

Original Article

PSA density as a better predictor of prostate cancer than percent-free PSA in a repeat biopsy

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Abstract

Background: The aim of our study was to identify the optimal predictor of prostate cancer among several prostate-specific antigen (PSA) derivatives in repeat prostate biopsy.

Methods: We retrospectively assessed the repeat prostate biopsy specimens, obtained between 1999 and 2008, of 212 patients with a total PSA (tPSA) of 4–10 ng/ml and normal digital rectal examination. Using a receiver operating characteristic (ROC) analysis, we assessed the predictive power of tPSA, percent free PSA (f/t PSA), PSA density (PSAD), and PSA velocity (PSAV) for the detection of prostate cancer.

Results: Repeat prostate biopsy specimens were positive for prostate cancer in the case of 26 patients and negative in the case of 186 patients. The areas under the receiver operating characteristic (ROC) curves for tPSA, f/tPSA, PSAD, and PSAV were 72.7%, 57.9%, 74.4%, and 64.8%, respectively. The ROC curve analysis revealed that PSAD was a better predictor of prostate cancer than f/t PSA. Moreover, when PSAD at an optimal cutoff of 0.18 ng/ml/cc was considered as the predictor, the detection of prostate cancer was found to have a high sensitivity and specificity (77% and 69%, respectively).

Conclusion: In a repeat prostate biopsy, PSAD is superior to f/t PSA as a predictor of prostate cancer. And, by assessing this predictor, an unnecessary repeat biopsy of patients with tPSA of 4–10 ng/ml can be avoided.

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Keywords: biopsy; density; men's health; prostate cancer; prostate-specific antigen; PSA

1. Introduction

Prostate cancer is a very common type of cancer in the United States and most western countries, but it is not as prevalent in Asian countries.^{1,2} During the past decade, however, the incidence of prostate cancer in Taiwan has been rising year after year. According to data from the Taiwan Cancer Registry, the incidence of prostate cancer in 2006 was ranked fifth among leading invasive cancers. Prostate cancer is an important health concern in Taiwan. Before the introduction

of prostate-specific antigen (PSA) in clinical practice, a digital rectal examination (DRE) was the most common method for the detection of prostate cancer. Serum total PSA (tPSA) is a useful serum marker for the early detection of prostate cancer.³ Several studies have indicated that the serum tPSA cutoff level of 4 ng/ml should be used for the screening of prostate cancer.⁴ Our current study was no exception. In a patient with abnormal serum tPSA levels or palpable nodules during a DRE, prostate biopsy is performed to confirm the diagnosis of prostate cancer. If the initial biopsy result reveals no malignancy, a repeat biopsy for those patients with persistently abnormal tPSA or DRE may be performed later.

A serum tPSA level between 4 and 10 ng/ml is considered as the diagnostic gray zone,⁵ because these levels may be indicative of either prostate cancer or benign prostatic

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hyperplasia (BPH). Negative results in the initial biopsy of patients with gray-zone serum tPSA and normal findings of DRE implied that considering only serum tPSA as the predictive factor in repeat prostate biopsy can result in a high rate of false negative prediction of prostate cancer. Therefore, increasing the sensitivity and the specificity of the serum tPSA testing is important to avoid unnecessary repeat prostate biopsy, which is invasive and costly. We retrospectively reviewed our database of prostate biopsies and sought to evaluate the predictive power of tPSA, percent free PSA (f/t PSA), PSA density (PSAD), and PSA velocity (PSAV).

2. Methods

From April 1999 to February 2008, 2987 patients (3625 prostate biopsies) underwent transrectal ultrasound (TRUS)-guided prostate biopsy in our hospital. Of these patients, 417 with elevated serum tPSA or abnormal DRE findings underwent repeat prostate biopsy. We excluded patients with abnormal DRE findings and serum tPSA levels > 10 ng/ml. Finally, 212 men with serum tPSA levels of 4–10 ng/ml and normal DRE findings were included for the statistical analysis.

