Chemo-radiotherapy in muscle invasive bladder cancer

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Overview

• Evidence base for cystectomy vs bladder preservation
• Chemo-radiotherapy vs radiotherapy alone
• Future directions:
  – Technical developments in radiotherapy
  – Trials
Cystectomy – “Gold standard”

Should be best way of treating majority of patients with a disease

Should give demonstrably better outcomes than alternatives

Should have solid evidence base to underpin its use
Fact

Bladder cancer outcomes have not significantly improved for 30 years

Age standardised 5 year survival rates in UK

Prepared by Cancer Research UK -
http://info.cancerresearchuk.org/cancerstats/
The best way of treating majority of patients?
Age at diagnosis

Median age in BA06 & SWOG 8710

Median age in USC series

Median age in BC2001 and BCON
Age distribution of cystectomy series – UK data

- Median age: 68
- Interquartile (midspread) range: 62-74
- Aged > 80y: 6%
- Incident cases >80y: approx 20%
- Cystectomy as primary treatment >80 years: 7%
Is survival better with surgery?

• Should give demonstrably better outcomes than alternatives

• Should have solid evidence base to underpin its use
Survival from UK cancer registry

453 UK patients, 1993-6

Ratio RT : Cystectomy 3:1

10 year survival:
RT 22% Surgery 24%

Primary vs Salvage Cystectomy

Are complication rates higher with Salvage Cystectomy?

<table>
<thead>
<tr>
<th>Complication</th>
<th>1970–2005</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Salvage cystectomy, % (No.)</td>
<td>Primary cystectomy, % (No.)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>5.1 (21)</td>
<td>3.8 (16)</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>1.7 (7)</td>
<td>0.5 (2)</td>
</tr>
<tr>
<td>Anastomotic bowel leak</td>
<td>1.4 (6)</td>
<td>1.1 (5)</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>4.8 (20)</td>
<td>4.2 (18)</td>
</tr>
<tr>
<td>Urinary leak</td>
<td>3.8 (16)</td>
<td>4 (17)</td>
</tr>
</tbody>
</table>

* More than 30 d postoperative; there was no statistically significant difference in either of the groups ($\chi^2$ test).

Canadian Cancer Registry – bladder cancer

• Variations in the use of cystectomy vs. radical radiotherapy were not associated with difference in survival

• Survival differences related to tumour related factors

Survival Cystectomy vs Radical Radiotherapy

- Stein et al: 1054 Cystectomy patients 5 & 10ys 60% and 43%
- Rödel et al: 415 RT patients 5 & 10ys 51% and 31%
- However, cystectomy series:
  - included 213 T0, Ta, Tis patients
  - excluded 112 inoperable patients

- If comparison is restricted to operable muscle-invasive disease, 5ys survival:
  Radical Cystectomy 47%
  Conservative therapy 45%

Stein JP et al JCO Feb 1 2001: 666-675
Is survival better with surgery?

No
Choice of Treatment

• Surgery and radiotherapy data relate to different segments of the population
• Neoadjuvant therapy data also mainly relate to younger patients
• Hence age/fitness is important factor in treatment decisions
Patients unsuitable for surgery

- Elderly
- Severe cardiovascular or chest problems
- Obese
- Diabetes
- Patients reluctant or unable to cope with stoma
Patients unsuitable for (Chemo) Radiotherapy

• Poor bladder function
• Highly symptomatic bladders
• Extensive CIS
• Prior pelvic RT
• Inflammatory bowel disease
• Certain genetic disorders
Bladder preservation
Bladder cancer is systemic disease

- No plateau in survival curves
- Patients die with metastatic disease
- Treatment needs to address both local control and systemic disease
- Most important factor for future study is how to improve systemic control
Mortality Rates From Breast Cancer US and the UK
### Organ preservation revisited

<table>
<thead>
<tr>
<th></th>
<th>Anal cancer</th>
<th>Bladder cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key study</strong></td>
<td>ACT 1</td>
<td>BC2001</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>5FU/MMC Radiotherapy 60Gy/31f</td>
<td>5FU/MMC Radiotherapy 64Gy/32f</td>
</tr>
<tr>
<td><strong>Loco regional failure</strong></td>
<td>~29%</td>
<td>33% (18%)</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td>58%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Salvage/alternative treatment</strong></td>
<td>Abdomino-perineal resection/colostomy</td>
<td>Cysto/prostatectomy Ileostomy</td>
</tr>
</tbody>
</table>
Neoadjuvant Chemotherapy

