Multidisciplinary Approaches to Cancer Symposium

Adjuvant vs Early Salvage Radiation Therapy for Prostate Cancer with Adverse Pathological Features on Radical Prostatectomy: Do We Finally have the Answer?

Scott Glaser, MD

Panel & Disclosures

Scott Glaser, MD
Associate Professor of Radiation Oncology
City of Hope

- *No relevant financial relationships*

This presentation and/or comments will be free of any bias toward or promotion of the above referenced company or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

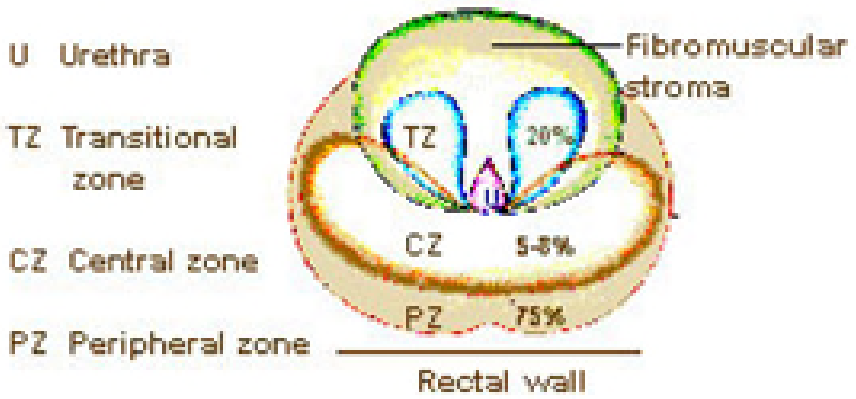
- *Disparities in cancer treatment.*
- *How bias can affect treatment decisions.*

Prostate Cancer Overview

- Most common noncutaneous malignancy in men
- Approximately 190,000 cases per year in the United States
- #2 cause of cancer death after lung cancer (29,000 for prostate and 91,000 for lung)
- Median age of diagnosis is 70, but in PSA era more common to see younger men

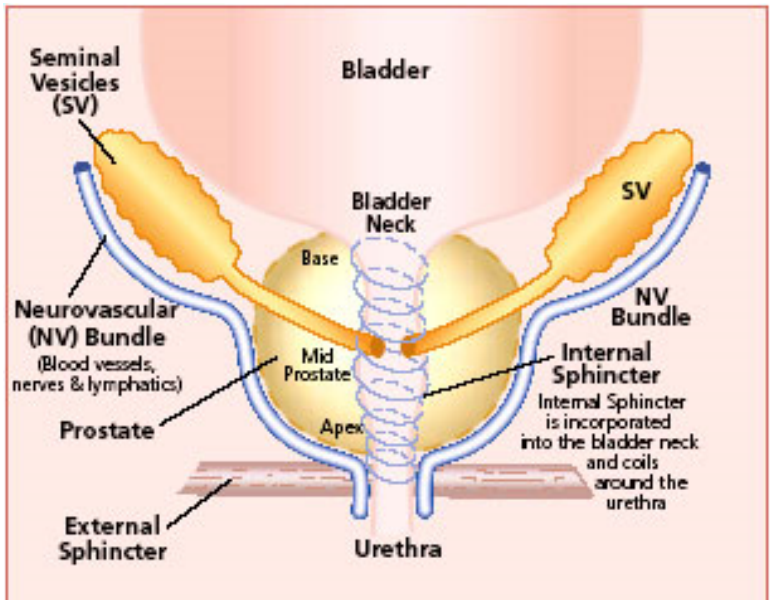
Prostate Cancer Overview

- Prostate gland consists of peripheral zone, central zone, transitional zone, and anterior fibromuscular stroma.
- Most cancers originate in the peripheral zone.



Prostate Cancer Overview

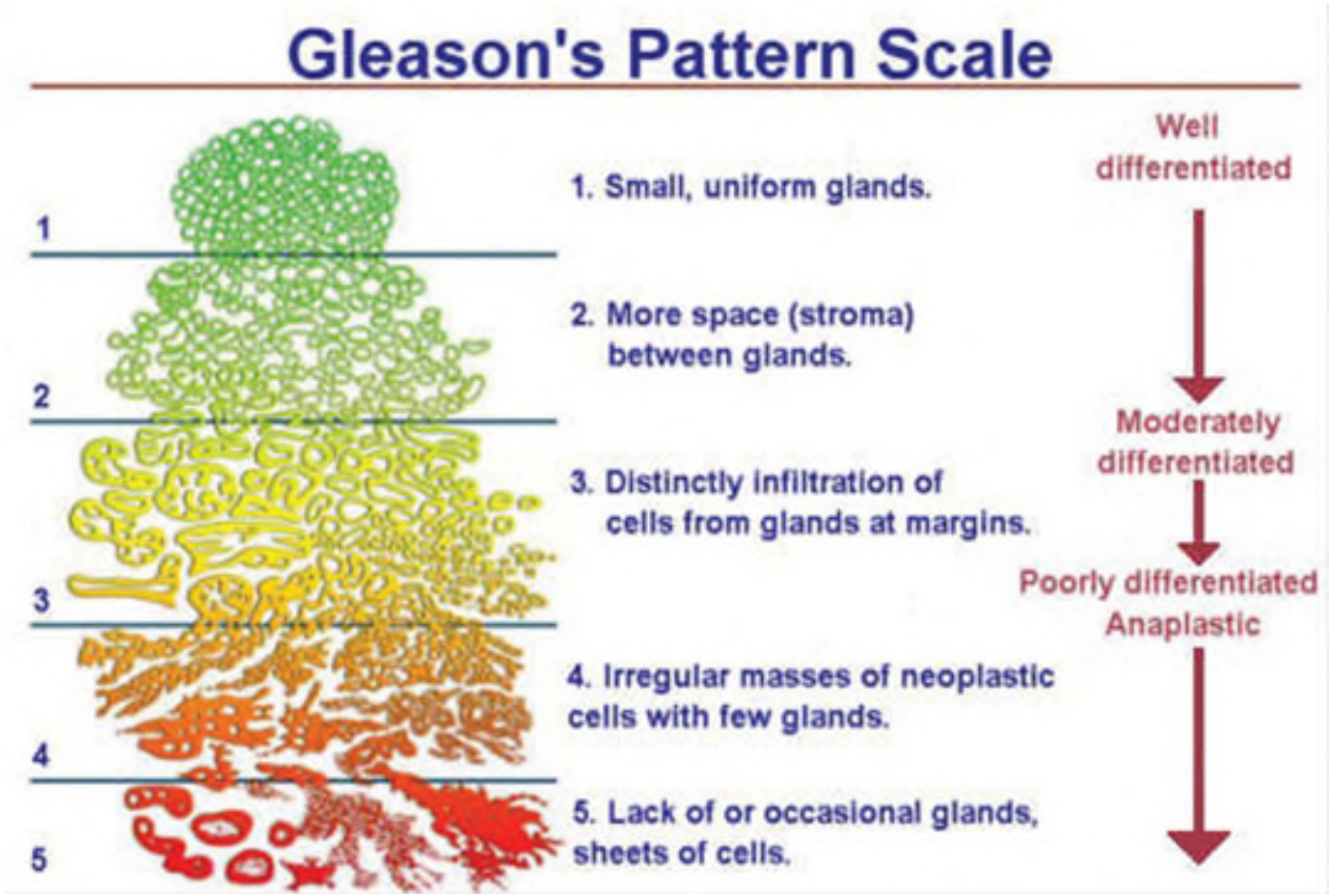
- Approximately 2/3 tumors involve the prostate apex and 85% of patients have multifocal disease in the prostate.
- At the apex, the capsule is not well-defined and it can be difficult to recognize true ECE.



Pathology

- Greater than 95% of prostate cancers are adenocarcinoma.
- Tumors are graded based on the Gleason scoring system ranging from slight disorganization with a score of 1 to anaplastic with a score of five.
- The most common pattern receives the first score and the second most common receives the second score (i.e. 5+4=9 or 3+4=7).

Pathology


Gleason's Pattern Scale
1
2
3
4
5
1. Small, uniform glands.
2. More space (stroma) between glands.
3. Distinctly infiltration of cells from glands at margins.
4. Irregular masses of neoplastic cells with few glands.
5. Lack of or occasional glands, sheets of cells.
Well differentiated
Moderately differentiated
Poorly differentiated
Anaplastic

Staging

Primary tumor (T) – clinical

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Clinically inapparent tumor neither palpable nor visible by imaging
- T1a: Tumor incidental histologic finding in 5% or less of tissue resected
- T1b: Tumor incidental histologic finding in more than 5% of tissue resected
- T1c: Tumor identified by needle biopsy (e.g., because of elevated PSA)

T2: Tumor confined within prostate*
- T2a: Tumor involves one-half of one lobe or less
- T2b: Tumor involves more than one-half of one lobe, but not both lobes
- T2c: Tumor involves both lobes

T3: Tumor extends through the prostate capsule**
- T3a: Extracapsular extension (unilateral or bilateral)
- T3b: Tumor invades seminal vesicle(s)

T4: Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

**Note*: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.
***Note*: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2

