PROSTATE BRACHYTHERAPY
UK & Ireland Conference 2024

PORTSMOUTH
25-26 APRIL
Action Stations,
HM Naval Base,
Portsmouth,
PO1 3LJ

SpaceOAR for Prostate Brachytherapy

Dr Roberto Alonzi

Mount Vernon Cancer Centre

Overview

- Evidence (……or lack of)
- SpaceOAR for LDR brachytherapy
- SpaceOAR for HDR brachytherapy
- SpaceOAR for EBRT plus brachytherapy boost
- SpaceOAR for salvage brachytherapy
- Summary

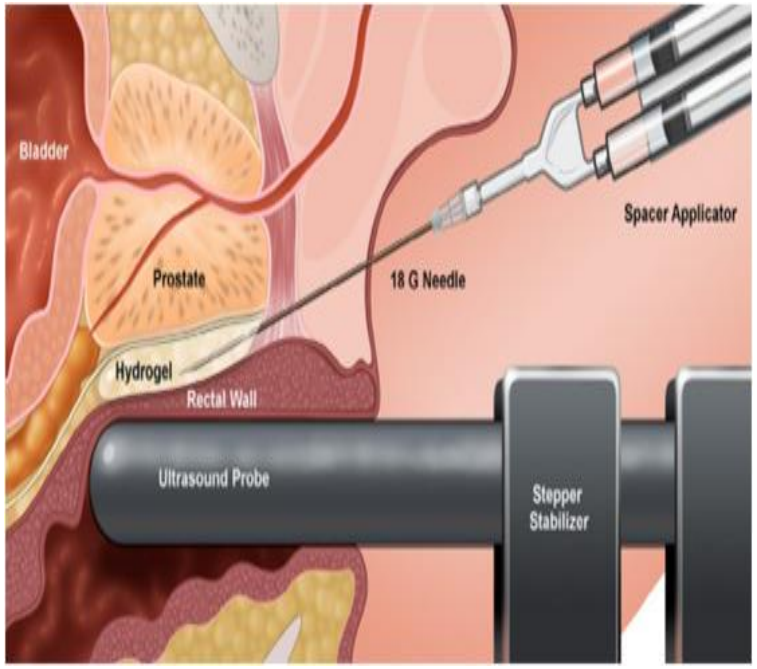
JAMA Network Open

Original Investigation | Oncology

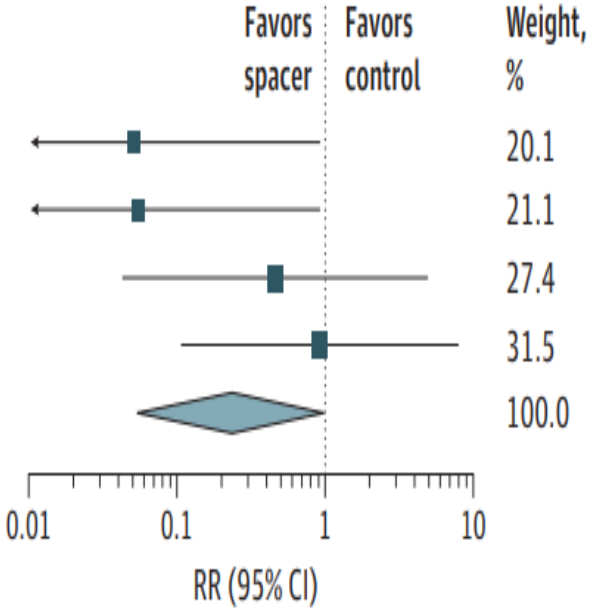
Association of the Placement of a Perirectal Hydrogel Spacer With the Clinical Outcomes of Men Receiving Radiotherapy for Prostate Cancer

A Systematic Review and Meta-analysis

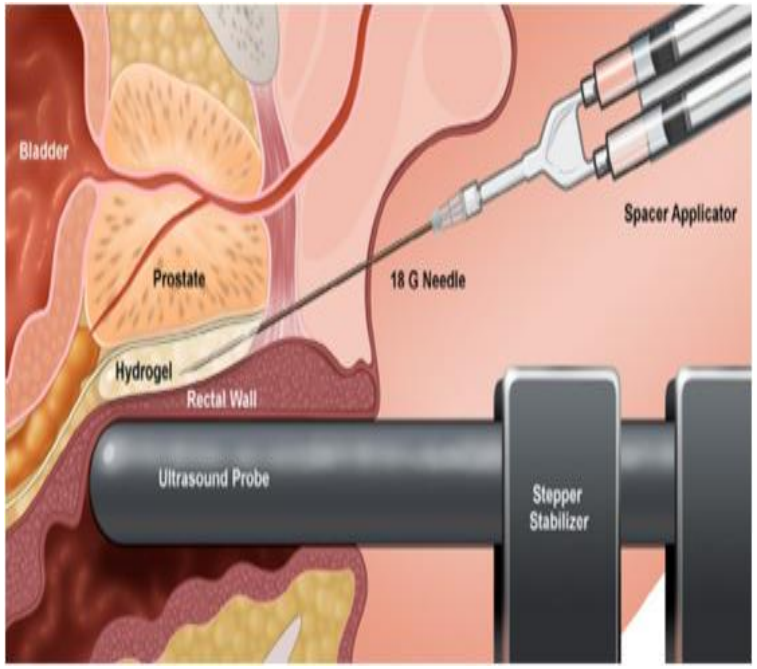
Larry E. Miller, PhD, PStat; Jason A. Efstathiou, MD, DPhil; Samir K. Bhattacharyya, PhD; Heather A. Payne, FRCR, FRCP; Emily Woodward, MSc; Michael Pinkawa, MD, PhD



- 1 phase III (222 patients) and 6 phase II trials
- 1011 men in total – 486 had spacer, 525 controls
- Successful placement in 97%
- 77% reduction in G2 or more late GI toxicity (1.5% vs 5.7%; risk ratio, 0.23; 95% CI, 0.06-0.99; P = 0.05)
- Improvement in long term bowel related QoL (mean difference, 5.4; 95% CI, 2.8-8.0; P < 0.001)



Evidence for spacer insertion with brachytherapy



- There are NO phase III trials that investigate the use of spacers in <u>brachytherapy</u>
- There are numerous studies that report toxicity outcomes which allowed the inclusion of spacers but did not specifically look at the toxicity benefit from the spacer
- There are 3 trials that specifically demonstrate the toxicity benefit of spacers in brachytherapy
  - 1 LDR only
  - 1 EBRT + LDR boost
  - 1 LDR only or EBRT + LDR boost

Cs-131 prostate brachytherapy boost and effect of hydrogel rectal spacer on long-term patient-reported rectal bleeding and bowel quality of life

Mohamed K Abdelhakiem [1], Andrew Keller [2], Rajesh R Bajpai [3], Ryan P Smith [1], Sushil Beriwal [4], Ronald Benoit [3]

- Retrospective
- 2007 – 2022
- 45Gy EBRT + 85Gy LDR
- 108 hydrogel spacer
- 233 no spacer
- Overall median follow-up was 48 months
- At 60 months, the **prevalence** of clinically significant rectal bleeding and bleeding bother were 2.2% and 2.2%, respectively
- The cumulative **incidence** of clinically significant long-term rectal bleeding was 2.8% and 18.9% in the hydrogel group and non-hydrogel group, respectively (Fisher's exact test, $p < 0.0001$)
- The cumulative **incidence** of clinically significant long-term bowel bother was 4.6% and 19.7% in the hydrogel group and non-hydrogel group, respectively (Fisher's exact test, $p < 0.001$).

Impact of hydrogel and hyaluronic acid rectal spacer on rectal dosimetry and toxicity in low-dose-rate prostate brachytherapy: a multi-institutional analysis of patients' outcomes

Yuan-Hong Lin [1], Wee Loon [1], Mark Tacey [1 2], Damien Bolton [3], Alwin Tan [4], Yee Chan [3], Chee Wee Cham [4], Huong Ho [5], Mario Guerrieri [5], Farshad Foroudi [1], Daryl Lim Joon [1], Kevin McMillan [6], George Koufogiannis [6], Paul Manohar [6], Madalena Liu [6], Trung Pham [6], Michael Chao [1 5]

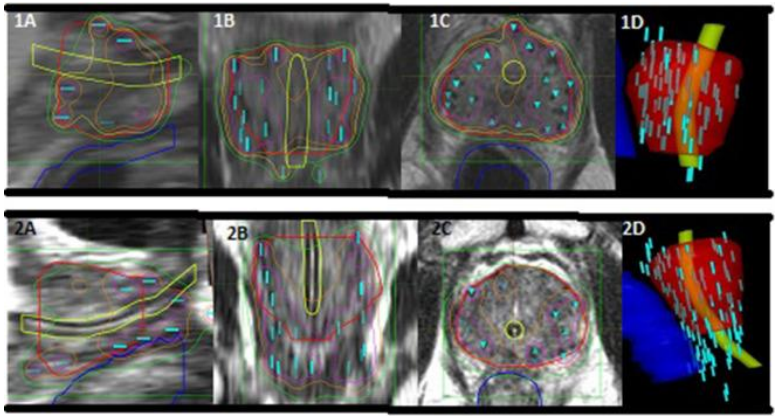
- 2017 – 2019
- LDR only
- 28 spacer
- 42 no spacer
- The median follow-up was 23.5 months
- There were significantly less grade 1 acute and late GI toxicities in RS-group when compared to non-RS group (0% vs. 24%, $p = 0.004$ for acute GI toxicity; 4% vs. 33%, $p = 0.003$ for late GI toxicity)
- There were no reported acute or late grade 2 or above GI toxicities.

