Surrogate End Point for Prostate Cancer–Specific Mortality After Radical Prostatectomy or Radiation Therapy

Anthony V. D'Amico, Judd W. Moul, Peter R. Carroll, Leon Sun, Deborah Lubeck, Ming-Hui Chen

Background: **The relationship between prostate-specific antigen (PSA)–defined recurrence and prostate cancer–specific mortality remains unclear. Therefore, we evaluated the hypothesis that a short post-treatment PSA doubling time (PSA-DT) after radiation therapy is a surrogate end point for prostate cancer–specific mortality by analyzing two multi-institutional databases.** ***Methods:*** **Baseline, treatment, and follow-up information was compiled on a cohort of 8669 patients with prostate cancer treated with surgery (5918 men) or radiation (2751 men) from January 1, 1988, through January 1, 2002, for localized or locally advanced, non-metastatic prostate cancer. We used a Cox regression analysis to test whether the post-treatment PSA-DT was a prognostic factor that was independent of treatment received. All statistical tests were two-sided.** ***Results:*** **The post-treatment PSA-DT was statistically significantly associated with time to prostate cancer–specific mortality and with time to all-cause mortality (all P_{Cox}<.001). However, the treatment received was not statistically significantly associated with time to prostate cancer–specific mortality after PSA-defined disease recurrence for patients with a PSA-DT of less than 3 months (P_{Cox} = .90) and for patients with a PSA-DT of 3 months or more (P_{Cox} = .28) when controlling for the specific value of the PSA-DT. Furthermore, after a PSA-defined recurrence, a PSA-DT of less than 3 months was statistically significantly associated with time to prostate cancer–specific mortality (median time = 6 years; hazard ratio = 19.6, 95% confidence interval = 12.5 to 30.9).** ***Conclusion:*** **A post-treatment PSA-DT of less than 3 months and the specific value of the post-treatment PSA-DT when it is 3 months or more appear to be surrogate end points for prostate cancer–specific mortality after surgery or radiation therapy. We recommend that consideration be given to initiating androgen suppression therapy at the time of a PSA-defined recurrence when the PSA-DT is less than 3 months to delay the imminent onset of metastatic bone disease. [J Natl Cancer Inst 2003;95:1376–83]**

Although generally found in an asymptomatic patient with prostate cancer, prostate-specific antigen (PSA)–defined disease recurrence after initial therapy with radical prostatectomy or external beam radiation therapy is considered to be treatment failure *(1)* and often triggers the start of secondary therapy *(2).* However, it remains unknown whether PSA-defined recurrence is a surrogate end point for prostate cancer–specific mortality, particularly for men with competing causes of mortality *(3).*

To identify patients for whom a PSA-defined recurrence is likely to translate into death from prostate cancer, investigators have tried to identify prognostic factors associated with the time to documentation of distant disease recurrence (i.e., positive bone scan) after PSA-defined recurrence. From these investigations *(4–8),* one post-treatment clinical parameter, a short post-treatment PSA doubling time (PSA-DT), was consistently found to be statistically significantly associated with the time to distant disease recurrence after PSA-defined recurrence.

Factors that were associated with the time to prostate cancer–specific mortality after PSA-defined recurrence were then determined. Specifically, D'Amico et al. *(9)* evaluated the determinants of time to prostate cancer–specific mortality after PSA-defined recurrence in patients treated with radiation therapy and found that, after a PSA-defined recurrence, patients with a short post-treatment PSA-DT had an estimated prostate cancer–specific mortality and an estimated all-cause mortality that were nearly identical. These results confirmed the findings of Sandler et al. *(10)* on the prognostic significance of a short post-treatment PSA-DT. Thus, a short post-treatment PSA-DT appeared to identify patients with PSA-defined recurrence after radiation therapy who were at high risk for prostate cancer–specific mortality.

In this study, we compiled baseline, treatment, and follow-up data on 8669 patients treated with radical prostatectomy or radiation therapy at multiple institutions throughout the United States and assessed whether a short post-treatment PSA-DT after radical prostatectomy or radiation therapy could serve as a surrogate end point for prostate cancer–specific mortality.

Patients and Methods

Patient Selection and Treatment

Patients in two multi-institutional databases, Cancer of the Prostate Strategic Urologic Research Endeavor *(11)* and the Center for Prostate Disease Research *(12),* containing baseline, treatment, and follow-up information on 8669 patients treated with radical prostatectomy (5918 men) or radiation therapy (2751 men) between January 1, 1988, and January 1, 2002, for clinical-stage T1c-4NX or N0M0 (i.e., localized or locally advanced, non-metastatic) prostate cancer formed the study cohort. An approved and signed Internal Review Board informed con-

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See "Notes" following "References."

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sent form was obtained on each patient before study entry. To be eligible for this study, patients treated surgically were permitted to have received up to 3 months of neoadjuvant androgen-suppression therapy, given that the 5-year results of a randomized trial *(13)* have shown no statistically significant impact on PSA outcome when 3 months of neoadjuvant androgen-suppression therapy was added to radical prostatectomy. The median age of the patients treated surgically or with radiation therapy at the time of initial therapy was 64.5 years (range = 34.3–96.8 years) and 71.1 years (range = 43.7–92.8 years), respectively. The pretreatment clinical characteristics of all patients stratified by the treatment received are shown in Table 1.

