PROSTATE BRACHYTHERAPY
UK & Ireland Conference 2015

The future of brachytherapy is HDR

Dr Roberto Alonzi

Senior Lecturer and
Consultant in
Clinical Oncology

Mount Vernon Cancer Centre, UK

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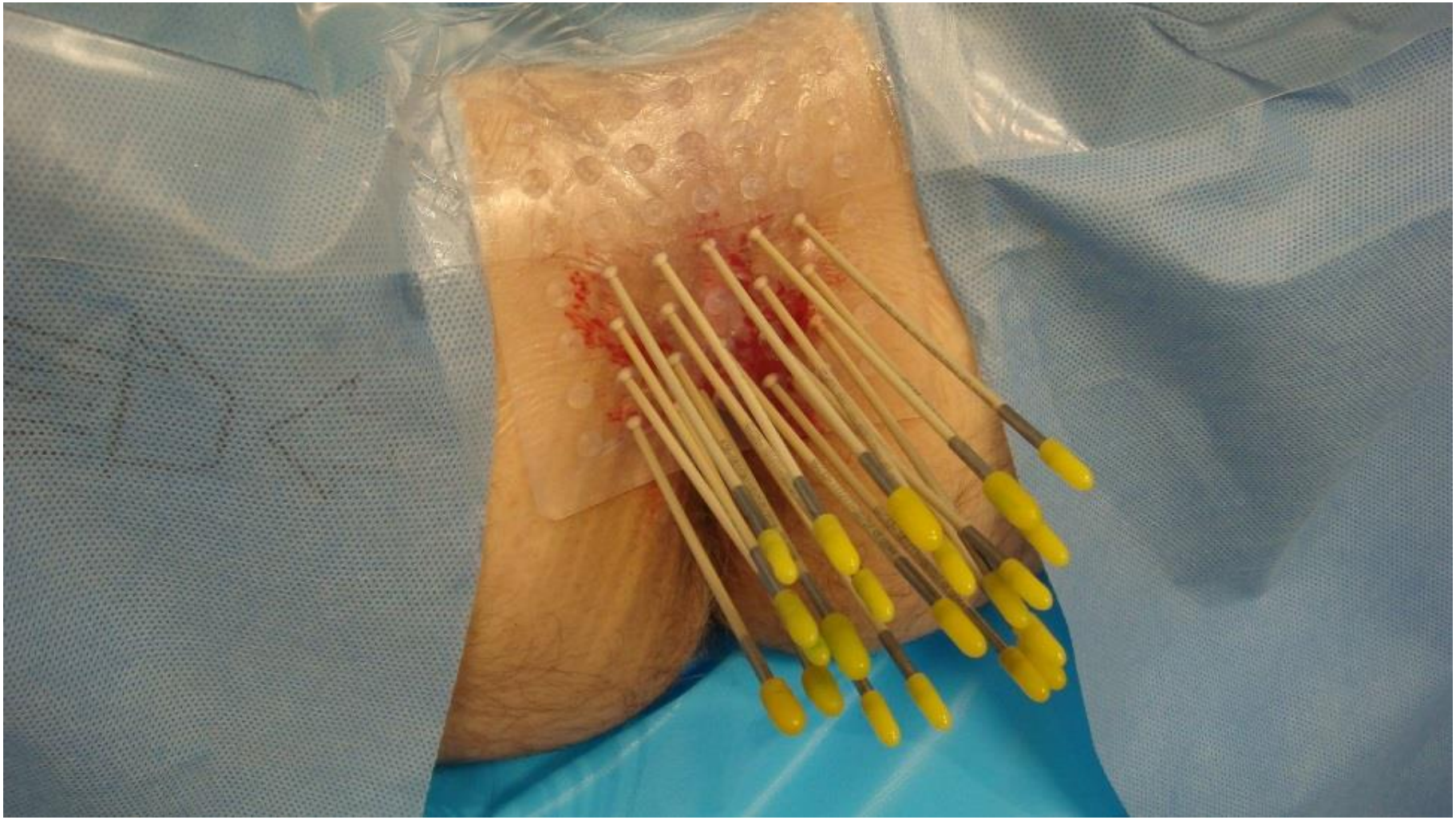
Overview

- 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

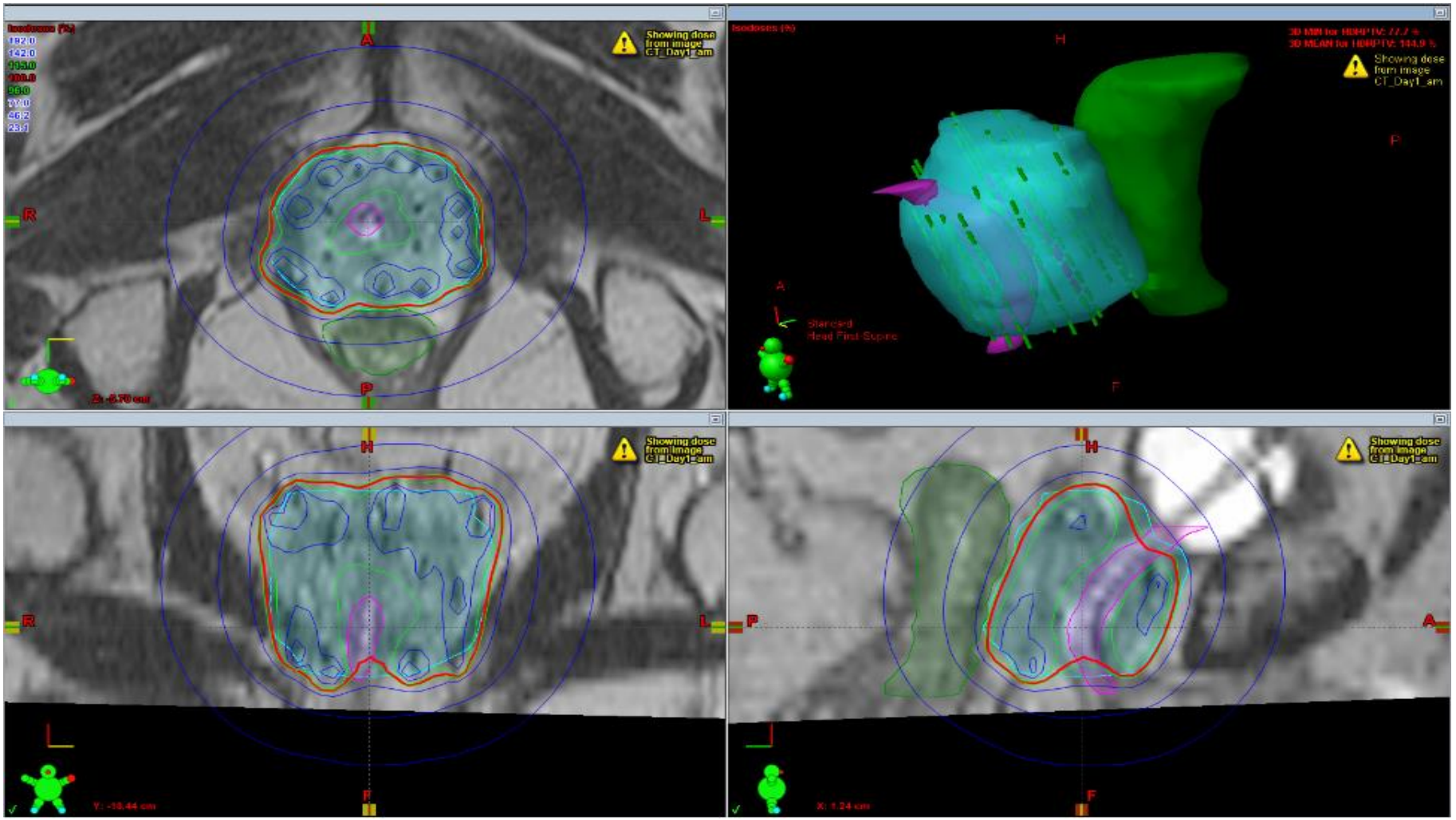
Brachytherapy Techniques

High Dose-Rate Brachytherapy

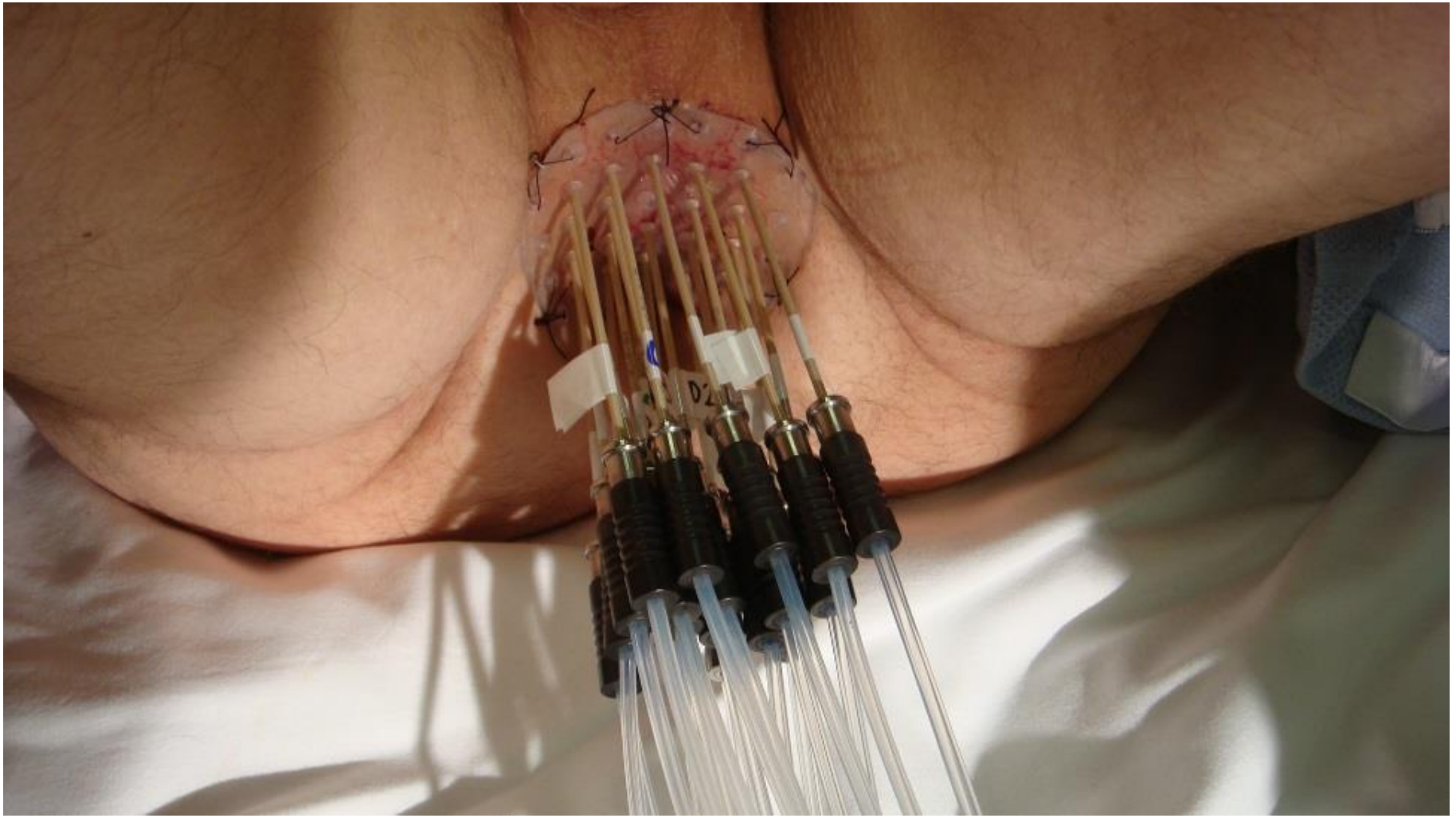
High Dose-Rate Brachytherapy



High Dose-Rate Brachytherapy



High Dose-Rate Brachytherapy



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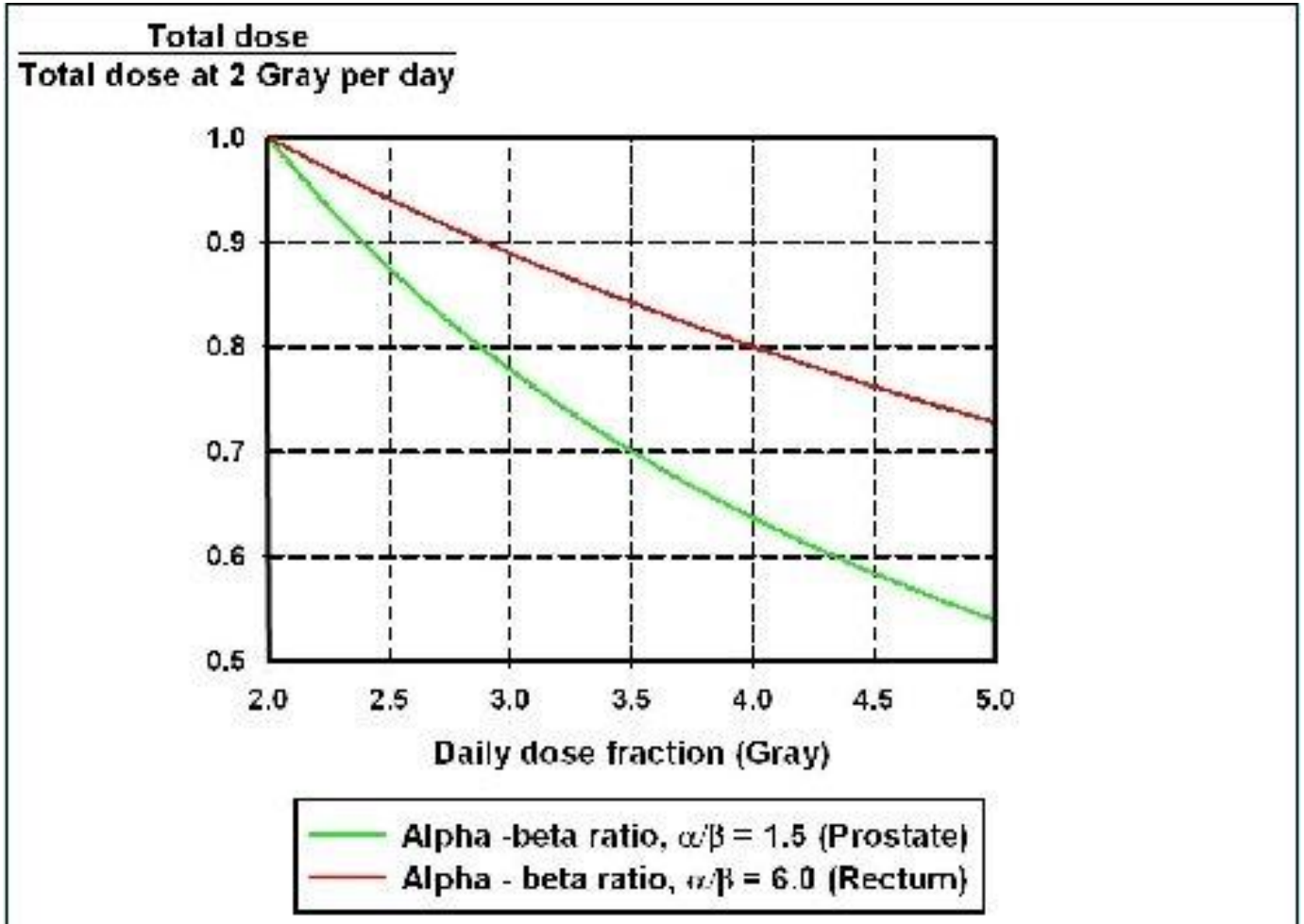
Biology

- 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



Iso-effect doses for different daily fractions and α/β ratios.

