# Risk of Prostate Cancer–Specific Mortality Following Biochemical Recurrence After Radical Prostatectomy

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**Context** The natural history of biochemical recurrence after radical prostatectomy can be long but variable. Better risk assessment models are needed to identify men who are at high risk for prostate cancer death early and who may benefit from aggressive salvage treatment and to identify men who are at low risk for prostate cancer death and can be safely observed.

**Objectives** To define risk factors for prostate cancer death following radical prostatectomy and to develop tables to risk stratify for prostate cancer–specific survival.

**Design, Setting, and Patients** Retrospective cohort study of 379 men who had undergone radical prostatectomy at an urban tertiary care hospital between 1982 and 2000 and who had a biochemical recurrence and after biochemical failure had at least 2 prostate-specific antigen (PSA) values at least 3 months apart in order to calculate PSA doubling time (PSADT). The mean (SD) follow-up after surgery was 10.3 (4.7) years and median follow-up was 10 years (range, 1-20 years).

**Main Outcome Measure** Prostate cancer–specific mortality.

**Results** Median survival had not been reached after 16 years of follow-up after biochemical recurrence. Prostate-specific doubling time (<3.0 vs 3.0-8.9 vs 9.0-14.9 vs ≥15.0 months), pathological Gleason score (≤7 vs 8-10), and time from surgery to biochemical recurrence (≤3 vs >3 years) were all significant risk factors for time to prostate-specific mortality. Using these 3 variables, tables were constructed to estimate the risk of prostate cancer–specific survival at year 15 after biochemical recurrence.

**Conclusion** Clinical parameters (PSADT, pathological Gleason score, and time from surgery to biochemical recurrence) can help risk stratify patients for prostate cancer–specific mortality following biochemical recurrence after radical prostatectomy. These preliminary findings may serve as useful guides to patients and their physicians to identify patients at high risk for prostate cancer–specific mortality following biochemical recurrence after radical prostatectomy to enroll them in early aggressive treatment trials. In addition, these preliminary findings highlight that survival in low-risk patients can be quite prolonged.

*JAMA. 2005;294:433-439* www.jama.com

RADICAL PROSTATECTOMY IS ONE of the most common treatments for prostate cancer and generally provides excellent cancer control. However, approximately 35% of patients will develop a prostate-specific antigen (PSA) recurrence within 10 years after surgery.[1-4] Due to the exquisite sensitivity of PSA to detect disease recurrence early, many patients have a long interval between biochemical recurrence and the development of local recurrence or distant metastasis. To help counsel these patients and their physicians, we previously analyzed a cohort of 304 men who had undergone radical prostatectomy and had a subsequent biochemical recurrence, of whom 131 had PSA doubling time (PSADT) data available.[5] In that report, the median time from biochemical recurrence to metastasis was 8 years and from metastasis to death was 5 years. Given this protracted natural history, we identified clinical variables to help stratify patients for risk of metastasis: time from surgery to biochemical recurrence, pathological Gleason score, and PSADT. Since our initial report, other series have confirmed that a short PSADT is a risk factor for clinical progression and prostate cancer–specific mortality.[6-8] To further de-

**See also pp 440 and 493.**

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fine the natural history of patients with biochemical relapse after radical prostatectomy, we sought to identify risk factors for prostate cancer–specific mortality following radical prostatectomy using an expanded cohort with a longer follow-up. We also attempted to identify patients who were at high risk for prostate cancer–specific mortality who would be candidates for clinical trials evaluating the role of early aggressive interventions.

## METHODS

### Patient Population

The institutional review board at Johns Hopkins University approved this study and when required, written informed consent was obtained from all study participants. We evaluated data from 5096 patients with prostate adenocarcinoma who had undergone radical prostatectomy at the Johns Hopkins Hospital from April 1982 to October 2000 with follow-up data available. During a mean (SD) of 6.0 (4.4) years and median follow-up of 5 years, 979 (19%) developed a biochemical recurrence, defined as a single postoperative PSA of at least 0.2 ng/mL. For this study, we only included patients with at least 2 PSA values separated by at least 3 months within 2 years after biochemical recurrence who did not receive adjuvant radiation or hormonal therapy prior to biochemical recurrence (n=411). Patients who received preoperative radiation (n=2) or hormonal therapy (n=10) were excluded. Patients who received salvage radiation with a durable PSA response (>2 years) were considered to have local-only recurrence and to have been cured by surgery plus radiation, and were excluded (n=20). Patients who underwent salvage radiation but did not achieve a durable PSA response were considered to have distant failure and were included (n=22). This resulted in a study population of 379 patients. Race was categorized using patient reported data and is reported for baseline demographic information purposes only. Because our study population was predominantly white, we did not include race in any statistical analyses.