Pathologic (pT)*

pT2: Organ confined
- pT2a: Unilateral, one-half of one side or less
- pT2b: Unilateral, involving more than one-half of side but not both sides
- pT2c: Bilateral disease

pT3: Extraprostatic extension
- pT3a: Extraprostatic extension or microscopic invasion of bladder neck**
- pT3b: Seminal vesicle invasion

pT4: Invasion of rectum, levator muscles, and /or pelvic wall

Risk Groups

- Per NCCN
  - Low risk: T1-2a and Gleason < or = 6 and PSA <10
  - Intermediate: T2b-T2c, and/or GS 7, and/or PSA 10-20
  - High: T3+, or GS8-10, or PSA>20

pT3 Prostate Cancer – Natural History

- Oregon data on observation for pT3 patients (Lowe et al, J Urol, 1997)
  - 35% of patients with cT1-T2 disease had pT3 disease
  - 114 cases of ECE, 22 SVI, 20 N+ were observed
  - 4 year risk of biochemical failure was 30% for ECE, 27% for SVI, and 80% for N+
  - Risk factors for failure were:
    - # of margins involved (1=20%, 2=40%, >3=50%)
    - Gleason Score (6=20%, 7=34%, >7=74%)
    - Pretreatment PSA (<10=17%, >10=45%)

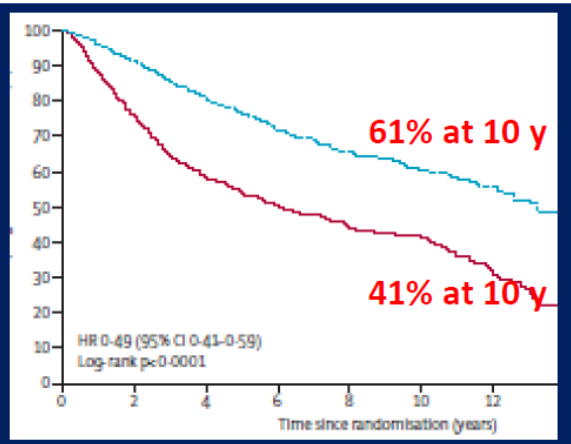
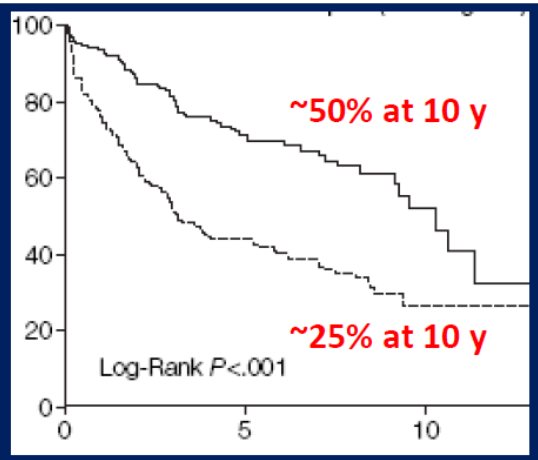
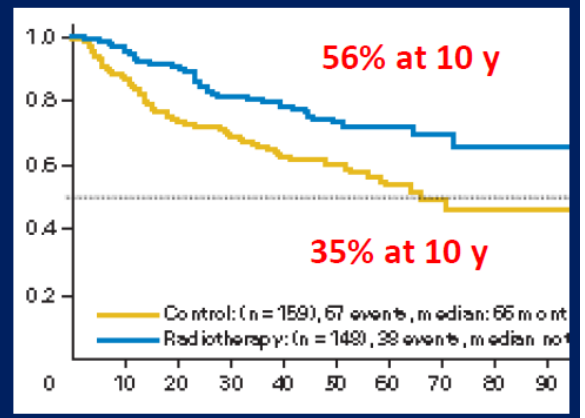
How to Handle High Risk Patients Post-Op?

- Option 1:
  - Offer all patients adjuvant treatment
- Option 2:
  - Observe all patients and treat at time of PSA failure
- Option 3:
  - Offer “high risk” patients adjuvant treatment and observe “low risk” patients (treatment at failure)

Historical Data:

The Data

	SWOG	German	EORTC
Years	1988-1997	1997-2004	1992-2001
Meadian f/u	12.6 years	9.4 years	10.6 years
n	425	307	1005
Inclusion	pT3 or +SM	<76y/o, pT3-T4, undectable	<75y/o, pT3 or +SM
End Point Improved	MFS 57% vs. 46%, OS 59% vs. 48% subset analysis MFS improved in undectable PSA	10 yr bPFS 63% vs 37% (underpowered for OS and MFS as only 43/307 patients died)	10 yr bPFS 61% vs. 41%, 10 yr LRF 7.3% vs. 16.6%
Toxicity		1 grade 3 late toxicity	grade 3 = 5.3% vs. 2.5%
median PSA at time of Salvage RT	0.75-1.0		1.7

	EORTC 22911	*SWOG 8794*	*ARO 9602*
bNED			

Making a Decision

- How to decide whether to offer adjuvant RT:
  - Is the treatment toxic / Do the risks of treatment outweigh the benefits?
    - Adjuvant RT appears to be well tolerated
      - One grade 3 event in EORTC trial using 3D planning
      - QOL data in SWOG trial showed initially more frequent urination and bowel dysfunction but long-term SS better QOL in RT arm. (Moninpour, JCO, 2008)
  - What endpoint is improved?
    - All trials show bPFS advantage
    - SWOG, which has longest follow-up, showed OS at 15 year publication, but not at 10 year publication
    - EORTC and German data only have 10 year publications
    - PSA recurrence predates clinical progression by median of 8 years (Pound, JAMA 1999;281:1591–7.)

Can't I Just Wait Until PSA Failure and Treat Then?

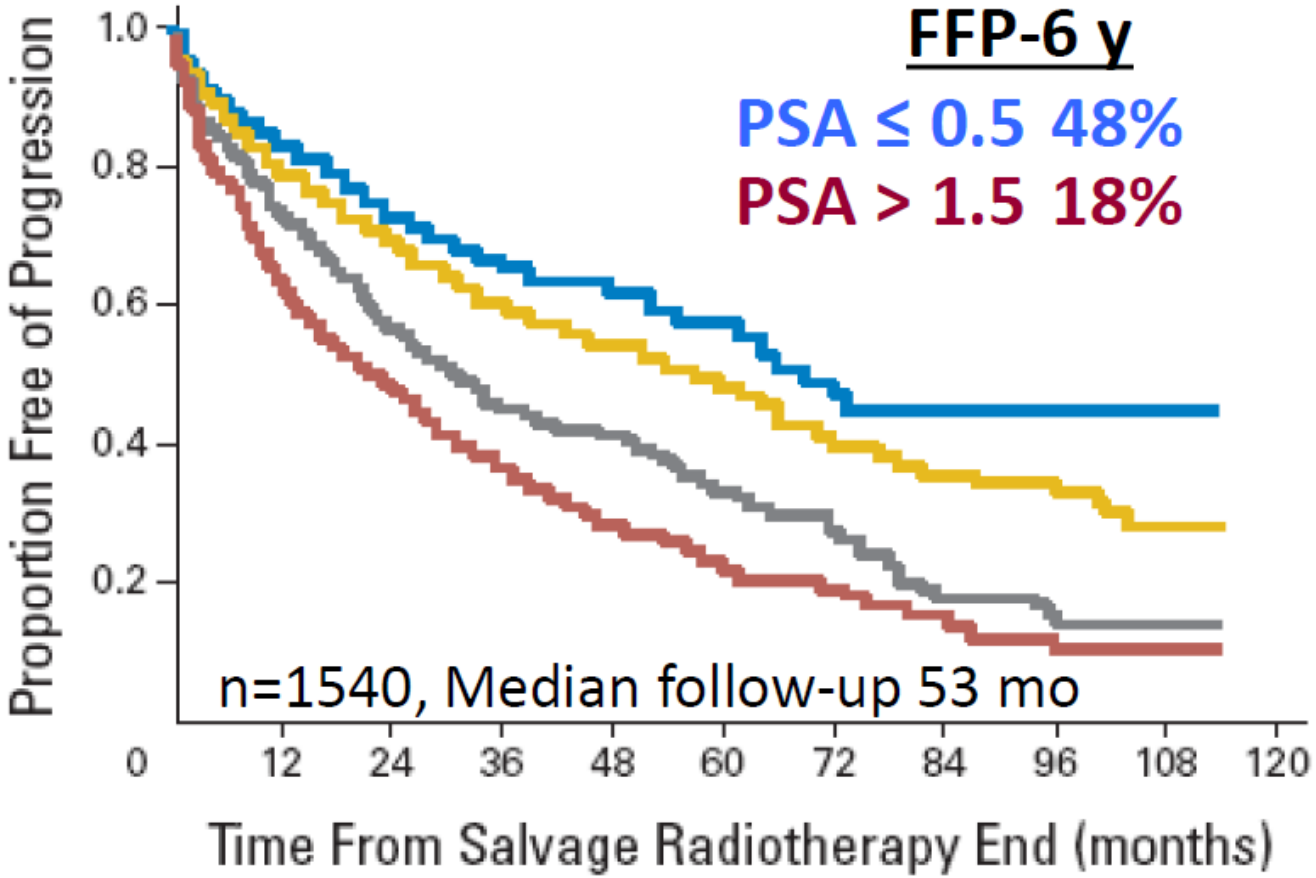
- Salvage radiation at time of PSA failure was frequently used in the observation arm of the trials previously discussed, although it's use was not mandated nor standardized
- Thus, the observation arms of these trials have been heavily criticized as sub-optimal and many clinicians believe early salvage RT to be equivalent with adjuvant RT

The Timing of Salvage RT

- Timing of Salvage RT is important
  - Control rates decrease with increasing pre-RT PSA (Stephenson AJ,JCO, 2007)
    - PreRT PSA < 0.5 had 6 year FFP of 48%
    - PreRT PSA .5-1.0 had 6 year FFP of 40%
    - PreRT PSA 1.0-1.5 had 6 year FFP of 28%
    - PreRT PSA >1.5 had 6 year FFP of 18%
  - Also seen in systematic review (King, IJROBP, 2012)
    - 5597 patients, 41 studies, 2.6% loss in relapse free survival for each incremental 0.1 rise in PSA at time of salvage RT. FFP of 64% with PSA<0.2

