PROSTATE BRACHYTHERAPY
UK & Ireland Conference 2016

The Paul Evans Memorial Lecture

Functional radiotherapy targeting using focused dose escalation

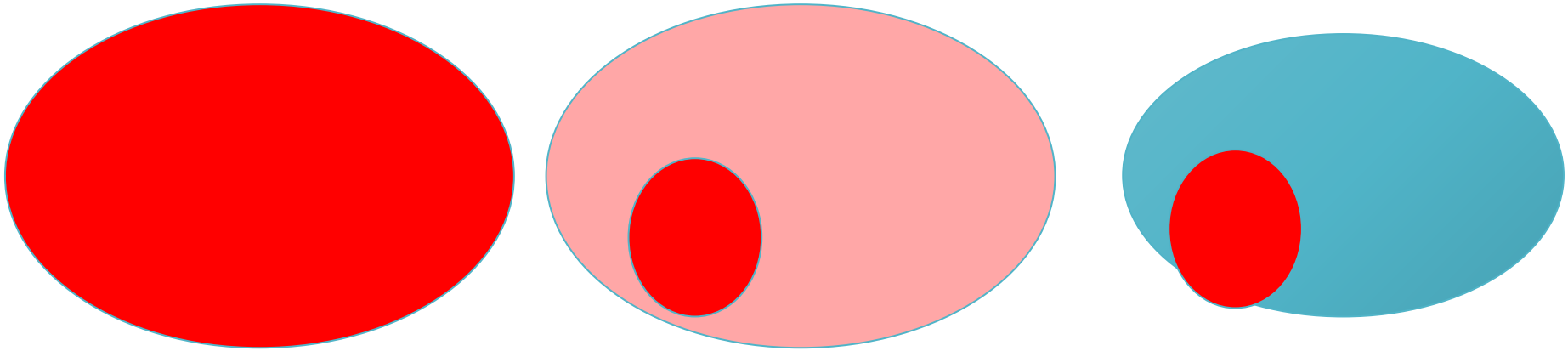
Roberto Alonzi

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



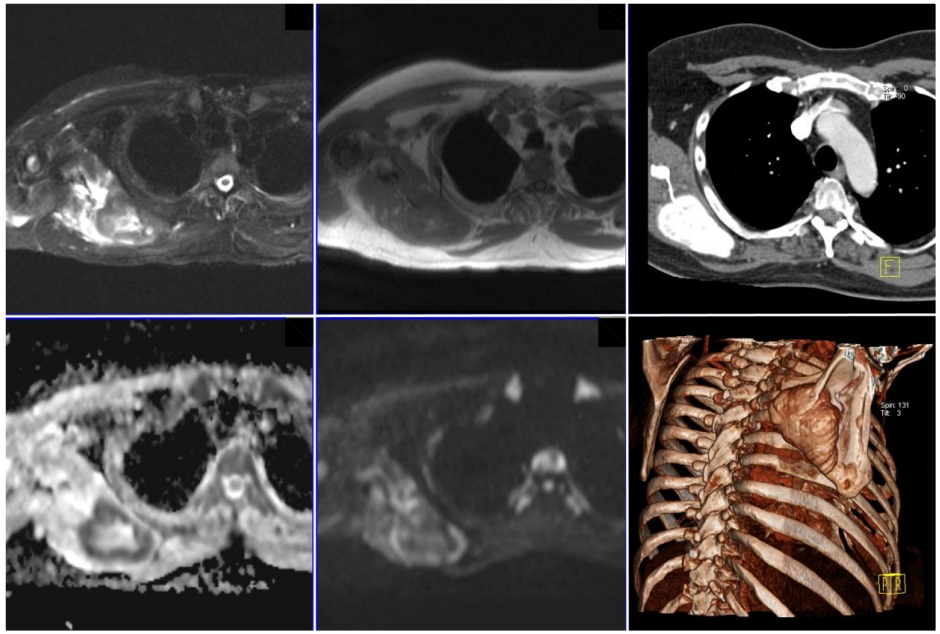
Whole Gland Therapy

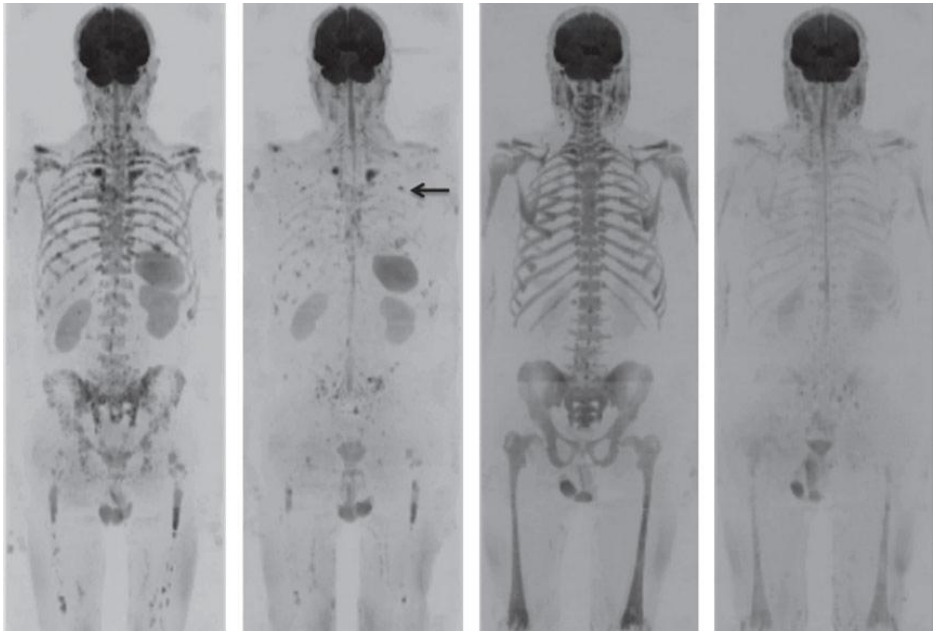
Focused Therapy or 'Focal Boost'

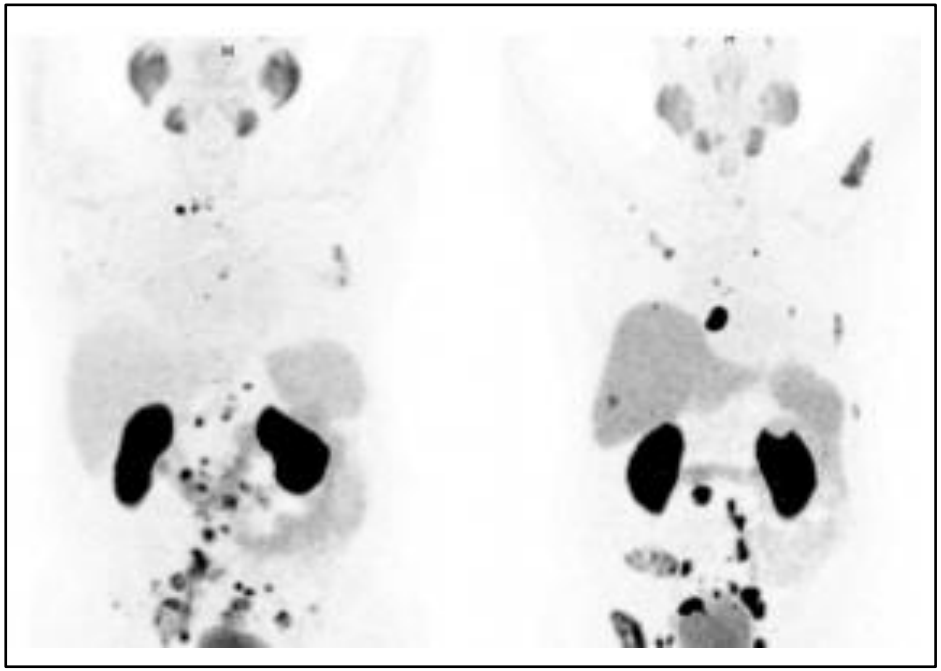
Focal Therapy

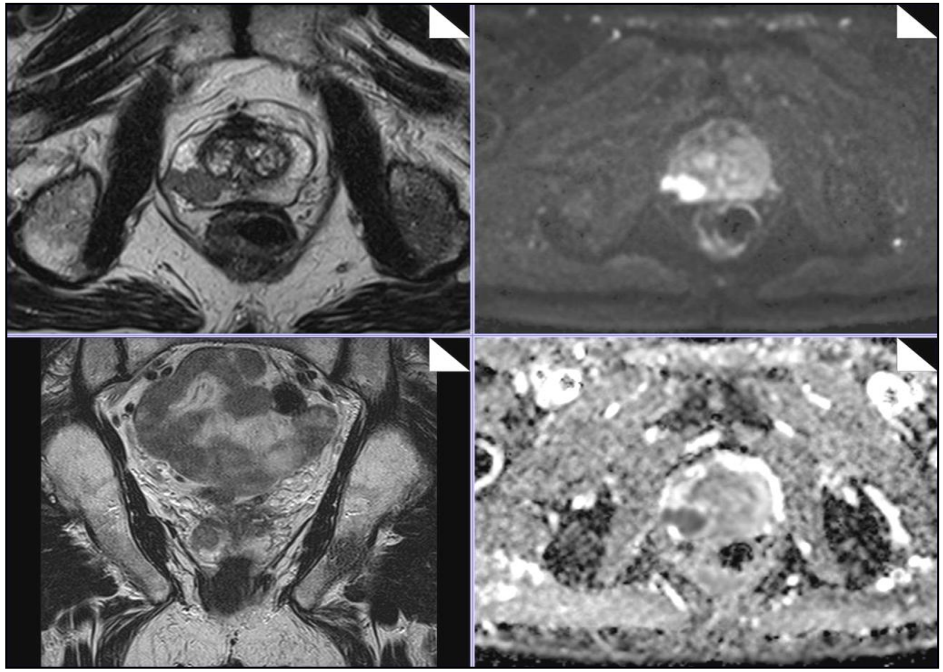
Why does radiotherapy fail?

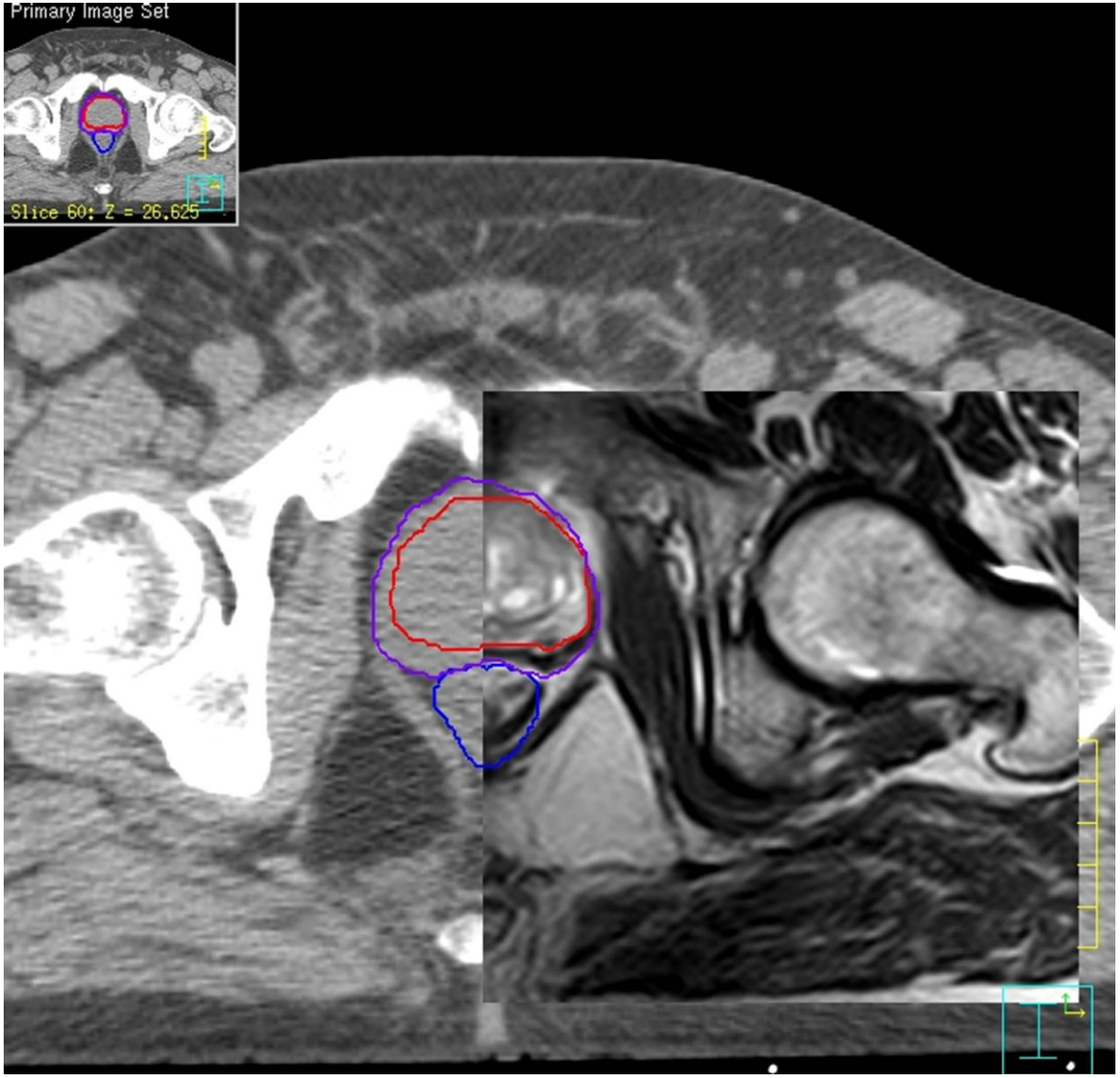
- Failure of staging
- Geographical miss
- Radioresistance







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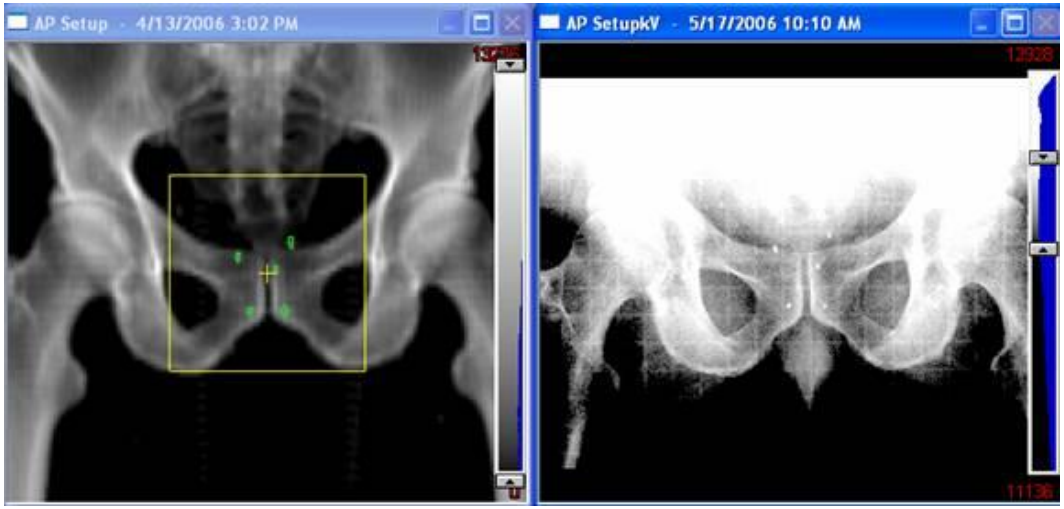
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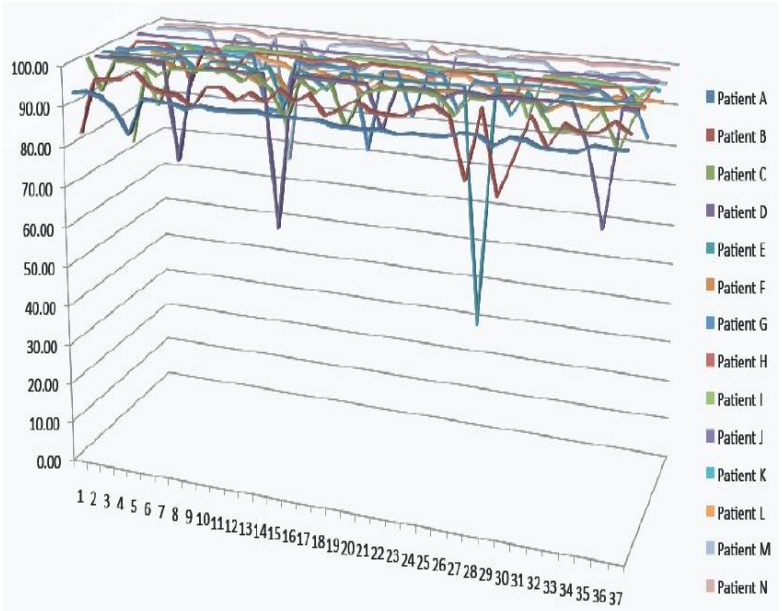
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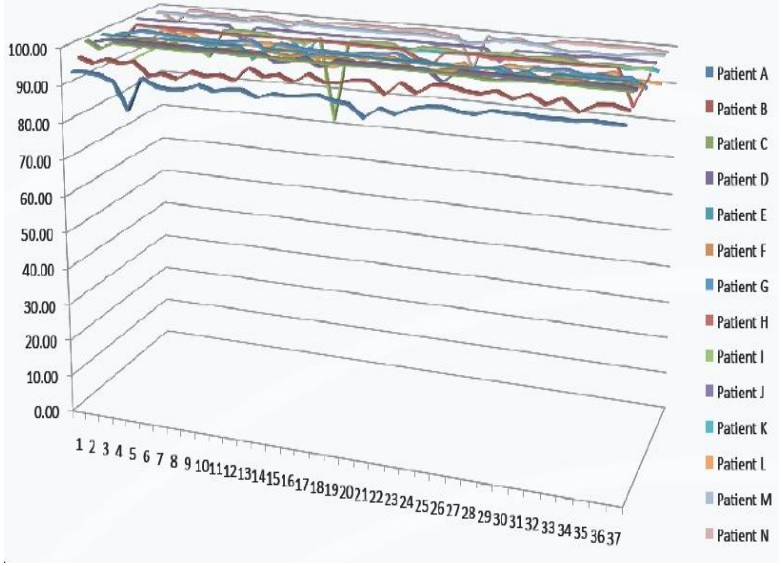
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Patient F
Patient G
Patient H
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Why does radiotherapy fail?

