Biomarkers vs Conventional Approaches: How these tools can help the management of biochemical recurrence?

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What is Treatment Failure after Radical Prostatectomy:

Defining Surgery Failure:

PSA > 0.6 ng/ml (Wash U 1994)

vs

> 0.4 ng/ml (UCLA 1992)

vs

> 0.2 ng/ml (Hopkins 1993)

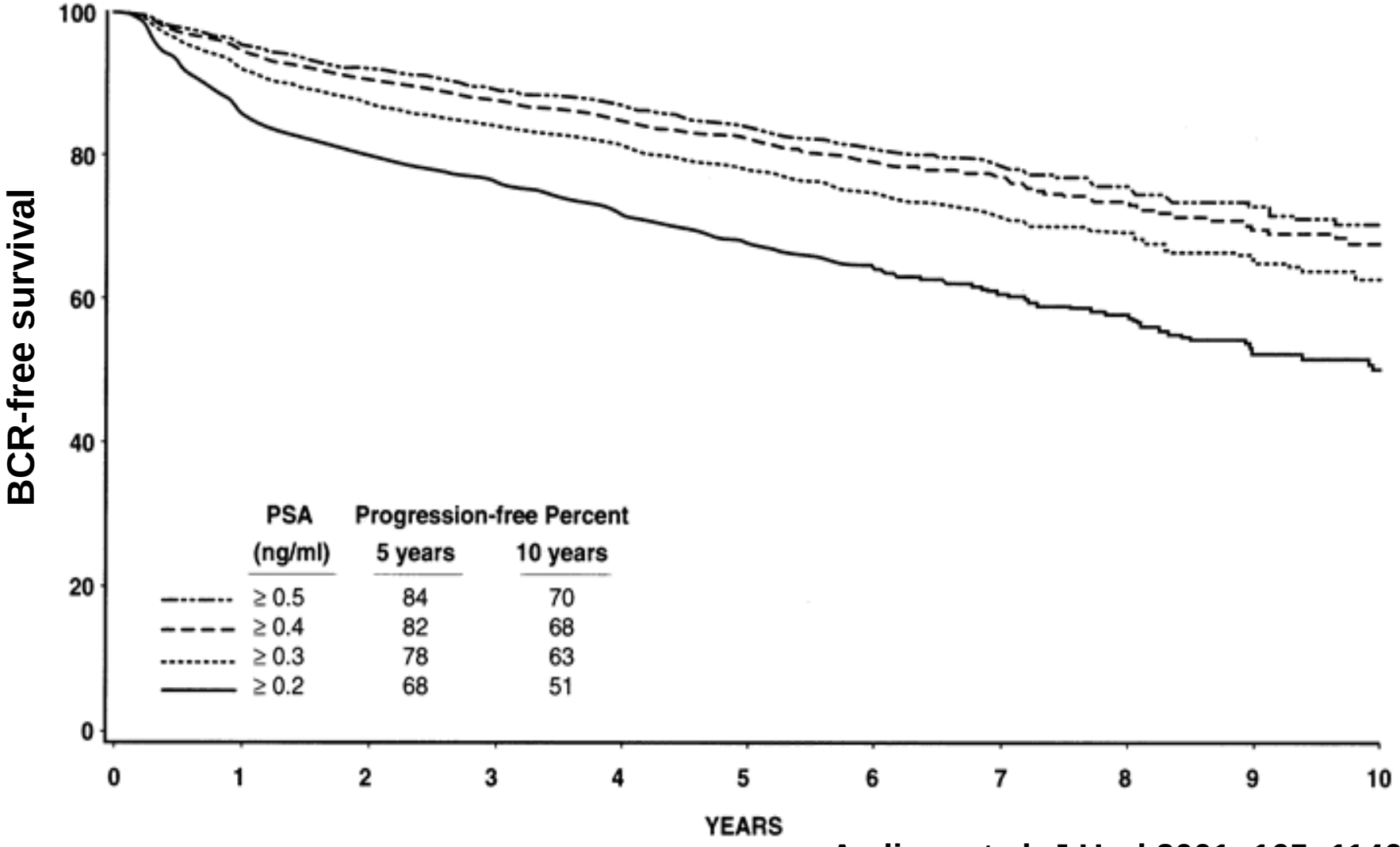
vs

= 0.1 ng/ml (UCSF 1995)

vs

"Ultra-sensitive" < 0.1 (Stanford 1995)

- Organ confined, pT2



Amling, et al. J Urol 2001; 165: 1146.

Post-Operative Radiotherapy (P-XRT) After Radical Prostatectomy (Px) Improves Progression-Free Survival (PFS) in pT3 Prostate Cancer (PC) (EORTC 22911)

Bolla et al. Lancet 366: 572-78, 2005

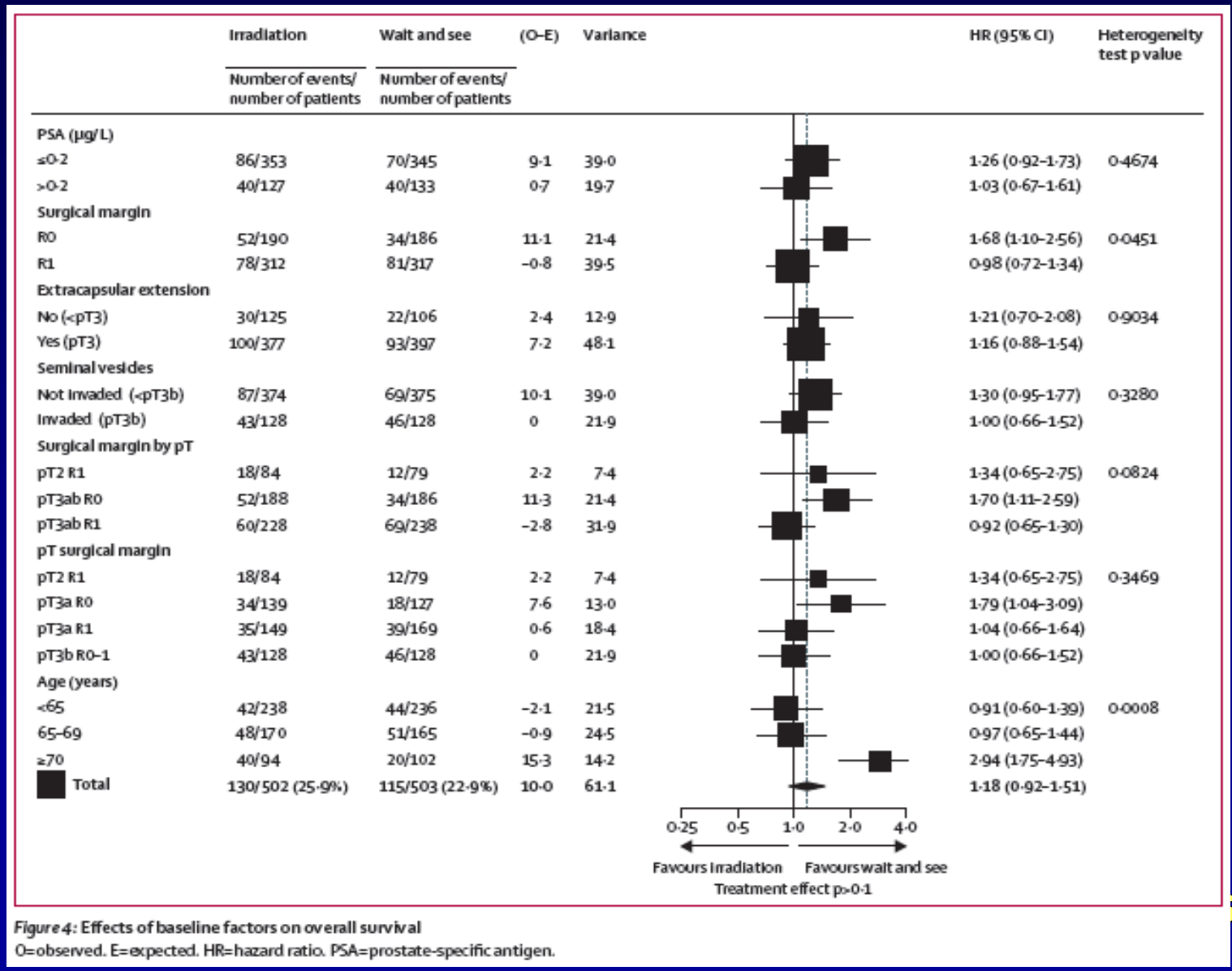
- **Phase III Trial initiated in 1992, N = 1005, eligibility:**
  - **–T3, pN0M0 with Cap pen., + margins, invas. SV**
  - **–Age < 76 years, WHO 0 or 1**
  - – 60 Gy (non-3D @ iso.) bed (SV to apex) ≤16 wks of RP
  - – Salvage dose in wait-and-see 70 Gy in most (some LHRH)

5-year estimates (median=5 yrs):

Relapse-free survival*	**74% vs 52%**	**p < 0.0001**
Clinical progression-free surv	**85% vs 75%**	**p = 0.0009**
Late grade 3**	**4.6 vs 2.6%**	**p = 0.0726**

Biochemical progression = * Increase > 0.2 ng/ml, **NS diff incont.

Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long term results of a randomised controlled trial (EORTC trial 22911). Bolla et al. Lancet 380: 2018-17, 2012



	Irradiation	Wait and see	(O–E)	Variance	HR (95% CI)	Heterogeneity test p value
	Number of events/ number of patients	Number of events/ number of patients				
PSA (µg/L)						
≤0·2	86/353	70/345	9·1	39·0	1·26 (0·92–1·73)	0·4674
>0·2	40/127	40/133	0·7	19·7	1·03 (0·67–1·61)	
Surgical margin						
R0	52/190	34/186	11·1	21·4	1·68 (1·10–2·56)	0·0451
R1	78/312	81/317	−0·8	39·5	0·98 (0·72–1·34)	
Extracapsular extension						
No (<pT3)	30/125	22/106	2·4	12·9	1·21 (0·70–2·08)	0·9034
Yes (pT3)	100/377	93/397	7·2	48·1	1·16 (0·88–1·54)	
Seminal vesicles						
Not invaded (<pT3b)	87/374	69/375	10·1	39·0	1·30 (0·95–1·77)	0·3280
Invaded (pT3b)	43/128	46/128	0	21·9	1·00 (0·66–1·52)	
Surgical margin by pT						
pT2 R1	18/84	12/79	2·2	7·4	1·34 (0·65–2·75)	0·0824
pT3ab R0	52/188	34/186	11·3	21·4	1·70 (1·11–2·59)	
pT3ab R1	60/228	69/238	−2·8	31·9	0·92 (0·65–1·30)	
pT surgical margin						
pT2 R1	18/84	12/79	2·2	7·4	1·34 (0·65–2·75)	0·3469
pT3a R0	34/139	18/127	7·6	13·0	1·79 (1·04–3·09)	
pT3a R1	35/149	39/169	0·6	18·4	1·04 (0·66–1·64)	
pT3b R0–1	43/128	46/128	0	21·9	1·00 (0·66–1·52)	
Age (years)						
<65	42/238	44/236	−2·1	21·5	0·91 (0·60–1·39)	0·0008
65–69	48/170	51/165	−0·9	24·5	0·97 (0·65–1·44)	
≥70	40/94	20/102	15·3	14·2	2·94 (1·75–4·93)	
Total	130/502 (25·9%)	115/503 (22·9%)	10·0	61·1	1·18 (0·92–1·51)	

Figure 4: Effects of baseline factors on overall survival
O=observed. E=expected. HR=hazard ratio. PSA=prostate-specific antigen.

Adjuvant Radiotherapy for Pathological T3N0M0 Prostate Cancer Significantly Reduces Risk of Metastases and Improves Survival: Long-Term Followup of a Randomized Clinical Trial. Thompson et al. J Urol 181: 956-62, 2009

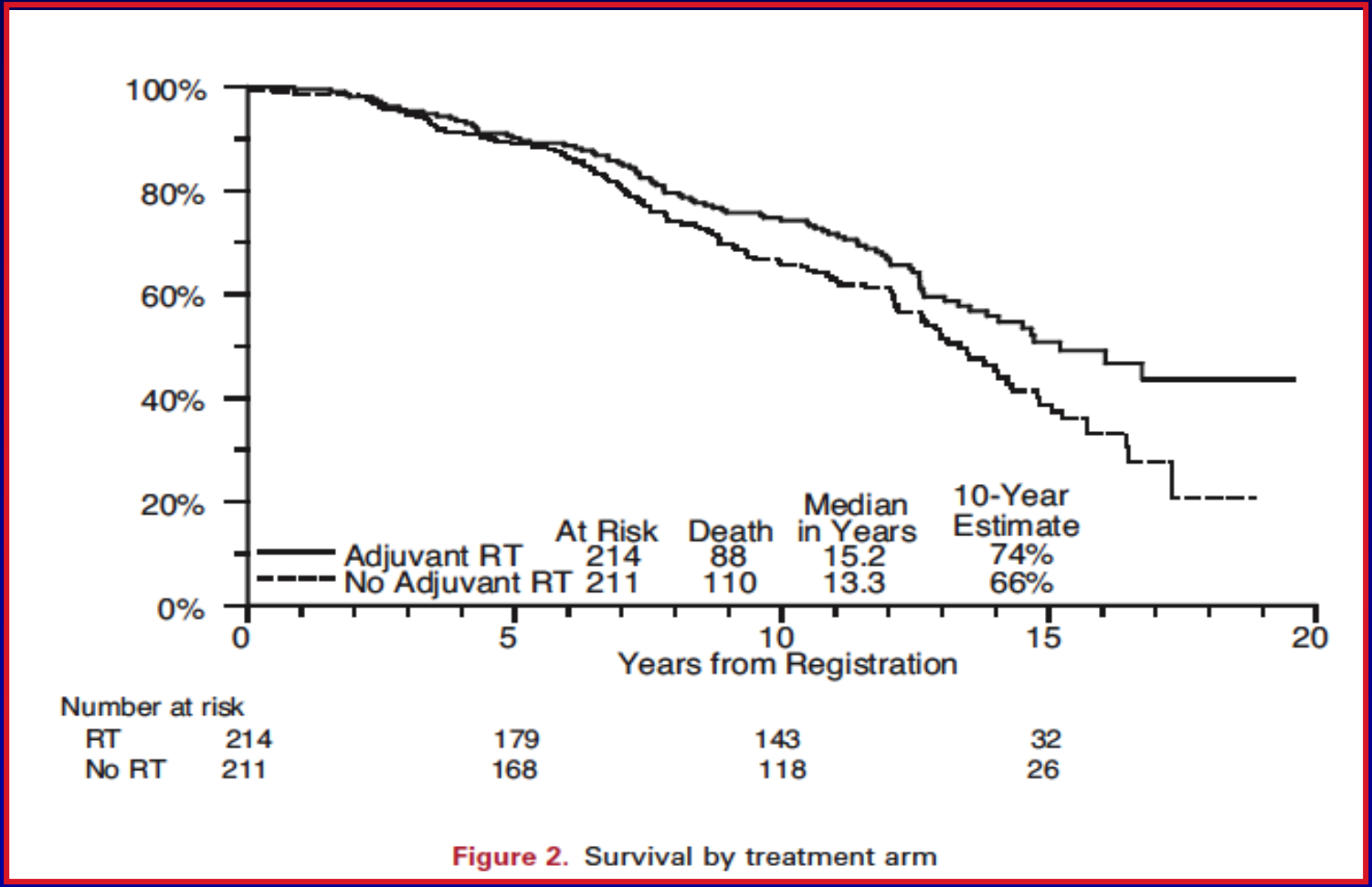


Figure 2. Survival by treatment arm

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Adjuvant Radiotherapy for Pathological T3N0M0 Prostate Cancer Significantly Reduces Risk of Metastases and Improves Survival: Long-Term Followup of a Randomized Clinical Trial. Thompson et al. J Urol 181: 956-62, 2009

