Re-Irradiation:
SBRT for Retreatment of Radiation Failures

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Accuray Disclaimers and Disclosure

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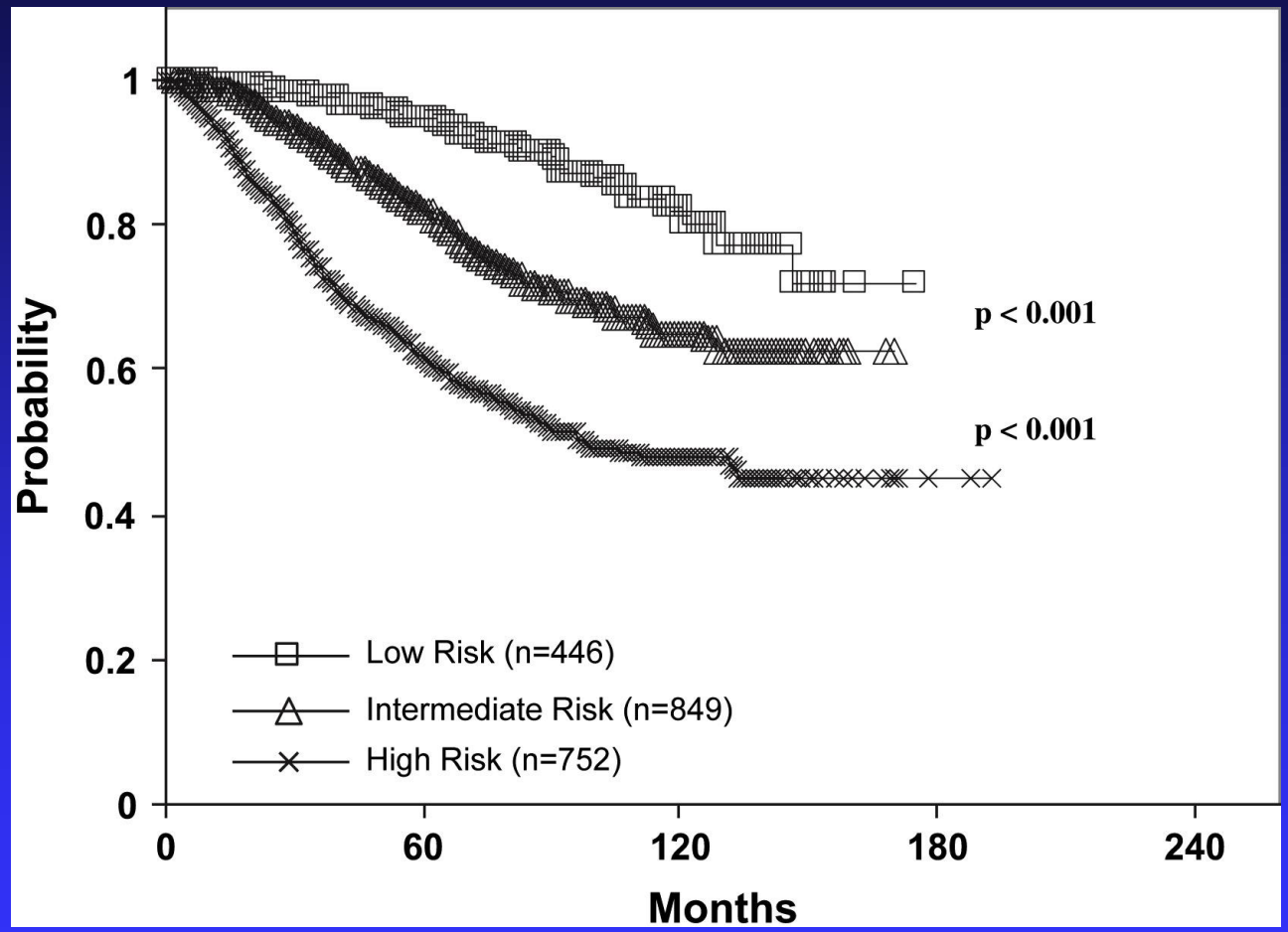
Disclosure

Accuray Clinical Consultant

PSA Failures Following Conventional Radiation Therapy

- BDFS (5 yrs)
  - Low 95%
  - Inter. 82%
  - High 62%



- *Zelefsky et al, IJROBP 2008*

Primary Reasons for Radiation Therapy Failures

- **Missed the Cancer**
  - The prostate moves during treatment

- **Radiation Dose Inadequate**
  - Post-treatment positive biopsy rate 30-40%
  - Dose limited by surrounding normal tissue tolerance

PSMA Determined Patterns of Recurrence Following Prostate IMRT

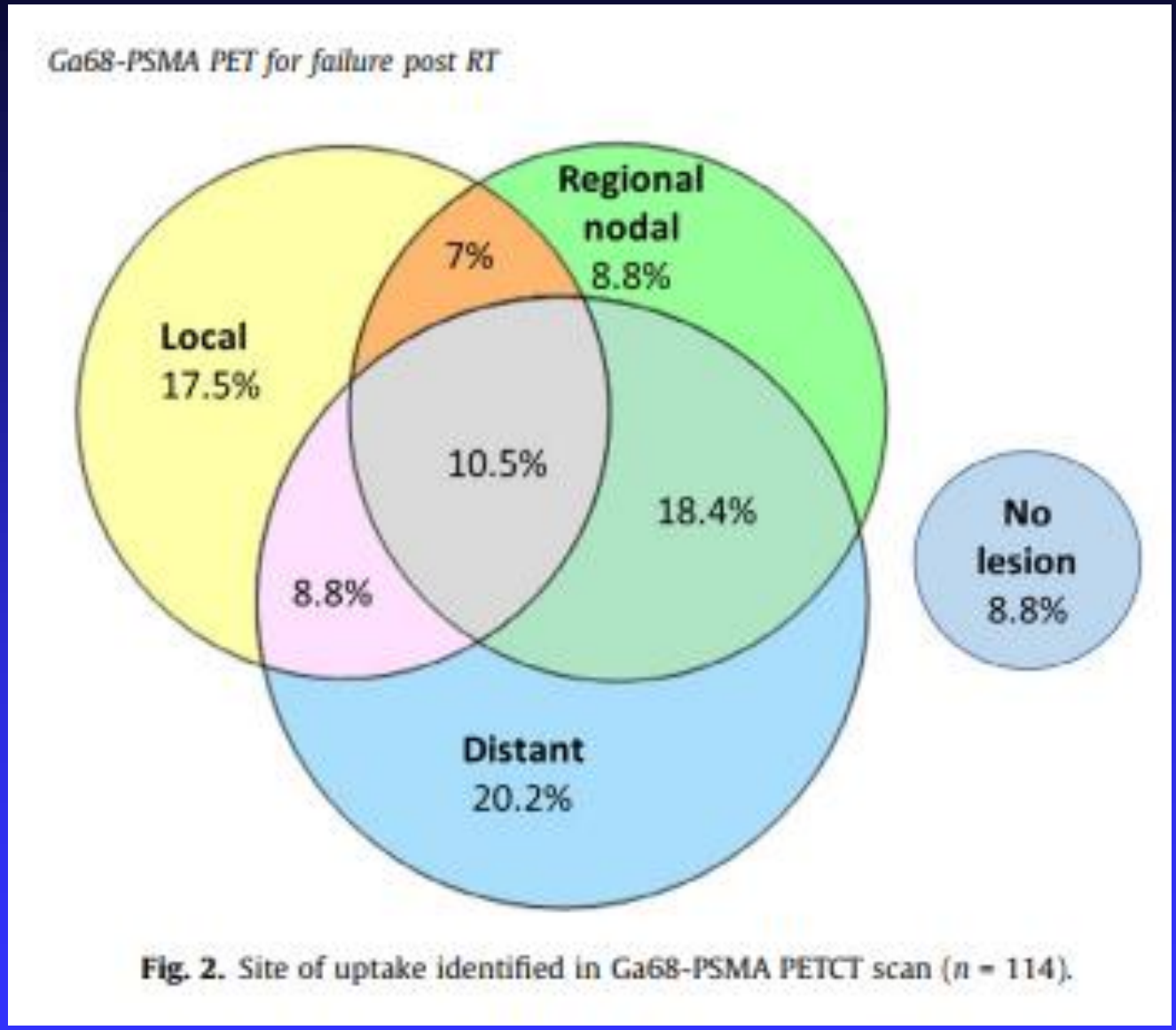
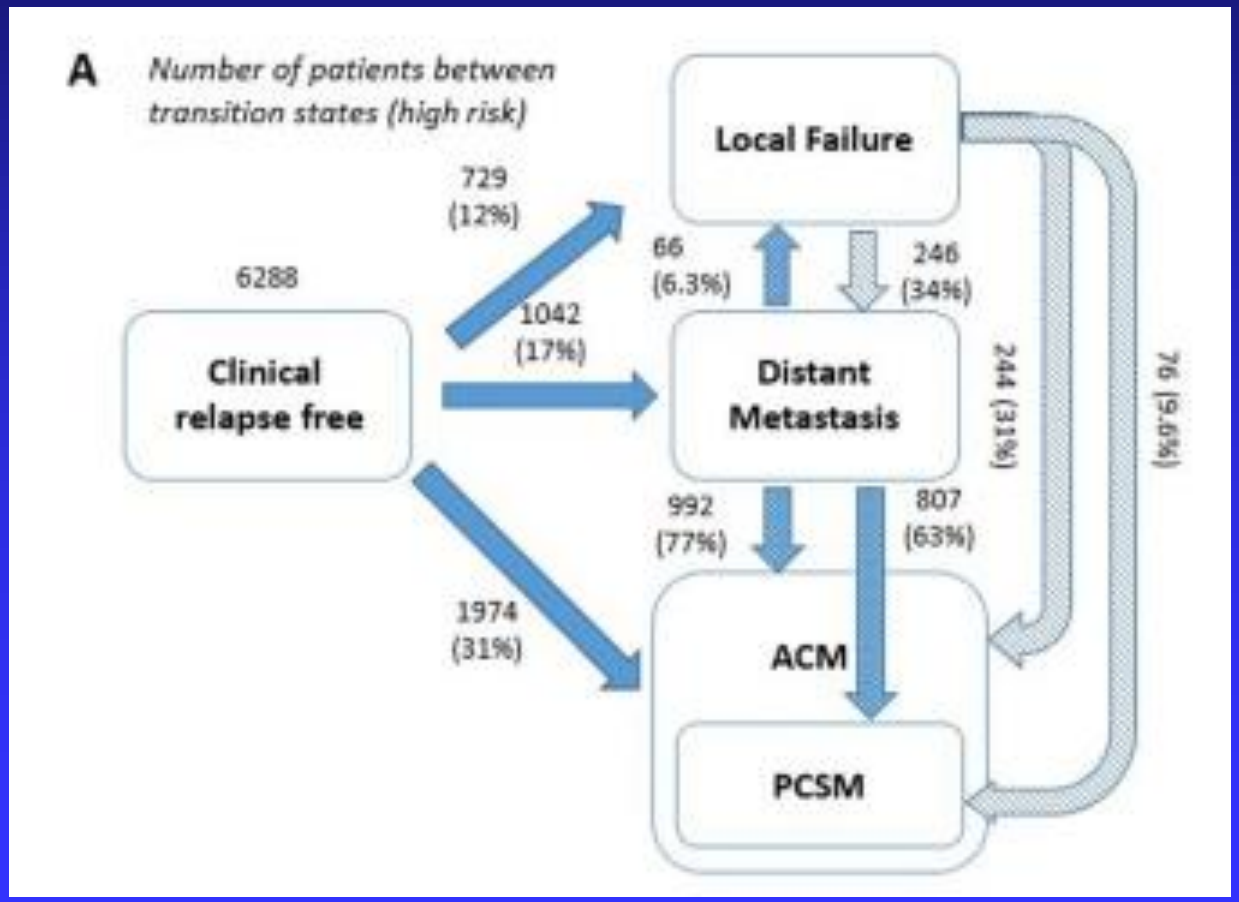