TRUS-guided prostate biopsy was performed using an 18-G needle. The number of core biopsy specimens in the first and second TRUS-guided prostate biopsy was the same. The number was between 8 and 14. The total prostate volume was measured using TRUS. PSAD was calculated as tPSA divided by total prostate volume.⁶

Serum tPSA and free PSA (fPSA) were measured using TPSA-RIACT and FPSA-RIACT kits (CIS-Bio International, France), respectively. The f/tPSA was calculated as fPSA divided by tPSA.⁷ For the determination of PSAV, the latest three values of tPSA were obtained, and PSAV was calculated using linear regression.⁸

3. Statistical analysis

Mann-Whitney *U* test was used to compare continuous data groups, and a *p* value less than 0.05 were considered statistically significant. The sensitivity and specificity were calculated for the overall study population. The ROC curves were prepared for each PSA derivative. The areas under the ROC curves were used to assess the accuracy of each test with PSA derivatives, and they were compared using the Mann-Whitney *U* test as modified by Bonferroni-Holm. The *p* values less than 0.05 were considered statistically significant.

4. Results

At our institution, the positive rates of prostate cancer detection in the first and second TRUS-guided prostate biopsy were 26.6% (795 of 2987) and 13.3% (63 of 474), respectively. Of the 212 patients with tPSA of 4–10 ng/ml and normal DRE who underwent repeat prostate biopsy, 26 patients (12.3%) were diagnosed with prostate cancer. Table 1 shows the patient age, total prostate volume, tPSA, fPSA, f/t PSA, PSAV, and PSAD. The values of tPSA, PSAD, and PSAV

Table 1

Age, prostate volume, and PSA results of 212 patients diagnosed with prostate cancer or benign prostatic hyperplasia after repeat prostate biopsy.

	BPH	prostate Cancer	<i>p</i> value
Number of patients	186	26	
Age	66.59 ± 9.92	73.42 ± 3.81	< 0.001
Total prostate volume (ml)	42.81 ± 18.15	32.75 ± 10.76	0.008
tPSA (ng/ml)	6.34 ± 1.66	7.37 ± 1.24	0.001
fPSA (ng/ml)	1.31 ± 0.65	1.64 ± 1.60	0.663
f/tPSA (%)	21.41 ± 8.83	21.72 ± 21.59	0.148
PSAD (ng/ml/cc)	0.182 ± 0.203	0.252 ± 0.099	< 0.001
PSAV (ng/ml/yr)	0.263 ± 1.713	0.832 ± 0.924	0.008

BPH = benign prostatic hyperplasia; fPSA = free PSA; f/t PSA = percent free PSA; PSA = prostate-specific antigen PSAD = PSA density; PSAV = PSA velocity; tPSA = total PSA.

of patients diagnosed with prostate cancer were significantly higher than those patients diagnosed with BPH (Mann-Whitney *U* test, *p* = 0.001, 0.000005, and 0.008, respectively). However, the values of fPSA and f/t PSA in both groups were not significantly different (*p* = 0.663 and 0.148, respectively).

The predictive ability of each PSA derivative in repeat prostate biopsy was analyzed using the ROC curves (Fig. 1). The areas under the ROC curves for each PSA derivative and their 95% confidence intervals are shown in Table 2. The areas under the curves for tPSA, f/tPSA, PSAD, and PSAV were 72.7%, 57.9%, 74.4%, and 64.8%, respectively. Comparison of f/t PSA, PSAV, or PSAD with tPSA revealed no statistically significant difference (Mann-Whitney *U* test as modified by Bonferroni-Holm, *p* = 0.106, 0.323, and 0.825, respectively). PSAD was observed to be a significantly better predictor of prostate cancer than f/t PSA (Mann-Whitney *U* test as modified by Bonferroni-Holm, *p* = 0.023).

To increase the specificity of repeat biopsy and to avoid unnecessary repeat biopsy, cutoffs that ensured good specificity and sufficiently high sensitivity were selected. Table 3 shows that optimal cutoffs of 6.44 ng/ml, 25%, 0.75 ng/ml/year and 0.18 ng/ml/cc for tPSA, f/t PSA, PSAV, and PSAD, respectively, were the most accurate in predicting positive repeat biopsy. The sensitivity and specificity of these optimal cutoffs are also shown in Table 3.

