BC CANCER
Provincial Health Services Authority

Update on Long term outcomes of HDR prostate brachytherapy

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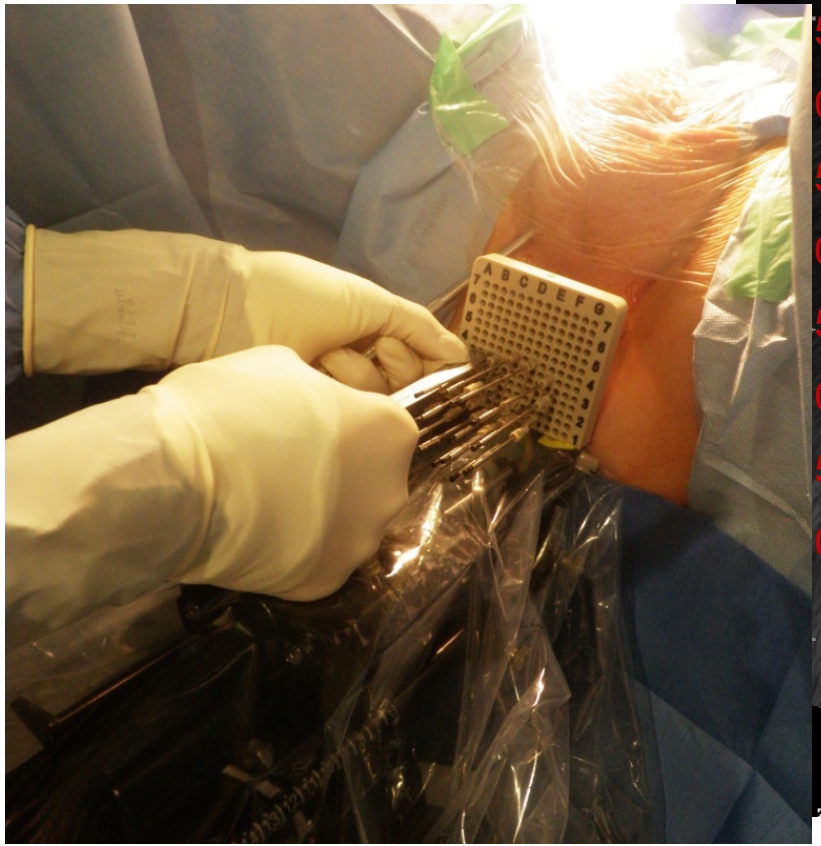
Disclosures

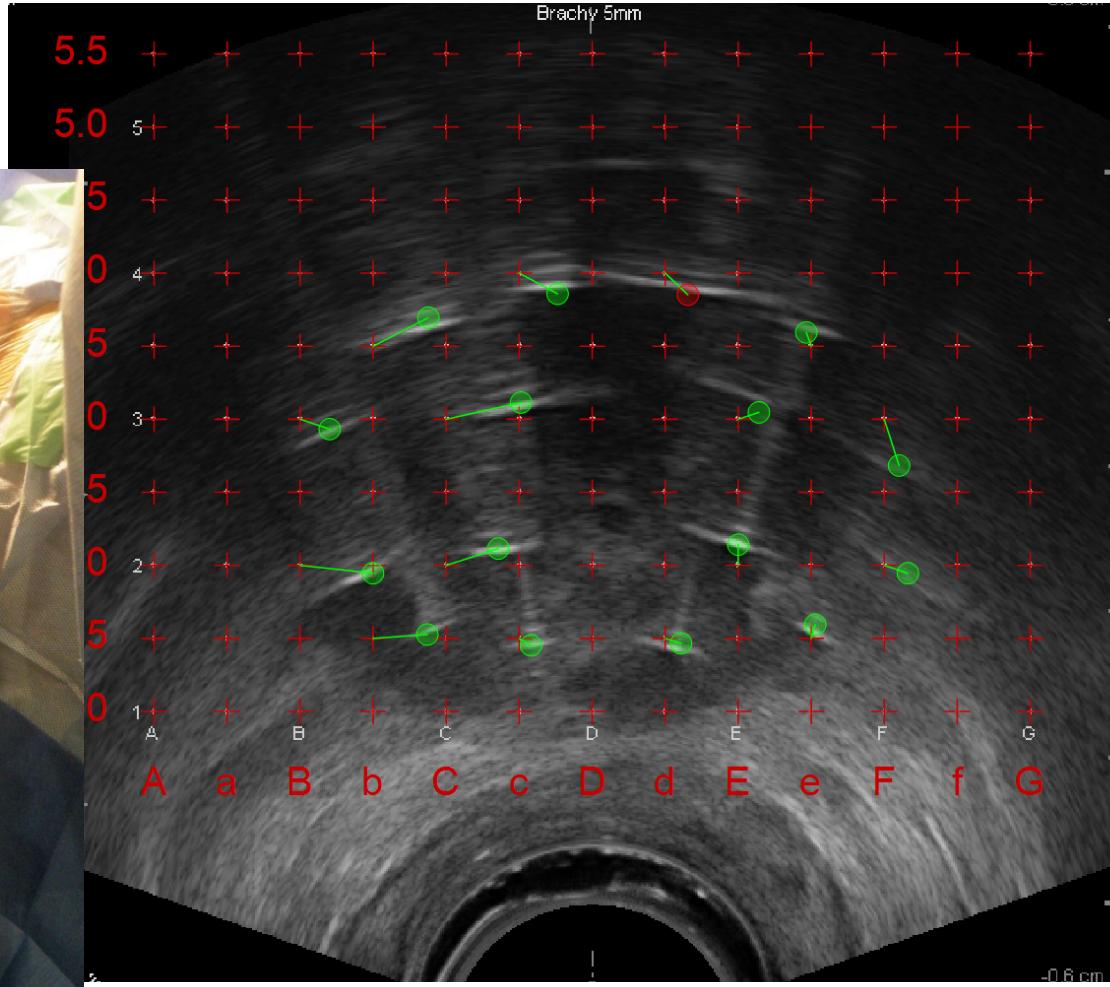
- Advisory Board/honoraria: Varian
- Advisory Board: Breast Microseed
- Speaker Honoraria: Abbvie
- Speaker Honoraria: Sanofi
- Research Funding: Ferring

