

PROSTATE CANCER DETECTION BY PROSTATE-SPECIFIC ANTIGEN-RELATED PARAMETERS

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Total serum prostate-specific antigen (PSA) levels, free-to-total PSA ratio (F/T ratio) and PSA density (PSAD) were compared to clarify the clinical significance of these parameters in the diagnosis of prostate cancer (CaP) with intermediate PSA concentrations (4–10 ng/ml). PSAD and F/T ratio were obtained during the period from May 1999 to April 2001 from 43 patients with serum PSA concentrations of 4–10 ng/ml who underwent ultrasound-guided systematic sextant biopsies. PSAD was compared with total serum PSA and F/T ratio via receiver operating characteristic (ROC) curves for diagnosis of CaP. Diagnosis of CaP and non-CaP was made in 12 (27.9%) and 31 (72.1%) of the 43 patients, respectively. Mean serum PSA, PSA density and F/T ratio were 7.308 ± 0.636 ng/ml, 0.271 ± 0.039 ng/ml/cm³ and $16.225 \pm 4.911\%$ in patients with CaP and 6.300 ± 0.289 ng/ml, 0.178 ± 0.020 ng/ml/cm³ and $15.213 \pm 0.980\%$ in those with non-CaP, respectively. The ROC curve analysis demonstrated that PSAD predicted the biopsy outcome significantly better than F/T ratio and total PSA in all 43 patients ($p < 0.05$). In distinguishing CaP patients, the cutoff value of 0.16 ng/ml/cm³ for PSAD yielded a specificity level of 71.0% at a sensitivity level of 83.3%. Our study revealed that PSAD is a significant predictor in distinguishing CaP from non-CaP in Japanese men.

(Acta Urol. Jpn. 49: 405–410, 2003)

Key words: Prostate cancer, PSA, F/T ratio, PSA density

INTRODUCTION

Accumulating evidence has demonstrated that serum prostate-specific antigen (PSA) is the most useful parameter for finding prostate cancer (CaP) and monitoring patients on CaP treatment¹⁾ However, the clinical usefulness of PSA in detecting CaP is decreased by the lack of specificity, particularly in patients with intermediate PSA concentrations between 4 and 10 ng/ml. Thus, additional parameters such as PSA velocity, PSA density (PSAD)²⁾ and percentage of free to total PSA (F/T ratio) have been proposed to increase the sensitivity and specificity of serum PSA concentrations. PSA consists of free PSA and its complexes with α -antichymotrypsin in serum³⁾. As the α -antichymotrypsin-bound form is preferentially elevated in CaP, F/T ratio has been recognized to be beneficial to the discrimination of CaP from non-CaP^{4,5)}, though a contrary result has also been reported⁶⁾. Few studies have simultaneously compared these parameters including PSAD and F/T ratio in patients with serum PSA levels of 4–10 ng/ml⁷⁾. The aim of our study is to clarify the role of PSA-based prostate parameters including PSAD and F/T ratio in Japanese patients. We compared the accuracy of total PSA (tPSA), PSAD and F/T ratio via receiver operating characteristic (ROC) curves in biopsy populations.

PATIENT'S MATERIALS AND METHODS

A total of 43 patients with serum PSA levels ranging from 4 to 10 ng/ml (Tandem-R; Hybritech. Inc., San Diego, CA, USA, cutoff < 4.0 ng/ml) were consecutively enrolled from May 1999 to April 2001 in this study. All the patients first visited the outpatient department of the Osaka Medical College Hospital for difficulty in voiding or screening CaP. Fifteen patients with overt urinary tract infection, acute urinary retention and known CaP were excluded. On digital rectal examination (DRE) nodules on the prostate were considered suspicious for prostate carcinoma (positive DRE finding), and no-nodule or no-induration on the prostate was interpreted as negative for prostate carcinoma (negative DRE finding). These examinations were basically performed in men younger than 80 years who would probably survive at least for 10 years. The mean age of the study subjects was 67.4 years (range 53–78). All the patients underwent blood drawing, and transrectal ultrasonography (TRUS) to calculate whole prostate volume and sextant biopsy of the prostate, as well as additional biopsy of the suspicious lesion of some sort. The nuclear grade, glandular differentiation and clinical staging of the tumor followed General Rule for Clinical and Pathological Studies on Prostate Cancer⁸⁾ and the Gleason system⁹⁾. To ensure consistency in the diagnosis of prostate cancer, a single experienced pathologist read all slides of biopsies.