5. Discussion

Prostate biopsy is the gold standard for diagnosing prostate cancer in men with elevated serum tPSA levels or abnormal DRE findings. Earlier, a sextant prostate needle biopsy was widely used for establishing the definitive diagnosis in patients suspected of having prostate cancer.⁹ However, a 1998 study revealed that the false negative rate of prostate cancer detection by this method was 30%.⁹ Thereafter, many studies recommended that the number of core biopsy specimens should be increased during repeat prostate biopsy.^{10,11} However, the optimal number of core biopsy specimens still remains controversial. In our study, we increased the number of core biopsy specimens from eight to 14 cores. Repeat prostate biopsy plays an important role in patients whose initial biopsy

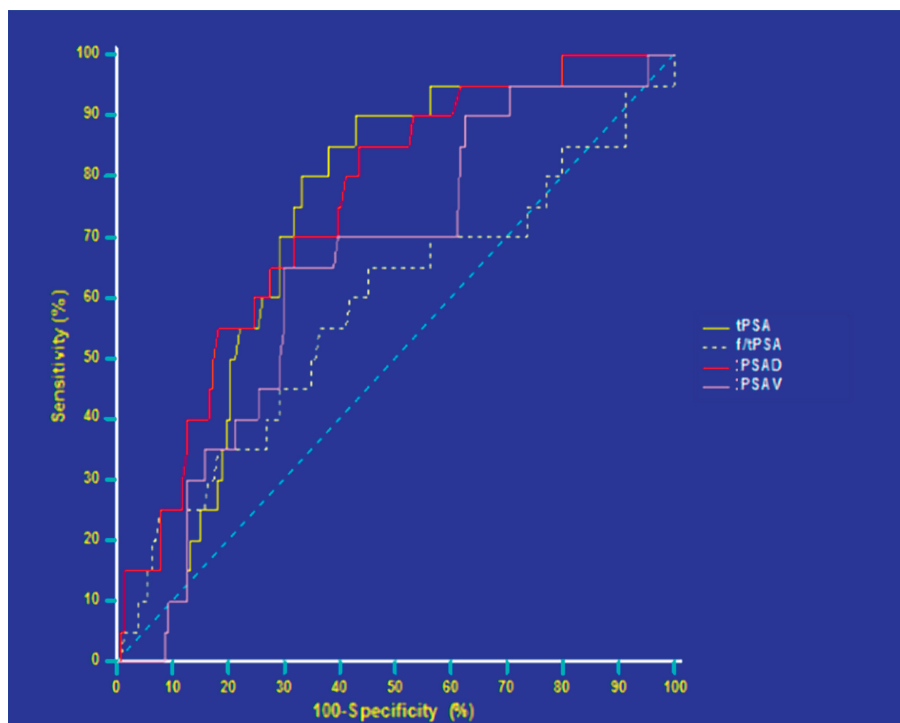


Fig. 1. ROC curves for prostate cancer detection in repeat prostate biopsy. tPSA (yellow), f/tPSA (yellow dash), PSAD (red), PSAV (purple).

specimens were negative for prostate cancer. Our goal was to identify markers to eliminate the need for repeat prostate biopsy, which is invasive and costly. We retrospectively evaluated the ability of tPSA, f/t PSA, PSAV, and PSAD to predict the results of repeat prostate biopsy.

Yang and colleagues conducted a prospective blinded study of patients with serum tPSA between 4 and 25 ng/ml by using f/tPSA for prostate cancer detection.¹² Optimal cutoff set at 30% could eliminate 30%–36% of unnecessary biopsies and ensure a reasonable sensitivity. However, this cutoff may not be suitable for patients who have already undergone prostate biopsy. When we set a cutoff of f/t PSA at 30% for our patients, the sensitivity and specificity of the test were observed to be 25% and 84%, respectively. This degree of sensitivity was not acceptable. Therefore, we observed that if the optimal cutoff of f/tPSA was set at 25%, then the sensitivity and specificity of this variable in the detection of prostate cancer were 65% and 53%, respectively. On the basis of

Table 2

Areas under the ROC curves of the PSA derivatives in repeat prostate biopsy.

	Area under the ROC Mean \pm SD (95% CI)	tPSA <i>p</i> value*	f/tPSA <i>p</i> value*
tPSA (ng/ml)	0.727 \pm 0.0674 (0.647–0.797)	—	0.106
f/tPSA (%)	0.579 \pm 0.066 (0.494–0.660)	0.106	—
PSAD (ng/ml/cc)	0.744 \pm 0.0663 (0.666–0.813)	0.825	0.023
PSAV (ng/ml/yr)	0.648 \pm 0.0706 (0.565–0.725)	0.323	0.461

f/t PSA = percent free PSA; PSA = prostate-specific antigen PSAD = PSA density; PSAV = PSA velocity; tPSA = total PSA; ROC = receiver operating characteristic.

* Comparison with tPSA or f/tPSA.

the above mentioned results, we considered that f/tPSA is not ideal for use as a predictor of prostate cancer.