The Problem With Waiting

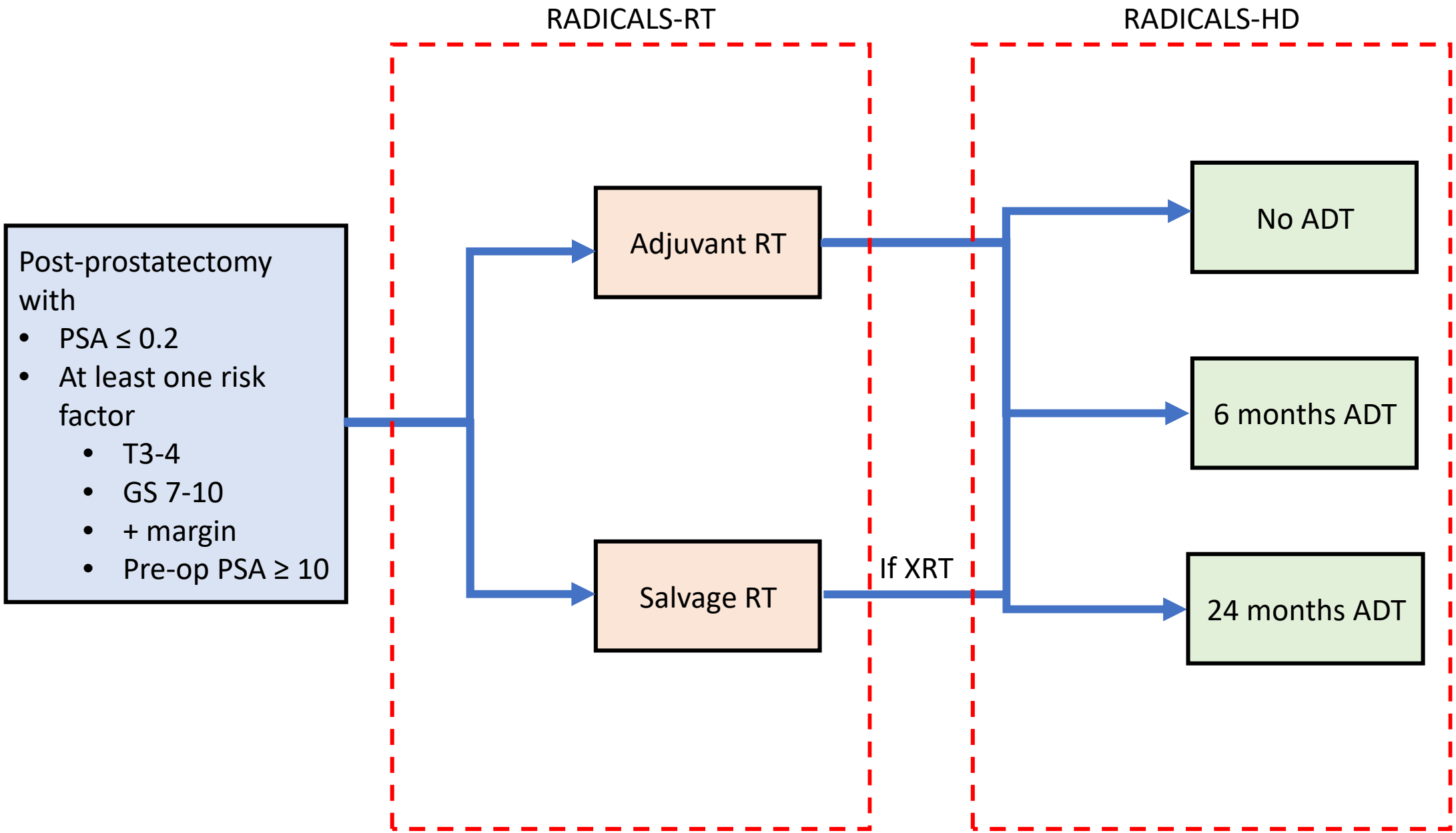
- When patient's do not receive adequate follow-up or do not receive appropriate referral for salvage RT at time of PSA failure post-prostectomy, outcomes are compromised – **Success rates are best at a low PSA**



Modern Data:

Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial

Christopher C Parker, Noel W Clarke, Adrian D Cook, Howard G Kynaston, Peter Meidahl Petersen, Charles Catton, William Cross, John Logue, Wendy Parulekar, Heather Payne, Rajendra Persad, Holly Pickering, Fred Saad, Juliette Anderson, Amit Bahl, David Bottomley, Klaus Brasso, Rohit Chahal, Peter W Cooke, Ben Eddy, Stephanie Gibbs, Chee Goh, Sandeep Gujral, Catherine Heath, Alastair Henderson, Ramasamy Jaganathan, Henrik Jakobsen, Nicholas D James, Subramanian Kanaga Sundaram, Kathryn Lees, Jason Lester, Henriette Lindberg, Julian Money-Kyrle, Stephen Morris, Joe O'Sullivan, Peter Ostler, Lisa Owen, Prashant Patel, Alvan Pope, Richard Popert, Rakesh Raman, Martin Andreas Røder, Ian Sayers, Matthew Simms, Jim Wilson, Anjali Zarkar, Mahesh K B Parmar, Matthew R Sydes


RADICALS-RT
RADICALS-HD
Post-prostatectomy with
• PSA ≤ 0.2
• At least one risk factor
• T3-4
• GS 7-10
• + margin
• Pre-op PSA ≥ 10
Adjuvant RT
Salvage RT
If XRT
No ADT
6 months ADT
24 months ADT

PSA Biochemical Progression

- 2 consecutive rises in PSA with PSA > 0.1 mg/ml
- 3 consecutive rises in PSA

Radiation

- Prostate bed +/- pelvic lymph nodes
- Fractionation
  - 66 Gy in 33 fx
  - 52.5 Gy in 20 fx
- Started within 26 weeks of RP or 2 months of PSA biochemical progression

Outcomes

- Primary
  - Disease-specific survival
- Secondary
  - Freedom from distant metastases (bone, liver, lung, distant node)

Outcomes

- Primary
  - Freedom from distant metastases
- Secondary
  - Survival
  - Disease-specific survival
  - Initiation of non-protocol hormone therapy
  - Treatment toxicity
  - Patient-reported outcomes
  - Freedom from biochemical progression
    - Added in 2018 to facilitate ARTISTIC meta-analysis with RAVES and GETUG-AFU 17

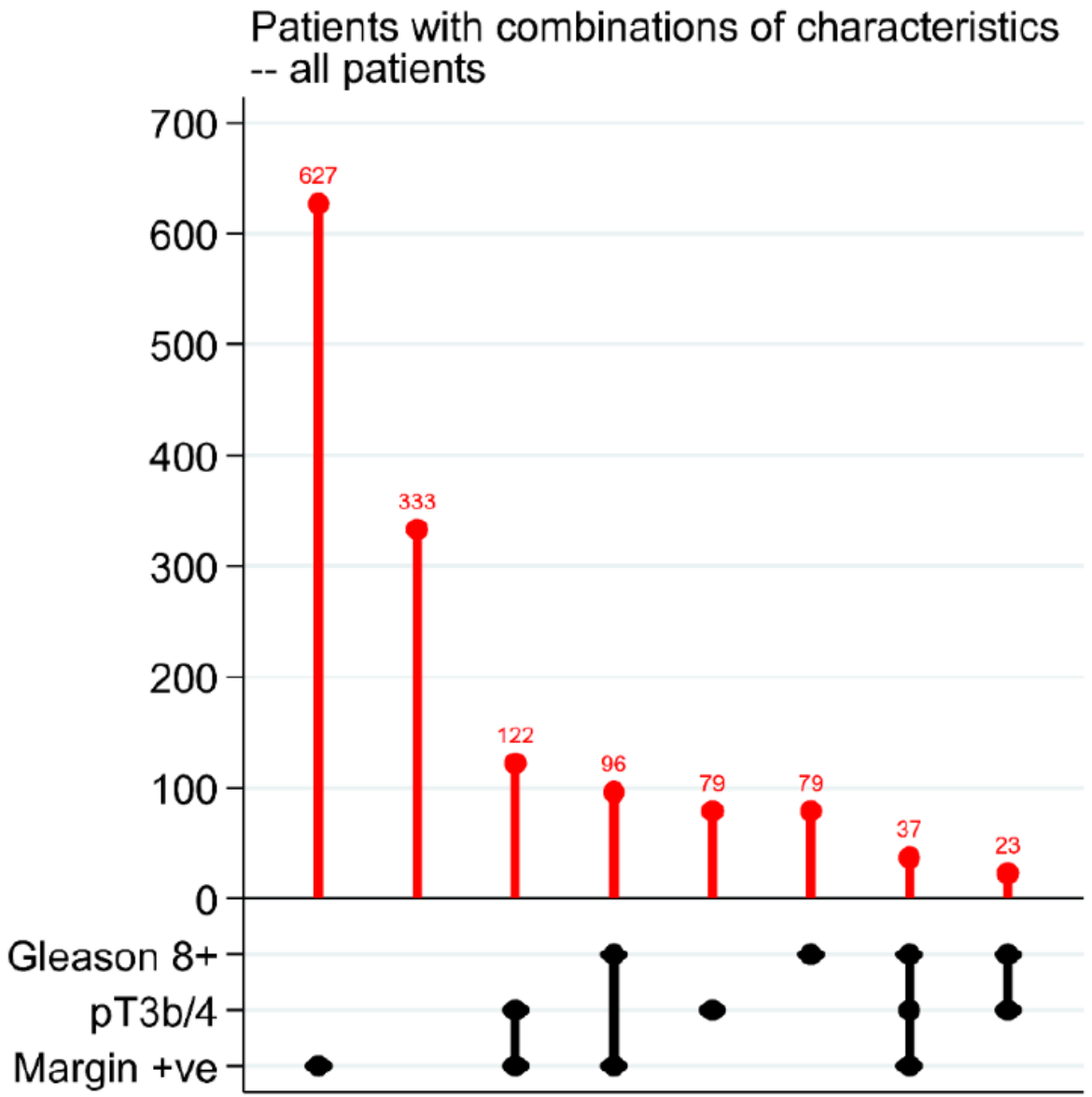
Biochemical Progression-Free Survival

- Freedom from
  - PSA ≥ 0.4 ng/ml following post-op radiation
  - PSA ≥ 2 at any time
  - Clinical progression
  - Initiation of non-protocol hormone therapy
  - Death from any cause