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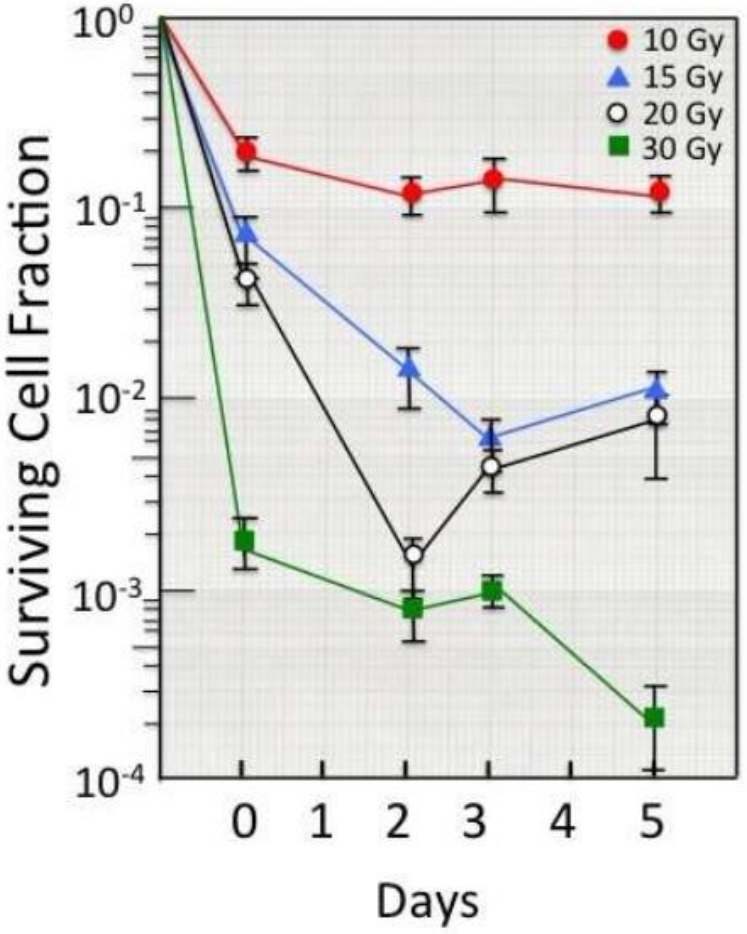
- **<u>Biology</u>**

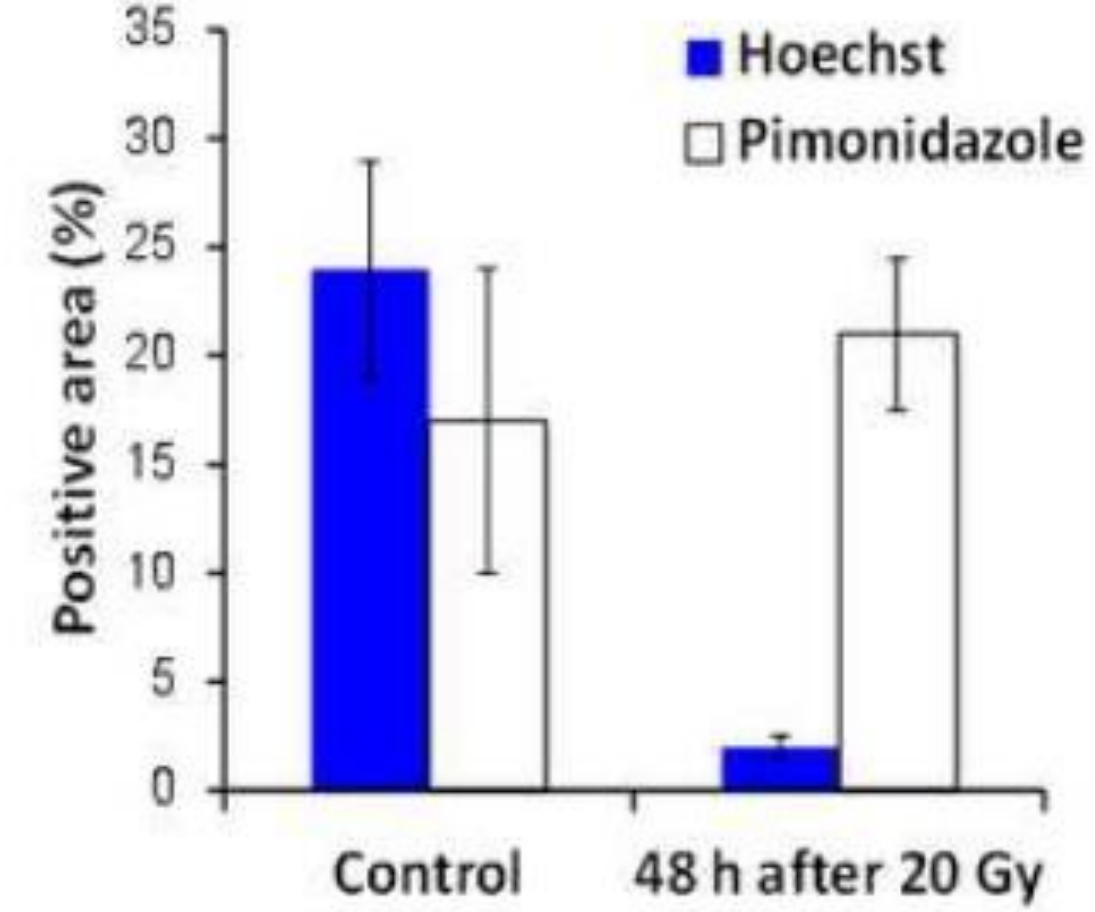
- Cell death induced by vascular damage at very high doses per fraction

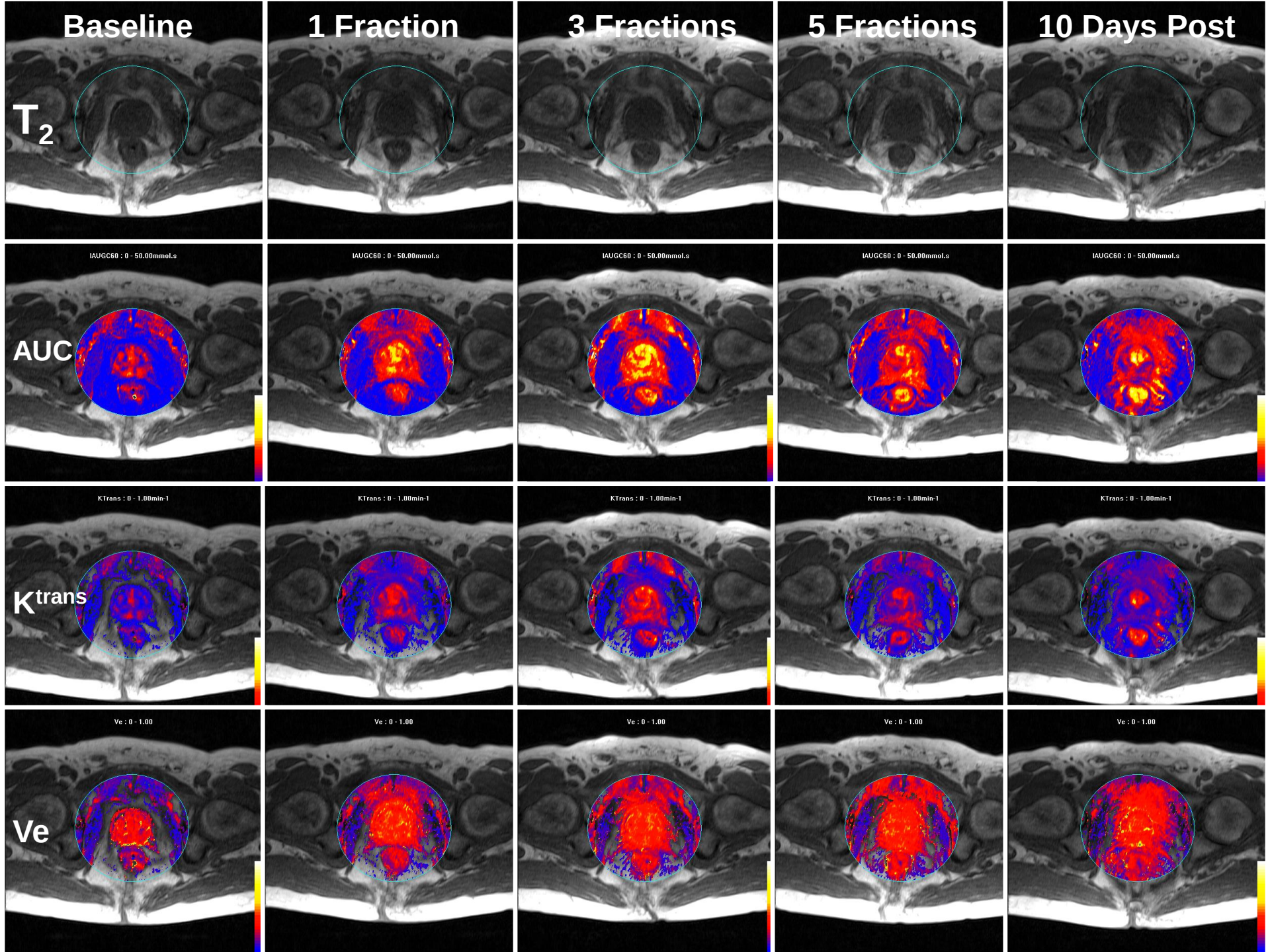
  - Wong et al. *Radiology* 1973;108:429–434.
  - Song et al. *Cancer Res* 1974;34:2344–2350.



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 tumors in situ for 1-5 days


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


Baseline
1 Fraction
3 Fractions
5 Fractions
10 Days Post
T2
AUC
Ktrans
Ve
IAUGC60 : 0 - 50.00mmol.s
KTrans : 0 - 1.00min-1
Ve : 0 - 1.00

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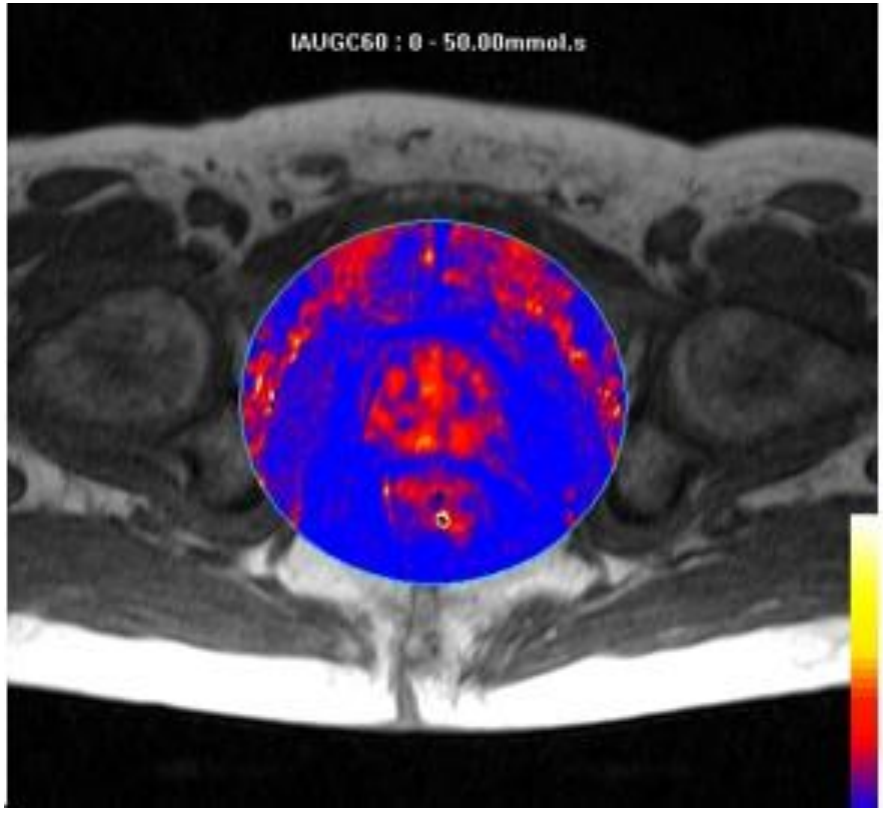

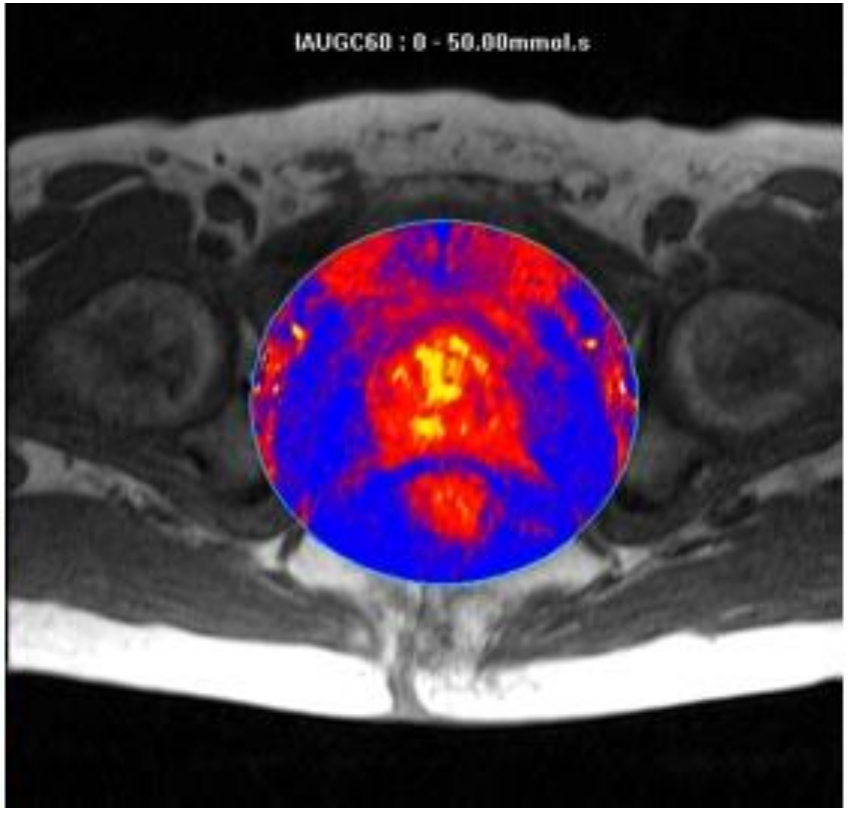

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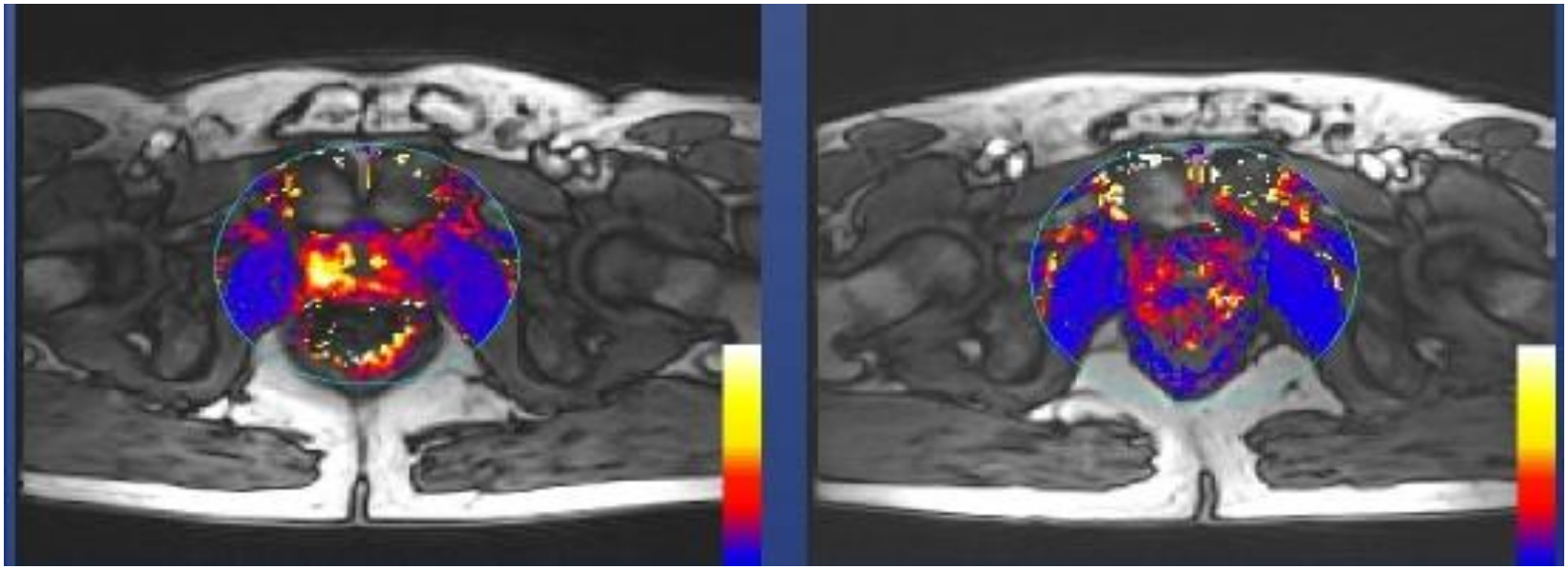

