THE SIGNIFICANCE OF PROSTATE-SPECIFIC ANTIGEN ALPHA-1-ANTICHYMOTRYPSIN COMPLEX AND ITS INDICES FOR THE DETECTION OF PROSTATE CANCER

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We examined the usefulness of prostate specific antigen alph-1-antichymotrypsin complex (PSA-ACT) and its indices for the detection of prostate cancer in patients with a prostate specific antigen (PSA) level between 2.1 and 10.0 ng/ml. Between July 1999 and October 2001, 151 patients with a PSA level between 2.1 and 10.0 ng/ml underwent a systematic biopsy under transrectal ultrasound (TRUS) guidance. The clinical values of total PSA, PSA-ACT, PSA density (PSAD), PSA-ACT density (PSA-ACTD), PSA transition zone density (PSATZD) and PSA-ACT transition zone density (PSA-ACTTZD) for the detection of prostate cancer were compared by using receiver operating characteristic (ROC) curve analysis. Of the 151 patients, 36 (23.8%) were histologically confirmed as having prostate cancer. The differences between patients with prostate cancer and benign prostatic disease were significant with respect to the PSA and PSA-ACT related parameters examined in this study. According to ROC curve analysis, the area under the curve (AUC) of PSA-ACTTZD was the greatest of all the parameters. The differences was significant between the AUC of PSA-ACTTZD and total PSA (p<0.05). The cutoff value of PSA-ACTTZD with 0.20 ng/ml^2 showed the highest sum of sensivitity (90%) and specificity (55%). Also, in 86 patients with a PSA level between 2.1 and 6.0 ng/ml, the AUC of PSA-ACTTZD was the greatest of all the parameters. Measuring the level of PSA-ACT and its indices may provide a better differentiation of prostate cancer and benign prostatic disease than total PSA alone in patients with intermediate PSA levels. PSA-ACTTZD is the most useful indicator among PSA-ACT and its volume indices.

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Key words: Prostate cancer, Prostate specific antigen alpha-1-antichymotrypsin, Transition zone

INTRODUCTION

Serum prostate specific antigen (PSA) has unequivocally proved its clinical usefulness as a serum marker for prostate cancer. However, it is difficult to differentiate between prostate cancer and benign prostatic disease in patients with intermediate PSA levels, since elevated serum levels of PSA can be found in patients with benign prostatic hypertrophy and prostatitis[1]. Therefore, in order to avoid unnecessary biopsies and to increase specificity in the diagnosis of prostate cancer, the values of several PSA-related parameters have been developed, including age-specific references for PSA[2], PSA density (PSAD)[3], PSA velocity (PSAV)[4], and free-to-total PSA (F/T) ratio[5]. Despite promising results in recent studies, it remains unclear which method is superior in practical use.

Recent studies have demonstrated that PSA exists in different molecular forms. The majority of PSA is complexed with several enzyme inhibitors, including α-1-antichymotrypsin, α-1-antitrypsin, α-2-macro-globlin and C protein, whereas the minority of PSA is not bound to serum proteins and is called free PSA. Moreover, several studies have shown that serum from patients with prostate cancer contains a higher proportion of prostate specific antigen α-1-antichymotrypsin complex (PSA-ACT) than that from patients with benign prostatic disease[6]. Thus, PSA-ACT appears to be more closely associated with the progression of prostate cancer than PSA. Although the accurate measurement of PSA-ACT has been difficult because of technical problems, the recent development of a PSA-ACT assay may be of clinical value.

Many investigators have shown the importance of PSA adjusted for prostate volume to detect prostate cancer[7]. It has been reported that the PSA transition zone density (PSATZD) may be a more valuable method than PSAD. However, few studies evaluating the value of serum PSA-ACT and its volume indices have been published and their conclusions are not consistent[11,12].

In this study, we examined the usefulness of PSA-

ACT and its volume indices, including PSA-ACTD and PSA-ACTTZD for detecting prostate cancer in patients with intermediate serum PSA levels.