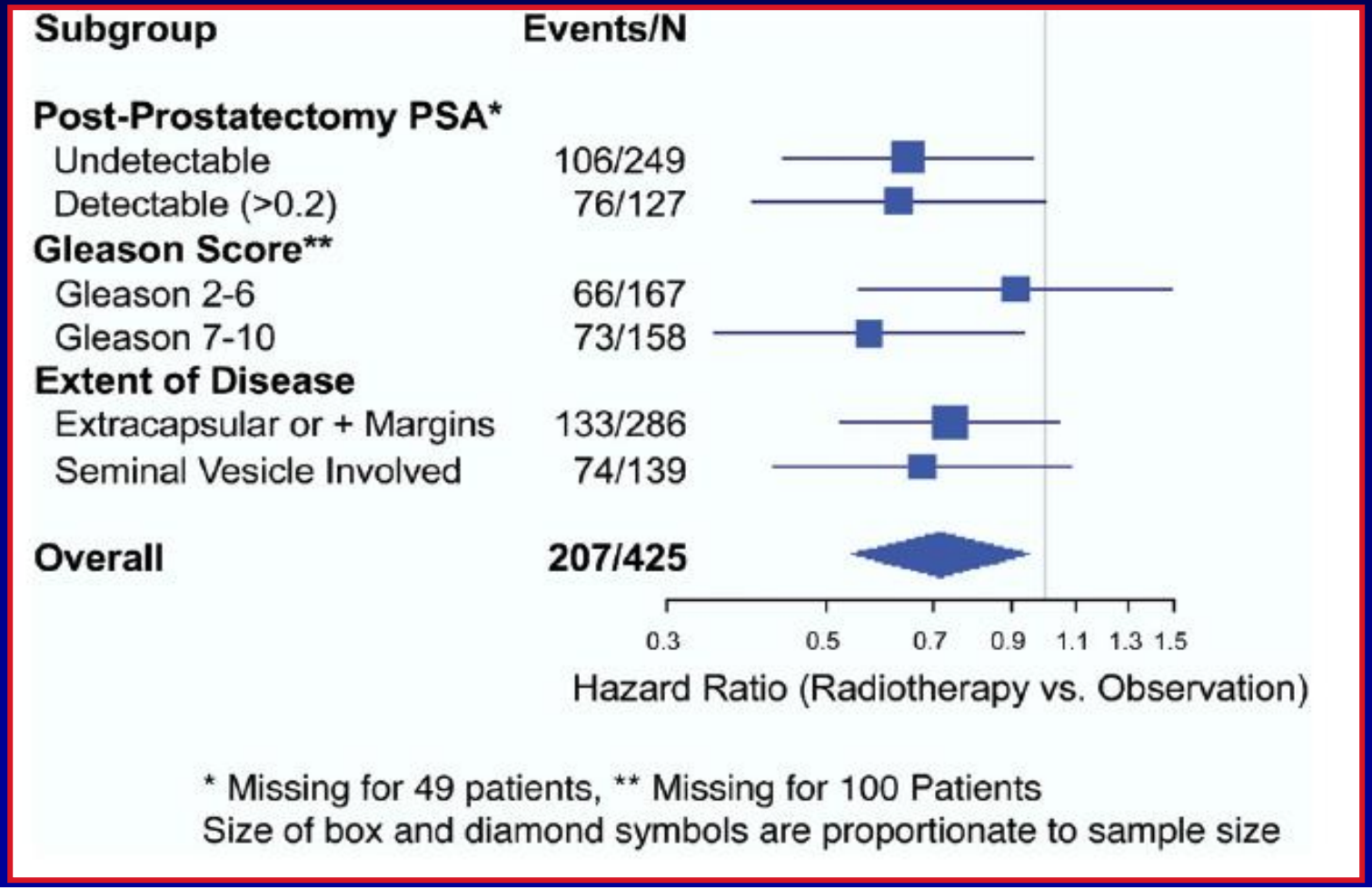

Figure 3. Metastasis-free survival HR estimates and corresponding 95% CI for subsets of patients based on baseline risk factors

Purpose: Discuss the Status of Post Operative Radiotherapy for Localized Prostate Cancer:

- **When?**
  - **Salvage**
  - **Adjuvant**
  - **Salvage vs Adjuvant?**

Predominant Treatment Failure in Prostatectomy Patients Is Local: Analysis of Patterns of Treatment Failure in SWOG 8794

Swanson et al. JCO 25: 2225-2229, 2007

70% @ ~2 yrs vs 8 yrs

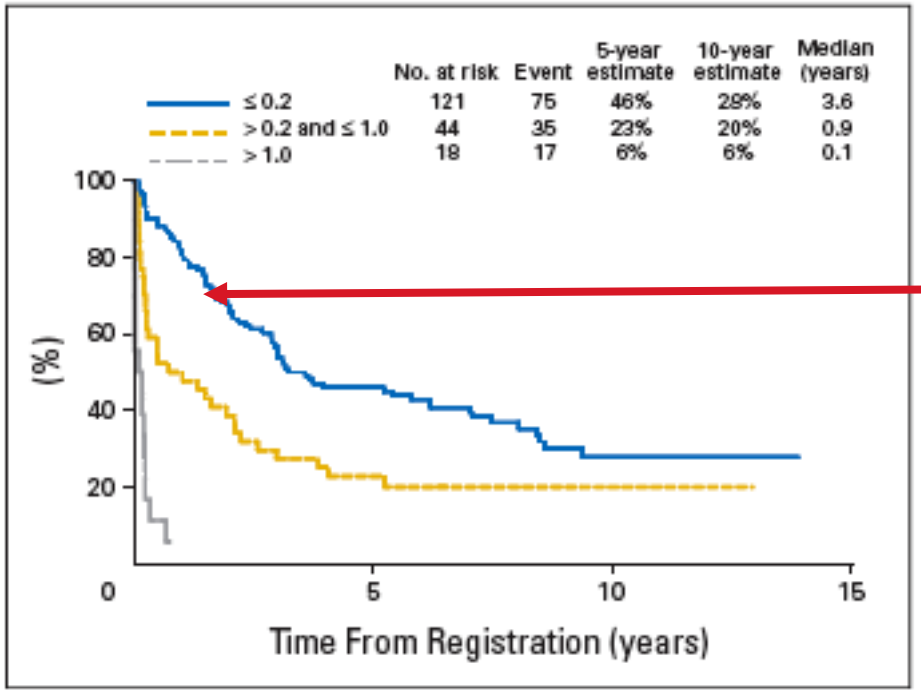

Fig 1. Kaplan-Meier estimates of freedom from prostate-specific (PSA) failure by postprostatectomy PSA subgroup in patients randomly assigned to observation. Median time to PSA failure given in years.

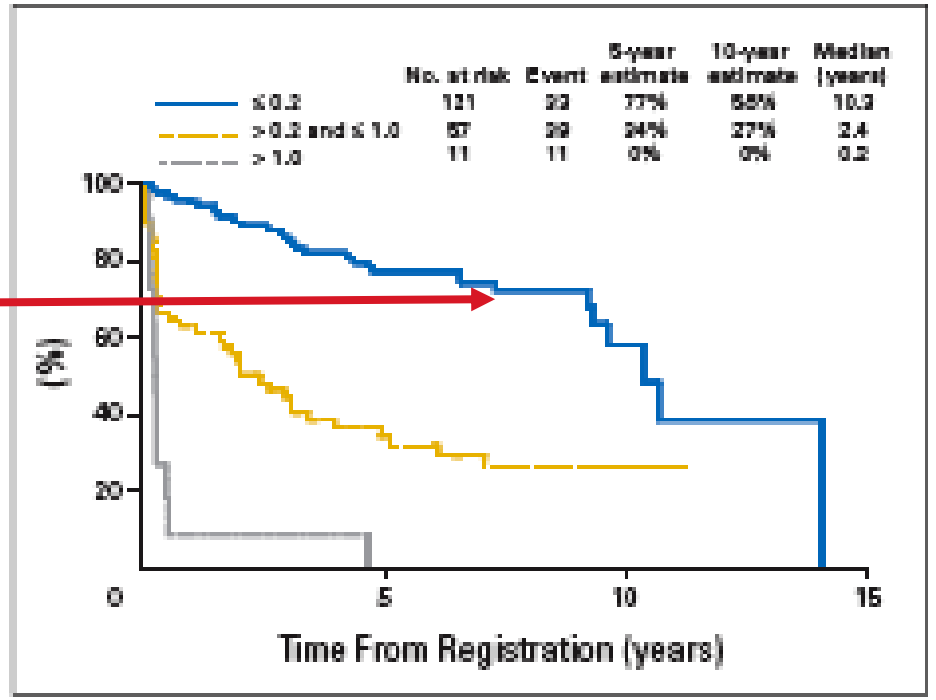

Fig 2. Kaplan-Meier estimates of freedom from prostate-specific antigen (PSA) failure by postprostatectomy PSA subgroup in patients randomly assigned to adjuvant radiotherapy. Median time to PSA failure given in years.

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Predominant Treatment Failure in Prostatectomy Patients Is Local: Analysis of Patterns of Treatment Failure in SWOG 8794 Swanson et al. JCO 25: 2225-2229, 2007

Table 2. PSA Failure-Free Rates by Post-RP PSA Subgroup Among Patients Who Received Immediate or Delayed Radiation

Post-RP PSA (ng/mL)	No. of Patients	5-Year PSA Failure-Free Rate (%)
≤ 0.2		
Immediate XRT	122	77*
XRT at failure	34	38†
> 0.2 and ≤ 1.0		
Immediate XRT	57	34*
XRT at failure	17	18†

Abbreviations: RP, radical prostatectomy; PSA, prostate-specific antigen; XRT, radiation therapy.

*Time to PSA failure = registration date to date of first PSA ≥ 0.4 ng/mL.

†Time to PSA failure = date of initiation of salvage RT to first subsequent date of PSA ≥ 0.4 ng/mL.

