Biofocussed prostate cancer RadioTherapy: The BiRT project

Presented by

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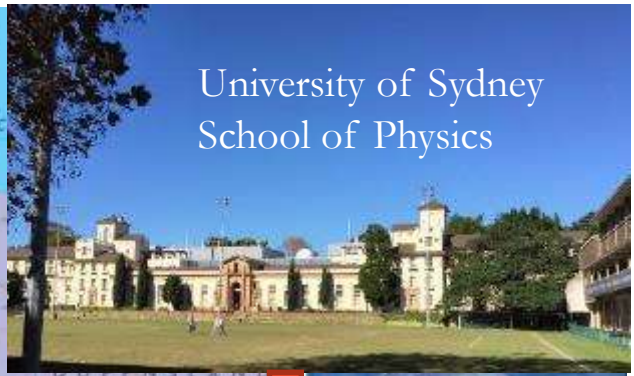


The University of Sydney

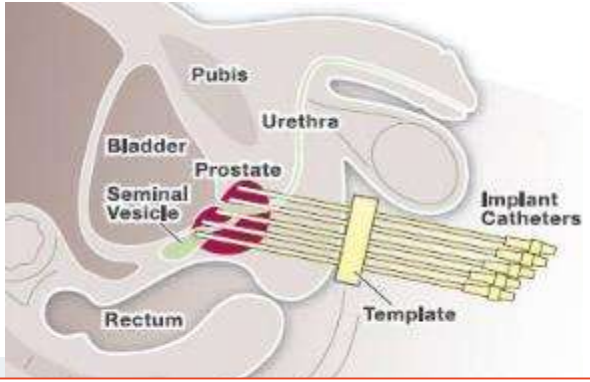
Peter MacCallum Cancer Centre

Biofocussed RadioTherapy

BiRT

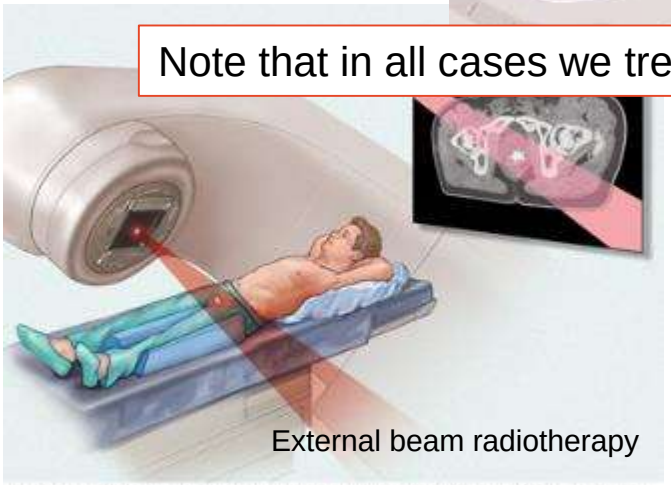
How do we treat prostate cancer?

Surgery

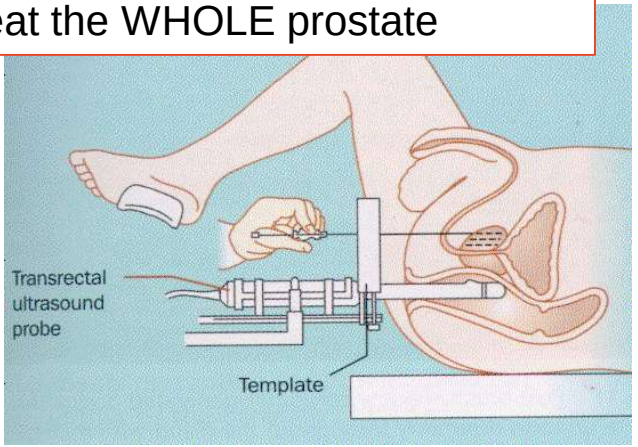


Brachytherapy

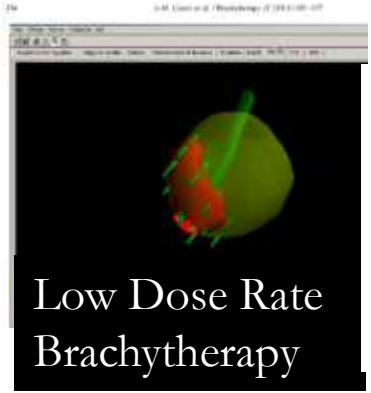
Note that in all cases we treat the WHOLE prostate



External beam radiotherapy

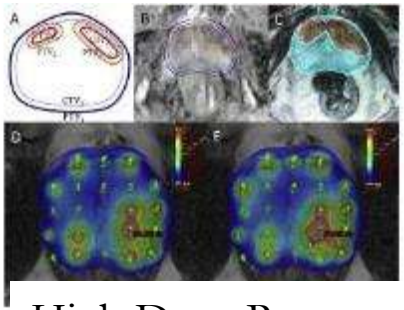


Current approaches to focal / boost-focal approaches



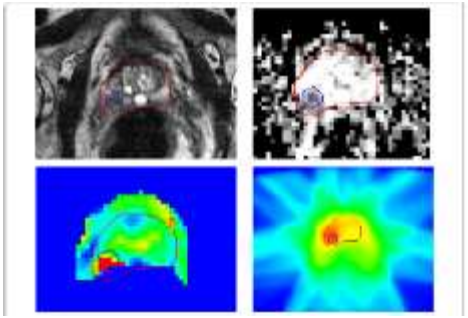
Low Dose Rate Brachytherapy

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



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

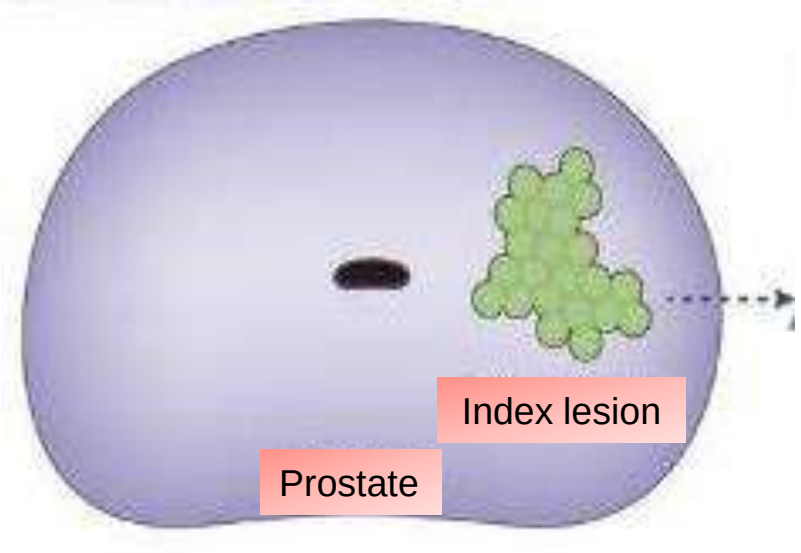
Why focal therapy?

- 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

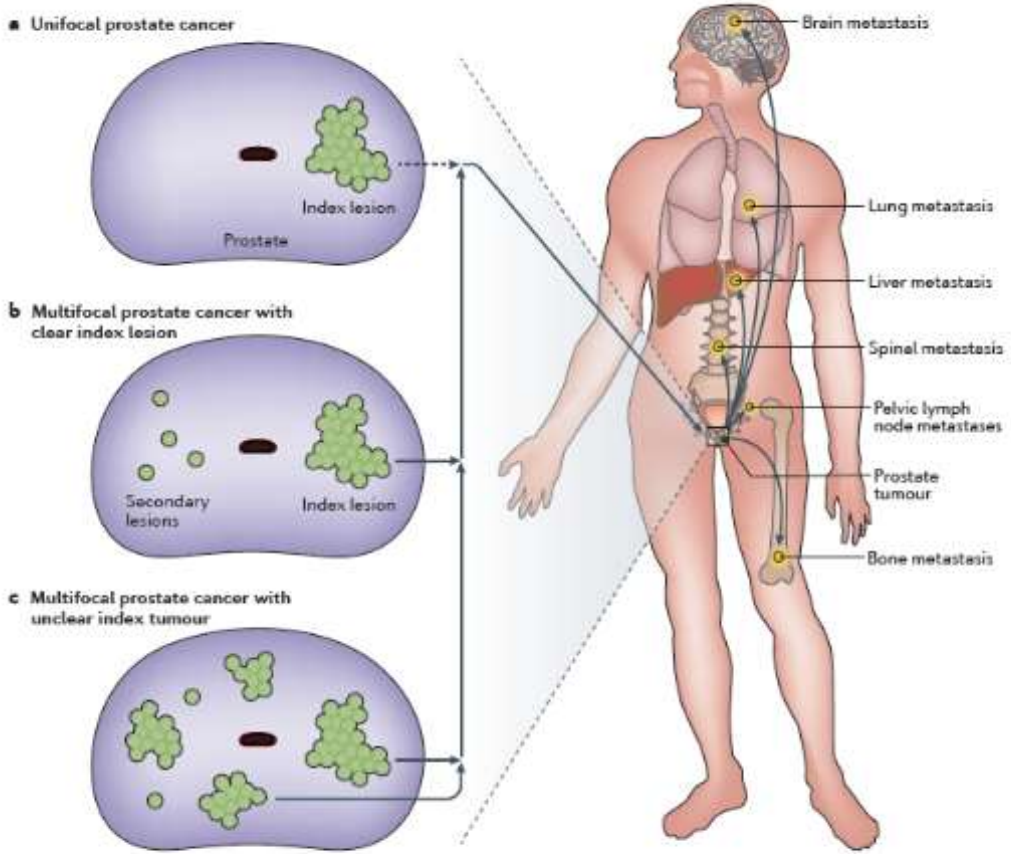


Figure 1 | **Metastatic properties of prostate cancer. a** | Unifocal prostate cancer. **b** | Multifocal prostate cancer with clear index lesion and one or more separate secondary tumour foci with smaller volumes (most common). **c** | Multifocal cancer with unclear index tumour.

Perera et al Nature Reviews Urology 2016

What volume?