Rationale for HDR

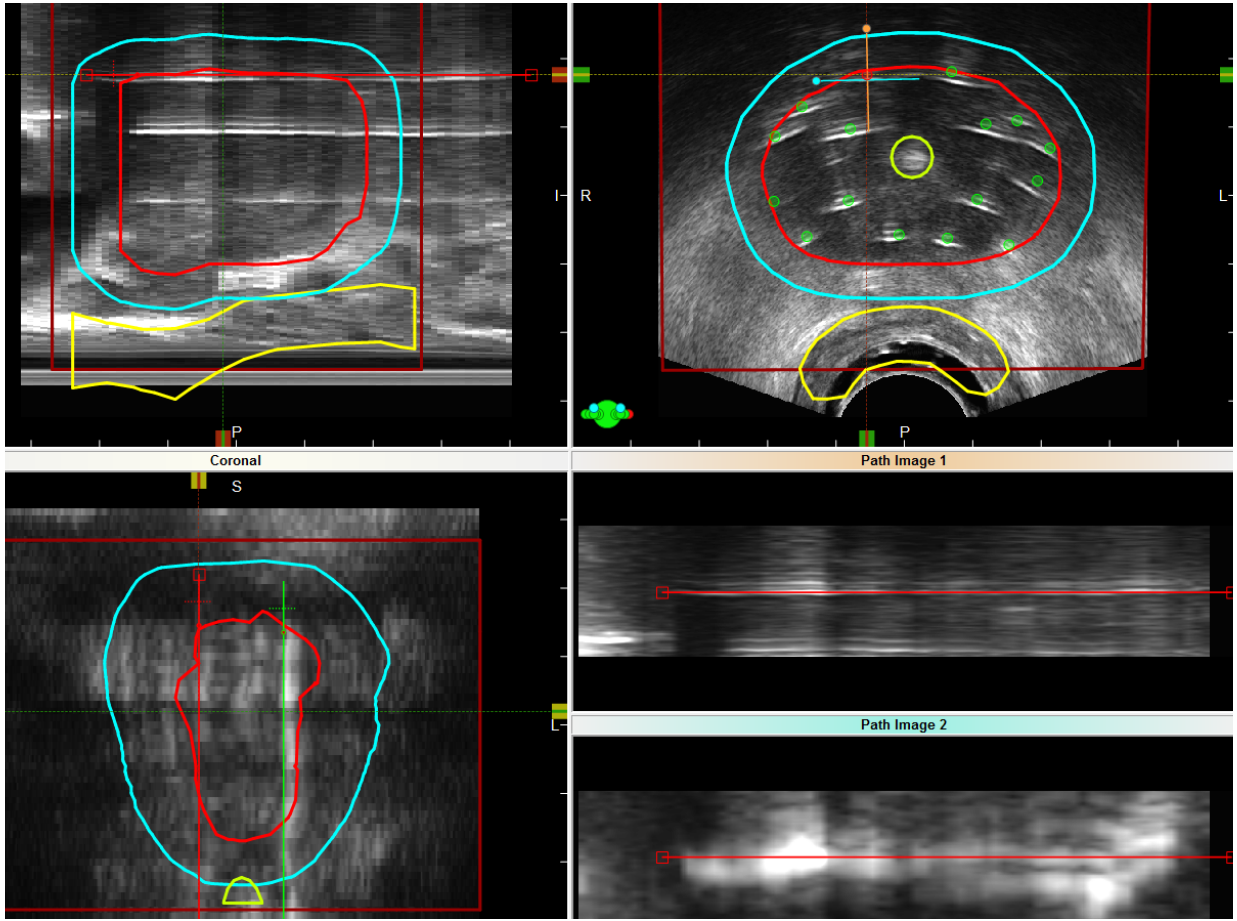
- Radiobiologic:
  - Low α/β ratio for prostate cancer favors large dose per fraction
- Technical
  - Exquisite dose optimization through manipulation of source dwell positions and durations
  - No organ motion or set-up error
  - No seed migration
  - No alteration of delivered dose because of edema
- Economical
  - One Ir-192 source for multiple treatments over 90 days

