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**Optimizing Pelvic Radiotherapy in
the PSMA PET Era:
When and How to Integrate SBRT for
Nodal Management**

Goal: Discuss Pelvic Radiotherapy in the PSMA PET Era and the Role of SBRT (30 min.)

- 1. Who are we talking about here?**
 - a. Clinically node + (e.g. imaging) vs path node +?**
 - b. Definitive vs post Op?**
 - c. High risk for occult node + Dz?**
- 2. Endpoints?**
 - a. Overall Survival , Cause Specific Survival, Mets ...**
 - b. PSA control**
 - c. Biopsies**
 - d. QoL?**
- 3. Level of evidence?**
- 4. Technical RT Details?**
 - a. SBRT vs ENRT**
 - b. Prophylactic Irradiation**

Optimum Use of Pelvic RT in the PSMA PET?

- 1. No prophylactic RT?**
 - a) Ignore POP-RT, RTOG 0534**
 - b) NRG 0924 "a negative trial"**
- 2. Selective?**
 - a) Node + (e.g., PSMA PET)**
 - b) Very High Risk**
 - c) Biomarker driven?**
- 3. SIB (simultaneous integrated boost?)**
- 4. SBRT alone?**
- 5. Short Course (Hypofractionated)?**
 - a) i.e., 500 cGy x 5 ("98% effective")**

Clinical outcomes of definitive whole pelvic radiotherapy for clinical lymph node metastatic prostate cancer.

Tsuchida et al. Cancer Medicine 2020

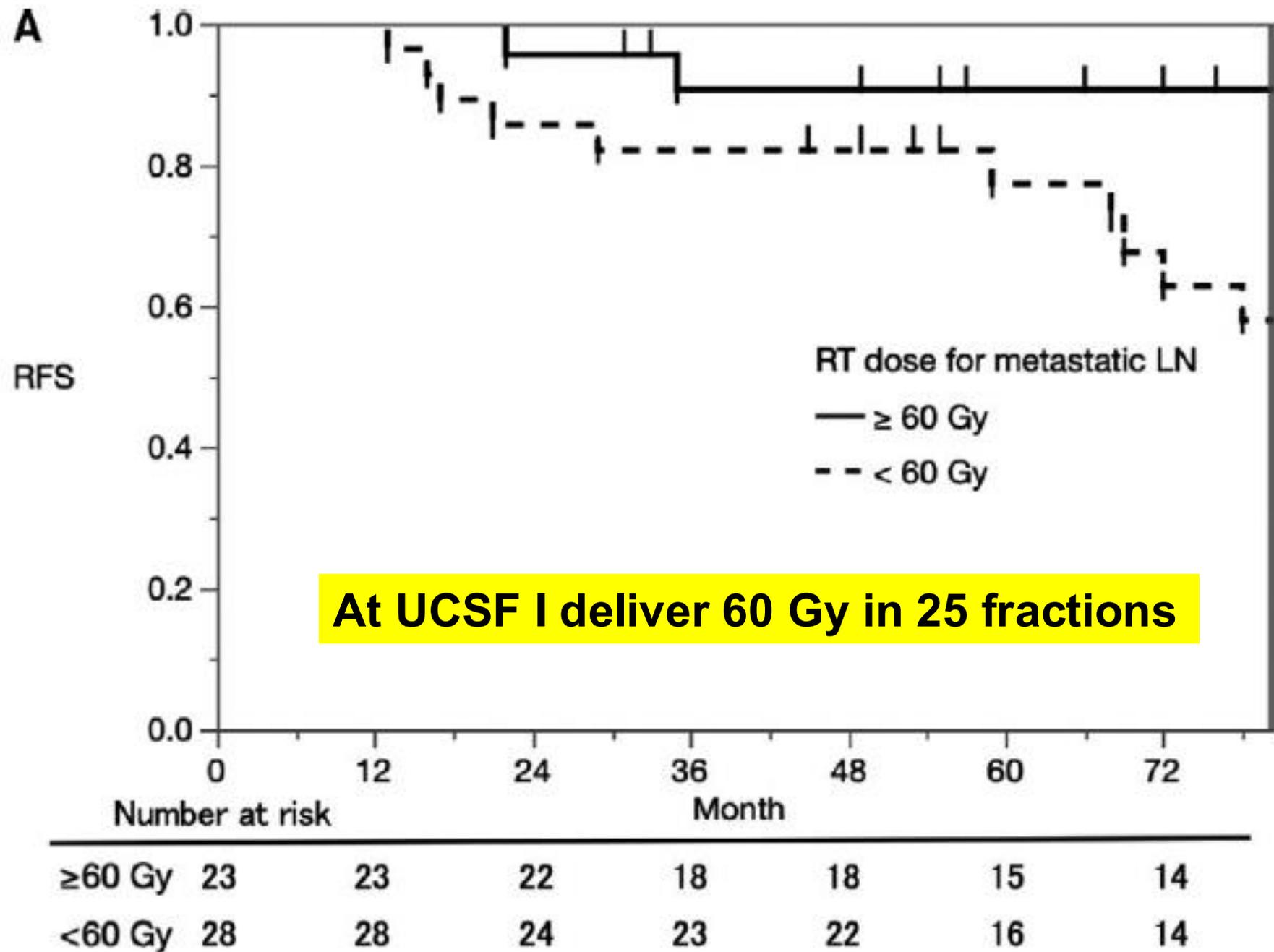
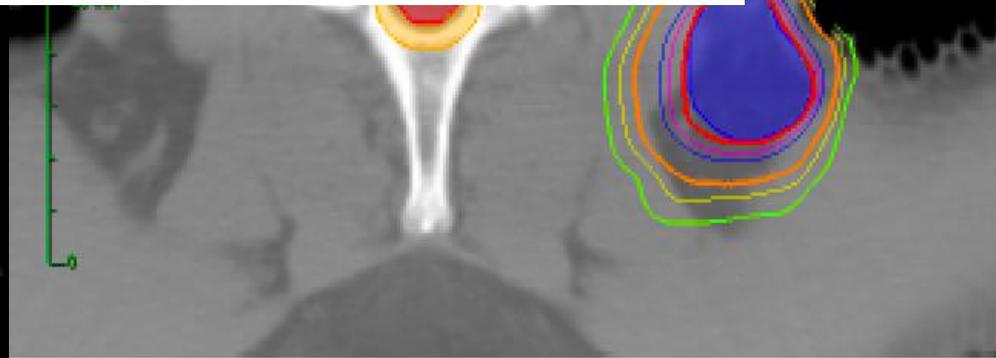
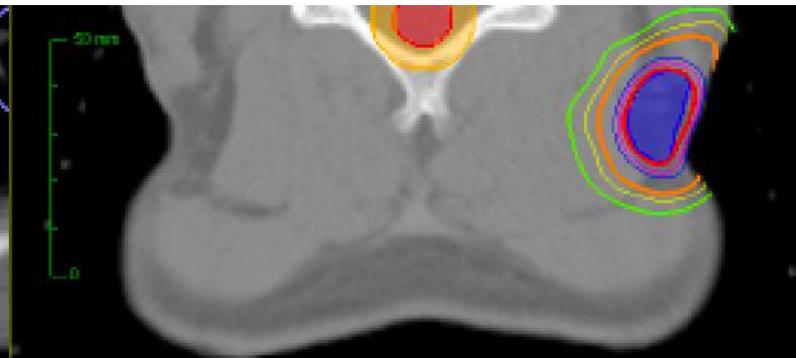
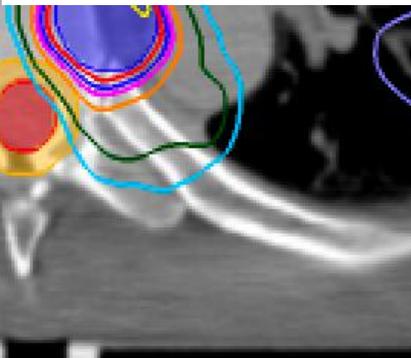
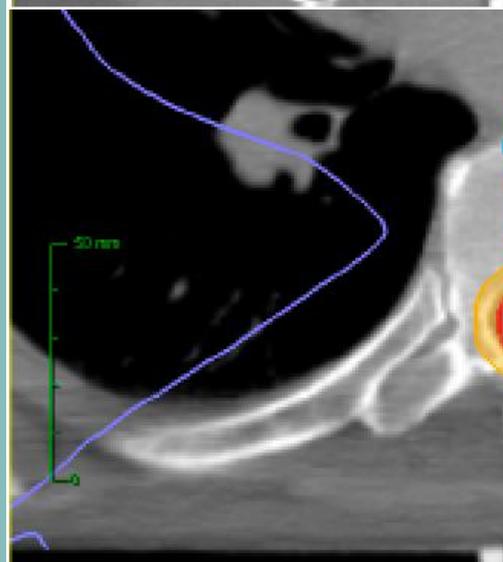
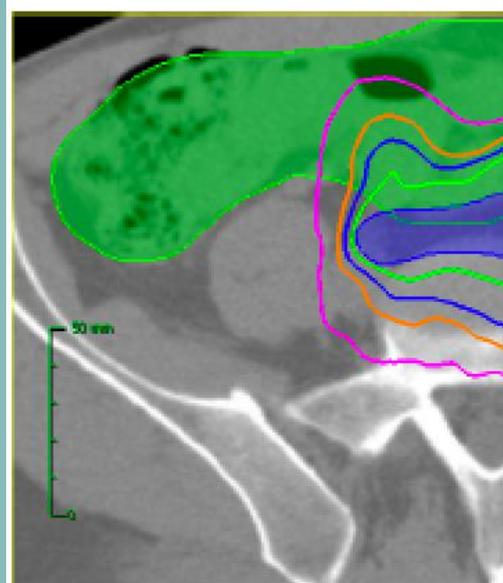
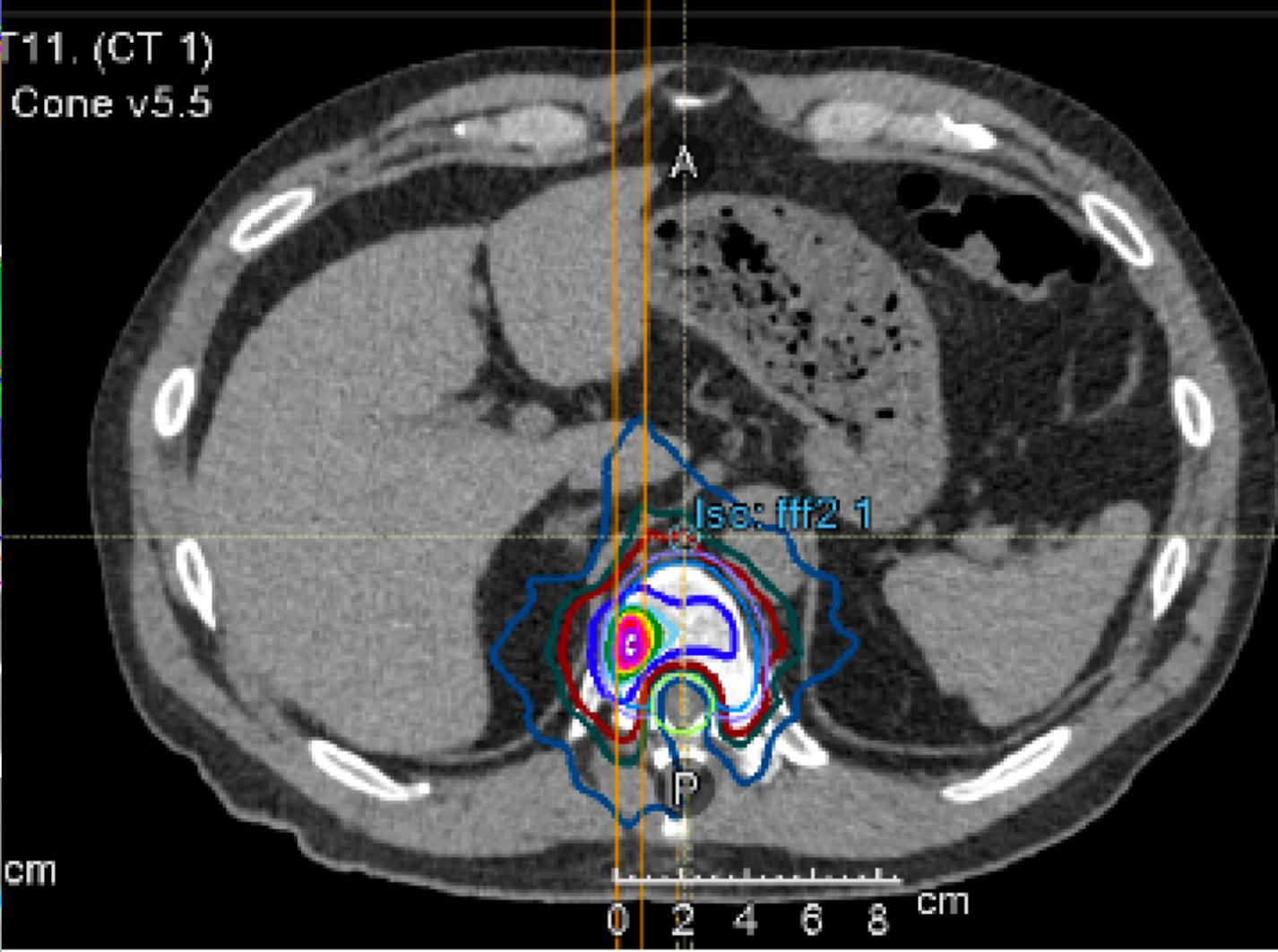
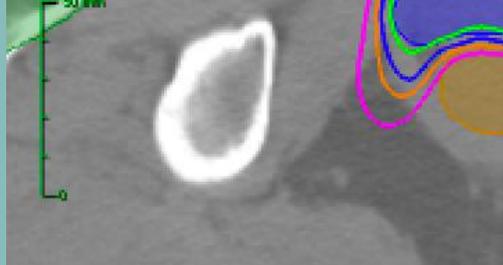
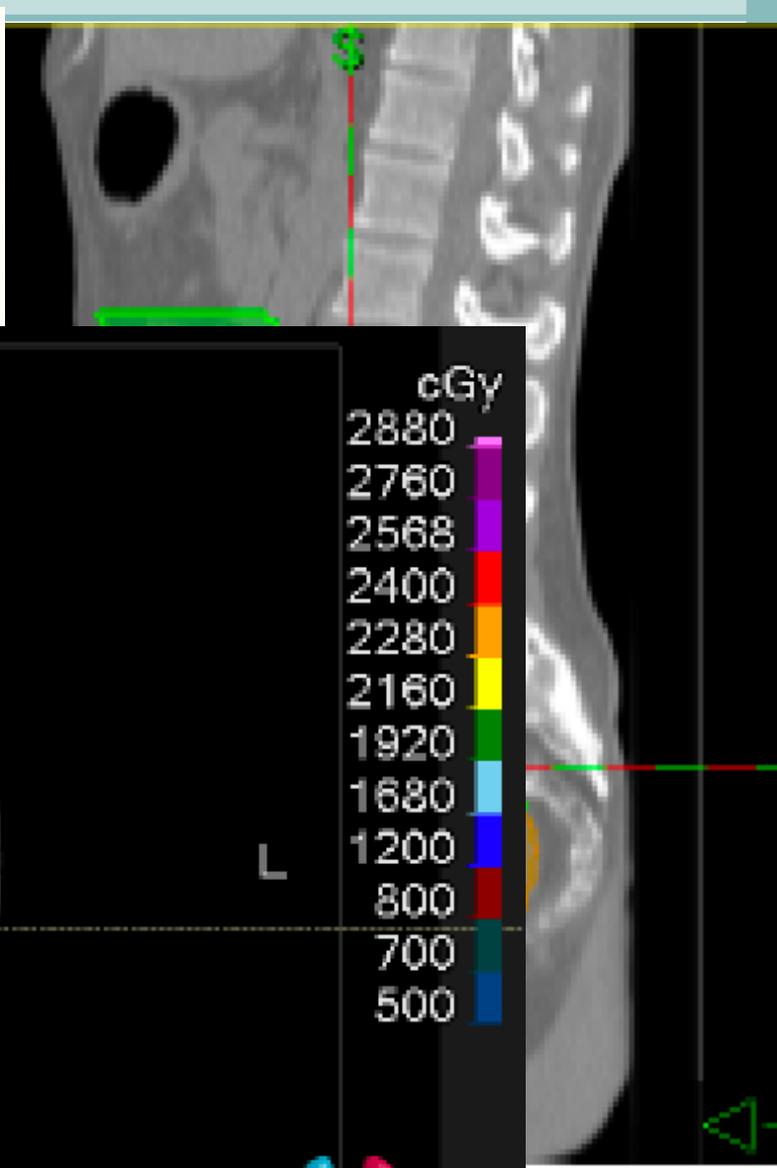
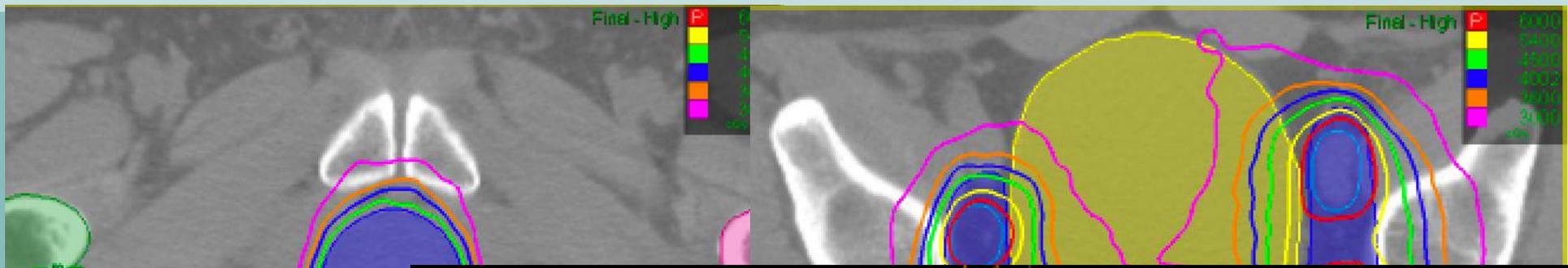


Fig. 1 Kaplan-Meier estimates for comparison of relapsefree survival (RFS) between higher lymph node (LN) RT dose (60 Gy or more) group and lower LN RT dose (less than 60 Gy) group



Research

JAMA Oncology | Original Investigation

Diagnostic Accuracy of 68Ga-PSMA-11 PET for Pelvic Nodal Metastasis Detection Prior to Radical Prostatectomy and Pelvic Lymph Node Dissection

A Multicenter Prospective Phase 3 Imaging Trial

Table 1. Baseline Characteristics

Characteristic	No. (%)			P value
	Total	Surgery cohort	Nonsurgery cohort	
No. (%)	764 (100)	277 (36)	487 (64)	NA
Age, median (IQR), y	69 (63-73)	67 (61-71)	70 (65-75)	<.001
PSA, median (IQR), ng/mL	11.4 (6.7-21.2)	11.1 (6.5-18.0)	11.9 (6.8-24.0)	.07
≥20	202 (26)	59 (21)	143 (29)	.73
ISUP grade group ^a				
1	30 (4)	8 (3)	22 (5)	.65
2	128 (17)	49 (18)	79 (22)	
3	151 (20)	59 (21)	92 (19)	
4	186 (25)	63 (23)	123 (26)	
5	264 (35)	98 (35)	166 (34)	
D'Amico risk ^a				
Intermediate	166 (22)	49 (18)	117 (24)	.12
High	590 (78)	225 (81)	365 (75)	

Optimizing
Pelvic RT in
the PSMA
PET Era ...
Integrating
SBRT

Hope et al. JAMA Oncology 7; 11:1635-1642, 2021

Research

JAMA Oncology | Original Investigation

Diagnostic Accuracy of ⁶⁸Ga-PSMA-11 PET for Pelvic Nodal Metastasis Detection Prior to Radical Prostatectomy and Pelvic Lymph Node Dissection

A Multicenter Prospective Phase 3 Imaging Trial

Table 2. ⁶⁸Ga-PSMA-11 Test Characteristics for the Composite 3 Blinded Reads and Overall Majority Rule Read