BJUI SUPPLEMENTS

2012

Report of a consensus meeting on focal low dose rate brachytherapy for prostate cancer

Stephen Langley[1], Hashim U. Ahmed[2], Bashar Al-Qaisieh[3], David Bostwick[4], Louise Dickinson[2], Francisco Gomez Veiga[5], Peter Grimm[6], Stefan Machtens[7], Ferran Guedea[8] and Mark Emberton[2]

Ultra-Focal Therapy | Focal Therapy | Focused Therapy

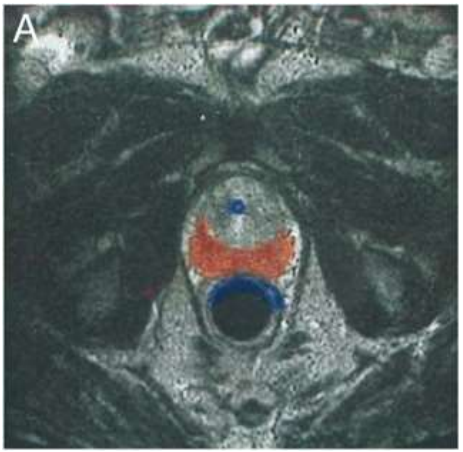
What dose?

Updated Results of Magnetic Resonance Imaging Guided Partial Prostate Brachytherapy for Favorable Risk Prostate Cancer: Implications for Focal Therapy

JOURNAL OF UROLOGY 2012

Paul L. Nguyen,* Ming-Hui Chen, Yuanye Zhang, Clare M. Tempany, Robert A. Cormack, Clair J. Beard, Mark D. Hurwitz, W. Warren Suh and Anthony V. D'Amico

- 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?

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Prostate brachytherapy

MRI guided focal HDR brachytherapy for localized prostate cancer: Toxicity, biochemical outcome and quality of life

Metha Maenhout [a], Max Peters [a], Marinus A. Moerland [a], Richard P. Meijer [b], Maurice A.A.J. van den Bosch [c], Steven J. Frank [d], Paul L. Nguyen [e], Marco van Vulpen [a], Jochem R.N. van der Voort van Zyp [a,*]

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

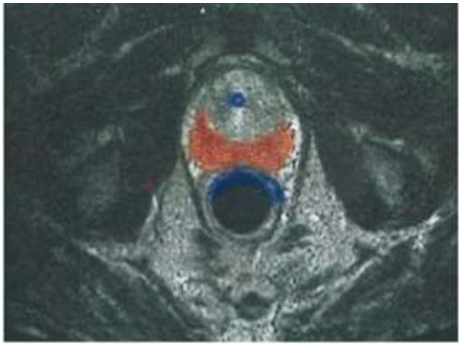


Image from Nguyen 2012 showing PZ

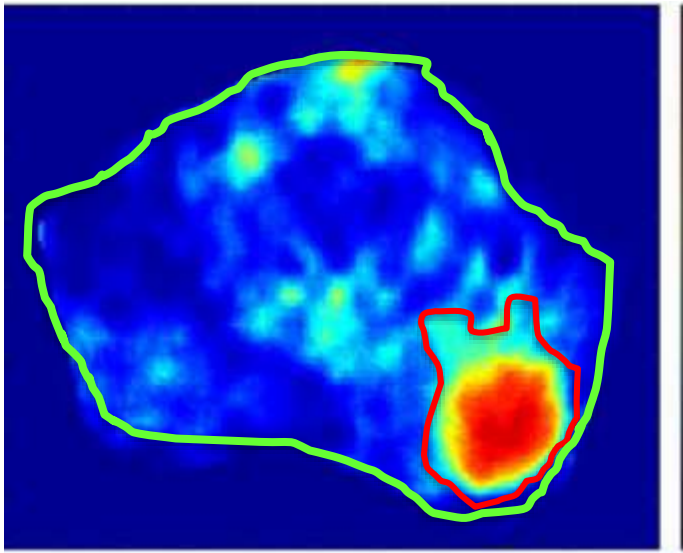
Biofocussed RadioTherapy

BiRT

Hypothesis

With the use of imaging biomarkers we can:

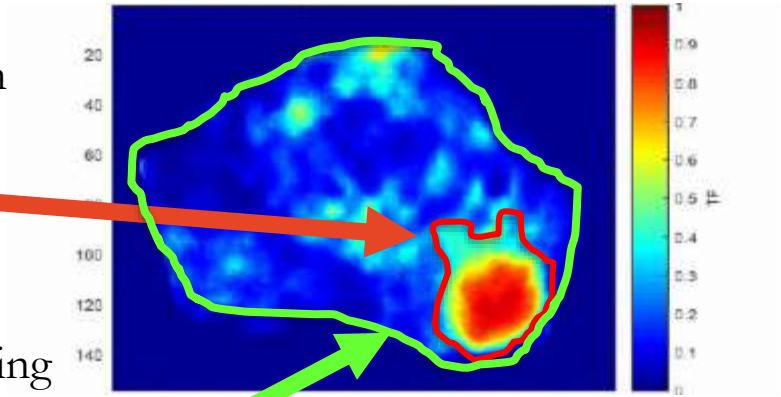
- Identify **where** high doses of radiation should be delivered
- Quantitative imaging will tell us **how much** radiation



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

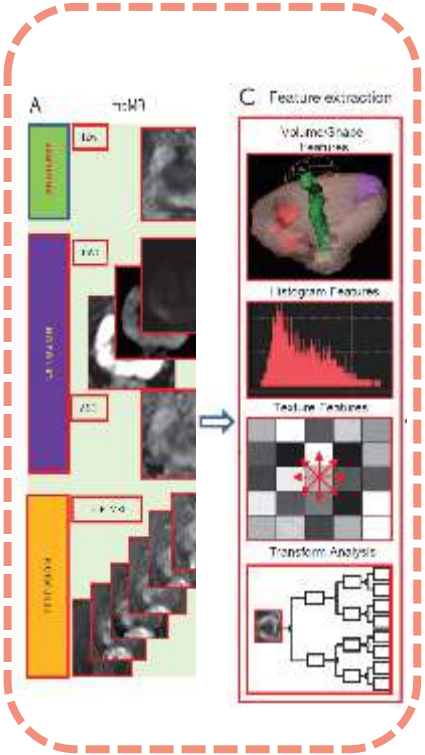


Our goal is to deliver the right dose to the right place

'Biofocussed RadioTherapy'

BiRT

Building imaging biomarkers



RADIOMICS

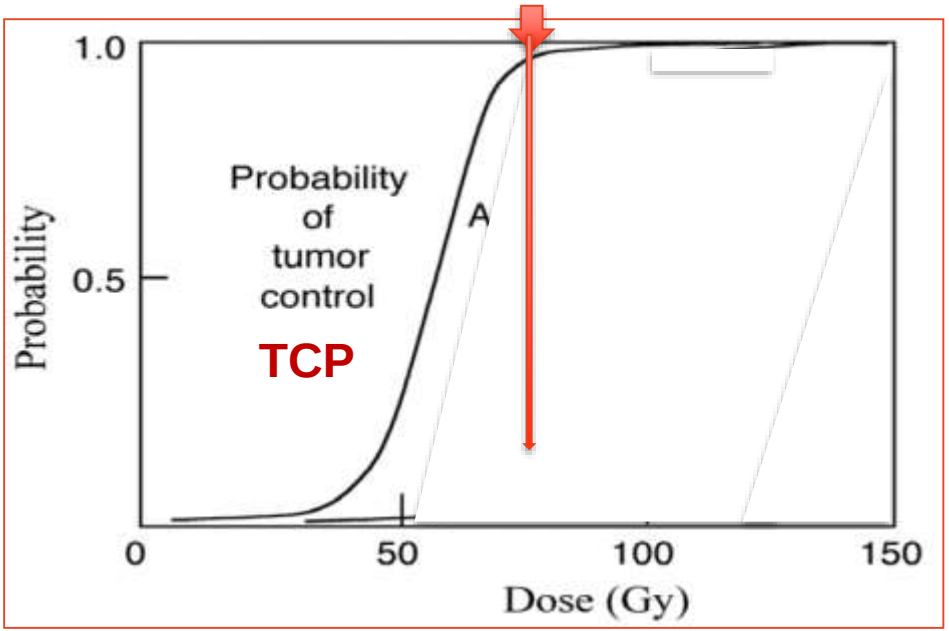
Machine learning

Predictive Model

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

… radiomics… extract quantitative features from medical images

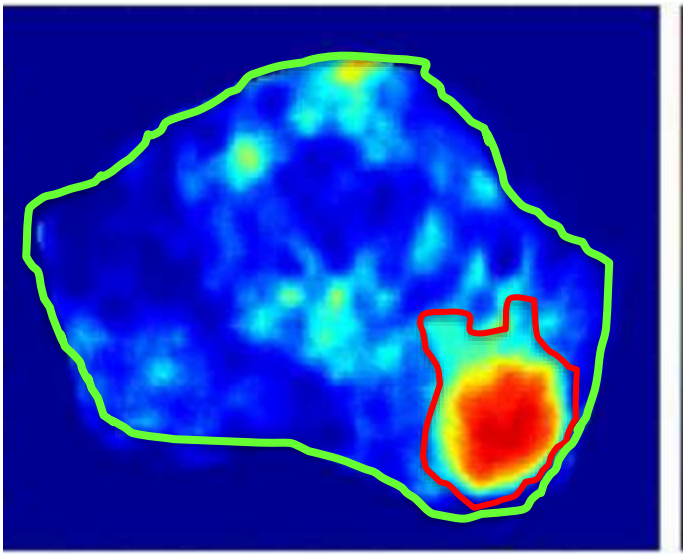
Our goal is to maximise the therapeutic ratio by delivering a dose distribution customised to tumour biology



