LDR Monotherapy vs. HDR Monotherapy

Is it time for LDR to retire?

Gerard Morton

Radiation Oncology
UNIVERSITY OF TORONTO

Sunnybrook
HEALTH SCIENCES CENTRE

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update

Joseph Chin, R. Bryan Rumble, Marisa Kollmeier, Elisabeth Heath, Jason Efstathiou, Tanya Dorff, Barry Berman, Andrew Feifer, Arthur Jacques,† and D. Andrew Loblaw

Recommendations

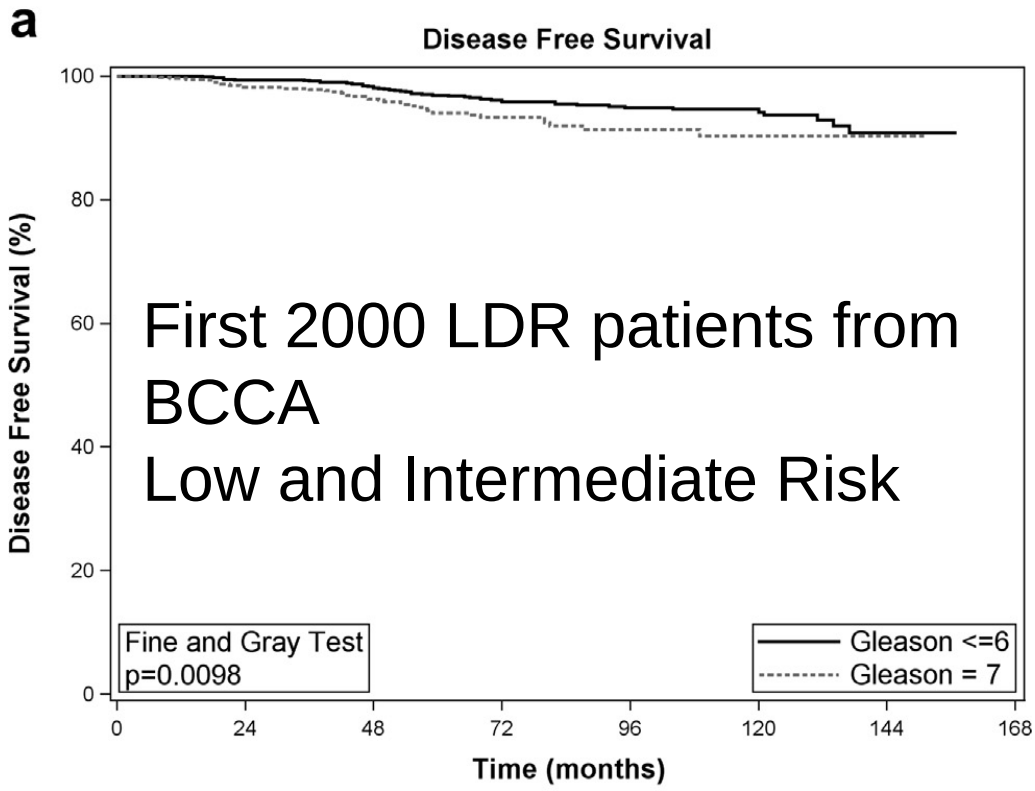
For patients with low-risk prostate cancer who require or choose active treatment, low–dose rate brachytherapy (LDR) alone, EBRT alone, and/or radical prostatectomy (RP) should be offered to eligible patients. For patients with intermediate-risk prostate cancer choosing EBRT with or without androgen-deprivation therapy, brachytherapy boost (LDR or high–dose rate [HDR]) should be offered to eligible patients. For low-intermediate risk prostate cancer (Gleason 7, prostate-specific antigen < 10 ng/mL or Gleason 6, prostate-specific antigen, 10 to 20 ng/mL), LDR brachytherapy alone may be offered as monotherapy. For patients with high-risk prostate cancer receiving EBRT and androgen-deprivation therapy, brachytherapy boost (LDR or HDR) should be offered to eligible patients. Iodine-125 and palladium-103 are each reasonable isotope options for patients receiving LDR brachytherapy; no recommendation can be made for or against using cesium-131 or HDR monotherapy. Patients should be encouraged to participate in clinical trials to test novel or targeted approaches to this disease.

Additional information is available at www.asco.org/Brachytherapy-guideline and www.asco.org/guidelineswiki.

J Clin Oncol 35.

LDR Seed Brachytherapy

LDR Implant



Morris et al, Brachytherapy 2014

LDR Seed Brachytherapy

LDR Implant

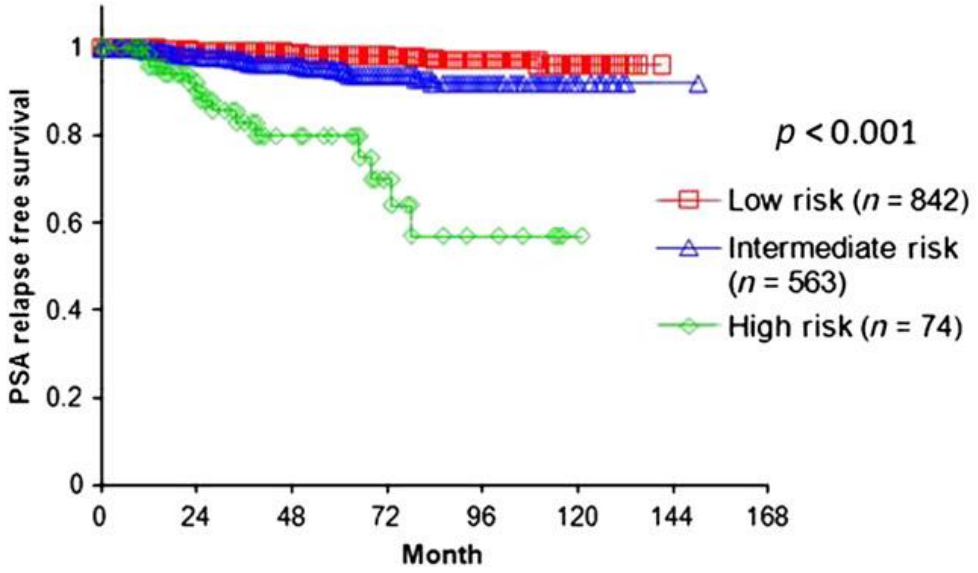


Fig. 1. PSA relapse-free survival for favorable-, intermediate-, and high-risk prostate cancer patients treated with brachytherapy ($p < 0.001$). PSA = prostate-specific antigen.

