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RELAPSE AFTER RADICAL PROSTATECTOMY CORRELATES WITH PREOPERATIVE PSA VELOCITY AND TUMOR VOLUME: RESULTS FROM A SCREENING POPULATION

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ABSTRACT

Objectives. To evaluate, in a screening population, the impact of tumor volume and prostate volume on prostate-specific antigen (PSA) velocity (PSAV) and to find predictors of biochemical failure after radical prostatectomy. Longitudinal PSA changes in men with prostate cancer have been reported to be significantly different from those without prostate cancer.

Methods. PSAV was assessed in 102 men undergoing radical retropubic prostatectomy. The pathologic findings of specimens obtained at radical retropubic prostatectomy and pelvic lymph node dissection were analyzed separately for all patients.

Results. The median preoperative PSA in the 102 patients was 6.4 ng/mL, the median prostate volume was 32.8 cm^3, and the median tumor volume was 1.27 cm^3. The PSAV correlated significantly with tumor volume ($P < 0.05$) but not with prostate volume ($P = 0.142$). The median tumor volume in men with biochemical progression after radical retropubic prostatectomy was 2.55 cm^3 versus 0.94 cm^3 in men who were free of disease 5 years after surgery. The median PSAV in the year before diagnosis in men with relapse after radical prostatectomy was 1.98 ng/mL/yr versus 1.05 ng/mL/yr in men who had no evidence of disease.

Conclusions. The results of our study have shown that the main factor contributing to the PSAV in patients with prostate cancer is cancer load and that prostate volume is not significantly associated with the PSAV. Men with a PSAV of more than 2 ng/mL/yr in the year before cancer diagnosis are at a high risk of relapse. The PSAV may be helpful in identifying patients with small tumors and thus increase the detection rate of potentially curable prostate cancers. UROLOGY **68:** 1067–1071, 2006.

Longitudinal prostate-specific antigen (PSA) changes in men with prostate cancer have been shown to differ significantly from those in men without prostate cancer. However, differences exist between screening and nonscreening populations.[1,2]

The aim of prostate cancer screening is the detection of potentially curable cancer that is either life-threatening or reduces the man's quality of life. However, controversy still exists about prostate cancer screening in asymptomatic men, and the PSA threshold warranting further evaluation is still a matter of discussion. Several studies have shown that patients with cancer and pretreatment total PSA levels of up to 4 ng/mL have a good chance of cure, but patients with greater levels are less likely to have organ-confined tumors.[3–5] According to recent studies, prostate cancer in patients with a total PSA level less than 4 ng/mL may exhibit all the features of advanced tumors and are thus potentially life-threatening.[6,7] It has been shown that men whose PSA levels increase by more than 2.0 ng/mL in the year before diagnosis have a high risk of death from prostate cancer even if they undergo radical prostatectomy.[8]

In patients with prostate cancer, the tumor volume has been found to correlate with numerous adverse prognostic indicators.

The present study was performed to evaluate the impact of tumor volume and prostate volume on the PSA velocity (PSAV). Moreover, the value of

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TABLE I. *Demographic data and pathologic findings*

Patients (n)	102
Age (yr)	
Mean	63
Range	47–76
Preoperative PSA (ng/mL)	
Mean	6.35
Range	1.1–56.6
Prostate volume (cm^3)	
Mean	32.8
Range	12–80
Cancer volume (cm^3)	
Mean	1.27
Range	0.01–15.13
Gleason score (n)	
<7	62 (60.7)
7	27 (26.5)
>7	13 (12.7)
Tumor stage (n)	
pT2	79 (77.5)
pT3–pT4	23 (22.5)
Lymph node involvement (n)	
No	98 (96.1)
Yes	4 (3.9)
Seminal vesicle involvement (n)	
No	91 (89.2)
Yes	11 (10.8)
Margin status	
Negative	85 (83.3)
Positive	17 (16.7)

KEY: PSA = prostate-specific antigen.
Data in parentheses are percentages.

PSAV in identifying patients who are likely to have biochemical relapse after radical retropubic prostatectomy was assessed in a screening population.