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Table 1 - Percentage change in each mpMRI parameter before and after catheter insertion into the prostate				
Patient	R_2^*	K^{trans}	$IAUGC_{60}$	ADC
1	-27.3	-49.7	-14.4	2.3
2	0	-35.6	-7.3	5.1
3	-2.9	-	-	3.8
4	27.0	-19.7	-0.3	-12.7
5	-25.9	-11.2	-19.4	3.4
6	-14.0	74.6	114.3	-4.2
Average	*-7.2*	*-8.4*	*14.6*	*-0.4*

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ELSEVIER

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]

[a] Cancer Centre, Mount Vernon Hospital, Northwood, UK; [b] St. James's Institute of Oncology, St. James's University Hospital, Leeds, UK

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- T1c-T3b
- PSA < 50ng/ml

- 55Gy in 20# control arm

v

- 37.75Gy in 13# plus HDR boost of 17Gy in 2#

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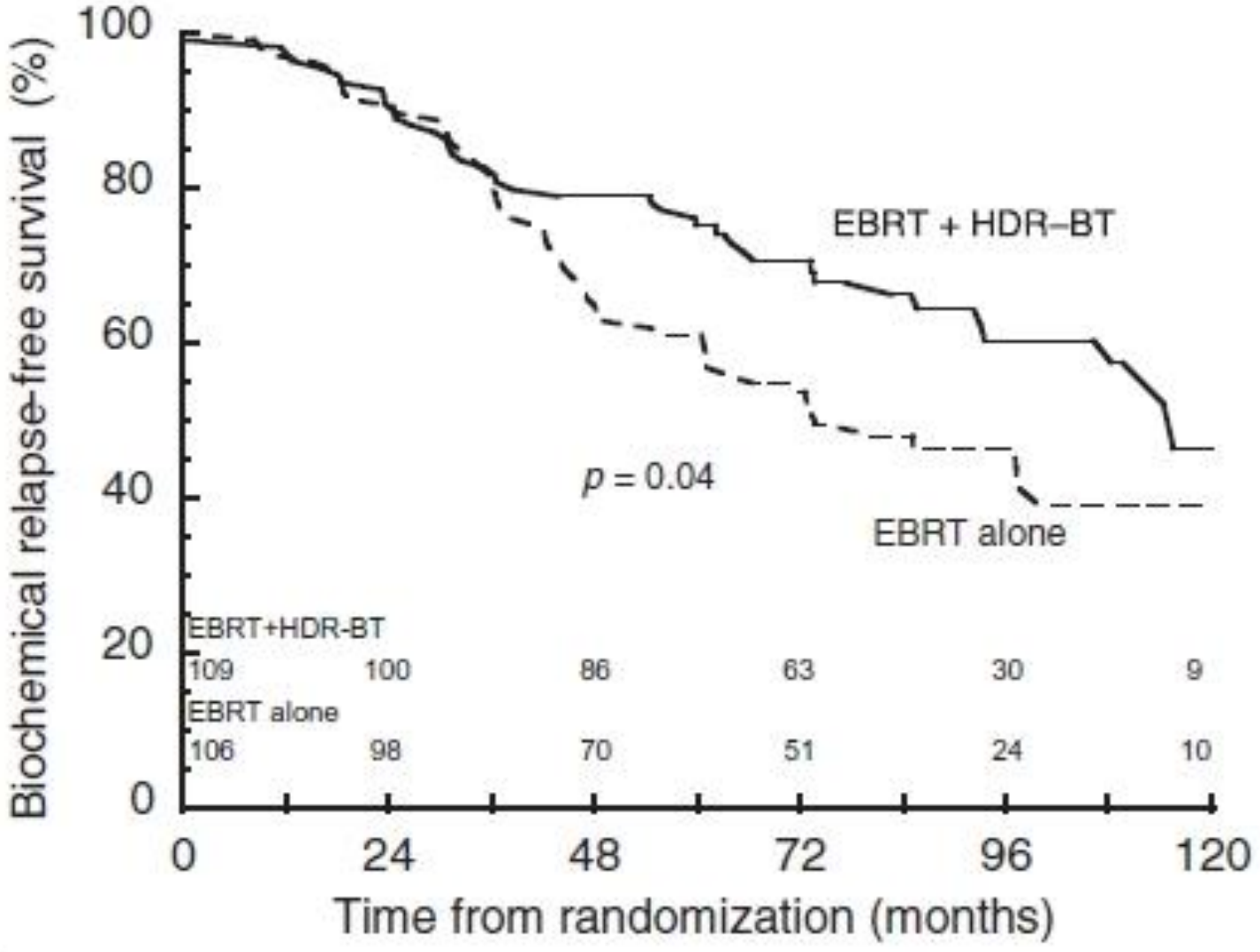

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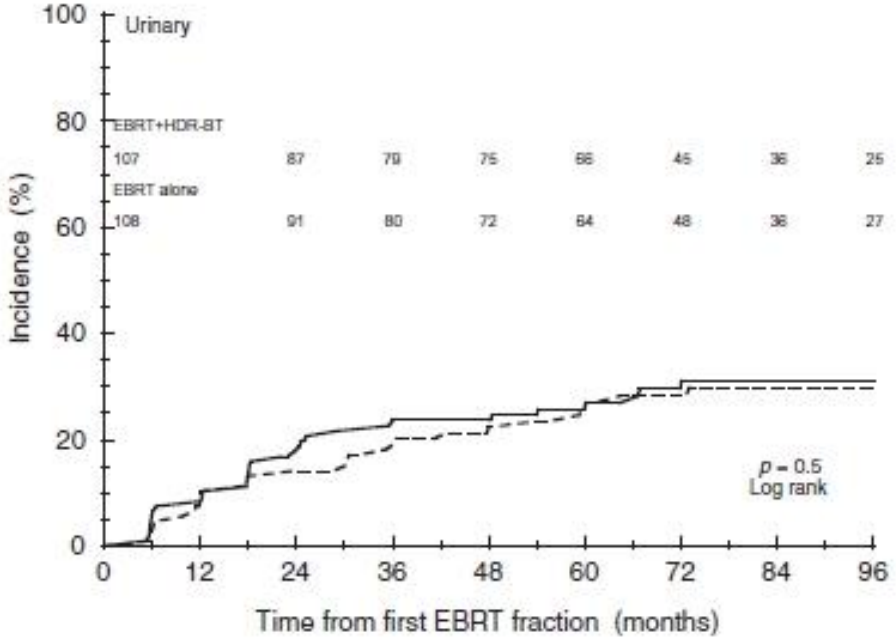
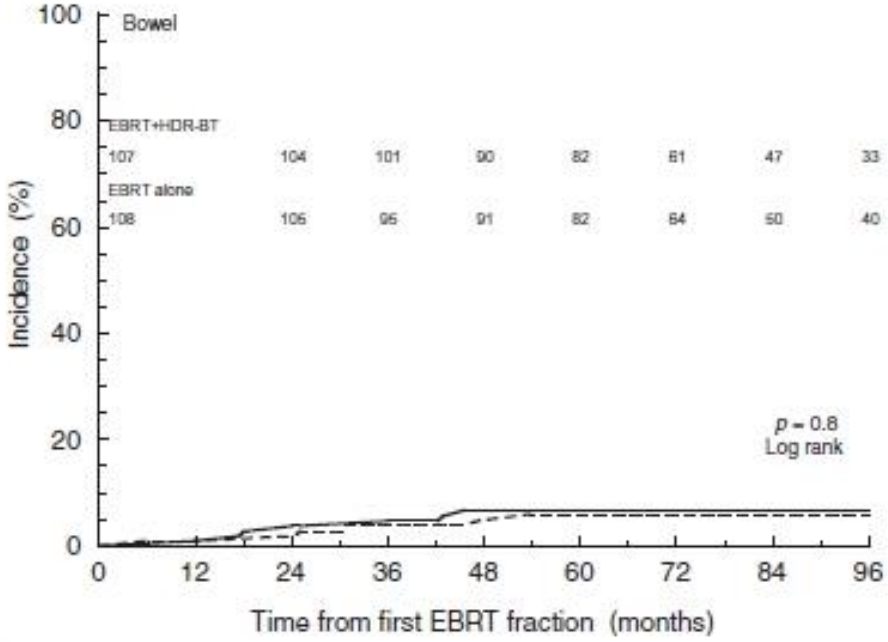
- Median time to relapse of 116 months v 74 months
- The 5-, 7- and 10-year estimates are:

  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	Analytical procedure	At 5 years	At 7 years	*p* value
bRFS				
Arm 1	K–M	61%	48%	0.04
Arm 2		75%	66%	
OS				
Arm 1	K–M	89%	88%	0.2
Arm 2		88%	81%	
Genito-urinary				
Arm 1	K–M	26%	30%	0.5
Arm 2		26%	31%	
Genito-urinary				
Arm 1	Prevalence	9%	4%	5 year: 1.0
Arm 2		8%	11%	7 year: 0.4
Urethral strictures				
Arm 1	K–M	2%	2%	0.1
Arm 2		6%	8%	
Gastro-intestinal				
Arm 1	K–M	6%	6%	0.8
Arm 2		7%	7%	
Gastro-intestinal				
Arm 1	Prevalence	0%	2%	7 year: 1
Arm 2		0%	0%	

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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

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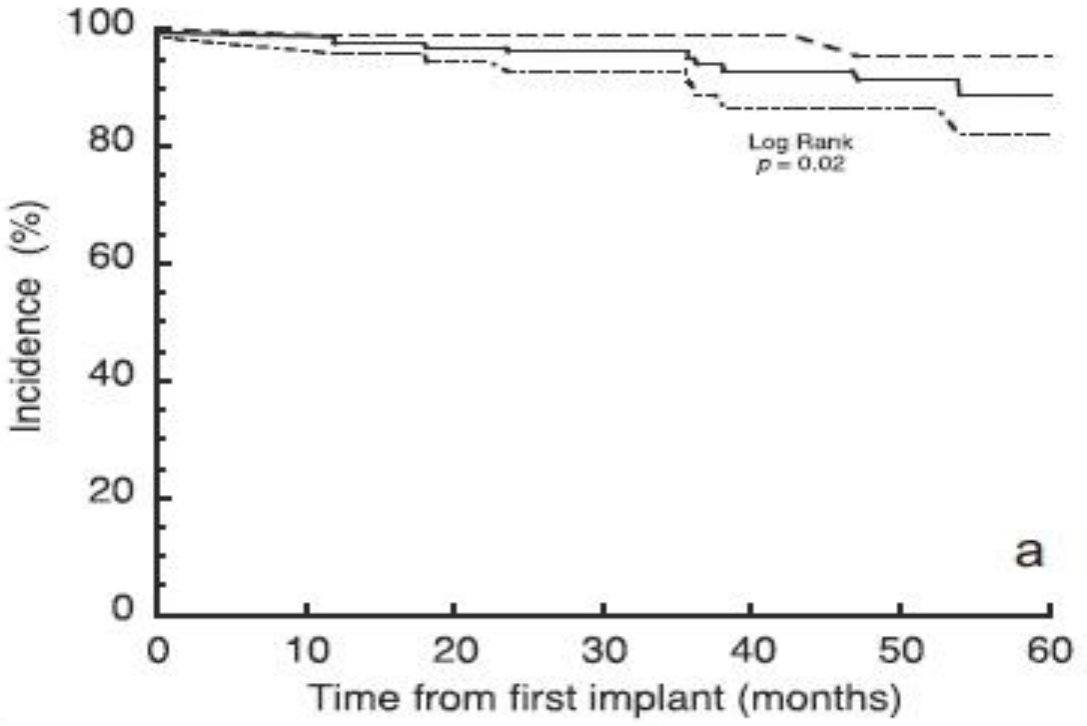
High Dose-Rate Brachytherapy - Monotherapy



227 Patients

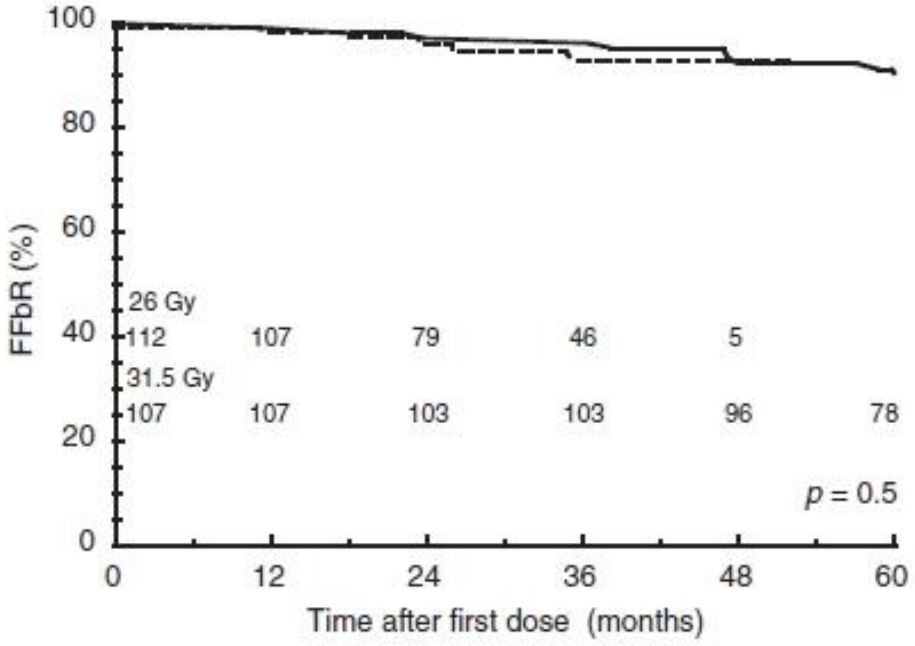
3-year DFS:

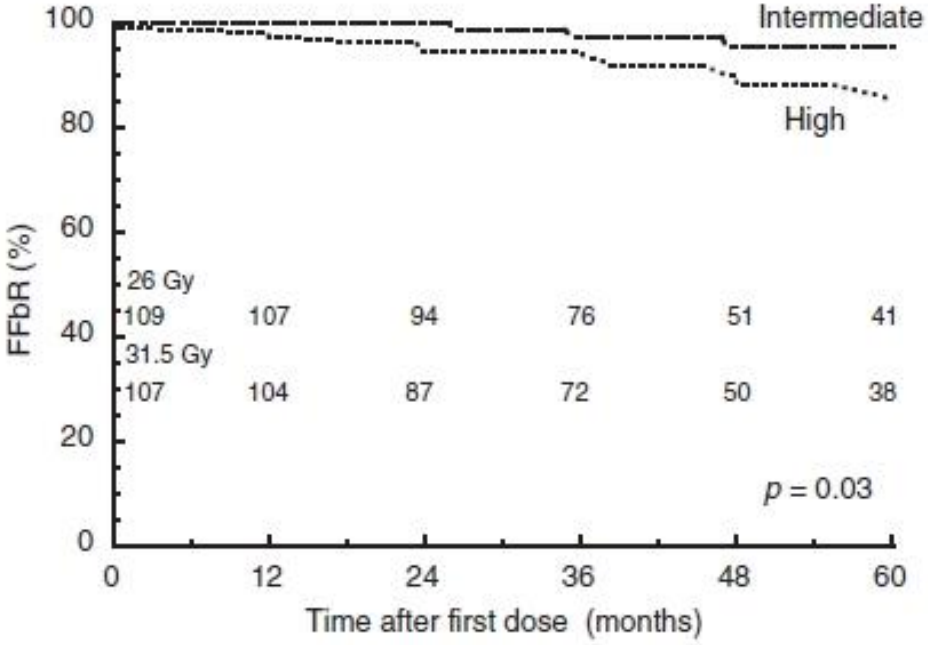
Intermediate Risk = 99%
High Risk = 91%

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





	Dose	[a]K–M estimate (%)	[b]p	Prevalence	[b]p
Urinary					
Grade ⩾ 1	26 Gy	24	<0.001	8% (4/52)	0.2
	31.5 Gy	48		16% (15/91)	
Grade ⩾ 2	26 Gy	10	<0.001	0	0.3
	31.5 Gy	32		4% (4/91)	
Grade 3	26 Gy	2	0.01	0	1
	31.5 Gy	11		1% (1/91)	
IPSS					
Scores ⩾ 8	26 Gy	56	0.6	25% (13/52)	1
	31.5 Gy	52		24% (22/90)	
Scores 21–35	26 Gy	8	0.03	6% (3/52)	0.4
	31.5 Gy	17		2% (2/90)	
Bowel					
Grade ⩾ 1	26 Gy	21	0.01	11% (6/53)	1
	31.5 Gy	42		12% (11/92)	
Grade ⩾ 2	26 Gy	3	0.6	4% (2/53)	0.6
	31.5 Gy	5		1% (1/92)	
Grade 3	26 Gy	0	0.3	0	
	31.5 Gy	1		0	

