Localised tumours in vulnerable older adults: choosing the best treatment

Bladder Cancer

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Disclosure

I have the following conflict(s) of interest to declare:

• Membership of MR-Linac Elekta international consortium (bladder cancer lead)
• Meeting attendance sponsorship by MSD
Introduction

- Bladder cancer is 9th most frequently diagnosed cancer
- Ranks 13th in terms of cause of cancer death
- Spectrum
  - Non-muscle invasive
  - Muscle invasive
  - Metastatic
- Histology
  - Europe/North America (90%) transitional cell carcinomas. Aetiological association with smoking in 37% cases.
  - North Africa/Asia (75%) squamous cell carcinoma. Aetiological association with urinary schistosomiasis

T stage

- Non-invasive (75-80%)
- Muscle invasive (20-25%)

https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#bladder
https://pathways.nice.org.uk/pathways/bladder-cancer
Transurethral resection of bladder tumour (TURBT)

Surgery
- Cystectomy & pelvic node dissection

Radiosensitiser
- Neoadjuvant chemotherapy

Radiation Therapy
- Bladder (radio sensitisers)

Regular cystoscopy

Residual or recurrent invasive disease
- Salvage cystectomy

Non muscle invasive disease
- Local treatment
Challenges in MIBC

Advancing age

- Nationwide registries demonstrate that curative treatment approaches vary based on age
- % of patients receiving curative treatment
  - 52% vs 12% for those aged <60yrs vs >80yrs

Original data sources are available from http://www.cancerresearchuk.org/cancer-info/cancerstats/
Challenges in MIBC

- Fear of treatment related morbidity
- Estimated short life expectancy from perceived frailty
- Comorbidities

<table>
<thead>
<tr>
<th>Characteristic comorbidity</th>
<th>Total</th>
<th>%</th>
<th>Mean age at diagnosis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>919</td>
<td>37</td>
<td>67</td>
</tr>
<tr>
<td>One</td>
<td>748</td>
<td>31</td>
<td>71</td>
</tr>
<tr>
<td>Two of more</td>
<td>778</td>
<td>32</td>
<td>74</td>
</tr>
<tr>
<td>Type of comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>285</td>
<td>12</td>
<td>74</td>
</tr>
<tr>
<td>Hypertension</td>
<td>472</td>
<td>19</td>
<td>73</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>753</td>
<td>31</td>
<td>74</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>315</td>
<td>13</td>
<td>73</td>
</tr>
</tbody>
</table>

n=2445

Challenges in MIBC

- Many patients deemed unfit for standard approaches radical treatment
- But many may survive significant time period
- Without treatment at risk of significant cancer related morbidity and/or die of ‘curable’ bladder cancer
- Cancer-specific mortality is highest in the oldest patient groups.

Would hypofractionated radiotherapy offer solution?

Role of radiotherapy in bladder cancer

Standard options - localised ≥ T2

- Selective bladder preservation
  - Neo-adjuvant chemotherapy/Induction CRT
  - Radiosensitised radiotherapy
- Radiosensitised radiotherapy
- Radiotherapy alone
- Hypofractionated radiotherapy

How do you assess fitness?
Role of hypofractionated radiotherapy

RCT in those unfit or unsuitable for radical treatment

<table>
<thead>
<tr>
<th></th>
<th>35Gy 10f</th>
<th>21Gy 3f</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>248</td>
<td>252</td>
</tr>
<tr>
<td>Local control</td>
<td>18/33 (55%)</td>
<td>14/37 (38%)</td>
</tr>
<tr>
<td>Symptom control</td>
<td>71%</td>
<td>64%</td>
</tr>
<tr>
<td>Median survival</td>
<td>7.5 months</td>
<td>7.5 months</td>
</tr>
<tr>
<td>2yr survival</td>
<td>19%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Time to deterioration of bladder related symptoms

Overall survival

Role of hypofractionated radiotherapy

Delivering 6Gy per fraction

<table>
<thead>
<tr>
<th>Study</th>
<th>Schedule</th>
<th>n</th>
<th>2Gy equivalent dose</th>
<th>Local control (3 month cystoscopy)</th>
<th>Symptom control</th>
<th>Toxicity &gt;gd2</th>
<th>Survival median</th>
<th>2 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21Gy/3f</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21Gy/3f/1w</td>
<td>252</td>
<td></td>
<td>42.0</td>
<td>14/37(38%)</td>
<td>64%</td>
<td>7.5 months</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>36Gy/6f/6w</td>
<td>43</td>
<td></td>
<td>64.8</td>
<td>10/43(23%)</td>
<td>64%</td>
<td>7.5 months</td>
<td>19%</td>
</tr>
</tbody>
</table>

Overall, local control 83%, symptom control 50-75% >G2 toxicity <10%

RMH 243 patients 5% >G2 toxicity, median survival 12.6 months, 2 year survival 33%
Challenges in bladder radiotherapy

