Update on Bladder Cancer

Summary of EAU and AUA 2016 meetings

Albert El Hajj, MD
Assistant Professor
• Basic Science

• NMIBC

• MIBC

  • Surgery in bladder cancer
  • Chemotherapy
  • Novel therapies
Basic science

Exosomes

- membrane-enclosed 30-100 nm vesicles that cells release into the environment
- can be found and isolated from bodily fluids
  - blood
  - urine
  - semen

• MP45-01: Exosomal miRNAs: key regulators of cell-cell communication between bladder cancer cells and tumor microenvironment (Baumgart et. al.)
  • found that exosomes from invasive and non-invasive bladder cancer cell lines have distinct miRNA signatures and can be taken up by naïve fibroblasts
• MP45-15: Non-invasive Urothelial Cancer Biomarkers (Harada et. al.)
  • presented a 38 gene panel from urinary exosomes that could be used to develop a new assay for detection of urothelial carcinoma

• PD38-10: Bladder cancer exosomes from high-grade muscle invasive bladder cancer contain long non-coding RNA and messenger RNA (Berrondo et. al.)
  • showed increased levels of tumor-associated mRNA and IncRNA such as HOTAIR in exosomes isolated from patients with MIBC.
• MP83-01: Urinary shed bladder cancer exosomes have distinct mRNA profiles and have potential as urinary biomarkers (Blackwell et. al.)
  • discovered bladder cancer cell lines shed exosomes at much higher quantities compared with non-transformed urothelial cell lines and have distinct mRNA expression profiles
Exosomes

- can be isolated with proper technique
- macromolecular profiles can be used to distinguish benign bladder disease from bladder cancer
- future studies are needed to investigate
  - effect on bladder cancer progression
  - therapeutic potential of artificial exosomes

Finasteride Reduces Risk of Bladder Cancer in a Large Prospective Screening Study


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EUROPEAN UROLOGY 63 (2016) 407–410

Self-reported use of finasteride was associated with a decreased risk of bladder cancer development (HR = 0.634; 95% CI 0.493-0.816)
Basic science

- **MP83-14: Genomic Expression Evidence for Androgen Receptor Axis Activation in Urothelial Carcinoma: Data from the Cancer Genome Atlas (Morales et. al.)**
  - analyzed gene expression data from TCGA and found that expression of 5-α reductase isozyme subtype and genes involved in androgen signaling associated with TCGA bladder cancer cluster type

- **MP83-20: Enzalutamide as an androgen receptor inhibitor prevents urothelial tumorigenesis (Kawahara et. al.)**
  - found that anti-androgens can inhibit colony formation in vitro and growth in a xenograft model of a carcinogen-transformed, androgen-receptor expressing urothelial cell line

- Androgen receptor activation may play a role in bladder carcinogenesis and can potentially serve as a therapeutic target.
• Basic Science
  • NMIBC
• MIBC
  • Surgery in bladder cancer
  • Chemotherapy
  • Novel therapies
The survival prognosis for patients with NMIBC is relatively favorable, with the cancer-specific survival (CSS) in high-grade disease ranging from approximately 70-85% at 10 years and a much higher rate for low-grade disease.

The rates of recurrence and progression to MIBC are important surrogate endpoints for prognosis in NMIBC, as these are major determinants of long-term outcome.

Risk stratification in NMIBC aids personalized treatment decisions and surveillance strategies as opposed to a generalized ‘one-size fits all’ approach.

Palou 2012; Cookson 1997; Leblanc 1999
## AUA Risk Stratification System

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>LG&lt;sup&gt;a&lt;/sup&gt; solitary Ta ≤ 3cm</td>
<td>Recurrence within 1 year, LG Ta</td>
<td>HG T1</td>
</tr>
<tr>
<td>PUNLMP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Solitary LG Ta &gt; 3cm</td>
<td>Any recurrent, HG Ta</td>
</tr>
<tr>
<td></td>
<td>LG Ta, multifocal</td>
<td>HG Ta, &gt;3cm (or multifocal)</td>
</tr>
<tr>
<td></td>
<td>HG&lt;sup&gt;c&lt;/sup&gt; Ta, ≤ 3cm</td>
<td>Any CIS&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>LG T1</td>
<td>Any BCG failure in HG patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any variant histology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any LVI&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any HG prostatic urethral involvement</td>
</tr>
</tbody>
</table>

*LG = low grade; PUNLMP = papillary urothelial neoplasm of low malignant potential; HG = high grade; CIS = carcinoma in situ; LVI = lymphovascular invasion*
6. An experienced genitourinary pathologist should review the pathology of a patient with any doubt in regards to variant or suspected variant histology (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid), extensive squamous or glandular differentiation, or the presence/absence of lymphovascular invasion. (Moderate Recommendation; Evidence Strength: Grade C)

7. If a bladder sparing approach is being considered in a patient with variant histology, then a clinician should perform a restaging TURBT within four to six weeks of the initial TURBT. (Expert Opinion)

8. Due to the high rate of upstaging associated with variant histology, a clinician should consider offering initial radical cystectomy. (Expert Opinion)
GUIDELINE: URINE MARKERS

9. In surveillance of NMIBC, **a clinician should not use urinary biomarkers in place of cystoscopic evaluation.** (Strong Recommendation; Evidence Strength: Grade B)

Direct comparisons between markers are difficult, and given the uncertainty in sensitivity, these tests cannot be use to replace cystoscopy.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMP22®</td>
<td>Protein-based; identifies nuclear matrix protein involved in the mitotic apparatus</td>
</tr>
<tr>
<td>BTA®</td>
<td>Protein-based; identifies a basement membrane antigen related to complement factor H</td>
</tr>
<tr>
<td>UroVysion® FISH</td>
<td>Cell-based; identifies altered copy numbers of specific chromosomes using fluorescent probes</td>
</tr>
<tr>
<td>ImmunoCyt™</td>
<td>Cell-based; identifies three cell surface glycoproteins</td>
</tr>
<tr>
<td>Cxbladder™</td>
<td>Cell-based; identifies the presence of five mRNA fragments</td>
</tr>
</tbody>
</table>

Tomasini 2013; O’Sullivan 2012
19. In an intermediate-risk patient who completely responds to an induction course of intravesical chemotherapy, a clinician may utilize maintenance therapy. (Conditional Recommendation; Evidence Strength: Grade C)

20. In an intermediate-risk patient who completely responds to induction BCG, a clinician should consider maintenance BCG for one year, as tolerated. (Moderate Recommendation; Evidence Strength: Grade C)