Influence of hydrogel spacer placement with prostate brachytherapy on rectal and urinary toxicity

Achiraya Teyateeti [1] [2], Craig Grossman [1], Marisa A Kollmeier [1], Megan Fiasconaro [3], Margaret Hopkins [1], Sean McBride [1], Daniel Gorovets [1], Daniel Shasha [1], Gilad Cohen [4], Zhigang Zhang [3], David J Lesser [1], Antonio Damato [4], Michael J Zelefsky [1]

- 2016 – 2019
- LDR or EBRT + LDR boost
- 224 patients with spacer
- Matched with 139 controls
- The **incidence** rates of overall rectal toxicity were lower in patients with spacer insertion compared to patients who did not undergo spacer insertion:
  - Any grade - 12% vs 31% and
  - Grade ≥2 - 1.8% vs 5.8
- The 3-year cumulative **incidence** of overall rectal toxicity was significantly lower with HSP than without (15% vs 33%; $P < 0.001$)
- Overall rectal toxicity reduction on univariable analysis (hazard ratio 0.45, 95% confidence interval 0.28-0.73; $P = 0.001$).

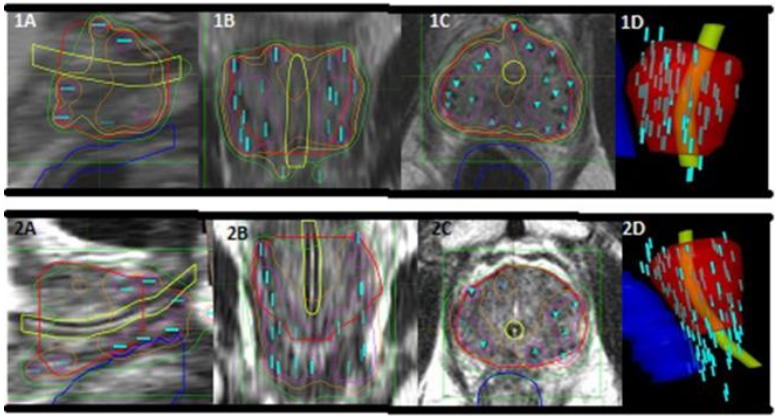
LDR Brachytherapy
Indications



Author and year	GI outcomes
Nakai, 2022	5 years: Grade 2 – 3.3% 10 Years: Grade 2 – 3.3%
Sakurai, 2021	5 years: Grade 2 – 6.4%, Grade 3 – 0%
Ollivier, 2020	2 years: Grade 2 – 1%
Serrano, 2016	5 years: Grade 2 – 2.5%, Grade 3 – 0.2%

Significant rectal / GI toxicity is <u>rare</u>

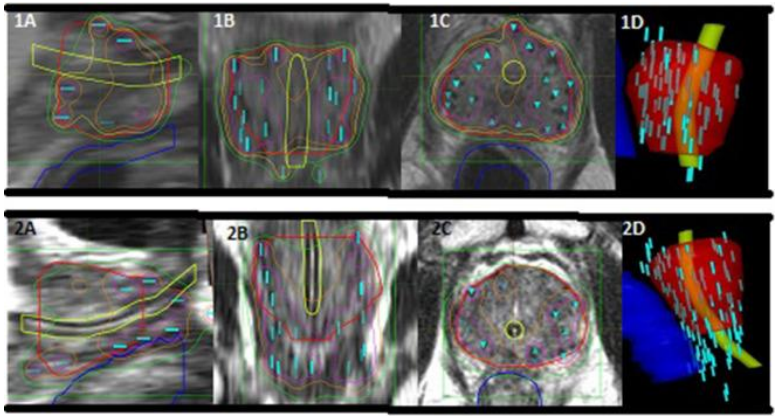
LDR Brachytherapy
Indications



- Carefully consider the suitability of spacer devices for routine use with standard LDR prostate brachytherapy cases – probably unwarranted

- Use in patients with increased risk of rectal toxicity
  - Previous rectal surgery
  - Inflammatory bowel disease
  - Anticoagulation use
  - Diabetes
  - (Smoking)