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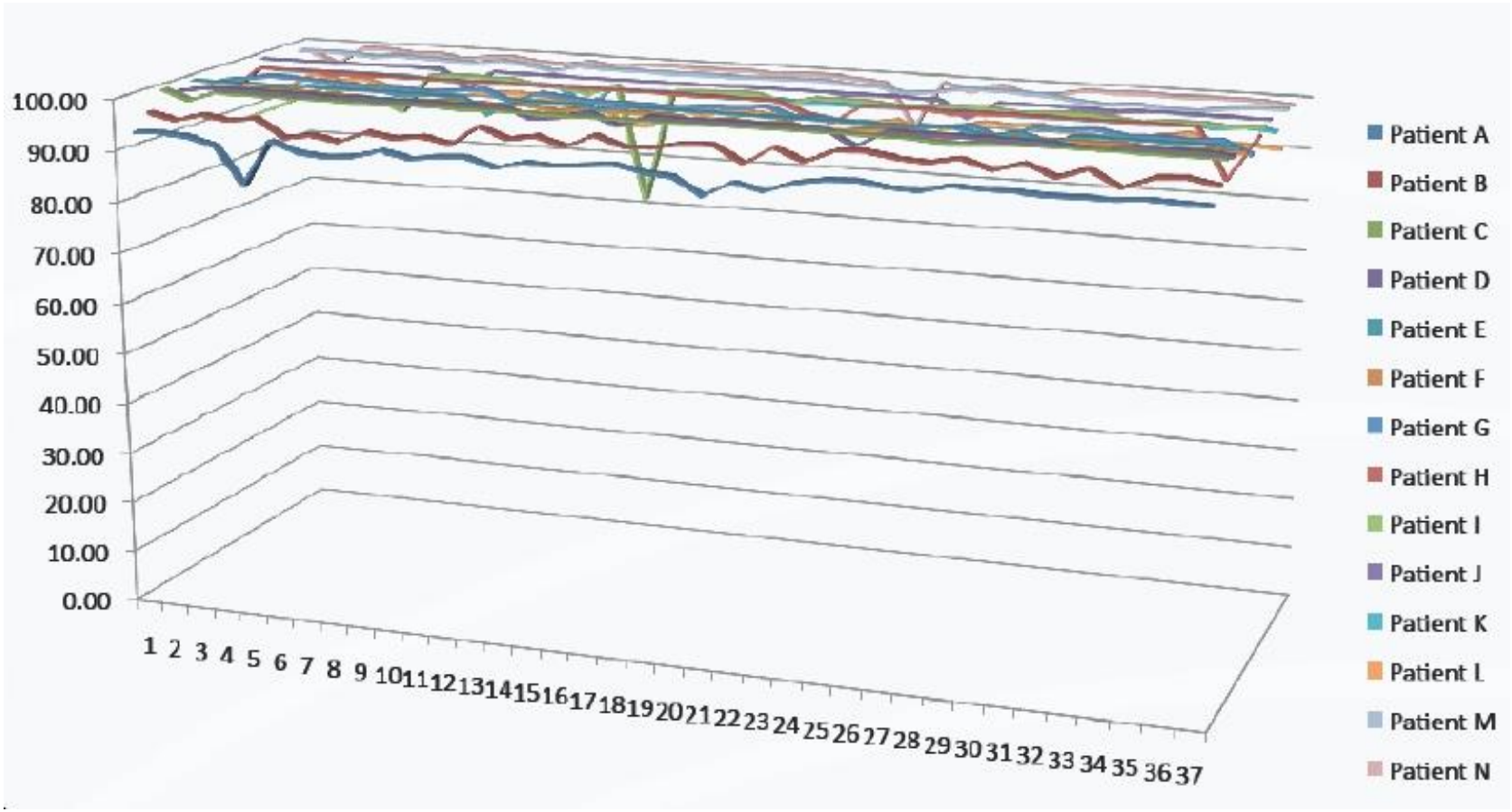
- Geographical Miss



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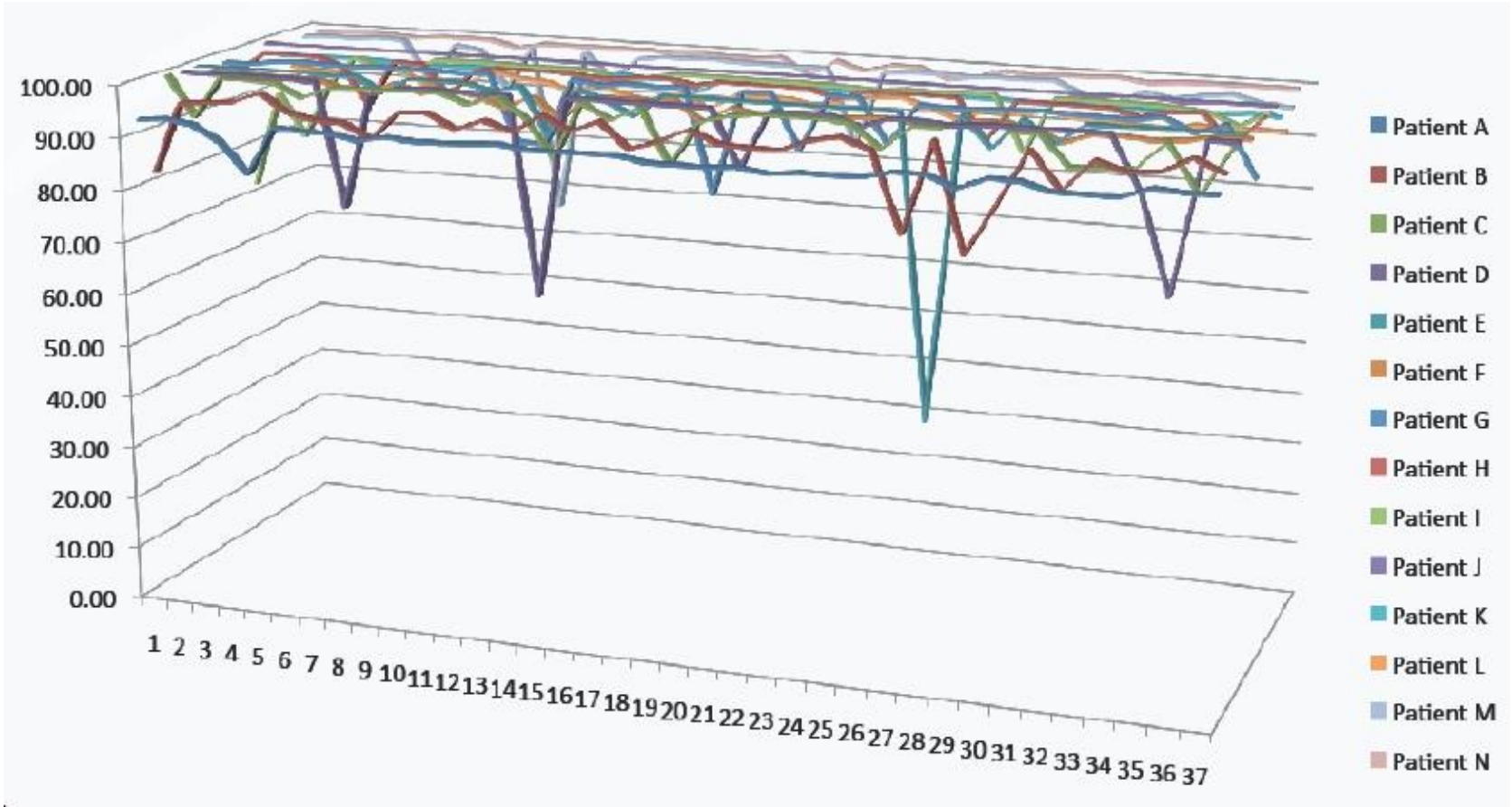
- Geographical Miss



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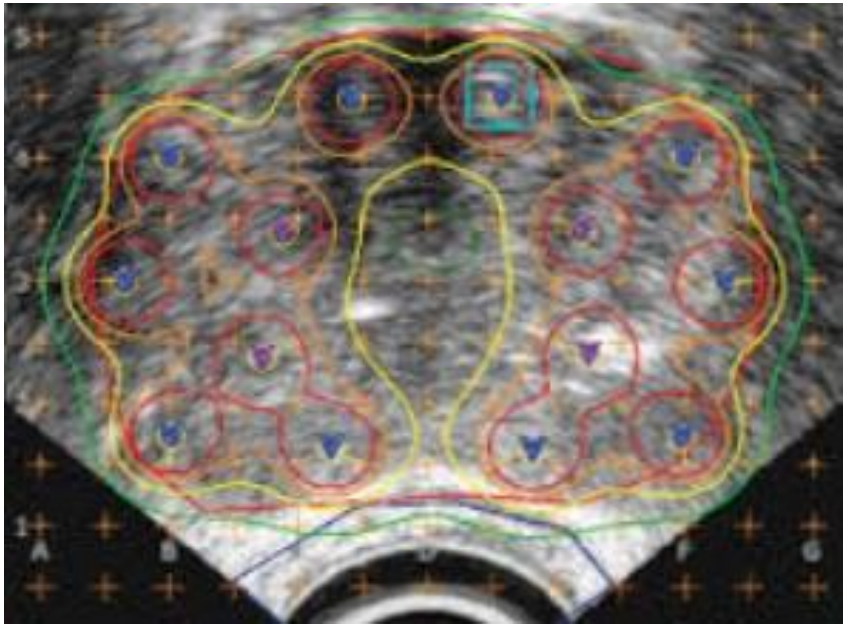
- Geographical Miss



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Ability to treat large prostate glands

Le et al. Int J Radiat Oncol Biol Phys. 2013 Oct 1;87(2):270-4

- 164 patients
- November 2003 to July 2009

- Median prostate volume = 60cc (15-208 cc)

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Table 2. Evidence of biochemical disease after high dose rate brachytherapy alone

Volume	Patients on ADT	*p* value	ADT mean duration	bNED %	*p* value	Mean TTF
≤ median	73	0.01	12.1	80	0.0042	71
> median	59		15.3	93		70

Abbreviations: ADT = androgen deprivation therapy, bNED = no evidence of biochemical disease, TTF = time to failure
Time measured in months

Figure 2

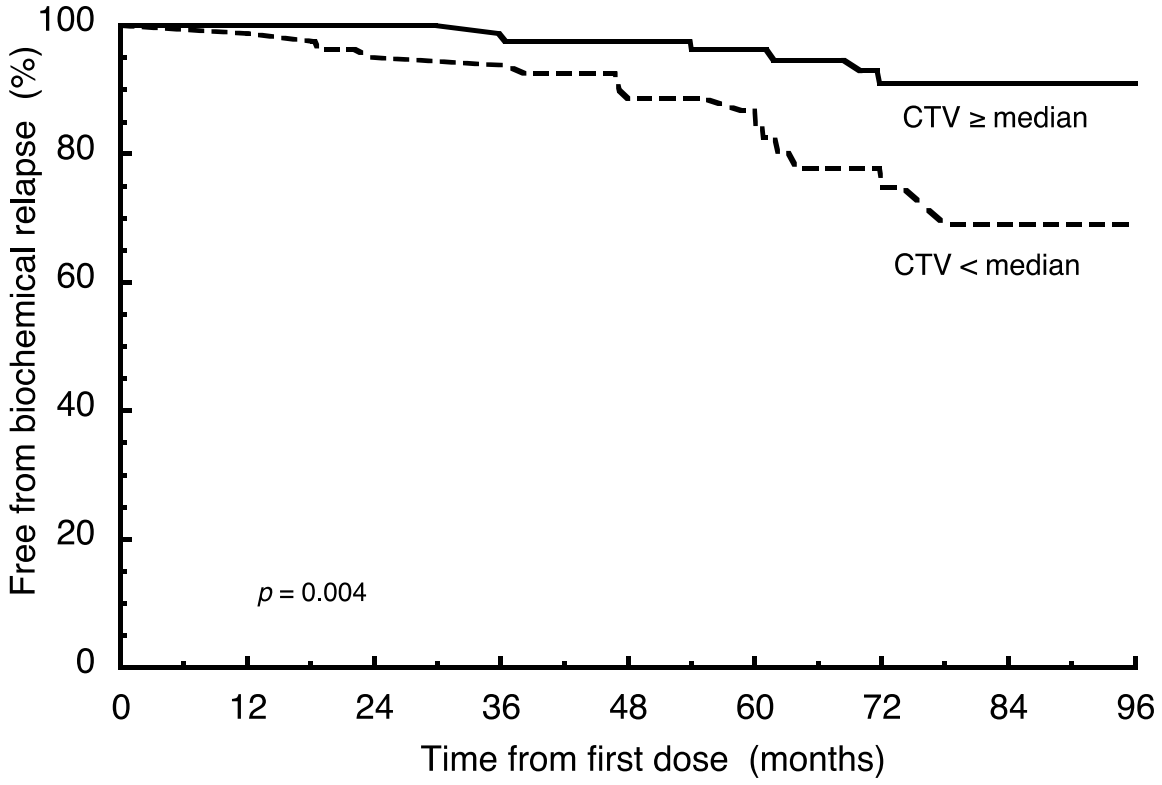
100
80
60
40
20
0
Free from biochemical relapse (%)
CTV ≥ median
CTV < median
p = 0.004
0
12
24
36
48
60
72
84
96
Time from first dose (months)

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

Volume	n	IPSS 8 - 19	IPSS ≥ 20	Strictures
≤ median	82	49 (30)	13 (8)	6 (4)
> median	82	52 (32)	18 (11)	7 (4)

Abbreviations: IPSS = International Prostate Symptom Score
Numbers in parentheses are percentages

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Focussed dose escalation

- Rationale
- Examples

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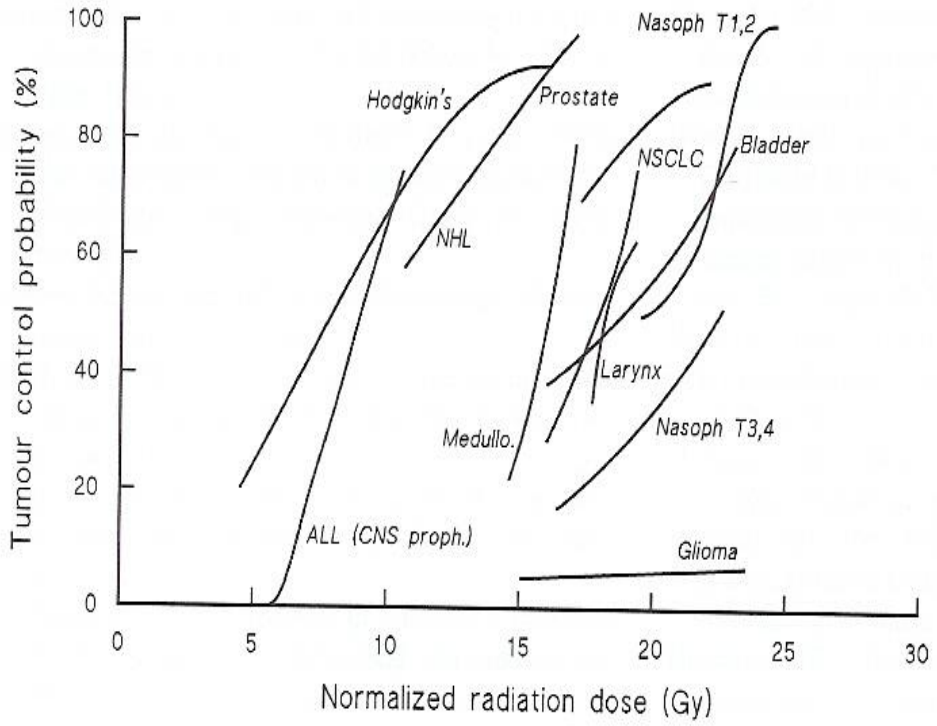
Dose Response Relationship in Prostate Cancer



