BLADDER PRESERVATION STRATEGIES FOR THE MANAGEMENT OF MUSCLE INVASIVE BLADDER CANCER

STATE OF THE ART LECTURE SERIES
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Objectives:

- Epidemiology of Muscle Invasive Bladder Cancer (MIBC)
- Natural history of MIBC and Impact Radical Cystectomy
- Historical Overview of Monotherapy Alternatives to Cystectomy
- Multimodal Therapy for Bladder Preservation Therapy (BPT)
- Bladder Preservation Failures and Non-Ideal patients
- Quality of Life outcomes
- The Troubles with Multi-Disciplinary Disease Research
Epidemiology

- Fourth most common cancer in men
- 7th most common in women
- 6th leading cause of cancer death in the US (ACS 2009)
- Slight decrease in bladder cancer deaths in NA, with no clear difference in muscle invasive disease
- Increasing incidence globally with the majority of growth in third world countries (exposure)
- 15-20% of bladder cancer is muscle invasive bladder cancer (MIBC)
Cystectomy + Lymph node dissection

• Radical cystectomy was introduced in 1867 in Germany
• First long term outcomes reported in 1962 showing 5-year survival rates of 21-49% (Whitmore and Marshall, 1962)
• Bowel diversion strategies have attempted to improve QoL in cystectomy patients
• Although mortality rates with radical cystectomy have decreased by 50% over the last 20 years, survival rates with surgery alone have remained steady, with 5-year survival rates have slowly improved
• MIBC still has a poor long term prognosis, related to depth of involvement and nodal status
# Natural History

- Radical Cystectomy (Stein, 2001)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Recurrence</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 year</td>
<td>10 year</td>
</tr>
<tr>
<td></td>
<td>5 year</td>
<td>10 year</td>
</tr>
<tr>
<td>T2</td>
<td>-N</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>+N</td>
<td>50</td>
</tr>
<tr>
<td>T3a</td>
<td>-N</td>
<td>78</td>
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<tr>
<td></td>
<td>+N</td>
<td>41</td>
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<tr>
<td>T3b</td>
<td>-N</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>+N</td>
<td>29</td>
</tr>
<tr>
<td>T4a</td>
<td>-N</td>
<td>50</td>
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<tr>
<td></td>
<td>+N</td>
<td>33</td>
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</tbody>
</table>
Comparison of 5y survival for Radical cystectomy based on pathologic stage

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N)</th>
<th>No Residual Disease at Cystectomy (%)</th>
<th>Operative Mortality (%)</th>
<th>Survival by Pathologic Stage (%)</th>
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</thead>
<tbody>
<tr>
<td>Ritchie et al. (1975)</td>
<td>134</td>
<td>8</td>
<td>8.5</td>
<td>40 P2 20 P3 18 P4</td>
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<tr>
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<td>174</td>
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<td>4</td>
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<td>Mathur et al. (1981)</td>
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<td>7</td>
<td>3.4</td>
<td>77 P2 33 P3 29 P4</td>
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<td>Skinner and Lieskovsky (1984)</td>
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<td>Montie et al. (1984)</td>
<td>99</td>
<td>10</td>
<td>9</td>
<td>69 P2 57 P3 36 P4</td>
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<tr>
<td>Giuliani et al. (1985)</td>
<td>202</td>
<td>—</td>
<td>12</td>
<td>56 P2 19 P3 0 P4</td>
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<tr>
<td>Roehrborn et al. (1991)</td>
<td>280</td>
<td>—</td>
<td>2.1</td>
<td>63 P2 36 P3 24 P4</td>
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<tr>
<td>Pagano et al. (1991)</td>
<td>261</td>
<td>9</td>
<td>1.8</td>
<td>57 P2 15 P3 21 P4</td>
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<td>Wishnow and Tenney (1991)</td>
<td>188</td>
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<td>1.1</td>
<td>79 P2 46 P3 33 P4</td>
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<td>Waehre et al. (1993)</td>
<td>227</td>
<td>25</td>
<td>—</td>
<td>61 P2 36 P3 29 P4</td>
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<td>Vieweg et al. (1999)</td>
<td>686</td>
<td>—</td>
<td>—</td>
<td>58 P2 22 P3 15 P4</td>
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<td>Stein et al. (2001)</td>
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<td>3</td>
<td>72 P2 48 P3 33 P4</td>
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<td>Dalgarni et al. (2001)</td>
<td>284</td>
<td>10.7</td>
<td>—</td>
<td>59 P2 25 P3 29 P4</td>
</tr>
<tr>
<td>Madersbacher et al. (2003)</td>
<td>507</td>
<td>—</td>
<td>4.5</td>
<td>74 P2 52 P3 36 P4</td>
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<tr>
<td>Grossman et al. (2003)</td>
<td>154</td>
<td>15</td>
<td>0.6</td>
<td>75 P2 24 P3 24 P4</td>
</tr>
</tbody>
</table>

* Southwest Oncology Group (SWOG) 8710 trial cystectomy-alone arm.
† Pathologic stage T3 and T4a combined.

Sternburg, 2007
Natural History - Cystectomy

Cystectomy for MIBC:
- Complete excision of tumor burden
  - Up to 30% of patients are upstaged with cystectomy pathology
  - pT2-Ta tumors with +N disease 15-20%
- Complications
  - Reported peri-op morbidity mortality
    - 0.5-2% mortality
    - 61% Low grade morbidity, 13% high grade morbidity within 90d
      - Bowel 29%, Infectious 25%, Wound 15%
  - Long term morbidity/complications
- Quality of life
Why Bladder Preservation?
Is there away to avoid morbidity of a radical cystectomy with equivalent oncologic and survival outcomes?
Consider:

The Patient

Radical TUR
Chemotherapy
Radiotherapy
Intra-arterial chemotherapy
Partial cystectomy
Combination of all above

The Disease

Tumor stage/Grade
Resection and re-resection pathologic outcomes
Treatment response
Hydronephrosis
LN involvement
CIS
<4 or 5cm lesion
Which is your patient:

- **Limited Stage**
  - RCT and cystectomy possible
- **Limited Stage**
  - Cystectomy not possible (comorbidities)
- **Advanced Stage**
  - Cystectomy not adequate (distant metastases)

RT/RCT for palliation.

