

Optimal fractionation in HDR brachytherapy

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Sunnybrook
HEALTH SCIENCES CENTRE

Objectives

- **Choose a dose and fractionation to use for HDR boost**
- **Interpret recent clinical trial results to select dose and fractionation for HDR monotherapy**
- **Assess ongoing clinical trials of monotherapy**

American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy

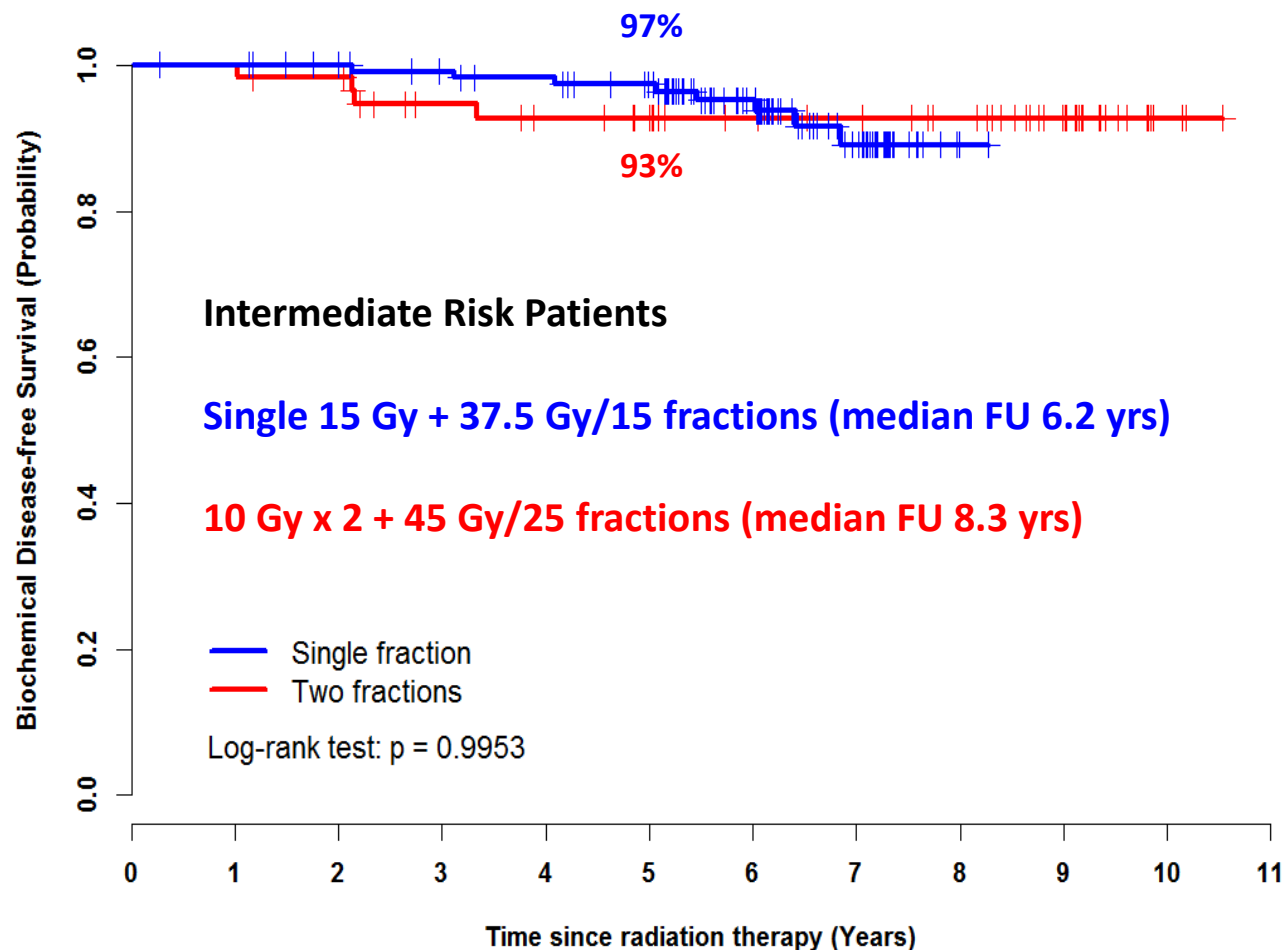
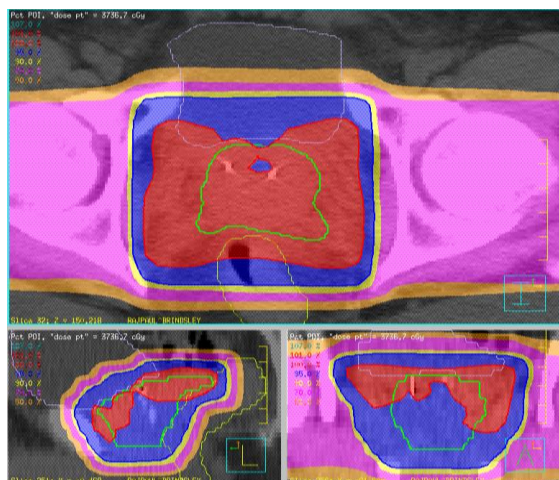
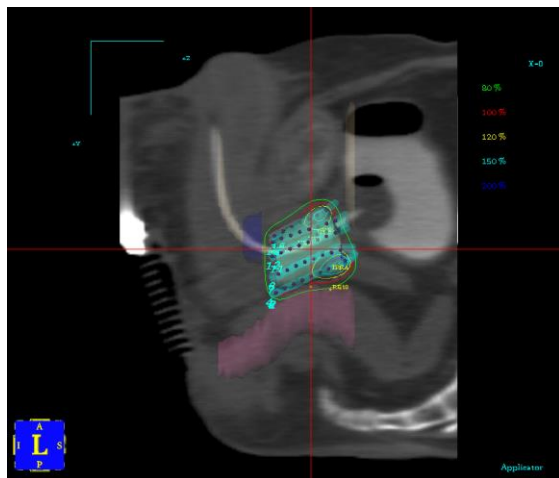
Yoshiya Yamada^{1,*}, Leland Rogers², D. Jeffrey Demanes³, Gerard Morton⁴,
Bradley R. Prestidge⁵, Jean Pouliot⁶, Gil'ad N. Cohen⁷, Marco Zaider⁷,
Mihai Ghilezan⁸, I-Chow Hsu⁶

“Given the heterogeneity of prescription doses described in the literature, all reporting similar excellent outcomes in terms of toxicity and disease control, no particular dose fractionation schedule can be recommended.”

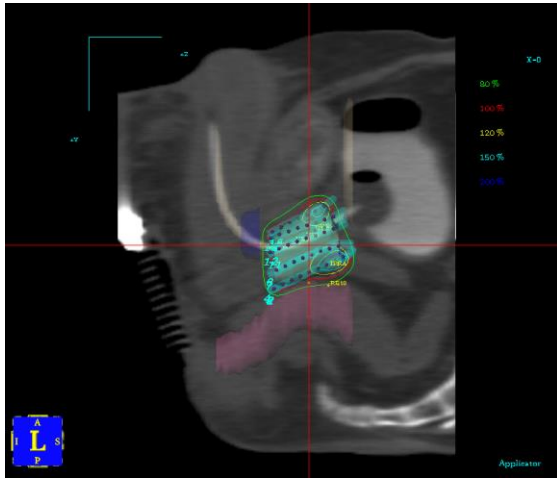
Equivalent dose at 2 Gy/fraction

Radiation Schedule	$\alpha/\beta=2$	$\alpha/\beta=3$	$\alpha/\beta=10$
10 Gy x 2 HDR + 45 Gy/25f	102	95	77
15 Gy x1 HDR + 37.5 Gy/15f	106	95	62

Sunnybrook HDR Boost Protocols

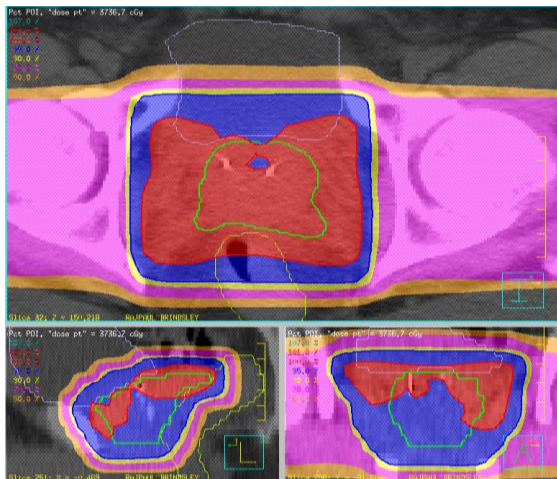


Single 15 Gy HDR Boost + 37.5 Gy/15 f EBRT



Findings

- Nadir PSA: 0.05 ng/ml
- Positive biopsy rate at 2 years < 1%
- 5-year bDFS: >97%
- Late Grade 3 toxicity 3%



Morton, Radiother Oncol 2011
Helou et al, Radiother Oncol 2015
D'Alimonte et al, Brachytherapy 2015
Shahid et al, Clin Oncol 2017