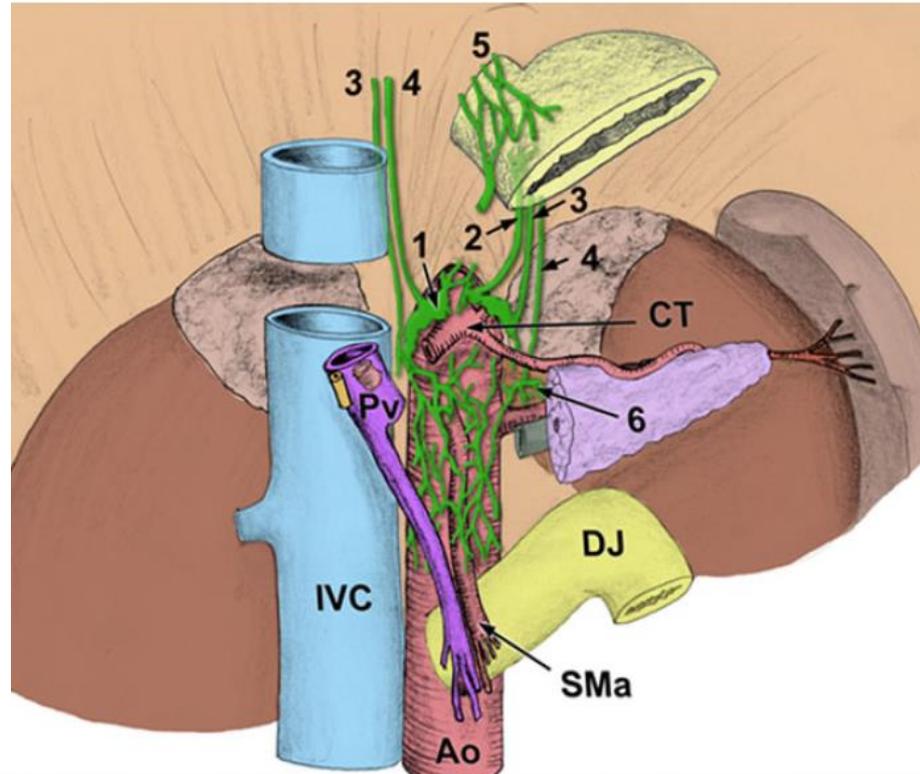
Test characteristic	Read 1	Read 2	Read 3	Majority read
True positive	30	33	29	30
False positive	13	16	15	10
True negative	189	186	187	192
False negative	45	42	46	45
Sensitivity ^a	0.40 (0.30-0.51)	0.44 (0.33-0.55)	0.39 (0.28-0.50)	0.40 (0.30-0.51)
Specificity ^a	0.94 (0.89-0.96)	0.92 (0.88-0.95)	0.93 (0.88-0.95)	0.95 (0.91-0.97)
PPV ^a	0.70 (0.55-0.81)	0.67 (0.53-0.79)	0.66 (0.51-0.78)	0.75 (0.60-0.86)
NPV ^a	0.81 (0.75-0.85)	0.82 (0.76-0.86)	0.80 (0.75-0.85)	0.81 (0.76-0.85)

Optimizing
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Be Aware: False + Results on PSMA PET

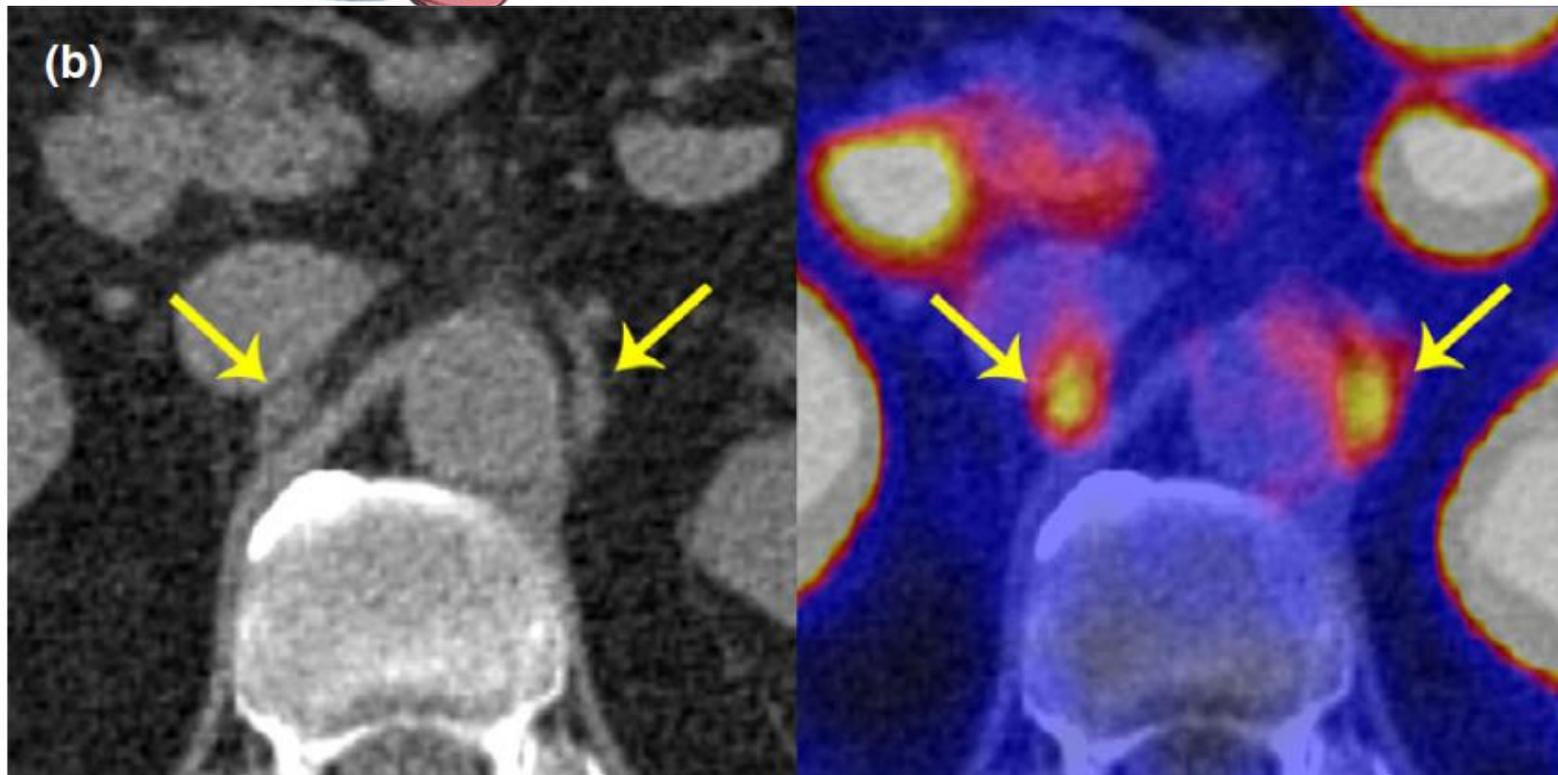
- 1. Solitary rib lesions (Chen et al. BJUI 2020; 126: 361-401)**
 - a) "... 62 had PSMA uptake in a solitary rib ... (98.4%) met the criteria for a benign rib lesion. One man had a false-negative malignant lesion."
- 2. Bone Uptake in recurrences (Letang et al. CNMed 2022)**
 - a) "most bone uptakes at PSMA PET/CT were benign lesions ... patient, tumor characteristics and SUV_{max} could help ..."
- 3. Tracheobronchial uptake in 31% Osman et al. JNM '24**
- 4. Paraesophageal Schwannomas (Ries et al. CNM 2019)**
- 5. Misc. False positives (e.g., post RP) (Orevi et al. Frontiers in Surg) : ~80% with undetectable PSAs**
- 6. Sympathetic ganglia uptake**

Uptake in sympathetic ganglia on ⁶⁸Ga-PSMA-HBED PET/CT: A potential pitfall in scan interpretation. Kanthan et al.



The celiac plexus with its right left ganglia.

- 1 – Right coeliac ganglion,
- 2 – Posterior vagal trunk contributing to celiac plexus,
- 3 – Greater splanchnic nerve to the celiac plexus,
- 4 – Lesser splanchnic nerve to aorticorenal plexus,
- 5 – Anterior vagal trunk and hepatic nerve,
- 6 – Aorticorenal plexus,



Pv, portal triad; IVC, inferior vena cava; Ao, aorta; DJ, duodeno-jejunal junction; SMA, superior mesenteric artery. The splenic vein is removed at its termination on the Pv. The renal vein and pancreas are cut to expose the aorticorenal plexus.

Prostate Cancer

A Novel Nomogram to Identify Candidates for Extended Pelvic Lymph Node Dissection Among Patients with Clinically Localized Prostate Cancer Diagnosed with Magnetic Resonance Imaging-targeted and Systematic Biopsies. Gandaglia, Ploussard ... Briganti

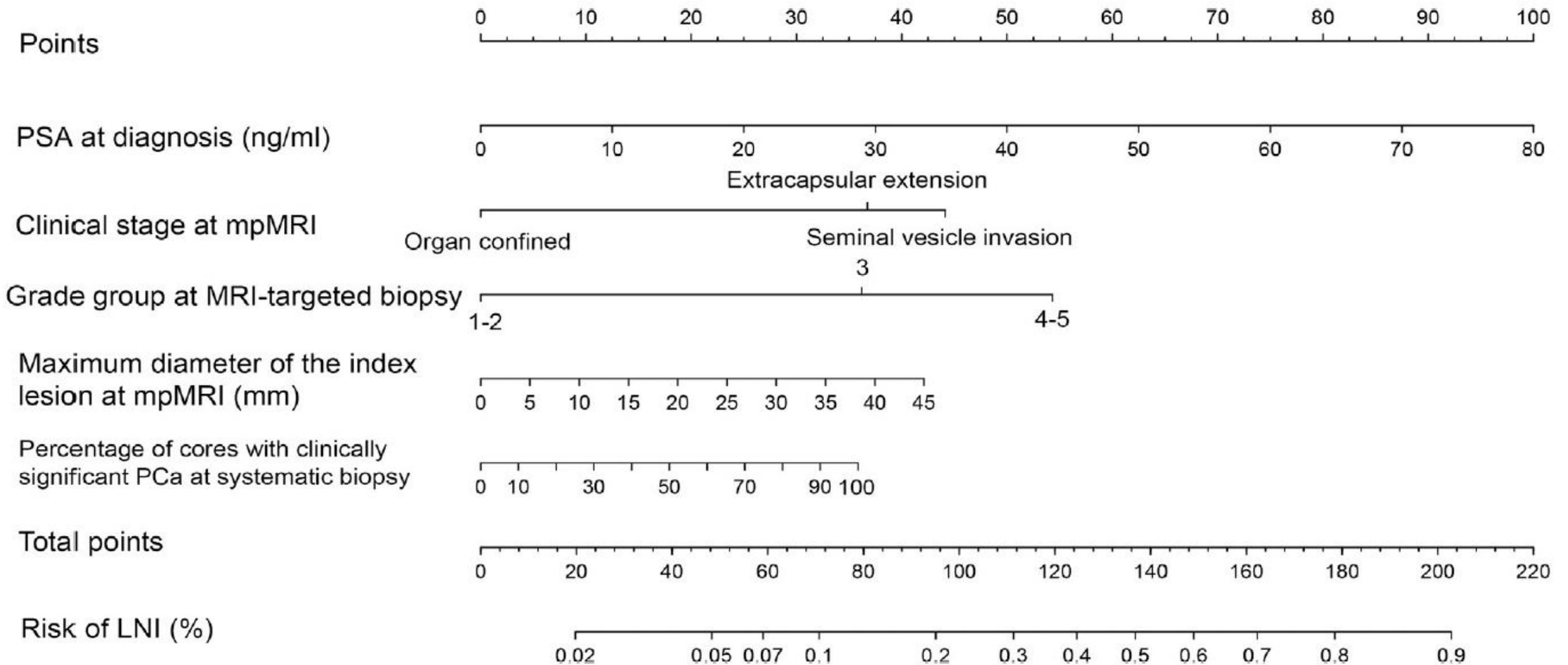


Fig. 1 – Novel nomogram predicting the probability of lymph node invasion (LNI) for patients diagnosed via targeted biopsies and treated with radical prostatectomy and extended pelvic lymph node dissection. mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; PSA = prostate-specific antigen.

Prostate Cancer

External Validation of Nomograms for the Identification of Pelvic Nodal Dissection Candidates Among Prostate Cancer Patients with Negative Preoperative Prostate-specific Membrane Antigen Positron Emission Tomography. Gandaglia ... Briganti

**Clinical implications according to treatment option:
(MSKCC vs Briganti 2017 vs Briganti 2019 vs Amsterdam-Brisbane-Sydney vs Briganti 2023)**

Treatment option	Patients in whom PLND is not recommended according to the cutoff (below cutoff)	Patients below cutoff with histological LNI	Patients in whom PLND is recommended according to the cutoff (above cutoff)	Patients above cutoff with histological LNI
MSKCC, 5% cutoff	27 (9.6)	1 (3.7)	255 (90)	35 (14)
MSKCC, 7% cutoff	39 (14)	2 (5.1)	243 (86)	34 (14)
MSKCC, 10% cutoff	53 (19)	3 (5.7)	229 (81)	33 (14)
Briganti 2017, 5% cutoff	45 (16)	1 (2.2)	237 (84)	35 (15)
Briganti 2017, 7% cutoff	52 (18)	1 (1.9)	230 (82)	35 (15)
Briganti 2017, 10% cutoff	74 (26)	2 (2.7)	208 (74)	34 (16)
Briganti 2019 ^a , 5% cutoff	38 (14)	2 (5.3)	234 (86)	33 (14)
Briganti 2019 ^a , 7% cutoff	51 (19)	3 (5.9)	221 (81)	32 (14)
Briganti 2019 ^a , 10% cut-off	74 (27)	4 (5.4)	198 (73)	31 (16)
Amsterdam-Brisbane-Sydney, 5% cutoff	12 (4.3)	1 (8.3)	270 (96)	35 (13)
Amsterdam-Brisbane-Sydney, 7% cutoff	30 (11)	3 (10)	252 (89)	33 (13)
Amsterdam-Brisbane-Sydney, 10% cutoff	59 (21)	6 (10)	223 (79)	30 (14)
Briganti 2023, 5% cutoff	133 (47)	5 (3.8)	149 (53)	31 (21)
Briganti 2023, 7% cutoff	174 (62)	8 (4.6)	108 (38)	28 (26)
Briganti 2023, 10% cutoff	213 (76)	15 (7)	69 (24)	21 (30)

LNI = lymph node invasion; MSKCC = Memorial Sloan Kettering Cancer Center; PLND = pelvic lymph node dissection.

^a Available for 272 patients.

WPRT for Prostate Cancer: Important & Challenging

- **Practical issues:**
 - Small field vs Big Field?
 - Potential Morbidity
 - Cost (time and money)?
- **Challenge – tough to prove:**
 - e.g. 1200 pts with 1/3rd (33%) having + nodes
 - ... then study really based on n=400 pts
 - ... if disease beyond pelvis in 25% down to n=300 pts
 - ... and local failures 1/3rd to n=200 pts
 - ... competing causes of death (e.g. 50%) n=100
 - ... improved “salvage” treatments, delaying deaths
 - ... “study too small?”

Thus, RTOG 0924: n=2580 (@2592 pts)!

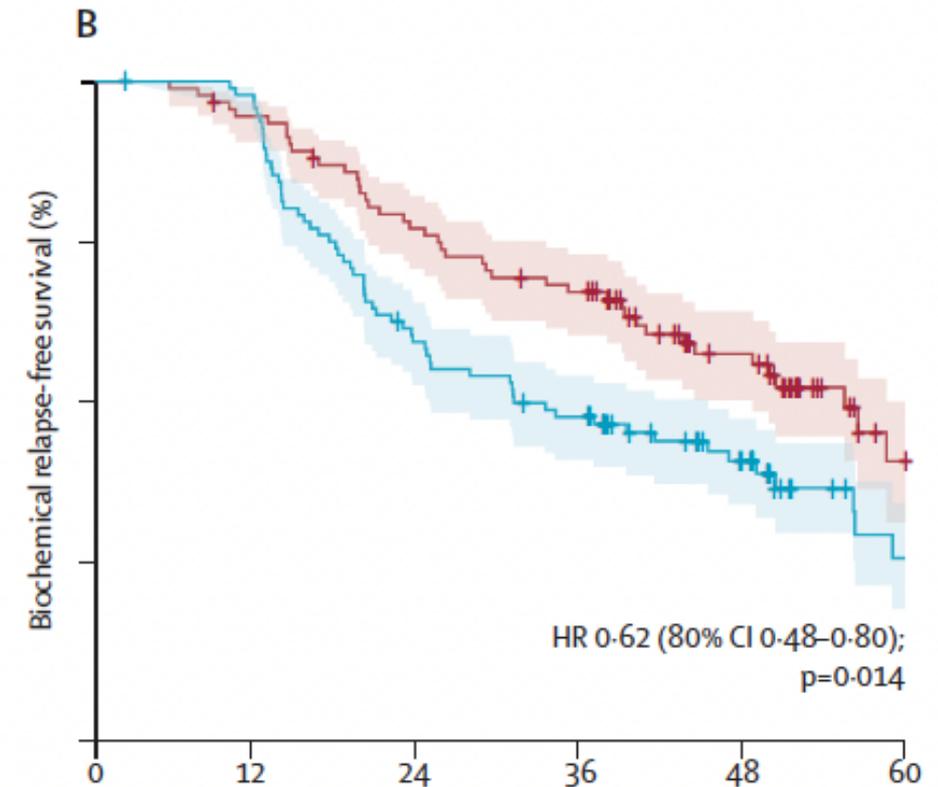
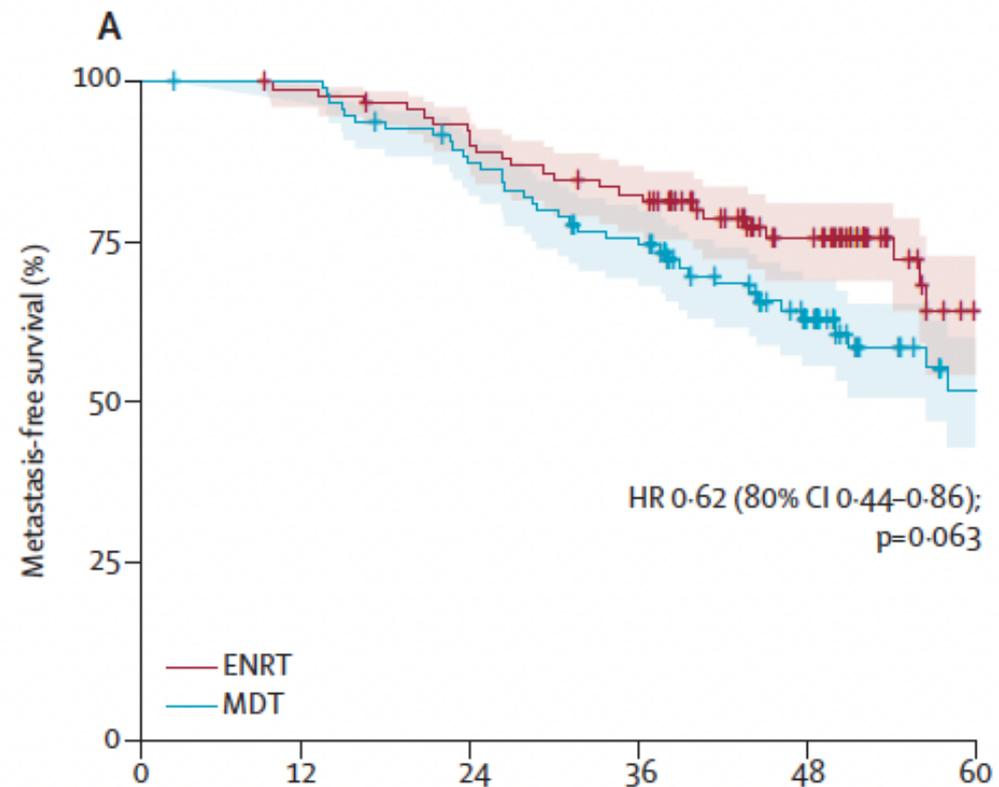
Important Trials Addressing MDT

Trial (Au) yr (ref)	Design	Results	Conclusions
PEACE V-STORM (Ost) 2025 (1)	SBRT (30 Gy 3 fx's) vs ENRT (45 Gy + SIB to 65 Gy) meta. Oligo nodes (6 mo.)	MFS 63 vs 76% (SBRT vs ENRT) (p=0.063)	ENRT better?
RADIOSA (Marvaso) 2025 (2)	SBRT (30 Gy 3 fx's) +/- ADT (6 mo.)	PFS 15.1 vs 32.2 mo. (p=0.001)	Short term ADT doubles PFS
EXTEND Trial (Sherry) 2025 (3)	Continuous ADT +/- SBRT:	PFS: 47 vs 22 mo. (0.036)	MDT improves PFS
GROUQ-PCS 9) (Niazi) 2025 (4)	ADT-ENZA vs ADT-ENZA + SBRT (24 Gy 2 fx's or fractionated 30 to 60 Gy)	Rad PFS 4.6 vs 2.3 yrs (0.014)	MDT improves rad PFS
RAVENS (Wang) 2025 (5)	SBRT +/- Radium-223 for bone dominant disease	Rad PFS 11.8 vs 10.5 yrs (0.24)	No benefit to bone targeting agent
LUNAR (Kishan) 2025 (6)	SBRT +/- 177 LU-PNT2002	7.4 vs 17.6 mo. (p,<0.0001))	Benefit to Radioisotope targeting PSMA occult disease

1. Lancet Oncol 2025; 26: 695-706
2. Lancet Oncol 2025; 26: 300-311
3. European Urology 2025; 88: 496-509
4. Lancet Oncol 2025; 26: 1158-67
5. JCO 2025 43: 2059-2068
6. ASTRO 2025, SF CA.

