original reports

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

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abstract

PURPOSE Adjuvant compared with early salvage radiation therapy (sRT) following radical prostatectomy (RP) has not been shown to reduce progression-free survival in randomized controlled trials. However, these trials might have missed a benefit in men with adverse pathology at RP given that these men were under-represented and immortal time bias might have been present; herein, we investigate this possibility.

METHODS We evaluated the impact of adjuvant versus early sRT on all-cause mortality (ACM) risk in men with adverse pathology defined as positive pelvic lymph nodes (pN1) or pGleason score 8-10 prostate cancer (PC) and disease extending beyond the prostate (pT3/4). We used a treatment propensity score to minimize potential treatment selection bias when estimating the causal effect of adjuvant versus early sRT on ACM risk and a sensitivity analysis to assess the impact that varying definitions of adverse pathology had on ACM risk adjusting for age at RP, PC prognostic factors, site, and the time-dependent use of post-RP androgen deprivation therapy.

RESULTS After a median follow-up (interquartile range) of 8.16 (6.00-12.10) years, of the 26,118 men in the study cohort, 2,104 (8.06%) died, of which 539 (25.62%) were from PC. After excluding men with a persistent prostate-specific antigen, adjuvant compared with early sRT was associated with a significantly lower ACM risk among men with adverse pathology at RP when men with pN1 PC were excluded (0.33 [0.13-0.85]; $P = .02$) or included (0.66 [0.44-0.99]; $P = .04$).

CONCLUSION Adjuvant radiation therapy should be considered in men with pN1 or pGleason score 8 to 10 and pT3/4 PC given the possibility that a significant reduction in ACM risk exists.

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INTRODUCTION

Adjuvant radiation therapy (aRT) to the prostatic bed versus surveillance following radical prostatectomy (RP) in men with extra-prostatic extension, seminal vesicle invasion (SVI), or positive surgical margins halved the risk of progression[1-3] before the routine use of post-RP prostate-specific antigen (PSA) monitoring was practiced. Subsequently, three randomized controlled trials (RCTs)[4-7] where post-RP PSA monitoring was used investigated whether adjuvant versus early salvage radiation therapy (sRT) was superior[5-7] or whether early salvage versus aRT was noninferior[4] with a primary end point of progression-free survival (PFS) in two studies (GETUG-AFU 17[5,6] and RAVES[4]) and metastasis-free survival in one study (RADICALS RT[7]).

While not significant, the point estimate of the PFS hazard ratio (HR) comparing adjuvant with sRT was > 1.0 in the largest study[7] and in high-risk subsets including SVI and prostatectomy (p) Gleason score 8-10 in the next largest study,[4] suggesting that early sRT may be superior to aRT with respect to PFS. At best, PFS following early sRT could be equivalent to aRT, but not superior given the delay in the administration of treatment when the PSA is detectable (ie, early salvage) compared with undetectable (ie, adjuvant).

A possible explanation for these findings is immortal time bias.[8] Specifically, a patient randomly assigned to the 2-month course of aRT initiated treatment with an undetectable PSA, whereas on the sRT arm, men were required to start the 2-month course of sRT within 4 months of exceeding the PSA trigger level (> 0.1 ng/mL[7] or > 0.2 ng/mL[4-6]) for recurrence with an assessment for progression (PSA level ≥ 0.4 ng/mL) within 3 months following sRT. Therefore, men on the sRT arm would not be assessable for progression for several months following the PSA trigger level to initiate sRT.

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Did prior randomized trials miss the benefit of delivering adjuvant compared with early salvage radiation therapy (sRT) in men with adverse prostate cancer pathology at radical prostatectomy (RP) because of inadequate power and/or the presence of immortal time bias?

Knowledge Generated

Adjuvant compared with early sRT was associated with a reduction in the risk of death among men with adverse pathology at RP, which included those with prostatectomy Gleason score 8-10 prostate cancer and extension of the cancer beyond the prostate and/or involved pelvic lymph nodes.

Relevance

Three randomized trials and an associated meta-analysis found no difference in progression-free survival when comparing adjuvant with early sRT, which can cause many physicians to not offer adjuvant radiation therapy, irrespective of the pathologic findings at RP. We provide evidence to support that adjuvant compared with early sRT may lower the risk of death in men with adverse pathology at RP.

Men with adverse pathology at RP are at high risk for recurrence[9] and include those with pelvic lymph node–positive (pN1) disease or prostatectomy (p) Gleason score 8-10 and extra-prostatic extension (pT3a) or SVI (pT3b) or invasion into adjacent organs (pT4). When these men recur, their PSA typically increases rapidly[9] and can result in PSA rise from the trigger PSA level of 0.1 ng/mL or 0.2 ng/mL to 0.4 ng/mL (ie, progression), while sRT is being planned and delivered and before the PSA response following sRT is assessed.[8] If this occurs, then men with adverse pathology would be scored as having progressed on the early sRT arm at a later time compared with men on the aRT arm explaining why early sRT tended toward superiority compared with aRT.[7] Therefore, the question of whether men with adverse pathology at RP benefit from adjuvant compared with early sRT remains unknown and was retrospectively investigated in the current study.

