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NADiA® ProsVue™ PSA Slope Is an Independent Prognostic Marker for Identifying Men at Reduced Risk for Clinical Recurrence of Prostate Cancer after Radical Prostatectomy

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Abstract

Objectives—To validate the hypothesis that men displaying serum PSA slopes ≤2.0 pg/mL/month postprostatectomy, measured with a new immuno-PCR diagnostic test (NADiA® ProsVue™) were at a reduced risk of clinical recurrence as determined by positive biopsy, imaging or death due to prostate cancer.

Methods—From 4 clinical sites, we selected a cohort of 304 men followed up to 17.6 years postprostatectomy for clinical recurrence. We assessed the prognostic value of a PSA slope cutpoint of 2.0 pg/mL/month against established risk factors to identify men at very low risk of clinical recurrence using uni- and multivariate Cox proportional hazards regression and Kaplan-Meier analysis.

Results—The univariate HR (95% CI) of a PSA slope >2.0 pg/mL/month was 18.3 (10.6–31.8), compared to a slope ≤2.0 pg/mL/month (P <0.0001). Median disease-free survival was 4.8 years

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versus >10 years in the 2 groups (P <0.0001). Multivariate HR for PSA slope with the covariates of preprostatectomy PSA, pathologic stage and Gleason score was 9.8 (5.4–17.8), an 89.8% risk reduction, for men with PSA slopes ≤2.0 pg/mL/month (P <0.0001). Gleason Score (<7 vs. ≥7) was the only other significant predictor (HR 5.4, 2.1–13.8, P = 0.0004).

Conclusions—Clinical recurrence following radical prostatectomy is often difficult to predict since established factors do not reliably stratify risk. We demonstrate that a NADiA ProsVue slope ≤2.0 pg/mL/month postprostatectomy is prognostic for reduced risk of prostate cancer recurrence and adds predictive power to established risk factors.

Keywords

NADiA Pros Vue; PSA; prostate cancer; prostatectomy

INTRODUCTION

Prostate cancer is the most prevalent male malignancy in the United States. With PSA screening, the age at diagnosis has decreased with a concomitant increase in the number of men diagnosed with early-stage or clinically localized disease.[1,2] Radical prostatectomy (RP) is an increasingly common treatment for localized prostate cancer perhaps due to wider adoption of robotic-assisted laparoscopic technology. While surgery can result in long-term cancer control,[3–6] more men are living longer with prostate cancer. This has resulted in a proportionately larger number of men at risk for cancer recurrence heralded by a rising PSA that exceeds a defined cutpoint (0.2–0.4 ng/mL, or 200–400 pg/mL). Biochemical recurrence (BCR) is conservatively estimated to affect around 50,000 men each year.[7] As a result, both physicians and the men treated by RP are interested in estimating the risk of clinical recurrence.

Post-RP risk stratification approaches are based on a number of factors, but rely heavily on pathologic findings such as Gleason score, percentage of grade 4–5 disease, surgical margin involvement, extracapsular extension, seminal vesicle invasion and lymph node involvement. Multivariate models (nomograms) that incorporate these factors predict the likelihood of BCR and are not suitably generalizable for identifying individual men at high or low risk of clinical recurrence, either locally or systemically.[8] The serum PSA nadir value following RP can be an indicative factor since undetectable levels <0.01 ng/mL (<10 pg/mL) are associated with better prognosis when BCR is used as the endpoint.[9–12] However these assays cannot quantitate post-RP PSA concentrations <10 pg/mL, thus they are unable to distinguish between men that are at increased risk of recurrence and those that may be at reduced risk of recurrence.[12–14]

The inability to differentiate clinical recurrence risk is unfortunate for several reasons. From a healthcare management perspective, the intensity of serum PSA and urologic follow-up could be reduced in men at low risk for meaningful clinical recurrence. In addition, empiric use of adjuvant therapies could be reduced or eliminated, which could also reduce healthcare costs. From a patient perspective, quality of life would improve with the avoidance of unneeded radiotherapy or hormonal therapy, safer treatment of hypogonadism, and the unquantifiable yet important alleviation of psychological stress.