HDR Monotherapy Dose Fractionations



6 Gy x 9

6 Gy x 8

7 Gy x 6

7.25 Gy x 6

6.5 Gy x 6

6 Gy x 6

6 Gy x 6

7 Gy x 4

9 Gy x 4

9.5 Gy x 4

9.5 Gy x 4

10 Gy x 3

10.5 Gy x 3

11.5 Gy x 3

13 Gy x 2

13.5 Gy x 2

19 Gy x 1

20.5 Gy x 1

HDR Monotherapy – 4 and more fractions

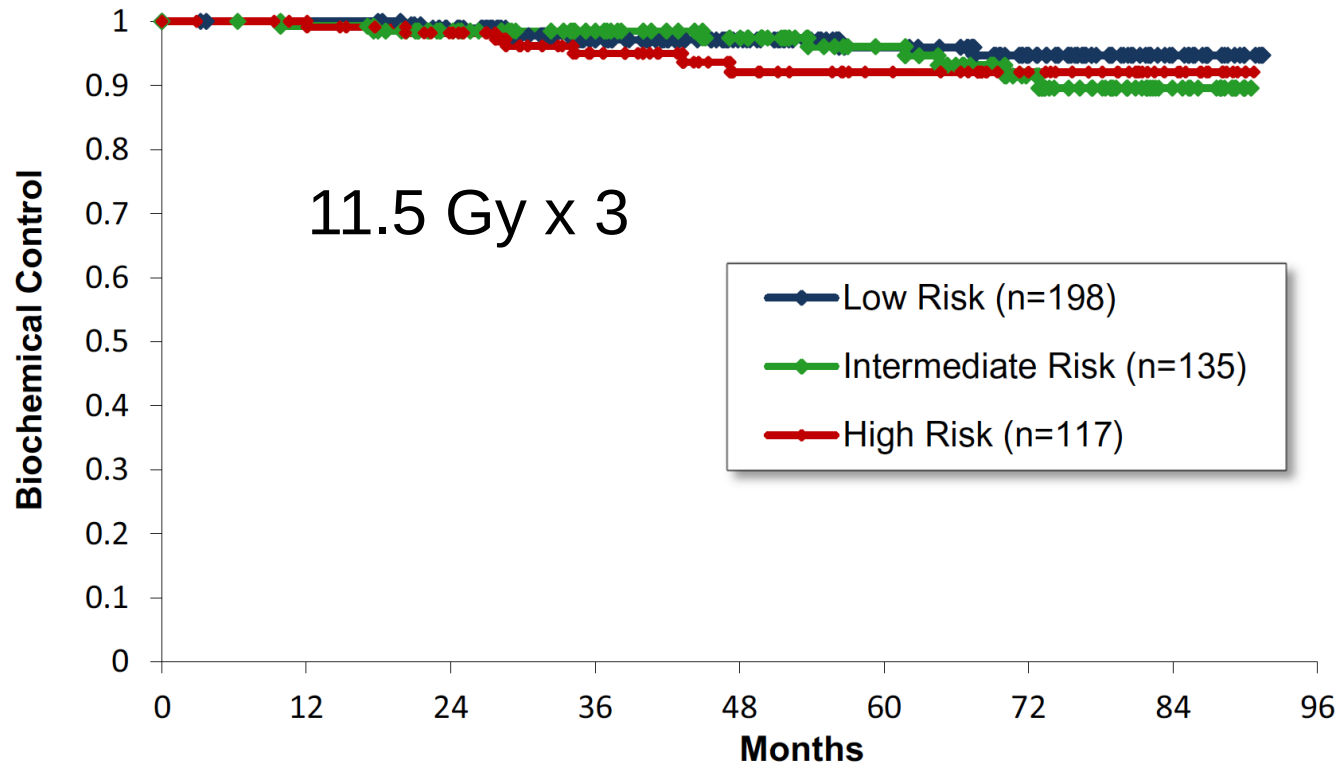
Author	n	Gy x f	Dose (Gy)	Median FU (yrs)	bDFS		
					LR	IR	HR
Yoshioka	190	6 x 8	48	7.6		93%	81%
		6 x 9	54				
		6.5 x 7	45.5				
Hauswald	448	7-7.25 x 6	42-43.5	6.5	99%	95%	
Rogers	284	6.5 x 6	39	2.7		94%	
Mark	301	7.5 x 6	45	8		88%	
Demanes	157	7 x 6	42	5.2	97%		
Patel	190	7.25 x 6	43.5	6.2		90%	
Martinez	171	9.5 x 4	38	4.6	91%		
Zamboglou	492	9.5 x 4	38	5-7.7	95%	93%	93%

HDR Monotherapy: 2-3 fractions

Author	n	Gy x f	Dose (Gy)	Median FU (yrs)	bDFS		
					LR	IR	HR
Barkati	19	10 x 3	30	3.3	85%		
	19	10.5 x 3	31.5				
	19	11 x 3	33				
	22	11.5 x 3	34.5				
Strouthos	450	11.5 x 3	34.5	4.7	96%	96%	92%
Kulkielka	77	15 x 3	45	4.7	97%		
Jawad	319	9.5 x 4	38	5.5	98%		
	79	12 x 2	24	3.5	92%		
	96	13.5 x 2	27	2.9	100%		
Hoskin	55	8.5-9 x 4	34-36	5	99%		
	109	10.5 x 3	31.5	9	91%		
	138	13 x 2	26	5.25	93%		

HDR Monotherapy by Risk Group

)



Patients at risk

low risk	198	197	185	145	112	85	63	22
intermediate risk	135	134	119	102	88	68	51	19
high risk	117	115	107	80	58	48	33	17

Linear Quadratic Calculations

For $\alpha/\beta = 1.5$

HDR Dose x Fractions	BED	Equivalent EBRT Dose
6 Gy x 9	270	116 Gy
7.5 Gy x 6	270	116 Gy
9.5 Gy x 4	278	120 Gy
11.5 Gy x 3	286	122 Gy
13.5 Gy x 2	270	116 Gy
19 Gy x 1	260	112 Gy

$$\text{BED} = nd (1 + d/\alpha/\beta)$$

Linear Quadratic Calculations

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$$\text{BED} = nd (1 + d/\alpha/\beta) + C + D$$

C = Caution

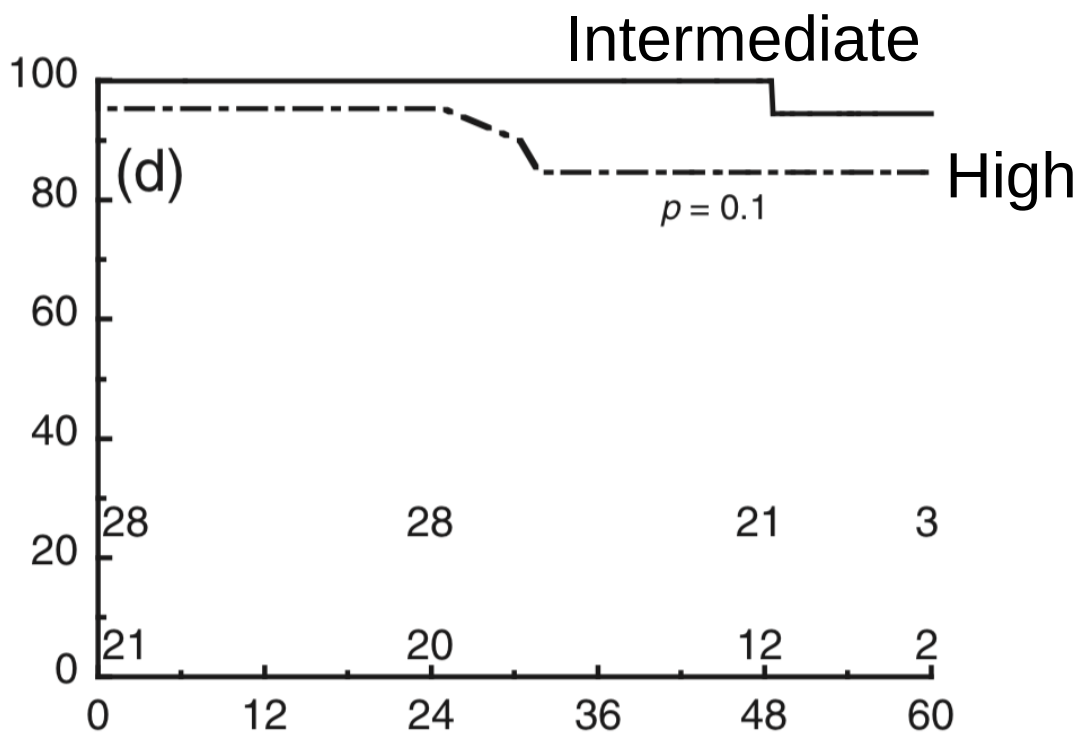
D = Doubt

Single-dose high-dose-rate brachytherapy compared to two and three fractions for locally advanced prostate cancer

Peter Hoskin, Ana Rojas*, Peter Ostler, Robert Hughes, Roberto Alonzi, Gerry Lowe

19 Gy (n=23)
20 Gy (n=26)
Median FU 49 mos
Interm/High Risk: 28/21
74% had ADT

4 yr bDFS: 94%



High-dose-rate interstitial brachytherapy as monotherapy in one fraction for the treatment of favorable stage prostate cancer: Toxicity and long-term biochemical results

Pedro J. Prada^{a,*}, Juan Cardenal^a, Ana García Blanco^a, Javier Anchuelo^a, María Ferri^a, Gema Fernández^c, Elisabeth Arrojo^c, Andrés Vázquez^b, Maite Pacheco^b, José Fernández^d