LDR Brachytherapy
Technique



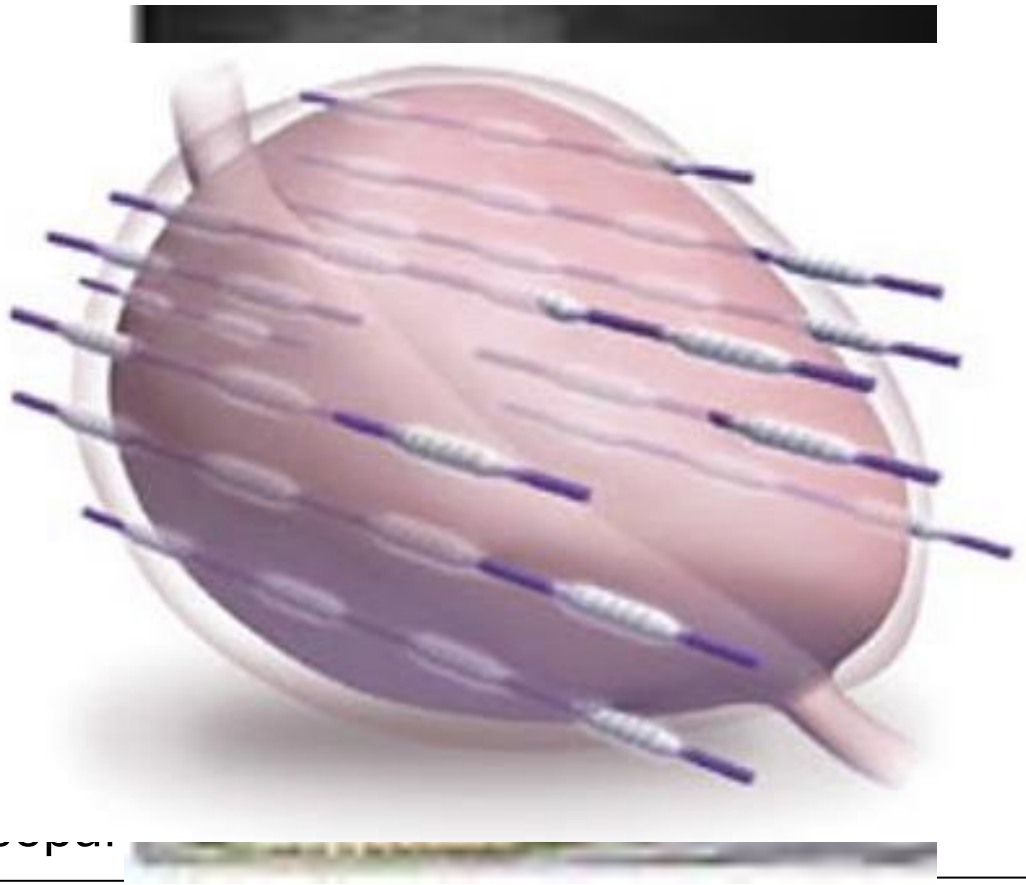
Spacer **ant**

Disadva

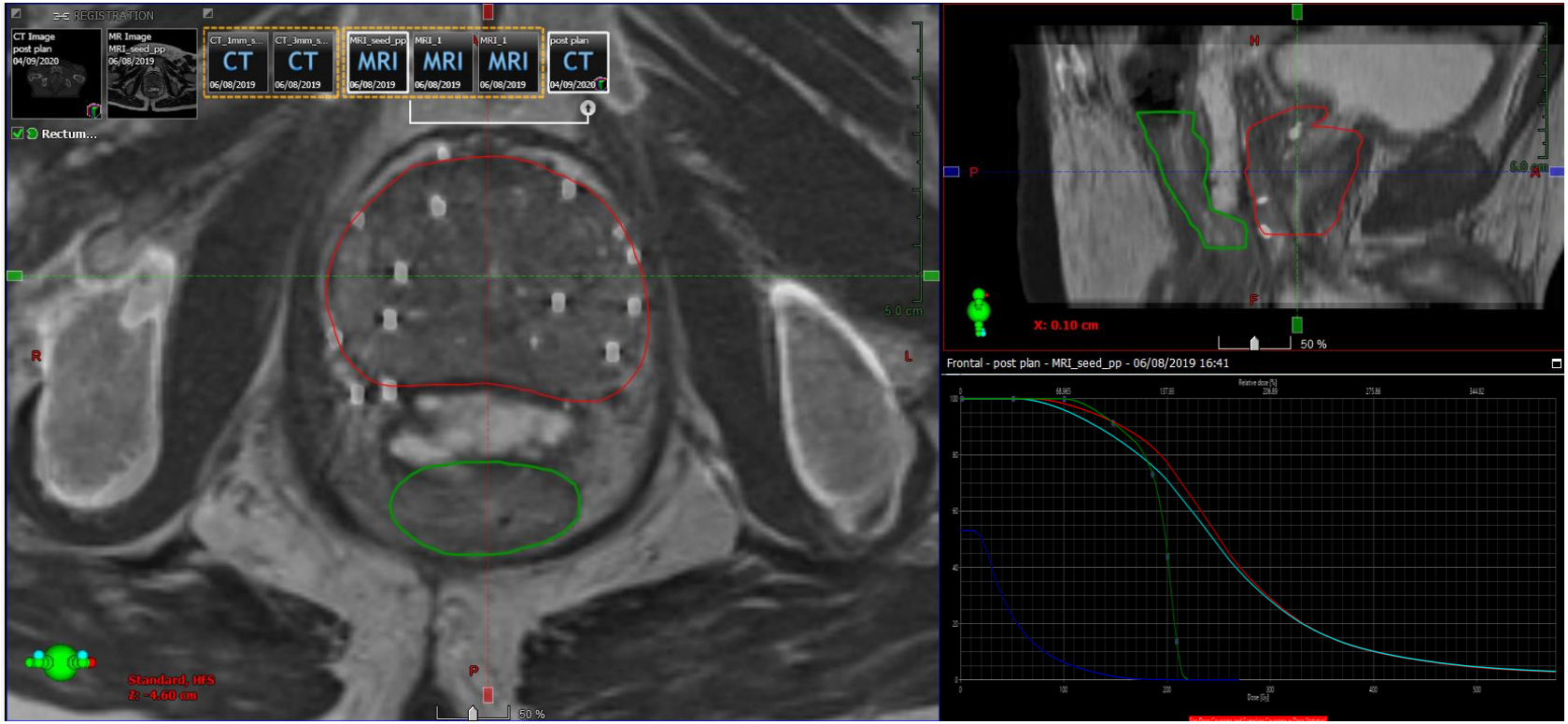
- 2 visit nd try
- Pubic nsertion

Advanta

- Excell
- No im
- Better sues

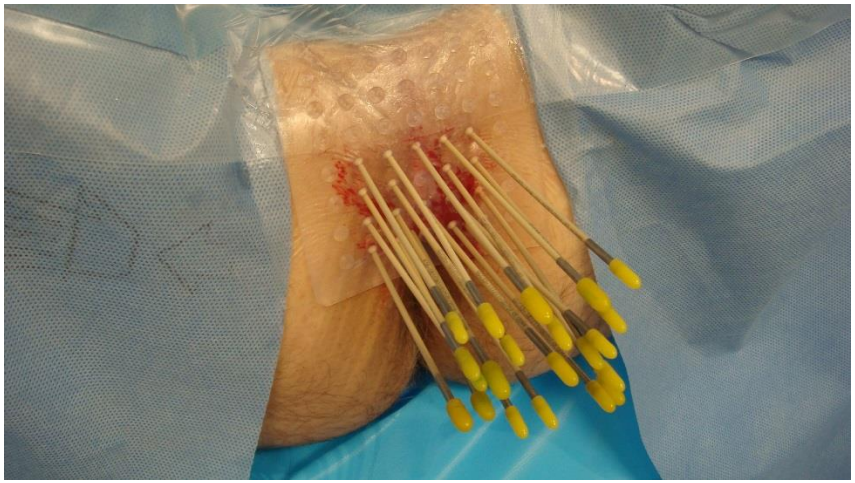


LDR brachytherapy



- Pre-implant spacer placement
  - Consider using 5-7mls only to avoid pubic arch issues
  - No compromise to dosimetry
  - Easier spacer insertion
  - Best US views for LDR implant

HDR Brachytherapy
Indications



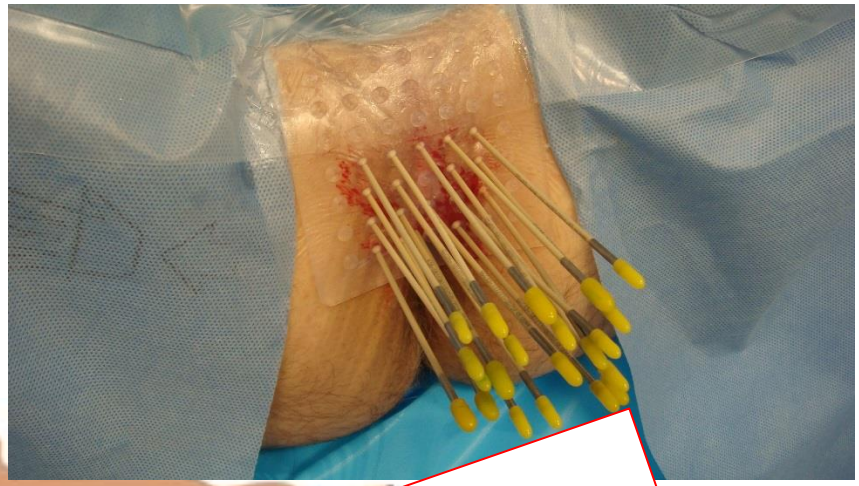
Parzen et al. 2020 545 patients 7.5 years median follow up	
Symptom	GI outcome
Grade ≥2 diarrhoea	0.7%
Pain / Tenesmus	0.6%
Grade ≥2 rectal bleeding	1.3%
Proctitis	0.9%
Any Grade ≥2 GI toxicity	2.4%

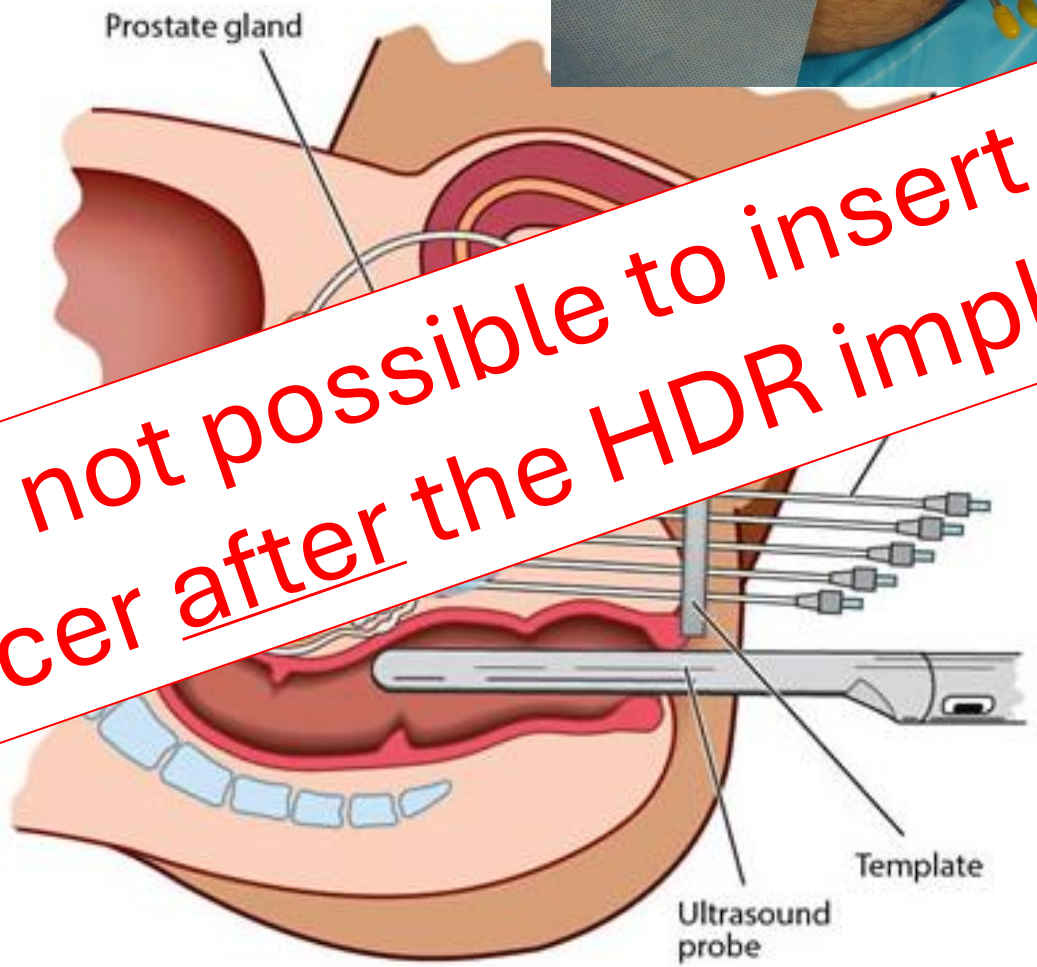
As with LDR brachytherapy, significant GI / rectal toxicity is rare

