Neoadjuvant vs. Adjuvant Chemotherapy for Muscle-Invasive Bladder Cancer

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Cleveland Clinic
Invasive Bladder Cancer

- Usually a lethal disease...

- Cancer Statistics:
  - US → 70,530 cases in 2010 (~ 23,000 HG TCC)
  - → 14,680 deaths (majority from HG TCC)
Invasive Bladder Cancer

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  Incidence : Mortality for HG TCC → 1.6 : 1

Jemal et al. CA Cancer J Clin 2010
Invasive Bladder Cancer

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Jemal et al. CA Cancer J Clin 2010
### Cystectomy: Too Often Too Late!

<table>
<thead>
<tr>
<th></th>
<th>PT0-2</th>
<th>PT3-4</th>
<th>PN1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSKCC, USA</strong></td>
<td>52%</td>
<td>48%</td>
<td>22%</td>
</tr>
<tr>
<td><strong>USC, USA</strong></td>
<td>51%</td>
<td>49%</td>
<td>23%</td>
</tr>
<tr>
<td><strong>Bern, SUI</strong></td>
<td>48%</td>
<td>52%</td>
<td>24%</td>
</tr>
<tr>
<td><strong>Leissner et al., GER</strong></td>
<td>52%</td>
<td>48%</td>
<td>28%</td>
</tr>
<tr>
<td><strong>Shariat et al., USA</strong></td>
<td>57%</td>
<td>43%</td>
<td>23%</td>
</tr>
<tr>
<td><strong>Herr et al., USA</strong></td>
<td>55%</td>
<td>45%</td>
<td>20%</td>
</tr>
</tbody>
</table>
Post-Cystectomy Survival

- pT2, N0
- pT3-4, N0
- pN+

Stein et al. *J Clin Oncol* 2001
Radical Cystectomy: Optimizing Outcomes

- “Timely” cystectomy for T1, TaHG, CIS
- Quality of radical cystectomy
- Extended pelvic lymphadenectomy
- Peri-operative systemic therapy
- Improve morbidity and HRQOL
Perioperative Chemotherapy

- National Cancer Database (USA)
  - 1998-2003
  - Only 11.6% of eligible cystectomy patients received any form of perioperative chemotherapy
    - 16.8% in 2003
  - Majority received adjuvant chemotherapy (10.4%)
  - Few patients received neoadjuvant therapy (1.2%)

David et al. J Urol 2007
Neoadjuvant MVAC Chemotherapy: SWOG 8710

- All-cause mortality: 25% RRR
- 5-yr survival: 57% vs. 43%
- Bladder cancer-specific mortality: 40% RRR ($P = .002$)
- Benefit observed across all stages
Neoadjuvant MVAC Chemotherapy: SWOG 8710

Unadjusted Survival Curves by Treatment and Nodes
For SWOG 8710 Patients Receiving Cystectomy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At Risk</th>
<th>Death</th>
<th>Median in Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVAC+RC, &gt;= 10 nodes</td>
<td>71</td>
<td>33</td>
<td>NR</td>
</tr>
<tr>
<td>RC, &gt;= 10 nodes</td>
<td>67</td>
<td>36</td>
<td>5.6</td>
</tr>
<tr>
<td>MVAC+RC, &lt; 10 nodes</td>
<td>64</td>
<td>43</td>
<td>5.0</td>
</tr>
<tr>
<td>RC, &lt; 10 nodes</td>
<td>66</td>
<td>47</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Years from Cystectomy

Cleveland Clinic
Dotan et al ASCO 2005
# Optimal Therapy for Invasive Bladder Cancer

