The future of brachytherapy is HDR

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Overview

• Brief summary of the procedure
• Biological rationale for HDR
• Clinical evidence for HDR
• Possible technical advantages of HDR
• Focussed dose escalation
• Focal salvage for radio-recurrent disease
Brachytherapy Techniques
High Dose-Rate Brachytherapy
High Dose-Rate Brachytherapy
High Dose-Rate Brachytherapy
High Dose-Rate Brachytherapy
Biology

• Low $\alpha/\beta$ ratio for prostate cancer
  
  • Acta Oncol. 2005;44(3):265-76.
Iso-effect doses for different daily fractions and $\alpha/\beta$ ratios.
• **Biology**

• Cell death induced by vascular damage at very high doses per fraction

  • Song et al. *Cancer Res* 1974;34:2344–2350.
FSaII fibrosarcoma grown subcutaneous (s.c.) in the hind limb of C3H mice

The cell survival was determined immediately after irradiation or after leaving the irradiated tumors in situ for 1-5 days.
<table>
<thead>
<tr>
<th>Patient</th>
<th>$R_2^*$</th>
<th>$K_{trans}$</th>
<th>IAUGC$_{60}$</th>
<th>ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-27.3</td>
<td>-49.7</td>
<td>-14.4</td>
<td>2.3</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>-35.6</td>
<td>-7.3</td>
<td>5.1</td>
</tr>
<tr>
<td>3</td>
<td>-2.9</td>
<td>-</td>
<td>-</td>
<td>3.8</td>
</tr>
<tr>
<td>4</td>
<td>27.0</td>
<td>-19.7</td>
<td>-0.3</td>
<td>-12.7</td>
</tr>
<tr>
<td>5</td>
<td>-25.9</td>
<td>-11.2</td>
<td>-19.4</td>
<td>3.4</td>
</tr>
<tr>
<td>6</td>
<td>-14.0</td>
<td>74.6</td>
<td>114.3</td>
<td>-4.2</td>
</tr>
<tr>
<td>Average</td>
<td>-7.2</td>
<td>-8.4</td>
<td>14.6</td>
<td>-0.4</td>
</tr>
</tbody>
</table>
Phase III randomised trial

Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer

Peter J. Hoskin\textsuperscript{a}, Ana M. Rojas\textsuperscript{a,*}, Peter J. Bownes\textsuperscript{b}, Gerry J. Lowe\textsuperscript{a}, Peter J. Ostler\textsuperscript{a}, Linda Bryant\textsuperscript{a}

\textsuperscript{a} Cancer Centre, Mount Vernon Hospital, Northwood, UK; \textsuperscript{b} St. James’s Institute of Oncology, St. James’s University Hospital, Leeds, UK
T1c-T3b
PSA < 50ng/ml

55Gy in 20# control arm

37.75Gy in 13# plus HDR boost of 17Gy in 2#
• Median time to relapse of 116 months v 74 months
• The 5-, 7- and 10-year estimates are:

  75%, 66% and 46% for EBRT + HDR
  61%, 48% and 39% for EBRT alone (log rank p = 0.04)

• Significant covariates for risk of biochemical relapse on univariate and multivariate analysis:

  Treatment arm
  Risk category
### Endpoint Analysis:

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Analytical procedure</th>
<th>At 5 years</th>
<th>At 7 years</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>bRFS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm 1</td>
<td>K-M</td>
<td>61%</td>
<td>48%</td>
<td>0.04</td>
</tr>
<tr>
<td>Arm 2</td>
<td></td>
<td>75%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm 1</td>
<td>K-M</td>
<td>89%</td>
<td>88%</td>
<td>0.2</td>
</tr>
<tr>
<td>Arm 2</td>
<td></td>
<td>88%</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td><strong>Genito-urinary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm 1</td>
<td>K-M</td>
<td>26%</td>
<td>30%</td>
<td>0.5</td>
</tr>
<tr>
<td>Arm 2</td>
<td></td>
<td>26%</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td><strong>Urethral strictures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm 1</td>
<td>K-M</td>
<td>2%</td>
<td>2%</td>
<td>0.1</td>
</tr>
<tr>
<td>Arm 2</td>
<td></td>
<td>6%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td><strong>Gastro-intestinal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm 1</td>
<td>K-M</td>
<td>6%</td>
<td>6%</td>
<td>0.8</td>
</tr>
<tr>
<td>Arm 2</td>
<td></td>
<td>7%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm 1</td>
<td></td>
<td>0%</td>
<td>2%</td>
<td>7 year: 1</td>
</tr>
<tr>
<td>Arm 2</td>
<td></td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