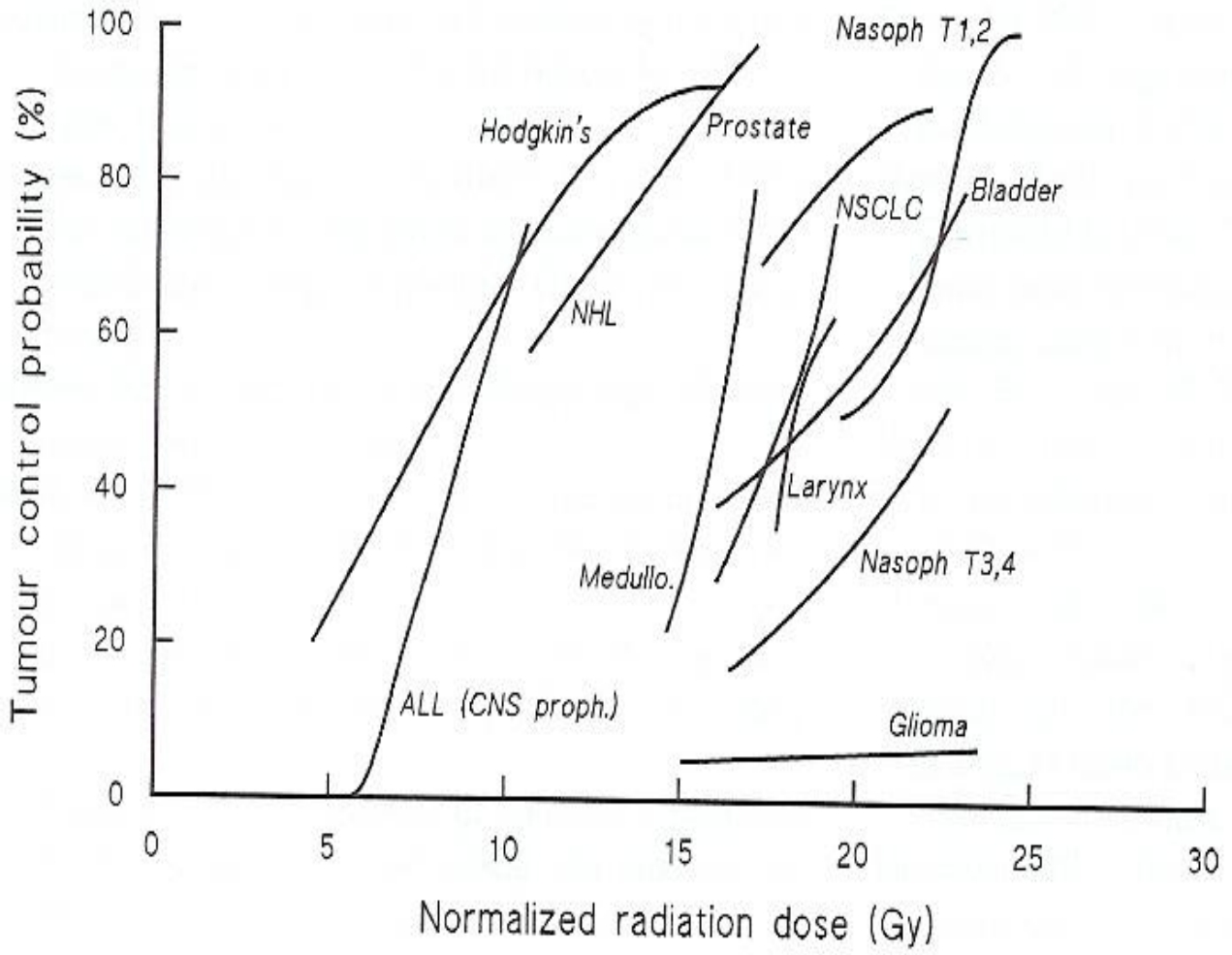
- Failure of staging
- Geographical miss
- Radioresistance

Rationale

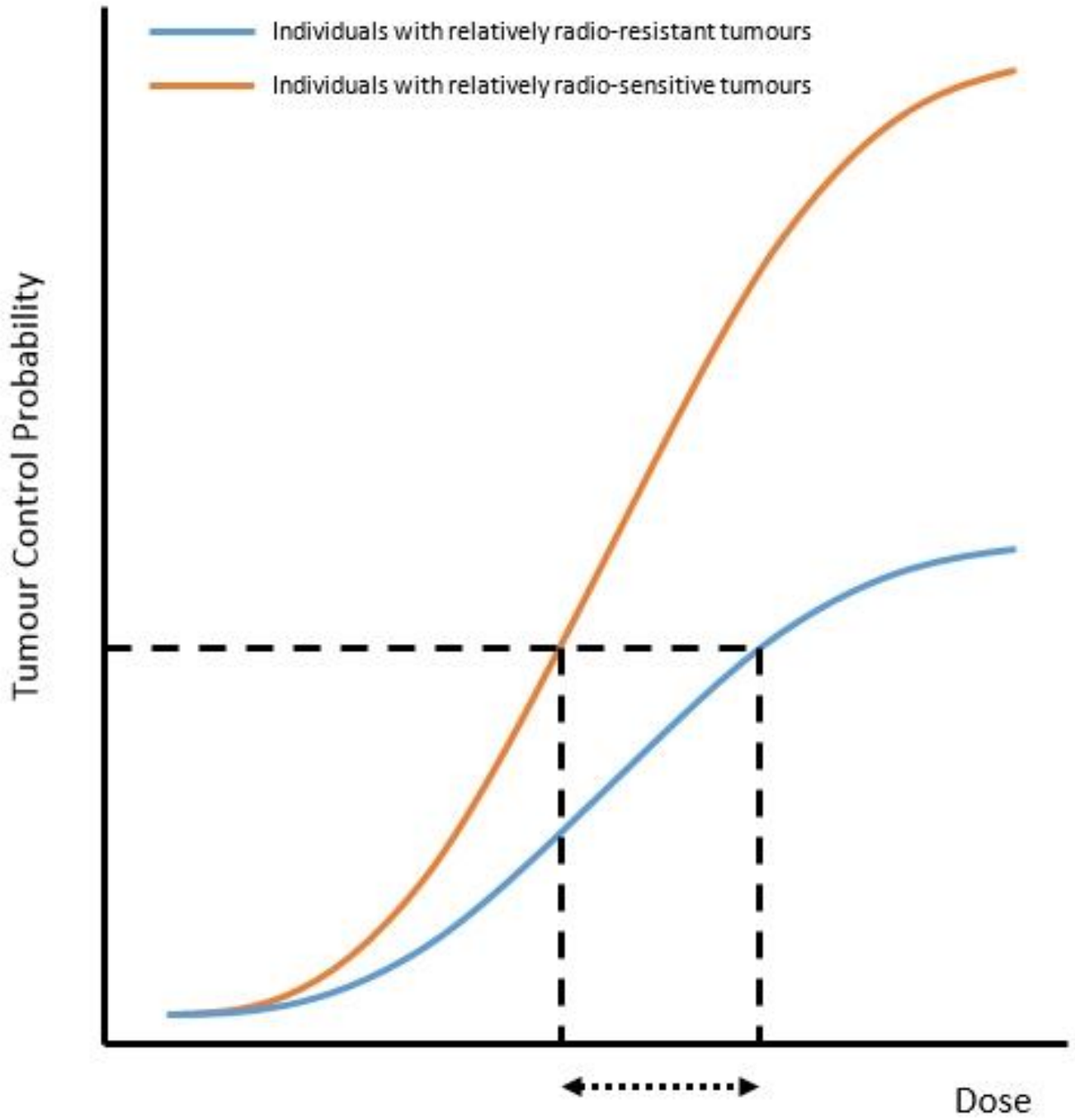
Focused dose escalation is based upon the principle that areas of tumour with relative radio-resistance can be overcome by administering a higher biologically effective radiation dose (BED).

- Higher total dose
- Higher dose per fraction

Dose Response Relationship in Cancer

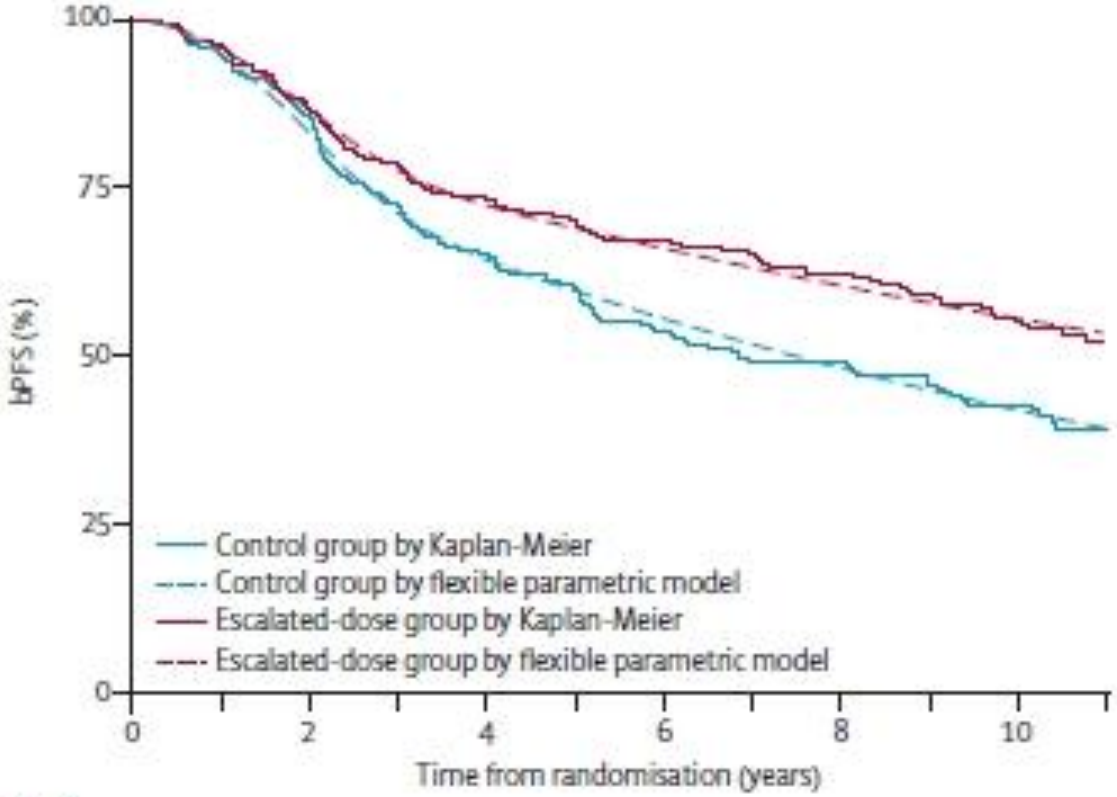


Individual variation in radio-sensitivity



Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial

David P Dearnaley, Gordana Jovic, Isabel Syndikus, Vincent Khoo, Richard A Cowan, John D Graham, Edwin G Aird, David Bottomley, Robert A Huddart, Chakiath C Jose, John H L Matthews, Jeremy L Millar, Claire Murphy, J Martin Russell, Christopher D Sarase, Mahesh K B Parmar, Matthew R Sydes



Number at risk						
Control group	417	351	255	189	154	71
Escalated-dose group	418	351	282	237	197	99

Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 4, pp. 1028–1033, 2008

0360-3016/08/$–see front matter

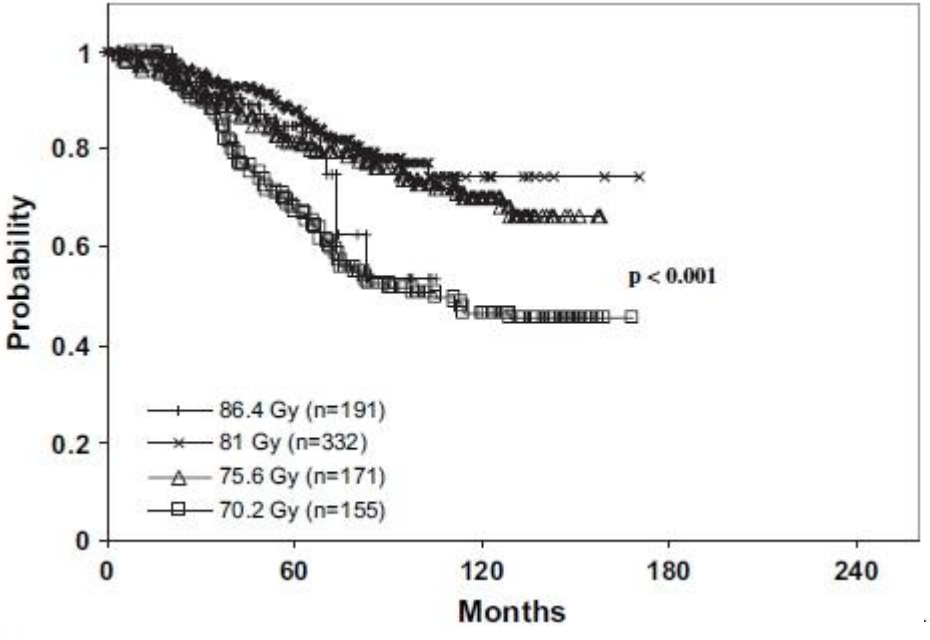
ELSEVIER

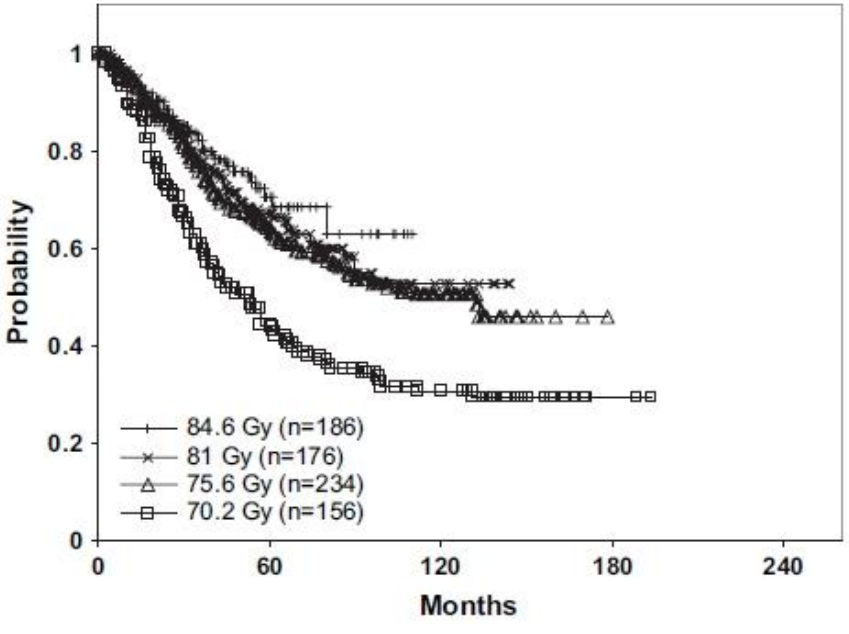
doi:10.1016/j.ijrobp.2007.11.066

CLINICAL INVESTIGATION **Prostate**

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 CAHLON, M.D.,* JESSICA PARK, B.A.,* AND ALISON SHIPPY, B.A.*





Dose Escalation in Prostate Cancer

Taken from Dearnaley *et al.* Lancet Oncology 2014;15:464-73

	N	Accrual period	Total radiation dose (Gy/number of fractions)		NAADT	NCCN risk		Median age (years)	Data last reported	Median follow-up (years)	PSA failure (N [%])	Absolute reduction in PSA failure in dose escalated group	Survival in escalated-dose group	Prostate cancer deaths (N [%])	Non-prostate-cancer deaths (N [%])
			Control	Escalated		Inter-mediate	High								
MRC RT01	843	1998–2001	64/32	74/37	All	37%	43%	67	2012	10·0	365 (43%)	13% (10 year)	70% (10 year)	91 (11%)	145 (17%)
NKI[3]	664	1997–2003	68/34	78/39	22%	27%	55%	69	2013	9·2	329 (50%)	6% (10 year)	67% (10 year)	88 (13%)	117 (18%)
PROG 95-09[8]	393	1996–99	70·2/39	79·2/44	No	37%	4%	67	2010	8·9	83 (21%)	16% (10 year)	83% (NS)	6 (1·5%)	55 (14%)
MDACC[5]	301	1993–98	70/35	78/39	No	46%	34%	69	2008	8·7	61 (20%)	19%* (8 year)	79% (8 year)	10 (3%)	70 (23%)
ICR-RMH[9]	126	1995–97	64/32	74/37	All	27%	53%	67	2013	13·7	64 (51%)	8% (12 year)	About 60% (14 year)	19 (15%)	32 (25%)
GETUG 06[10]	306	1999–2002	70/35	80/35	No	NS	29%	67	2011	5·1	85 (28%)	8·5% (5 year)	(NS)	10 (3·3%)	16 (5·2%)
Total	2633	..	..	..	..	..	..	..	..	..	987	..	..	224	435

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.

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

Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 3, pp. 773–783, 2010

0360-3016/$–see front matter

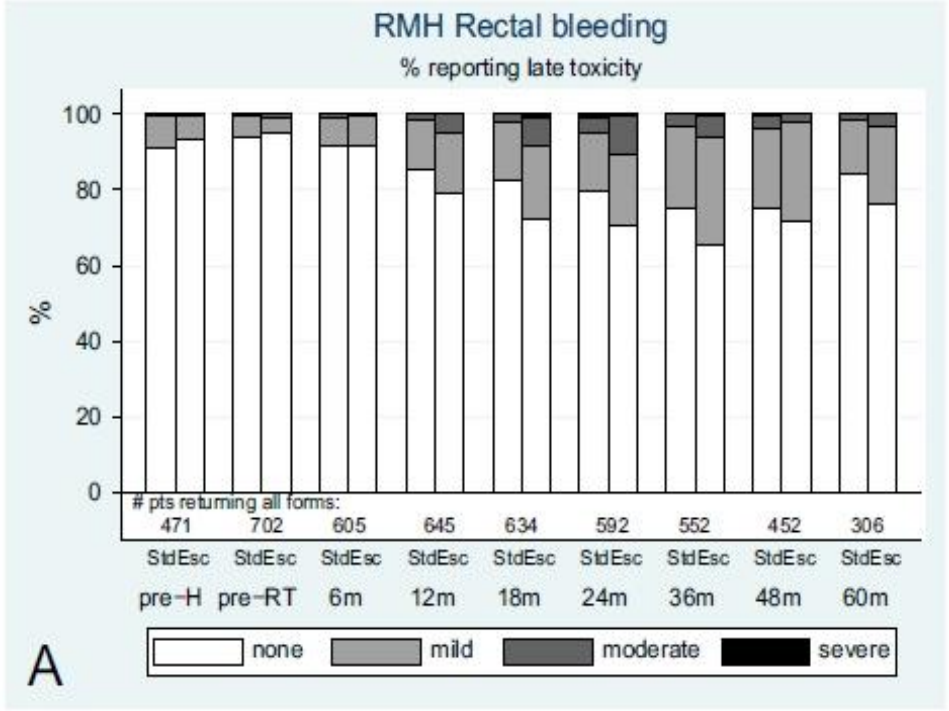
ELSEVIER

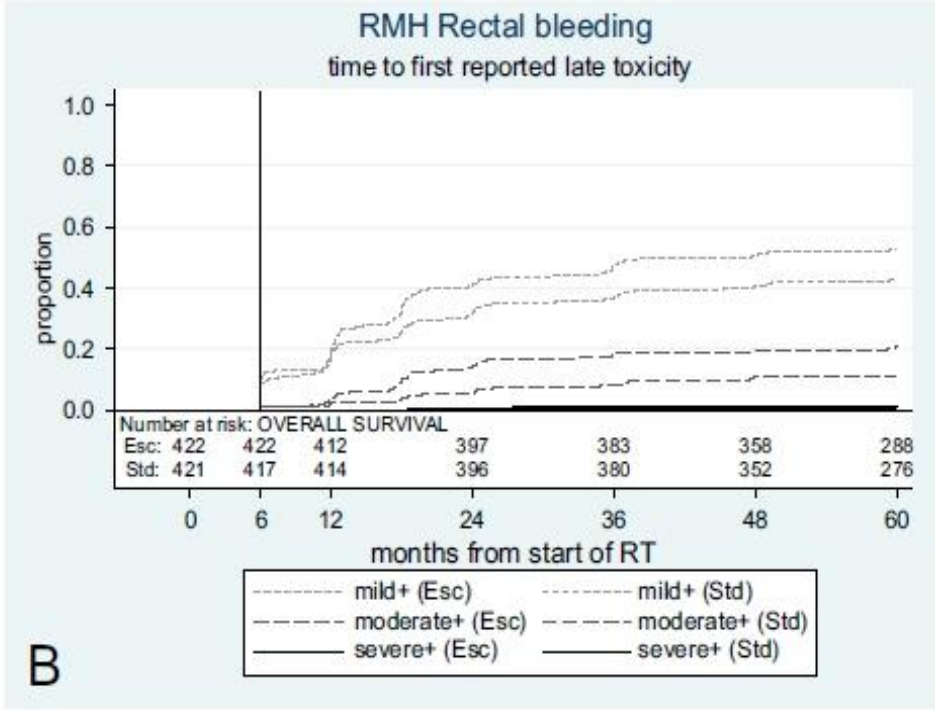
doi:10.1016/j.ijrobp.2009.05.052

CLINICAL INVESTIGATION **Prostate**

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

ISABEL SYNDIKUS, F.R.C.R.,* RACHEL C. MORGAN, M.SC.,† MATTHEW R. SYDES, C.STAT.,†
JOHN D. GRAHAM, F.R.C.R.,‡ AND DAVID P. DEARNALEY, F.R.C.R.,§ ON BEHALF OF THE MRC RT01 COLLABORATORS





Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 3, pp. 773–783, 2010

0360-3016/$–see front matter

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doi:10.1016/j.ijrobp.2009.05.052

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Toxicity	M. D. Anderson (1)	NKI (2, 3)	PROG 9509 (4)	RMH pilot (5)	MRC RT01 (6, 7)
RT dose Gy	70 vs. 78	68 vs. 78	70.2 vs 79.2	64 vs. 74	64 vs. 74
Setting	US	The Netherlands	US	UK	UK, Australia, New Zealand
Sites	Single site	Multisite	Single site	Single site	Multisite
RT technique	CFRT photon CFRT boost	CFRT photon CFRT boost	CFRT photon Proton boost	CFRT photon CFRT boost	CFRT photon CFRT boost
No. of patients randomized	301	669	393	126	843
Toxicity scale	RTOG-LENT modified*	RTOG/EORTC	RTOG	RTOG original	RTOG original
Median follow-up (years)	8.7	5.8	5.5	6.2	5.3
Grade ≥2 64 Gy vs. 74 Gy	13% vs. 26% ($p = 0.013$)	25% vs. 35% ($p = 0.04$)	9% vs. 18% ($p = 0.005$)	11% vs. 23% ($p = 0.02$)	24% vs. 33% ($p = 0.005$)
Analysis time point and type	By 10 years cumulative	By 7 years cumulative	"Late" snapshot	By 2 years cumulative	By 5 years cumulative