Zelefsky et al, Brachytherapy 2012 : 11(4): 245-9

LDR Seed Brachytherapy

LDR Implant

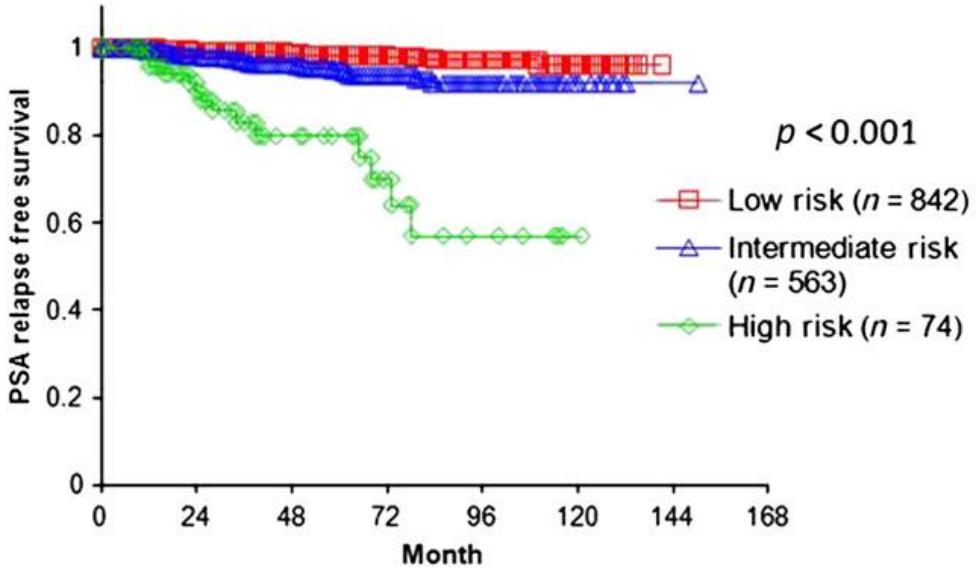
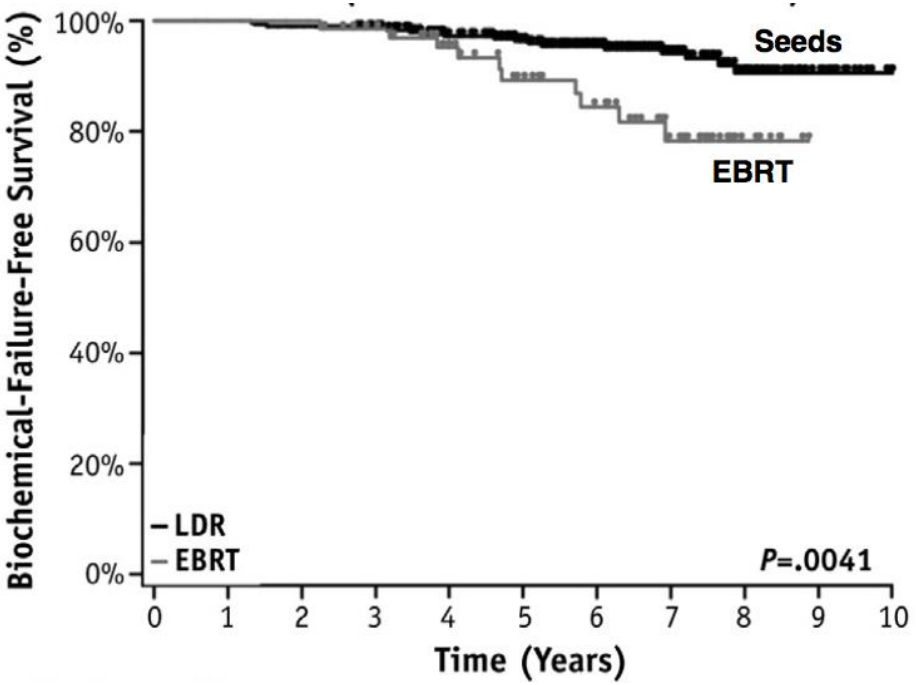


Fig. 1. PSA relapse-free survival for favorable-, intermediate-, and high-risk prostate cancer patients treated with brachytherapy ($p < 0.001$). PSA = prostate-specific antigen.

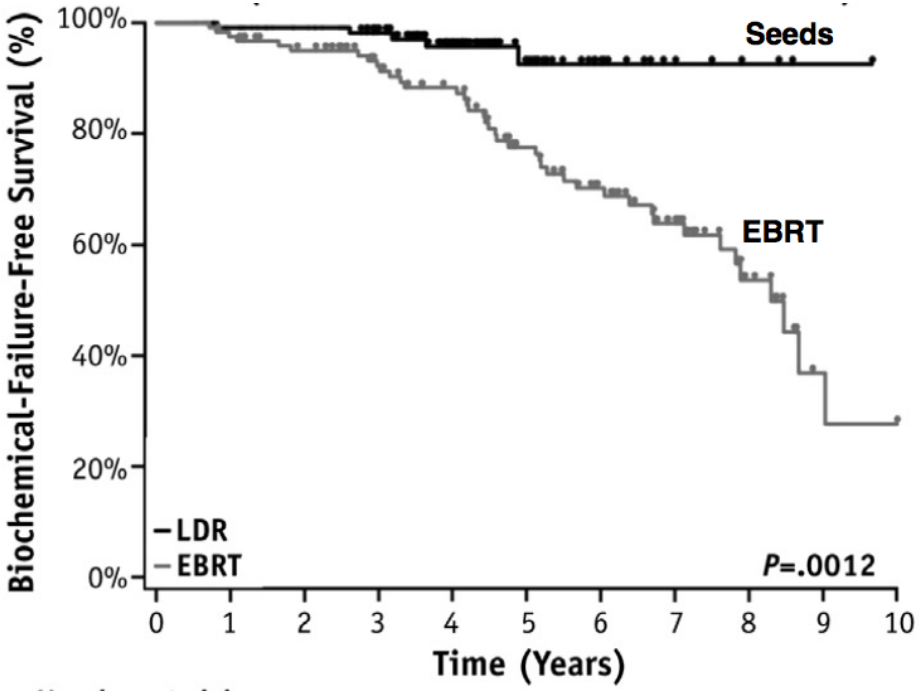
Zelefsky et al, Brachytherapy 2012 : 11(4): 245-9