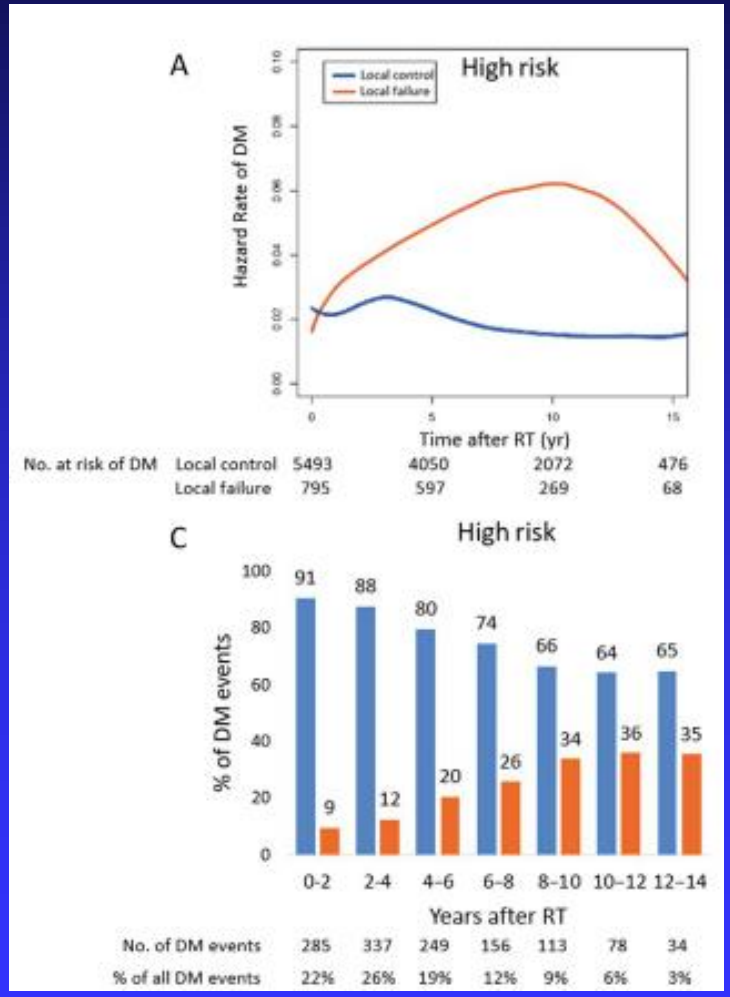
Fig. 2. Site of uptake identified in Ga68-PSMA PETCT scan (n = 114).

- ***Maitre et al, Radiotherapy and Oncology, 2022***

Local Failure Events in Prostate Cancer Treated with Radiotherapy: A Pooled Analysis of 18 Randomized Trials from the Meta-analysis of Randomized Trials in Cancer of the Prostate Consortium (LEVIATHAN)

- **Local Failure is an Independent Predictor of OS, PCSS and DMFS in High-Risk PC!**





- *Ma et al, Eur Urol. 2022*

Under-utilization of Local Therapy After Radiation Therapy for Prostate Cancer

- **Only 2% of Patients that are Eligible for Local Salvage Therapy Receive It**
  - **Elderly Patient Population**
  - **Excessive Toxicity**
  - **Lack of Experience**

Table 3
Salvage therapy after radiation therapy (n = 257)

Primary salvage	Secondary salvage	Tertiary salvage	Frequency (%)
Observation			126 (49.0)
Observation	None		61 (23.7)
	CADT		12 (4.7)
	IADT	None	42 (16.3)
		Orchiectomy	1 (0.4)
		Brachytherapy	1 (0.4)
	Orchiectomy		3 (1.2)
	Unspecified ADT		6 (2.3)
ADT (within 1 y of BCR)			119 (46.3)
CADT			39 (15.2)
IADT	None		65 (25.3)
	Orchiectomy		1 (0.4)
Orchiectomy	None		7 (2.7)
Unspecified ADT	None		7 (2.7)
Clinical trial drug	Observation	ADT	1 (0.4)
Salvage brachytherapy			1 (0.4)
Salvage RP	ADT		2 (0.8)
	None		1 (0.4)
Unknown			7 (2.7)

CADT = continuous androgen-deprivation therapy; IADT = intermittent androgen-deprivation therapy; RP = radical prostatectomy.

- ***Tran et al, Urol. Onc. 2014***

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

Table 2 – Covariate-adjusted estimates of efficacy and toxicity across salvage modalities

	2-yr RFS (95% CI)	5-yr RFS (95% CI)	Severe GU toxicity (95% CI)	Severe GI toxicity (95% CI)
RP	69 (64–74)	54 (49–59)	21 (16–27)	1.9 (0.6–3.7)
Number of studies	26	21	43	43
Number of patients	1439	1488	1617	1617
Heterogeneity (95% PI)	48–84	34–73	0.1–58	0.0–13
Cryotherapy	68 (62–73)	50 (44–56)	15 (10–22)	1.7 (1.0–2.7)
Number of studies	24	18	23	22
Number of patients	3887	3616	2618	2475
Heterogeneity (95% PI)	40–87	28–73	0.0–48	0.2–4.1
HIFU	54 (48–60)	53 (43–63)	23 (17–29)	1.6 (0.9–2.4)
Number of studies	14	7	19	19
Number of patients	1092	236	1737	1737
Heterogeneity (95% PI)	36–71	34–71	4.2–49	0.9–2.4
SBRT	62 (47–74)	60 (N/A)	4.2 (0.8–9.1)	0.0 (0.0–0.1)
Number of studies	5	1	8	8
Number of patients	206	50	261	261
Heterogeneity (95% PI)	49–73	NA	0.0–15	0.0–0.1
HDR	77 (70–83)	60 (52–67)	8.0 (5.1–11)	0.0 (0.0–0.2)
Number of studies	14	7	16	15
Number of patients	456	350	586	571
Heterogeneity (95% PI)	55–90	45–73	2.3–16	0.0–0.2
LDR	81 (74–86)	56 (48–63)	8.1 (4.3–13)	1.5 (0.2–3.4)
Number of studies	22	16	26	26
Number of patients	495	511	664	660
Heterogeneity (95% PI)	57–93	33–76	0.0–31	0.0–5.7

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; PI = prediction interval; RFS = recurrence-free survival; RP = radical prostatectomy; SBRT = stereotactic body radiotherapy.

Valle et al, Eur Urol. 2021

MASTER Conclusions:

- Recurrence Free Survival (5 years)
  - 50-60%
  - No Significant Difference Between any Modality and RP
- Severe GU Toxicity
  - Significant Lower with RT than RP (21%)
    - LDR Brachytherapy 8.1%
    - HDR Brachytherapy 8.0%
    - SBRT 4.2%
- Severe GI Toxicity
  - Significant Lower with SBRT/HDR Brachy (0%) than RP (1.9%)

Valle et al, Eur Urol. 2021

Retreatment for Local Recurrence After Prior Irradiation: Low Dose Rate Brachytherapy (RTOG 0526)

- **Patient Selection:**
  - **Low or Intermediate Risk Prostate Cancer**
  - **Biopsy-Proven Local Recurrence**
  - **Local Recurrence > 30 Months Post-EBRT**
  - **PSA < 10 ng/ml**
  - **Negative Bone and Pelvic CT Scan**
  - **IPSS < 15**
  - **No Residual Grade $\geq$ 2 GU or GI Toxicities**

Crook et al, IJROBP 2022

Retreatment for Local Recurrence After Prior Irradiation: Low Dose Rate Brachytherapy (RTOG 0526)

- 92 Patients
- Median FU = 6.7 yrs
- ADT = 16%
- GU/GI Grade 3 = 14%
- OS (10 yrs) = 70%
  - Death
    - PC 5
    - Other 10
    - ??? 4

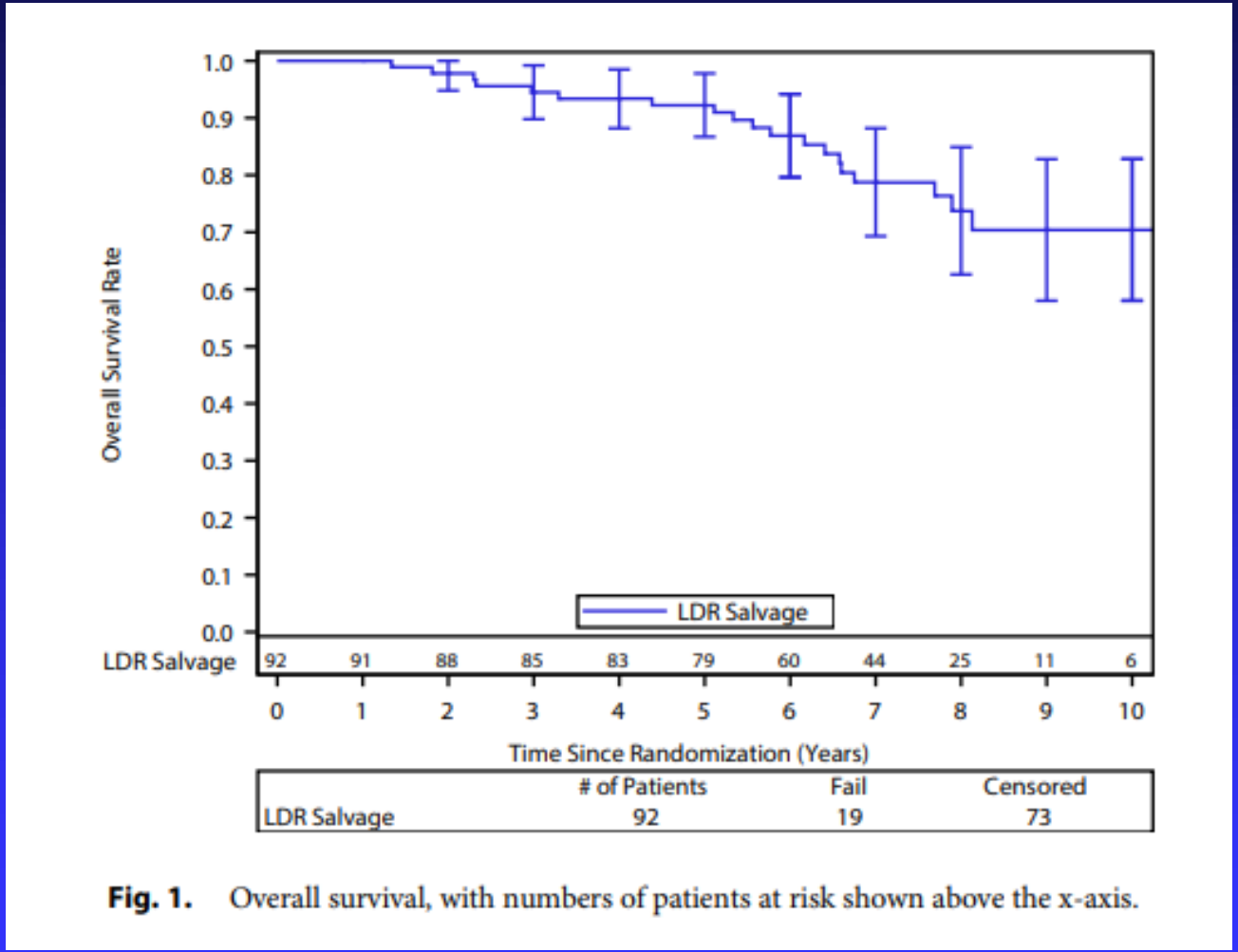


Fig. 1. Overall survival, with numbers of patients at risk shown above the x-axis.