Contents lists available at SciVerse ScienceDirect

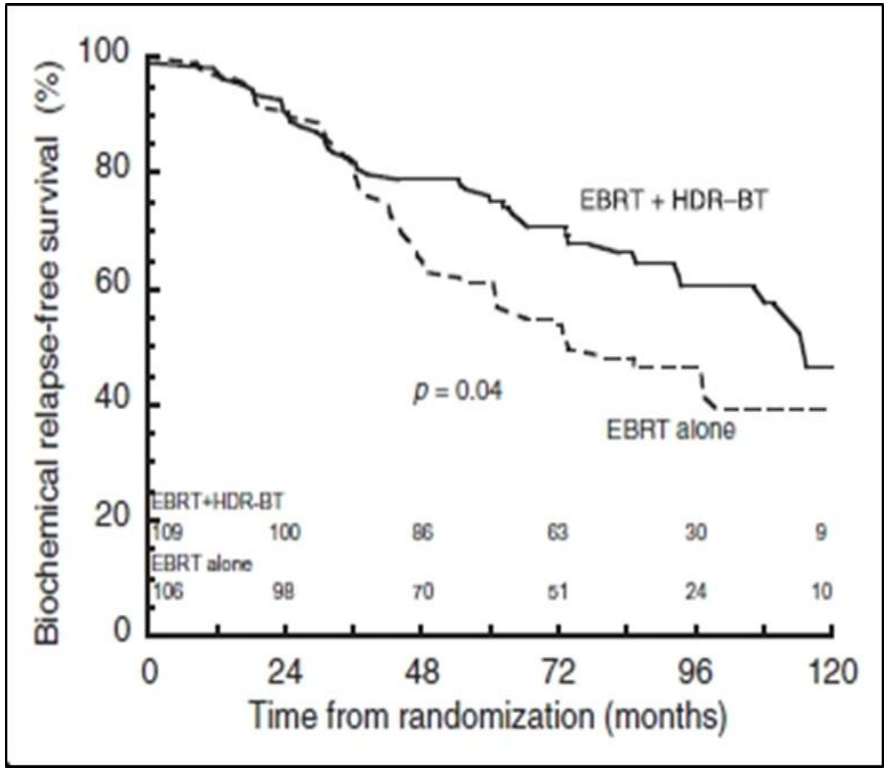
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

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[a], Ana M. Rojas[a,*], Peter J. Bownes[b], Gerry J. Lowe[a], Peter J. Ostler[a], Linda Bryant[a]



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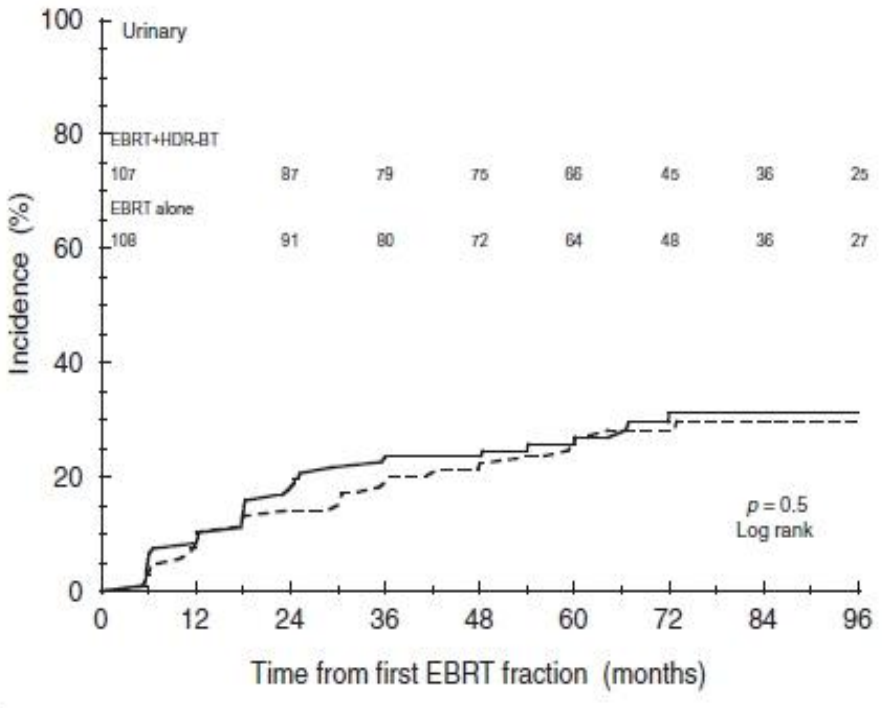
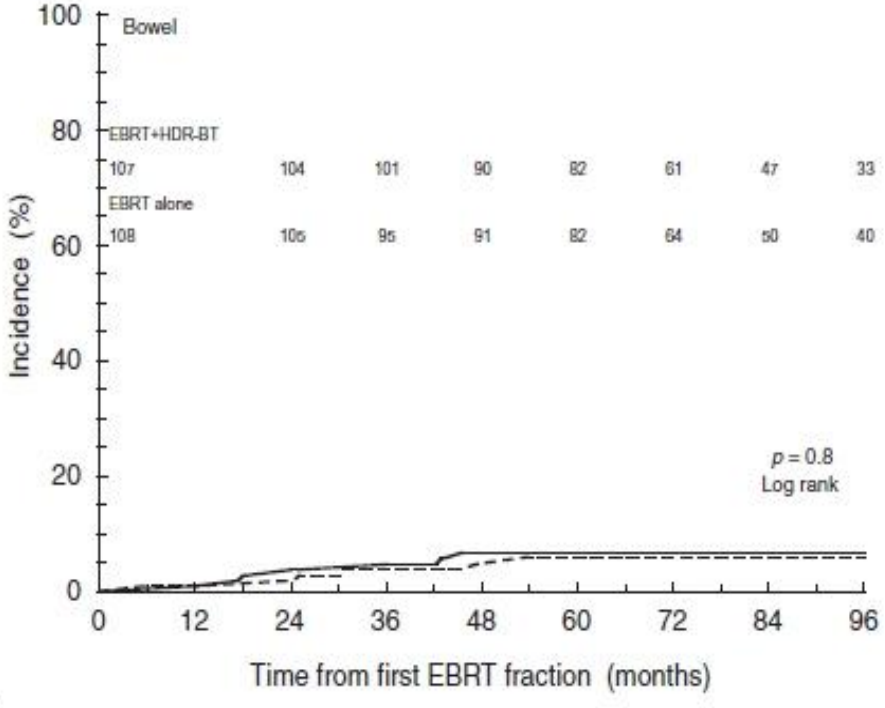




Rationale for focused dose escalation

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

Rationale for focused dose escalation

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?

AJR American Journal of Roentgenology
Diagnostic Imaging and Related Sciences

Accuracy of Multiparametric MRI for Prostate Cancer Detection: A Meta-Analysis

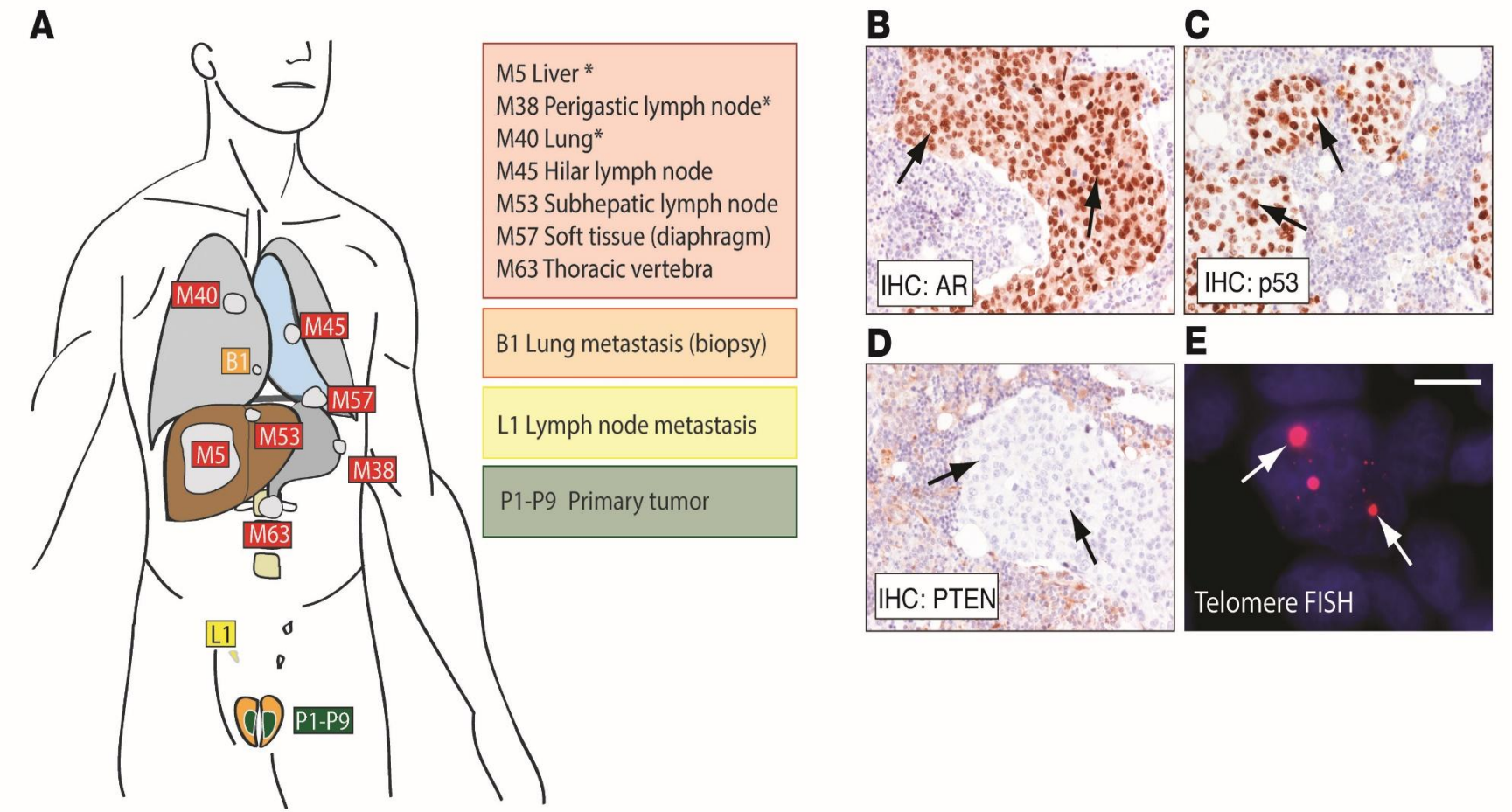
Maarten de Rooij[1], [2], Esther H. J. Hamoen[1], [3], Jurgen J. Fütterer[1], Jelle O. Barentsz[1] and Maroeska M. Rovers[2], [4]

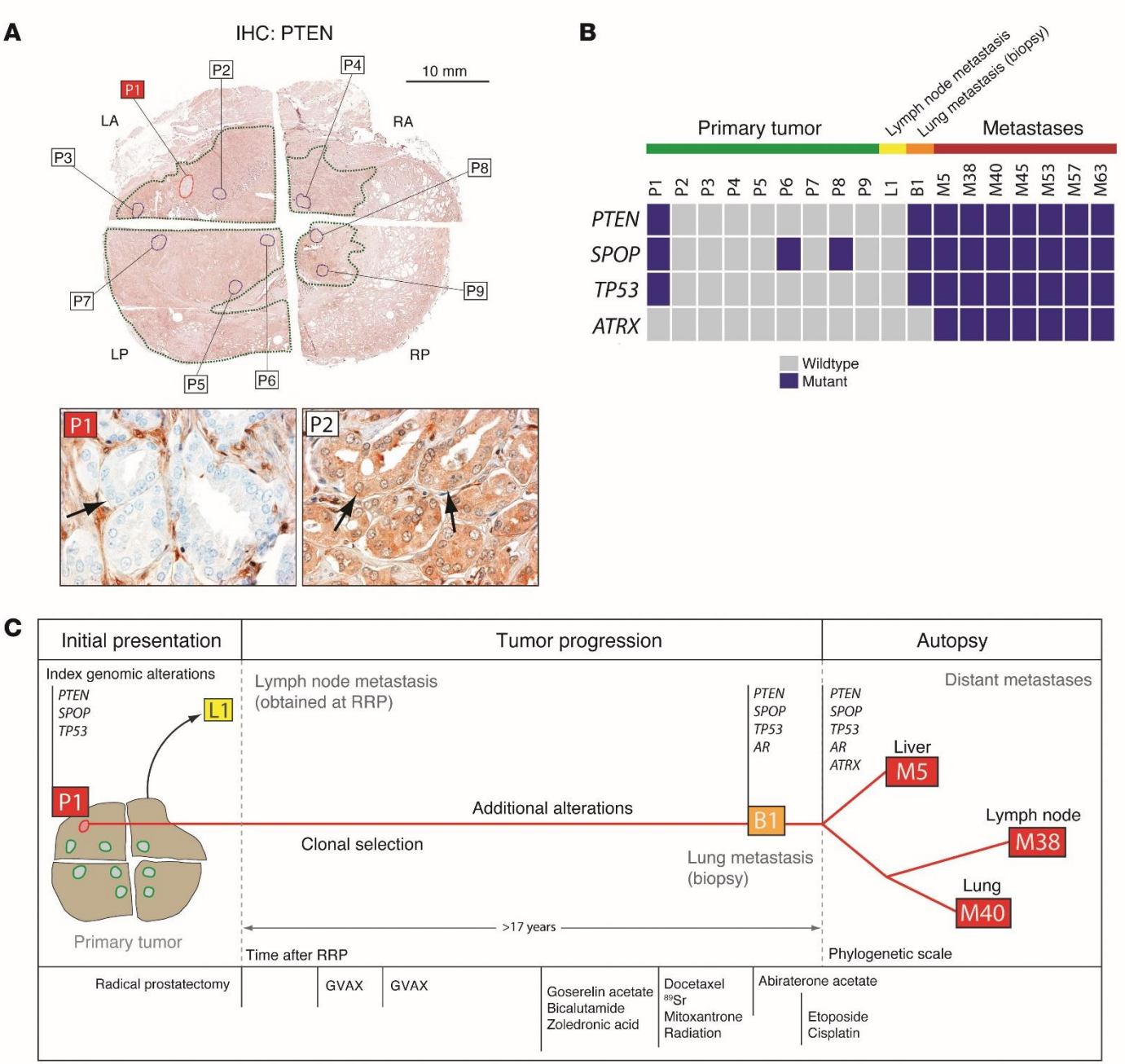
- Meta-analysis of 7 studies
- All T2W + DCE + DWI at least
- Compared to radical prostatectomy
- Specificity of 0.88 (95% CI, 0.82–0.92)
- Sensitivity of 0.74 (95% CI, 0.66–0.81)
- Negative predictive values (NPVs) ranging from 0.65 to 0.94

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 Yegnasubramanian[1]

J Clin Invest. 2013 Nov;123(11):4918-22.

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P2
P3
P4
P5
P6
P7
P8
P9
LA
RA
LP
RP
B
Primary tumor
Lymph node metastasis
Lung metastasis (biopsy)
Metastases
P1 P2 P3 P4 P5 P6 P7 P8 P9 L1 B1 M5 M38 M40 M45 M53 M57 M63
PTEN
SPOP
TP53
ATRX
Wildtype
Mutant
C
Initial presentation
Tumor progression
Autopsy
Index genomic alterations
PTEN
SPOP
TP53
L1
P1
Primary tumor
Lymph node metastasis
(obtained at RRP)
Additional alterations
Clonal selection
PTEN
SPOP
TP53
AR
B1
Lung metastasis
(biopsy)
Distant metastases
PTEN
SPOP
TP53
AR
ATRX
Liver
M5
Lymph node
M38
Lung
M40
>17 years
Time after RRP
Phylogenetic scale
Radical prostatectomy
GVAX
GVAX
Goserelin acetate
Bicalutamide
Zoledronic acid
Docetaxel
89Sr
Mitoxantrone
Radiation
Abiraterone acetate
Etoposide
Cisplatin

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)

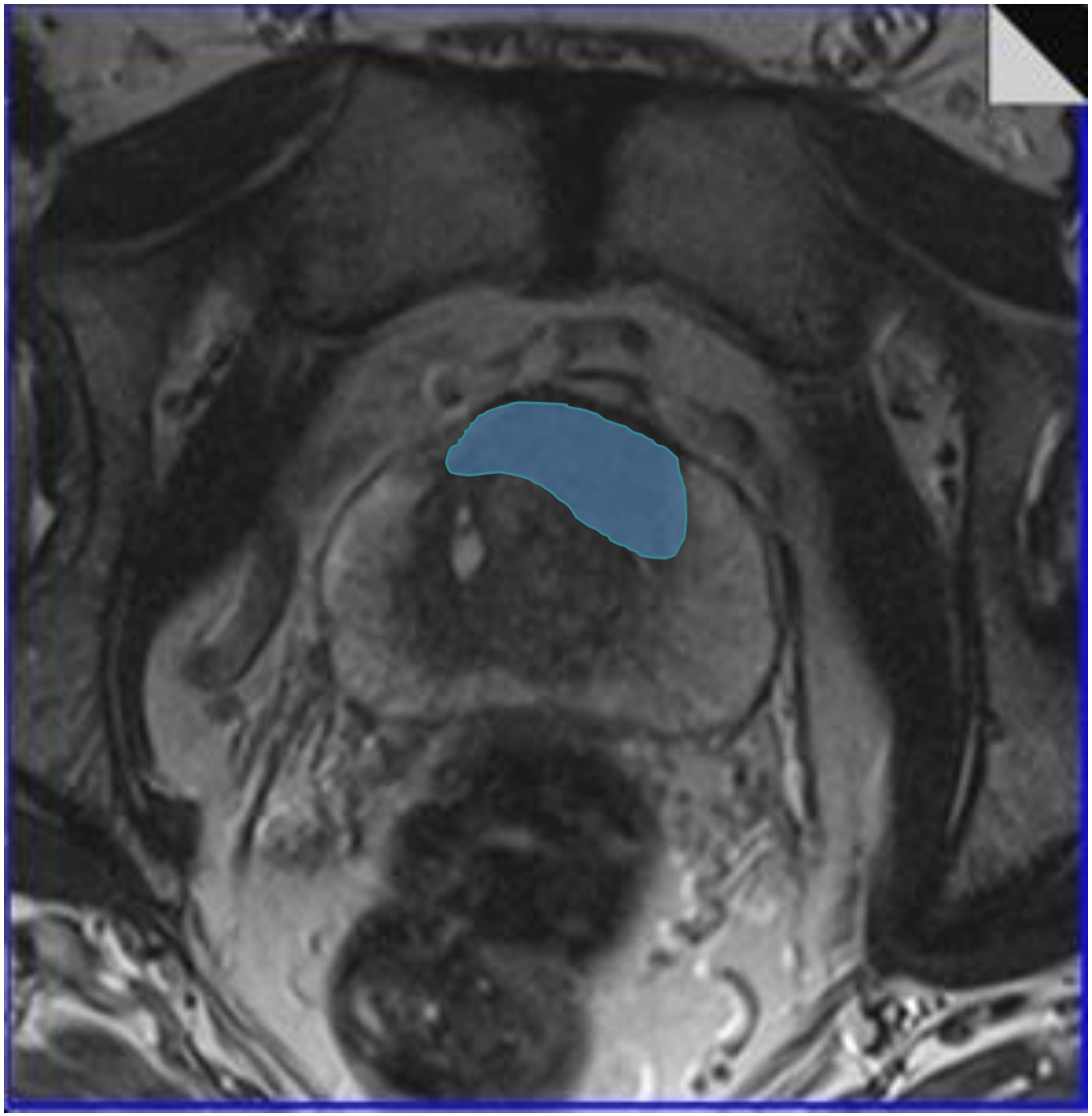
Validated biomarker groups that may serve as targets for pharmacological radio-sensitisation or focused dose escalation

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

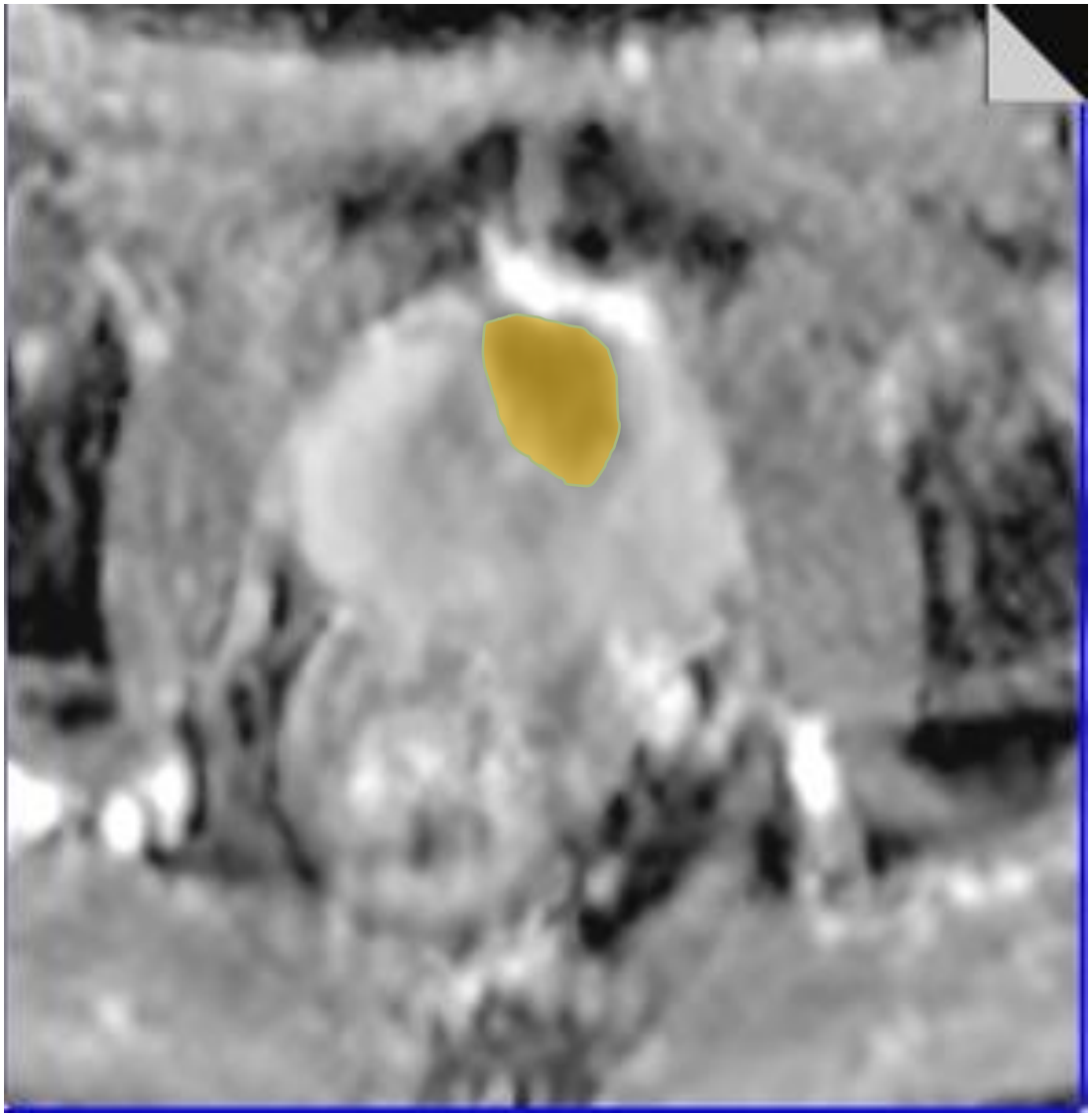
These may exist in complex arrangements……..

