Original Article

Salvage Radiation in Men After Prostate-Specific Antigen Failure and the Risk of Death

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BACKGROUND: A survival benefit has been observed with salvage radiation therapy (RT) for prostate-specific antigen (PSA) failure after radical prostatectomy (RP) in men with rapid rises in PSA doubling time (DT, <6 months). Whether such a benefit exits in men with a protracted PSA rise in DT (≥6 months) is unclear and was examined in the current study. **METHODS:** Of 4036 men who underwent RP at Duke University between 1988 and 2008, 519 experienced a PSA failure, had complete data, and were the subjects of this study. Univariate and multivariate Cox regression analyses were performed to evaluate whether salvage RT in men with either a rapid (<6 months) or a protracted (≥6 months) PSA DT was associated with the risk of all-cause mortality adjusting for age at the time of PSA failure, known prostate cancer prognostic factors, and cardiac comorbidity. **RESULTS:** After a median follow-up of 11.3 years after PSA failure, 195 men died. Salvage RT was associated with a significant reduction in all-cause mortality for men with either a PSA DT of <6 months (adjusted hazard ratio [AHR], 0.53; $P = .02$) or a PSA DT of ≥6 months (AHR, 0.52; $P = .003$). In a subset of patients with comorbidity data at the time of PSA failure, salvage RT remained associated with a significant reduction in all-cause mortality for both men with a PSA DT of <6 months (AHR, 0.35; $P = .042$) or a PSA DT of ≥6 months (AHR, 0.60; $P = .04$). **CONCLUSIONS:** Salvage RT for PSA DTs less than or in excess of 6 months is associated with a decreased risk in all-cause mortality. ***Cancer*** **2011;117:3925–32.** © *2011 American Cancer Society.*

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Twenty to 40 percent of men undergoing radical prostatectomy will have a PSA failure within 10 years.[1-4] Without salvage therapy, approximately 1 in 3 of these men will develop distant metastases within 5 years of PSA failure.[5]

Salvage radiation to the prostatic fossa after a PSA recurrence provides the potential for long-term cancer control.[6,7] Ideally, local salvage therapy should be recommended to those men who have both a high probability of a local-only recurrence and who are expected to live long enough to realize the benefits of successful local treatment. Salvage radiation is more effective at prolonging PSA recurrence-free survival in men who have classically indolent disease with lower Gleason scores and increased PSA DT.[7] This likely reflects the finding that men with a protracted PSA rise (ie, PSA DT of ≥6 months) are those most likely to harbor a local-only recurrence and, therefore, are more likely to benefit from salvage radiation. Paradoxically, a survival benefit for salvage RT after biochemical failure after RP has been seen only in men with a PSA DT of ≤6 months, whereas no survival benefit has been noted in men with a PSA DT of >6 months in the same study with a median follow-up after PSA failure limited to 6 years.[8] No studies, to date, have shown that the prolonged PSA recurrence-free survival seen after salvage RT for men with indolent disease (PSA DT of >6 months) corresponds to a survival

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Dr. Chen had full access to all data in the study, and Drs. Cotter and D'Amico take responsibility for the integrity of the data and the accuracy of the data analysis.

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benefit. Evaluation of comorbidity and extended follow-up are needed to determine whether salvage RT will lead to a survival benefit in men with comparatively indolent disease where competing risks can significantly contribute to overall mortality.[9] Therefore, the purpose of this study was to assess whether salvage RT was associated with a decreased risk of all-cause mortality for men with either a rapid or protracted PSA rise after RP adjusting for known prostate cancer prognostic factors, cardiac comorbidity, and age at the time of PSA failure.

MATERIALS AND METHODS

Patient Selection and Treatment

At Duke University Medical Center (Durham, NC) between January 1988 and October 2008, 4036 men underwent radical prostatectomy with or without pelvic lymph node dissection for clinical stage T1c to T3 prostate cancer. These men had an initial postprostatectomy PSA value of <0.2 ng/mL and no pathologic evidence of nodal involvement. After exclusion of 188 men who received adjuvant radiation or hormone therapy before PSA failure, 443 men lacking documentation of baseline characteristics, and 361 men with insufficient data to calculate PSA doubling time, 3044 men remained evaluable. A surgical pathologist with expertise in genitourinary pathology generally evaluated the RP specimens for determination of prostatectomy Gleason (pGleason) score, margin status, and stage.