- *Crook et al, IJROBP 2022*

Retreatment for Local Recurrence After Prior Irradiation: Low Dose Rate Brachytherapy (RTOG 0526)

- **Local Recurrence (10 yrs) = 5%**

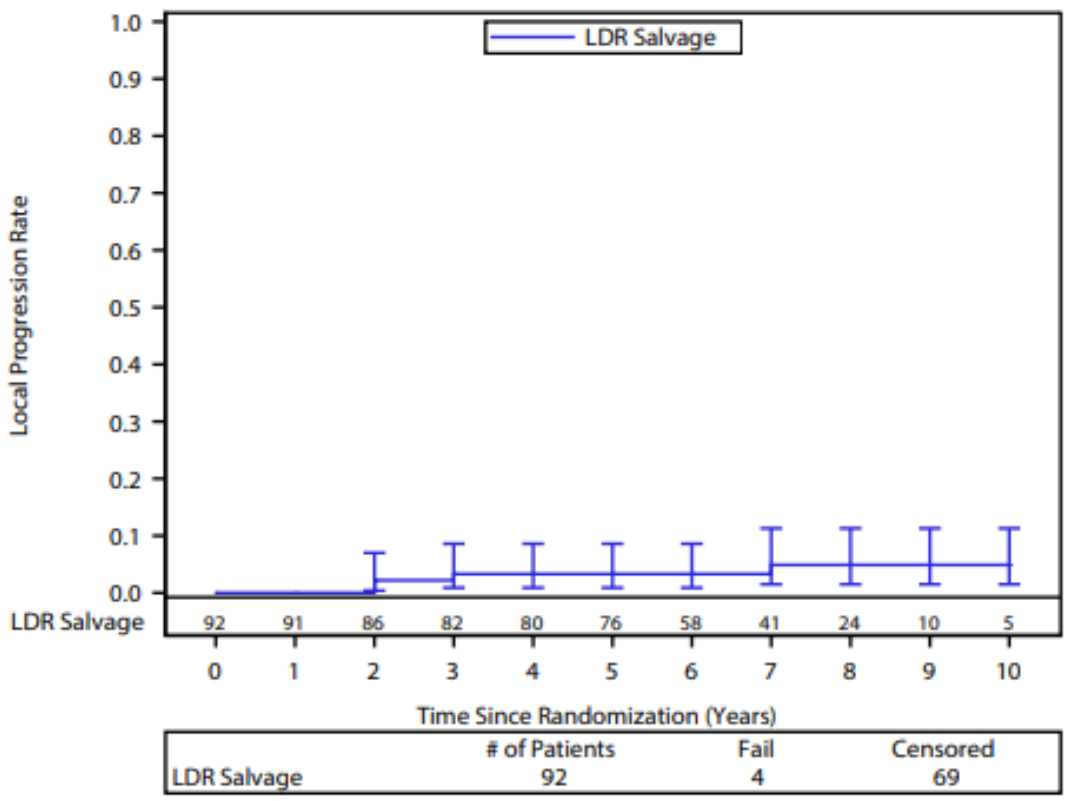


Fig. 2. Actuarial local failure after salvage brachytherapy, with numbers of patients at risk are shown above the x-axis.

- *Crook et al, IJROBP 2022*

Retreatment for Local Recurrence After Prior Irradiation: Low Dose Rate Brachytherapy (RTOG 0526)

- **Biochemical Failure (10 yrs) = 46%**

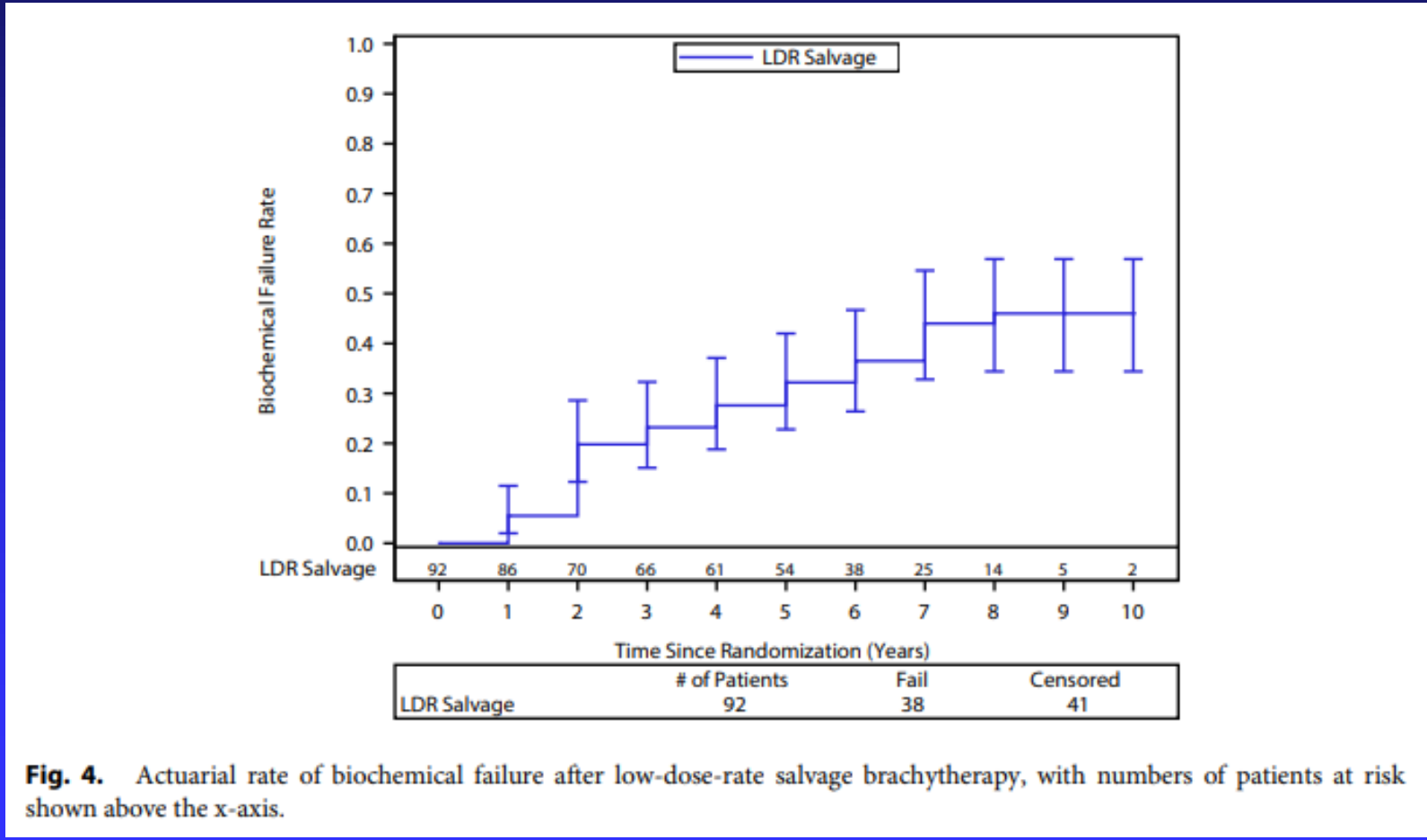


Fig. 4. Actuarial rate of biochemical failure after low-dose-rate salvage brachytherapy, with numbers of patients at risk shown above the x-axis.

- ***Crook et al, IJROBP 2022***

Retreatment for Local Recurrence After Prior Irradiation: Low Dose Rate Brachytherapy (RTOG 0526)

- **GU/GI Grade 3 = 14%**

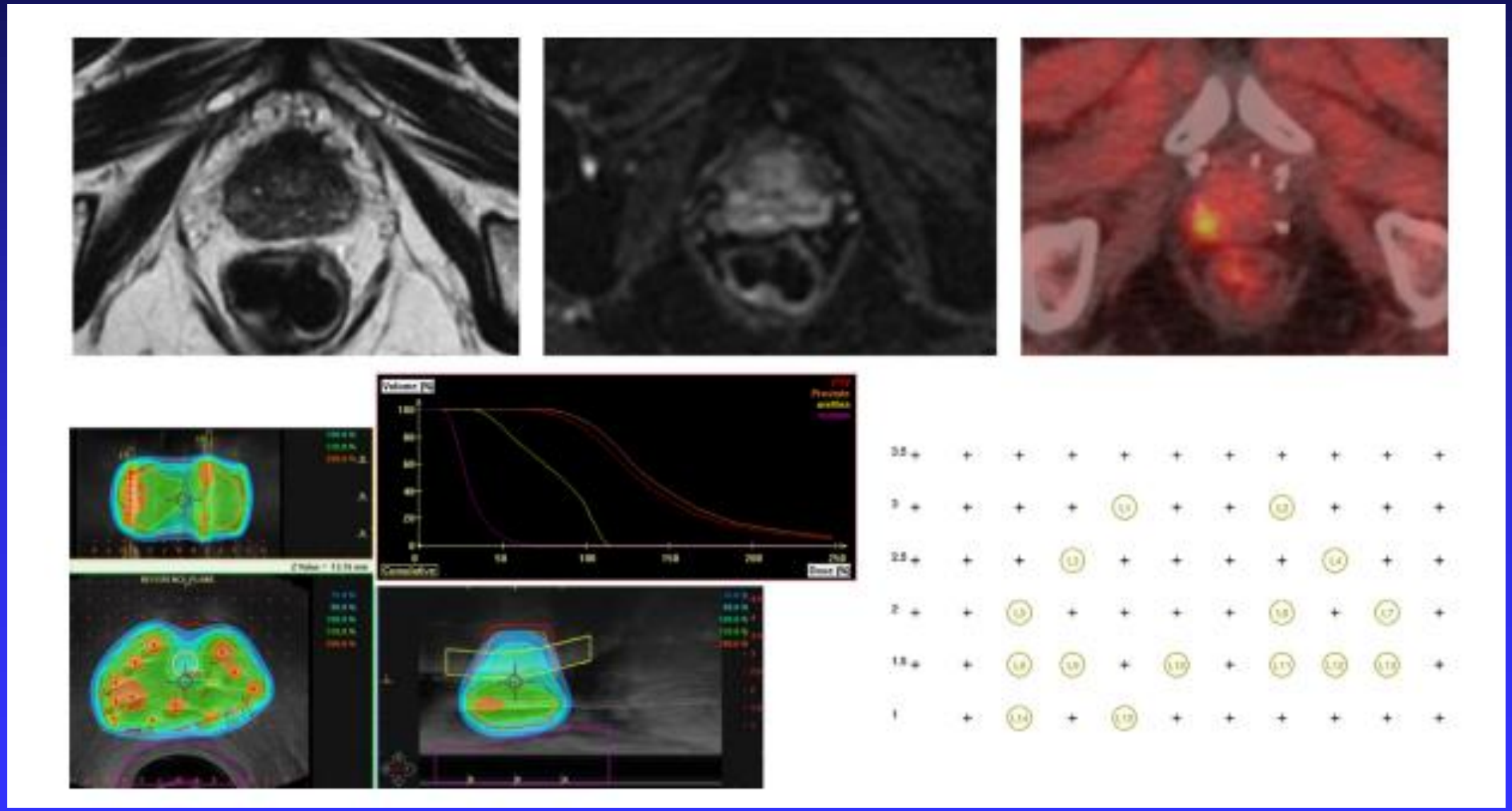
Table 6 Early grade 3 or higher treatment-related gastrointestinal or genitourinary adverse effects occurring 9 months (39 weeks) or less from treatment

