

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

Shaojun Nong
Duangai Wen
Caibin Fan

Department of Urology, the First Affiliated
Hospital of Suzhou University, Suzhou
215006, China.

Correspondence to: Duangai Wen
E-mail: wdg501025@sina

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-

Received July 9, 2007; accepted September 6, 2007.

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 5 α -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 radioim-

unoassay. 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).

Statistical analysis

We explored differences in the distribution of clinicopathological characteristics among PSA groups of less than 10 ng/ml, 10 to 19.9 ng/ml and 20 ng/ml or greater and among PSAD groups of less than 0.15, 0.15~0.25 and 0.26 ng/ml/cm³ or greater using ANOVA for continuous variables and the chi-square test for categorical variables. The association among PSAD and PSA and clinicopathological characteristics was evaluated using the Spearman correlation. All statistical analyses were performed using SAS (version 6.12) software. Statistical significance was ascribed to P values less than 0.05.

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 ($P = 0.018$).

Table 1. Clinical and pathological features in patients undergoing RP with preoperative PSA.

Item	PSA (ng/ml)			χ^2	P
	Less than 10	10~19.9	20 or greater		
Patients	17	35	13		
Age (M±SD)	56.8±5.2	59.7±6.0	64.3±5.6		<0.01
Clinical stage				5.585	0.018
T1c	11	20	5		
T2a	4	10	2		
T2b	1	3	2		
T2c	1	2	2		
T3	0	0	2		
Gleason score				6.065	0.014
<6	12	17	3		
6~8	3	10	5		
>8	2	8	5		
Positive surgical margins	1	3	5	5.753	0.016
Capsular penetration	5	17	10	6.431	0.011
Seminal vesicle invasion	1	3	5	5.753	0.016
Positive lymph nodes	1	3	4	3.739	0.053

M±SD=Mean± Standard Deviation

Table 2. Clinical and pathological features in patients undergoing RP with preoperative PSAD.

Item	PSA (ng/ml)			χ^2	P
	Less than 0.15	0.15~0.25	0.26 or greater		
Patients	15	36	14		
Age (M±SD)	55.8±6.2	57.9±7.3	65.5±5.6		<0.01
Clinical stage				5.063	0.024
T1c	10	10	4		
T2a	2	10	3		
T2b	2	10	3		
T2c	1	5	3		
T3	0	1	1		
Gleason score				5.899	0.015
<6	10	16	3		
6~8	3	11	5		
>8	2	9	6		
Positive surgical margins	1	2	6	7.519	0.006
Capsular penetration	4	18	10	5.729	0.017
Seminal vesicle invasion	1	2	6	4.738	0.030
Positive lymph nodes	1	2	5	5.351	0.021

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 does 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^[10,11], but not all studies^[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_s 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.^[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^[13] and diagnose^[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 elliptic volumetric measurements, the mechanism by which TRUS determines the volume, and multislice 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

- 1 Stamey TA, Johnstone IM, McNeal JE, et al. Preoperative serum prostate specific antigen levels between 2 and 22 ng/ml correlate poorly with post-radical prostatectomy cancer morphology: prostate specific antigen cure rates appear constant between 2 and 9 ng/ml. *J Urol* 2002; 167: 103-111.
- 2 Benson MC, Whang IS, Pantuck A, et al. Prostate specific antigen density: a means of distinguishing benign prostate hypertrophy and prostate cancer. *J Urol* 1992; 147: 815-816.
- 3 Antenor JA, Han M, Roehl KA, et al. Relationship between initial prostate specific antigen level and subsequent prostate cancer detection in a longitudinal screening study. *J Urology* 2004; 172: 90-93.
- 4 Wolff JM, Boeckmann W, Effert PJ, et al. Evaluation of patients with diseases of the prostate using prostate-specific antigen density. *Br J Urol* 1995; 76: 41-46.
- 5 Catalona WJ, Southwick PC, Slawin KM, et al. Comparison of percent free PSA, PSA density, and age-specific PSA cutoffs for prostate cancer detection and staging. *Urology* 2000; 56: 255-260.
- 6 Freedland SJ, Wieder JA, Jack GS, et al. Improved risk stratification for biochemical recurrence after radical prostatectomy using a novel risk group system based on prostate specific antigen density and biopsy Gleason score. *J Urol* 2002; 168: 110-115.
- 7 Datta MW, Dhir R, Dobbin K, et al. Prostate cancer in patients with screening serum prostate specific antigen values less than 4.0 ng/ml: results from the cooperative prostate cancer tissue resource. *J Urol* 2005; 173:546-1551.
- 8 Stamey TA, Caldwell M, McNeal JE, et al. The prostate specific antigen era in the United States is over for prostate cancer: what happened in the last 20 years? *J Urol* 2004; 172: 1297-1301.
- 9 Noguchi M, Stamey TA, Neal JE, et al. An analysis of 148 consecutive transition zone cancers: clinical and histological characteristics. *J Urol* 2000; 163: 1751-1755.
- 10 Aleman M, Karakiewicz PI, Kupelian P, et al. Age and PSA predict likelihood of organ-confined disease in men presenting with PSA less than 10 ng/ml: implications for screening. *Urology* 2003; 62: 70-74.
- 11 Freeland SJ, Aronson WJ, Kane CJ, et al. Biochemical outcome after radical prostatectomy among men with normal preoperative serum prostate-specific antigen levels. *Cancer* 2004; 101: 748-753.
- 12 Gonzalez CM, Roehl KA, Antenor JV, et al. Preoperative PSA level significantly associated with interval to biochemical progression after radical retropubic prostatectomy. *Urology* 2004; 64: 723-728.
- 13 Freeland SJ, Kane CJ, Presti JC, et al. Comparison of preoperative prostate specific antigen density and prostate specific antigen for predicting recurrence after radical prostatectomy: results from the search data base. *J Urol* 2003; 169: 969-973.
- 14 Sozen S, Eskicorapci S, Kupeli B, et al. Complexed prostate specific antigen density is better than the other PSA derivatives for detection of prostate cancer in men with total PSA between 2.5 and 20 ng/ml: results of a prospective multicenter study. *European Urology* 2005; 47: 302-307.
- 15 Ohi M, Ito K, Suzuki K, et al. Diagnostic significance of PSA density adjusted by transition zone volume in males with PSA levels between 2 and 4 ng/ml. *European Urology* 2004; 45: 92-97.