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Significance of preoperative PSA velocity in men with low serum PSA and normal DRE

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Abstract

Objectives—A PSA velocity (PSAV) >0.35 ng/ml/year approximately 10–15 years prior to diagnosis is associated with a greater risk of lethal prostate cancer. Some have recommended that a PSAV >0.35 ng/ml/year should prompt a prostate biopsy in men with a low serum PSA (<4 ng/ml) and benign DRE. However, less is known about the utility of this PSAV cutpoint for the prediction of treatment outcomes among men undergoing radical prostatectomy (RP).

Methods—Between 1992 and 2007, 339 men underwent RP at our institution with a preoperative PSA <4 ng/ml, benign DRE, and multiple preoperative PSA measurements. PSAV was calculated by linear regression analysis using all PSA values within 18 months prior to diagnosis. Kaplan–

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Meier survival analysis was performed, and biochemical progression rates were compared between PSAV strata using the log-rank test.

Results—The preoperative PSAV was >0.35 ng/ml/year in 124 (36.6%) of 339 men. Although there were no significant differences in clinicopathological characteristics based upon PSAV, men with a PSAV >0.35 ng/ml/year were significantly more likely to experience biochemical progression after RP at a median follow-up of 4 years ($P = 0.022$).

Conclusions—In this low-risk population with a preoperative PSA <4 ng/ml and benign DRE, approximately 1/3 had a preoperative PSAV >0.35 ng/ml/year. Physicians should carefully monitor men with a preoperative PSA >0.35 ng/ml/year as they are at increased risk of biochemical progression following RP.

Keywords

Prostate cancer; Radical prostatectomy; Pathologic stage; PSA; PSAV; Gleason score

Introduction

In 1994, the U.S. Food and Drug Administration approved PSA for prostate cancer screening using a threshold value of 4 ng/ml [1]. However, a considerable proportion of prostate cancer is detected at PSA levels less than 4 ng/ml. For example, in the Prostate Cancer Prevention Trial, men with a PSA <4 ng/ml and negative digital rectal examination throughout the 7-year study period were offered an end-of-study biopsy [2]. This revealed that biopsy-detectable prostate cancer was present in 15.2% of these men.

It is well-established that men with lower total PSA levels have more favorable treatment outcomes. In 2804 men with clinical stage T1c prostate cancer, Antenor et al. showed that the 10-year progression-free survival rates were 88, 80, 76, and 61% for men with total PSA levels from 2.6 to 4.0, 4.1 to 7.0, 7.1 to 10.0, and >10.0 ng/ml, respectively ($P = 0.0001$) [3]. At Johns Hopkins, Han et al. reported 10-year actuarial progression-free survival rates of 91, 79, 57, and 48% for men with PSA levels ≤ 4.0 , 4.1 to 10.0, 10.1 to 20.0, and >20.0 ng/ml, respectively [4]. A subsequent study demonstrated men with PSA <4 ng/ml, had lower rates of high-risk pathology and demonstrated a trend toward decreased biochemical recurrence [5].

Several recent studies have demonstrated a relationship between preoperative PSA velocity and disease-specific outcomes [1,6]. Less is known about the optimal predictors of tumor aggressiveness and treatment outcomes in the specific sub-population of men with clinical stage T1c prostate cancer and a PSA level <4 ng/ml. Therefore, our objective was to evaluate the prognostic value of PSA velocity for men meeting these criteria from a large radical prostatectomy database.

Methods

From 1992 to 2007, 3705 men underwent surgery at the Johns Hopkins Medical Institutions by one of three of the highest volume surgeons, who collected data on all available preoperative PSA measurements. We excluded men with PSA of 4 ng/ml or greater (2,875), those with clinical stage greater than T1c (256), those with only a single preoperative PSA measurement (234), and those with missing pathology reports (1). This left a study cohort of 339 men with multiple preoperative PSA measurements available to enable a PSA velocity determination. Data on the serial PSA measurements recorded prior to diagnosis were obtained retrospectively from the medical record. None of the men in the study sample

received neoadjuvant therapy. The institutional review board at Johns Hopkins approved this study and, when required, written informed consent was obtained from study participants.

PSA velocity was calculated by linear regression using all available PSA values measured in the 18 months prior to diagnosis. The chi-square (categorical variables) and Mann–Whitney *U* (continuous variables) tests were used to compare clinical and pathological features between men with a PSAV ≤ 0.35 ng/ml/year and > 0.35 ng/ml/year. Logistic regression was used to determine the odds ratios for pathological outcomes.

Biochemical progression was defined as a postoperative PSA level ≥ 0.2 ng/ml [7]. Biochemical progression-free survival curves were created using the Kaplan–Meier method and were compared with the log-rank test. STATA (College Station, TX) was used for all statistical analysis.

Results

A total of 339 patients had clinical stage T1c prostate cancer and a preoperative PSA < 4 ng/ml. The PSAV was ≤ 0.35 ng/ml/year in 215 (63%) and > 0.35 ng/ml/year in the remaining 124 (37%). Table 1a shows the demographics of the study population stratified by PSAV. The majority of men were white in both groups, and the date of surgery was similar. There were no statistically significant differences in age, preoperative PSA, or biopsy Gleason score between the groups.

Table 1b demonstrates the surgical pathology findings in the radical prostatectomy specimen. Overall, 296 (87.3%) had organ-confined disease, 15 (4.4%) had positive surgical margins, and 3 (0.9%) had seminal vesicle invasion. None had lymph node metastases. There was no significant difference in the odds of adverse pathological features between men with PSAV ≤ 0.35 ng/ml/year and > 0.35 ng/ml/year (Table 2).

