

Diagnostic Approach to Prostate Cancer using Total Prostate Specific Antigen-Based Parameters Together

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Abstract. This prospective study investigated the value of serum total prostate specific antigen (tPSA)-based parameters in the diagnosis of prostate cancer (PCa). Serum tPSA, free to tPSA ratio (f/tPSA), PSA density (PSAD), and PSA transition zone (PSAT) were evaluated in 110 patients with histologically confirmed benign prostate hyperplasia (BPH) and 98 patients with PCa. Once the serum tPSA was elevated (greater than 4 ng/ml) or digital rectal examination (DRE) was suspicious, transrectal ultrasound-guided biopsies were recommended. The tPSA, f/tPSA, PSAD, and PSAT levels were significantly different between the BPH and PCa groups. In patients with a tPSA level of 4.1-9.9 ng/ml or an abnormal DRE finding, only PSAT was found to have discriminating power. The cut-off values were 0.15 for f/tPSA, 0.30 for PSAT, and 0.15 for PSAD. The diagnostic sensitivity of a positive result for one of these parameters in the whole group was 84%, but 75% in patients with a tPSA of 4.1-9.9 ng/ml or an abnormal DRE finding. The diagnostic specificity of positive results for 3 parameters was 92% in the whole group and 93% in patients with a tPSA of 4.1-9.9 ng/ml or an abnormal DRE finding. All parameters were influenced by the histological grades. Histological grades showed a negative correlation ($r = -0.56$) with f/t PSA and a positive correlation ($r = 0.44$) with PSAT. No diagnostic marker investigated heretofore was able to rule out or detect early PCa in patients with a PSA level of 4.1-9.9 ng/ml. Using the PSA-based parameters together can be helpful in management of these patients. If all of the PSA-based parameters are negative, biopsy might be postponed; patients who have three positive PSA-based parameters should be biopsied. In case of one or two of the parameters, the patient's age and race should be considered in clinical decision-making. (received 14 July 2001, accepted 13 October 2001)

Keywords: serum total prostate specific antigen, ratio of free/total prostate specific antigen, prostate cancer.

Introduction

Prostate specific antigen (PSA) is the initial screening test and most useful marker for early detection of prostate cancer (PCa). If the serum PSA level is elevated, a standard urologic evaluation is performed. Since PSA may also be elevated in benign prostate hyperplasia (BPH), PSA is not specific for cancer [1-4]. The discrimination between PCa and BPH is

particularly more problematic in patients with serum PSA values between 4.1-9.9 ng/ml. Several methods have been proposed to identify cancer patients with intermediate PSA levels, including f/tPSA, PSA density (PSAD, ie, tPSA divided by prostate volume), PSA transition zone (PSAT, ie, PSA divided by the volume of the transition zone), and free PSA (fPSA, ie, the portion of PSA not bound to serum proteins) [5-7]. However, whether one of these assays is superior to another as a guide to clinical management has remained unclear in practice.

PSA is a 34 kD monomeric glycoprotein, a product of a locus on chromosome 19, and a

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member of the human tissue kallikrein family. PSA is a serine protease produced by the epithelial cells that line the acini and ducts of the prostate gland. It is secreted into the lumen of the ducts to liquefy the seminal coagulum [8]. The half-life of serum PSA is 2 to 3 days. Therefore, 2 to 3 wk should pass after any event that causes PSA to rise, to ensure a stable baseline value.

Serum PSA exists in various molecular forms: approximately 70-90% of total PSA (tPSA) is bound to α 1-antichymotrypsin (ACT), and smaller amounts are bound to α 1-antitrypsin and protein C. A portion of PSA that is complexed with α 2-macroglobulin (AMG) can be measured only if the complex is cleaved and the PSA epitopes become accessible. Because of failure to detect AMG-PSA, owing to concealment of antigenic epitopes, most of the complexed PSA that is measured in commercial immunoassays is ACT-PSA.