Salvage metastasis-directed therapy versus elective nodal radiotherapy for oligorecurrent nodal prostate cancer metastases (PEACE V-STORM): a phase 2, open-label, randomised controlled trial

Piet Ost, Shankar Siva, Sigmund Brabrand, Piet Dirix, Nick Liefhooghe, François-Xavier Otte, Alfonso Gomez-Iturriaga, Wouter Everaerts, Mohamed Shelan, Antonio Conde-Moreno, Fernando López Campos, Alexandros Papachristofilou, Matthias Guckenberger, Marta Scorsetti, Almudena Zapatero, Ana-Elena Villafranca Iturre, Clara Eito, Felipe Couñago, Paolo Muto, Wim Duthoy, Nicolas Mach, Valérie Fonteyne, Daniel Moon, Kristian Thon, Carole Mercier, Vérane Achard, Karin Stellamans, Els Goetghebeur, Dries Reynders, Thomas Zilli

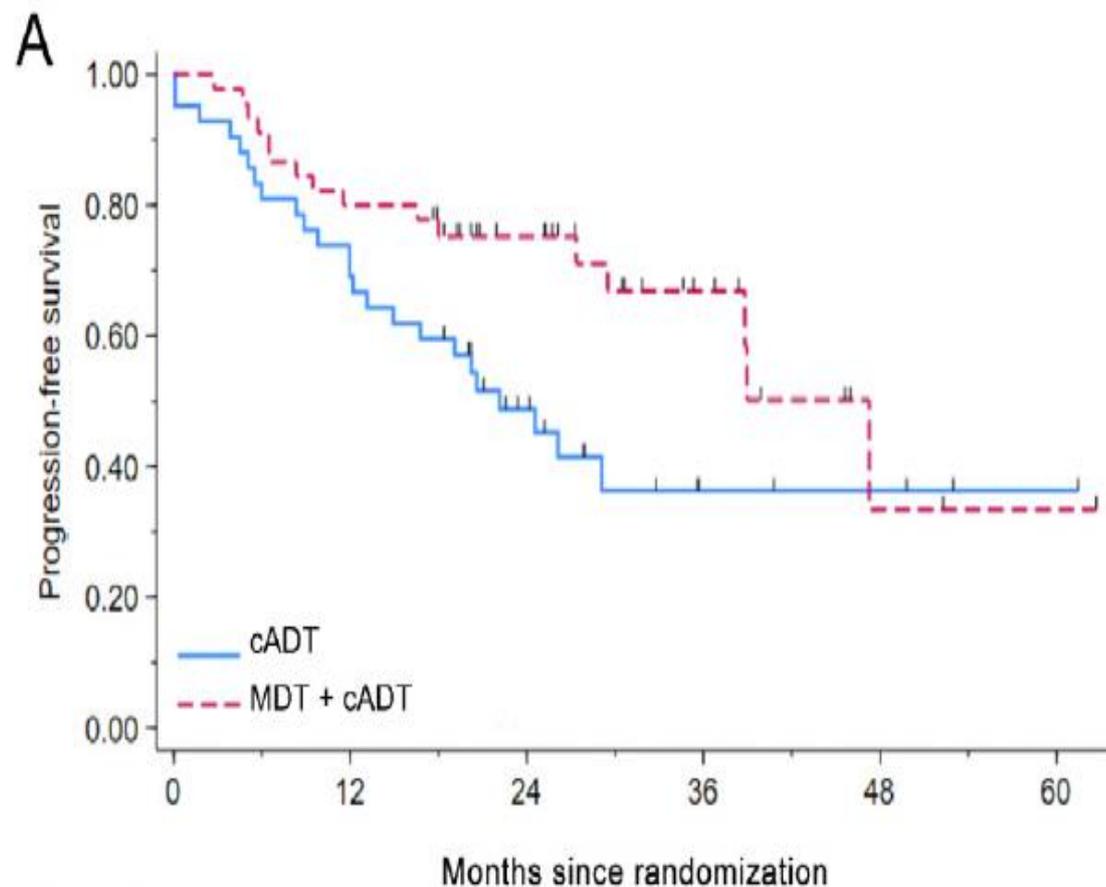


Number at risk (number censored)		0	12	24	36	48	60	0	12	24	36	48	60
ENRT	93 (0)	91 (1)	82 (2)	74 (3)	46 (26)	13 (57)	93 (0)	87 (1)	70 (2)	60 (3)	35 (21)	9 (42)	
MDT	97 (0)	96 (1)	82 (3)	68 (5)	39 (25)	15 (45)	97 (0)	91 (1)	56 (2)	44 (3)	24 (18)	7 (30)	

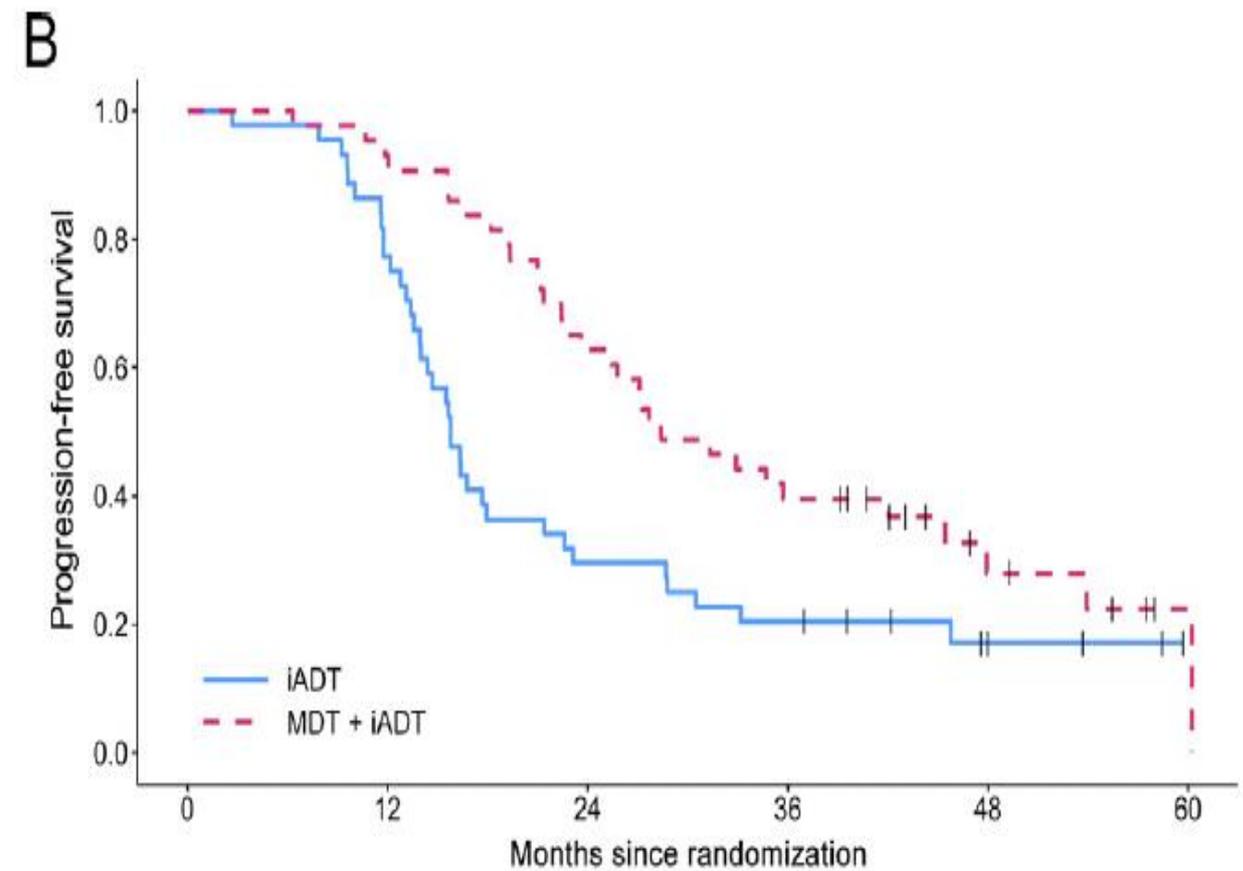
Optimizing
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Continuous Androgen Deprivation Therapy with or Without Metastasis-directed Therapy for Oligometastatic Prostate Cancer: The Multicenter Phase 2 Randomized EXTEND Trial.

Sherry et al. *EUROPEAN UROLOGY* 88 (2025) 496–509



No. at risk (events)	0	12	24	36	48	60					
cADT	42	(13)	29	(8)	15	(3)	4	(0)	3	(0)	1
MDT + cADT	45	(9)	36	(2)	23	(2)	10	(3)	2	(0)	1



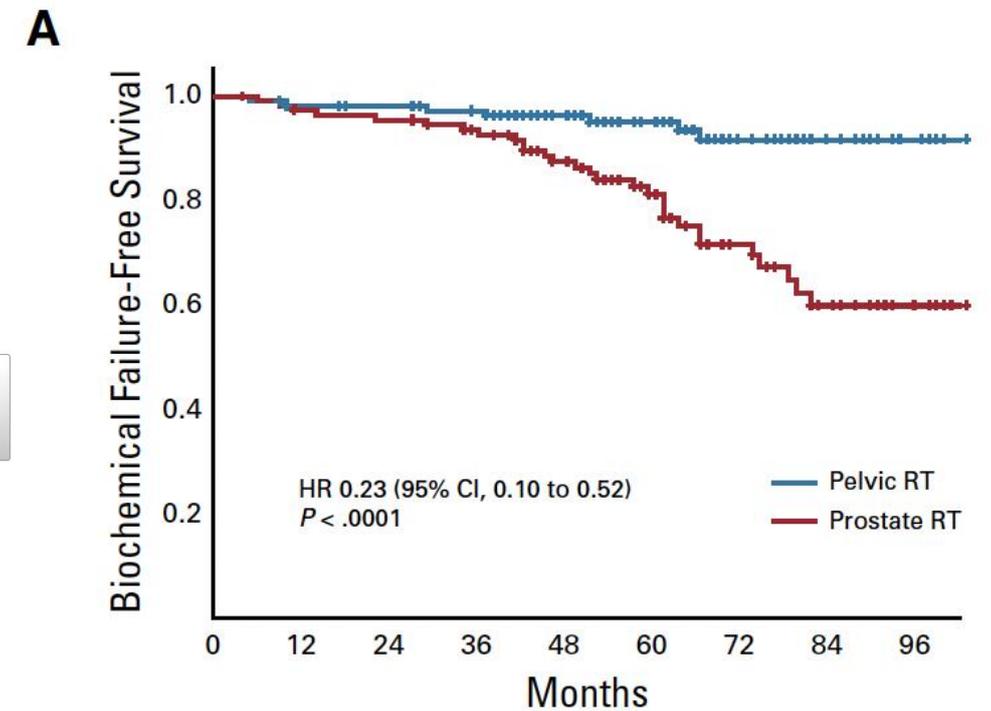
No. at risk (events)	0	12	24	36	48	60					
iADT	44	(10)	34	(21)	13	(4)	9	(1)	3	(0)	0
MDT + iADT	43	(3)	40	(13)	27	(10)	17	(3)	6	(1)	1

original reports

Prostate-Only Versus Whole-Pelvic Radiation Therapy in High-Risk and Very High-Risk Prostate Cancer (POP-RT): Outcomes From Phase III Randomized Controlled Trial



Vedang Murthy, MD¹; Priyamvada Maitre, MD¹; Sadhana Kannan, MSc²; Gitanjali Panigrahi, MSc¹; Rahul Krishnatry, MD¹; Ganesh Bakshi, MCh³; Gagan Prakash, DNB³; Mahendra Pal, DNB³; Santosh Menon, MD⁴; Reena Phurailatpam, MSc⁵; Smruti Mokul, MSc²; Dipika Chaurasiya, BSc¹; Palak Popat, DNB⁶; Nilesh Sable, MD⁶; Archi Agarwal, DNB⁷; Venkatesh Rangarajan, DNB⁷; Amit Joshi, DM⁸; Vanita Noronha, DM⁸; Kumar Prabhash, DM⁸; and Umesh Mahantshetty, MD¹

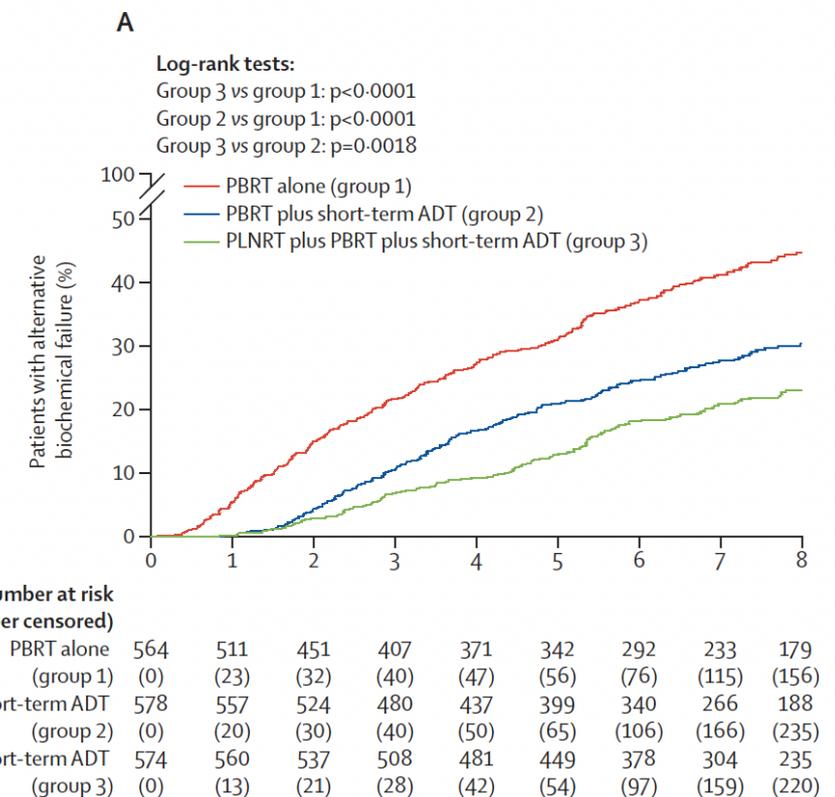


No. at risk	0	12	24	36	48	60	72	84	96
WPRT	110	106	104	100	81	64	40	20	10
PORT	112	106	104	97	77	55	34	22	10



The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial

Alan Pollack, Theodore G Karrison, Alexander G Balogh, Leonard G Gomella, Daniel A Low, Deborah W Bruner, Jeffrey S Wefel, Andre-Guy Martin, Jeff M Michalski, Steve J Angyalfi, Himanshu Lukka, Sergio L Faria, George B Rodrigues, Marie-Claude Beauchemin, R Jeffrey Lee, Samantha A Seaward, Aaron M Allen, Drew C Monitto, Wendy Seiferheld, Oliver Sartor, Felix Feng, Howard M Sandler



Optimizing Pelvic RT in the PSMA PET Era ... Integrating SBRT

The Distribution of Pelvic Nodal Metastases in Prostate Cancer Reveals Potential to Advance and Personalize Pelvic Radiotherapy

Filimonova et al. *Frontiers in Oncology* 2020

1. **Conclusions:** ... common iliac level should extend to the left psoas major & obturator levels should extend posteriorly 5 mm beyond the obturator internus.
2. **Incomplete coverage by NRG-consensus mostly due to perirectal involvement.**