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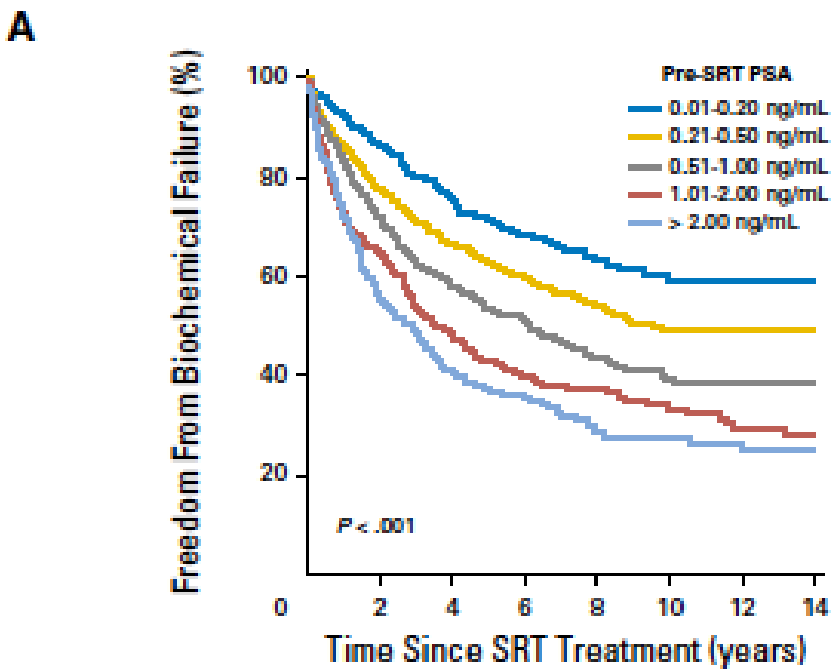
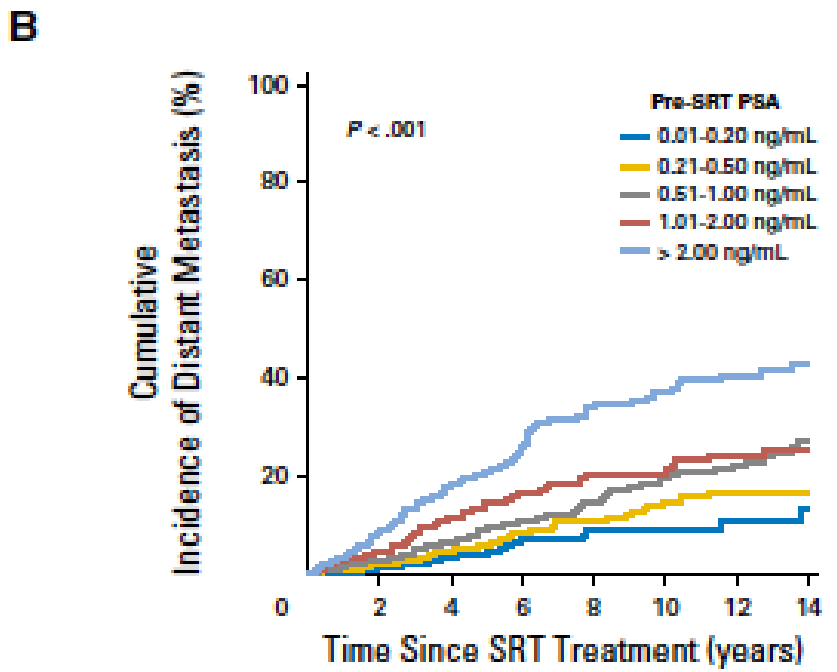
ORIGINAL REPORT

Contemporary Update of a Multi-Institutional Predictive Nomogram for Salvage Radiotherapy After Radical Prostatectomy. Tendulkar et al. JCO 2016



No. at risk by pre-SRT PSA								
0.01-0.20 ng/mL	441	283	168	108	62	41	23	15
0.21-0.50 ng/mL	822	513	339	203	121	65	34	14
0.51-1.00 ng/mL	533	314	203	138	82	51	32	22
1.01-2.00 ng/mL	341	184	112	70	47	30	20	11
> 2.00 ng/mL	323	145	83	53	26	19	14	5



No. at risk by pre-SRT PSA								
0.01-0.20 ng/mL	441	318	202	137	87	60	32	21
0.21-0.50 ng/mL	822	636	462	304	201	109	55	23
0.51-1.00 ng/mL	533	419	319	238	162	110	75	41
1.01-2.00 ng/mL	341	272	210	148	102	71	54	36
> 2.00 ng/mL	323	234	167	120	75	57	40	22

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RTOG 96-01 Schema

RANDOMIZE

Arm 1 → **RT (64.8 Gy) plus AAT*** **Bicalutamide 150 mg QD****

Arm 2 → **RT (64.8 Gy) plus placebo QD****

Protocol Eligibility

pT3 pN0 or pT2 pN0 with positive margins

An elevated PSA no higher than 4.0 ng/ml

Abdominal / pelvic CT & bone scan negative

* AAT = Anti – Androgen Therapy

** During and after RT for 24 months

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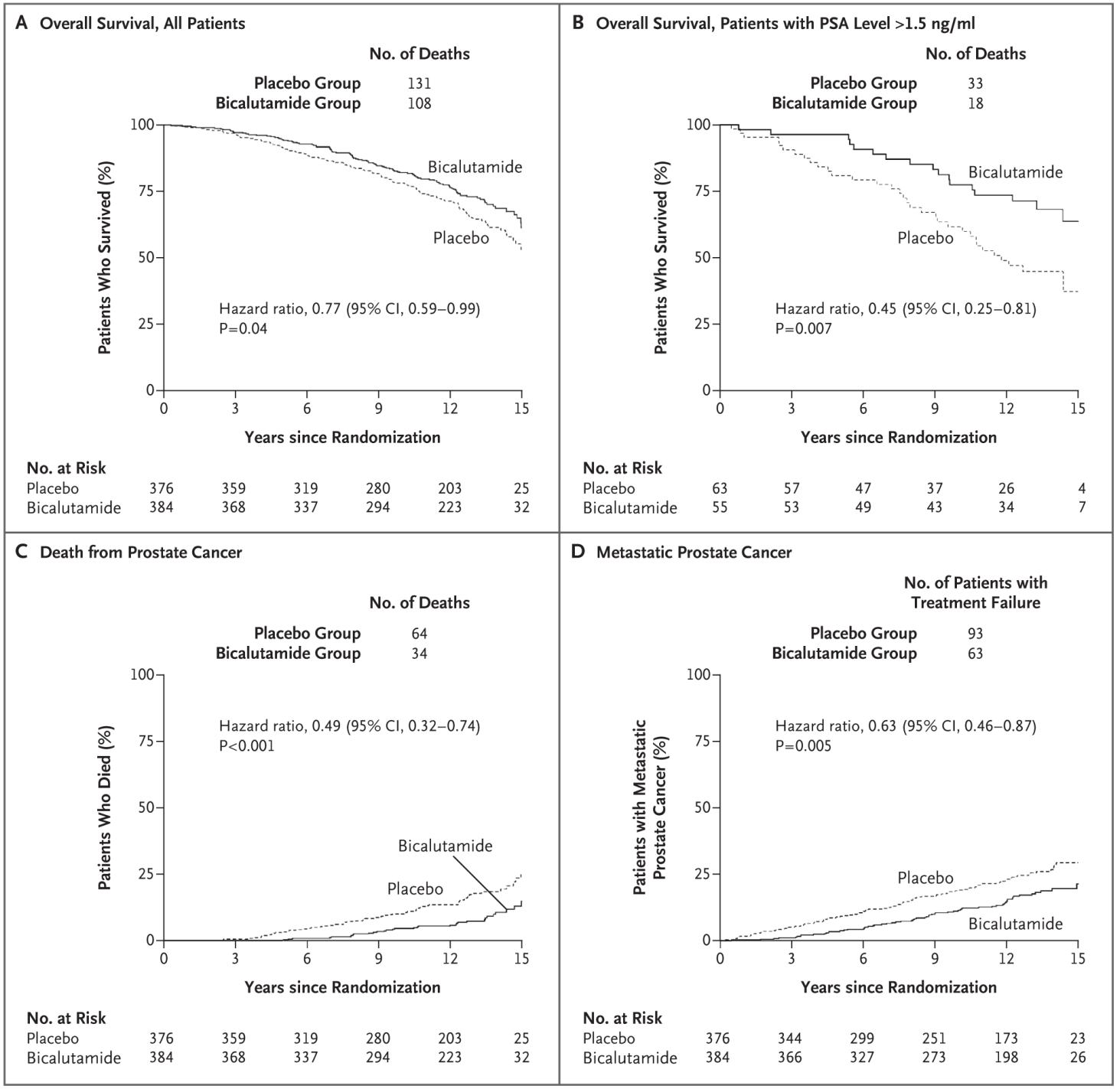
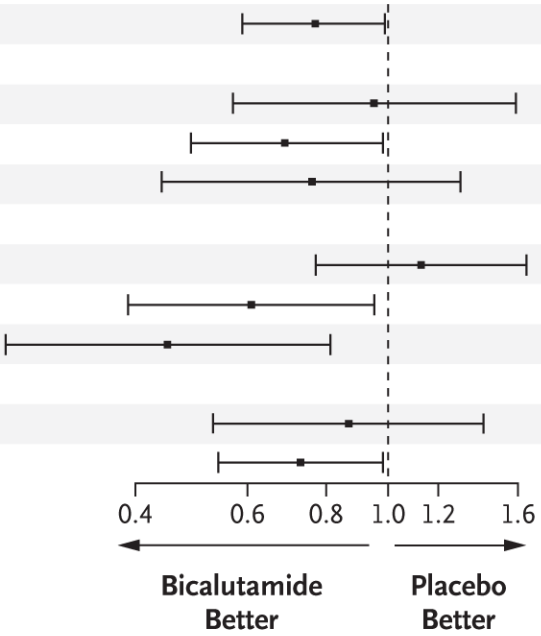