Staging

In all patients, the evaluation of stage involved a history and physical examination including a digital rectal exam, determination of serum PSA level, and a transrectal ultrasound-guided needle biopsy of the prostate; the Gleason score was determined by histologic examination *(14)*. The prostate biopsy was generally performed transrectally with an 18-gauge Tru-Cut needle (Travenol Laboratories, Deerfield, IL). Before 1996, patients generally had a computerized tomographic scan of the pelvis and a bone scan. After 1996, patients with a pretreatment PSA level of less than 10 ng/mL and a biopsy Gleason score of 6 or less did not generally undergo radiologic staging because of the less than 1% chance that these studies would reveal metastatic disease *(15)*. The clinical stage was obtained from the results of the digital rectal examination and the 2002 American Joint Commission on Cancer staging system *(16)*. Radiologic and biopsy information was not used to determine clinical stage. PSA levels were commonly measured with assays from Hybritech (San Diego, CA), Tosoh (Foster City, CA), or Abbott Laboratories (Chicago, IL).

Table 1. Distribution of pretreatment clinical characteristics of the 5918 patients treated surgically and the 2751 patients treated with radiation therapy in the study cohort*

Clinical characteristic	Surgery, %	Radiation therapy, %
PSA level		
≤4 ng/mL	18	11
>4–10 ng/mL	58	45
>10 ng/mL	17	26
>20 ng/mL	8	19
Biopsy Gleason score		
≤6	74	61
7	21	26
8–10	5	13
2002 AJCC category		
T1c	40	32
T2a	33	29
T2b	20	20
T2c	4	8
T3a	2	8
T3b	0.1	2
T4	0.1	1
Age		
<50 y	4	1
50–59 y	28	7
60–69 y	55	37
70–74 y	12	31
75–79 y	1	20
≥80 y	0.3	4

*PSA = prostate-specific antigen; AJCC = American Joint Commission on Cancer *(16)*; age = age at the time of initial therapy. The two-sided χ^2 test was used to compare the distribution of pretreatment clinical factors between patients treated surgically and with radiation therapy. All $P_{\chi 2}$ values were less than .001. Percentages may not sum to 100 because of rounding.

Follow-up

The median follow-up for the entire study cohort of 5918 patients treated surgically and 2751 patients treated with radiation therapy was 7.1 years (range = 0.5–14.3 years) and 6.9 years (range = 0.8–14.5 years), respectively; follow-up started on the first day of treatment. Before PSA-defined recurrence, as specified by the American Society for Therapeutic Radiology and Oncology consensus criteria *(17)*, patients generally had a serum PSA measurement and digital rectal examination every 3 months after radiation therapy for 2 years, then every 6 months for an additional 3 years, and then annually thereafter. The median follow-up after PSA-defined recurrence for the 611 patients receiving radical prostatectomy and 840 patients treated with radiation therapy who experienced a PSA-defined recurrence was 4.1 years (range = 0.3–11.8 years) and 3.8 years (range = 0.3–12.0 years), respectively. Overall, there were 154 deaths, 110 of which were from prostate cancer. Determination of the cause of death was made from death certificates.

Statistical Analysis

Calculation of the PSA-DT. Unlike patients treated surgically, patients treated with radiation therapy do not necessarily have an undetectable PSA level (PSA<0.2 ng/mL) but often have a finite nadir PSA level, typically less than 1.0 ng/mL within 2 years after radiation therapy. Therefore, to be certain that the magnitude of the PSA-DT would be the same for patients treated surgically and those treated with radiation therapy who experienced the same absolute increase in PSA level, the nadir PSA level was subtracted from the post-radiation PSA level before the PSA-DT was determined. The PSA-DT was calculated by assuming first-order kinetics and by using a minimum of three PSA measurements, each separated by a minimum of 3 months and each with a PSA increase of more than 0.2 ng/mL. Therefore, the minimum PSA level that was used to calculate the PSA-DT needed to be more than 0.2 ng/mL for all study patients. If a patient had one or two consecutive increases in his PSA level from an undetectable PSA level (<0.2 ng/mL) after surgery or from the PSA nadir after radiation therapy but before salvage therapy was initiated, his PSA-DT could not be calculated; such patients were excluded from the analysis. An example of the PSA measurements used to calculate the PSA-DT for patients treated surgically and with radiation therapy follows. If one assumes that serum PSA levels are obtained at 6-month intervals and that a surgically managed patient has the following consecutive 6-month PSA values of less than 0.2 (or 0), 0.3, 0.6, and 1.2 ng/mL, then the PSA-DT is approximately 6 months. If a patient treated with radiation therapy has the following consecutive 6-month PSA values of 0.6 (nadir), 0.9, 1.2, and 1.8 ng/mL, then, without correcting for the nadir of 0.6, a PSA-DT of approximately 12 months is obtained. However, if the PSA nadir of 0.6 is subtracted from each post-radiation PSA value, then the PSA-DT for patients treated surgically and with radiation is the same.