METHODS

Patient Population and Treatment

The study cohort comprised 26,118 men of median [interquartile range (IQR)] age 62 (57-67) years with pT2-4N0 or N1M0 prostate cancer (PC) consecutively treated between June 23, 1989, and July 26, 2016, with RP and pelvic lymph node assessment and then followed for possible treatment with adjuvant or early sRT at the University Hospital Hamburg-Eppendorf (Hamburg, Germany), Charité University Hospital (Berlin, Germany), University Hospital Ulm (Ulm, Germany), and two academic centers in the United States including University of California, San Francisco, and Johns Hopkins Medical Institution. The use of aRT, early sRT, or no radiation therapy (RT) among the 26,188 men is stratified by the presence or absence of adverse pathology (Fig 1).

Prostatectomy specimens underwent review by a pathologist with expertise in genitourinary pathology. In accord with federal and institutional guidelines, men signed an institutional review board–approved, protocol-specific informed consent form permitting prospective collection of deidentified data at baseline and follow-up, which were entered into a secure, password-protected database for outcome analysis. A minority of data were collected retrospectively.

Follow-up and Determination of the Cause of Death

Follow-up started on the day of RP and concluded on the date of last follow-up or the date of death, whichever came first; no patient was lost to follow-up. The database was last updated on October 2, 2020. During follow-up, patients had a PSA test and rectal examination and were seen every 3 months for 1 year, every 6 months for an additional 4 years, and then annually thereafter. To assign PC-specific mortality (PCSM) as the cause of death, castrate-resistant metastatic PC on the basis of a rising PSA level in the setting of a testosterone level < 20 ng/dL before death needed to be confirmed.

Statistical Analysis (Protocol, online only)

Comparison of the distribution of clinical factors and post-operative treatment. Comparisons of the distribution of clinical factors and post-RP treatment stratified by no or adjuvant versus early sRT among men with no adverse pathology or adverse pathology including and excluding pN1 PC were made using a Mantel-Haenszel χ^2 metric[10] for categorical covariates; in the case of a small sample size, a Fisher exact test[11] was used. For continuous covariates, such as age and year of treatment, medians and their distributions were compared using a Wilcoxon 2-sample test.[12]

Univariable and multivariable hazard ratios for all-cause mortality risk. Univariable and multivariable regression using method by Cox[13] was used to evaluate whether all-cause mortality (ACM) risk was significantly associated with the use of adjuvant versus early sRT in an interaction model[13] among men with or without evidence of adverse pathology at RP. The same RT timing question was asked among men with evidence of adverse pathology at RP but

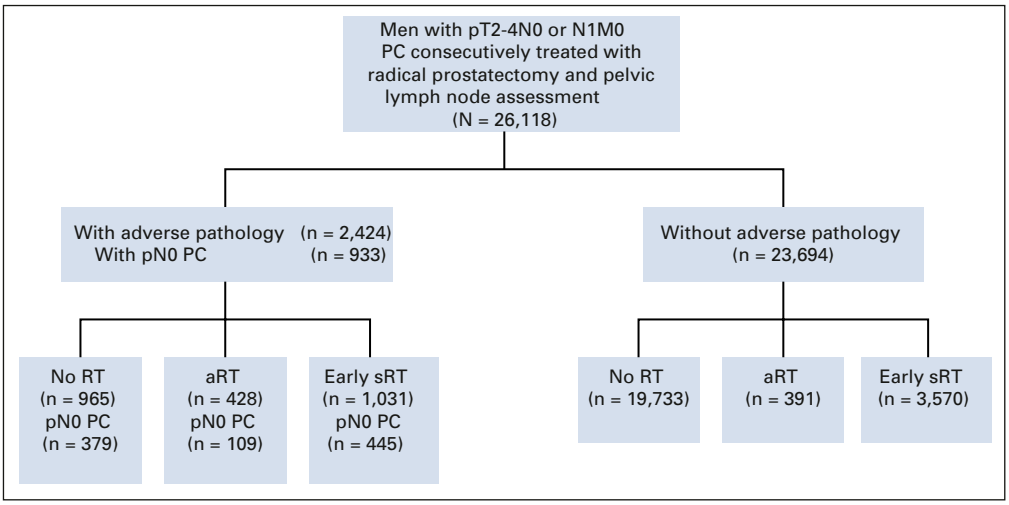

FIG 1. CONSORT diagram illustrating the distribution of adjuvant, early salvage, or no RT use over the study period among the 26,118 men in the study cohort stratified by the presence or absence of adverse pathology. aRT, adjuvant radiation therapy; PC, prostate cancer; RT, radiation therapy; sRT, salvage radiation therapy; T, tumor category.

excluding men with pN1 PC given that these men were not included in two of three RCTs.[4-6] We define early sRT (t) as the time-dependent baseline group and report the results for adjuvant versus early sRT (t) and no RT versus early sRT (t) among men with or without adverse pathology at RP. In addition to PC prognostic factors, all models were adjusted for site with University Hospital Hamburg-Eppendorf as the reference group, age at RP, and the time-dependent use[14] of post-RP androgen deprivation therapy (ADT), which could be in the adjuvant or salvage setting. Finally, an assessment of treatment in men with and without adverse pathology by institution interaction[13] was performed. Time zero was defined as the date of RP.

Treatment propensity score. The treatment propensity score (PS)[15] represents the probability of treatment assignment conditional on observed baseline prognostic covariates. PSs were estimated using multinomial logistic regression, with treatment (aRT, early sRT, and no RT) as the outcome and age in years at RP (continuous) and year of RP categorized about the median, ln (initial pre-RP PSA level, continuous), and margin status (+ *v* –) as prognostic covariates. To minimize the potential bias when estimating treatment effect of aRT, early sRT, or no RT on ACM risk in the Cox model,[13] we adjust using a treatment PS. Age is used twice in the adjusted model because physicians incorporate age in decisions regarding treatment selection and age is also prognostic for ACM risk.