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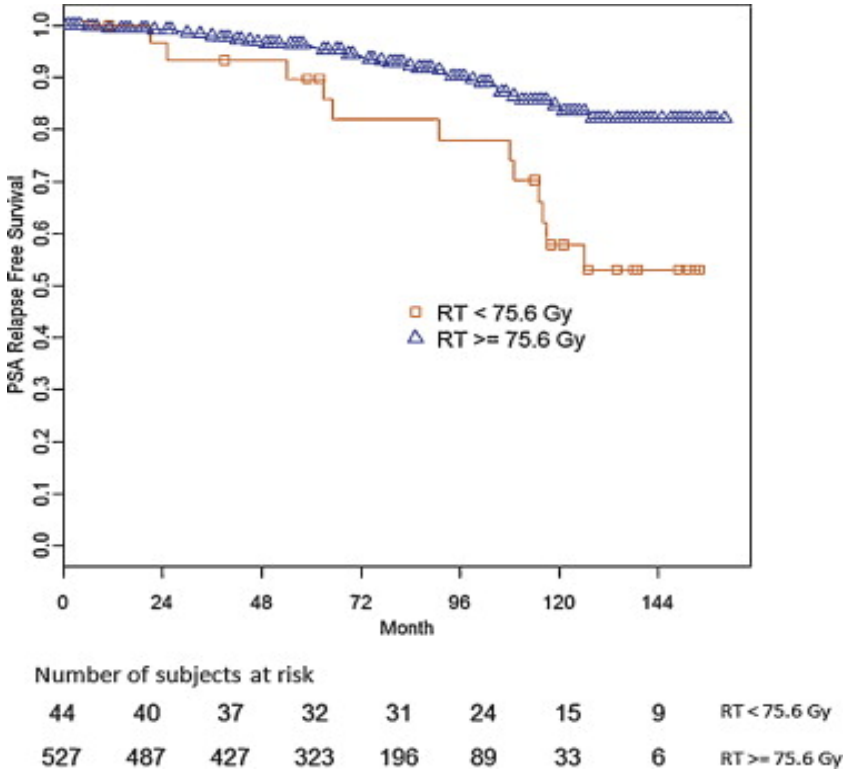
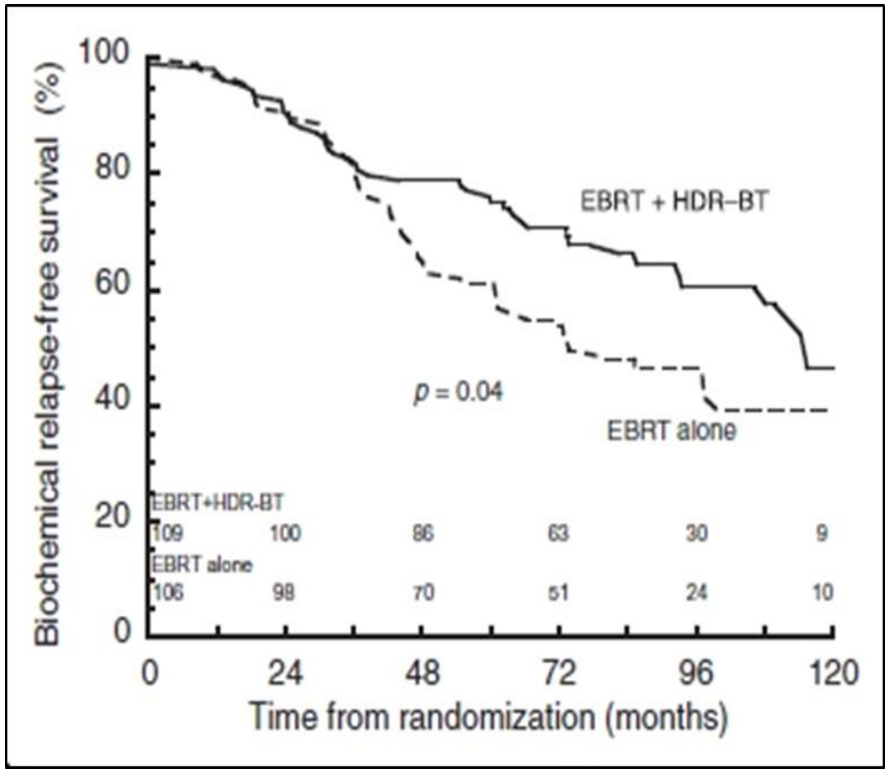


Ten-year prostate-specific antigen (PSA) relapse–free survival for low-risk patients was 84% and 70% for patients treated with ≥75.6Gy and with lower doses, respectively (p=0.04).RT=radiotherapy. Zelefsky et al, 2011



Kaplan–Meier survival curves for patients free of biochemical and or clinical
Failure. Solid line: EBRTplus HDR brachytherapy boost. Dashed line: EBRT alone. Hoskin et al 2012

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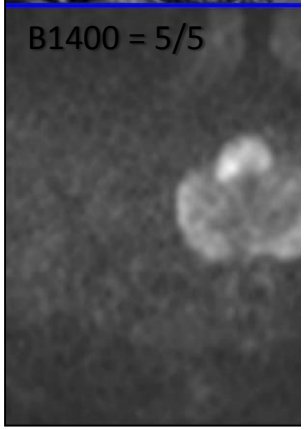
Detecting disease with T2W-MRI

- 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

*Langer DL, et al. Radiology 2008; 249:900-908
**Wang L. et al. Radiology 2008; 246:168-176
**Peng Y et al. Radiology 2013 doi:10.1148/radiol.13121454

61 yrs; cT1; TRUS Gl 3+4; PSA 8.7 ng/ml (intermediate risk)

Partins table: organ confined 59%; EPE 34%; SVI 6%; LN 1%)

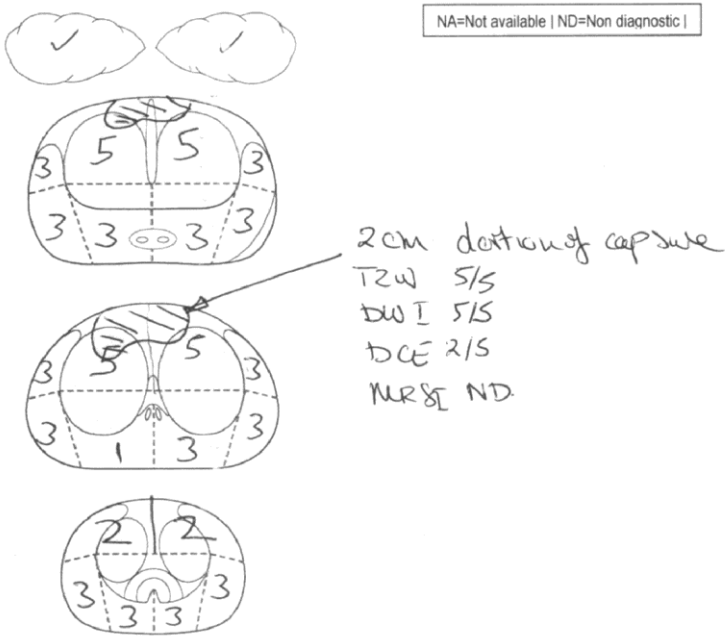


T2W ☑ DW-MRI ☑ MRSI ☑ DCE-MRI ☑

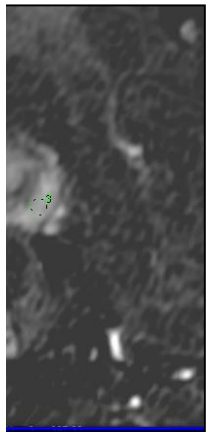
GLAND SIZE: 5.1 x 4 x 4 cms (1.5T) / 3T

Detection ☑ Staging ☐ Localisation ☐ Surveillance ☐ Response/Relapse ☐

NA=Not available | ND=Non diagnostic |



Clinically significant disease - highly unlikely (1) ↔ Clinically significant disease - unlikely (2) ↔ indeterminate ↔ Clinically significant cancer likely (4) ↔ Clinically significant disease - highly likely (5)



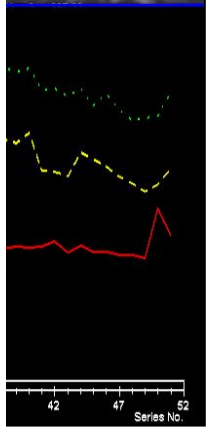


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Figure 1. *Sagittal View, Transperineal Template Biopsy*

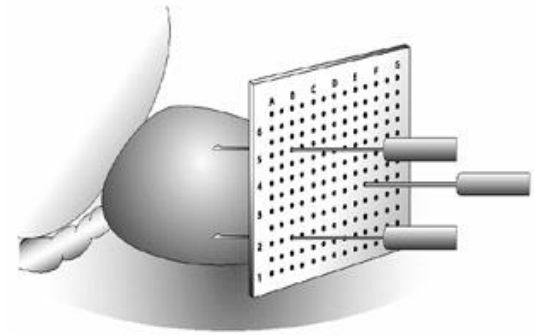
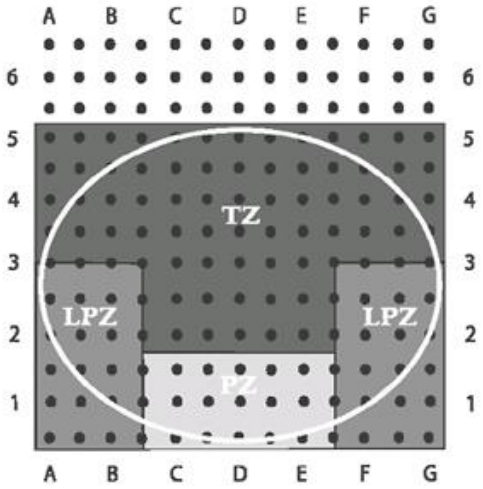
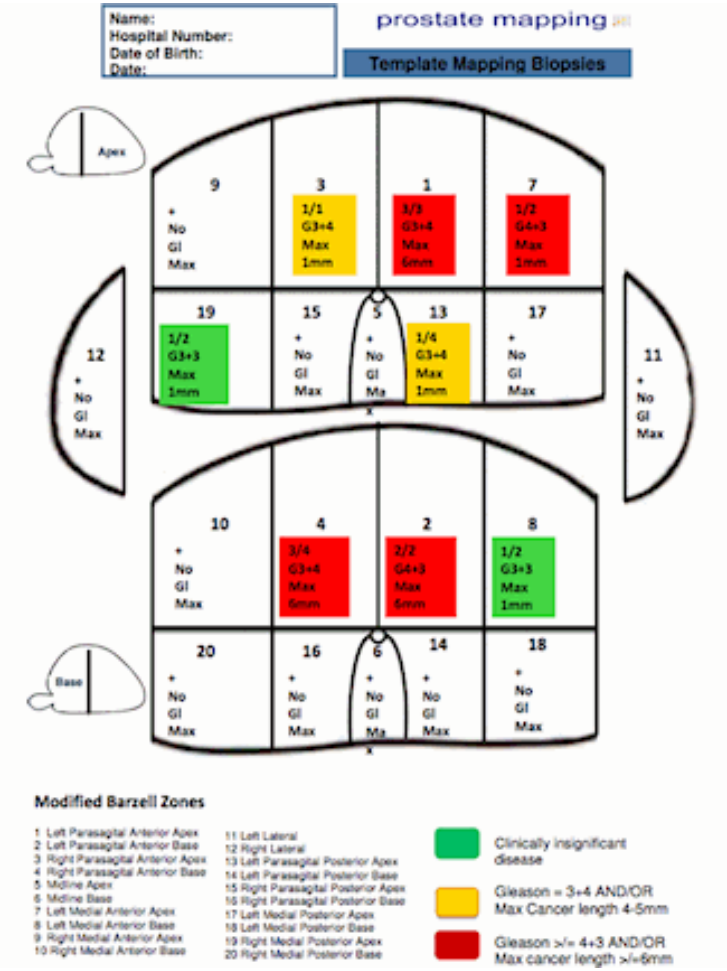


Figure 2. *Template Grid Illustration, Mid-Prostate Transverse Plane. (TZ, Transition Zone. LPZ, Lateral Peripheral Zone. PZ, Peripheral Zone.)*





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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

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Workflow for focussed dose escalation

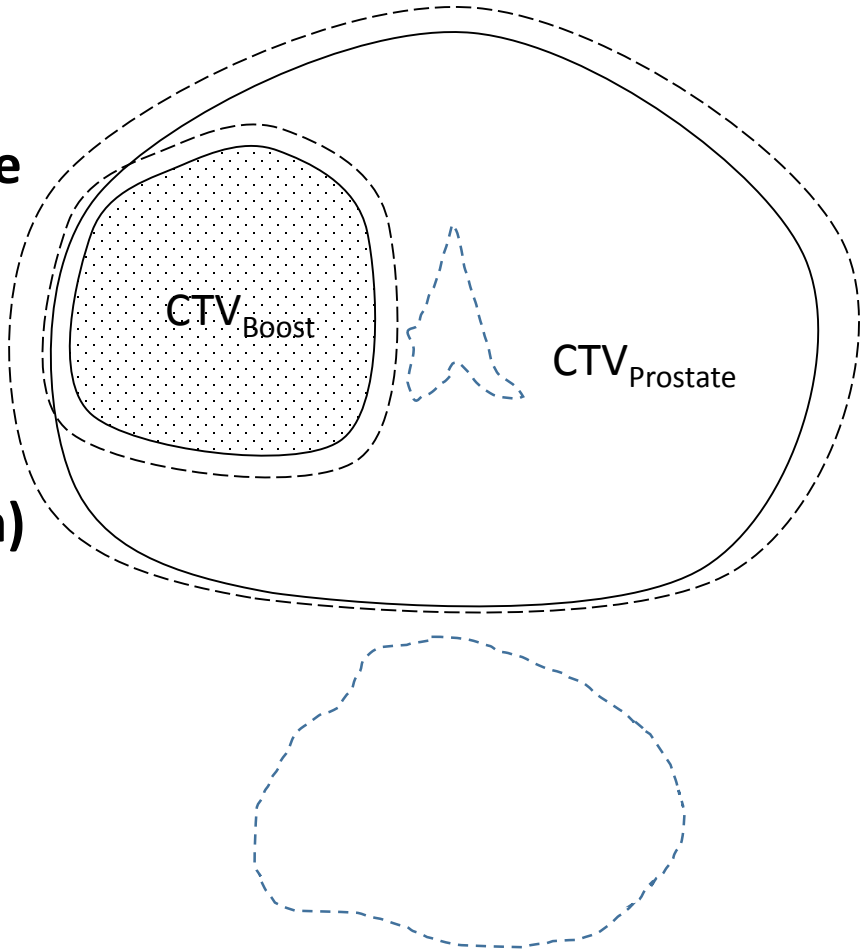
- Pre-Implant Multi-Parametric MRI Scan
  - T2
  - Diffusion Weighted
  - Dynamic Contrast Enhanced MRI
- Images available in the operating theatre during implantation
  - Currently no US-MRI fusion capability in theatre
- Conventional Whole gland needle placement
- 5mm spacing across dominant region
- 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} + 3mm) - Rectum**
- **PTV_{Comb} = ($CTV_{Prostate}$ + 3mm) – Rectum**
- **$PTV_{NonBoost}$ = PTV_{Comb} - PTV_{boost}**