PATIENTS AND METHODS

Between July 1999 and October 2001, 151 patients with a PSA level of 2.1 and 10.0 ng/ml underwent systematic sextant transrectal prostate biopsies under the guidance of transrectal ultrasound (TRUS) in our hospital. The indications for prostate biopsies were a serum PSA level greater than 4.0 ng/ml and/or a suspicious digital rectal examination (DRE) irrespective of TRUS findings. The patient ages ranged from 50 years to 89 years (mean, 70.0 years). No patients with a poor diagnosis of prostate cancer or hormonal manipulation were included.

The prostate volume (whole gland and transition zone volume) was determined using the volumetric formula for a prolate spheroid, i.e., $\pi/6 \times$ (transverse width)$^2 \times$ (anteroposterior dimension or height)[13] Serum was obtained before a digital rectal examination or TRUS. Total PSA was measured using a Cosmedi · F-PSA (International Reagent Corporation) and the values for PSA-ACT were determined using the PSA-ACT kit (Chugai Pharmaceutical Company, Japan). PSAD, PSATZD, PSA-ACTD and PSA-ACTTZD were calculated by dividing the serum PSA and PSA-ACT values by the whole prostate volume and the transition zone volume, respectively.

Receiver operating characteristic (ROC) curves were plotted as graphical presentations of the sensitivity against 100 minus the corresponding specificity. Based on the fact that the ROC curves move leftward and upward with increases in sensitivity and specificity, ROC curves have been utilized to compare the diagnostic usefulness of tumor markers. The area under the curve (AUC) was calculated, and results compared as described by Hanley and McNeil[14]. Values from patients with and without cancer were compared using the Mann-Whitney U-test for non parametric analyses, and p<0.05 was considered statistically significant.

RESULTS

Of the 151 patients with a PSA level between 2.1 and 10.0 ng/ml, 36 (23.8%) were histologically confirmed as having prostate cancer, and the remaining 115 (76.2%) were diagnosed with benign prostatic disease. The differences between patients with prostate cancer and benign prostatic disease were significant with respect of PSA, PSA-ACT, PSAD, PSA-ACTD, PSATZD and PSA-ACTTZD, although not to age (Table 1).

We then calculated the specificity of each assay within the range of 80% to 95% sensitivity (Table 2). At sensitivities of 95, 90, 85 and 80%, PSA-ACTTZD had the highest specificity. The cutoff value of PSA-ACTTZD with 0.20 ng/ml^2 showed the highest sum of sensitivity (90%) and specificity (55%). The cutoff value of 0.20 reduced the number of biopsies from 151 to 84 (i.e., reduced the number of biopsies by 44%).

ROC curves in those showing serum PSA values of 2.1 to 10 ng/ml were evaluated in order to determine the clinical usefulness of PSA, PSA-ACT, PSAD, PSATZD, PSA-ACTD and PSA-ACTTZD in the differentiation of prostate cancer and non-cancer. ROC analysis revealed that the AUCs of PSA, PSA-ACT, PSAD, PSA-ACTD, PSATZD, and PSA-ACTTZD were 0.6374, 0.7154, 0.7242, 0.7597, 0.7544, and 0.7945, respectively. Although the AUCs of PSATZD and PSA-ACTTZD were greater than those of their corresponding parameters (i.e., PSA, PSAD and PSA-ACT, PSA-ACTD, respectively), there were no significant differences. The AUC of PSA-ACTTZD was the greatest of all the parameters. The difference was significant between the AUC of PSA-ACTTZD and PSA (p<0.05) (Fig. 1). In a subgroup of 86 patients with PSA levels between 2.1 and 6.0 ng/ml, the AUC of PSA-ACTTZD was the

Table 1. The characteristics of patients with total PSA levels between 2.1 and 10.0 ng/ml