T2-weighted MRI

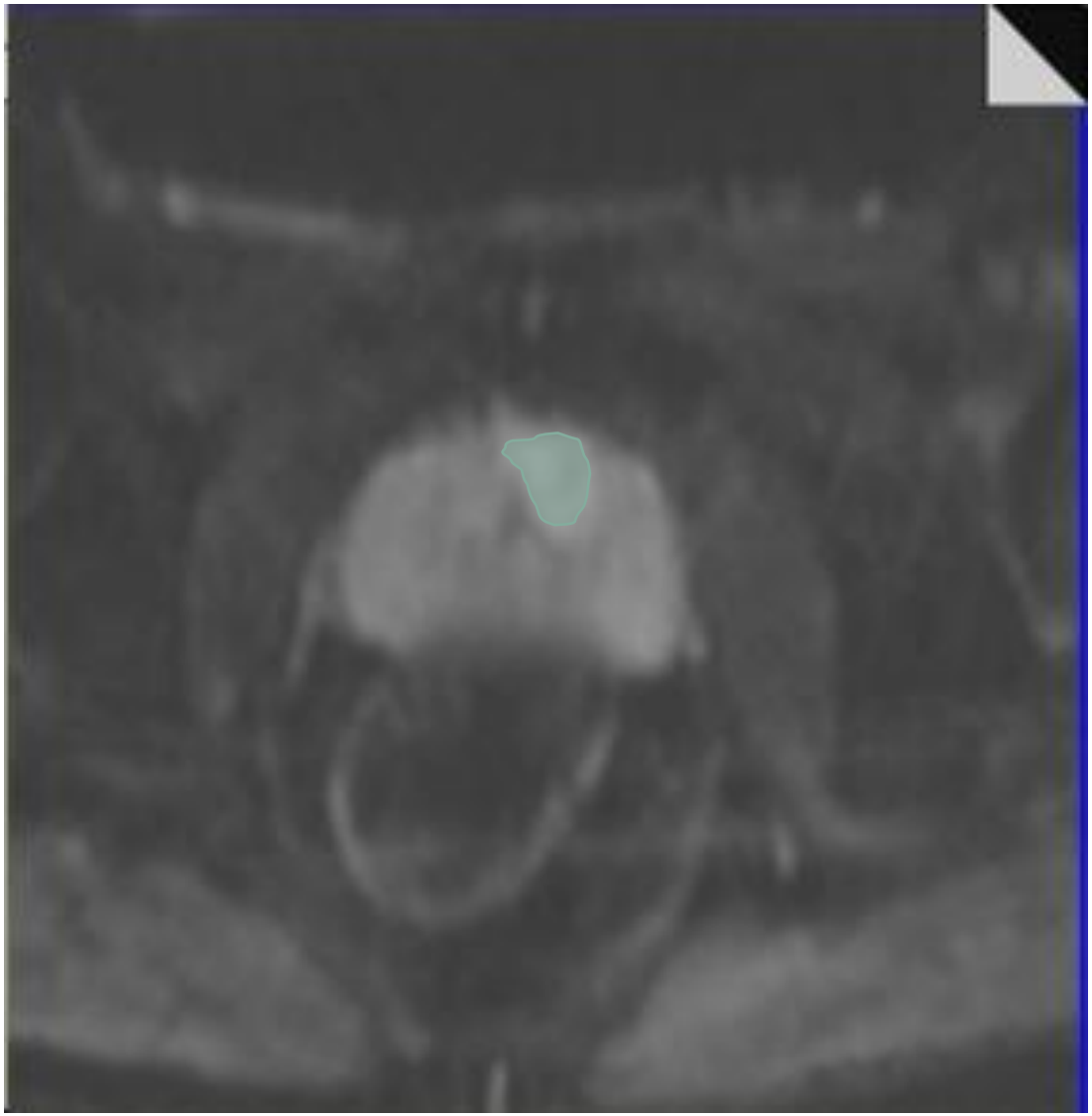
67 year old man with a Gleason 4+3 carcinoma



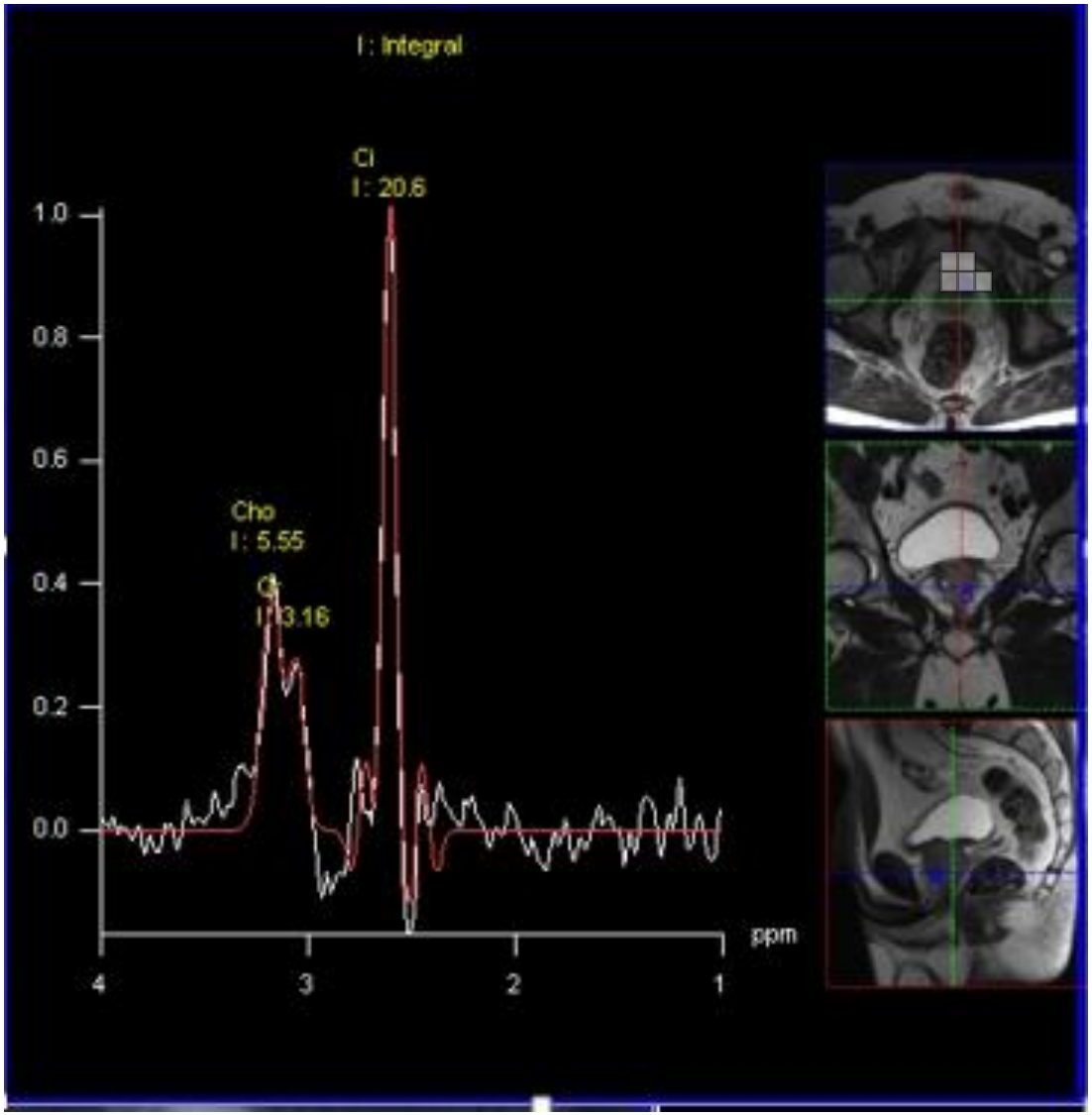
Diffusion Weighted MRI



Dynamic Contrast Enhanced MRI



Magnetic Resonance Spectroscopy



Which biological map to choose?

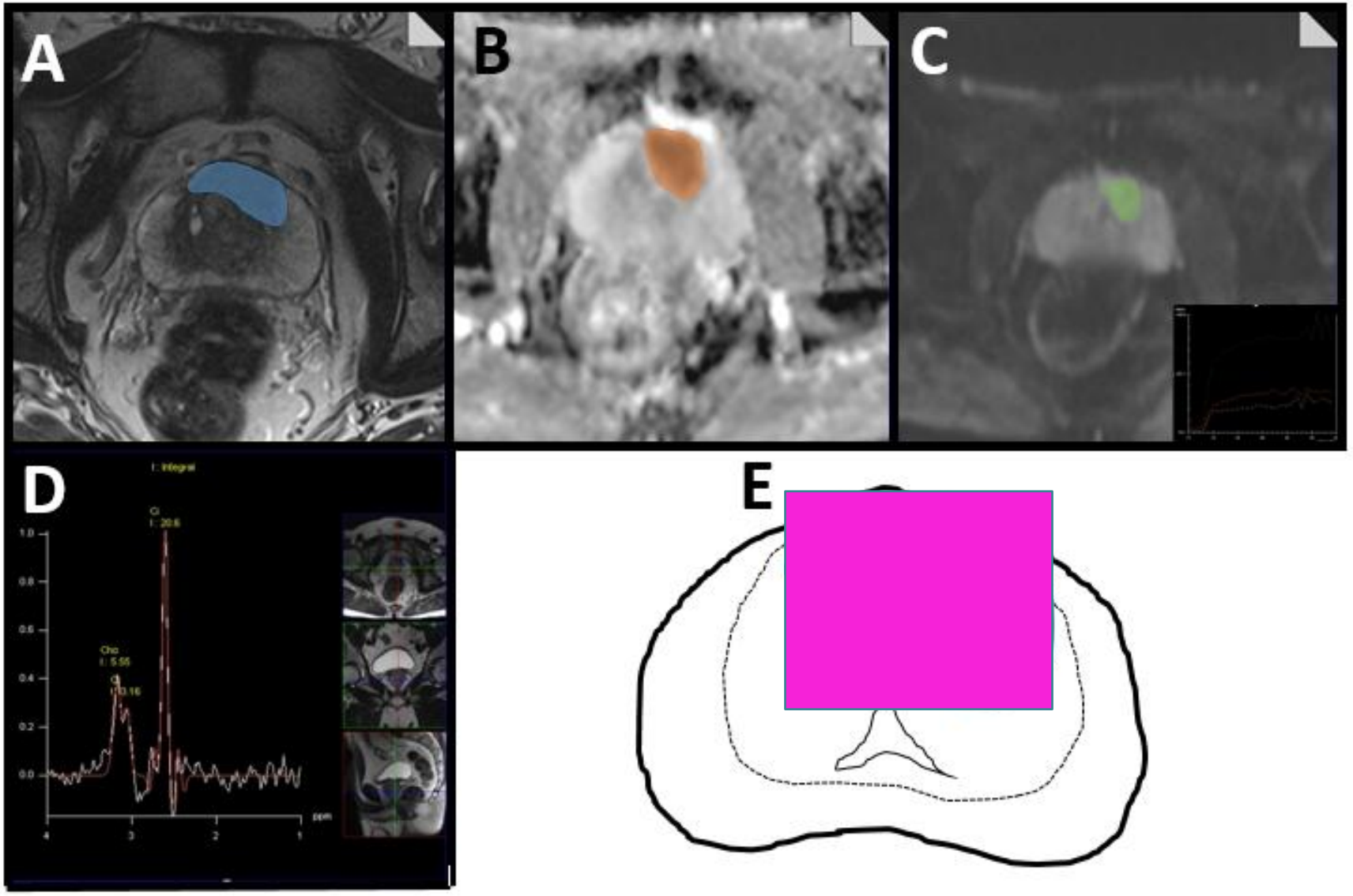


Image Registration

- Rigid fusion - Linear Transformations
  Rotation, Scaling, Translation

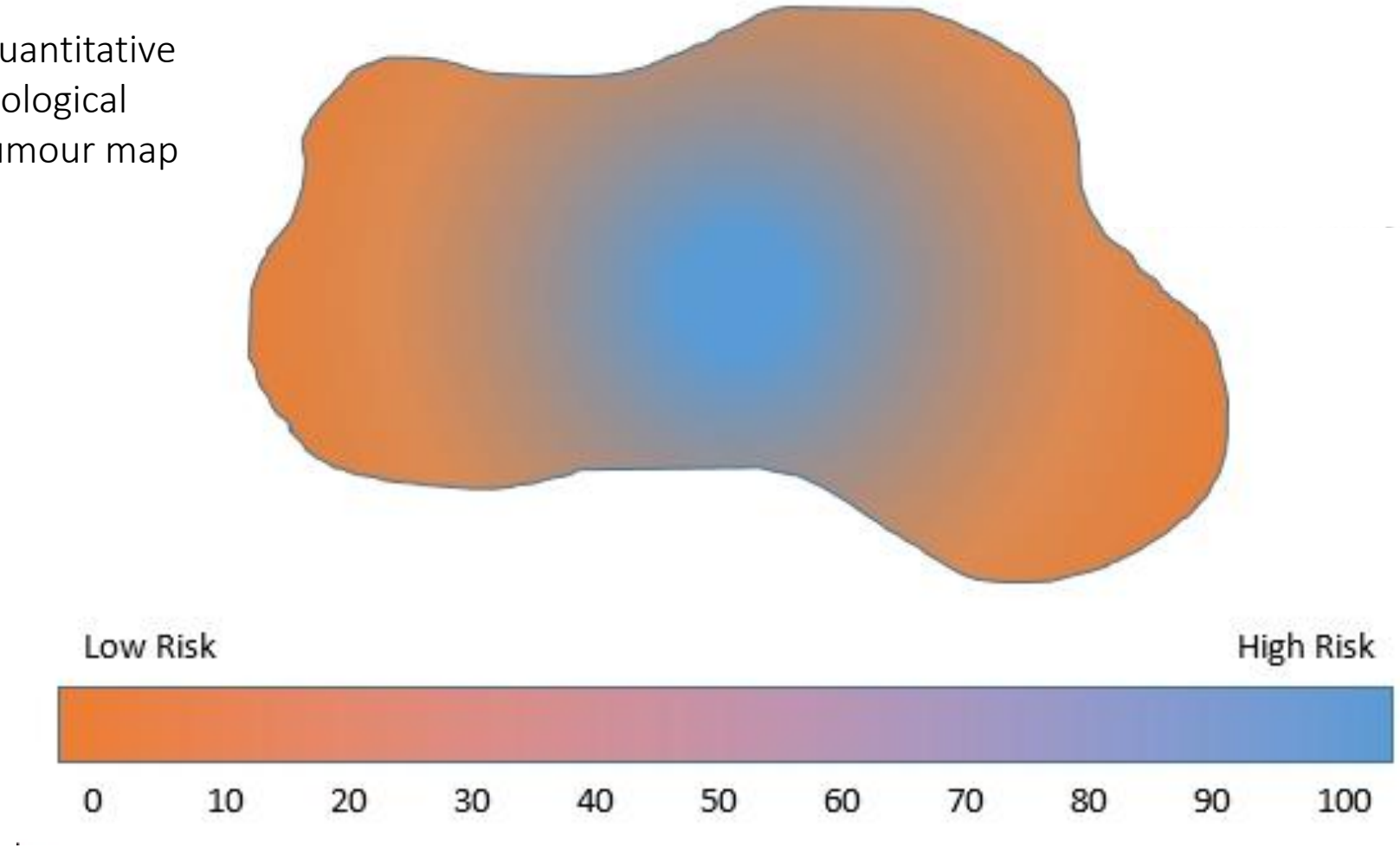
- Non-rigid fusion - Warping
  Multiple points, Contours

A confident registration with a measurement of uncertainty is critical.

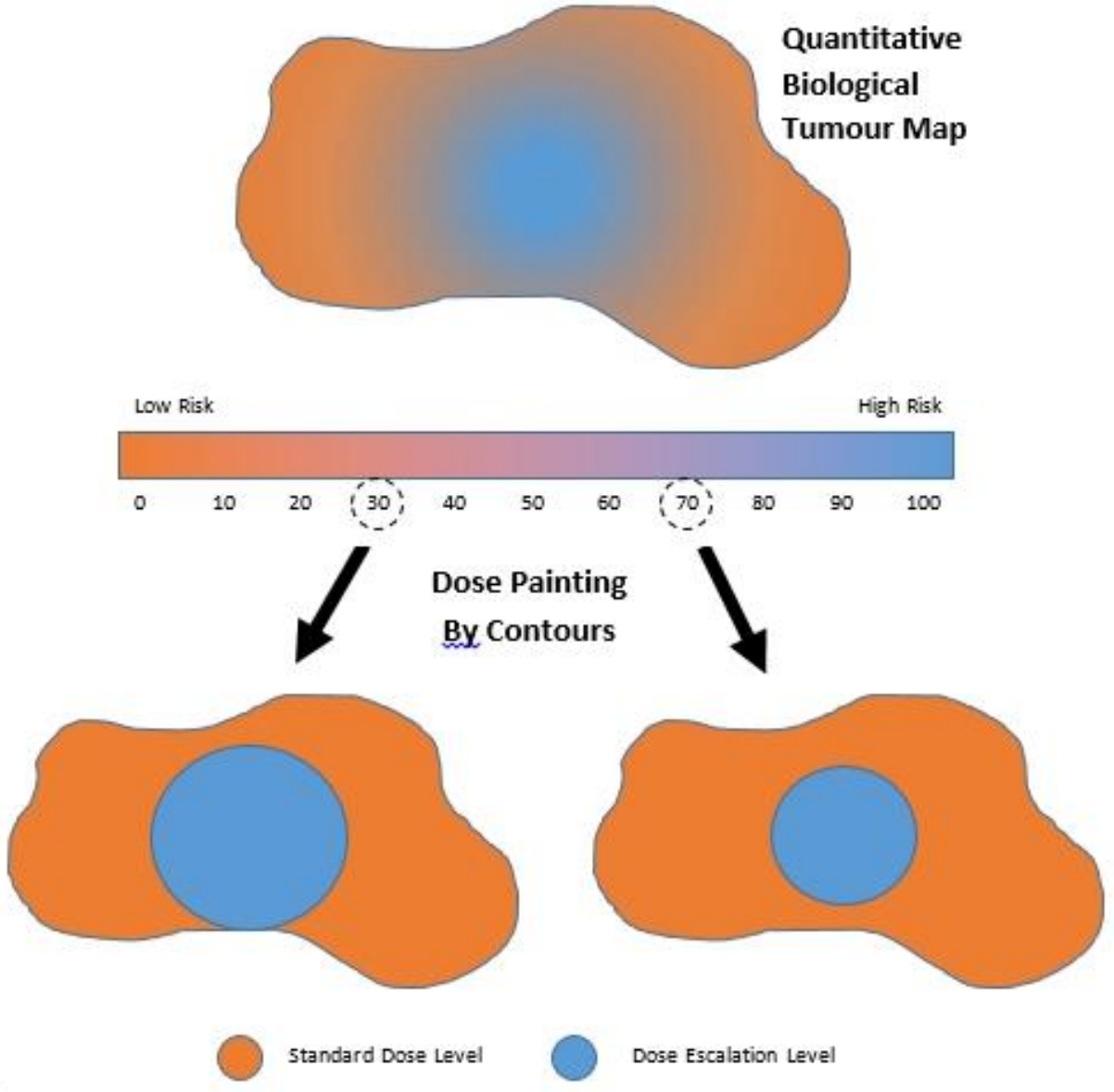
This level of uncertainty must then be incorporated into the margins chosen for CTV to PTV expansion.