### Follow-up

Patients were followed up postoperatively with PSA determinations and rectal examinations every 3 months for the first year, semiannually for the second year, and annually thereafter. After biochemical progression, imaging was performed at the discretion of the primary care physician. Fifty-four patients (14%) received hormonal therapy before developing metastasis, of whom 6 went on to develop metastasis while 48 remained metastasis-free at last follow-up. Following progression after hormonal therapy, patients returned to their primary oncologist for treatment and follow-up. Prostate cancer death was defined as death in any patient with metastasis that showed any progression following hormonal therapy. Because of the limited number of non–prostate cancer deaths (n=15) in this relatively healthy cohort, the prostate cancer–specific mortality approached the all-cause mortality, so data are only reported for prostate cancer–specific mortality. When the 15 men with non–prostate cancer deaths were excluded vs informatively censored at the time of death, the results of the multivariable analyses did not materially change. Therefore, these men were censored at the time of death and included in the analyses.

### Determination of PSADT

Prostate-specific antigen doubling time was calculated by the natural log of 2 (0.693) divided by the slope of the linear regression line of log of the PSA over time. As previously described, we used all PSA values within 2 years after biochemical recurrence (≥0.2 ng/mL).[5] Patients (n=7) with a negative or 0 PSADT (no increase in PSA) were assigned a value of 100 months for ease of calculations. All PSA values were taken prior to subsequent therapy (radiation or hormonal) and therefore subsequent therapy had no effect on PSADT calculation. In a small subset (n <100), frozen banked serum samples collected prior to the introduction of the PSA assay were used to measure PSA concentration retrospectively.

### Statistical Analysis

Significant risk factors for time from biochemical recurrence to prostate cancer–specific mortality were examined using log-rank survivorship analysis and Cox proportional hazards regression. Univariable exploratory analyses showed that grouping Gleason score as 7 or less vs 8 through 10 and time from surgery to biochemical recurrence as 3 years or less vs more than 3 years provided the greatest likelihood $\chi^2$ ratio for estimating time to prostate cancer–specific mortality; therefore, these groupings were used in the multivariable model. For multivariable analysis, a forward-stepwise Cox proportional hazards model was used with $P<.15$ determining which variables should be entered into the model at each step. The variables considered for entry into the model included PSADT, pathological Gleason score, time from surgery to biochemical recurrence, age at radical prostatectomy, surgical margin status, extraprostatic extension, seminal vesicle invasion, and lymph node metastasis. The possibility of a time effect was examined by comparing the Kaplan-Meier survivorship curves for patients treated before 1990 vs 1990 or later. Because these curves were almost identical and the Cox model estimates were also representative of the curves, we concluded that any time effect in this data was minimal.

The proportional hazards assumption of the Cox model was tested through the graphical examination of the log-log plots of the variables used in the model. These plots formed approximate parallel straight lines as required. In addition, internal validation of the model was tested by comparing the Kaplan-Meier and Cox estimated values for several subsets that were defined using factors not included in the Cox model. In these cases, the estimated points at the death times appeared randomly scattered about the Kaplan-Meier curves. The predictive performance of the model was as-

sessed using the concordance index C.[9] The 5-, 10-, and 15-year actuarial risk of prostate cancer–specific survival from biochemical recurrence was calculated using the coefficients of the multivariable Cox model. The 95% confidence intervals (CIs) were calculated as previously described.[10] The estimated variance of the survivorship estimate (f) was determined using a bootstrapping technique with 1000 replicates. The effective sample size (ESS) was calculated using the following formula: ESS = [f × (1–f)]/variance. The asymmetric binomial distribution CI was then calculated using the Wilson Quadratic Formula. All statistical analyses were performed using STATA 8.0 (STATA Corp; College Station, Tex), and $P<.05$ was considered statistically significant.