Type	No. of patients	Attribution	Grade	Time since implant (wk)
Rectal bleed	1	Definitely	3	32
Rectal pain	2	Possibly	3	26, 17
Retention	2	Definitely	3	7, 6
Frequency	3	Possibly, definitely, probably	3	4, 11, 14
Frequency/retention	1	Definitely	3	8/8
Urethral stricture	1	Probably	3	36
Frequency/retention/obstruction	1	Definitely	3	1/1/1
Incontinence	1	Probably	3	30

- ***Crook et al, IJROBP 2019***

Retreatment for Local Recurrence After Prior Irradiation: High Dose Rate Brachytherapy

- **HDR Brachy May Have Lower Toxicity than LDR Brachy**



- ***Kissel et al, Brachytherapy 2022***

Retreatment for Local Recurrence After Prior Irradiation: High Dose Rate Brachytherapy

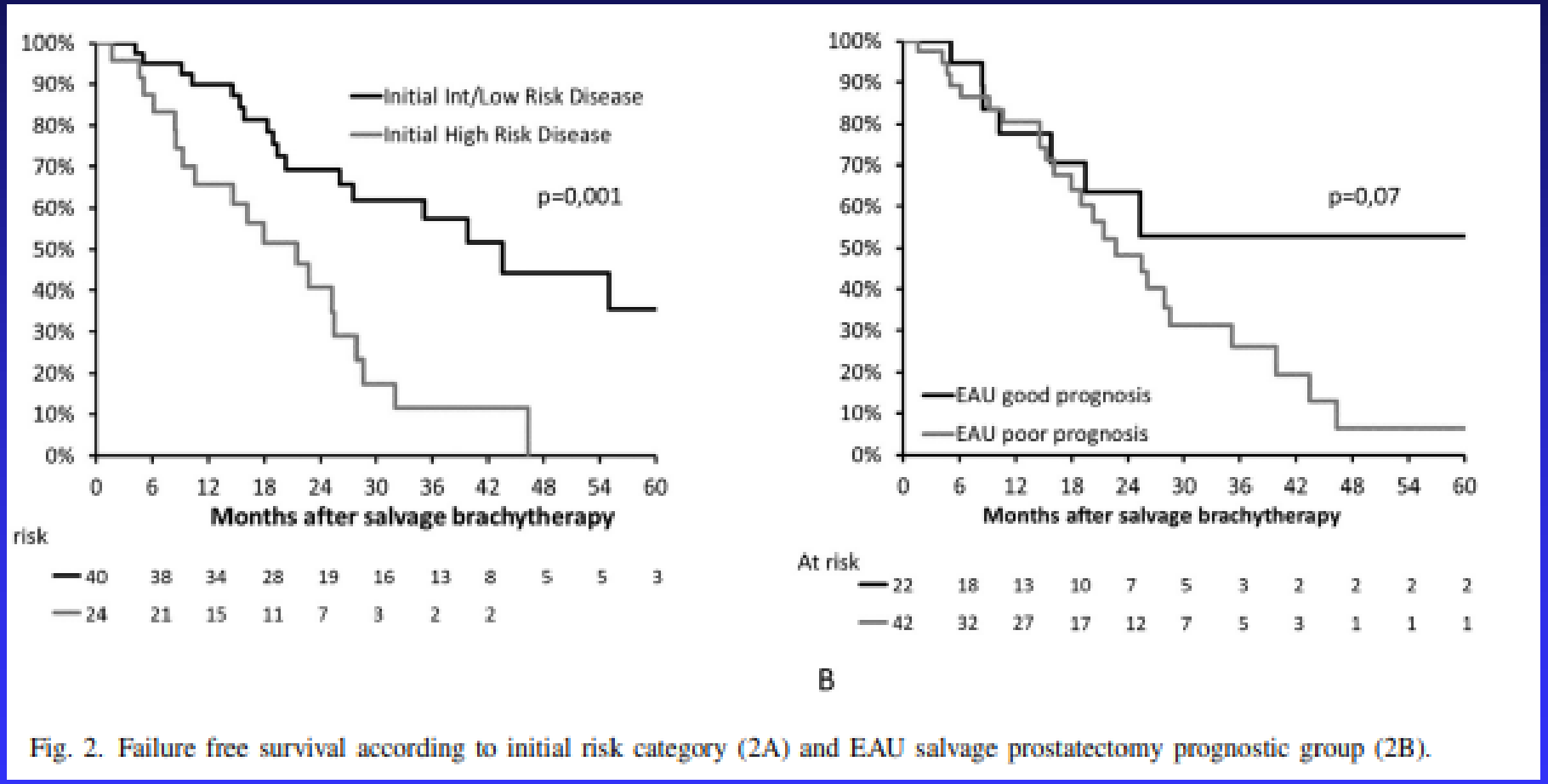


Fig. 2. Failure free survival according to initial risk category (2A) and EAU salvage prostatectomy prognostic group (2B).

Kissel et al, Brachytherapy 2022

Retreatment for Local Recurrence After Prior Irradiation: High Dose Rate Brachytherapy

Table 3
Univariate and multivariate analyses for failure-free survival.

Patient characteristics		Univariate		Multivariate	
		HR (95% CI)	*p*	HR (95% CI)	*p*
EAU prognostic group	Adequate for salvage RP	1	0.07		
	Not adequate for salvage RP	2.01 (0.94; 4.58)			
Time between first RT and salvage BT	>10y	1	0.49		
	5–10y	0.79 (0.41; 1.53)			
Salvage BT dose	24 Gy	1	0.74		
	26 Gy	0.94 (0.65; 1.36)			
D90	>95% of prescribed dose	1	0.57		
	<95% of prescribed dose	1.23 (0.60; 2.50)			
Hormone sensitivity at relapse	Yes	1	0.12		
	No	1.79 (0.86; 3.75)			
ADT with salvage BT	No	1	0.47		
	Yes	0.48 (0.065; 3.57)			
Gleason score at relapse	≤7	1	0.08		
	8–10	1.81 (0.93; 3.52)			
PSA at relapse	<10 ng/mL	1	0.60	1	0.14
	>10 ng/mL	1.23 (0.56; 2.74)		1.90 (0.81; 4.44)	
Initial high risk	No	1	0.001	1	0.0005
	Yes	3.07 (1.56; 6.04)		3.59 (1.75; 7.39)	

EAU = European Association of Urology; RT = radiotherapy; D90 = dose received by 90% of the CTV; ADT = androgen deprivation therapy; BT = brachytherapy.

Table 4
Acute and late toxicities.

	Grades 0–1	Grade 2	Grade 3	Grades 4–5
Acute GU	41 (68.5%)	18 (30%)	1 (1.5%)	0
Acute GI	58 (100%)	0	0	0
Late GU	51 (80%)	12 (18.5%)	1 (1.5%)	0
Late GI	62 (97%)	1 (1.5%)	1 (1.5%)	0

GU = genito-urinary; GI = gastro-intestinal.

Kissel et al, Brachytherapy 2022

Retreatment for Local Recurrence After Prior Irradiation: HDR-Like SBRT

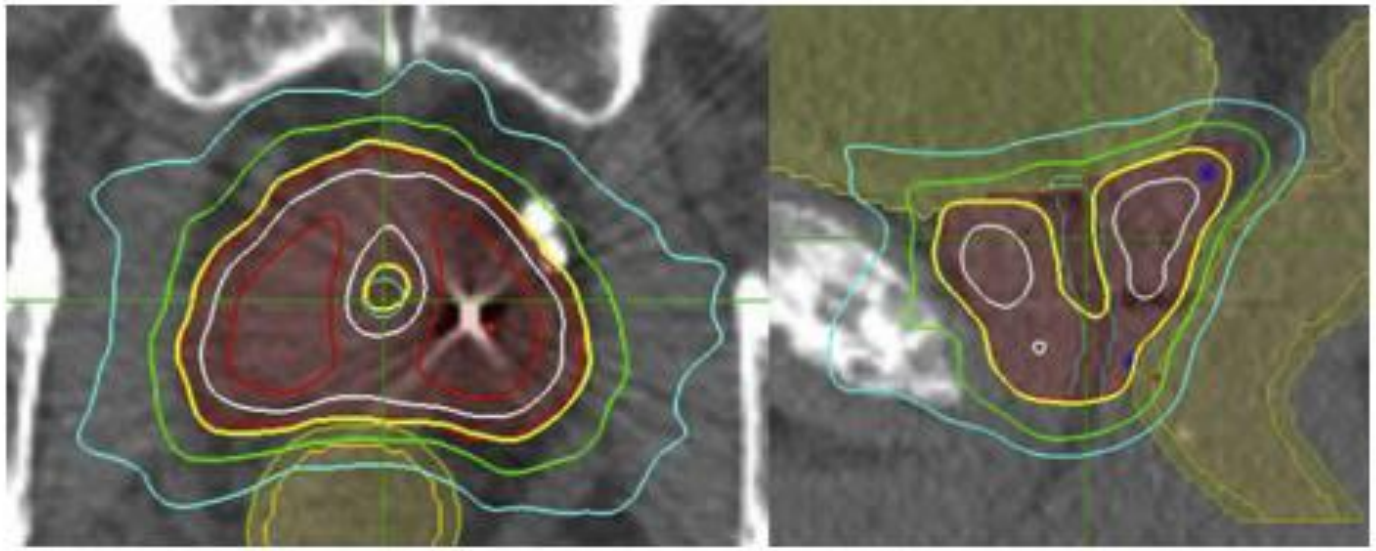
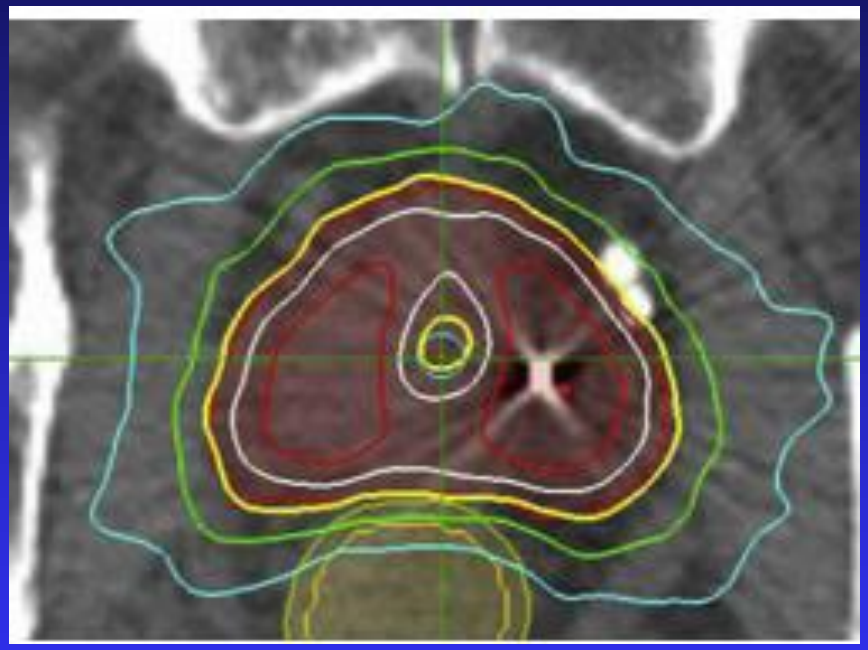


Fig. 1. Typical salvage prostate "high dose-rate (HDR)-like" stereotactic body radiation therapy (SBRT) treatment plan. Zero margin expansion of prescription isodose line (yellow) beyond prostate against adjacent bladder and rectum. Relative central periurethral isodose sparing and HDR-like dose escalation within the peripheral zone of the prostate (white:125% isodose line; red: 150% isodose line).

