Prognostic and Predictive Performance of a 24-Gene Post-Operative Radiation Therapy Outcomes Score (PORTOS) in a Phase 3 Randomized Trial of Dose-Intensified Salvage Radiotherapy after Radical Prostatectomy (SAKK 09/10)

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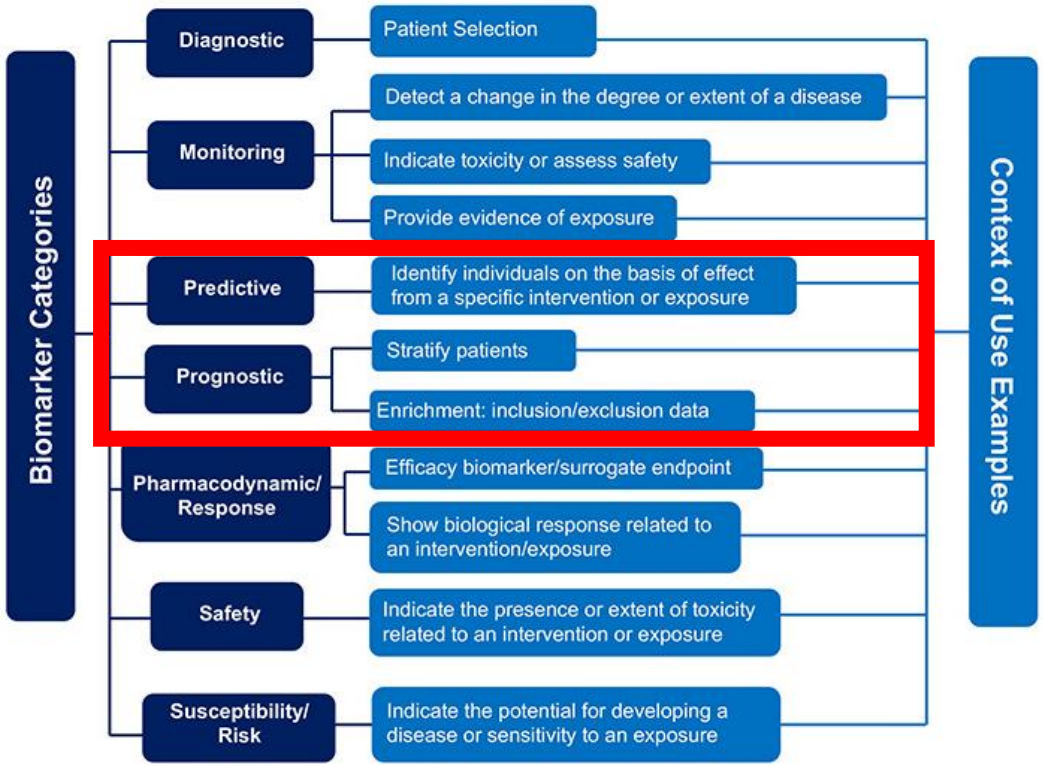
Prognostic vs. Predictive Biomarkers



https://www.fda.gov/drugs/biomarker-qualification-program/context-use

Prognostic Biomarkers:

Indicate long-term outcome for patients untreated or receiving SOC treatment **independent of treatment received**.

Predictive Biomarkers:

Identify who is likely or unlikely to **benefit from a specific treatment**.

NCCN Prostate 2023

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PRINCIPLES OF RISK STRATIFICATION