Haworth et al PMB 2016

Tumour Control Probability - TCP

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



Haworth et al *Brachytherapy* 2013

Tumour Control Probability - TCP

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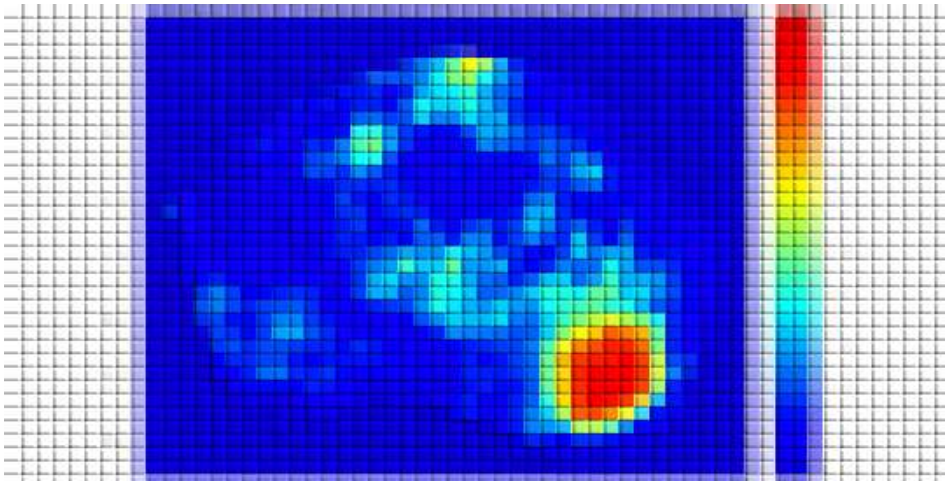
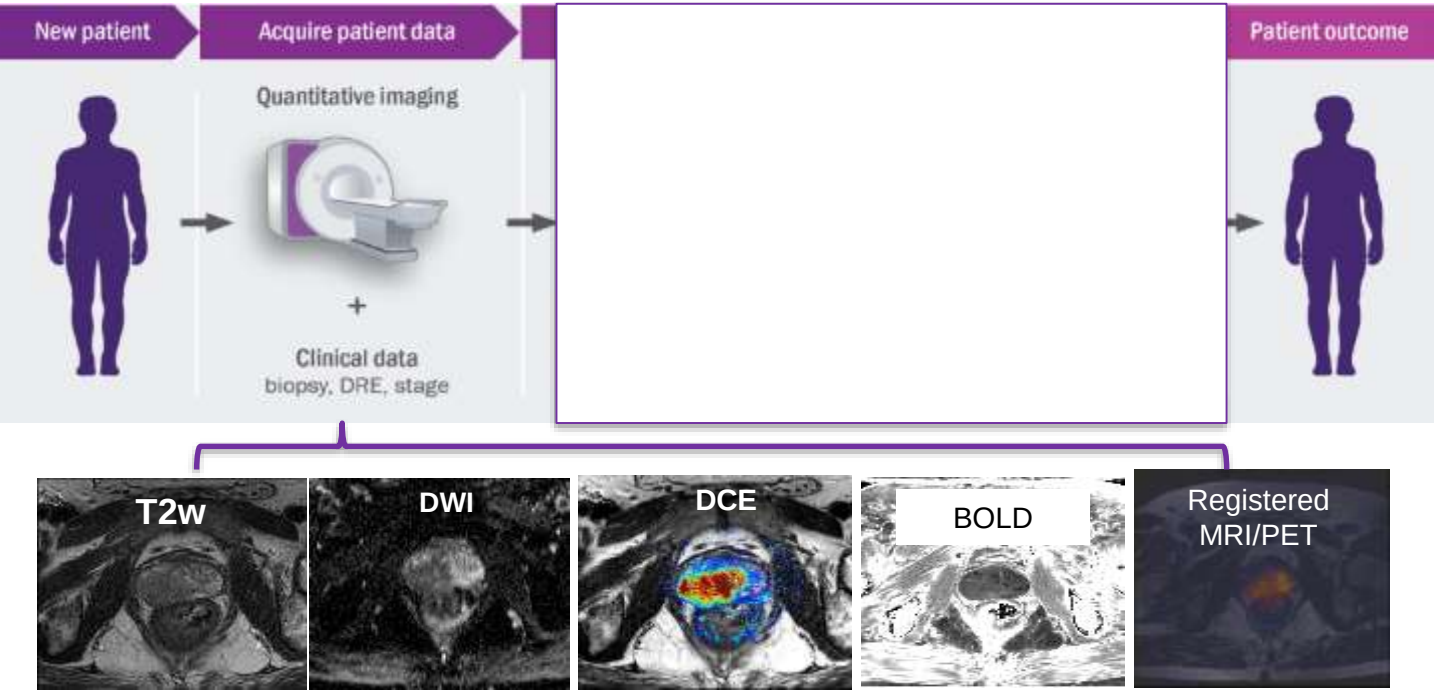
To work out what dose goes where



Haworth et al *Brachytherapy* 2013

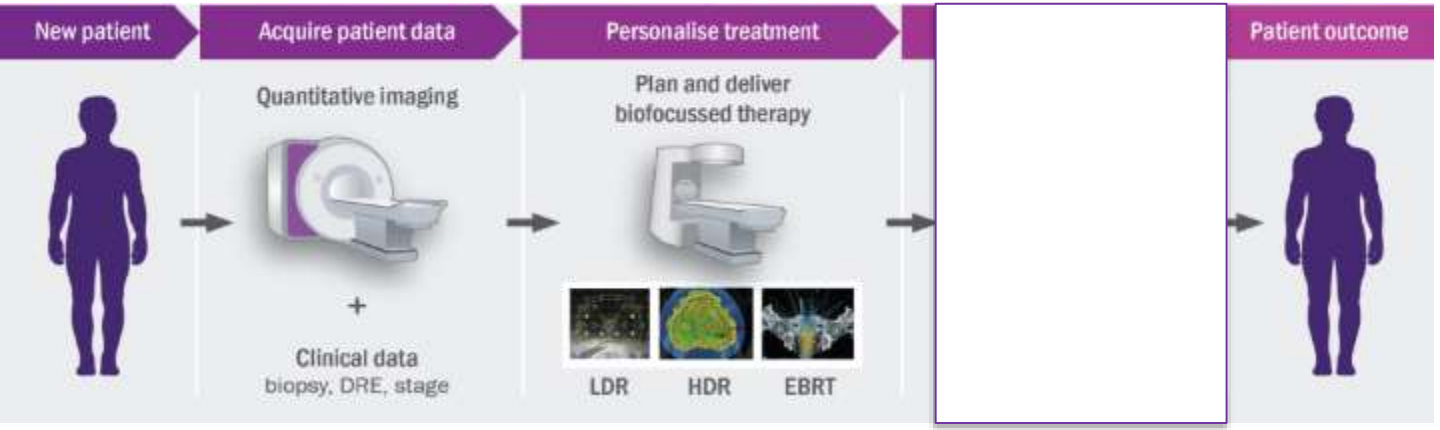
The BiRT Project

The BiRT Project (overview)

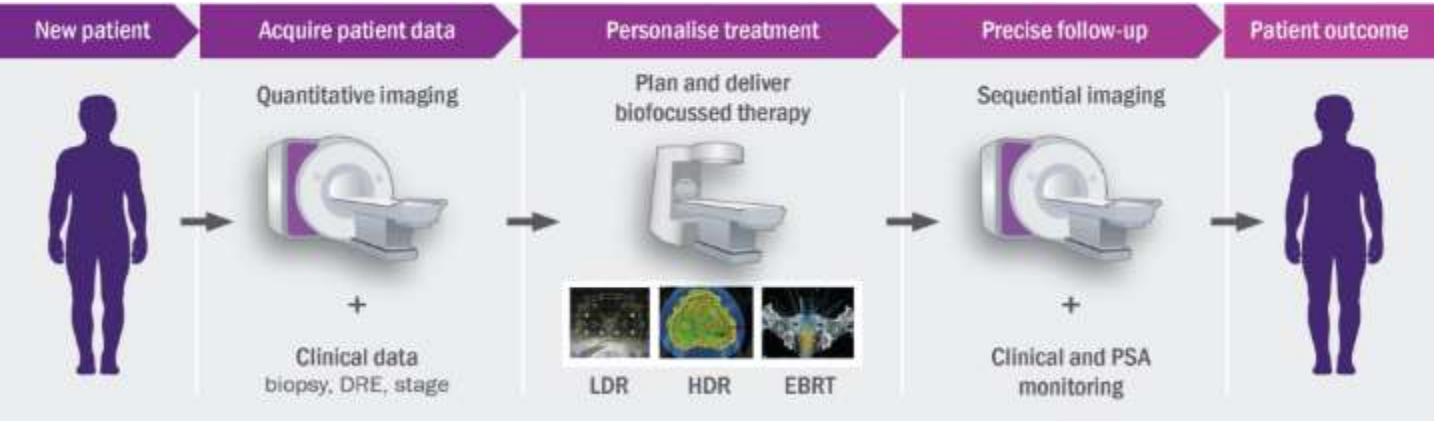


Magnetic Resonance Imaging (MRI) + PET

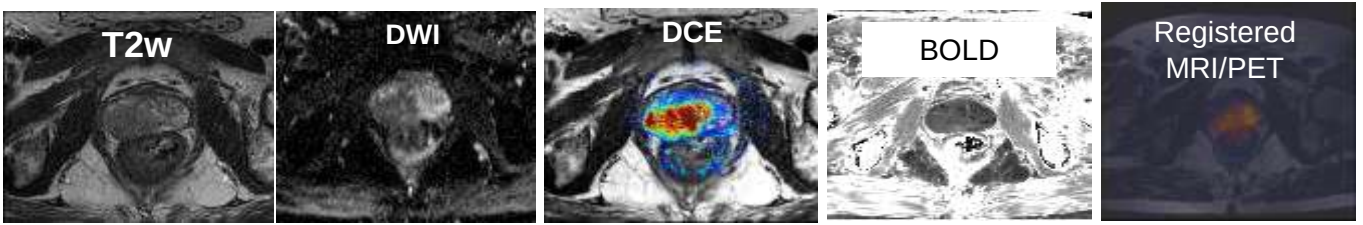
The BiRT Project (overview)



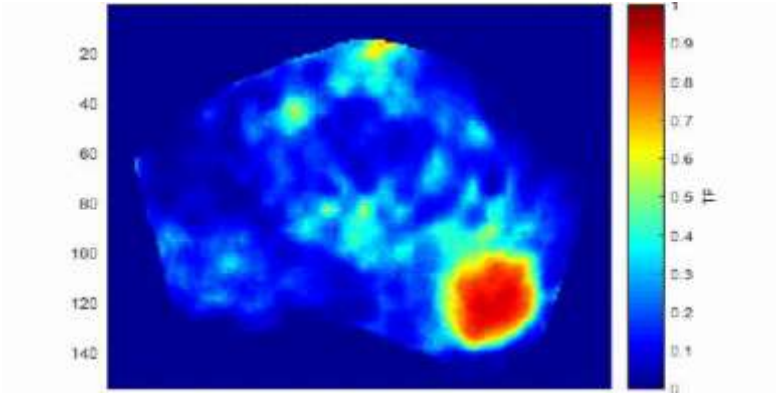
The BiRT Project (overview)



