PROSTATIC VOLUME AND VOLUME-ADJUSTED PROSTATE-SPECIFIC ANTIGEN AS PREDICTIVE PARAMETERS FOR T1c PROSTATE CANCER

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We examined the usefulness of the volume-adjusted prostate-specific antigen (PSA) parameters for prediction of T1c prostate cancer on 210 patients who had abnormal PSA levels but no abnormal findings in digital transrectal examination (DRE) or transrectal ultrasonography (TRUS). PSA, prostate volume (PV), transition zone volume (TZV), PSAD (PSA/PV) and PSATZD (PSA/TZV) were assessed with the receiver operating characteristic (ROC) curve and the area under the curve (AUC). Simple and stepwise logistic regression models were used to calculate the odds ratios of these parameters. Fifty-three (25.2%) of all 210 patients and 31 (19.9%) of 156 patients with intermediate PSA levels had biopsy-proved prostate cancer. The ROC curves of all patients revealed that PSA, PV, TZV, PSAD and PSATZD had significant predictive values, while AUCs of PV, PSAD and PSATZD had significant predictive values as compared to that of PSA. In the patients with intermediate PSA levels, the ROC curves revealed that PV, TZV, PSAD and PSATZD had significant predictive values, but there were no significant differences in AUCs among these parameters. The stepwise logistic regression analysis showed that PV and PSATZD were significant predictive parameters in all patients and that PSATZD was the only significant predictive parameter in the patients with intermediate PSA levels. In conclusion, not only PSAD and PSATZD but also PV and TZV had significant predictive values in discriminating prostate cancer. However, the multivariate analysis showed that PSATZD had the strongest predictive value in all patients and in those with intermediate PSA levels.

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Key words : Prostate cancer, PSAD, PSATZD, Systematic needle biopsy, Cancer prediction

INTRODUCTION

According to the recent increase in patients showing abnormal elevation of the prostate-specific antigen (PSA) value but having no abnormal findings in transrectal digital examination (DRE) or transrectal ultrasonography (TRUS), the incidence of T1c[1)] prostate cancer has increased. Most patients with T1c prostate cancer have intermediate PSA levels of less than 10 ng/ml. In the patients with an intermediate PSA level, the detection rate of cancer is not high due to the low specificity of PSA value for cancer. To improve this disadvantage in the patients with intermediate PSA value, many investigators have studied the usefulness of various volume-adjusted parameters including PSA density (PSAD), PSA transition zone density (PSATZD), complexed PSA density (cPSAD) and complex PSA transition zone density (cPSATZD) for accurate diagnosis of prostate cancer, as well as the serum PSA fractions such as free PSA, complex PSA and free/total PSA ratio[2–16)].

In this study, we retrospectively investigated our series of patients with abnormal PSA value but no abnormal findings in DRE or TRUS and elucidated which volumetric parameter or volume-adjusted PSA parameter is available and useful for discriminating T1c prostate cancer from non-cancer including benign prostate hyperplasia (BPH) in this population of patients.

METHODS

Between August 1996 and April 2004, 618 consecutive patients who were suspected of having prostate cancer based on abnormal PSA value or DRE findings or TRUS findings underwent systematic prostate needle biopsies at Nara Medical University Hospital. Out of these patients, 210 patients with no abnormal findings in DRE or TRUS were enrolled in this study as T1c category. Their mean age was 69.9 years (range : 41 to 88 years) and their mean PSA value was 10.1 ng/ml (range : 4.1 to 120 ng/ml). These patients were not selected from a screening population but from a community-based practice.

PSA was measured (normal value : 3.7 ng/ml or less) using a TOSOH E test (kit : AIA-PACK PA, Immuno-Enzymometric Assay, TOSOH Corp., Tokyo, Japan) before performing DRE and TRUS. Patients who had acute or chronic prostatitis, urinary retention, urinary

tract infection and indwelling urethral catheter were excluded from this study.

