

Can Complexed Prostate Specific Antigen Enhance Prostate Cancer Detection in Japanese Men?

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Abstract

Backgrounds: The aim of this study is to ascertain whether Bayer complexed PSA (cPSA) and volume referenced cPSA could enhance the detection of prostate cancer in Japanese men.

Methods: A total of 214 Japanese men whose serum total PSA (tPSA) values ranged from 1.2 ng/ml to 4600 ng/ml were enrolled from two institutions. Serum samples for tPSA, free PSA, PSA- α -1-antichymotripsin (PSA-ACT) and cPSA (ADVIA-Centaur) were obtained in all cases. In addition, total gland (TGV) as well as transition zone volume (TZV) were determined in all cases who underwent ultrasound guided prostate biopsy (sextant and two additional transition zone biopsies). Biopsy outcome was correlated to the following parameters: tPSA, cPSA, PSA-ACT, free to total (F/T) PSA ratio, 2 complex to total (C/T) PSA ratios and 6 volume referenced parameters.

Results: Prostate cancer was detected in 85 of 214 patients (40%). The area under the receiver operating characteristic curve in non-volume referenced variables was highest for cPSA (0.736), followed by PSA-ACT (0.735), tPSA (0.722), F/T PSA ratio (0.613) and C/T PSA ratio (0.591). Comparing tPSA with the cutoff value of 4.0 ng/ml, the cutoff value with a 2.8 ng/ml of cPSA detected one more positive biopsy patient, decreasing one more cancer missed case and 8 more false positive cases. At sensitivities of 85% to 95% in men with tPSA between 4.00 and 10.00 ng/ml ($n = 116$), there were no significant differences in the corresponding specificities between tPSA and cPSA, or between cPSA and PSA-ACT. At sensitivities of 90% to 95%, the corresponding specificities of PSA-ACT adjusted for transition zone volume revealed best performance. As for the performance in men with a tPSA less than 4.0 ng/ml, the specificities of cPSA performed best, and differed significantly from PSA-ACT and F/T PSA at sensitivities of 80% to 90%.

Conclusion: Bayer cPSA could replace the first screening test by total PSA and can enhance cancer detection, compared with PSA-ACT. However, cPSA did not provide additional value in differentiating cancer from non-cancer cases in men with a tPSA between 4.00 and 10.00 ng/ml.

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1. Introduction

In 1998, a novel assay for Bayer complexed PSA, which avoided the use of antibodies to ACT [1], was

developed. Since the first reports, several retrospective and prospective studies focusing on the clinical usefulness of Bayer complexed PSA with European and American populations have been reported, and the majority of these articles concluded that Bayer complexed PSA could enhance prostate cancer detection in men with a serum total PSA range between 4 and

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10 ng/ml [2,3] and with less or equal to 4.0 ng/ml [4–6]. This novel complexed PSA assay is stable by prostatic manipulation and not temperature sensitive compared with total PSA [7,8]. Furthermore, using this new assay, several investigators have demonstrated that Bayer complexed PSA could be applied as a staging predictor in men undergoing radical prostatectomy [9,10]. However, its usefulness with regard to the Japanese population remains undetermined because of the lack of retro and prospective studies.

We conducted the first study for the new developed Bayer complexed PSA (the Bayer ADVIA-Centaur complexed PSA) in Japanese men. The aim of this study is to ascertain whether new complexed PSA can be used as a tool to detect prostate cancer in the Japanese population. In addition, we compared the diagnostic performance of total PSA, complexed PSA, free PSA, their respective ratios (C/T PSA and F/T PSA) and their volume referenced indexes to clarify the optimum total PSA range for each test.

2. Materials and methods

Between January 1999 and December 2002, Japanese serum samples archived on an outpatient referral basis were obtained before prostatic manipulation and tested retrospectively at 2 sites, the Kyoto Prefectural University of Medicine (Kyoto), Kyoto, Japan and the Matsushita Memorial Hospital (Matsushita), Osaka, Japan. Participants with a personal history of prostate cancer or symptoms of acute prostatitis and/or urinary tract infection were excluded from this study. A total of 214 men (Kyoto: 140, Matsushita: 74) underwent transperineal ultrasound guided prostate needle biopsy (sextant biopsy from peripheral zone and 2 additional transition zone biopsies). Men with serum PSA value greater or equal to 4.00 ng/ml were indicated prostate biopsy without exception regardless of DRE findings. In addition, in men with serum PSA less than 4.00 ng/ml, prostate biopsy was indicated if DRE was abnormal.

The ages of these 214 men ranged from 52 to 85 years (median 66). A blood sample was drawn to measure total PSA (the Hybritech Tandem-R), free PSA (the Hybritech Tandem-R assays), PSA- α -1-antichymotrypsin (PSA-ACT, Markit ACT PSA assay, Dainippon Pharmaceuticals, Tokyo, Japan) and complexed PSA (cPSA, The Bayer ADVIA-Centaur complexed PSA).