So how do we develop imaging biomarkers

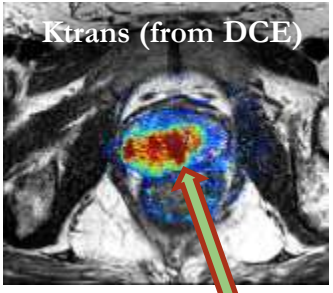


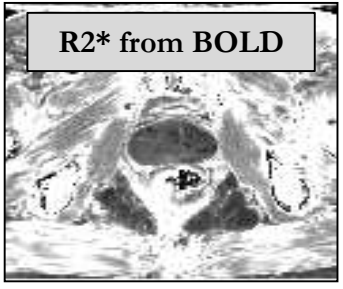
So that we can deliver a non-uniform dose distribution

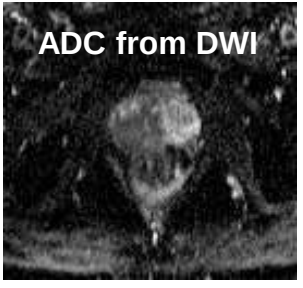


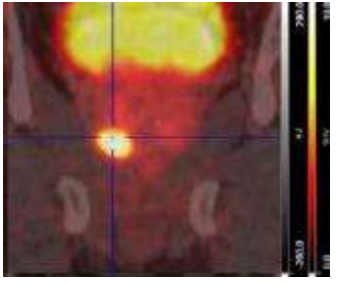
mpMRI, PSMA PET and Quantitative Imaging (Radiomics)

Angiogenesis	Hypoxia	Proliferation	Metabolism









Ktrans, Ve, etc

R2*

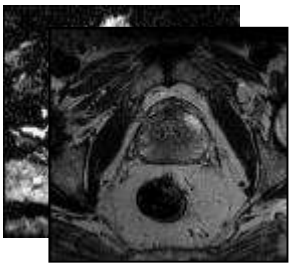
ADC

PSMA PET

180	120	480	350
250	50	25	300
0	0	200	250
0	200	350	400

Kim 2016; Zelhof 2009; Hoskin 2007; Schiller 2017

Building predictive models



Feature Extraction

RADIOMICS*

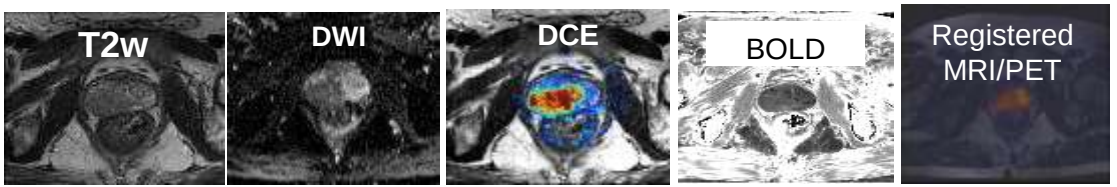
Machine learning

Predictive Model

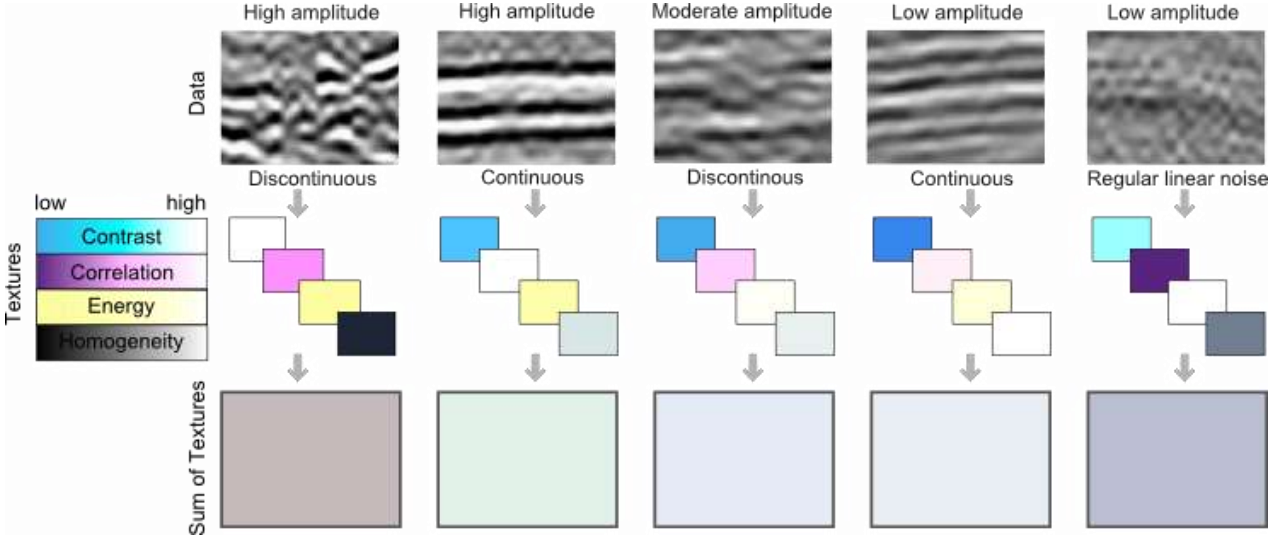
- Tumour location
- Tumour aggressiveness
- Tumour cell density
- Tumour hypoxia

… radiomics… extract quantitative features from medical images

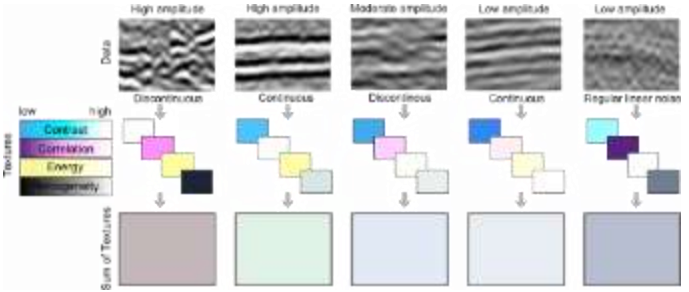
How do we build biology models from MRI + PET?

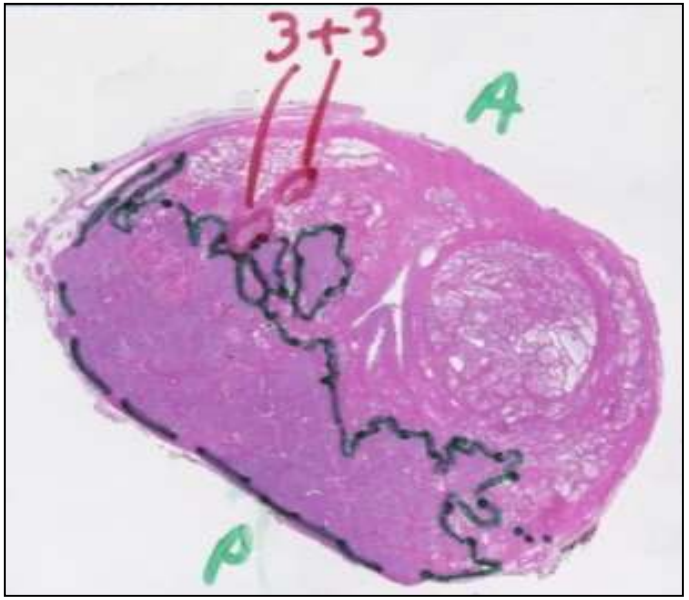


First step "feature extraction"



We then correlate these features with pathology





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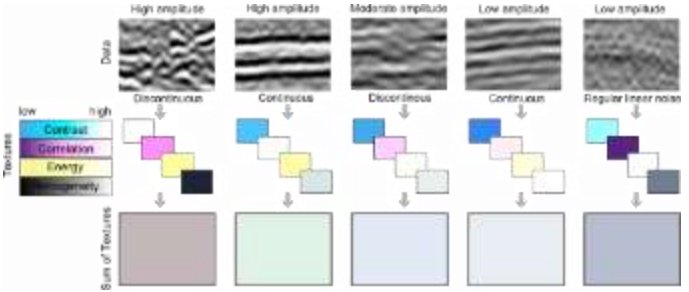
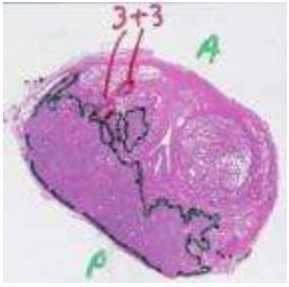
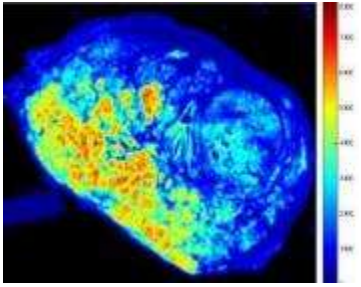
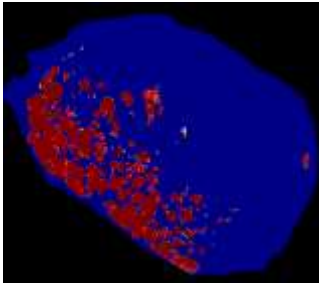




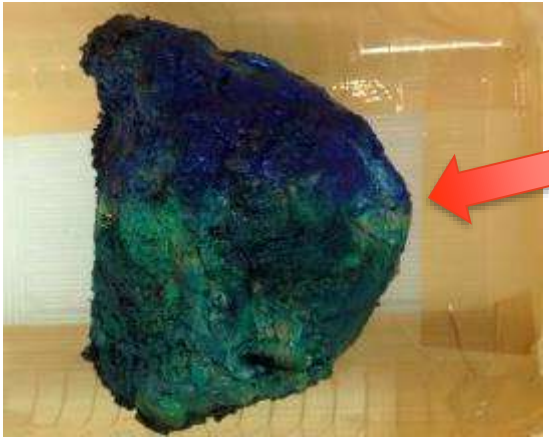


Cell density map
(1)