Systematic sextant prostate needle biopsies were performed using an automatic biopsy gun and with an 18-gauge needle under TRUS guidance. Since March 2003, octant systematic needle biopsies have been adopted, besides the sextant biopsies plus additional 2 biopsies to the bilateral far peripheral zones. Of all patients, 164 patients (78.1%) received sextant needle biopsy and 46 patients (21.9%) received octant needle biopsy, respectively. We used a 7.5 MHz biplane transducer to obtain axial and sagittal images. PV and TZV were calculated using a formula for a prostate ellipsoid (transverse width × transverse length × longitudinal height × 0.52). PSAD and PSATZD were calculated through dividing PSA by PV and TZV, respectively.

Prostate intraepithelial neoplasms and atypia were not considered as prostate cancer. To examine the differences in these volumetric and volume-adjusted PSA parameters between the patients with prostate cancer and non cancer patients, we used Mann-Whitney's U test for bivariate analyses on age, PSA, PV, TZV, PSAD and PSATZD. Analysis using receiver operating characteristic (ROC) curves was employed for diagnosis of prostate cancer among PSA, PV, TZV, PSAD and PSATZD and calculated each area under the curve (AUC), comparing it with the Hanley and McNeil method[17,18]. In the ROC analysis, the reciprocal plots were adopted for PV and TZV. Furthermore, as the age parameter and all parameters were significantly predictive in the simple logistic regression analysis, stepwise logistic regression models were used to calculate the odds ratios for prostate cancer diagnosis. All p values less than 0.05 were considered as statistically significant.

The institutional reviewer board approved this retrospective study and obtaining informed consent from the patients was exempted in the respect of the aim and methods of this study.

RESULTS

Background of volume parameters and volume-adjusted PSA parameters of enrolled patients

Of 618 patients who underwent systematic prostate needle biopsies, 261 patients (42.2%) had biopsy-proved prostate cancer and 210 patients (34.0%) showed only abnormal PSA levels without any abnormal findings in DRE or TRUS. Of these 210 patients showing abnormal PSA levels only, 53 patients (25.2%) had biopsy-proved T1c prostate cancer (N0M0) and 156 patients (74.3%) showed intermediate PSA values (4.1–10.0 ng/ml). Of these 156 patients with intermediate PSA level, 31 patients (19.9%) had biopsy-proved prostate cancer.

Table 1 shows the characteristics of 210 patients showing only abnormal PSA levels without any abnormal findings of DRE or TRUS. Regarding these patients, the mean levels of PSA, PSAD and PSATZD in the prostate cancer group were significantly greater than those in the non-cancer group. On the other hand, both PV and TZV in the prostate cancer group were significantly smaller than those in the non-cancer group. In the 156 patients with intermediate PSA levels, there were no significant differences in the PSA values between the prostate cancer group and the non-cancer group. The mean levels of PSAD and PSATZD in the prostate cancer group were significantly greater than those in the non-cancer group and both PV and TZV in the prostate cancer group were significantly smaller than those in the non-cancer group.

Analysis by receiver operating characteristic curves and area under the curve

The ROC curve analyses of all 210 patients revealed that PSA, PV, TZV, PSAD and PSATZD had significant predictive values in discriminating prostate cancer (Fig. 1A). However, analysis of differences in AUC among PV, TZV, PSAD, PSATZD and PSA, revealed that each AUC of PV, PSAD and PSATZD had significant predictive values as compared to that of PSA, while there was no significant difference in AUC between TZV and PSA (Table 2). On the other hand, the ROC

Table 1. Background of patients showing abnormal prostate-specific antigen value without abnormal findings in transrectal digital or ultrasound examination