Sensitivity analysis. A sensitivity analysis[16] was performed using different definitions of adverse pathology including the three definitions used in the three RCTs[4-7] to ascertain the impact of varying definitions of adverse pathology on the adjusted HR of ACM for men who underwent adjuvant versus early sRT. For the Cox model,[13] an event was defined as any death. The assumptions of the Cox model[13] were tested, and no evidence was found that these assumptions were violated. Unadjusted and adjusted HRs for ACM, with associated 95% CIs and *P* values, were calculated for each covariate.

Adjusted estimates of ACM. For the purpose of illustration, adjusted estimates of ACM (1 minus Kaplan-Meier[17] estimates of overall survival [OS]) following RP stratified by no RT and the time-dependent treatment groups of aRT or early sRT among men with adverse pathology or all others were calculated using the extended Kaplan-Meier method with time-dependent treatment groups.[14] These estimates were adjusted for the treatment PS[16] and the fixed covariates of age at RP,[18] institution with University Hospital Hamburg-Eppendorf as the baseline institution, and the time-dependent use[14] of post-RP ADT. A 2-sided *P* value $\leq$ .05 was considered statistically significant, and the Bonferroni method[19] was used for multiplicity adjustment of six comparisons such that the smallest *P* value needed to be $\leq$ .05/.06 or $\leq$ .0083 to be considered significant. *P* values for the adjusted plots were calculated using the Cox[13] model and were adjusted for both fixed and time-dependent covariates. R (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) was used to calculate Kaplan-Meier estimates with time-dependent treatment covariates. SAS (version 9.4; SAS Institute Inc, Cary, NC) was used for all other calculations.

RESULTS

Description and Comparison of the Distribution of Clinical Factors and Postoperative Treatment

Of the 26,118, 819 (3.14%) received aRT (ie, PSA level $<$ 0.1 ng/mL) generally within 6 months of RP and

4,601 (17.72%) underwent early sRT at a median PSA of 0.30 ng/mL (IQR: 0.20-0.62). Of the 4,601 men who received early sRT, 655 had a persistent PSA (14.24%) defined as the PSA level ≥ 0.1 ng/mL postoperatively and were categorized into the early sRT group. Adjuvant ADT and salvage ADT (sADT) were used in 352 (1.35%) and 2,532 (9.69%) men, respectively. aRT was delivered at a median of 3.55 months (IQR: 2.79-4.50 months) after RP to the prostatic bed (median dose: 68.4 Gy) and 45.0 Gy to the pelvic lymph nodes if involved and at the discretion of the treating physician. Adjuvant ADT was given for a median of 9.17 months (IQR: 3.94-23.49 months). Among 26,118 men, 1,491 (5.71%) were found to have pN1 PC (median number of lymph nodes removed: 12 [IQR: 7-19]), of which 319 (21.4%) received aRT and 241 (16.16%) received adjuvant ADT. sADT was delivered following PSA failure and clinical or radiographic evidence of progression after receiving aRT or early sRT. Men who received neither aRT nor early sRT (ie, No RT group) never experienced PSA failure during the conduct of the study or were treated with sADT alone at progression (Table 1).

As shown in Table 1, men with adverse pathology including pN1 PC who underwent adjuvant compared with early sRT had a significantly higher proportion of pT3a or higher (97.90% *v* 94.48%; $P = .002$) and margin-positive PC (82.71% *v* 45.68%: $P < .001$), whereas sADT use was significantly lower (36.21% *v* 47.53%; $P < .001$). Similarly, among men undergoing adjuvant compared with early sRT with adverse pathology excluding pN1 PC, the proportion of men with margin-positive PC was significantly higher (88.07% *v* 45.17%; $P < .001$) and sADT use was less (35.78% *v* 45.84%; $P = .06$).

Univariable and Multivariable HRs for ACM Risk

Men included in the study had a minimum follow-up of 4 years and a maximum follow-up of 28.41 years and initiated treatment within 4-6 weeks of diagnosis. After a median follow-up (IQR) of 8.16 (6.00-12.10) years, 2,104 (8.06%) men died, of which 539 (25.62%) were from PC. As shown in Table 2, adjuvant compared with early sRT was associated with a significantly lower ACM risk among men with adverse pathology at RP when men with pN1 PC were excluded (0.31 [0.12-0.78]; $P = .01$) or included (0.61 [0.41-0.89]; $P = .01$), whereas no significant association was observed in men without adverse pathology at RP ($P \geq .28$).

Sensitivity Analysis

The results of the sensitivity analysis are shown in Table 3. After excluding men with adverse pathology who had a persistent PSA from the early sRT cohort, the association of a reduced ACM risk with adjuvant as compared with early sRT remained significant (0.33 [0.13-0.85]; $P = .02$) (0.66 [0.44-0.99]; $P = .04$) when men with pN1 PC were excluded or included, respectively. There was a significant association with adjuvant as compared with sRT use and decreased ACM risk in men with a positive margin and ≥ pT3a PC (0.55 [0.34-0.90]; $P = .02$), but this significance was lost when excluding men with a persistent PSA (0.67 [0.37-1.001]; $P = .0504$). When defining adverse pathology as per the patient selection criteria from the three RCTs,[4-7] adjuvant as compared with early sRT was not significantly associated with lower ACM risk ($P_{RADICALS\text{-}RT} = .49$, $P_{RAVES} = .22$, and $P_{GETUG\text{-}AFU\ 17} = .0504$).