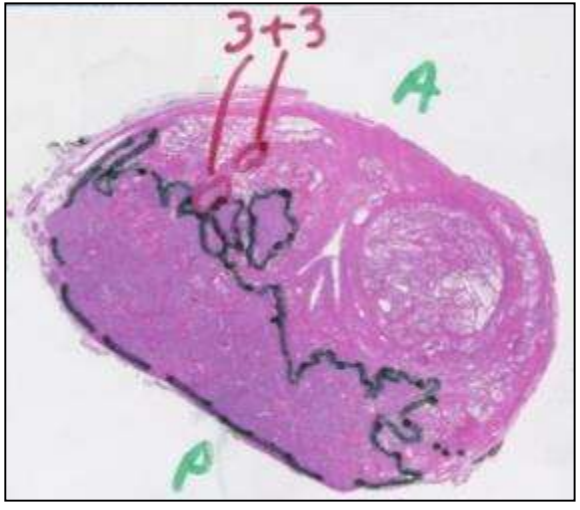


Prediction of high grade tumour location
(2)

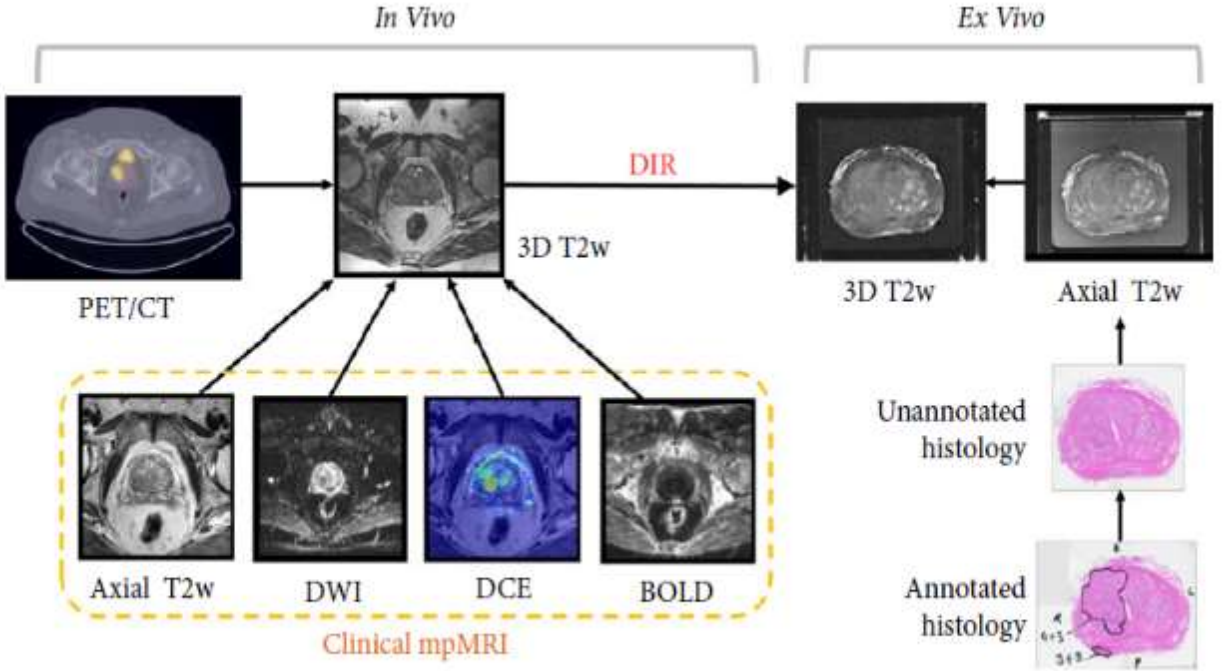
1. Reynolds H, et al (2014) Proc. SPIE Medical Imaging
2. DiFranco MD, et al (2015) SPIE Medical Imaging



Prostate after it has been removed from the patient

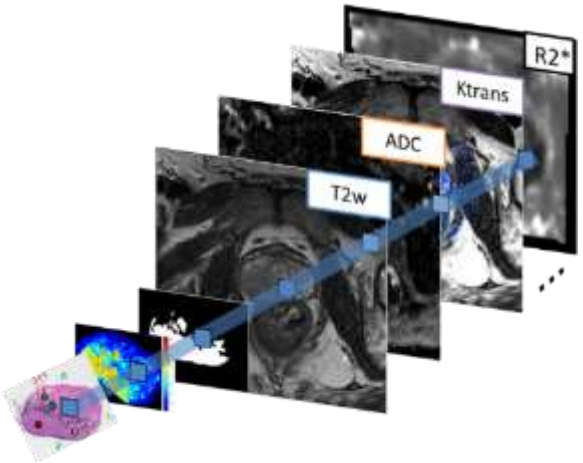


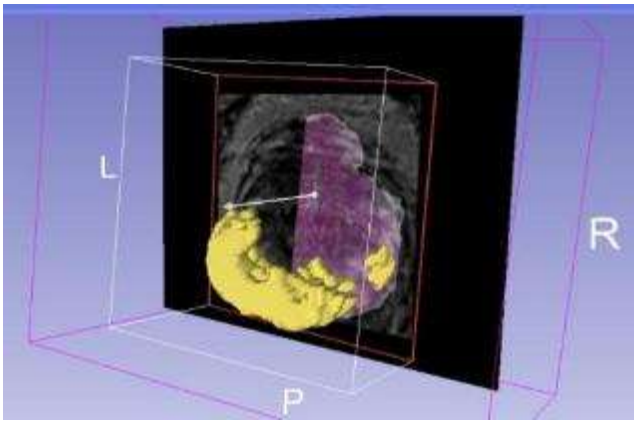
Co-registration of "ground truth" histology and imaging



Reynolds et al Med Phys 2015, BJUI 2018

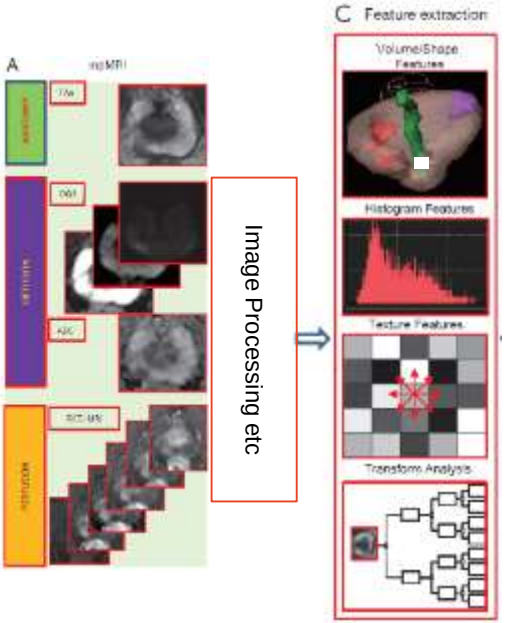
Co-registration of "ground truth" histology and imaging





Reynolds et al Med Phys 2015

Quantitative mpMRI - Radiomics



Ground truth from histology

Predictive model

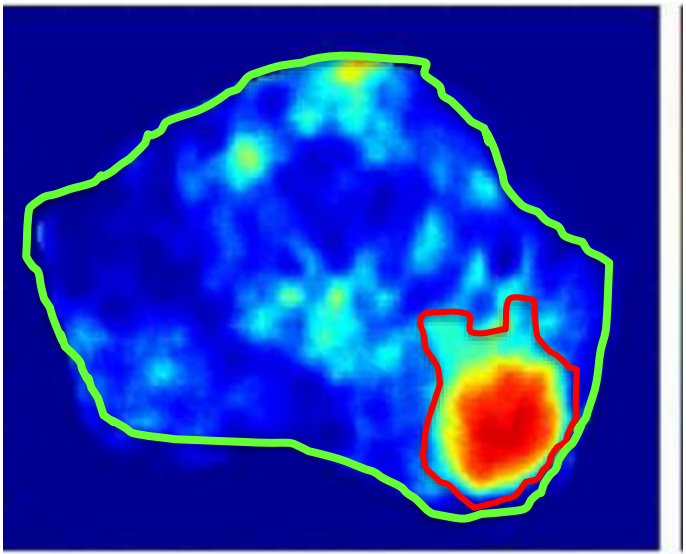
In future patients have the potential to determine:

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

Stoyanova et al. Transl Cancer Res 2016

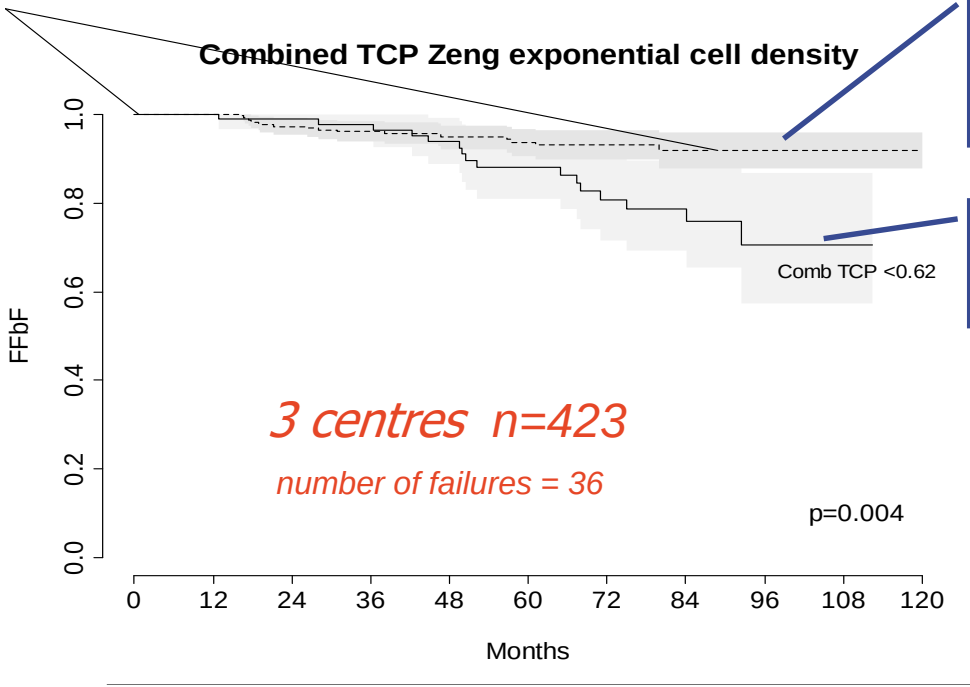
Tumour Control Probability - TCP

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



Haworth et al *Brachytherapy* 2013

What TCP value predicts for treatment failure?