MATERIAL AND METHODS

In the present retrospective study, we reviewed the charts of 102 consecutive men undergoing radical retropubic prostatectomy for clinically localized prostate cancers. Patients with a history of prostate surgery, men taking 5-alpha-reductase inhibitors, and those undergoing chemotherapy were excluded from the study.

In all subjects, the prostates were examined using the Stanford technique[9] of 3-mm step sections. The pathologic stage, postoperative Gleason score (Table I), and PSAV for a 3-year period were obtained, as were the PSA values for at least 5 postoperative years. The PSAV was defined as the average annual rate of change in the PSA level between the first and last visit. At least three PSA values were available for every patient. Biochemical failure was defined as a PSA value of more than 0.2 ng/mL.

In 1993, a mass screening project using PSA determination as the only screening test was launched in the Federal State of Tyrol, Austria. From 1988 to 1992, both PSA determination and digital rectal examination were used in the diagnostic workup of patients with suspected prostate cancer, and occasionally of asymptomatic men as well. Age-referenced PSA levels,[10] in combination with percent-free PSA of less than 22%, were used as biopsy criteria. Since October 1995, bisected PSA levels[11] have been used, together with a percent-free PSA of 18% (Table II). In addition, patients with PSA levels greater than 10 ng/mL or suspicious findings on digital rectal examination were advised to undergo biopsy.

TABLE II. *Bisected, age-specific reference ranges for PSA*

Age Range (yr)	PSA Range (ng/mL)
40–49	0–1.25
50–59	0–1.75
60–69	0–2.25
70–79	0–3.25

KEY: PSA = prostate-specific antigen.

The serum total and percent-free PSA levels were assessed using the Abbott IMx Immunoassay (Abbott Laboratories, Abbott Park, Ill).

The pathologic findings of the specimens obtained at radical retropubic prostatectomy and pelvic lymph node dissection were analyzed for all patients. The radical prostatectomy specimens were inked and perfused with formalin. They were then sectioned in 3-mm steps and processed in standard cassettes. The prostatic capsule, fibromuscular junction between the peripheral and transition zones, urethra, and the boundaries of each cancer lesion were traced with continuous ink lines for each slice on the glass slide. The outlines were then transferred to tracing paper so that the tumor area could be determined and digitized for each slice. The tumor volume was calculated as the sum of the tumor areas in each slice multiplied by the slice thickness and a shrinkage factor of 1.33.

Data are expressed as the mean ± standard deviation (SD), median, and 25th and 75th percentiles; $P < 0.05$ was considered statistically significant.

The Statistical Package for Social Sciences for Windows, version 11.5, software (SPSS, Chicago, Ill) was used for the analyses. Differences between subgroups were analyzed with the Kruskal-Wallis test. If it indicated statistical significance, post hoc tests were performed with the Mann-Whitney *U* test. Statistical significance was defined as $P < 0.05$. After Bonferroni correction for comparisons, corrected *P* values were considered to indicate statistical significance, depending on the number of compared subgroups. Multivariate analysis (forward stepwise logistic regression analysis) was performed to evaluate the influence of different parameters on tumor progression.

RESULTS

Whole mount sections obtained from 102 patients with prostate cancer with a median preoperative PSA value of 6.35 ng/mL (25th percentile, 4.07 ng/mL; 75th percentile, 10.63 ng/mL) were analyzed with regard to tumor volume (Stanford protocol), PSAV, Gleason score, pathologic stage, and PSA values at a median of 7.6 years (range 5 to 9) after surgery. Biochemical failure was defined as repeated PSA values of 0.2 ng/mL or more. The median patient age at surgery was 63.1 years (range 47 to 76).