## RESULTS

Most patients had pathologically extraprostatic disease and high-grade disease (TABLE 1). Mean (SD) and median follow-up after surgery among the 379 patients was 10.3 (4.7) and 10 years, respectively (range, 1-20 years). Mean (SD) and median time from surgery to biochemical recurrence was 3.5 (3.0) and 2 years, respectively, and mean (SD) and median follow-up after biochemical recurrence was 6.8 (3.8) and 6 years, respectively. During this time, 66 of the 379 patients (17%) died from prostate cancer. Median prostate cancer–specific survival of the study cohort of 379 patients with PSADT data available who experienced a biochemical recurrence has not been reached. Among this cohort, the 5-, 10-, and 15-year cause-specific survival from the respective time of biochemical recurrence was 93% (95% CI, 90%-96%), 73% (95% CI, 66%-79%), and 55% (95% CI, 41%-67%; FIGURE 1).

On multivariable analysis, pathological Gleason score (hazard ratio [HR], 2.33; 95% CI, 1.38-3.95; $P=.002$), time from surgery to biochemical recurrence (HR, 2.55; 95% CI, 1.15-5.62; $P=.02$), and PSADT as a continuous variable (HR, 0.86; 95% CI, 0.81-0.91; $P<.001$) were the only significant independent risk factors for time to prostate cancer–specific mortality following biochemical recurrence. The importance of time from surgery to biochemical recurrence (≤3 vs >3 years) and Gleason score (≤7 vs 8-10) for estimating prostate cancer–specific mortality are shown in Figure 1 and FIGURE 2, respectively.

We explored various PSADT cut points by dividing patients into groups based on every 3 months in PSADT: <3.0, 3.0-5.9, 6.0-8.9, 9.0-11.9 months, etc. Due to limited patient numbers and few cancer deaths in patients with longer PSADT, patients with a PSADT of at least 24 months were combined into 1 group. The PSADT groups were then examined as a categorical variable in multivariable analysis and categories with similar HRs for prostate cancer–specific mortality were combined. This resulted in PSADT being divided into the following groups: <3.0, 3.0-8.9, 9.0-14.9, ≥15.0 months (FIGURE 3). The PSADT categories remained significantly associated with time to prostate cancer–specific mortality in multivariable analysis, along with pathological Gleason score and time from surgery to biochemical recurrence (TABLE 2). Within each PSADT category, the HR of PSADT as a continuous variable for prostate cancer–specific mortality was exactly 1.0 except for the group with a PSADT less than 3 months in which there were only 23 patients (HR, 0.85; 95%, 0.37-1.96).

The concordance index C of the model using PSADT as a continuous variable to estimate time to prostate cancer–specific mortality was 0.83, and with PSADT as a categorical variable, it was 0.84. The bias of the predictive-performance characteristic of the model with PSADT as a categorical variable was assessed using a bootstrap resampling procedure with 1000 replicates, which demonstrated that the bias in each coefficient of the 3 significant variables (time from surgery to biochemical recurrence, pathological Gleason score, and PSADT) was <8% (range, 1.8%-7.7%), the value of the coefficient.

Using the pathological Gleason score, time from surgery to biochemical recurrence, and PSADT, patients could be stratified into high- and low-risk groups for prostate cancer–specific mortality. For example, patients with a PSADT in less than 3 months (n = 23) had a median survival of 6 years. Patients with a PSADT in less than 3 months, biochemical recurrence 3 years or less after surgery, and a pathological Gleason score of 8-10 (n = 15) had a median survival of 3 years. On the contrary, patients with a PSADT of 15 or more months and a biochemical recurrence more than 3 years after surgery (n = 82) had a 100% cause-specific survival.