EBRT Challengers

Low Risk



Intermediate Risk



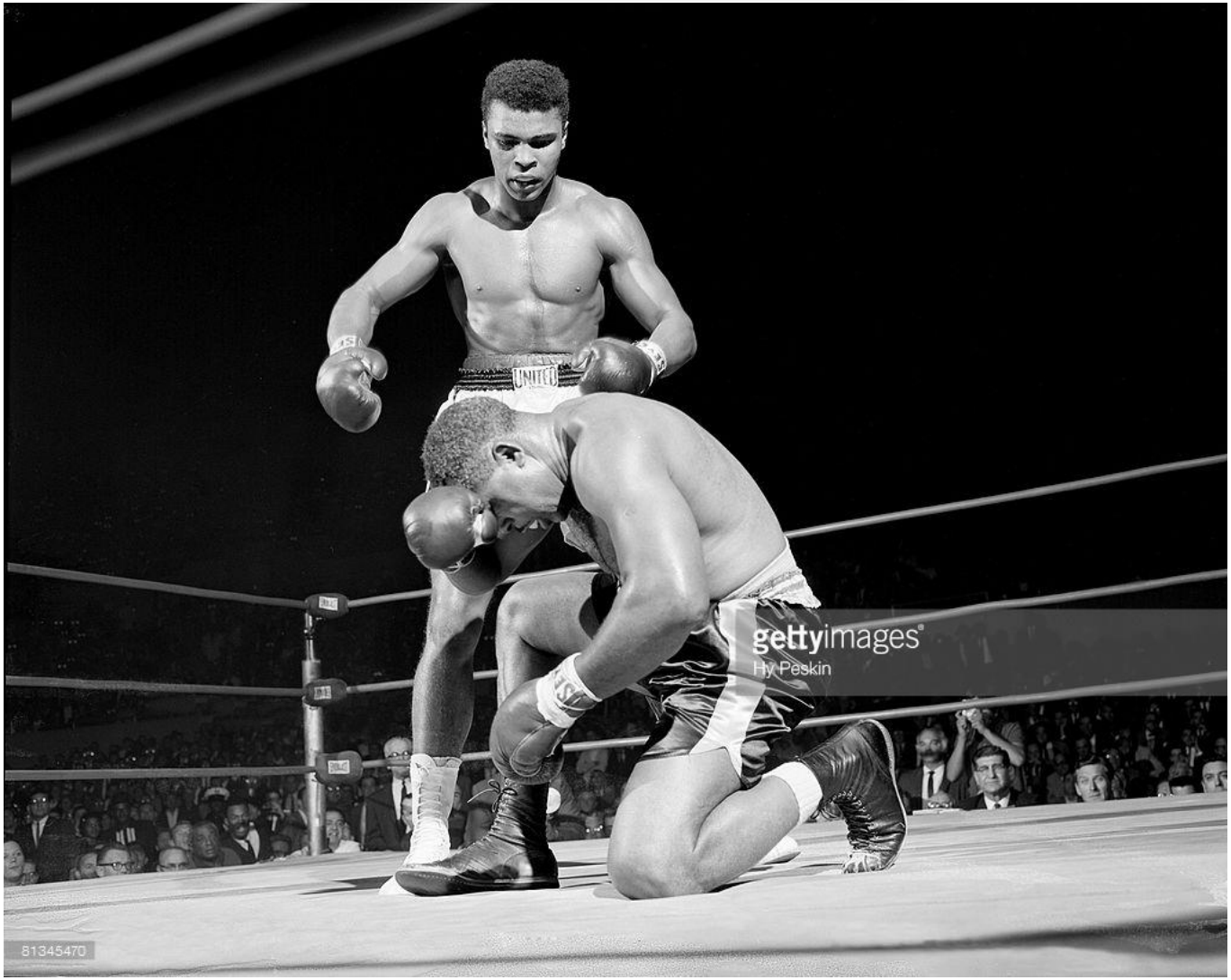
PROCARS Database

Smith et al, Int J Radiother Oncol Biol Phys 91:505-16, 2015

LDR Monotherapy

- **The undefeated champion for low and favourable intermediate risk prostate cancer**
- **Has defeated all challengers**
  - **Nadir PSA values: typically < 0.05 ng/ml**
  - **bDFS: typically > 90%**

LDR vs. HDR?



However – LDR seed implants have some disadvantages..

- Seeds displacement – so dose delivered may differ from that planned
- Cost of seeds
- Dose is delivered slowly
  - so may not be best for more rapidly growing cancers
  - so side-effects take months to resolve

HDR Monotherapy

- Consistent Dosimetry – no seed displacement
- Reusable source
- Rapid dose delivery
  - Repopulation not a problem
  - Rapid resolution of side effects

HDR Monotherapy – the safe!

Author	n	Gy x f	Dose (Gy)	Median FU (yrs)	bDFS		
					LR	IR	HR
Yoshioka	190	6 x 8 6 x 9 6.5 x 7	48 54 45.5	7.6		93%	81%
Komiya	51	6.5 x 7	45.5	1.4	-	-	-
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%		

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

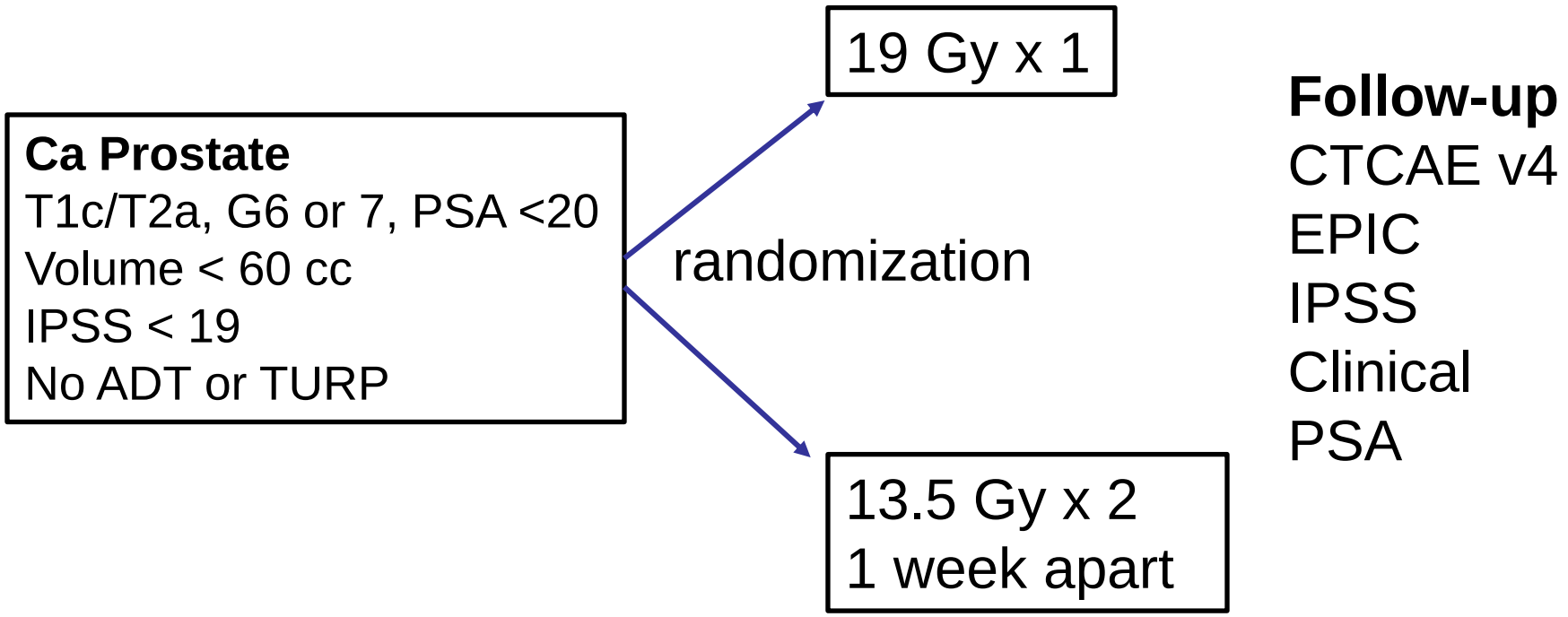
HDR Monotherapy: the daring!

Author	n	Gy x f	Dose (Gy)	Median FU (yrs)	bDFS		
					LR	IR	HR
Barkati	19 19 19 22	10 x 3 10.5 x 3 11 x 3 11.5 x 3	30 31.5 33 34.5	3.3	85%		
Zamboglou	492 226	9.5 x 4 11.5 x 3	38 34.5	5-7.7 2.1	95%	93%	93%
Kulkielka	77	15 x 3	45	4.7	97%		
Jawad	319 79 96	9.5 x 4 12 x 2 13.5 x 2	38 24 27	5.5 3.5 2.9	98% 92% 100%		
Hoskin	30 25 109 33	8.5 x 4 9 x 4 10.5 x 3 13 x 2	34 36 31.5 26	5 4.5 3 0.5		99%	91%

HDR Monotherapy: the bold!