21. In a high-risk patient who completely responds to induction BCG, a clinician should continue maintenance BCG for three years, as tolerated. (Moderate Recommendation; Evidence Strength: Grade B)
## GUIDELINE: INTRAVESICAL THERAPY

<table>
<thead>
<tr>
<th>Events / Patients</th>
<th>Statistics</th>
<th>HR &amp; CI*</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 yr</td>
<td>3 yr</td>
<td>(O−E)</td>
<td>Var.</td>
</tr>
<tr>
<td>1/3 dose – intermediate risk</td>
<td>106/192</td>
<td>97/218</td>
<td>15.2</td>
</tr>
<tr>
<td>Full dose – intermediate risk</td>
<td>72/191</td>
<td>81/188</td>
<td>-4.8</td>
</tr>
<tr>
<td>1/3 dose – high risk</td>
<td>60/149</td>
<td>48/119</td>
<td>0.2</td>
</tr>
<tr>
<td>Full dose – high risk</td>
<td>73/146</td>
<td>49/146</td>
<td>14.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>311/678</td>
<td>275/671</td>
<td>25</td>
</tr>
</tbody>
</table>

**Test for heterogeneity**
Chi-square = 7.79, df = 3: $p = 0.05$

**Fig. 5 – Disease-free interval: 1 yr of maintenance versus 3 yr of maintenance according to dose and risk group. HR = hazard ratio; CI = confidence interval; df = degrees of freedom.**

**Oddens 2013**
32. After completion of the initial evaluation and treatment of a patient with NMIBC, a clinician should perform the first surveillance cystoscopy within three to four months. (Expert Opinion)

33. For a low-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent surveillance cystoscopy six to nine months later, and then annually thereafter; surveillance after five years in the absence of recurrence should be based on shared-decision making between the patient and clinician. (Moderate Recommendation; Evidence Strength: Grade C)

34. In an asymptomatic patient with a history of low-risk NMIBC, a clinician should not perform routine surveillance upper tract imaging. (Expert Opinion)

35. In a patient with a history of low-grade Ta disease and a noted sub-centimeter papillary tumor(s), a clinician may consider in-office fulguration as an alternative to resection under anesthesia. (Expert Opinion)
36. For an intermediate-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every 3-6 months for 2 years, then 6-12 months for years 3 and 4, and then annually thereafter. (Expert Opinion)

37. For a high-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every three to four months for two years, then six months for years three and four, and then annually thereafter. (Expert Opinion)

38. For an intermediate- or high-risk patient, a clinician should consider performing surveillance upper tract imaging at one to two year intervals. (Expert Opinion)
- Basic Science
- NMIBC
  - MIBC
    - Surgery in bladder cancer
- Chemotherapy
- Novel therapies
• Prehabilitation
  • Radical cystectomy is often performed on elderly and frail patients.
  • Functional capacity after major abdominal surgery can decrease by 40% to 60%.
  • Neoadjuvant chemotherapy can contribute to decreased physical fitness.
  • Goal – develop preoperative program using exercise and nutrition-supplementation to facilitate postoperative recovery
MIBC-Surgery: Rehabilitation

- MP38-14: Implementing a Multimodal Prehabilitation Program in a High-volume Bladder Cancer Center (Jensen et. al.)
- MP63-02: A Phase I/II Trial of Prehabilitation in Patients Undergoing Cystectomy for Bladder Cancer (Montgomery et. al.)

- Relatively short (2-3 week) programs
- Good patient compliance (~75-80%)
- Measurable improvement in post-operative fitness and endurance

- Prehabilitation is feasible and safe in this population, and future studies can focus on determining the optimum program for cystectomy patients.
Systematic literature review and cumulative analysis of pathologic, oncologic, and functional outcomes of RARC in comparison with ORC and LRC.

105 papers, 87 of which reported on pathologic, oncologic and functional outcomes.
**Lymph node dissection:**

22% positive rate (extended template, on range of 3-55 nodes removed)

**Fig. 2** – Comparison of lymph node yields following robot-assisted or open radical cystectomy.  
CI = confidence interval; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy; SD = standard deviation.

**No differences between RARC and ORC**
Surgical approach: what is new?

Positive surgical margins (PSMs)

PSMs rates: 5.6%
1–1.5% in pT2
0–25% in pT3 and higher disease

PSM rates did not appear to decrease with sequential case numbers.