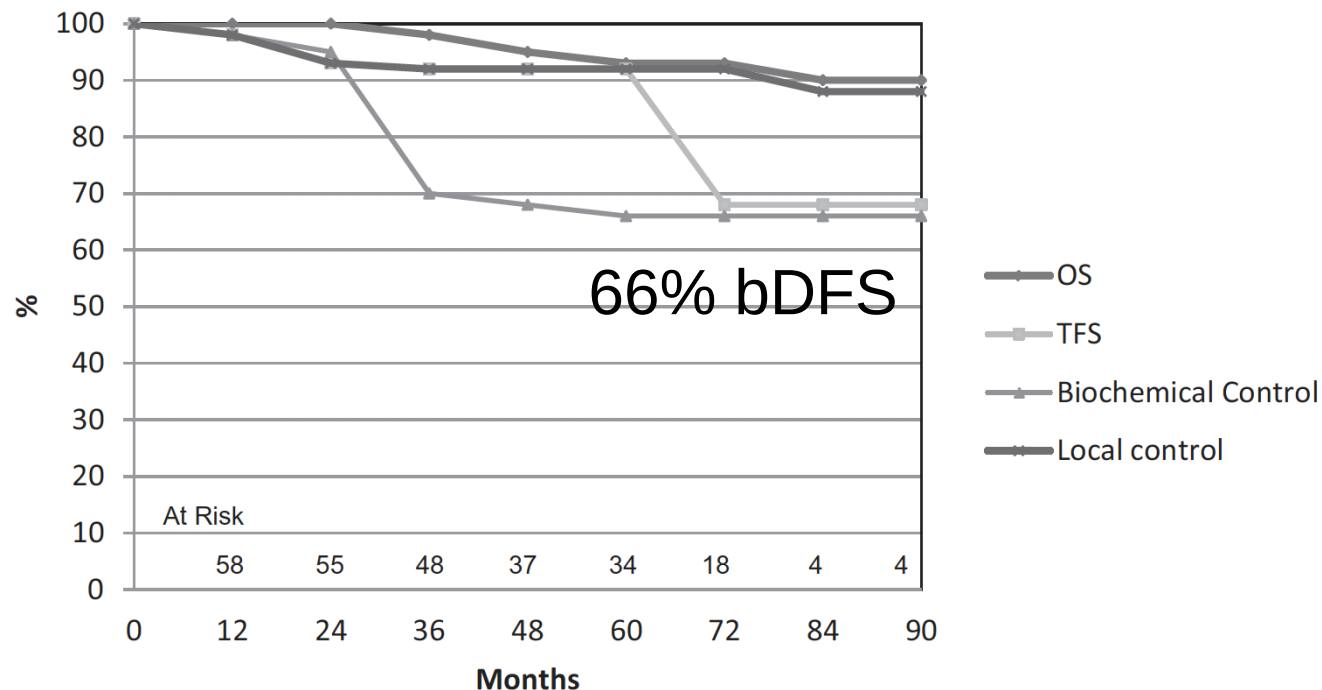
19 Gy x 1

N=60

Low/Interm: 44/16

1/3 had ADT

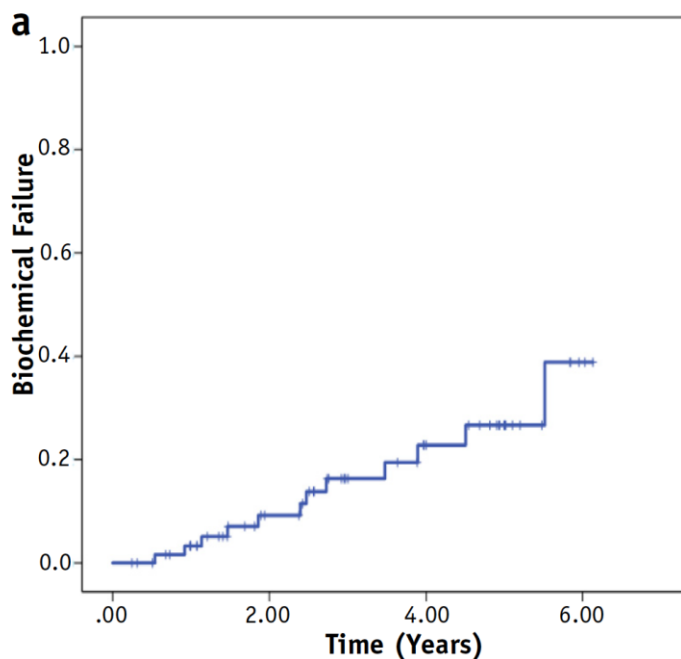
Median FU 6 yrs



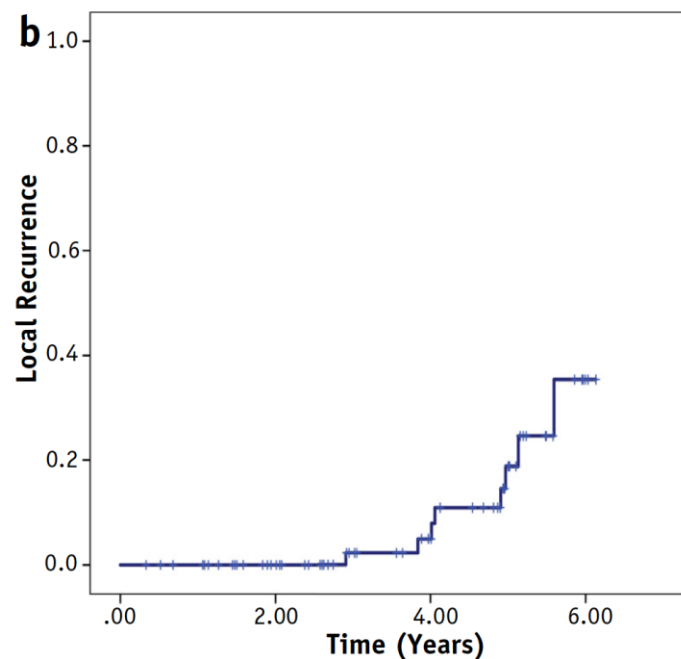
Five-Year Outcomes of a Single-Institution Prospective Trial of 19-Gy Single-Fraction High-Dose-Rate Brachytherapy for Low- and Intermediate-Risk Prostate Cancer

Zaid A. Siddiqui, MD,* Gary S. Gustafson, MD,* Hong Ye, PhD, MPH,*
 Alvaro A. Martinez, MD,† Beth Mitchell, RN,* Evelyn Sebastian, BS,*
 Amy Limbacher, BS, RTT,* and Daniel J. Krauss, MD*

68 patients
 med FU 3.9 yrs
 5 yr bDFS: 77%

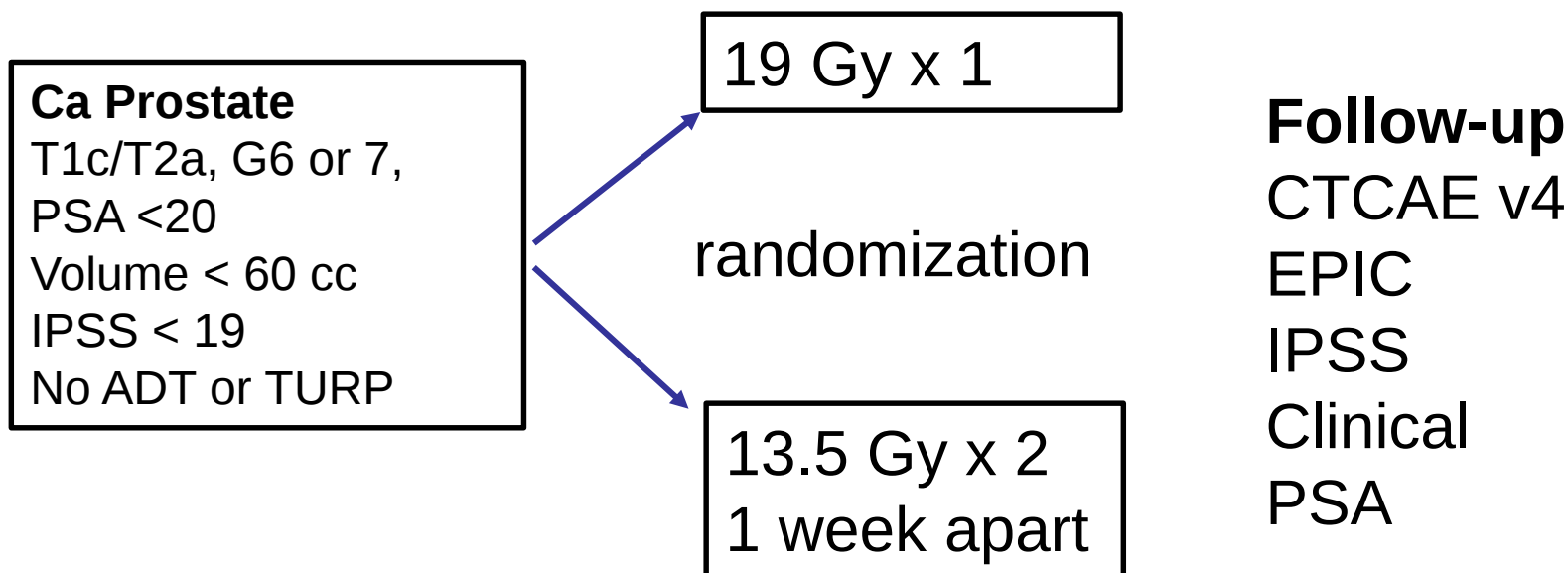


# of Events	1	2	3	4	5
12	3.3%	9.2%	16.3%	22.8%	26.6%



# of Events	1	2	3	4	5
8	0%	0%	2.3%	4.9%	18.8%

Sunnybrook Randomized Trial



170 patients accrued June 2013 to April 2015

Patient Characteristics

	19 Gy x 1 (n=87)	13.5 Gy x 2 (n=83)
Median Age (range)	65 (46,80)	65 (49,80)
Stage		
T1c	67	63
T2a	20	20
Median PSA (range)	6.4 (1.1,13.7)	6.3 (2.0,16.0)
Gleason Score		
Gleason 6	28 (32%)	19 (23%)
Gleason 7	59 (68%)	64 (77%)
Risk Grouping		
Low	21 (24%)	12 (14%)
Fav Intermediate	40 (46%)	46 (56%)
Unfav Intermediate	26 (30%)	25 (30%)