Author	n	Gy x f	Dose (Gy)	Median FU (yrs)	bDFS		
					LR	IR	HR
Prada	60	19 x 1	19	6	66% (6 yrs)		
Hoskin	115 24 26	13 X 2 19 x 1 20 x 1	26 19 20	-	-	-	-
Krauss	63	19 x 1	19	2.9	93% (3 yrs)		

Sunnybrook Randomized Trial



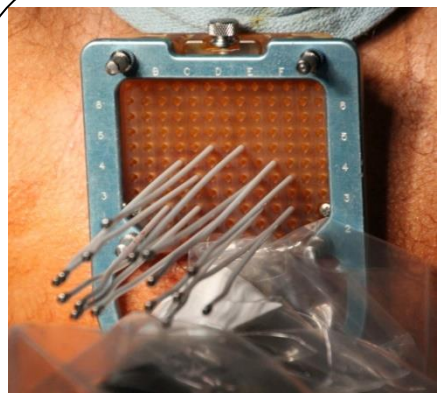
170 patients accrued June 2013 to April 2015

Patient Characteristics

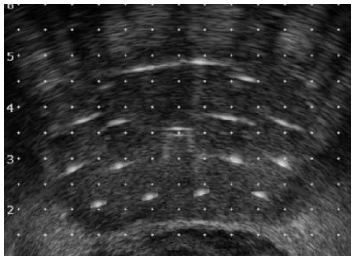
	19 Gy x 1 (n=87)	13.5 Gy x 2 (n=83)	P-value
Median Age (range)	65 (46,80)	65 (49,80)	0.7364
Stage			
T1c	67	63	0.8648
T2a	20	20	
Median PSA (range)	6.4 (1.1,13.7)	6.3 (2.0,16.0)	0.9366
Gleason Score			
Gleason 6	28 (32%)	19 (23%)	0.2298
Gleason 7	59 (68%)	64 (77%)	
Risk Grouping			
Low	23 (26%)	16 (19%)	0.5295
Intermediate	64 (74%)	67 (81%)	

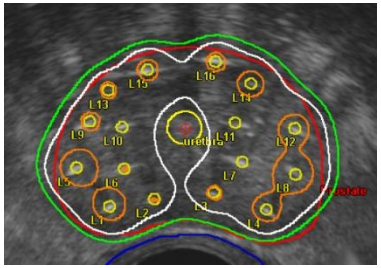
Median Follow-up 30 months

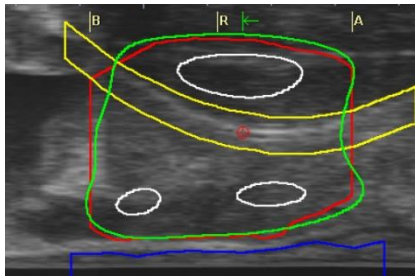
Treatment Details



TRUS Guided







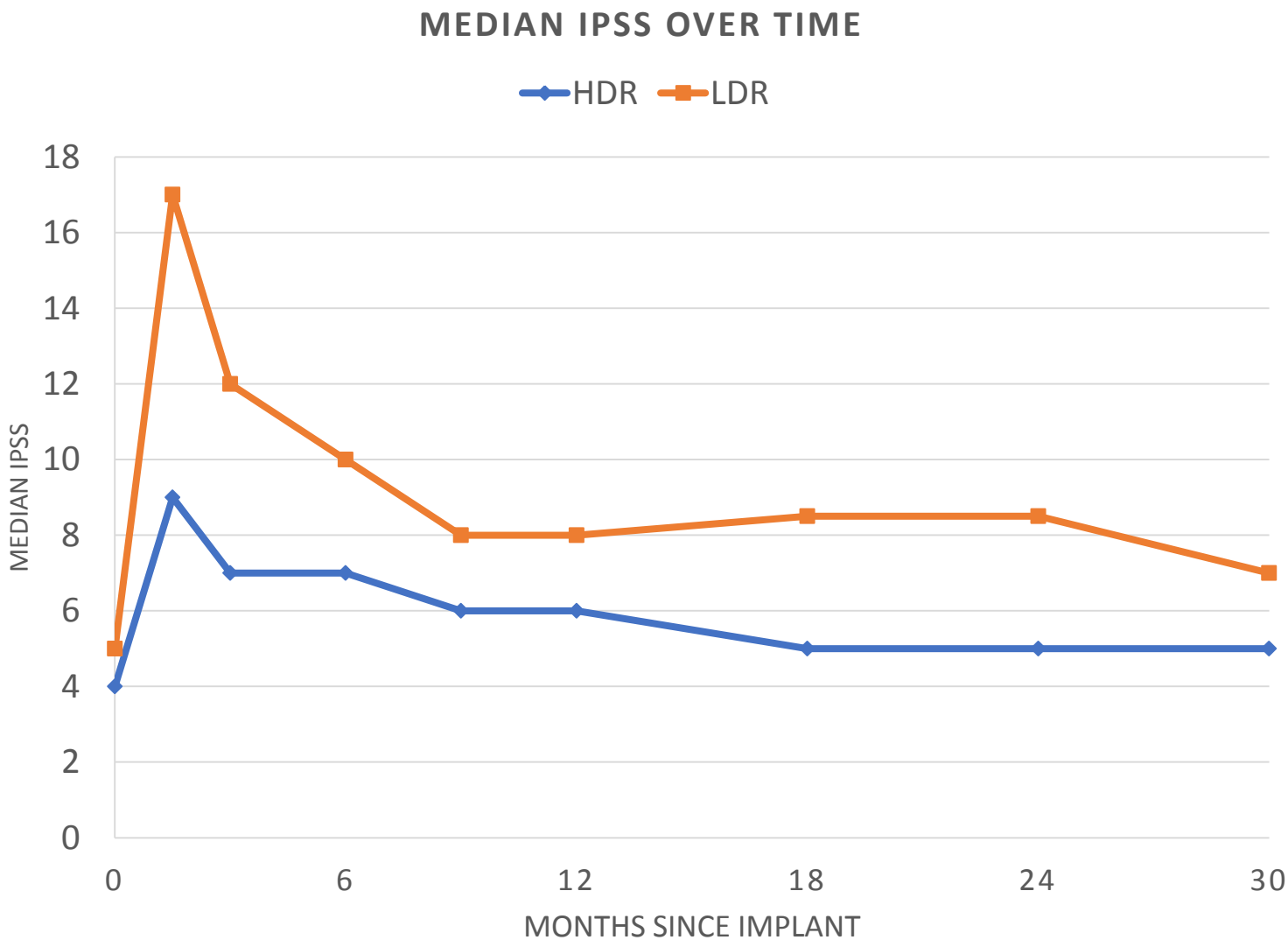
- PTV = prostate +0-3 mm
- Median V100 = 97%
- Median V200 = 11%
- Median D90 = 110%
- Median urethra max = 120%
- Relative dosimetry same in both arms

