Comparison of Prostate Specific Antigen and Prostate Specific Antigen Density for Predicting the Degree of Gleason Score of Prostate Cancer

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Abstract: *Introduction*: In this study we evaluate the relationship of PSA and PSAD with the degree of Gleason's score of prostate cancer in transrectal ultrasound guided biopsy specimens.

Methods: From March 2003 to October 2009, 1025 transractal ultrasound guided biopsies were performed in our hospital. PSA was measured by monoclonal antibody method and PSAD was calculated. The Gleason grade of the detected tumors in the biopsy specimens was classified as low, moderate and high grade. Data were analyzed by SPSS software.

Results: 292 patients were diagnosed to have prostate adenocarcinoma. There was an acceptable correlation between PSA (P=0.001) and PSAD of the specimens (*P* = 0.013) with Gleason grades. PSA level showed a statistically significant difference between the low and high grade groups (P=0.005) and the intermediate and high grade groups (p=0.014). A statistically significant difference of PSAD level was seen only between the low and high grade (P=0.006) groups

Conclusions: PSA and PSAD are both effective diagnostic tools for detection of prostate cancer; PSA level has a valuable role in predicting Gleason pattern higher than 7/10 and it can be the predictor of advanced pathological features but PSAD is effective in prediction of Gleason pattern lower than 5/10.

Keywords: Prostate specific antigen, Prostate cancer, Gleason's score, Tumor Grading, Gleason Grading.

INTRODUCTION

Prostate cancer is one of the major causes of cancer related death. In 2004, 230000 prostate cancer patients were diagnosed in the United States, 29900 of whom died [1]. These statistics enforce the need for early diagnosis of prostate cancer and its differentiation from benign disorders. Although controversy exists regarding the benefits of early diagnosis, this can be achieved using a combination of digital rectal examination (DRE), serum prostate-specific antigen (PSA), and transrectal ultrasound-guided prostate biopsy [2, 3]. Age, medications, race, benign prostate hyperplasia, prostatitis, elevated body mass index, and perineal trauma can change the level of PSA [4]. PSA has predictive value for estimation of tumor grade [5]. PSA measurement in the same person may have some variations in different sampling sessions [6]. So, using PSA alone especially for intermediate values of PSA between 4 and 10 ng/ml may lead to an increased number of suspicious cases for malignancy and unnecessary biopsies. For reducing the effect of these limitations, PSA density (PSAD) can be used [7, 8]. PSAD is the PSA value divided by the prostate volume. There are difficulties in measuring PSA density, including inherent errors of prostate volume measurement by either ultrasonography or MRI [9].

Controversy exists concerning the utility of serum PSA for prediction of prostate cancer, as well as its role in determining the primary tumor burden and post-treatment recurrence [10]. Mc Neal *et al*. reported that prostate cancers with Gleason grade 4 and 5 were more aggressive than lesser grade prostate cancer [11]. Later, Stamey *et al*. reported that the cancer volume and percentage of Gleason pattern 4/5 were a strong predictor of biochemical progression [12]. Albertsen PC showed that the patients with high-grade prostate cancers (Gleason scores 7-10) had more chance of disease progression and death if managed expectantly than the patients with low grade prostate cancers (Gleason scores 6 or less) [13].

Although some studies have found a correlation between PSAD and adverse pathologic features, others have found no benefit using this parameter [8]. The differences in results could be due to different sample sizes as well as using multivariate analysis in some studies [14].

Because of the racial differences mentioned in the literature, we previously performed a retrospective study to delineate a specific cut off for PSA and PSAD in our country men to determine the patients at higher risk of prostate cancer who should undergo TRUS guided biopsy [15]. However, since PSA itself is no longer a valid tool for predicting the outcome of prostate cancer [16], along with our previous study, we

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performed another statistical analysis of PSA and PSA density in 1025 consecutive males to determine the relationship between PSA and PSAD with Gleason grade of prostate cancer.

