Debate: Adjuvant vs. Neoadjuvant Therapy for Urothelial Cancer

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Director of Centre of Applied Urological Research  
Queen’s University  
Kingston, Ontario
Debate: Touchpad Questions
Do you refer all patients who undergo cystectomy to medical oncology?

1. Yes
2. No

Summary of Responses

<table>
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<tbody>
<tr>
<td>%</td>
<td>39%</td>
<td>61%</td>
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</table>
What percentage of your patients receive neoadjuvant chemotherapy?

1. < 10%
2. 10–30
3. 30–50
4. > 50%

Summary of Responses

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<td>%</td>
<td>19%</td>
<td>22%</td>
<td>28%</td>
<td>31%</td>
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What percentage of your patients receive adjuvant chemotherapy?

1. < 10%
2. 10–30
3. 30–50
4. > 50%

Summary of Responses

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<th>21%</th>
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<th>12%</th>
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Point-Counter-Point Debate
Neoadjuvant vs Adjuvant for MIBC

Mount Tremblant
January 19, 2017

Kala S. Sridhar MD, MSc, FRCPC
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Head, GU Medical Oncology Site Group
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Toronto, ON
Introduction

• MIBC is a potentially curable disease
• Cystectomy and pelvic node dissection
• Many patients will recur and die of this disease
• Due to the presence of micrometastases
• Chemotherapy given early can potentially eradicate micrometastases and prevent recurrence
• Recent studies performed after 2010, suggest that use of NC is increasing
• Suggests real progress!

Quek ML, J Urol 2005
Top Ten Reasons to give Neoadjuvant Chemotherapy
1. MIBC is a Systemic Disease!

- Major cause of death is **not** due to local disease but micrometastatic disease

- NC is the quickest and most efficient way to deal with the biggest threat to the patient

- NC is given when the disease burden is at its lowest and so has the greatest chance for benefit
2. Evidence that NC is better

Systematic Review and Metaanalysis

NC improves 5 year OS by 5%, decreased risk mortality by 14% (p=0.003)

European Urology 2005
2. Evidence that NC is Better

• This degree of evidence is acceptable breast and colon cancers

• **Breast**
  – A meta-analyses of 17723 women showed a survival benefit of 7% and 15% decreased mortality at 10yrs for women ≤50 – SOC

• **Colon**
  – Pooled analysis of 3302, showed a survival benefit of 7% at 5 years – SOC

EBCTCG Lance 1998
Gill S, JCO 2004
3. pCR linked to better OS

- Patients who achieve a pCR have a better survival

- Grossman et al – with MVAC 38% had a pCR at cystectomy and 5 year OS was 85%!!

Grossman HB, NEJM 2003
4. Guidelines

- Guidelines in both North America and Europe support the use of NC
5. Assessment of Chemosensitivity

- Midway imaging can determine if a patient is responding and continues full course, or is not and stops early and goes to surgery

- ‘Personalizing treatment’
6. Ease of Administration

- Patients are elderly, frail, with comorbidities
- Chemotherapy is better tolerated before surgery
- In 1142 patients, 30% have Gr 2+ post op complications within 90 days of surgery
- In upper tract disease nephrectomy can compromise renal function and ability to give chemoetherapy
- **Bottom Line:** Many patients planned for AC – will simply never get it

Donat SM, Euro Urol 2009
7. Many patients are upstaged!

- High discrepancy between clinical staging and pathological staging (using current imaging strategies – role for PET??)

- 43-73% of patients with T2 disease pre-cystectomy were upstaged on pathology – and miss the window for NC

- At the time of cystectomy and pelvic node dissection 16-22% of patients with T2 disease will have microscopic lymph-node metastases

Canter D, BJUInt 2011
Dickstwein RJ JCO 2011
Ghoneim M, Jurol 1997
Leissner, J, BJUI 2000
Stein J, JCO 2001
8. A solution to surgical wait times?

• In most centers NC can be initiated quickly and may even be completed before a surgical date is available.

• A recent study by Park would suggest that delay in time to surgery is not an issue in patients getting NC.

Park JC et al J Urol 2015
9. Eligibility for Immunotherapy Trials

- Trials of immunotherapy in the perioperative setting are ongoing

- Many trials allow cisplatin-based neoadjuvant chemotherapy, but NOT adjuvant chemotherapy as this is the setting where immunotherapy is given
10. NC provides the ideal setting for Clinical Trials, Biomarkers, Imaging...