Needle insertion under anesthesia

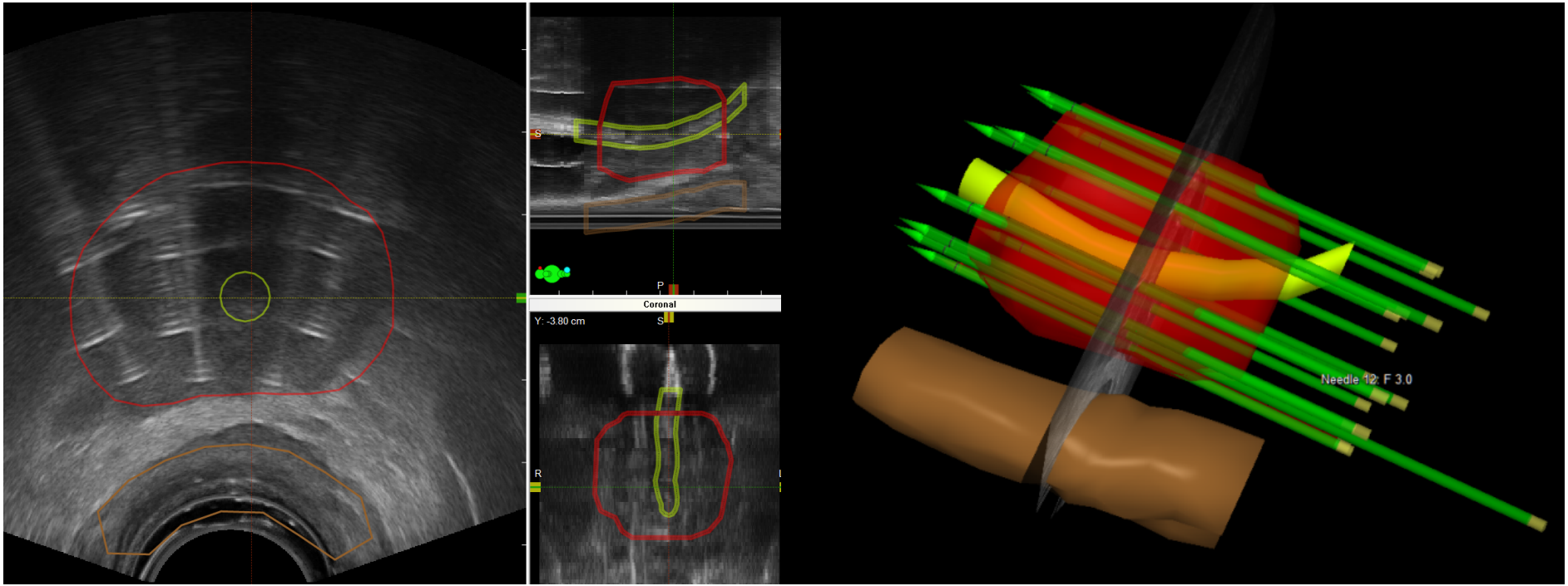


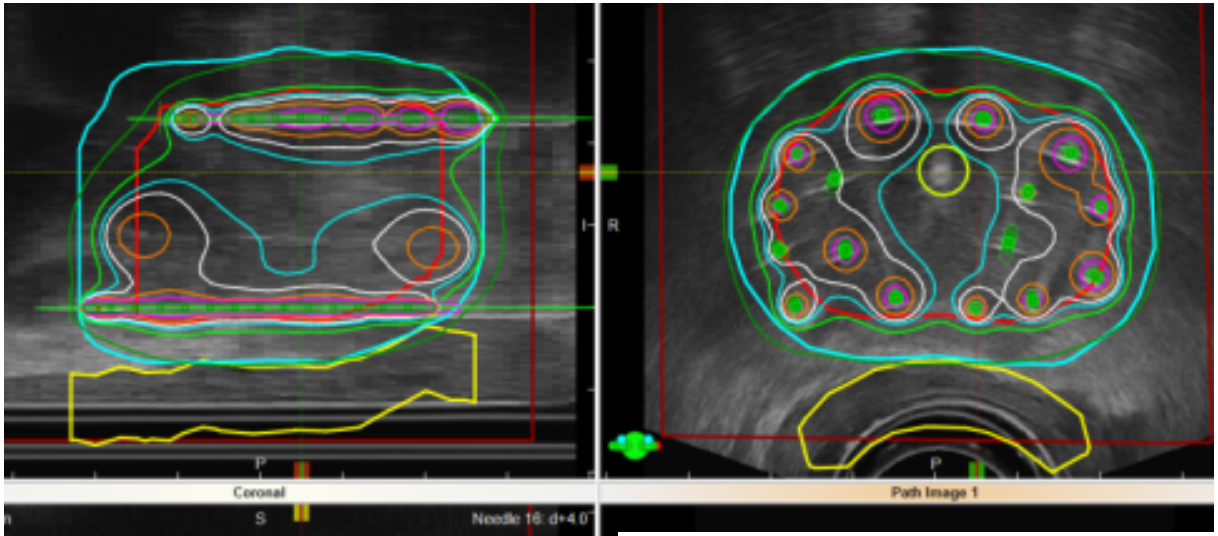


Needle track identification

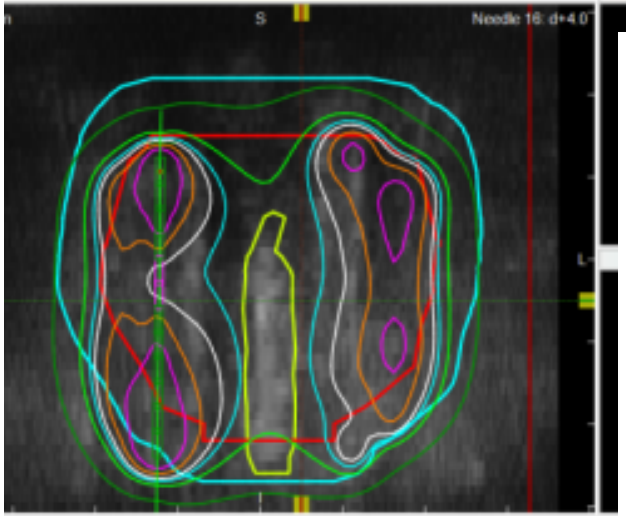


Contouring of prostate and adjacent organs





Inverse Planning



Pre set dose constraints

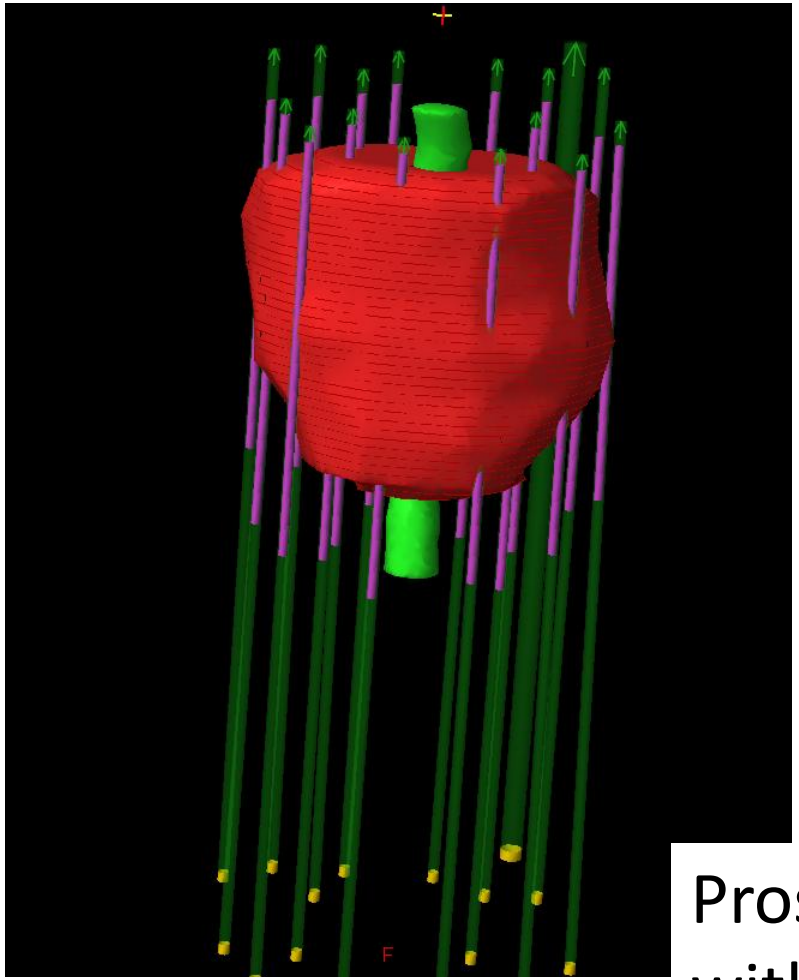
Prostate V100> 98%

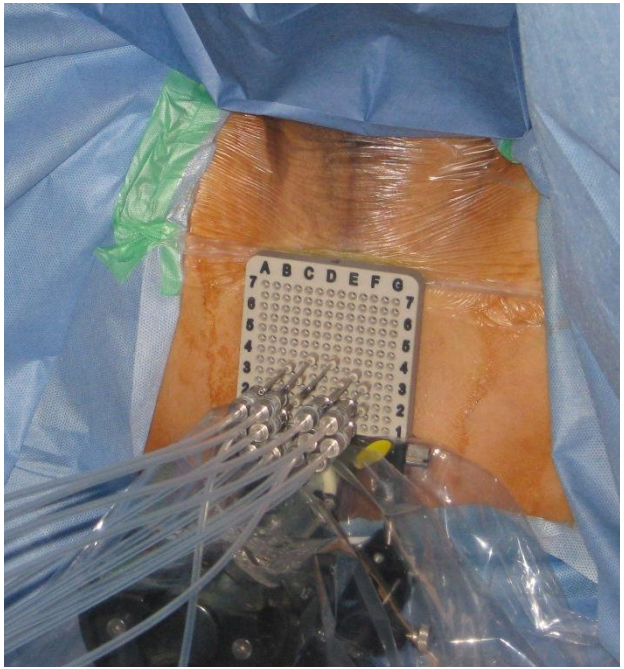
V125 55-63%

V150 27-32%

Urethral V115: 0%

Rectal D1cc < 7 Gy (70%)





