The Paul Evans Memorial Lecture

Functional radiotherapy targeting using focused dose escalation

Roberto Alonzi

Mount Vernon Cancer Centre
Overview

• Introduction and rationale for focused dose escalation
• Options for focused therapy
• Requirements for focused dose escalation
• Focused dose escalation using high dose rate brachytherapy as monotherapy
• Hypoxia as a target for focused dose escalation for prostate cancer
Concepts and Terminology

Whole Gland Therapy

Focused Therapy or ‘Focal Boost’

Focal Therapy
Why does radiotherapy fail?

• Failure of staging

• Geographical miss

• Radioresistance
Why does radiotherapy fail?

• Failure of staging

• Geographical miss

• Radioreistance
Rationale

Focused dose escalation is based upon the principle that areas of tumour with relative radio-resistance can be overcome by administering a higher biologically effective radiation dose (BED).

- Higher total dose
- Higher dose per fraction
Dose Response Relationship in Cancer
Individual variation in radio-sensitivity

Tumour Control Probability

Dose

Individuals with relatively radio-resistant tumours
Individuals with relatively radio-sensitive tumours
Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial

LONG-TERM RESULTS OF CONFORMAL RADIOTHERAPY FOR PROSTATE CANCER: IMPACT OF DOSE ESCALATION ON BIOCHEMICAL TUMOR CONTROL AND DISTANT METASTASES-FREE SURVIVAL OUTCOMES

MICHAEL J. ZELEFSKY, M.D.,* YOSHIYA YAMADA, M.D.,* ZVI FUKS, M.D.,* ZHIGANG ZHANG, PH.D.,† MARGIE HUNT, B.S.,‡ OREN CAHLOM, M.D.,* JESSICA PARK, B.A.,* AND ALISON SHIPPY, B.A.*
# Dose Escalation in Prostate Cancer

**Table 3:** Data from randomised controlled trials of dose-escalated external beam radiotherapy for prostate cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Accrual period</th>
<th>Total radiation dose (Gy/number of fractions)</th>
<th>NAADT</th>
<th>NCCN risk</th>
<th>Median age (years)</th>
<th>Data last reported</th>
<th>Median follow-up (years)</th>
<th>PSA failure (N [%])</th>
<th>Absolute reduction in PSA failure in dose escalated group</th>
<th>Survival in escalated-dose group</th>
<th>Prostate cancer deaths (N [%])</th>
<th>Non-prostate-cancer deaths (N [%])</th>
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<tbody>
<tr>
<td>MRC RT01</td>
<td>843</td>
<td>1998-2001</td>
<td>64/32, 74/37</td>
<td>All</td>
<td>37%</td>
<td>67</td>
<td>2012</td>
<td>10.0</td>
<td>365 (43%)</td>
<td>13% (10 year)</td>
<td>70% (10 year)</td>
<td>91 (11%)</td>
<td>145 (17%)</td>
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<tr>
<td>NKI</td>
<td>664</td>
<td>1997-2003</td>
<td>68/34, 78/39</td>
<td>No</td>
<td>37%</td>
<td>69</td>
<td>2013</td>
<td>9.2</td>
<td>329 (50%)</td>
<td>6% (10 year)</td>
<td>67% (10 year)</td>
<td>88 (13%)</td>
<td>117 (18%)</td>
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<tr>
<td>PROG 95-99</td>
<td>393</td>
<td>1996-99</td>
<td>70-2/39, 79-2/44</td>
<td>No</td>
<td>37%</td>
<td>67</td>
<td>2010</td>
<td>8.9</td>
<td>83 (21%)</td>
<td>16% (10 year)</td>
<td>83% (NS)</td>
<td>6 (1.5%)</td>
<td>55 (14%)</td>
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<tr>
<td>MDACC</td>
<td>301</td>
<td>1993-98</td>
<td>70/35, 78/39</td>
<td>No</td>
<td>46%</td>
<td>69</td>
<td>2008</td>
<td>8.7</td>
<td>61 (20%)</td>
<td>19%* (8 year)</td>
<td>79% (8 year)</td>
<td>10 (3%)</td>
<td>70 (23%)</td>
</tr>
<tr>
<td>ICR-RMH</td>
<td>126</td>
<td>1995-97</td>
<td>64/32, 74/37</td>
<td>All</td>
<td>27%</td>
<td>67</td>
<td>2013</td>
<td>13.7</td>
<td>64 (51%)</td>
<td>8% (12 year)</td>
<td>About 60% (14 year)</td>
<td>19 (15%)</td>
<td>32 (25%)</td>
</tr>
<tr>
<td>GETUG 06</td>
<td>306</td>
<td>1999-2002</td>
<td>70/35, 80/35</td>
<td>No</td>
<td>NS</td>
<td>67</td>
<td>2011</td>
<td>5.1</td>
<td>85 (28%)</td>
<td>8.5% (5 year)</td>
<td>(NS)</td>
<td>10 (3.3%)</td>
<td>16 (5.2%)</td>
</tr>
</tbody>
</table>