Adjusted Estimates of ACM

After adjustment for six comparisons, as illustrated in Figure 2A, men with adverse pathology including pN1 PC had adjusted ACM estimates that were significantly lower with aRT ($P < .001$), but not no RT ($P = .09$) compared with early sRT. Similarly, men with adverse pathology excluding pN1 PC had adjusted ACM estimates that were significantly lower with aRT ($P = .003$), but not no RT ($P = .36$) compared with early sRT as shown in Figure 2B. These respective comparisons had *P* values of .57 and .11 among men without adverse pathology as shown in Figure 2C.

Ten-year adjusted point estimates of ACM and associated 95% CI were 13.78% (95% CI, 8.43 to 22.12), 27.32% (95% CI, 22.54 to 32.88), and 21.98% (95% CI, 18.30 to 26.27) for men with adverse pathology including pN1 PC who received adjuvant, no, or early sRT, respectively. These respective estimates were 5.13% (95% CI, 2.00 to 12.82), 25.32% (95% CI, 18.95 to 33.34), and 22.15% (95% CI, 17.55 to 27.74) for men with adverse pathology excluding pN1 PC and 7.82% (95% CI, 4.55 to 13.28), 8.81% (95% CI, 7.35 to 10.54), and 7.95% (95% CI, 6.82 to 9.24) for men without adverse pathology. The differences in the 10-year adjusted point estimates of ACM for men undergoing aRT versus early sRT with adverse pathology including or excluding pN1 PC were –8.20% (95% CI, –15.96 to –0.43) and –17.02% (95% CI, –24.00 to –10.05), respectively. Given that the 95% CI of the difference in the 10-year adjusted point estimates of ACM excluded 0.00 verifies that the 10-year adjusted point estimates for aRT and early sRT are significantly different and given the magnitude of these differences, also clinically relevant.

DISCUSSION

We found that among men with adverse pathology at RP including pN1 or pGleason score 8-10 and pT3a or higher PC, adjuvant compared with early sRT was associated with a significant reduction in ACM risk. This association of reduced ACM risk with adjuvant compared with early sRT is strengthened given that men who underwent adjuvant compared with early sRT had less favorable PC prognostic factor distributions, which should have placed them at higher risk for needing sADT and dying. However, they had lower rates of sADT use and a lower ACM risk.

The clinical significance of this finding is that there exists a subset of men with adverse pathology at RP who may experience a lower ACM risk when adjuvant as opposed to early sRT is delivered. Yet, three randomized trials[4-7] and a

TABLE 1. Comparison of the Distribution of Clinical Factors and Post-RP Treatment Stratified by No or Adjuvant as Compared With Early sRT Among Men With No Adverse Pathology or Adverse Pathology Including and Excluding pN1 Prostate Cancer

		Adverse Pathology Including pN1 (n = 2,424)				Adverse Pathology Excluding pN1 (n = 933)				No Adverse Pathology (n = 23,694)			
Clinical Factors, Post-RP Treatment	All Men (N = 26,118)	No RT	aRT[a]	sRT[a]	*P*: No RT *v* sRT, aRT *v* sRT	No RT	aRT[a]	sRT[a]	*P*: No RT *v* sRT, aRT *v* SRT	No RT	aRT[a]	sRT[a]	*P*: No RT *v* sRT, aRT *v* sRT
Median age at RP, years (IQR)	62 (57-67)	64 (58-78)	64 (60-69)	64 (58-68)	.92, .18	63 (58-68)	65 (61-68)	64 (58-68)	.72, .048	62 (57-67)	64 (59-68)	62 (57-67)	.03, < .001
Median year of RP (IQR)	2008 (2003-2012)	2009 (2000-2013)	2012 (2009-2014)	2011 (2007-2013)	< .001, < .001	2007 (1999-2012)	2011 (2008-2013)	2009 (2005-2012)	< .001, < .001	2008 (2003-2012)	2009 (2006-2012)	2008 (2003-2011)	.04, < .001
Pre-RP PSA level, ng/mL													
< 4	3,275 (12.54%)	72 (7.46%)	20 (4.67%)	52 (5.04%)	< .001, .94	42 (11.08%)	10 (9.14%)	37 (8.31%)	.003, .88	2,861 (14.50%)	16 (4.09%)	254 (7.11%)	< .001, < .001
4-10	15,635 (59.86%)	394 (40.83%)	152 (35.51%)	361 (35.01%)		191 (50.04%)	47 (43.12%)	184 (41.35%)		12,540 (63.55%)	197 (50.38%)	1,991 (55.77%)	
> 10	7,208 (27.60%)	499 (51.71%)	256 (59.81%)	618 (59.94%)		146 (38.52%)	52 (47.71%)	224 (50.34%)		4,332 (21.95%)	178 (45.52%)	1,325 (37.11%)	
AJCC prostatectomy stage													
T2	17,184 (65.79%)	65 (6.74%)	9 (2.10%)	61 (5.92%)	.45, .002	—	—	—	NA	15,344 (77.76%)	55 (14.07%)	1,650 (46.22%)	< .001, < .001
T3a or higher	8,934 (34.21%)	900 (93.26%)	419 (97.90%)	970 (94.48%)		379	109	445		4,389 (22.24%)	366 (85.93%)	1,920 (53.78%)	
Prostatectomy Gleason score													
7 or less	24,258 (92.88%)	391 (40.52%)	168 (39.25%)	380 (36.86%)	.09, .39	—	—	—	NA	19,475 (98.69%)	383 (97.95%)	3,461 (96.95%)	< .001, .26
8-10	1,860 (7.12%)	574 (59.48%)	260 (60.75%)	651 (63.14%)		379	109	445		258 (1.31%)	8 (2.05%)	109 (3.05%)	
Prostatectomy margin status													
Negative	21,498 (82.31%)	673 (69.74%)	74 (17.29%)	560 (54.32%)	< .001, < .001	287 (75.73%)	13 (11.93%)	224 (54.83%)	< .001, < .001	17,632 (89.35%)	45 (11.51%)	2,514 (70.42%)	< .001, < .001
Positive	4,620 (17.69%)	292 (30.26%)	354 (82.71%)	471 (45.68%)		92 (24.27%)	96 (88.07%)	201 (45.17%)		2,101 (10.65%)	346 (88.49%)	1,056 (29.58%)	
Prostatectomy nodal status													
Negative	24,627 (94.29%)	379 (39.27%)	109 (25.47%)	445 (43.16%)	.08, < .001	379	109	445	NA	19,733	391	3,750	NA
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	8 (2.11%)	24 (22.02%)	18 (4.04%)	.11, < .001	23 (0.12%)	26 (6.65%)	12 (0.34%)	.002, < .001
No	25,766 (98.65%)	912 (94.51%)	270 (63.08%)	951 (92.24%)		371 (97.89%)	85 (77.98%)	427 (95.96%)		19,710 (99.89%)	365 (93.35%)	3,558 (99.66%)	
sADT[a]													
Yes	2,532 (9.69%)	232 (24.04%)	155 (36.21%)	490 (47.53%)	< .001, < .001	61 (16.09%)	39 (35.78%)	204 (45.84%)	< .001, .06	449 (2.28%)	59 (15.09%)	1,147 (32.13%)	< .001, < .001
No	23,586 (90.31%)	733 (75.96%)	273 (63.79%)	541 (52.47%)		318 (83.91%)	70 (64.22%)	241 (54.16%)		19,284 (97.72%)	332 (84.91%)	2,423 (67.87%)	