Target motion

Presumed empty bladder on two different occasions

Influence of rectal filling
Challenges in bladder radiotherapy

Target motion

Bladder assumed to be in same place
Influence of margins on volume

Third-power relationship between radius of a sphere and volume \((4/3\pi r^3)\)

<table>
<thead>
<tr>
<th>Margin</th>
<th>size (cm)</th>
<th>Volume (cm^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>GTV-CTV</td>
<td>0.5</td>
<td>34</td>
</tr>
<tr>
<td>CTV-PTV</td>
<td>1.5</td>
<td>180</td>
</tr>
<tr>
<td>CTV-PTV</td>
<td>0.5</td>
<td>65</td>
</tr>
</tbody>
</table>

Bladder radiotherapy solutions

Key tool: cone beam CT

Plan of the day (Library of plan)

Following automatic bone registration, PTV contours (small, medium, large) overlaid, assessment made to determine appropriate PTV contour covering bladder (with minimal normal tissue irradiation) made. Treatment delivered with corresponding plan.
Bladder radiotherapy solutions

**APPLY study**

*Adaptive predictive planning for hypofractionated bladder radiotherapy*


Apply study

Patient characteristics

55 patients
- Not suitable for daily radical RT
- 36Gy in 6f
- Plan of the Day adaptive RT
- Median age 86yrs

<table>
<thead>
<tr>
<th>Age</th>
<th>Median 86 years (range 68-97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31</td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
</tr>
<tr>
<td>Stage at presentation</td>
<td></td>
</tr>
<tr>
<td>T2N0M0</td>
<td>36</td>
</tr>
<tr>
<td>T3N0M0</td>
<td>11</td>
</tr>
<tr>
<td>T4N0M0</td>
<td>3</td>
</tr>
<tr>
<td>TanyN1-N3M0</td>
<td>3</td>
</tr>
<tr>
<td>TanyN+M1</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Charlson comorbidity index (age adjusted)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>21 (0)</td>
</tr>
<tr>
<td>1</td>
<td>11 (0)</td>
</tr>
<tr>
<td>2</td>
<td>12 (0)</td>
</tr>
<tr>
<td>3</td>
<td>3 (2)</td>
</tr>
<tr>
<td>4</td>
<td>5 (18)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>6 (35)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of fractions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Assessment of response 3 months post radiotherapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystoscopy</td>
<td>30</td>
</tr>
<tr>
<td>Radiology alone</td>
<td>6</td>
</tr>
<tr>
<td>Not assessed</td>
<td>19</td>
</tr>
</tbody>
</table>

Apply study

Plan selections

139 RT fractions assessed
- 68 (49%) small, 63 (45%) medium, and 8 (6%) large selected
- 3 (12%) same plan throughout the course

Dosimetric advantage

Standard Radiotherapy
PTV-CTV_{cb} = 401\text{cm}^3 (SD, 122; range, 176-714).

The average PTV applied was reduced by 42%

Plan of day/ library of plans
PTV-CTV_{cb} = 182\text{cm}^3 (SD, 86; range, 52-428).

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Toxicity

Acute toxicity (CTCAE v3)
GU grade 2 and grade 3 was seen in 40% and 18% respectively.
GI grade 2 and grade 3 acute toxicity was seen in 38% and 4% respectively.
No grade 4 genito-urinary or gastro-intestinal toxicity was seen.

Late toxicity (RTOG)
Grade 2 late toxicity (any) at 6 and 12 months was 19% and 13%
Grade 3 late toxicity at 6 and 12 months was 6.5% and 4%
Efficacy

**Local control assessed in 60%**
- 33/36 local control at 3 months
- 28/30 on cystoscopy
- ~at least 51%
- Estimated local control at 1 yr 91% (CI 82-99%)

**Median survival at 1 year**
- 66% (CI 51%-77%)
Clinical outcomes of the first randomised trial of adaptive hypofractionated radiotherapy in bladder cancer (HYBRID - CRUK/12/055)


*Chief Investigator

on behalf of all HYBRID Investigators
HYBRID
Non comparative randomised phase II trial

65 patients recruited
12 UK sites
April 2014-August 2016

32 Standard
33 Adaptive

Median FU: 25 months
58 patients with 3 month follow-up:
29 Standard & 29 Adaptive

62 patients with pT2-T4a N0 M0 bladder carcinoma unsuitable for standard daily radiotherapy

Due to receive six 6Gy fractions of radiotherapy delivered weekly (total dose: 36Gy over 6 weeks)

Randomise 1:1

Groups 1: STANDARD PLANNING (CONTROL)
Groups 2: ADAPTIVE PLANNING (CONTROL)