Defining the PSA-DT for study. The PSA-DT (e.g., <12, <6, <4, <3, or <2 months) selected for testing via Prentice's criteria *(18)* as a possible surrogate end point for prostate cancer–specific mortality in patients treated surgically or with radiation therapy corresponded to the maximum PSA-DT that

minimized the difference in estimates of prostate cancer–specific mortality from the cumulative incidence plots *(19)* and estimates of all-cause mortality from the Kaplan–Meier plots *(20),* as shown in Table 2. An additional test to identify the candidate surrogate was the marginal proportion of the variation in prostate cancer–specific mortality *(21),* calculated for different PSA-DTs to ensure that the PSA-DT identified by comparing the estimates of prostate cancer–specific mortality and of all-cause mortality also maximized the marginal proportion of the variation in prostate cancer–specific mortality explained by the surrogate end point (mPVE). The 95% confidence intervals (CIs) for the mPVE values were calculated by a bootstrapping technique with 1000 replications *(22).*

Assessment of PSA-DT by Prentice's criteria. Prentice's criteria *(18)* require that the surrogate end point be a prognostic factor and that, when a patient achieves the surrogate end point, the time to prostate cancer–specific mortality be independent of the treatment received. These criteria were tested with a Cox regression analysis *(23).* Because patients were not randomly assigned to treatment arms, the Cox regression analyses were also adjusted for factors that have been shown to be prognostic and, therefore, could confound the analyses *(24).* These factors included age (continuous variable) at the time of initial therapy, pretreatment PSA level (continuous variable), biopsy Gleason score (continuous variable, with integral values of 2–10, inclusive), and the clinical tumor (T) category *(16)* (categorical variable: T1c [baseline], T2a, T2b, T2c, T3a, T3b, or T4). Specifically, we used a Cox regression analysis *(23)* to determine whether the proposed surrogate end point violated the Prentice criteria—that the surrogate end point be statistically significantly associated with the time to prostate cancer–specific mortality after PSA-defined recurrence but not be associated with the initial treatment. To that end, we compared the categorical variable of a PSA-DT of less than 3 months with the baseline category of patients with a PSA-DT of 3 months or more and compared treatments among those patients not in the baseline category (i.e., those with PSA-DT <3 months) for their association with time to prostate cancer–specific mortality after PSA-defined recurrence. Age (continuous) at the time of PSA-defined recurrence was also included in the analysis that evaluated time to all-cause mortality after PSA-defined recurrence.

The impact of treatment and the specific value of the PSA-DT on time to prostate cancer–specific mortality after a PSA-defined recurrence was also assessed for patients with a PSA-DT of 3 months or more. Specifically, a single Cox regression analysis was used to compare the continuous variable of PSA-DT of 3 months or more with the baseline category of patients with a PSA-DT of less than 3 months and also compared the initial treatment received among those patients not in the baseline category (i.e., PSA-DT ⩾3 months). Age (continuous) at the time of PSA-defined recurrence was also included in the analysis that evaluated time to all-cause mortality after PSA-defined recurrence.

Further testing was performed to assess the proposed surrogate end point by determining the proportion of the treatment effect that was explained by the proposed surrogate end point (PTE) *(25).* Evidence to support Prentice's criteria corresponds to a PTE of 1.0, signifying that 100% of the treatment effect can be explained by the proposed surrogate end point. The PTE and its 95% confidence interval were calculated *(25)* for the proposed surrogate end point.

As a final test of the proposed surrogate end point, we determined the partial proportion of the variation in the prostate cancer–specific mortality data and all-cause mortality data explained by the proposed surrogate end point (pPVE) *(21)* by using a Cox regression model containing the candidate surrogate end point and the treatment received. The data used met the assumptions for using the Cox model, and 95% confidence intervals were calculated by a bootstrapping technique *(22)* with 1000 replications. Evidence to support Prentice's criteria corresponds to a partial proportion of the variation in the prostate cancer–specific mortality data and all-cause mortality data explained by the surrogate end point (pPVE) of 0 *(21),* when the treatment received was added to a Cox regression model *(23)* containing the proposed surrogate end point. We performed this analysis for the end points of time to prostate cancer–specific mortality and time to all-cause mortality after PSA-defined recurrence.

For all Cox regression analyses *(23),* time zero was taken as the day of PSA-defined recurrence, which was defined as the midpoint between the PSA nadir and the first increase in the PSA level *(17).* For all analyses, the assumptions of the Cox model were tested and met. The treatment hazard ratio and the associated 95% confidence intervals were calculated *(26)* and reported before and after adjustment for the potential baseline confounding factors and also after adjustment for the potential confounding factors and the proposed surrogate end point. The PSA-DT hazard ratios were calculated *(26)* for all patients and for the individual cohorts of men treated with surgery or radiation therapy. For the purpose of illustration, estimates of prostate cancer–specific mortality after PSA-defined recurrence were calculated by the cumulative incidence method *(19)* and esti-

Table 2. Estimates of prostate cancer–specific and all-cause mortality after prostate-specific antigen (PSA)–defined recurrence stratified by the post-treatment PSA-doubling time (DT) and initial treatment*