### Graphs:

- **Urinary**
  - EBRT + HDR-BT:
    - At 5 years: 87%
    - At 7 years: 75%
  - EBRT alone:
    - At 5 years: 80%
    - At 7 years: 64%

- **Bowel**
  - EBRT + HDR-BT:
    - At 5 years: 107%
    - At 7 years: 82%
  - EBRT alone:
    - At 5 years: 108%
    - At 7 years: 82%

### Statistics:

- p = 0.5
- Log rank
High Dose-Rate Brachytherapy - Monotherapy

- T1c-T3b
- PSA < 40ng/ml

- 34 Gy in 4 fractions
- 36 Gy in 4 fractions
- 31.5 Gy in 3 fractions
- 26 Gy in 2 fractions
- 19 Gy single fraction
- 20 Gy single fraction
High Dose-Rate Brachytherapy - Monotherapy

227 Patients

3-year DFS:

Intermediate Risk = 99%
High Risk = 91%

The 3-year actuarial rate of Grade 3 toxicity:

GU = 3-16%
GI = 1%

• Geographical Miss
• Geographical Miss
• Geographical Miss
Ability to treat large prostate glands


• 164 patients
• November 2003 to July 2009
• Median prostate volume = 60cc (15-208 cc)
Table 2. Evidence of biochemical disease after high dose rate brachytherapy alone

<table>
<thead>
<tr>
<th>Volume</th>
<th>Patients on ADT</th>
<th>$p$ value</th>
<th>ADT mean duration</th>
<th>bNED %</th>
<th>$p$ value</th>
<th>Mean TTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ median</td>
<td>73</td>
<td>0.01</td>
<td>12.1</td>
<td>80</td>
<td>0.0042</td>
<td>71</td>
</tr>
<tr>
<td>&gt; median</td>
<td>59</td>
<td>15.3</td>
<td>93</td>
<td>70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: ADT = androgen deprivation therapy, bNED = no evidence of biochemical disease, TTF = time to failure*

Time measured in months
Figure 2

Free from biochemical relapse (%)

CTV ≥ median

CTV < median

Time from first dose (months)

$p = 0.004$
Table 3. Late genitourinary toxicity International Prostate Symptom Score after high dose rate brachytherapy alone

<table>
<thead>
<tr>
<th>Volume</th>
<th>n</th>
<th>IPSS 8 - 19</th>
<th>IPSS ≥ 20</th>
<th>Strictures</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ median</td>
<td>82</td>
<td>49 (30)</td>
<td>13 (8)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>82</td>
<td>52 (32)</td>
<td>18 (11)</td>
<td>7 (4)</td>
</tr>
</tbody>
</table>

*Abbreviations: IPSS = International Prostate Symptom Score
Numbers in parentheses are percentages*
Focussed dose escalation

• Rationale
• Examples
Dose Response Relationship in Prostate Cancer
Ten-year prostate-specific antigen (PSA) relapse–free survival for low-risk patients was 84% and 70% for patients treated with ≥75.6 Gy and with lower doses, respectively (p = 0.04). RT = radiotherapy. Zelefsky et al, 2011

Detecting disease with T2W-MRI

- Good at detecting cancers in the PZ. More difficult in the TZ & CZ.
- Better for more advanced disease / higher risk disease
- Better at depicting densely cellular cancers than sparse infiltrating disease*
- Signal intensity of tumours does not consistently correlate with grade**
- False positives in PZ: scars, BPH in PZ, prostatitis, PIN, atypical ductal hyperplasia, glandular atrophy, haemorrhage & treatment effects

61 yrs; cT1; TRUS GI 3+4; PSA 8.7 ng/ml (intermediate risk)
Partins table: organ confined 59%; EPE 34%; SVI 6%; LN 1%
Figure 1: Sagittal Plane, Transperitoneal Template Biopsy