No differences between RARC and ORC
### Survival outcomes

**Table 5 - Survival outcomes in robot-assisted radical cystectomy series**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Institution</th>
<th>IDEAL stage</th>
<th>Cases, no.</th>
<th>Study design</th>
<th>Follow-up, mo</th>
<th>Neoadjuvant chemotherapy, %</th>
<th>Adjuvant chemotherapy, %</th>
<th>DFS estimates, %</th>
<th>CSS estimates, %</th>
<th>OS estimates, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruthi et al., 2008 [15]</td>
<td>UNC</td>
<td>26</td>
<td>50</td>
<td>Retrospective</td>
<td>13.2</td>
<td>0</td>
<td>-</td>
<td>94 (15 mo)</td>
<td>90 (13 mo)</td>
<td>-</td>
</tr>
<tr>
<td>Murphy et al., 2008 [12]</td>
<td>Guy's Hospital</td>
<td>2a</td>
<td>23</td>
<td>Retrospective</td>
<td>12</td>
<td>28</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Josephson et al., 2010 [4]</td>
<td>City of Hope Cancer Center</td>
<td>2a</td>
<td>58</td>
<td>Retrospective</td>
<td>12</td>
<td>22</td>
<td>-</td>
<td>76 (2 y)</td>
<td>76 (2 y)</td>
<td>-</td>
</tr>
<tr>
<td>Kong et al., 2010 [25]</td>
<td>T Multicenter</td>
<td>2a</td>
<td>194</td>
<td>Retrospective</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>96 (2 y)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kaufman et al., 2011 [77]</td>
<td>Cornell</td>
<td>2a</td>
<td>83</td>
<td>Retrospective</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>79 (2 y)</td>
<td>83 (2 y)</td>
<td>83 (2 y)</td>
</tr>
<tr>
<td>Martin et al., 2010 [86]</td>
<td>Mayo Arizona</td>
<td>2a</td>
<td>99</td>
<td>Retrospective</td>
<td>21</td>
<td>17</td>
<td>62</td>
<td>71 (2 y)</td>
<td>72 (2 y)</td>
<td>-</td>
</tr>
<tr>
<td>Pruthi et al., 2008 [14]</td>
<td>T Multicenter</td>
<td>2a</td>
<td>100</td>
<td>Retrospective</td>
<td>24</td>
<td>3</td>
<td>-</td>
<td>94 (21 mo)</td>
<td>90 (23 mo)</td>
<td>-</td>
</tr>
<tr>
<td>Carra et al., 2012 [33]</td>
<td>T Multicenter</td>
<td>2a</td>
<td>37</td>
<td>Not reported</td>
<td>6</td>
<td>-</td>
<td>4</td>
<td>85 (6 mo)</td>
<td>89 (6 mo)</td>
<td>-</td>
</tr>
<tr>
<td>Nisei et al., 2013 [49]</td>
<td>Mayo Arizona</td>
<td>2a</td>
<td>56</td>
<td>Retrospective</td>
<td>41</td>
<td>12</td>
<td>46</td>
<td>43 (2 y)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Truex et al., 2012 [49]</td>
<td>T Multicenter</td>
<td>2a</td>
<td>93</td>
<td>Retrospective</td>
<td>15</td>
<td>0</td>
<td>-</td>
<td>94 (15 mo)</td>
<td>93 (15 mo)</td>
<td>-</td>
</tr>
<tr>
<td>Collins et al., 2014 [52]</td>
<td>K Multicenter</td>
<td>2a</td>
<td>141</td>
<td>Retrospective</td>
<td>25</td>
<td>14</td>
<td>-</td>
<td>84 (5 y)</td>
<td>80 (5 y)</td>
<td>-</td>
</tr>
<tr>
<td>Khan et al., 2013 [60]</td>
<td>T Multicenter</td>
<td>1</td>
<td>144</td>
<td>Prospective</td>
<td>84</td>
<td>28</td>
<td>14</td>
<td>75 (2 y)</td>
<td>64 (2 y)</td>
<td>-</td>
</tr>
<tr>
<td>Nepple et al., 2013 [62]</td>
<td>T Multicenter</td>
<td>2a</td>
<td>56</td>
<td>Retrospective</td>
<td>12</td>
<td>6</td>
<td>-</td>
<td>67 (2 y)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sturz-Uzz et al., 2014 [61]</td>
<td>T Multicenter</td>
<td>2a</td>
<td>17</td>
<td>Retrospective</td>
<td>87</td>
<td>-</td>
<td>-</td>
<td>81 (2 y)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tyrer et al., 2013 [50]</td>
<td>T Multicenter</td>
<td>2a</td>
<td>20</td>
<td>Retrospective</td>
<td>20</td>
<td>24</td>
<td>-</td>
<td>81 (2 y)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Xylinas et al., 2013 [57]</td>
<td>T Multicenter</td>
<td>2a</td>
<td>195</td>
<td>Retrospective</td>
<td>37</td>
<td>-</td>
<td>67</td>
<td>63 (2 y)</td>
<td>68 (2 y)</td>
<td>60 (2 y)</td>
</tr>
<tr>
<td>Rana et al., 2014 [50]</td>
<td>C Multicenter</td>
<td>2a</td>
<td>98</td>
<td>Retrospective</td>
<td>73</td>
<td>6</td>
<td>29</td>
<td>76 (2 y)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yu et al., 2014 [58]</td>
<td>T Multicenter</td>
<td>2a</td>
<td>162</td>
<td>Retrospective</td>
<td>32</td>
<td>23</td>
<td>-</td>
<td>74 (2 y)</td>
<td>81 (2 y)</td>
<td>-</td>
</tr>
</tbody>
</table>

CSS = cancer-specific survival; DFS = disease-free survival; OS = overall survival; UNC = University of North Carolina.
Surgical approach: what is new?

Potency

### Table 7 - Erectile function in robot-assisted radical cystectomy series

<table>
<thead>
<tr>
<th>Reference</th>
<th>Institution</th>
<th>IDEAL stage</th>
<th>Cases, no.</th>
<th>Nerve-sparing surgery, %</th>
<th>Study design</th>
<th>Follow-up, mo</th>
<th>Method of data collection</th>
<th>Potency definition</th>
<th>Potency at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mottrie et al. 2007 [9]</td>
<td>O.L.V. Clinic Guy's Hospital</td>
<td>2a</td>
<td>27</td>
<td>29</td>
<td>Retrospective</td>
<td>10.2</td>
<td>IIEF</td>
<td>IIEF &gt;21 with or without PDEx-1</td>
<td>86%</td>
</tr>
<tr>
<td>Murphy et al. 2005 [32]</td>
<td></td>
<td>2a</td>
<td>23</td>
<td>20</td>
<td>Retrospective</td>
<td>17</td>
<td>IIEF</td>
<td>IIEF &gt;21 with or without PDEx-1</td>
<td>75%</td>
</tr>
<tr>
<td>Palou Redorta et al., 2009</td>
<td>Barcelona Autonomous University</td>
<td>2a</td>
<td>9</td>
<td>100</td>
<td>Retrospective</td>
<td>7</td>
<td>IIEF</td>
<td>IIEF &gt;21 with or without PDEx-1</td>
<td>100%</td>
</tr>
<tr>
<td>Akbulut et al., 2011 [32]</td>
<td>Ankara Ataturk Training and Research Hospital</td>
<td>2a</td>
<td>12</td>
<td>82 bilateral, 9 unilateral</td>
<td>Not reported</td>
<td>7.1</td>
<td>IIEF</td>
<td>None provided</td>
<td>A single patient with IIEF &gt;18</td>
</tr>
<tr>
<td>Canak et al., 2012 [33]</td>
<td>Ankara Ataturk Training and Research Hospital</td>
<td>2a</td>
<td>27</td>
<td>89</td>
<td>Not reported</td>
<td>6</td>
<td>IIEF</td>
<td>None provided</td>
<td>A single patient with IIEF &gt;18</td>
</tr>
<tr>
<td>Jonsson et al., 2011 [33]</td>
<td>Karolinska Institute</td>
<td>2b</td>
<td>36</td>
<td>55</td>
<td>Prospective</td>
<td>25</td>
<td>IIEF</td>
<td>Adequate for penetration with or without PDEx-1</td>
<td>61% at 12 mo</td>
</tr>
<tr>
<td>Tyrkow et al., 2013 [56]</td>
<td>Karolinska Institute</td>
<td>2b</td>
<td>70</td>
<td>56 bilateral, 8 unilateral</td>
<td>Retrospective</td>
<td>12</td>
<td>IIEF</td>
<td>Adequate for penetration with or without PDEx-1</td>
<td>63% at 12 mo</td>
</tr>
</tbody>
</table>

IIEF = International Index of Erectile Function; PDEx-1 = phosphodiesterase type 5 inhibitors.