Curative intention:
- RCT as alternative to radical cystectomy.

Ott et al., 2009
Which is your patient:

Ott et al., 2009
Is there a way to reduce the morbidity of cystectomy and diversion?

Attempts at single therapy

- Radical TUR
  - Whitmore et al. 1977
  - Barns et al., 1977
  - Solsona et al., J Urol, 1998
- Partial Cystectomy
  - MSK, 2002
  - MD Anderson, 2004
- Radical EBRT
- Primary Chemotherapy
Radical TUR
Radical TUR


- 10 year follow-up of 463 MIBC patients undergoing ‘Radical TUR for bladder cancer’
- TURBT, followed by a second restaging TUR (deep to scar, peripheral normal tissue)
- Conservative management or cystectomy +/- BCG

- Followed for 10y:
  - 35% (n=145) offered bladder preservation
    - pT0 (96), or down staged to pT1 (55)
  - 36% elected immediate cystectomy
Survival of all patients undergoing BP

Survival of patients undergoing BP with T0 disease

Survival of Patients undergoing BP with T1 disease
Bladder Preservation Rates

Overall Survival for T1 v T0

Progression Free Survival for T1 v T0
Herr, 1979-1989

Of those undergoing upfront cystectomy

- 35% of patients were upstaged:
  - pT0 19%, pT1 25%, pT2 17%, pT3 17%, N+ 9%
  - 75% survival at 10 years

“18% of late recurrences leading to mortalities could have been prevented with upfront cystectomy”

Concluded:

- In select patient radical TUR alone has 10y survival comparable to radical cystectomy
- pT0 10y survival 85%, with 68% retained bladders
- pT1 10y survival 57% with 27% retained bladders

- Prospective follow-up (58) radical TUR, with bladder preservation for T2/t3a bladder cancer between 1981 and 1986 for 5 years,
  - Compared to radical TUR (1987-1991) w f/u 5y
  - Compared to control group of T2-T3a,N0-3,M0 patients treated with cystectomy
- Recurrence: urothelial tumor limited to the mucosa
- Progression: MIBC, M+, recurrence with need for cystectomy

- **Five year results:**
  - Bladder preservation
  - 48% RFS, 75% PFS
  - 41% with bladder insitu
  - Lower progression with time (27% 1981-86, 17% 1986-91)
  - Lower DSM with time (25.4% 1981-86, 14.8% 1986-91)

- **Ten year results:**
  - Disease Free Survival 23.7%
  - Cancer specific mortality 25%
  - Mortality-unrelated to bladder cancer 50%

- **Compared to cystectomy patients**
  - DSS was equal
  - CIS: poorer PFS, RFS in TUR but not in cystectomy patients
  - Cystectomy patients were all comers, however TUR patients were selected as N0 disease
Partial Cystectomy
Advantages of partial cystectomy

- Minimal morbidity
- Minimal sexual dysfunction
- Improved body image
- Quality of life improvements
- Maintenance of continuity of GU tract
- Full thickness tissue for pathologic staging

Resection of a “free-wall,” without trigone involvement, or the need for ureteric reimplant. Bilateral pelvic node dissection +/- 2cm margins, with frozen sections
## Partial Cystectomy

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>N=37, F/U</td>
<td></td>
<td>N=57, F/U=33m</td>
</tr>
<tr>
<td>Adjuvant:</td>
<td></td>
<td>Adjuvant:</td>
</tr>
<tr>
<td>RT 3%, Chemo 24%,</td>
<td></td>
<td>Chemo 20%</td>
</tr>
<tr>
<td>BCG 8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>67%</td>
<td>5y OS</td>
<td>69%</td>
</tr>
<tr>
<td>87%</td>
<td>5y DFS</td>
<td>67%</td>
</tr>
<tr>
<td>39%</td>
<td>5y RFS</td>
<td></td>
</tr>
<tr>
<td>65%</td>
<td>Bladder <em>in situ</em></td>
<td>75%</td>
</tr>
<tr>
<td>24% Superficial</td>
<td>Recurrence</td>
<td>12% Superficial</td>
</tr>
<tr>
<td>24% Advanced</td>
<td></td>
<td>26% Advanced</td>
</tr>
</tbody>
</table>
• MD Anderson: solitary initial tumor, without CIS, and resection margin >2cm
  • 5% of cases in literature → 2.5% of cases
  • 5y Mortality: 16% mortality vs. 30-40% with cystectomy
  • Of those with superficial recurrence ½ were treated with TUR and BCG
  • Several had late recurrences over 138m, therefore important to recognize lifetime follow-up
  • Adjuvant treatment should be considered in all patients who have node positive or T3b tumors, as they are associated with advanced recurrence)
All partial cystectomy patients reviewed:
- All had frozen sections, and LN dissections performed
- 6.2% of total candidates underwent partial cystectomy
- 26% CIS, 9% multifocal disease, 60% T2 lesions
- 4 pt with positive margins. 3 had false-negative FS
- 9% +N

**Regression analysis:**
- multi-focality, CIS, location affect RFS rate.
- CIS and +N associated with advanced recurrence (T3/4 or metastatic disease)

**Complication rate 10%**
- Survival rate = to cystectomy rates (though <5 years f/u, most recurrences occur within 2y) and equal to Shipley trimodal protocol without use of RT in the majority of patients.
Radical Radiotherapy
Radical Radiotherapy

- Initiated in the 1970-1980s was trialed as radical therapy for bladder TCC
- Felt to aid in local control, when extra-vesical involvement could not be managed by surgical resection alone