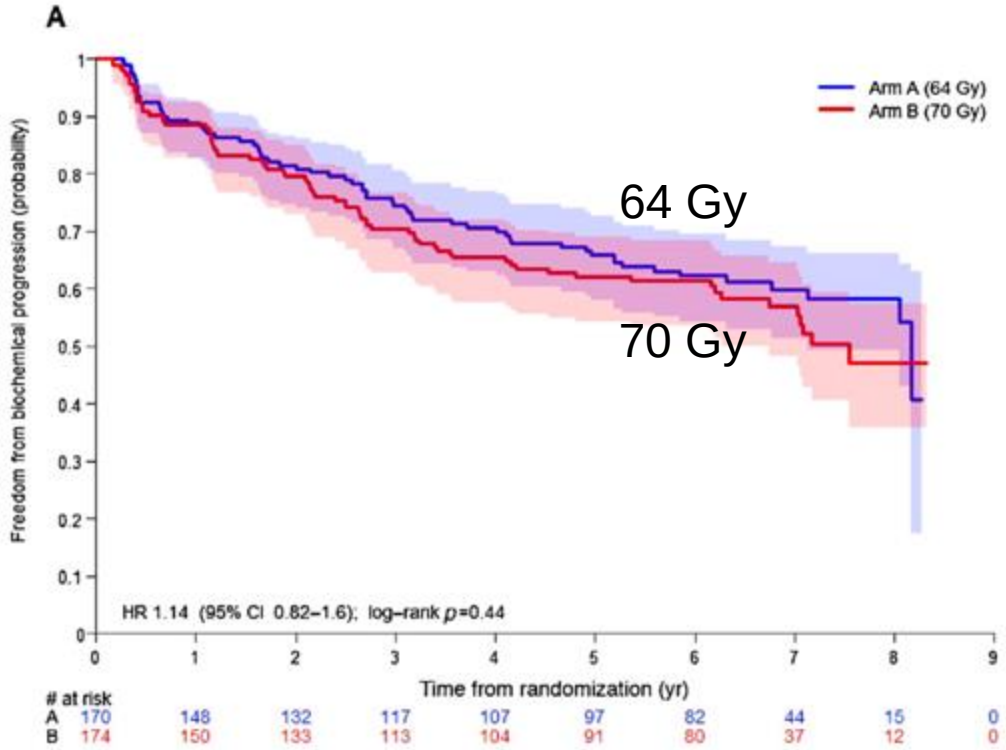
Table 1. Initial Risk Stratification for Clinically Localized Disease

Category	Tool	Predictive	Prognostic	Endpoint Trained For[a]	Level of Evidence for Validation[b]
Clinical	NCCN	No	Yes	See note[c]	1
	STAR-CAP[2]	No	Yes	PCSM	3
	CAPRA[11,d]	No	Yes	BCR	3
	MSKCC[12]	No	Yes	BCR and PCSM[f]	3
AI	ArteraAI Prostate (category 2B)[5,e]	No	Yes	BCR, DM, PCSM[g]	1
Gene Expression Testing	Decipher[13]	No	Yes	DM	1
	Prolaris[14]	No	Yes	See note[h]	3
	Oncotype[15]	No	Yes	Adverse pathology	3
Germline	HRR	No	Uncertain	See note[i]	4

No predictive biomarkers currently available

SAKK 09/10 phase 3 trial:
Dose-escalation not superior to 64Gy

- Multicenter, randomized phase 3 trial performed in 24 centers in Switzerland, Germany, and Belgium.
- N= 350 patients
- Patients with biochemical progression (PSA >0.1 to 2 ng/mL) randomized to 64 Gy vs 70 Gy to the prostate bed.
- No ADT or pelvic nodal radiotherapy.