Serum fPSA accounts for 10-30% of tPSA. A lower ratio of fPSA to tPSA (f/tPSA) in patients with PCa has been found in numerous studies and this ratio appears to be a helpful tool for distinguishing between PCa and BPH [7-10]. Recently, an assay for PSA coupled to serum proteins except α 2-macroglobulin (cPSA) was developed. However, there was not any difference between cPSA/tPSA and fPSA/tPSA [11].

PSAD may be helpful in discriminating between PCa and BPH and may be especially useful in patients with intermediate PSA levels. It seems likely that the serum PSA level is related to the volume of prostatic epithelium. Serum PSA level was strongly correlated with the volume of epithelium in the transition zone. Transrectal ultrasonography (TRUS) provides an accurate means of assessing the total prostatic volume (PV), as well as the transition zone volume (TZV). Recent studies suggest that the PSAT parameter is better than PSAD for detecting PCa [5-7,12].

The goal of this investigation was to improve the detection of PCa using 3 PSA-based parameters (f/tPSA, PSAT, and PSAD) in patients with serum tPSA levels greater than 4 ng/ml and in patients with abnormal prostate findings by digital rectal examination (DRE).

Materials and Methods

Between October 1998 and December 2000, 208 consecutive male patients were examined, including 110 patients with histologically confirmed BPH (median age 63.6 yr; range 44-72 yr) and 98 patients with PCa (median age 66.9 yr; range 52-82 yr). The study group was derived from a community-based urology practice and does not represent a screening population.

Indications for biopsy of prostate were abnormal digital rectal examination (DRE) findings and/or serum PSA levels greater than 4 ng/ml. Of 208 men (whole group, WG), 136 had tPSA levels between 4.1-9.9 ng/ml, or abnormal DRE findings (intermediate group, IG). Blood samples were taken before diagnostic procedures or at least 6 wk after DRE, prostate biopsy, or TRUS to avoid possible errors caused by release of PSA from prostate and different elimination kinetics of their forms from blood. The samples were collected in evacuated tubes and centrifuged at 2000 g for 10 min. The sera were stored at -80°C until further processing.

Serum tPSA and fPSA were measured according to the manufacturer's instructions (Diagnostics Products Corp., Los Angeles, CA). In the present study, the mean intra-assay and inter-assay coefficients of variations for fPSA and tPSA assays were 3.4-5.1% and 2.8-4.2%, respectively. The detection limits for tPSA and fPSA were 0.04 ng/ml and 0.03 ng/ml, respectively.

An attending urologist performed DRE in the dorsolithotomy position. DRE finding was classified as normal or abnormal. Transrectal biopsy was performed under TRUS guidance. Whole PV and TZV were determined using the volumetric formula for a prostate spheroid, $\pi/6 \times (\text{transverse width})^2 \times (\text{anteroposterior height})$. The largest transverse and anteroposterior dimensions of the gland were measured in the transaxial view. PV for PSAD and TZV for PSAT were calculated by dividing tPSA value.

For each patient the DRE and biopsy were performed by the same urologist. After imaging by an experienced ultrasonography technician, systematic sextant biopsies were performed using the automated biopsy gun and an 18-gauge needle

Table 1. Measurements of PSA-based parameters in patients with prostate cancer (PCa) and benign prostatic hyperplasia (BPH): results and statistical differences in the whole group (WG) and the intermediate group (IG).