The estimated 5-, 10-, and 15-year risk of prostate cancer–specific sur-

**Table 1.** Preoperative Clinical and Pathological Characteristics of Men Who Experienced a Biochemical Recurrence After Radical Prostatectomy*

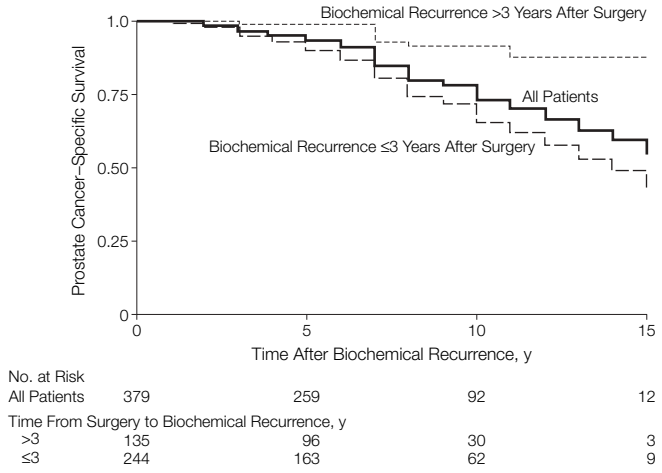
| Characteristics | No. (%) |
|---|---|
| No. of patients | 379 |
| Age at time of surgery, mean (SD), y | 59.7 (6.2) |
| Preoperative PSA, ng/mL | |
| Mean (SD) | 14.4 (15.0) |
| Median | 10.6 |
| Biopsy Gleason score† | |
| 2-6 | 173 (47) |
| 7 | 146 (39) |
| 8-10 | 53 (14) |
| Race | |
| White | 360 (95) |
| Black | 14 (4) |
| Nonblack-nonwhite | 5 (1) |
| Clinical stage† | |
| T1b | 6 (2) |
| T1c | 73 (19) |
| T2a | 130 (34) |
| T2b | 119 (32) |
| T2c | 29 (8) |
| T3 | 20 (5) |
| Pathological Gleason score | |
| 2-6 | 54 (14) |
| 7 | 195 (51) |
| 8-10 | 130 (34) |
| Positive surgical margins | 178 (47) |
| Extracapsular extension | 337 (89) |
| Seminal vesicle invasion | 143 (38) |
| Positive lymph nodes | 124 (33) |
| PSADT after biochemical recurrence, mo | |
| Median | 12.1 |
| <3 | 23 (6) |
| 3.0-5.9 | 55 (15) |
| 6.0-8.9 | 64 (17) |
| 9.0-11.9 | 46 (12) |
| 12.0-14.9 | 33 (9) |
| 15.0-17.9 | 33 (9) |
| 18.0-20.9 | 20 (5) |
| 21.0-23.9 | 17 (4) |
| ≥24 | 88 (23) |

Abbreviation: PSADT, prostate-specific antigen doubling time.
*Percentages may not sum to 100 due to rounding.
†Seven patients had missing data for biopsy Gleason score, and 2 patients had missing data for clinical stage.

vival following biochemical recurrence stratified by pathological Gleason score, time from surgery to biochemical recurrence, and PSADT is shown in TABLE 3.

Of the 379 patients, 54 received hormonal therapy prior to the development of metastasis. To investigate whether these patients influenced the results, we analyzed the data excluding these patients. When these patients were excluded, pathological Gleason score, time from surgery to biochemical recurrence, and PSADT remained significant risk factors for prostate cancer–specific mortality and the 5-, 10-, and 15-year risk of prostate cancer survival following biochemical recurrence fell within the 95% CIs of the estimates when the full cohort was examined. For example, the 5-, 10-, and 15-year risk of prostate cancer survival for a patient not treated with early hormonal therapy with a PSADT in less than 3 months, recurrence 3 or more years after surgery, and a Gleason score between 8 and 10 was 50%, 1%, and less than 1%, respectively. For a similar patient but with a PSADT between 3.0 and 8.9 months, the 5-, 10-, and 15-year risk of prostate cancer survival was 78%, 19%, and <1%, respectively.