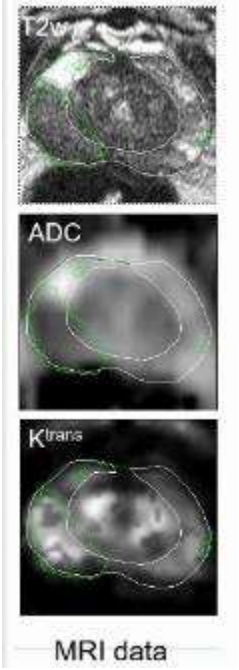


High TCP_{comb}
FFbF 93.7%
(95% CI 90.4-96.4%)

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

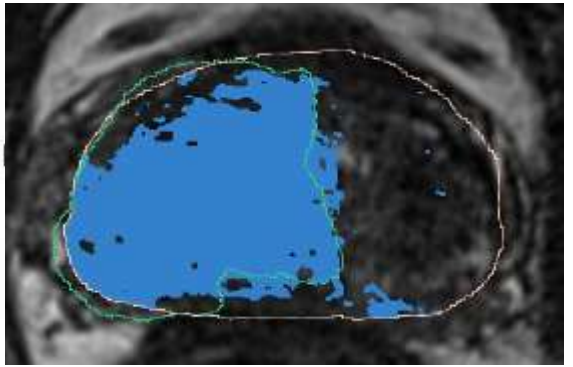
Haworth et al *Brachytherapy* 2013

Machine Learning to generate Predictive Model



mpMRI data
&
histology
From multiple
patients

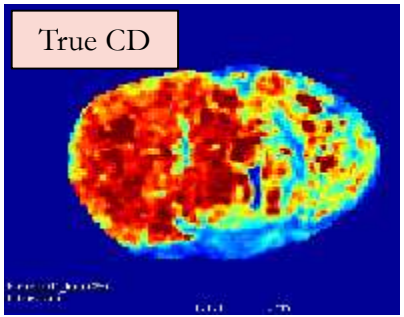
Predictive
model

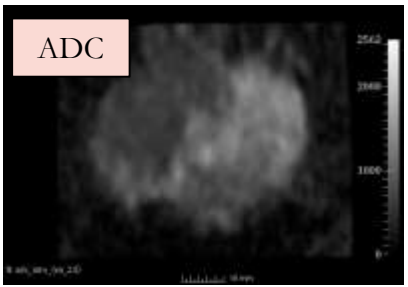


Dinh 2016; Sun 2017

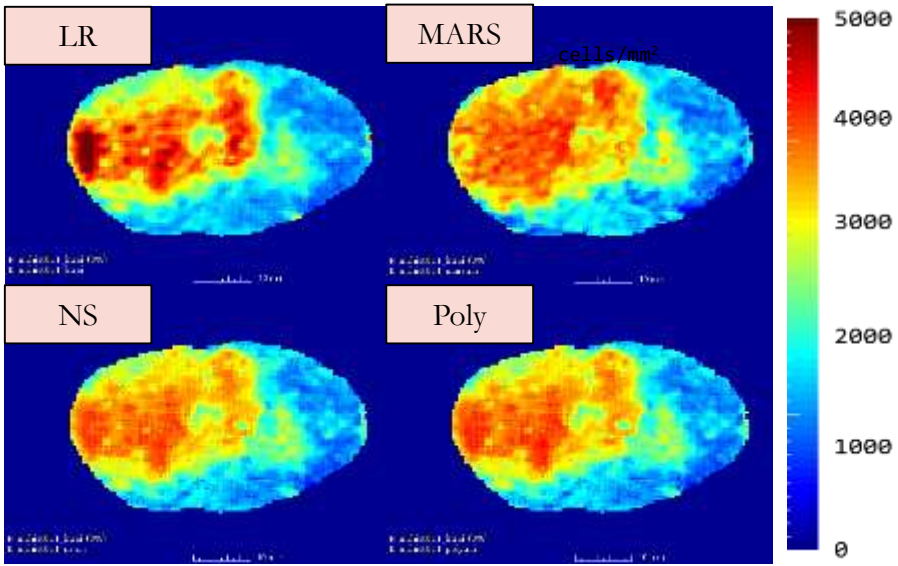
Predicting Cell Density from mpMRI

True cell density from histology





Predicted cell density from mpMRI

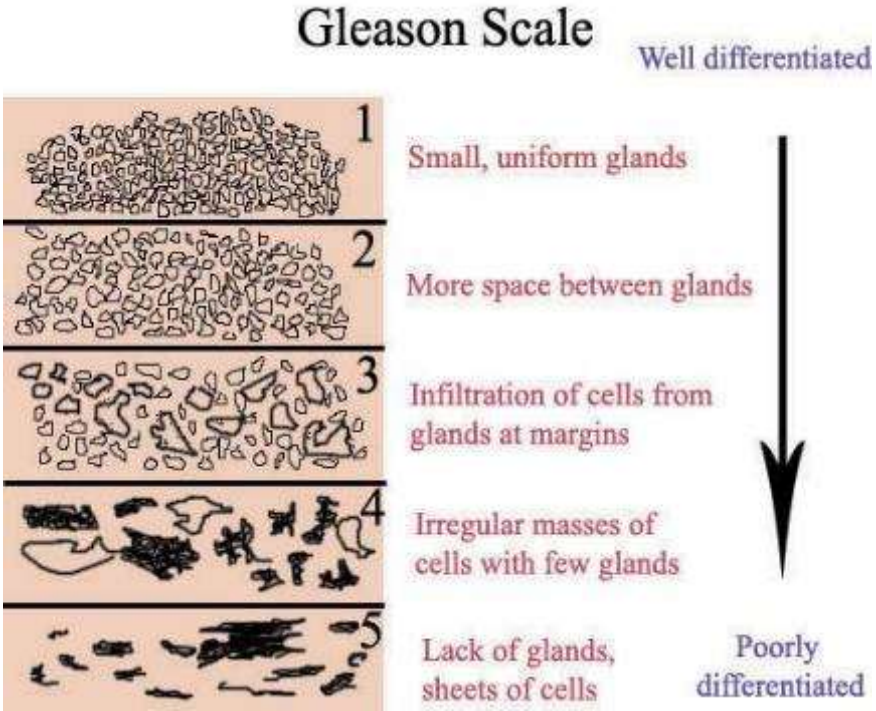


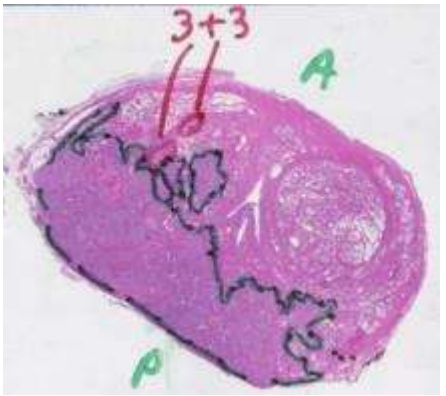
Multivariate adaptive regression splines: Region-wise linear regressions. Generalised additive model (GAM): Extends linear models to non-linear models; functions of $natural\ splines\ (NS)$ $or\ polynomials\ (poly)$

RMS error:
1.06 x 10^3 cells / mm^2
(relative error 13%)

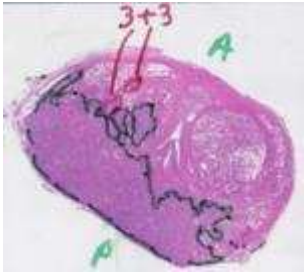
Sun et al (Acta Oncologica 2018)

Correlating imaging with tumour grade



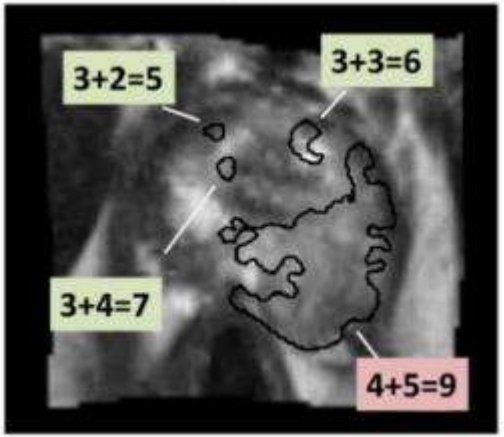


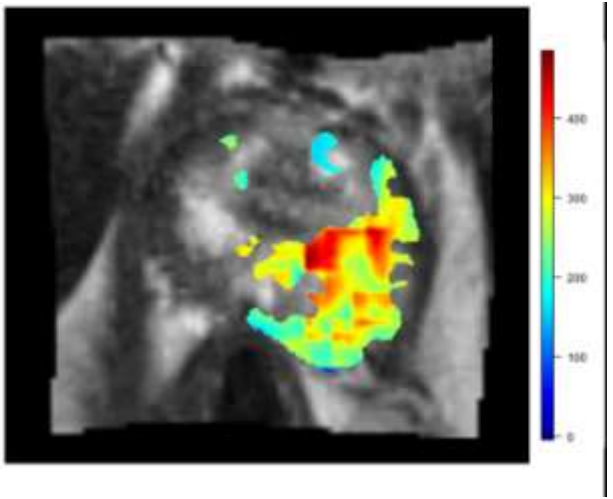
Correlating imaging with tumour grade



(not the same patient!)