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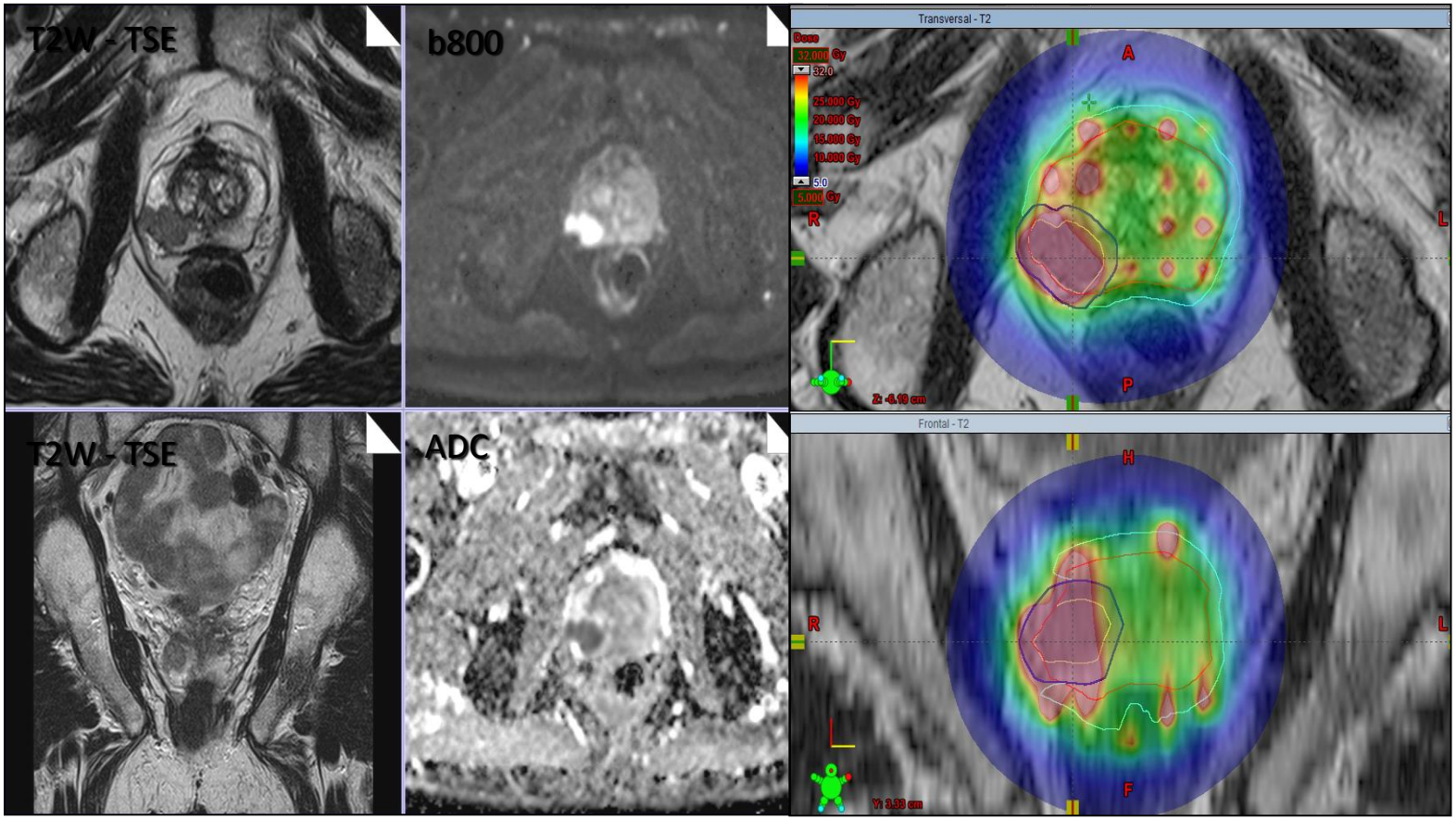
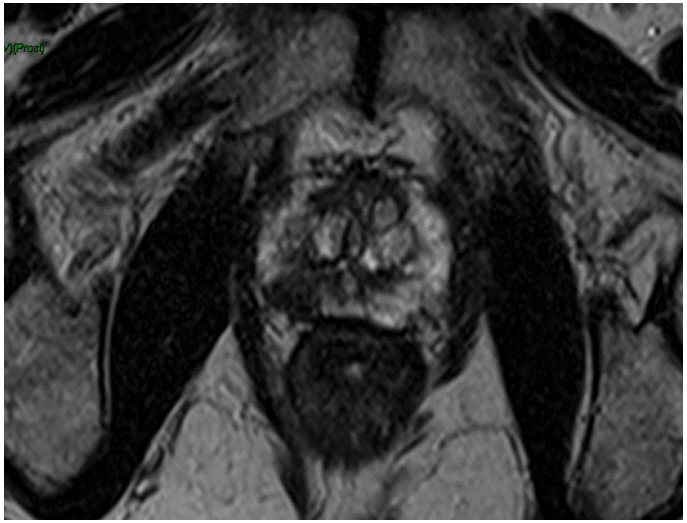
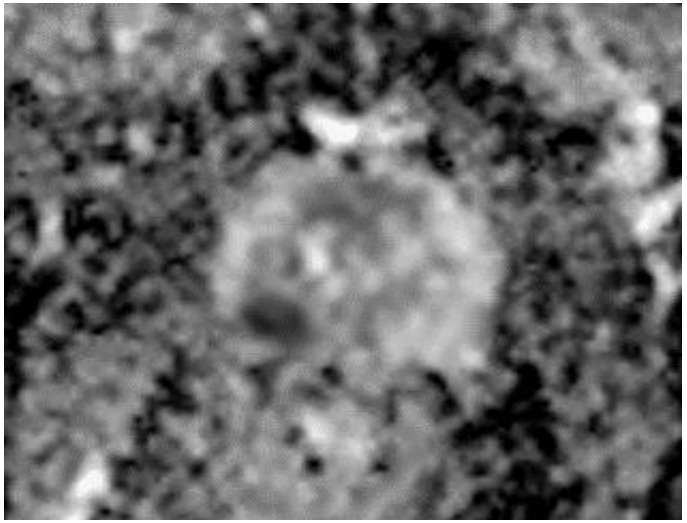
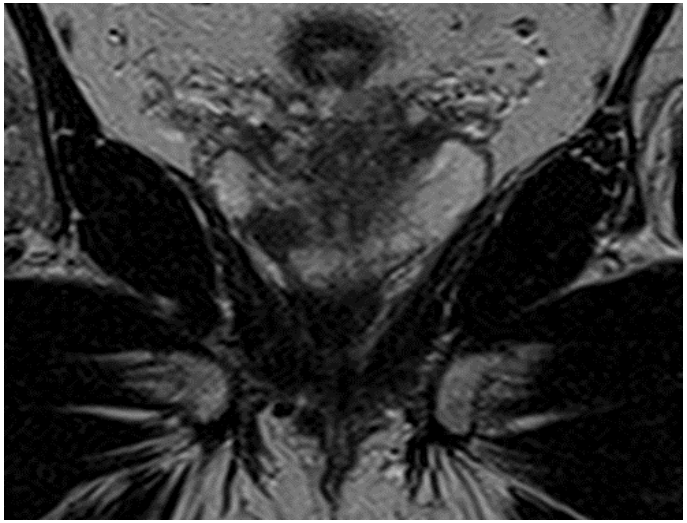
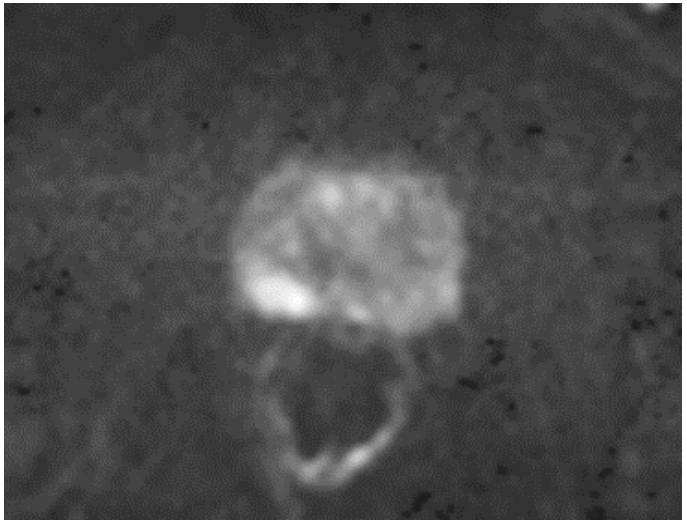


75 year old man, PSA 18ng/ml, T3a No Mo, Gleason 4+3 in 5/12 TRUS biopsy cores, all Right Sided







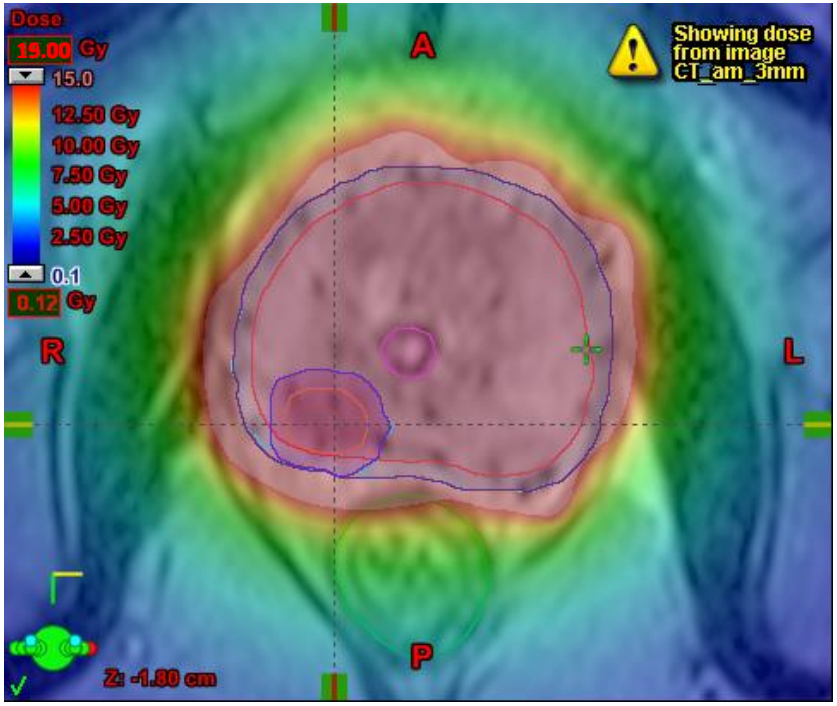


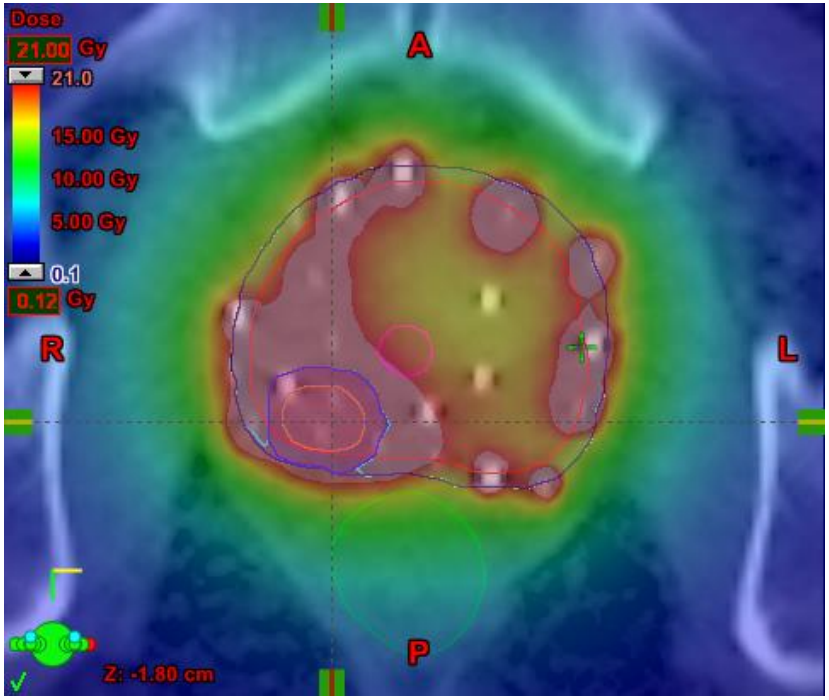
64 year old man

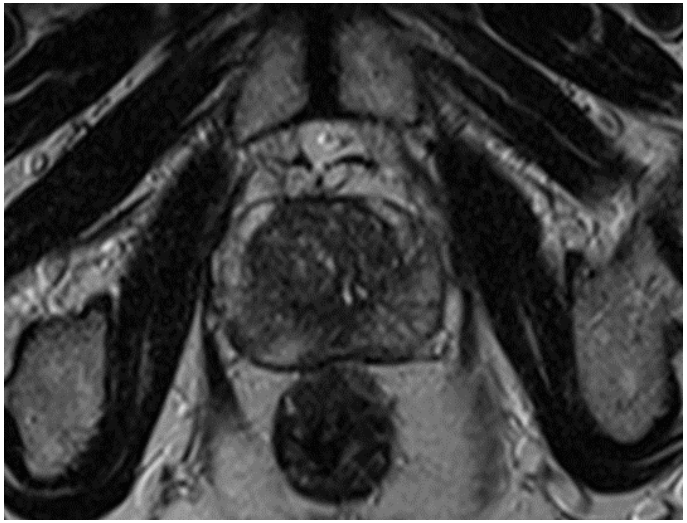
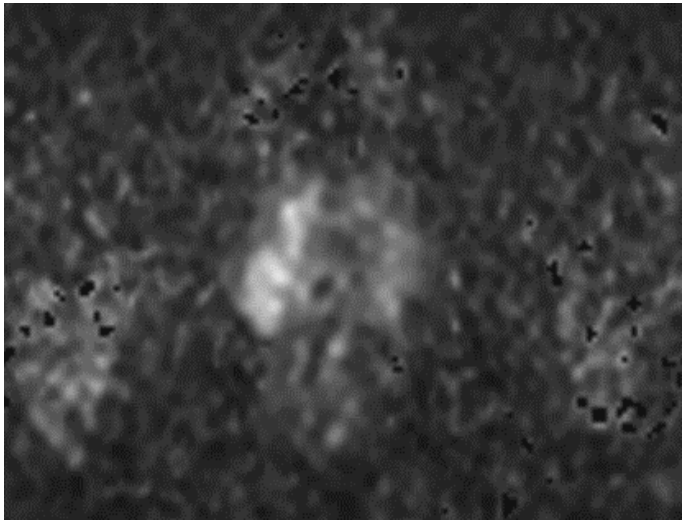
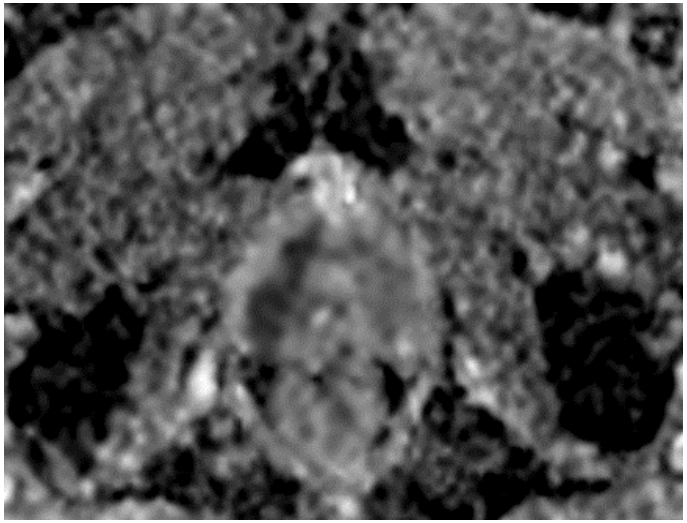
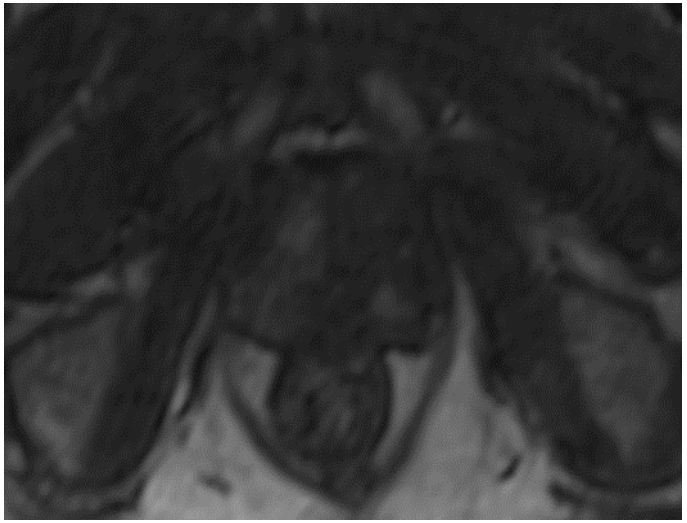
PSA 8.9ng/ml

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
Showing dose from image CT_am_3mm
R
L
P
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

