The Relationship of PSA, PSAD and Clinicopathological Stage in Patients with Prostate Cancer

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OBJECTIVE  To investigate the relationship between the clinicopathological stage and serum prostate specific antigen (PSA) concentration and PSA density (PSAD) in patients with prostate cancer.

METHODS  The clinicopathological stage was determined on the basis of a pathological examination and clinical data in 65 prostate cancer patients treated by radical prostatectomy. PSA and PSAD were measured before the operation. The Spearman rank correlation was applied to evaluate the relationship between the clinicopathological stage, serum PSA concentration and PSAD.

RESULTS  Patients with higher PSA and PSAD were significantly more likely to have higher clinical stages, a higher Gleason score, positive surgical margins, capsular penetration, and seminal vesicle invasion (each \( P < 0.05 \)). But there was no significant association between PSA and lymph node metastasis (\( P = 0.053 \)). The levels of serum PSA concentration and PSAD were significantly correlated with the clinical stage (\( P < 0.05 \)) in the prostate cancer patients.

CONCLUSION  The level of both PSA and PSAD were significantly correlated with the clinical stage (\( P < 0.05 \)) in the prostate cancer patients. But PSAD may be a more powerful predictor of clinical stage and prognosis than PSA.

KEYWORDS: prostate cancer, prostate specific antigen, prostate specific antigen density

INTRODUCTION

Preoperative serum PSA has long been held as one of the most important prognostic and diagnostic variables in prostate cancer patients. Controversy exists concerning the utility of serum prostate-specific antigen (PSA) as a screening tool for prostate cancer, as well as for its prognostic value in determining the tumor burden, post treatment biochemical recurrence and survival. Moreover, tumor volume and biochemical recurrence might not be predicted by a pretreatment PSA level\(^1\). With the advent of more rigorous screening efforts and ensuing stage increase, most cancers detected presently fall within relatively low PSA values. It is now a challenge to search for a more reliable prognostic and diagnosis marker to assess these tumors accurately, and assist in preoperative planning and subsequent follow-up.

The original research concerning PSA density (PSAD) by Benson et al.\(^2\) focused on its utility in improving the sensitivity and specificity of PSA in prostate cancer screening. Less investigation has been done on evaluating its role as a predictor of tumor characteristics. It has been predicted that, on average, 1 g of benign prostatic hyperplastic tissue increases the serum PSA concentra-
tion by about 0.3 ng/ml. However, 1 g of prostate cancer tissue increases the serum PSA level by about 3.5 ng/ml[3]. Thus, the hypothesis could be developed that the PSAD would be a more accurate marker of the pathological stage, extracapsular extension, and eventual PSA recurrence. PSAD was used in predicting regional lymph node involvement and it was found that PSAD had a 30% greater sensitivity than PSA alone when using a value of 0.15 ng/mL/cm³ and 10 ng/ml, respectively[4]. It has also been demonstrated that for a PSAD of less than 0.15 ng/mL/cm³, favorable pathologic features (organ confinement, Gleason score less than 7, and tumor volume less than 10%) can be predicted with a sensitivity of 74%[5]. More recently, it has been shown that PSAD is a strong predictor of biochemical failure after prostatectomy[6]. Our goal was to research the relationship among PSA and PSAD with the clinicopathologic stage in patients with prostate cancer.

MATERIAL AND METHODS

Clinical data

Data from a total of 110 patients who had been hospitalized with prostate cancer during the period from June 2000 to June 2004 were analyzed. Two men with missing PSA data were excluded. Thirty-five patients, who were treated with preoperative hormonal (anti-androgen or 5α-reductase type II inhibitor) therapy, chemotherapy or radiation therapy, were excluded. Eight patients diagnosed from a transurethral resection specimen (clinical stage T1a and T1b) also were excluded because this could affect PSA measurements. Therefore, 65 patients with prostate cancer were studied. Radical prostatectomy or bilateral pelvic lymphadenectomy was conducted in all the patients, by various surgeons using standardized techniques. The extirpated specimens were evaluated by a limited sampling technique using frozen sections at surgery and subsequently employing paraffin-embedded sections the following day. Gross characteristics of the patients are shown in Tables 1 and 2.

Clinicopathological characteristics

Pathologic data were obtained proceeding the radical prostatectomy to document prostate size, tumor number, individual and total tumor volume, positive surgical margins, pathologic stage, Gleason score, capsular penetration, seminal vesicle invasion and positive lymph nodes. The stage was classified using the 1992 AJCC staging guidelines (Tables 1,2).

PSA and PSAD measurements

All serum PSA levels were determined by radioimunoassay. Preoperative PSA was defined as the PSA measurement which prompted a diagnostic transrectal ultrasound guided prostate biopsy. Preoperative PSAD was measured by transrectal ultrasonography (TRUS PSAD).

RESULTS

Patient types

The demographics of our study group consisted of a mean age of 63 years (range, 51~78 years). The clinical parameters consisted of a mean PSA level of 13.4 ng/ml (range, 5.8~41.5 ng/ml), mean TRUS volume of 51.2 cm³ (range, 39.5~131.4 cm³) and mean TRUS PSAD of 0.19 ng/ml/cm³ (range, 0.09~0.39 cm³).