Dosimetry Data

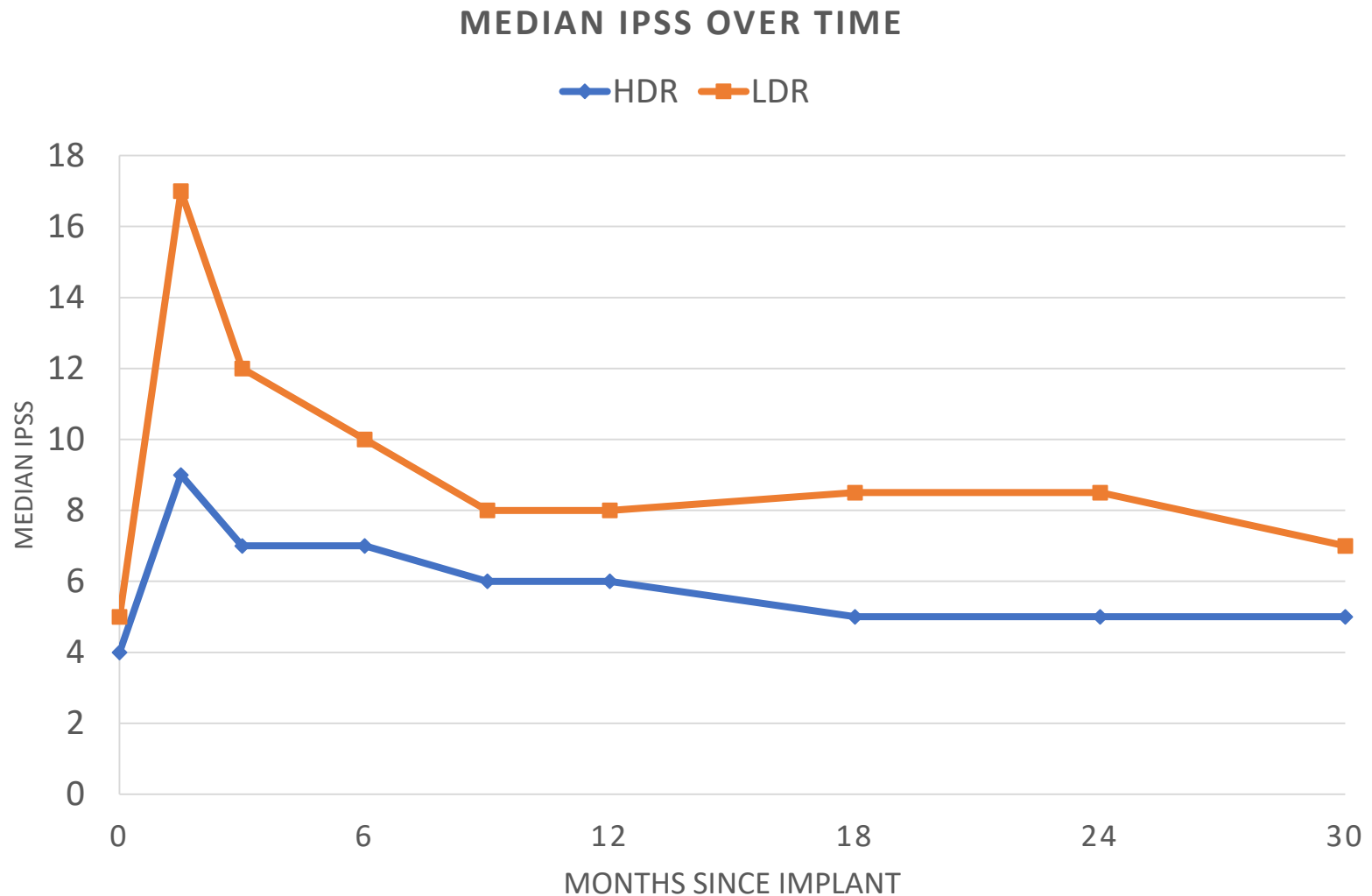
	19 Gy x 1	13.5 Gy x 2	
		#1	#2
Mean PTV cc	46.9 (14.2)	44.6 (11.4)	51 (13.8)
Mean V100	97.2 (1.7)	96.9 (1.5)	97.3 (1.2)
Mean V150	36.0 (4.8)	34.5 (5.3)	35.6 (6.1)
Mean V200	11.4 (3.3)	11.4 (3.9)	11.2 (3.3)
D 90 %	110.6 (3.1)	109.6 (2.9)	110.0 (2.5)
Urethra D max %	122.9 (2.6)	122.4 (8.3)	121.1 (7.1)
Urethra D10 %	116.4 (1.1)	116.2 (1.2)	116.2 (1.1)
Rectal D max %	84.5 (9.9)	81.0 (10.6)	81.6 (13.1)
Rectal V 80 (cc)	0.17 (0.2)	0.11 (0.18)	0.08 (0.16)

Acute Toxicity

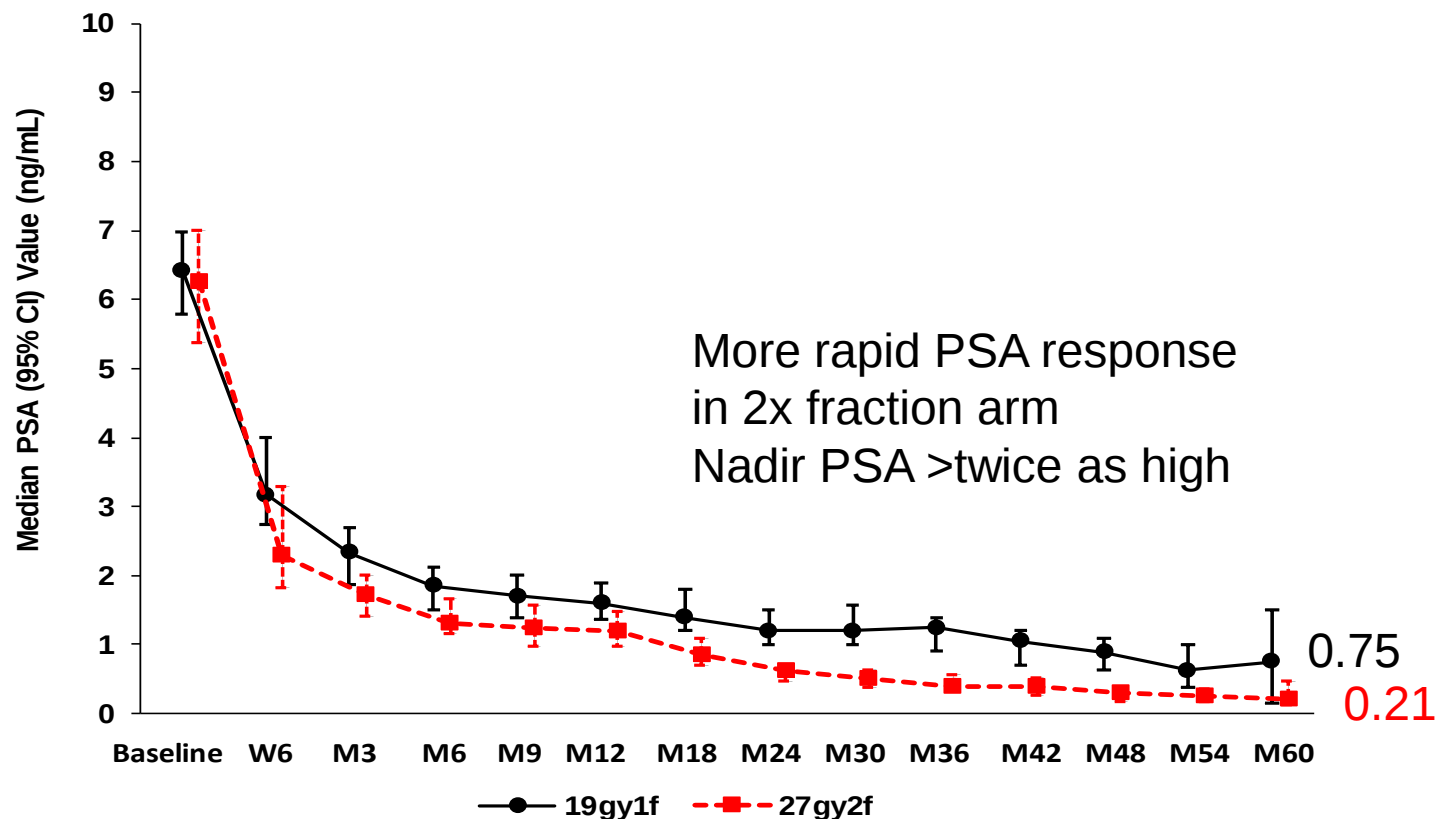
- Minimal acute toxicity in either arm
- Acute retention rate 2%
- 1 acute Grade 3 toxicity (haematuria)

Radiother Oncol 122: 87-92, 2017

Urinary Symptoms: HDR vs. LDR



PSA Response by treatment arm



Conclusions from Sunnybrook Trial

- **13.5 Gy x 2 is the clear winner**
- **Treatment with either 1 or 2 fractions is very well tolerated**
- **Toxicity from single fraction slightly less in first 12 months but slightly worse beyond 3 years**
- **13.5 Gy x 2 is highly effective, looks similar to LDR**
- **19 Gy x 1 has unacceptable local failure rate, usually at site of initial disease**

So what should we do?

- **Stick to 2 fractions**
- **Increase single fraction dose to whole gland**
- **Use dose painting to increase dose to dominant lesion**
- **Something else**

Higher Whole Gland Dose



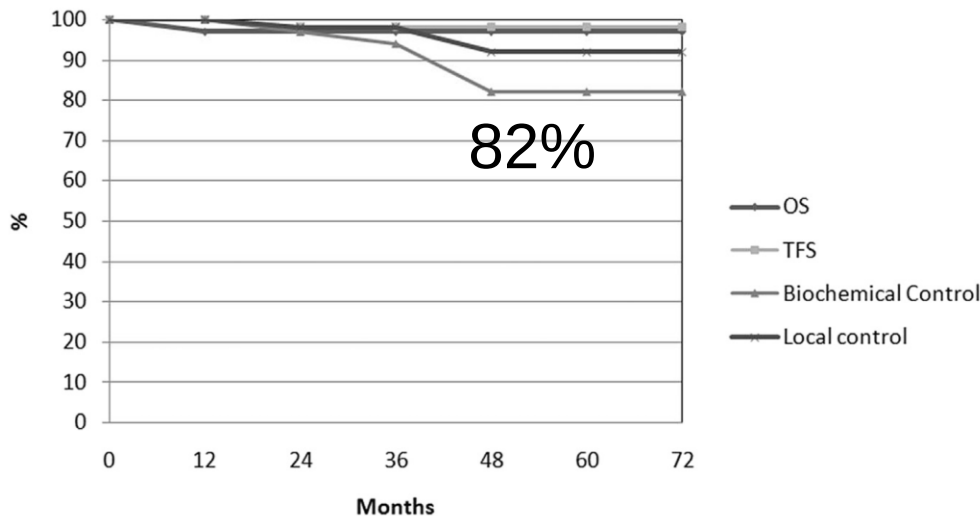
Brachytherapy 17 (2018) 845–851

BRACHYTHERAPY

Prostate

High-dose-rate interstitial brachytherapy as monotherapy in one fraction of 20.5 Gy for the treatment of localized prostate cancer: Toxicity and 6-year biochemical results

Pedro J. Prada^{1,*}, María Ferri¹, Juan Cardenal¹, Ana García Blanco¹, Javier Anchuelo¹, Iván Díaz de Cerio¹, Andrés Vázquez², Maite Pacheco², Ignacio Raba², Samuel Ruiz²



N=60

Median FU 51 mos

63% Gleason 6
37% Gleason 7
68% PSA < 10
43% ADT

bDFS

Low Risk: 82%

Int Risk: 79%

G6: 87%

G7: 62%

Higher Whole Gland Dose?