<table>
<thead>
<tr>
<th></th>
<th>Survival</th>
<th>Local Rec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant Chemo, RC, &gt; 10 LN</td>
<td>81%</td>
<td>9%</td>
</tr>
<tr>
<td>RC, &gt; 10 LN removed</td>
<td>66%</td>
<td>10%</td>
</tr>
<tr>
<td>Neoadjuvant Chemo, RC, ≤ 10 LN</td>
<td>55%</td>
<td>23%</td>
</tr>
<tr>
<td>RC, ≤ 10 LN removed</td>
<td>39%</td>
<td>44%</td>
</tr>
<tr>
<td>No cystectomy</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>

Dotan et al. ASCO 2005
Neoadjuvant CMV Chemotherapy: BA06 30894

- $N = 976$, 1989-1995, median FU 8 yrs, 58% RC
- Mortality: $HR = 0.8$; 95% CI: 0.7-0.99; $P = .037$
- 10-yr survival: 36% vs. 30%
- Mets: $HR = 0.8$; 95% CI: 0.7-0.9; $P = .001$
Neoadjuvant Chemotherapy

- **Meta-analysis**: 6 RCT, 2116 pts
- **Mortality**: HR 0.9; 95% CI: 0.8-0.95; *P* = .003
- **5% absolute survival benefit at 5 years**

<table>
<thead>
<tr>
<th>Number of events/total</th>
<th>Neoadjuvant</th>
<th>Control</th>
<th>O-E</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single agent platinum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallace11</td>
<td>59/83</td>
<td>50/76</td>
<td>2.74</td>
<td>27.18</td>
</tr>
<tr>
<td>Martinez-Martinez9</td>
<td>34/41</td>
<td>37/95</td>
<td>5.85</td>
<td>16.91</td>
</tr>
<tr>
<td>Raghavan14</td>
<td>43/62</td>
<td>38/99</td>
<td>0.33</td>
<td>20.11</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>136/186</td>
<td>125/190</td>
<td>8.92</td>
<td>63.80</td>
</tr>
<tr>
<td>Platinum-based combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malmström11</td>
<td>68/151</td>
<td>84/160</td>
<td>-9.97</td>
<td>37.94</td>
</tr>
<tr>
<td>Bassi11</td>
<td>53/102</td>
<td>60/104</td>
<td>-1.95</td>
<td>28.13</td>
</tr>
<tr>
<td>Cortesi (unpublished)</td>
<td>43/82</td>
<td>41/71</td>
<td>-1.87</td>
<td>20.84</td>
</tr>
<tr>
<td>Sengelov13</td>
<td>70/78</td>
<td>60/75</td>
<td>1.79</td>
<td>31.96</td>
</tr>
<tr>
<td>MRC/EORTC</td>
<td>275/491</td>
<td>301/485</td>
<td>-23.69</td>
<td>143.61</td>
</tr>
<tr>
<td>Sriniv12</td>
<td>79/158</td>
<td>90/159</td>
<td>-6.37</td>
<td>42.18</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>588/1062</td>
<td>636/1054</td>
<td>-42.06</td>
<td>304.66</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>724/1248</td>
<td>761/1244</td>
<td>-33.14</td>
<td>368.45</td>
</tr>
</tbody>
</table>

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Why Not Adjuvant Instead of Neoadjuvant?

- Similar evidence exists for a survival benefit with adjuvant chemotherapy?
- Over-treatment: Many cT2 patients with have organ-confined bladder cancer and are cured with cystectomy alone?
- Chemotherapy delays surgery and leads to increased complications?
- Patients are just as likely to receive 3-4 cycles of chemotherapy in the adjuvant setting as the neoadjuvant setting?
Survival Benefit with Adjuvant Chemotherapy?

- **Meta-analysis:** 4 RCT, 491 pts
- **Insufficient power**
- **Mortality:** 0.8; 95% CI: 0.6-0.96; \( P = .002 \)
Survival Benefit with Adjuvant Chemotherapy?