Transfer tubes connected and ready to treat

Prostate reconstructed with catheters

Patient selection

- Gland size > 70-80 cc
- Previous TURP within 3 months
- IPSS > 20 or obstructed voiding/retention
- Significant pubic arch interference
- Lithotomy position not possible
- Not fit for anesthesia

Evolution of HDR over 2 decades

- Multiple smaller fractions ➔fewer larger fractions
- Overnight hospitalization ➔ out patient procedure
- Boost ➔ Monotherapy
- CT-based planning (6 hours with multiple patient movements) ➔ US-based planning (2 hours from probe-in to treatment finished)

BED OF EBRT+ HDR BOOST

DOSE LEVEL	BED $\alpha/\beta = 1.2$	BED Total
5.50 Gy x 3	92	215
6.00 Gy x 3	108	231
6.50 Gy x 3	125	248
8.25 Gy x 2	130	253
8.75 Gy x 2	145	268
9.50 Gy x 2	169	292
10.50 Gy x 2	205	327
11.50 Gy x 2	243	366
15 Gy x 1	165	272

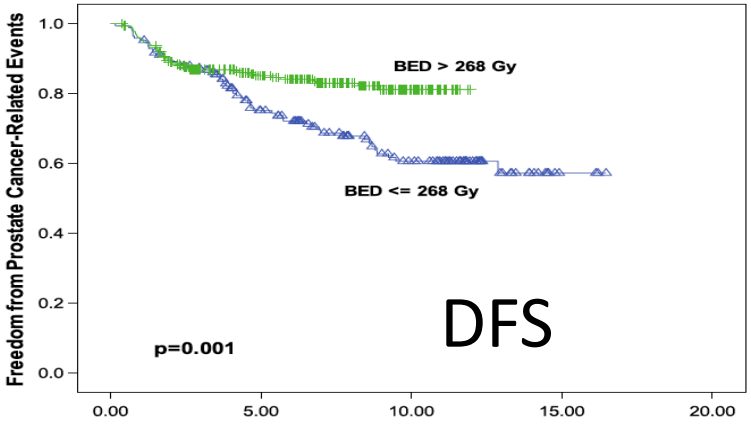
EBRT 46Gy/23fx

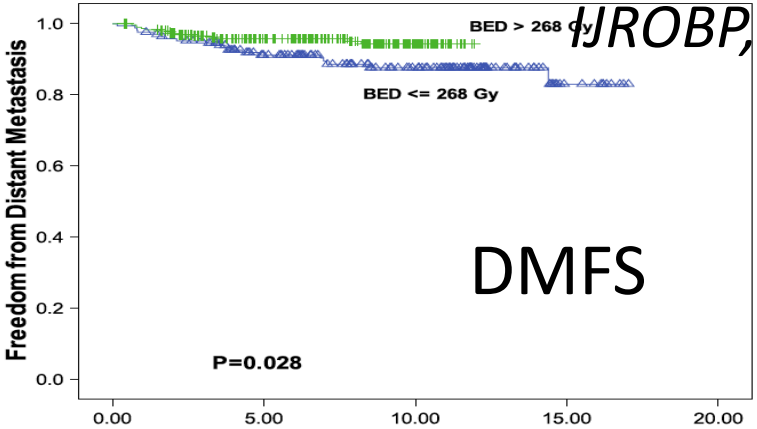
= 123 Gy

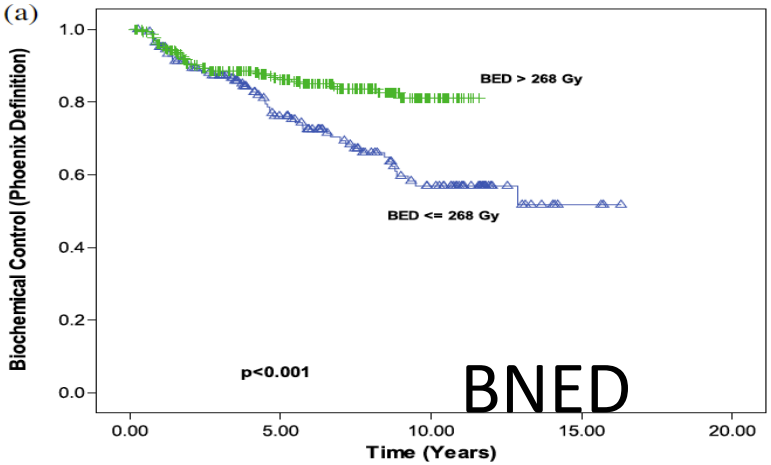
86.4Gy/48fx

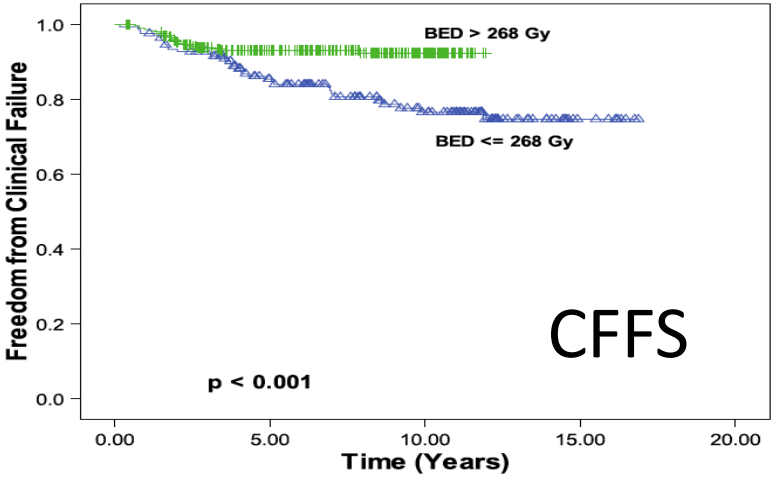
=216 Gy

10-year results by BED dose levels *Martinez et al, IJROBP, 2011*









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Efficacy: HDR Boost

Author	year	# pts	ADT	HDR	EBRT	Risk	bNED	F-up
Falk	2017	159	77%	3 x 6 2 x 9 1 x 14	46/23	IR HR	92% (IR) 85% (HR)	5.1
Joseph	2016	95	97%	1 x 12.5 Low dose!	37.5/15	IR HR	82% 78%	6.5
Ishiyama	2017	3424	28%(8) 44%(28	2 x 9	39/13	IR HR	91% (5) 81% (10)	5.5 (17)
Lakosi	2017	52	96%	1 x 8-10	46-60	IR HR	97%	6.1
Olarte	2016	249	100% 2 yrs	4 x 4.75 2 x 9.5	54 Gy	HR	88% (7)	7.4
Vigneault	2017	832	40%	3 x 6-6.5 2 x 9.5-11 1 x 15	40-45/20-25 37.5/15	IR HR	95% (5) 93% (10)	6.5
Yaxley	2017	507	100% 6 m	3 x 6.5 Low dose!	46/23	IR HR	93% (5), 87% (10) 79% (5), 56% (10)	10.3