Dose Painting

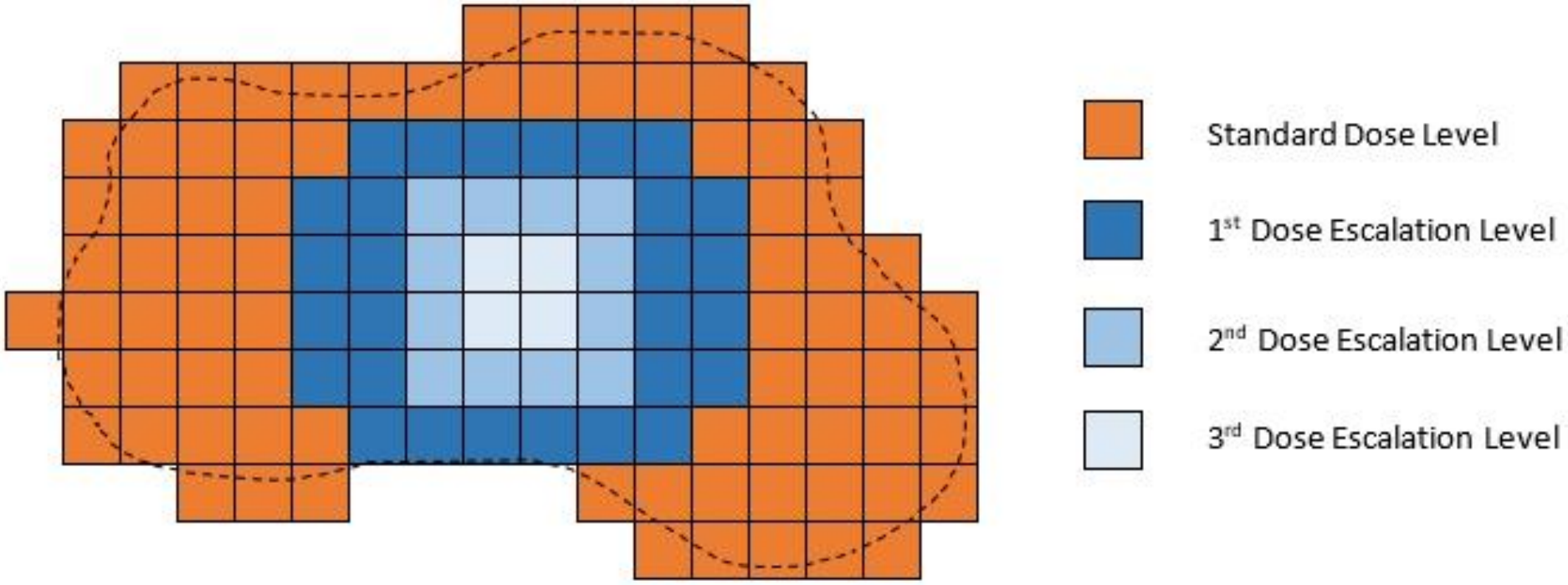
Quantitative biological tumour map



Dose Painting by contours



Dose Painting By Numbers



Focused dose escalation using high dose rate brachytherapy as monotherapy for prostate cancer

Biology

Low α/β ratio for prostate cancer

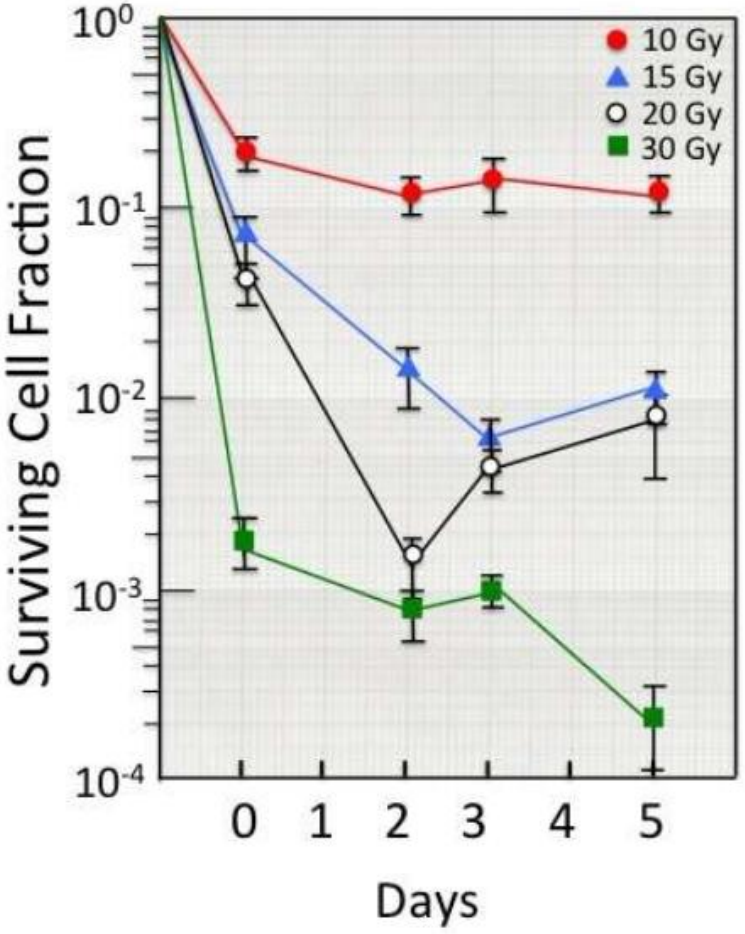
Anticancer Res. 2013 Mar;33(3):1009-11.
Int J Radiat Oncol Biol Phys. 2003;55:194-203.
Acta Oncol. 2005;44(3):265-76.
Int J Radiat Oncol Biol Phys. 2013 Jan 1;85(1):89-94

Biology

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

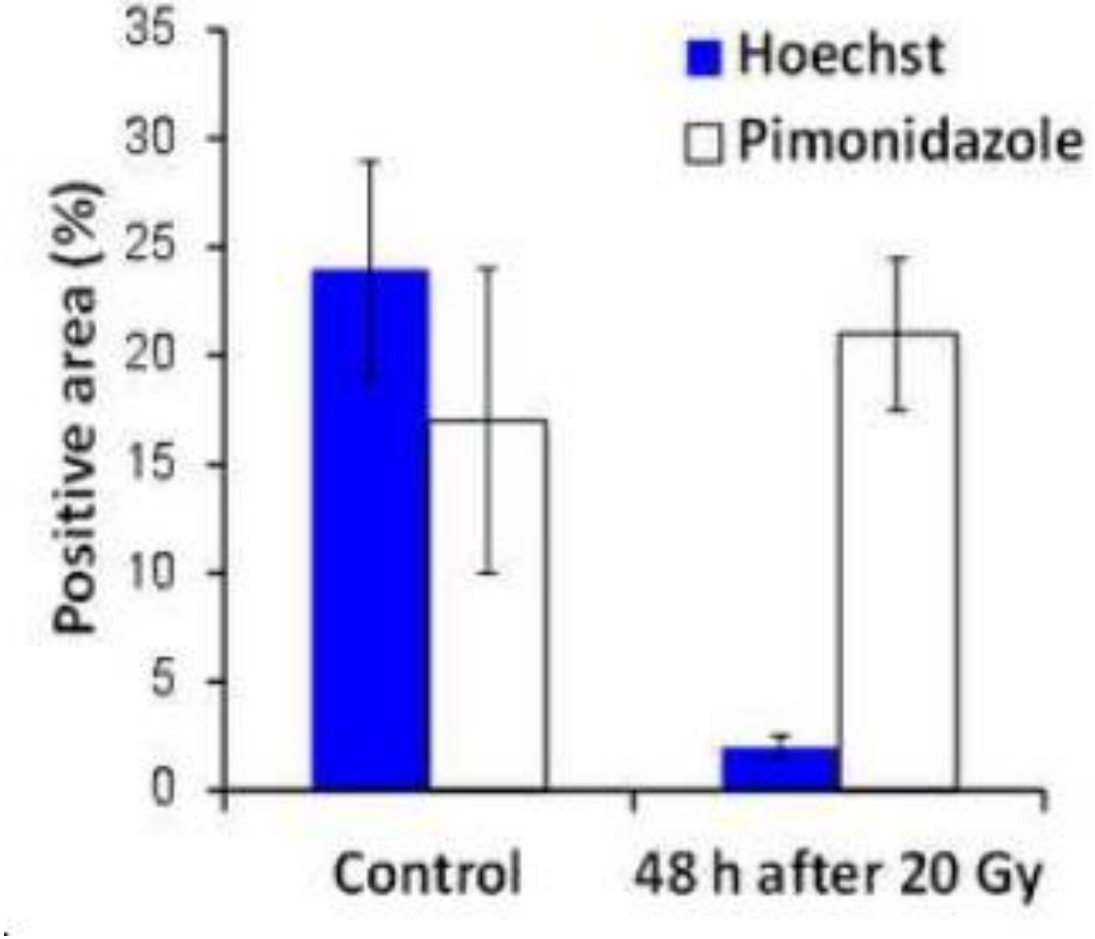
Wong et al. Radiology 1973;108:429–434.

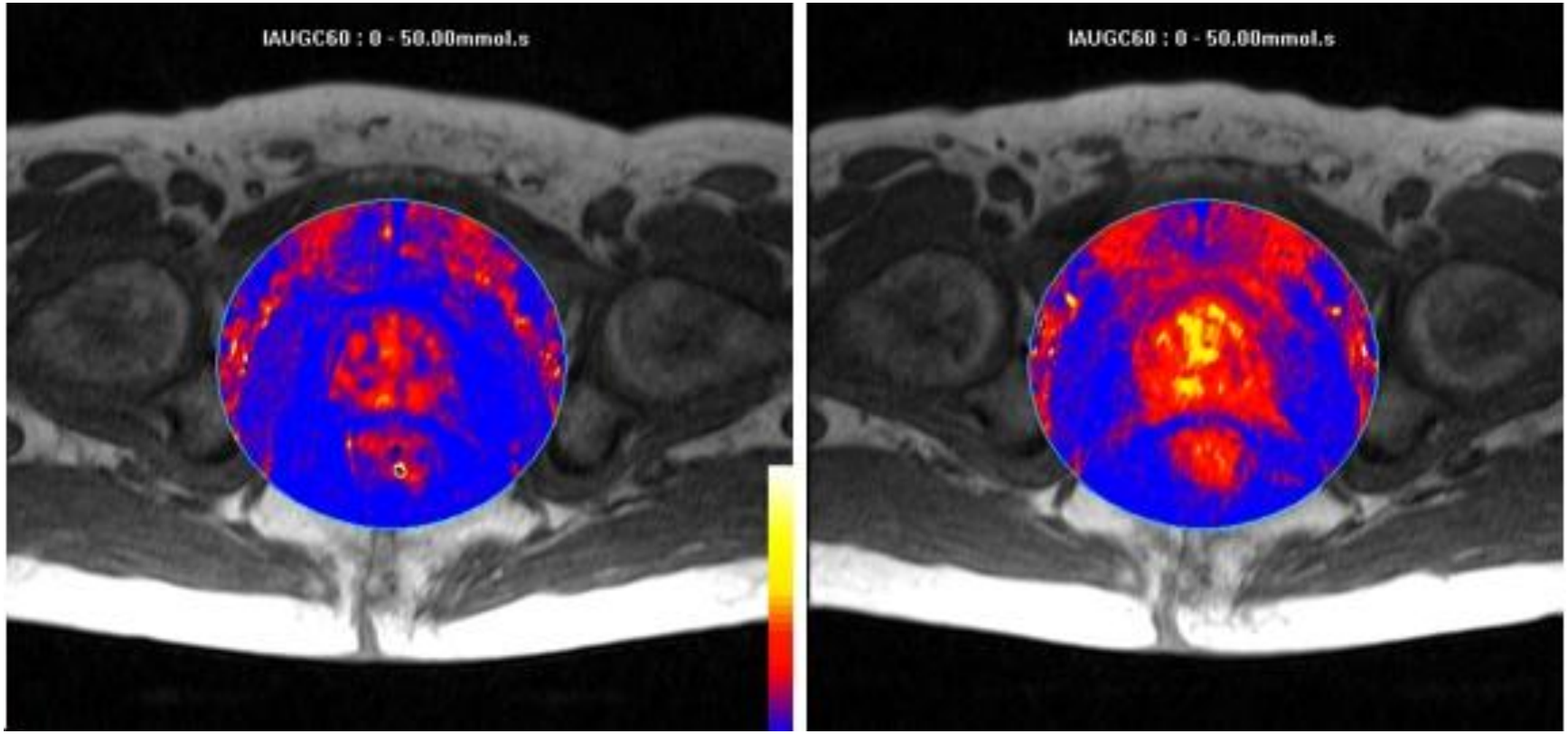
Song et al. Cancer Res 1974;34:2344–2350.



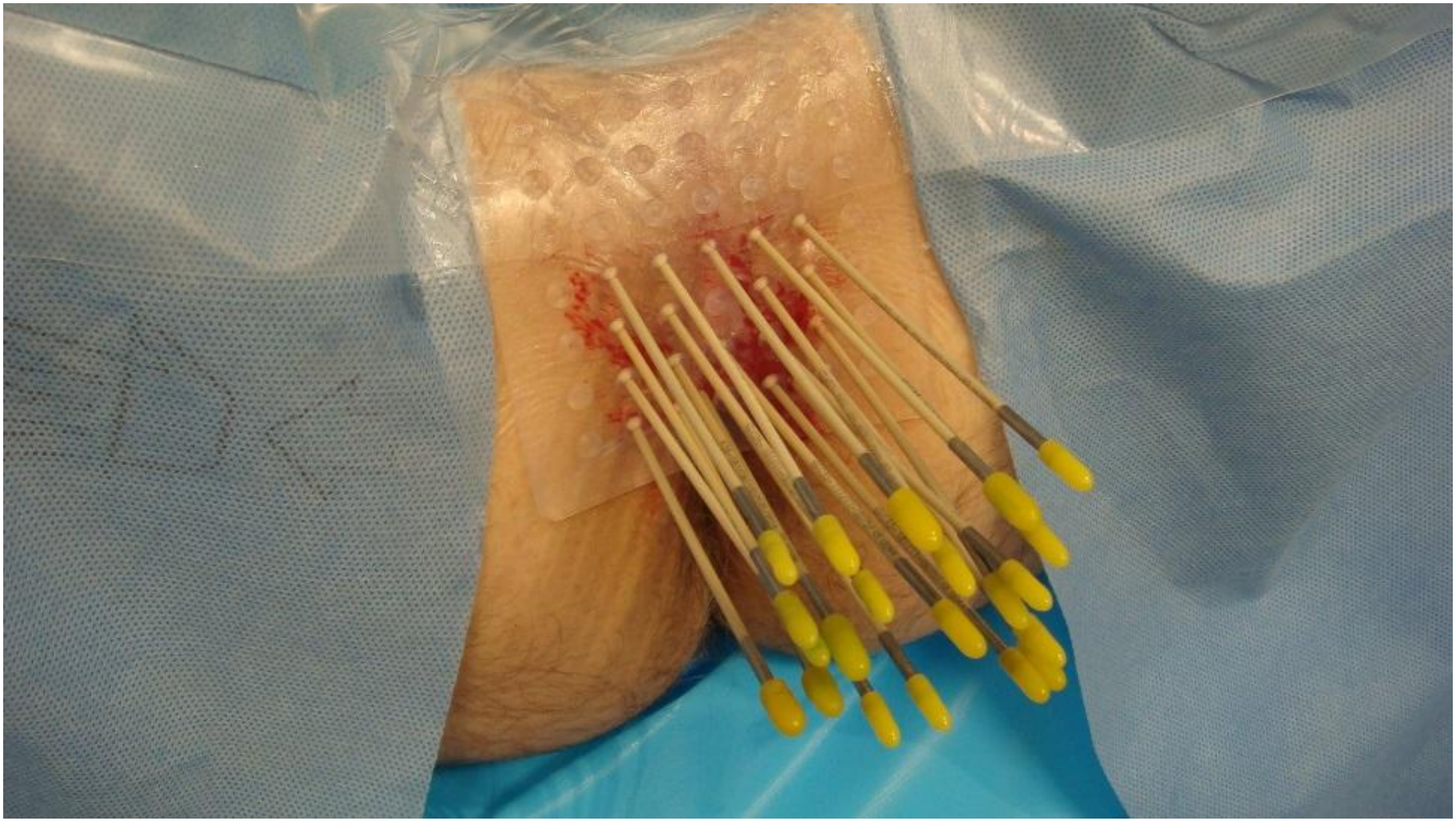
FSaII fibrosarcoma grown subcutaneous (s.c.) in the hind limb of C3H mice

The cell survival was determined immediately after irradiation or after leaving the irradiated tumours in situ for 1-5 days

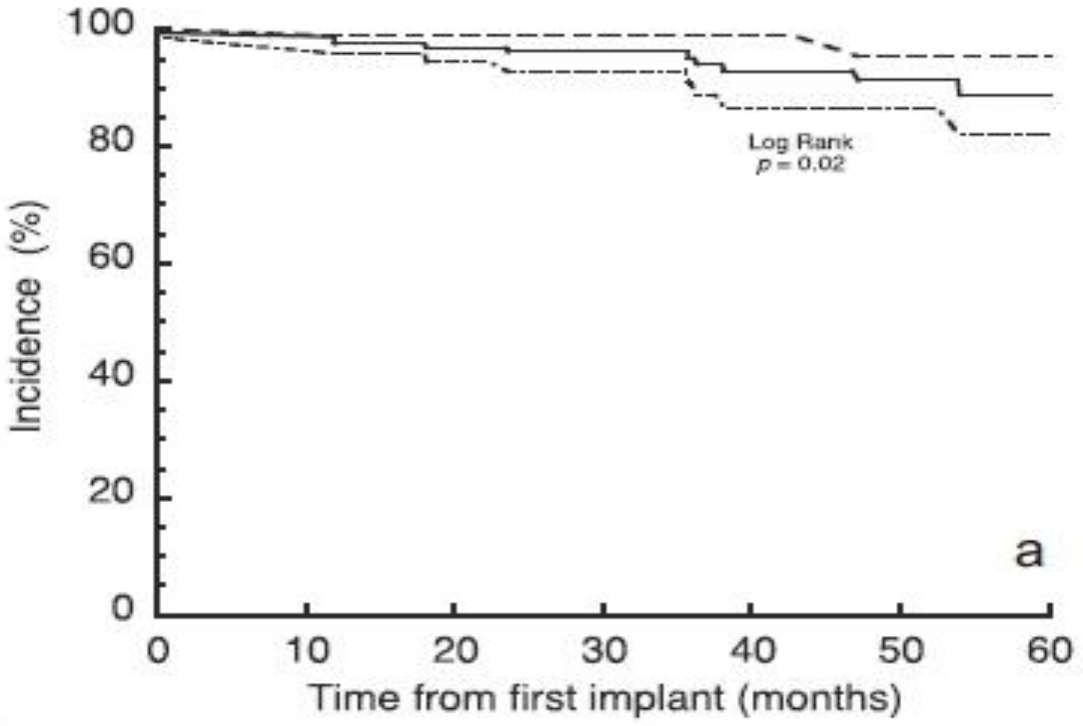

Hoechst
Pimonidazole
Positive area (%)
35
30
25
20
15
10
5
0
Control
48 h after 20 Gy