The Bayer ADVIA-Centaur cPSA assay is a simultaneous sandwich immunoassay that uses magnetic particles as the solid phase. Basically, Centaur cPSA assay uses the same measuring method theory with Immuno1 cPSA assay. In Immuno1 assay, however, free PSA is prevented from reacting with the total PSA antibodies by incubating the sample with a free PSA-specific monoclonal mouse antibody (ME2), and cPSA antibody conjugate was labeled by alkaliphosphatase (ALP). In contrast, light reagent with polyclonal goat anti-PSA antibody with acridinium eater is applied in Centaur assay [11]. Those differences between Immuno1 and Centaur assay lead to continuous operation and cost-effective workstation consolidation in Centaur cPSA assay. Although the minimum detection sensitivity of Immuno1 cPSA is 0.2 ng/ml, Centaur cPSA can be measured to 0.03 ng/ml. Moreover, sample throughput in Centaur cPSA and Immuno1 can perform 240 tests/

hour and 100 tests/hour, respectively. As for the comparison of time of the first result, Centaur cPSA can save 29 minutes (Centaur: 17 minutes and Immuno1: 46 minutes).

All serum samples were drawn before digital rectal examination (DRE). In this study, blood samples were centrifuged and the serum was immediately decanted and stored as -70°C until analysis. The minimum specimen volume was 0.7 ml. To determine free to total PSA (F/T PSA), the Hybritech free and total PSA assays were used. The Bayer complexed to total PSA ratio (C/T PSA) and PSA-ACT to total PSA ratio (ACT/T PSA) were determined using the combination Bayer complexed PSA with total PSA and the combination PSA-ACT with total PSA.

In each outpatient clinic, all the cases consented to transrectal ultrasound examination including prostate volume study under the insurance coverage to assess the suspicious lesions inside the prostate before biopsy. Total prostate volume as well as transition zone volume were routinely measured by the three dimensional method using transrectal ultrasound in all 214 cases. In the results, a total of 12 variables using serum assays were used in this study, including total, PSA-ACT, cPSA, F/T PSA, C/T PSA, ACT/T PSA, PSA density (PSAD), PSA-ACT density (PSA-ACTD), cPSA density (cPSAD), PSA density adjusted for transition zone volume (PSAD-TZ), PSA-ACT density adjusted for transition zone volume (PSA-ACTD-TZ) and cPSA adjusted for transition zone volume (cPSAD-TZ). In addition, volume variables (total and transition zone volume: TGV and TZV, respectively) were compared with the 12 assay parameters in terms of diagnostic ability.

The χ^2 -test was used for each statistical comparison between two specificities at the same sensitivity. For continuous variables, a *t*-test or analysis of variance was used to compare groups. Receiver operating characteristic (ROC) curves were generated by plotting the sensitivity versus (1-specificity). The area under the curve (AUC) was likewise calculated for the 12 assays and 2 volume variables. All statistical calculations were performed with the SAS (SAS Institute Cary, NC, USA) or SPSS 10.0 (SPSS Inc, Chicago, IL, USA) software package; $p < 0.05$ was taken as the level of statistical significance.

3. Results

Of the 214 men with complete sample collection, 85 had positive biopsy results for prostate cancer (Kyoto: 60, Matsushita: 25), while 129 men had no evidence of malignancy on biopsy including histologic confirmation of prostatitis ($n = 8$) and prostatic intra-epithelial neoplasia (PIN, $n = 3$). Comparing the patient populations from each institution, there was no significant difference in mean ages (Kyoto: 68.6 ± 8.3 , Matsushita: 66.2 ± 9.4) as well as no significant difference in cancer proportion (Kyoto: 43%, Matsushita: 34%).

The correlation of the total PSA with cPSA plus free PSA was excellent, within the assay range ($n = 214$, $r = 0.96$, and $y = 0.96x - 0.84$, $y = \text{cPSA} + \text{free PSA}$, $x = \text{total PSA}$). In addition, the correlation of the cPSA with PSA-ACT was also excellent, within the assay range ($n = 214$, $r = 0.987$, and $y = 1.36x - 0.84$, $y = \text{cPSA}$, $x = \text{PSA-ACT}$). Table 1 shows the distribution of cancer and patients with no evidence of malignancy

Table 1

Distributions in 214 men with and without prostate cancer detected by biopsy

	No. with Ca	No. without Ca	Total no.
Hybritech total PSA (ng/ml)			
0.00–3.99	9	36	45
4.00–10.00	40	76	116
Greater than 10.01	36	17	43
Total	85	129	214
PSA-ACT (ng/ml)			
0.00–3.99	25	77	102
4.00–10.00	30	47	77
Greater than 10.01	30	5	35
Total	85	129	214
Bayer complexed PSA (ng/ml)			
0.00–3.99	27	81	108
4.00–10.00	27	42	69
Greater than 10.01	31	6	37
Total	85	129	214

stratified by total PSA, PSA-ACT and cPSA. Hybritech total PSA (tPSA) ranged from 1.2 to 4600 ng/ml (median 8.6 ng/ml). In 45 patients with a tPSA less than 4.00 ng/ml, prostate biopsies were performed based on abnormal results for the patients' DRE. There was no significant difference for patient age between men with and without prostate cancer (Table 2). Comparing the *p* values of the other 14 variables, transition zone volume differed the most significantly ($p < 0.0001$) between men with cancer and those without, followed by PSA-ACT ($p = 0.0007$), tPSA ($p = 0.0015$) and cPSA ($p = 0.0017$).