5-10 yrs

5,318

IR: 91-97% HR: 85-93%

Late grade 3 GI/GU toxicity

Author	year	# pts	HDR	EBRT	GU gr 3	GI gr 3	F-up
Shahid	2017	125	1 x 15	37.5/15	4%	0	5.2
Ishiyama	2017	3424	2 x 9	39/13	5% (5) 10%(10)	0.5% 0.6%	5.5 (max 17)
Lakosi	2017	52	1 x 8-10	46-60	1%	0	6.1
Olarte	2016	249	4 x 4.75 2 x 9.5	54 Gy	8%	3%	7.4
Vigneault	2017	832	3 x 6-6.5 2 x 9.5-11 1 x 15	40-45 37.5/15	5%	2%	6.5
Yaxley	2017	507	3 x 6.5	46/23	Stricture 29%→4% (after 2005)		10.3

HDR Monotherapy results

Author	year	# pts	HDR	ADT	Risk	F-up	BNED	GI gr3	GU gr3
Hauswald Demanes	2016	448	6 x7.25	9%	LR IR	6.5 Max15	98% (10)	0	4.7%
Hoskin	2017	293	1 x19-20 2 x 13 3 x 10.5	75% 6m	IR HR	4.1 5.2 9	94% (4y) 93% 91%	0 1%	2% 11%
Jawad Martinez Krauss	2016	494	4 x 9.5 2 x 12 2 x 13.5	14%	LR IR	5.5 3.5 2.9	97% 87% 90%	0	2% str 2% inc 7% hem
Patel	2017	190	6 x 7.25	0	IR	6.2	97% (5) 90% (8)	0	3.7% Str/inc
Prada	2016	60	1 x 19	33%	LR IR	6	66% (6)	0	0
Strouthos	2017	450	3 x 11.5	13%	IR HR	4.8	95%	0	0.8%
Yoshioka	2017	524	2 x 13.5 7 x 6.5-7 9 x 6	70%	LR IR HR	5.9	95% 94% 89%	0	1%