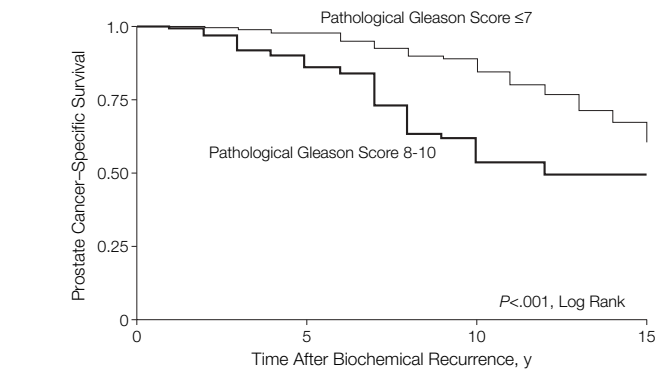
**Figure 1.** Fifteen-Year Actuarial Kaplan-Meier Prostate Cancer–Specific Survival Curves by Time of Recurrence




| No. at Risk | | | | |
|---|---|---|---|---|
| All Patients | 379 | 259 | 92 | 12 |
| Time From Surgery to Biochemical Recurrence, y | | | | |
| >3 | 135 | 96 | 30 | 3 |
| ≤3 | 244 | 163 | 62 | 9 |

Biochemical recurrence stratified by all comers vs early biochemical recurrence (within 3 years following surgery) vs late biochemical recurrence (>3 years following surgery).

**Figure 2.** Fifteen-Year Actuarial Kaplan-Meier Prostate Cancer–Specific Survival Curves by Gleason Score




| No. at Risk | | | | |
|---|---|---|---|---|
| Pathological Gleason Score | | | | |
| ≤7 | 252 | 166 | 68 | 10 |
| ≥8 | 127 | 93 | 24 | 2 |

Biochemical recurrence segregated by pathological Gleason score among patients who experienced a biochemical recurrence.

## COMMENT

The natural history of prostate cancer following biochemical recurrence can be quite long.[5] A short PSADT is associated with increased risk of clinical progression, metastasis, and prostate cancer–specific mortality.[6-8] However, whether other clinical variables add information to PSADT is less clear. Using a cohort of patients all having biochemical recurrence after radical prostatectomy with prolonged follow-up, we identified 3 significant risk factors for prostate cancer–specific mortality: PSADT, pathological Gleason score, and time from surgery to biochemical recurrence. Using these variables, tables were constructed to estimate the 5-, 10-, and 15-year risk of prostate cancer–specific survival. Although the number of patients in the current study was relatively small requiring that the findings be viewed as preliminary, these tables may serve as useful guides to patients and their physicians to assess the risk of prostate cancer–specific mortality after a biochemical recurrence after radical prostatectomy.

Following radical prostatectomy, approximately 35% of patients will experience a biochemical recurrence within 10 years.[1-4] Biochemical recurrence is associated with increased need for secondary treatment, which can negatively impact quality of life.[11] It has become increasingly recognized that many patients who develop a biochemical recurrence will have an indolent clinical course.[5] We previously studied 304 patients treated with radical prostatectomy who had a biochemical recurrence, of whom 131 had PSADT data available.[5] In that prior study, the median time from biochemical recurrence to metastasis was 8 years and from metastasis to death was 5 years. Rela-

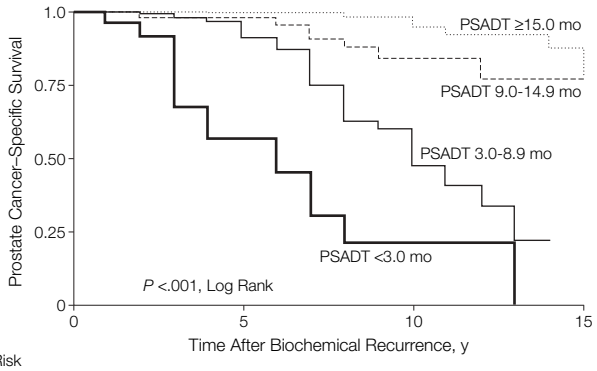
 

tive to our earlier study,[5] the current study included a larger patient population (379 vs 131) and longer mean follow-up after surgery (10.3 vs 5.3 years). In the current study, the median time from biochemical recurrence to prostate cancer–specific mortality was not reached after 16 years of follow-up. However, using the clinical variables of PSADT, Gleason score, and time to biochemical recurrence, patients could be stratified into groups with a varying risk of survival at year 15 of 94% vs <1%, although the CIs for many of the subgroups were large.