Recently, we developed an immuno-polymerase chain reaction (IPCR) assay for total serum PSA and validated its analytical performance in human samples.[15] Our nucleic acid detection immunoassay (NADiA®) incorporates a double-stranded (ds) DNA label for high-sensitivity analyte detection and resists non-specific binding to improve precision. The limit of quantification (LOQ) is 0.00065 ng/mL (0.65 pg/mL), more than an order of magnitude lower than the most sensitive commercial PSA assays. Further, the assay employs a calculation of PSA slope (PSA change over time) as a unique prognostic factor. In pilot studies using NADiA PSA, we found that 90% of men without BCR have serum PSA concentrations below 5 pg/mL in the first several months following RP.[16] In addition, the superior sensitivity and precision of this assay provided a unique opportunity to evaluate the kinetics of PSA at these very low post-RP concentrations. We found that PSA change over time (slope) exhibited first-order kinetics in non-recurring men and that the slope (in pg/mL/month) was significantly different from men that clinically recurred and that slope was a stronger prognostic factor than PSA nadir.[17] These studies determined the potential clinical utility of a NADiA PSA slope cutpoint of 2.0 pg/mL/month and formed the hypothesis that men displaying a slope ≤2.0 pg/mL/month post-RP could be at a reduced risk of clinical recurrence.

The study protocol was reviewed with the US Food and Drug Administration through the pre-IDE process. Its objective was to validate the hypothesis that men displaying PSA slopes ≤2.0 pg/mL/month post-RP were at a reduced risk of clinical recurrence in an appropriately powered case-cohort designed trial.[18] The results provided the basis for United States 510(k) clearance of NADiA ProsVue™ as a post-RP prognostic marker.

PATIENTS AND METHODS

Study design

The required sample size assuming a type I error rate of 5%, 80% power, and a univariate hazard ratio (HR) for PSA slope of 1.4 (estimated from pilot studies) based on a two-sided test was 262. Assuming 20% prevalence for recurrence, a minimum of 52 men with recurrence was required. A cohort random sampling of eligible men was performed within four strata arising from categorization as above or below median patient age (61.4 years) and median sample storage time (13.5 years). The final selected study population consisted of 64 men with clinical recurrence and 240 controls (prevalence 21.1%). Post-RP PSA slope (ProsVue result) was calculated in units of pg/mL vs. time in months for each man using least squares linear regression. ProsVue results were then expressed as a binary categorical variable with the cutpoint set at 2.0 pg/mL/month. ProsVue results ≤2.0 were pre-specified for identifying men at reduced risk of recurrence, therefore results >2.0 identified men “not at reduced risk of recurrence.”

Study population

The study was prospectively designed and incorporated archived serum samples from men treated by RP at four investigational sites (Duke University, Eastern Virginia Medical School, Memorial Sloan-Kettering Cancer Center, and the University of Washington) during 1990–2001. Institutional review boards at all sites approved the study protocol. Study

samples were de-identified except for dates of birth, death, and clinical procedures, which were used to calculate age at RP, time to recurrence or length of follow-up. Inclusion criteria consisted of men with biopsy-confirmed prostate cancer treated by RP with a PSA value in the first post-RP sample <0.1 ng/mL (<100 pg/mL) using standard-of-care immunoassays for PSA. Three serum samples obtained between 1.5 and 20 months post-RP were required with at least a two-month interval between each sample draw date. Documentation of pre-RP PSA, pathologic stage and Gleason score was required to serve as covariates in multivariate analyses. Findings of positive surgical margins, extracapsular extension, seminal vesicle invasion, bladder neck invasion and positive lymph nodes were also recorded if documentation was available. Men categorized by the sites as non-recurrent required a minimum post-RP follow-up of 8 years. Exclusion criteria were radiation treatment administered in the first 12 months post-RP, androgen deprivation therapy administered in the first 20 months post-RP, and serum samples stored longer than 20 years.

Criteria for response

Men categorized by the sites as recurrent required documented evidence of local recurrence by biopsy, evidence of metastases by imaging (MRI, CT, bone scan, or ^{111}In capromab pendetide immunoscintigraphy in conjunction with CT), or death due to prostate cancer. Men categorized as non-recurrent were followed after RP a median of 11.0 (IQR, 9.6–12.9) years vs. a median of 4.7 (IQR, 2.7–8.4) years for men with clinically recurrent disease. Men with BCR without documented evidence of disease (stage D0) were categorized as non-recurrent.

Clinical samples

Serum samples from 433 men treated by RP were available for this study. Samples were stored at ≤–70 °C in each site's biorepository. The sample dra w dates and the PSA immunoassay method used were documented in medical records. Samples from 24 men could not be used because the men either did not meet protocol eligibility or were excluded because secondary treatment was administered during the sample collection period. A total of 1,227 archived samples from the 409 men eligible for cohort selection were shipped on dry ice.