Figure 1

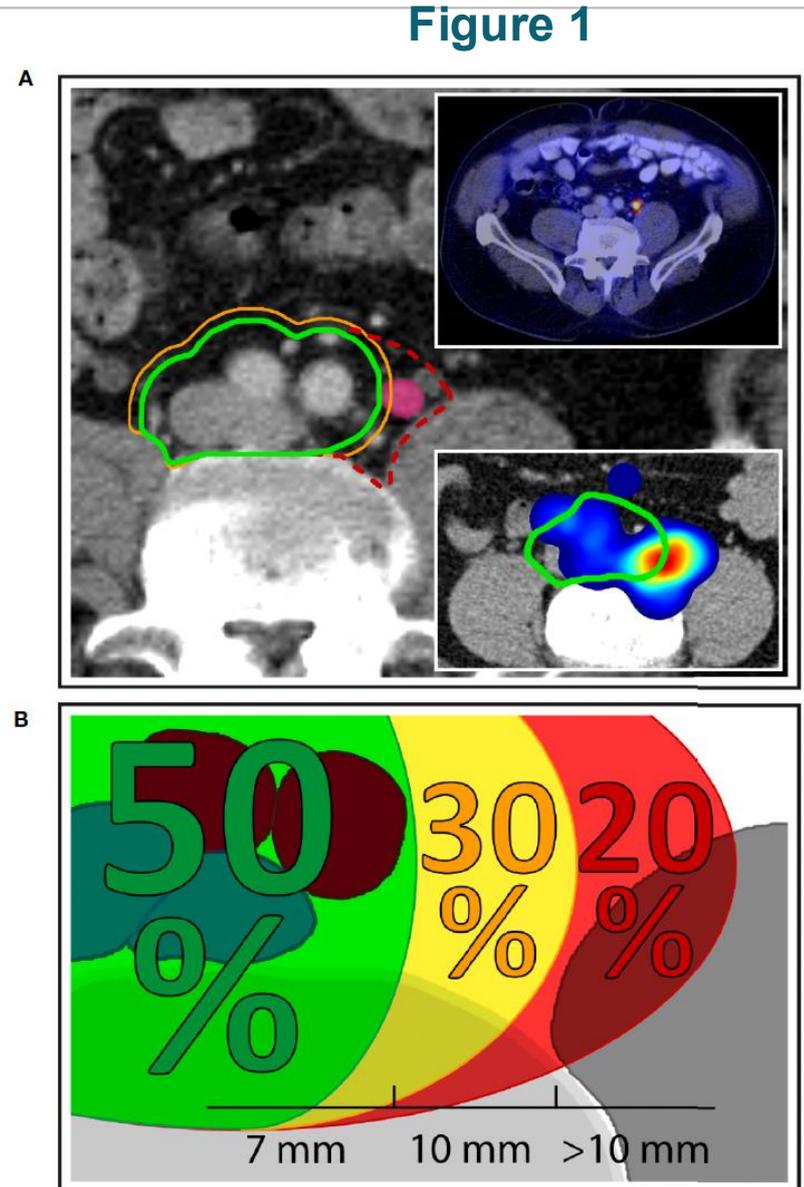


Figure 2

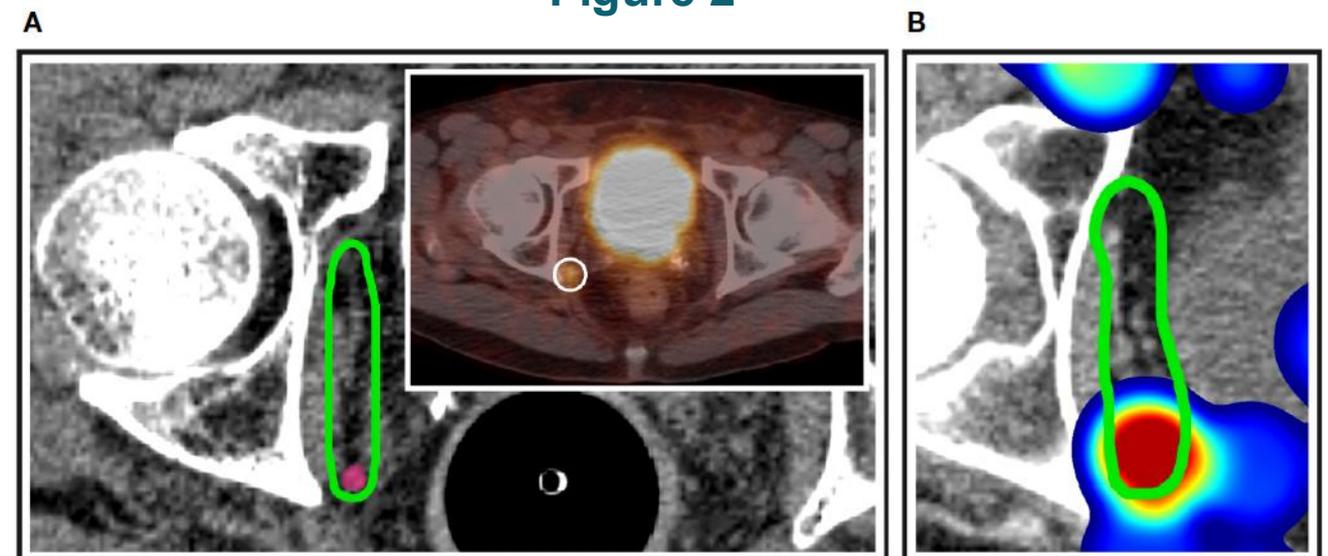


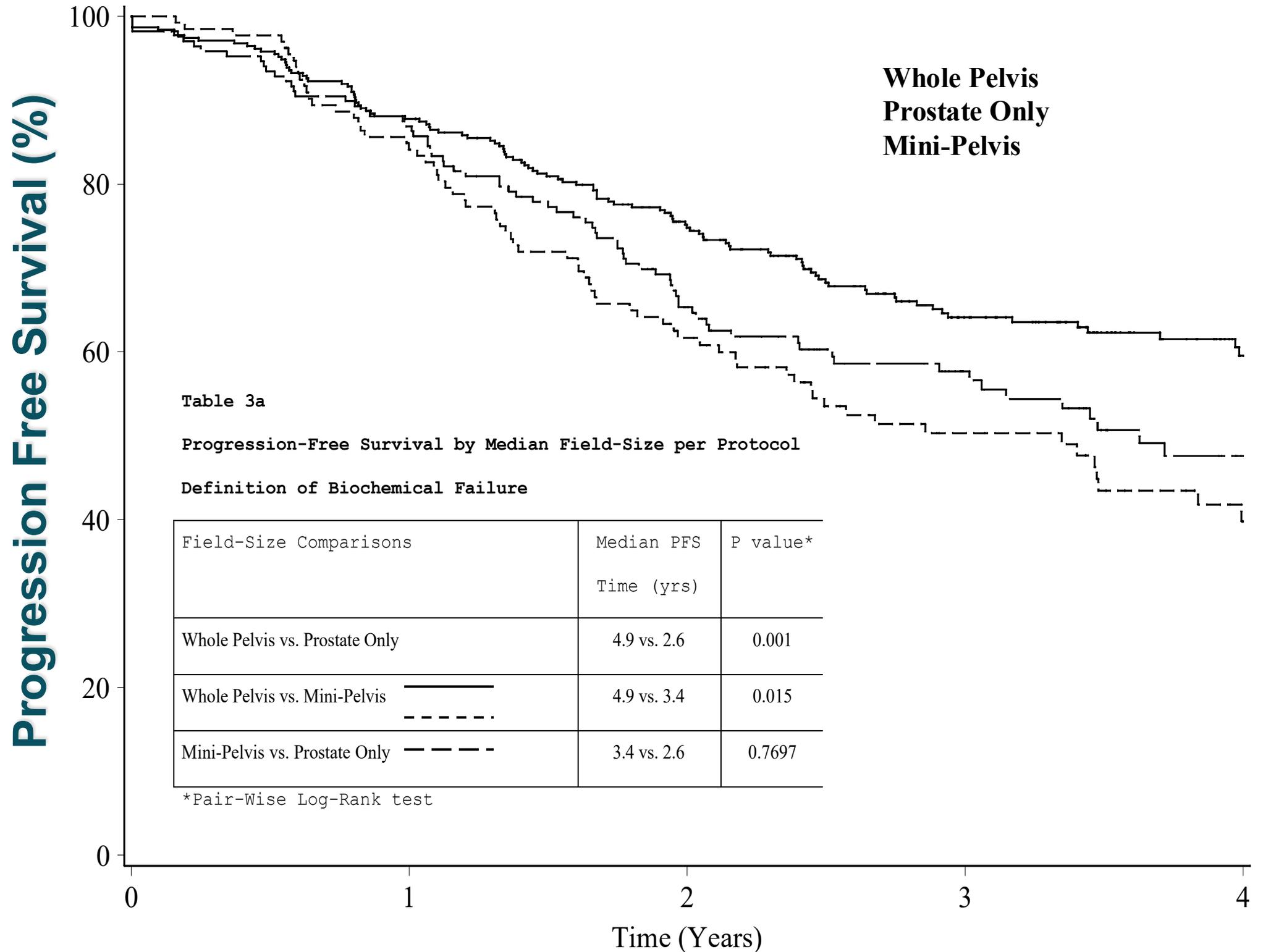
FIGURE 2 | Obturator nodes at the posterior edge of the NRG consensus CTV. (A) ... case with a PSMA-avid nodal metastasis (inset) right at the posterior edge of the NRG obturator level. (B) ... mapping analysis ... high-probability hotspot near the posterior edge of the NRG CTV ...

FIGURE 1 | Left common iliac nodal metastases outside NRG consensus CTV. (A) Exemplary patient ... with a left common iliac nodal metastasis outside the NRG CTV ... using margin options of 7 mm (green contour) and 10 mm (orange contour) ... Dashed red contour: proposed ... CTV to the medial surface of the left major psoas ...

Top right inset: PSMA-PET/CT ... demonstrating PSMA uptake. **Bottom right inset:** ... high-probability hotspot that extends beyond the left boundary of the NRG CTV recommendation. (B) 10 mm margin encompassed all nodal metastases in an additional 30.0% ... 20.0% of pts with left common iliac ... node metastases that extended ... beyond the 10-mm margin.

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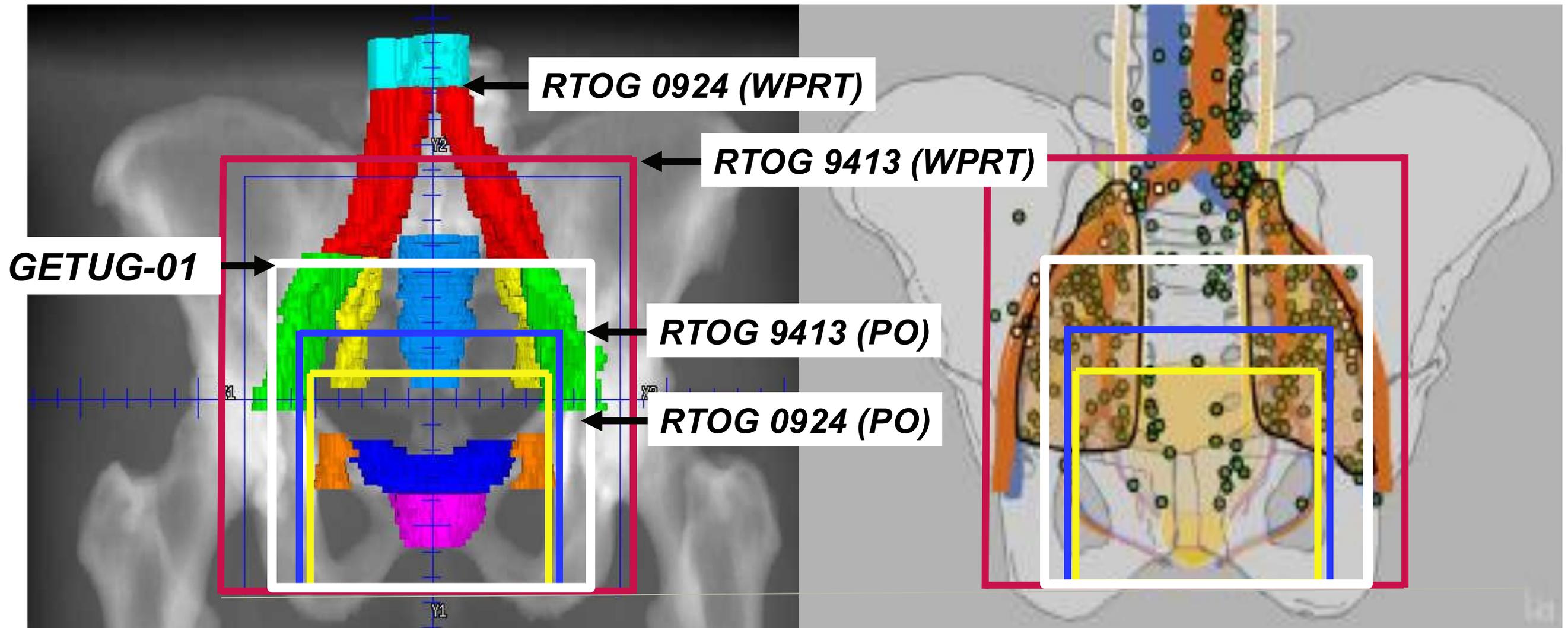
Progression-Free Survival: Protocol Definition



Optimizing Pelvic RT in the PSMA PET Era ... Integrating SBRT

The Template of the Primary Lymphatic Landing Sites of the Prostate Should be Revisited: Results of a Multimodality Mapping Study.

Mattei ... Studer. EAU 53:118-125, 2008



Nodal recurrence patterns on PET/CT after RTOG-based nodal radiotherapy for prostate cancer. Liskamp et al.

“Purpose: ... if current RTOG-based elective nodal fields ... considered optimal ... evaluated recurrence patterns on PET/CT after RT for PCN+ ... to explore options for improved nodal target definition.

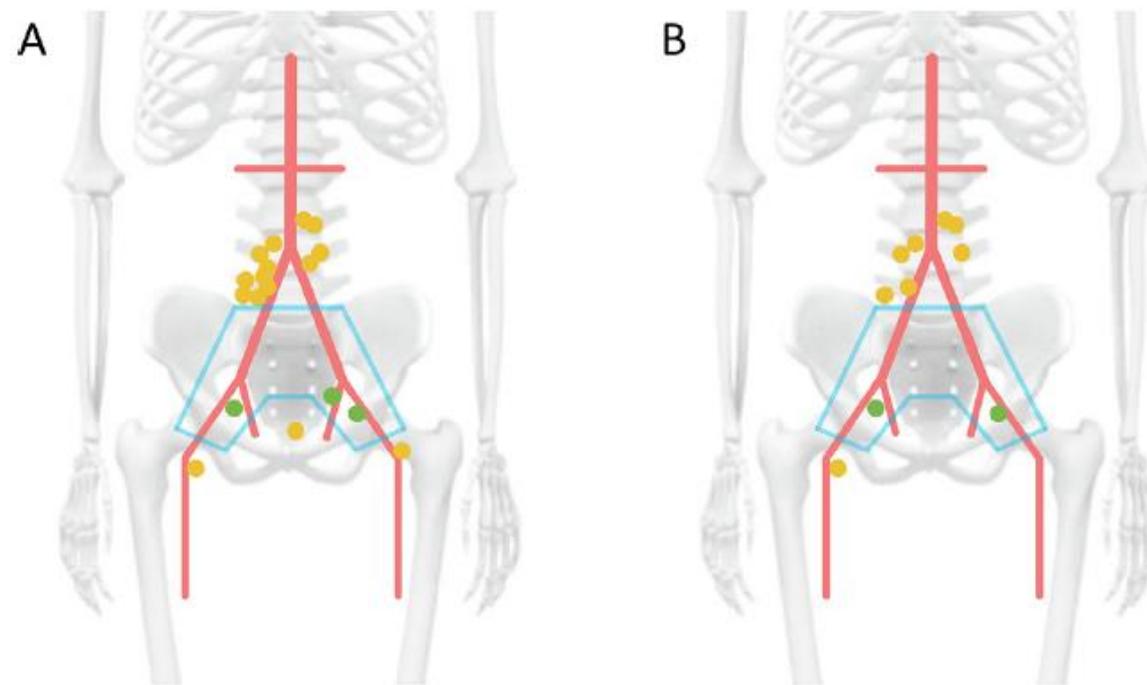


Fig. 2 Schematic distribution of nodal recurrences. Schematic overview of anatomical locations of nodal recurrences (A) in all patients and (B) in patients with only nodal recurrence. Red = large arteries for anatomical reference. Blue box = RTOG-based elective nodal radiotherapy field. Green ● = in-field nodal recurrence. Yellow ● = out-field nodal recurrence, indicating the node closest to the elective field for each involved anatomical region.

Conclusions: Current RT with RTOG-based nodal fields for PCN+ provides ... frequent out-field nodal recurrences ... Expanding elective fields to include the aorta bifurcation may prolong recurrence-free survival.”

“Realistic Survival Expectations” after Treatment of Clinically Localized Prostate Cancer

A. Active Surveillance data

1. Recent population based data *

B. Post RP

1. *Gleason 7 (Mayo Clinic)* *
2. Cause of Death population based (JH) *
3. *SPCG-4 (Sweden)* *
4. *PIVOT (2012 vs 2020)*

C. Post Radiotherapy

1. *RTOG 0815*
2. *RTOG 8531*
3. *MDA long term results of Dose escalation* *

D. Mixed

1. *PROTECT*

ORIGINAL RESEARCH

Metastasis and Mortality in Men With Low- and Intermediate-Risk Prostate Cancer on Active Surveillance. Courtney et al. J Natl Compr Canc Netw 2022

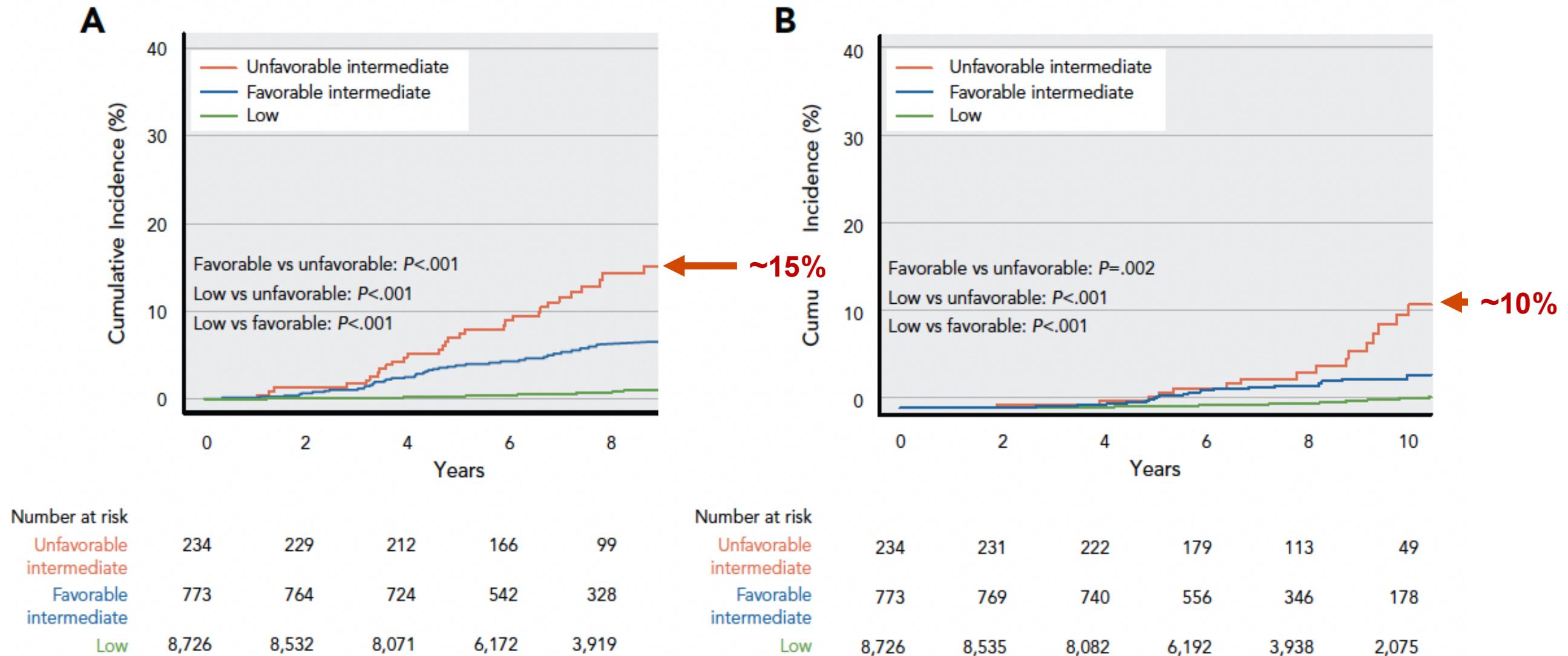


Figure 1. Cumulative incidences of (A) metastasis and (B) prostate cancer–specific mortality, with Gray’s test for equality P values between prostate cancer risk groups.

Long-Term Prognostic Significance of Primary Gleason Pattern in Patients With Gleason Score 7 Prostate Cancer: Impact on Prostate Cancer Specific Survival

Tollefson et al. The Journal of Urology Vol. 175, 547-551 (2006)

Pretreatment Characteristics:

Age: 65

PSA=7.8 ng/mL

8% T3/4

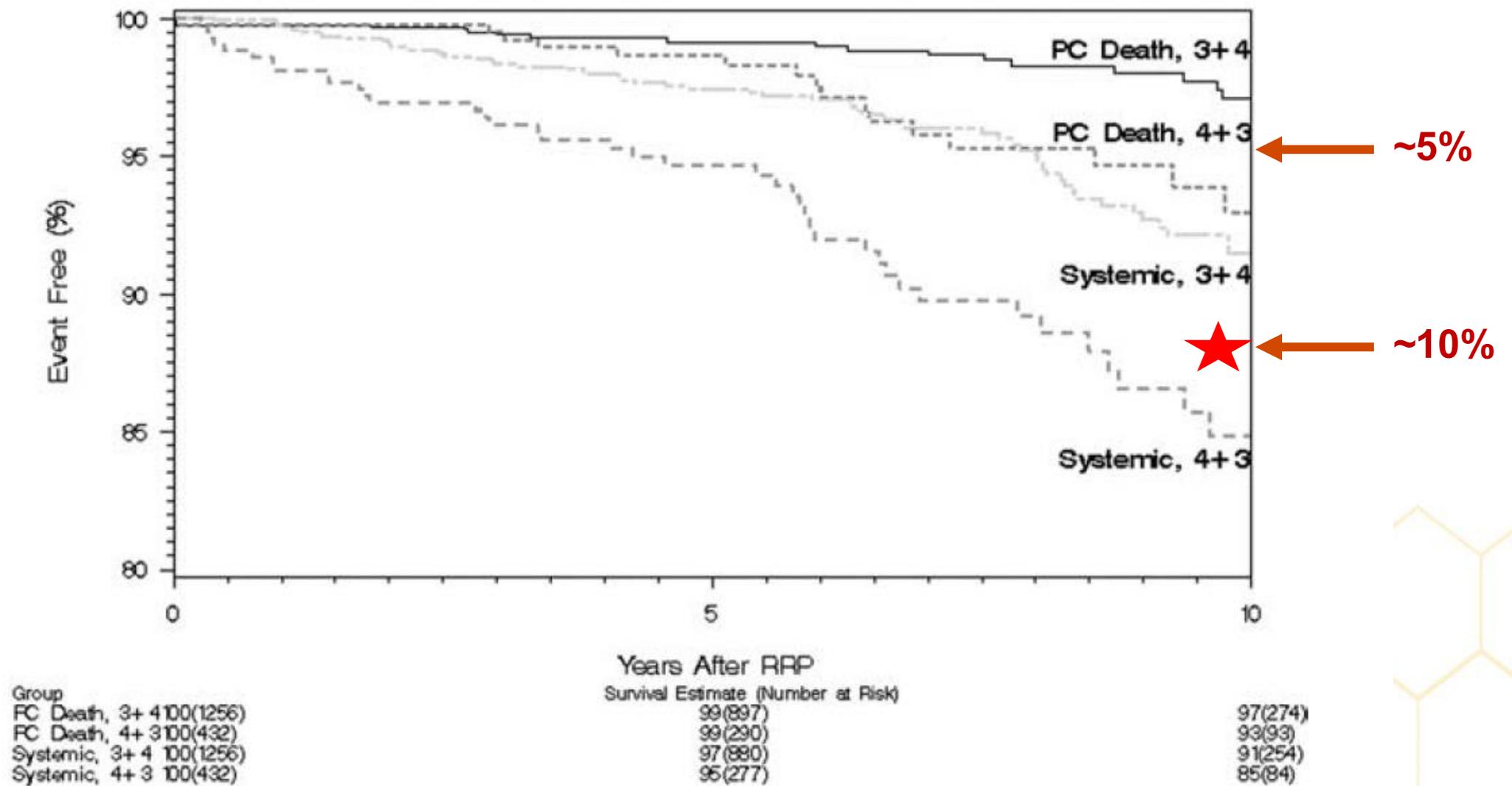


FIG. 2. Systemic progression and PC specific death rates by primary Gleason pattern.