	All patients (n=210)			Patients with intermediate PSA levels (n=156)		
	Cancer (n=53) mean±SD	Non-cancer (n=157) mean±SD	p-value*	Cancer (n=31) mean±SD	Non-cancer (n=125) mean±SD	p-value*
Age (yrs)	71.3±6.4	69.5±6.6	0.089	70.4±6.2	69.2±6.7	0.368
PSA (ng/ml)	13.6±18.1	8.9±6.3	0.037	6.5±1.7	6.6±1.7	0.658
PV (cm^3)	24.7±10.2	41.4±23.0	<0.001	24.4±10.0	39.9±22.2	<0.001
TZV (cm^3)	11.6±6.3	21.8±15.1	<0.001	11.3±6.5	20.3±13.6	<0.001
PSAD	0.65±0.88	0.28±0.30	<0.001	0.32±0.21	0.21±0.10	<0.001
PSATZD	1.51±1.77	0.61±0.81	<0.001	0.88±1.03	0.47±0.33	<0.001

PSA: prostate-specific antigen; PV: prostate volume; TZV: transition zone volume; PSAD: PSA density; PSATZD: PSA transition zone density; SD: standard deviation; *: Mann-Whitney's U test.

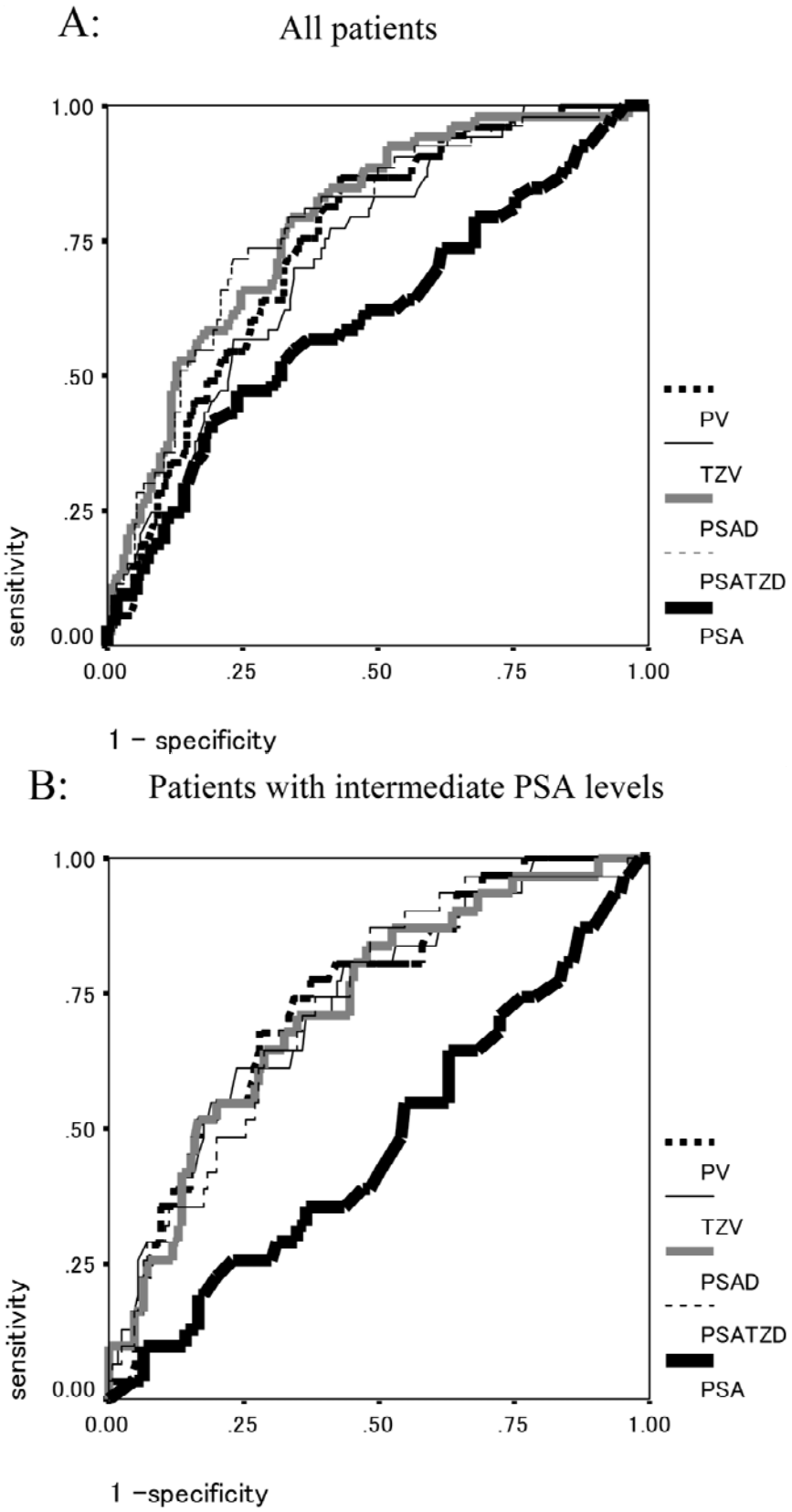

Fig. 1. The receiver operating characteristic curves of PSAD, PSATZD, PV, TZV and PSA in all patients (A ; n=210) and in those with intermediate PSA levels (B ; n=156).

curve analysis of patients with intermediate PSA levels revealed that PV, TZV, PSAD and PSATZD had significant predictive values in discriminating prostate cancer, whereas PSA had no significant predictive value (Fig. 1B). Moreover, there were no significant differences in discriminating prostate cancer among PV, TZV, PSAD and PSATZD (Table 2).

The cutoff values of each parameter corresponding to

Table 2. Analyses of receiver operating characteristic curves of PV, TZV, PSAD, PSATZD and PSA