	PSA-DT<12 mos		PSA-DT<6 mos		PSA-DT<4 mos		PSA-DT<3 mos		PSA-DT<2 mos	
Treatment	PCSM, %	ACM, %	PCSM, %	ACM, %	PCSM, %	ACM, %	PCSM, %	ACM, %	PCSM, %	ACM, %
Surgery										
Year 5	7.6	7.6	13.9	13.9	20.0	20.0	31.2	31.2	47.8	47.8
Year 8	12.5	15.5	21.5	21.5	38.8	38.8	48.5	48.5	62.1	63.1
Year 10	17.5	10.5	34.1	35.5	49.0	49.0	67.8	67.8	81.5	81.5
Radiation										
Year 5	15.9	19.1	27.0	30.4	34.1	35.7	38.4	39.0	49.3	49.3
Year 8	30.5	38.2	43.8	48.5	54.7	58.3	58.4	59.0	72.0	72.0
Year 10	39.6	47.7	60.6	65.2	74.1	75.7	76.6	77.2	86.0	86.0

*Time zero is the date of PSA-defined recurrence. PCSM = prostate cancer–specific mortality; ACM = all-cause mortality.

mates of all-cause mortality after PSA-defined recurrence were calculated by the Kaplan–Meier method *(20)*. Cancer-specific and all-cause survival were then graphically displayed, stratified by the PSA-DT and the initial treatment received. Comparisons of survival were made with the log-rank test. All statistical tests were two-sided.

RESULTS

Identifying the PSA-DT for Study

The maximum value of the PSA-DT that minimized the difference in the estimates of prostate cancer–specific mortality and all-cause mortality after PSA-defined recurrence for patients who were treated with surgery or radiation therapy was less than 3 months, as shown in Table 2. Among the patients who had a PSA-defined recurrence, including 611 patients treated surgically and 840 patients treated with radiation therapy, 12% (95% CI = 9% to 15%) and 20% (95% CI = 18% to 23%), respectively, had a PSA-DT of less than 3 months (Figs. 1 and 2). In addition, the marginal proportion of the variation in prostate cancer–specific mortality value explained by the PSA-DT (mPVE) was nearly maximized for a PSA-DT of less than 3 months. Specifically, for patients treated surgically, these values were 11% (95% CI = 8% to 13%), 12% (95% CI = 9% to 15%), 14% (95% CI = 10% to 17%), and 14.3% (95% CI = 10% to 17%) for a PSA-DT of less than 5, 4, 3, and 2 months, respectively; for patients treated with radiation therapy, these values were 7% (95% CI = 5% to 10%), 7.4% (95% CI = 5% to 10%), 9% (95% CI = 6% to 12%), and 9.3% (95% CI = 6% to 12%), respectively.

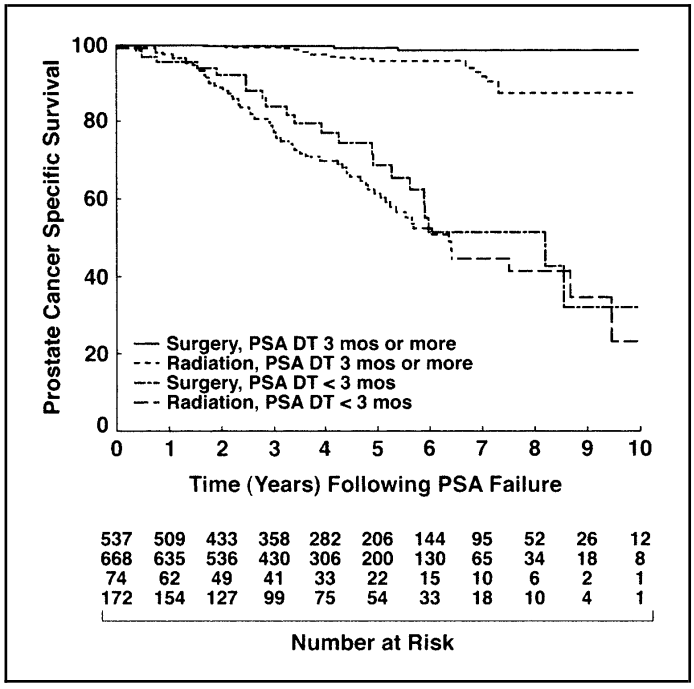

Fig. 1. Prostate cancer–specific survival after prostate-specific antigen (PSA)–defined recurrence stratified by treatment received and the value of the post-treatment PSA doubling time (PSA-DT). A pairwise two-sided log-rank test was used. *P* values are as follows: for a PSA-DT of less than 3 months (surgery versus radiation), $P = .38$; for PSA-DT of 3 months or more (surgery versus radiation), $P<.001$; for PSA-DT of less than 3 months versus PSA-DT of 3 months or more (surgery), $P<.001$; for PSA-DT of less than 3 months versus PSA-DT of 3 months or more (radiation), $P<.001$. For PSA-DT of 3 months or more (surgery), at 3 years, 99.8 (95% confidence interval [CI] = 99.4 to 100); at 5 years, 99.4 (95% CI = 98.6 to 100); at 8 years, 98.9 (95% CI = 97.6 to 100). For PSA-DT of 3 months or more (radiation), at 3 years, 99.6 (95% CI = 99.1 to 100); at 5 years, 96.1 (95% CI = 94 to 98.2); at 8 years, 87.6 (95% CI = 81.2 to 94). For PSA-DT of less than 3 months (surgery), at 3 years, 84.1 (95% CI = 74.4 to 93.8); at 5 years, 68.8 (95% CI = 55 to 82.6); at 8 years, 51.5 (95% CI = 34.8 to 68.3). For PSA-DT of less than 3 months (radiation), at 3 years, 79.1 (95% CI = 72.5 to 85.8); at 5 years, 61.6 (95% CI = 53 to 70.4); at 8 years, 41.6 (95% CI = 29.8 to 53.4).