N=2459

Yoshioka et al, grade 2 and 3 toxicity

IJROBP 2017

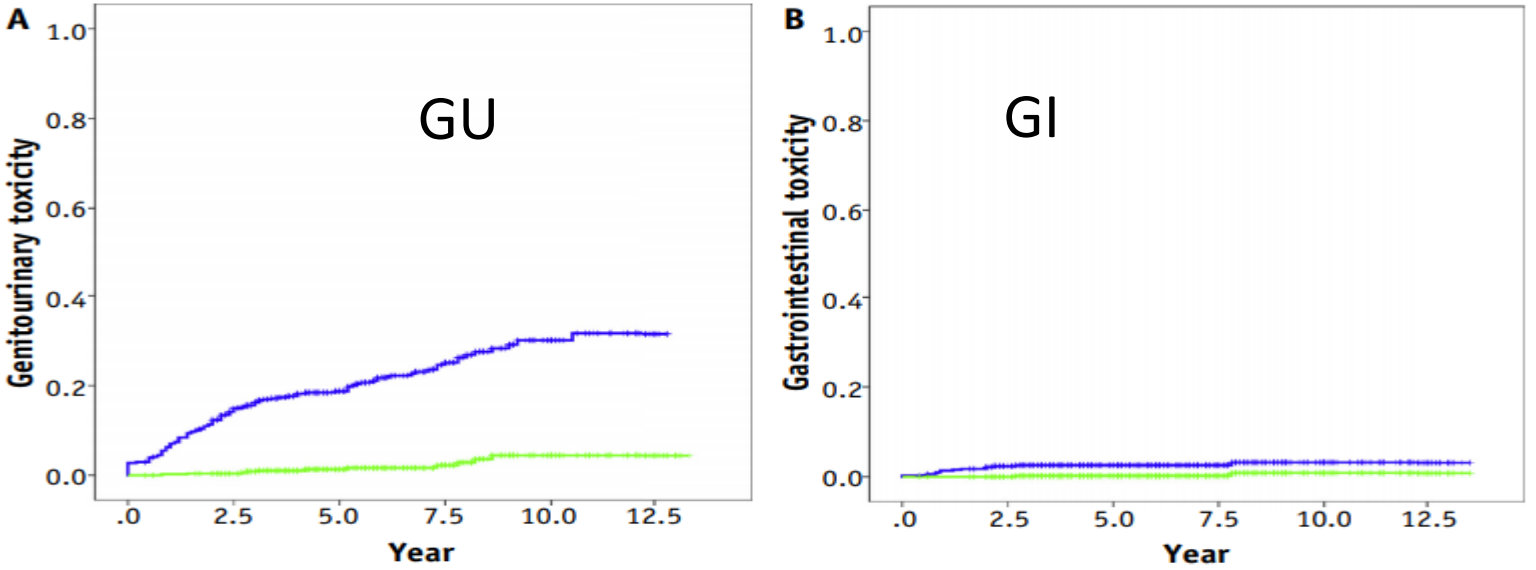


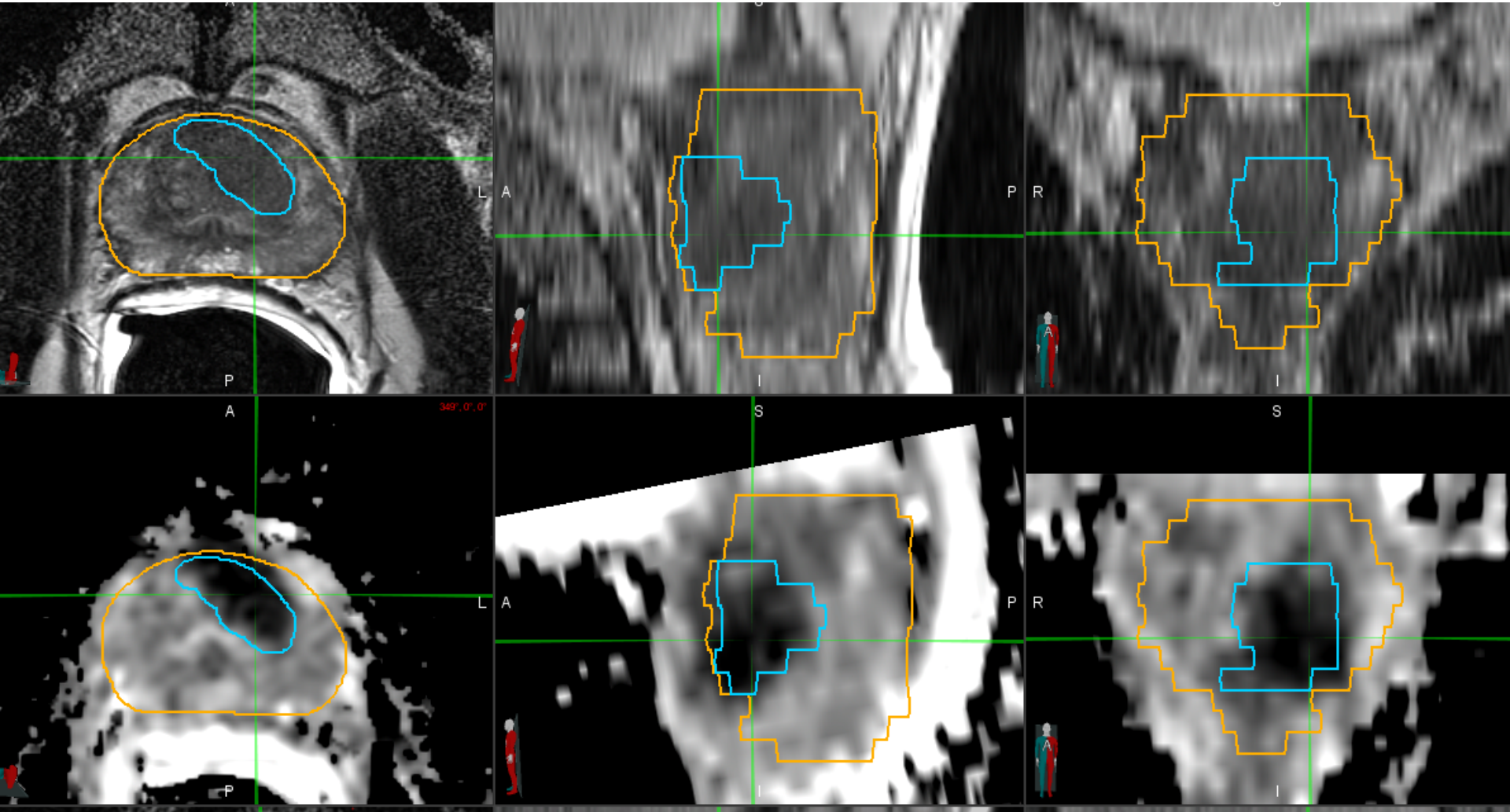
Fig. 2. Cumulative incidence of grade 2 to 3 (blue) and grade 3 (green) late toxicity. Grading was based on the Common Terminology Criteria for Adverse Events, version 4.0. (A) Genitourinary toxicity. (B) Gastrointestinal toxicity. (A color version of this figure is available at www.redjournal.org.)

Summary: HDR prostate

- Highly effective treatment with low toxicity
- Optimal boost dose established at 15 Gy /1
- Optimal monotherapy dose and fractionation still evolving
  - Linear-quadratic model for calculating biologic equivalent dose may be less accurate at fraction size > 10-15 Gy
  - Single fraction loses opportunity to take advantage of “sensitization” by previous treatment
    - Re-oxygenation
    - Re-distribution of cells into sensitive phase of cell cycle
    - Immunologic and transcriptional changes in tumor

HDR monotherapy Case 1: JY

- Age 65, T1c, PSA 7.5, GS 7
- TRUS volume: 24 cc
- 2 cores: 30% pattern 4, Left TZ 5 mm, Right TZ 2 mm
- mpMRI: 1.3 x 2 cm reduced T2 signal with smudged margins in left paracentral and anterior TZ, restricted diffusion on ADC
- PI-RADS 5
- Prescribed dose 2 X 13.5 Gy whole gland with focal escalation to DIL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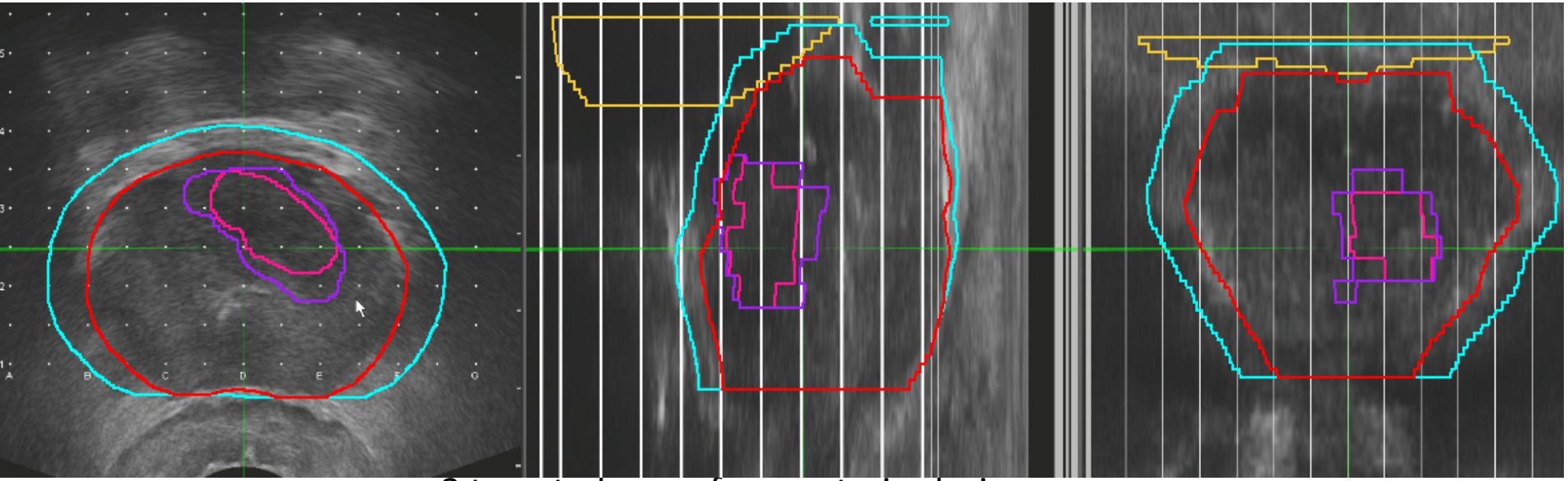
Target localization transferred from mpMRI to TRUS