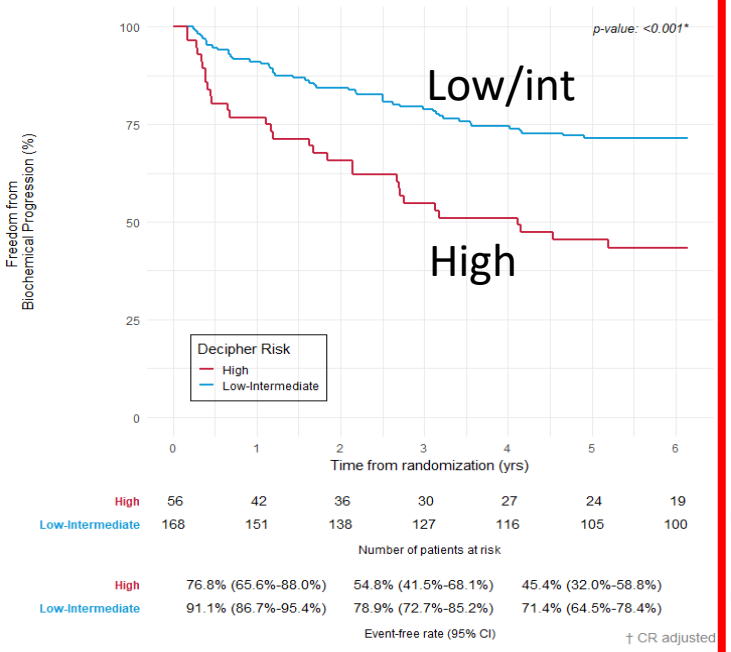


No difference in FFBP at median FU 6 yrs

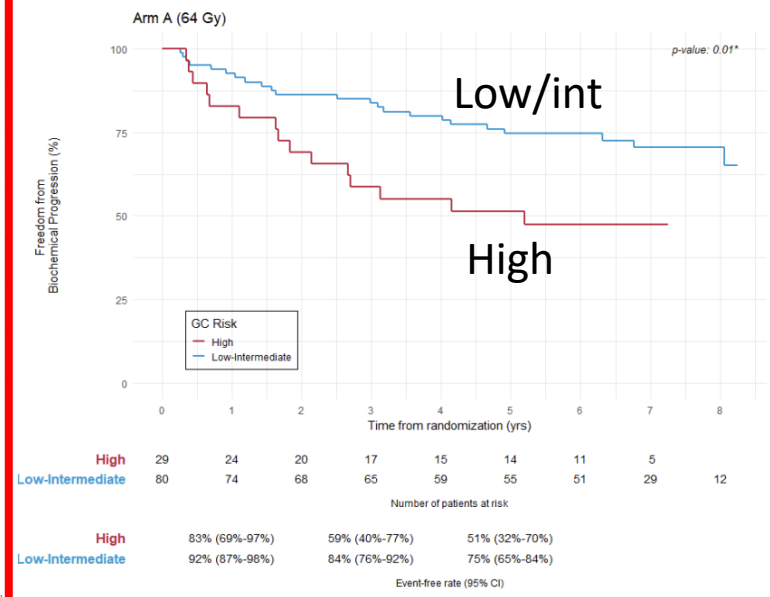
Ghadjar et al., Eur Urol 2021

Decipher is a strong prognostic marker, but did not predict benefit from dose escalation