	Salvage radiotherapy (n=699)	Adjuvant radiotherapy (n=697)	All (n=1396)
Age, years	65 (60–68)	65 (60–68)	65 (60–68)
PSA at diagnosis, ng/mL	8·0 (5·6–11·6)	7·8 (5·8–11·4)	7·9 (5·7–11·5)
Gleason score			
<7	48 (7%)	48 (7%)	96 (7%)
3+4	338 (48%)	349 (50%)	687 (49%)
4+3	190 (27%)	188 (27%)	378 (27%)
≥8	123 (18%)	112 (16%)	235 (17%)
Pathological T-stage			
2	176 (25%)	163 (23%)	339 (24%)
3a	389 (56%)	407 (58%)	796 (57%)
3b	130 (19%)	122 (18%)	252 (18%)
4	4 (1%)	5 (1%)	9 (1%)
Positive margins			
Present	443 (63%)	439 (63%)	882 (63%)
Absent	256 (37%)	258 (37%)	514 (37%)
Lymph node involvement			
Node positive	28 (4%)	38 (5%)	66 (5%)
Node negative	374 (54%)	335 (48%)	709 (51%)
No dissection	297 (42%)	322 (46%)	619 (44%)
CAPRA-S score			
Low (0–2)	55 (8%)	58 (8%)	113 (8%)
Intermediate (3–5)	384 (55%)	382 (55%)	766 (55%)
High (6+)	260 (37%)	257 (37%)	517 (37%)
Country			
UK	573 (82%)	574 (82%)	1147 (82%)
Denmark	92 (13%)	95 (14%)	187 (13%)
Canada	28 (4%)	22 (3%)	50 (4%)
Ireland	6 (1%)	6 (1%)	12 (1%)

Data are n (%) or median (IQR). PSA=prostate-specific antigen. CAPRA-S=Cancer of the Prostate Risk Assessment post-surgical.

Table 1: **Baseline characteristics**

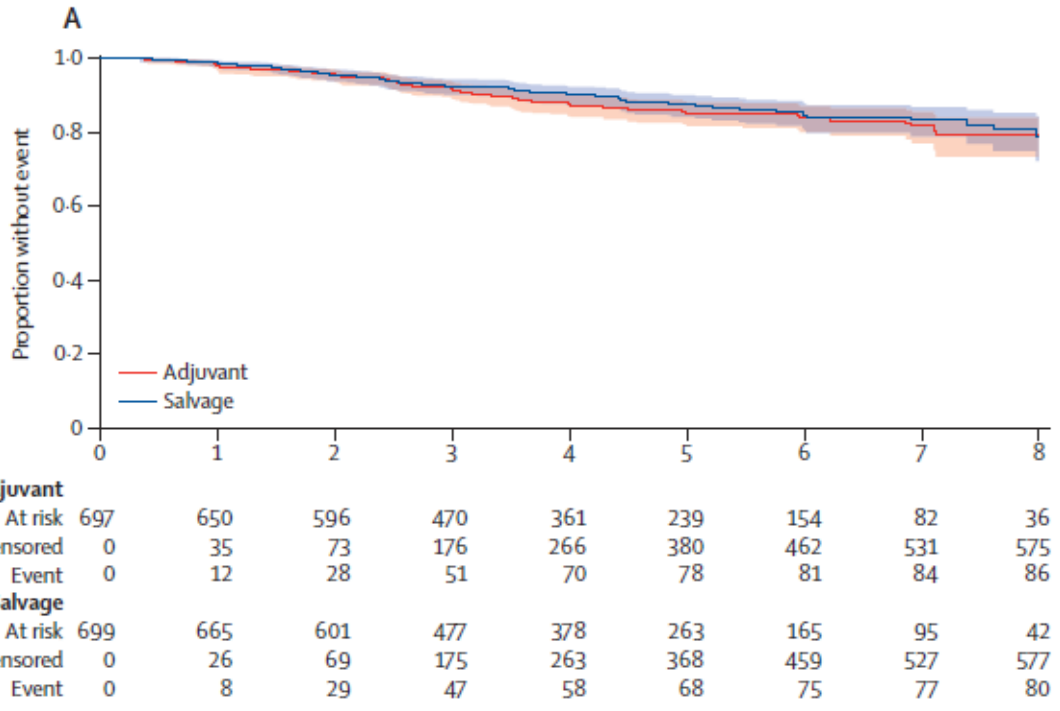

Patients with combinations of characteristics
-- all patients
700
600
500
400
300
200
100
0
627
333
122
96
79
79
37
23
Gleason 8+
pT3b/4
Margin +ve

Radiation Received

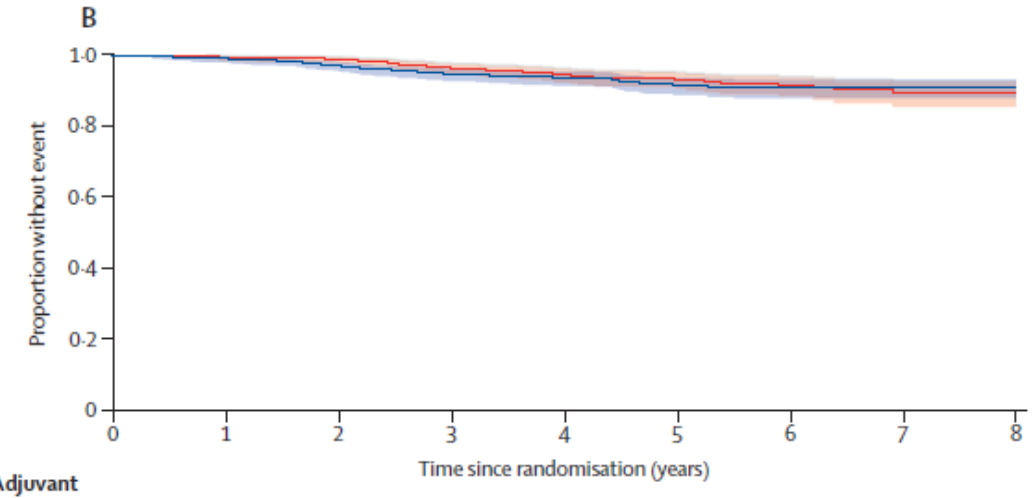
- 61% received 66 Gy in 33 fx
- Pelvic radiation
  - 3% of salvage radiation patients
  - 7% of adjuvant radiation patients

ADT

- 24% of adjuvant radiotherapy patients received ADT
- 27% of salvage radiotherapy patients received ADT



Adjuvant									
At risk	697	650	596	470	361	239	154	82	36
Censored	0	35	73	176	266	380	462	531	575
Event	0	12	28	51	70	78	81	84	86
Salvage									
At risk	699	665	601	477	378	263	165	95	42
Censored	0	26	69	175	263	368	459	527	577
Event	0	8	29	47	58	68	75	77	80



Adjuvant									
At risk	697	671	632	511	408	291	200	119	58
Censored	0	22	58	165	259	371	458	536	597
HT	0	4	7	21	30	35	39	42	42
Salvage									
At risk	699	688	646	517	412	305	208	125	62
Censored	0	5	34	148	248	347	442	525	588
HT	0	6	19	34	39	47	49	49	49

Figure 2: Biochemical progression-free survival (A) and freedom from non-protocol HT (B)
HT=hormone therapy.

Other outcomes

- Data not mature enough to report outcome for
  - Freedom from distant metastases
  - Overall survival

	Early (<2 years)				Late (≥2 years)			
	All (n=1372)	Salvage radiotherapy (n=696)	Adjuvant radiotherapy (n=676)	p value	All (n=1220)	Salvage radiotherapy (n=621)	Adjuvant radiotherapy (n=599)	p value
Diarrhoea								
Grade 1 or 2	372 (27%)	112 (16%)	260 (38%)	<0·0001	153 (13%)	50 (8%)	103 (17%)	<0·0001
Grade 3	13 (1%)	3 (<1%)	10 (1%)	..	7 (1%)	2 (<1%)	5 (1%)	..
Grade 4	0	0	0	..	1 (<1%)	0	1 (<1%)	..
Proctitis								
Grade 1 or 2	196 (14%)	47 (7%)	149 (22%)	<0·0001	111 (9%)	34 (5%)	77 (13%)	<0·0001
Grade 3	11 (1%)	3 (<1%)	8 (1%)	..	7 (1%)	1 (<1%)	6 (1%)	..
Grade 4	0	0	0	..	0	0	0	..
Cystitis								
Grade 1 or 2	255 (19%)	84 (12%)	171 (25%)	<0·0001	122 (10%)	42 (7%)	80 (13%)	<0·0005
Grade 3	16 (1%)	5 (1%)	11 (2%)	..	10 (1%)	4 (1%)	6 (1%)	..
Grade 4	1 (<1%)	0	1 (<1%)	..	0	0	0	..
Haematuria								
Grade 1 or 2	96 (7%)	25 (4%)	71 (11%)	<0·0001	95 (8%)	25 (4%)	70 (12%)	<0·0001
Grade 3	22 (2%)	2 (<1%)	20 (3%)	..	26 (2%)	2 (<1%)	24 (4%)	..
Grade 4	0	0	0	..	0	0	0	..
Urethral stricture								
Grade 1 or 2	62 (5%)	21 (3%)	41 (6%)	0·020	55 (5%)	19 (3%)	36 (6%)	0·0025
Grade 3	64 (5%)	27 (4%)	37 (5%)	..	39 (3%)	13 (2%)	26 (4%)	..
Grade 4	5 (<1%)	3 (<1%)	2 (<1%)	..	3 (<1%)	3 (<1%)	0	..