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Toxicity and 6-year biochemical results

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Table 2
Dosimetric value

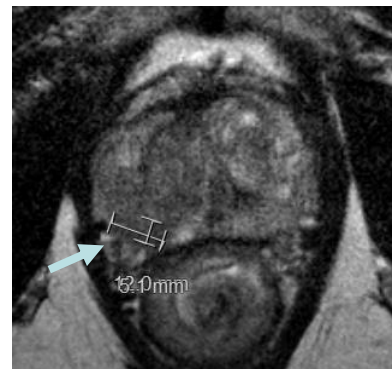
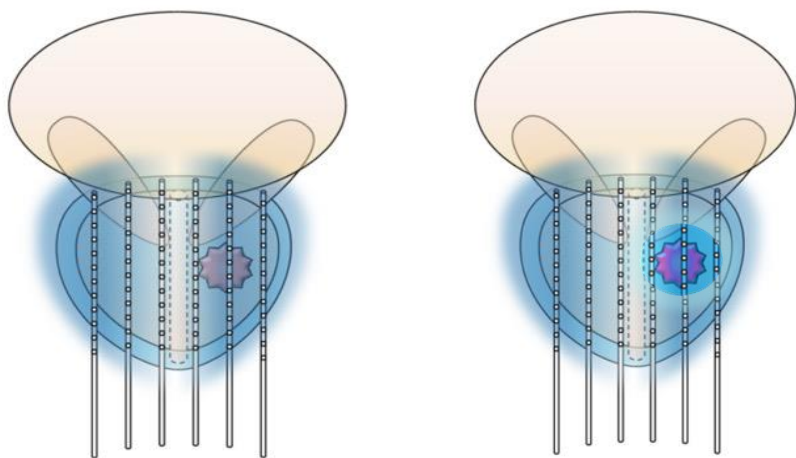
Variable	V ₉₀ (%)	V ₁₅₀ (%)	V ₂₀₀ (%)	D ₉₀ (Gy)	V ₁₀₀ (%)
Mean	97	17	4	21	91
Median	98	18	5	22	92
Minimum	96	11	2	19	81
Maximum	100	23	7	22	96

Sunnybrook Dosimetry (19Gy)

	D90 (Gy)
Mean	21
Median	21.1
Minimum	18.9
Maximum	22.2

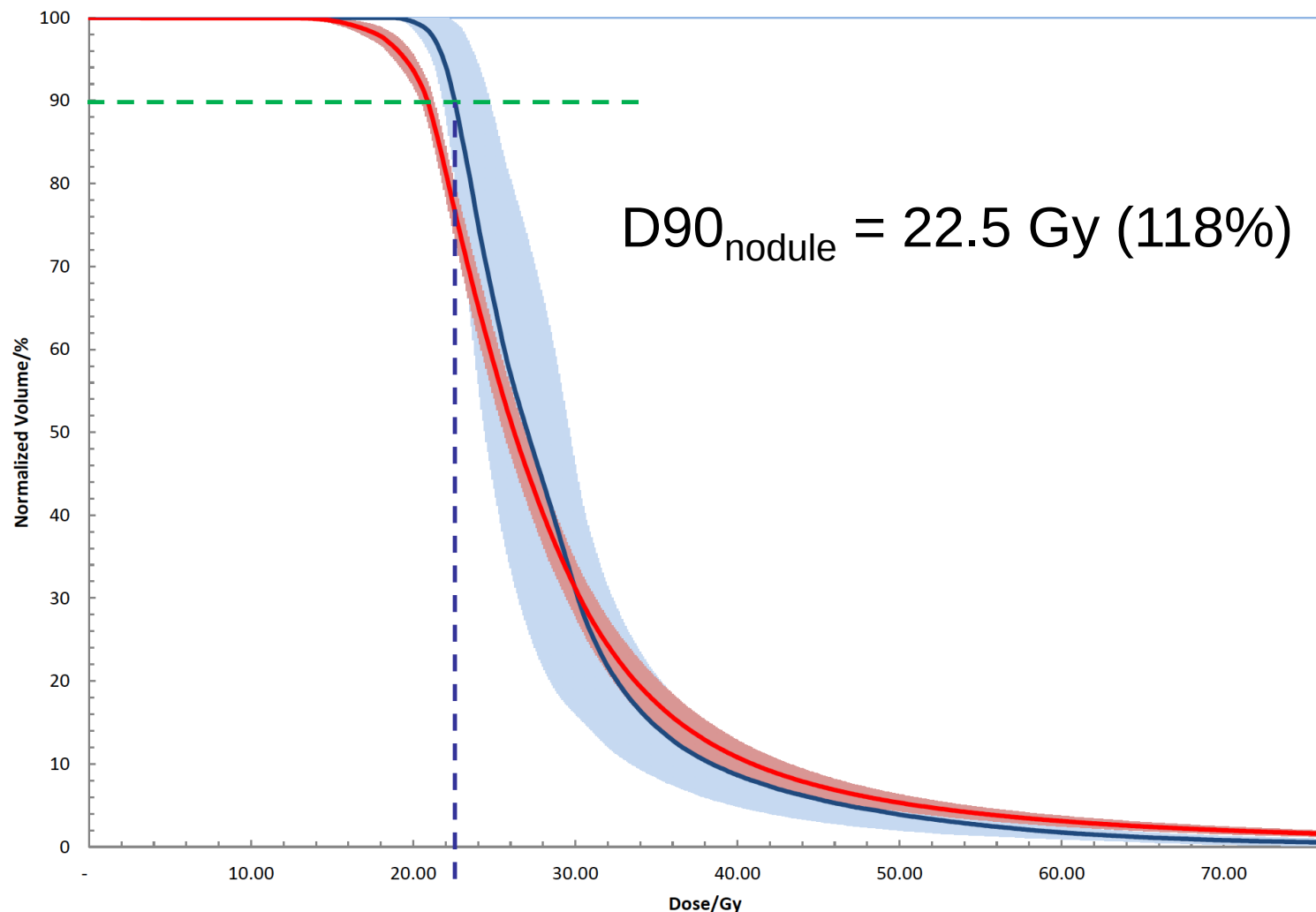
Increasing Dose to Dominant Lesion

- Failure occurs at site of initial bulk disease
- Can we improve results by dose escalating to site of dominant disease?



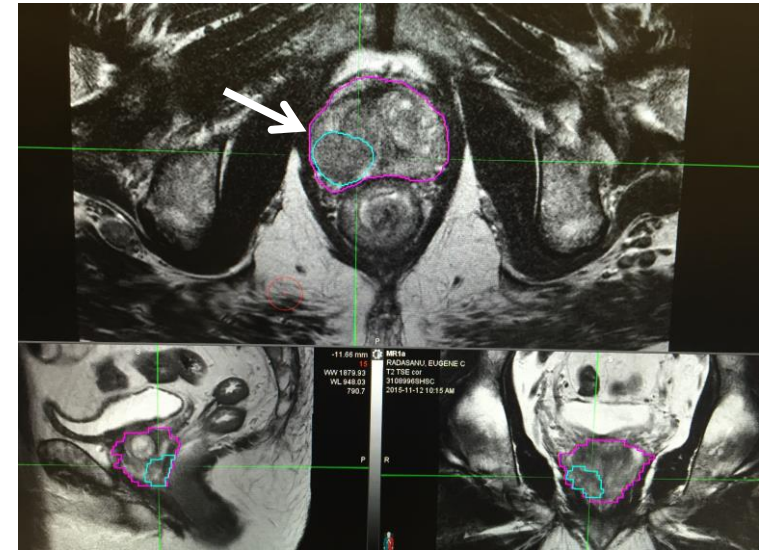
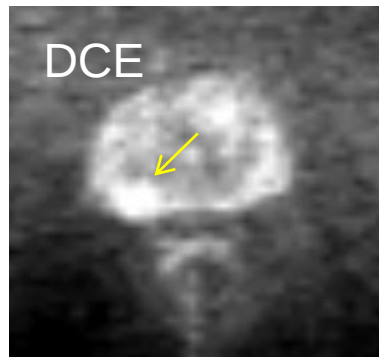
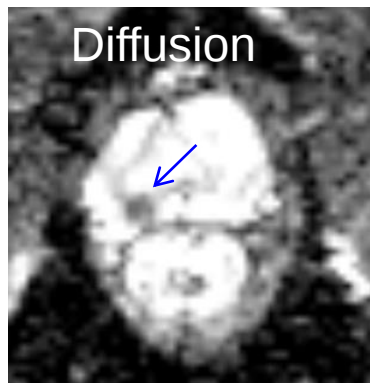
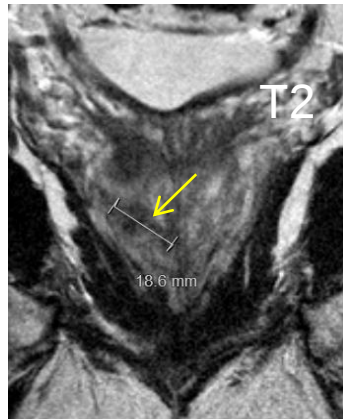
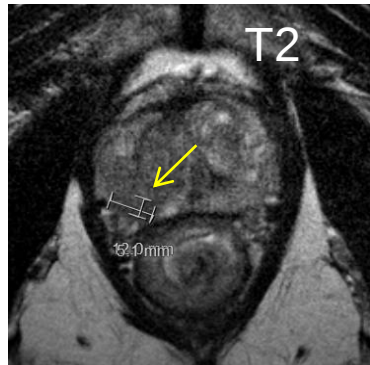
Dosimetry of Local Failures with 19 Gy Whole Gland