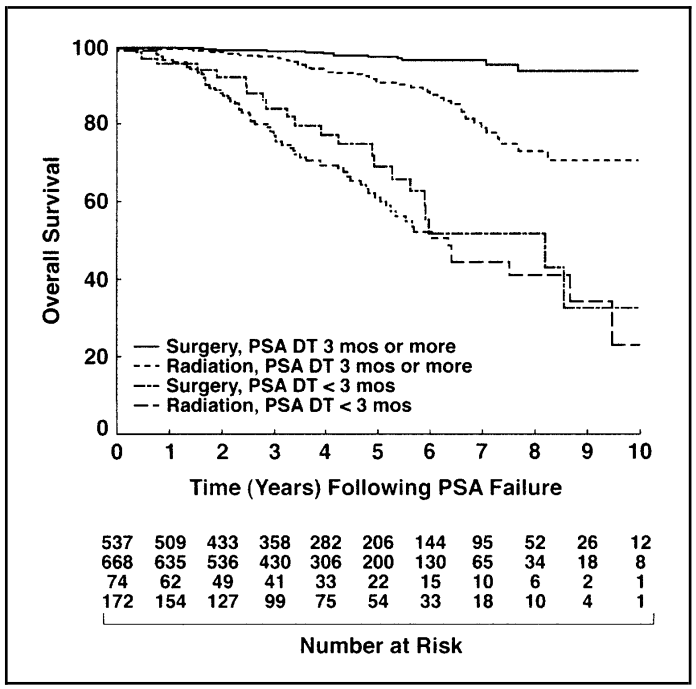

Fig. 2. Overall survival after prostate-specific antigen (PSA)–defined recurrence stratified by treatment received and the value of the post-treatment PSA doubling time (PSA-DT). A pairwise two-sided log-rank test was used. *P* values are as follows: for PSA-DT of less than 3 months (surgery versus radiation), $P = .34$; for PSA-DT of 3 months or more (surgery versus radiation), $P<.001$; for PSA-DT of less than 3 months versus PSA-DT of 3 months or more (surgery), $P<.001$; for PSA-DT of less than 3 months versus PSA-DT of 3 months or more (radiation), $P<.001$. For PSA-DT of 3 months or more (surgery), at 3 years, 99.1 (95% confidence interval [CI] = 98.2 to 100); at 5 years, 97.6 (95% CI = 95.9 to 99.3); at 8 years, 93.9 (95% CI = 89.7 to 98.1). For PSA-DT of 3 months or more (radiation), at 3 years, 97.7 (95% CI = 96.4 to 98.9); at 5 years, 91.7 (95% CI = 88.9 to 94.6); at 8 years, 73 (95% CI = 64.8 to 81.4). For PSA-DT of less than 3 months (surgery), at 3 years, 84.1 (95% CI = 74.4 to 93.8); at 5 years, 68.8 (95% CI = 55 to 82.6); at 8 years, 51.5 (95% CI = 34.8 to 68.3). For PSA-DT of less than 3 months (radiation), at 3 years, 78.5 (95% CI = 71.8 to 85.3); at 5 years, 61 (95% CI = 52.1 to 69.8); at 8 years, 41 (95% CI = 29.1 to 52.8).

Assessment of Prentice's Criteria

As shown in Table 3 and Figs. 1 and 2, after a PSA-defined recurrence, a PSA-DT of less than 3 months was statistically significantly associated with time to prostate cancer–specific mortality ($P_{Cox}<.001$) and time to all-cause mortality ($P_{Cox}<.001$). The hazard ratio for men with a PSA-DT of less than 3 months for prostate cancer–specific mortality after a PSA-defined recurrence was 19.6 (95% CI = 12.5 to 30.9) as detailed in Table 4. It is important to note that when unadjusted or adjusted only for the potential confounding factors and not the PSA-DT of less than 3 months, the initial treatment received was statistically significantly associated with time to prostate cancer–specific mortality and all-cause mortality, as shown in Table 3. However,

Table 3. Cox regression analyses *(23)* to assess prostate-specific antigen doubling time (PSA-DT) as a surrogate end point for prostate cancer–specific mortality (PCSM) after PSA-defined recurrence*