Follow up is too short to get conclusions
Surgical approach: what is new?

RARC Pasadena Consensus Panel – Review
Editorial by Monish Arora and Inderbir S. Gill on pp. 261–262 of this issue

Systematic Review and Cumulative Analysis of Perioperative Outcomes and Complications After Robot-assisted Radical Cystectomy

Giacomo Novara, James W.F. Catto, Timothy Wilson, Magnus Annerstedt, Kevin Chan, Declan G. Murphy, Alexander Motttrie, James O. Peabody, Eila C. Skinner, Peter N. Wiklund, Khurshid A. Guru, Bertram Yuh

195 papers finally included in the systematic review

80 surgical series

70 surgical series reporting data on perioperative outcomes and complications

25 comparative studies

23 comparative studies reporting data on perioperative outcomes and complications
Surgical approach: what is new?

Operative time

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RAARC Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 Randomized studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parekh 2013</td>
<td>308</td>
<td>77</td>
<td>20</td>
<td>288</td>
<td>60</td>
<td>20</td>
<td>9.5%</td>
<td>20.00 [22.78, 22.78]</td>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>Bochner 2014</td>
<td>456</td>
<td>82</td>
<td>60</td>
<td>329</td>
<td>77</td>
<td>58</td>
<td>11.3%</td>
<td>127.00 [188.11, 179.56]</td>
<td>2014</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>80</td>
<td></td>
<td></td>
<td>78</td>
<td></td>
<td></td>
<td>20.6%</td>
<td>74.73 [30.11, 179.56]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: ( \hat{Tau}^2 = 5379.12; \chi^2 = 16.57, df = 1 (p &lt; 0.0001); I^2 = 94% )</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: ( Z = 1.40 (p = 0.16) )</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

| **1.1.2 Nonrandomized studies** | | | | | | | | | |
| Rhee 2006 | 628 | 46 | 7 | 507 | 110 | 23 | 8.1% | 131.00 [74.59, 187.41] | 2006 |
| Ng 2010 | 375 | 90 | 68 | 357 | 132 | 104 | 10.7% | 18.90 [-13.91, 49.91] | 2010 |
| Shy 2012 | 455 | 100 | 50 | 349 | 87 | 100 | 10.2% | 106.00 [72.46, 139.54] | 2012 |
| Sung 2012 | 578 | 153 | 35 | 501 | 110 | 104 | 8.2% | 77.00 [22.08, 131.92] | 2012 |
| Gando 2012 | 408.5 | 55.8 | 11 | 363 | 111.2 | 15 | 7.2% | 45.50 [-19.72, 110.72] | 2012 |
| March 2013 | 410 | 68 | 100 | 351 | 92 | 42 | 10.8% | 59.00 [28.15, 89.85] | 2013 |
| Tretman 2013 | 372 | 73 | 96 | 259 | 70 | 102 | 11.6% | 113.00 [93.06, 132.94] | 2013 |
| Anderson 2012 | 403 | 93 | 103 | 281 | 77 | 375 | 11.9% | 122.00 [102.42, 141.58] | 2013 |
| **Subtotal (95% CI)** | 865 | | | 853 | | | 79.4% | 85.32 [56.80, 113.83] | |
| Heterogeneity: \( \hat{Tau}^2 = 1235.79; \chi^2 = 42.64, df = 7 (p < 0.00001); I^2 = 84% \) |
| Test for overall effect: \( Z = 5.66 (p < 0.00001) \) |

**Total (95% CI)**

<table>
<thead>
<tr>
<th>RAARC Mean</th>
<th>SD</th>
<th>Total</th>
<th>ORC Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>565</td>
<td>943</td>
<td>100%</td>
<td>83.60 [57.06, 110.14]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favors in ORC
Surgical approach: what is new?

Trasfusion rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RARC</th>
<th>ORC</th>
<th>Odds Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Random, 95% CI</td>
<td></td>
</tr>
<tr>
<td>1.1.1 Randomized studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parsh 2013</td>
<td>8 20 10 20</td>
<td>0.67 [0.19, 2.33]</td>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>29 20 20 8.8%</td>
<td>0.67 [0.19, 2.33]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>8 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 0.63 (p = 0.53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1.2 Nonrandomized studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galich 2000</td>
<td>2 13 18 24</td>
<td>0.06 [0.02, 1.02]</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Alves 2006</td>
<td>4 7 20 23</td>
<td>4.3%</td>
<td>0.20 [0.03, 1.37]</td>
<td>2006</td>
</tr>
<tr>
<td>Richards 2010</td>
<td>6 35 25 35</td>
<td>7.3%</td>
<td>0.08 [0.01, 1.26]</td>
<td>2010</td>
</tr>
<tr>
<td>Styn 2012</td>
<td>2 50 24 100</td>
<td>5.8%</td>
<td>0.13 [0.03, 0.58]</td>
<td>2012</td>
</tr>
<tr>
<td>Sung 2012</td>
<td>4 35 59 104</td>
<td>21%</td>
<td>0.10 [0.03, 0.30]</td>
<td>2012</td>
</tr>
<tr>
<td>Gondo 2012</td>
<td>2 11 6 15</td>
<td>2.3%</td>
<td>0.06 [0.05, 1.24]</td>
<td>2012</td>
</tr>
<tr>
<td>Khan 2012</td>
<td>2 48 30 52</td>
<td>5.7%</td>
<td>0.01 [0.01, 0.15]</td>
<td>2012</td>
</tr>
<tr>
<td>Marx 2011</td>
<td>1 14 4 14</td>
<td>3.3%</td>
<td>0.19 [0.07, 0.90]</td>
<td>2013</td>
</tr>
<tr>
<td>Mosh 2013</td>
<td>27 100 25 42</td>
<td>9.2%</td>
<td>0.25 [0.12, 0.54]</td>
<td>2013</td>
</tr>
<tr>
<td>Nepple 2013</td>
<td>14 36 24 59</td>
<td>7.1%</td>
<td>0.13 [0.04, 0.43]</td>
<td>2013</td>
</tr>
<tr>
<td>Trentman 2013</td>
<td>10 96 61 102</td>
<td>10.0%</td>
<td>0.31 [0.17, 0.60]</td>
<td>2013</td>
</tr>
<tr>
<td>Knoe 2013</td>
<td>13 58 68 84</td>
<td>6.6%</td>
<td>0.01 [0.00, 0.05]</td>
<td>2013</td>
</tr>
<tr>
<td>Kader 2013</td>
<td>13 100 47 100</td>
<td>9.6%</td>
<td>0.20 [0.10, 0.39]</td>
<td>2013</td>
</tr>
<tr>
<td>Ahdoos 2014</td>
<td>11 51 17 51</td>
<td>8.5%</td>
<td>0.53 [0.23, 1.28]</td>
<td>2014</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>654 775 93.2%</td>
<td>0.15 [0.09, 0.25]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>115 428</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Tau^2 = 0.55; \chi^2 = 37.00, df = 13 (p = 0.0004); I^2 = 66%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 7.30 (p &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total (95% CI)</td>
<td>674 795 100.0%</td>
<td>0.16 [0.10, 0.27]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>114 438</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Tau^2 = 0.58; \chi^2 = 40.82, df = 14 (p = 0.0002); I^2 = 66%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 7.04 (p &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for subgroup differences: Tau^2 = 4.82, df = 1 (p = 0.03), I^2 = 79.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favors in RARC
# Intraoperative complication rates