Average Dose-Volume histogram for recurrent nodule and prostate



27

Monotherapy: HDR 19 Gy with Focal Boost



Dose escalation to GTV
using MR/TRUS fusion

PR.19

A Randomized Phase II Trial Evaluating High Dose Rate Brachytherapy and Low Dose Rate Brachytherapy as Monotherapy in Localized Prostate Cancer

Study Chairs: Eric Vigneault
Gerard Morton

Senior Investigator (SI): Wendy Parulekar

Senior Biostatistician: Keyue Ding

Study Coordinator (SC): Kate Whelan

Activated: Nov 2016

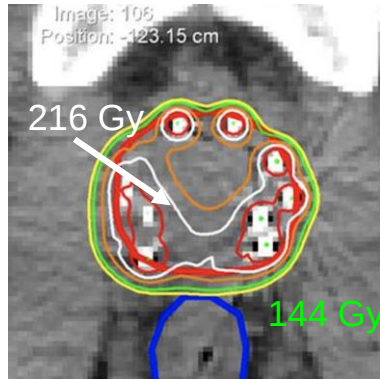
Accrual to March 2019: 100/232

PR.19 Schema

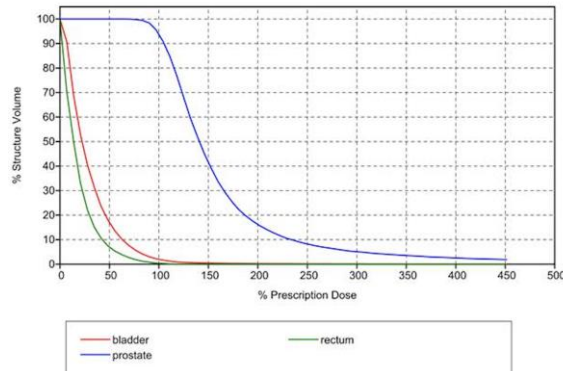
<u>Eligibility criteria:</u> - Prostate carcinoma - cT1- T2 and PSA < 20 and Gleason = 6 Or - cT1-T2 and PSA < 15 and Gleason = 7 (3+4) and ≤ 50% of positive cores	R A N D O M I Z E	<u>Arm 1:</u> LDR brachytherapy with I-125 to a total dose of 144 Gy <u>Arm 2:</u> HDR brachytherapy: 19 Gy in 1 fraction with intraprostatic boost to GTV
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PR.19 Treatment Arms

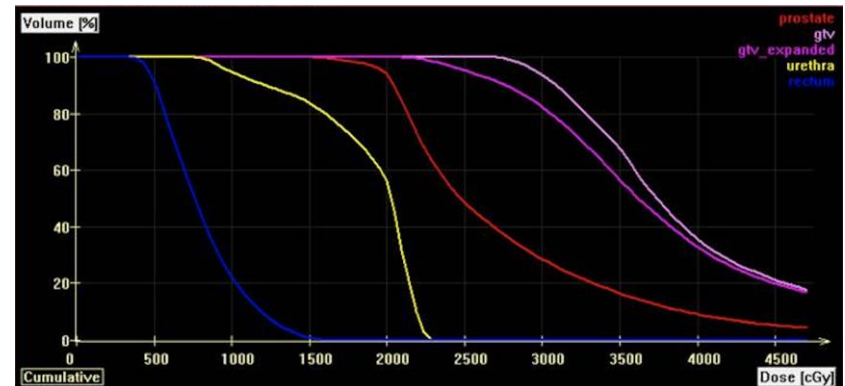
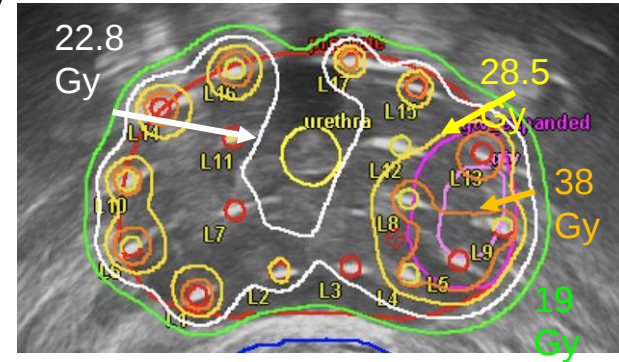
Arm 1: LDR 144 Gy



Cumulative DVH

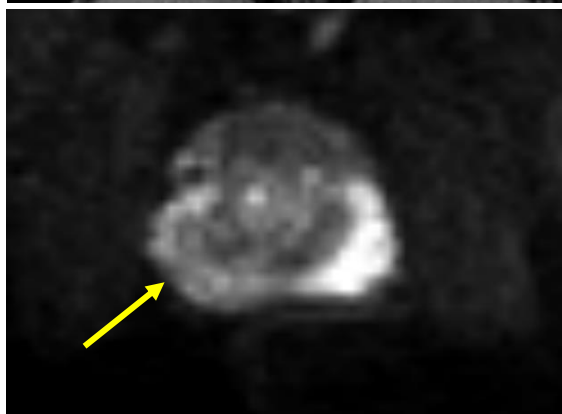


Arm 2: HDR 19 Gy + GTV boost to 28.5 Gy

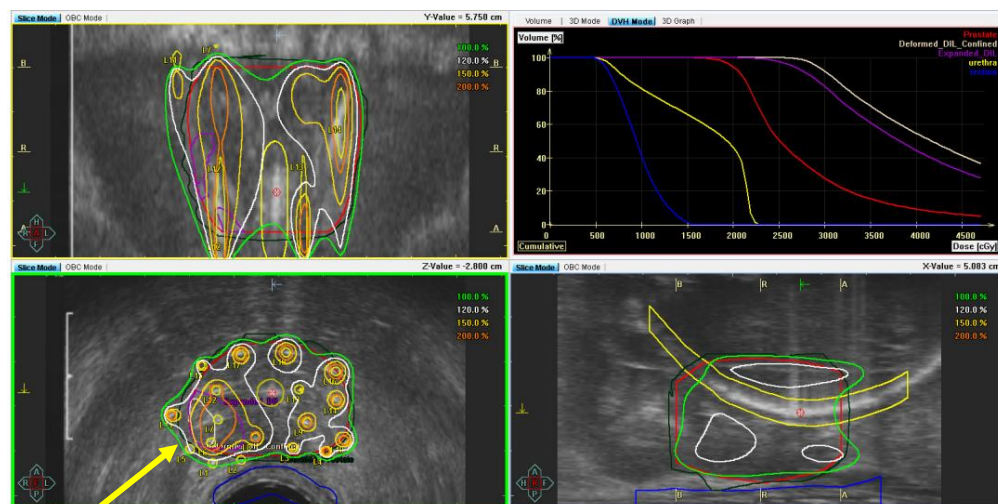


Single Fraction with GTV Boosting

- 65 yr old with PSA 7.85
- Gleason 3+4 in 3/12 cores at right apex, 25% p4
- MRI: PIRAD 4 right apex