Toxicity

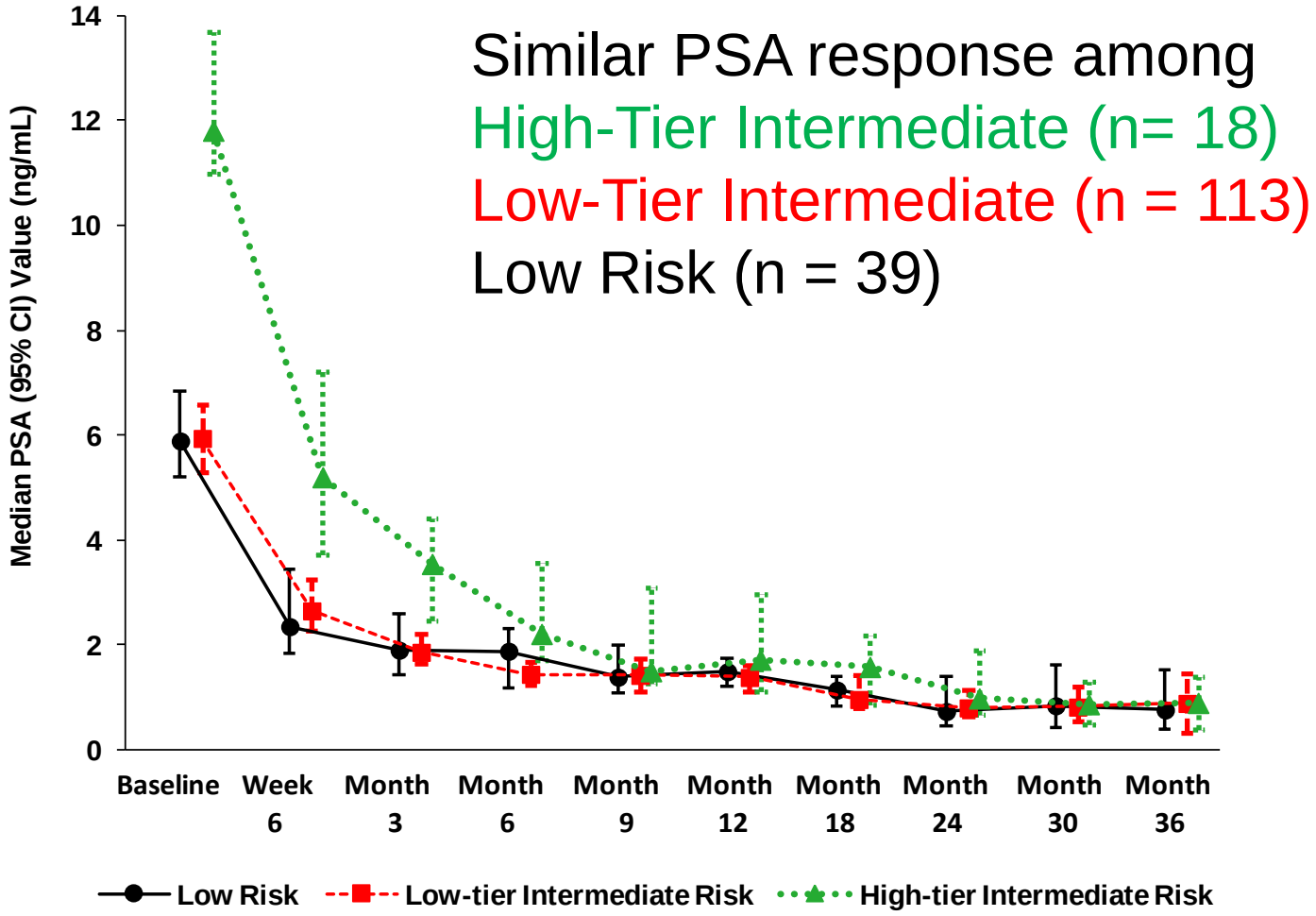
- Minimal toxicity in either arm
- No GI toxicity
- Acute retention rate 2.4%
- 1 acute Grade 3 toxicity (haematuria)
- 1 late Grade 3 toxicity (stricture)
- Less urinary symptoms and less erectile dysfunction in single fraction arm within first year