NADiA PSA assay

NADiA is a re-engineered IPCR assay that utilizes a non-native dsDNA label for analyte detection (IRIS International, Inc.). Details of the NADiA PSA assay procedure have been previously described.[15] Briefly, the monoclonal antibody (MAb)-DNA conjugate is reacted with sample in a microtiter plate format to form a first immune complex with PSA. The complex is then captured onto paramagnetic microparticles coated with the second capture MAb. Excess reporter MAb-DNA conjugate is removed from the microparticles by several cycles of magnetic capture and re-suspension. The specifically bound DNA label is amplified using PCR and the quantification cycles (Cq) of standards and samples are measured by qPCR. Cq values are calculated from the calibration curve and converted to PSA concentrations (pg/mL). ProsVue results are calculated from three NADiA PSA values using ProsVue Software. The linear range of the NADiA PSA assay extends beyond its reportable range (0.65–100 pg/mL), and intra-assay precision is <9.0%.[15]

Statistical analyses

The primary outcome measure was clinical recurrence-free survival defined as being alive with no detectable disease on biopsies or imaging studies. Univariate and multivariate Cox proportional hazards regression models were performed to determine the predictive capability of the binary expression of ProsVue results and covariates for clinical recurrence-free survival. Supportive survival analyses employed the Kaplan-Meier method with results of both Wilcoxon and log-rank tests reported. Sensitivity, specificity and positive and negative predictive values (PPV, NPV) were calculated via a standard 2x2 contingency table of clinical recurrence category vs. ProsVue risk category and exact binomial 95% confidence intervals (CI) were determined for each parameter. Comparisons of clinicodemographic factors between recurrent and non-recurrent groups were performed using the Wilcoxon rank sum test for continuous variables, and the Pearson chi-square or Fisher's Exact tests, as appropriate, for categorical variables. SAS V9.1 (SAS Institute, Cary, NC), JMP v5.01 (SAS Institute), and NCSS 2007 (NCSS Inc., Kaysville, UT) were used for the statistical analyses. All tests were two-sided and P <0.05 was considered significant.

RESULTS

Study population

Patient characteristics are listed in Table 1. For discrete covariates, category frequencies are provided, and for continuously valued covariates, mean, median and interquartile ranges (IQR) are given. Overall, 56.1% of men had organ-confined disease, and 3% had evidence of nodal spread. Forty-six percent had Gleason scores of 6 or lower, whereas 76.6% had PSA values ≤10 ng/mL at the time of RP. Comparing the recurrent and non-recurrent groups, pre-RP PSA, tumor volume, pT3/pT4 disease, Gleason score ≥7, positive surgical margins, extracapsular extension, seminal vesicle invasion and bladder neck invasion tended to be higher in value or percentage incidence in the recurrent vs. non-recurrent groups, indicating a higher proportion of aggressive cancers in the clinically recurrent group.

NADiA PSA results

Median sampling times across the study cohort were 4.9, 8.5 and 12.8 months post-RP. Median NADiA PSA concentrations in the first post-RP serum samples were 3.1 (IQR 1.8–6.6) and 14.1 (IQR 4.1–48.4) pg/mL in the non-recurrent and recurrent groups, respectively (P <0.0001). Median PSA values in the second and third samples showed minimal change over time in the non-recurrent group but showed a significant rise across the three sampling points in the recurrent group. Median ProsVue results calculated from the three samples were 0.03 (IQR, −0.04–0.24) pg/mL/month in the non-recurrent group compared to 5.6 (1.6–22.0) in the clinically recurrent group (P <0.0001).

Efficacy analysis

Clinical recurrence was documented in 64/304 (21.1%) men; 15 initially recurred with biopsy-proven localized cancer and 49 initially recurred with distant metastases. Skeletal metastases was the initial presentation in 24/64 (37.5%) cases. Of the men that recurred, 46/64 (71.9%) were correctly classified as “not at reduced risk” of recurrence based on a

ProsVue result >2.0 pg/mL/month. Of the men that did not recur, 227/240 (94.5%) were correctly classified as "at reduced risk" of recurrence based on a ProsVue result ≤2.0. Although the purpose of the study was to validate the hypothesis that ProsVue results ≤2.0 pg/mL/month identified men at a reduced risk of clinical recurrence, the sensitivity, specificity, PPV and NPV for clinical recurrence were also determined. Sensitivity (95% CI) was 71.9% (59.2–82.4%) at 94.6% (90.9–97.1%) specificity. PPV and NPV were 78.0% (65.3–87.7%) and 92.7% (88.6–96.5%), respectively at the 21.1% prevalence of recurrence in this study.