Our model predicts tumour grade





Courtesy Yu Sun

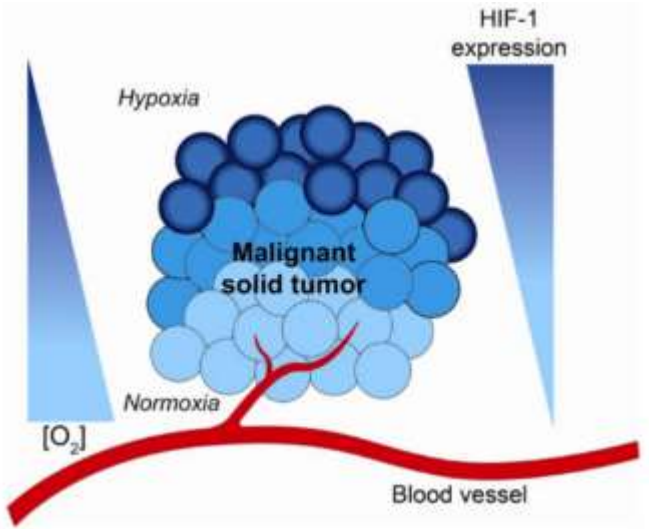
Sun et al Acta Oncol accepted Mar 2019

But now we are exploring hypoxia

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

Michael Milosevic[1,5], Padraig Warde[1,5], Cynthia Ménard[1,5], Peter Chung[1,5], Ants Toi[2,6], Adrian Ishkanian[1,5], Michael McLean[1,5], Melania Pintilie[3], Jenna Sykes[3], Mary Gospodarowicz[1,5], Charles Catton[1,5], Richard P. Hill[4,5,7], and Robert Bristow[1,4,5,7]

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



http://www.mdpi.com/proteomes/proteomes-01-00087/article_deploy/html/images/proteomes-01-00087-g002-1024.png

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

PETER J. HOSKIN, M.D., F.R.C.R.,* DAWN M. CARNELL, F.R.C.R.,*‡ N. JANE TAYLOR, PH.D.,†
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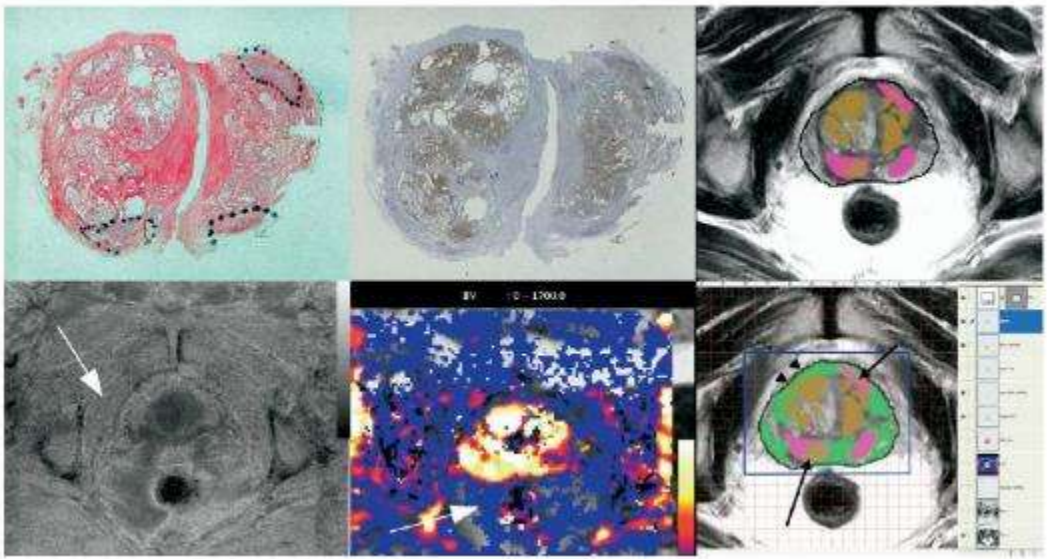
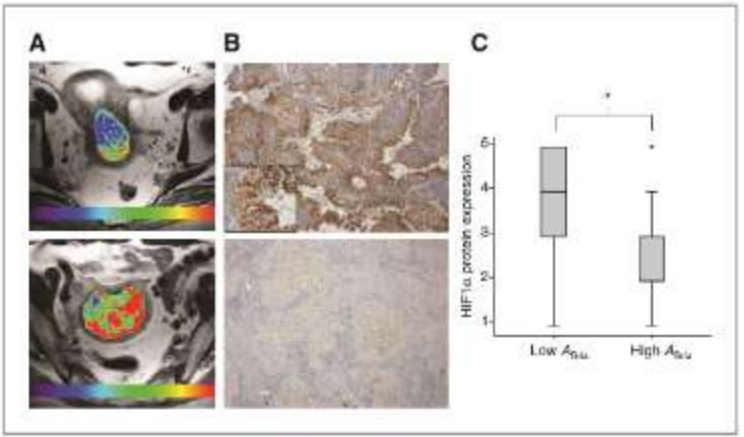
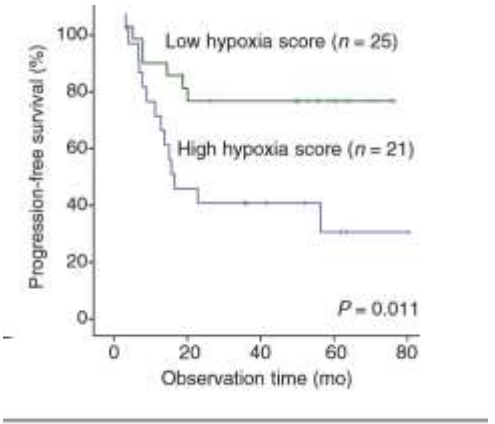
1068 I. J. Radiation Oncology ● Biology ● Physics Volume 68, Number 4, 2007



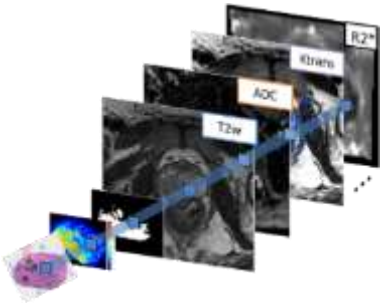
Hypoxia – correlation of DCE with genetic signatures for hypoxia in cervix

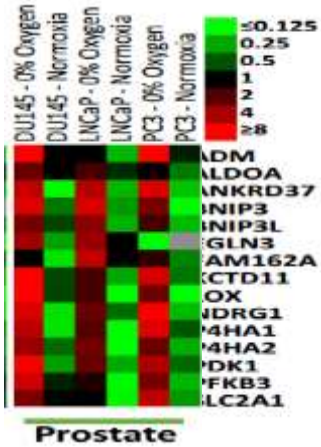




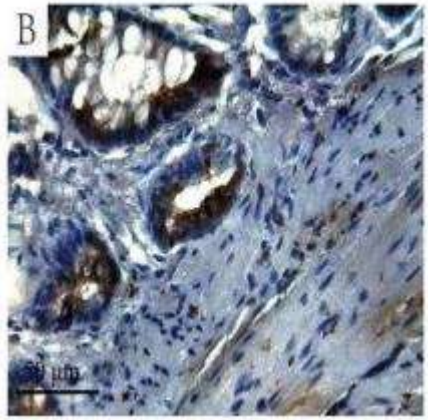
Lyng et al Cancer Research 2012

An alternative to pimonidazole





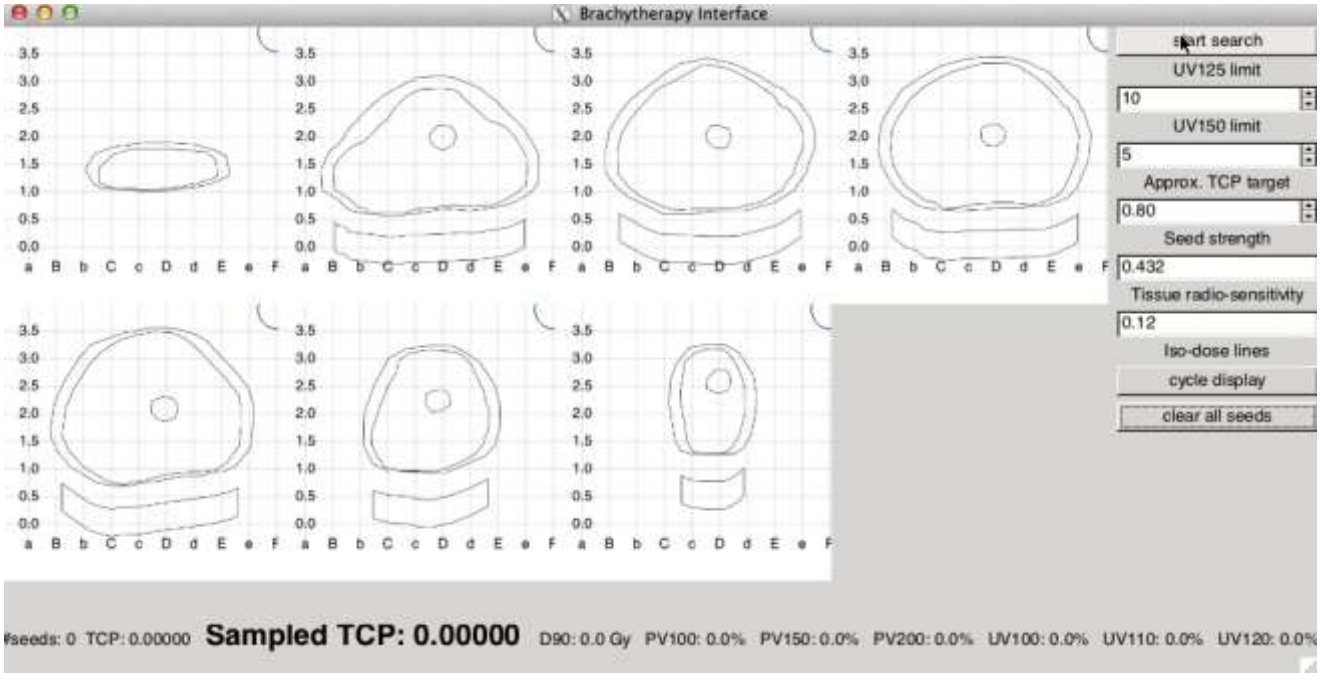
Method 1: Genetic signatures for hypoxia



Method 2: IHC (Immunohistochemistry*) Hypoxia-related markers HIF-lα, GLUT-1, CAIX