IAUGC60 : 0 - 50.00mmol.s
IAUGC60 : 0 - 50.00mmol.s

High Dose-Rate Brachytherapy



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%

*Hoskin *et al.* Int J Radiat Oncol Biol Phys. 2012 Mar 15;82(4):1376-84

Contents lists available at ScienceDirect

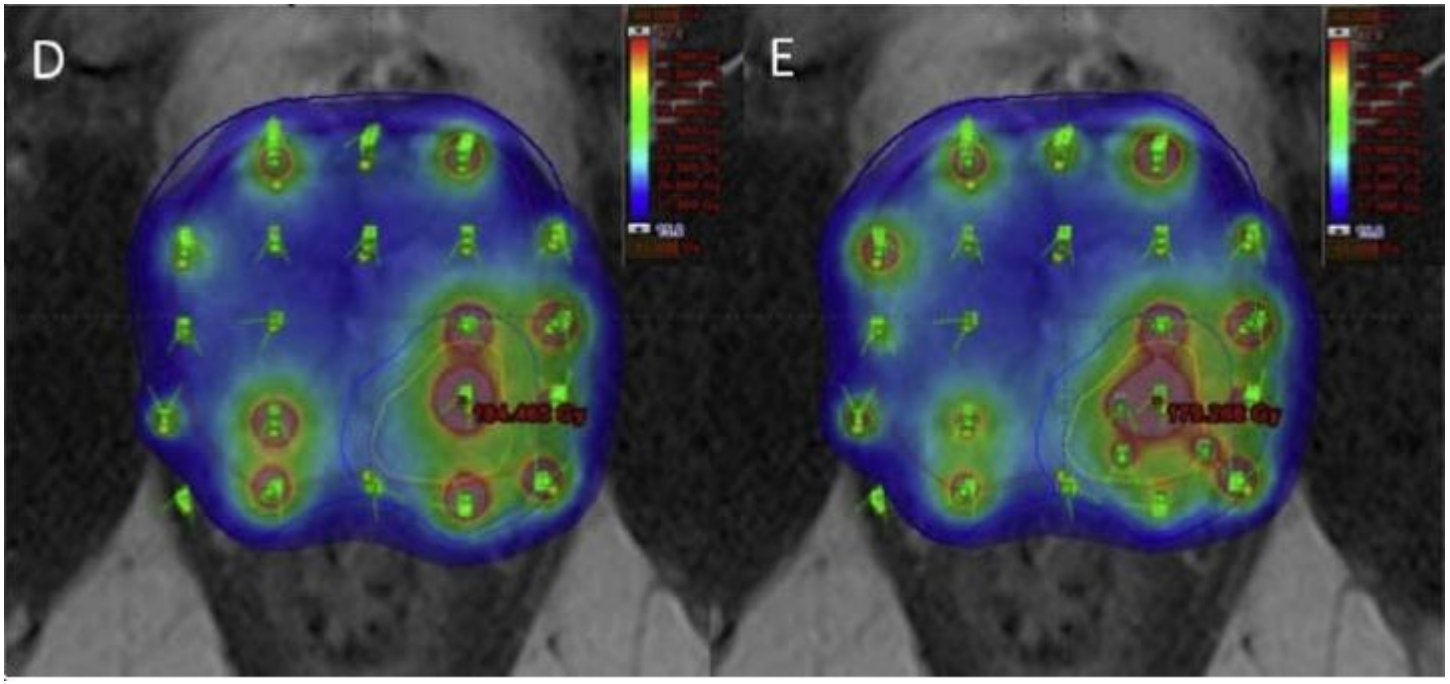
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Prostate brachytherapy

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

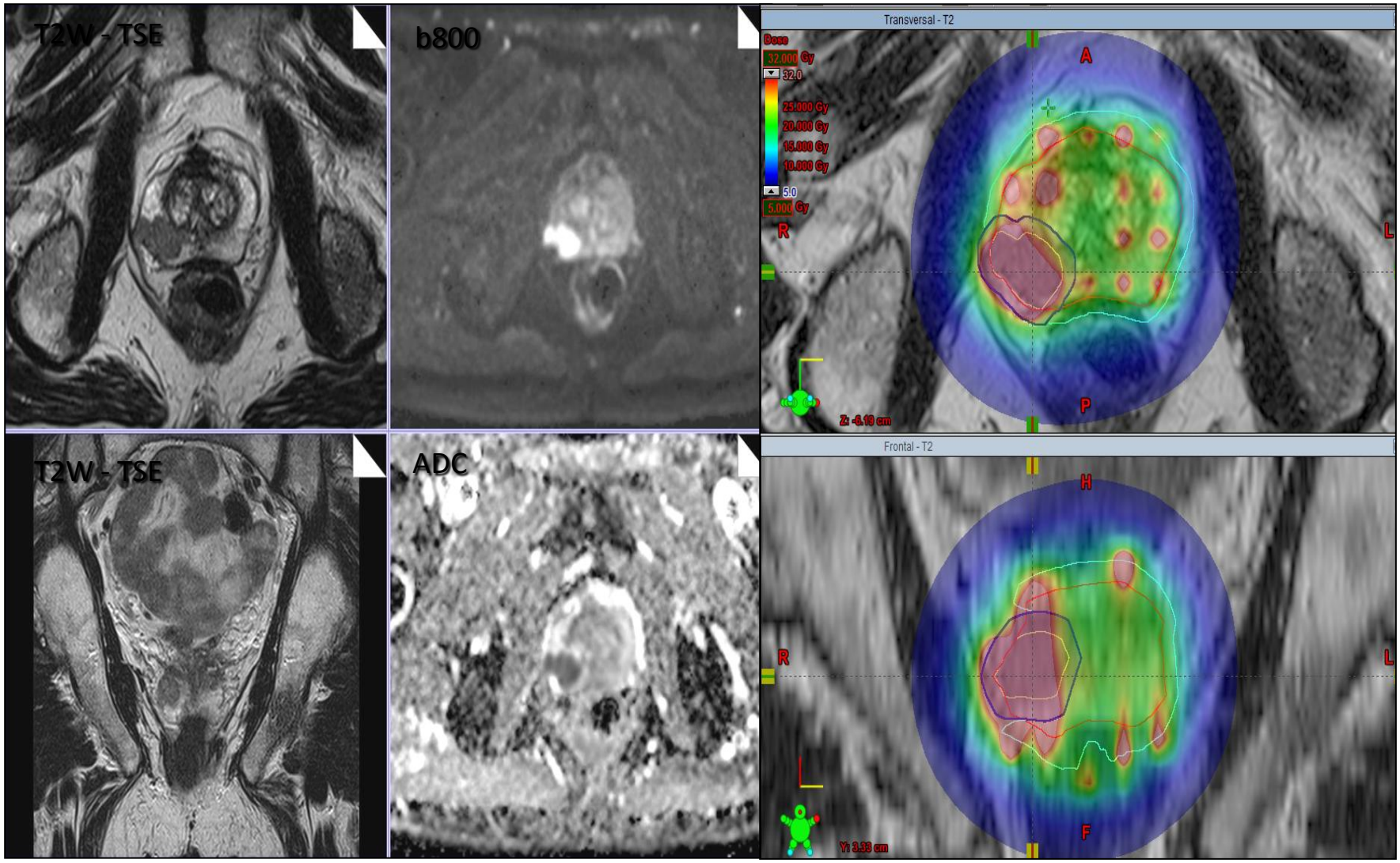
Pittaya Dankulchai [a,b,*], Roberto Alonzi [a], Gerry J. Lowe [a], James Burnley [a], Anwar R. Padhani [c], Peter J. Hoskin [a]



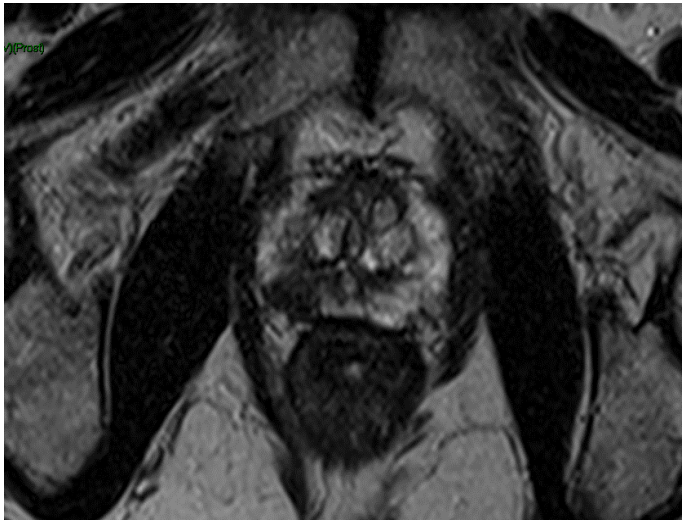
1st cohort – 25 patients

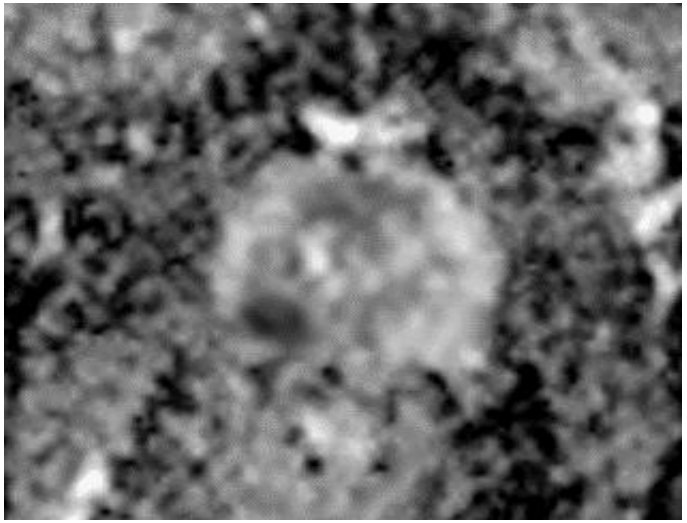
Quality Indices

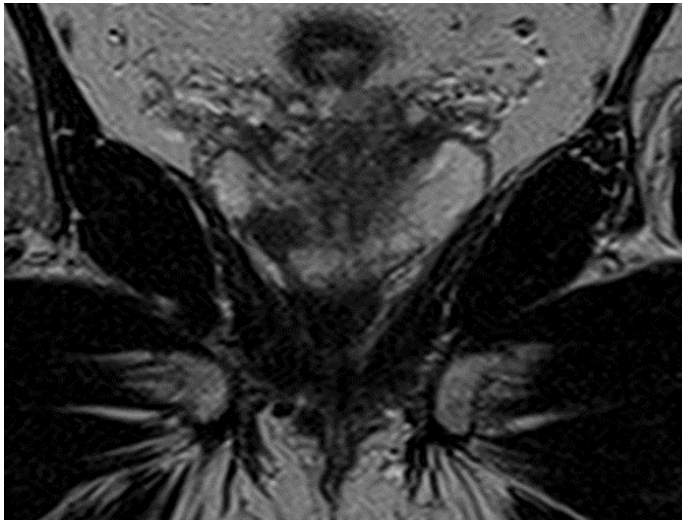
Structure	Index		Target Value
HDR PTVBoost	V100 [% of volume]	Is more than	95
HDR PTVNonBoost	V19Gy [% of volume]	Is less than	75
HDR Urethra	D30 [Gy]	Is less than	20.8
HDR Urethra	D10 [Gy]	Is less than	22
HDR Urethra	V150 [cm^3]	Is less than	.01
HDR Rectum	V19Gy [cm^3]	Is less than	.01
HDR Rectum	D2.0cc [Gy]	Is less than	15
HDR PTVNonBoost	V19Gy [% of volume]	Is more than	65
HDR PTVNonBoost	V15Gy [% of dose]	Is more than	95

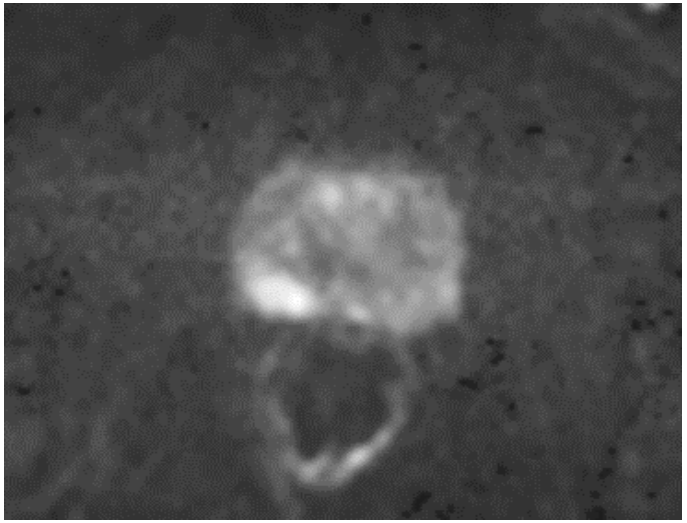


75 year old man, PSA 18ng/ml, T3a No Mo, Gleason 4+3 in 5/12 TRUS biopsy cores, all Right Sided







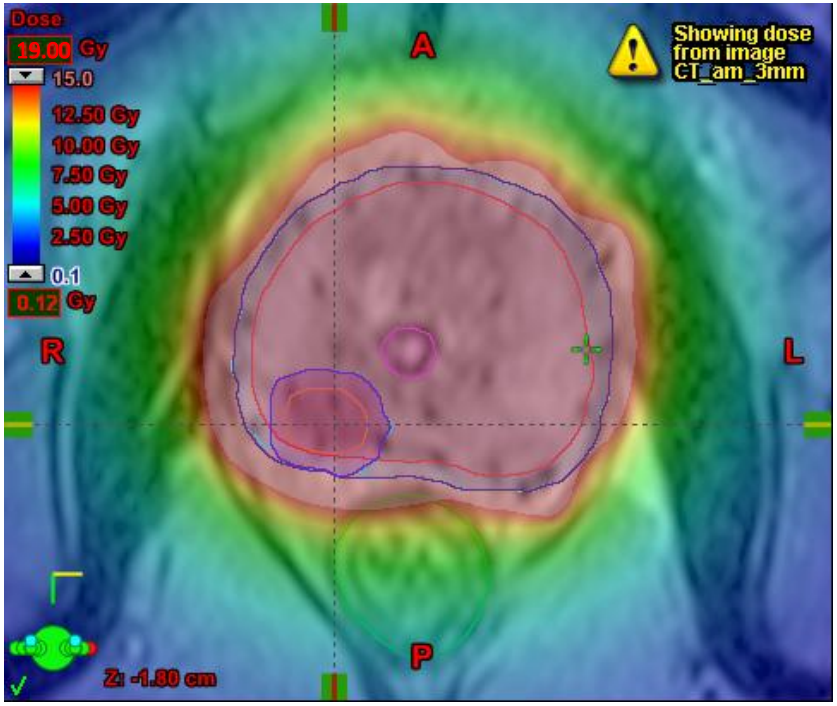


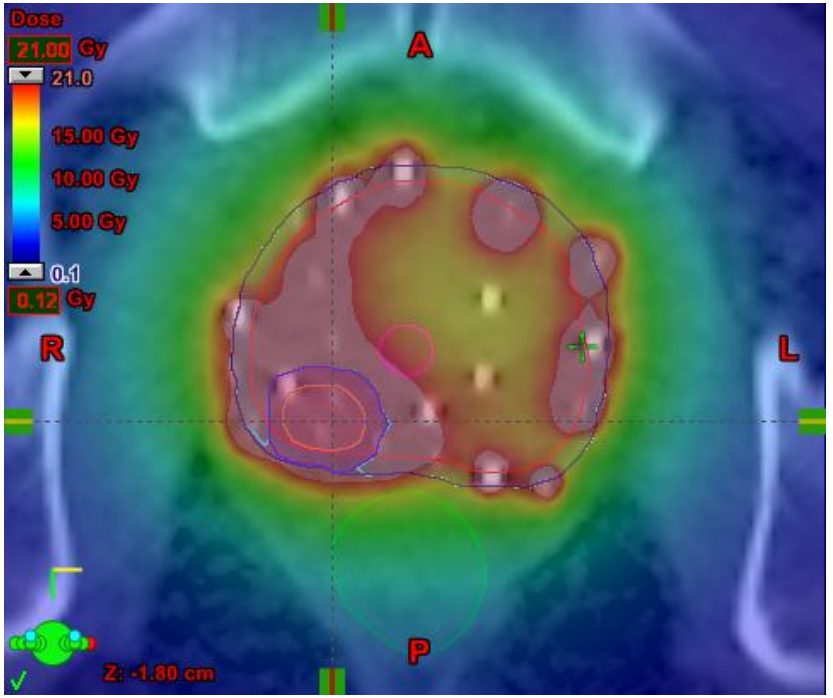
64 year old man

PSA 8.9ng/ml

T2a No Mo

Gleason 3+4 in 2/12 TRUS biopsy cores, all Right Sided

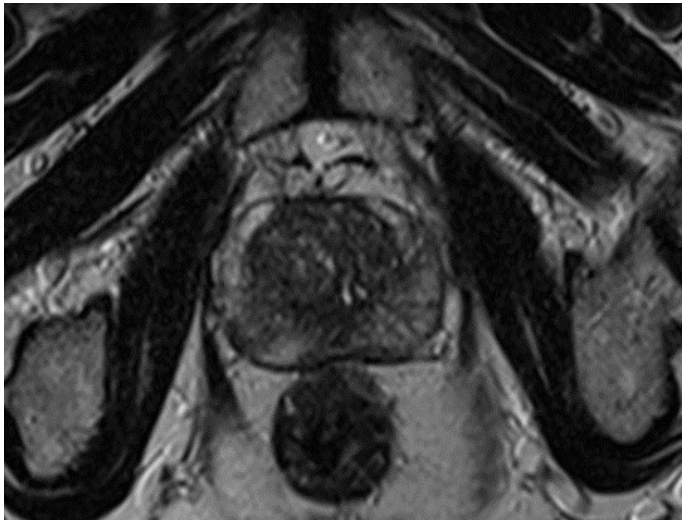
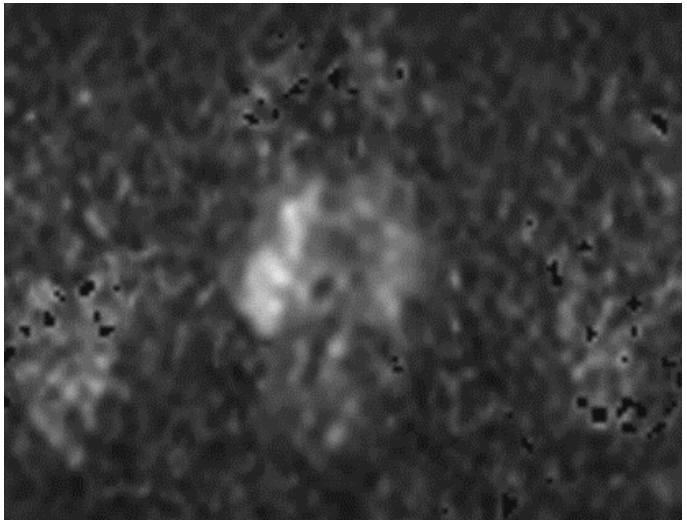
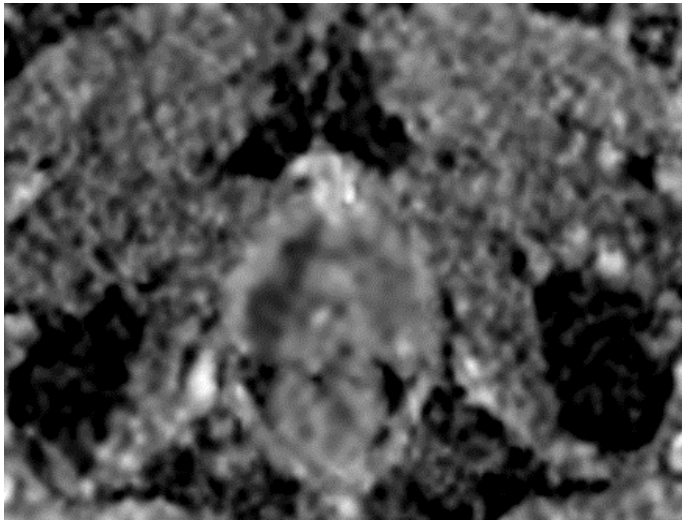
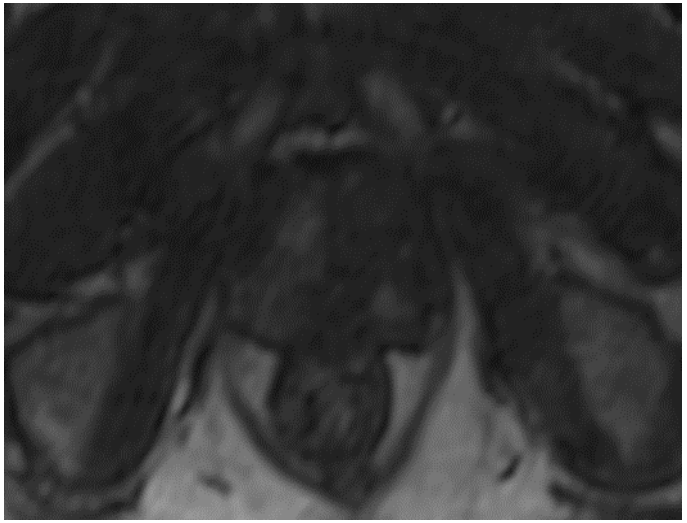

Dose
19.00 Gy
15.0
12.50 Gy
10.00 Gy
7.50 Gy
5.00 Gy
2.50 Gy
0.1
0.12 Gy
A
R
L
P
Showing dose from image CT_am_3mm
Z: -1.80 cm


Dose
21.00 Gy
21.0
15.00 Gy
10.00 Gy
5.00 Gy
0.1
0.12 Gy
A
R
L
P
Z: -1.80 cm

2nd cohort – 25 patients (21 treated so far)