NADiA ProsVue results and pathological variables

The risk of clinical recurrence in relation to ProsVue results and pathological variables is listed in Table 2. A ProsVue result ≤2.0 was significantly associated with a reduced risk of clinically recurrent prostate cancer by univariate Cox proportional hazards regression analysis (HR 18.3, 95% CI, 10.6–31.8, P <0.0001). Most covariates and other pathological variables were also significantly associated with clinical recurrence using univariate analysis. In the multivariate model that included pre-RP PSA, pathological stage, and Gleason score as covariates, the ProsVue HR was minimally attenuated to 9.8 (95% CI, 5.4–17.8, P <0.0001) and was an independent predictor of recurrence risk. The inverse of the HR yields a ratio of 0.102 for an 89.8% reduction in risk of recurrence for men with a ProsVue result ≤2.0. Of the covariates, only Gleason score was significantly associated with recurrence risk (HR 5.4, 95% CI, 2.1–13.8, P = 0.0004) for an 81.4% reduction in risk for men with Gleason score <7.

Figure 1 is a Kaplan-Meier plot of clinical recurrence-free survival based on the ProsVue cutpoint of 2.0 pg/mL/month. The plots diverge within the first two years of follow-up (Wilcoxon P <0.0001) and continue to separate due to fewer clinically recurrent events in men with ProsVue results ≤2.0. Median clinical recurrence-free survival was 4.8 years vs. >17.6 years when ProsVue results were >2.0 and ≤2.0, respectively (log-rank P <0.0001). Figure 2 is a Kaplan-Meier plot of clinical recurrence-free survival based on the ProsVue cutpoint in groups of men with pathological Gleason scores <7 (N=140) and ≥7 (N=164). The plots for the groups with Gleason <7 and ≥7 and ProsVue results >2.0 also diverge within the first two years post-RP, whereas the separation of the plots for the groups with Gleason <7 and ≥7 and ProsVue results ≤2.0 diverge more slowly due to fewer clinically recurrent events in men with ProsVue results ≤2.0 (log-rank P <0.0001 for Gleason scores <7 and ≥7).

In the Gleason score ≥7 subset, sensitivity was 71.2% (57.9–82.2%) at 91.4% (84.4–96.0%) specificity and PPV and NPV were 82.4% (69.1–91.6%) and 85.0% (77.0–91.0%) respectively. Multivariate Cox proportional hazards regression analysis including pre-RP PSA and pathological stage (T3-T4 vs. T0-T2) as covariates showed minimal attenuation of the HR for ProsVue to 8.1 (95% CI, 4.5–14.7, P <0.0001) and it remained the strongest independent predictor of recurrence risk.

COMMENT

Prostate cancer is a complex disease, and it has proved difficult to predict clinical outcomes accurately in individual men following RP.[8] Previous studies have linked undetectable PSA levels <0.01 ng/mL (<10 pg/mL) post-RP to relapse-free survival[12] and nadir values to a lower likelihood for BCR.[14] However, the risk of BCR is not informative as a predictor of clinical endpoints because of the unpredictable kinetics of post-RP PSA values after a BCR event occurs.[19–23] For this reason, the NADiA ProsVue pre-IDE protocol stipulated that efficacy must be defined by clinically documented prostate cancer recurrence rather than BCR. Patients with ProsVue results ≤2.0 pg/mL/month enjoyed a ~90% reduction in risk of clinical recurrence in multivariate analyses. The multivariate model included pre-RP PSA, pathological stage and Gleason score and demonstrated that a ProsVue result ≤2.0 was the most powerful independent prognostic factor for identifying men at reduced risk for clinical recurrence (HR 9.8, P <0.0001). While Gleason score was also found to be a prognostic factor (HR 5.4), ProsVue demonstrated significant utility for identifying men at low risk of clinical recurrence in the subset of men having Gleason score ≥7 prostate cancer.

Limitations of this study include its reliance on archived serum samples. Because of this, the timing of serum sampling was not standardized and ProsVue calculations were determined from varying post-RP timepoints. However, this reflects real-world usage of PSA for post-treatment monitoring since routine testing does not always occur at fixed intervals. Further analysis of our data showed that the prognostic performance of ProsVue was not significantly different when all three NADiA PSA samples were collected within or outside of a one year time period (P = 0.17, data not shown). To address potential selection bias, we compared the demographic and clinicopathological characteristics of the men selected for this study against those of >10,000 RP cases in three published series.[6,24,25] Results revealed similar distributions of demographic and clinicopathological characteristics to the men in this study. Importantly, the pre-IDE protocol was not designed to assess the utility of ProsVue results for identifying men at high risk for clinical recurrence and it was not intended to select men for additional post-RP treatment.