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cases (n)</th>
<th>Median follow-up (months)</th>
<th>T category</th>
<th>5-year overall survival (%)</th>
<th>5-year overall survival, bladder preserved (%)</th>
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</thead>
<tbody>
<tr>
<td>Stein et al. [64]</td>
<td>1024</td>
<td>122</td>
<td>T1, T2-4</td>
<td>74, 55</td>
<td>51, 38</td>
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<tr>
<td>Dalbagni et al. [65]</td>
<td>300</td>
<td>65</td>
<td>T1, T2</td>
<td>64, 59</td>
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<td>Madersbacher et al. [66]</td>
<td>507</td>
<td>45</td>
<td>T1, T2, T3-4</td>
<td>63, 59, 26</td>
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<td>Hautmann et al. [67]</td>
<td>788</td>
<td>35</td>
<td>T1, T2, T3-4</td>
<td>58, 63, 35</td>
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<td>Shariat et al. [68]</td>
<td>888</td>
<td>39</td>
<td>T1-4</td>
<td>59</td>
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<td>Erlangen data [19,21,45]</td>
<td>525</td>
<td>35</td>
<td>T1, T2-4</td>
<td>71, 56</td>
<td></td>
</tr>
</tbody>
</table>

Ott et al., 2009
Radical Radiotherapy

Analysis of failure:

- **Shipley, 1985**
  - 5y survival subgroup analysis (50-60gy)
    - Sessile lesion 0% (vs. papillary lesion 62%)
    - Incomplete TUR 17% (vs. 54% with complete TUR)
    - Hydronephrosis 14% (vs. 47% without hydro)
    - T4 Bladder cancer 9% (vs. 45% T2-3)

- **Gospodarowicz, 1989**
  - Overall 5y survival: 31.6%, DSS 44%
    - 27% alive with bladder *in situ*
    - Tumor configuration (Amenable to TUR, size <4cm)
    - Hemoglobin
    - Clinical stage
    - CIS
Radical Radiotherapy

- Alternate methods of Radiotherapy were delivered due to the subtle nature of mucosal involvement of TCC
- Intra-operative radiotherapy was developed by Japanese directing energy directly at the tumor base
- Brachytherapy using radium needle implants were used for superficial and invasive TCC, leading to 5y survival rates of 31%
- Very good local control and DSS rates were seen for Ta and T1 disease
Radical Radiotherapy

- Data for invasive disease was fueled by successful trials with superficial disease, giving superior results over intra-vesical chemotherapy
- Intra-operative RT +/- Brachy and EBRT had promising preliminary results, with higher morbidity

<table>
<thead>
<tr>
<th>Series</th>
<th>Treatment</th>
<th>No.</th>
<th>5y local control</th>
<th>5y survival</th>
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</thead>
<tbody>
<tr>
<td>Tokyo</td>
<td>IORT</td>
<td>38</td>
<td>82%</td>
<td>62%</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>EBRT, IO-Brachy</td>
<td>328</td>
<td>77%</td>
<td>56%</td>
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<tr>
<td>Amsterdam</td>
<td>EBRT IO-Brachy</td>
<td>85</td>
<td>74%</td>
<td>55%</td>
</tr>
<tr>
<td>Creteil</td>
<td>EBRT, IO-brachy</td>
<td>24</td>
<td>93%</td>
<td>58%</td>
</tr>
</tbody>
</table>
Chemotherapy
Chemotherapy for MIBC

• Introduced in 1980, has been used in conjunction with TUR and surgical resection of primary tumor burden.
• Since 1976 platinum based chemotherapy has been shown to be efficacious in advanced bladder cancer (Yagoda, 1976)
• Has been found to minimally affect toxicity, while acting synergistically with RT, confirmed phase I-II studies 1980-1982
• Help treat microscopic disease outside the bladder, and any residual micro-metastases (most likely in normal radiographic appearing lymph nodes)
## Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Neoadjuvant Arm</th>
<th>Standard Arm</th>
<th>Patients (N)</th>
<th>Survival</th>
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<tbody>
<tr>
<td><strong>Cisplatin chemotherapy</strong></td>
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<td></td>
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<tr>
<td>Australia/UK(^{17})</td>
<td>Cis/RT</td>
<td>RT</td>
<td>255</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>Cis/RT or preop</td>
<td>RT or preop</td>
<td>99</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>RT+cytectomy</td>
<td>RT+cytectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada/NCI(^{18})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain (CUETO)(^{19})</td>
<td>Cis/cystectomy</td>
<td>Cystectomy</td>
<td>121</td>
<td>No difference</td>
</tr>
<tr>
<td><strong>Combination chemotherapy</strong></td>
<td></td>
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<tr>
<td>EORTC/MRC(^{11})</td>
<td>CMV/RT or cystectomy</td>
<td>RT or cystectomy</td>
<td>976</td>
<td>5.5% difference in favor of CMV (P = 0.06)</td>
</tr>
<tr>
<td>SWOG Intergroup(^{20})</td>
<td>M-VAC/cystectomy</td>
<td>Cystectomy</td>
<td>298</td>
<td>Benefit with M-VAC</td>
</tr>
<tr>
<td>Italy (GUONE)(^{16})</td>
<td>M-VAC/cystectomy</td>
<td>Cystectomy</td>
<td>206</td>
<td>No difference</td>
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<td>Italy (GISTV)(^{21})</td>
<td>M-VEC/cystectomy</td>
<td>Cystectomy</td>
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<td>No difference</td>
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<td>Genoa(^{22})</td>
<td>Cis/5-FU/RT/cystectomy</td>
<td>Cystectomy</td>
<td>104</td>
<td>No difference</td>
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<td>Nordic I(^{24})</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>
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<tr>
<td>Nordic II(^{16})</td>
<td>MTX/Cis/cystectomy</td>
<td>Cystectomy</td>
<td>317</td>
<td>No difference</td>
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<tr>
<td>Abol-Enein et al.(^{23})</td>
<td>CarboMV/cystectomy</td>
<td>Cystectomy</td>
<td>194</td>
<td>Benefit with CarboMV</td>
</tr>
</tbody>
</table>
Earliest Study:

- 57 patients underwent high dose methotrexate (+/- Leucovorin) after TUR.
- 6 months post chemotherapy re-resection showed:
  - 57% pt tumor free
  - 8.7% superficial recurrence
  - 22.8% persistent T2 disease
  - 5% progression in stage
  - 5% mortality secondary to methotrexate
- 2 year DFS with bladder in situ rate: 79%
111 patients with MIBC disease, who on re-TUR had residual pT2 received MVAC x 4
54% complete responders (pT0 on TUR) and were advised to undergo local surgical management (if feasible)
Post MVAC complete responders:
- 28 managed with TUR (refused definitive surgery)
- 15 had partial cystectomy
- 17 had radical cystectomy
- None received radiotherapy
Follow-up 10 years (8-13y)
- 76% of T2 and 64% of T3 survived @ 10 years
Not randomly assigned to each treatment arm

Majority of RC patients were T3 patients

53% salvage cystectomy
(7)

47% died of recurrence
(6)

<2y: mets from original
(2)
tumor

>2y: mets from recurrence

Herr, Bajorin, Scher, 1998

<table>
<thead>
<tr>
<th>Sx</th>
<th>No patients</th>
<th>Invasive relapse</th>
<th>10y OS</th>
<th>Bladder intact</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUR</td>
<td>28</td>
<td>29% (6)</td>
<td>75%</td>
<td>61%</td>
</tr>
<tr>
<td>PC</td>
<td>15</td>
<td>33% (7)</td>
<td>73%</td>
<td>53%</td>
</tr>
<tr>
<td>RC</td>
<td>17</td>
<td>0</td>
<td>65%</td>
<td>0</td>
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</tbody>
</table>
Results:

- **Those who respond favorably to chemotherapy have an increased rate of survival (70%@10y)**
- Only 1 partial cystectomy patient was upstaged, therefore 30% upstaging from TUR to RC pathology does not necessarily apply to post-chemo
- **Preventable CSM:**
  - Mets after 2 years, were attributed to “Metastasis from recurrence” and thus 9% of patients could have been spared CSM with upfront cystectomy
  - Up to 15% if all mets after pT0 status are counted
Sternberg et al., 2003

MVAC and Survival/Recurrence for Local disease

- 104 patients MIBC
  - 3 cycles MVAC, then re-staged and clinically assigned to
    - 60% TURBT alone
      - Complete response, or down staged to superficial disease
    - 37.5% radical cystectomy
      - Poor responder to MVAC
    - 12.5% partial cystectomy
      - CR or PR to MVAC, solitary lesion at dome/lateral wall, first episode of TCC, no CIS, good bladder capacity
Sternberg et al., 2003

Median survival for entire group: 7.5y

**TUR:**
- 60% survival at 5y
- and 44% with bladder *in situ*

**Partial Cystectomy:**
- 5y survival 69%
- only 1 of 7 required salvage cystectomy

**MVAC**
- 5y survival: pT0: 69%
  - ≥pT2: 26%

**Octogenarian Survival**
- 67% @ 5y, median survival 9y
- 47% maintained their bladder
EORTC-MRC

- Randomized CMV neoadjuvant Tx to clinically selected treatment modalities
  - CMV x3 vs. No Chemo
  - followed by
    - Radical Radiotherapy
    - RT + Cystectomy
    - Cystectomy

- 976 patient with T2-4a N0M0 Bladder Cancer
  - (106 hospitals, 20 countries)
EORTC MRC

- Complete Response:
  - Cystectomy: 32% with CMV and 12% without

- CMV:
  - **3 year 5.5% absolute survival benefit** (50% vs 55.5% with chemotherapy)
  - Median survival 44m vs. 37.5m
  - 15% risk reduction of death, 21% decrease in metastatic disease

- 1% mortality due to CMV compared to 3.7% due to cystectomy
- No accounting for salvage therapy, unknown intention to treat

These results are statistically unreliable as the study was powered to detect a 10% change (risking these number are due to chance). Should this study be powered to detect a 5% difference, 3500 pt’s would need to be enrolled.
EORTC MRC – 10 year follow up

- Follow up analysis of CMV neo-adjuvant chemotherapy
  - 3y survival benefit (50→56%)
  - 10y survival benefit (30→36%)
  - 16% risk of death reduction
- Local relapse for definitive mgt
  - Definitive RT: 49% with CMV, without CMV48%
  - Cystectomy: 40% with CMV, without CMV39%
- Improved Progression and survival rates if only cystectomy patients accounted for (survival improvement of 25%, however, patients were clinically selected to this population)
- Identical numbers to ABC Meta-analysis (Lancet, 2003) reviewing 2700 patients
Multimodal Bladder Preservation
Bladder Preservation Protocols

Initial + f/u TUR

Rads/Chemo

Restaging TUR

Non-Responder

Residual Tumor

MIBC

Superficial

Salvage Cystectomy

CR

Relapse

Superficial

MIBC

TUR w/out Intravesical Tx

Neo-adjuvant Rads/Chemo

Restaging TUR

Non-Responder

CR

Immediate Cystectomy

Consolidative Rads

Relapse
Bladder Preservation Protocols

1. TUR, reTUR
   - Chemo+Rads
     - Restaging TUR
       - Non-Responder
         - Residual Tumor
           - MIBC Superficial
             - Salvage Cystectomy
           - Superficial MIBC
             - TUR w/out Intravesical Tx
       - CR
         - Relapse
           - MIBC Superficial
             - Immediate Cystectomy
               - Consolidative Rads
                 - Relapse
     - Neo-adjuvant Rads/Chemo
       - Restaging TUR
         - Non-Responder
           - CR
             - Immediate Cystectomy
               - Consolidative Rads
Only prospective randomized trial

**Neo-adjuvant cisplatin** to rads + cystectomy or Radical RT with **MIBC**

- 99 patients (t2-4) followed for 6.5y
  - 36% T2-3a
  - 64% T3b-4
- **Randomized**: Concurrent chemo vs. No chemo
- **Clinically selected**: Radical RT vs. Consolidative RT+cystectomy
NCIC CTG 1996 (continued)

