Biofocussed prostate cancer RadioTherapy: The BiRT project

Presented by
Professor Annette Haworth
Institute of Medical Physics,
School of Physics
These slides may not be reproduced without the author’s permission. Please contact Annette.Haworth@Sydney.edu.au
Biofocussed RadioTherapy

BiRT
How do we treat prostate cancer?

Note that in all cases we treat the WHOLE prostate.
Current approaches to focal / boost-focal approaches

- Cosset 2013
- 145 Gy to MRI defined “focal volume”
  - Generous margin
  - ~ 1/3 prostate volume

Low Dose Rate Brachytherapy

High Dose Rate Brachytherapy

- Dankulchai et al Radiother Oncol 2014

EBRT focal lesion

- Lips et al Trials 2011 FLAME trial
- 77 Gy whole gland vs 77 Gy+ 18 Gy microboost in 35 fractions
Why focal therapy?

- Reduce the dose to OARs
  - Good for low risk disease
  - where Active Surveillance is now mostly indicated
- Dose escalation of the dominant lesion
  - Good for intermediate/ high risk disease
  - Where dose escalation has shown to benefit local control
- Improve the therapeutic ratio
  - Ie maximise tumour control & minimise toxicity
Starting a focal therapy program

- No consensus on the volume (CTV) that should be treated
- No consensus on the prescribed dose
- No consensus on how to monitor treatment response
What volume?

We currently treat the whole prostate

Because we don’t know where the tumour is inside the prostate
Figure 1 | Metastatic properties of prostate cancer. 

- a) Unifocal prostate cancer
- b) Multifocal prostate cancer with clear index lesion
- c) Multifocal prostate cancer with unclear index tumour
Report of a consensus meeting on focal low dose rate brachytherapy for prostate cancer

Stephen Langley¹, Hashim U. Ahmed², Bashar Al-Qaisieh³, David Bostwick⁴, Louise Dickinson², Francisco Gomez Veiga⁵, Peter Grimm⁶, Stefan Machtens⁷, Ferran Guede⁸ and Mark Emberton²

Ultra-Focal Therapy  Focal Therapy  Focused Therapy
What dose?

I-125 137 Gy to peripheral zone or
  - EBRT 45 Gy prostate & SV plus I-125 PZ boost to 90 Gy

Low & favourable intermediate risk patients

Median FU 5.1 years

LR: FFbF 95%

Favourable IR : FFbF 73%

Was this dose insufficient?
What dose?

- 19 Gy single fraction to peripheral zone
- Favourable risk patients
- At 24-months 5/30 biochemical recurrence
- Was this dose insufficient?

Image from Nguyen 2012 showing PZ
Biofocussed RadioTherapy
Hypothesis

With the use of imaging biomarkers we can:

- Identify **where** high doses of radiation should be delivered

- Quantitative imaging will tell us **how much** radiation
Our goal is to deliver a dose distribution customised to tumour biology

‘Biofocussed RadioTherapy’

- High dose to tumour
  - Actual dose depends on specific tumour characteristics

- Lower dose to surrounding prostate to mop up any stray cancer cells
Our goal is to deliver the right dose to the right place

‘Biofocussed RadioTherapy’

BiRT
Building imaging biomarkers

RADIOMICS

- Tumour location
- Tumour aggressiveness
- Tumour cell density
- Tumour hypoxia

Machine learning

Predictive Model

… radiomics… extract quantitative features from medical images
Our goal is to maximise the therapeutic ratio by delivering a dose distribution customised to tumour biology.

Haworth et al PMB 2016
**Tumour Control Probability - TCP**

\[
TCP = \prod_{i=1}^{N} TCP_i = \prod_{i=1}^{N} \exp \left[ -\rho_i V_i \exp \left( -\alpha d_i R E_i + \ln(2) \left( \frac{T_{i \text{ crit}}}{T_{\text{ pot}}} \right) \right) \right]
\]

Haworth et al *Brachytherapy* 2013
Tumour Control Probability - TCP

\[
TCP = \prod_{i=1}^{N} TCP_i = \prod_{i=1}^{N} \exp \left[ -\rho_i V_i \exp \left( -\alpha d_i RE_i + \ln(2) \left( \frac{T_{crit}^i}{T_{pot}} \right) \right) \right]
\]

To work out what dose goes where
The BiRT Project
The BiRT Project (overview)

Magnetic Resonance Imaging (MRI) + PET
The BiRT Project (overview)
The BiRT Project (overview)
So how do we develop imaging biomarkers

So that we can deliver a non-uniform dose distribution
mpMRI, PSMA PET and Quantitative Imaging (Radiomics)

Angiogenesis

Hypoxia

Proliferation

Metabolism

Ktrans (from DCE)

R2* from BOLD

ADC from DWI

Ktrans, Ve, etc

<table>
<thead>
<tr>
<th></th>
<th>180</th>
<th>120</th>
<th>480</th>
<th>350</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>200</td>
<td></td>
<td>350</td>
<td>400</td>
</tr>
</tbody>
</table>

Kim 2016; Zelhof 2009; Hoskin 2007; Schiller 2017
Building predictive models

RADIOMICS*

- Tumour location
- Tumour aggressiveness
- Tumour cell density
- Tumour hypoxia

Feature Extraction

Machine learning

Predictive Model

... radiomics... extract quantitative features from medical images
How do we build biology models from MRI + PET?