Ultrasound of the prostate

TRUS equipped with a biplane probe (7.5 MHz transducer) was applied to evaluate the estimated volume of the prostate by a single urologist experienced in TRUS. The volume of the total prostate was calculated by using the formula for a prolate spheroid ($V = \pi/6 \times \text{transverse width} \times \text{transverse height} \times \text{longitudinal length}$)^{10,11)} All diameters were obtained from the maximal plane of the transverse and longitudinal sections.

The prostate biopsy under guidance of TRUS was performed as previously described¹¹⁾ In brief, the specimens were obtained with a spring-loaded biopsy gun (Biopsy®; C.R. Bard, GA), using an 18-gauge "Tru-cut" biopsy needle under the sonographic guidance. If hypoechoic areas were noted on TRUS, a specimen was taken from each of these areas. In addition, systematic biopsy was performed. Biopsies were taken from the prostate apex, and from the middle and base of the peripheral zone in each lobe. Informed consent was given by all the patients.

PSA assays

tPSA was measured by an immunoenzymatic assay (Tandem-R). For the quantification of free PSA an immunoradiometric assay was used¹²⁾ PSAD was calculated by dividing the tPSA value by the total prostate volume¹¹⁾

Statistical analysis

Statistical analysis was carried out using the Expert StatView system (version 4.5) on a Macintosh computer (Apple Computers, Cupertino, CA, USA). Mann-Whitney U-test was employed to assess the difference between the two groups (patients' age, prostatic volumes and other parameters) as univariate analysis and Kruskal-Wallis test was done to compare each parameter with glandular differentiation or advanced stage of the tumors. A *p*-value of less than 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were calculated to demonstrate the sensitivity and specificity of tPSA, PSAD and F/T ratio. ROC curves illustrate the reciprocal relationship between sensitivity and specificity by plotting true positive (sensitivity) versus false positive (one minus the specificity values). The closer the ROC curves were to the upper left of the graph and the larger the area under the curve (AUC), the better was the test. Statistical analysis of the different AUC was calculated with Hanley and McNeil's test^{13,14)}.

RESULTS

A mean of 7.5 cores per patient were taken for biopsy (range, 6–8 cores). Of the 43 patients, 12 (27.9%) and 31 (72.1%) were diagnosed as CaP and non-CaP, respectively. The mean age of the patients with CaP was 70.5 years and that of those with non-CaP 66.4 years (*p*=0.065). The patients with non-

CaP had significantly larger prostate glands than those with CaP (45.6 vs. 34.3 cm³, *p*=0.0199). Of all the 43 patients for whom DRE finding were available, 13 (30.2%) had suspicious DRE. CaP was found in 23.3% (7 out of 30) and 38.5% (5 out of 13) of the patients with normal and suspicious DRE finding, respectively. In addition, it was found in 50% (3 out of 6) and 24.3% (9 out of 37) of the patients with normal and abnormal TRUS findings. DRE and TRUS methods showed 41.7% (5 out of 12) and 50% (6 out of 12) sensitivity in 74.2% (17 out of 31) and 75.7% (28 out of 37) specificity, respectively. The positive predictive value of each method is 35.7% (5 out of 14) and 50% (3 out of 6). Combination of the two methods resulted in a sensitivity and specificity of 38.5% (5 out of 13) and 74.2% (23 out of 31), respectively. The 12 cancers were classified clinically as stage B0 in 7 patients, B1 in 1, C and D2 each in 2. The glandular differentiation of the tumors was well differentiated in 5, moderately in 3 and poorly in 4. Five patients showed Gleason score 2 to 4, 5 showed 5 to 7 and 2 showed 8 to 10. In our study, 25% of the patients with carcinoma had insignificant tumors based on pathologic and clinical findings¹⁵⁾. Of the non-CaP patients, 20 had benign prostatic disease including benign prostate hypertrophy (BPH) and 5 had prostatitis. Total PSA, but neither F/T ratio nor PSAD, was associated with glandular differentiation of the tumors (*p*=0.0414). None of the three parameters were associated with clinically advanced disease. The mean and standard error median for tPSA, F/T ratio and PSAD in each group are shown in Table 1. The mean PSAD was significantly higher in the CaP patients than in the non-CaP patients. There was no statistically significant difference in the tPSA value or F/T ratio between the CaP and the non-CaP groups. The cutoff value of 11 percent for F/T ratio yielded a specificity level of 50% at a sensitivity level of 77.4% in all the patients (data not shown). Fig. 1 shows the ROC curves of tPSA, PSAD and F/T ratio obtained from all 47 patients. The area under the curve

Table 1. Several parameters in patients

	Prostate cancer (n=12)	Non-cancer (n=31)	<i>p</i> -value
tPSA (ng/ml)			
Mean	7.308	6.300	0.2612
SEM	0.636	0.289	
F/T ratio (%)			
Mean	16.225	15.213	0.1673
SEM	4.911	0.980	
PSAD (ng/ml/cm ³)			
Mean	0.271	0.178	0.0109
SEM	0.039	0.020	

SEM: standard error of mean. Statistical analysis of the data was performed with the Mann-Whitney U test.