Response to RT
• CR: Cisplatin arm 47% vs. Control 29% (p=.16)

Overall Survival
• Median f/u 6.5y: Cisplatin 47% vs. Control 33% (p=.34)
  • Clinical stage (T2-3a vs. 3b-4), absence of elevated WBC were favorable, and cisplatin effect was not significant
• No difference in chemo/RT SE
• No complications affecting surgery. 11 Radical RT required salvage cystectomy
NCIC CTG 1996 (continued)

Progression Free Survival
• No difference

Failure pattern
• Pelvic relapse @2y: Cisplatin 33% vs. Control 53%
  @5y: Cisplatin 40% vs. control 59%
• significant effects on local control: stage, grade, cisplatin use

Conclusions:
• Some benefits for local control
• Downstaged cystectomy pathology to pT0 in 54% of patients vs. 40% in control groups
• Single agent cisplatin does not affect survival
• Underpowered to adequately display effect
• Confirmed via meta-analysis
• 190 patients from 1987-1997, T2-4a disease
  *during various phase I-II protocols*
• Triple therapy:
  • TURBT with Chemotherapy and induction RT (40Gy)
    • Cisplatin or MCV
  • Re-evaluated and CR received concurrent chemo and RT (65Gy)
    • If incomplete response: radical cystectomy
Shipley et al., 2002 (continued)

- 66 Radical cystectomy (35%)
  - 41 for incomplete response
  - 25 for salvage, 0 for bladder cripple
- Stage
  - 5y Survival: T2 (75%), T3-4a (57%)
  - Rate of Mets: T2 (22%), T3-4a (37%)
- Intact bladder and T2 dz:
  - 5y survival 57%, 10y survival 50%
  vs. T3-4a: 5y 35%, 10y survival 24%
- Hydronephrosis
  - Reduced CR (37% vs 68%)
- Tumor Grade, Neo-adjuvant Chemo
  - No improvement to CR, OS, DSS, Met free survival

- Cystectomy OS
  5y: 48%, 10y: 41%
  (No diff between salvage and upfront cystectomy)
Importance of Resection Status:
• 473 patients were prospectively followed in several protocols, and analyzed with up to 15year follow up
  • 70% Radical TURBT with Chemo/Rads
    Cis/Carbo/5FU/Gem: single or combo
  • 30% Radical TURBT with Rads
    • Due to Age, Comorbidities, ECOG
Significant prognostic indicators
Non-Responders

- 62% had pR1,2 disease after rads +/- chemo
- 26% (125) underwent surgical intervention
  - 51% salvage cystectomy
  - 49% re-TUR +/- intravesical therapy

All Patients

- Medial survival 57.5m
- OS 5y:50%, 10y: 30%, 15y:19%
- Predictors of Outcomes
  - Stage
  - LVI, and +LN
  - Resection status
- NO DIFFERENCE
  - CIS, Multi-focality, Grade
Table III. Estimated median survival time in months and 5-, 10- and 15-year survival rates (YSRs) according to the Kaplan-Meier method (95% confidence intervals in brackets) for 473 patients following TURBT and RCT or RT.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median survival (months)</th>
<th>5-YSR (%)</th>
<th>10-YSR (%)</th>
<th>15-YSR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>119 (89-166)</td>
<td>71 (62-80)</td>
<td>48 (39-59)</td>
<td>30 (21-44)</td>
</tr>
<tr>
<td>T2/3</td>
<td>44 (32-61)</td>
<td>45 (40-51)</td>
<td>26 (22-32)</td>
<td>16 (12-22)</td>
</tr>
<tr>
<td>T4</td>
<td>17 (11-22)</td>
<td>15 (7-33)</td>
<td>7 (2-26)</td>
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<tr>
<td><strong>Acc. Cis</strong></td>
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<td></td>
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</tr>
<tr>
<td>Cis</td>
<td>62 (37-93)</td>
<td>52 (43-63)</td>
<td>29 (21-41)</td>
<td>15 (8-28)</td>
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<tr>
<td>No Cis</td>
<td>58 (40-66)</td>
<td>48 (43-53)</td>
<td>30 (26-36)</td>
<td>19 (15-24)</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>58 (42-71)</td>
<td>49 (42-57)</td>
<td>29 (23-37)</td>
<td>17 (11-24)</td>
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<tr>
<td>III</td>
<td>49 (34-68)</td>
<td>47 (41-54)</td>
<td>29 (24-36)</td>
<td>21 (16-28)</td>
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<tr>
<td><strong>cN</strong></td>
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<td></td>
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</tr>
<tr>
<td>0</td>
<td>63 (49-75)</td>
<td>52 (47-57)</td>
<td>32 (28-38)</td>
<td>19 (15-25)</td>
</tr>
<tr>
<td>+</td>
<td>20 (16-26)</td>
<td>14 (6-34)</td>
<td>10 (4-30)</td>
<td>10 (4-30)</td>
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<tr>
<td><strong>pL</strong></td>
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</tr>
<tr>
<td>1</td>
<td>26 (19-38)</td>
<td>37 (31-45)</td>
<td>22 (16-29)</td>
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<tr>
<td>0</td>
<td>74 (62-96)</td>
<td>56 (51-63)</td>
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<tr>
<td>Uni</td>
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<td>29 (24-36)</td>
<td>18 (13-24)</td>
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<td><strong>Response</strong></td>
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</tr>
<tr>
<td>CR</td>
<td>80 (70-98)</td>
<td>60 (55-66)</td>
<td>38 (33-44)</td>
<td>23 (18-29)</td>
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<tr>
<td>NR</td>
<td>17 (14-21)</td>
<td>23 (16-31)</td>
<td>12 (8-20)</td>
<td>9 (5-17)</td>
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<td><strong>Resection</strong></td>
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<tr>
<td>R0</td>
<td>116 (92-168)</td>
<td>70 (63-78)</td>
<td>46 (37-56)</td>
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<tr>
<td>R1</td>
<td>54 (36-70)</td>
<td>47 (39-55)</td>
<td>30 (23-38)</td>
<td>16 (10-23)</td>
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<tr>
<td>R2</td>
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<td>16 (11-23)</td>
<td>7 (4-13)</td>
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<tr>
<td><strong>Therapy</strong></td>
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</tr>
<tr>
<td>R1</td>
<td>29 (23-42)</td>
<td>36 (29-45)</td>
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<td>8 (4-14)</td>
</tr>
<tr>
<td>RCT</td>
<td>70 (58-85)</td>
<td>54 (49-60)</td>
<td>36 (31-43)</td>
<td>24 (19-30)</td>
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</tbody>
</table>