Parameter	WG (n=208) (mean±SD)			IG* (n=136) (mean±SD)		
	PCa (n=98)	BPH (n=110)	p	PCa (n=56)	BPH (n=80)	p
Age (yr)	66.9 ± 7.9	63.6 ± 5.9	0.06	63.0 ± 9.4	61.8 ± 2.8	0.73
tPSA (ng/ml)	21.5 ± 4.21	9.01 ± 0.79	0.005	7.32 ± 2.22	6.23 ± 2.57	0.07
fPSA (ng/ml)	2.47 ± 2.48	1.69 ± 1.18	0.05	1.21 ± 0.66	1.25 ± 0.71	0.80
f/tPSA	0.16 ± 0.10	0.20 ± 0.08	0.01	0.18 ± 0.10	0.21 ± 0.09	0.12
PV (ml)	60.6 ± 43.1	52.7 ± 22.2	0.27	54.1 ± 41.4	50.9 ± 24.1	0.69
TZV (ml)	30.7 ± 22.1	33.0 ± 19.0	0.57	23.7 ± 10.9	31.8 ± 20.8	0.07
PSAD (ng/ml/ml)	0.36 ± 0.19	0.19 ± 0.15	0.001	0.17 ± 0.09	0.14 ± 0.08	0.11
PSAT (ng/ml/ml)	0.71 ± 0.63	0.36 ± 0.42	0.002	0.36 ± 0.22	0.26 ± 0.16	0.03

*IG: patients with PSA levels 4.1-9.9 ng/ml or positive findings on digital rectal examination.

Table 2. Specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) in the whole group (WG) and intermediate group (IG), ie, patients with serum PSA levels 4.1-9.9 ng/ml or positive DRE findings.

Parameter (cutoff value)	WG (n=208)				IG (n=136)			
	Specificity %	Sensitivity %	PPV %	NPV %	Specificity %	Sensitivity %	PPV %	NPV %
tPSA (10 ng/ml)	68.42	44.90	64.71	49.06				
tPSA (4 ng/ml)	21.05	93.88	60.53	72.73	29.63	89.29	56.82	72.73
f/tPSA (0.15)	57.14	73.68	73.68	57.14	50.00	74.07	66.67	58.82
PSAD (0.15)	75.51	42.11	62.71	57.14	57.14	55.56	57.14	55.56
PSAT (0.3)	65.31	55.26	65.31	55.26	42.86	66.67	57.14	52.94
1 test *	34.21	83.67	62.12	61.90	40.74	75.00	56.76	61.11
2 test *	76.32	53.06	74.29	55.77	66.67	50.00	60.87	56.25
3 test *	92.11	30.61	83.33	50.72	92.59	25.00	77.78	54.35

* Positive test number of each f/tPSA, PSAT, and PSAD.

Table 3. The correlation results between all PSA-based parameters in the entire population, in patients with benign prostatic hyperplasia (BPH) and prostate cancer (PCa).

Parameter	Group	f/tPSA	PV	TZV	PSAD	PSAT	Age
tPSA	Total	-0,318**	0,468**	0,476**	0,706**	0,595**	0,336**
	BPH	-0,263	0,142	0,064	0,833**	0,735**	0,100
	PCa	-0,313*	0,516**	0,712**	0,682**	0,586**	0,321*
f/t PSA	Total		-0,028	-0,035	-0,323**	-0,262**	-0,070
	BPH		-0,043	-0,044	-0,218	-0,145	0,071
	PCa		0,024	-0,060	-0,297*	-0,237	-0,010
PV	Total			0,957**	-0,037	-0,119	0,308**
	BPH			0,967**	-0,318**	-0,318**	0,047
	PCa			0,969**	-0,017	-0,105	0,397**
TZV	Total				-0,049	-0,183	0,114
	BPH				-0,356**	-0,382**	-0,014
	PCa				0,116	-0,035	0,261
PSAD	Total					0,952**	0,271*
	BPH					0,955**	0,183
	PCa					0,961**	0,174
PSAT	Total						0,301**
	BPH						0,273*
	PCa						0,182

* p<0.05, ** p<0.01.

Table 4. Parameters in prostate cancer patients (medians and ranges), stratified by Gleason scores.