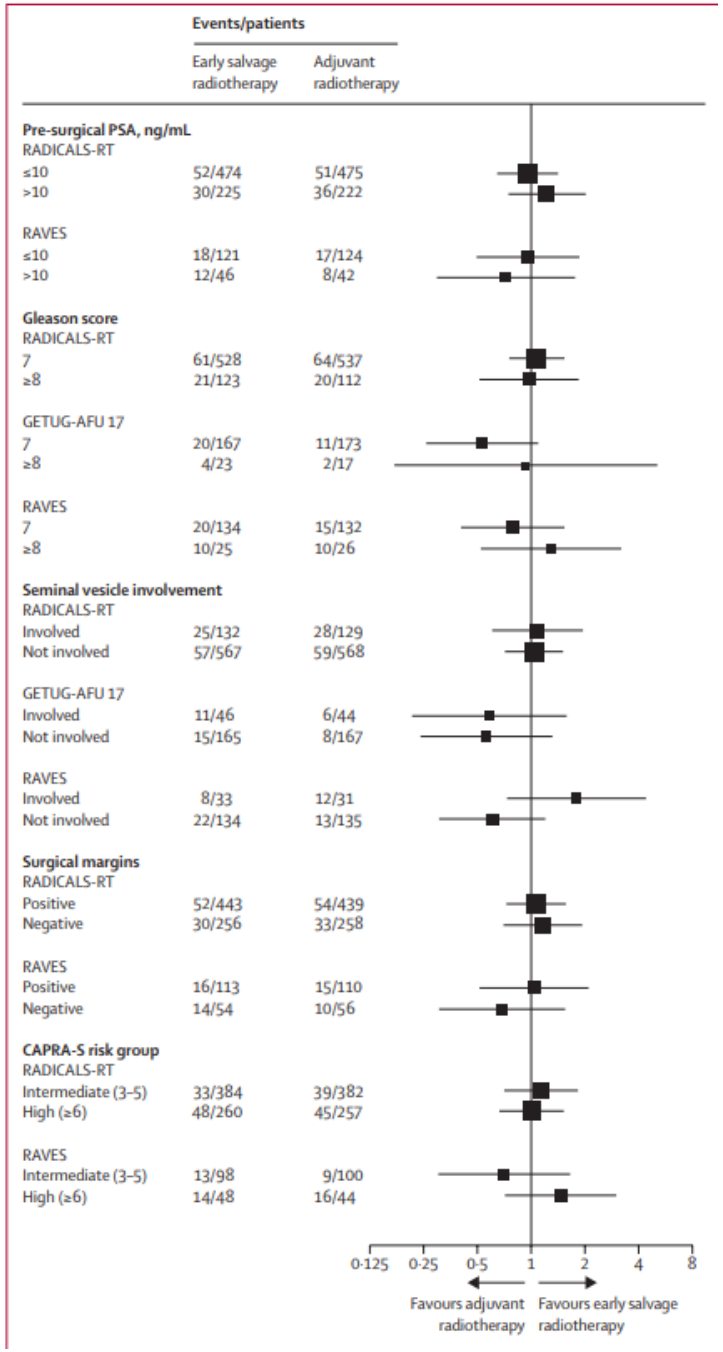
Data are n (%). p values represent adjuvant versus salvage, χ^2 test. No grade 5 events reported.

Table 2: **Radiation Therapy Oncology Group toxicity**

Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data

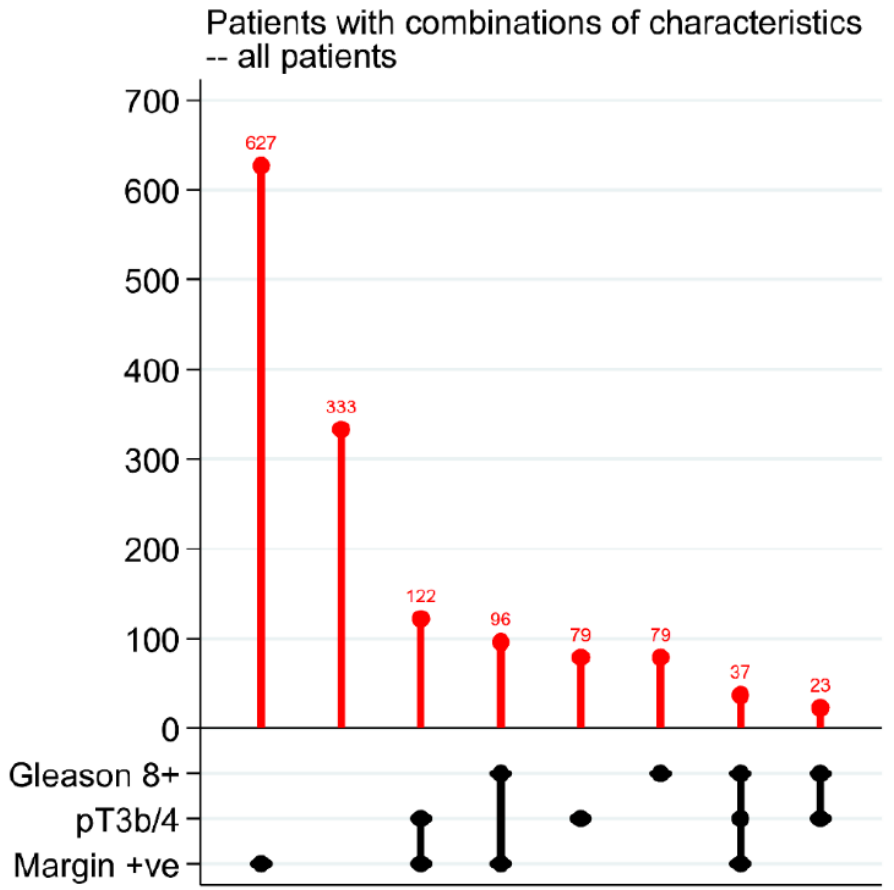
Claire L Vale, David Fisher, Andrew Kneebone, Christopher Parker, Maria Pearse, Pierre Richaud, Paul Sargos, Matthew R Sydes, Christopher Brawley, Meryem Brihoum, Chris Brown, Sylvie Chabaud, Adrian Cook, Silvia Forcat, Carol Fraser-Browne, Igor Latorzeff, Mahesh K B Parmar, Jayne F Tierney, for the ARTISTIC Meta-analysis Group

***Lancet* 2020; 396: 1422–31**



Conclusion

- No clear benefit from adjuvant over salvage radiation in the post-prostatectomy setting
- **Adjuvant radiation does increase the risk of urinary and bowel toxicity**
- A majority of patients on these three trials were Gleason 7… do the results apply to men with Gleason 8+ disease or those with multiple high risk factors?
- Node positive patients were not included on the RTCs. Adjuvant RT is currently still the standard of care for men with N+.



ORIGINAL REPORTS | Genitourinary Cancer

Adjuvant Versus Early Salvage Radiation Therapy for Men at High Risk for Recurrence Following Radical Prostatectomy for Prostate Cancer and the Risk of Death

Derya Tilki, MD[1,2]; Ming-Hui Chen, PhD[3]; Jing Wu, PhD[4]; Hartwig Huland, MD[1]; Markus Graefen, MD[1]; Thomas Wiegel, MD[5]; Dirk Böhmer, MD[6]; Osama Mohamad, MD, PhD[7]; Janet E. Cowan, MA[8]; Felix Y. Feng, MD[7,8]; Peter R. Carroll, MD, MPH[8]; Bruce J. Trock, MPH, PhD[9]; Alan W. Partin, MD, PhD[10]; and Anthony V. D'Amico, MD, PhD[11]