The relation of PSA and clinicopathological characteristics

Patients with higher PSA were significantly more likely to have higher clinical stages (P=0.018) and a higher Gleason score (P=0.014) in the radical prostatectomy (RP) specimens. A higher PSA was related to positive surgical margins, capsular penetration, and seminal vesicle invasion (each P<0.05, Table 1). There was no significant association between the PSA level and lymph node metastasis (P=0.053). Preoperative PSA levels were also significantly related to age at surgery with men in whom PSA was less than 10 ng/ml, 10~19.9 ng/ml and 20 ng/ml or greater (P<0.01). A Spearman correlation coefficient between PSA and the clinical stage was 0.42 (P=0.021).

The relation of PSAD and clinicopathological characteristics

Patients with a higher PSAD were significantly associated with older age (P<0.01). Furthermore, higher PSAD levels also were also significantly associated with higher clinical stages (P=0.024) and a higher Gleason score in the RP specimens (P=0.05). Moreover, higher PSADs were correlated with positive
surgical margins, capsular penetration, lymph node metastasis and seminal vesicle invasion (each \(P<0.05\), respectively, Table 2). A Spearman correlation coefficient between PSADs and the clinical stage was 0.47 (\(P=0.018\)).

**DISCUSSION**

Prostate specific antigen (PSA) has been known as a valuable tool for detecting early stage prostate cancer. However, recently, the value of PSA to detect incident disease has been questioned due to evidence from two sources. The first is increasing awareness that men with normal PSA can have prostate cancer. This was exemplified by the Prostate Cancer Prevention Trial, where at the end of study, biopsies of almost 15% of men with a PSA of less than 4 ng/ml had prostate cancer on sextant biopsy[7]. The second evidence to question the value of the PSA comes from a study, which found that the PSA was only weakly associated with prostate cancer volumes in men treated with a radical prostatectomy (RP)[8]. However, in an analysis of 65 men treated with a RP, we found that the PSA was still strongly and significantly associated with the clinical and pathological stage. A Spearman correlation coefficient between the PSA and the clinical stage was 0.42. Although there was no significant association between the PSA and lymph node metastasis, the current data support the notion that PSA remains one of the best and prognostic markers of the biological potential of newly diagnosed prostate cancer, which strongly suggests that the PSA era is alive and well.

However, tumor volume dose not always correlate with clinical outcome. For example, large transition zone tumors progress more often than equal sized peripheral zone tumors[9]. Therefore, rather than tumor
volume, a better end point is the biological potential of the cancer. When this type of analysis has been performed using biochemical progression as a substitute end point, some\textsuperscript{10,11} but not all studies\textsuperscript{12} have found that lower PSA values were associated with better outcomes in men with a PSA less than 10 ng/ml.

Although it has been controversial as to whether tumor volume is associated with the clinicopathological stage and predictive of prostate cancer, we sought to determine whether PSAD could preoperatively substitute for the tumor volume. We found that both PSA and PSAD have an association with the clinicopathology in prostate cancer. The higher PSA and PSAD were significantly more likely to have higher clinical stages, higher grades of cancer in the RP specimens, positive surgical margins, capsular penetration, and seminal vesicle invasion, but there was no significant association between the PSA and lymph node metastasis ($P>0.05$). PSAD was significantly associated with lymph node metastasis ($P<0.05$). Furthermore, Spearman $r$, for PSAD ($r=0.47$) was higher than the PSA ($r=0.42$). Therefore, as in other studies, the results indicate that PSAD was a more powerful predictor of the clinical stage, pathological stage and prognosis than PSA. For example, Freedland et al.\textsuperscript{[6]} showed that the PSAD was associated with the Gleason score and pathological stage. Furthermore, PSAD was the only clinical variable that was a significant independent predictor of margin status, extracapsular extension, and seminal vesicle involvement, whereas PSA alone was not an independent predictor of these pathologic parameters in multivariate analysis. Other studies also showed that PSAD had a benefit in determining cancer recurrence\textsuperscript{[13,14]} and diagnosis\textsuperscript{[14,15]}

But some may argue that the use of TRUS PSAD has an inherent inaccuracy owing to the reliance on volumetric measurements, which may bias its comparison with PSA. We evaluated elliptical volumetric measurements, the mechanism by which TRUS determines the volume, and multisytle volume calculations. The error was only 5% to 10% in comparative measurements. Our data indicated that the TRUS PSAD was significantly associated with older age and clinical stage, and can provide a biomarker for prostate cancer. However, the purpose of this analysis was not to emphasize the predictive ability but to evaluate the relationship of these two values and clinicopathological stage.

Our study had a number of limitations. First, the PSA subgroup analysis (PSA less than 4, 4.0 to 10.0, and greater than 10 ng/mL) did not provide a definitive value for analysis. Second, the PSA and PSAD subdivisions might have been somewhat broad for present day comparisons. Third, the cohort of patients in our data was only 65 cases. More cases are required to fully understand the relationship of PSA and PSAD to the clinicopathological stages of prostate cancer. As our knowledge of prostate cancer continues to evolve, future studies will be crucial in characterizing the role of PSA and PSAD in this disease.

REFERENCES