Of the evaluable men, 519 developed a PSA failure, defined as 2 consecutive rising PSA levels of at least 0.2 ng/mL separated by at least 3 months, and they comprised the study cohort. These men received either no salvage therapy, salvage radiation alone, salvage radiation and androgen-deprivation therapy, or androgen-deprivation therapy alone. Among men who received both radiation and androgen-deprivation therapy, these treatments were considered concurrent if both were initiated within a 6-month period. Age at surgery, prostatectomy Gleason score, prostatectomy stage, time to and date of PSA failure, margins status, timing of and type of salvage therapies, and date and cause of death were recorded.

The study was performed with the approval of the institutional review board at Duke University (NCT # 00978991).

Definition of Cardiac Comorbidity

Men with a history of myocardial infarction, coronary artery disease, or congestive heart failure at or before the time of PSA failure were considered to have cardiac comorbidity, whereas those without any of these conditions at the time of PSA failure were documented to be free of significant cardiac comorbidity. At the time of PSA failure, 87 of the 519 men were without documented comorbidity data and were excluded from subsequent comorbidity analyses.

Follow-Up

Routine follow-up at Duke University generally included history and serum PSA measurements, every 3 months for 2 years, then every 6 months for an additional 3 years, and annually thereafter. Digital rectal examination was generally performed only after PSA recurrence. Follow-up began on the day of RP and continued until last observation or death, through January 23, 2009. No patient in this cohort was lost to follow-up.

Salvage radiation and/or androgen-deprivation therapy after PSA failure were delivered at the discretion of the treating physician. Androgen-deprivation therapy could also be administered after salvage radiation failure at the discretion of the treating physician.

Radiation Treatment and Androgen-Deprivation Therapy

Patients receiving salvage radiation at Duke University were treated to a radiation field that included the surgical bed and ansatamosis, generally to a total dose of 66 Gray (Gy) and within 1 year after the first measurement of a detectable PSA. Pelvic lymph nodes were generally not treated. Radiation was delivered daily in conventional 1.8-Gy to 2-Gy fractions during a 7-week treatment period. Androgen-deprivation therapy consisted of continuous administration of a luteinizing hormone-releasing hormone (LHRH) agonist and/or antiandrogen therapy when given alone at the time of initial PSA failure or when administered after salvage RT failure. When part of a combined regimen, androgen-deprivation therapy was given for a minimum of 6 months surrounding a radiation course, but could be extended after radiotherapy completion at the discretion of the treating physician.

Statistical Methods

Calculation of the PSA Doubling Time

The PSA DT was calculated by assuming first-order kinetics and by using all detectable PSA values after RP but before the start of salvage therapy. Each PSA value was separated by at least 3 months. When a patient had only 1 increase in his PSA level after surgery, but before salvage

therapy was initiated, a PSA DT could not be derived. PSA DT was categorized as greater or less than 6 months for comparison to previously published cohorts.[8,10]

Distribution of Clinical and Pathologic Factors of the Study Cohort Stratified by the value of the PSA DT

Descriptive statistics were used to evaluate baseline patient characteristics at study entry. A Mantel-Haenszel chi-square metric was used to compare the distributions of clinical characteristics among men with PSA DT of ≥6 months or PSA DT of <6 months.[11] The continuous variable of age at the time of PSA failure was compared by using a nonparametric Wilcoxon test.[12]

Risk of All Cause Mortality

The primary endpoint of the study was the risk of all-cause mortality. Survival time was defined as the time from the date of PSA failure to the date of death or to the date of last follow-up for living patients. Univariate and multivariate Cox regression analyses were performed to evaluate whether salvage RT in men with either a rapid (<6 months) or slow (≥6 months) PSA DT was associated with the risk of all-cause mortality adjusting for age at the time of PSA failure, known prostate cancer prognostic factors, and comorbidity.[13] Categorical covariates in the multivariate model included the 1992 American Joint Commission on Cancer (AJCC) pathologic tumor stage (T2 vs T3/4), pGleason score (Gleason 6 or less vs Gleason 7, Gleason 6 or less vs Gleason 8-10), and margin status. The age at the time of PSA failure was incorporated as a continuous variable. Baseline groups for the categorical covariates were pT2 disease, pGleason 6 or less disease, and negative margins. No significant cardiac comorbidity was the baseline in the subgroup analysis of men with comorbidity documentation.