Radiother Oncol 122: 87-92, 2017

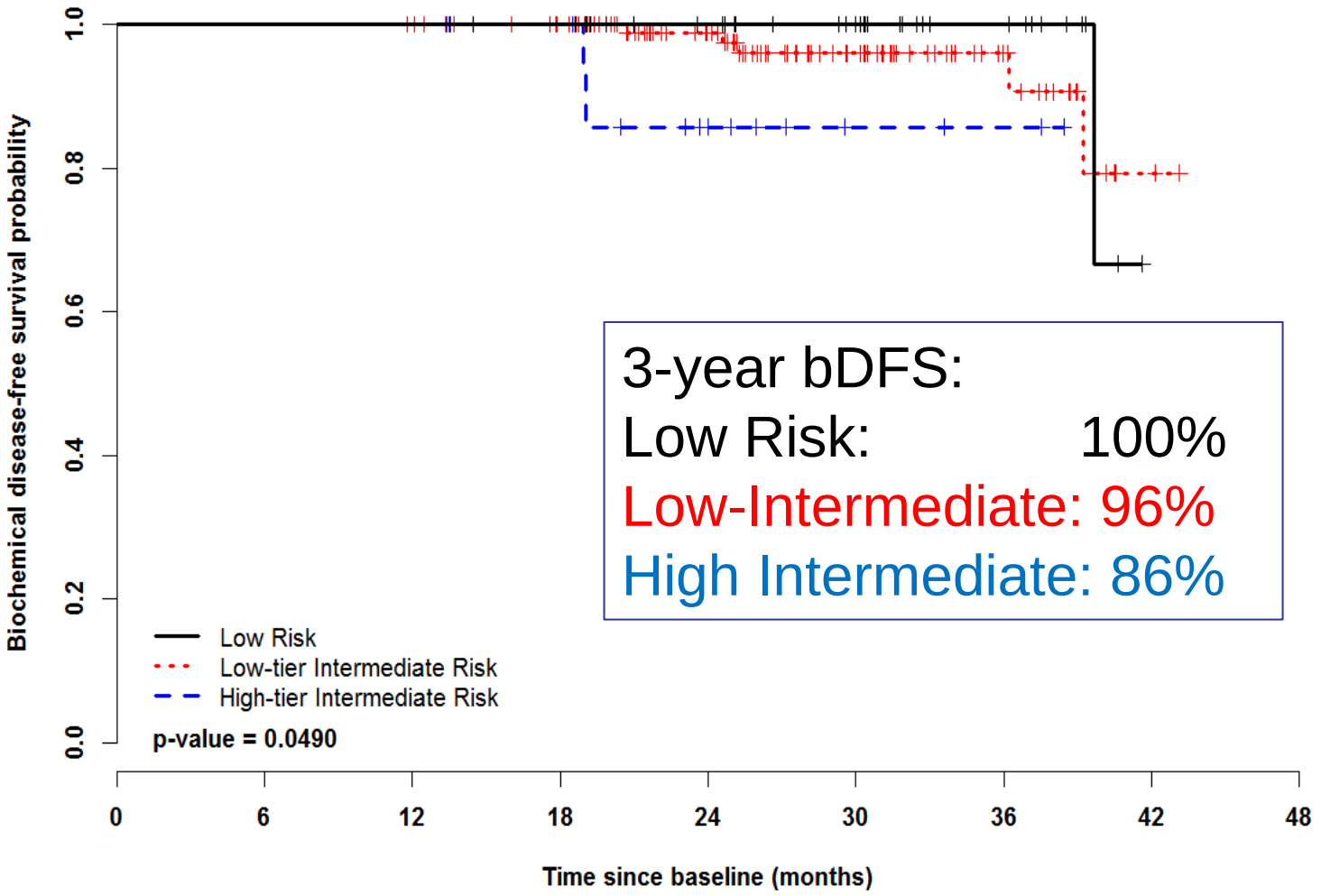
Urinary Symptoms: HDR vs. LDR



HDR PSA Response

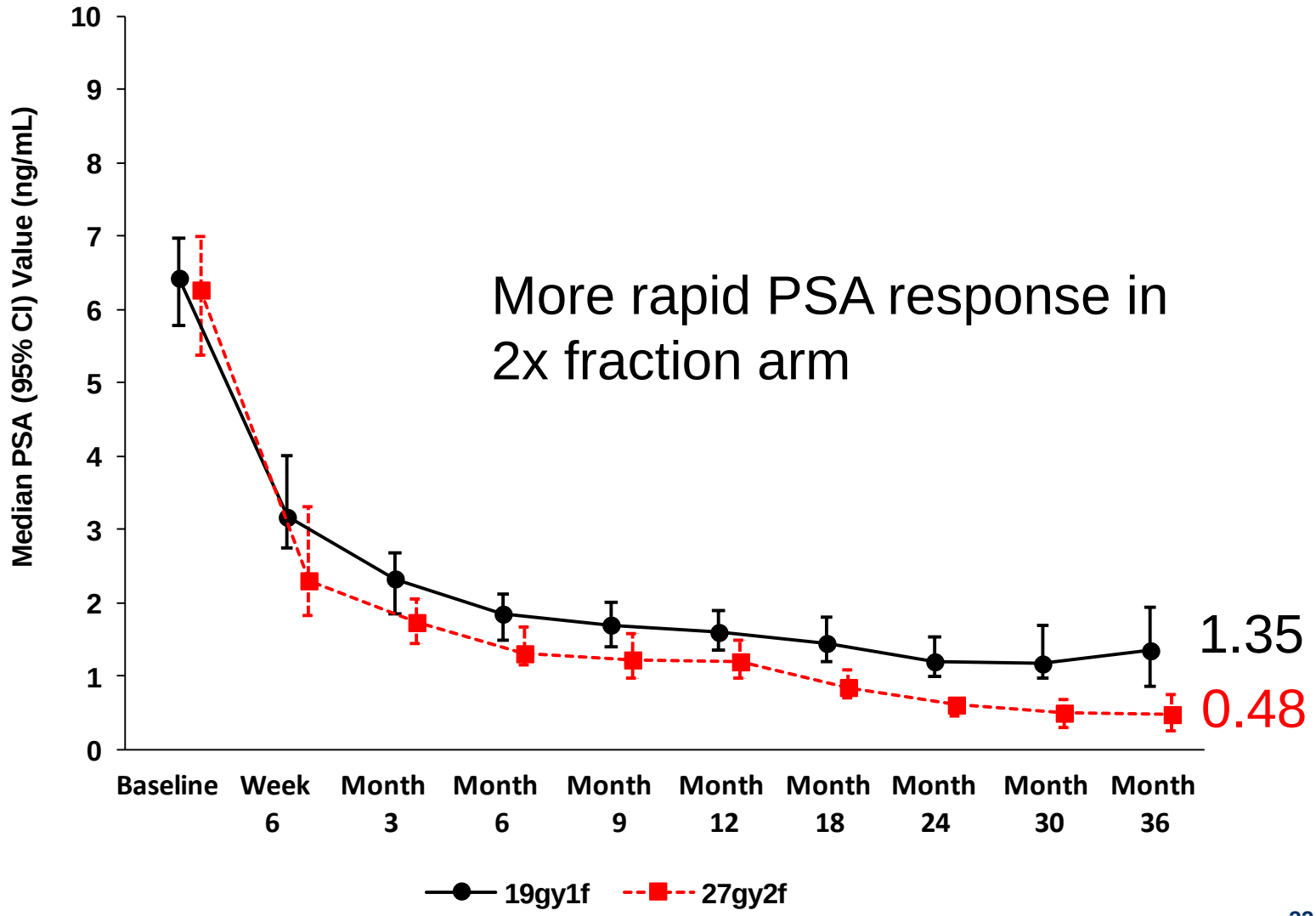


bDFS by Risk Groups (all patients)

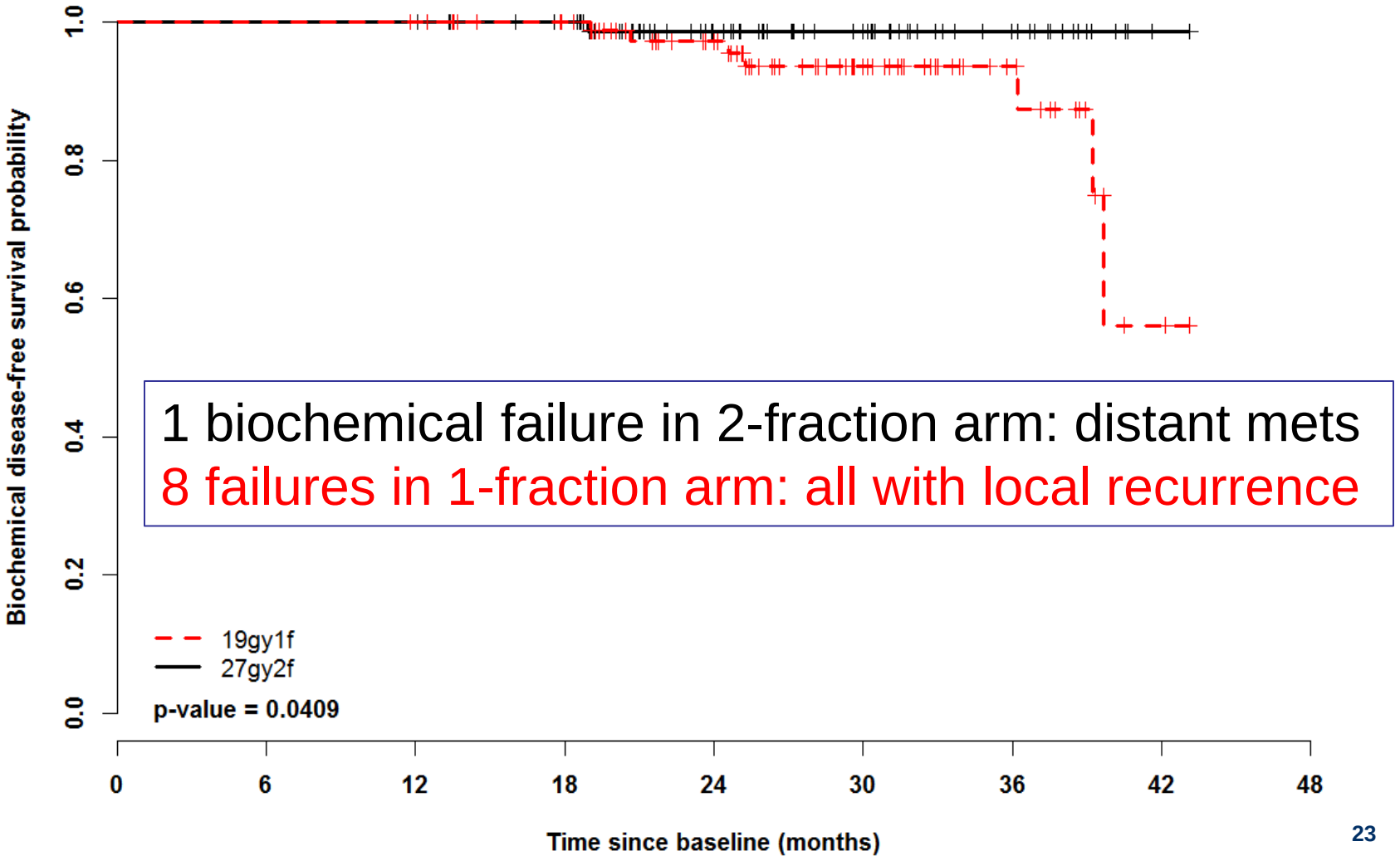


3-year bDFS:
Low Risk: 100%
Low-Intermediate: 96%
High Intermediate: 86%

PSA Response by treatment arm



Disease-Free Survival by treatment arm



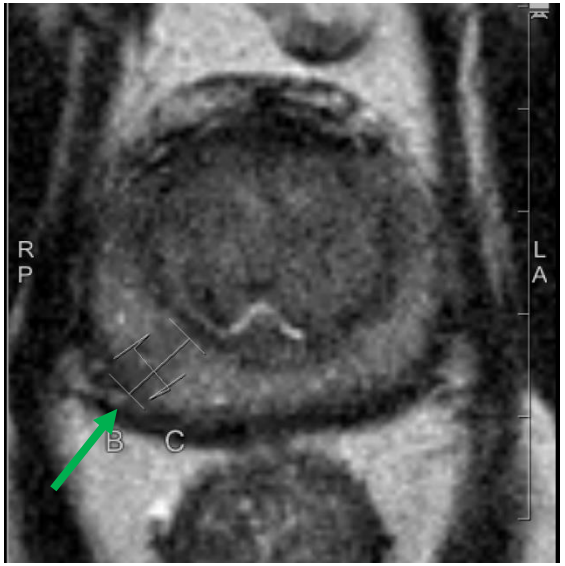
1 biochemical failure in 2-fraction arm: distant mets