A Overall Survival, All Patients
No. of Deaths
Placebo Group 131
Bicalutamide Group 108
Patients Who Survived (%)
100
75
50
25
0
Bicalutamide
Placebo
Hazard ratio, 0.77 (95% CI, 0.59–0.99)
P=0.04
0 3 6 9 12 15
Years since Randomization
No. at Risk
Placebo 376 359 319 280 203 25
Bicalutamide 384 368 337 294 223 32
B Overall Survival, Patients with PSA Level >1.5 ng/ml
No. of Deaths
Placebo Group 33
Bicalutamide Group 18
Patients Who Survived (%)
Bicalutamide
Placebo
Hazard ratio, 0.45 (95% CI, 0.25–0.81)
P=0.007
Years since Randomization
No. at Risk
Placebo 63 57 47 37 26 4
Bicalutamide 55 53 49 43 34 7
C Death from Prostate Cancer
No. of Deaths
Placebo Group 64
Bicalutamide Group 34
Patients Who Died (%)
Hazard ratio, 0.49 (95% CI, 0.32–0.74)
P<0.001
Bicalutamide
Placebo
Years since Randomization
No. at Risk
Placebo 376 359 319 280 203 25
Bicalutamide 384 368 337 294 223 32
D Metastatic Prostate Cancer
No. of Patients with Treatment Failure
Placebo Group 93
Bicalutamide Group 63
Patients with Metastatic Prostate Cancer (%)
Hazard ratio, 0.63 (95% CI, 0.46–0.87)
P=0.005
Placebo
Bicalutamide
Years since Randomization
No. at Risk
Placebo 376 344 299 251 173 23
Bicalutamide 384 366 327 273 198 26

Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer Shipley et al. NEJM 2017

Subgroup	No. of Patients (%)	Bicalutamide Group	Placebo Group	Hazard Ratio (95% CI)	P Value
		12-yr overall survival rate (%)			
Overall	760 (100.0)	76.3	71.3	0.77 (0.59–0.99)	0.04
Gleason score					
2–6	214 (28.2)	79.5	79.2	0.95 (0.57–1.59)	0.84
7	413 (54.5)	78.5	70.9	0.69 (0.49–0.98)	0.04
8–10	131 (17.3)	63.9	58.4	0.76 (0.44–1.30)	0.32
PSA level at trial entry					
<0.7 ng/ml	405 (53.3)	76.8	80.7	1.13 (0.77–1.65)	0.53
0.7–1.5 ng/ml	237 (31.2)	77.0	67.5	0.61 (0.39–0.95)	0.03
>1.5 ngl/ml	118 (15.5)	73.5	48.9	0.45 (0.25–0.81)	0.007
Positive surgical margin					
No	191 (25.1)	73.5	72.9	0.87 (0.53–1.41)	0.56
Yes	569 (74.9)	77.3	70.7	0.73 (0.54–0.98)	0.04



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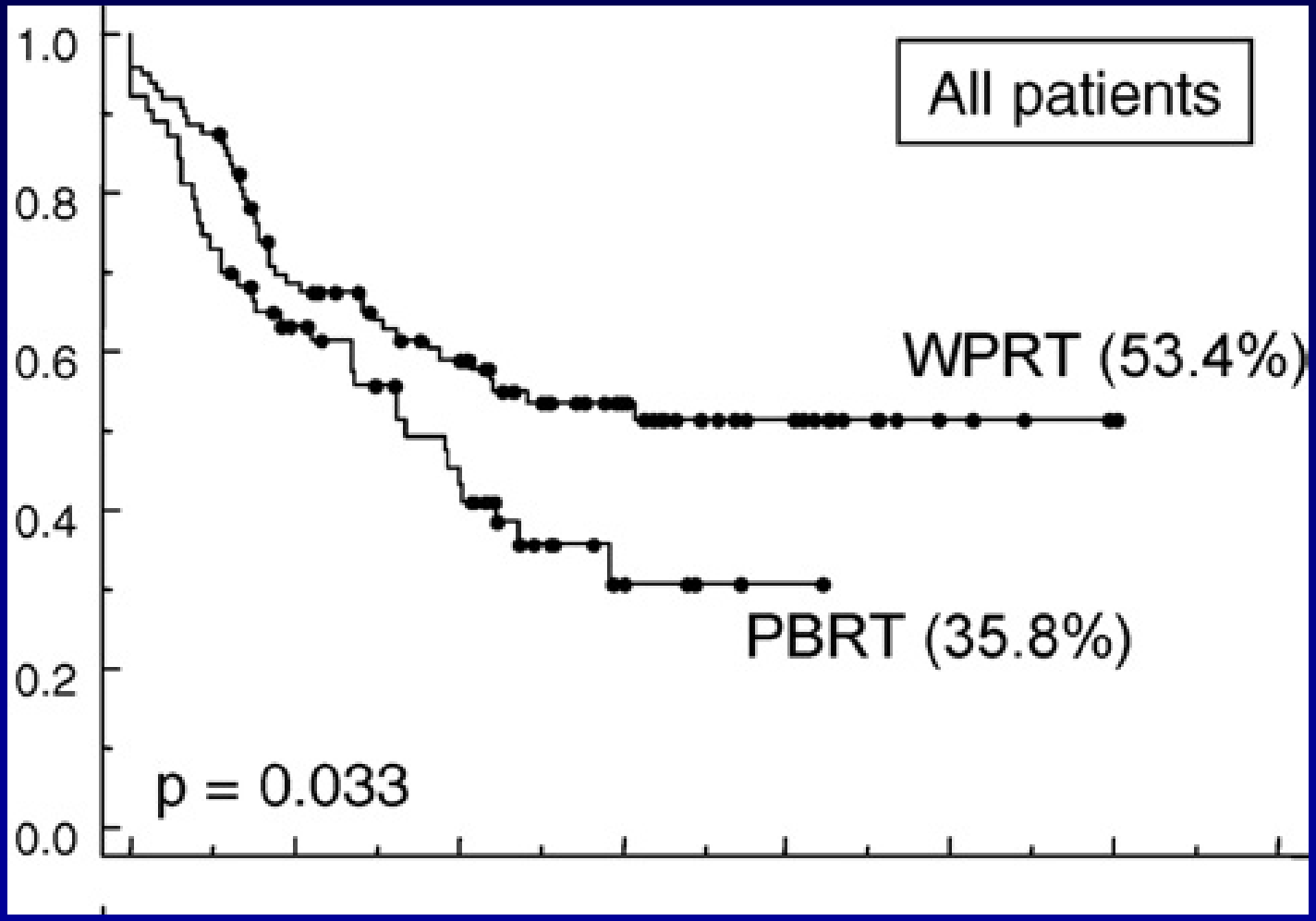
Purpose: Discuss the Status of Post Operative Radiotherapy for Localized Prostate Cancer:

- **What?**
  - **Pelvic +/- Para-aortic Nodes**
  - **Anastomosis**

RADIOTHERAPY AFTER PROSTATECTOMY: IMPROVED BIOCHEMICAL RELAPSE-FREE SURVIVAL WITH WHOLE PELVIC COMPARED WITH PROSTATE BED ONLY HIGH-RISK PATIENTS

Spiotto et al. IJROBP 2007



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A PHASE III TRIAL OF PBRT ALONE VS PBRT+STAD VS WPRT+STAD FOR PATIENTS WITH A RISING PSA AFTER RADICAL PROSTATECTOMY (RTOG)

S	SV Involvement	R	Arm 1: PBRT Alone
	1. No	A	PBRT 64.8 – 70.2 Gy
T	2. Yes		
		N	vs
	Prostatectomy Gleason score		
R	1. Gleason ≤7	D	Arm II: PBRT+ STAD
	2. Gleason 8-10		PBRT 64.8 – 70.2 Gy +
A		O	STAD for 4 mo, beginning 2 mo pre RT
	Pre-Radiotherapy PSA Level		
T	1. PSA ≤1 ng/ml	M	vs
	2. PSA >1 ng/ml		
I		I	Arm III: WPRT + STAD
	Use of IMRT		WPRT to 45 Gy & PBRT to 64.8 – 70.2 Gy
F	1. No	Z	STAD for 4 mo, beginning 2 mo pre RT
	2. Yes		
Y		E	