The importance of PSADT as a marker of prostate cancer biology among patients with biochemical recurrence after definitive treatment and prior to hormonal therapy was recognized more than 10 years ago.[12-14] Subsequent studies have confirmed that after PSADT treatment is strongly associated with clinical progression and development of metastasis.[5,7,8,15-20] Only recently have data emerged linking shorter PSADT before hormonal therapy with prostate cancer–specific mortality.[6,21-24] In the current study, PSADT was one of the strongest risk factors for prostate cancer–specific mortality. Although the number of patients with a PSADT in less than 3 months in the current study was small, median survival of these patients was 6 years, identical to the findings from an earlier large multicenter study.[6] Thus, patients with a short PSADT are at high-risk for prostate cancer–specific mortality and should be offered early aggressive salvage treatment and participation in clinical trials. Conversely, patients with a long PSADT (≥15 months) are at low risk for prostate cancer–specific mortality and can potentially be spared the effects of secondary treatment because it is unlikely to significantly prolong life in patients with such a low risk.

A prior study from D'Amico et al[6] examined patients treated with both external beam radiation therapy and radical prostatectomy and found that a posttreatment PSADT in less than 3 months was significantly associated with risk of prostate cancer–specific

**Figure 3.** Fifteen-Year Actuarial Kaplan-Meier Prostate Cancer–Specific Survival Curves by PSADT




| No. at Risk PSADT, mo | | | | |
|---|---|---|---|---|
| <3.0 | 23 | 10 | 2 | 0 |
| 3.0-8.9 | 119 | 85 | 19 | 0 |
| 9.0-14.9 | 79 | 51 | 19 | 3 |
| ≤15 | 158 | 113 | 52 | 9 |

Biochemical recurrence segregated by prostate-specific antigen doubling time among patients who experienced a biochemical recurrence. PSADT indicates prostate-specific antigen doubling time.

**Table 2.** Cox Proportional Hazards Analysis of Factors Estimating Time to Prostate Cancer–Specific Death After Biochemical Recurrence Following Radical Prostatectomy

| Variables | HR (95% CI) | β (SE) | *P* Value |
|---|---|---|---|
| PSADT (relative to ≥15.0 mo) | | | |
| <3.0 mo | 27.48 (10.66-70.85) | 3.314 (0.483) | <.001 |
| 3.0-8.9 mo | 8.76 (3.74-20.50) | 2.170 (0.434) | <.001 |
| 9.0-14.9 mo | 2.44 (0.88-6.81) | 0.893 (0.523) | .09 |
| Years from radical prostatectomy to recurrence (≤3 vs >3) | 3.53 (1.59-7.84) | 1.262 (0.407) | .002 |
| Pathological Gleason score (≥8 vs <8) | 2.26 (1.35-3.77) | 0.815 (0.262) | .002 |

Abbreviations: CI, confidence interval; HR, hazard ratio; PSADT, prostate-specific antigen doubling time.

**Table 3.** Estimate of the Risk of Prostate Cancer–Specific Survival After Biochemical Recurrence Following Radical Prostatectomy

| | Risk Estimate, % (95% Confidence Interval) | | | |
|---|---|---|---|---|
| | Recurrence >3 y After Surgery | | Recurrence ≤3 y After Surgery | |
| Prostate-Specific Antigen Doubling Time, mo | Gleason Score <8 | Gleason Score ≥8 | Gleason Score <8 | Gleason Score ≥8 |
| 5-y Estimate | | | | |
| ≥15.0 | 100 (98 to 100) | 99 (98 to 99) | 99 (96 to 100) | 98 (90 to 100) |
| 9.0-14.9 | 99 (70 to 100) | 98 (75 to 100) | 97 (76 to 100) | 94 (63 to 99) |
| 3.0-8.9 | 97 (81 to 100) | 94 (74 to 99) | 91 (67 to 98) | 81 (46 to 95) |
| <3.0 | 92 (70 to 98) | 83 (52 to 96) | 74 (37 to 93) | 51 (19 to 82) |
| 10-y Estimate | | | | |
| ≥15.0 | 98 (96 to 100) | 96 (93 to 98) | 93 (80 to 98) | 86 (61 to 96) |
| 9.0-14.9 | 95 (75 to 99) | 90 (58 to 98) | 85 (49 to 97) | 69 (30 to 92) |
| 3.0-8.9 | 84 (62 to 94) | 68 (37 to 89) | 55 (25 to 82) | 26 (7 to 62) |
| <3.0 | 59 (29 to 83) | 30 (10 to 63) | 15 (3 to 53) | 1 (<1 to 55) |
| 15-y Estimate | | | | |
| ≥15.0 | 94 (87 to 100) | 87 (79 to 92) | 81 (57 to 93) | 62 (32 to 85) |
| 9.0-14.9 | 86 (57 to 97) | 72 (35 to 92) | 59 (24 to 87) | 31 (7 to 72) |
| 3.0-8.9 | 59 (32 to 81) | 30 (10 to 63) | 16 (4 to 49) | 1 (<1 to 51) |
| <3.0 | 19 (5 to 51) | 2 (<1 to 38) | <1 (<1 to 26) | <1 (<1 to 2) |