Characteristics	Prostate cancer mean±SD	Benign prostate disease mean±SD	p value[a]	Total mean±SD
No. of patients	36	115		151
Age (years)	72 ± 6.2	70 ± 8.1	0.18	71 ± 7.7
Total PSA (ng/ml)	6.3 ± 2.1	5.3 ± 1.9	<0.01	5.5 ± 2.0
PSA-ACT (ng/ml)	5.2 ± 1.9	3.8 ± 1.6	<0.001	4.1 ± 1.8
Prostate volume (cm^3)	28.8 ±12.2	42.6 ±23.0	<0.001	39.3 ±21.7
Transition zone volume (cm^3)	10.7 ± 7.4	20.4 ±15.1	<0.001	18.1 ±14.3
PSAD	0.29± 0.13	0.17± 0.14	<0.001	0.19± 0.15
PSATZD	0.83± 0.52	0.44± 0.41	<0.001	0.54± 0.46
PSA-ACTD	0.22± 0.15	0.13± 0.12	<0.001	0.15± 0.13
PSA-ACTTZD	0.70± 0.49	0.33± 0.34	<0.001	0.42± 0.41

PSA, prostate specific antigen; PSA-ACT, α-1-antichymotrypsin-PSA complex; PSAD, PSA density; PSATZD, PSA transition zone density; PSA-ACTD, PSA-ACT density; PSA-ACTTZD, PSA-ACT transition zone density.
[a] Statistical analysis of the data between prostate cancer and benign prostate disease.

Table 2. Sensitivity of the cutoff values of the different PSA assays at selected sensitivities in patients with total PSA levels between 2.1 and 6.0 ng/ml

	Sensitivity	Total PSA	PSA-ACT	PSAD	PSATZD	PSA-ACTD	PSA-ACTTZD
95.0%	Specificity (%)	2.3	13	17	29	35	43
	Cut-off value	2.41	1.97	0.076	0.19	0.067	0.16
90.0%	Specificity (%)	17	28	45	45	46	55
	Cut-off value	3.08	2.61	0.12	0.25	0.085	0.20
85.0%	Specificity (%)	32	44	46	47	51	60
	Cut-off value	4.03	3.29	0.12	0.28	0.095	0.23
80.0%	Specificity (%)	35	52	57	47	59	61
	Cut-off value	4.43	3.64	0.15	0.29	0.11	0.25

PSA, prostate specific antigen ; PSA-ACT, α-1-antichymotrypsin-PSA complex ; PSAD, PSA density ; PSATZD, PSA transition zone density ; PSA-ACTD, PSA-ACT density ; PSA-ACTTZD, PSA-ACT transition zone density.
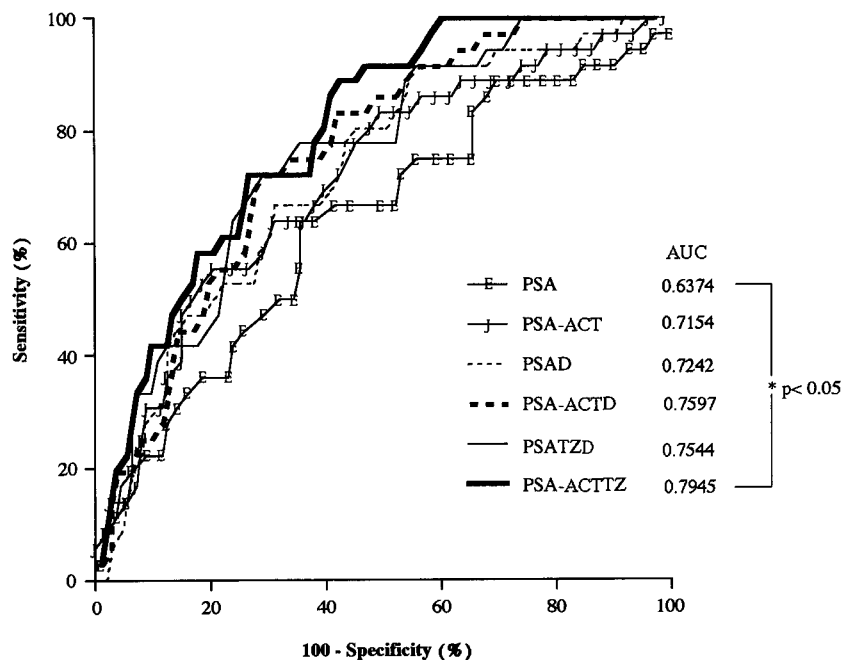

Fig. 1. Receiver operating characteristic curve analysis of total prostate specific antigen (PSA), α-1-antichymotrypsin-PSA complex (PSA-ACT), PSA density (PSAD), PSA-ACT density (PSA-ACTD), PSA transition zone density (PSATZD) and PSA-ACT transition zone density (PSA-ACTTZD) in 151 patients with a PSA level between 2.1 and 10.0 ng/ml. * p<0.05

greatest of all the parameters and was significantly greater than that of total PSA (p<0.05) (Fig. 2).