End point	Factor tested	*P* value†	Treatment hazard ratio (95% confidence interval)	Interpretation
Time to PCSM after PSA-defined recurrence	PSA-DT<3 mo	<.001	NA	PSA-DT<3 mo = adverse prognostic factor for this end point
	Treatment	.90	1.0 (0.6 to 1.9)† 8.7 (5.6 to 13.4)‡ 11.4 (7.8 to 16.8)§	Initial treatment did not predict this end point after adjusting for a PSA-DT<3 mo and potential confounding factors
Time to ACM after PSA-defined recurrence	PSA-DT<3 mo	<.001	NA	PSA-DT<3 mo = adverse prognostic factor for this end point
	Age (continuous) at the time of PSA-defined recurrence	<.001	NA	Advancing age = adverse prognostic factor for this end point
	Treatment	.83	0.9 (0.5 to 1.7)† 5.0 (3.4 to 7.3)‡ 5.5 (4.0 to 7.6)§	Initial treatment did not predict this end point after adjusting for a PSA-DT<3 mo and potential confounding factors
Time to PCSM after PSA-defined recurrence	PSA-DT≥3 mo (continuous)	<.001	NA	Decreasing PSA-DT = adverse prognostic factor for this end point for patients with a PSA-DT≥3 mo
	Treatment	.28	1.0 (0.5 to 1.7)‖ 0.4 (0.2 to 0.6)¶ 0.3 (0.2 to 0.5)#	Initial treatment did not predict this end point after adjusting for the value of the PSA-DT and the potential confounding factors
Time to ACM after PSA-defined recurrence	PSA-DT≥3 mo (continuous)	<.001	NA	Decreasing PSA-DT = adverse prognostic factor for this end point for patients with a PSA-DT≥3 mo
	Age (continuous) at the time of PSA-defined recurrence	<.001	NA	Advancing age = adverse prognostic factor for this end point
	Treatment	.10	0.7 (0.5 to 1.1)‖ 0.6 (0.4 to 0.9)¶ 0.5 (0.4 to 0.8)#	Initial treatment did not predict this end point after adjusting for the value of the PSA-DT and potential confounding factors

*ACM = all-cause mortality; NA = not applicable. All statistical tests were two-sided and assessed the ability of the proposed surrogate and treatment to predict time to PCSM after PSA-defined recurrence or assessed the ability of the proposed surrogate, age at the time of PSA recurrence, and treatment to predict time to ACM after PSA-defined recurrence.

†Adjusted for a PSA-DT<3 mo and potential confounding factors.

‡Adjusted for the potential confounding factors.

§Unadjusted. The baseline groups included men treated with surgery and who had a PSA-DT<3 mo and all men with a PSA-DT≥3 mo independent of treatment.

‖Adjusted for the potential confounding variables and the value of the PSA-DT.

¶Adjusted for the potential confounding variables.

#Unadjusted. The baseline group included men treated with surgery and who had a PSA-DT≥3 mo and all men with a PSA-DT<3 mo, independent of treatment.

Table 4. Summary of the PSA-DT hazard ratios (HRs) for the time to prostate cancer–specific mortality (PCSM) and all-cause mortality (ACM) for all patients and for patients treated with surgery or radiation therapy*

	HR (95% confidence interval)		
	Surgery	Radiation	All
Time to PCSM			
PSA-DT<3 mo	62.9 (18.8 to 210.1)	12.2 (7.5 to 20.1)	19.6 (12.5 to 30.9)
PSA-DT≥3 mo (continuous)	0.61 (0.51 to 0.73)	0.83 (0.78 to 0.87)	0.78 (0.74 to 0.82)
Time to ACM			
PSA-DT<3 mo†	18.2 (8.9 to 37.2)	4.8 (3.4 to 7.0)	6.9 (5.0 to 9.5)
PSA-DT≥3 mo (continuous)†	0.84 (0.78 to 0.90)	0.95 (0.93 to 0.98)‡	0.93 (0.91 to 0.95)

*All *P* values are less than .001, except as indicated. All statistical tests were two-sided.

†These analyses are adjusted for age at the time of PSA-defined recurrence.

‡$P = .001$.

after adjusting for the potential baseline confounding factors and the PSA-DT of less than 3 months in Cox multivariable regression analyses, the initial treatment received was not statistically significantly associated with time to prostate cancer–specific mortality ($P_{Cox} = .90$) or with time to all-cause mortality ($P_{Cox} = .83$), whereas age at the time of PSA-defined recurrence was a statistically significant covariate ($P_{Cox}<.001$). Specifically, as illustrated in Figs. 1 and 2, the differences in the estimates of prostate cancer–specific mortality ($P_{log\text{-}rank} = .38$) and all-cause mortality ($P_{log\text{-}rank} = .34$) after PSA-defined recurrence were not statistically significantly different for patients with a PSA-DT of less than 3 months who were treated with surgery or radiation, respectively. Moreover, the proportion of treatment effect (PTE) explained by the PSA-DT when its estimate was less than 3 months was 0.98 (95% CI = 0.7 to 1.3).