Quality Indices

Structure	Index		Target Value
HDR PTVBoost	V100 [% of volume]	Is more than	95
~~HDR PTVNonBoost~~	~~V19Gy [% of volume]~~	~~Is less than~~	~~75~~
HDR Urethra	D30 [Gy]	Is less than	20.8
HDR Urethra	D10 [Gy]	Is less than	22
HDR Urethra	V150 [cm^3]	Is less than	.01
HDR Rectum	V19Gy [cm^3]	Is less than	.01
HDR Rectum	D2.0cc [Gy]	Is less than	15
~~HDR PTVNonBoost~~	~~V19Gy [% of volume]~~	~~Is more than~~	~~65~~
HDR PTVNonBoost	V15Gy [% of dose]	Is more than	95

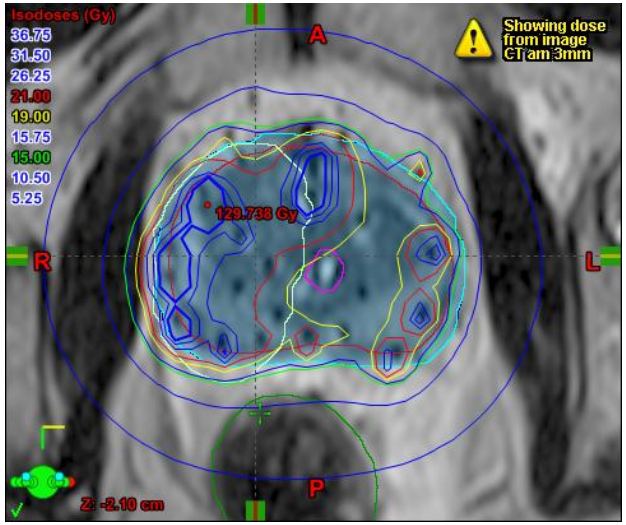





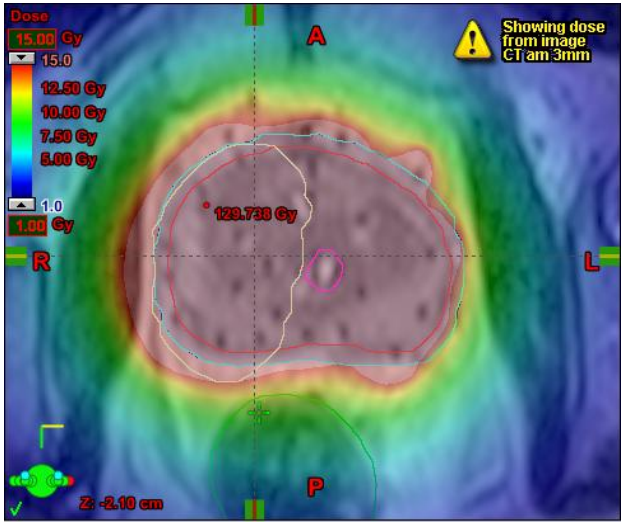
67 year old man

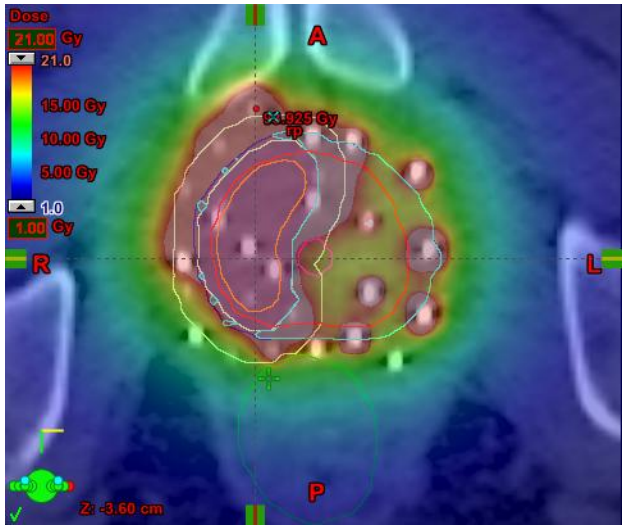
PSA 14.7ng/ml

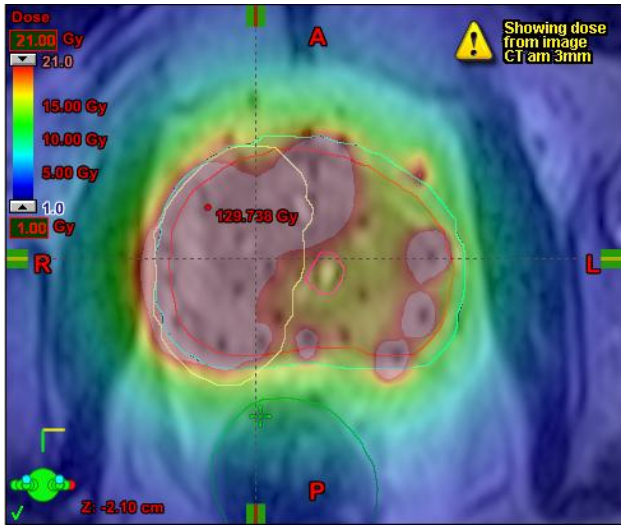
T2b No Mo

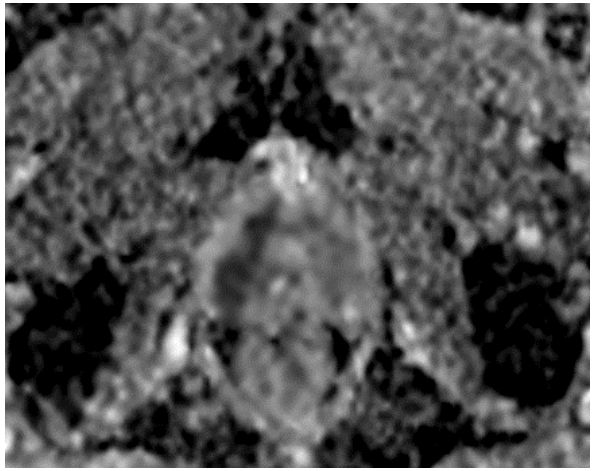
Gleason 3+4 in 4/12 TRUS biopsy cores, all Right Sided


Isodoses (Gy)
36.75
31.50
26.25
21.00
19.00
15.75
15.00
10.50
5.25
Showing dose from image CT am 3mm
129.738 Gy
A
R
L
P
Z: -2.10 cm


Dose
15.00 Gy
15.0
12.50 Gy
10.00 Gy
7.50 Gy
5.00 Gy
1.0
1.00 Gy
Showing dose from image CT am 3mm
129.738 Gy
A
R
L
P
Z: -2.10 cm


Dose
21.00 Gy
21.0
15.00 Gy
10.00 Gy
5.00 Gy
1.0
1.00 Gy
A
R
L
P
Z: -3.60 cm


Dose
21.00 Gy
21.0
15.00 Gy
10.00 Gy
5.00 Gy
1.0
1.00 Gy
Showing dose from image CT am 3mm
129.738 Gy
A
R
L
P
Z: -2.10 cm



Published articles with toxicity results for focused therapies in prostate cancer

1st Author	Citation	Patient Number	Modality	Technique	Whole Gland Dose	Dose to Dominant Lesion
Aluwini	Radiat Oncol. 2013;8:84	50	SBRT	Integrated Boost	38Gy in 4#	49 Gy in 4#
Schild	OMICS J Radiol. 2014;3(4).	78	IMRT	Integrated Boost	77.4Gy in 43#	81 Gy in 43#
Wu	Asian J Androl. 2011;13(3): 499-504	120	EBRT + HiFU	Sequential Boost	65-70Gy	HiFU

Hypoxia as a target for focused dose escalation for prostate cancer

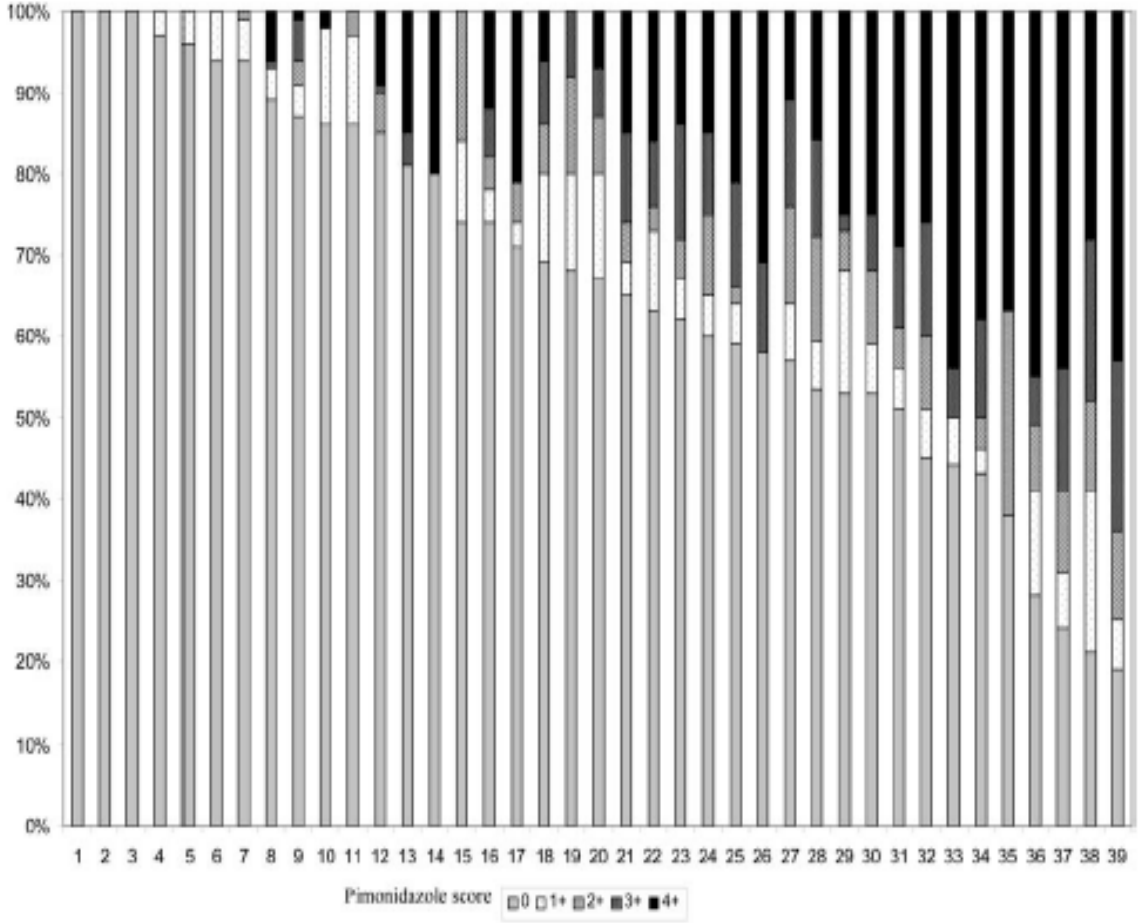
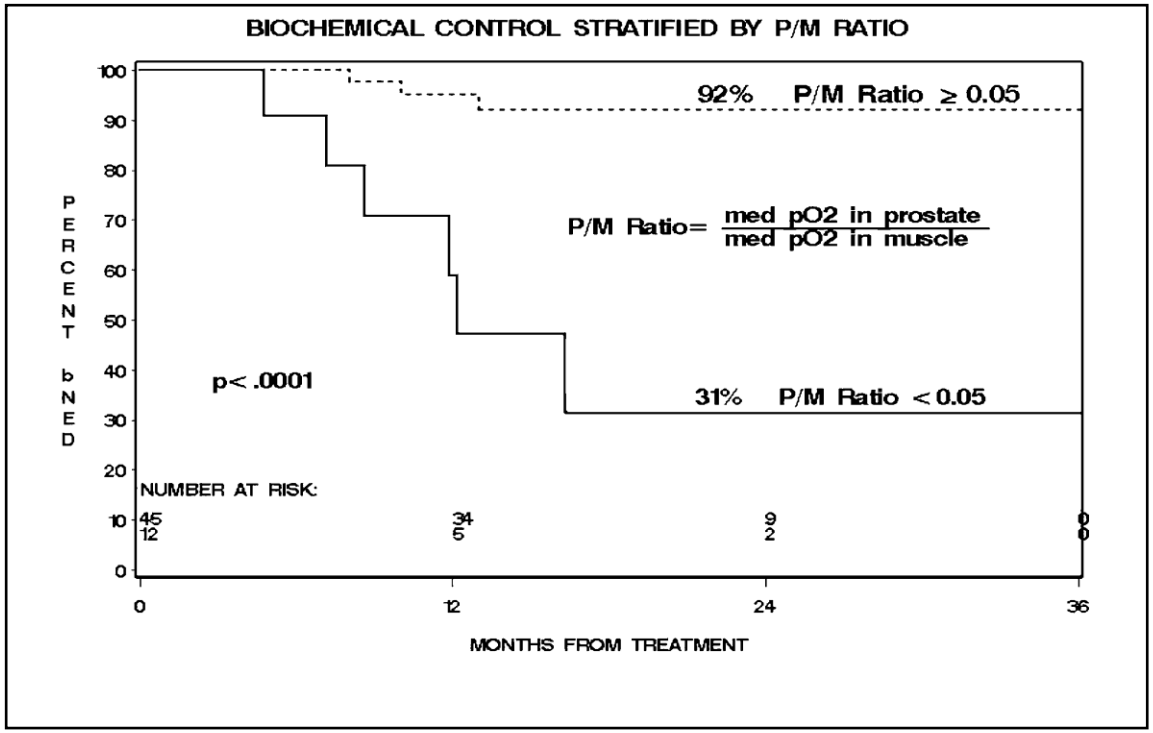


FIGURE 2. *Histogram of pO_2 measurements from prostate cancer nodule.*

Hypoxia in Prostate Cancer

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

Hypoxia predicts for poor outcomes in prostate cancer



Hypoxic ratio of prostate pO_2 / muscle pO_2 predicts biochemical failure after RT

Immunohistochemistry

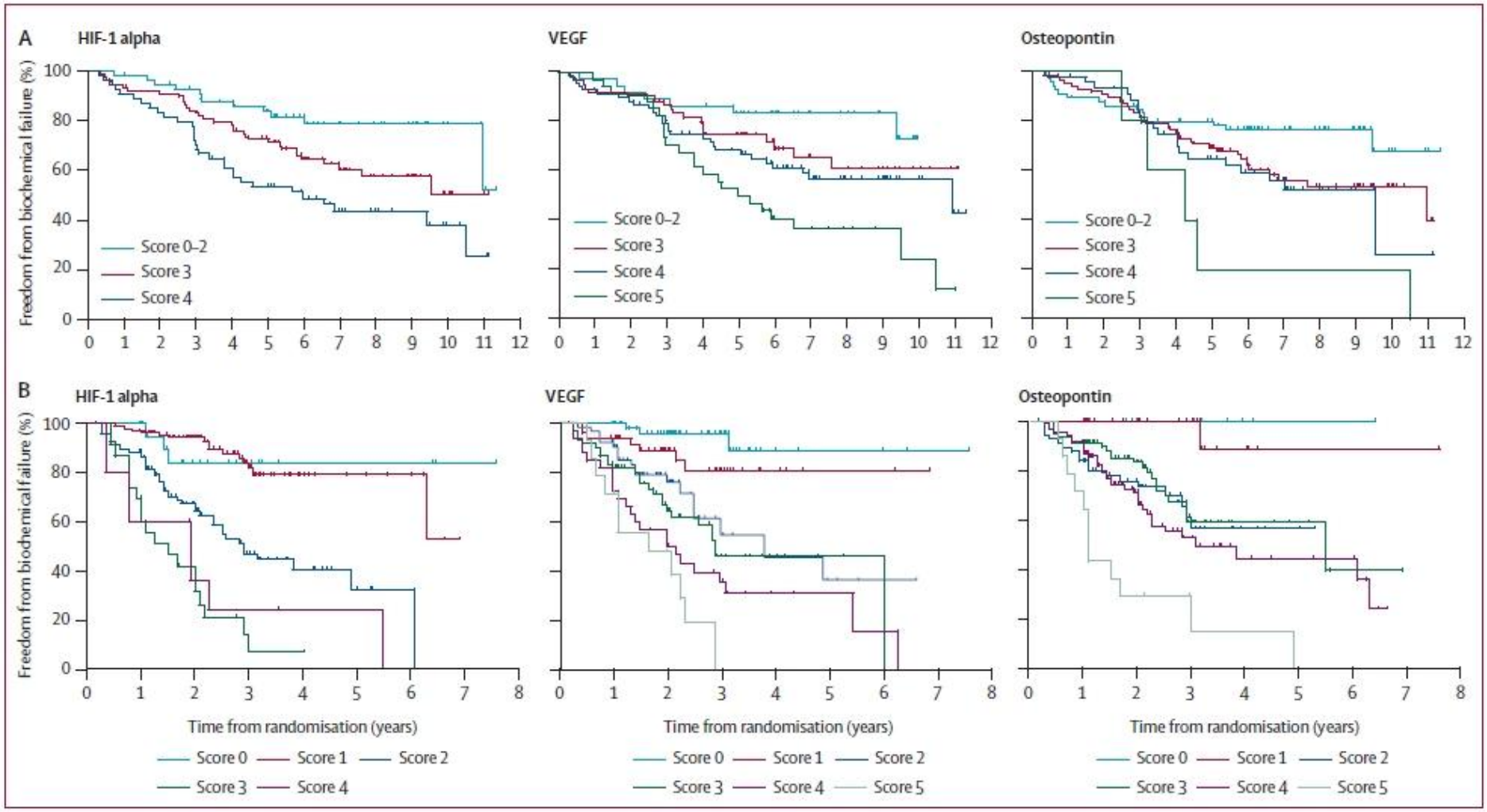
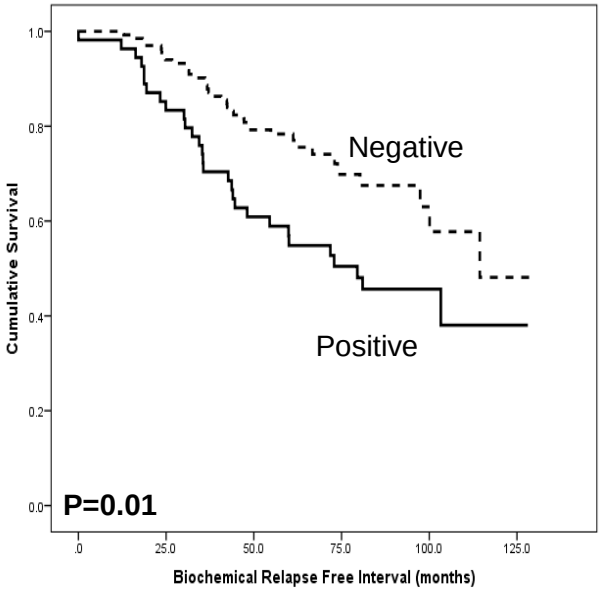
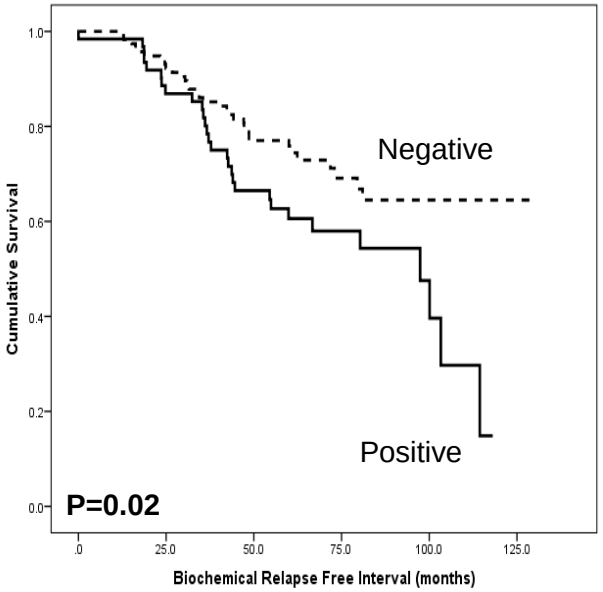


Figure 2: **Freedom from biochemical failure (%) against time (years) with respect to expression of intrinsic markers of tumour hypoxia and angiogenesis***
(A) Radiotherapy cohort. (B) Radical prostatectomy cohort. *Marker categories pooled where fewer than ten patients in one category.