Use in patients with increased risk of rectal toxicity:

- Previous rectal surgery
- Inflammatory bowel disease
- Anticoagulation use
- Diabetes
- (Smoking)

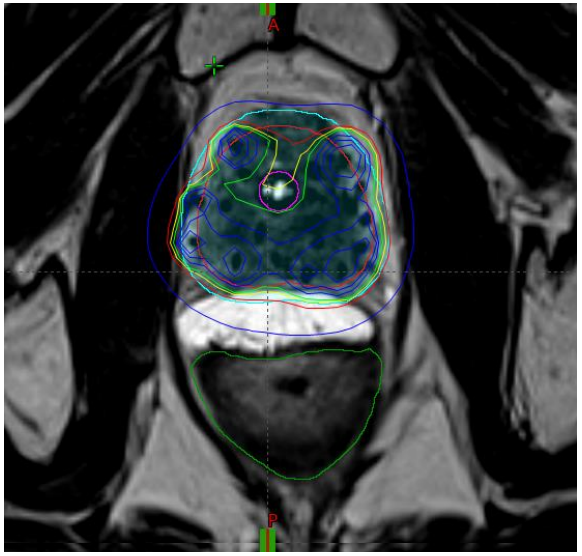
HDR Brachytherapy
Technique

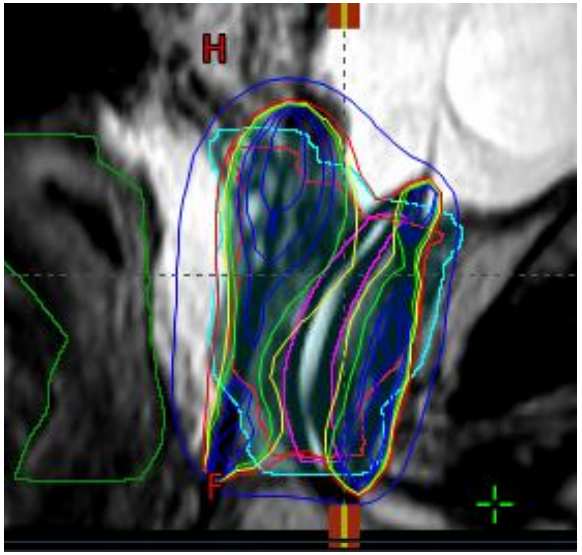


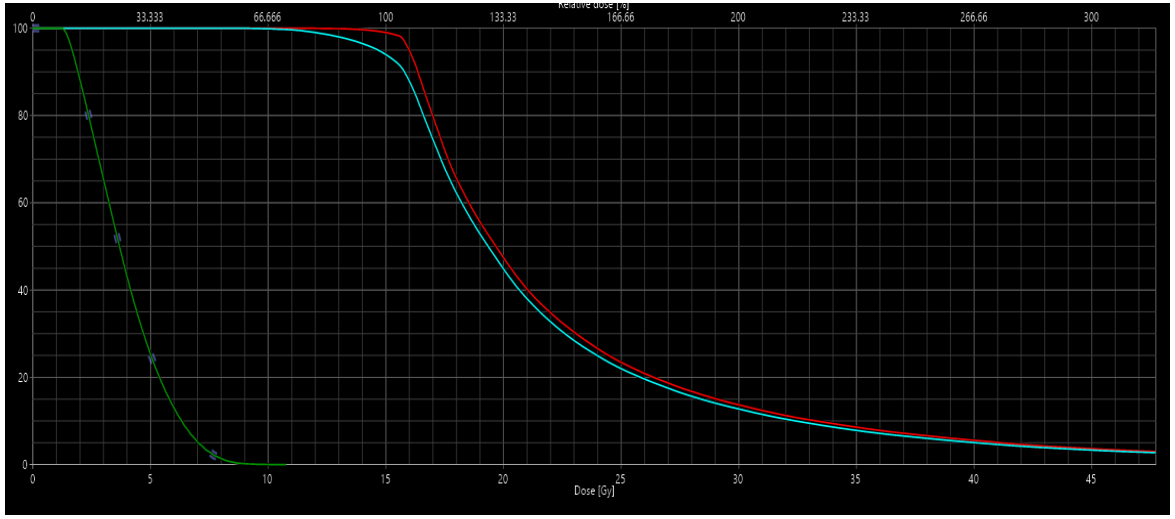


It is not possible to insert a spacer after the HDR implant

HDR brachytherapy







- Pre-implant spacer placement
- Spacer insertion 2-3 weeks pre-implant
- Maximum separation
- Improves US views
- Optimum dosimetry
- Less issue of pubic arch issues compared to LDR
- Easy to implant SVs through gel
- *2 visits*

EBRT plus brachytherapy boost

- ASCENDE-RT: *An Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer*. 2016

Table 2 Crude incidence of acute GU and GI morbidity

Grade	By treatment received: DE-EBRT (n = 195)	LDR-PB (n = 188)	χ^2 *P*
Acute GU morbidity			
0	79 (40.5)	36 (19.1)	<.0001*
1	70 (35.8)	75 (39.8)	.562
2	31 (15.8)	64 (30.0)	<.0001*
3	1 (0.5)	5 (2.5)	.121
4-5	0	0	N/A
Acute GI morbidity			
0	88 (45.1)	87 (46.2)	.961
1	65 (33.3)	74 (39.3)	.271
2	28 (14.3)	17 (9.0)	.090
3-5	0	0	N/A

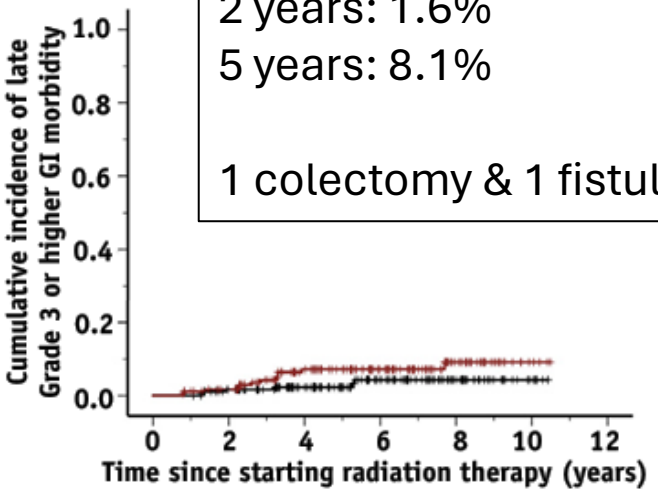
Abbreviations: GI = gastrointestinal; GU = genitourinary. Other abbreviations as in Table 1.

Values are number (percentage).

* Statistically significant.

Late Grade 3 GI toxicity:
2 years: 1.6%
5 years: 8.1%

1 colectomy & 1 fistula (1%)

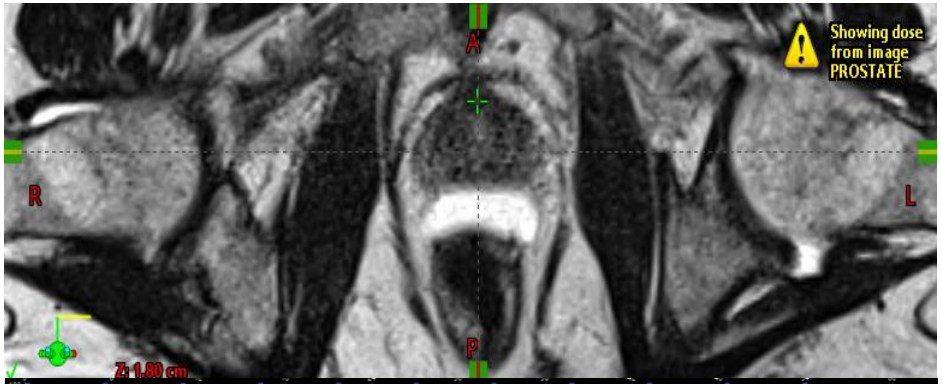


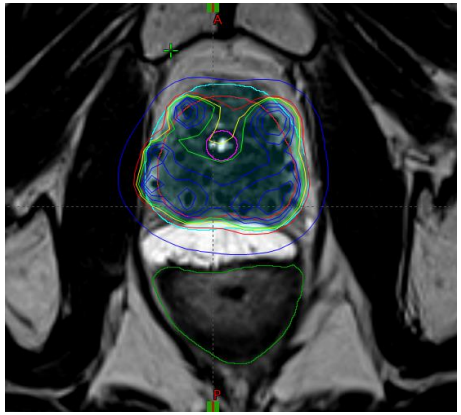
Numbers at risk:

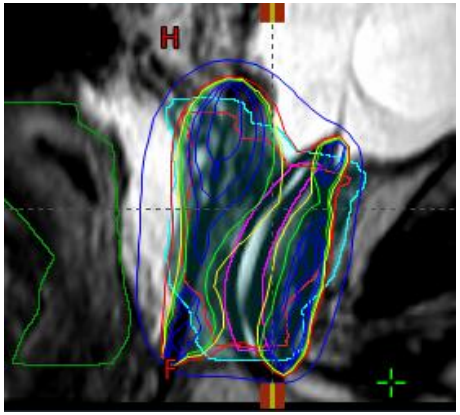
Years	0	2	4	6	8	10
DE-EBRT	195	172	129	80	41	9
LDR-PB	188	168	119	80	36	4

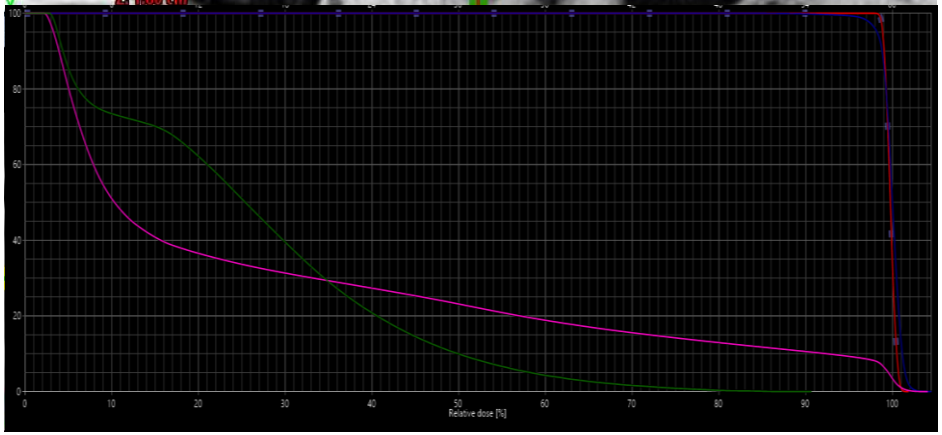
EBRT plus brachytherapy boost

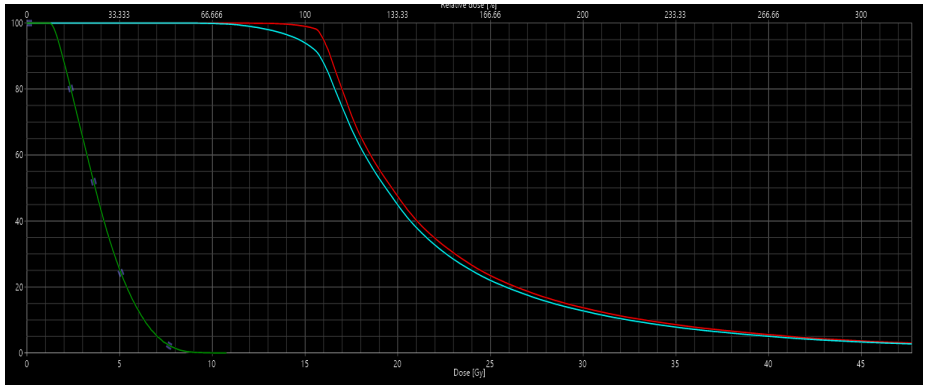
- Potential for significant rectal toxicity
- Therefore, there is rationale for offering spacer placement for all patients
- Benefit during both EBRT and brachytherapy components