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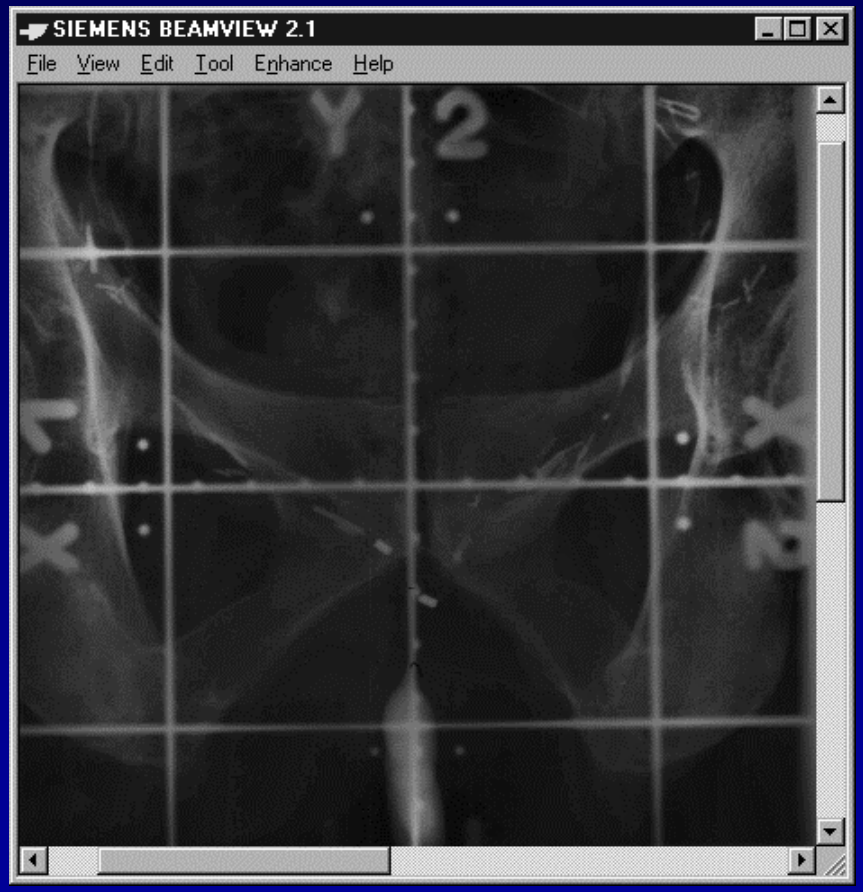
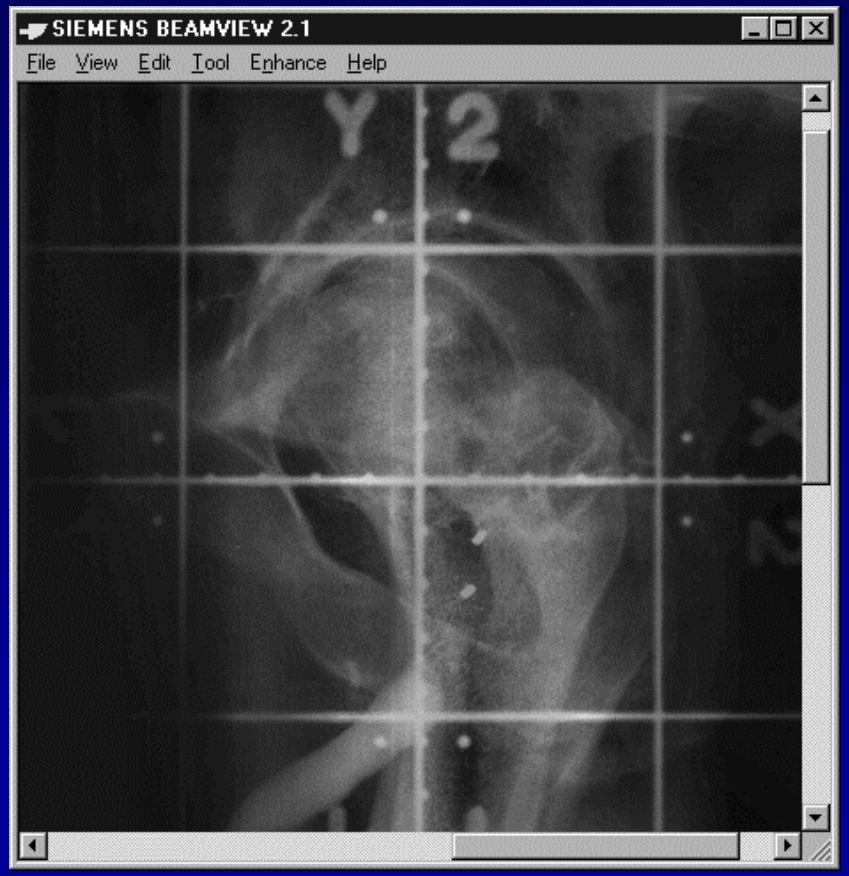
Purpose: Discuss the Status of Post Operative Radiotherapy for Localized Prostate Cancer:

- How (IGRT):
  - Localization of the anatomosis
  - IMRT to nodes
  - Metal density artifacts & Dose calculations
  - Dynamic changes during treatment?

Organ Movement + set-up error In a Post-operative patient?





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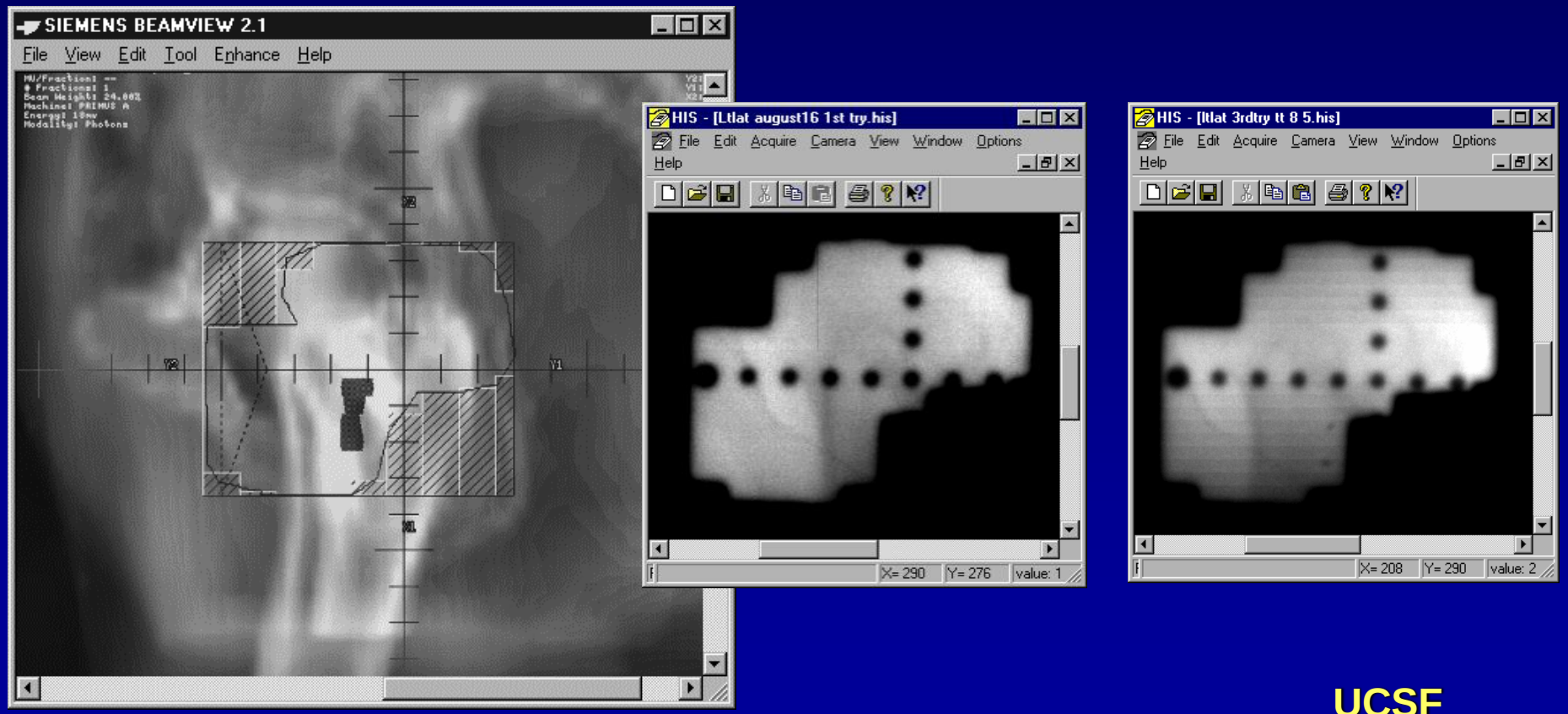
Organ Movement + set-up error?