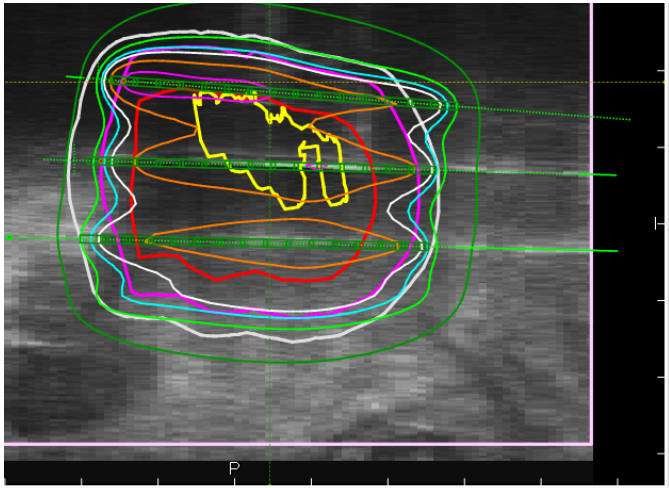


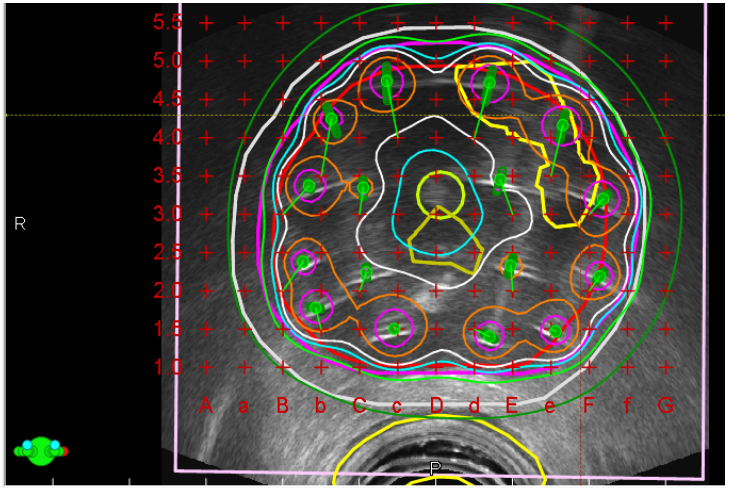
2 targeted cores from anterior lesion

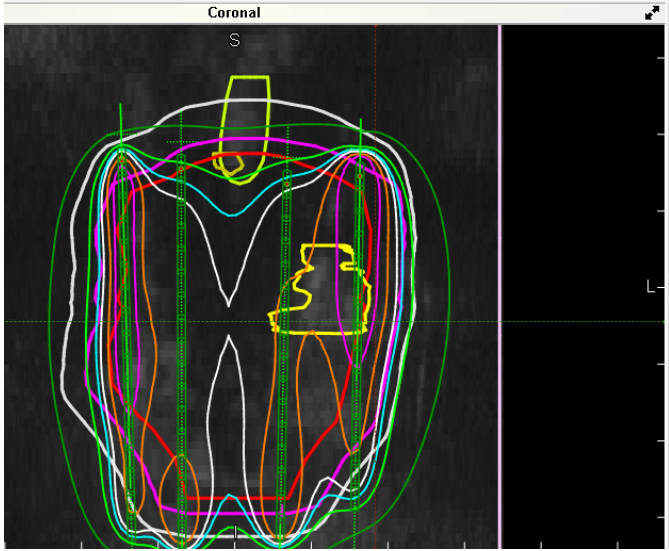
JY

Overall 60% pattern 4

One core 90-95% pattern 4







Path Image 1

Prostate: prescribed 13.5 Gy
D90 whole prostate: 15.2 Gy
D90 DIL: 135%= 18.2 Gy

Path Image 2

Urethra max < 115%
Rectum 1cc: 7.2 Gy

Fraction #1 of 2

Is there an optimal single dose?

- Single fraction for boost (15 Gy) OK because followed by EBRT
- Single 19 Gy as monotherapy mixed results
  - *Hoskin et al*: OK at 4 years
  - *Prada et al*: BNED only 66% at 6 years
  - *Mendez, Morton et al*: 10% LF at site of original DIL after 19 Gy (D90 to DIL 23 Gy and mean dose 29 Gy)
- Single dose monotherapy remains investigational

What is optimal fractionation for monotherapy?

- Demanes results using 6 fractions of 7.25 Gy in 2 implants are excellent
  - 2 procedures
  - 2 hospitalizations with overnight stays
- Results maturing for 2 fractions of 13 to 13.5 Gy
  - Hoskin BNED 93% with 5.2 yr med f-up
  - Yoshioka only used 2 x 13.5 Gy for 13% of pts but did not report different efficacy @ 5.9 yrs compared to std fractionation of 6 x 6.5-7 Gy
  - Jawad reports only 2.9 year follow-up for 2 x 13.5 with BNED 90%

BED equivalence: *Yoshioka et al 2017*

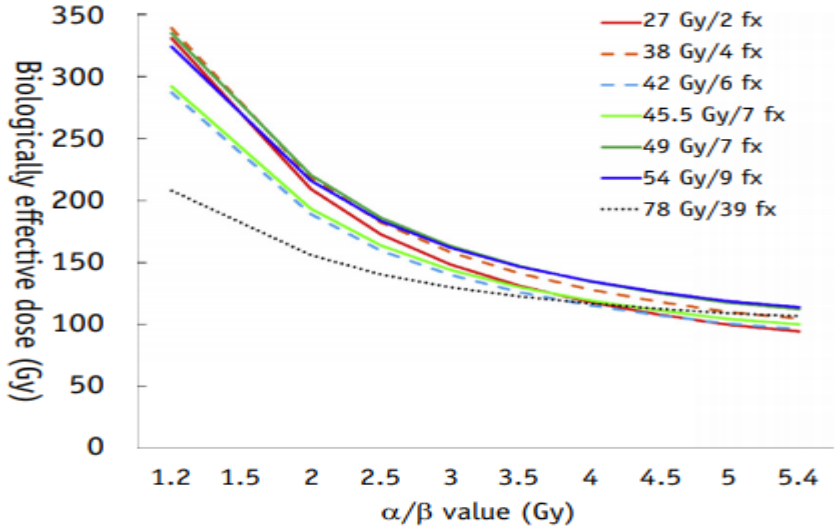


Fig. 3. Biologically effective doses from various regimens of high-dose-rate brachytherapy as monotherapy that were used in the present study (solid lines) or in the literature (reference 27; dashed lines), at different α/β ratios,

But what happens with a single fraction??