Predicting 15-Year Prostate Cancer Specific Mortality After Radical Prostatectomy.
Scott E. Eggener et al. THE JOURNAL OF UROLOGY. Vol. 185, 869-875, March 2011

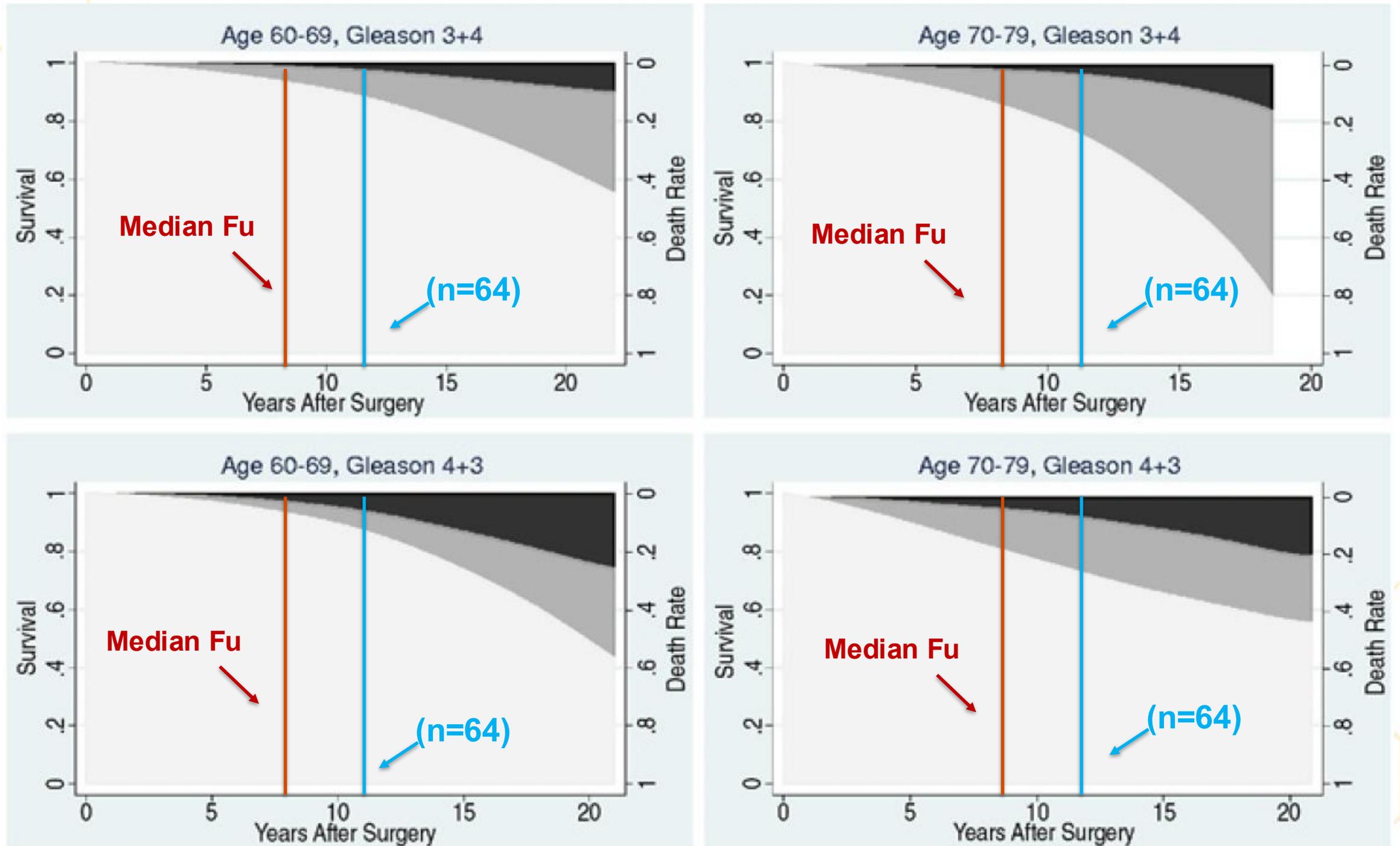


Figure 3. PCSM (black areas) and mortality from competing causes (gray areas) by pathological Gleason score and patient age at diagnosis.

Table 2

Predicting 15-Year Prostate Cancer Specific Mortality After Radical Prostatectomy*

Year	Age 60 – 69	Age 70 – 79	Average
	GS = 3+4	GS = 3+4	GS = 7
5yr	≤ 1%	≤ 1%	≤ 1%
10yr	1.5%	2.5%	2.0%
15 yr	4%	7.5%	5.8%
			Estimated % PCSM yr 10 to 15: ~ 66%
	GS = 4 + 3	GS = 4 + 3	Average
5yr	≤ 1%	≤ 1%	≤ 1%
10yr	4%	5%	4.5%
20 yr	25%	19%	22.0%
			Estimated % PCSM yr 10 to 20: ~ 80%

PCSM = prostate cancer mortality; *(Modified estimates from Fig. 3, Eggener et al. J of Urol 2011). Based on an analysis of 11,521 men post RP from four academic institutions

Table 3**No. of events observed, cumulative PCSM & OM at 5-Yr increments (Holmberg modified) SPCG-4***

Mortality Endpoint	RP Group (n=347)		WW Group (n=348)		Absolute risk reduction	NNT
PCS	Events	CIE % (95% CI)	Events	CIE % (95% CI)	% (95% CI)	(95% CI)
5yr	10	2.9 (2.6 - 3.2)	16	4.6 (4.1 - 5.1)	1.7 (-1.1 to 4.5)	58 (22 - ∞)
10yr	37	10.7 (9.7 - 11.8)	53	15.2 (13.8 - 16.8)	4.6 (-0.4 to 9.6)	22 (11 - ∞)
20 yr	78	22.5 (20.5 - 24.7)	124	35.6 (32.7 - 38.8)	13.2 (6.5 - 20.3)	7.6 (5.0 - 15)
OM	Events	CIE % (95% CI)	Events	CIE % (95% CI)	% (95% CI)	(95% CI)
5yr	27	7.8 (2.9 - 20.7)	34	9.8 (7.1 - 13.5)	2.0 (-2.2 to 5.9)	50 (17 - ∞)
10yr	90	25.9 (16.8 - 40.0)	110	31.6 (27.1 - 36.9)	5.7 (-1.1 to 11.3)	18 (8.9 - ∞)
20 yr	226	65.1 (52.1 - 81.5)	264	75.9 (71.5 - 80.5)	10.7 (4.0 - 19.9)	9.3 (5.0 - 25)

CI = confidence interval; CIE = cumulative incidence estimate; PCSM = prostate cancer mortality; NNT = number needed to treat; OM = overall mortality; RP = radical prostatectomy; WW = watchful waiting. ^a As no adjustments were planned for multiplicity, significance levels are not shown for comparisons by follow-up interval. All analyses are on an intention-to-treat basis. ^b The CI widths have not been adjusted for multiplicity.

***Time Dependence of Outcomes in the SPCG-4 Randomized Trial Comparing Radical Prostatectomy and Watchful Waiting in Early Prostate Cancer. Holmberg et al. Eur Uro, 2025**

Dose Escalation for Prostate Adenocarcinoma: A Long-Term Update on the Outcomes of a Phase 3, Single Institution Randomized Clinical Trial.

Pasalic et al. IJROBP 2019

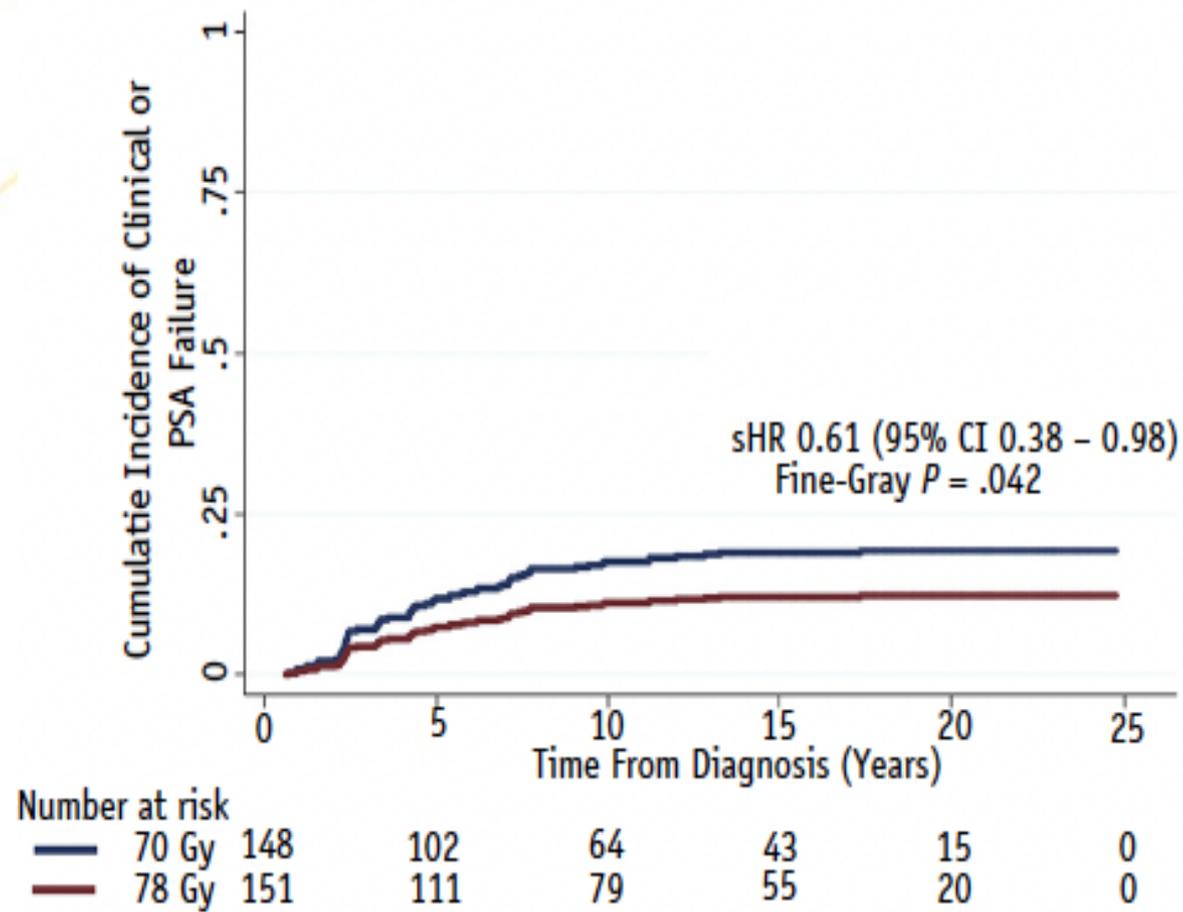


Fig. 1. Cumulative incidence of biochemical or clinical failure for the entire patient cohort treated to 70 Gy versus 78 Gy. Biochemical or clinical failure at 15 and 20 years was significantly better for patients receiving 78 Gy (red line; 12.0% and 12.2%, respectively) compared to 70 Gy (blue line; 18.9% and 19.2%, respectively) (subhazard ratio, 0.61; 95% confidence interval, 0.38-0.98; Fine-Gray p < 0.042).

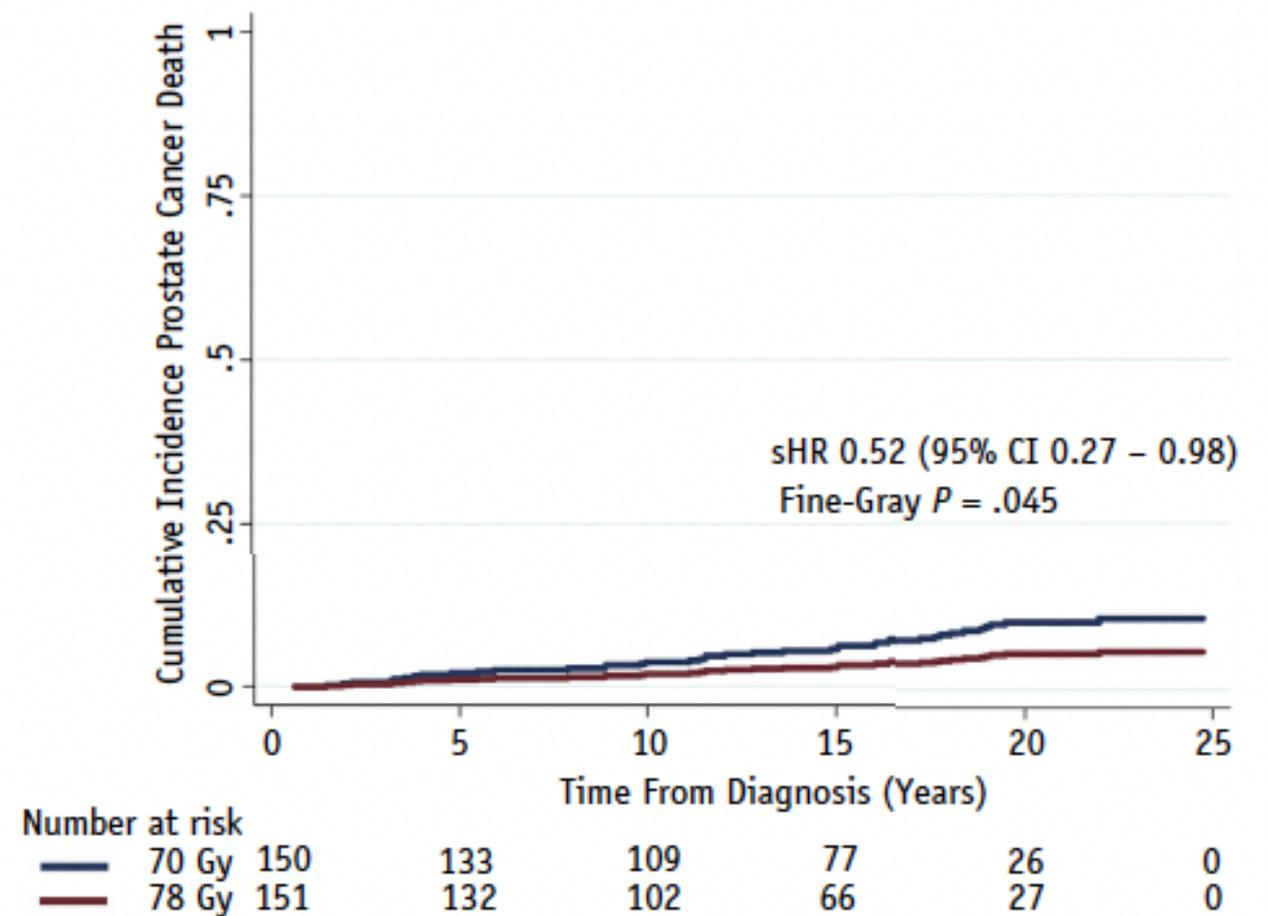


Fig. 4. Cumulative incidence of prostate cancer specific mortality for the entire patient cohort treated to 70 Gy versus 78 Gy. Cumulative incidence of prostate cancer specific mortality at 15 and 20 years was significantly higher in the patients receiving 70 Gy (blue line; 6.2% and 10.2%, respectively) compared to 78 Gy (red line; 3.2% and 5.4%, respectively) (subhazard ratio, 0.52; 95% confidence interval, 0.27-0.98; Fine-Gray p < 0.045).

Dose Escalation for Prostate Adenocarcinoma: A Long-Term Update on the Outcomes of a Phase 3, Single Institution Randomized Clinical Trial. Pasalic et al. IJROBP 2019

Outcome type

Prostate cancer-specific mortality			Other-cause mortality			Overall survival		
Univariate			Univariate			Univariate		
15-year (%)	sHR (95% CI)	<i>P</i> value	15-year (%)	sHR (95% CI)	<i>P</i> value	15-year (%)	HR (95% CI)	<i>P</i> value
6.2	1 [Ref]	.045	45.7	1 [Ref]	.061	53.4	1 [Ref]	.469
3.2	0.52 (0.27-0.98)		55.6	1.33 (0.99-1.79)		48.9	1.10 (0.84-1.45)	

Table 2

Cumulative incidence of prostate cancer-specific mortality, other-cause mortality, and overall survival hazard ratios by treatment arm (modified)

Identifying the Optimal Candidate for Salvage Lymph Node Dissection for Nodal Recurrence of Prostate Cancer: Results from a Large, Multi-institutional Analysis. Fossati et al. *Eur Urol.* 2019 (176 – 183)

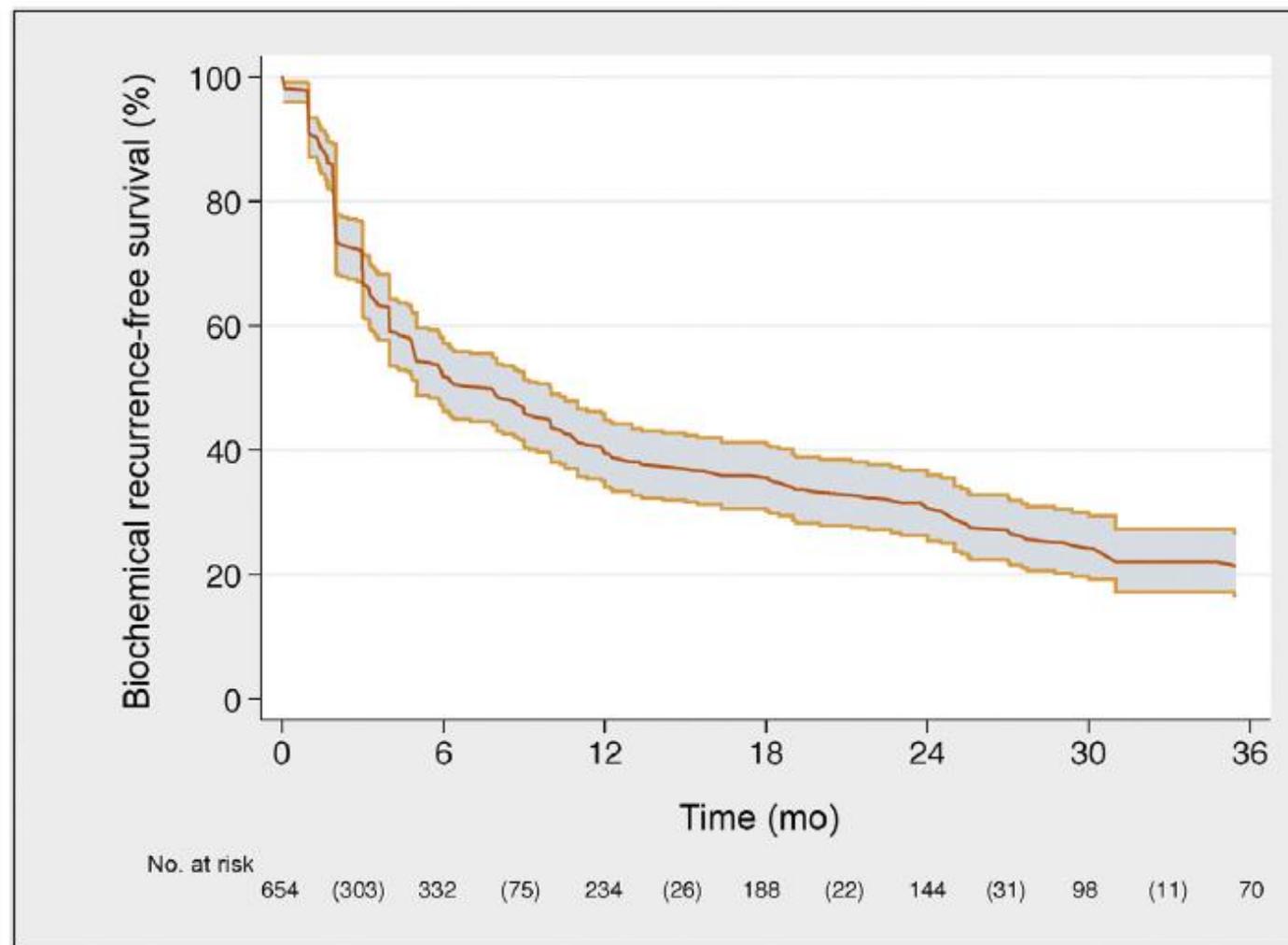


Fig. 2 – Kaplan-Meier plot depicting biochemical recurrence-free survival in the overall population.