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Daily Electronic Portal Imaging of Implanted Gold Seed Fiducials in Patients Undergoing Salvage Radiotherapy After Radical Prostatectomy. Schiffner, … and Roach

Total positioning errors (set-up and movement)

Total Fractions (163)	RL	IS	AP
# Shifts Negative	92	77	88
# Shifts Positive	71	86	75
Systematic Error (Mean, mm)	0.2	1.2	-0.3
Standard Deviation (mm)	4.5	5.1	4.5
% Shifts > 5mm	14.1 %	38.7 %	28.2 %
Range	- 16.5 to 22.3	- 9.4 to 12.7	- 11.6 to 9.9

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Why “Taylor” …

- Most Urologist don’t want their pts to get irradiated unless they really “need it” (5% vs 25% vs 50%?)
- … Most patients don’t either
- Many Radiation Oncologist favor error on the side of treatment

	Gen-Probe, Inc	intended use for men who have a suspicion of PCa based on PSA level and/or DRE and/or one or more negative biopsy results	measures the concentration of prostate ca. gene 3 (PCA3) and PSA RNA molecules and calculates the ratio of PCA3 RNA molecules to PSA RNA molecules (PCA3 score) in postdigital rectal examination (DRE) urine specimens	Not relevant to intermediate risk CaP. Weakest test
	NA	the most prevalent form in tumor extracts, which suggests a role for these molecular forms of PSA for the early detection of PCa, and for possibly identifying aggressive PCa	contains a seven amino acid pro leader peptide, is a molecular form of free PSA (fPSA), and is more likely to be associated with PCa has been identified as the most prevalent form in tumor extracts	Not relevant to int risk CaP
	Beckman Coulter, Inc	to distinguish PCa from benign conditions in men ≥ 50 years and PSA between 4 and 10 ng/ml, and in whom the DRE is not suspicious	a mathematical formula of three biomarkers –(p2PSA/fPSA) × PSA1/2	Not relevant to int risk CaP: > PCA3=4K
		used to distinguish between pathologically insignificant and aggressive disease and reduce unnecessary biopsies	A panel of four kallikriens – total PSA, free PSA, intact PSA, and kallikrein-related peptide 2 (hK2), combined to generate the 4K score (without hK2, the other three PSA isoforms are similar to (PHI).	Available 2014 (?) > PCA3=PHI
	Metabolon & Boswick Labs	to aid in the decision for initial or repeat Bx in men with - DRE and modestly elevated PSA	DRE urine test is based on a proprietary metabolic signature … profile improved prediction of organ confinement (AUC from 0.53 to 0.62) and 5-year recurrence (AUC 0.53–0.64)	Like PCA3
	MDxHealth, Inc	to distinguish pts who have a true negative Bx from those who may have occult cancer with a 90% negative predictive value (NPV).	12-core Bx (minimum of 8 cores) … test of epigenetic field effect based on DNA methylation … able to diagnosis PCa in specimens that are otherwise histologically benign because of a 'halo effect'	
	Metamark Genetics	biopsy-based PCa prognostic test	Bx detecting multiple protein biomarkers (n =8) using a fully automated immunofluorescent imaging platform	Available 2014 (?)
	GenomeDx Biosciences	Probability of Mets after surgery (n=2000) validation) 22 RNA biomarkers	Path from RP or Bx, recommendations for post op RT?	Predicts Grade (Gl 4/5), 5 yr mets, 10 yr pros ca. death RP
	Genomic Health (~$4500)	with NCCN risk criteria, GPS improves discrimination of PCa into very low, low and modified int. risk to select candidates for AS	Fixed paraffin-embedded Bx tissue. Measures the expression of 12 cancer-related genes from 4 different pathways … algorithmically combined to calculate the Genomic Prostate Score (GPS)	Used before or after treatment
	Myriad Genetics, Inc (~3400)	low expression is associated with a low risk of disease progression BUT WHETHER ACTIONABLE OR NOT AND HOW IF SO UNDEFINED	fixed paraffin-embedded tissue obtained by Bx or RP, Myriad tests 46 gene expressions, which include 31 cell cycle progression (CCP) genes + 15 housekeeper genes selected because of correlation with proliferation of PCa	Used before or after treatment

Modified from Sartori and Chan (Johns Hopkins) JNCI 2014

JOUNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Genomic Classifier Identifies Man with Adverse Pathology After Radical Prostatectomy Who Benefits from Adjuvant Radiation Therapy. Den et al. JCO, 2015

PURPOSE: To test the hypothesis that a genomic classifier (GC) would predict biochemical failure (BF) & distant metastasis (DM) in men receiving RT after RP.

M & M: Among pts … 139 were identified for pT3 or + margins, who did not receive NHT & had paraffin-embedded specimens. RNA was extracted from the highest Gleason grade focus & applied to a high-density-oligonucleotide microarray.

ROC characteristic … and Cox regression analyses were performed to assess GC performance for predicting BF and DM after post-RP RT in comparison with clinical nomograms.

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JOUNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Genomic Classifier Identifies Man with Adverse Pathology After Radical Prostatectomy Who Benefits from Adjuvant Radiation Therapy . Den et al. JCO, 2015

RESULTS: ROC of Stephenson model was 0.70 for BF & DM, … addition of GC sign. improved the ROC to 0.78 & 0.80.

Stratified by GC risk groups, 8-yr … was 21%, 48%, & 81% for BF (P<.001) & DM 0%, 12%, & 17% (P=.032) for low, int, & high GC ...

At 8 yrs, the DM for pts with high GC & RT with undetectable PSA was 3%, compared with 23% with detectable PSA (P=0.03).

No outcome diff. were for low GC between the Tx groups.

CONCLUSION: The GC predicted BF and metastasis after post-RP irradiation. Pts with lower GC risk may benefit from delayed RT, as opposed to those with higher GC ...

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Problems with data?:

1. Should these data be used in the clinic?
2. Follow-up adequate (mets are a late event)!
3. To define role of RT +/- ADT?

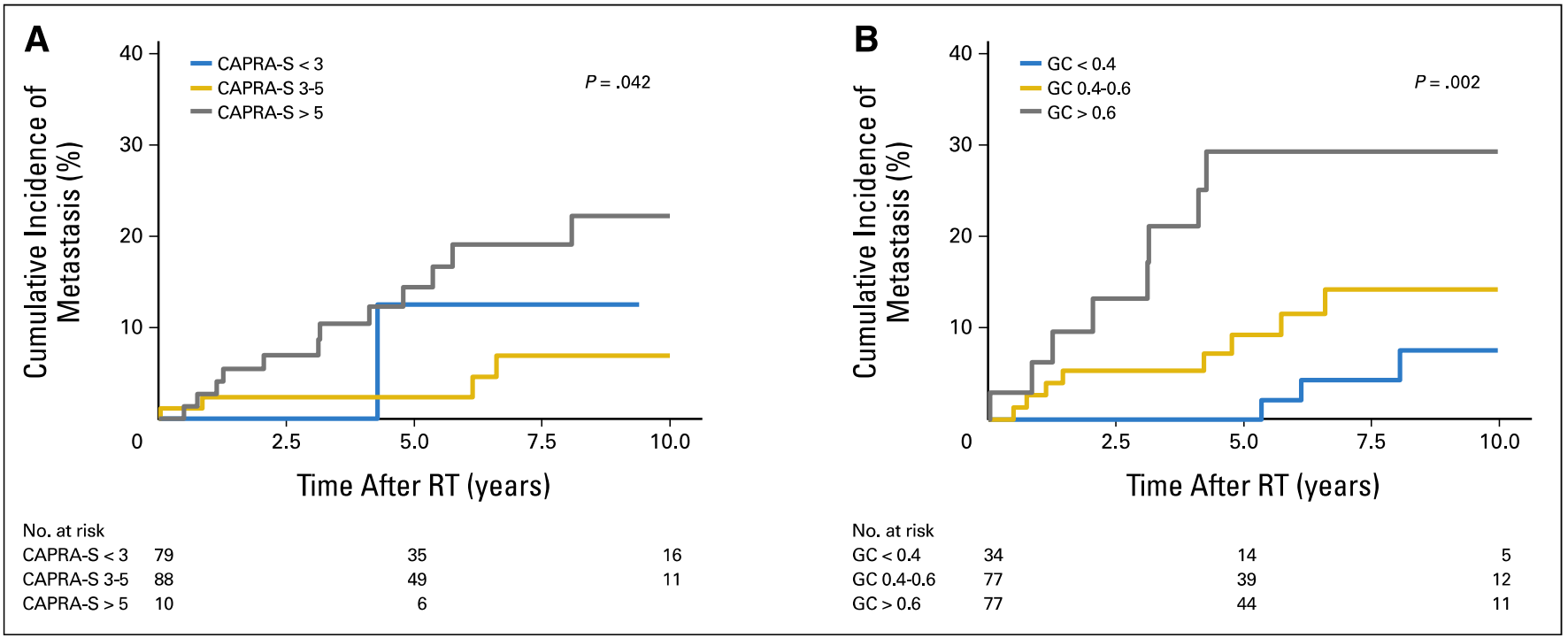

Fig 2. Cumulative incidence curves stratified by (A) Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score and (B) genomic classifier (GC) to evaluate their prognosis for postradiotherapy metastasis. RT, radiotherapy.

