Neoadjuvant chemotherapy for bladder cancer: fighting between evidence 1 level and real life.

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Introduction

• Radical cystectomy (RC) + pelvic lymphadenectomy (LAD): gold standard.

• 5-yrs survival rate depends on T and N stage:
  - 52-77% for organ confined node negative (cT2N0M0)
  - 40-50% extravescical extension of primary (cT3-4)
  - 15-35% node positive disease (anyT)

• 50% develop distant metastasis within 2 yrs

• BC is the most expensive diagnosis for lifetime among all cancer
Improve outcomes!

Improve surgical techniques

perioperative systemic therapy
Advantages of NAC

• Evaluate response to chemotherapy upfront.
• Better tolerance pre surgery.
• Downstaging local tumor for better resectability
• Early targeting of micrometastasis
• Make possible preoperative pCR
• Improve survival.
Disadvantages of NAC

• Potential disease progression in chemo resistant.

• Overtreat pts upstaged

• Delay surgery for toxicity.

• Possible increase in post surgical complications
**ABC Meta-analysis Collaboration: update on 11 trials, 3005 pts**

HR 0.86; 14% risk death. Absolute Surv benefit 5%; 50% 5yrs

<table>
<thead>
<tr>
<th>Author/year</th>
<th>No. patients</th>
<th>Stage</th>
<th>NC regimen</th>
<th>Definitive treatment</th>
<th>OS benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallace/1991</td>
<td>159</td>
<td>T2-4NXM0</td>
<td>Cisplatin 100 mg/m²</td>
<td>45-50 Gy in 22F</td>
<td>No</td>
</tr>
<tr>
<td>Raghavan/1991</td>
<td>96</td>
<td>T2-4NXM0</td>
<td>Cisplatin 70 mg/m²</td>
<td>65 Gy in 22F + RC + pelvic lymphadenectomy</td>
<td>No</td>
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<tr>
<td>Martinez-Pineiro/1995</td>
<td>122</td>
<td>T2-4ANX-2M0</td>
<td>Cisplatin 100 mg/m²</td>
<td>RC + pelvic lymphadenectomy</td>
<td>No</td>
</tr>
<tr>
<td>Malmstrom/1996</td>
<td>325</td>
<td>T1 (grade3)</td>
<td>Doxorubicin 30 mg/m²</td>
<td>20 Gy in 5F + RC + pelvic lymphadenectomy</td>
<td>No</td>
</tr>
<tr>
<td>Abol-Enein/1997</td>
<td>196</td>
<td>T2-4ANXM0</td>
<td>Methotrexate 50 mg/m²</td>
<td>Yes for T3-T4 (p=0.03)</td>
<td>No</td>
</tr>
<tr>
<td>Bassi/1999</td>
<td>206</td>
<td>T2-4N0M0</td>
<td>Methotrexate 30 mg/m²</td>
<td>Not reported</td>
<td>No</td>
</tr>
<tr>
<td>International Collaboration/1999,7 updated 2011</td>
<td>976</td>
<td>T2 (grade 3)</td>
<td>Cisplatin 100 mg/m²</td>
<td>60 Gy in 30F (or) 20 Gy in 5F + RC (or) RC and pelvic lymphadenectomy</td>
<td>Yes on 2011 update (p=0.037)</td>
</tr>
<tr>
<td>Sheriff/2002</td>
<td>317</td>
<td>T2-4ANXM0</td>
<td>Methotrexate 30 mg/m²</td>
<td>RC + pelvic lymphadenectomy</td>
<td>No</td>
</tr>
<tr>
<td>Sengelov/2002</td>
<td>153</td>
<td>T2-T4bN0NXM0</td>
<td>Methotrexate 250 mg/m²</td>
<td>60 Gy in 30F (or) RC</td>
<td>No</td>
</tr>
<tr>
<td>Cortesi/unpublished</td>
<td>171</td>
<td>T2-4N0M0</td>
<td>Methotrexate 30 mg/m²</td>
<td>RC</td>
<td>Not reported</td>
</tr>
<tr>
<td>Grossman/2003</td>
<td>317</td>
<td>T2-T4ANXM0</td>
<td>Methotrexate 30 mg/m²</td>
<td>RC</td>
<td>No</td>
</tr>
</tbody>
</table>

ABC Meta-analysis Collaboration: update on 3005 pts

Survival curve (platinum based combination trials only)

This fit all?

- review of inclusion criteria and pts characteristics on the 3 major trials (EORTC, SWOG and Nordic)
- 1913/3005 → 64%
- Compared with SEER database.
- No data on >80 years old pts
- No data on PS 2-3.

- In pts >70 years old the probability of PS <1 → 13%
- In pts >70 years old the probability of Cr Cl < 50 ml/min → 47%

- Pts > 70 years old are almost 1/3 of bladder pts
Take home message on NAC

• NAC is feasible with level I evidence data.