Fuller et al, IJROBP 2019

Retreatment for Local Recurrence After Prior Irradiation: HDR-Like SBRT

- **Protocol:**
  - **50 Patients**
  - **CyberKnife System**
  - **Fiducial Guidance**
  - **MRI/CT for Treatment Planning**
  - **34 Gy in 5 Fx**
  - **Whole Prostate**
  - **CTV = Prostate plus ECE**
  - **No PTV Margin**
  - **ADT = 14%**



- ***Fuller et al, IJROBP 2019***

Retreatment for Local Recurrence After Prior Irradiation: HDR-Like SBRT

- Mean Age = 74 yo
- Mean Volume = 22 cc
- Mean Interval = 8 yrs
- Mean Dose = 75.6 Gy

Table 1 Patient Characteristics

Patient characteristics		
Number treated with salvage protocol	50	
Follow-up postsalvage, median (range)	44 mo (3-110 mo)	
Age at salvage, median (range)	74 y	(50-89 y)
Prior RT modality	43 EBRT	7 other (5 brachytherapy, 1 SBRT, 1 radical prostatectomy + EBRT)
Interval to SBRT salvage, median (range)	98 mo (31-241 mo)	
Prior RT dose, median (range)	7560 cGy	(3500-14,500 cGy)
Presence of toxicity from initial RT course	20 pts with complications reported 30 pts with no complications reported	
T-stage at salvage (DRE)	# pts	
T1c	28	
T2a	6	
T2b	10	
T2c	4	
T3a	0	
T3b	1	
T3c	0	
Unknown	1	
PSA level at salvage, median (range)	3.97 ng/mL	(0.1-48.2 ng/mL)
Total Gleason score at recurrence	# pts	
6	9	
7	22	
3 + 4	9	
4 + 3	13	
8	10	
9	8	
4 + 5	5	
5 + 4	3	
ADT	7 pts reported ADT 4 pts neoadjuvant 3 pts CRPC	
Prostate volume at salvage (TRUS − LWH), median (range)	21.5 cc	(10.5-47.7 cc)

Abbreviations: ADT = androgen deprivation therapy; EBRT = external beam radiation therapy; RT = radiotherapy; SBRT = stereotactic body radiation therapy.

Fuller et al, IJROBP 2019

Retreatment for Local Recurrence After Prior Irradiation: HDR-Like SBRT

- **Rapid PSA Declines (0.6 ng/ml at 1 yr)**

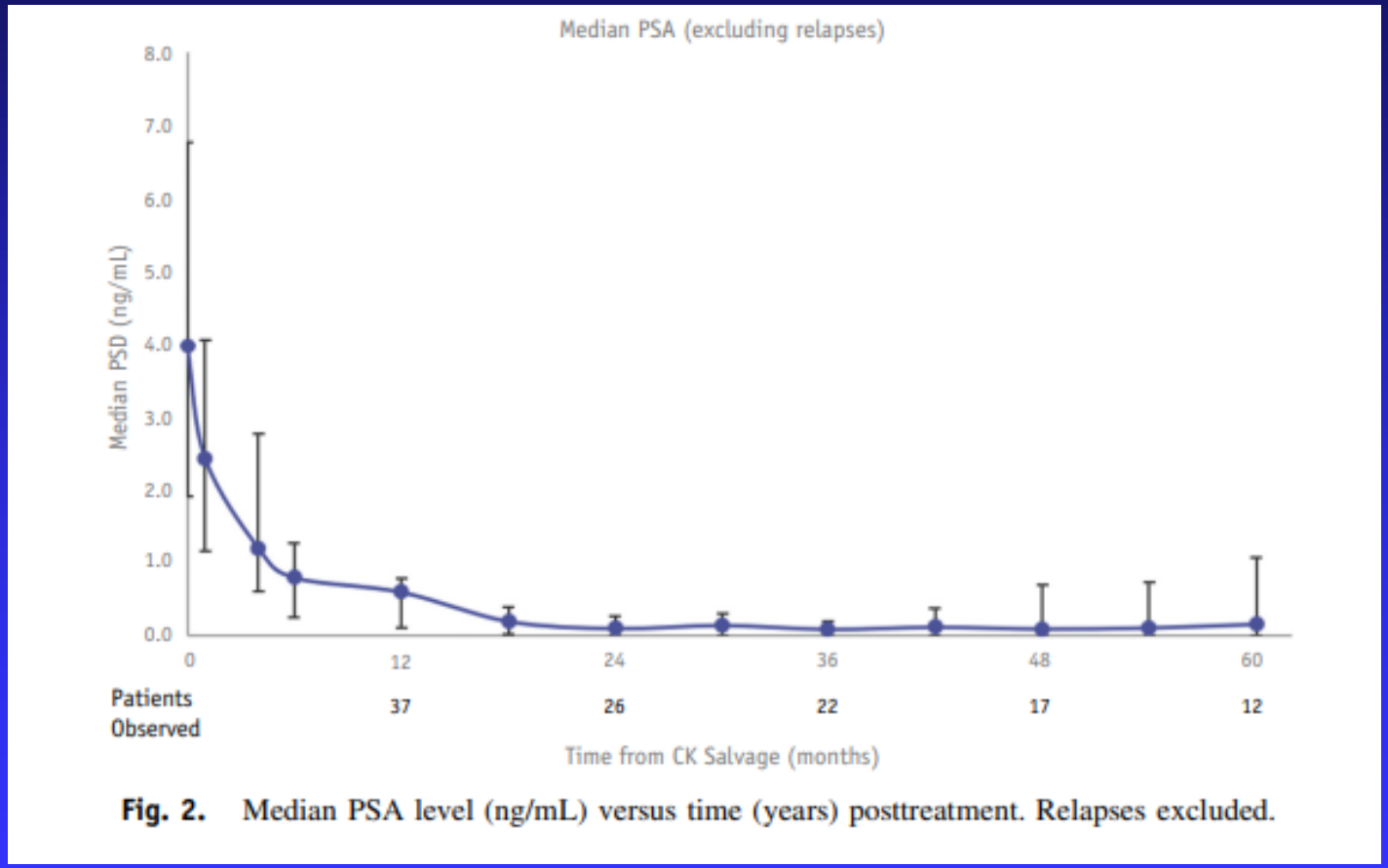
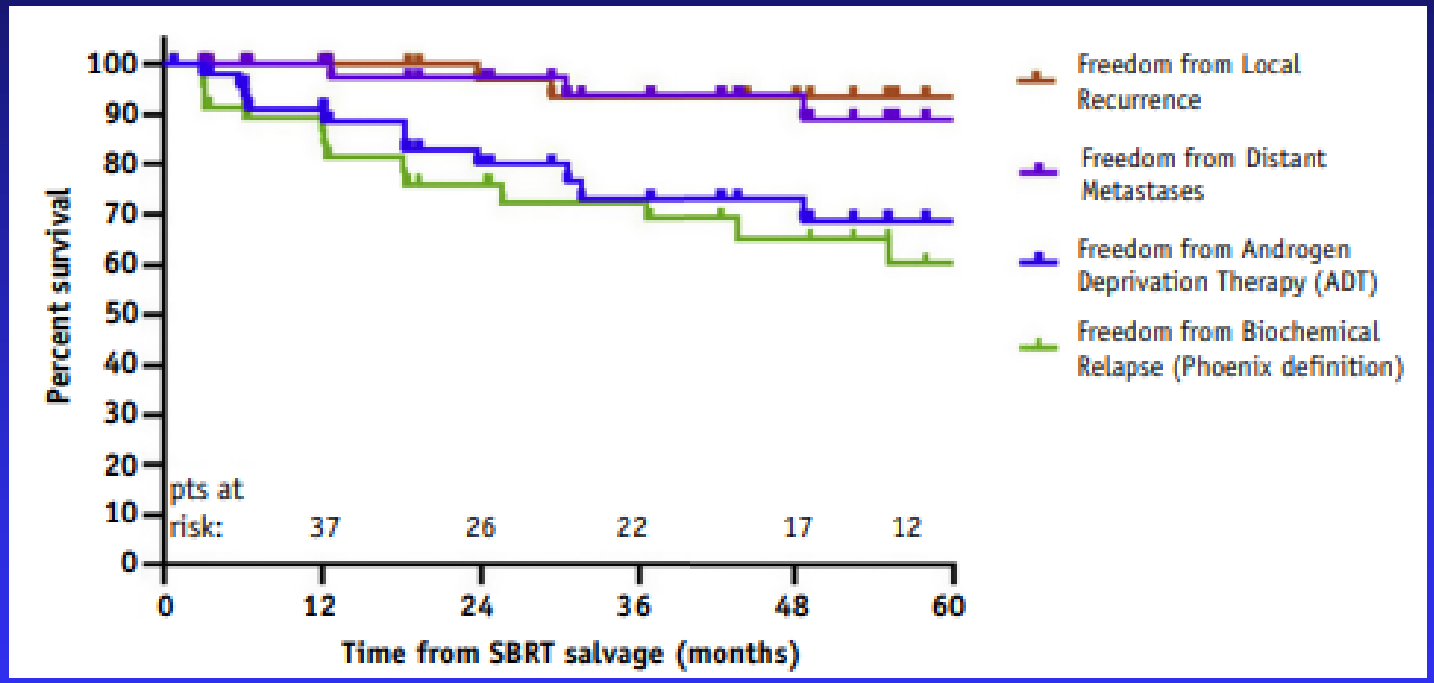


Fig. 2. Median PSA level (ng/mL) versus time (years) posttreatment. Relapses excluded.