The median tumor volume for all patients was 1.27 ± 3.1 cm^3 (25th percentile, 0.53 cm^3; 75th percentile, 2.66 cm^3), and the median prostate volume was 32.8 cm^3 (range 12 to 80). In the 32 men

TABLE III. *Correlation between PSA velocity and cancer volume*

Tumor Volume (cm^3)	PSAV (ng/mL/yr)		
	Median	25th Percentile	75th Percentile
0–0.5	0.59	0.43	1.23
0.51–1	1.11	0.65	2.55
>1	2.03	0.8	3.26
All	1.27	0.53	2.66

KEY: PSA = prostate-specific antigen; PSAV = PSA velocity.

with failure after surgery, the median tumor volume was 2.55 ± 4.17 cm^3 (25th percentile, 1.23 cm^3; 75th percentile, 5.9 cm^3) compared with 0.94 ± 1.23 cm^3 (25th percentile, 0.43 cm^3; 75th percentile, 1.99 cm^3) in the 70 patients who presented with undetectable PSA levels 5 years postoperatively ($P < 0.001$).

The PSAV in patients with tumors greater than 1 cm^3 was significantly greater than that in men with tumor loads of 0.5 to 1 cm^3 and men with tumors smaller than 0.5 cm^3 (Table III).

The median PSAV for men who postoperatively presented with biochemical failure was 1.98 ng/mL/yr compared with 1.05 ng/mL/yr for men without relapse within 5 years after surgery ($P < 0.05$).

Of the 102 men, 54 had a prostate volume of less than 30 cm^3, 42 had a prostate volume of 30 to 60 cm^3, and 6 had a prostate volume larger than 60 cm^3. The median PSAV in the first group was 0.78 ± 1.01 ng/mL/yr versus 1.08 ± 3.28 ng/mL/yr in the second group and 1.55 ± 1.27 ng/mL/yr in the third; this difference was not statistically significant ($P = 0.142$).

The Gleason score correlated strongly with the tumor volume ($P < 0.001$). In the 62 men with a Gleason score of less than 7, median tumor volume was 0.82 ± 1.03 cm^3 (25th percentile, 0.4 cm^3; 75th percentile, 1.72 cm^3). In the 27 men with a Gleason score of 7, the median tumor volume was 2.15 ± 2.39 cm^3 (25th percentile, 1.34 cm^3; 75th percentile, 4.01 cm^3), and in the 13 men with a Gleason score of 8 to 10, the median tumor volume was 8.49 ± 5.16 cm^3 (25th percentile, 2.61 cm^3; 75th percentile, 11.66 cm^3). A trend toward a greater PSAV was found in patients with a Gleason score of 7 or greater (median PSAV 1.07 ng/mL/yr) compared with men with a Gleason score of 7 (median PSAV 1.07 ng/mL/yr) and those with a Gleason score of less than 7 (median PSAV 0.83 ng/mL/yr); this difference was not statistically significant.

The median tumor volume in the 79 men with organ-confined cancer was 0.92 ± 0.97 cm^3 (25th percentile, 0.44 cm^3; 75th percentile, 1.85 cm^3), lower than in the 23 men with non-organ-confined cancer (median 4.95 ± 4.28 cm^3; 25th percentile, 2.67 cm^3; 75th percentile, 10.07 cm^3). This also applied to the PSAV (median 0.83 ng/mL/yr for Stage pT2 versus 1.23 ng/mL/yr for Stage pT3 and pT4; $P < 0.05$).

Multivariate analysis (forward stepwise logistic regression analysis) revealed that several parameters were associated ($P < 0.05$) with biochemical progression after surgery, including tumor volume ($P < 0.001$), Gleason score ($P < 0.05$), pathologic stage ($P < 0.001$), PSAV in the year before the diagnosis of prostate cancer ($P < 0.05$), surgical margin status ($P < 0.05$), and seminal vesicle involvement ($P < 0.05$). Prostate volume ($P = 0.490$), preoperative PSA level ($P = 0.093$), and age ($P = 0.165$) were not associated with biochemical progression.