Table IV. Estimated median survival time in months and 5-, 10- and 15-year survival rates (YSRs) according to the Kaplan-Meier method (95% confidence intervals in brackets) for 331 patients treated with TURBT and RCT.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median survival (months)</th>
<th>5-YSR (%)</th>
<th>10-YSR (%)</th>
<th>15-YSR (%)</th>
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</thead>
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<td><strong>pT</strong></td>
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</tr>
<tr>
<td>1</td>
<td>121 (104-166)</td>
<td>73 (68-83)</td>
<td>51 (41-64)</td>
<td>34 (23-50)</td>
</tr>
<tr>
<td>2/3</td>
<td>60 (42-75)</td>
<td>50 (44-57)</td>
<td>32 (26-39)</td>
<td>22 (17-30)</td>
</tr>
<tr>
<td>4</td>
<td>18 (10-50)</td>
<td>16 (6-45)</td>
<td>11 (3-39)</td>
<td>0</td>
</tr>
<tr>
<td><strong>cN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>77 (66-98)</td>
<td>58 (52-64)</td>
<td>39 (33-46)</td>
<td>27 (21-34)</td>
</tr>
<tr>
<td>+</td>
<td>20 (12-54)</td>
<td>14 (5-41)</td>
<td>10 (3-36)</td>
<td>0</td>
</tr>
<tr>
<td><strong>pL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>27 (23-67)</td>
<td>43 (35-53)</td>
<td>28 (21-37)</td>
<td>17 (11-26)</td>
</tr>
<tr>
<td>0</td>
<td>91 (68-119)</td>
<td>60 (54-67)</td>
<td>40 (34-48)</td>
<td>28 (21-37)</td>
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<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>93 (77-121)</td>
<td>64 (58-70)</td>
<td>43 (37-50)</td>
<td>27 (21-35)</td>
</tr>
<tr>
<td>NR</td>
<td>17 (14-24)</td>
<td>25 (17-37)</td>
<td>15 (8-26)</td>
<td>13 (7-24)</td>
</tr>
<tr>
<td><strong>Resection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>142 (93-168)</td>
<td>72 (64-81)</td>
<td>50 (41-62)</td>
<td>45 (35-59)</td>
</tr>
<tr>
<td>R1</td>
<td>61 (42-85)</td>
<td>52 (43-61)</td>
<td>35 (28-46)</td>
<td>22 (14-32)</td>
</tr>
<tr>
<td>R2</td>
<td>26 (17-50)</td>
<td>37 (29-48)</td>
<td>19 (12-29)</td>
<td>8 (4-18)</td>
</tr>
</tbody>
</table>

CR: Complete responder; NR: non-responder.
What happens when preservation fails?
Bladder Sparing: TUR $\rightarrow$ combo chemo/rad $\rightarrow$ reTUR
20% underwent salvage cystectomy for residual or recurrent tumor
- 37% were incomplete responders
- 15% with initial complete response developed relapse
- 35% of these patients were unable to undergo radical cystectomy or refused.

- Time to local failure
  - Non-responders: 6m
  - Complete Responders: 18m
  - Invasive relapse: 26m
- DSS: 50% @5y, and 45% @10y
- 2% (3) cystectomy for bladder cripples due to high dose RT
Incomplete Response and Metastatic Spread:
415 patients between 1982-2000 reviewed

Metastatic disease: 98 patients
• Metastatic free survival rate:
  • Complete Responders: 79%
  • Incomplete responders: 52%

Positive predictors of +M:
T Stage
+LN
Vascular involvement
Patients with MIBC underwent:
  • Radical TUR, Combo Chemo, Re-staging TUR
• Re-Staging TUR:
  >pT0(54%, n=40): underwent cystectomy
  pT0 (46%): 10 underwent immediate cystectomy, rest observed
  • 6/10 had residual pT2 TCC on pathology
• 2year OS:
  • All patients: 59%
  • cT0 patients: 75%
    • cT0 observation: 76%
    • cT0 immed. Cystectomy: 70%
Which is your patient:

- Limited Stage
  - RCT and cystectomy possible

- Limited Stage
  - Cystectomy not possible (comorbidities)

- Advanced Stage
  - Cystectomy not adequate (distant metastases)

Curative intention:
- RCT as alternative to radical cystectomy.

RT/RCT for palliation.

Ott et al., 2009
Who is a non-cystectomy candidate?

- No consensus on who is/not a candidate for cystectomy

<table>
<thead>
<tr>
<th>Age</th>
<th>Diabetes</th>
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</thead>
<tbody>
<tr>
<td>Functional Status</td>
<td>Renal insufficiency</td>
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<tr>
<td>Psychological state</td>
<td>Rheumatic disease</td>
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<tr>
<td>Cognitive status</td>
<td>Economic support</td>
</tr>
<tr>
<td>Nutritional status</td>
<td>Social support</td>
</tr>
<tr>
<td>Medical comorbidities</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary disease</td>
<td></td>
</tr>
</tbody>
</table>

- Many tools (Comprehensive Geriatric Assessment, Vulnerable Elders Survey 13, etc.) to help prognosticate older patients success with invasive therapy

- Patient preference
Bladder Cancer

Outcome of Patients Who Refuse Cystectomy after Receiving Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer

Harry W. Herr*

- Patients with MIBC for who had residual ≥T2 disease and underwent cisplatin based neo-adjuvant chemotherapy, to be followed with cystectomy
- Improved Re-TUR and (+/-improved CT scan): pts refused cystectomy, though fit for surgery
- Followed for a median of 7 years
63 patients @ median 6y f/u
- 64% MFS, 54% kept bladder
- 64% DSS, median survival 23m
- CR post-chemo Re-TUR
  - 93% survived
  - 38% of incomplete TUR patients survived (median survival 36m)
- Relapse survival
  - 64% had local recurrences
    - 60% MIBC at median 16mos with a 75% mortality rate (median survival 39m)
  - 57% recurrences at previous tumor site
14 Patients underwent salvage cystectomy
  - 42% (6) were salvaged
  - 58% (8) died of metastatic disease
No relapse: 83% survival
Herr, 2002 continued

• 30% of those who died had initial local recurrence (after complete response) and could have been prevented by upfront cystectomy
• Most mortalities had poor prognostic tumor features:
  • cT3–4 tumors (70%), multiple invasive primary tumors (61%), incomplete tumor resections (91%), palpable mass and larger tumors (52%), prior history of bladder tumors (63%), hydro (39%), bladder relapse w/in one year (83%)
• Patients who survived with an intact bladder had clinically confined good prognostic features:
  • (cT2) to the bladder (74%), solitary tumors (94%), tumors less than 5 cm in size (74%), a complete resection (62%), no palpable mass (82%), no hydro (85%), first TCC presentation (77%).
Octogenarians and Cystectomy

- SEER (1989-1999): Radical cystectomy and partial cystectomy had the greatest risk reduction from death in patients over 80. However, significantly less likely to receive surgical management (Hollenbeck et al., 2004)
- 1142 patients reviewed between 1995-2005, showing no increased incidence of complications in patients undergoing radical cystectomy (Donat et al. 2010)
Quality of Life
Quality of Life

- Bladder preservation has not been directly compared to cystectomy/diversion patients
- Neo-bladder, may have higher QoL scores than cystectomy, in highly selective patient population
- Long term consequences and sustained quality of life has been investigated only in patients with the best outcomes (long OS interval, long DFS interval)
Quality of Life

- Bowel Function is preserved in most patients
  - Some diarrhea and urgency
- Voiding function may decrease (urgency, urinary incontinence) at 3 years
- Sexual Function is preserved (6y)
  - 36% had full erections
  - 50% capable of
    - Penetration
    - Orgasm
    - Ejaculation
- Cystectomy patients
  - Lower overall QoL, Lower sexual function, and physical condition

(Lagrange et al., 2009) (Caffo et al., 2001)
Zeitman, 2003

- Bladder Function
  - UDS on 32 Bladder Preservation patients with median 6 year follow-up (currently disease free status)
  - 24/32 had normal bladder function (with
  - If Radiotherapy included in protocol
    - Compliance
    - Functional bladder filling
  - Women had more incont.
    - 20%, mixed
    - stress>urge
Quality of Life

- Katsuyoshi et al., 2008
  - Contacted all patients who underwent BPT in the previous 15 years who were still alive and free from recurrence. Compared them to new diagnosis of superficial bladder cancer patients and Japanese general public (age matched).
  - SF-36 QoL: groups

- IPSS: no significant difference
- EPIC: urinary irritability, obstructive sympt, bowel function worse in BPT. Bother, incontinence and sexual function were equal
The Future of Bladder Preservation

- **Randomized controlled trials** of preservation protocols: randomized to sparing vs. non sparing procedures (tumor criteria matched)
- **Expanding Radiation Technology**
  - Conformational
  - Brachy + EBRT
  - Photon tx
- **Chemotherapy**
  - Ideal combination
  - Hyperthermic chemotherapy
  - Intra-arterial chemotherapy
- **Patient stratification**
  - Genetic marker analysis
Problems with Multi-disciplinary Research
The Futility of Multi-Disciplinary Research

“Selective bladder preservation against radical excision trial (SPARE)” Dept of Urology, Royal Marsden Hospital, UK

- Randomized MIBC patients to Cystectomy vs. bladder preservation
- Preliminary planning was endorsed by
  - BUA, and UK Cancer Research Network
  - Multiple patient focus groups
  - External review boards
- Followed **ProtecT** trial which was well received
- Initiated in 2007, closed 2.5y for poor accrual
  - >800 eligible candidates, >250 not identified, 45 enrolled
- Several publications have addressed failure of accrual
Dis-SPARE, multidisciplinary bladder cancer research

- Complexity of patient pathway
  - Neo-adjuvant chemotherapy
  - Radiotherapy
  - Radical surgery
  - Endoscopic management
- Multiple departments offering concurrent care
  - Diagnosing urologist
  - Medical oncologist
  - Central urologist if cystectomy required
  - Radiation oncologist
  - Localized and centralized research nurses/teams
- Administrative restraints of Centralized and local ethics boards
- Patient and physician bias
Dis-SPARE, multidisciplinary bladder cancer research

Five challenges have been identified

• Investigators and recruiters had difficulty articulating the trial design in simple terms
• Complicated recruitment pathway involving staff across specialties/centers
• Communication between research staff and physicians often was inadequate
• Strong treatment preferences were expressed by many trial staff
• Eligibility of patients misjudged
Neo-adjuvant chemotherapy
3 cycles

Randomise (during 2nd cycle of chemotherapy)

Group 1
Surgery

Group 2
Selective Bladder Preservation

Cystoscopy (after 3 cycles)

Chemotherapy has worked well
Chemotherapy hasn't worked as well
Chemotherapy hasn't worked as well
Chemotherapy has worked well

Chemotherapy cycle 4
Chemotherapy cycle 4
Chemotherapy cycle 4
Radiotherapy

Surgery
Surgery
Surgery

*If the three cycles of chemotherapy do not clear your cancer well, you won’t receive a fourth cycle and will have surgery as soon as possible, whichever group you are in.
### Conclusion:

**Radical Cystectomy**
- Gold standard
- higher morbidity
- 5y OS: 45-70%
- Outcome related to:
  - LN+, Stage, time to cystectomy
- Improved survival with NA Chemo in MIBC
- Difficult to compare QoL

**Chemo/Radiation**
- Combo w Cisplatin
  - Cis, Gem, 5FU, Carbo, Vin, etc.
- Prognosticator
- Decreases Mets by 20%
- Preventable CSM of 10-20%
- Improved outcome:
  - Cystectomy
  - Complete response

**TURBT/Partial Cystectomy**
- OS: 57-85%, BP 68%
- 10% complication rate
- Preventable CSM of 18%
- Improved outcome:
  - T0 vs. T1
  - Size, solitary lesion
  - Nodes, frozen section

**Combination Therapy**
- Chemo + RT > RT alone (47 vs. 29%)
- Chemo + Sx > Sx alone
- 5yOS advantage: 5%
- Salvage cystectomy = outcomes (5yOS 48%)
- No long term bladder failure
Conclusion: Bladder Sparing

- **Benefits:**
  - In the appropriately selected patient, OS and DFS may be equivalent to the gold standard (Radical cystectomy).
  - High rates of bladder preservation over 5 years have been reported.
  - May be the only choice in some patients who are unfit for radical surgery, or due to patient preference.

- **Risk:**
  - Salvage cystectomy provides comparable survival outcomes, however preventable deaths have been reported from 19-30%.
  - Bladder preservation may lead to cystectomy for symptomatic relief of local therapy in a minority of patients.
  - Treatment dose radiation may prevent neobladder creation due to SB involvement.
  - Risk of metastatic disease without local recurrence.

- **Patient Satisfaction:**
  - Unclear in comparison to radical surgery.
  - Preserved bladder function and sexual function.
Conclusion:

If applied:

- **Tumor**: Best results from minimal disease
  - T2 > T3a > T3b-T4, <5cm, solitary lesion, not involving trigone, first presentation, no +LN/CIS/hydro
- Complete resection
- Complete response to chemo/radiation

- **Patient selection**: 
  - Able to undergo salvage cystectomy
  - Comorbidities do not preclude: chemotherapy/radiation
  - Able to understand complicated and changing clinical pathways
  - Reliable for intense follow-up

- **Follow-up**
  - H&P, cysto/cytology, Bloods, Imaging q3m x2years, then q6mx3y
  - If recurrence:
    - Salvage cystectomy
    - Superficial recurrence: TUR + Intravesical tx, though outcomes better with cystectomy
Objectives:

- Epidemiology of Muscle Invasive Bladder Cancer (MIBC)
- Natural history of MIBC and Impact Radical Cystectomy
- Historical Overview of Monotherapy Alternatives to Cystectomy
- Multimodal Therapy for Bladder Preservation Therapy (BPT)
- Bladder Preservation Failures and Non-Ideal patients
- Quality of Life outcomes
- The Troubles with Multi-Disciplinary Disease Research

Questions?
• Is bladder preservation a realistic long term goal
• Can initial attempt to spare the bladder fail to control progression of undetected invasive disease that may have been prevented by cystectomy
• Can recurrences progress, and spread to ultimately cause cancer death
  • YES
## SPARE Recommendation:

<table>
<thead>
<tr>
<th>Key issues</th>
<th>Findings</th>
<th>Changes/recommendations</th>
<th>Aspect of trial changed/recommendation for</th>
<th>Implementation</th>
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<tbody>
<tr>
<td>Difficulty in explaining the trial</td>
<td></td>
<td>Simplified flowchart</td>
<td>PI and protocol</td>
<td>Amended and ethical approval obtained</td>
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<tr>
<td>Randomisation period confusion</td>
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<td>Easy explanation of trial</td>
<td>Recruiter-patient interaction</td>
<td>Training session</td>
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<tr>
<td>Information overload</td>
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<td>Opened up randomisation period</td>
<td>Protocol</td>
<td>Amended and ethical approval obtained</td>
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<tr>
<td>Complex recruitment pathway</td>
<td></td>
<td>Two-stage information provision (chemo and post-chemo)</td>
<td>Recruitment and pre-recruitment interactions (also linked to streamlining of pathway)</td>
<td>Training session, Recruitment appointment tips document</td>
</tr>
<tr>
<td>Loaded terminology and unbalanced</td>
<td></td>
<td>Streamlining of recruitment pathway and information provision</td>
<td>Recruitment pathway</td>
<td>Streamlining recommendations document</td>
</tr>
<tr>
<td>Preferences</td>
<td></td>
<td>Use of neutral terms and equivalent information on both arms</td>
<td>PI</td>
<td>Amended and ethical approval obtained</td>
</tr>
<tr>
<td>Patients' strong treatment preferences</td>
<td></td>
<td>Eliciting and addressing concerns/preferences</td>
<td>Recruiter-patient interaction</td>
<td>Training session, Recruitment appointment tips document</td>
</tr>
<tr>
<td>Preferences</td>
<td>Patient preferences influenced by recruiter, and number of people in recruitment pathway</td>
<td>Acknowledging and reflecting on own preferences, Streamlining and limiting number of people involved in recruitment pathway</td>
<td>Recruiter-patient interaction Recruitment pathway</td>
<td>Training session, Streamlining recommendations document</td>
</tr>
</tbody>
</table>

*These changes of the PI and protocol were done together.

*These aspects were done at various points in the study, but it was not possible to monitor their implementation because of the closure of the trial.

The major findings and the subsequent changes and methods of implementation of the qualitative recruitment investigation are shown in Table 3.
Chemotherapy

Combination therapy
• Does not eliminate the risk of progression/recurrence in localized disease
• Can down-stage pathology and reduce the incidence of recurrence and progression
• Improved prognosis in patients who display pT0 CR
• May have an durable positive effect on overall survival

Agents:
• MVAC > CMV
• Cisplatin Combination > Cisplatin alone > Carboplatin