	All patients (n=210)				Patients with intermediate PSA levels (n=156)			
	AUC	SE	95% CI	*p*-value*	AUC	SE	95% CI	*p*-value*
PSA	0.596	0.048	0.502–0.689	0.037	0.474	0.059	0.360–0.589	0.658
PV	0.750	0.036	0.680–0.819	<0.001	0.740	0.047	0.649–0.831	<0.001
TZV	0.732	0.037	0.660–0.804	<0.001	0.730	0.048	0.638–0.826	<0.001
PSAD	0.772	0.036	0.701–0.843	<0.001	0.728	0.049	0.632–0.823	<0.001
PSATZD	0.776	0.035	0.708–0.845	<0.001	0.728	0.047	0.635–0.821	<0.001

* Null hypothesis : AUC=0.5

AUC : area under the curve ; SE : standard error ; CI : confidential interval.

Table 3. Cutoff values and diagnostic accuracy in all patients (n=210)

	Cutoff value	Sensitivity (%)	Specificity (%)	Efficacy (%)
PV (cm^3)	64.6	100.0	16.6	37.6
	40.0	94.3	38.9	52.9
	37.0	90.6	43.3	55.2
TZV (cm^3)	28.3	100.0	23.6	42.9
	22.0	94.3	37.6	51.9
	20.0	90.6	40.8	53.3
PSAD	0.090	100.0	7.6	31.0
	0.160	94.3	30.6	46.7
	0.191	90.6	40.8	56.7
PSATZD	0.141	100.0	3.4	27.6
	0.355	94.3	42.0	55.2
	0.381	90.6	47.1	58.1

Table 4. Cutoff values and diagnostic accuracy in patients with intermediate PSA values (n=156)

	Cutoff value	Sensitivity (%)	Specificity (%)	Efficacy (%)
PV (cm^3)	50.4	100.0	23.1	38.2
	40.0	93.5	35.7	47.1
	39.9	90.3	35.7	46.5
TZV (cm^3)	28.3	100.0	21.4	36.9
	22.0	93.5	34.1	45.9
	20.7	90.3	35.7	46.5
PSAD	0.090	100.0	9.5	27.4
	0.147	93.5	31.0	43.3
	0.160	90.3	36.5	47.1
PSATZD	0.141	100.0	4.8	23.6
	0.326	93.5	38.9	49.7
	0.355	90.3	45.2	54.1