Abbreviations: ADT, androgen deprivation therapy; AJCC, American Joint Commission of Cancer; aRT, adjuvant radiation therapy; IQR, interquartile range; NA, not available; pN1, prostatectomy node–positive; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy; sADT, salvage androgen deprivation therapy; sRT, salvage radiation therapy; T, tumor.

[a]Comparisons of the distribution of time-dependent postoperative treatment covariates are made retrospectively given that time 0 is defined as the date of RP.

TABLE 2. Treatment PS AHRs for the Risk of Death Including (Top Row) and Excluding (Bottom Row) Men With pN1 PC

				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)	—
Treatment PS							
PS for selection of aRT *v* (sRT or no RT)	26,118	2,104	539	1.02 (1.01 to 1.03)	.005	0.99 (0.98 to 0.993)	< .001
	24,627	1,876	392	1.01 (0.99 to 1.03)	.60	0.98 (0.97 to 0.99)	< .001
PS for selection of sRT *v* (aRT or no RT)	26,118	2,104	539	1.03 (1.02 to 1.03)	< .001	0.99 (0.98 to 1.01)	.43
	24,627	1,876	392	1.03 (1.02 to 1.03)	< .001	0.97 (0.95 to 0.997)	.03
Patient and PC prognostic factors							
Age at RP, years	26,118	2,104	539	1.08 (1.07 to 1.09)	< .001	1.07 (1.06 to 1.08)	< .001
	24,627	1,876	392	1.09 (1.08 to 1.10)	< .001	1.08 (1.07 to 1.09)	< .001
Adverse pathology							
Present	2,424	397	237	2.78 (2.29 to 3.38)	< .001	2.04 (1.68 to 2.50)	< .001
	933	169	90	2.82 (2.20 to 3.61)	< .001	2.15 (1.67 to 2.78)	< .001
Absent	23,694	1,707	302	1.0 (Ref)	—	1.0 (Ref)	—
	23,694	1,707	302	1.0 (Ref)	—	1.0 (Ref)	—
Institution[b]							
UCSF	735	97	17	1.45 (1.18 to 1.78)	< .001	1.51 (1.23 to 1.86)	< .001
	735	97	17	1.58 (1.28 to 1.95)	< .001	1.49 (1.21 to 1.85)	< .001
Johns Hopkins Medical Institute	7,560	717	229	0.73 (0.67 to 0.81)	< .001	1.05 (0.95 to 1.16)	.35
	7,358	651	174	0.74 (0.67 to 0.82)	< .001	1.05 (0.94 to 1.17)	.41
Charité University Hospital[c] and University Hospital Ulm[c]	505	55	2	1.16 (0.89 to 1.52)	.28	0.94 (0.71 to 1.24)	.65
	505	55	2	1.28 (0.98 to 1.68)	.08	0.91 (0.69 to 1.21)	.53
University Hospital Hamburg-Eppendorf	17,318	1,235	291	1.0 (Ref)	—	1.0 (Ref)	—
	16,029	1,073	199	1.0 (Ref)	—	1.0 (Ref)	—
Time-dependent ADT use							
Adjuvant ADT(t)	352	55	34	2.44 (1.86 to 3.20)	< .001	1.64 (1.21 to 2.21)	.001
	111	16	9	1.84 (1.12 to 3.01)	.02	1.70 (1.02 to 2.84)	.04
sADT(t)	2,532	488	295	3.33 (3.00 to 3.69)	< .001	2.37 (2.09 to 2.69)	< .001
	1,959	357	207	3.07 (2.74 to 3.45)	< .001	2.43 (2.11 to 2.79)	< .001

Abbreviations: ACM, all-cause mortality; ADT, androgen deprivation therapy; AHR, adjusted hazard ratio; aRT, adjuvant radiation therapy; HR, hazard ratio; PC, prostate cancer; pN1, prostatectomy node positive; PS, propensity score; Ref, reference or baseline group; RP, radical prostatectomy; RT, radiation therapy; sADT, salvage androgen deprivation therapy; sRT, salvage radiation therapy; t, time dependence; UCSF, University of California San Francisco.