Rationale

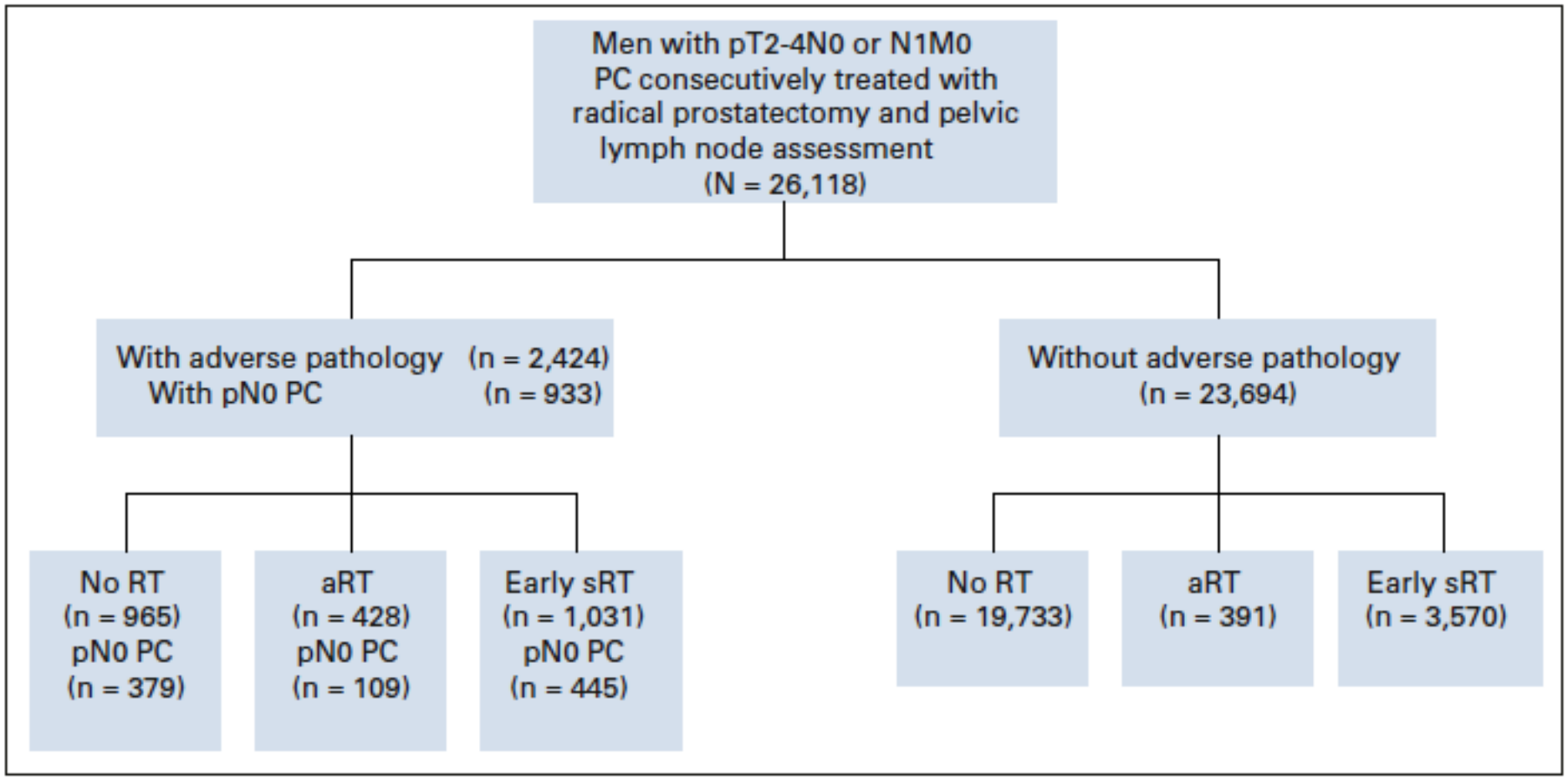
- Previous studies (3 randomized trials + an associated meta-analysis) found no difference in BPFS when comparing adjuvant vs. early salvage RT
- Based on this, many patients are not offered adjuvant RT, regardless of RP path findings
- prior randomized trials **may have missed the benefit of adjuvant RT** in those patients at high risk for recurrence (ie, adverse pathology at time of RP) either due to inadequate power or immortal time bias

Immortal Time Bias

- *immortal time*: period during which study outcome cannot occur
- *immortal time bias*: participants in one arm cannot experience the outcome and are basically “immortal”
- example: patient is randomly assigned to adjuvant RT with an undetectable PSA vs. on salvage arm, men are required to start RT within 4 months of exceeding “trigger level” (0.1 or 0.2 ng/mL) w PSA assessment within 3 months following salvage RT
- when men w adverse features on RP path recur, their PSA may rise rapidly (e.g. from 0.1 ng/mL to 0.4 ng/mL) while salvage RT is being planned and delivered but prior to the PSA response following salvage RT is assessed
- **men on salvage arm are not able to be assessed for progression for several months following PSA trigger level -** could explain why early salvage trended toward superiority

Methods

- Multi-institution, non randomized study including patients treated at one of 3 hospitals in Germany as well as UCSF and Johns Hopkins
- Cohort included 26,118 men with **pT2-4N0** or **N1M0** prostate cancer treated between 1989 and 2016
- s/p RP and pelvic lymph node assessment
- use of adjuvant, salvage, or no RT was stratified by presence (or absence) of adverse pathology
  - adverse features include: Gleason 8-10, extension of cancer beyond the prostate, and/or node positivity


Men with pT2-4N0 or N1M0 PC consecutively treated with radical prostatectomy and pelvic lymph node assessment (N = 26,118)
With adverse pathology (n = 2,424)
With pN0 PC (n = 933)
Without adverse pathology (n = 23,694)
No RT (n = 965) pN0 PC (n = 379)
aRT (n = 428) pN0 PC (n = 109)
Early sRT (n = 1,031) pN0 PC (n = 445)
No RT (n = 19,733)
aRT (n = 391)
Early sRT (n = 3,570)

Methods continued

- Prostatectomy specimens reviewed by GU pathologist
- Follow-up: started on day of RP and concluded on date of last follow up or death
- patients had a PSA test and rectal exam and were seen q3 mo. for 1 yr, q6 mo. for 4 yrs, then annually thereafter
- Prostate cancer specific mortality (PCSM) was determined by confirming castrate-resistant metastatic PC (i.e. rising PSA w testosterone level < 20 ng/dL before death)
- univariable and and multivariable regression was used to evaluate whether all cause mortality was associated with the use of adjuvant vs early salvage RT among men w or wo adverse features

Treatment Propensity Score

- represents the probability of treatment assignment conditional on observed baseline prognostic covariates
- estimated using multinomial logistic regression, with treatment as the outcome and age, year of RP, pre-op PSA< and margin status as prognostic covariates
- purpose is to minimize selection bias when estimating treatment effect by adjusting for variables

Sensitivity Analysis

- was performed using different definitions of “adverse pathology” per Raves, Getug, and Radicals to determine impact of diff definitions on the adjusted HR of all cause mortality

All Cause Mortality (ACM)

- adjusted estimates of ACM were calculated using the extended Kaplan Meier method
- adjusted for treatment propensity score, age, institution, and use of ADT
- $p<0.05$ considered SS

Results

- Of the 26,118 men included in the study:
- 819 received adjuvant RT (ie, PSA <0.1 ng/mL) at a median of 3.55 mo. (range 2.79-4.50 months) after RP; pelvic LN coverage at discretion of treating physician
- 4,601 underwent early salvage RT (median PSA 0.30 ng/mL, range 0.2-0.6)
- of those who received early salvage RT, 655 (14.24%) had persistent PSA >0.1 ng/mL
- adjuvant and salvage ADT were used in 1.35% and 9.69% of the men, respectively

Clinical Factors, Post-RP Treatment	All Men (N = 26,118)	Adverse Pathology Including pN1 (n = 2,424)			P: No RT vsRT, aRT v sRT
		No RT	aRT[a]	sRT[a]	
Median age at RP, years (IQR)	62 (57-67)	64 (58-78)	64 (60-69)	64 (58-68)	.92, .18
Median year of RP (IQR)	2008 (2003-2012)	2009 (2000-2013)	2012 (2009-2014)	2011 (2007-2013)	< .001, < .001
Pre-RP PSA level, ng/mL					
< 4	3,275 (12.54%)	72 (7.46%)	20 (4.67%)	52 (5.04%)	< .001, .94
4-10	15,635 (59.86%)	394 (40.83%)	152 (35.51%)	361 (35.01%)	
> 10	7,208 (27.60%)	499 (51.71%)	256 (59.81%)	618 (59.94%)	
AJCC prostatectomy stage					
T2	17,184 (65.79%)	65 (6.74%)	9 (2.10%)	61 (5.92%)	.45, .002
T3a or higher	8,934 (34.21%)	900 (93.26%)	419 (97.90%)	970 (94.48%)	
Prostatectomy Gleason score					
7 or less	24,258 (92.88%)	391 (40.52%)	168 (39.25%)	380 (36.86%)	.09, .39
8-10	1,860 (7.12%)	574 (59.48%)	260 (60.75%)	651 (63.14%)	
Prostatectomy margin status					
Negative	21,498 (82.31%)	673 (69.74%)	74 (17.29%)	560 (54.32%)	< .001, < .001
Positive	4,620 (17.69%)	292 (30.26%)	354 (82.71%)	471 (45.68%)	
Prostatectomy nodal status					
Negative	24,627 (94.29%)	379 (39.27%)	109 (25.47%)	445 (43.16%)	.08, < .001
Positive	1,491 (5.71%)	586 (60.73%)	319 (74.53%)	586 (56.84%)	
Adjuvant ADT[a]					
Yes	352 (1.35%)	53 (5.49%)	158 (36.92%)	80 (7.76%)	.04, < .001
No	25,766 (98.65%)	912 (94.51%)	270 (63.08%)	951 (92.24%)	
sADT[a]					
Yes	2,532 (9.69%)	232 (24.04%)	155 (36.21%)	490 (47.53%)	< .001, < .001
No	23,586 (90.31%)	733 (75.96%)	273 (63.79%)	541 (52.47%)	

- among men with adverse pathology: SS higher proportion who received adjuvant RT were pT3a+ or margin-positive PC