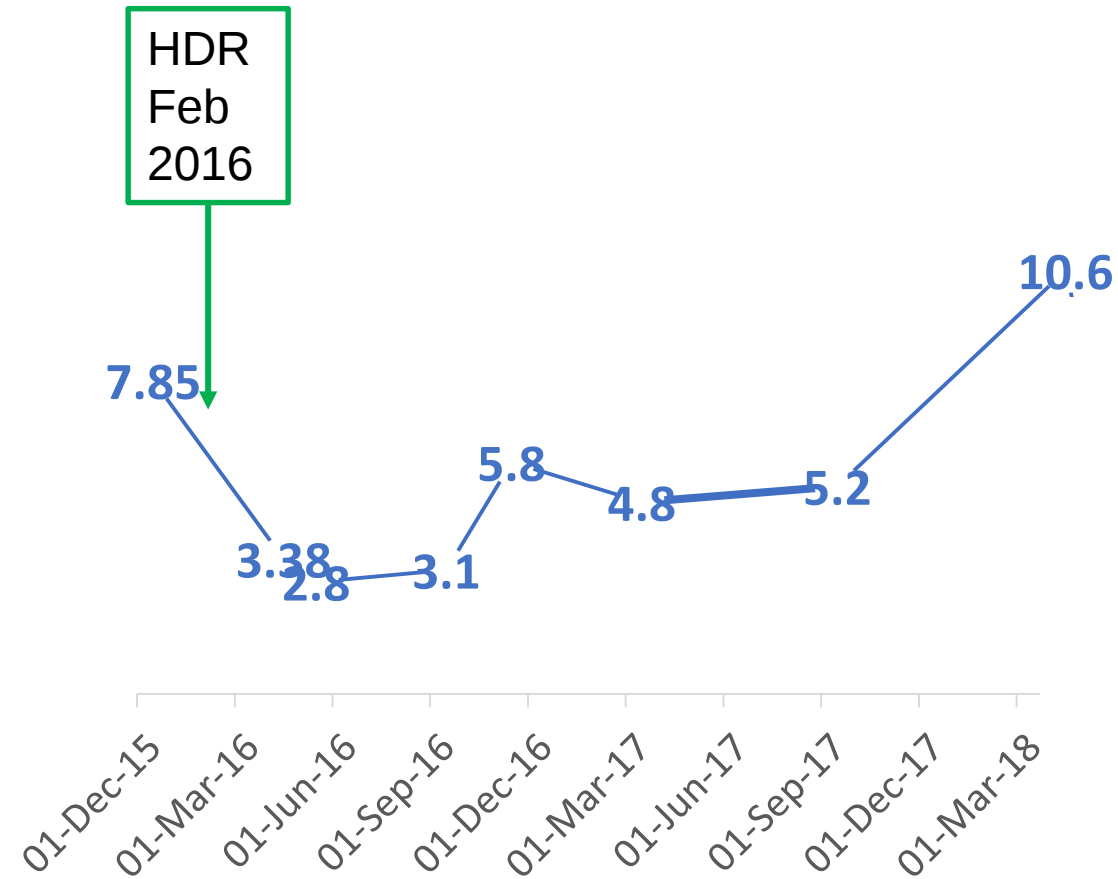
HDR 19 Gy + GTV Boost



Prostate V100: 97.6%
Prostate D90: 20.9 Gy

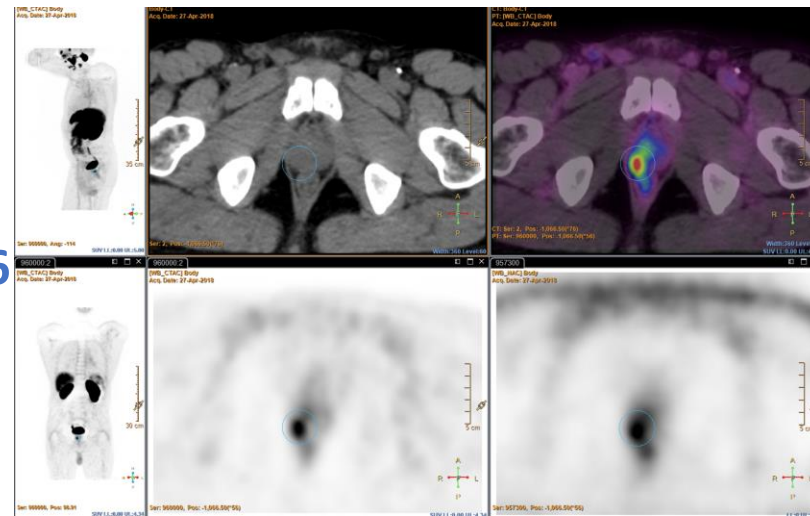
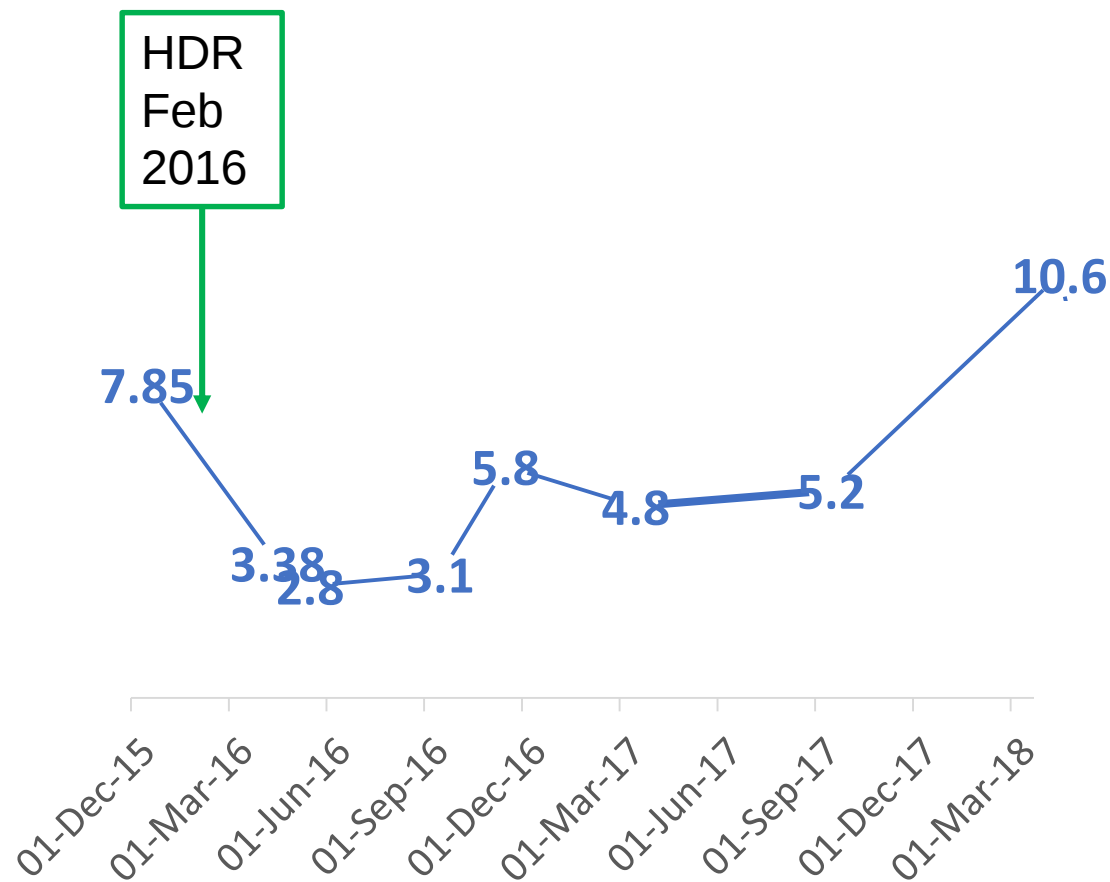
GTV D90: 30.5 Gy
Mean GTV: 45.3 Gy

PSA Profile



PSA Profile

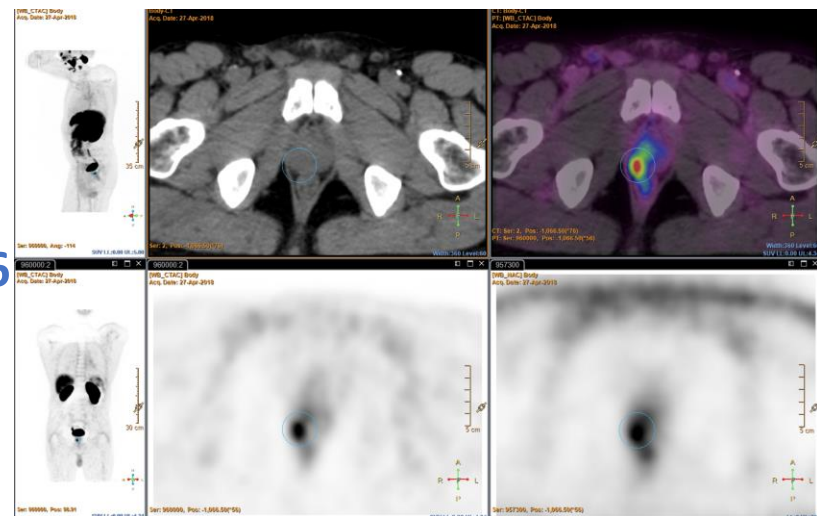
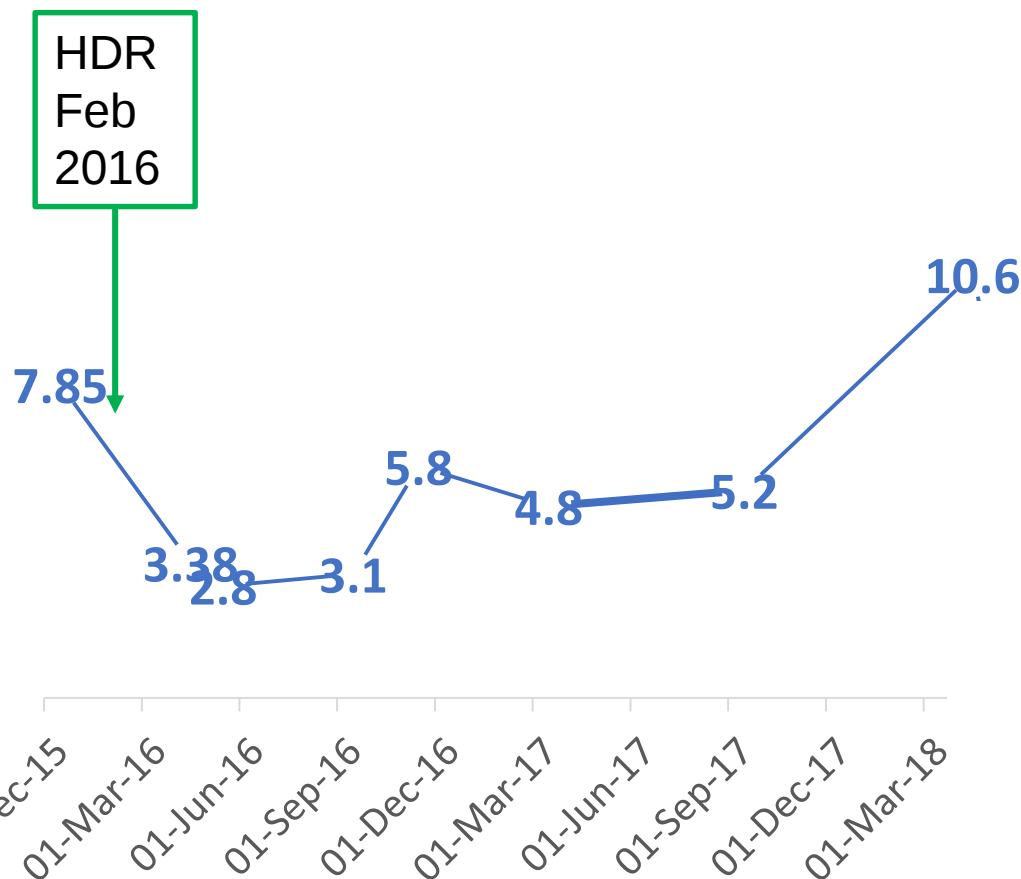
PSMA PET