PSA (SLND) = 2.1

No. PET +nodes

n=1 (51%)

n=2 (23%)

n=3 (17%)

n≥4 (9%)

No. +nodes PO

n=0 (9%)

n=1 (33%)

n=2 (14%)

n≥3 (54%)

**70% PSA ≥ 0.1
ng/ml PO**

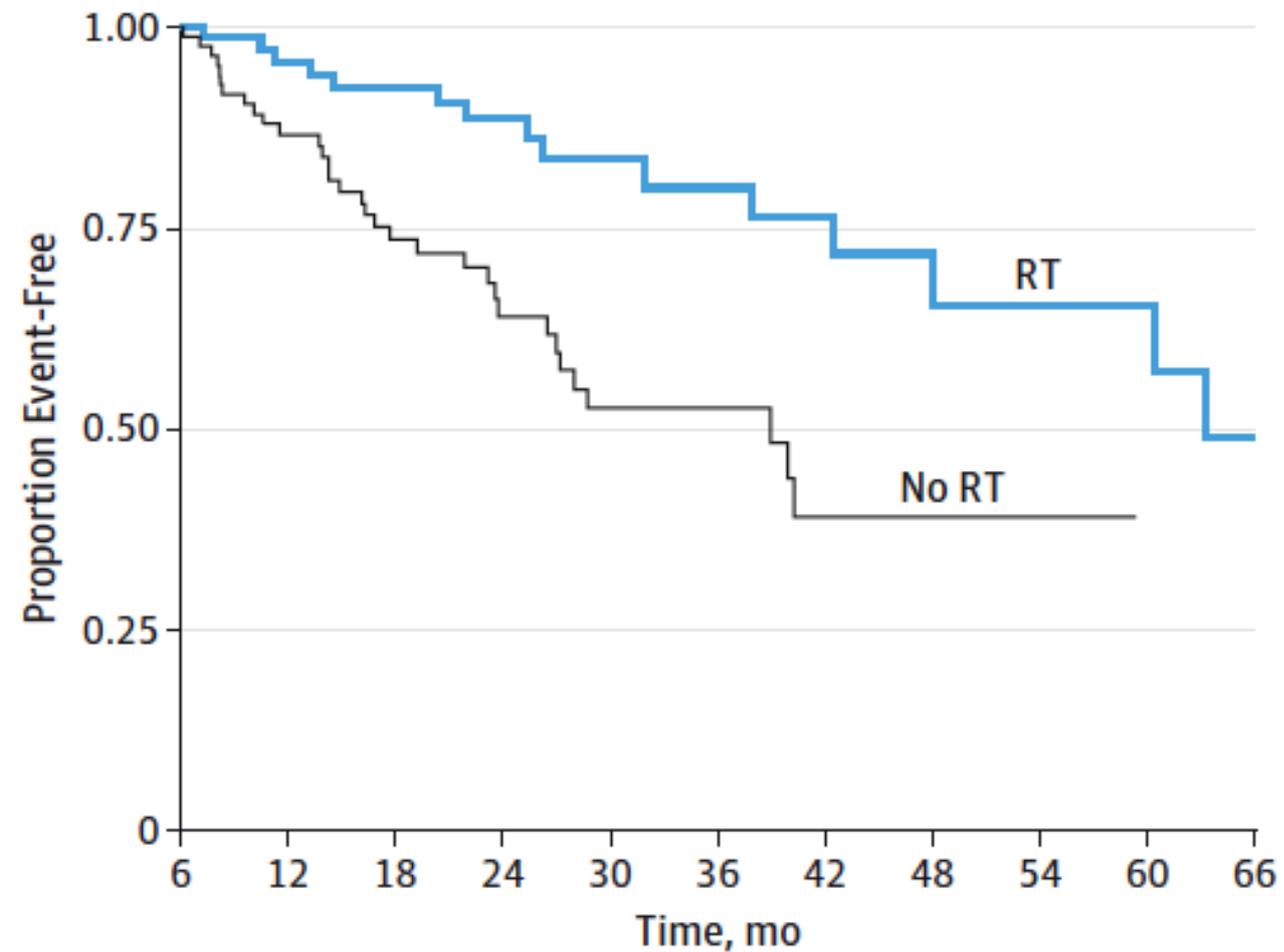
Analysis based on 654 pts ... PSA rise and nodal recurrence after RP and ... SLND ... Lymph node recurrence was documented by PET/CT using (11)C-choline or (68)Ga-labeled PSMA.

**Optimizing
Pelvic RT in
the PSMA
PET Era ...
Integrating
SBRT**

Failure-Free Survival and Radiotherapy in Patients With Newly Diagnosed Nonmetastatic Prostate Cancer

Data From Patients in the Control Arm of the STAMPEDE Trial

B N+M0 subcohort

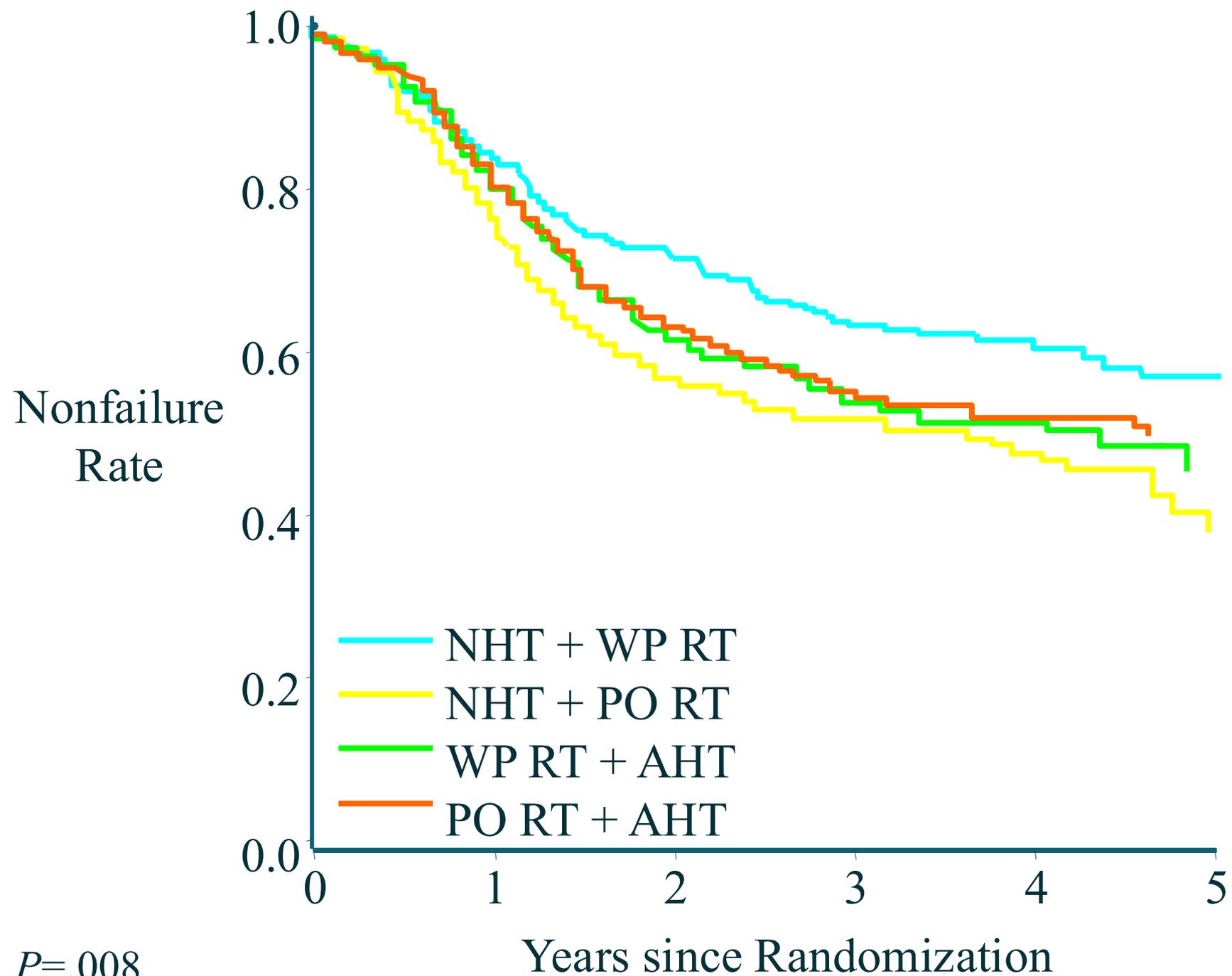


No. at risk (events)

No RT	86	(20)	47	(10)	20	(3)	8	(0)	6	(0)	3
RT	71	(5)	54	(4)	28	(2)	17	(2)	9	(2)	6

Figure 2.
Failure-Free Survival for Reported Radical Radiotherapy Status, in N+M0 Subcohort
James et al. JAMA Oncology 2016

Progression-Free Survival: RTOG 9413



Optimizing
Pelvic RT in
the PSMA
PET Era ...
Integrating
SBRT

NHT=neoadjuvant hormonal therapy; AHT=adjuvant hormonal therapy
JCO 2003 Roach, et al.

Basis of study design for RTOG 0924?

Table 12.6. 4-Yr PFS: Intermediate Risk (PSA <30 and GS 7-10 excluding Clinical Stages T2c-T4, or GS=6 with PSA <30, Gleason 2-6, and Clinical Stages T2c-T4, or PSA ≥30 and GS 2-6)

Treatment Arm	Failures	N	4-Yr Rate (%) [95% C.I.]	P-Value*
Hormones + RT Whole Pelvis+Boost	35	125	68.1 [58, 78]	0.027
Hormones + RT Prostate Alone	56	125	46.6 [36, 58]	
RT Whole Pelvis+Boost + Hormones	44	113	53.8 [42, 65]	
RT Prostate Alone + Hormones	50	118	49.8 [39, 61]	

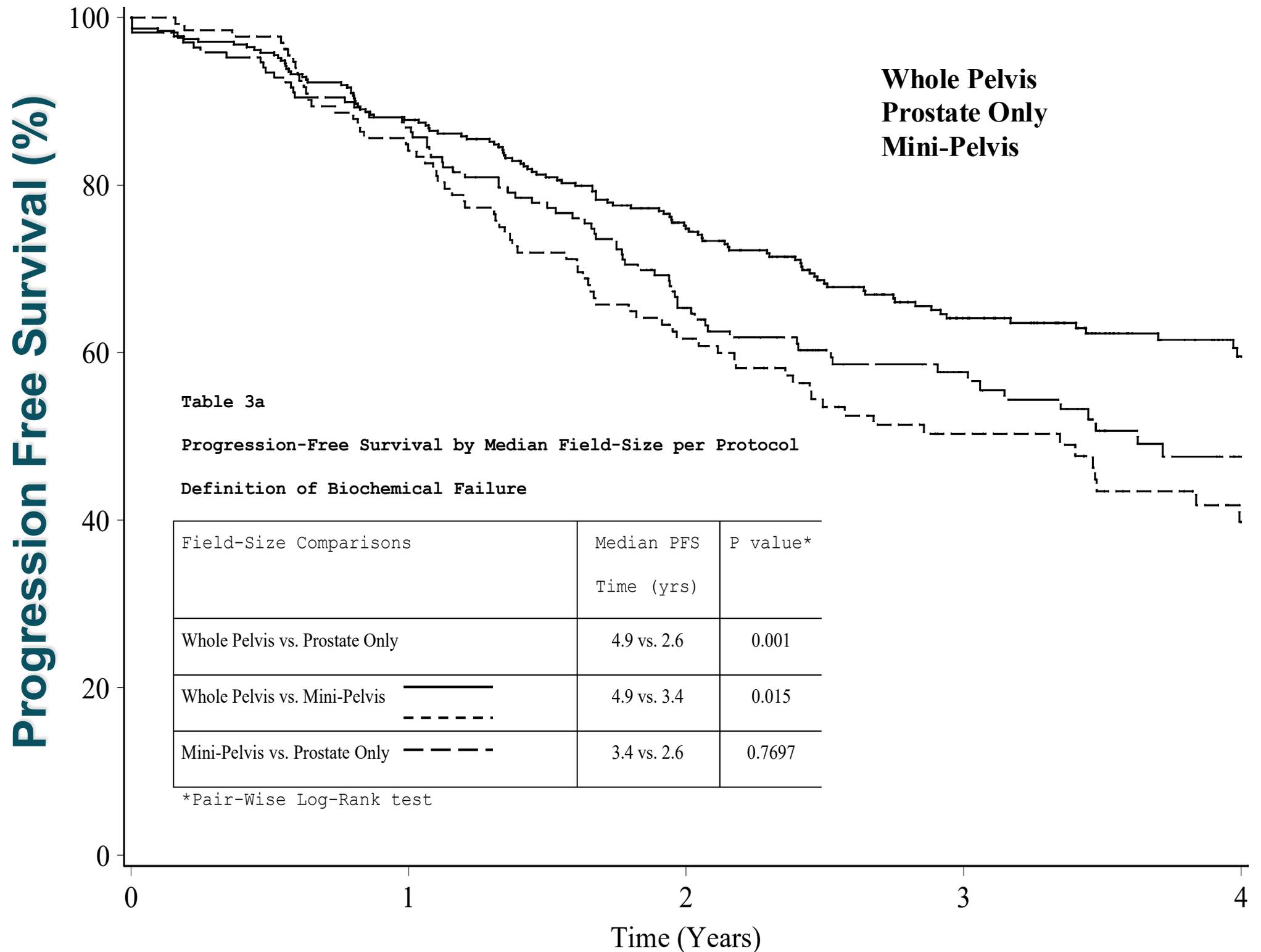
P-value from log-rank test for comparing the survival curves.

RTOG 9413* Subset middle stratification risk + nodes > 15% by Roach equation: (1) PSA <50 ng/ml & GS 7-10, T1c-T2b, or (2) GS=2-6 with Clinical Stages T2c-T4 or > 50% biopsies + & PSA <50 ng/ml, or (3) GS=2-6, PSA > 20 ng/ml and T1c-T2b

Group	10 yr CSS				
PO (n=145)	0.8497	0.1503	0.0358	16	52
WPRT (n=146)	0.9741	0.0259	0.0150	3	40
	<i>Diff = 13%</i>	<i>Log-Rank</i>	8.7735	1	0.0031

Max PSA < 100 ng/ml

Progression-Free Survival: Protocol Definition



Optimizing
Pelvic RT in
the PSMA
PET Era ...
Integrating
SBRT

**“If you want to prove something
doesn’t work,
design an underpowered study”**

- Mack Roach III, MD



Advancing Research. Improving Lives.™

Androgen Deprivation Therapy (ADT) and High Dose Definitive Radiotherapy (RT) +/- Whole Pelvic RT in Patients with Unfavorable Intermediate or Favorable High-Risk Prostate Cancer: Early Results of a Phase III Randomized Trial, NRG/ RTOG 0924

Mack Roach III, Theodore Karrison, Hans Chung, Albert J Chang, Leonard G Gomella, I-Chow Hsu, Gerard Morton, Robert E Wallace, Benjamin Movsas, Deborah Watkins Bruner, Adam P Dicker, Deborah Citrin, Isaac Kaufman, Jeff M Michalski, Eric Vigneault, Michael A Papagikos, Daniel Spratt, Ashesh B Jani, Trevor Johnson, Howard M Sandler

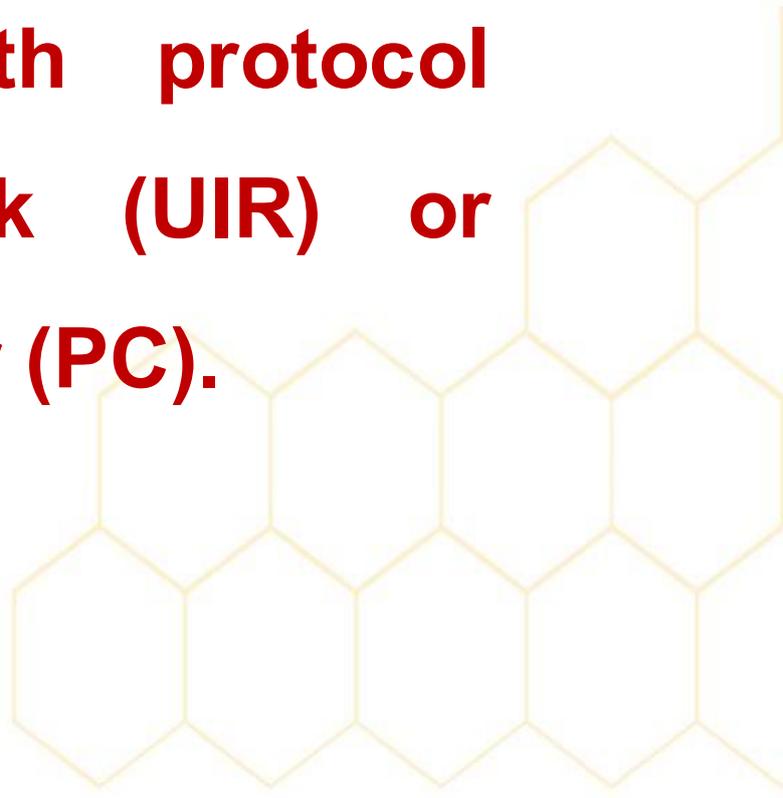
ASTRO 2025, 9/28/25





Purpose/Objectives:

Assess whether prophylactic whole pelvic radiotherapy (WPRT) improves overall survival (OS) compared to prostate only dose escalated radiotherapy (PORT) in patients with protocol defined unfavorable intermediate risk (UIR) or favorable high risk (FHR) prostate cancer (PC).



Background (continued):

RTOG 9413 demonstrated (~300 each arm) that with neoadjuvant ADT, WPRT improved PFS, and BF compared to PORT in men with a risk of + nodes > 15% (Lancet Oncol 2018).