Djavan and colleagues¹³ reported a prospective study of 1051 men with serum tPSA levels of 4–10 ng/ml. The positive rates of prostate cancer detection during the initial prostate biopsy and repeat biopsy were 22% (231 of 1051) and 10% (83 of 820), respectively. In these patients, f/t PSA and transitional-zone PSAD were the most accurate predictors of prostate cancer. They suggested that a repeat prostate biopsy of patients with f/t PSA levels less than 30% or transitional-zone PSAD of 0.26 ng/ml/cc or greater should be performed. In our study, the transitional-zone prostate volume was not measured for all of the included patients because the measurement bias of the transitional-zone volume in small-sized prostate (< 30 cc) was significant.¹⁴ In our patients, the transitional-zone PSAD was not found to be superior to PSAD when compared with both of the ROC curves. PSAD was significantly better than f/t PSA as a predictor of a positive result of a repeat prostate biopsy. Our results were different from those of Djavan and others but similar to those of Shen

Table 3

PSA results at optimal cutoffs for 212 patients after repeat prostate repeat biopsy.

	Optimal cutoff	Sensitivity (%)	Specificity (%)
tPSA (ng/ml)	6.44	81	61
f/tPSA (%)	25	65	53
PSAD (ng/ml/cc)	0.18	77	69
PSAV (ng/ml/yr)	0.75	65	70

f/t PSA = percent free PSA; PSA = prostate-specific antigen PSAD = PSA density; PSAV = PSA velocity; tPSA = total PSA.

and colleagues,¹⁵ who reported that PSAD had a greater clinical diagnostic value than f/tPSA for the diagnosis of prostate cancer in Chinese patients with tPSA level in the diagnostic gray zone. The differences between the patients of Asian and Caucasian descent may be attributed to the biologic aspects of ethnicity.

Vickers and colleagues¹⁶ reported a systematic review of pretreatment PSAV and doubling time as predictors for prostate cancer, showing that there is little evidence that the calculation of PSAV and doubling time in untreated patients provides predictive information beyond that provided by only tPSA level. In our study, the area under the ROC curve of PSAV was compared with those of tPSA, PSAD, and f/tPSA (Mann-Whitney *U* test, $p = 0.323$, 0.282 and 0.461 , respectively). We observed that PSAV was not a better predictor than other PSA derivatives. Our results were consistent with those of Vickers and others.¹⁶

An ideal test should have a high sensitivity and a high specificity, but such tests may not exist in the real world. Tests used to screen patients for cancer should be highly sensitive. This is because although cancer is associated with high mortality, it is curable if it is diagnosed in its early stages. In tests performed for lethal communicable diseases, such as human immunodeficiency virus, false positive results can lead to serious consequences. Therefore, in such cases, the tests should be highly specific. We used a serum tPSA level of 4 ng/ml as the cutoff for prostate cancer screening because this value has been shown to have a high sensitivity. However, using only a serum tPSA test would not be sufficient for further follow-up and the evaluation of the possibility of prostate cancer if the initial prostate biopsy showed BPH. Therefore, the specificity of this test is important to avoid an unnecessary repeat prostate biopsy. We need optimal cutoffs for these tests with the same weighting of sensitivity and specificity. Two methods are commonly used to identify the optimal cutoffs of tests.^{17,18} In our protocol, we considered the values closest to the (0,1) point on the ROC curve as the optimal cutoffs that corresponded to the specificity and sensitivity values. These values were considered as the best differentiators between people with disease and those without disease.^{17,18}

6. Limitations

First, we included patients with serum tPSA levels of 4–10 ng/ml and normal DRE findings, so the final conclusions could not be generalized to all repeat biopsy patients. Secondly, prostate volumes of all study patients were measured by multiple operators. Therefore, inter-operator bias might interfere with our results. Additionally, this was a retrospective study, so various biopsy intervals and different numbers of biopsy core were noted. However, there were no definite guidelines for these two issues. Thirdly, our small sample size and long study period could cause some biases. Further prospective studies with large sample sizes and meticulous designs will overcome these shortcomings.

In conclusion, we propose that PSAD is superior to f/t PSA as a predictor of prostate cancer in repeat prostate biopsy for

men with serum tPSA levels of 4–10 ng/ml. Using the optimal cutoff (0.18 ng/ml/cc) for PSAD, we can avoid unnecessary prostate biopsies and obtain an acceptable positive rate of prostate cancer detection from the core biopsy specimens.

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