MATERIALS AND MEHODS

This study is a retrospective one which was done from March 2003 to October 2009. A total of 1025 patients referred by urologists underwent TRUS-guided prostate biopsies because of abnormal DRE, abnormal previous US, elevated PSA, or combination of mentioned problems. Serum PSA was measured by an immune-radiometric test, with accuracy about 0.01ng/ml PSA level. The most recent serum PSA level in any patient was used for this study. TRUS was done by a radiologist, by using a GE Logiq 500 Ultrasonographic equipment with 6.0 to 8.0 MHZ, end-firing probe. The prostate volume was calculated according to following formulas:

Volume = (length × width × height) × 0.523, the length was measured in the longitudinal picture, but the width and the height were measured in the axial scans. PSAD was measured by dividing the last PSA value by the prostate volume which was calculated according to previous mentioned method. All the biopsies were performed under ultrasound guidance *via* the transrectal rout on an outpatient basis by automatic 18-gauge spring-driven biopsy needle. Fourteen specimens were taken from each patient. Additional biopsies were obtained at Ultrasonographic suspected regions for malignancy. All the specimens were sent to the same laboratory for pathological examination. Each biopsy specimen was categorized histologically (normal tissue, hyperplasia, inflammation, intraepithelial neoplasia, or cancer).Classification into Gleason grade of the tumor was according to following statements: Low-grade cancer=Gleason score 2, 3, 4; intermediate-grade cancer=Gleason score 5, 6, 7; and high-grade cancer= Gleason score 8, 9, 10. The highest reported Gleason score in the specimens was used for further statistical analysis. The individuals with preoperative hormonal therapy, missing TRUS data, or missing pathologic report or Gleason grade were excluded from the study.

All the data were classified and further analyzed by SPSS® 15.0 statistical software (Chicago, IL, USA). Kruskal-Wallis or Mann Whitney test was used to compare the means. Spearman method was used to evaluate the correlation of PSA and PSAD with Gleason grade. *P value less than* 0.05 was considered as statistically significant.

RESULTS

After excluding those whose medical records were not complete, 985 patients (mean age 66.7±9.5 y/o, 32-92 years) participated in this study. Among them, 292 (30.7%) were diagnosed to have prostate adenocarcinoma and the remaining specimens were negative for malignancy.

Table **1** shows age, PSA level, and PSAD in each group.

In those patients with adenocarcinoma, 8.2%, 36%, and 55.8% had low, intermediate and high grade adenocarcinoma, respectively. Mean PSAD increased from 0.24 ng/mL/mL in patients whose biopsy specimens were negative for malignancy to 0.38 ng/mL/mL in the low grade adenocarcinoma, to 0.59 ng/mL/mL in the intermediate grade and 0.68 ng/mL/mL in the high grade adenocarcinoma. Evaluation with Spearman method showed that there was correlation of PSA (P value=0.001, correlation coefficient=0.146) and PSAD of the specimens (*P value* =0.013, correlation coefficient=0.195) with Gleason grades.

As shown in Table **2**, mean PSA increased from 11.8 ng/mL in patients whose biopsy specimens were negative for malignancy to 16.1 ng/mL in low grade adenocarcinoma, to 21.3 ng/mL in intermediate grade and 28 ng/mL in high grade adenocarcinoma. Also, mean PSAD increased from 0.24 ng/mL/mL in patients whose biopsy specimens were negative for malignancy to 0.38 ng/mL/mL in the low grade adenocarcinoma, to

Table 1: Age, Mean PSA and PSA Density Level in each Group

	Positive for malignancy (n=292)	Negative for malignancy (n=696)
Age (year)	70.2±8.3	65.3±9.6
Mean PSA level (ng/ml)	24S	11.8
Mean PSA density (ng/ml/ml)	0.63	0.24

PSA, Prostatic Specific Antigen.

Table 2: Mean Rank, Mean and Median for PSA and PSAD

	Group	Mean rank (median)	Mean	Median	P (kruskal wallis)
PSA	Low	107.94	16.10	11.10	0.003
	I.M	134.22	21.32	13.30	
	High	160.09	28.04	19.60	
PSAD	Low	100.52	0.38	0.22	0.015
	I.M	139.11	0.59	0.38	
	High	152.51	0.68	0.45	

PSA: Prostatic Specific Antigen; PSAD: Prostatic Specific Antigen Density, I.M: intermediate.