mortality. We found very similar results in that patients with a PSADT less than 3 months were at very high-risk for death due to prostate cancer. However, other studies have suggested different cut points for stratifying low vs high risk including 6,[8,16,20] 10,[5] and 12[24] months. In the current study, a PSADT cut point of less than 3 months would result in 94% of patients being grouped into the low-risk category. To explore in an unbiased manner the possibility that there may be multiple PSADT cut points, we broke patients into groups by 3-month intervals in PSADT. After combining groups with small patient numbers and/or overlapping Kaplan-Meier curves, we identified 3 PSADT cut points that stratified patients into 4 groups. Within each group, PSADT as a continuous variable was not associated with prostate cancer–specific mortality, suggesting that further subdivision of these groups would not likely improve risk stratification in this data set. However, it is almost certain that the relationship between PSADT and prostate cancer–specific mortality is on a continuum rather than a discrete subdivision. This continuous relationship between PSADT and risk would explain why different investigators have found different subdivisions of PSADT that stratify patients into low- and high-risk groups.

In addition to PSADT, pathological Gleason score was significantly associated with death due to prostate cancer: patients with a Gleason score of 8 to 10 were more likely to die from prostate cancer than patients with a Gleason score of 7 or less. This is in agreement with our earlier study[5] and other studies[21,25] that found Gleason score was significantly associated with risk of metastasis and death from prostate cancer. However, not all studies found that Gleason score helps risk-stratify patients once the PSADT is known.[6,8,16,20] Differences in results between studies may relate to how Gleason score is coded. In the current study, the increased risk of prostate cancer–specific mortality was only observed among patients with a Gleason score of 8 to 10. Patients with a Gleason score of 7 (3 + 4 or 4 + 3), who are often considered high risk, had a similar risk of death as patients with lower Gleason scores.

The third variable that was significantly associated with prostate cancer–specific mortality was the time from surgery to biochemical recurrence. Although we previously found that patients who had recurrence in 2 or fewer years after surgery were at high risk of developing metastasis,[5] in the current analysis, when we examined multiple cut points, we found that segregating by biochemical recurrences in 3 or less vs more than 3 years after surgery provided the best risk stratification. Prior studies have also found an association between early biochemical recurrence and clinical progression and prostate cancer–specific mortality.[15,16,26] This is an important finding in that many studies examine biochemical recurrence as the end point. Although including data about PSADT following biochemical recurrence would be preferable, the current analysis suggests that time to biochemical recurrence may be a reasonable intermediate end point for study.