the sensitivity of 100, 94.3 and 90.6% in all patients and those of 100, 93.5 and 90.3% in the patients with intermediate PSA levels are summarized in Tables 3 and 4, respectively. On using the cutoff values of PV, TZV, PSAD and PSATZD at 100% sensitivity, the numbers of unnecessary biopsies were 28, 37, 12 and 5, respectively, in all patients. On using the cutoff values at 90.6% sensitivity of PV, TZV, PSAD and PSATZD, 68, 64, 71 and 74 unnecessary biopsies could be avoided, respectively, while 5 prostate cancers were missed (Table 3). On the other hand, on using the cutoff values of PV, TZV, PSAD and PSATZD at 100% sensitivity, the numbers of unnecessary biopsies were 29, 27, 12 and 6, respectively, in the patients with intermediate PSA levels. On using the cutoff value of PV, TZV, PSAD and PSATZD at 90.3% sensitivity, 45, 45, 46 and 57 unnecessary biopsies could be avoided, respectively, while 3 prostate cancers were missed (Table 4).

Bivariate and multivariate analysis on predictive values using age, volume parameters and volume-adjusted PSA parameters

Table 5. Simple logistic regression analyses

Variables	(Cutoff)	All patients (n=210)			(Cutoff)	Patients with intermediate PSA levels (n=156)		
		Odds ratio	95% CI	*p*-value		Odds ratio	95% CI	*p*-value
Age		1.04	0.994–1.10	0.086		1.03	0.97–1.09	0.351
PSA		1.04	1.01 –1.08	0.025		0.96	0.76–1.21	0.702
PV	(37.0)	7.33	2.77 –19.4	<0.001	(39.9)	5.19	1.49–18.0	0.010
TZV	(20.0)	6.61	2.49 –17.5	<0.001	(20.7)	5.19	1.49–18.0	0.010
PSAD	(0.191)	7.92	2.99 –21.0	<0.001	(0.160)	5.37	1.55–18.6	0.008
PSATZD	(0.381)	8.56	3.22 –22.6	<0.001	(0.355)	7.71	2.23–26.7	0.001

CI : confidential interval ; parenthesis : cutoff value at 90.6% of sensitivity in patients and at 90.3% in patients with intermediate PSA value.

Table 6. Stepwise logistic regression analyses

Variables	(Cutoff)	All patients (n=210)			(Cutoff)	Patients with intermediate PSA levels (n=156)		
		Odds ratio	95% CI	*p*-value		Odds ratio	95% CI	*p*-value
PSA		1.04	0.992–1.06	0.139		NA		
PV	(37.0)	3.36	1.07 –10.6	0.039		NA		
PSATZD	(0.381)	3.93	1.25 –12.3	0.019	(0.355)	7.71	2.23–26.7	0.001

CI : confidential interval ; parentheses : cutoff value at 90.6% of sensitivity in patients and at 90.3% in patients with intermediate PSA value, NA : not available in the logistic model.

Table 5 shows the results of simple logistic regression analyses. In all patients, PSA, PV, TZV, PSAD and PSATZD, but not age showed significant predictive values. In the patients with intermediate PSA levels, PV, TZV, PSAD and PSATZD, but not age and PSA, had significant predictive values.

The stepwise logistic regression analysis using age and all parameters that showed significant predictive values in the simple logistic regression analysis in all patients revealed that PV and PSATZD were significant independent predictive variables (Table 6). In the patients with intermediate PSA levels, the stepwise logistic regression analysis showed that PSATZD was the only significant independent predictive variable while the other variables showed no significances (Table 6).