Time-Dependent Covariates

Time-dependent covariates were used to adjust for the potential effect of the timing of salvage RT after PSA failure and the timing of androgen-deprivation therapy, which could be administered in addition to or in lieu of salvage RT, or after salvage RT failure.[13] Because we wished to evaluate whether salvage RT use was beneficial in men with short or long PSA DT, we evaluated the risk of all-cause mortality in these men by using a baseline group of no salvage RT and a short PSA DT (<6 months) and no salvage RT and a longer PSA DT (≥6 months), respectively. The baseline group for the salvage androgen-deprivation therapy covariate was no salvage androgen-deprivation therapy.

The date of PSA failure was defined as time zero for all covariates. Unadjusted (HR) and adjusted hazard ratios (AHR) and their associated 95% confidence intervals (CI) were estimated for all categorical, continuous, and time-dependent covariates.

For all analyses, 2-sided *P*-values of <.05 were considered statistically significant, except for instances where a Bonferroni adjustment for multiple comparisons was used. SAS version 9.2 (SAS Institute, Cary, North Carolina) was used for all calculations.

RESULTS

Distribution of Clinical and Pathologic Factors of the Study Cohort Stratified by the Value of the PSA Doubling Time

The median PSA DT for all men in the study cohort was 10.2 months (interquartile range [IQR], 5.0 months to 25.7 months). There were 158 (30.4%) men who had a PSA DT of <6 months, whereas 361 (69.6%) men had a PSA DT of ≥6 months. Baseline patient characteristics stratified by a PSA DT value of <6 months are compared with ≥6 months in Table 1. Men with a PSA DT of <6 months were younger at PSA failure (median age, 65.6 years vs 68.1 years; $P = .006$) and were more likely to have pGleason scores of 7 or higher (86% vs 72%, $P<.001$) and pT3/4 disease (76% vs 66%, $P = .02$) when compared with men with a PSA DT of ≥6 months. Prostatectomy margin positivity was similar (61% vs 58%, $P = .53$) in both PSA DT cohorts. During the study period, men with a PSA DT of ≥6 months received salvage treatment for PSA failure less often (57% vs 73%) when compared with men with a PSA DT of <6 months.

Comorbidity data was available for 432 of 519 (83%) patients. The median PSA DT in this subset was similar to the entire cohort at 11.4 months, with 313 of 432 (72.5%) men with a PSA DT of ≥6 months.

Risk of All-Cause Mortality

After a median follow-up of 11.3 (IQR, 5.8-16.4) years from the time of PSA failure, there were 195 (37.6%) deaths among the 519 men. Of these 195 deaths 115 of 361 (31.9%) were observed in men with a PSA DT of ≥6 months compared with 80 of 158 (50.6%) men with a PSA DT of <6 months.

Table 2 displays the unadjusted and adjusted risk of all-cause mortality for both clinical and pathologic factors.

Table 1. Distribution of Clinical and Pathologic Factors of the Study Cohort Stratified by the Value of the Prostate-Specific Antigen Doubling Time at the Time of Prostate-Specific Antigen Failure

	PSA DT ≥6 Months	PSA DT <6 Months	
	n=361	n=158	*P*
Age at PSA failure, y, median (IQR)	68.1 (63.0-72.5)	65.6 (60.0-71.2)	.006
pGleason score			<.001
6	99 (27%)	21 (13%)	
7	182 (50%)	67 (42%)	
8-10	80 (22%)	70 (44%)	
AJCC tumor category			.02
pT2	124 (34%)	38 (24%)	
pT3/4	237 (66%)	120 (76%)	
Margin status			.53
Negative	150 (42%)	61 (39%)	
Positive	211 (58%)	97 (61%)	
Treatment after PSA failure			[a]
No therapy	157 (43%)	42 (27%)	
RT	95 (26%)	39 (25%)	
RT+ADT (concurrent)	18 (5%)	11 (7%)	
RT → ADT	34 (9%)	18 (11%)	
ADT → RT	2 (1%)	2 (1%)	
ADT	55 (15%)	46 (29%)	