RTOG 0924 sought to demonstrate we could improve OS if we:

- 1. Quadrupled the size of the arms to yield greater statistical power.**
- 2. Made “big fields bigger” & “small fields smaller” (RTOG IJROBP, 2006).**
- 3. Leverage dose escalation to reduce late local recurrences.**
- 4. Refine our patient selection UIR & FHR (RTOG 9413, JCO 2003)**

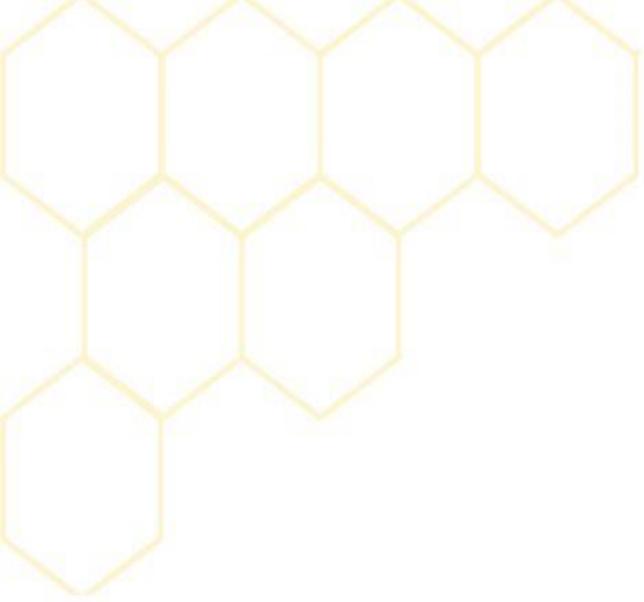
Materials/Methods:

- **Localized prostate ca. with estimated risk of + LN \geq 15% (Roach eq.)**
- **UIR or FHR (PSA <50 ng/ml clinical T1-2b, i.e., no T3's)**
 - *Predated NCCN risk group definitions*
- **Stratification variables:**
 - Risk group
 - RT boost: brachytherapy vs IMRT to 79.2 Gy
 - ADT duration (4 or 6 vs 32 mos)
- **WPRT had superior border at L4-5 interspace)**
- **Staging was based on conventional imaging.**

Eligibility and Stratification:

S T R A T I F Y	Pretreatment Variables	R A N D O M I Z E	Treatment
	<p>Risk Groups:</p> <ol style="list-style-type: none"> 1. GS 7-10 + T1c-T2b + PSA < 50 ng/mL 2. GS 6 + T2c-T4 or ≥ 50% Bx's + PSA <50 ng/mL 3. GS 6 + T1c-T2b + PSA > 20 ng/ml 		<p>Arm 1 (PORT): NADT + prostate & seminal vesicle RT, then a boost to prostate & proximal seminal Vesicles</p>
	<p>Type of RT Boost:</p> <ol style="list-style-type: none"> 1. IMRT 2. Brachytherapy (LDR using PPI or HDR) 		<p>Arm 2 (WPRT): NADT + WPRT** followed by a boost to prostate & proximal seminal vesicles</p>
	<p>Duration of ADT:</p> <ol style="list-style-type: none"> 1. Short Term (4 or 6 months) 2. Long Term (32 months) 		

*Neoadjuvant androgen deprivation therapy = NADT; **Whole Pelvic Radiotherapy (WPRT); ***(LDR) low dose rate; (PPI) permanent prostate implant; (HDR) high dose rate



Clarification of Eligibility

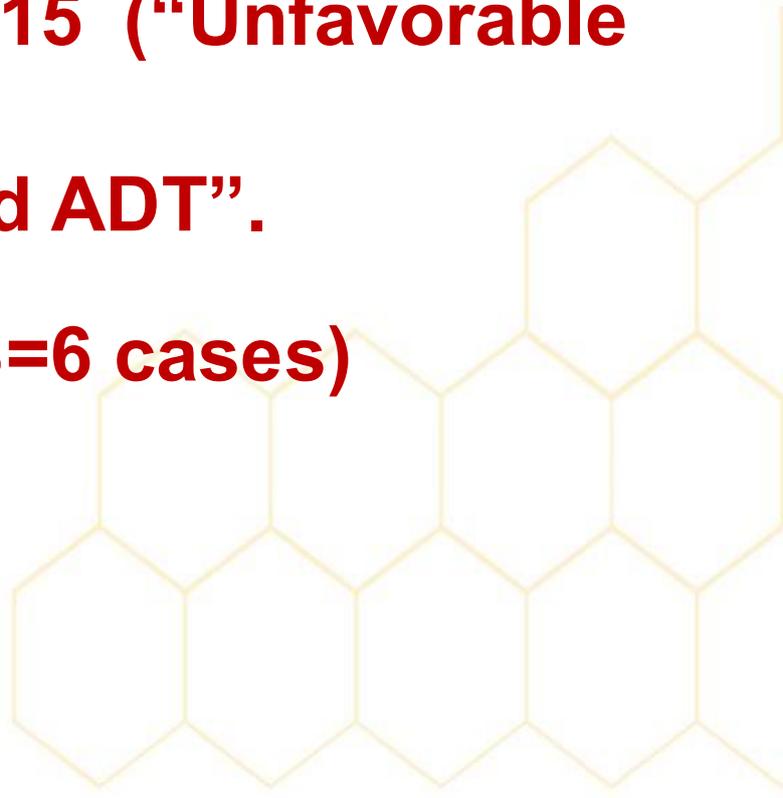
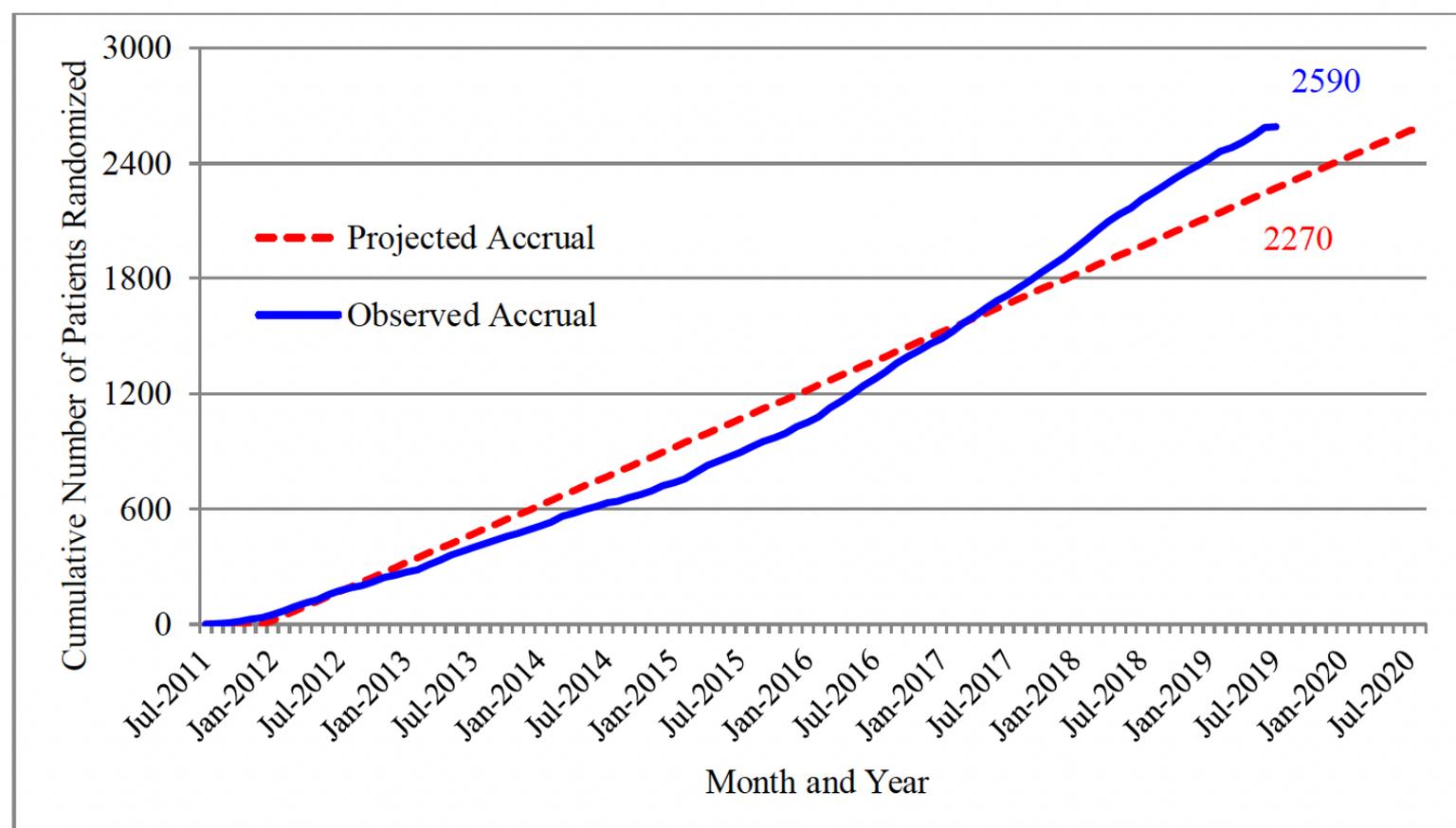
- 1. Not current NCCN Risk Groups (designed 5 yrs earlier)**
 - 2. “Intermediate” subset from RTOG 9413 (JCO 2003)**
 - 3. Sandwiched between RTOG 0815 (“favorable int. risk”) Dose Escalation +/- 4 to 6mo. ADT and RTOG 1115 (“Unfavorable HR”, T3 allowed) Dose Escalation +/- “enhanced ADT”.**
 - 4. Nearly all had GS > or = 7-10, (a few “bulky” GS=6 cases)**
- 

Figure 1
Cumulative Accrual for RTOG 0924 - Data as of 04/30/2024



From July 2011, thru June 24, 2019, 2590 patients were enrolled with 117 (4.5%) deemed ineligible, leaving 2473 for primary analysis.

Baseline Demographic and Clinical Characteristics

Variable		Arm 1 (n=1228)	Arm 2 (n=1245)
Age (Med) [Min-Max range]		69 [43 - 89]	69 [44 - 87]
Race	White	74.5%	75.5%
	Black/AA	18.3%	18.5%
	Other	7.2%	6.0%
Risk Group	UIR	563 (45.8)	567 (45.5)
	FHR	665 (54.2)	678 (54.5)
PSA	< 20 ng/ml	1035 (84.3%)	1043 (83.8%)
	>20 – 50 ng/ml	193 (15.8%)	202 (16.2%)
RT Modality	IMRT	79.1	78.7
	BT	20.9	21.3
ADT duration	4-6 months	841 (68.5%)	879 (70.6%)
	32 months	387 (31.5%)	366 (29.4%)

Study Design/Analysis Plan:

- Primary endpoint (OS) compared by logrank test with Cox hazard ratio (HR). Study designed to have 90% power to detect a HR of 0.82, based on one-sided test at 0.025 α -level: N=2,580.
- Secondary endpoints (PCS, DM, biochemical failure) evaluated using competing risks methods with cause-specific HRs.
- Quality of life (to be reported later) analyzed by mixed-effect modelling.
- Interim efficacy and futility analyses were specified:

“Although the p-value from the interim futility test, $p=0.018$, was not less than the protocol-specified $p<0.005$, the survival curves are very similar out to 9 yrs and the estimated hazard ratio (HR) is 1.0 (95% CI: 0.83-1.21). Given the much longer time it has taken to accumulate events, the decision was made to release the results now.”

****DSMC July 25, 2024***

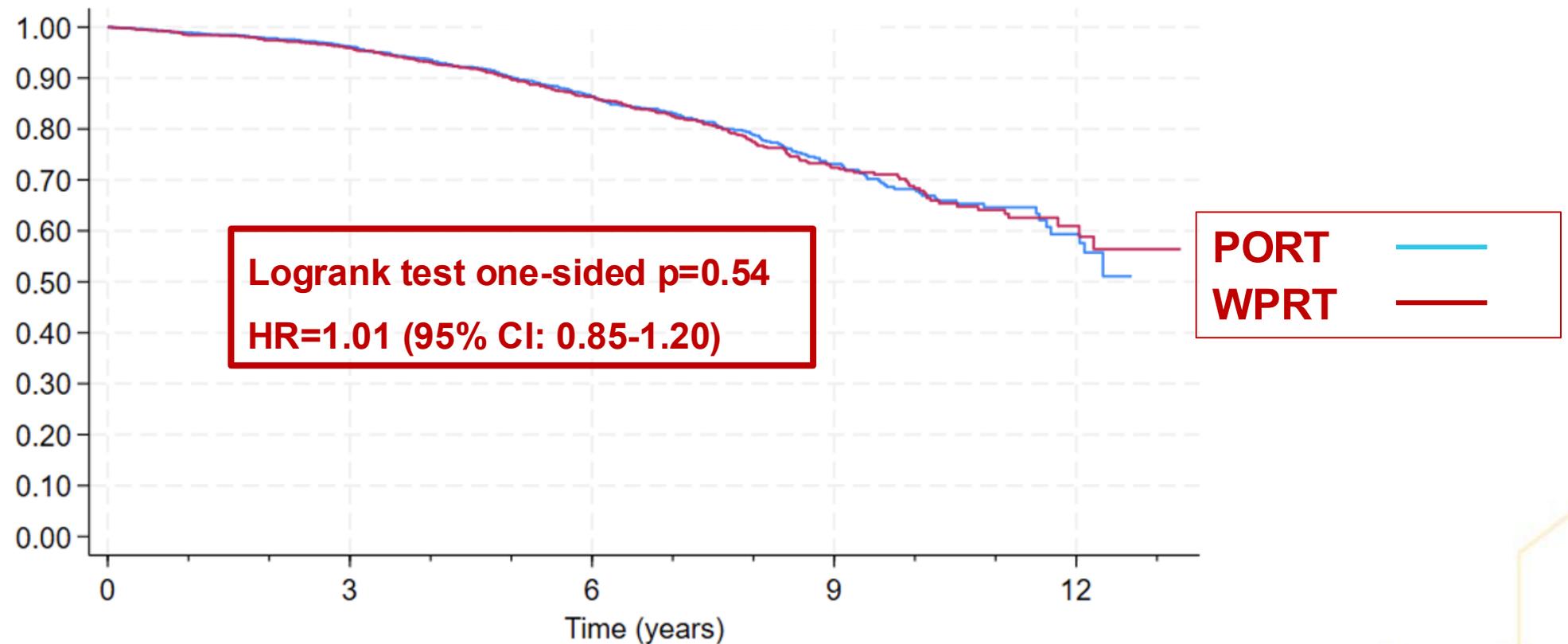
Results:

- 2473 (UIR=1130; FHR=1343) eligible/evaluable pts (med age 69 yrs)
 - 30% receiving long term ADT
 - 21% a BT boost
 - 98% had a GS = 7-10.
- Med. fu 7.3 yrs (IQR 6.1-9.2), only 64 pts with >12 yrs of Fu
- WPRT did not improve OS
 - 10-yr OS 68% both (HR 1.01, 95% CI: 0.85-1.20, *one-sided* p=0.54).

Among 514 total deaths, only 44 have been reported as due to prostate cancer, however an additional 139 were coded as "unknown" cause and are actively being adjudicated.

Time-to-event analysis (death due to any cause)

Overall Survival

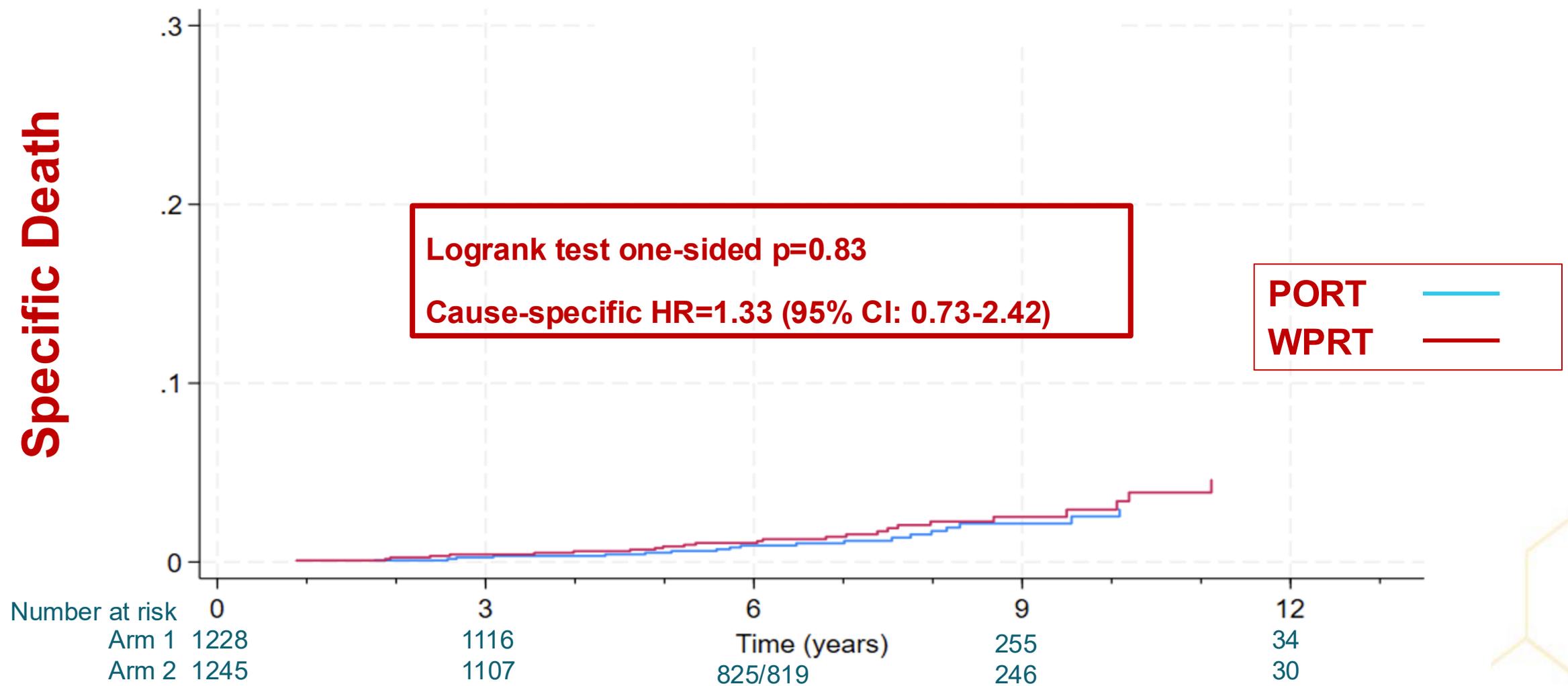


Number at risk

Arm 1	1228	(45)	1116	(107)	825	(77)	255	(25)	34
Arm 2	1245	(49)	1107	(104)	819	(81)	246	(21)	30

Overall survival by treatment arm. Blue: PORT (Arm 1), Red: WPRT (Arm 2)

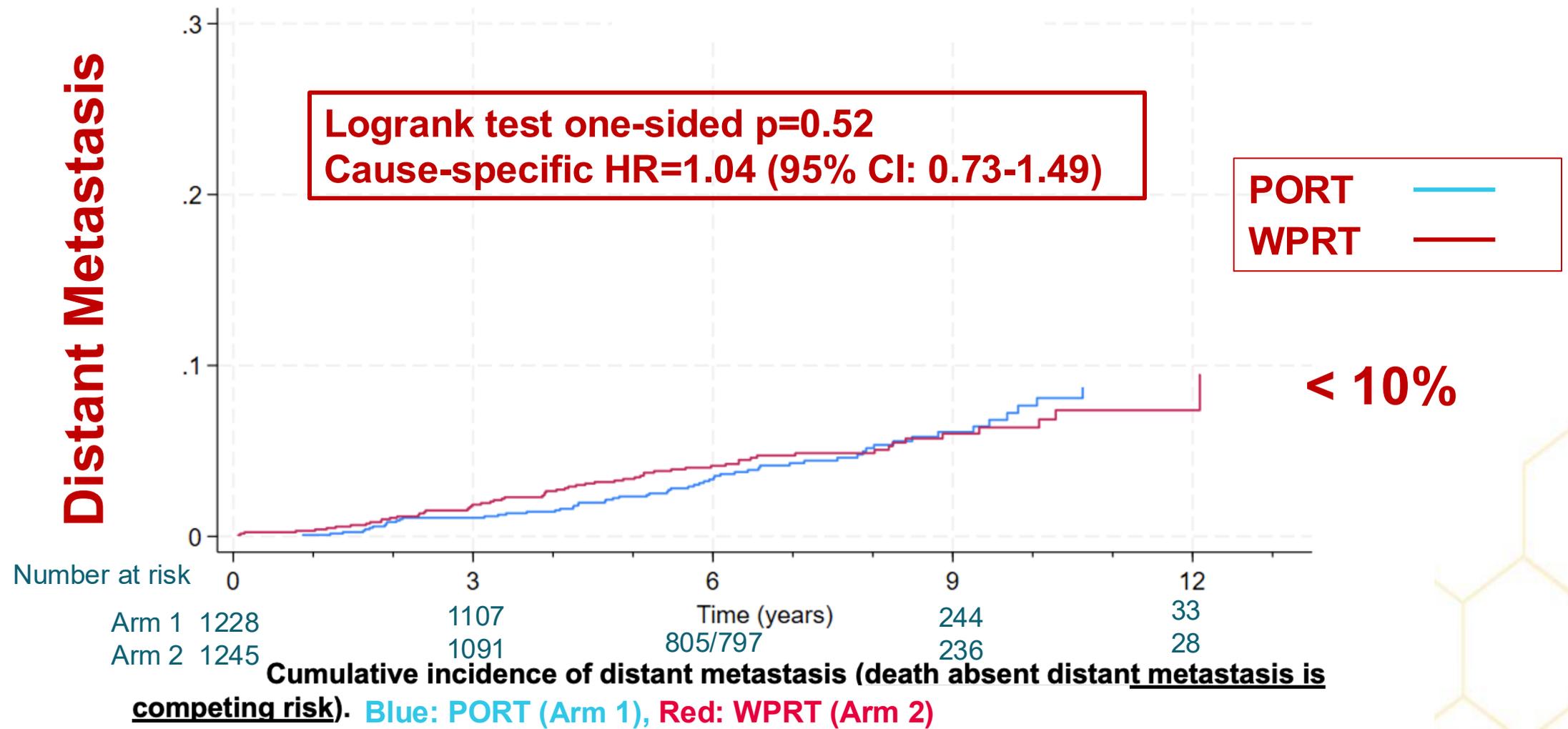
Prostate Cancer Specific Death



Cumulative incidence of prostate cancer death (*death from other causes is competing risk*). Blue: PORT (Arm 1), Red: WPRT (Arm 2)

Time-to-event analyses
Competing risks

Distant Metastasis



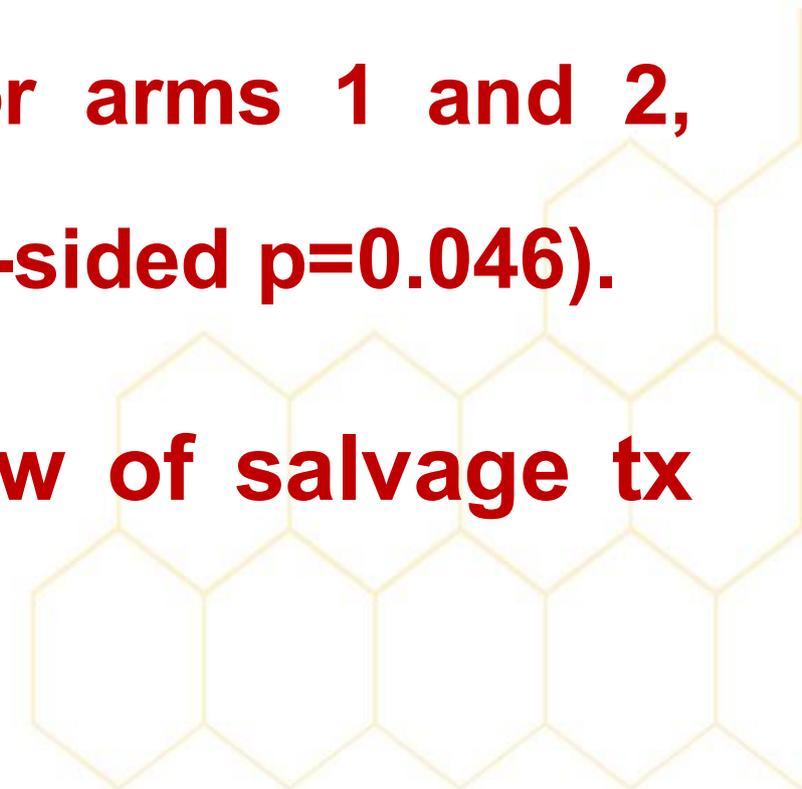


Results (continued):

No difference was noted in the risk of distant metastases (HR=1.04, 95% CI: 0.73-1.49, one-sided p=0.52).