At a median follow-up of 4 years (range, 1–9 years), biochemical progression occurred in 4% of men with a preoperative PSAV > 0.35 ng/ml/year and in none with a lower PSAV ($P = 0.017$, chi squared). Figure 1 shows the Kaplan–Meier progression-free survival curve, wherein a PSAV > 0.35 ng/ml/year was associated with a significantly greater risk of progression ($P = 0.022$).

In the subset with biochemical progression, the mean preoperative PSA and PSAV were 2.63 ng/ml and 1.00 ng/ml/year, respectively. Sixty-seven percent had non-organ-confined disease, and all demonstrated Gleason pattern 4 in the surgical specimen. The median time to failure was 3 years, with a mean postoperative PSA doubling time of 28.7 months.

Discussion

PSAV was initially described as a means to differentiate between benign conditions and prostate cancer in men with total PSA levels from 4 to 10 ng/ml [8]. In such men from the Baltimore Longitudinal Study of Aging, it was demonstrated that a PSAV > 0.75 ng/ml/year was significantly associated with prostate cancer. The use of PSAV to aid in prostate cancer diagnosis was subsequently confirmed in a screened population with PSA levels between 4 and 10 ng/ml [9].

However, the majority of men in the general population have total PSA levels < 4 ng/ml. Thus, recent studies have attempted to evaluate whether PSAV is also useful for prostate cancer detection among men with lower total PSA levels. Loeb et al. examined 11,792 men with total PSA levels < 4 ng/ml and demonstrated that PSAV was significantly associated with prostate cancer detection [10]. On multivariate analysis, PSAV remained a significant

independent predictor of prostate cancer even after adjusting for age, race, family history, and the total PSA level. However, a lower PSAV cutpoint of approximately 0.4 ng/ml/year was associated with the best performance characteristics in these men. In the Duke database, Moul et al. similarly showed that a cutpoint in the range of 0.4 ng/ml/year was useful for prostate cancer diagnosis [11].

The previous studies address the use of PSAV for prostate cancer detection; however, less is known about its role in prognostication for men with total PSA levels <4 ng/ml. Carter et al. showed that a PSAV threshold of 0.35 ng/ml/year 10–15 years prior to diagnosis (at a time when the PSA level was low) was associated with a 5-fold increased risk of prostate cancer death [12]. We wished to explore whether this threshold would also be useful for prognostication in the immediate pretreatment setting for patients with low PSA levels at the time of diagnosis. We therefore evaluated the association between PSAV and radical prostatectomy outcomes in men with a PSA <4 ng/ml and non-palpable disease. Indeed, we found that those men with a PSAV >0.35 ng/ml/year were at significantly greater risk for biochemical progression.

Some limitations of our study deserve mention. First, PSAV was calculated by regression of PSAs recorded in the 18 months prior to diagnosis, which differs from the method used in some other studies. A selection bias may also have been introduced into the study population as many of the men in our radical prostatectomy database either did not have sufficient serial preoperative PSA measurements to enable a PSAV calculation or were not able to provide these data. Based on our sample, we are unable to assess the characteristics of men without PSAVs and the reasons for which their PSAVs were unavailable. Additionally, while our sample has a substantial number of patients within it, our Kaplan–Meier and log-rank analyses are based on a small number of events.

Conclusions

A PSAV >0.35 ng/ml/year at 10–15 years prior to diagnosis has previously been associated with a greater risk of later prostate cancer-specific mortality. In our radical prostatectomy series, approximately 1/3 of men with clinical stage T1c disease and a preoperative PSA <4 ng/ml had a PSAV >0.35 ng/ml/year. In accord with prior studies, these men had a significantly greater risk of biochemical progression. Our results suggest that PSAV may be useful to further stratify the risk of adverse treatment outcomes in this low-risk patient population.

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Fig. 1.
Kaplan–Meier biochemical progression-free survival curve stratified by PSA velocity

Table 1

Comparison of (a) clinical and (b) pathological features between radical prostatectomy patients with a preoperative PSAV ≤ 0.35 versus >0.35 ng/ml/year

	PSAV ≤ 0.35 ng/ml/year	PSAV >0.35 ng/ml/year	P-value
(a)			
Race			
Non-black	96.3%	95.2%	0.431
Black	3.7%	4.8%	
Year of surgery (median)	2002	2002	0.386
Mean age (years)	56.1	55.0	0.092
Median PSA prior to diagnostic biopsy (ng/ml)	3.2	3.2	0.583
Biopsy Gleason score			
≤ 6	87.5%	90.3%	0.578
≥ 7	12.5%	9.7%	
(b)			
Organ-confined	84.7%	91.9%	0.052
Positive margins	5.1%	3.2%	0.415
Seminal vesicle invasion	0.9%	0.8%	0.907
Lymph node metastases	0	0	0.540
RP Gleason score			
≤ 6	87.5%	84.5%	0.701
≥ 7	12.5%	15.5%	
Biochemical progression	0	4.0%	0.017

Table 2

Odds of adverse pathological features in men with a pre-operative PSAV >0.35 ng/ml/year, relative to a PSAV ≤0.35 ng/ml/year

	Odds ratio (95% CI)	P-value
Non-organ-confined	0.5 (0.2–1.0)	0.056
Positive margins	0.6 (0.2–5.3)	0.880
Extraprostatic extension	3.3 (0.2–1.7)	0.289
Seminal vesicle invasion	1.01 (0.1–11.9)	0.993
Gleason score ≥7	1.5 (0.7–3.1)	0.267