In our earlier report,[5] no patient was treated with hormonal therapy before developing metastasis. Although this presents an ideal situation to study the natural history of prostate cancer because hormonal therapy can delay time to metastasis,[27,28] many patients today receive hormonal therapy before developing metastasis. Whether early hormonal therapy among patients with a biochemical recurrence after radical prostatectomy delays prostate cancer–specific mortality is debatable.[29] Due to the retrospective nature of our study, our overall small sample size (n=379), only 54 men receiving hormonal therapy before metastasis, and the inability to know from our data why these 54 men received hormonal therapy, we are unable to address this question in the current study. If early hormonal therapy does dramatically improve survival,[30] the estimates generated in the current study may underestimate the likelihood of survival. However, the variables identified in the current study as significant risk factors for death due to prostate cancer may help select men for enrollment in future clinical trials to address this extremely important question. In addition, external validation in other retrospective cohort studies or within the context of prospective clinical trials is necessary. Because our study population was predominantly white and no patient received adjuvant therapy prior to biochemical recurrence, our results may not apply to nonwhite patients or patients receiving adjuvant therapy before biochemical recurrence. Increased postoperative PSA concentrations and PSADT are likely to be time-dependent factors. In our calculation of PSADT, we used the log slope of the PSA concentration over time under the assumption that PSA levels increased exponentially, at least during the first 2 years after recurrence. Thus, though the PSADT may not have been calculable in some men until the end of the second year because no second PSA value was available until that point, the calculated PSADT at that point was presumed to be the PSADT at the time of biochemical recurrence. However, it is certainly plausible that in the long term PSADT values may not be stable. Future studies are needed to examine whether changes in PSADT over time may help further risk-stratify men with biochemical recurrence for death from prostate cancer.

Finally, what degree of risk for prostate cancer–specific mortality merits entry into a clinical trial is unknown. The decision to enroll in a clinical trial is ultimately up to the discretion of the patient and physician. Factors that should be considered include, but are not limited to, the risk of death, the perceived benefit of the intervention, individual patient preferences, and the age and overall health of the patient (ie, the expected life-span of the patient in the absence of recurrent prostate cancer). Thus, the risk of death that would prompt entry into a clinical trial is different for each patient. Ultimately, the value of assessing risk of prostate cancer–specific mortality is expected to be even more important in the future when better and less toxic adjuvant therapies exist.

Using the current data, patients at high risk of death due to prostate cancer can be identified. These patients should be offered aggressive combined multimodality treatment using hormonal and cytotoxic chemotherapy, particularly in light of recent data suggesting that chemotherapy can modestly, but significantly, prolong survival in patients with hormone refractory disease.[31,32]

In a cohort of patients who all experienced a biochemical recurrence after radical prostatectomy, the time to death varied although the median time to death had not been achieved after 16 years of follow-up. Using PSADT, pathological Gleason score and time from surgery to biochemical recurrence, patients could be stratified into groups with varying risk of prostate cancer–specific survival ranging from 94% to <1% 15 years after biochemical recurrence although the CIs for many of the subgroups were large. Using these 3 variables, tables were constructed to estimate the risk of prostate cancer survival at 5, 10, and 15 years after biochemical recurrence. These tables may serve as useful guides to patients and their physicians to assess the risk of prostate cancer survival following biochemical recurrence after radical prostatectomy.

**Author Contributions:** Dr Freedland had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Freedland, Eisenberger, Walsh, Partin.
*Acquisition of data:* Freedland, Humphreys, Mangold, Walsh, Partin.
*Analysis and interpretation of data:* Freedland, Dorey, Partin.
*Drafting of the manuscript:* Freedland, Humphreys, Mangold, Dorey, Partin.
*Critical revision of the manuscript for important intellectual content:* Freedland, Humphreys, Eisenberger, Dorey, Walsh, Partin.
*Statistical analysis:* Freedland, Dorey.
*Obtained funding:* Freedland, Partin.
*Administrative, technical, or material support:* Freedland, Humphreys, Mangold, Partin.
*Study supervision:* Eisenberger, Dorey, Walsh, Partin.
**Financial Disclosures:** None reported.
**Funding/Support:** This study was supported by SPORE Grant P50CA58236 from the National Institutes of Health and National Cancer Institute, the Prostate Cancer Foundation, the Department of Defense Prostate Cancer Research Program grant PC030666, and the American Foundation for Urological Disease/ American Urological Association Education and Research Scholarship Award.
**Role of the Sponsor:** The role of the funding sources was to provide salary support, particularly for Ms Humphreys and Dr Freedland. Otherwise, the funding sources had no direct or indirect involvement in the design and conduct of the study nor the collection, management, analysis, and interpretation of the data nor in the preparation, review, or approval of the manuscript.
**Disclaimer:** Views and opinions of, and endorsements by the author or authors do not reflect those of the US Army or the Department of Defense.

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