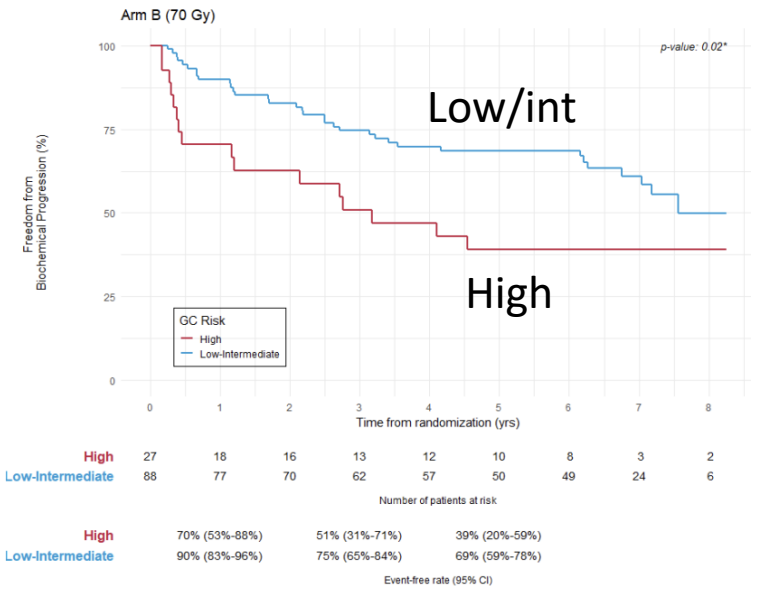
Full cohort



64 Gy arm



70 Gy arm



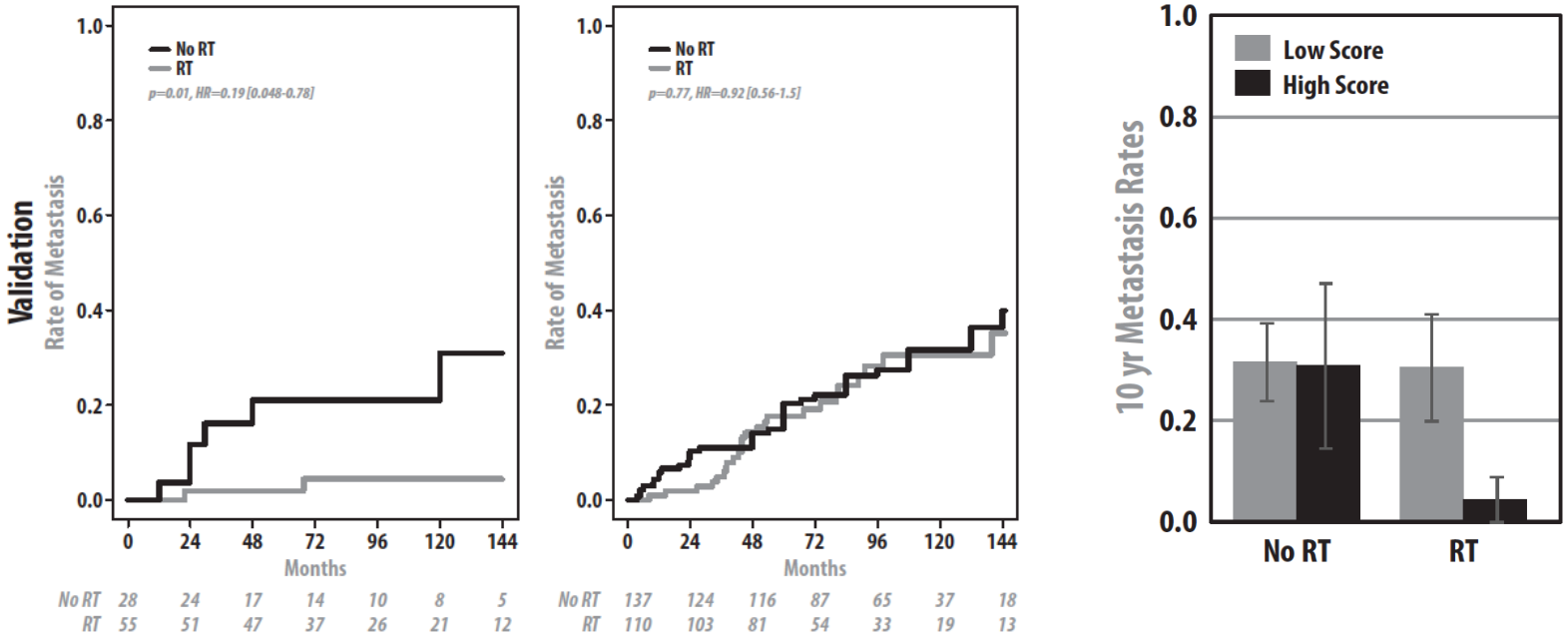
Similar estimates in the 64- vs. 70-Gy arms within GC high and within GC low–intermediate; no SS interaction between Decipher status and RT dose

Dal Pra et al., Ann Oncol 2022

Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis

Shuang G Zhao*, S Laura Chang*, Daniel E Spratt, Nicholas Erho, Menggang Yu, Hussam Al-Deen Ashab, Mohammed Alshalalfa, Corey Speers, Scott A Tomlins, Elai Davicioni, Adam P Dicker, Peter R Carroll, Matthew R Cooperberg, Stephen J Freedland, R Jeffrey Karnes, Ashley E Ross, Edward M Schaeffer, Robert B Den, Paul L Nguyen†, Felix Y Feng†

PORTOS is an expression signature of 24 DNA damage repair, and immune pathway genes



Patients with high PORTOS scores may benefit from post-op RT

Zhao et al., Lancet Oncol 2016

Materials and methods:

- The SAKK 09/10 phase 3 trial (NCT01272050)
- After central review, the highest-grade tumors were profiled using the Decipher whole-transcriptome assay (Veracyte, San Diego, CA) to generate PORTOS.
- The independent prognostic ability and interaction effects were examined with Cox, Fine and Gray (in the presence of competing risks), or logistic (binary endpoints) multivariable and interaction analyses (MVA).
- Biochemical progression, clinical progression-free survival (CPFS), receipt of salvage hormone therapy, and metastasis-free survival endpoints
- Categorical analyses used the published threshold for PORTOS radiotherapy response (High PORTOS, higher RT response vs Lower PORTOS, average RT response, Zhao et al., Lancet Oncol 2016).

Patient characteristics by PORTOS.

Variables	PORTOS		Overall	P-value
	Average RT Response	Higher RT Response		
Total	189 (83.6)	37 (16.4)	226 (100.0)	
Age				
Median (Q1, Q3)	66 (62, 70)	67 (64, 73)	66 (62, 70)	0.201[a]
WHO performance status				
0	178 (94.2)	35 (94.6)	213 (94.2)	1.000[b]
1	11 (5.8)	2 (5.4)	13 (5.8)	
Pre-op PSA				
Median (Q1, Q3)	8.15 (5.55, 12.1)	7.65 (5.56, 11.2)	8.05 (5.55, 12.1)	0.613[a]
Positive surgical margins				
No	91 (48.7)	19 (52.8)	110 (49.3)	0.717[b]
Yes	96 (51.3)	17 (47.2)	113 (50.7)	
Extraprostatic extension				
No	99 (52.7)	21 (56.8)	120 (53.3)	0.720[b]
Yes	89 (47.3)	16 (43.2)	105 (46.7)	
Seminal vesicle invasion				
No	165 (88.2)	31 (83.8)	196 (87.5)	0.424[b]
Yes	22 (11.8)	6 (16.2)	28 (12.5)	
Lymphovascular invasion				
No	166 (88.3)	30 (81.1)	196 (87.1)	0.280[b]
Yes	22 (11.7)	7 (18.9)	29 (12.9)	
Lymphadenectomy type				
Limited lymph node dissection	118 (63.1)	27 (75.0)	145 (65.0)	0.337[b]
Extended lymph node dissection	44 (23.5)	7 (19.4)	51 (22.9)	
None	25 (13.4)	2 (5.6)	27 (12.1)	