US Intergroup Trial

BA06 EORTC 30894

Surgery +/- MVAC chemotherapy

Surgery or RT +/- CMV chemotherapy


MRC/EORTC Trial - Loco-regional and metastatic control

Neoadjuvant Chemotherapy – meta analysis

ABC MAC 2003 Lancet 361 p1927-1934
Synchronous Chemo-Radiotherapy

- Numerous phase I/II studies showing feasibility and safety
- Three phase III studies
  - RT vs RT + Cisplatinum (NCIC)
  - RT vs RT + 5FU/MMC (BC2001)
  - RT vs RT + nicotinamide/carbogen (BCON)
Patients with muscle invasive bladder cancer

RANDOMISE

CT
- Standard volume RT⁺ + synchronous chemotherapy

No CT
- Standard volume RT⁺

sRT

Reduced high
dose volume RT⁺ + synchronous chemotherapy

RHDV RT

Reduced high
dose volume RT⁺

Pragmatic design: Centres could offer double or either single randomisation
• Bladder radiotherapy challenges

- Deformable
  - Empty bladder
  - ‘Empty’ bladder

- Mobile
  - Empty rectum
  - Full rectum
Conventional Radiotherapy - Empty Bladder

1.5 to 2cm margins

Courtesy of Fiona McDonald
Cone beam CT

Planning CT

Cone beam CT

Pre bone match

Post bone match

Systematic error

Random error

On-line correction strategy

3 planes of couch adjustability
CTV coverage according to margin and set up technique

Foroudi et al 2012 Clin Oncol 24 673-681

<table>
<thead>
<tr>
<th></th>
<th>CTV+0.5</th>
<th>CTV+1.0</th>
<th>CTV+1.5</th>
<th>CTV+2.0</th>
<th>CTV+2.5</th>
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<tbody>
<tr>
<td>Skin</td>
<td>0</td>
<td>19</td>
<td>56</td>
<td>93</td>
<td>96</td>
</tr>
<tr>
<td>Bone</td>
<td>0</td>
<td>41</td>
<td>63</td>
<td>89</td>
<td>96</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>52</td>
<td>89</td>
<td>96</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Retrospective analysis of 30 patients having daily CBCT set up by skin, bone or soft tissue match
Concomitant boost (partial bladder)
Chemotherapy regimen

Target volume tumour + bladder + 1.5-2cm
Chemotherapy via peripherally inserted central line as outpatient therapy
Patient demographics

- Mean (SD) 70.5 (8.2) years
- Median (IQR) 71.9 (64.1 - 76.2) years
- Older than patients in previously published trials including SWOG 8710\(^1\) (median 63 y) and BA06\(^2\) (median 64 y)

Performance status

- Male = 289/360 (80%)

Age at randomisation

Acute toxicity

- Proportions with a grade 3/4 at any time on treatment:
  - 62/179 (34.6%) CT vs. 49/172 (28.5%) No CT (% of pts with data)
  - Stratified Chi-square test p=0.19

Worst grade of on-treatment toxicity by week
RTOG 6 month toxicity outcomes

n= 291, 145 RT only, 146 chemo-radiotherapy
Loco-regional disease free survival in chemotherapy randomisation

Loco-regional control (invasive and non-invasive)

Invasive loco-regional control

James et al, Radiotherapy with or without chemotherapy for invasive bladder cancer. NEJM 2012 366, 1477-1488
OS in chemotherapy randomisation

- **2-yr OS**: 62% (95% CI: 54%, 68%)
- **5-yr OS**: 50% (42%, 58%)

**HR** = 0.82 (95% CI: 0.61, 1.10); **p** = 0.16

**N at risk (events)**

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>No CT</th>
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<tbody>
<tr>
<td>182</td>
<td>141</td>
<td>178</td>
</tr>
<tr>
<td>104</td>
<td>95</td>
<td>139</td>
</tr>
<tr>
<td>72</td>
<td>68</td>
<td>139</td>
</tr>
<tr>
<td>56</td>
<td>33</td>
<td>139</td>
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<tr>
<td>37</td>
<td>19</td>
<td>139</td>
</tr>
<tr>
<td>18</td>
<td>11</td>
<td>139</td>
</tr>
</tbody>
</table>
# LRDFS - consistency across subgroups