Thirteen men had ProsVue results >2.0 pg/mL/month but showed no clinical evidence of disease recurrence after a minimum 8-year follow-up (i.e., false positive result). In three (23.1%) men, the PSA rise was not sustained and all values declined to <0.05 ng/mL as determined by standard PSA assays and remained <0.05 ng/mL throughout follow-up. Ten men were staged as D0 based on BCR and negative imaging findings, 8 of whom received salvage RT and/or ADT. None of these men had clinical disease recurrence or died from prostate cancer during follow-up.

It should be noted that the men in this study underwent RP between 1991 and 2001 and Gleason grade patterns were assigned by each institution according to the grading system used at that time. The criteria for Gleason grading was refined in 2005[26] therefore we attempted to adjust for these changes so that our results would better correlate with men classified by today's criteria. We combined Gleason score 4, 5 and 6 tumors into one group (≤6). Most cases initially reported as pattern 2 would now be graded pattern 3 since pathologists seldom assign a grade less than 3 to tumors. Scores for higher-grade tumors

were unified to account for certain patterns originally graded as pattern 3 that would now be graded as pattern 4. We were unable to adjust for any Gleason 3+3=6 tumors that might have been upgraded to 3+4=7 using the new scoring system.

CONCLUSIONS

This is the first study of a prognostic assay for risk stratification of clinical prostate cancer recurrence with >10 years median follow-up. NADiA ProsVue is also the first assay to receive FDA clearance based on linear slope of tumor marker concentrations over time. A ProsVue result was the most powerful indicator of reduced risk of clinical recurrence and added prognostic value to established risk factors. ProsVue testing could possibly reduce healthcare costs by reducing the intensity of follow-up in men identified at a reduced risk for recurrence. Further studies will assess method performance and define the role of the assay in risk models and nomograms.

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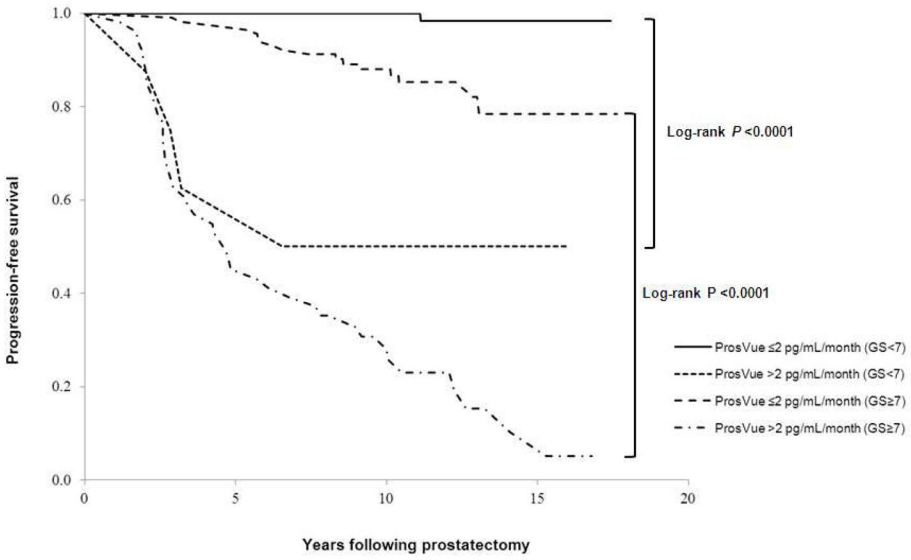

Figure 1.

Kaplan-Meier plot of clinical progression-free survival probabilities for patients categorized as at reduced risk for clinical recurrence (dashed line) and not at reduced risk for recurrence (solid line) by ProsVue results.