[a]Mann-Whitney U test

[b]Fisher's exact test

Missing values: 3 (Positive surgical margins & Lymphadenectomy type); 1 (Extraprostatic extension & Lymphovascular invasion); 2 (Seminal vesicle invasion)

Variables	Average RT Response	Higher RT Response	Overall	P-value
Pathological stage				
pT2	99 (52.9)	21 (56.8)	120 (53.6)	
pT3a	66 (35.3)	10 (27.0)	76 (33.9)	0.508[a]
pT3b	22 (11.8)	6 (16.2)	28 (12.5)	
Pathological Gleason group				
≤ 6	25 (13.3)	3 (8.1)	28 (12.4)	
7	136 (72.3)	29 (78.4)	165 (73.3)	0.766[a]
8-10	27 (14.4)	5 (13.5)	32 (14.2)	
Post-Op PSA				
Median (Q1, Q3)	0.04 (0.019, 0.09)	0.04 (0.01, 0.09)	0.04 (0.0142, 0.09)	0.582[b]
Persistent PSA after RP				
Undetectable (< 0.1 ng/mL)	144 (76.2)	31 (83.8)	175 (77.4)	0.393[a]
Detectable (≥ 0.1 ng/mL)	45 (23.8)	6 (16.2)	51 (22.6)	
EAU High-risk				
No	48 (25.4)	7 (18.9)	55 (24.3)	0.530[a]
Yes	141 (74.6)	30 (81.1)	171 (75.7)	
GETUG High-risk				
No	39 (20.6)	8 (21.6)	47 (20.8)	1.000[a]
Yes	150 (79.4)	29 (78.4)	179 (79.2)	
PSA at randomization				
≤ 0.5 ng/mL	141 (74.6)	24 (64.9)	165 (73.0)	0.229[a]
> 0.5 ng/mL	48 (25.4)	13 (35.1)	61 (27.0)	
RT technique				
3D-CRT	91 (48.1)	15 (40.5)	106 (46.9)	0.472[a]
IMRT/Rotational techniques	98 (51.9)	22 (59.5)	120 (53.1)	

[a]Fisher's exact test

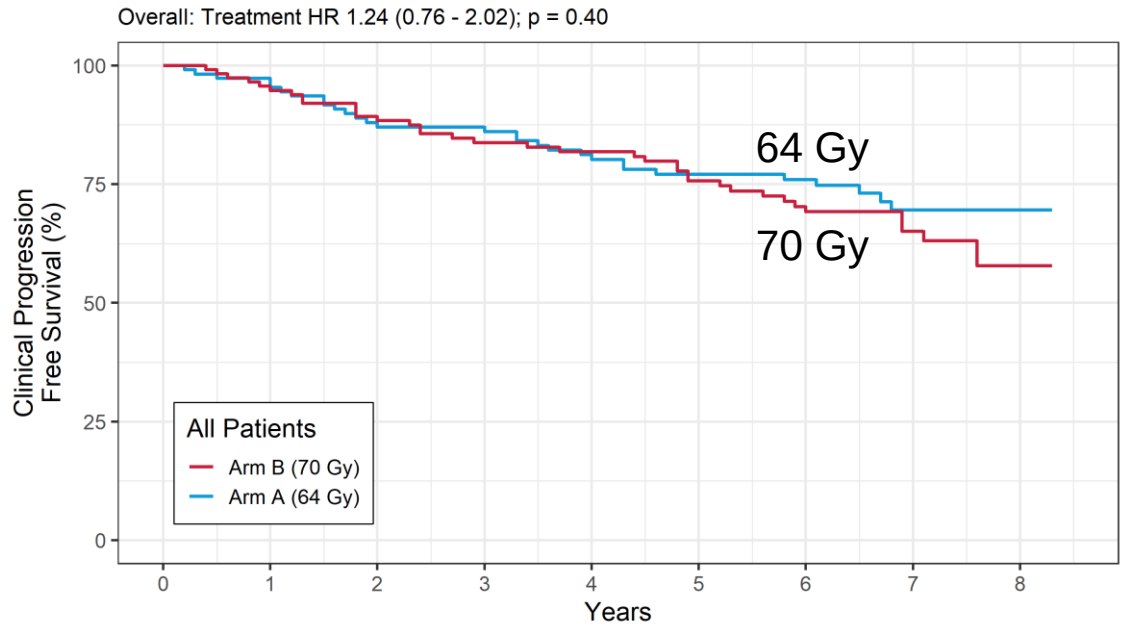
[b]Mann-Whitney U test

Missing values: 2 (Pathological stage); 1 (Pathological Gleason group)