Figure 2: Template Grid Illustration, Mid-Prostate Transverse Plane. (TZ, Transition Zone; LPZ, Lateral Peripheral Zone; PZ, Peripheral Zone.)
Rationale for focussed dose escalation

• Proven dose-response relationship for prostate cancer

• Ability to geographically map the distribution of ‘clinically significant’ prostate cancer using modern imaging and template biopsy

• Belief that outcome may determined by the behaviour of the most aggressive tumour focus
Workflow for focussed dose escalation

- Pre-Implant Multi-Parametric MRI Scan
  - T2
  - Diffusion Weighted
  - Dynamic Contrast Enhanced MRI
- Images available in the operating theatre during implantation
  - Currently no US-MRI fusion capability in theatre
- Conventional Whole gland needle placement
- 5mm spacing across dominant region
- Post-Implant CT and MRI scans
- Overlay of Pre-Implant MRI sequences
Volumes
• $CTV_{Prostate} =$ Entire Prostate
• $CTV_{Boost} =$ Boost volume
• Organs at risk, rectum, urethra etc.

Expansions
• $PTV_{Boost} = (CTV_{Boost} + 3\text{mm}) - \text{Rectum}$
• $PTV_{Comb} = (CTV_{Prostate} + 3\text{mm}) - \text{Rectum}$
• $PTV_{NonBoost} = PTV_{Comb} - PTV_{boost}$
75 year old man, PSA 18ng/ml, T3a No Mo, Gleason 4+3 in 5/12 TRUS biopsy cores, all Right Sided
64 year old man

PSA 8.9ng/ml

T2a No Mo

Gleason 3+4 in 2/12
TRUS biopsy cores, all Right Sided
67 year old man

PSA 14.7ng/ml

T2b No Mo

Gleason 3+4 in 4/12

TRUS biopsy cores, all Right Sided
Salvage Treatment for radio-recurrent prostate cancer

• Rationale and Clinical Need
• Examples
• Design For Proposed Clinical Trial
Among those treated with external beam radiotherapy at the dose of 74 Gray in 37 fractions, 29% will experience biochemical relapse within 5 years (Dearnaley et al 2007).

Out of all the patients with biochemical relapse, over a quarter (26-32%) will have local recurrence without detectable extraprostatic spread (Lee et al 1997, Murat et al 2007).

Therefore, we can estimate that in the UK (population 60,000,000) between 1500 and 1850 patients will experience local failure per year.
• Local recurrence remains a neglected area of study
• Standard therapy is immediate or deferred androgen deprivation therapy
  • flushing, sexual dysfunction, gynaecomastia, weight gain, mood changes muscular and joint pains and osteoporosis
• Endocrine therapy is expensive
  • £1000 per year, rising to upto £5000 with the combined use of LHRH analogues and anti-androgen therapy
65 year old man
EBRT 74Gy 2009

At primary diagnosis:
- PSA 12.7ng/ml
- T2a No Mo
- Gleason 3+4 in
- 6/12 TRUS biopsy cores, all Right Sided

Biochemical relapse
February 2014 (Phoenix criteria)

Bone scan, mp MRI pelvis, whole body diffusion weighted MRI = No, Mo

Template biopsy – 6 cores +ve R posterior apex and base, rest of gland negative
PSA at 6 months < 0.1
Failure after $^{125}$I brachytherapy
Salvage treatment for local recurrence in prostate cancer

Trial Schema

PSA failure after radical external beam RT or seed brachytherapy

Already on hormones?

Yes

Patient not eligible for trial entry

No

PSA < 10

Yes

Patient not eligible for trial entry

No

Experimental Arm

Randomisation (3:1)

Standard Arm

Commencement of hormone at clinician’s discretion

Whole body CT & 99mTc bone scan ± Whole body diffusion weighted MRI scan or ¹¹C / ¹⁸F-Choline PET

Evidence of distal metastases?

Yes

Commencement of hormone at clinician’s discretion

No

True local recurrence confirmed by either template biopsy or image guided biopsy?

Yes

Focal High Dose Rate Brachytherapy Salvage – 19Gy single fraction

No

Commencement of hormone at clinician’s discretion