[a]Adverse pathology includes pGleason scores 8-10 plus pT3a or higher PC with or without pN1 PC.

[b]An assessment of treatment in men with and without adverse pathology by US versus German institution(s) interaction was performed and found not to be significant when pN1 PC was included ($P = .52$) or excluded ($P = .77$) from the definition of adverse pathology.

[c]Institutions are combined given that they represent all men treated following RP in the same way by the two authors (Wiegel and Bohmer); one author (Wiegel) moved from Berlin to Ulm in 2005.

TABLE 3. Sensitivity Analysis Using Different Definitions of Adverse Pathology and Associated Treatment Propensity Score AHRs for the Risk of Death Following Adjuvant Versus Early Salvage Radiation Therapy

		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

Abbreviations: AHR, adjusted hazard ratio; N, node; pGL, prostatectomy Gleason score; PSA, prostate-specific antigen; RP, radical prostatectomy; T, tumor category.

[a]Patient eligibility criteria for the RAVES[4] trial; one patient in the RAVES trial had pN1 prostate cancer.

[b]Patient eligibility criteria for the GETUG-AFU 17[5,6] trial.

[c]Exact $P = .0504$.

[d]Patient eligibility criteria for the RADICALS-RT[7] trial.

meta-analysis[20] on the basis of PFS primarily driven by PSA failure suggest no difference when using adjuvant compared with early sRT, which can lead physicians to not offer aRT to any patient,[21] which could result in an increased risk of death in the subset of men with adverse pathology at RP.

Several points require further discussion. First, selection bias can exist in nonrandomized comparisons. For example, men selected for adjuvant as compared with early sRT might have been healthier and, therefore, survived longer, leading to less death from non-PCSM. Therefore, the magnitude of the reduction in ACM risk we report that is associated with adjuvant as compared with sRT may overestimate the actual reduction (Appendix, online only). Second, fewer men have undergone salvage as compared with aRT on the RADICALS RT[7] AND GETUG-AFU 17[6] trials where concurrent post-RP ADT with RT was used in some or all men, respectively. This difference raises the question as to the reliability of the PFS end point as assessed in the recent RCTs[4-7] and meta-analysis[20] given that ADT use can delay time to progression. Third, although the RADICALS RT trial[7] was designed to evaluate metastasis-free survival, this end point can also be confounded by the timing of post-RP sADT use unless strict rules for its use are detailed and followed on both randomized treatment arms (eg, to start within 1 month of documenting PSA failure), whereas OS should not be confounded by the timing of post-RP sADT use and therefore would be the ideal end point. However, the RADICALS RT study might not be powered to assess OS. Moreover, the cohort of men in whom we identified a possible reduction in ACM risk in the current study are those with pGleason score 8-10 and pT3a or higher PC who comprised at most 9%-17% of men enrolled in the three randomized trials[4-7] that investigated the question of adjuvant versus early sRT. Therefore, whether a future meta-analysis of the three RCTs[4-7] will be adequately powered to evaluate the impact of adjuvant versus early sRT on OS in this important high-risk subgroup[22,23] remains to be answered. Until then, we addressed this question by using a large international and multi-institutional database using a treatment PS[15] to minimize potential treatment selection bias when estimating the causal treatment effect of adjuvant, early salvage, or no RT on ACM risk and adjusted for age at RP, PC prognostic factors, site, and post-RP ADT use as a time-dependent covariate[14] and not as a dichotomous categorical covariate.[24] Moreover, we required a minimum follow-up of 4 years yielding a median follow-up time of 8.16 years permitting evaluation of the long-term outcome of ACM. Finally, the Radiation Therapy Oncology Group 0534[25] and GETUG-AFU 16[26] studies observed a PFS benefit in the salvage setting when elective pelvic lymph node RT was added to prostatic bed RT and short-course ADT and when 6 months of ADT was added to pelvic lymph node and prostatic bed RT, respectively. Also, an OS benefit was observed in RTOG 9601[27] when long-course ADT was added to sRT. However, whether the addition of pelvic RT and/or supplemental ADT can reduce the risk of ACM when delivered in conjunction with aRT as opposed to sRT in men with adverse pathology at RP remains to be