- ***Fuller et al, IJROBP 2019***

Retreatment for Local Recurrence After Prior Irradiation: HDR-Like Whole Gland SBRT

- **BDFS (5 yr) = 60%**
- **LC (5 yr) = 94%**
- **MFS (5 yr) = 89%**
- **ADT FS (5 yrs) = 69%**



- ***Fuller et al, IJROBP 2019***

Retreatment for Local Recurrence After Prior Irradiation: HDR-Like SBRT

- **GU Grade ≥ 3 = 8% - Most Prior Brachy/SBRT**

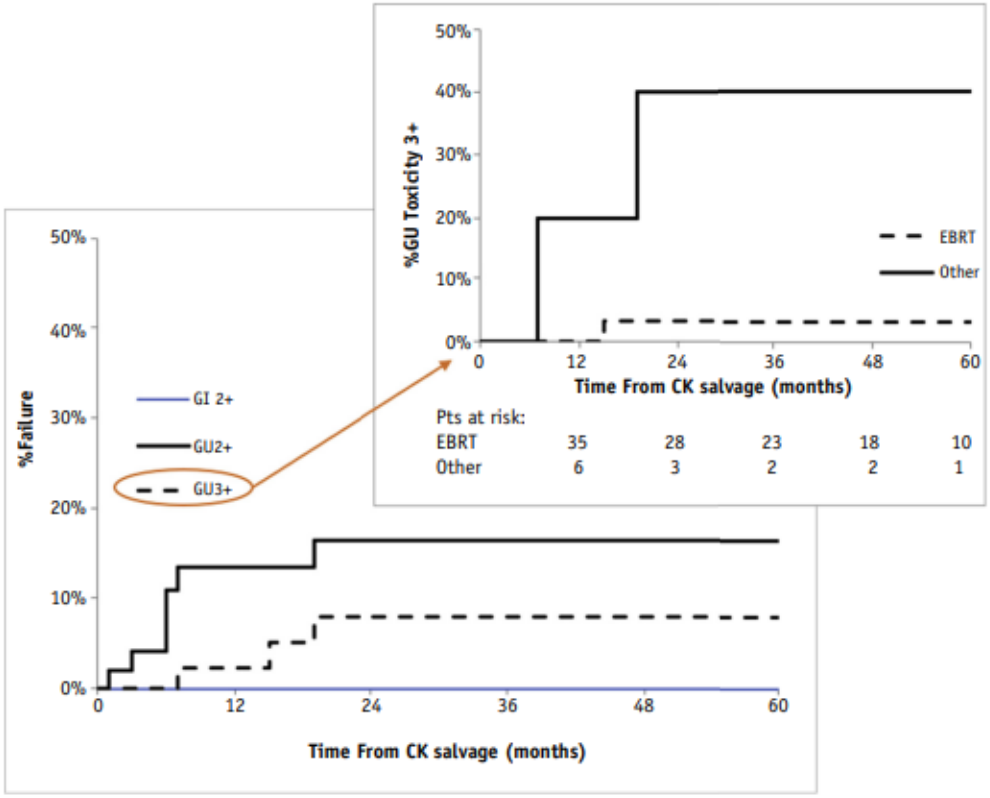


Fig. 4. Actuarial rate of grade 2 + GU and gastrointestinal (GI) complications for entire series (left panel) and subdivision of the actuarial rate of grade 3 + GU complications by initial radiation therapy modality received. Conventional fractionation EBRT versus other.

- ***Fuller et al, IJROBP 2019***

Local Failure After Prostate SBRT Predominantly Occurs in the Dominant Intraprostatic Lesion (DIL)

- Men with PI-RADS 4-5 DILs have a Higher Risk of Recurrence

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European Association of Urology

Prostate Cancer

Local Failure after Prostate SBRT Predominantly Occurs in the PI-RADS 4 or 5 Dominant Intraprostatic Lesion

Daniel Gorovets [a,*], *Andreas G. Wibmer* [b], *Assaf Moore* [a,c], *Stephanie Lobaugh* [d], *Zhigang Zhang* [d], *Marisa Kollmeier* [a], *Sean McBride* [a], *Michael J. Zelefsky* [a]

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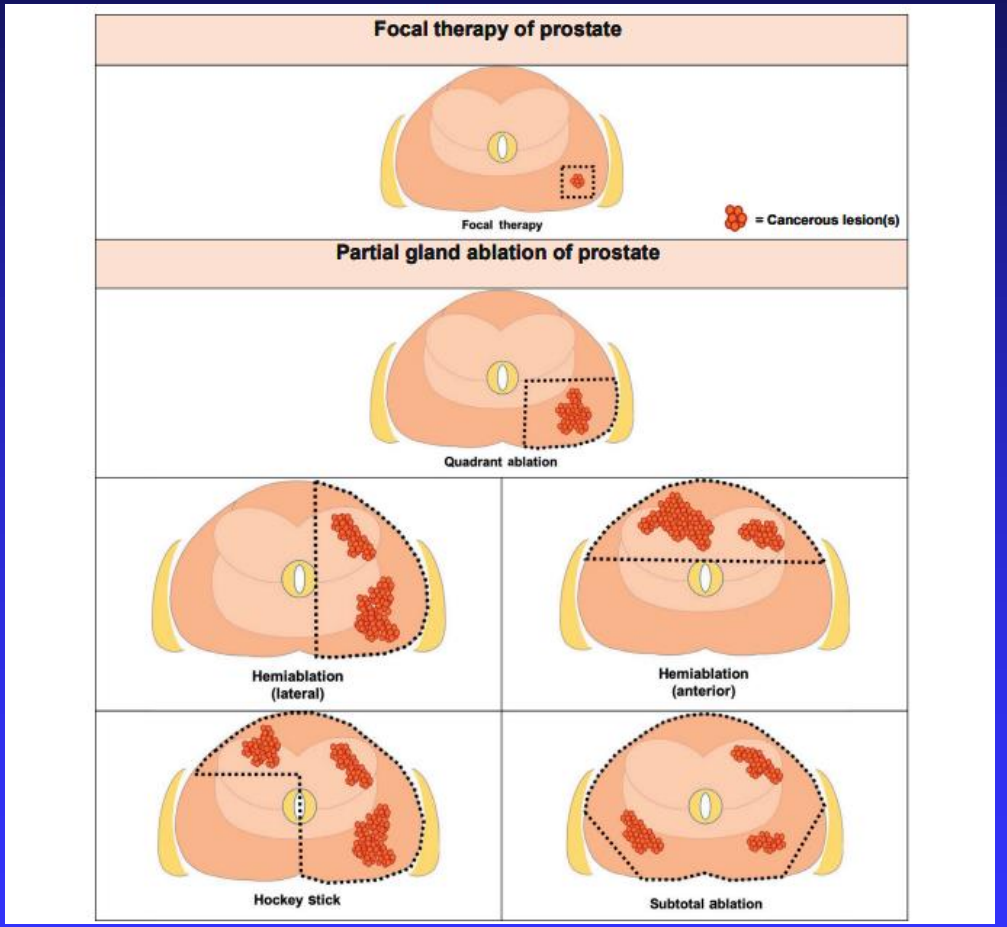
FOCAL SBRT: Target Volume?

- **With Improved Imaging and Treatment Guidance, Is It Time for Focal Re-Irradiation?**

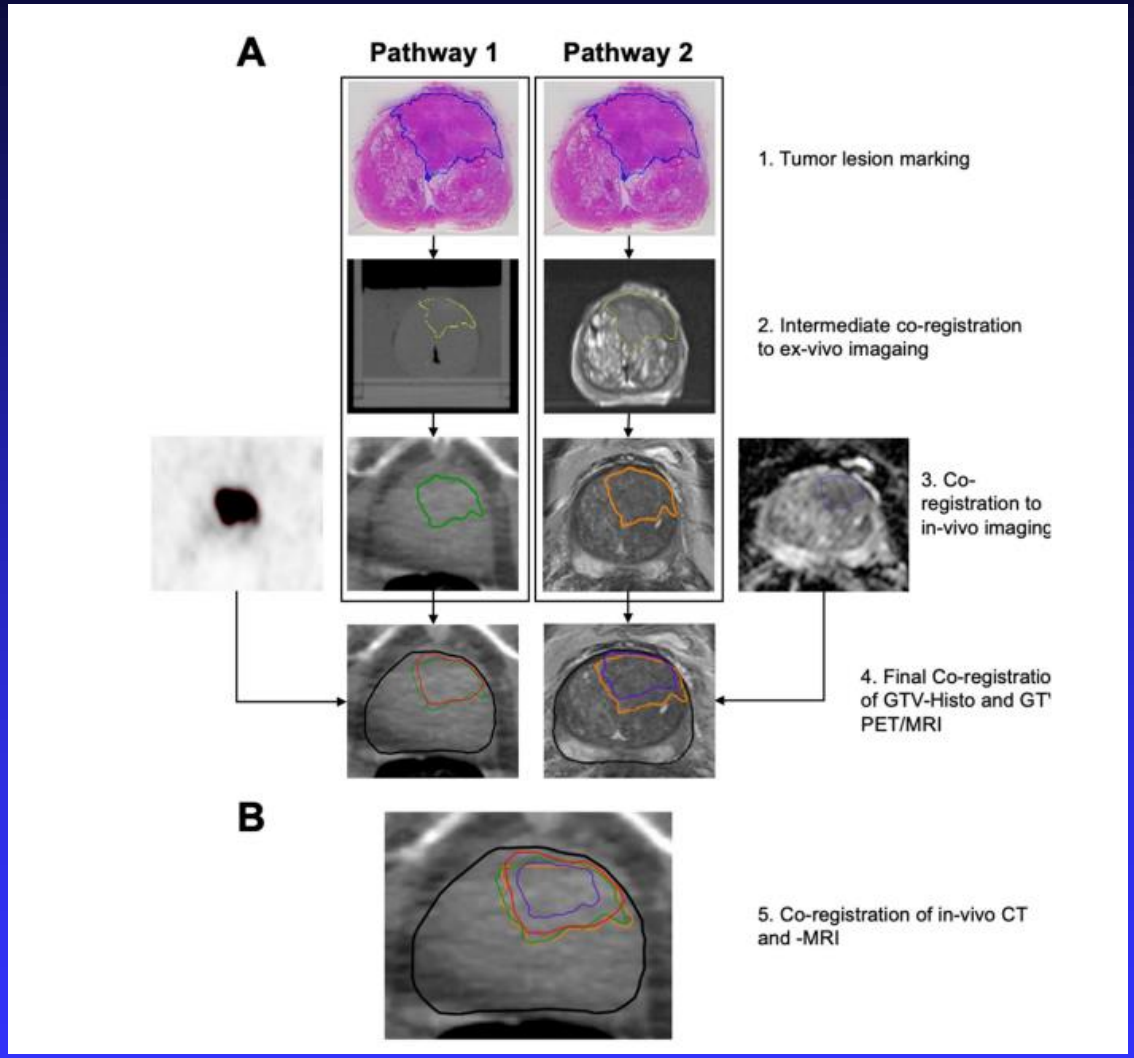
- **Post-Brachy/SBRT?**
  - **Dominant Lesion**
  - **Toxic WG Re-treatment**



- ***Lebastchi et al, Sci Rep 2021***

FOCAL SBRT: Target Volume?