- A strategy using NC permits collection of tumor pre and post treatment, imaging studies etc

- Will help us develop novel approaches in the future
Neoadjuvant chemotherapy should be the standard of care in all eligible patients *

• However, for those who cannot receive NC - I will concede AC has a role..
Thank you for your attention
Peri-operative Chemotherapy for MIBC: Adjuvant Hits the Mark

2017 ICUC Debate
@siemensr
siemensr@kgh.kari.net
Peri-operative Chemotherapy for MIBC: Adjuvant Hits the Mark

2017 ICUC Debate
@siemensr
siemensr@kgh.kari.net
Peri-operative Chemotherapy for MIBC: When EBM Goes Wrong!

2017 ICUC Debate
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siemensr@kgh.kari.net
MIBC Population Level Survival

- Among all cases in Ontario
  - 5 yr OS 30% (95% CI 28-31%)
  - 5 yr CSS 34% (95% CI 32-36%)

Booth, Cancer, 2014
The Quality of Health Care Delivered to Adults in the United States

Cystectomy for Muscle-Invasive Bladder Cancer: Patterns and Outcomes of Care in the Medicare Population

Effectiveness of Adjuvant Chemotherapy for Locally Advanced Bladder Cancer

EUROCare-3: Survival of Cancer Patients Diagnosed 1990–94—Results and Commentary

Effect of Preoperative Delay on Survival in Patients With Bladder Cancer Undergoing Cystectomy in Quebec: A Population Based Study

From the Departments of Oncology (SMM), Surgery (Urology) (SMM, BF, NF, ST, AGA) and Epidemiology and Biostatistics (SMM), McGill University, Montreal, Quebec, Canada
What is **KNOWN** about Neoadjuvant Chemotherapy for MIBC?

- RCTs and 2 meta-analyses suggest modest (~5%) improvement in OS with NACT
  - Treatment guidelines recommend use of NACT in MIBC
- Poor uptake in the general population
  - 1-15% in Canada and US
  - Delay definitive therapy, limited risk stratification, real-world effectiveness?

ABC Meta-Analysis Eur Urol 2005
Grossman NEJM, 2003
Griffiths JCO, 2011
ABC meta-analysis, Lancet 2003
What is **KNOWN** about Adjuvant Chemotherapy for MIBC?

- RCTs for ACT are limited with conflicting results
  - Cochrane meta-analysis shows a 9% improvement in OS. However quality of evidence is “poor”.
  - Current guidelines do not strongly endorse ACT given the limited evidence

- Still utilized more frequently than NACT!

ABC Meta-Analysis Eur Urol 2005
Sternberg Urology 2007
Winquist J Urol 2004
Paz-Ares JCO 2010
Cogentti Ann Oncol 2012
Sternberg Lancet Oncol 2015
Segal Can J Urol 2002
What is **NOT KNOWN** about NACT/ACT for MIBC?

- Predictive clinical/biomarkers for benefit
- Factors associated with utilization and how to improve utilization in routine practice
- What are the toxicities of NACT/ACT in the general population?
- **Does ACT improve survival in this disease?**
Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence

<table>
<thead>
<tr>
<th>RCTs</th>
<th>Population-based studies</th>
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<tbody>
<tr>
<td>Precise measures of efficacy under ideal conditions</td>
<td>Difficulty in eliminating bias and confounders of effect</td>
</tr>
<tr>
<td>Poor measure of effectiveness under real life conditions</td>
<td>Can estimate effectiveness in the general population</td>
</tr>
<tr>
<td>Limited information on toxicity</td>
<td>Assess toxicity under real life conditions</td>
</tr>
<tr>
<td>Applicability to clinical practice can be limited</td>
<td>Evaluate uptake of treatment in general population</td>
</tr>
</tbody>
</table>
Health Services Research
Queen’s Cancer Research Institute

- Population-based database
  - Ontario Cancer Registry
  - Hospital discharge data
  - Statistics Canada
  - Regional cancer center clinical databases
  - ICES

- 1990-2014
  - 81,566 prostate cancer
  - 6,145 bladder cancer
  - 1,490 testes cancer
Ontario: NACT/ACT Utilization

2944 MIBC cases

2003: Pivotal SWOG RCT reports improved survival with NACT
2003: Cancer Care Ontario Guideline does not endorse ACT

2005: MRC meta-analysis reports survival benefit with NACT
2005: Cancer Care Ontario Guideline endorses NACT
2005: MRC meta-analysis reports survival benefit with ACT

1999. Pivotal MRC RCT reports improved survival with NACT

Proportion of cases treated with chemotherapy

Year of surgery

Adjuvant chemotherapy
Neoadjuvant chemotherapy
Utilization across regions (NACT%/ACT%)
Ontario Referral Patterns

MIBC Cystectomy
N=2944

- Seen by MO pre-op
  N= 520 (18%)
- Not seen by MO pre-op
  N= 2424 (82%)

- NACT
  N= 128 (25%)
- No NACT
  N= 392 (75%)

Small fraction of patients (18%) seen by MO pre-op
- higher T stage, younger age, low co-morbidity