PSA DT indicates prostate-specific antigen doubling time; IQR, interquartile range; p, prostatectomy; AJCC, American Joint Commission on Cancer staging system; RT, radiation therapy; ADT, androgen-deprivation therapy.
Percentages may not sum to 100 because of rounding.
[a] *P* not given because these treatments can be given over time.

The use of salvage radiation therapy for PSA failure was associated with a significant reduction in all-cause mortality for men with both a PSA DT of <6 months (AHR, 0.53; 95% CI, 0.31-0.90; $P = .02$) or a PSA DT of ≥6 months (AHR, 0.52; 95% CI, 0.34-0.80; $P = .003$).

In addition, pGleason score 8 to 10 disease (AHR, 1.93; 95% CI, 1.28-2.92; $P = .002$) and increasing age in years (AHR, 1.05; 95% CI, 1.02-1.07; $P < .0001$) at the time of PSA failure were associated with a significant increase in the risk of all-cause mortality. The addition of salvage androgen-deprivation therapy for PSA failure was associated with a significant reduction in all-cause mortality (AHR, 0.53; 95% CI, 0.35-0.81; $P = .003$).

Risk of All-Cause Mortality—Men With Cardiac Comorbidity Data

To adjust for the possibility that the decision to provide salvage RT may have been influenced by comorbidity status, we analyzed the subset of men in whom cardiac comorbidity data at the time of PSA failure was documented. Among these 432 men, at a median follow-up of 9.6 (IQR, 5.0-14.4) years from the time of PSA failure, there were 131 (30.3%) deaths. Of these 131 deaths, 83 occurred in the 313 (26.5%) men with a PSA DT of ≥6 months compared with 48 in the 119 (40.3%) men with a PSA DT of <6 months.

Table 3 displays the unadjusted and adjusted risk of all-cause mortality for both clinical and pathologic factors, adjusting for cardiac comorbidity. The use of salvage radiation therapy for PSA failure was associated with a significant reduction in all-cause mortality for men with both a PSA DT of <6 months (AHR, 0.35; 95% CI, 0.17-0.72; $P = .004$) or a PSA DT of ≥6 months (AHR, 0.60; 95% CI, 0.37-0.98; $P = .04$).

The presence of a cardiac comorbidity was significantly associated with an increased risk of all-cause mortality (AHR, 4.73; 95% CI, 2.30-9.75; $P < .001$). In addition, pGleason score 8 to 10 disease (AHR, 1.93; 95% CI, 1.18-3.15; $P = .009$), positive margin status at RP (AHR, 1.55; 95% CI, 1.07-2.26; $P = .02$), and increasing age (AHR, 1.05; 95% CI, 1.02-1.08; $P = .001$) were all associated with an increased risk of all-cause mortality, whereas salvage androgen-deprivation therapy was associated with a decreased risk of all-cause mortality (AHR, 0.54; 95% CI, 0.31-0.94; $P = .03$).

Table 2. Adjusted and Unadjusted Risk of All Cause Mortality After Postoperative Prostate-Specific Antigen Failure for Clinical, Pathologic, and Treatment Factors