## Study or Subgroup

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RARC Events</th>
<th>Total</th>
<th>ORC Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruthi 2007</td>
<td>1</td>
<td>20</td>
<td>0</td>
<td>24</td>
<td>9.9%</td>
<td>3.77 [0.15, 97.74]</td>
<td>2007</td>
</tr>
<tr>
<td>Gondo 2012</td>
<td>1</td>
<td>11</td>
<td>0</td>
<td>15</td>
<td>8.8%</td>
<td>4.43 [0.16, 119.48]</td>
<td>2012</td>
</tr>
<tr>
<td>Sung 2012</td>
<td>1</td>
<td>104</td>
<td>0</td>
<td>35</td>
<td>17.2%</td>
<td>1.03 [0.04, 25.84]</td>
<td>2012</td>
</tr>
<tr>
<td>Musch 2013</td>
<td>3</td>
<td>100</td>
<td>2</td>
<td>42</td>
<td>64.1%</td>
<td>0.62 [0.10, 3.84]</td>
<td>2013</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>235</strong></td>
<td></td>
<td><strong>116</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.34 [0.37, 4.77]</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total events</th>
<th>6</th>
</tr>
</thead>
</table>

Heterogeneity: $\chi^2 = 1.61$, $df = 3$ ($p = 0.66$); $I^2 = 0\%$

Test for overall effect: $Z = 0.45$ ($p = 0.65$)

## Odds Ratio

Favors RARC  | Favors ORC
---|---

No differences between RARC and ORC
Surgical approach: what is new?

Hospital stay

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RARC</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>ORC</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parekh 2013</td>
<td>9.2</td>
<td>7.8</td>
<td>20</td>
<td>8.9</td>
<td>5.6</td>
<td>20</td>
<td>5.9</td>
<td>20</td>
<td>3.5%</td>
<td>0.30 [-3.91, 4.51]</td>
<td>2013</td>
</tr>
<tr>
<td>Bouchner 2014</td>
<td>8</td>
<td>3</td>
<td>60</td>
<td>8</td>
<td>5</td>
<td>58</td>
<td>30.8%</td>
<td>78</td>
<td>34.7%</td>
<td>0.03 [-1.37, 1.44]</td>
<td>2014</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: $\chi^2 = 0.02$, df = 1 ($p = 0.90$); $I^2 = 0$
| Test for overall effect: $Z = 0.05$ ($p = 0.96$) |

1.5.2 Nonrandomized studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RARC</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>ORC</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhie 2006</td>
<td>11.2</td>
<td>9</td>
<td>11</td>
<td>13</td>
<td>3</td>
<td>23</td>
<td>18.6%</td>
<td>23</td>
<td>-2.00 [-1.92, -0.08]</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Gonda 2012</td>
<td>40.2</td>
<td>9.2</td>
<td>11</td>
<td>37</td>
<td>9.9</td>
<td>15</td>
<td>1.3%</td>
<td>15</td>
<td>3.20 [-4.19, 10.59]</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>Sung 2012</td>
<td>28.9</td>
<td>11.9</td>
<td>35</td>
<td>27.1</td>
<td>13.4</td>
<td>104</td>
<td>3.1%</td>
<td>104</td>
<td>1.80 [-2.91, 6.51]</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>Sny 2012</td>
<td>9.5</td>
<td>8.8</td>
<td>50</td>
<td>10.2</td>
<td>8.4</td>
<td>100</td>
<td>7.5%</td>
<td>100</td>
<td>-0.70 [-3.64, 2.24]</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>Trenkman 2013</td>
<td>7.1</td>
<td>5.8</td>
<td>96</td>
<td>9.8</td>
<td>5</td>
<td>102</td>
<td>30.0%</td>
<td>102</td>
<td>-2.70 [-4.21, -1.19]</td>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>Musch 2013</td>
<td>17.1</td>
<td>7.6</td>
<td>100</td>
<td>19.9</td>
<td>12</td>
<td>42</td>
<td>4.5%</td>
<td>42</td>
<td>-2.80 [-6.72, 1.12]</td>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>299</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65.3%</td>
<td></td>
<td>-1.94 [-2.96, -0.91]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: $\chi^2 = 6.12$, df = 5 ($p = 0.29$); $I^2 = 18$
| Test for overall effect: $Z = 3.71$ ($p = 0.0002$) |

Total (95% CI)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RARC</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>ORC</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>379</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
<td></td>
<td>-1.26 [-2.08, -0.43]</td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: $\chi^2 = 11.06$, df = 7 ($p = 0.14$); $I^2 = 37$
| Test for overall effect: $Z = 2.97$ ($p = 0.003$) |
| Test for subgroup differences: $\chi^2 = 4.92$, df = 1 ($p = 0.03$); $I^2 = 79.7$

Favors in RARC
Robotic surgery

• MP38-05: Tumor Dissemination during Robot-Assisted Radical Cystectomy: Does the Emperor Have No Clothes? (Hussein et. al.)
  • Investigated potential of tumor dissemination under pneumoperitoneum.
  • Authors examined mRNA expression and epithelial cell markers from intravesical and pelvic washes in patients undergoing robotic cystectomy.
  • Intravesical washes were positive for bladder cancer markers but pelvic irrigations were not.
  • Epithelial markers were detected in the pelvis in one patient with node positive disease.