PORTOS is not a prognostic marker for clinical outcomes

No treatment effect was observed

Dose-escalation treatment effect



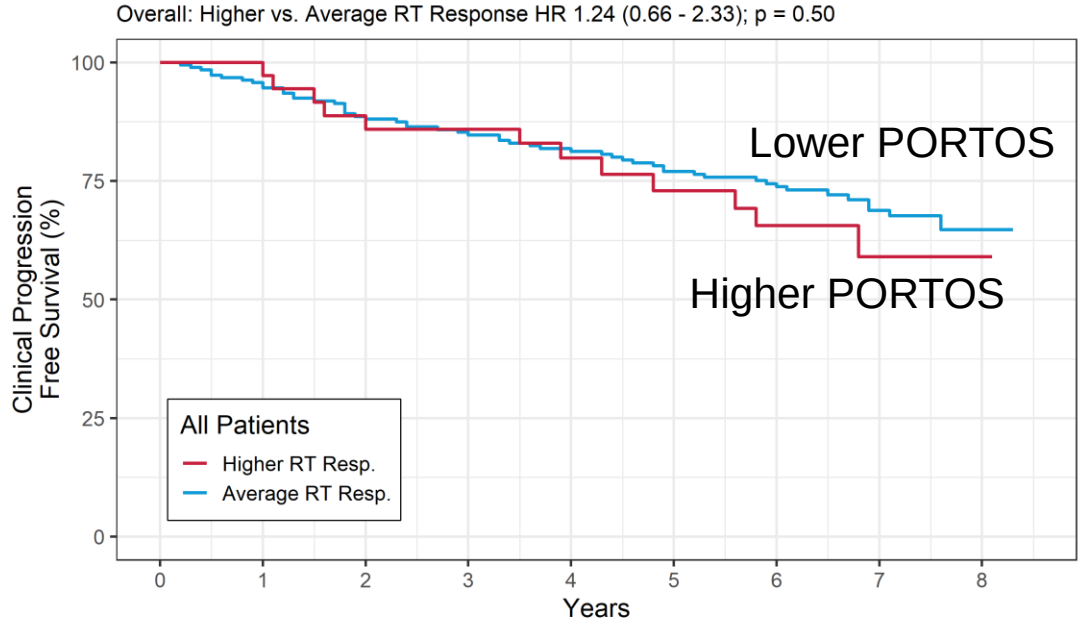
Arm B (70 Gy)	115	106	97	90	85	73	63	32	9
Arm A (64 Gy)	110	103	93	92	81	74	66	36	12

Number of Patients at Risk

Arm B (70 Gy)	95%	84%	76%	65%
Arm A (64 Gy)	95%	86%	77%	70%

Event Rate

PORTOS prognostic effect



Higher RT Resp.	37	35	30	30	26	21	18	9	4
Average RT Resp.	188	174	160	152	140	126	111	59	17