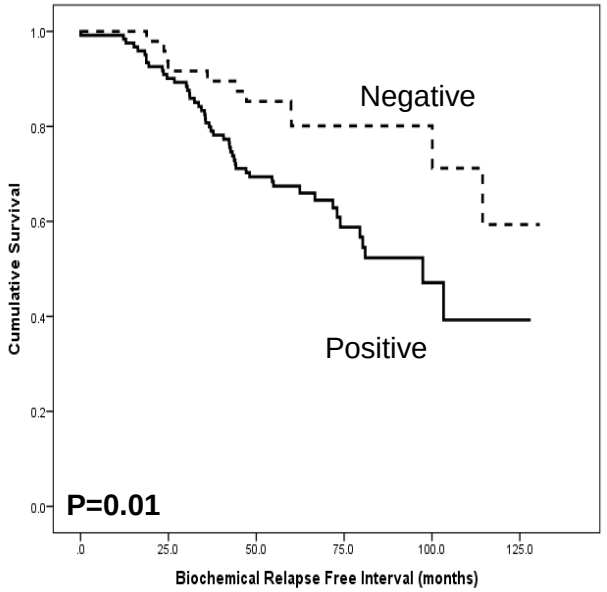
GLUT1



HIF1α



OPN



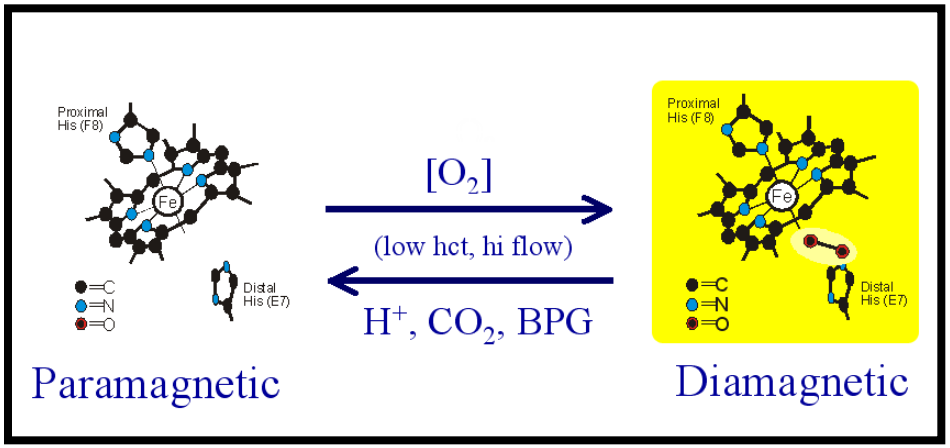
Intrinsic susceptibility weighted (BOLD) MRI

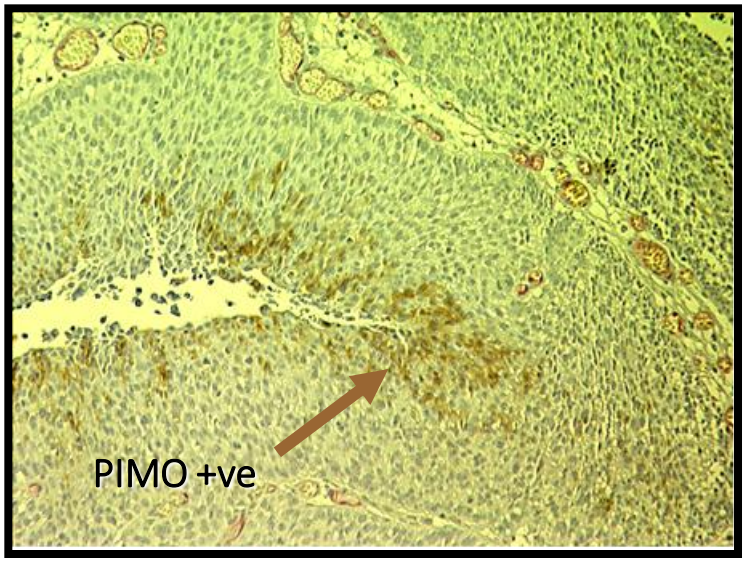
Primary source of BOLD image contrast is deoxyhaemoglobin

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 ($\uparrow R_2$*)

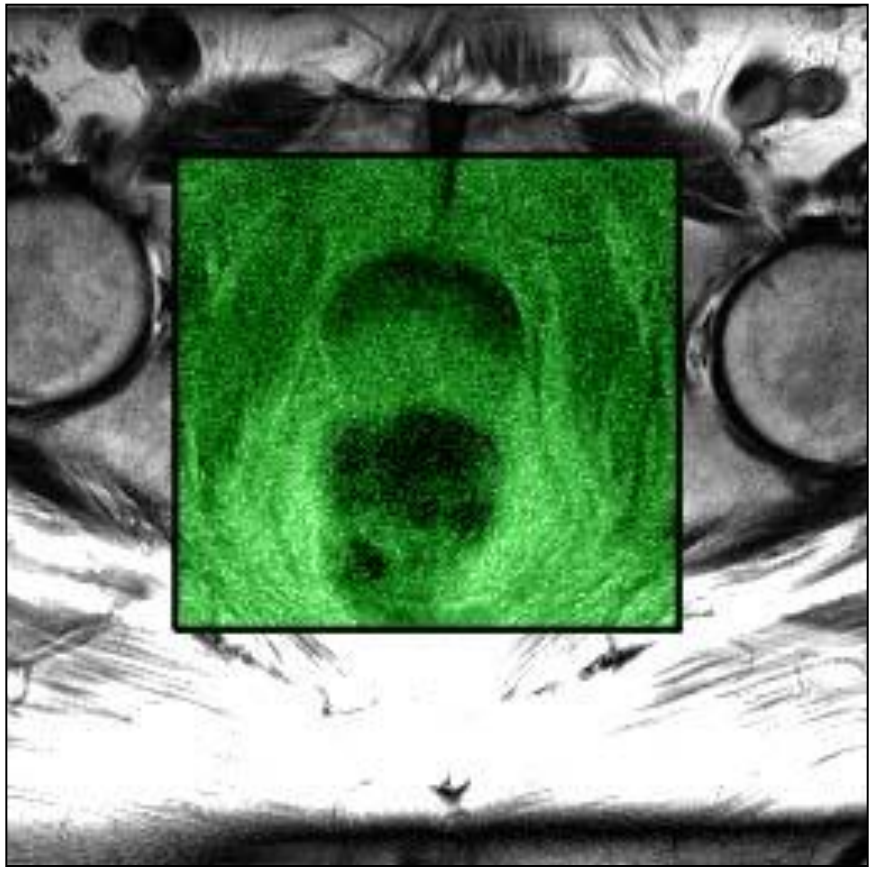
Oxygenation of Hb is proportional to blood pO_2 which is in equilibrium with tissue pO_2





BOLD-MRI ~ [deoxyhaemoglobin] ~ blood p_aO_2 ~ tissue pO_2

Example of BOLD MRI

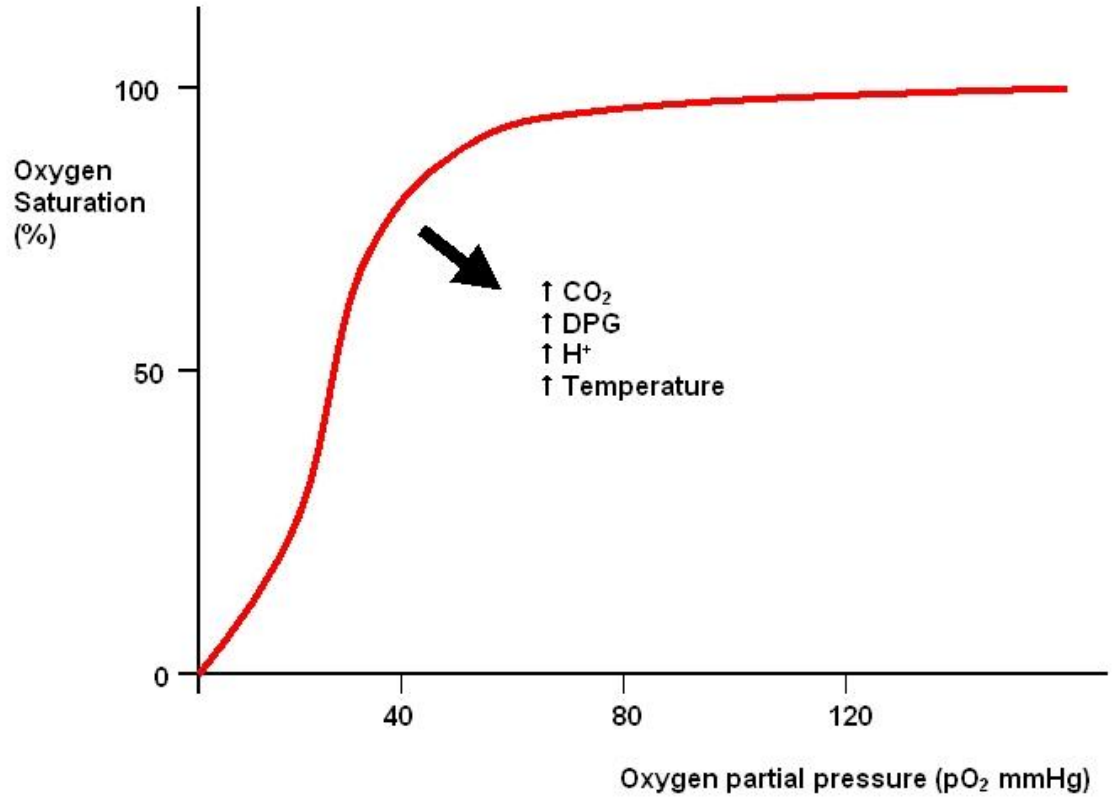


The ‘probe’ is in the wrong place!

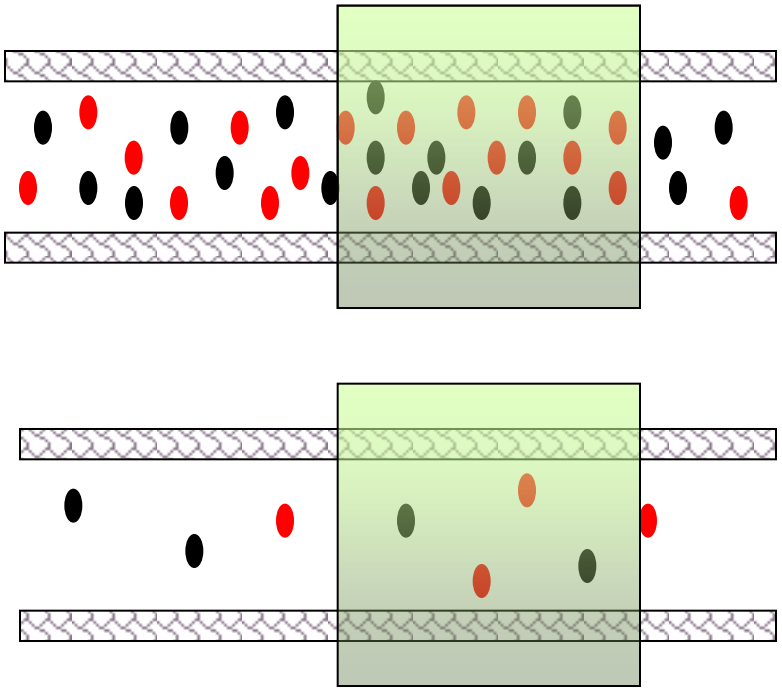
We are interested in the pO_2 in the immediate vicinity of tumour cells not the *intravascular* deoxyhaemoglobin concentration

However……

Deoxyhaemoglobin concentration ~ paO2 ~ tissue pO2



Blood Volume Dependency



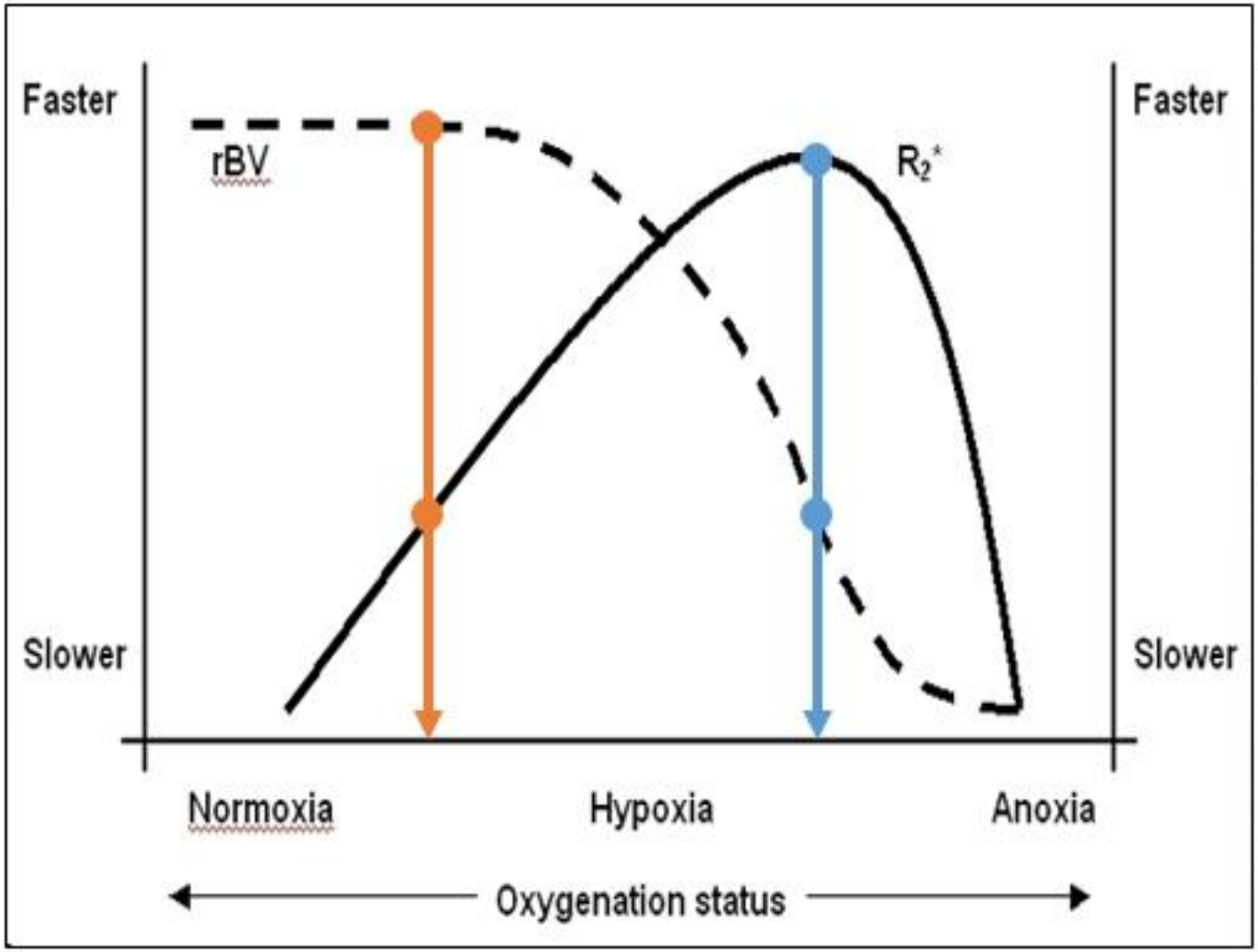
High Blood Volume

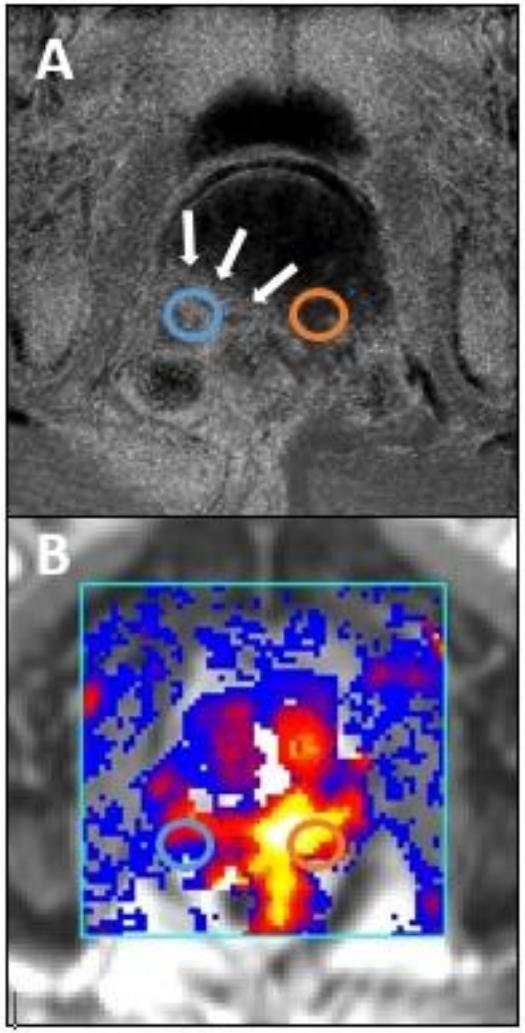
Low Blood Volume

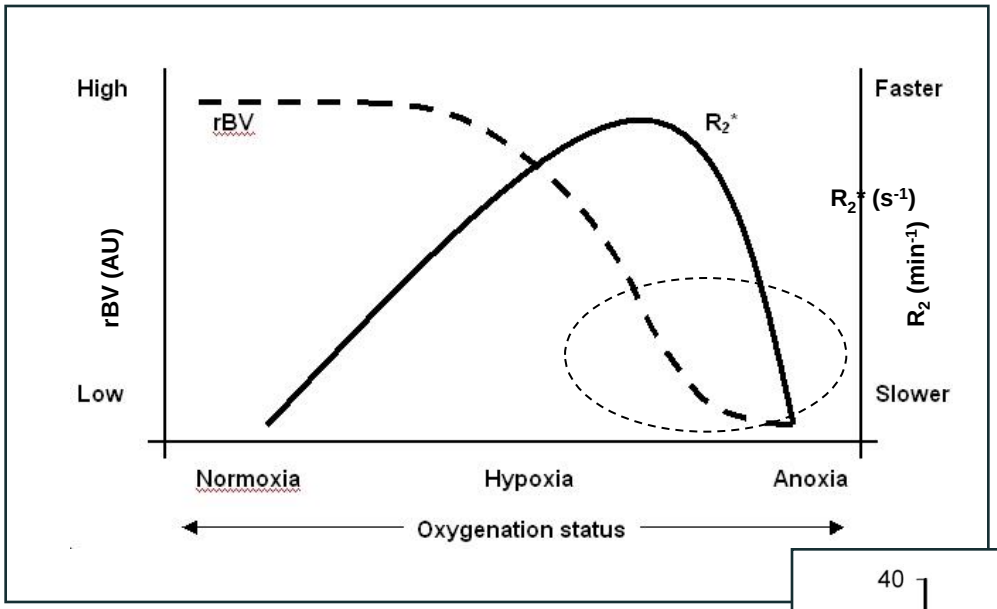
Oxyhemoglobin

Deoxyhemoglobin

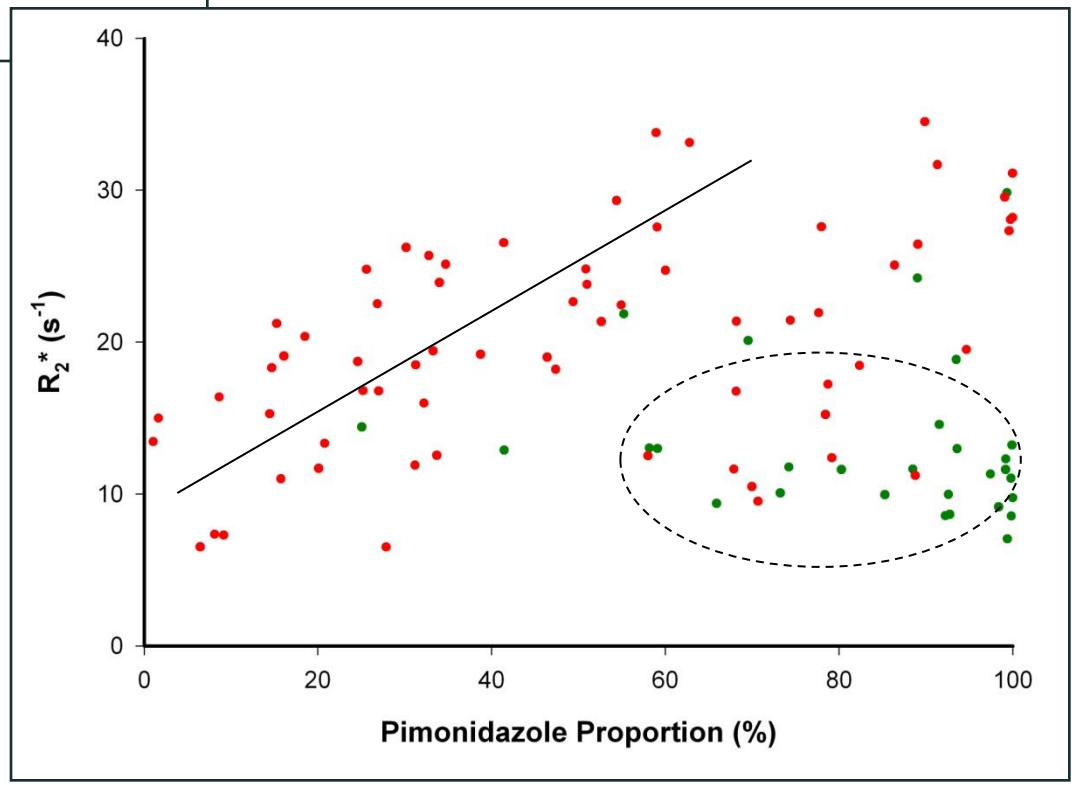
For BOLD-MRI to work, red blood cells have to be delivered to tissues







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