- 114 pts pT1-2, N0 and p53+ randomized to adjuvant MVACx3 vs. observation
  - Only 67% pts randomized to adjuvant MVAC received 3 cycles
  - Under-powered → 50% recurrence rate in control arm, planned accrual 190 pts

Stadler et al. *J Clin Oncol* 2011
Survival Benefit with Adjuvant Chemotherapy?

- 194 pts with pT2-4, N0-2 bladder cancer randomized to adjuvant GCx4 vs observation
  - Powered to detect 20% improvement in OS at 2 years, planned accrual 610 pts

HR 1.29 95% CI: 0.84-1.99, P=0.24
Many clinical T2 patients have organ-confined bladder cancer and are cured by cystectomy alone?

- Clinically localized → Pathologically advanced
  - Clinical T2 (67-82%) → 49% pT3-4, 23% pN+
  - Clinical T3-4 (18-33%) → 84% pT3-4, 26-60% pN+
Many clinical T2 patients have organ-confined bladder cancer and are cured by cystectomy alone?

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- **pT2N0 bladder cancer → 25-30% mortality at 5 yrs**

Are your patients satisfied with a 1 in 3 risk of death?
Neoadjuvant chemotherapy delays surgery and leads to increased morbidity?

• SWOG 8710: Radical cystectomy performed in 82% MVAC arm vs. 81% control
  – Median time to cystectomy in MVAC arm 115 days (11-169)
Neoadjuvant chemotherapy delays surgery and leads to increased morbidity?

• SWOG 8710: Radical cystectomy performed in 82% MVAC arm vs. 81% control
  – Median time to cystectomy in MVAC arm 115 days (11-169)

• MD Anderson: RCT of neoadjuvant vs. adjuvant chemotherapy in 140 pts w/ locally advanced bladder cancer
  – No difference in failure to undergo cystectomy (3 vs. 5)
  – No significant difference in OR time, EBL, transfusion rate
  – No significant difference in complications

Patients are just as likely to receive 3-4 cycles of chemotherapy if it is deferred to adjuvant setting?

• **Neoadjuvant:**
  - SWOG 8710: 87% received MVAC arm received 1 cycle
  - BA6 3094: 80% of CMV arm received 3+ cycles
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  - 97% (68 of 70) randomized to neoadjuvant arm received 2 cycles MVAC vs. 77% (54 of 70) in adjuvant arm
  - 13% in adjuvant arm received no chemotherapy
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  - 13% in adjuvant arm received no chemotherapy

- **Adjuvant:**
  - 25-38% of pts in 3 of 5 trials received no chemotherapy
Are patients likely to receive 3-4 cycles of chemotherapy if it is deferred to adjuvant setting?

- MSKCC: 1142 pts, 1995-2005
  - All complications within 90 days of surgery, modified Clavien system
  - 64% (N=735) experienced a complication; 83% grade II-V
  - 26% (N=298) required readmission
  - 30% (N=347) may not be eligible to receive postoperative chemotherapy due to important postoperative complications*

  * Defined as grade II-V complication occurring within 6-12 wks of surgery
It’s not just about giving chemotherapy before cystectomy!!

- Cleveland Clinic, 2006-2007
  - 29 of 117 (25%) RC patients received neoadjuvant chemotherapy
    - pT0: 7%  pT3-4 or pN+: 62%
      - In SWOG 8710 → 38% pT0 and 31% pT3-4
    - Chemotherapy:
      - 14% MVAC, 69% GC, 17% other regimens
    - Median time to cystectomy: 208 days (IQR: 149-327)
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It’s about appropriate chemotherapy and timely cystectomy!
Neoadjuvant vs. Adjuvant Chemotherapy

• Cystectomy alone is insufficient for majority of patients with muscle-invasive bladder cancer

• Perioperative chemotherapy is associated with 5-14% improvement in survival at 5 years
  – The best evidence is for neoadjuvant chemotherapy

• Patients are more likely to receive the optimal therapy if chemotherapy is administered before cystectomy

• ‘Timely’ cystectomy is critical in this equation!!!