• These data are preliminary and further studies are needed to assess whether pneumoperitoneum can potentially alter the pattern of spread.
Robotic vs Open Radical Cystectomy
Recurrence Pattern

Abstr. 625 (J. Collins, Stockholm, Sweden) Multi-institutional database (7 countries)
N=621 with > 3 mo. F-U

4 (0.6%) peritoneal carcinomatosis
1 (0.2%) port site metastasis
49 (7.9%) local recurrences

Early recurrences associated with pN1-2 and pT3-pT4 and appear consistent with publishes open series

Abstr. 630 (T.P.D Nguyen, New York, USA) n=310 robotic cases, median F-U 23 mo.
79 recurrences

13 (4.2%) peritoneal carcinomatosis (6 pT3, 3 pT4, 7 pN1-2)
Robotic surgery

- Robotic cystectomy
  - Utilization has increased over time to ~20%-30%, depending on population studied.
  - Peri-operative and short-term outcomes such as length of stay, complications, and readmission rates are similar to open cystectomy.
  - No significant difference in long term oncologic outcomes were seen.
  - Need for studies reporting comparison of late postoperative complications such as ureterointestinal and urethroidintestinal anastomotic strictures, renal function deterioration, etc.
Complications in Radical Cystectomy
Surgical Volume

Abstr. 516 (M.Vetterlein, Hamburg, Germany) Multicenter Germany+Austria

n=479 radical cystectomies
High volume hospitals ≥ 45 cases/year
High volume surgeon ≥ 15 cases/year

High volume hospitals with lower complication rate.
No difference between surgeon volume groups for complication or quality of care

Coordination of care at high volume centers confers a more important factor in postop. complications than surgeon experience

Abstr. 517 (C.Llorente, Madrid, Spain)

n=8663 radical cystectomies
277 hospitals – only 12 did >35 cases/year
Mortality rate at 30 days 2.8% and 90 day 6%

90 day mortality decreased 12.3% per 10 extra cystectomies/year
Complications of Othotopic Neobladders after 10 years

Abstr. 622 (M.Furrer, Bern, Switzerland) n=200 Studer Neobl., retrospective review

During first 10 years: 46% of patients with complications

Most common:

- 5% Bowel obstruction – related to cystectomy
- 24% Reservoir outlet obstruction (84% treated endourologically)

After first 10 years: 21% of patients with complications

<table>
<thead>
<tr>
<th></th>
<th>10 yrs</th>
<th>15 yrs</th>
<th>20 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime continence</td>
<td>91%</td>
<td>90%</td>
<td>79%</td>
</tr>
<tr>
<td>Night continence</td>
<td>70%</td>
<td>66%</td>
<td>55%</td>
</tr>
<tr>
<td>Median GFR</td>
<td>74%</td>
<td>68.5%</td>
<td>60%</td>
</tr>
</tbody>
</table>

10% of patients suffered pyelonephritis

Voiding every 4 h.
• Basic Science

• NMIBC

• MIBC

  • Surgery in bladder cancer

  • Chemotherapy

• Novel therapies
Guideline on Muscle-Invasive and Metastatic Bladder Cancer (European Association of Urology guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement

Matthew I. Milowsky, R. Bryan Rumble, Christopher M. Booth, Timothy Gilligan, Libni J. Eapen, Ralph J. Hauke, Pat Boumansour, and Cheryl T. Lee

1. Multidisciplinary input via tumor board discussions and/or directed consultations is critical to the optimal management of patients with MIBC and metastatic bladder cancer (eg, referral to a medical oncologist should be made for a discussion of neoadjuvant chemotherapy and referral to a radiation oncologist for a discussion of bladder preservation in patients with muscle-invasive disease). Implementation of these guidelines requires the integration of urology and medical and radiation oncology expertise to provide the highest level of care to patients.

2. Neoadjuvant chemotherapy is recommended for T2-T4a, cN0M0 bladder cancer and should always be cisplatin-based combination therapy.
Duration of Survival (n=976)
J Clin Oncol June 2011;29:2171-2177

Median Follow Up = 8 years

16% reduction in risk of death
HR = 0.84, 95% CI 0.72 – 0.99
Logrank test: p = 0.037

OS benefit 6% at 10 years

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Number of patients at risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>309</td>
<td>485</td>
<td>270 201 151 93 48 11</td>
</tr>
<tr>
<td>282</td>
<td>491</td>
<td>301 228 185 121 60 8</td>
</tr>
</tbody>
</table>

Treatment:
- No CMV
- CMV
ABC Meta-analysis Collaboration: Platinum-based combination Neo-adjuvant chemotherapy trials only
Overall survival

Absolute benefit of 5% at 5 years

# Advanced Bladder Cancer (ABC) Meta-analysis Collaboration

## 11 Neo-adjuvant Trials: Overall Survival

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>NeoCT</th>
<th>Control</th>
<th>O-E</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single agent cisplatin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMURG</td>
<td>59/83</td>
<td>50/76</td>
<td>2.74</td>
<td>27.18</td>
</tr>
<tr>
<td>CUETO 84005</td>
<td>43/62</td>
<td>38/59</td>
<td>0.33</td>
<td>20.11</td>
</tr>
<tr>
<td>ABCSG URO 84834/41</td>
<td>37/55</td>
<td>37/55</td>
<td>5.85</td>
<td>16.51</td>
</tr>
<tr>
<td><strong>Sub-total</strong></td>
<td>136/186</td>
<td>125/190</td>
<td>8.92</td>
<td>63.80</td>
</tr>
<tr>
<td><strong>Platinum-based combinations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GISTV</td>
<td>43/82</td>
<td>41/71</td>
<td>-1.87</td>
<td>20.84</td>
</tr>
<tr>
<td>SWOG</td>
<td>98/158</td>
<td>108/159</td>
<td>-13.61</td>
<td>51.00</td>
</tr>
<tr>
<td>GUONE</td>
<td>53/102</td>
<td>60/104</td>
<td>-1.95</td>
<td>28.13</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>Nordic 1</td>
<td>68/151</td>
<td>84/160</td>
<td>-9.97</td>
<td>37.94</td>
</tr>
<tr>
<td>Nordic 2</td>
<td>79/158</td>
<td>90/159</td>
<td>-6.37</td>
<td>42.18</td>
</tr>
<tr>
<td>Daveca</td>
<td>70/78</td>
<td>60/75</td>
<td>1.79</td>
<td>31.96</td>
</tr>
<tr>
<td><strong>Sub-total</strong></td>
<td>686/1220</td>
<td>744/1213</td>
<td>-55.67</td>
<td>355.65</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>822/1406</td>
<td>869/1403</td>
<td>-46.75</td>
<td>419.45</td>
</tr>
</tbody>
</table>

**Hazards Ratio Diagram**

- HR = 1.15, p = 0.264
- HR = 0.86, p = 0.003
- HR = 0.89, p = 0.022

*Eur Urol. 2005 Aug;48(2):202-5*
Trends in the Use of Perioperative Chemotherapy for Localized and Locally Advanced Muscle-invasive Bladder Cancer: A Sign of Changing Tides

POC use for MIBC increased from 2006 to 2010, with this increase disproportionally due to rising NAC utilization.