8 failures in 1-fraction arm: all with local recurrence

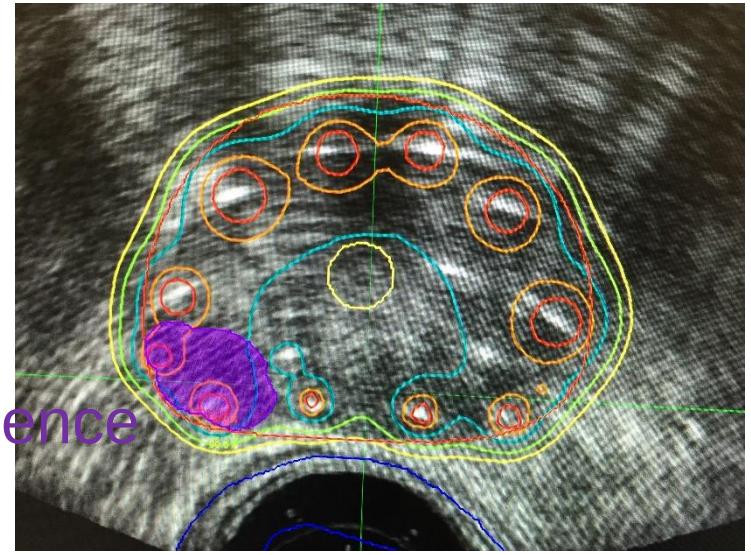
HDR Monotherapy Randomized Trial

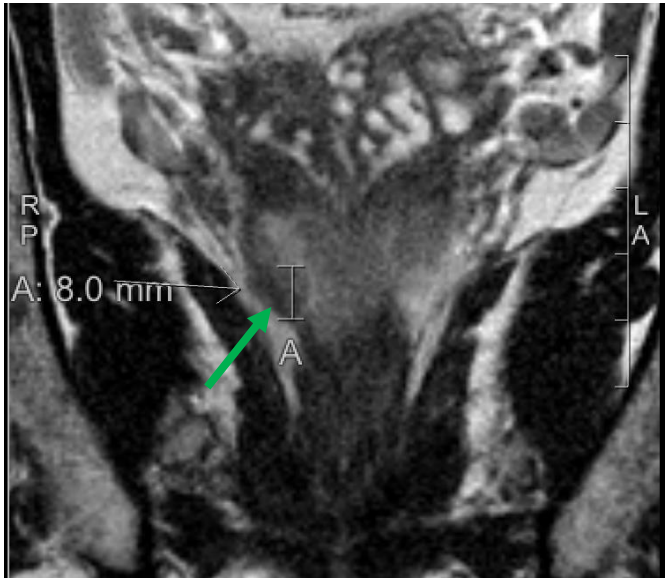
- HDR Monotherapy in 1 or 2 fractions is really well tolerated
- Less urinary symptoms than LDR
- High local recurrence rate with single 19 Gy, almost always at site of initial disease
  - Potential for further dose escalation