			Univariate Analysis		Multivariate Analysis	
Clinical Factor	No. of Deaths	No. of Men	HR (95% CI)	*P*	AHR (95% CI)	*P*
Age at PSA failure, y	195	519	1.05 (1.03 to 1.07)	<.001	1.05 (1.02 to 1.07)	<.001
pGleason score						
6	38	120	1.00		1.00	
7	79	249	1.27 (0.86 to 1.87)	.24	1.36 (0.91 to 2.04)	.13
8-10	78	150	1.85 (1.26 to 2.74)	.002	1.93 (1.28 to 2.92)	.002
AJCC tumor category						
pT2	48	162	1.00		1.00	
pT3/4	147	357	1.12 (0.81 to 1.55)	.50	0.90 (0.63 to 1.28)	.55
Margin status						
Negative	80	211	1.00		1.00	
Positive	115	308	1.40 (1.05 to 1.87)	.02	1.35 (0.99 to 1.84)	.06
Salvage ADT use						
No	91	333	1.00		1.00	
Yes	104	186	1.12 (0.82 to 1.53)	.49	0.53 (0.35 to 0.81)	.003
Salvage RT Use						
DT <6 mo, no salvage RT	46	88	1.00		1.00	
DT <6 mo, plus salvage RT	34	70	0.81 (0.52 to 1.26)	.34	0.53 (0.31 to 0.90)	.02
DT ≥6 mo, no salvage RT	65	212	0.69 (0.47 to 1.00)	.05	0.66 (0.44 to 0.99)	.04
DT ≥6 mo, plus salvage RT	50	149	0.44 (0.29 to 0.66)	<.001	0.34 (0.21 to 0.57)	<.001
DT ≥6 mo, no salvage RT[a]	65	212	1.00		1.00	
DT ≥6 mo, plus salvage RT	50	149	0.64 (0.44 to 0.93)	.02	0.52 (0.34 to 0.80)	.003

HR indicates hazard ratio; CI, confidence interval; AHR, adjusted hazard ratio; PSA, prostate-specific antigen; p, prostatectomy; AJCC, American Joint Commission on Cancer staging system; ADT, androgen-deprivation therapy; DT, prostate-specific antigen doubling time; RT, radiation therapy.
[a] This group was set as the baseline group to allow a direct and clear comparison of the DT ≥6 mo group with or without RT.

Table 4 displays the adjusted risk of all-cause mortality in the men free of comorbidity at the time of PSA failure. Among these 342 men, there were 119 (34.8%) deaths. Salvage RT led to a decreased risk of all-cause mortality in healthy men with a PSA DT of <6 months (AHR, 0.37; 95% CI, 0.17-0.83; $P = .02$) or a PSA DT of ≥6 months (AHR, 0.55; 95% CI, 0.37-0.92; $P = .02$). In addition, pGleason score 8 to 10 disease, positive margin status at RP, and increasing age were all associated with an increased risk of all-cause mortality, whereas salvage androgen-deprivation therapy remained associated with a decreased risk of all-cause mortality. Among those with a documented cardiac comorbidity, the total number of men and events were too small for meaningful multivariate analysis.

DISCUSSION

This retrospective study comparing observation to salvage radiation, with an 11.3-year median follow-up after PSA failure, provides the first evidence of an overall survival benefit for patients with long PSA DTs. Specifically, we examined a cohort of 519 men with PSA failure after radical prostatectomy. The administration of salvage radiation was significantly associated with a lower risk of all-cause mortality in both men with a PSA DT of ≥6 months (AHR, 0.52; $P = .003$) and men with a PSA DT of <6 months (AHR, 0.53; $P = .02$). This association remained for men with a PSA DT of ≥6 months (AHR, 0.60; $P = .04$) or a PSA DT of <6 months (AHR, 0.35; $P = .004$) when controlling for comorbidity in a subset analysis. Furthermore, when men free of comorbidity were analyzed independently, salvage RT remained associated with a decreased risk of all-cause mortality in both men with a PSA DT of ≥6 months (AHR, 0.55; $P = .02$) or a PSA DT of <6 months (AHR, 0.37; $P = .02$).

The clinical significance of this finding is that it appears that healthy men with both classically indolent and more aggressive PSA failure after RP benefit from salvage RT. The majority of men in this and previous studies of PSA failure after RP have a PSA DT of ≥6 months.[8,10] Although previous retrospective studies have shown that

Table 3. Adjusted and Unadjusted Risk of All Cause Mortality After Postoperative Prostate-Specific Antigen Failure for Clinical, Pathologic, and Treatment Factors Adjusting for Comorbidity