• Careful patients selection:
  - T2-T4a N0-x
  - ECOG 0-1
  - Creatinine clearance > 50 ml/min

• Adequate pre treatment staging and clinical evaluation

• pCR: 30-40% and correlate with survival (less benefit with GC but less toxicity)
Take home message on NAC

• NO platinum in monotherapy: no benefit
• NO Regimen other than cisplatinum based

• Optimal regimen unknown (MVAC; ddMVAC; GC)
• 4 cycles before surgery

• UC of the upper tract or urethra and mixed squamous and/or glandular differentiation can be considered
National Cancer Database (NCDB)

David et al. J Urol. 2007:
11.6% perioperative CT
10.4% AC - 1.2% NAC

40388 pts after metanalysis (Fedeli and Coll, 2013):
NAC 2003 → 2007
6% → 13%

5692 pts after metanalysis (Zaid and Coll, 2014):
NAC 2006 → 2010 (overall use: 16.9%)
10.2% → 20.9%
Trends in the Utilization of Neoadjuvant Chemotherapy in Muscle-invasive Bladder Cancer: Results From the National Cancer Database


Figure 1. Use of neoadjuvant chemotherapy (NAC) increased with time for patients undergoing radical cystectomy (RC). The difference between 2006 (7.6%) and 2010 (20.9%) reached significance ($P < .01$).

Zaid et Al J. Urol, 2013
Indipendent factors in receiving NAC

• Younger age
• Higher clinical stage
• Lower comorbidity

• Married status
• North east location (USA)
• Higher income

• Academic or tertiary structure

Zaid et Al J. Urol, 2013
Understanding Avoidance, Refusal, and Abandonment of Chemotherapy Before and After Cystectomy for Bladder Cancer
Shabnam Rehman, Alice Crane, Rakeeba Din, Syed Johar Raza, Yi Shi, Gregory Wilding, Ellis G. Levine, Saby George, Roberto Pili, Donald L. Trump, and Khurshid A. Guru, 2013

Increasing Utilization of Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer in the United States

Neoadjuvant Chemotherapy Use in Bladder Cancer: A Survey of Current Practice and Opinions

Cost-effectiveness of neoadjuvant chemotherapy before radical cystectomy for muscle-invasive bladder cancer.
Scott M. Stevenson, Matthew R. Danzig, Rashed A. Ghandour, Christopher M. Deibert, G. Joel Decastro, Mitchell C. Benson, James M. McKiernan, * Urologic Oncology 2014
Figure 2. Yearly proportions of patients who received neoadjuvant chemotherapy (NAC) and patients in the non-NAC group, who were not referred to medical oncology due to patient or surgeon factors. (The year 2005 was omitted from the x-axis due to surgeon’s brief initial tenure at the institution.)
First: try to understand

Figure 5: “What are your major concerns about recommending NAC? (Select all that apply.)”

Cowan et Al Advances in Urology, 2014
Clarifying doubts:

- Age should not be an exclusion criteria on its own.

- Similar mean time from diagnosis to RC (3.3 mons RC alone vs 3.8 mons in NAC+RC)
  - No increase in perioperative complications.

- The % of pts excluded for comorbidity is similar in NAC and surgery arm.

- High probability to achieve pCR and so to improve survival.

- T2G3: high probability to be upstaged at surgery.
Enhance multidisciplinarity
Stringent multidisciplinary approach

Figure 1. Multidisciplinary management algorithm at Roswell Park Cancer Institute (RPCI).

Rehman et Al J. Urol, 2013
Figure 2. Yearly proportions of patients who received neoadjuvant chemotherapy (NAC) and patients in the non-NAC group, who were not referred to medical oncology due to patient or surgeon factors. (The year 2005 was omitted from the x-axis due to surgeon’s brief initial tenure at the institution.)
About cost effectiveness

Table 4
Survival and summary of costs

<table>
<thead>
<tr>
<th></th>
<th>Radical cystectomy</th>
<th>Neoadjuvant chemotherapy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>119 (65.4%)</td>
<td>63 (34.6%)</td>
<td></td>
</tr>
<tr>
<td>Median follow-up, mo</td>
<td>22.3</td>
<td>29.6</td>
<td></td>
</tr>
<tr>
<td>Percentage who died during</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median survival, mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>26.6</td>
<td>46.2</td>
<td>0.027</td>
</tr>
<tr>
<td>QALY</td>
<td>21.9</td>
<td>40.4</td>
<td>0.029</td>
</tr>
<tr>
<td>5-Y overall survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>31.7%</td>
<td>42.5%</td>
<td>0.034</td>
</tr>
<tr>
<td>QALY</td>
<td>21.9%</td>
<td>42.9%</td>
<td>0.021</td>
</tr>
<tr>
<td>Mean total cost</td>
<td>$42,890</td>
<td>$52,429</td>
<td>0.005</td>
</tr>
<tr>
<td>Percentage of total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radical cystectomy</td>
<td>35.8</td>
<td>17.7</td>
<td></td>
</tr>
<tr>
<td>Early surgical complications</td>
<td>11.8</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Related hospital admissions</td>
<td>22.9</td>
<td>24.3</td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>0</td>
<td>26.2</td>
<td></td>
</tr>
<tr>
<td>Outpatient visits/procedures</td>
<td>20.6</td>
<td>26.4</td>
<td></td>
</tr>
<tr>
<td>Adjuvant/salvage chemotherapy</td>
<td>8.9</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

Stevenson, Urolonc, 2014
To cut a long story short

Underutilization and disparities in NAC represent an opportunity to improve multidisciplinarity.

Implement dedicated programs and discuss every case together can be the right way.

Educate community doctors towards best practice and evidence based practice guidelines.
Thanks for your attention!