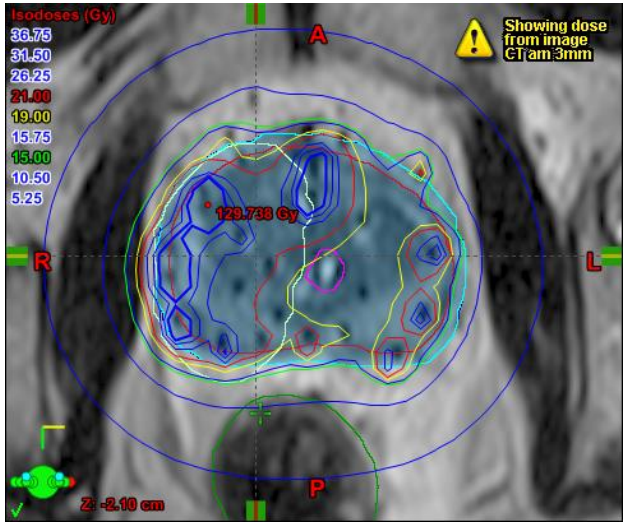





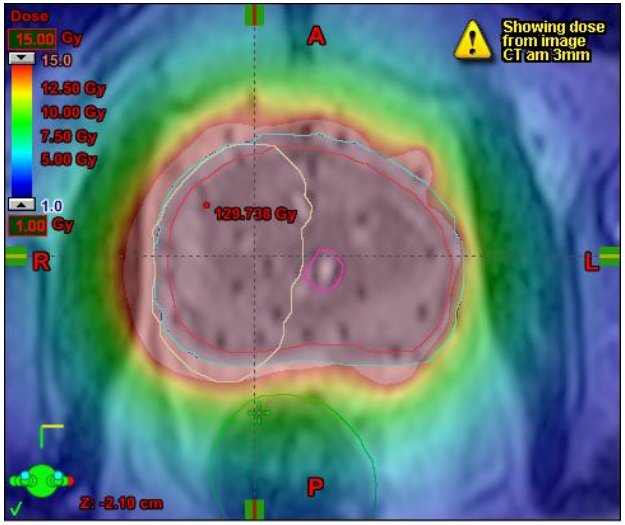
67 year old man

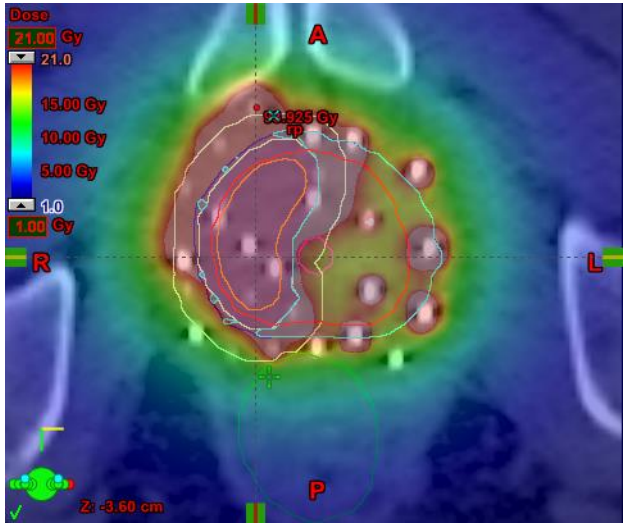
PSA 14.7ng/ml

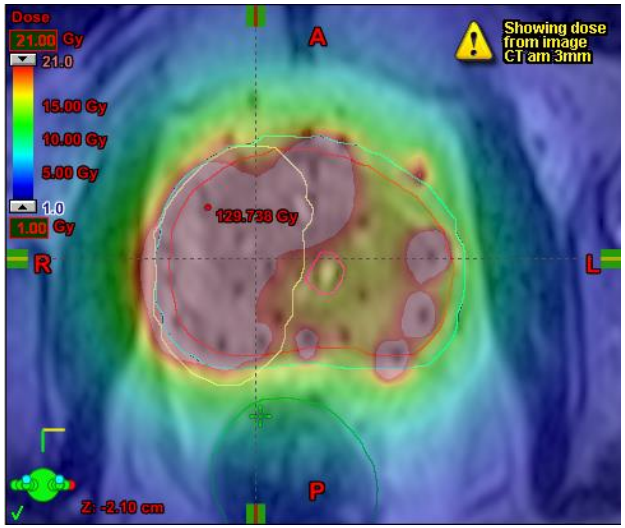
T2b No Mo

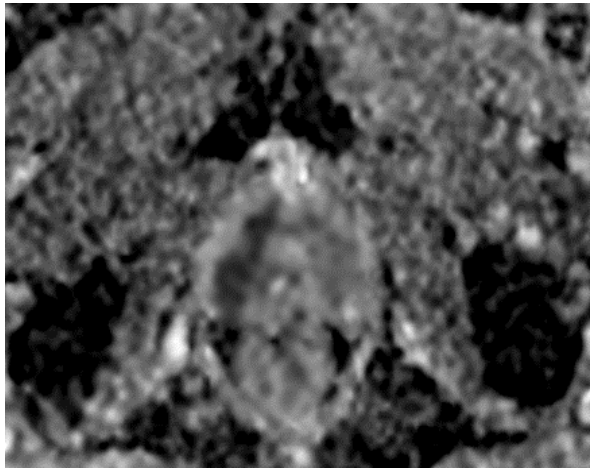
Gleason 3+4 in 4/12 TRUS biopsy cores, all Right Sided


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



PROSTATE BRACHYTHERAPY
UK & Ireland Conference 2015

Salvage Treatment for radio-recurrent prostate cancer

- Rationale and Clinical Need
- Examples
- Design For Proposed Clinical Trial

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UK & Ireland Conference 2015

- 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.

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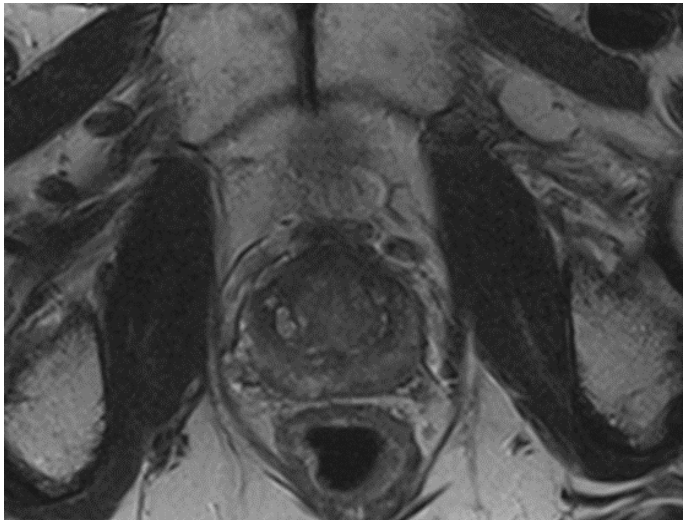
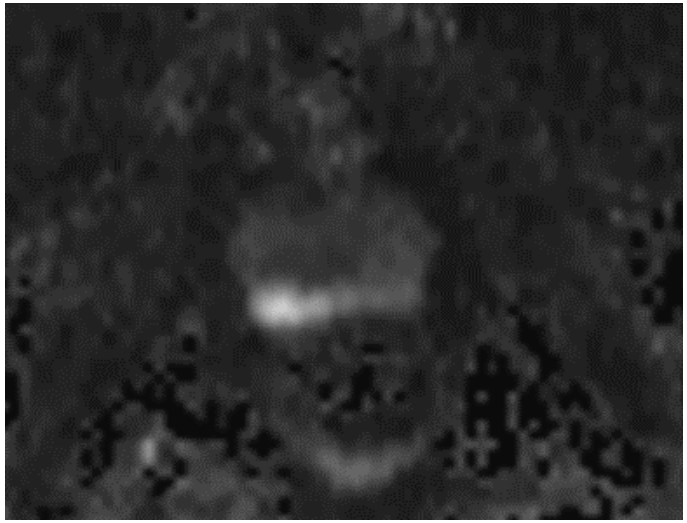
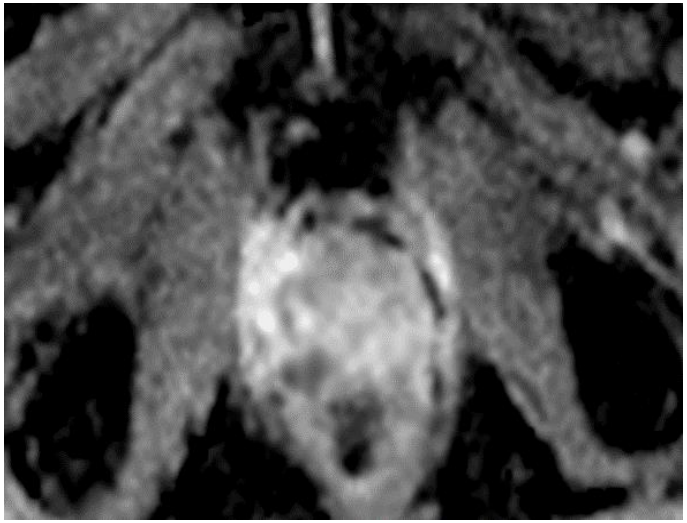
- Local recurrence remains a neglected area of study
- Standard therapy is immediate or deferred androgen deprivation therapy
  - flushing, sexual dysfunction, gynaecomastia, weight gain, mood changes muscular and joint pains and osteoporosis
- Endocrine therapy is expensive
  - £1000 per year, rising 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

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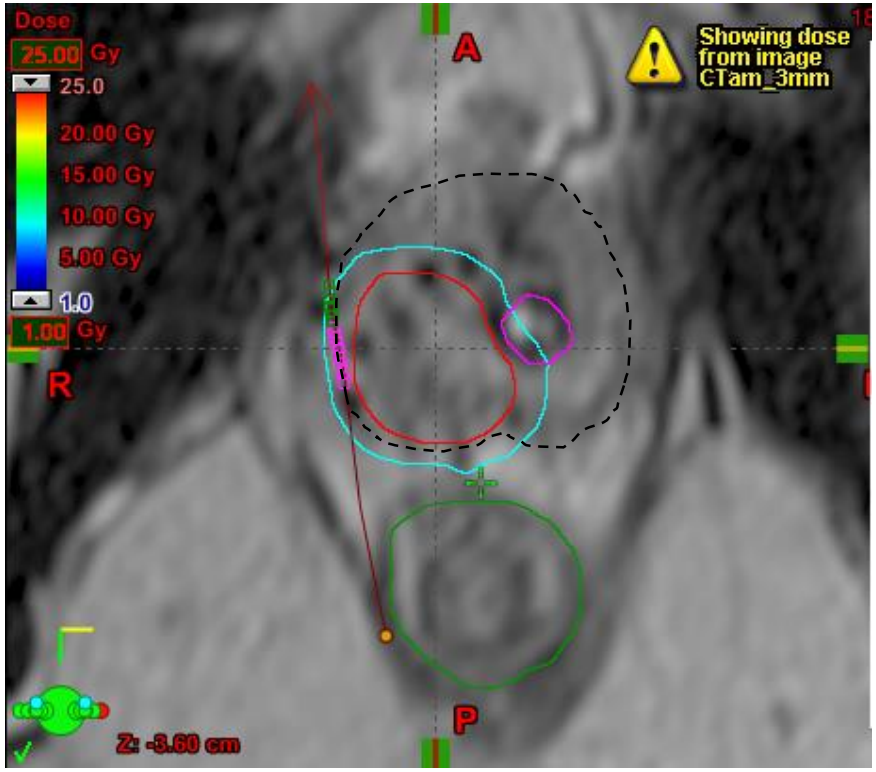
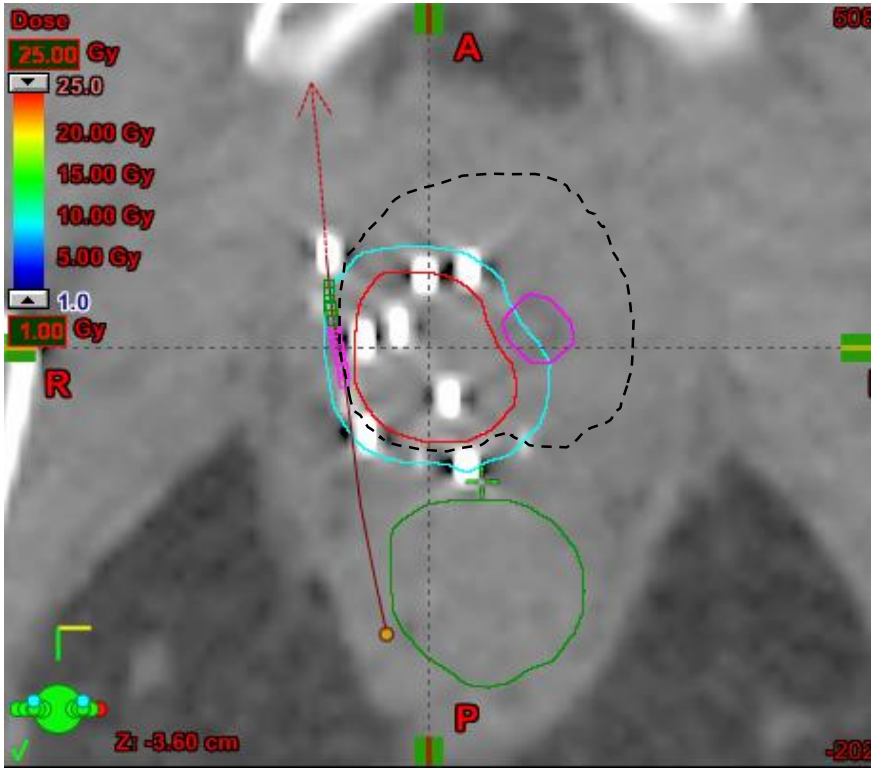
UK & Ireland Conference 2015





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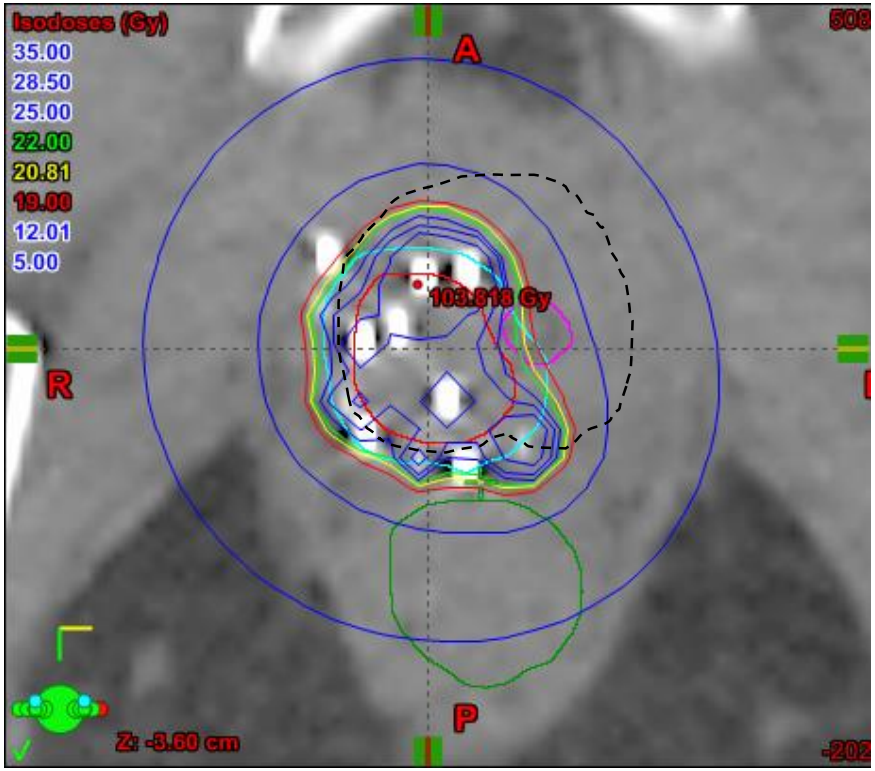
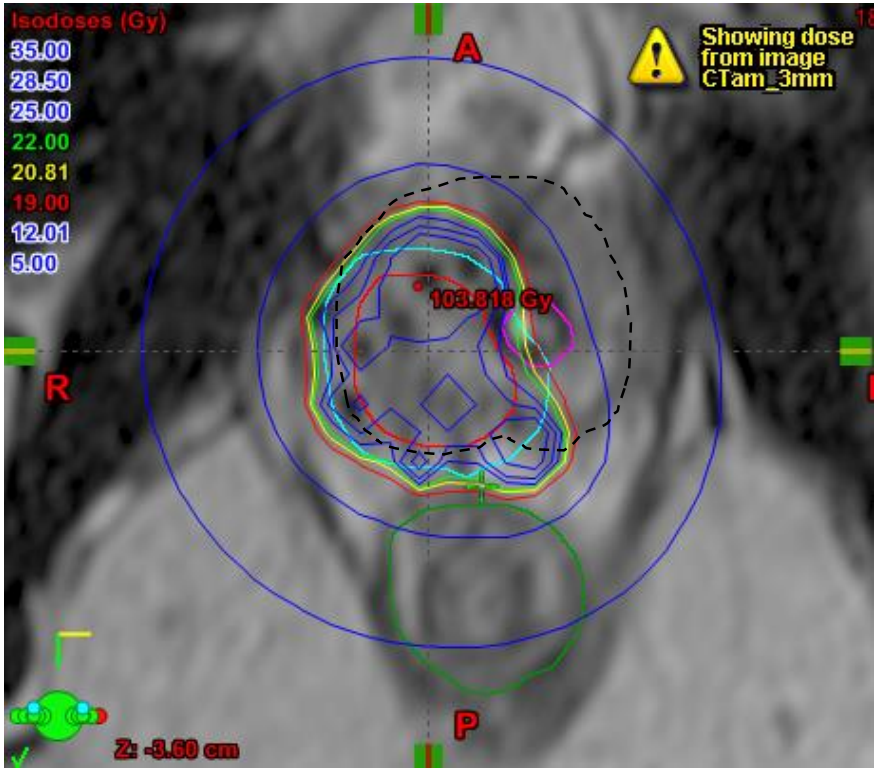
UK & Ireland Conference 2015