N - number of patients randomised. NAADT - short course neoadjuvant androgen deprivation therapy. NCCN - National Comprehensive Cancer Network. PSA - prostate-specific antigen. NS - not stated. *Freedom from biochemical (PSA) or clinical failure.
LATE GASTROINTESTINAL TOXICITY AFTER DOSE-ESCALATED CONFORMAL RADIOTHERAPY FOR EARLY PROSTATE CANCER: RESULTS FROM THE UK MEDICAL RESEARCH COUNCIL RT01 TRIAL (ISRCTN47772397)


A

RMH Rectal bleeding
% reporting late toxicity

B

RMH Rectal bleeding
time to first reported late toxicity

Number at risk: OVERALL SURVIVAL
Esc: 422 412 397 383 358 288
Std: 421 417 414 396 380 352 276

months from start of RT

- mild+ (Esc)
- mild+ (Std)
- moderate+ (Esc)
- moderate+ (Std)
- severe+ (Esc)
- severe+ (Std)
CLINICAL INVESTIGATION

LATE GASTROINTESTINAL TOXICITY AFTER DOSE-ESCALATED CONFORMAL RADIOTherapy FOR EARLY PROSTATE CANCER: RESULTS FROM THE UK MEDICAL RESEARCH COUNCIL RT01 TRIAL (ISRCTN47772397)


<table>
<thead>
<tr>
<th>Toxicity</th>
<th>M. D. Anderson (1)</th>
<th>NKI (2, 3)</th>
<th>PROG 9509 (4)</th>
<th>RMH pilot (5)</th>
<th>MRC RT01 (6, 7)</th>
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</thead>
<tbody>
<tr>
<td>RT dose Gy Setting</td>
<td>70 vs. 78 US</td>
<td>68 vs. 78 The Netherlands</td>
<td>70.2 vs 79.2 US</td>
<td>64 vs. 74 UK</td>
<td>64 vs. 74 UK, Australia, New Zealand</td>
</tr>
<tr>
<td>Sites</td>
<td>Single site</td>
<td>Multisite</td>
<td>Single site CFRT photon</td>
<td>Single site CFRT photon</td>
<td>Single site Multisite</td>
</tr>
<tr>
<td>RT technique</td>
<td>CFRT photon</td>
<td>CFRT photon</td>
<td>CFRT photon Proton boost</td>
<td>CFRT photon</td>
<td>CFRT photon CFRT boost</td>
</tr>
<tr>
<td>No. of patients randomized</td>
<td>301</td>
<td>669</td>
<td>393</td>
<td>126</td>
<td>843</td>
</tr>
<tr>
<td>Toxicity scale</td>
<td>RTOG-LENT modified*</td>
<td>RTOG/EORTC</td>
<td>RTOG</td>
<td>RTOG original</td>
<td>RTOG original</td>
</tr>
<tr>
<td>Median follow-up (years)</td>
<td>8.7</td>
<td>5.8</td>
<td>5.5</td>
<td>6.2</td>
<td>5.3</td>
</tr>
<tr>
<td>Grade ≥2 64 Gy vs. 74 Gy</td>
<td>13% vs. 26% (p = 0.013)</td>
<td>25% vs. 35% (p = 0.045)</td>
<td>9% vs. 18% (p = 0.005)</td>
<td>11% vs. 23% (p = 0.02)</td>
<td>24% vs. 33% (p = 0.005)</td>
</tr>
<tr>
<td>Analysis time point and type</td>
<td>By 10 years cumulative</td>
<td>By 7 years cumulative</td>
<td>“Late” snapshot</td>
<td>By 2 years cumulative</td>
<td>By 5 years cumulative</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}
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Rationale for focused dose escalation