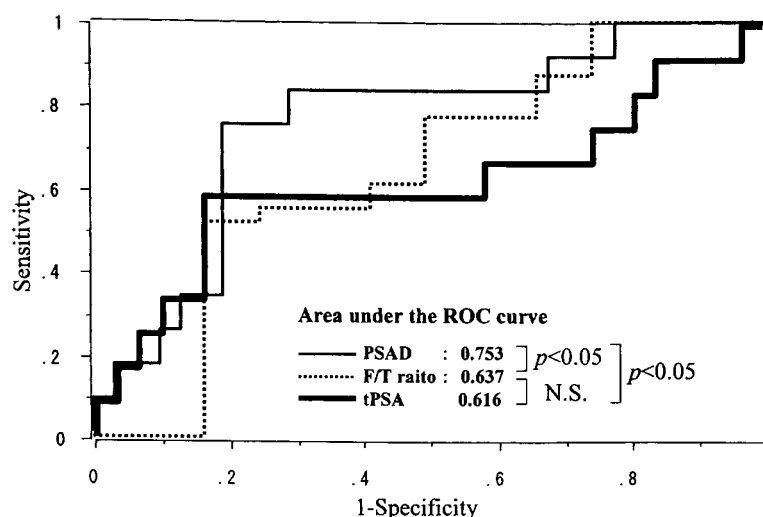


Fig. 1. Receiver operating characteristic (ROC) curves of total prostate-specific antigen (tPSA), PSA density (PSAD) and free-to-total PSA ratio (F/T ratio) obtained from all 43 patients. Area under curve was 0.616, 0.753 and 0.637, respectively. The closer the ROC curves is to the upper left of graph, the better is the test.

Table 2. Performance of different PSAD in patients with intermediate serum PSA concentrations

Cutoff value (ng/ml/cm ³)	Sensitivity (%)	Specificity (%)	Overall accuracy (%)	PPV (%)	NPV (%)
0.13	83.3	48.4	40.3	38.5	88.2
0.14	83.3	48.4	40.3	38.5	88.2
0.15	83.3	61.3	51.1	45.5	90.5
0.16	83.3	71.0	59.1	52.6	91.7
0.17	75.0	74.2	55.6	52.9	88.5
0.18	75.0	77.4	58.1	56.3	88.9
0.19	75.0	77.4	58.1	56.3	88.9

PPV: positive predictive value; NPV: negative predictive value.

(AUC) was 0.616, 0.753 and 0.637, respectively. The difference was significant between PSAD and F/T ratio ($p < 0.05$) and between PSAD and tPSA ($p < 0.05$) but not between F/T ratio and PSA. The sensitivity and specificity of PSAD were 83.3% (10 of 12) and 71.0% (22 of 31), at a cutoff value of 0.16, respectively (Table 2). The cutoff value of PSAD used (0.16) would prevent 71.0% (22 of 31) of unnecessary negative biopsy, but 16.7% of the tumors (2 of 12) would be overlooked.

DISCUSSION

Serum tPSA is useful for screening prostate carcinoma in combination with DRE and TRUS. Differential diagnosis is important in patients with intermediate PSA concentrations of 4.1–10.0 ng/ml because most of them have organ-confined cancers and are potential candidates for therapy^{16,17}. With the combination of PSA, DRE, and TRUS, however, it is difficult to differentially diagnose prostate carcinoma from benign prostatic disease in patients with intermediate PSA concentrations.

PSAD was superior to F/T ratio in ROC curve

analysis in all patients. These results were consistent with previous reports^{10,18}. PSAD was confirmed useful as an aid in differentiating BPH from CaP in the range, 4.1 to 10.0 ng/ml, in which the two conditions overlapped the most.

Several studies, however, indicated that the PSAD in the Japanese population is higher than that in white American men and the usefulness of PSAD in the Japanese population is still unclear^{11,19}. On the other hand, Catalona et al. reported that PSAD was less useful than serum PSA²⁰. They detected difficulty in measuring accurate prostate volume that influenced the usefulness of PSAD. In our study, TRUS was performed by a single expert to decrease the interobserver variability in measuring the prostate volume.

In many studies PSA-related parameter cut points are necessary to maintain at least 90% sensitivity^{17,21}. Therefore, we concluded that 0.16 ng/ml/cm³ was the best cutoff of PSAD because this cutoff value yielded high specificity at a sensitivity level of about 90%. In Western countries, the PSAD cutoff value of 0.15 is generally used^{2,10,18,20}.