For patients with a PSA-DT of 3 months or more, the distributions of PSA-DT ($P_{\chi 2}<.001$) and of age at the time of PSA-defined recurrence ($P_{\chi 2}<.001$) were statistically significantly different between patients treated surgically and patients treated with radiation therapy (Table 5). In addition, as shown in Table 3, treatment received was statistically significantly associated with both time to prostate cancer–specific mortality and all-cause mortality in unadjusted analyses and in analyses that were adjusted only for the baseline confounding factors. However, after adjusting for the specific value of the PSA-DT and baseline confounding factors in the time to prostate cancer–specific mortality analysis and adjusting for the specific value of the PSA-DT, baseline confounding factors, and age at the time of PSA-defined recurrence in the time to all-cause mortality analysis, treatment received was not statistically significantly associated with time to prostate cancer–specific mortality ($P_{Cox} = .28$) or time to all-cause mortality ($P_{Cox} = .10$) (Table 3). Age at the time of PSA-defined recurrence was a statistically significant covariate ($P_{Cox}<.001$) in the time to all-cause mortality analysis. The value of the proportion of treatment effect (PTE) explained

Table 5. Distribution of the age at prostate-specific antigen (PSA)–defined recurrence and the post-treatment prostate-specific antigen doubling time (PSA-DT) for patients with a PSA-DT of 3 months or greater, stratified by initial treatment received*

Clinical factor	Surgery, %†	Radiation, %†
PSA-DT		
3–5.99 mo	18	23
6–11.99 mo	32	37
⩾12 mo	50	40
Age at PSA-defined recurrence		
<50 y	0.4	0.2
50–59 y	15	3
60–69 y	51	23
70–74 y	22	31
75–79 y	10	29
⩾80 y	1.5	15

*The two-sided χ^2 statistical test was used to compare the distributions of post-treatment PSA-DT and age at the time of PSA recurrence among patients treated with surgery as opposed to radiation therapy. Both *P* values were <.001. All statistical tests were two-sided.

†Percentages may not sum to 100 because of rounding.

by the value of the PSA-DT for patients in whom this estimate was 3 months or more was 0.96 (95% CI = 0.5 to 1.4).

The lack of an impact of the treatment received on the time to prostate cancer–specific mortality and all-cause mortality after PSA-defined recurrence for patients with a PSA-DT of less than 3 months was further supported by the partial proportion of the variation in prostate cancer–specific mortality. Specifically, after a PSA-defined recurrence, the additional information obtained by adding treatment received to the Cox model that contained a PSA-DT of less than 3 months was very small (<1%), corresponding to the partial proportion of the variation in the time to prostate cancer–specific mortality of 0.06% (95% CI = 0.0003% to 0.63%) and 0.01% (95% CI = 0.00008% to 0.38%) for the time to all-cause mortality.

Discussion

Randomized trials comparing surgery and radiation therapy for patients with localized prostate cancer often take more than a decade from inception to reporting because of the long natural history of the disease after primary therapy. To more quickly obtain information about the efficacy of new treatments, risk groups have been defined *(27)* and nomograms have been developed *(28)* to identify patients with prostate cancer who are at high risk of PSA-defined recurrence after surgery or radiation therapy based on pretreatment parameters *(27,28),* post-treatment parameters *(29,30),* or both *(31),* so that they can be entered onto randomized clinical trials. However, not all patients who are at high risk for PSA-defined disease recurrence will experience a recurrence and, of those who do, only a fraction will die of prostate cancer.

Identification of a surrogate end point for prostate cancer–specific mortality would alter randomized clinical trial design comparing different treatments (e.g., radical prostatectomy versus radiation therapy) or different regimens of the same treatment (e.g., radiation therapy doses of 70 Gy versus 78 Gy). A smaller sample size and a shorter follow-up period could be used if the power calculation for the study was based on the surrogate end point rather than on a survival end point, providing results of the trial more rapidly. Moreover, a surrogate end point for prostate cancer–specific mortality could be used to identify patients at high risk for such mortality after primary local treatment failure who could be given more aggressive therapy earlier and perhaps could be selected for clinical trials of novel systemic therapies.

Recent data suggest that patients with a short post-treatment PSA-DT have an estimated prostate cancer–specific mortality and an estimated all-cause mortality that are nearly identical *(9),* providing the basis for the hypothesis that a short PSA-DT after radiation therapy may serve as a surrogate end point for prostate cancer–specific mortality. Therefore, the purpose of this study was to validate or refute this hypothesis by assessing whether Prentice's criteria *(18)* that define a surrogate end point were violated by outcome data taken from two large multi-institutional databases on patients with prostate cancer who were treated with surgery or radiation therapy.