	Low grade (n=34)	Medium grade (n=48)	High grade (n=16)	p†	r§
Age (year)	67 (53-80)	68 (52-82)	70 (63-80)	0.134	0.122
tPSA (ng/ml)	8.2 (6.2-73.2)	7.9 (1.6-76.0)	26.9 (4.2-145)	<0.001	0.115
f/t PSA (ng/ml)	0.19 (0.1-0.31)	0.13 (0.05-0.48)	0.09 (0.06-0.12)	<0.001	-0.556**
PV (ml)	56.2 (19.5-205)	45.4 (20.5-83.1)	48.25 (24.8-182)	0.001	-0.275*
TZV (ml)	33.6 (8.4-121.7)	20.05 (9.1-53.8)	24.52 (10.05-116)	0.009	-0.350*
PSAD (ng/ml/ml)	0.17 (0.04-1.14)	0.19 (0.03-1.15)	0.48 (0.17-0.81)	<0.001	0.366*
PSAT (ng/ml/ml)	0.26 (0.06-2.23)	0.39 (0.05-2.31)	1.06 (0.42-1.60)	<0.001	0.436**

† Group differences (p) computed by Kruskal-Wallis test.

§ Correlation coefficient (r) of Gleason scores versus other parameters.

* p < 0.01.

** p < 0.001.

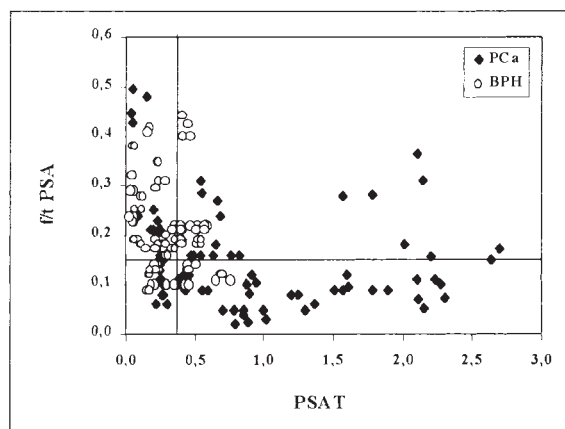
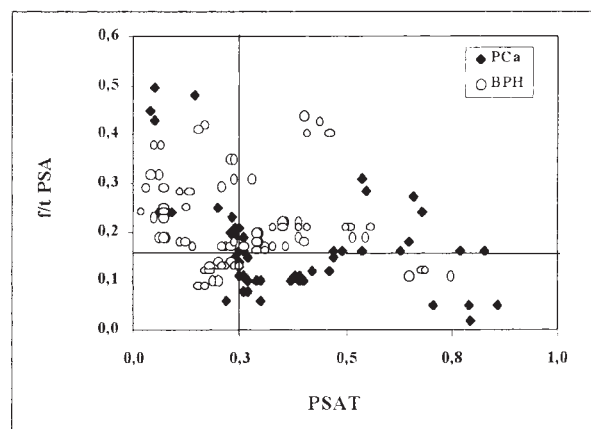
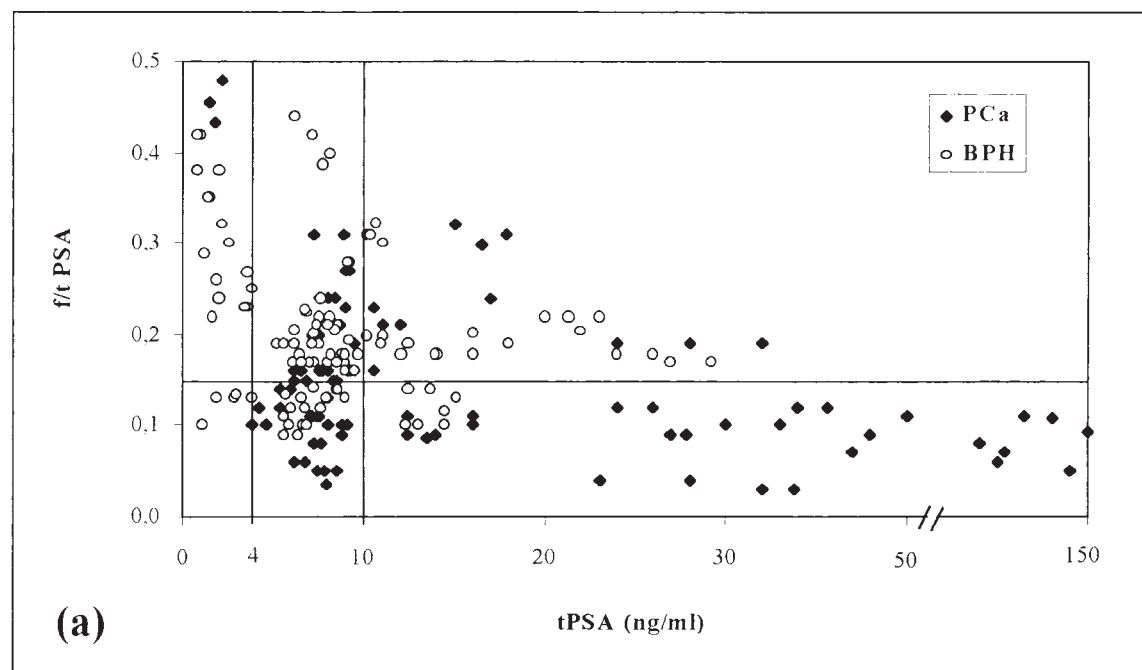