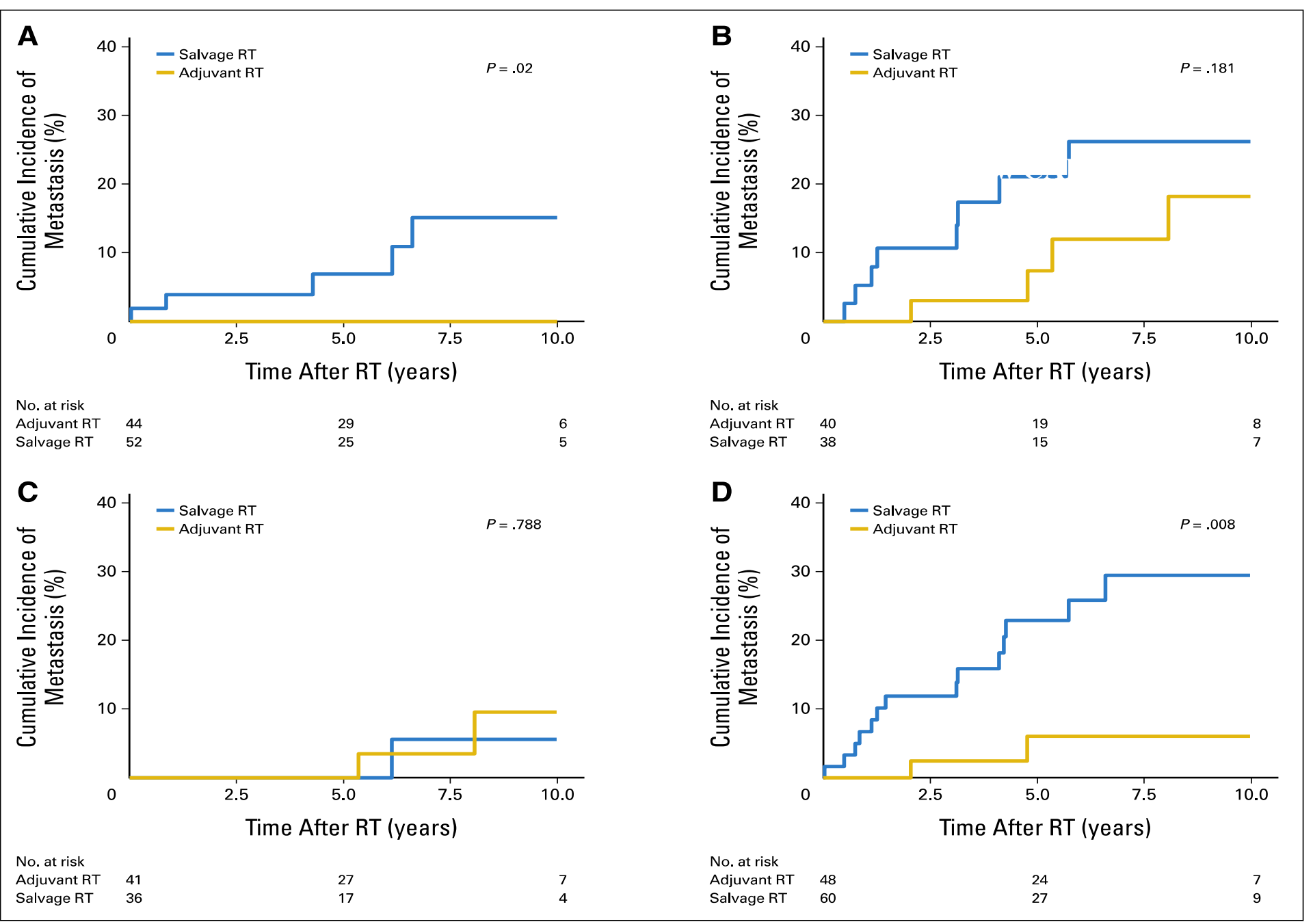

Fig 3. Cumulative incidence curves to evaluate benefit from adjuvant radiotherapy (RT) versus salvage RT stratified by (A and B) Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score and (C and D) genomic classifier (GC).

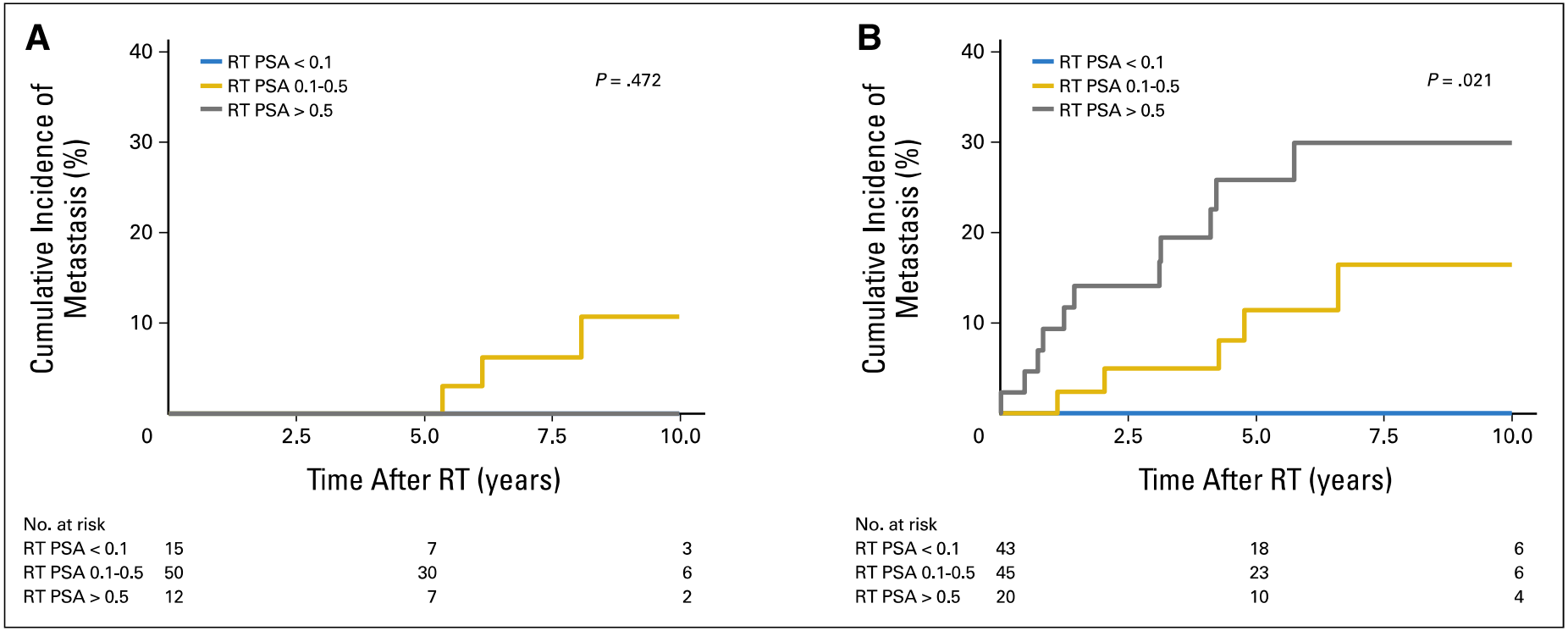

Fig 4. Cumulative incidence curves to evaluate benefit for three preradiotherapy prostate-specific antigen (PSA) levels (< 0.1, 0.1 to 0.5, and > 0.5 ng/mL) stratified by (A) low genomic classifier (GC) score (< 0.4) and (B) high GC score (≥ 0.4). RT, radiotherapy.

Bottom-line:

1. **Focus on cutting out RT too dangerous**
2. **May be useful for guiding addition of ADT?**
3. **More data needed!**

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Adjuvant vs Salvage Radiation After Radical Prostatectomy: Conclusions

- **Adjuvant RT: delays PSA recurrences**
  - **Favored level I evidence**
- **Salvage RT: long term Dz free survival**
  - **It Works!**
- **Morbidity is be low for post op RT**
- **ADT improves survival with EBRT in salvage setting**
- **Future Directions:**
  - WPRT? - RTOG salvage Trial
  - Newer agents with EBRT?

“If you don’t treat for Cure,
you won’t cure those you treat”