Nonetheless, there is persistent variation in the likelihood of receiving POC secondary to non clinical factors.
Selection for preoperative chemotherapy

Socio-economic factors
- Private insurance
- Higher median income
- Higher education
- Short distance to facility

Patient's characteristics
- ECOG 0 & age ↓
- Comorbidity ↓

Medical factors
- Multidisciplinary tumor board
- Surgeon's decision

Limitations of Neoadjuvant chemotherapy

**Patient's characteristics**
- Advanced age & ECOG PS >1
- High comorbidities & impaired renal function

**Surgeon's concerns:**
- Operation time ↑
- Rate of bleeding and blood transfusion ↑
- Respiratory and cardiovascular complications ↑
- Wound infection and sepsis ↑
- Hospital stay and readmission ↑
- Perioperative mortality ↑
- Worsening renal function

Tyson et al, Canad J Urol 2014; Thompson et al, BJU int 2014
Neoadjuvant chemotherapy for bladder cancer does not increase risk of perioperative morbidity

Retrospective Review (NSQIP) from 2005 – 2011:
Cystectomy (n=564) versus NAC plus cystectomy (n=78)
Complication rate 30 days after surgery

• Operation time
• Rate of bleeding and blood transfusion
• Respiratory and cardiovascular complications
• Wound infection and sepsis
• Hospital stay and readmission
• Perioperative mortality

Multivariable Analysis:
No statistical difference

Johnson et al, BJU Int 2014
Neoadjuvant chemotherapy: Morbidity?

The Effect of Neoadjuvant Chemotherapy on Perioperative Outcomes in Patients Who Have Bladder Cancer Treated with Radical Cystectomy: A Population-based Study

Giorgio Gandaglia, Ioana Popa, Firas Abdollah, Jonas Schiffmann, Shahrokh F. Shariat, Alberto Briganti, Francesco Montorsi, Quoc-Dien Trinh, Pierre I. Karakiewicz, Maxine Sun

Retrospective Review (SEER-Medicare linked database) from 2000 – 2009:
Cystectomy (n=1664) versus NAC plus cystectomy (n=416)
Complication rate 30 and 90 days after surgery

- Respiratory & cardiovascular complications
- Genitourinary complications
- Rate of blood transfusion
- Wound infection
- Hospital stay and readmission
- Perioperative mortality

Multivariable Analysis:
No statistical difference

Gandaglia et al, Eur Urol 2014
Refining Patient Selection for Neoadjuvant Chemotherapy before Radical Cystectomy

The presence of high risk features identifies patients with a poor prognosis who are most likely to benefit from NAC.

Many of those with low risk disease can undergo surgery up front with good expectations and avoid chemotherapy associated toxicity.
**ERBB2 Mutations Characterize a Subgroup of Muscle-invasive Bladder Cancers with Excellent Response to Neoadjuvant Chemotherapy**

Floris H. Groenendijk, Jeroen de Jong, Elisabeth E. Fransen van de Putte, Magali Michaut, Andreas Schlicker, Dennis Peters, Arno Velds, Marja Nieuwland, Michel M. van den Heuvel, Ron M. Kerkhoven, Lodewijk F. Wessels, Annegien Broeks, Bas W.G. van Rhijn, René Bernards, Michiel S. van der Heijden

**Fig. 2** - Circos plot showing ERBB2 missense mutations, ERBB2 amplifications, and ESRRC2 missense mutations in the 36 complete responders and 33 nonresponders to neoadjuvant chemotherapy in this study. Individual patients are represented as colored circles. N/A = not available; pCR = pathologic complete response.

**ERBB2** missense mutations characterize a subgroup of MIBC patients with an excellent response to NAC.
Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials


Study ID

<table>
<thead>
<tr>
<th>Cisplatin-based combinations</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bono</td>
<td>0.65 (0.34-1.25)</td>
<td>9.83</td>
</tr>
<tr>
<td>Freiha</td>
<td>0.74 (0.36-1.53)</td>
<td>8.61</td>
</tr>
<tr>
<td>Otto</td>
<td>0.62 (0.48-1.20)</td>
<td>12.37</td>
</tr>
<tr>
<td>Skinner</td>
<td>0.15 (0.48-1.15)</td>
<td>14.22</td>
</tr>
<tr>
<td>Lessmann</td>
<td>0.57 (0.31-1.05)</td>
<td>10.57</td>
</tr>
<tr>
<td>Stadler</td>
<td>1.11 (0.45-2.73)</td>
<td>4.35</td>
</tr>
<tr>
<td>Subtotal (I² = 0.0%, p = 0.880)</td>
<td>0.74 (0.58-0.94)</td>
<td>61.95</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Single agent cisplatin</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stadler</td>
<td>1.02 (0.57-1.83)</td>
<td>11.09</td>
</tr>
<tr>
<td>Subtotal (I² = 0.0%, p = 0.880)</td>
<td>1.02 (0.57-1.83)</td>
<td>11.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gemcitabine–cisplatin comb.</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italian</td>
<td>1.29 (0.86-1.99)</td>
<td>14.83</td>
</tr>
<tr>
<td>Spanish</td>
<td>0.58 (0.32-0.95)</td>
<td>12.13</td>
</tr>
<tr>
<td>Subtotal (I² = 91.5%, p = 0.000)</td>
<td>0.71 (0.21-2.35)</td>
<td>26.98</td>
</tr>
<tr>
<td>Overall</td>
<td>0.77 (0.69-1.00)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random-effects analysis.
Thoughts on a Systematic Review and Meta-analysis of Adjuvant Chemotherapy in Muscle-invasive Bladder Cancer

Cora N. Sternberg\textsuperscript{a,*}, Richard Sylvester\textsuperscript{b}

\textsuperscript{a} Department Medical Oncology, San Camillo-Forlanini Hospital, Rome, Italy. \textsuperscript{b} EORTC, Brussels, Belgium

The randomized trials had a number of limitations, including differing definitions of disease-free survival (DFS).

The time at which patients were randomized also differed among the trials.

The results are not strong, and we still do not know which patients, if any, may actually benefit.