Follow up
- Weekly on treatment (Acute toxicity using CTCAE v.4)
- 4 weeks post last treatment (Acute toxicity using CTCAE v.4)
- 3 months post last treatment (Acute toxicity using CTCAE v.4, GA cystoscopy)
- 6 & 12 months (late toxicity using CTCAE v.4 and RTOG, flexible cystoscopy)
- 24 months (late toxicity using CTCAE v.4 and RTOG, disease control assessment)
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Standard planning (N=32)</th>
<th>Adaptive planning (N=33)</th>
<th>Total (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Range</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Age</td>
<td>85 (81, 89)</td>
<td>71, 91</td>
<td>84 (80, 87)</td>
</tr>
<tr>
<td>Months from histological confirmation</td>
<td>1.7 (1.2, 2.1)</td>
<td>0.3, 19.8</td>
<td>1.4 (1.0, 2.1)</td>
</tr>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24</td>
<td>75.0</td>
<td>20</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>25.0</td>
<td>13</td>
</tr>
<tr>
<td>Multiple tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>18.8</td>
<td>7</td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>78.1</td>
<td>25</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>3.1</td>
<td>1</td>
</tr>
<tr>
<td>Histological tumour type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCC</td>
<td>30</td>
<td>93.8</td>
<td>30</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2*</td>
<td>6.3</td>
<td>2**</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>1</td>
<td>3.1</td>
<td>0</td>
</tr>
<tr>
<td>G3</td>
<td>31</td>
<td>96.9</td>
<td>33</td>
</tr>
</tbody>
</table>

* Small cell carcinoma, Urothelial Carcinoma; **High grade sarcomatoid urothelial cancer with squamous differentiation; TCC + SCC
Results: Local disease control at 3 months

Aim: To rule out a control rate lower than 40% (target 60%)

- 39/51 (77%) patients with no evidence of residual tumour at 3 month follow-up

<table>
<thead>
<tr>
<th></th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death before 3 months</td>
<td>6</td>
</tr>
<tr>
<td>Assessed at 3 months</td>
<td>48</td>
</tr>
<tr>
<td>Disease present</td>
<td>9</td>
</tr>
<tr>
<td>Disease absent</td>
<td>39</td>
</tr>
<tr>
<td>Not assessed at 3 months</td>
<td>11</td>
</tr>
<tr>
<td>Disease present</td>
<td>3</td>
</tr>
<tr>
<td>Disease absent</td>
<td>1</td>
</tr>
</tbody>
</table>

*One patient had no cystoscopy at his 6-month follow-up. This patient was an inpatient at the time of visit and one patient had no assessment done at both 6 and 12 month follow-up visit per his preference.

^4 patients died due to their bladder cancer between 3.2 and 3.8 month and one died due to cardio-renal failure urosepsis, urinary tract infection.

Assuming unassessed patients to have failed (except for early death from other causes (n=4) and if no evidence of failure in 12 months (n=2))

Local control rate is 41/61 (65%)
Median overall survival: 18 months (IQR; 7.6-not reached)
Proportion surviving (95% CI):
6 months: 82% (70%, 89%)
12 months: 60% (47%, 71%)
24 months: 39% (26%, 53%)
Results: Adaptation rate

Aim: clinical benefit of adaptive planning would be anticipated if more than 25% of all fractions or more than one fraction per patient required intervention (i.e. smaller or larger margins than standard used)

- 76 of 193 (39.4%, 95% CI: 32%, 47%) fractions benefited from adaptive planning [46/193 (24%) small plan & 30/193 (16%) large]

- 28/33 pts (85%) benefited from adaptive planning (95% CI: 68%, 95%)
Results: Toxicity

**Acute**

**Aim:** To rule out an upper limit of 40% any grade 3+ acute adverse event with hypofractionated radiotherapy.

- 13/65 patients (20%; 90% CI: 12%-30%) had ≥G3
- 9/64 (14%; 90% CI: 8-23%) pts had ≥G3 treatment related GU acute AEs
- 3/65 (5%; 90% CI: 1-11%) had ≥G3 treatment related GI acute AEs

**Late**

RTOG toxicity (6 and 12 months)
Future

Daily plan re-optimisation

- The mean percentage reduction in volume with PTVre-opt compared to clinical plan selected from the library
  - 46% (SD 11.5, range 21.3-68.5).
  - 97% (29/30) fractions PTVre-opt was smaller PTV small
  - Statistically significant reduction all dose levels for bowel and at V17 and V28 for rectum
Conclusion

- A significant proportion of patients with MIBC are not fit for standard treatment approaches
- Using hypofractionated radiotherapy is a pragmatic approach to address their needs
- Prospective studies show that most patients can tolerate 6Gy weekly fractions
- This approach has modest short and long term toxicity
- Local control can be achieved in the majority
- Using adaptive therapy may improve accuracy and tolerability
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Our patients

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