PSA at 6 months <0.1

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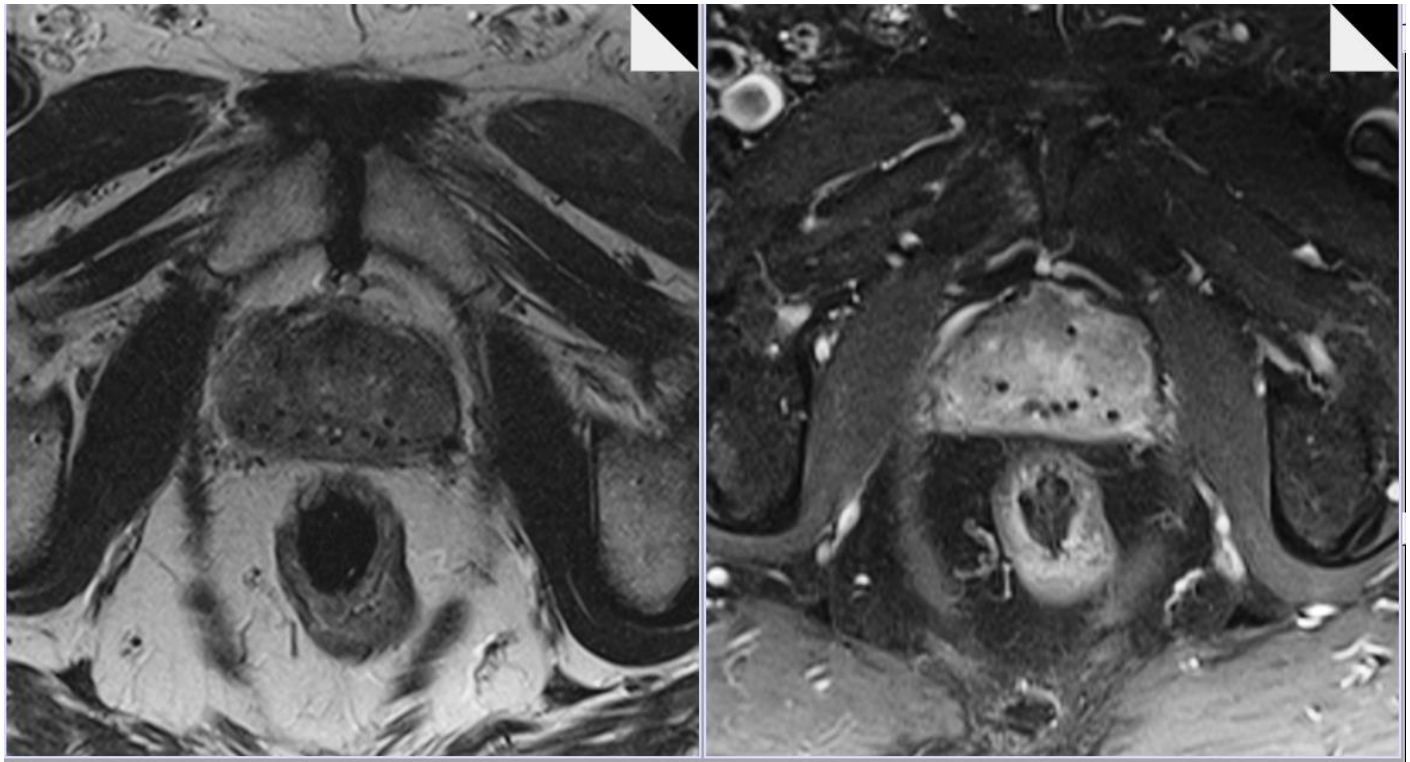
Failure after I^{125} brachytherapy



PROSTATE BRACHYTHERAPY

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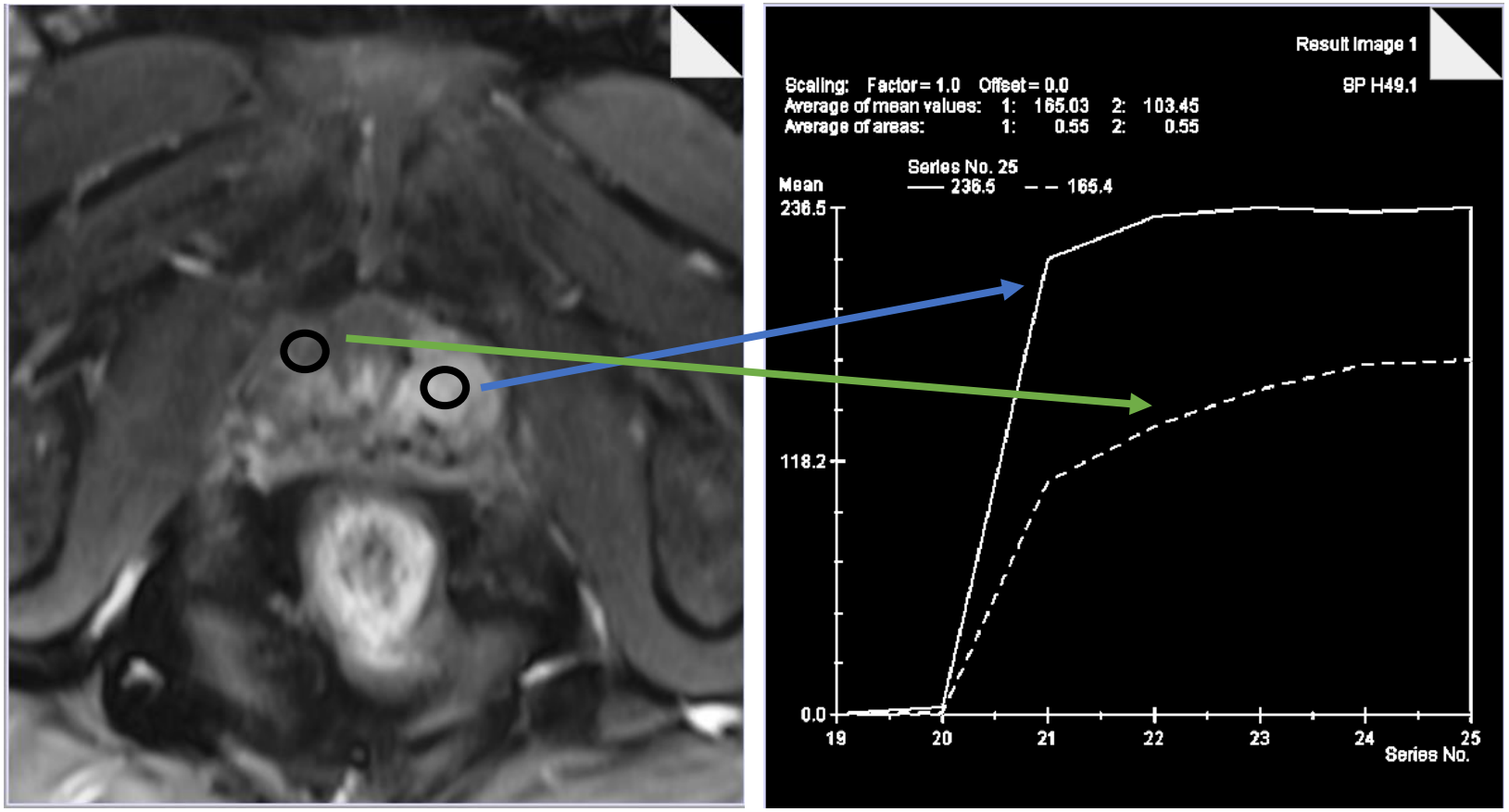

PROSTATE BRACHYTHERAPY

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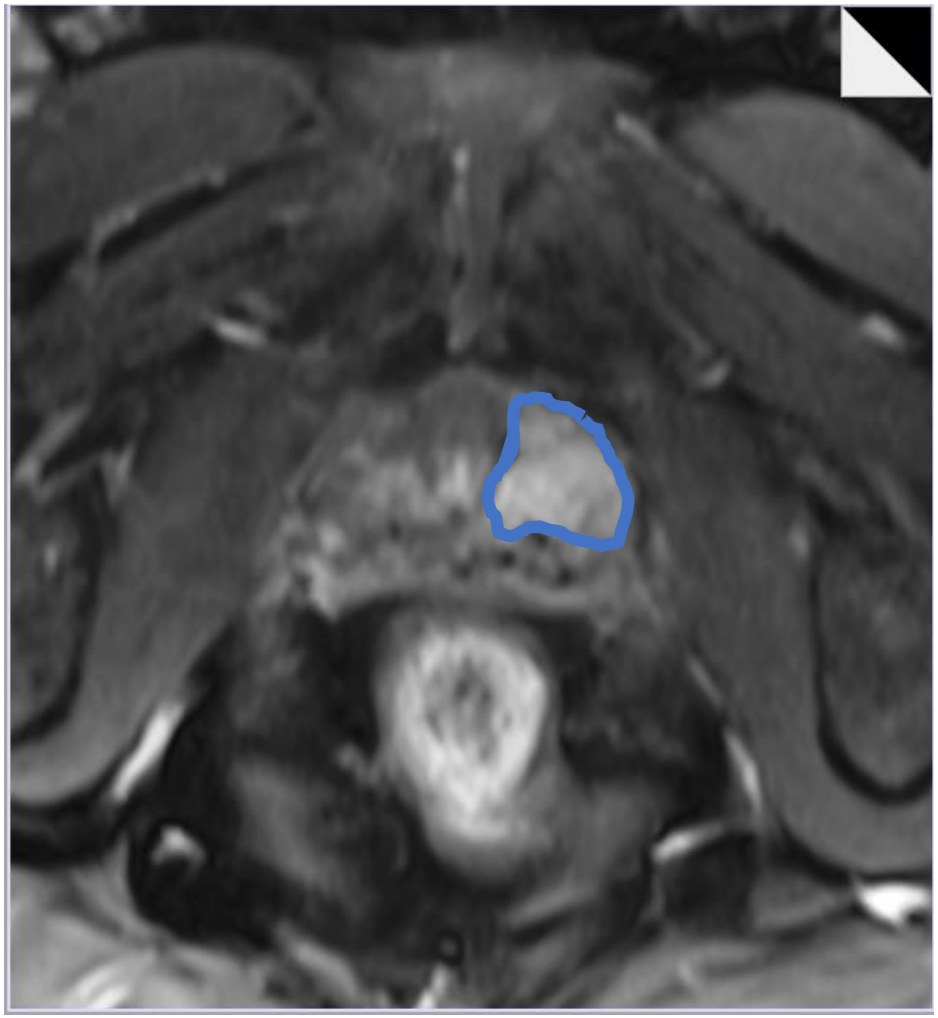
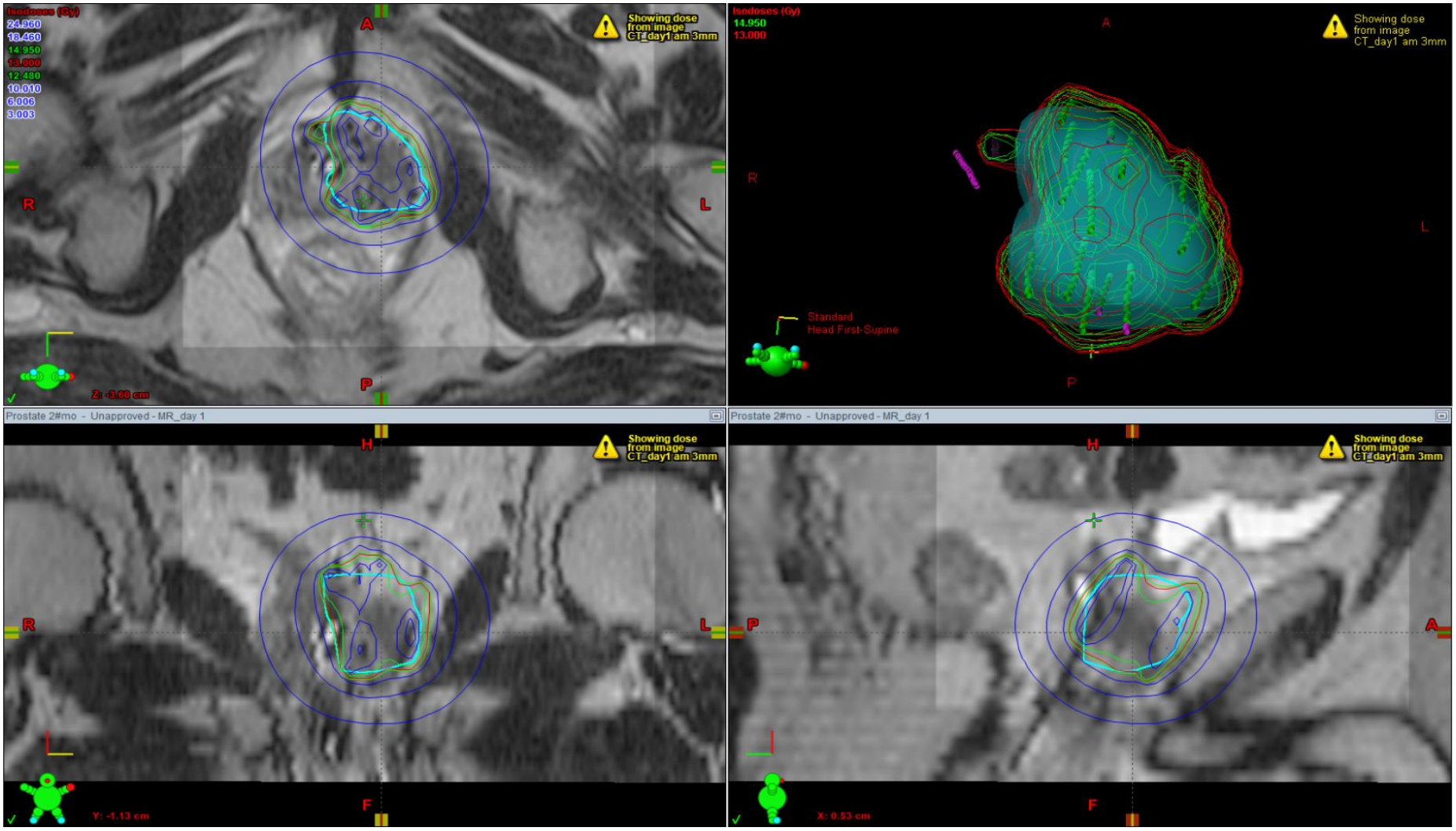


PROSTATE BRACHYTHERAPY

UK & Ireland Conference 2015



Salvage treatment for local recurrence in prostate cancer

Trial Schema