Fig. 1. Comparison of f/t PSA and tPSA levels in all patients with PCa or BPH (panel a); comparison of f/t PSA and PSAT levels in patients with PCa or BPH and tPSA levels from 4.1-9.9 ng/ml, or positive findings on digital rectal examination (panel b); comparison of f/t PSA and PSAT levels in all patients with PCa or BPH (panel c).

with transverse ultrasound guidance. Sextant biopsies comprised quadrant peripheral zone and 2 transition zone biopsies. In selected cases, additional biopsies were directed toward suspicious areas noted on the ultrasound image. All specimens were adequate for pathological diagnosis and Gleason scores were recorded [13]. Histological grades were

classified as low for Gleason scores of 1-4, medium for scores of 5-7, or high for scores of 8-10.

The Ethical Committee of the Gülhane School of Medicine, Ankara, Turkey, approved the protocol for the present study.

Data were analyzed using the statistical software package SPSS 10.0 for Windows. Data were

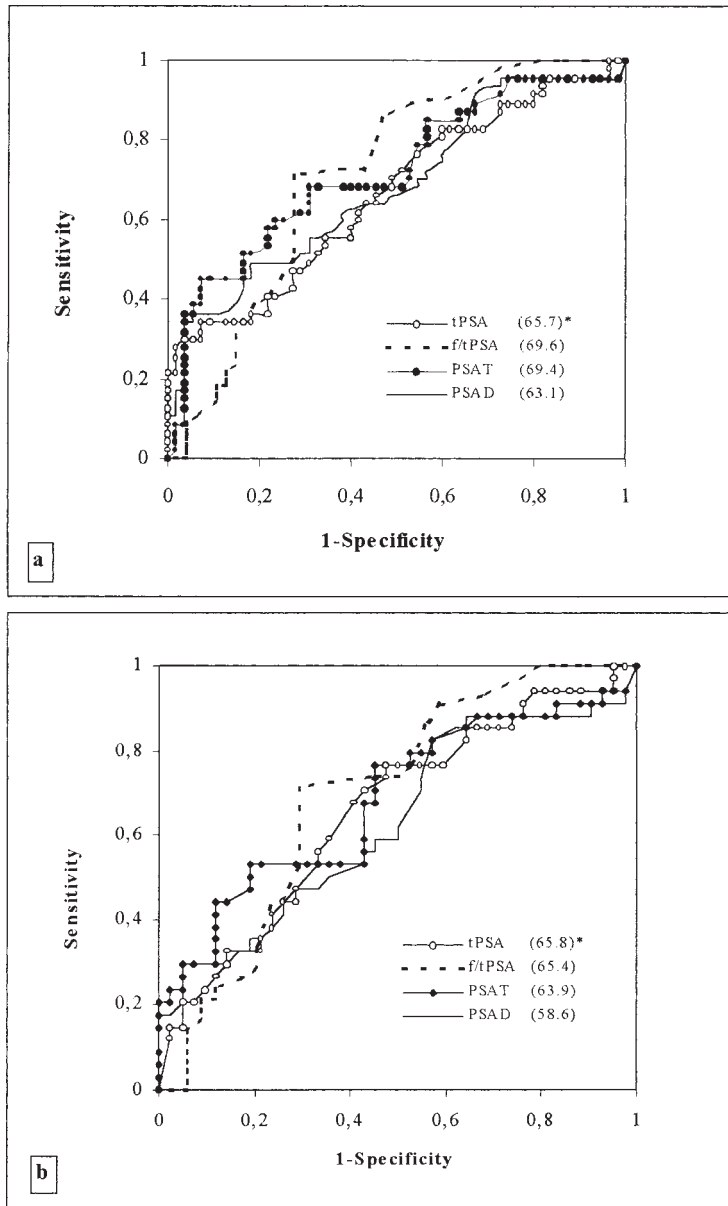


Fig. 2. Receiver-operator characteristic curves and areas under the curves (%) for the results of PSA-based parameters (tPSA, f/tPSA, PSAT, PSAD) for all patients (panel a) and for patients with tPSA levels from 4.1 to 9.9 ng/ml or positive findings on digital rectal examination (panel b).

expressed as mean and standard deviation, or median and range (minimum to maximum). All results were analysed by the one-sample Kolmogorow Simirnov test to determine the normal distribution. Inter-group comparisons were made by the independent-sample t test. The Kruskal-Wallis test was used to analyze the Gleason scores of patients with PCa. Correlations of histopathological results with other parameters were calculated with Spearman's correlation test. Receiver-operator characteristic

(ROC) curves to illustrate the reciprocal relationship between sensitivity and specificity were prepared by plotting true positives (sensitivity) versus false positives (1-specificity). The area under the curve (AUC) was calculated and compared for tPSA, f/t PSA, PSAD, and PSAT. The positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity for all parameters were calculated. P values < 0.05 was considered statistically significant.