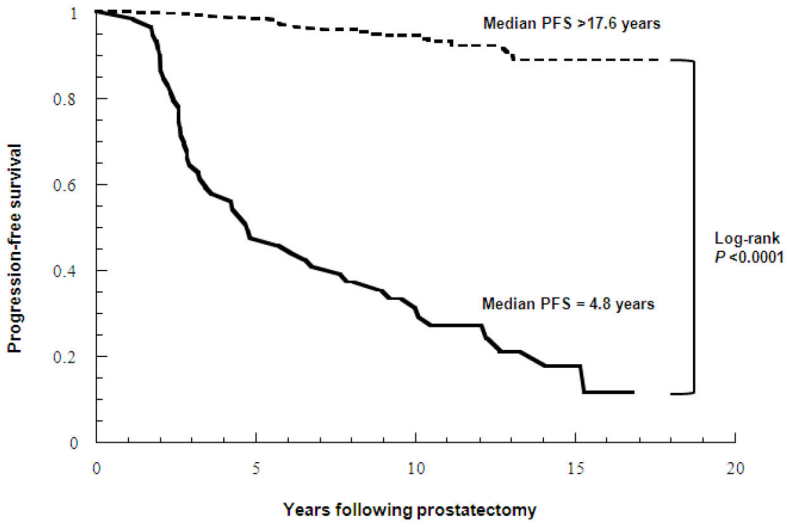

Figure 2.

Kaplan-Meier plot of clinical progression-free survival probabilities for patients categorized as at reduced risk for clinical recurrence and not at reduced risk for recurrence based on ProsVue results in relation to groups of men with pathologic Gleason score <7 and ≥7 prostate cancers.

Table 1

Clinicopathologic characteristics of the studied population

Characteristic	N	Pct.	Mean	Median (IQR)
Age at RP (years)	304	–	61.3	61.4 (59.6–66.1)
Percent tumor volume	65	–	18.3	15.0 (6.5–25.0)
Pre-RP treatment	59	19.4		
Pre-RP PSA (ng/mL)				
≤4.0	70	23.0		
4.0–10.0	163	53.6		
10.1–20.0	57	18.8		
>20.0	14	4.6		
Pathologic GS				
<6	44	14.5		
6	96	31.6		
7	126	41.4		
>7	38	12.5		
Pathologic stage				
T0	2	0.7		
T2	168	55.4		
T3	120	39.4		
T4	14	4.6		
Other pathologic findings[1]				
Surgical margin positive	95	31.3		
Extracapsular extension	125	41.4		
Seminal vesicle involvement	37	12.4		
Bladder neck invasion	18	11.0		
Lymph node involvement	8	3.0		
Race[1]				
African-American	25	8.3		
Asian	6	2.0		
Caucasian	270	89.7		
Ethnicity[1]				
Hispanic	8	4.4		
Non-Hispanic	173	95.6		

[1]Data for these characteristics were not documented in all 304 men in the study

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Table 2

Univariable and multivariate Cox regression analysis of the risk of clinical recurrence according to the post-RP ProsVue slope and pathologic variables

Clinicopathological variables	N	Median years of follow-up	No. Events	Univariate Analysis		Multivariate Analysis	
				HR (95% CI)	P	HR (95% CI)	P
NADiA ProsVue result							
≤2.0 pg/mL/month	245	10.6	18	1.0		1.0	
>2.0 pg/mL/month	59	7.8	46	18.3 (10.6–31.8)	<0.0001	9.8 (5.4–17.8)	<0.0001
Pre-RP PSA level (ng/mL)							
Continuous variable	304	8.6	64	1.1 (1.03–1.08)	<0.0001	1.0 (0.98–1.03)	0.647
Pathological Gleason score							
4, 5, 6	140	10.9	5	1.0		1.0	
7, 8, 9	164	10.0	59	12.1 (4.8–30.1)	<0.0001	5.4 (2.1–13.8)	0.0004
Pathological stage							
pT0–pT2	170	10.8	13	1.0		1.0	
pT3–pT4	134	9.7	51	5.8 (3.2–10.7)	<0.0001	1.7 (0.9–3.4)	0.105
Other pathological findings[1]							
Percent tumor volume							
Continuous variable	65	10.1	16	1.0 (1.0–1.1)	0.059		ND[2]
Surgical margins							
Negative	209	10.5	27	1.0			
Positive	95	9.9	37	3.3 (2.0–5.4)	<0.0001		ND
Extracapsular extension							
Absent	177	10.8	15	1.0			
Present	125	9.7	48	5.3 (3.0–9.5)	<0.0001		ND
Seminal vesicle invasion							
Absent	261	10.5	40	1.0			
Present	37	8.8	24	5.3 (3.2–8.8)	<0.0001		ND
Bladder neck invasion							
Absent	146	10.5	24	1.0			
Present	18	9.8	7	2.8 (1.2–6.5)	0.016		ND

[1] Data for other pathologic findings were not documented in all 304 patients;

[2] ND = not included in multivariate model