DISCUSSION

The total PSA level is considered to be a useful parameter for the detection of prostate cancer. However, it is difficult to discriminate between prostate cancer and benign prostatic disease among patients with intermediate PSA levels. Although PSA-related parameters, such as the F/T PSA ratio, PSAD, and PSATZD have been examined in order to reduce the number of unnecessary biopsies without missing a significant number of clinically important cancers, the most important parameter in the detection of prostate cancer remains controversial. Therefore, in this study, we examined whether the measurement of PSA-ACT and its volume adjusted

parameters could improve the diagnostic accuracy of prostate cancer among patients with intermediate serum PSA levels.

PSA-ACT is the major component of serum PSA and is apparently directly related to prostate cancer[6] Brawer et al. reported that PSA-ACT alone performed better than PSA and F/T PSA in patients with total PSA values between 4.0 and 10.0 ng/ml[15] Maeda showed the superiority of PSA-ACT over PSA and F/T PSA in intermediate serum PSA levels[11] The results of our study using ROC analysis showed the same trend as these earlier studies, although the difference between the AUC of PSA and PSA-ACT was not significant, probably because of the small number of patients.

Volume adjusted PSA might have an advantage in the detection of prostate cancer, since benign
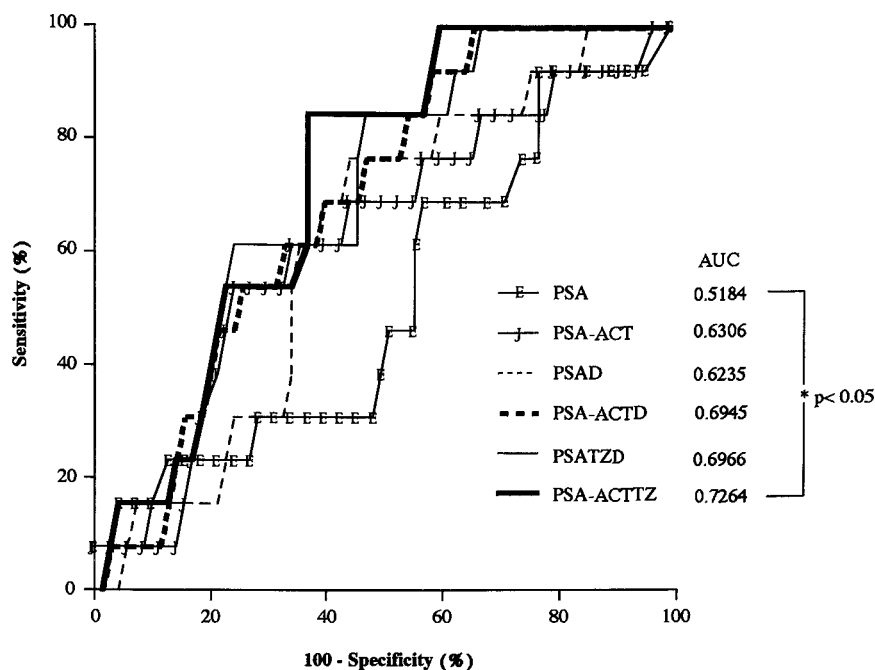
Fig. 2.   Receiver operating characteristic curve analysis of total prostate
specific antigen (PSA), α-1-antichymotrypsin-PSA complex (PSA-
ACT), PSA density (PSAD), PSA-ACT density (PSA-ACTD), PSA
transition zone density (PSATZD) and PSA-ACT transition zone
density (PSA-ACTTZD) in 84 patients with a PSA level between 2.1
and 6.0 ng/ml.   * p<0.05