Clinical Factors, Post-RP Treatment	All Men (N = 26,118)	Adverse Pathology Excluding pN1 (n = 933)			
		No RT	aRT[a]	sRT[a]	P: No RT *v* sRT, aRT *v* SRT
Median age at RP, years (IQR)	62 (57-67)	63 (58-68)	65 (61-68)	64 (58-68)	.72, .048
Median year of RP (IQR)	2008 (2003-2012)	2007 (1999-2012)	2011 (2008-2013)	2009 (2005-2012)	< .001, < .001
Pre-RP PSA level, ng/mL					
< 4	3,275 (12.54%)	42 (11.08%)	10 (9.14%)	37 (8.31%)	.003, .88
4-10	15,635 (59.86%)	191 (50.04%)	47 (43.12%)	184 (41.35%)	
> 10	7,208 (27.60%)	146 (38.52%)	52 (47.71%)	224 (50.34%)	
AJCC prostatectomy stage					
T2	17,184 (65.79%)	—	—	—	NA
T3a or higher	8,934 (34.21%)	379	109	445	
Prostatectomy Gleason score					
7 or less	24,258 (92.88%)	—	—	—	NA
8-10	1,860 (7.12%)	379	109	445	
Prostatectomy margin status					
Negative	21,498 (82.31%)	287 (75.73%)	13 (11.93%)	224 (54.83%)	< .001, < .001
Positive	4,620 (17.69%)	92 (24.27%)	96 (88.07%)	201 (45.17%)	
Prostatectomy nodal status					
Negative	24,627 (94.29%)	379	109	445	NA
Positive	1,491 (5.71%)	—	—	—	
Adjuvant ADT[a]					
Yes	352 (1.35%)	8 (2.11%)	24 (22.02%)	18 (4.04%)	.11, < .001
No	25,766 (98.65%)	371 (97.89%)	85 (77.98%)	427 (95.96%)	
sADT[a]					
Yes	2,532 (9.69%)	61 (16.09%)	39 (35.78%)	204 (45.84%)	< .001, .06
No	23,586 (90.31%)	318 (83.91%)	70 (64.22%)	241 (54.16%)	

- Among men w adverse pathology *excluding pN1*, SS more margin positivity in adjuvant vs. early salvage RT. Salvage ADT use was less in those who received adjuvant vs early salvage RT.

All Cause Mortality

- at median f/u of 8.16 yrs, 8.06% of men had died, 25.62% were from prostate cancer

- **Among men with adverse pathologic features** (both including and excluding pN1), **adjuvant RT was associated with a lower all-cause mortality risk** compared w those who received early salvage RT (0.31 [0.12-0.78]; P=0.01 for adverse path including pN1) and (0.61 [0.41-0.89]; P=0.01 for adverse path excluding pN1)
- No significant association was observed in men without adverse pathology at RP

				Univariable Analysis		Multivariable Analysis	
Covariate	No. of Men	No. of Deaths	No. of PC Deaths	ACM, HR (95% CI)	*P*	ACM, AHR (95% CI)	*P*
Adverse pathology[a] present							
aRT(t)	428	37	20	0.79 (0.55 to 1.14)	.21	0.61 (0.41 to 0.89)	.01
	109	5	1	0.38 (0.16 to 0.95)	.04	0.31 (0.12 to 0.78)	.01
No RT(t)	965	210	130	0.80 (0.65 to 0.99)	.04	1.09 (0.88 to 1.36)	.42
	379	87	46	0.70 (0.52 to 0.96)	.03	1.14 (0.83 to 1.57)	.42
sRT(t)	1,031	150	87	1.0 (Ref)	—	1.0 (Ref)	—
	445	77	43	1.0 (Ref)	—	1.0 (Ref)	—
Adverse pathology[a] absent							
aRT(t)	391	21	7	0.82 (0.52 to 1.27)	.37	0.78 (0.50 to 1.22)	.28
	391	21	7	0.83 (0.53 to 1.29)	.42	0.81 (0.52 to 1.27)	.36
No RT(t)	19,733	1,364	156	0.70 (0.62 to 0.79)	< .001	1.07 (0.93 to 1.23)	.33
	19,733	1,364	156	0.71 (0.63 to 0.80)	< .001	1.09 (0.95 to 1.26)	.22
sRT(t)	3,570	322	139	1.0 (Ref)	—	1.0 (Ref)	—
	3,570	322	139	1.0 (Ref)	—	1.0 (Ref)	—

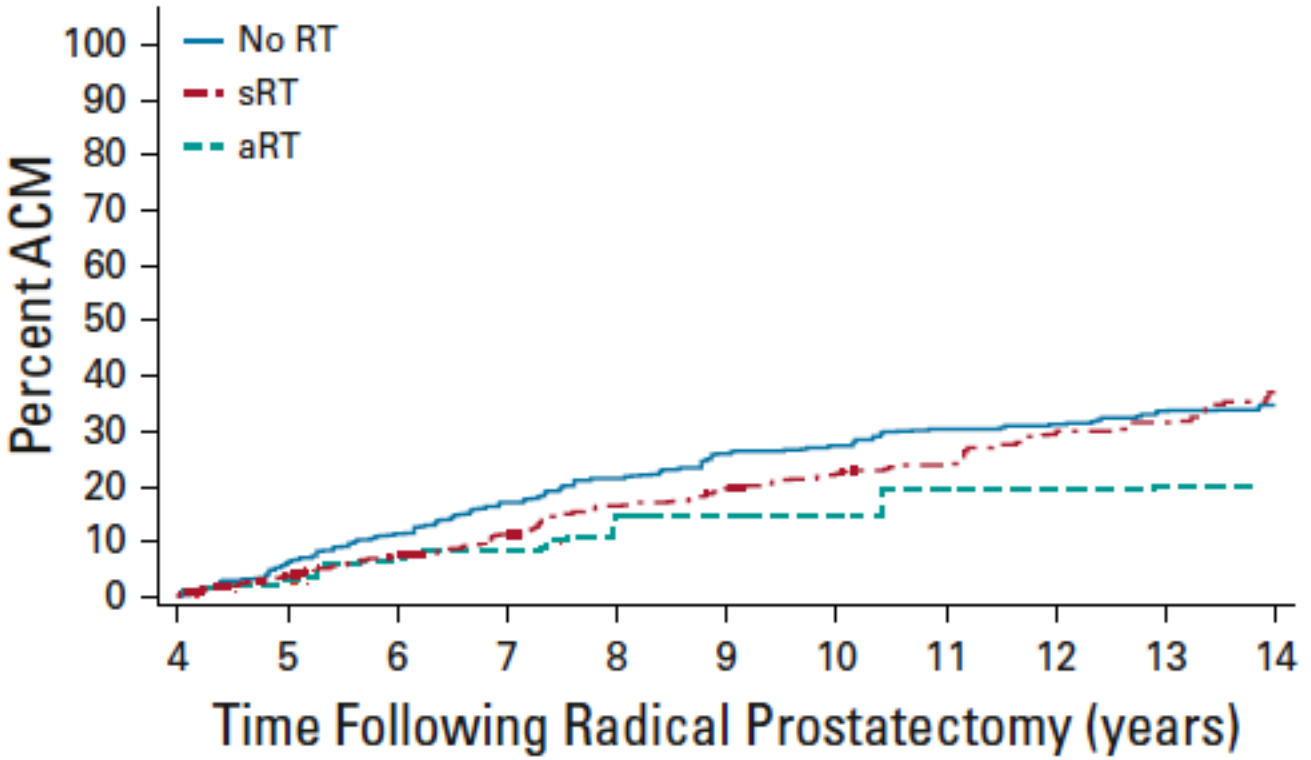
Sensitivity analysis:

- After excluding men w adverse pathology who had a persistent PSA from the early salvage cohort, the association of reduced ACM with adjuvant RT remained significant (0.33 [0.13-0.85], P=0.02 excluding pN1) (0.66 [0.44-0.99]; P=0.04 including pN1)
- Significant association w adjuvant RT and decrease ACM risk in men with positive margin and ≥pT3a disease (0.55 [0.34-0.90];P=0.02), but significance lost when excluding men with persistent PSA (0.67 [0.37-1.001]; P=0.0504)
- No SS difference when defining adverse path per Radicals (P=0.49), Raves (P=0.22), and Getug (P=0.05)

		Adverse Pathology Present	
Definition of Adverse Pathology	**No. of Men (%)**	**AHR (95% CI)**	***P***
(≥ pT3 and ≥ pGL 8) or pN1	2,424 (9.28)	0.61 (0.41 to 0.89)	.01
As above excluding men with a persistent PSA	2,106 (8.27)	0.66 (0.44 to 0.99)	.04
(≥ pT3 and ≥ pGL 8) and pN0	933 (3.79)	0.31 (0.12 to 0.78)	.01
As above excluding men with a persistent PSA	826 (3.42)	0.33 (0.13 to 0.85)	.02
(≥ pT3 OR margin +) and pN0	9,083 (36.88)	0.70 (0.46 to 1.05)	.09
As above excluding men with a persistent PSA[a]	8,719 (36.05)	0.77 (0.51 to 1.17)	.22
(≥ pT3 AND margin +) and pN0	2,387 (9.69)	0.55 (0.34 to 0.90)	.02
As above excluding men with a persistent PSA[b]	2,192 (9.06)	0.61 (0.37 to 1.001)	.05[c]
Pre-RP PSA ≥ 10 ng/mL OR ≥ pT3 OR margin + OR ≥ pGL 7 (can include pN1)	20,518 (78.56)	0.78 (0.58 to 1.06)	.11
As above excluding men with a persistent PSA[d]	19,875 (78.05)	0.89 (0.66 to 1.21)	.49
(Pre-RP PSA ≥ 10 ng/mL OR ≥ pT3 OR margin + OR ≥ pGL 7) and pN0	19,029 (77.27)	0.79 (0.52 to 1.19)	.25
As above excluding men with a persistent PSA	18,597 (76.90)	0.89 (0.59 to 1.35)	.59

After adjusting for age, institution, propensity score, and ADT use , men with adverse pathology on RP including pN1 had adjusted ACM estimates that were significantly lower with adjuvant compared to salvage RT (P<0.001), though not SS lower compared to no RT (P=0.09)