			Univariate Analysis		Multivariate Analysis	
Clinical Factor	**No. of Deaths**	**No. of Men**	**HR (95% CI)**	***P***	**AHR (95% CI)**	***P***
Age at PSA failure, y	131	432	1.05 (1.02 to 1.08)	.001	1.05 (1.02 to 1.08)	.001
pGleason score						
6	28	102	1.00		1.00	
7	52	213	1.24 (0.78 to 1.97)	.37	1.20 (0.74 to 1.94)	.46
8-10	51	117	2.22 (1.40 to 3.53)	.001	1.93 (1.18 to 3.15)	.009
AJCC tumor category						
pT2	31	141	1.00		1.00	
pT3/4	100	291	1.09 (0.73 to 1.64)	.67	0.86 (0.56 to 1.32)	.48
Margin status						
Negative	50	172	1.00		1.00	
Positive	81	260	1.53 (1.07 to 2.19)	.02	1.55 (1.07 to 2.26)	.02
Salvage ADT use						
No	65	284	1.00		1.00	
Yes	66	148	1.19 (0.79 to 1.79)	.41	0.54 (0.31 to 0.94)	.03
Comorbidity						
Negative	119	342	1.00		1.00	
Positive	12	90	4.60 (2.33 to 9.08)	<.001	4.73 (2.30 to 9.75)	<.001
Salvage RT Use						
DT <6 mo, no salvage RT	23	62	1.00		1.00	
DT <6 mo, plus salvage RT	25	57	0.56 (0.32 to 0.99)	.05	0.35 (0.17 to 0.72)	.004
DT ≥6 mo, no salvage RT	43	180	0.36 (0.22 to 0.60)	<.001	0.31 (0.17 to 0.56)	<.001
DT ≥6 mo, plus salvage RT	40	133	0.25 (0.15 to 0.43)	<.001	0.19 (0.09 to 0.38)	<.001
DT ≥6 mo, no salvage RT[a]	43	180	1.00		1.00	
DT ≥6 mo, plus salvage RT	40	133	0.71 (0.46 to 1.09)	.12	0.60 (0.37 to 0.98)	.04

HR indicates hazard ratio; CI, confidence interval; AHR, adjusted hazard ratio; PSA, prostate-specific antigen; p, prostatectomy; AJCC, American Joint Commission on Cancer staging system; ADT, androgen-deprivation therapy; DT, prostate-specific antigen doubling time; RT, radiation therapy.
[a] This group was set as the baseline group to allow a direct and clear comparison of the DT ≥6 mo group with or without RT.

those men with protracted PSA DTs are more likely to obtain extended biochemical disease-free survival, no survival advantage has previously been reported. This may be due to the increased interval from the time of PSA failure to both distant metastasis and prostate cancer death in those men with relatively indolent disease, defined by prolonged PSA DTs, lower Gleason scores, and extended time to PSA failure after RP.[5,9,14] In these cases, extended follow-up after PSA failure, as provided in this study, and stratification by competing risks are likely necessary to note a survival benefit.

The decision to recommend salvage radiation needs to be individualized, taking into account: 1) patient longevity, including a consideration of comorbidity; 2) the probability that recurrent disease is localized and, therefore, amenable to salvage local treatment; and 3) the aggressiveness of the recurrence, represented, at least in part, by PSA DT. In this way, only those men with a reasonable chance of benefit would be offered salvage RT and be put at risk for treatment toxicities, which, based on the results of a randomized trial of RP alone versus RP and 3D-conformal RT, include urethral stricture (17.8% for RP and RT vs 9.5% for RP alone), total urinary incontinence (6.5% vs 2.8%), and proctitis (3.3% vs 0%).[15]

The importance of cardiac comorbidity assessment in the selection of men for salvage therapy in the setting of PSA failure is supported by the markedly increased risk of all-cause mortality in those men with documented cardiac comorbidity in this study (AHR, 4.73; $P < .001$). While healthy men benefit from salvage RT regardless of PSA DT, the same may not be true for those with documented comorbidity at the time of PSA failure.