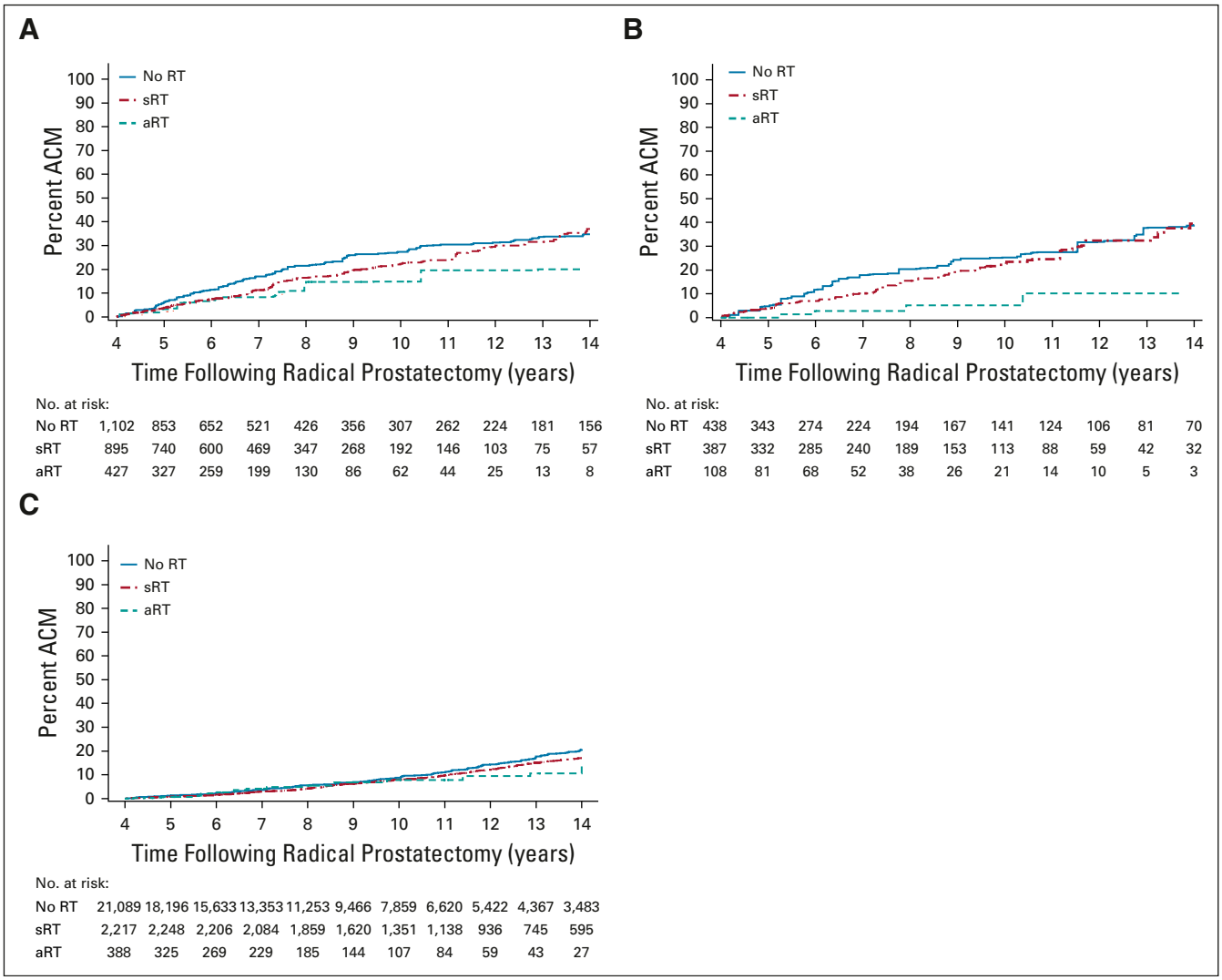

FIG 2. Adjusted estimates of ACM among (A) the 2,424 men with adverse pathology including pN1 and (B) 933 excluding pN1 prostate cancer and (C) 23,694 without adverse pathology comparing time-dependent adjuvant or no RT with time-dependent early salvage RT. *x*-axis begins at the minimum follow-up time of 4 years. ACM, all-cause mortality; aRT, adjuvant radiation therapy; RT, radiation therapy; sRT, salvage radiation therapy.

answered as well as the role of genomic classifiers[28] in identifying men who may benefit from adjuvant as compared with sRT.