There is evidence that:

1. There is a dose response relationship in prostate cancer
2. Dose escalation achieves better survival outcomes
3. Dose escalation to the whole gland using External Beam RT is associated with increased toxicity
4. Dose escalation to the whole gland using HDR Brachytherapy may be associated with a smaller penalty in terms of toxicity

We now have reliable imaging and mapping biopsy technology to define sub-volumes of ‘higher risk’ disease within the prostate gland
So is it possible to further increase the therapeutic ratio by delivering a differential dose to the region of the gland considered at highest risk compared to the remainder of the prostate?

Or, now that we can visualise most intermediate and high risk tumours with MRI, shouldn't we just go straight for focal therapy?
Meta-analysis of 7 studies
- All T2W + DCE + DWI at least
- Compared to radical prostatectomy
- Specificity of 0.88 (95% CI, 0.82–0.92)
- Sensitivity of 0.74 (95% CI, 0.66–0.81)
- Negative predictive values (NPVs) ranging from 0.65 to 0.94
Tracking the clonal origin of lethal prostate cancer

Michael C. Haffner,¹ Timothy Mosbruger,¹ David M. Esopi,¹ Helen Fedor,² Christopher M. Heaphy,² David A. Walker,¹ Nkosi Adejola,¹ Meltem Gürel,¹ Jessica Hicks,² Alan K. Meeker,¹,²,³ Marc K. Halushka,² Jonathan W. Simons,⁴ William B. Isaacs,¹,²,³ Angelo M. De Marzo,¹,²,³ William G. Nelson,¹,²,³ and Srinivasan Yegnasubramanian¹

Focused Boosting – ‘The Best Of Both Worlds’

Whole gland dose escalation improves outcome but at the price of increased toxicity

Focal therapy to a ‘dominant’ intra-prostatic lesion without treatment of the entire gland risks leaving a potentially lethal, clonally distinct, tumour focus
Options For Focused Therapy

EBRT to the whole gland

+ Focal therapy to the ‘dominant’ intra-prostatic lesion

- HDR
- LDR
- Stereotactic RT
- HiFU
- Cryotherapy
- Electroporation

Integrated Concomitant Boost

- HDR
- LDR
- Stereotactic RT
Requirements for focused dose escalation

1) Firstly, an accurate geographical map of tumour radio-resistance (or at least a map of a biomarker or combination of biomarkers that can act as a surrogate for the risk of progression following radiotherapy).

2) Secondly, a radiotherapy technique that can produce high dose gradients that are sufficient to facilitate dose escalation to sub-volumes within tumours without increasing dose to the whole tumour and surrounding normal tissues.
Definition of the biological target.

Key Imaging Requirements

1. The chosen imaging biomarker must have a proven association with radiotherapy outcome for that particular tumour type.
2. Stable physiological process
3. Range of biomarker values on which to base the differential dose
4. Reproducibility and Repeatability
5. Volumetric acquisition capability
6. Co-registration with anatomical map
7. (Repeat assessment)
Validated biomarker groups that may serve as targets for pharmacological radio-sensitisation or focused dose escalation

- Hypoxia
- Vascularity / Blood flow
- Cellular Proliferation
- Clonogen density

These may exist in complex arrangements........
T2-weighted MRI

67 year old man with a Gleason 4+3 carcinoma
Diffusion Weighted MRI
Dynamic Contrast Enhanced MRI
Magnetic Resonance Spectroscopy
Which biological map to choose?
Image Registration

- Rigid fusion - Linear Transformations
  Rotation, Scaling, Translation

- Non-rigid fusion - Warping
  Multiple points, Contours

A confident registration with a measurement of uncertainty is critical.