"...It is difficult to draw any real conclusion from this meta-analysis... ...it should be interpreted with caution."
**Neoadjuvant**

- Higher level of evidence
- Better tolerance
- No ↑ in perioperative complications
- Clinical Staging

**Adjuvant**

- Lower level of evidence
- Worse tolerance
- Postoperative complications in 30%
- Pathological Staging
• Basic Science

• NMIBC

• MIBC
  
  • Surgery in bladder cancer
  
  • Chemotherapy
  
  • Novel therapies
Why tumours are able to evade and suppress the immune response?

1. Inhibition of tumour antigen presentation, eg, down-regulation of MHC I
2. Secretion of immunosuppressive factors, eg, TGF-β
3. Inhibition of attack by immune cells, eg, disruption of T-cell checkpoint pathways
4. Recruitment of immunosuppressive cell types, eg, Treg
5. Other Mechanisms, eg, Poor immunogenicity/Rapid growth

APC, antigen-presenting cell; MHC, major histocompatibility complex; TGF, transforming growth factor; T-reg, regulatory T cell.
Secondary Signal: Checkpoint Pathways

Activation of T cells depends on the balance of the co-stimulatory and co-inhibitory signals, which are also known as checkpoint pathways\textsuperscript{1,2}

---

APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.
Checkpoint Pathways

Tumours are able to escape the immune system surveillance by expressing molecules that "activate the brakes" to the immune reaction (PD-L1, B7.1)

Blocking the interaction between those molecules and their receptor arises as a valid treatment strategy (ANTI-PD1/PD-L1, ANTI-CTLA4)

Targeting the CTLA-4 and PD-1 Checkpoint Pathways

Over the last several years, multiple compounds targeting CTLA-4 or PD-1/PD-L1 have been developed:

**PD-1:**
- Nivolumab [BMS]
- Pembrolizumab [MSD]
- Pidilizumab [Meditation]
- AMP-514 [MedImmune/Amplimmune]
- AMP-224 [MedImmune/Amplimmune]
- PDR001 [Novartis]

**CTLA-4:**
- Ipilimumab [BMS]
- Tremelimumab [MedImmune/AZ]

**PD-L1:**
- Atezolizumab [Roche/Genentech]
- BMS-936559 [BMS]
- Durvalumab [MedImmune/AZ]
- Avelumab [EMD Serono/Merck KGaA/Pfizer]

CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed death-1; PD-L1, programmed death ligand-1.
Immunotherapy: Why Bladder

Fig: Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs.

Bladder tumors along with other malignancies such as lung and melanoma display a high number of somatic mutations rendering these tumors more immunogenic

MS Lawrence et al. Nature 499, 214–218 (11 July 2013)
* I-O therapies under investigation as monotherapy and combination regimens

1L, first-line; 2L, second-line; BCG, Bacillus Calmette-Guerin; I-O, immuno-oncology
Efficacy of IT in bladder cancer

**LETTER**

MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer

Thomas Powles, Joseph Paul Eden, Craig D. Fene, Fadi S. Braicheh, Johann Loriot, Cristina Cruz, Neugim Bollimunt, Howard A. Burtis, Daniel P. Petrylak, Siwei-Jeng Teng, Xiaodong Shen, Zachary Boyd, Priti S. Hegde, Daniel S. Chen, & Nicholas J. Vogelzang

- 67 “bad” patients
- 50% RR (70% CB) in pts TILs + for PDL-1 (IHC 3)
- 8% RR (50% CB) in pts TIL – for PDL-1 (IHC-0)
Novel therapies: Anti-PD-L1

- **IMvigor 210 (Dreicer et al.)**
  - Phase II trial of atezolizumab (anti-PD-L1 antibody) in platinum-treated locally advanced or metastatic urothelial carcinoma
  - 311 patients received atezolizumab 1200 mg IV every 3 weeks until loss of clinical benefit.
  - PD-L1 IHC was performed to determine % of PD-L1+ immune cells and patients were classified as IC2/3 (≥5%), IC1 (≥1 but <5%), and IC0 (<1%).
  - Primary endpoints were
    - confirmed ORR by RECIST v1.1 per central review (IRF)
    - modified (m) RECIST per investigator
**Novel therapies: Anti-PD-L1**

<table>
<thead>
<tr>
<th>Table: Efficacy</th>
<th>n</th>
<th>IC2/3</th>
<th>n</th>
<th>IC1/2/3</th>
<th>n</th>
<th>All Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed IRF ORR, % (95% CI)</strong></td>
<td>100</td>
<td>27 (19, 37)</td>
<td>208</td>
<td>18 (13, 24)</td>
<td>311</td>
<td>15 (11, 20)</td>
</tr>
<tr>
<td>P value vs historical control (10%)</td>
<td>&lt; .0001</td>
<td>.0004</td>
<td>.0058</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prognostic subgroups confirmed IRF ORR, % (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral mets</td>
<td>66</td>
<td>17 (9, 28)</td>
<td>152</td>
<td>12 (7, 18)</td>
<td>243</td>
<td>10 (6, 14)</td>
</tr>
<tr>
<td>Liver mets</td>
<td>27</td>
<td>15 (4, 34)</td>
<td>60</td>
<td>7 (2, 16)</td>
<td>96</td>
<td>6 (2, 13)</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>59</td>
<td>19 (10, 31)</td>
<td>128</td>
<td>13 (7, 20)</td>
<td>193</td>
<td>10 (6, 15)</td>
</tr>
<tr>
<td>Hb &lt; 10 g/dL</td>
<td>24</td>
<td>21 (7, 42)</td>
<td>50</td>
<td>12 (5, 24)</td>
<td>69</td>
<td>9 (3, 18)</td>
</tr>
<tr>
<td>CrCl &lt; 60 mL/min</td>
<td>38</td>
<td>13 (4, 28)</td>
<td>66</td>
<td>17 (9, 28)</td>
<td>107</td>
<td>14 (8, 22)</td>
</tr>
<tr>
<td><strong>Overall DOR, median (range), mo</strong></td>
<td>27</td>
<td>NE (2.1+, 8.3+)</td>
<td>38</td>
<td>NE (2.1+, 8.3+)</td>
<td>47</td>
<td>NE (2.1+, 8.3+)</td>
</tr>
</tbody>
</table>

* Includes IC0, IC1 and IC2/3 pts.
* NE, not estimable.
Novel therapies: Anti-PD-L1

- IMvigor 210 (Dreicer et. al.)
  - Atezolizumab demonstrated significantly improved ORR vs. historical controls.
  - Responses were durable and associated with higher PD-L1 expression by IHC.
  - Poor prognostic factors did not preclude response.
  - Atezolizumab was well tolerated.
EAU-AUA Updates 2016