DISCUSSION

In this study, we focused on the patients who had an abnormal PSA level, but no abnormal findings in DRE or TRUS. Many previous reports likewise focused on similar groups of patients. Presti et al.[9] reported that PSAD had no predictive value to discriminate prostate cancer in 81 patients with intermediate PSA levels but no abnormal findings of DRE or TRUS. Brawer et al.[5] and Cookson et al.[8] also reported a similar result, but the numbers of their patients were small (41 and 44 patients, respectively) and they did not mention the TRUS findings. On the other hand, Rommel et al.[6] and Arai et al.[10] concluded that PSAD had predictive value superior to PSA and Egawa et al.[13] reported that PSAD and PSATZD had similar predictive values in discriminating prostate cancer, but they did not mention the TRUS findings. Bazinet et al.[7] reported that PSAD was useful in discriminating prostate cancer from BPH in the patients without any abnormal findings in DRE or TRUS and whose PSA levels were above 4.0 ng/ml or in intermediate PSA levels. On the other hand, Matsuyama et al.[16] reported that the percent free PSA was a significant useful predictor in the Japanese patients with intermediate PSA levels and normal DRE findings among PSAD, PSATZD, PV and percent free PSA in discriminating prostate cancer from BPH. Djavan et al.[12] also reported that the free PSA was more effective in prostates less than 30 cc in volume. Accordingly, the usefulness of volume-adjusted parameters including PSAD and PSATZD, or the serum PSA fractions such as free PSA has been controversial.

Our results of the ROC curve analyses demonstrated that PSA, PV, TZV, PSAD and PSATZD had significant predictive powers in discriminating prostate cancer in the patients without abnormal findings of DRE or TRUS. Interestingly, the AUCs of PV, PSAD and PSATZD were significantly larger than that of PSA. Nonetheless, there was no significant difference in AUC between TZV and PSA, possibly because this group included patients with relatively high PSA levels. Although PSA had no significant predictive value to discriminate prostate cancer in our patients, PV, TZV, PSAD and PSATZD still had predictive values. Among these four parameters, there were no significant differences in the AUC analysis. In other words, these four parameters had similar predictive values in prostate cancer detection and this implies that not only PSAD and PSATZD but also PV and TZV can be helpful in order to avoid unnecessary biopsy of the prostate.

On the other hand, the stepwise logistic regression analysis provided some additional suggestion that PV and PSATZD conclusively remained as predictive parameters in the patients without abnormal findings in DRE or TRUS and that PSATZD had the most significant predictive value. In the patients with intermediate PSA levels, PSATZD only remained as a significant predictive parameter. These findings lead to the possibility that PSATZD may be the strongest predictive parameter among PSA, PV, TZV, PSAD and PSATZD in discriminating prostate cancer. However, we have to keep in mind that the AUCs of PV, TZV, PSAD and PSATZD were similar and showed no statistically significant differences among them.

There may be several criticisms against this study. First, this study was a retrospective study. Second, we altered the method of biopsy from sextant to octant. Third, we demonstrated that a large prostate had a low incidence of prostate cancer. Now, our question is whether the number of biopsy cores was enough for a large prostate. A volume-adjusted number of biopsy cores would be necessary. In order to resolve these problems we have started a novel prospective study.

CONCLUSION

PSAD and PSATZD were significant volume-

adjusted parameters in discriminating T1c prostate cancer, while PV and TZV were also simple and significant predictive parameters as well as PSAD and PSATZD. We concluded that PSATZD may be the most powerful predictive parameter in discriminating T1c prostate cancer, especially in the patients with intermediate PSA levels.