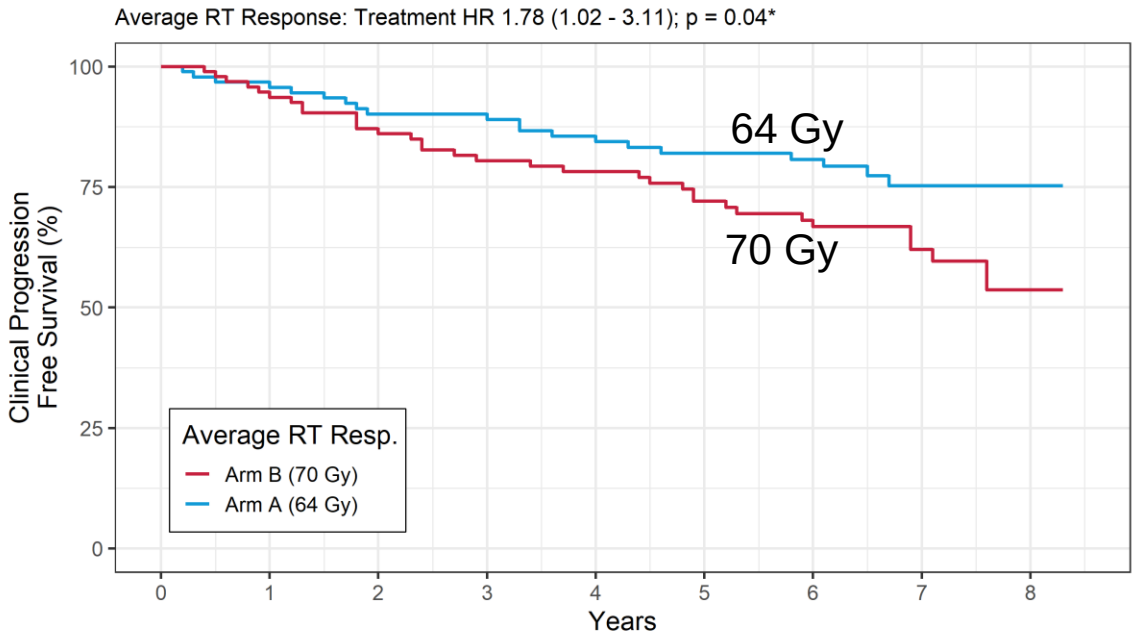
Number of Patients at Risk

Higher RT Resp.	97%	86%	73%	59%
Average RT Resp.	95%	85%	77%	69%

Event Rate

PORTOS is predictive of response to higher RT dose

Lower PORTOS



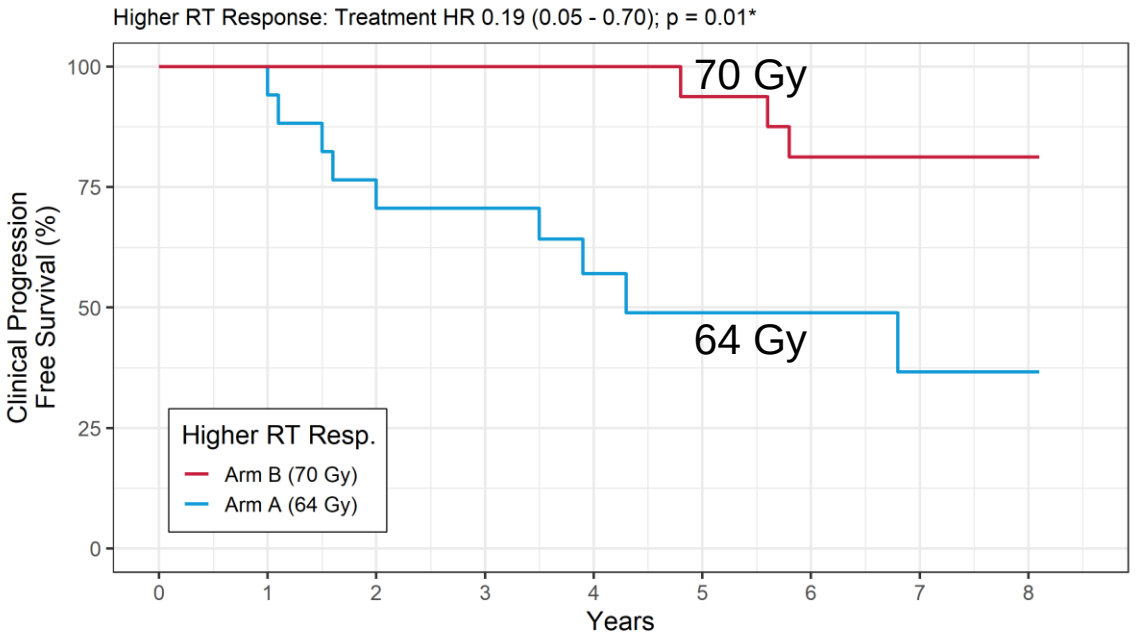
Arm B (70 Gy)	95	87	79	72	67	58	50	26	7
Arm A (64 Gy)	93	87	81	80	73	68	61	33	10