In conclusion, three randomized trials[4-7] and a meta-analysis[20] found no difference in PFS for adjuvant compared with early sRT use. However, a benefit might have been missed in men with adverse pathology at RP because of inadequate power and the presence of immortal time bias.[29] We provide evidence to support that adjuvant compared with early sRT may lower ACM risk in these men.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Bolla M, van Poppel H, Tombal B, et al: Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: Long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 380:2018-2027, 2012
2. Thompson IM, Tangen CM, Paradelo J, et al: Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: Long-term follow up of a randomized clinical trial. J Urol 181:956-962, 2009
3. Wiegel T, Bartkowiak D, Bottke D, et al: Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. Eur Urol 66:243-250, 2014
4. Kneebone A, Fraser-Browne C, Duchesne GM, et al: Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): A randomised, controlled, phase 3, non-inferiority trial. Lancet Oncol 21:1331-1340, 2020
5. UNICANCER: Triptorelin and radiation therapy in treating patients who have undergone surgery for intermediaterRisk stage III or stage IV prostate cancer. 2008. NLM identifier: NCT00667069. https://clinicaltrials.gov/ct2/show/NCT00667069
6. Sargos P, Chabaud S, Latorzeff I, et al: Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): A randomised, phase 3 trial. Lancet Oncol 21:1341-1352, 2020
7. Parker CC, Clarke NW, Cook AD, et al: Timing of radiotherapy after radical prostatectomy (RADICALS-RT): A randomised, controlled phase 3 trial. Lancet 396: 1413-1421, 2020
8. Suissa S: Immortal time bias in pharmacoepidemiology. Am J Epidemiol 167:492-499, 2008
9. Markowski MC, Chen Y, Feng Z, et al: PSA doubling time and absolute PSA predict metastasis-free survival in men with biochemically recurrent prostate cancer after radical prostatectomy. Clin Genitourin Cancer 17:470-475, 2019
10. Agresti A: Categorical Data Analysis (ed 3). Hoboken, NJ, John Wiley & Sons, 2012
11. Fisher RA: On the interpretation of X^2 from contingency tables, and the calculation of P. J R Stat Soc 85:87-94, 1922
12. Hollander M, Wolfe D, Chicken E: Nonparametric Statistical Methods (ed 3). Hoboken, NJ, John Wiley & Sons, 2014
13. Klein J, Moeschberger M: Survival Analysis: Techniques for Censored and Truncated Data. Norwell, MA, Springer, 2013
14. Snapinn S, Jiang Q, Iglewicz B: Illustrating the impact of a time-varying covariate with an extended Kaplan-Meier estimator. Am Stat 59:301-307, 2005
15. Newgard CD, Hedges JR, Arthur M, et al: Advanced statistics: The propensity score—A method for estimating treatment effect in observational research. Acad Emerg Med 11:953-961, 2004
16. Velentgas P, Dreyer NA, Nourjah P, et al (eds): Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide. Sensitivity Analysis Chapter 11. Rockville, MD, Agency for Healthcare Research and Quality (US), 2013
17. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958
18. Cupples LA, Gagnon DR, Ramaswamy R, et al: Age-adjusted survival curves with application in the Framingham Study. Stat Med 14:1731-1744, 1995
19. Kutner M, Nachtshein C, Neter J: Analysis of factor level means, in Applied Linear Regression Models (ed 5). New York, NY, McGraw-Hill/Irwin, 2005, pp 756-759
20. Vale CL, Fisher D, Kneebone A, et al: 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. Lancet 396:1422-1431, 2020
21. Knipper S, Sadat-Khonsari M, Boehm K, et al: Impact of adherence to multidisciplinary recommendations for adjuvant treatment in radical prostatectomy patients with high risk of recurrence. Clin Genitourinary Cancer 18:e112-e121, 2020
22. Pierorazio PM, Guzzo TJ, Han M, et al: Long-term survival after radical prostatectomy for men with high Gleason sum in the pathological specimen. Urology 76: 715-721, 2010
23. He J, Albertsen PC, Moore D, et al: Validation of a contemporary five-tiered Gleason grade grouping using population-based data. Eur Urol 71:760-763, 2017
24. Hwang WL, Tendulkar RD, Niemierko A, et al: Comparison between adjuvant and early-salvage postprostatectomy radiotherapy for prostate cancer with adverse pathological features, JAMA Oncol 4:e175230, 2018
25. Pollack A, Karrison TG, Balogh AG Jr, et al: Short term androgen deprivation therapy without or with pelvic lymph node treatment added to prostate bed only salvage radiotherapy: The NRG Oncology/RTOG 0534 SPPORT Trial. Int J Radiat Oncol Biol Phys 102:1605, 2018

26. Carrie C, Magné N, Burban-Provost P, et al: Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): A 112-month follow-up of a phase 3, randomised trial. Lancet Oncol 20:1740-1749, 2010
27. Shipley WU, Seiferheld W, Lukka HR, et al: Radiation with or without antiandrogen therapy in recurrent prostate cancer. N Engl J Med 376:417-428, 2017
28. Den RB, Yousefi K, Trabulsi EJ, et al: Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. J Clin Oncol 33(8):944-951, 2015
29. MacDuffie E, D'Amico AV: Adjuvant vs salvage radiation therapy for high-risk prostate cancer following radical prostatectomy. JAMA Oncol 6:1165-1166, 2020

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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APPENDIX

Sub-Distribution of Adjusted Hazard Ratios for Prostate Cancer–Specific and Non–Prostate Cancer-Specific Mortality

Although men selected for radical prostatectomy are generally healthy, selection bias can still exist in nonrandomized comparisons. Specifically, men selected for adjuvant as compared with early salvage radiation therapy (sRT) might have had less comorbidity and, as a result, survived longer, leading to less death from nonprostate cancer–specific mortality (PCSM). As a result, the magnitude of the reduction in all-cause mortality (ACM) risk we report that is associated with adjuvant as compared with early sRT may overestimate the actual reduction in ACM risk. To address this possibility, we ran a Fine and Grays competing risk (Fine J, et al: J Am Stat Assoc 94:496-509, 1999) multivariable interaction model for the end points of PCSM and non-PCSM, which was analogous to the model by Cox (Klein J and Moeschberger M, Norwell, MA, Springer, 2013) that we ran for the ACM end point, to assess whether the association of a reduction in ACM risk with adjuvant as compared with early sRT was the result of less PCSM risk or less non-PCSM risk or both.

We found that a reduction in PCSM risk appeared to be the main contributor to the reduction in ACM risk given that adjusted hazard ratio (AHR) comparing adjuvant radiation therapy with early sRT for PCSM (AHR: 0.62; $P = .08$ and AHR: 0.14; $P = .06$) was lower and closer to significance when comparing these results for non-PCSM (AHR: 0.74; $P = .33$ and AHR: 0.66; $P = .48$) when men with or without pN1 prostate cancer were included in the definition of adverse pathology, respectively.

Therefore, although we show that the reduction in PCSM risk was the primary contributor to the reduction in ACM risk, the possibility that there was also some contribution to this reduction in ACM risk from a reduction in non-PCSM risk cannot be excluded. This means that the ACM risk reduction we report may overestimate the actual reduction.