COMMENT

Widespread acceptance of serum PSA testing for the early detection of prostate cancer has been hampered by its low specificity, the resulting costs, and complications resulting from unwarranted biopsies. However, about 1 in 4 men with a PSA level of 2.5 to 4 ng/mL will have prostate cancer at biopsy. More than one half of these lesions are aggressive tumors detected in the window of opportunity for cure.[12] Also, it has been estimated that 40% of all detectable cancers are encountered in men with a total PSA level of less than 4 ng/mL.[13]

PSAV has been used as a means of enhancing the specificity of PSA testing. A recent study has shown that the PSAV in the year before radical prostatectomy allows for predicting the risk of death from prostate cancer. According to that study, a PSAV of more than 2 ng/mL/yr is an independent predictor of the risk of death from prostate cancer.[8] Although demographic differences might be present between the above-mentioned population and that of the present study (purely white screening population), it seems noteworthy that in the present study cohort, a similar PSAV (ie, median 1.98 ng/mL/yr) was associated with relapse. Also, those with a median PSAV of 1.05 ng/mL/yr in the year before radical prostatectomy did not present with biochemical failure for at least 5 years postoperatively. As the number of men diagnosed with prostate cancer on the basis of PSA screening has increased, small-volume cancers have become more common. It has been suggested that the serum PSA level reflects the size of the prostate rather than the presence of cancer.[14] This might be true for total PSA but not for the PSAV. The present data have shown that it is the cancer load, rather than the prostate volume, that contributes to the PSAV. Therefore, patients with a rapid increase in PSA might not be good candidates for watchful waiting. Although the PSAV did not prove to be a predictor of biochemical relapse after prostatectomy in a

study including a nonscreening population,[15] a large study recently published has clearly demonstrated that PSAV is a useful predictor of postoperative outcome.[16] This is supported by the present data, which have confirmed the usefulness of PSA kinetics for predicting the postprostatectomy outcome. However, not all men with recurrence die of prostate cancer, and the Gleason score and pathologic stage are additional determinants of recurrence.

The results of the present study have indicated that the impact of prostate size on PSAV can be neglected. Although it is generally accepted that large prostates release more PSA into the circulation, which results in greater baseline levels, a large study of 2462 men without prostate cancer has demonstrated that they had almost no PSA increase (PSAV of 0.03 ng/mL/yr during a 10-year period) despite high total PSA levels and large prostate volumes.[2] Also, 24.5% of men with no evidence of malignant disease after 10 years of PSA screening had PSA values that were even lower than their initial levels. A continuous PSA increase over time, however, may indicate a significant tumor burden, provided that infection, instrumentation, recent ejaculation, and digital rectal examination have been excluded.

From the data provided by D'Amico *et al.*,[8] Sengupta *et al.*,[16] and the present study, we believe that the results of reports claiming that a PSAV of up to 2.5 ng/mL is predictive of a good prognosis[17] might not be valid for a screening population. The PSAV indicating a favorable outcome after surgery seems to be lower.

Patients with organ-confined cancer had significantly lower annual PSAVs, as well as lower tumor loads, than men with pT3 disease and/or high-grade prostate cancer. The results of the present study have suggested that the tumor volume and PSAV in the year before radical prostatectomy may be used as prognostic factors for relapse after prostate cancer surgery.

A potential limitation of the present study was that all participants were white men; thus, the results obtained might not be representative of other ethnic groups. Evidence has shown that black men have a greater prevalence of prostate cancer and a propensity for more advanced stages at diagnosis.[18] With regard to cancer curability, a striking difference was found between black and white men with total PSA levels greater than 5.0 ng/mL, although both whites and blacks had reasonably high cure rates when the total PSA level was 4.0 ng/mL or less.[19] Additional studies are necessary before recommendations for biannual PSA testing can be made for black men.

CONCLUSIONS

The results of our study have shown that the main factor contributing to PSAV in patients with prostate cancer is cancer load. In contrast, prostate volume correlated with PSAV only insignificantly. In the present study, a correlation between the preoperative PSAV and PSA recurrence was found in men undergoing radical prostatectomy. A low PSAV was shown to be associated with a low tumor volume and a high PSAV with a high tumor burden. Consequently, rapidly increasing preoperative PSA levels may indicate rapid tumor growth and a high risk of relapse. PSAV determination may be helpful in identifying patients with small tumors and thus increase the detection rate of potentially curable prostate cancer.

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