Several points deserve additional discussion. First, this is a retrospective single-institution study that generates the hypothesis that salvage RT may benefit men regardless of the value of the PSA DT. Proof of this

Table 4. Adjusted and Unadjusted Risk of All Cause Mortality After Postoperative PSA Failure for Clinical, Pathologic, and Treatment Factors Among Healthy Men

			Univariate Analysis		Multivariate Analysis	
Clinical Factor	No. of Deaths	No. of Men	HR (95% CI)	*P*	AHR (95% CI)	*P*
Age at PSA failure, y	119	342	1.06 (1.03 to 1.09)	<.001	1.06 (1.02 to 1.09)	.001
pGleason score						
6	25	86	1.00		1.00	
7	47	161	1.30 (0.80 to 2.12)	.30	1.32 (0.80 to 2.20)	.27
8-10	47	95	2.36 (1.45 to 3.84)	<.001	2.12 (1.26 to 3.55)	.004
AJCC tumor category						
pT2	27	103	1.00		1.00	
pT3/4	92	239	1.13 (0.74 to 1.74)	.57	0.87 (0.55 to 1.37)	.55
Margin status						
Negative	47	142	1.00		1.00	
Positive	72	200	1.50 (1.03 to 2.18)	.03	1.51 (1.02 to 2.22)	.04
Salvage ADT use						
No	57	210	1.00		1.00	
Yes	62	132	1.11 (0.72 to 1.72)	.64	0.53 (0.29 to 0.96)	.04
Salvage RT Use						
DT <6 mo, no salvage RT	17	44	1.00		1.00	
DT <6 mo, plus salvage RT	24	47	0.69 (0.37 to 1.28)	.23	0.37 (0.17 to 0.83)	.02
DT ≥6 mo, no salvage RT	41	137	0.44 (0.25 to 0.77)	.004	0.36 (0.19 to 0.70)	.003
DT ≥6 mo, plus salvage RT	37	114	0.29 (0.16 to 0.52)	<.001	0.20 (0.09 to 0.44)	<.001
DT ≥6 mo, no salvage RT[a]	41	137	1.00		1.00	
DT ≥6 mo, plus salvage RT	37	114	0.67 (0.43 to 1.05)	.08	0.55 (0.33 to 0.92)	.02

HR indicates hazard ratio; AHR, adjusted hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; p, prostatectomy; AJCC, American Joint Commission on Cancer staging system; ADT, androgen-deprivation therapy; DT, prostate-specific antigen doubling time; RT, radiation therapy.
[a] This group was set as the baseline group to allow a direct and clear comparison of the DT ≥6 mo group with or without RT.

hypothesis requires prospective evaluation. Given that randomized studies examining this question are not planned, ongoing, or completed means that these data represent the best available evidence to date for RT use in the setting of PSA failure after radical prostatectomy in men with long PSA DTs. Second, the decision to initiate salvage therapy and the type of therapy administered were influenced by prognostic factors that differed between treatment groups. However, all of the known predictive factors are adjusted in the multivariate analysis. Unknown prognostic factors not included in the analysis may have had an impact on the results. Third, data to construct a validated comorbidity metric were not available; however, cardiac comorbidity as defined in this study was significantly associated with an increased risk of death on the adjusted analysis, as expected, given that cardiac death is the leading noncancer cause of death in the United States for men in this age group.[16] Given that recent studies have shown the importance of comorbidities in determining the risk of competing causes of death,[17-19] inclusion of a validated comorbidity metric such as the Adult Comorbidity Evaluation-27 (ACE-27) Test[20] in future studies will help define a population where treatment is unlikely to be of benefit. Finally, although androgen-deprivation therapy was associated with a decreased risk of all-cause mortality in this study and has previously been shown to delay clinical metastases in aggressive disease in a separate retrospective cohort of patients with PSA failure after RP,[21] its use in combination with RT requires prospective testing. Such a study, the Radiation Therapy Oncology Group (RTOG) 96-01 (NCT#00002874), a randomized trial of salvage radiation plus 2 years of androgen-deprivation therapy has been completed and will either refute or validate the association of a reduction in the risk of all-cause mortality found in this study for androgen-deprivation therapy.

In conclusion, this study has the longest follow-up to date after PSA failure after RP and provides the first evidence of a decrease in the risk of death with the use of salvage RT after RP regardless of the numerical value of the PSA DT.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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