This level of uncertainty must then be incorporated into the margins chosen for CTV to PTV expansion.
Dose Painting

Quantitative biological tumour map
Dose Painting by contours
Dose Painting By Numbers
Focused dose escalation using high dose rate brachytherapy as monotherapy for prostate cancer
Biology

Low $\alpha/\beta$ ratio for prostate cancer

Biology

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

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 tumours in situ for 1-5 days.
High Dose-Rate Brachytherapy
High Dose-Rate Brachytherapy - Monotherapy

3-year DFS:
Intermediate Risk = 99%
High Risk = 91%

The 3-year actuarial rate of Grade 3 toxicity:
GU = 3-16%
GI = 1%

Prostate brachytherapy

Optimal source distribution for focal boosts using high dose rate (HDR) brachytherapy alone in prostate cancer

Pittaya Dankulchai\textsuperscript{a,b,*}, Roberto Alonzi\textsuperscript{a}, Gerry J. Lowe\textsuperscript{a}, James Burnley\textsuperscript{a}, Anwar R. Padhani\textsuperscript{c}, Peter J. Hoskin\textsuperscript{a}
1<sup>st</sup> cohort – 25 patients

<table>
<thead>
<tr>
<th>Structure</th>
<th>Index</th>
<th>Target Value</th>
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<tbody>
<tr>
<td>HDR PTVBoost</td>
<td>V100 [% of volume]</td>
<td>Is more than</td>
</tr>
<tr>
<td>HDR PTVNonBoost</td>
<td>V19Gy [% of volume]</td>
<td>Is less than</td>
</tr>
<tr>
<td>HDR Urethra</td>
<td>D30 [Gy]</td>
<td>Is less than</td>
</tr>
<tr>
<td>HDR Urethra</td>
<td>D10 [Gy]</td>
<td>Is less than</td>
</tr>
<tr>
<td>HDR Urethra</td>
<td>V150 [cm³]</td>
<td>Is less than</td>
</tr>
<tr>
<td>HDR Rectum</td>
<td>V19Gy [cm³]</td>
<td>Is less than</td>
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<tr>
<td>HDR Rectum</td>
<td>D2.0cc [Gy]</td>
<td>Is less than</td>
</tr>
<tr>
<td>HDR PTVNonBoost</td>
<td>V19Gy [% of volume]</td>
<td>Is more than</td>
</tr>
<tr>
<td>HDR PTVNonBoost</td>
<td>V15Gy [% of dose]</td>
<td>Is more than</td>
</tr>
</tbody>
</table>
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
2\textsuperscript{nd} cohort – 25 patients (21 treated so far)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Index</th>
<th>Target Value</th>
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<tbody>
<tr>
<td>HDR PTVBoost</td>
<td>V100 [% of volume]</td>
<td>Is more than</td>
</tr>
<tr>
<td>HDR PTVNonBoost</td>
<td>V19Gy [% of volume]</td>
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<td>HDR Urethra</td>
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<td>Is less than</td>
</tr>
<tr>
<td>HDR Urethra</td>
<td>D10 [Gy]</td>
<td>Is less than</td>
</tr>
<tr>
<td>HDR Urethra</td>
<td>V150 [cm(^3)]</td>
<td>Is less than</td>
</tr>
<tr>
<td>HDR Rectum</td>
<td>V19Gy [cm(^3)]</td>
<td>Is less than</td>
</tr>
<tr>
<td>HDR Rectum</td>
<td>D2.0cc [Gy]</td>
<td>Is less than</td>
</tr>
<tr>
<td>HDR PTVNonBoost</td>
<td>V19Gy [% of volume]</td>
<td>Is more than</td>
</tr>
<tr>
<td>HDR PTVNonBoost</td>
<td>V15Gy [% of dose]</td>
<td>Is more than</td>
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67 year old man

PSA 14.7ng/ml

T2b No Mo

Gleason 3+4 in 4/12
TRUS biopsy cores, all Right Sided
## Published articles with toxicity results for focused therapies in prostate cancer