Only a small fraction seen by MO actually received NACT

Booth et al Urol Oncol 2014
### Adjuvant Chemotherapy: Survival

<table>
<thead>
<tr>
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<th>Overall Survival</th>
<th>Cancer Specific Survival</th>
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<tbody>
<tr>
<td></td>
<td>5 year OS</td>
<td>Multivariate analysis</td>
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<tr>
<td></td>
<td></td>
<td>HR (95%CI)</td>
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<tr>
<td><strong>Age, years</strong></td>
<td></td>
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</tr>
<tr>
<td>20-49 (n=88)</td>
<td>42%</td>
<td>0.6 (0.5-0.8)</td>
</tr>
<tr>
<td>50-59 (n=305)</td>
<td>39%</td>
<td>0.7 (0.6-0.8)</td>
</tr>
<tr>
<td>60-69 (n=646)</td>
<td>35%</td>
<td>0.7 (0.6-0.8)</td>
</tr>
<tr>
<td>70-79 (n=1051)</td>
<td>28%</td>
<td>0.9 (0.8-1.0)</td>
</tr>
<tr>
<td>80+ (n=524)</td>
<td>21%</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Charlson co-morbidity score</strong></td>
<td></td>
<td></td>
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<tr>
<td>0 (n=1799)</td>
<td>32%</td>
<td>0.7 (0.6-0.8)</td>
</tr>
<tr>
<td>1-2 (n=676)</td>
<td>26%</td>
<td>0.8 (0.7-1.0)</td>
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<tr>
<td>3+ (n=139)</td>
<td>16%</td>
<td>Ref</td>
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<tr>
<td><strong>T stage</strong></td>
<td></td>
<td></td>
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<tr>
<td>&lt;T3 (n=754)</td>
<td>50%</td>
<td>Ref</td>
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<tr>
<td>T3-T4 (n=1860)</td>
<td>22%</td>
<td>1.7 (1.6-2.0)</td>
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<tr>
<td><strong>N stage</strong></td>
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<tr>
<td>N negative (n=1132)</td>
<td>42%</td>
<td>Ref</td>
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<tr>
<td>N positive (n=672)</td>
<td>18%</td>
<td>1.9 (1.7-2.1)</td>
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<tr>
<td>NX (n=810)</td>
<td>24%</td>
<td>1.4 (1.3-1.6)</td>
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<tr>
<td><strong>ACT</strong></td>
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<tr>
<td>Yes (n=514)</td>
<td>30%</td>
<td>0.7 (0.6-0.8)</td>
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<tr>
<td>No (n=2100)</td>
<td>30%</td>
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</table>

- ACT is associated with improved OS (HR 0.70) and improved CSS (HR 0.70).
- Results consistent in propensity score analysis
Effectiveness of Adjuvant Chemotherapy for Locally Advanced Bladder Cancer

Matthew D. Galsky, Kristian D. Stensland, Erin Moshier, John P. Sfakianos, Russell B. McBride, Che-Kai Tsao, Martin Casey, Paolo Boffetta, William K. Oh, Madhu Mazumdar, and Juan P. Wisnivesky

See accompanying editorial on page 777 and article on page 780
<table>
<thead>
<tr>
<th>Age, years</th>
<th>HR</th>
<th>95% CL</th>
<th>No. of Patients</th>
<th>P*</th>
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<tr>
<td>&lt; 70</td>
<td>0.7</td>
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<td>2,782</td>
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<td>70–85</td>
<td>0.62</td>
<td>0.55 to 0.71</td>
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<td>Sex</td>
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<td>Male</td>
<td>0.69</td>
<td>0.63 to 0.76</td>
<td>4,162</td>
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<td>Female</td>
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<td>0.59 to 0.81</td>
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<td>Nodal status</td>
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<td>Nx</td>
<td>0.77</td>
<td>0.6 to 0.98</td>
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<td>Negative</td>
<td>0.77</td>
<td>0.66 to 0.9</td>
<td>1,228</td>
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<td>Positive</td>
<td>0.62</td>
<td>0.56 to 0.69</td>
<td>3,434</td>
<td>.2147</td>
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<tr>
<td>No. of nodes removed</td>
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<td></td>
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<td>&lt; 15</td>
<td>0.66</td>
<td>0.6 to 0.74</td>
<td>3,434</td>
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<td>&gt; 15</td>
<td>0.72</td>
<td>0.6 to 0.85</td>
<td>1,228</td>
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*Favors AC: 0.5 to 1, Favors Obs: 1 to 1.5*
Clinical Implications

Case #1: 54 year old male with minimal co-morbidity
T3 tumor, node positive disease

Predicted 5 yr OS
- Surgery alone = 12% (95%CI 8-19%)
- Surgery with ACT = 23% (95%CI 17-31%)

Case #2: 76 year old female with moderate co-morbidity
T2 tumor, N0 disease, LVI

Predicted 5 yr OS
- Surgery alone = 32% (95%CI 16-29%)
- Surgery with ACT = 45% (95CI 27-45%)
Conclusions

1. Contrary to treatment guidelines use of NACT is low and use of ACT is high and increasing.

2. ACT is associated with a substantial improvement in OS and CSS in the general population.

3. Despite the current level of “evidence” and guidelines most urologists and many MO appear to prefer ACT.