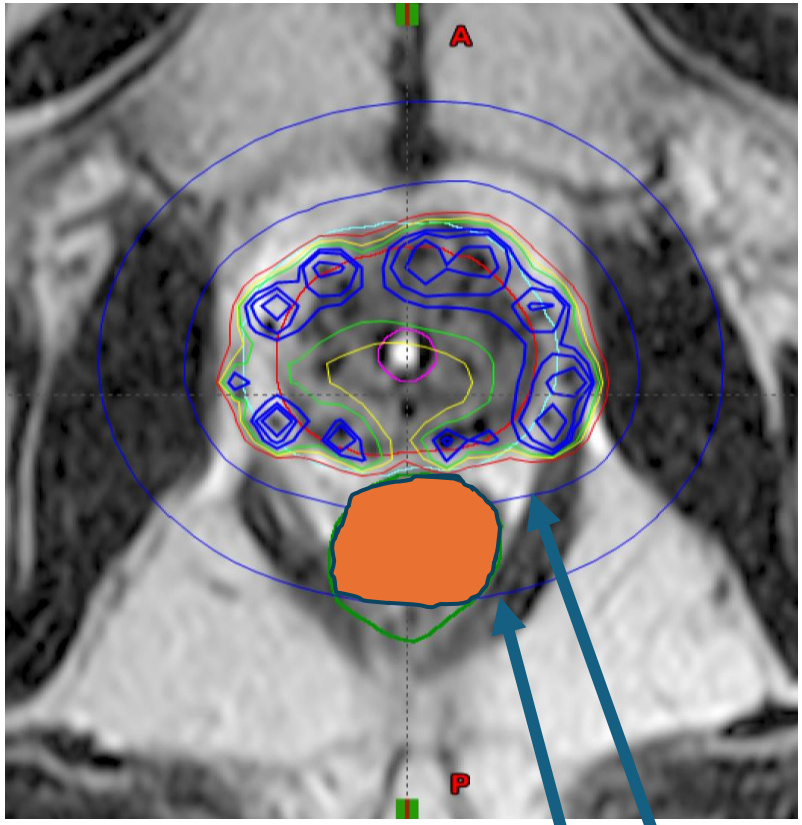


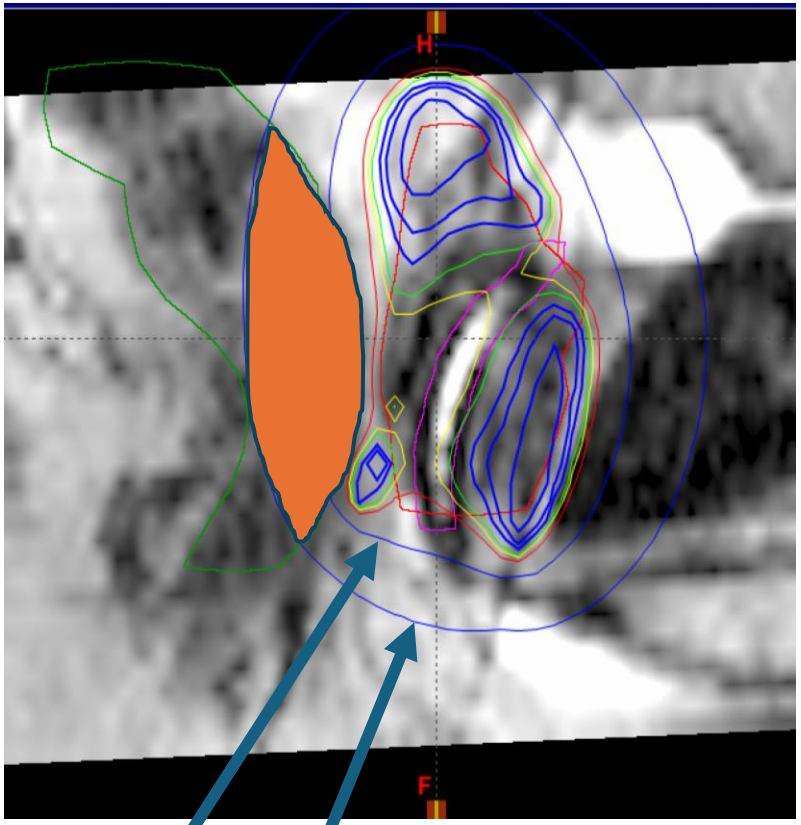






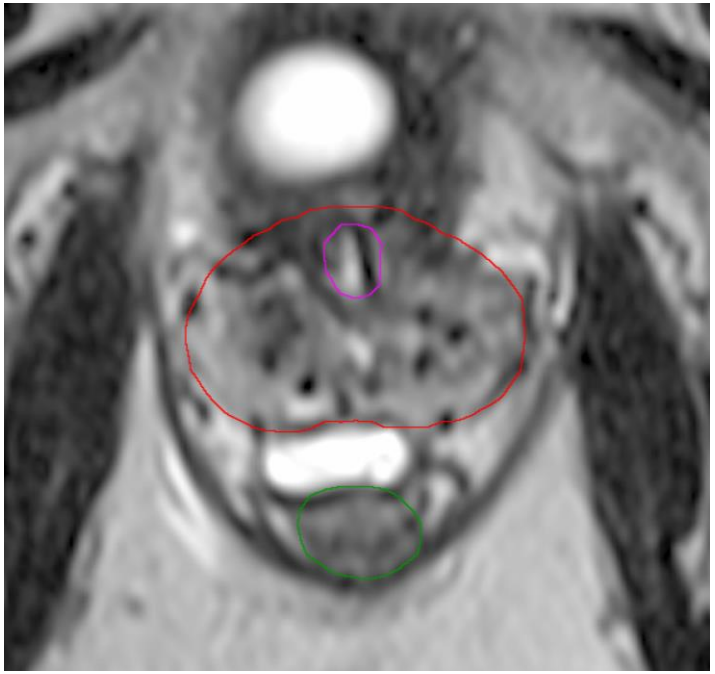


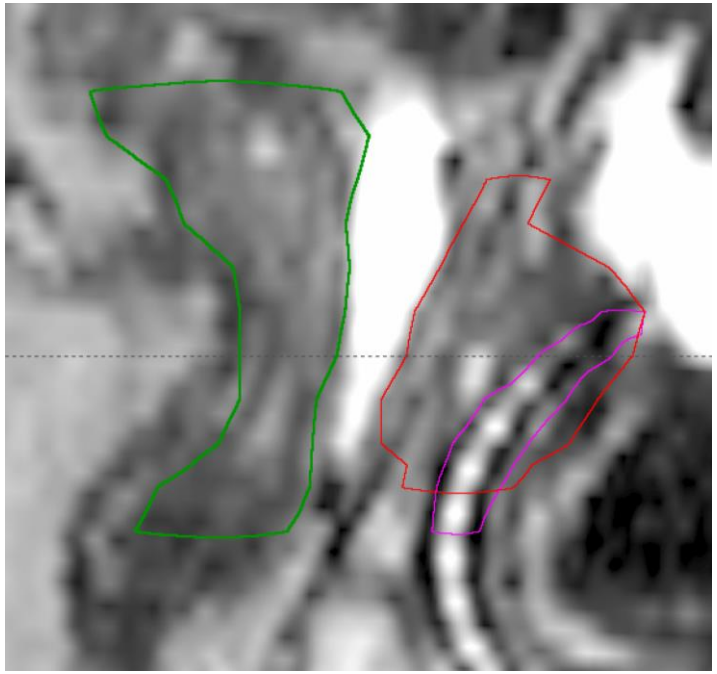


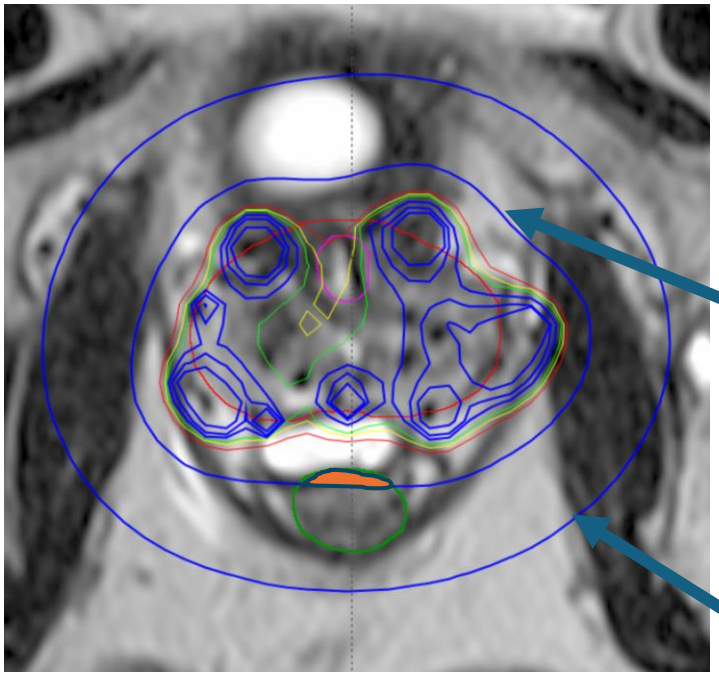


66% of the prescribed dose

33% of the prescribed dose

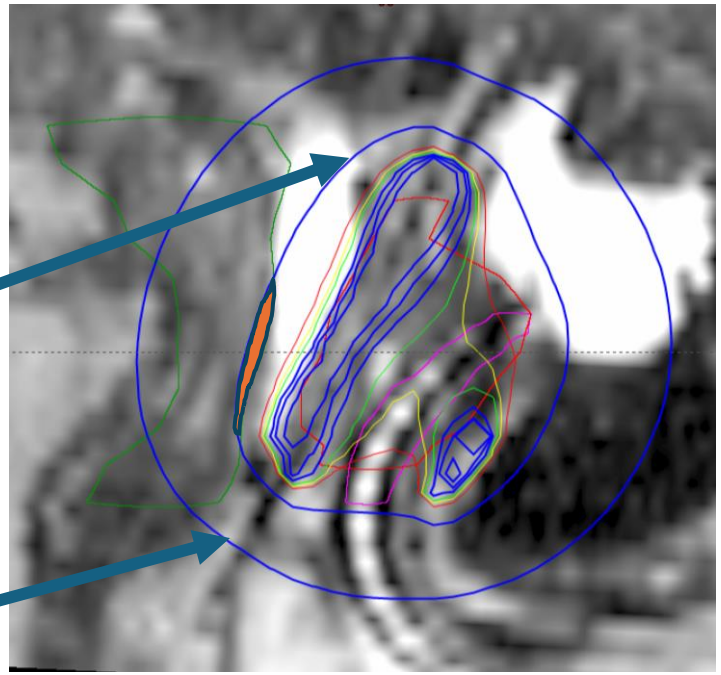






33% of the prescribed dose

15% of the prescribed dose



Salvage Brachytherapy

A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER)

Luca F. Valle [a,†], Eric J. Lehrer [b,†], Daniela Markovic [c], David Elashoff [c], Rebecca Levin-Epstein [a], R. Jeffery Karnes [d], Robert E. Reiter [e], Matthew Rettig [f,g], Jeremie Calais [h], Nicholas G. Nickols [a,i], Robert T. Dess [j], Daniel E. Spratt [j], Michael L. Steinberg [a], Paul L. Nguyen [k], Brian J. Davis [l], Nicholas G. Zaorsky [m], Amar U. Kishan [a,e,]*

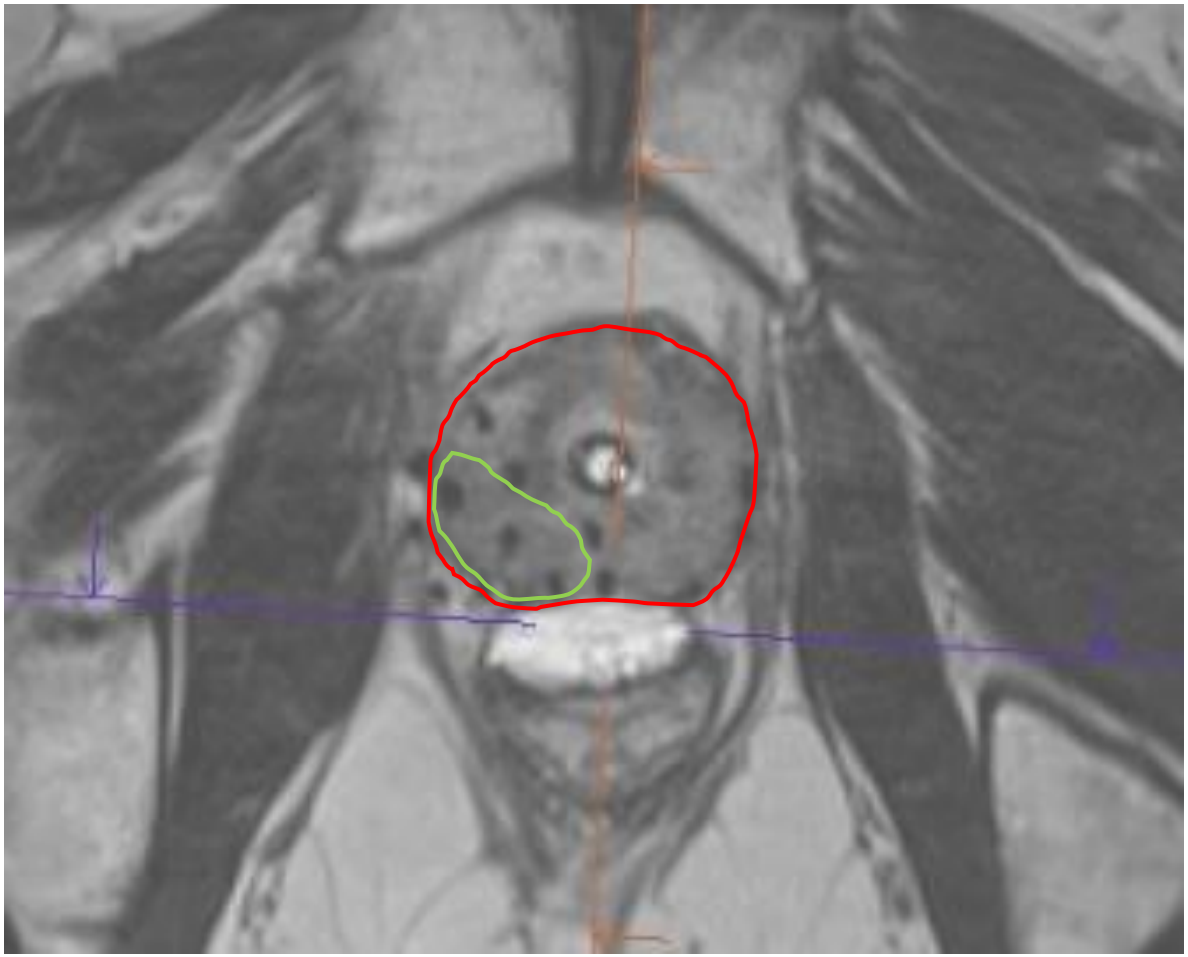
- 160 studies
- 11,322 patients
- (Each study only had 70 patient on average)
- All phase 1b/2 studies