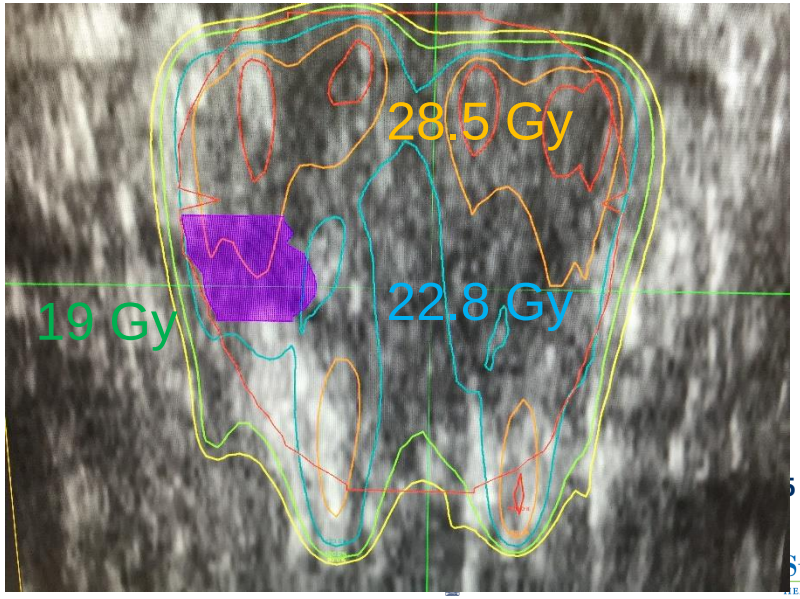
Local Recurrence Analysis



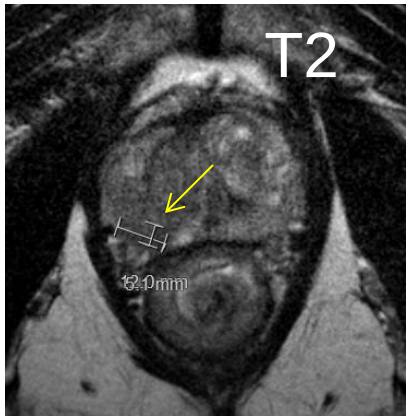
Recurrence

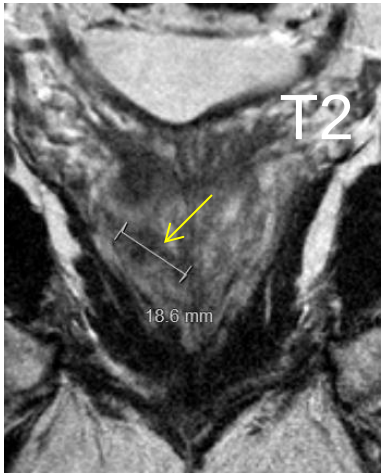


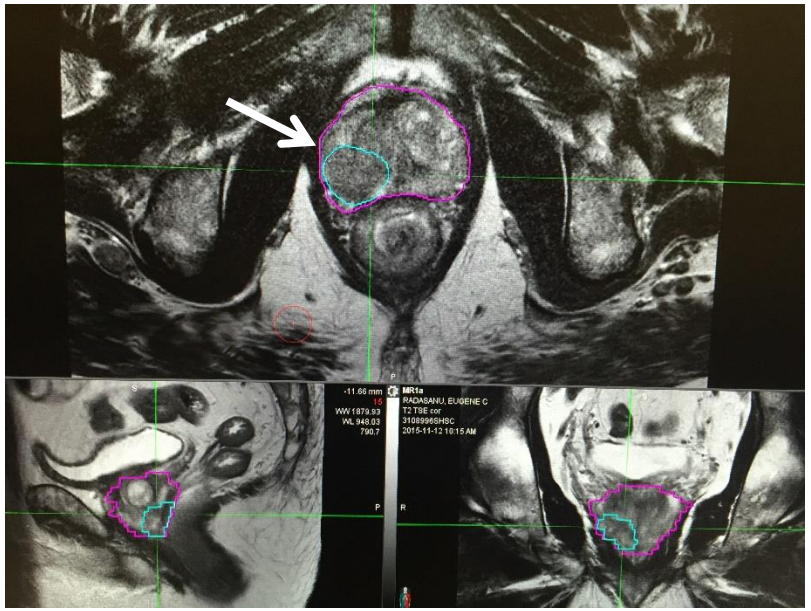


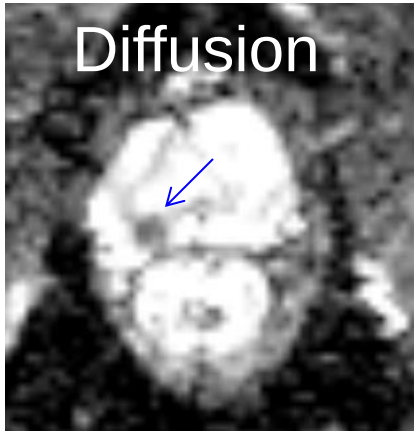


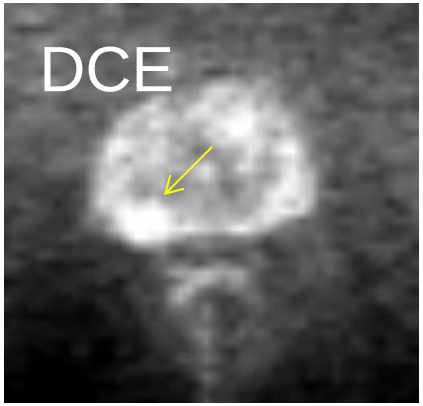
Dose escalation to GTV with HDR

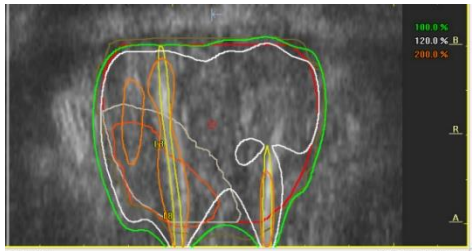


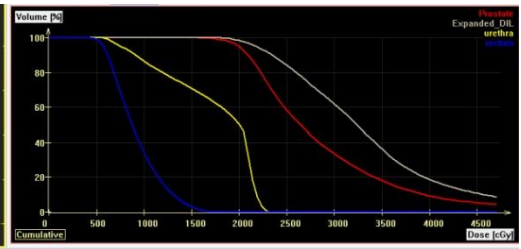






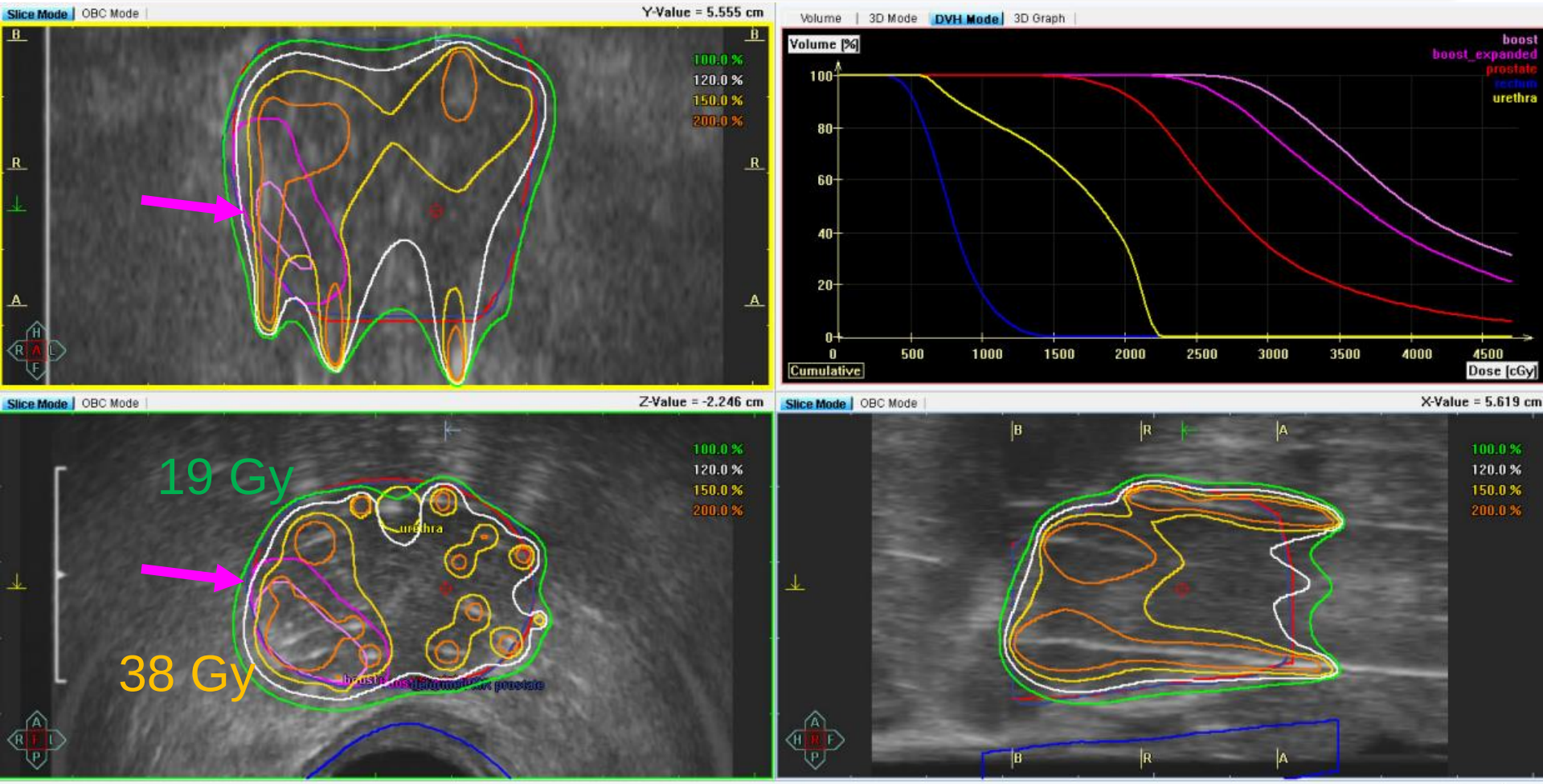






Dose escalation to GTV using MR/TRUS fusion

Dose escalation to GTV with HDR



Prostate: V100 96%, D90 109% (21 Gy), Mean dose 30 Gy

GTV: V100 100%, D90 163% (31 Gy), Mean Dose 47 Gy

Time for the old champ to retire?

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

Eligibility criteria:

- 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

RANDOMIZE

Arm 1:
LDR brachytherapy with I-125 to a total dose of 144 Gy

Arm 2:
HDR brachytherapy: 19 Gy in 1 fraction with intraprostatic boost to GTV

N=232

Conclusions

- LDR Monotherapy
  - Delivers ablative dose to the prostate
  - Durable long term cancer control
  - Short to medium term urinary toxicity
- HDR Monotherapy
  - Well fractionated protocols likely have same efficacy as LDR
  - Less short to medium term urinary toxicity
  - Single fraction protocols attractive but unproven
  - GTV dose painting
- Await our randomized trial!