prostatic enlargement can result in PSA elevation in the absence of prostate cancer[16] Although some investigators have confirmed the ability of PSAD to discriminate between prostate cancer and benign prostatic hyperplasia[5], others have questioned its validity[17]. Adjusting for transition zone volume may be a more useful parameter than using PSAD, since the transition zone is thought to account for PSA leakage into serum. Kalish et al. first indicated that PSATZD was superior to PSAD[8] Kurita et al. stressed the clinical usefulness of PSATZD in Japanese patients, with an optimal cutoff value of 0.3 ng/ml[2,9]. Conversely, Gohji et al. reported that PSATZD had no additional effect in predicting prostate cancer in Japanese men with intermediate serum PSA levels (2.1–10 ng/ml) and recommended that PSA should be used as an indicator for prostate biopsy[18] The use of PSATZD is now controversial.

In this study, the AUC of PSA-ACTTZD was the greatest among the volume-adjusted PSA-related parameters. At a sensitivity of 90% (missing 4 tumors), PSA-ACTTZD would have prevented unnecessary biopsies in 63 of 115 patients without prostate cancer (specificity 55%), whereas PSA, PSA-ACT, PSAD, PSA-ACTD, and PSATZD would have prevented unnecessary biopsies in 20, 32, 52, 52, and 53 patients, respectively. We believe that PSA-ACTTZD is superior in practical utility and can help to avoid more unnecessary biopsies. Recently, the importance of detecting cancer in a patient with a lower PSA level has been emphasized and it is

necessary to improve diagnostic accuracy in patients with a lower PSA. In our study, the AUC of PSA-ACTTZD was also the greatest in patients with a PSA level of 2.0–6.0 ng/ml. PSA-ACTTZD might be a useful indicator of prostate cancer in patients with a lower PSA level.

Djavan et al. reported a disadvantage of PSATZD in discriminating prostate cancer in men with smaller prostates, because it is difficult to measure the transition zone of small prostates by TRUS[19] Although we studied a subgroup of 105 patients with a smaller prostate volume (less than 45 ml), no significant differences in the discrimination between prostate cancer and benign prostatic disease were found among these six parameters (data not shown). We need careful ultrasonographic imaging, especially in patients with a small prostate, because the accuracy of the transition zone volume measurement depends on ultrasonography.

In this study we adopted transrectal sextant biopsy. Because the sextant biopsy technique described by Hodge et al. has in the past been considered to be standard[20]. However, Keetch et al. demonstrated that the positive biopsy rate for a second set of sextant biopsies was 20% in those with initially negative biopsies[21] This observation implied that more biopsies might increase the detection rate of prostate cancer. Further studies involving a large number of samples would be needed to re-evaluate the usefulness of PSA-ACTTZD under an ideal biopsy method. In conclusion, measuring the level of PSA-ACT and its

volume indices may provide a better differentiation of prostate cancer and benign prostatic disease than total PSA alone in patients with intermediate and lower PSA levels. PSA-ACTTZD might be one of the most useful indicators for prostate cancer among PSA-ACT and its volume indices.

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和文抄録

前立腺癌診断における PSA-ACT および PSA-ACT volume index の有用性についての検討

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　前立腺癌診断における PSA-ACT および PSA-ACT volume index の有用性について検討した．対象は1999年 7 月から2001年10月の間に当院にて超音波ガイド下経直腸的前立腺生検を施行した PSA 2.0〜10.0 ng/ml の症例151例で，PSA, PSA-ACT, PSAD, PSATZD, PSA-ACTD, PSA-ACTTZD を測定し，ROC 解析を用いてこれらのパラメーターを比較検討した．

　系統的 6 カ所生検にて151例中36例（23.8％）から前立腺癌が検出された．ROC 解析では今回われわれが検討したパラメーターのうち PSA-ACTTZD の AUC が最大となり，PSA-ACTTZD は有意差をもって（$p < 0.05$）PSA 単独より有用な指標と考えられた．PSA-ACTTZD のカットオフ値を $0.20 \, ng/ml^2$ を設定することにより，感度90％，特異度55％で不必要な生検を回避できる可能性が示唆された．PSA 軽度上昇例における前立腺癌診断については PSA より PSA-ACT の方が有用で，生検の適応を考慮する際には PSA-ACTTZD が最も有用なパラメーターのひとつになりうると思われた．

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