However, the cumulative incidence of biochemical failure (BF) (Phoenix*) at 10 yrs was 17% and 13% for arms 1 and 2, respectively (HR=0.82, 95% CI: 0.65-1.03, one-sided p=0.046).

***Based on current review of salvage tx administration**



Biochemical Failure

10 yr rates 17% & 13%, PORT vs WPRT, respectively,
(Logrank test one-sided p=0.045),
HR=0.82 (95% CI: 0.65-1.03)

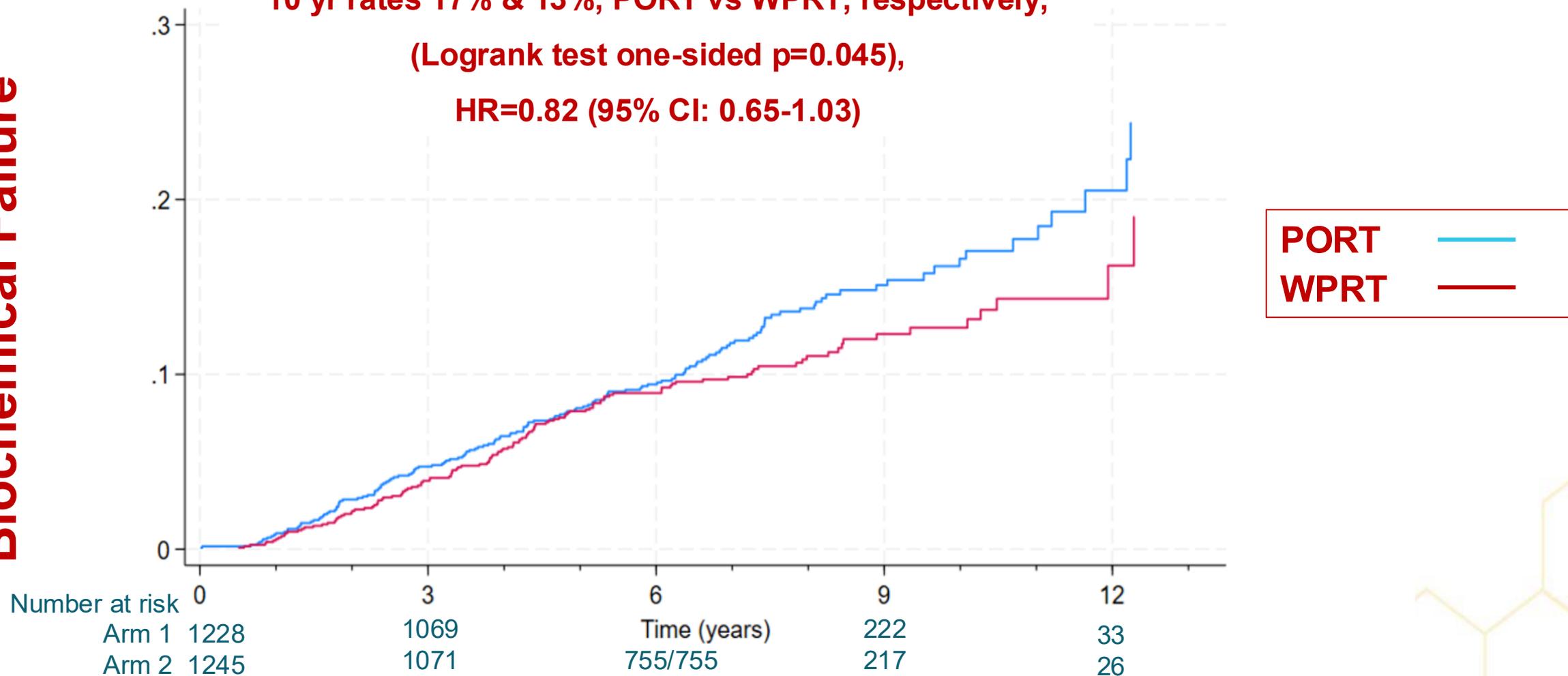


Figure 3 Cumulative incidence of biochemical failure (death absent biochemical failure is competing risk). Blue: PORT (Arm 1), Red: WPRT (Arm 2)

Biochemical Failure by Risk Group: Unfavorable Intermediate (UIR) vs Favorable High Risk (FHR)

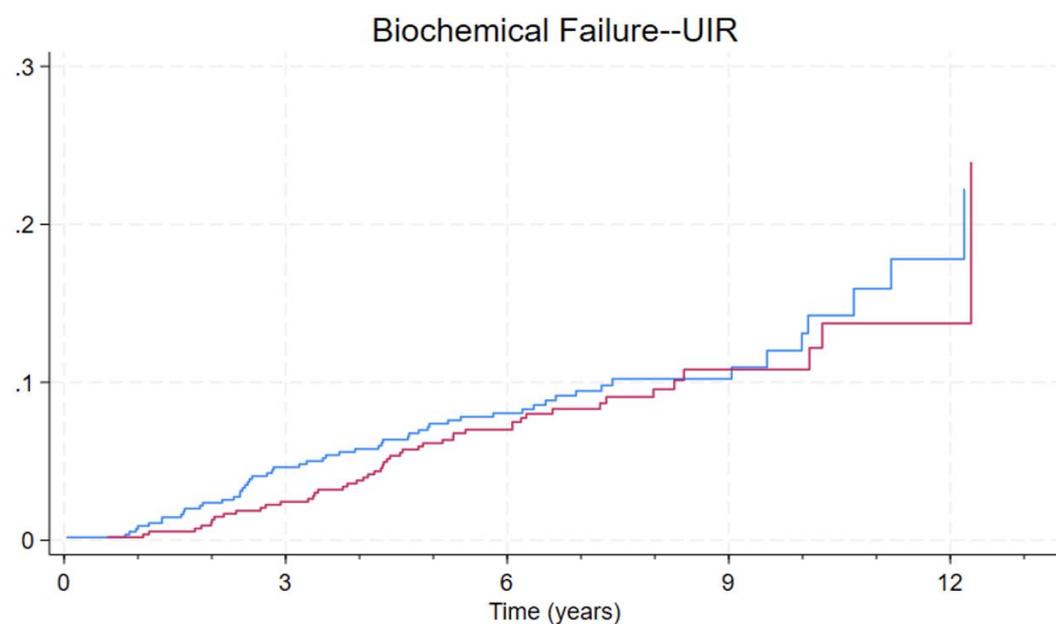


Figure 3 Cumulative incidence of biochemical failure (death absent biochemical failure is competing risk). Blue: Arm 1, Red: Arm 2

Cause-specific logrank test $1p=0.30$

Cause-specific HR=0.90 (95% CI: 0.61-1.32), $1p=0.30$

Fine-Gray SHR=0.88 (95% CI: 0.60-1.29), $p=0.26$

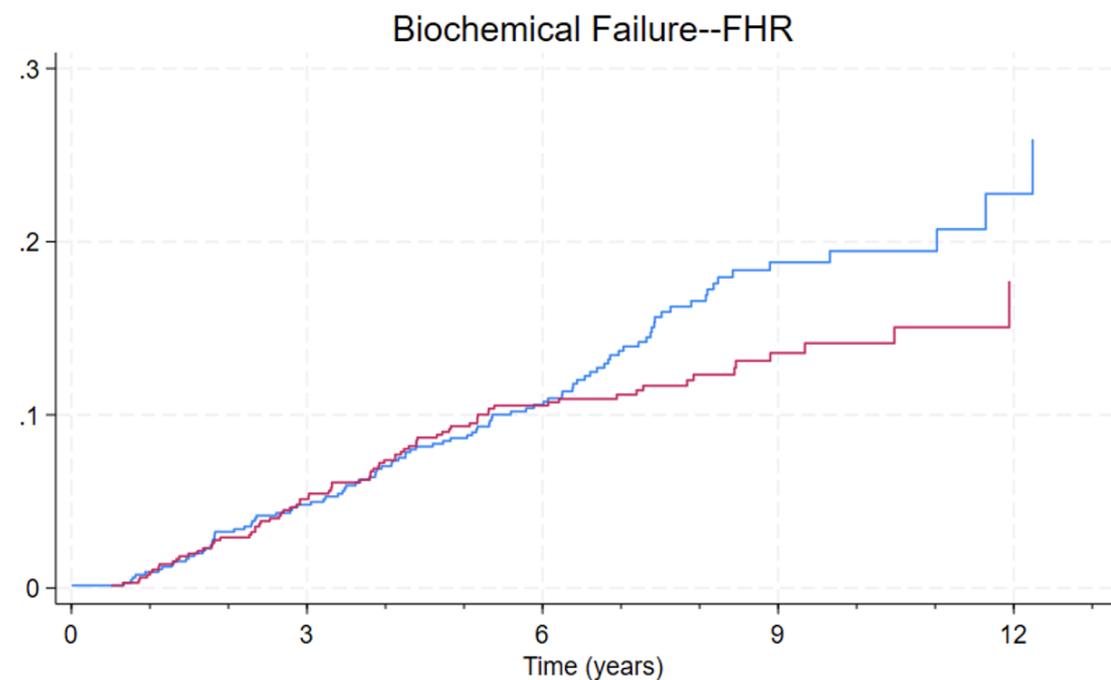


Figure 3 Cumulative incidence of biochemical failure (death absent biochemical failure is competing risk). Blue: Arm 1, Red: Arm 2

Cause-specific logrank test $1p=0.039$

Cause-specific HR=0.77 (95% CI: 0.57-1.03), $1p=0.039$

Fine-Gray SHR=0.78 (95% CI: 0.58-1.05), $1p=0.051$



Results (continued):

Gastrointestinal grade ≥ 2 (CTCAE version 4) adverse event rate:

- **18.1% vs 22.1% for PORT vs WPRT arm (p=0.0085, one-sided).**

However, there was no difference in grade ≥ 3 GI adverse events:

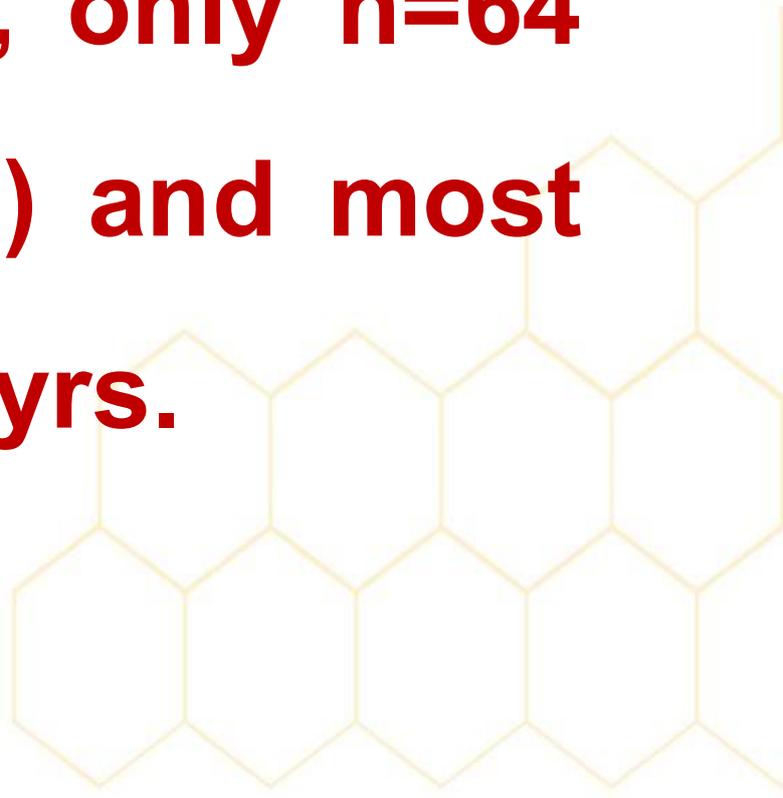
- **3.4% vs 3.3% for PORT vs WPRT arm.**

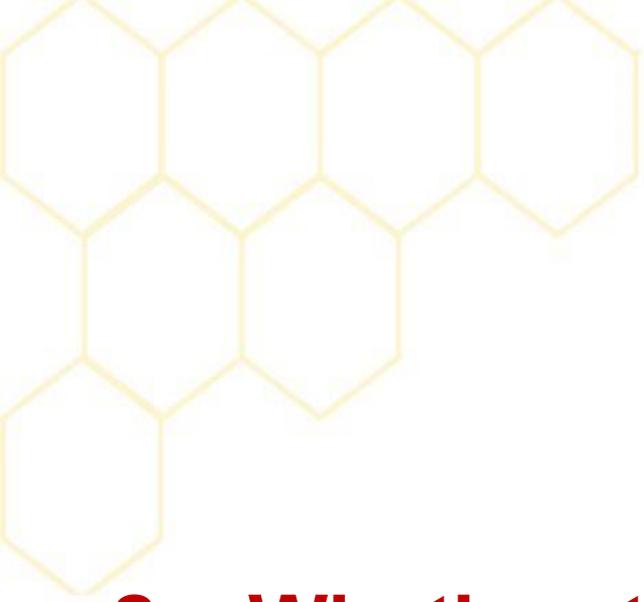
The rate of grade ≥ 2 and ≥ 3 urinary frequency was 25.3% and 0.5% with PORT, respectively, vs 27.2% and 0.7% with WPRT.



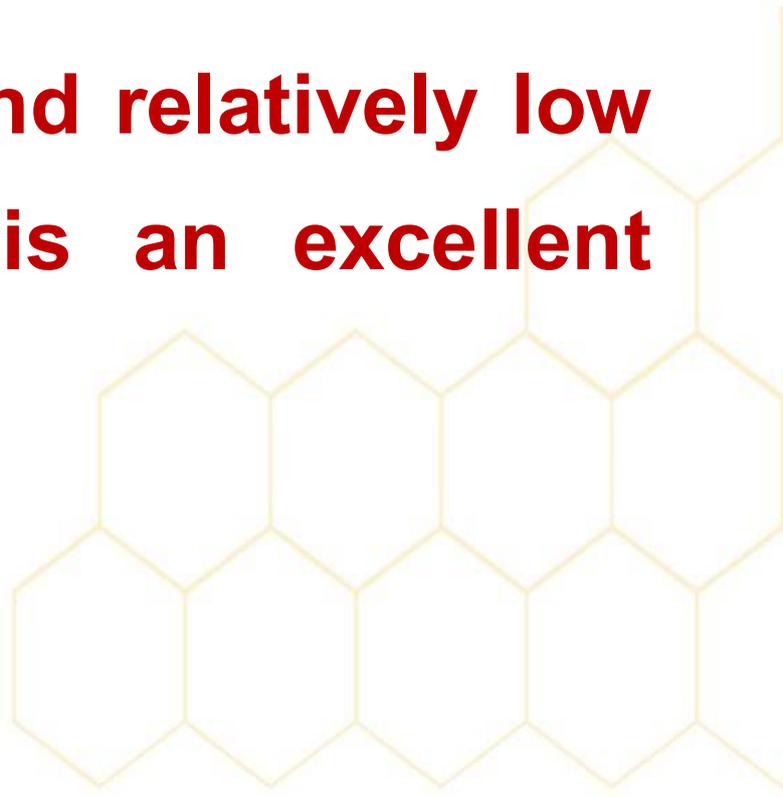


Conclusions:

- 1. At 10 yrs, WPRT did *not* appear to improve OS for UIR or FHR PC. However, follow-up is relatively short (med 7.3 yrs, only n=64 (~2.5% of enrollment) at 12 yrs) and most PC related deaths expected >10 yrs.**
- 



Conclusions:

- 2. Whether the early modest trends in BF will translate into differences in PCs and ultimately OS remains to be seen.**
 - 3. Future studies incorporating biomarkers may help identify subsets of pts who might benefit from WPRT.**
 - 4. The high prostate cancer survival rates and relatively low morbidity confirms that ADT + PORT is an excellent treatment option for UIR or FHR PC.**
- 



**“Thou shalt not declare a trial “negative”,
before it’s time!”**

According to the gospel of Roach

(e.g., PIVOT; RTOG 8531; ...)



Pelvic Regional Control With 25Gy in 5 Fractions in Stereotactic Radiation Therapy for High-Risk Prostate Cancer: Pooled Prospective Outcomes From the SHARP Consortium

***Purpose:* ... efficacy of 25Gy in 5 fractions ... nodal irradiation ... during ... (SBRT) for high-risk prostate cancer.**

***Methods and Materials:* ... multinational SHARP consortium ... treated with curative-intent prostate SBRT for high-risk prostate cancer was queried ... Phoenix-defined biochemical failure and location of recurrence (local, regional, or distant) were extracted. Five-year bio-chemical failure-free survival (BFFS), metastasis-free survival, and overall survival ... Impact of potential prognostic factors (tumor stage, grade group [GG], ... dose, and ... (ADT) duration) was analyzed ...**

Pelvic Regional Control With 25Gy in 5 Fractions in Stereotactic Radiation Therapy for High-Risk Prostate Cancer: Pooled Prospective Outcomes From the SHARP Consortium

***Results:* ... 171 patients ... Two-thirds ... had GG 4-5 cancer. Prostate was irradiated to 40Gy/5# in 51.5% of the cohort, where as the rest received 35 to 36.25 Gy/5#.**

Median ADT duration was 15 months ... Overall median follow-up of 51 months, biochemical failure was ... (11.1%) ... Restaging with ... (PSMA)-Positron Emission Tomography (PETCT) showed recurrence within the pelvic nodes in 3 patients ... Overall pelvic control was 98.2% ...

***Conclusions:* For high-risk prostate cancer treated with SBRT, prophylactic pelvic nodal irradiation with 25Gy/5# achieved near universal regional control.**

**“You can fool all the people some of the time
and some of the people all of the time,
but you can’t fool all the people all the time.”**

Abraham Lincoln

CLINICAL INVESTIGATION

Pelvic Regional Control With 25Gy in 5 Fractions in Stereotactic Radiation Therapy for High-Risk Prostate Cancer: Pooled Prospective Outcomes From the SHARP Consortium

My critique: “a short cut ... pursued by the young investigators”

- 1. Does WPRT really work?**
- 2. What was the incidence of occult + nodes**
- 3. What should be the duration of follow-up be (status of Testosterone)?**
- 4. How accurate was the assessment?**
 - a) Med duration ADT 15 mos (longer for HR (Nabid et al))**
 - b) Pattern of failure 84% PET**
 - c) 10% distant mets**
- 5. My conclusions:**
 - a) Showed that 500 x 5 is reasonably well tolerated.**
 - b) The value of WPRT remains to be proven.**
 - c) Follow-up is too short.**

Regarding the “PSMA PET era” (in the meantime I recommend):

- 1. Treat all PET + nodes (SIB to ~60 Gy) and prophylactic WPRT in high risk patients.**
- 2. SBRT only to avoid previously irradiated fields, otherwise I use extended nodal RT.**
- 3. Avoid prophylactic WPRT in most intermediate risk patients**



**"Not everything that counts can be counted,
and not everything that can be counted counts."**

Albert Einstein

(Sign in his office at Princeton)

"Count what you can count and hope that it counts!"

Mack Roach III