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>P-value</th>
<th>Hazard ratio (95% CI)</th>
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<tbody>
<tr>
<td>Randomised sRT</td>
<td>63</td>
<td>0.63</td>
<td>0.77 (0.33, 1.75)</td>
</tr>
<tr>
<td>Randomised RHDV</td>
<td>58</td>
<td></td>
<td>0.97 (0.35, 2.69)</td>
</tr>
<tr>
<td>Elect sRT</td>
<td>239</td>
<td></td>
<td>0.59 (0.38, 0.92)</td>
</tr>
<tr>
<td>RT dose 55Gy/20F</td>
<td>140</td>
<td>0.73</td>
<td>0.72 (0.39, 1.32)</td>
</tr>
<tr>
<td>RT dose 64Gy/32F</td>
<td>212</td>
<td></td>
<td>0.63 (0.40, 0.98)</td>
</tr>
<tr>
<td>Neoadjuvant CT</td>
<td>118</td>
<td>0.60</td>
<td>0.58 (0.31, 1.09)</td>
</tr>
<tr>
<td>No neoadjuvant CT</td>
<td>242</td>
<td></td>
<td>0.72 (0.46, 1.11)</td>
</tr>
<tr>
<td>Primary analysis</td>
<td>360</td>
<td></td>
<td>0.66 (0.46, 0.94)</td>
</tr>
</tbody>
</table>

Favours CT: 1, Favours no CT: 2
Patterns of recurrence after ChemoRT

Any recurrence: 93/182 pts

Loco-regional recurrence: 53
- Non-muscle invasive: 25
- Muscle invasive: 18
- Pelvic nodes: 6

Distant recurrence or second primary: 40
- Metastasis: 29
- Second primary: 11
BCON: Aim and endpoints

• To determine whether hypoxia-modifiers Carbogen (95% O2/5% CO2) and Nicotinamide increase efficacy of RT in TCC

• Primary endpoint - cystoscopic control

• Secondary endpoints: overall survival (OS), local relapse-free survival (RFS), urinary and rectal morbidity
**BCON Results**

Relapse-free survival

Overall survival

Outcome of BCON according to presence of necrosis  Eustace et al R&O 2013
**SPARE trial**

**Feasibility study:**
110 patients

**Main study:**
1015 patients
SPARE Trial Screening data (to end 2009)

- Screened: N=744
- Ineligible: n=450
- Eligible: N=294
- Not approached: N=143
- Approached: N=151
- Declined: N=109
- Consented: N=42

Huddart et al ASTRO 2012
SPARE: Overall Survival

Hazard ratio: 1.49, 95% CI (0.52, 4.3), P=0.46
Lessons from SPARE

• Lower than expected patient number eligible for chemotherapy, radiotherapy and surgery

• Impact of strong physician preferences

• Impact of strong patient preferences (patients find it difficult to be randomised and wish to make their own choice of treatment)

• The importance of excellent consistent and clear communication and patient information
Low tumor expression of DNA strand break signaling proteins would be associated with better outcome following radical radiotherapy in bladder cancer due to decreased DNA repair

Would not expect it to be related to outcome following surgery, as not mediated via DNA damage mechanisms
MRE11 hypothesis

T2-3 TCC
PS 0-1
Suitable for RT or Cystectomy

Biomarker determined treatment [MRE11]

Randomise

Recommend RT
Recommend Cystectomy

Accepts
Declines
Accepts

Radiotherapy
Cystectomy

Patient choice

Radiotherapy
Cystectomy
Conclusions

- No convincing evidence surgery superior to primary bladder preservation with salvage surgery
- Neoadjuvant chemotherapy improves overall survival
- Synchronous chemo-radiation is safe and improves pelvic control and hence is complementary to neoadjuvant treatment
- Markers are emerging which now need prospective evaluation

Acknowledgements: Professors Peter Hoskin, Nick James and Dr Robert Huddart