First step “feature extraction”
We then correlate these features with pathology.
We then correlate these features with pathology


**Cell density map**

**Prediction of high grade tumour location**
Prostate after it has been removed from the patient.
Co-registration of “ground truth” histology and imaging

Reynolds et al Med Phys 2015, BJUI 2018
Co-registration of “ground truth” histology and imaging

Reynolds et al Med Phys 2015
In future patients have the potential to determine:

- Location of disease
- Tumour cell density
- Proliferation
- Hypoxia

Stoyanova et al. Transl Cancer Res 2016
Tumour Control Probability - TCP

\[
TCP = \prod_{i=1}^{N} TCP_i = \prod_{i=1}^{N} \exp\left[-\rho_i V_i \exp\left(-\alpha d_i R E_i + \ln(2) \left(\frac{T_{i, crit}}{T_{pot}}\right)\right)\right]
\]

Haworth et al. *Brachytherapy* 2013
What TCP value predicts for treatment failure?

Combined TCP Zeng exponential cell density

High TCP_{\text{comb}}
\text{FFbF} 93.7% 
(95\% CI 90.4-96.4%)

Low TCP_{\text{comb}}
\text{FFbF} 88.8% 
(95\% CI 81.3-94.5%)

3 centres n=423
number of failures = 36

p=0.004
Machine Learning to generate Predictive Model

mpMRI data & histology From multiple patients

Predictive model

Dinh 2016; Sun 2017
Predicting Cell Density from mpMRI

True cell density from histology

Predicted cell density from mpMRI

True CD

LR

MARS
cells/mm²

NS

Poly

ADC

Multivariate adaptive regression splines: Region-wise linear regressions. Generalised additive model (GAM): Extends linear models to non-linear models; functions of natural splines (NS) or polynomials (poly)

RMS error: 1.06 x 10³ cells / mm² (relative error 13%)

Sun et al (Acta Oncologica 2018)
Correlating imaging with tumour grade

Gleason Scale

1. Small, uniform glands
2. More space between glands
3. Infiltration of cells from glands at margins
4. Irregular masses of cells with few glands
5. Lack of glands, sheets of cells

Well differentiated

Poorly differentiated

3+3

The University of Sydney
Correlating imaging with tumour grade

Our model predicts tumour grade

Sun et al Acta Oncol
accepted Mar 2019
But now we are exploring hypoxia

Tumor Hypoxia Predicts Biochemical Failure following Radiotherapy for Clinically Localized Prostate Cancer

- Higher potential to metastasize
- Higher resistance to RT
- Not well understood in prostate cancer

HYPOXIA IN PROSTATE CANCER: CORRELATION OF BOLD-MRI WITH PIMONIDAZOLE IMMUNOHISTOCHEMISTRY—INITIAL OBSERVATIONS


The University of Sydney
Hypoxia – correlation of DCE with genetic signatures for hypoxia in cervix

Lyng et al Cancer Research 2012
An alternative to pimonidazole

Method 1: Genetic signatures for hypoxia

Method 2: IHC (Immunohistochemistry*)
Hypoxia-related markers HIF-1α, GLUT-1, CAIX
Translating to clinical practice
Creating a plan using biological optimisation

Low Dose Rate Brachytherapy Approach

Credit to Chris Mears & team at Monash University, Haworth et al PMB 2015

The University of Sydney
Translating to clinical practice
Creating a plan using biological optimisation

Urethral Doses

Rectal Doses

Low Dose Rate Brachytherapy Approach

Credit to Chris Mears & team at Monash University, Haworth et al PMB 2015
Treatment response: DCE looks promising

Fig. 2 Example patients treated with primarily EBRT (a-c) and LDR brachytherapy (d) with histopathology delineations propagated to MRI (in blue) and tumor-suspected regions delineated by the experienced uro-radiologists (in yellow and red).

Fernandes et al European Radiology 2018
Fig. 1. Mp-MRI images for a patient whose original treatment was I-125 seeds, anterior tumor is visible as increased enhancement on DCE-MRI. In the DWI ADC map there are possible darker areas of restricted diffusion, but artifacts generated by the implanted seeds make this image hard to interpret. The tumor is not visible on the T2W images. Targeted biopsy confirmed presence of tumor in anterior cores only.
Our planned study: mapping biological changes to predict treatment response

1. Multi-centre Clinical trial (ANZCTR UTN U1111-1221-9589)
2. Phantom studies for inter- intra-scanner variability
The BiRT Project
Biofocussed radiotherapy: delivering personalised medicine

Using MRI + PET to guide treatment and monitor treatment response
Acknowledgements

Team Leaders
Prof Annette Haworth
A/Prof Scott Williams
Prof Martin Ebert
Dr Hayley Reynolds

Computer Scientists
Matthew Di Franco
(Vienna)
Jason Dowling

Monash University:
John Betts
Chris Mears,
Guido Tack,
Kevin Leo

NICTA:
Chris Leckie,
David Rawlinson,
Cheng Soon Ong,
Rajib Chakravorty,
Alan Zhang

Consumer
John Stubbs

Imaging
Bimal Parameswaran
Mary Finnegan
Gary Liney
Michael Hofman
Rodney Hicks

Statistics
Darren Wraith

Pathology
Dr Catherine Mitchell

Urology
Declan Murphy

Students
Yu Sun
Emily Her
Michaela Weingant
Mohammad Ali Jan
Ghasab
Jie Liu
Erin Wang

My former colleagues at Peter Mac