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Citation</th>
<th>Patient Number</th>
<th>Modality</th>
<th>Technique</th>
<th>Whole Gland Dose</th>
<th>Dose to Dominant Lesion</th>
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<tbody>
<tr>
<td>Aluwini</td>
<td>Radiat Oncol. 2013;8:84</td>
<td>50</td>
<td>SBRT</td>
<td>Integrated Boost</td>
<td>38Gy in 4#</td>
<td>49 Gy in 4#</td>
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<td>Schild</td>
<td>OMICS J Radiol. 2014;3(4).</td>
<td>78</td>
<td>IMRT</td>
<td>Integrated Boost</td>
<td>77.4Gy in 43#</td>
<td>81 Gy in 43#</td>
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<tr>
<td>Wu</td>
<td>Asian J Androl. 2011;13(3):499-504</td>
<td>120</td>
<td>EBRT + HiFU</td>
<td>Sequential Boost</td>
<td>65-70Gy</td>
<td>HiFU</td>
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</table>
Hypoxia as a target for focused dose escalation for prostate cancer
Hypoxia in Prostate Cancer

There is evidence to support the presence of clinically significant hypoxia in prostate tumours.

FIGURE 2. Histogram of pO₂ measurements from prostate cancer nodule.
Hypoxia predicts for poor outcomes in prostate cancer

Hypoxic ratio of prostate pO$_2$/muscle pO$_2$ predicts biochemical failure after RT
Immunohistochemistry

Figure 2: Freedom from biochemical failure (%) against time (years) with respect to expression of intrinsic markers of tumour hypoxia and angiogenesis*
(A) Radiotherapy cohort. (B) Radical prostatectomy cohort. *Marker categories pooled where fewer than ten patients in one category.
GLUT1

HIF1α

OPN

Negative

Positive

Negative

Positive

Negative

Positive

P=0.01

P=0.01

P=0.02

P=0.01

Cumulative Survival

Biochemical Relapse Free Interval (months)
Intrinsic susceptibility weighted (BOLD) MRI

Primary source of BOLD image contrast is deoxyhaemoglobin

Deoxyhaemoglobin (dHb) is paramagnetic and confined within RBCs (acts like intravascular contrast medium)

dHb decreases SI of blood and surrounding tissues on $T_2^*$ images ($R_2^*$)

Oxygenation of Hb is proportional to blood $pO_2$ which is in equilibrium with tissue $pO_2$

BOLD-MRI $\sim$ [deoxyhaemoglobin] $\sim$ blood $p_aO_2$ $\sim$ tissue $pO_2$
Example of BOLD MRI
The ‘probe’ is in the wrong place!

We are interested in the \( pO_2 \) in the immediate vicinity of tumour cells not the *intravascular* deoxyhaemoglobin concentration.
However......

Deoxyhaemoglobin concentration ~ paO2 ~ tissue pO2
Blood Volume Dependency

High Blood Volume

Low Blood Volume

Oxyhemoglobin
Deoxyhemoglobin
For BOLD-MRI to work, red blood cells have to be delivered to tissues.
Validating $R_{2}^{*}$ with pimonidazole immunostaining in prostate cancer

- Blood volume high > 42AU
- Blood volume low < 42AU

Alonzi et al, ISMRM 2008
Blood volume adjusted BOLD MRI for the detection of prostate cancer hypoxia

Test Criteria:

Hypoxia should be diagnosed if:
- rBV is less than 42 a.u. OR,
- rBV is greater than 42 a.u. AND $R_2^*$ is greater than 21.3s$^{-1}$

Sensitivity: 80% (68% - 89%)
Specificity: 77% (59% - 90%)
PPV: 88% (77% - 95%)
NPV: 65% (47% - 80%)
BOLD MRI

BOLD-MRI alone is not sufficient to accurately map hypoxia within prostate tumors.

Combined BOLD-MRI and DSC-MRI can produce a test of high positive predictive value for hypoxia mapping.

→ Criteria need independent verification
→ Requires validation using alternative hypoxia markers
Conclusions

Modelling suggests that there could be large gains in therapeutic ration from focused dose escalation.

We need a better understanding of the relationship between imaging biomarkers and radiosensitivity.

We need to establish imaging biomarker priority.