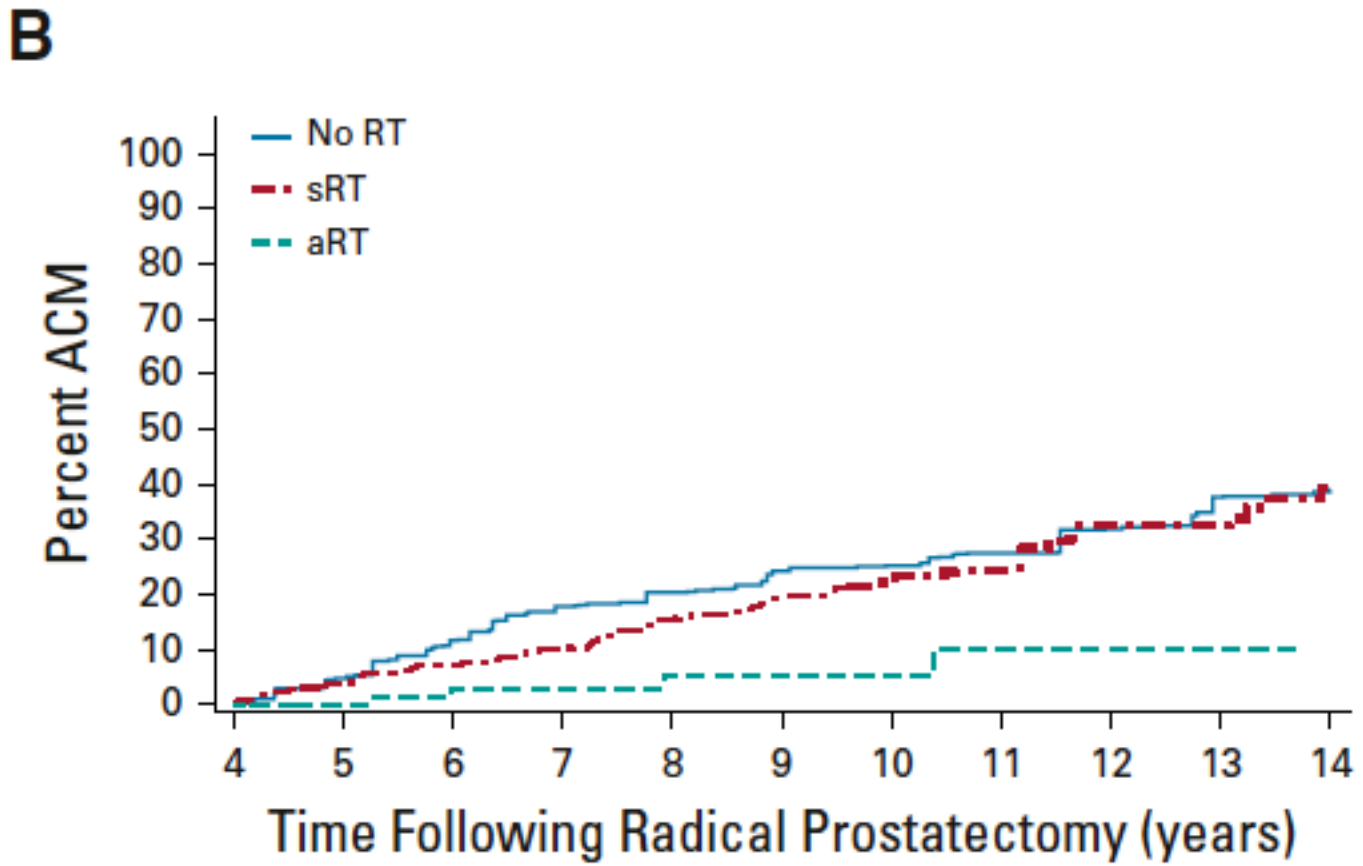
A



No. at risk:

No RT	1,102	853	652	521	426	356	307	262	224	181	156
sRT	895	740	600	469	347	268	192	146	103	75	57
aRT	427	327	259	199	130	86	62	44	25	13	8

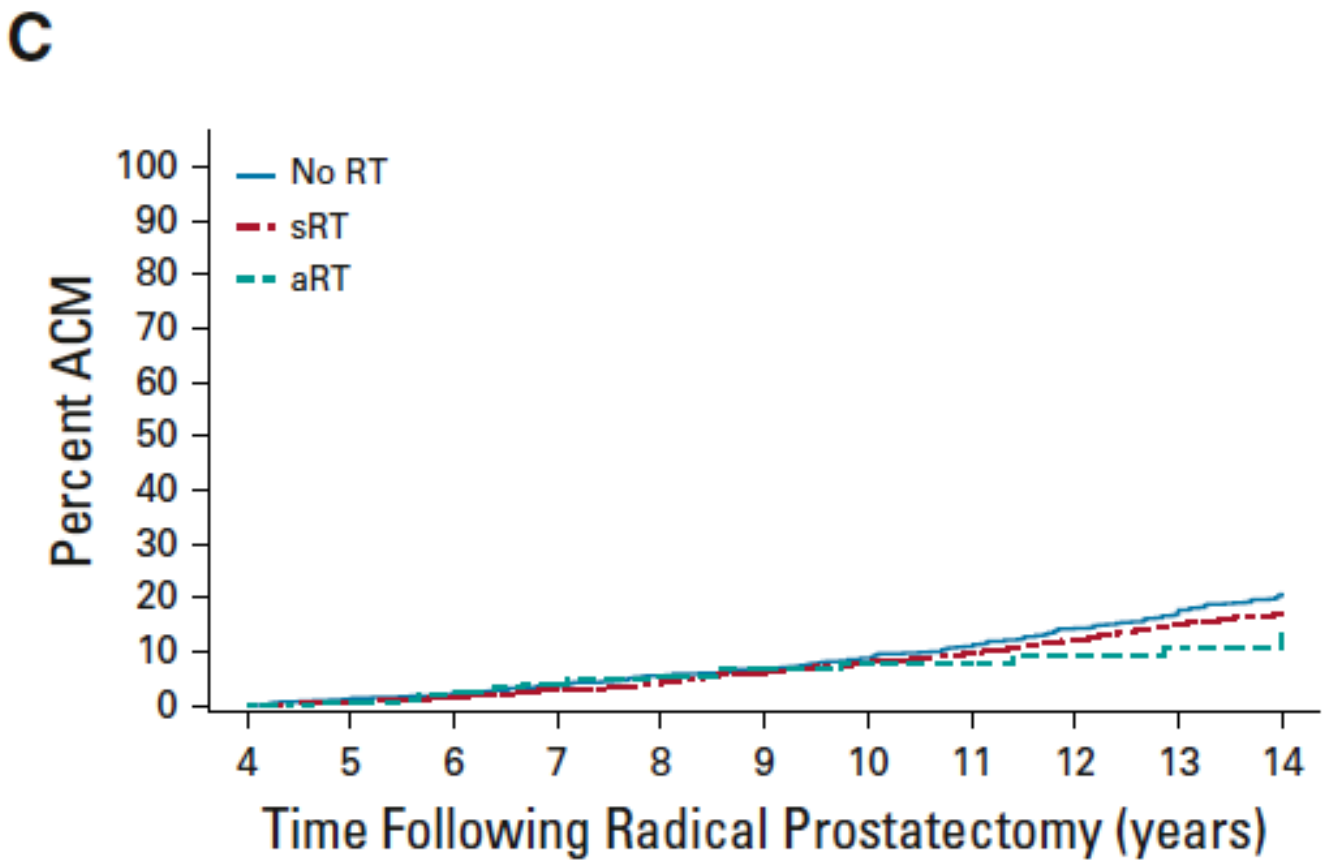
Similarly, **after adjustments for age, institution, propensity score, and ADT use,** men with adverse pathology *excluding pN1* prostate cancer who received adjuvant RT had **significantly lower ACM estimates** compared with those who received salvage RT (P=0.003) but not compared with no RT (P=0.36)



No. at risk:

No RT	438	343	274	224	194	167	141	124	106	81	70
sRT	387	332	285	240	189	153	113	88	59	42	32
aRT	108	81	68	52	38	26	21	14	10	5	3

After adjustments for variables, among men **lacking adverse pathologic features**, there was **no SS difference in ACM estimates** between those receiving adjuvant vs. salvage RT.



No. at risk:

No RT	21,089	18,196	15,633	13,353	11,253	9,466	7,859	6,620	5,422	4,367	3,483
sRT	2,217	2,248	2,206	2,084	1,859	1,620	1,351	1,138	936	745	595
aRT	388	325	269	229	185	144	107	84	59	43	27

Summary

- Men treated with adjuvant RT had less favorable prognostic factors (higher proportion of + margins and T3a+ disease), placing them at higher risk for needing salvage ADT and death – despite this, adjuvant RT had better outcomes compared to early salvage
- These findings support the idea that there exists a subset of men with adverse pathology at RP who may benefit from adjuvant RT, suggesting that the findings of Raves/Radicals/Getug/Artistic do not apply to everyone

Considerations

- Median PSA in early salvage was 0.3 – does this accurately reflect the PSAs seen in clinical practice?
- Nonrandomized studies at risk for selection bias: men selected for adjuvant RT may have been healthier and thus survived longer; thus the results of this study may be overestimating the reduction in all cause mortality
- Fewer men received ADT in this study compared with prior RCTs. ADT delays time to progression, so how reliable is PFS as an endpoint in the setting of ADT use?
- what is the benefit of pelvic RT or supplemental ADT in men with adverse pathology
- what is the role of genomic profiling in identifying benefit from adjuvant vs. early salvage RT

Opinion:
This nonrandomized data should not be practice changing in the context of 3 randomized controlled trials having shown equivalence between adjuvant vs. early salvage. Data is interesting and does suggest possible benefit of adjuvant RT for men w adverse path features.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