Persistent disease right apex

PSA Profile

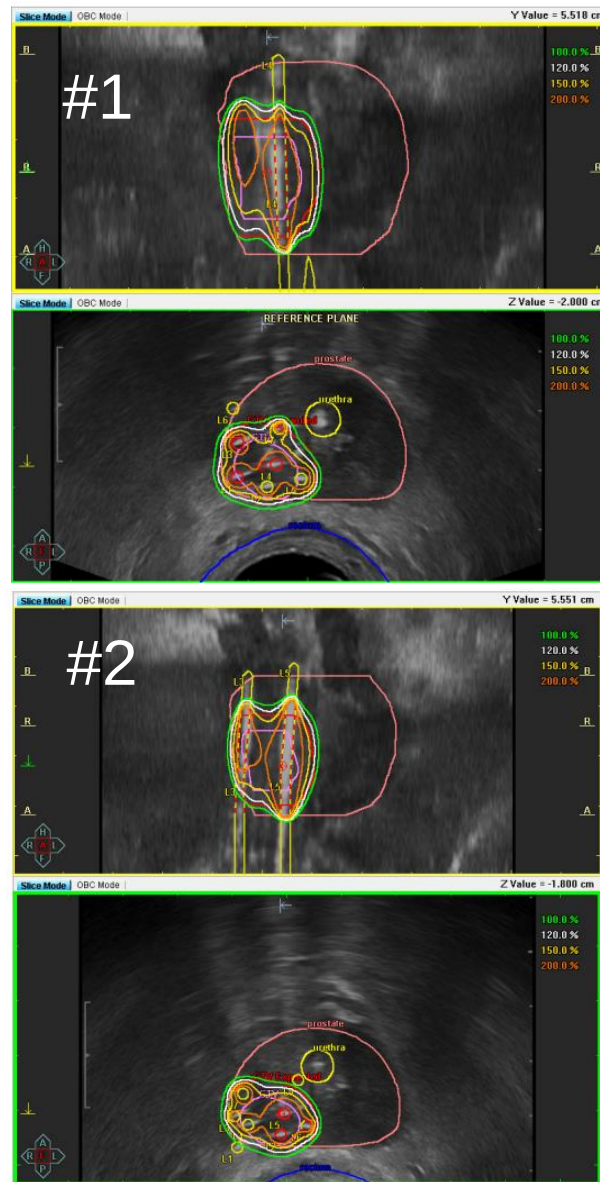
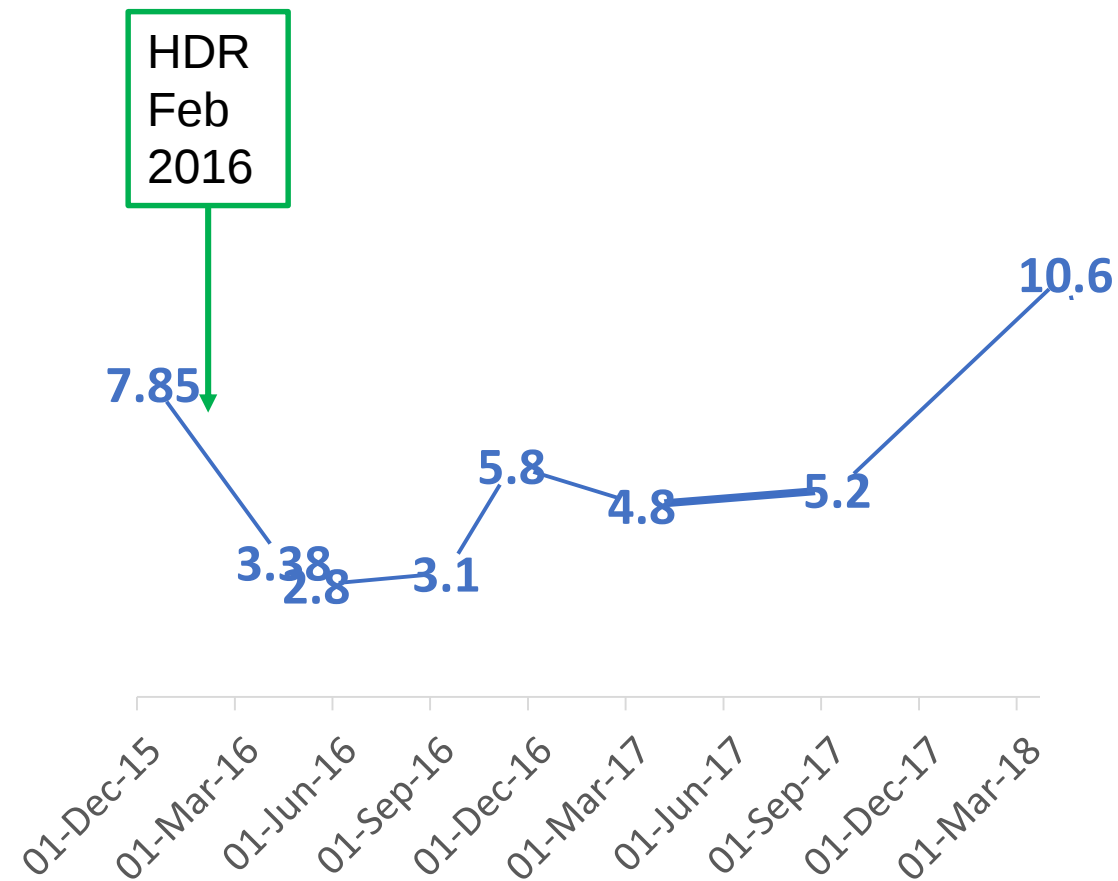
PSMA PET



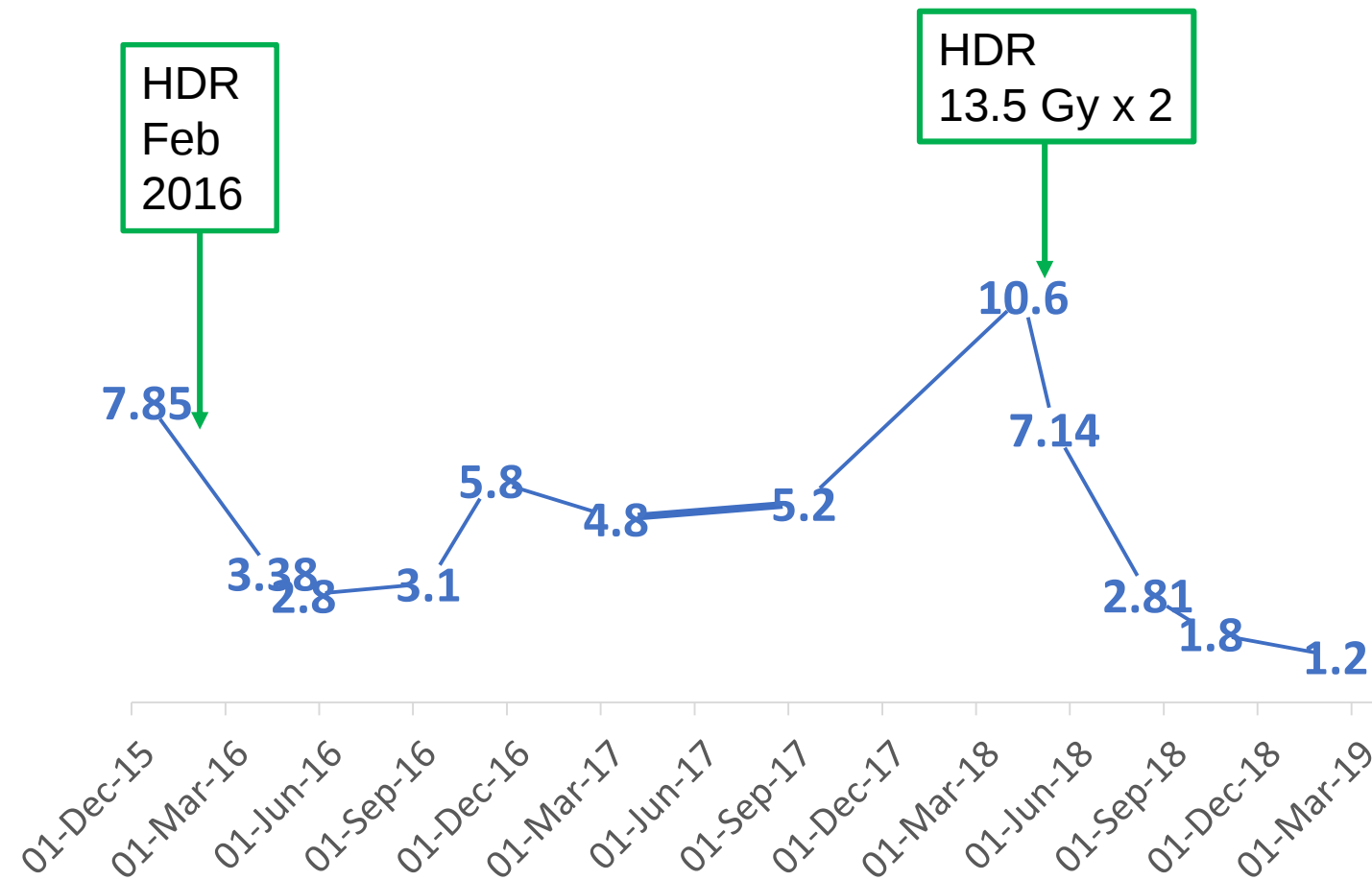
Biopsy:
G4+3 right apex 3/3
cores, 90% pattern 4
Systematic bx negative

PSA Profile

HDR 13.5 Gy x 2



PSA Profile



Conclusions

- **HDR Monotherapy in 2 or more fractions works really well**
 - **13.5 Gy x 2, 11.5 Gy x 3, 9.5 Gy x 4**
- **19 Gy x 1 may be associated with more late urinary symptoms and has unacceptably high local failure rate**
- **Not yet sure if single fraction with dose escalation to nodule will result in better outcome**