- **Accurate Delineation:**
  - **MRI**
    - **Gold Standard**
    - **Underestimates TV**
  - **PSMA-PET**
    - **Similar Specificity**
    - **Increased Sensitivity**



- ***Zamboglou et al, Sci Rep 2021***

Rationale for Utilization of PSMA Scan to Define Focal Target Volume

- **PSMA Scan May Aid in Selectively Identifying Aggressive Cancers**

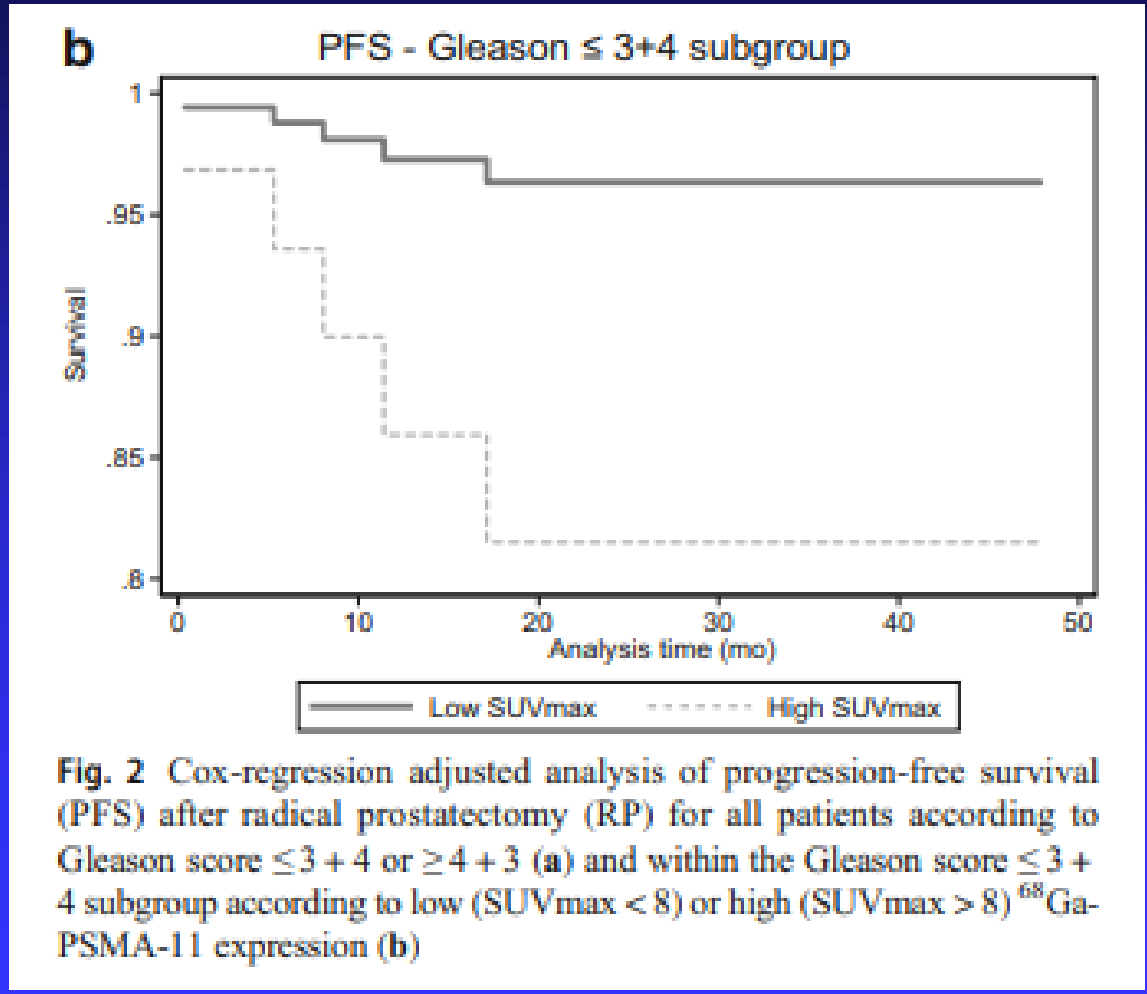
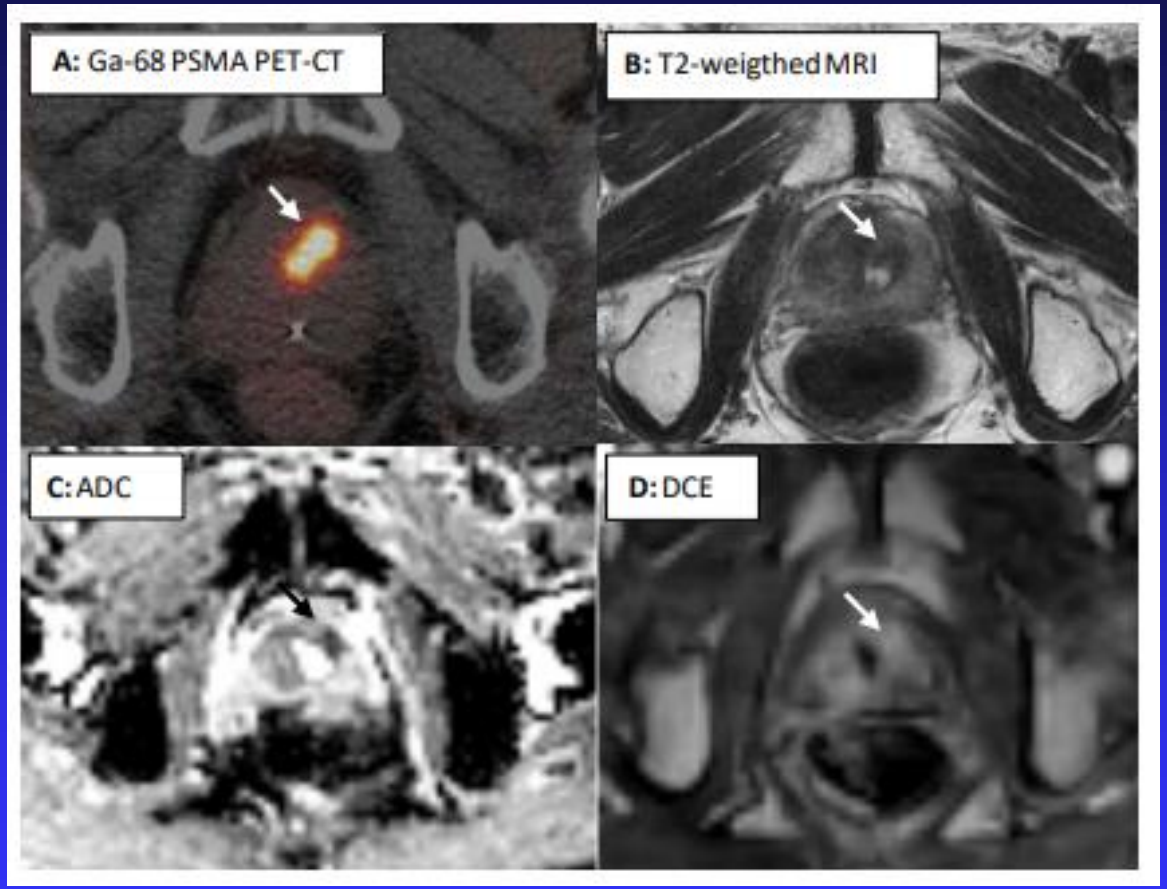


Fig. 2 Cox-regression adjusted analysis of progression-free survival (PFS) after radical prostatectomy (RP) for all patients according to Gleason score ≤ 3 + 4 or ≥ 4 + 3 (**a**) and within the Gleason score ≤ 3 + 4 subgroup according to low (SUVmax < 8) or high (SUVmax > 8) ^{68}Ga-PSMA-11 expression (**b**)

- ***Roberts et al, Eur J Nucl Med Mol Imaging. 2021***

FOCAL SBRT: Prostate Biopsy?

- **MRI and PSMA:**
  - **Positive Predictive Value**
    - **≥ 97.6%**
  - **Gleason Grading is Inaccurate**
  - **No Need for Biopsy**



- ***Raising et al, Cancers 2022***

Retreatment for Local Recurrence After Prior Irradiation: Focal HDR Versus SBRT

- **Both have Rapid Dose Fall Off**
- **Both are Heterogeneous**
- **SBRT may be Easier to Implement**

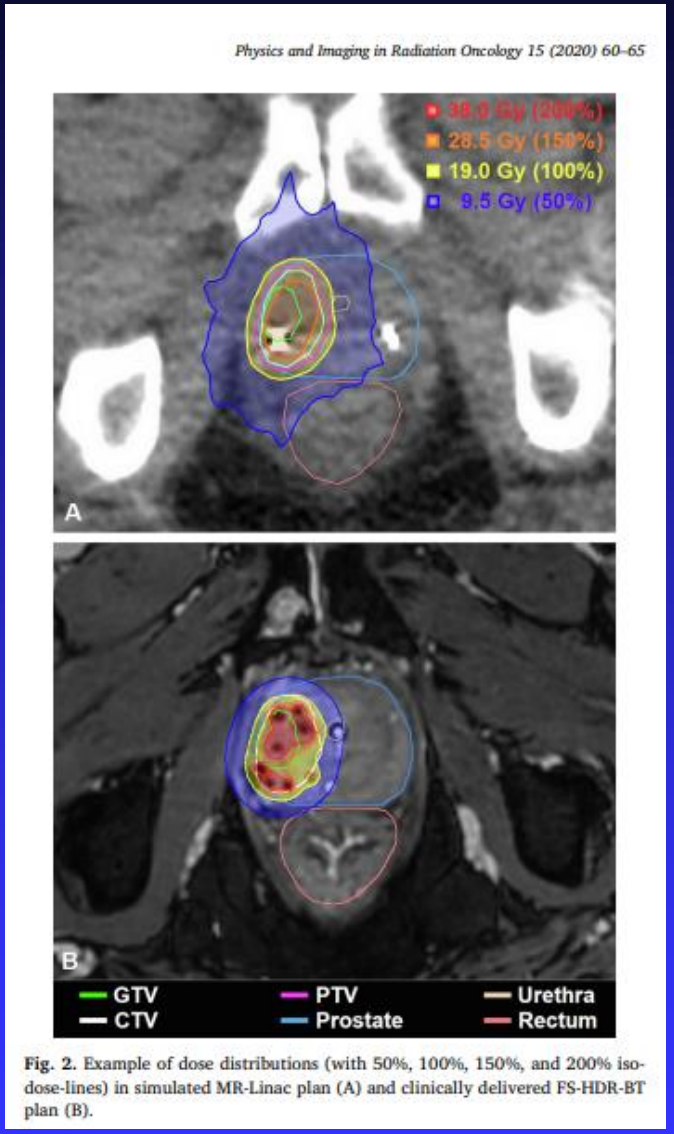


Fig. 2. Example of dose distributions (with 50%, 100%, 150%, and 200% iso-dose-lines) in simulated MR-Linac plan (A) and clinically delivered FS-HDR-BT plan (B).