Our results indicate that the post-treatment PSA-DT (the combination of a PSA-DT of less than 3 months and the specific value of the PSA-DT when it is 3 months or more) is a surrogate end point for prostate cancer–specific mortality. First, using Cox regression analysis, we found that, after PSA-defined recurrence in patients treated with surgery or radiation therapy, a PSA-DT of less than 3 months or the specific estimate of the PSA-DT when it was 3 months or more was statistically significantly associated with time to prostate cancer–specific mortality (P_{Cox}<.001) and with time to all-cause mortality (P_{Cox}<.001), as shown in Table 3. Although the initial treatment received was statistically significantly associated with time to prostate cancer–specific and all-cause mortality when unadjusted or adjusted for the potential baseline confounding factors (Table 3), the treatment received was not statistically significantly associated with time to prostate cancer–specific mortality after PSA-defined recurrence when adjusted for PSA-DT of less than 3 months (P_{Cox} = .90) or the specific value of the PSA-DT when it was 3 months or more (P_{Cox} = .28). Second, after a PSA-defined recurrence, the additional information obtained by adding treatment received to the Cox model that contained a PSA-DT of less than 3 months was very small (<1%), corresponding to the partial proportion of the variation in prostate cancer–specific mortality of 0.06%. Finally, the proportion of treatment effect (PTE) analysis *(25)* revealed that more than 95% of the treatment effect could be explained by the proposed surrogate end point; i.e., given the surrogate end point, the dependence of the time to prostate cancer–specific mortality after PSA-defined recurrence on treatment was small and was consistent with the results of the pPVE *(21)* and Cox regression *(23)* analyses.

The shorter post-treatment PSA-DT and the higher median age at PSA-defined recurrence for patients treated with radiation therapy than for patients treated surgically (Table 5) may be explained by the fact that surgical treatment is generally recommended for younger patients with less advanced disease (Table 1). However, even after adjusting for the shorter PSA-DT and older age at PSA-defined recurrence in a Cox regression analysis, initial treatment received was almost statistically significantly associated with the time to all-cause mortality after PSA-defined recurrence (P_{Cox} = .10; Table 3). A likely explanation for this result may be that patients selected for external beam radiation monotherapy, at any given age, are generally less healthy than those selected for surgery. As a result, age alone may not reflect the competing risks for all-cause mortality in patients treated with radiation therapy compared with those in patients treated surgically.

Of clinical importance, 12% of all patients treated surgically and 20% of all patients treated with radiation therapy in this study who experienced a PSA-defined recurrence had a PSA-DT of less than 3 months. Given that the median survival after PSA-defined recurrence in such patients is only 6 years (Fig. 2) and the hazard ratio is 19.6 (Table 4) for prostate cancer–specific mortality after a PSA-defined recurrence, they probably already harbor occult micrometastatic prostate cancer. In addition, given that a short PSA-DT has been shown to be associated with a short time to distant disease recurrence after PSA-defined recurrence *(4–8),* patients with a PSA-DT of less than 3 months are at very high risk for developing metastatic bone disease and subsequent pathologic fracture and spinal cord compression in a relatively short time after PSA-defined recurrence. Therefore, these are the men who are most likely to benefit from an extended, relatively symptom-free interval provided by the early salvage hormonal therapy. Consequently, patients with a PSA-DT of less than 3 months should be given the opportunity to begin androgen-suppression therapy. These patients should also be referred for entry onto clinical trials that are examining new forms of systemic therapy that may further benefit them.

A few potential limitations of this study need to be considered. First, although we cannot claim that Prentice's criteria have been completely satisfied in this study *(32–37),* we did use three different approaches *(21,23,25)* to test for Prentice's criteria and did not obtain any evidence that Prentice's criteria were violated in our dataset. We did not consider the timing of salvage hormonal therapy in this study, however. Specifically, if early rather than delayed salvage hormonal therapy after PSA-defined recurrence is shown to prolong survival, then the proposed surrogate end point would need to be reevaluated in a study in which all men received salvage hormonal therapy at a prespecified point (e.g., a specific PSA level) after PSA-defined recurrence to ensure that the Prentice's criteria had not been violated.

Second, to be certain that the magnitude of the PSA-DT would be the same for patients treated surgically and those treated with radiation therapy who experienced the same absolute elevations in PSA level, the nadir PSA level was subtracted from the PSA level after radiation therapy and then the PSA-DT was calculated. This normalization decreased the calculated PSA-DT in the patients treated with radiation therapy. In the hypothesis-generating study in which a near equivalence of cancer-specific and all-cause mortality was noted *(9)* and which this study sought to validate, normalization of the PSA-DT was not performed. However, when the data from that study *(9)* were normalized, the 12-month value of the PSA-DT was reduced to 6 months. Therefore, although the results of the current study support a near equivalence of prostate cancer–specific and all-cause mortality after PSA-defined recurrence for patients with a PSA-DT of less than 3 months but not a PSA-DT of less than 6 months, if future studies find the true surrogate end point to include a PSA-DT of less than 6 months as part of their definition, then a PSA-DT of less than 3 months would also satisfy the requirements for a surrogate end point.

Despite these potential limitations, after either surgery or radiation therapy in patients with clinically localized or locally advanced prostate cancer, the results of this study indicate that a PSA-DT of less than 3 months or the specific value of the PSA-DT when it is 3 months or more is apparently a surrogate for prostate cancer–specific mortality. In light of the relatively short time interval from PSA-defined failure to prostate cancer–specific mortality (Fig. 1) and the nearly 20-fold increased risk of prostate cancer–specific mortality for patients with a post-treatment PSA-DT of less than 3 months (Table 4), consideration should be given to promptly initiating hormonal therapy in these men at the time of the PSA-defined recurrence to delay the imminent sequelae of metastatic bone disease and to referring the patient for entry onto clinical trials investigating new forms of systemic therapy for prostate cancer.

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NOTES

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