RADIOGENOMICS

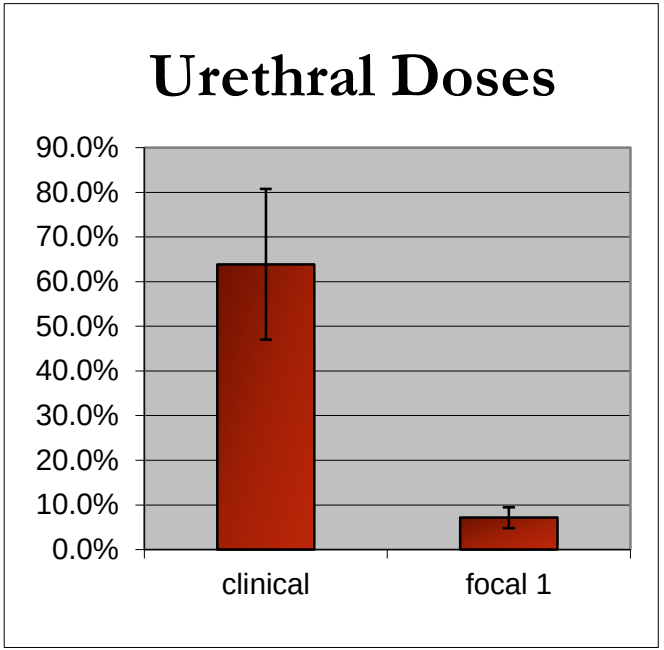
Translating to clinical practice
Creating a plan using biological optimisation

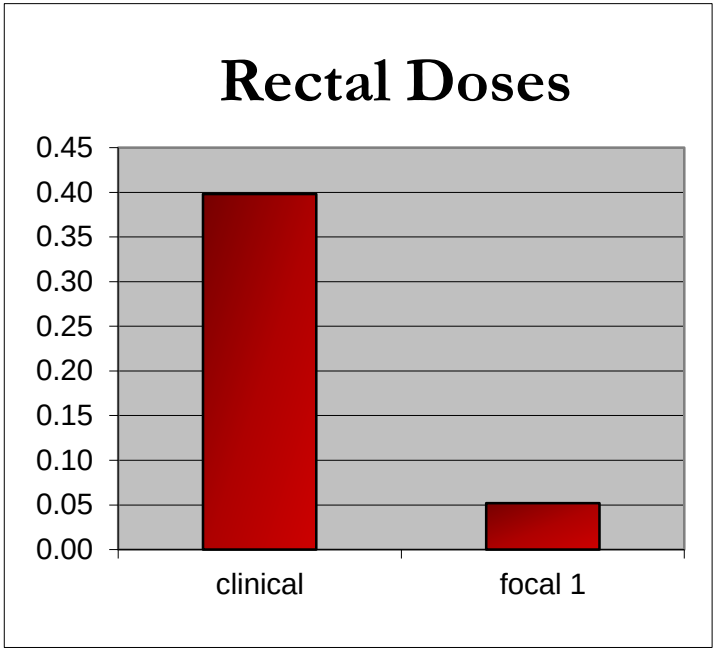


Low Dose Rate Brachytherapy Approach

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

Translating to clinical practice
Creating a plan using biological optimisation

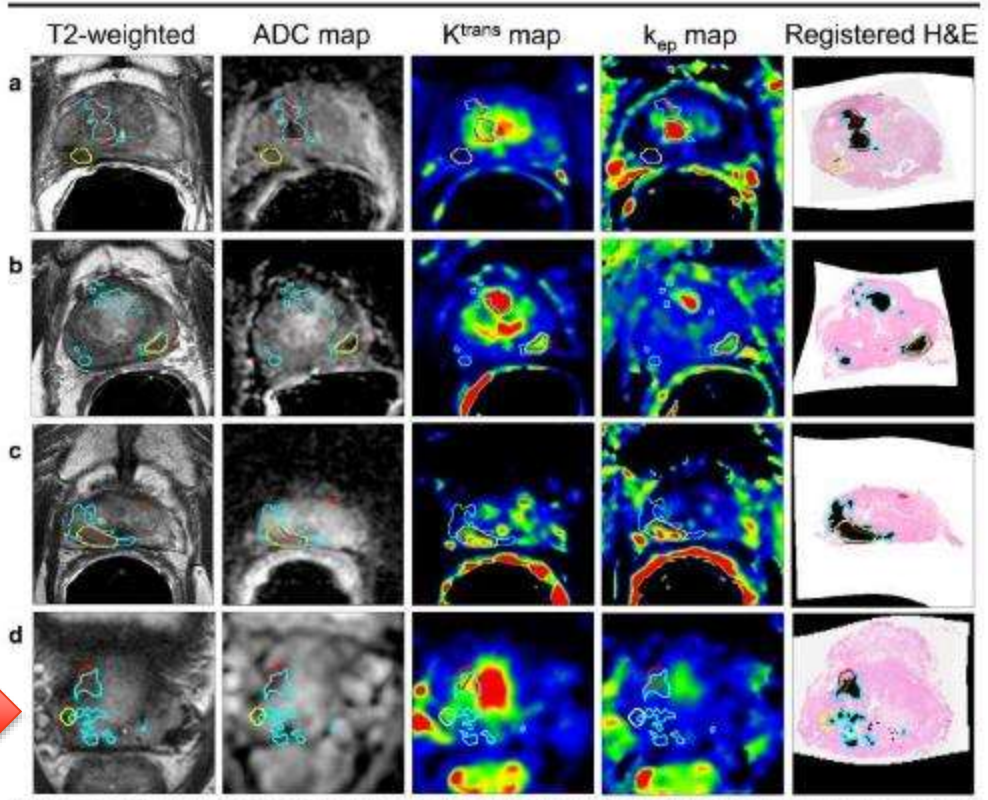




Low Dose Rate Brachytherapy Approach

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

Treatment response: DCE looks promising



LDR

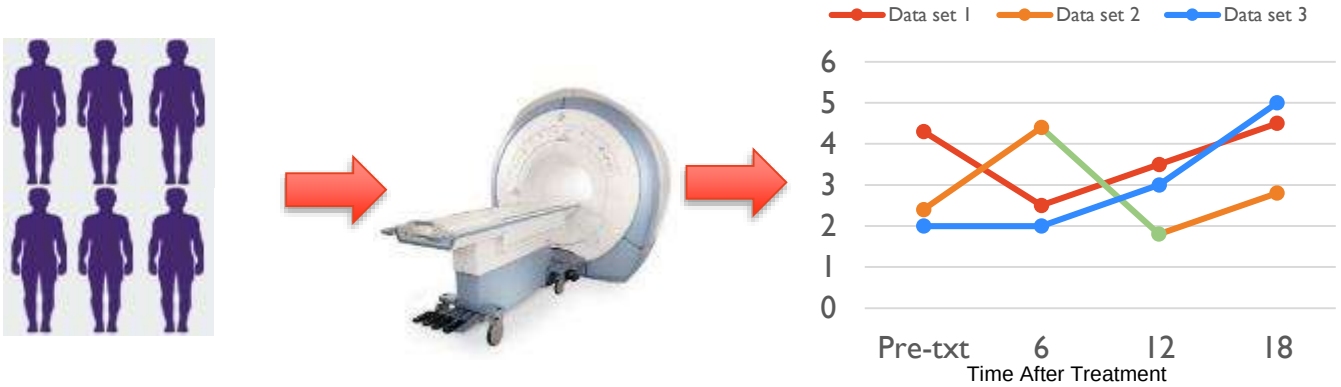
Fig. 2 Example patients treated with primarily EBRT (a-c) and LDR brachytherapy (d) with histopathology delineations propagated to MRI (in blue) and tumor-suspected regions delineated by the experienced uro-radiologists (in yellow and red)

Fernandes et al European Radiology 2018

Mason et al J Contemp Brachytherapy 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

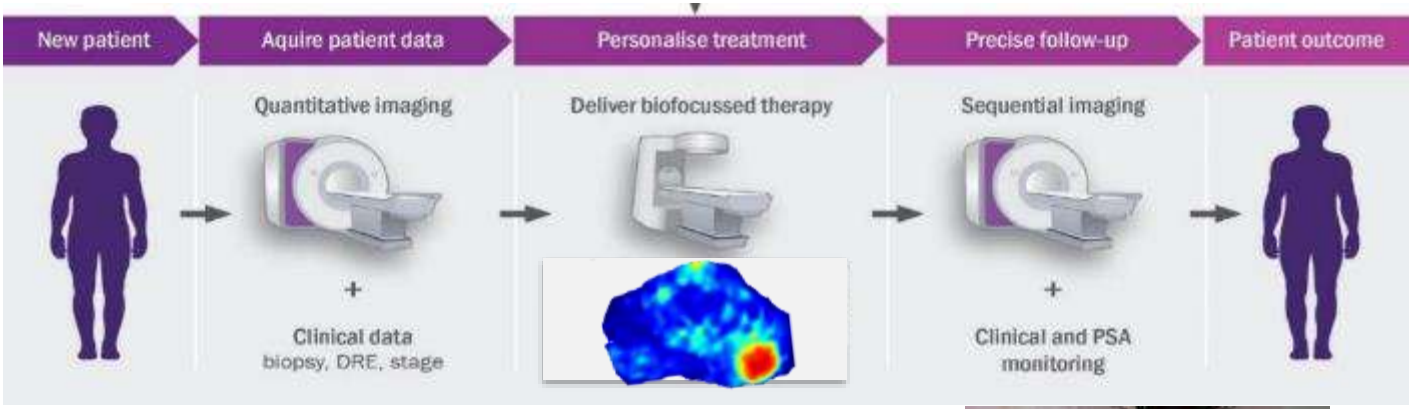
Our planned study: mapping biological changes to predict treatment response



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

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Computer Scientists

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Alan Zhang

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Gary Liney
Michael Hofman
Rodney Hicks

Statistics

Darren Wraith

Pathology

Dr Catherine Mitchell

Urology

Declan Murphy

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

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MONASH University

THE UNIVERSITY OF WESTERN AUSTRALIA

My former colleagues at Peter Mac

Australian Government
National Health and Medical Research Council

Prostate Cancer Foundation of Australia

Australian Government
Cancer Australia

Australian Government
Department of Health and Ageing

THE UNIVERSITY OF SYDNEY