Results

Table 1 shows the age, tPSA, fPSA, f/tPSA, PV, TZV, PSAD, and PSAT values for patients with BPH and PCa. There were significant differences between BPH and PCa patients in tPSA, f/tPSA, TZV, PV, PSAT, and PSAD values in the whole group (WG). The only significant difference in PSAT levels between patients with BPH and PCa were observed in the intermediate group (IG).

Individual tPSA and f/tPSA values in PCa and BPH are shown in Fig. 1a, f/tPSA and PSAT values in WG are compared in Fig. 1b, and those in IG are compared in Fig. 1c. All parameters, including cut-off levels, sensitivity, specificity, PPV, and NPV, both for WG and for IG, are shown in Table 2.

The ROC curve and AUC results of tPSA, f/tPSA, PSAD, and PSAT levels for WG and for IG are shown in Fig. 2a and Fig. 2b, respectively. Results were not significant between both groups, so that none was superior to results in the other.

The correlations of tPSA, PSAT and f/tPSA with prostate volume are shown in Table 3 and Fig. 1. Among patients with PCa, total prostate volume was significantly and positively correlated with the tPSA and f/tPSA, while it was significantly and negatively correlated with the PSAT. Also, there were significant correlations among tPSA, PV, and TZV in PCa, but not BPH.

Gleason scores were low-grade in 34 patients, medium-grade in 48 patients, and high-grade in 16 patients. In the various histopathological groups, all of the parameters were significantly different. Negative correlations were found with f/tPSA, PV, and TZV, and positive correlations were found with PSAT and PSAD (Table 4).

Discussion

Increasing evidence indicates that PSA-based diagnostic parameters and f/tPSA, in addition to tPSA, can improve the sensitivity and specificity of PCa detection, though some authors reported contrary results [2,9,14-17]. PSAD and PSAT provide a more reliable indication for biopsy of the prostate than PSA alone [12,18-22]. However, some authors concluded that PSAD did not enhance the prediction of carcinoma [17,23].