What happens between 2 fractions of HDR brachytherapy? *Keam et al, IJROBP 2018*

- 5 patients treated with 2 x 10 Gy, 2 weeks apart
- Biopsy before 1st fraction and before 2nd fraction
- Used genome-wide 3'RNA sequencing on total RNA from 10 biopsies → quantitative expression data for 13,244 genes
- 1.5x ↑ or ↓expression in > 80% of samples

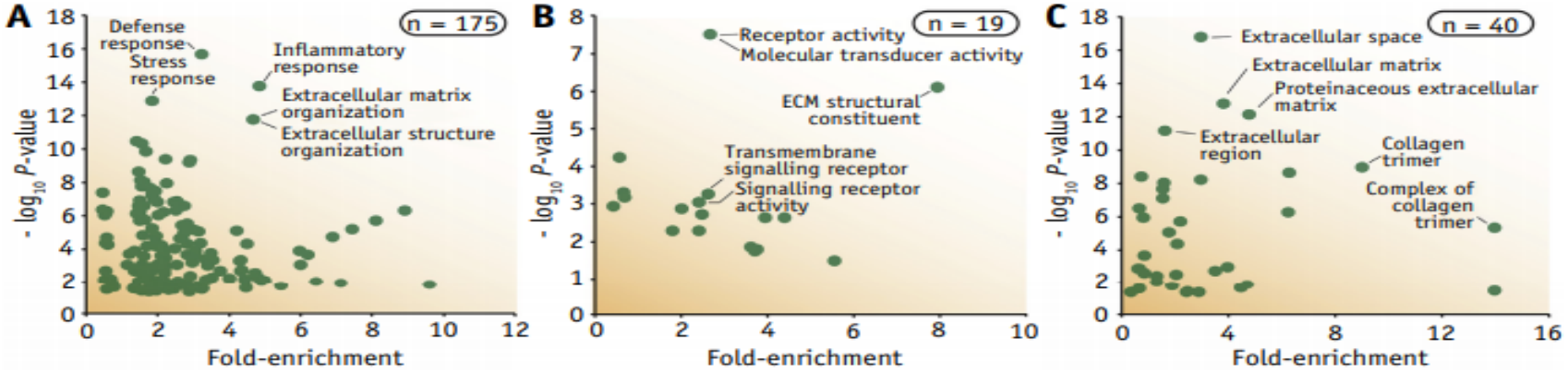
Between fractions….

- Strong up-regulation of p53 pathway
- Interstitial remodelling, extracellular matrix proteins, focal adhesion pathways and inflammation all up-regulated
- Clustering of changes inherent in apoptosis, programmed cell death, extracellular matrix organization and immune regulation

Genes exhibiting increased expression after HDR:

Keam et al, 2018

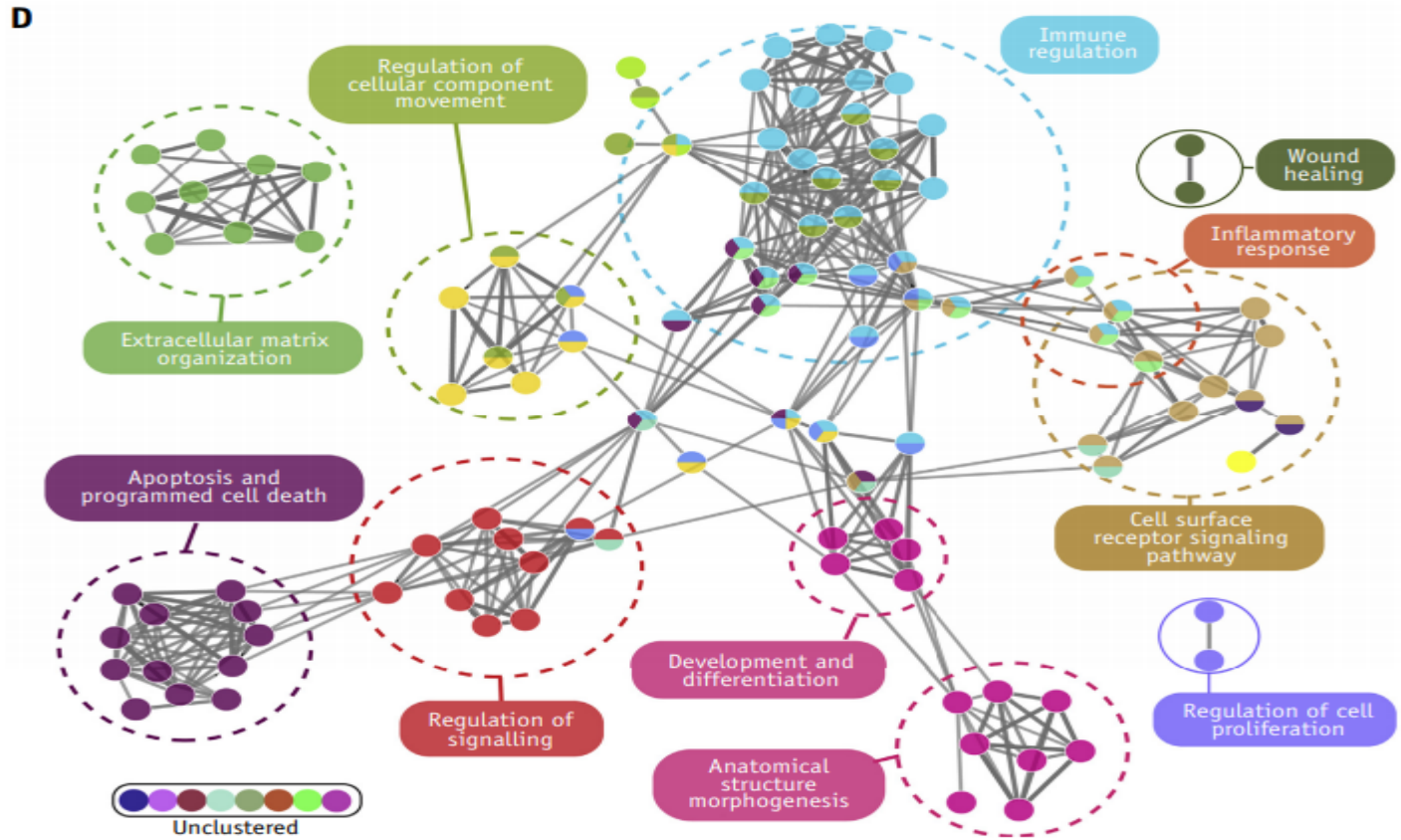
Fig. 2. Gene ontology enrichments and ClueGO network analyses within genes exhibiting increased expression after high-dose-rate brachytherapy. Ontology classes include (A) biologic processes, (B) molecular functions, and (C) cell localization



Biologic processes

Molecular functions

Cell localization



449 up-regulated genes with clustering: *Keam et al 2018*

Future directions

- Incorporation of results of advanced imaging with mpMRI into treatment planning and workflow allows focal dose escalation to sites of dominant disease
- mpMRI-TRUS fusion feasible for this purpose adding < 10 minutes to total procedure time with no change in standard technique of TRUS-based needle guidance and planning
- HDR allows precise dose painting to targets within prostate