0.59 ng/mL/mL in the intermediate grade and 0.68 ng/mL/mL in the high grade adenocarcinoma.

Mean rank, mean and median for PSA and PSAD are shown in Table **2**.

Further evaluation with Spearman method showed that there was correlation between PSA and PSAD level with Gleason grade of the specimen (*P* = 0.001 and 0.013, correlation coefficient=0.195 and 0.146, respectively).

According to the results of Kruskal-Wallis test, PSA and PSAD showed acceptable differences between all grades of Gleasons score (Ppsa=0.003, Ppsad=0.015) so Comparison between each group using Mann Whitney test was done (by corrected α =0.05/3=0.017).

Mann-Whitney test showed that there was no statistically acceptable difference between PSA level of the low and intermediate grade groups (P= 0.151) and also PSAD of the intermediate and high grade adenocarcinoma (P=0.19) and low and intermediate grade (p=0/034). PSA level shows a statistically acceptable difference between low and high grade adenocarcinoma (P=0.005) and intermediate and high grade adenocarcinoma (p=0.014). A statistically acceptable difference of PSAD level was seen between low and high grade (P=0.006) adenocarcinoma.

DISCUSSION

According to previously mentioned results, a significant correlation between PSA and PSAD and the degree of Gleason score exists. Using PSA, we notes a significant difference between high grade prostate adenocarcinoma and the other two types. Regarding the PSAD, low grade adenocarcinoma can be well differentiated from higher grade ones. There is one possible explanation for this difference: As the grade of adenocarcinoma increases, the level of secreting PSA is not significantly increased with respect to tumor volume. Corcoran *et al.* explained this as decrease in level of PSA secretion with increase in tumor grade [17]. We think, it might be due to under differentiation of tumor with increase in size and increase of staging of tumor. Also Corcoran *et al.* explained that underestimation of tumor grade can be secondary to sampling errors [18]. However, this fact does not seems to have any importance in the course of the disease and in treatment strategies. We report this relationship only as a fact in the course and the nature of the disease.

In addition to its ability as a screening tool, PSA is an indicator of adverse pathological features [14]. Other studies concluded that PSA density is a strong predictor of adverse pathological findings. In many studies, multi-variant analysis had not been performed and in the others the sample size was small. We examined both PSA and PSA density and their correlation with 3 degrees of Gleasons score in a large number of patients. Although many studies have looked at the performance of PSA and PSAD in prostate cancer detection in white and black men, [6, 7, 19] few investigations have been done on Iranian population [15, 20-22].

In a recent study, PSAD was mentioned as a strong predictor of advanced prostate pathological feature [14]. Our data reflect that PSAD shows no statistically acceptable differences between the high and intermediate groups (P=0.190) and also low and intermediate groups (p=0/034).

A more recent study by Bradley *et al*. indicated that even in the late PSA era, PSA level has retained its predictive value for the percentage of Gleason pattern 4/5 [23]. Freedland *et al.* reported that high preoperative PSA concentrations were associated with higher grade cancers [8]. Our results show that PSA

has acceptable statistical differences between the intermediate and high groups (P=0.014) and also low and high ones (p=0.005). So, these data suggest that PSA remains useful in predicting high grade Gleason score 8/10 in contrast to Gleason score 5-7/10 than PSAD and it is beneficial to use PSA due to the ease of acquisition, universal use and ability to more accurate obtaining.

CONCLUSION

Although PSA and PSAD are diagnostic tools for detection of prostate cancer, with a valuable correlation of PSA and PSAD with all 3 grades of Gleason score, as shown in this study, PSA level has retained its role in predicting Gleason pattern higher than 8/10 rather than that between 2-7/10 and it can be a predictor of advanced pathological features but PSAD is effective in prediction of Gleason pattern lower than 5/10.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article. No any founding or supporting company do exist for this manuscript. This study is affiliated to Shiraz University of Medical Sciences.

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