Another study showed that the best cutoff value of PSAD with intermediate PSA was 0.18¹¹⁾. This discrepancy might result from the difference in design (prospective vs. retrospective), or cohort size of the studies. Although several cutoffs for the PSAD have been proposed, the cutoff selected should be individualized according to the expectations of each physician and patient. Therefore, if one wishes to improve the sensitivity and detect more cancers, our results would favor 0.16 as the ideal PSAD cutoff. Using this cutoff, the specificity is maintained at a level similar to the use of DRE and TRUS findings (74.2%), but the proportion of cancer detection would increase from 38.5% to 83.3%. In addition, if the goal is to avoid unnecessary biopsies while maintaining a similar prostate detection rate, a cutoff of 0.16 should also be used on our data.

A previous report showed that a 25% rate of positive biopsy results would be obtained in a population of men with a PSA value between 4.0 and 10.0 ng/ml and normal finding on DRE²²⁾. Thus, we thought that the positive rate in this study (27.9%) was slightly higher than that of the other reports. The proportion of subjects with suspicious DRE findings would influence the rate of positive biopsy.

Several investigators found that the F/T ratio in patients with CaP was significantly smaller than that in those with BPH, and it significantly differentiated benign and malignant prostatic diseases, whereas tPSA did not^{17,23)}. Luderer et al. examined the clinical usefulness of free PSA in the differential diagnosis of CaP in patients with intermediate PSA concentrations. With PSAD, there is difficulty in accurately measuring prostate volume. The F/T ratio may surpass PSAD as a detector of cancer because it does not depend on prostate volume data²³⁾. However, several studies showed that the difference in cutoff value of free PSA was due to prostate volume and race population^{17,24)}. Thus, the cutoff value of F/T ratio in our data was lower compared to other data. Several studies have shown various cutoff values of F/T ratio between 12 and 15 percent²⁵⁻²⁷⁾. Such discrepancies may depend on the difference in assay systems used to determine free and total PSA concentrations and the study design, or the cohort size. The standard sextant method detected 90% of the patients with PSA greater than 10 ng/ml²⁸⁾. Most of our patients had only sextant biopsies performed, which could have affected our cancer detection. Recently, several investigators showed enhanced detection compared to conventional sextant biopsies by adding a variable number of biopsies at the transitional zone and the lateral aspects of peripheral zone²⁹⁻³¹⁾. Additional biopsies over the standard sextant zones may be needed in patients with a serum PSA of less than 10 ng/ml.

In conclusion, sensitivity and specificity were better for the F/T ratio than for tPSA but inferior for PSAD. The F/T ratio might not be a useful diagnostic tool for detecting prostate cancer in Japanese patients with intermediate tPSA concentrations (4 to 10 ng/ml). PSAD may be a better index than F/T ratio in detecting prostate cancer in patients with these tPSA concentrations. Further prospective studies with larger cohorts will define the benefit and optimal cutoff value of PSAD in finding prostate cancer in Japanese men by sampling additional areas.

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(Received on September 19, 2002)
 (Accepted on April 15, 2003)

和文抄録

前立腺癌診断における前立腺特異抗原 (PSA) 関連パラメーターの
有用性の検討：血清 PSA 値が Gray zone を示す症例

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血清 PSA 値 4~10 ng/ml を示す症例について 前立腺癌診断における total PSA (tPSA), PSA density (PSAD), free to total PSA ratio (F/T 比) の有用性を検討した。1999年5月から2001年4月までに経直腸的エコー下前立腺生検を施行した43例を対象とし, ROC 曲線を用いて各検査法の有用性を検討した。43例中, 前立腺癌: 12例 (27.9%), 非癌: 31例 (72.1%)。tPSA, PSAD 値, F/T 比の mean $\pm$ SEM は癌症例でそれぞれ 7.308 ± 0.636 ng/ml, 0.271 ± 0.039 ng/ml/cm³, $16.225\pm4.911\%$ であるのに対し, 非癌

症例は 6.300 ± 0.289 ng/ml, 0.178 ± 0.020 ng/ml/cm³, $15.213\pm0.980\%$ であった。全症例における PSAD, tPSA, F/T 比の ROC 曲線右下部分の面積を比較すると有意差をもって PSAD のみが高かった ($p<0.05$)。PSAD 値において cutoff 値を 0.16 ng/ml とすると感度は83.3%, 特異度は71.0%であった。日本人で血清 PSA 値が gray zone にある症例において PSAD の測定は最も有用であることが示唆された。

(泌尿紀要 49 : 405-410, 2003)