Number of Patients at Risk

Arm B (70 Gy)	94%	80%	72%	62%
Arm A (64 Gy)	96%	89%	82%	75%

Event Rate

Higher PORTOS



Arm B (70 Gy)	20	19	18	18	18	15	13	6	2
Arm A (64 Gy)	17	16	12	12	8	6	5	3	2

Number of Patients at Risk

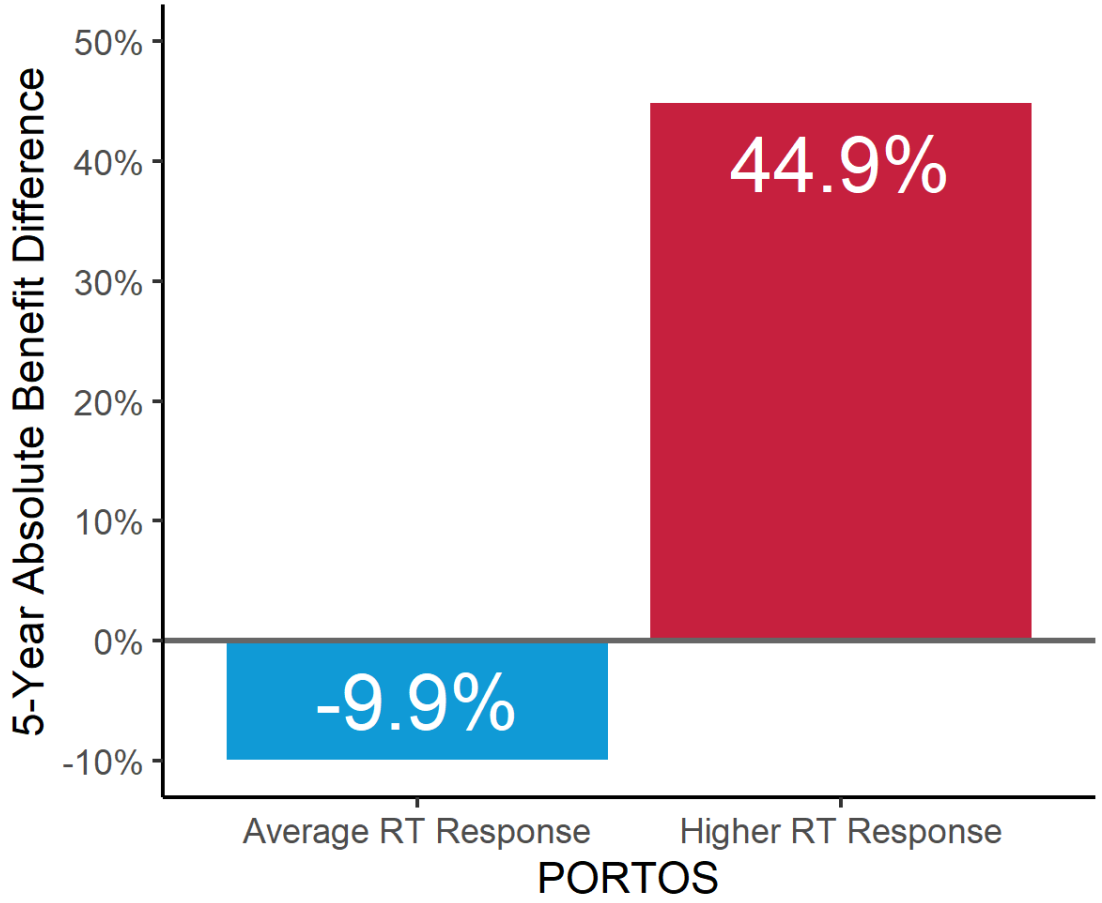
Arm B (70 Gy)	100%	100%	94%	81%
Arm A (64 Gy)	94%	71%	49%	37%

Event Rate

CPFS Kaplan-Meier plots (unadjusted arm interaction p = 0.003*, adjusted p = 0.008)

Large absolute CPFS benefit observed for dose-escalation in higher PORTOS tumors and significant biomarker-by-treatment interactions observed

Absolute CPFS difference between dose-escalated and standard dose arms at 5 years, stratified by PORTOS



Biomarker-by-treatment interactions observed for most endpoints

	Interaction p-value
BCF	0.04*
Rapid BCF	0.15
CPFS	0.003*
HT	0.06
Metastasis	0.69
MFS	0.04*
PFS	0.01*

Discussion

- Although there are strong prognostic biomarkers such as Decipher, we urgently need predictive biomarkers.
- How to explain the dose-escalation benefit in higher PORTOS tumors?
  - DDR pathway, differential immune profiling, hypoxia
- In view of SAKK 09/10 trial results, PORTOS could help select patients for dose-escalation (e.g., 70Gy) vs. lower doses to the prostate bed.
- Retrospective study of a phase 3 trial, exploratory analysis
  - Further validation is required

Conclusions

- In a phase 3 trial testing RT dose intensification after RP, patients with higher PORTOS scores had significantly better outcomes with dose-escalated RT, suggesting that higher doses could be considered in this subgroup.
- Further studies are warranted to validate PORTOS as the first predictive biomarker to help personalize radiotherapy dose in the postoperative setting.

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