Prostate volume was reported to be significantly and positively correlated with f/tPSA and negatively correlated with PSAT. A low f/tPSA was most useful for detecting PCa, especially in patients with prostate volume <40 ml; a high PSAT was also useful when the prostate volume was >40 ml [22]. Djavan et al [24] found that at a cut-off of 30%, f/tPSA results detected 90% of PCa and eliminated 50% of unnecessary biopsies.

In the present study, tPSA, f/tPSA, PSAD, and PSAT levels were significantly different between BPH and PCa groups in the WG. But in the IG subset, only PSAT showed a discrimination power. This is in accordance with the results of ROC analysis, which are not significantly different in the WG and IG. In our study, the cut-off value was 0.15 for f/tPSA, 0.30 for PSAT, and 0.15 for PSAD. Positive test sensitivity just for one parameter in the WG was 84%, but 75% in IG. Specificity with the positivity of 3 parameters was 92% for WG and 93% for IG.

Our results of ROC analysis indicate that the AUC for all samples was greater when f/tPSA and PSAT parameters were used together, compared to the tPSA parameter alone. It was previously reported that the use of the f/tPSA enhances sensitivity and specificity for PCa. Brawer et al [17] reported that the AUC was 75% for f/tPSA, versus 65% for tPSA. The different results of various studies may be associated with differences in the selection of the patient populations, and problems with the accurate determination of free and total PSA [17,25].

Serum f/tPSA was reported to show significant associations with prostate volume and Gleason score in patients with PCa. Serum tPSA levels greater than 4 ng/ml correlated with tumor volume and grade, but no significant correlation was found between f/tPSA and tumor volume [18,26]. Weir et al [12] showed that the gland volume and tumor volume were independently correlated with tPSA. Moreover, tissue PSA intensity was inversely correlated with the histological grade of the tumor. Pannek et al [27] reported that f/tPSA was a significant predictor of pathological stage. Serum f/tPSA \geq 0.15 was a good predictor of organ-confined prostate cancer when used with favorable needle biopsy findings [27].

Catalona et al [28] found that higher f/tPSA values (>0.15), or lower PSAD values (<0.15),

tended to indicate less aggressive disease. In our study, we found significant correlation among tPSA, PV, and TZV in PCa, but not in BPH. In addition, we found significant changes in all of the parameters in relation to histological score; f/tPSA and PSAT values were highly correlated with the Gleason score.

Problematic results in fPSA measurements have been reported due to analytical factors. Nixon et al [20] showed that the results of different assays are not interchangeable. Clinicians should be aware that different fPSA cut-off values need to be used, depending on the particular free and tPSA assays, and that all assays do not have the same diagnostic performance [28,29]. Different laboratories have different cut-off values, because of analytical problems [24,29-31]. Thus, fPSA measurements should be monitored by external quality assurance programs.

Paus et al [16] studied the in vitro stability of fPSA and tPSA in serum of patients with PCa or BPH. They concluded that serum samples should be stored frozen if not analyzed immediately or acidified to pH 5.5 [16].

The serum tPSA has been shown to correlate with both prostate volume and age, so the possibility cannot be dismissed that volume- and age-related variability may also apply to additional PSA-based parameters [15,27].

In conclusion, in patients with serum tPSA levels of 4.1-9.9 ng/mL, no diagnostic marker alone is reliable for the differential diagnosis of benign and malignant prostate disease; for early detection of PCa only PSAT has discriminating power. Based on the present results, in patients with serum tPSA between 4.1-9.9 ng/ml, if none of the PSA-based parameters is positive, biopsy can be postponed and the patients should be followed; on the other hand, patients with three positive parameters should be biopsied. If only one or two of the parameters are positive, the patient's age, race, and clinical findings should be considered in decision-making. Hence, the combined use of all markers can increase sensitivity and specificity.

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