- ***Willigenburg et al, Phy Imaging Radiat Oncol 2020***

Retreatment for Local Recurrence After Prior Irradiation: Focal SBRT (GETUG-AFU 31)

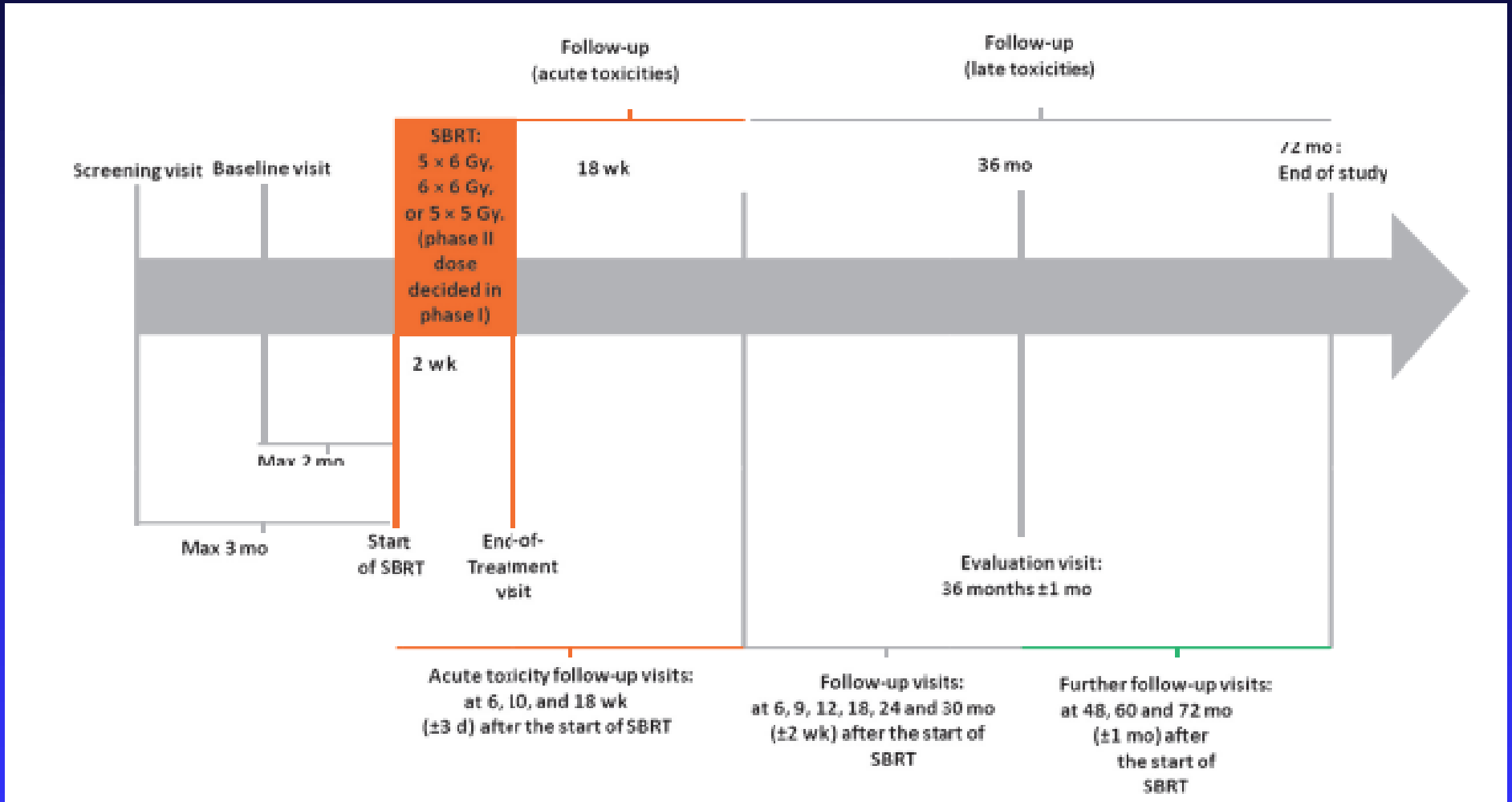


Fig. 1 – Study design. SBRT = stereotactic body radiation therapy.

Pasquier et al, Eur Urol Oncol. 2023

Retreatment for Local Recurrence After Prior Irradiation: Focal SBRT (GETUG-AFU 31)

Table 2 – Patient and disease characteristics at study inclusion

Characteristics (n = 21)	Total (N = 21)[a]	
Age (yr), median (IQR)	76.8	(72.2–80.8)
BMI (kg/m^2)—missing data (n = 2), median (IQR)	26.3	(24.2–27.5)
Number of biopsy cores, median (IQR)	14.0	(14.0–17.0)
Number of positive biopsy cores, median (IQR)	3.0	(2.0–5.0)
Gleason total score at recurrence—missing data (n = 1), n (%)		
6	2	(10)
7 (3 + 4)	11	(55)
7 (4 + 3)	4	(20)
8	1	(5)
9–10	2	(10)
PSA at recurrence (ng/ml), median (IQR)	2.9	(2.6–3.3)
PSA at study entry (ng/ml), median (IQR)	4.2	(3.2–6.0)
PSA doubling time (mo), median (IQR)	25.4	(18.1–48.0)
T stage on DRE at study entry—missing data (n = 4), n (%)		
T1	6	(35)
T1c	8	(47)
T2b	3	(18)

BMI = body mass index; DRE = digital rectal examination; IQR = interquartile range; PSA = prostate-specific antigen.

[a] The percentages may not add up to 100% because of rounding.

Pasquier et al, Eur Urol Oncol. 2023

Retreatment for Local Recurrence After Prior Irradiation: Focal SBRT (GETUG-AFU 31)

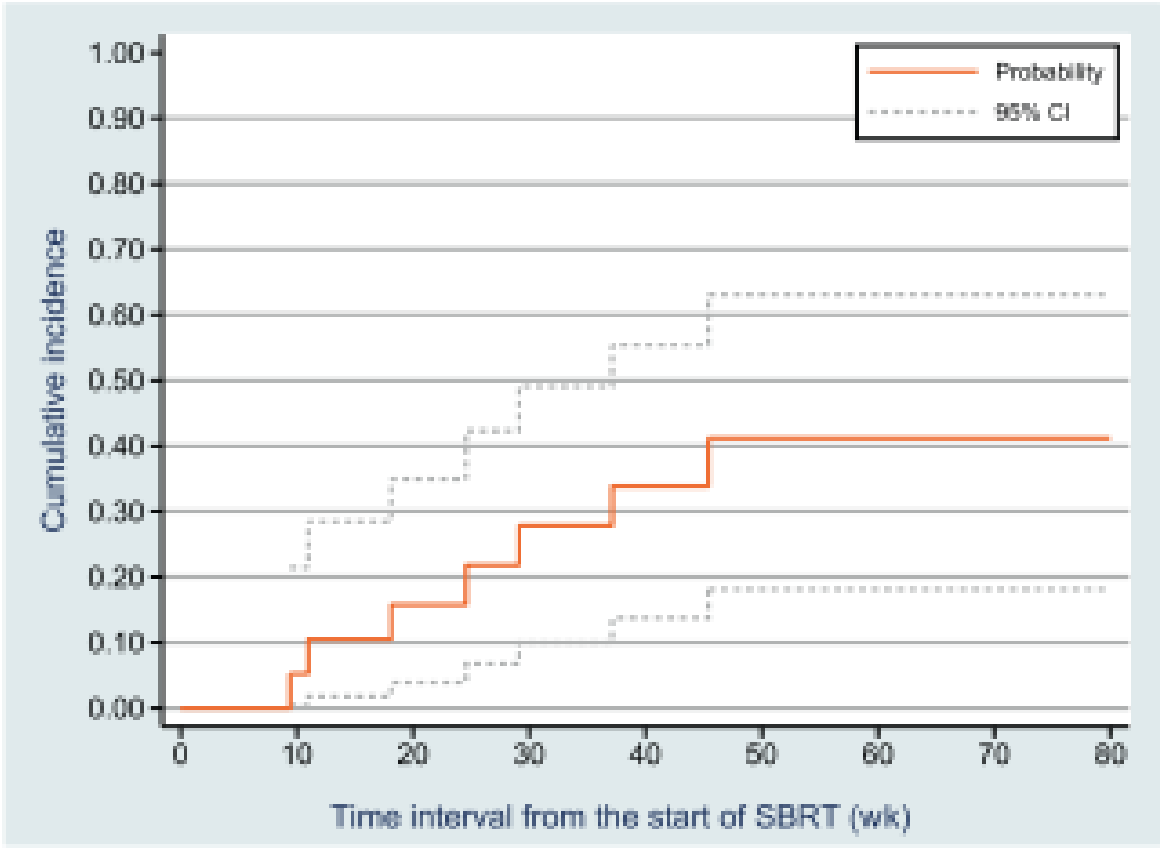


Fig. 2 – Cumulative incidence of late grade ≥2 genitourinary toxicities. CI = confidence interval.

Pasquier et al, Eur Urol Oncol. 2023

Recurrence Characteristics After Focal Salvage MRI-Guided HDR Brachytherapy (19 Gy x 1): a Cautionary Note

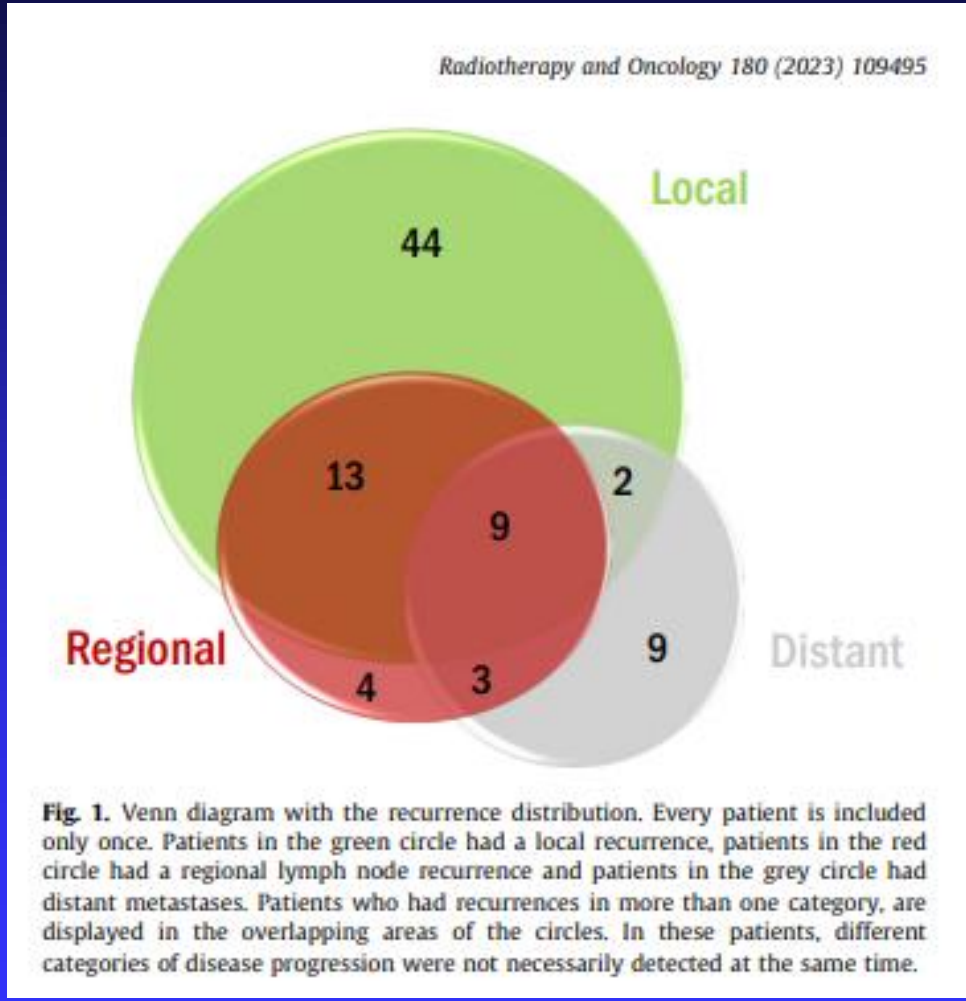


Fig. 1. Venn diagram with the recurrence distribution. Every patient is included only once. Patients in the green circle had a local recurrence, patients in the red circle had a regional lymph node recurrence and patients in the grey circle had distant metastases. Patients who had recurrences in more than one category, are displayed in the overlapping areas of the circles. In these patients, different categories of disease progression were not necessarily detected at the same time.

- ***Rasing et al, Radiotherapy and Oncol. 2023***

Thank You for Your Attention!