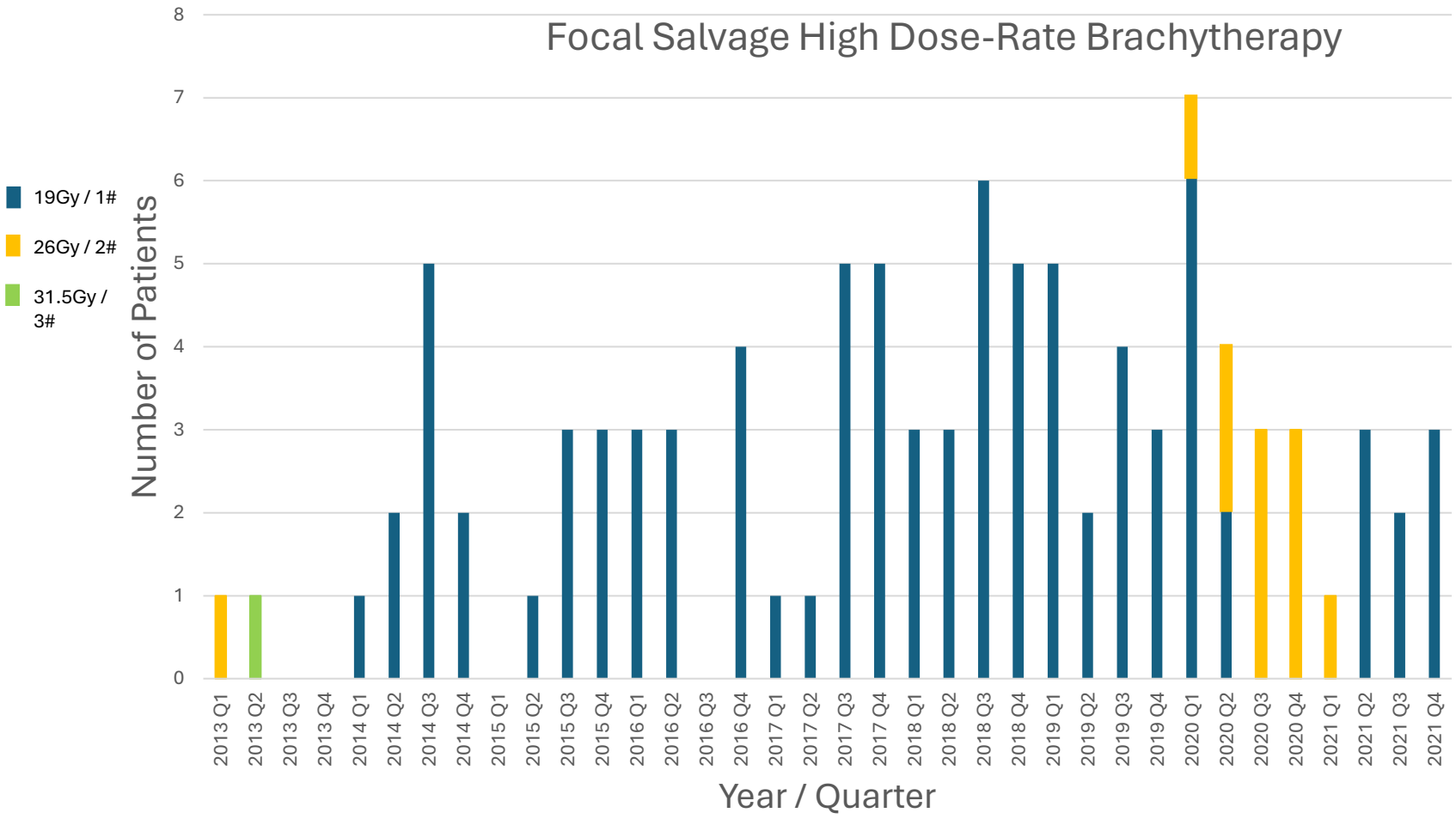
	Age (yr)	Whole-gland salvage (%)	Biopsy-proven recurrence (%)	Presalvage PSA (ng/mL)	Perisalvage ADT use (%)	Interval from initial treatment to recurrence or salvage (mo)	Median follow-up (mo)	Number of studies (*n*)	Number of patients (*n*)
RP	65	100	99	6.0	16	50	47	52	2686
Cryotherapy	66	93	99	5.8	35	63	32	32	5153
HIFU	69	86	100	5.0	18	63	33	20	1783
SBRT	72	61	81	4.0	37	89	26	8	261
HDR	71	85	94	4.5	43	61	40	16	586
LDR	69	92	95	5.5	37	67	52	32	853

ADT = androgen deprivation therapy; HDR = high-dose-rate brachytherapy; HIFU = high-intensity focused ultrasound; LDR = low-dose-rate brachytherapy; PSA = prostate-specific antigen; RP = radical prostatectomy; SBRT = stereotactic body radiotherapy.

	2-yr RFS	5-yr RFS	Severe GU toxicity	Severe GI toxicity
Radical prostatectomy				
Adjusted percent[a] (95% CI)	72% (66–78%)	53% (46%–59%)	21% (16%–26%)	1.5% (0.4%–3.2%)
Odds ratio (95% CI)	1.0	1.0	NA	NA
p value	Reference	Reference	Reference	Reference
R^2 (%)	0.0	0.0	0.0	0.0
Cryotherapy				
Adjusted percent[a] (95% CI)	66% (59–72%)	57% (49–65%)	15% (8–23%)	0.9% (0.3–1.8%)
Odds ratio (95% CI)	0.74 (0.49–1.12)	1.20 (0.80–1.79)	NA	NA
p value	0.2	0.4	0.2	0.5
R^2 (%)	25	0.0	8.2	27
HIFU				
Adjusted percent[a] (95% CI)	52% (45%–59%)	46% (37%–55%)	23% (17%–30%)	0.8% (0.1%–2.1%)
Odds ratio (95% CI)	0.42 (0.28–0.64)	0.76 (0.48–1.21)	NA	NA
p value	<**0.001**	0.2	0.5	0.4
R^2 (%)	0.0	41	15	22
SBRT				
Adjusted percent[a] (95% CI)	58% (46–69%)	56% (37–73%)	5.6% (1.4–12%)	0.0% (0.0–1.2%)
Odds ratio (95% CI)	0.52 (0.30–0.93)	1.13 (0.50–2.58)	NA	NA
p value	0.03	0.8	<**0.001**	0.07
R^2 (%)	55	4.2	0.00	0.0
HDR				
Adjusted percent[a] (	77% (69–8	58% (52–64%)	9.6% (6.0–13.9%)	0.0% (0.0–0.3%)
Odds ratio (95% CI)	1.26 (0.77–2.09)	1.25 (0.88–1.78)	NA	NA
p value	0.4	0.2	**0.002**	**0.003**
R^2 (%)	0.0	91	0.0	0.0
LDR				
Adjusted percent[a] (95% CI)	79% (72–85%)	53% (43–63%)	9.1% (5.2–14%)	2.1% (0.6–4.0%)
Odds ratio (95% CI)	1.49 (0.89–2.50)	1.02 (0.63–1.67)	–	–
p value	0.13	0.9	**0.001**	0.6
R^2 (%)	4.3	5.2	12	20%

CI = confidence interval; GI = gastrointestinal; GU = genitourinary; HDR = high-dose-rate brachytherapy; HIFU = high-intensity focused ultrasound; LDR = low-dose-rate brachytherapy; NA = not available; RFS = recurrence-free survival; SBRT = stereotactic body radiotherapy.
Significant p-values after Bonferroni correction appear in bold.
[a] Back-transformed regression coefficients for ease of interpretation.