REFERENCES

1) Sobin LH and Wittekind C : International Union Against Cancer (UICC) : TNM Classification of Malignant Tumors (5th ed.). Wiley-Liss, 170–173, New York, 1997
2) Benson MC, Whang IS, Pantuck A, et al. : Prostate specific antigen density : a means of distinguishing benign prostatic hypertrophy and prostate cancer. J Urol **147** : 815–816, 1992
3) Benson MC, Whang IS, Olsson CA, et al. : The use of prostate specific antigen density to enhance the predictive value of intermediate level of serum prostate specific antigen. J Urol **147** : 817–821, 1992
4) Kalish J, Cooner WH and Graham SD Jr : Serum PSA adjusted for volume of transition zone (PSAT) is more accurate than PSA adjusted for total gland volume (PSAD) in detecting adenocarcinoma of the prostate. Urology **43** : 601–606, 1994
5) Brawer MK, Aramburu EAG, Chen GL, et al. : The inability of prostate specific antigen index to enhance the predictive value of prostate specific antigen in the diagnosis of prostatic carcinoma. J Urol **150** : 369–373, 1993
6) Rommel FM, Agusta VE, Breslin JA, et al. : The use of prostate specific antigen and prostate specific antigen density in the diagnosis of prostate cancer in a community based urology practice. J Urol **151** : 88–93, 1994
7) Bazinet M, Péloquin F, Meshref AW, et al. : Prospective evaluation of prostate-specific antigen density and systematic biopsies for early detection of prostate carcinoma. Urology **43** : 44–52, 1994
8) Cookson MS, Floyd MK, Ball TP, et al. : The lack of predictive value of prostate specific antigen density in the detection of prostate cancer in patients with normal rectal examinations and intermediate prostate specific antigen levels. J Urol **154** : 1070–1073, 1995
9) Presti JC Jr, Hovey R, Carroll PR, et al. : Prospective evaluation of prostate specific antigen and prostate specific antigen density in the detection of nonpalpable and stage T1c carcinoma of the prostate. J Urol **156** : 1685–1690, 1996
10) Arai Y, Maeda H, Ishitoya S, et al. : Prospective evaluation of prostate specific antigen density and systematic biopsy for detecting prostate cancer in Japanese patients with normal rectal examinations and intermediate prostate specific antigen levels. J Urol **158** : 861–864, 1997
11) Maeda H, Arai Y, Ishitoya S, et al. : Prostate specific antigen adjusted for the transition zone volume as an indicator of prostate cancer. J Urol **158** : 2193–2196, 1997
12) Djavan B, Zlotta AR, Byttebier G, et al. : Prostate specific antigen density of the transition zone for early detection of prostate cancer. J Urol **160** : 411–419, 1998
13) Egawa S, Suyama K, Takashima R, et al. : Prospective evaluation of prostate cancer detection by prostate-specific antigen-related parameters. Int J Urol **6** : 493–501, 1999
14) Maeda H, Arai Y, Aoki Y, et al. : Complexed prostate-specific antigen and its volume indexes in the detection of prostate cancer. Urology **54** : 225–228, 1999
15) Kikuchi E, Nakashima J, Ishibashi M, et al. : Prostate specific antigen adjusted for transition zone volume. Cancer **89** : 842–849, 2000
16) Matsuyama H, Baba Y, Yamanaka G, et al. : Diagnostic value of prostate-specific antigen-related parameters in discriminating prostate cancer. Int J Urol **7** : 409–414, 2000
17) Hanley JA and McNeil BJ : The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology **143** : 29–36, 1982
18) Hanley JA and McNeil BJ : A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology **148** : 839–843, 1983

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和文抄録

T1c 前立腺癌診断における予測因子としての前立腺体積および volume-adjusted prostate-specific antigen の検討

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T1c 立腺癌の診断における PSA density（PSAD）および PSA transition zone density（PSATZD）の有用性について，生検前に PSA のみに異常を認めた210例について検討した．210例中53例（25.2%），生検前 PSA 値がグレーゾーン（4.1～10.0 ng/ml）を示した156例中31例（19.9%）が癌と診断された．ROC 曲線解析では，全体210例では，PSA，PSAD，PSATZD，前立腺体積（PV）および移行域体積（TZV）が癌診断の有効なパラメータであった．グレーゾーンを示した156例では，PSAD，PSATZD，PV および TZV が癌診断の有効なパラメータであった．多変量解析では PSATZD が最も有効なパラメータであった．T1c 前立腺癌を疑う症例において，PSATZD が最も有用性が高いことが示された．

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