Focal Salvage High Dose-Rate Brachytherapy
19Gy / 1#
26Gy / 2#
31.5Gy / 3#
Number of Patients
0
1
2
3
4
5
6
7
8
2013 Q1
2013 Q2
2013 Q3
2013 Q4
2014 Q1
2014 Q2
2014 Q3
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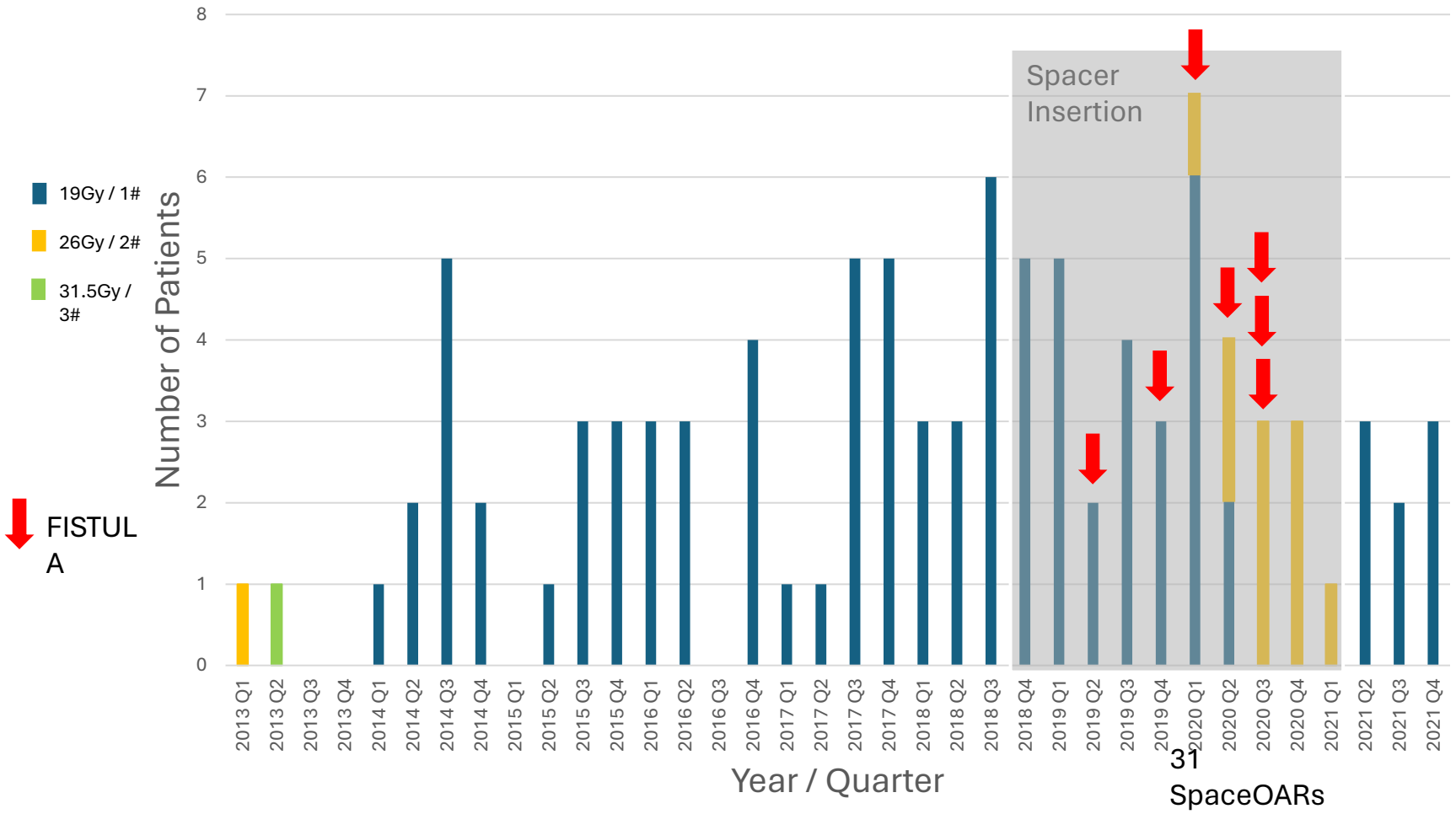

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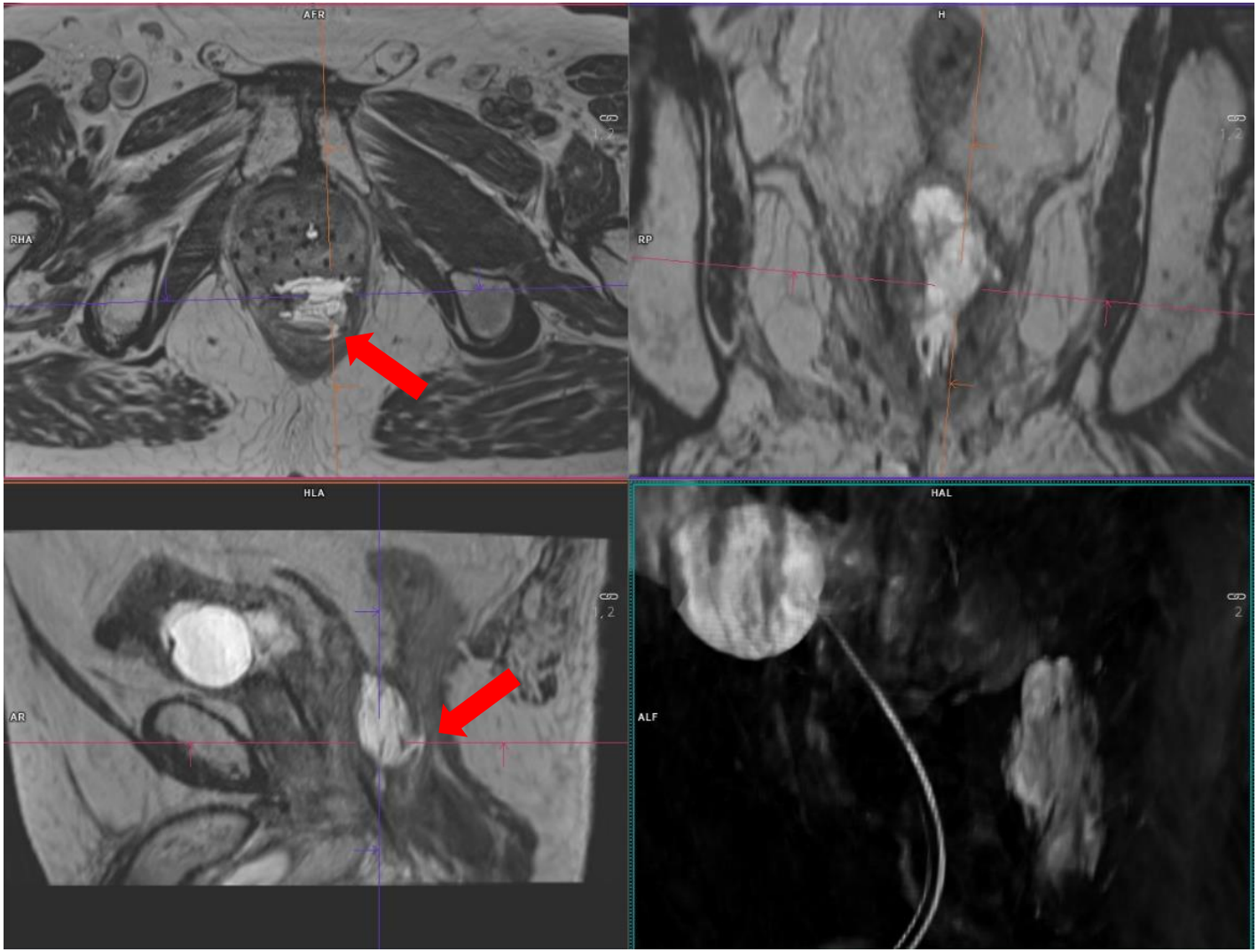
SpaceOARs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HAL
ALF

Fistula patients - outcome

	1	2	3	4	5	6	7
Time from salvage HDR to fistula	5 months	4 months	6 months	6 months	6 months	7 months	5 months
Treatment	Colostomy + Bilateral Nephrostomy	Bilateral Nephrostomy (Awaiting Colostomy)	Ileal Conduit	Ileal Conduit	Loop Colostomy	Ileal Conduit	Ileal Conduit
PSA (follow-up)	0.07 (22 months)	0.09 (11 months)	0.40 (16 months)	<0.06 (15 months)	1.2 (20 months)	0.11 (9 months)	0.06 (26 months)

Summary

- SpaceOAR and SpaceOAR Vue can be used for prostate brachytherapy
- Good rationale and dosimetric evidence for likelihood of benefit
- Extensive retrospective, non-randomised evidence for safety and toxicity benefit for LDR and combined LDR and EBRT
- Probable benefit in all EBRT + brachytherapy boost patients
- Selected use in LDR or HDR monotherapy cases
- More evidence needed:
  - Evidence for benefit in HDR brachytherapy
  - Phase 3 studies
- **Do NOT use spacers in any pre-irradiated pelvic cases**