We compared the numbers of patients with a cancer missed or a false positive result based on tPSA, PSA-ACT and cPSA (Table 3). The numbers of cancers missed and false-positive results using a tPSA cutoff value of 4.0 ng/ml were 9 and 93, respectively. The number of cancer patients using a tPSA cutoff value of 4.0 ng/ml was 76, while that with the optimal cutoff

Table 2

Age and various variables results for men without and with prostate cancer

	Median (interquartile range)		<i>p</i> value
	Without Ca	With Ca	
Age	68 (62)	70 (65)	0.1324
Hybritech total PSA	5.10 (3.70)	8.30 (5.10)	0.0015
PSA-ACT	3.50 (2.40)	6.00 (3.80)	0.0007
Bayer complexed PSA	3.42 (2.32)	5.97 (3.49)	0.0017
Free-to-total PSA	17.07 (10.52)	13.04 (8.64)	0.0039
ACT-to-total PSA	65.96 (58.33)	70.59 (64.04)	0.0143
Complexed-to-total PSA	63.33 (52.38)	66.70 (57.03)	0.0133
Total PSA density	0.1711 (0.1209)	0.377 (0.2385)	0.0085
PSA ACT density	0.1114 (0.0727)	0.290 (0.1576)	0.0038
Complexed PSA density	0.1058 (0.0669)	0.3062 (0.1515)	0.0090
Total PSA density/transition zone	0.3306 (0.2142)	1.2346 (0.5338)	0.0149
PSA ACT density/transition zone	0.2090 (0.1361)	0.8590 (0.3525)	0.0074
Complexed PSA density/transition zone	0.1909 (0.1229)	0.7346 (0.3293)	0.0162
Prostate volume	32.50 (23.33)	27.50 (18.90)	0.0059
Transition zone volume	16.25 (10.28)	12.20 (7.20)	<0.0001

Table 3

Comparison between total PSA, complexed PSA and PSA-ACT at various cutoff values

	Hybritech Total PSA	PSA-ACT			Bayer Complexed PSA		
	≥4.0	≥2.8	≥2.5	≥2.7	≥2.8	≥2.9	≥3.0
No. with Ca	76	77	78	77	77	74	73
No. with Ca missed	9	8	7	8	8	11	12
No. false positive	93	91	89	87	85	81	78
No. vs. Hybritech total PSA with a 4.0 ng/ml							
Ca missed		–1	–2	–1	–1	+2	+3
False positive		–2	–4	–6	–8	–12	–15
No. vs. PSA-ACT at the same cutoff values							
Ca missed			+3	+2	±0	±0	–1
False positive			–2	+5	+6	+11	+14

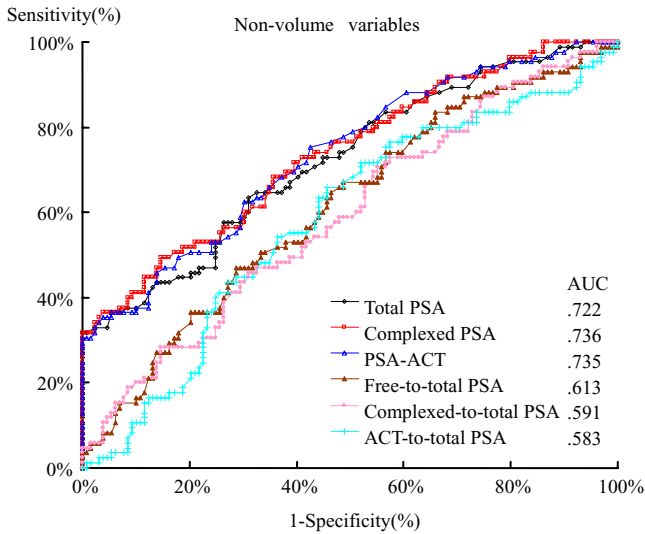


Fig. 1. Comparison of ROC curves without volume referenced variables in 214 samples. The AUC for cPSA (0.736) was greatest, followed by PSA-ACT (0.735), tPSA (0.722), F/T PSA (0.613), C/T PSA (0.591) and ACT/T PSA (0.583). The AUC value for cPSA differed significantly from the values for F/T PSA ($p < 0.005$), C/T PSA ($p < 0.001$) and ACT/T PSA ($p < 0.001$). However, that for cPSA did not differ significantly from PSA-ACT and tPSA.

values (2.8 ng/ml) of cPSA was equivalent to that of PSA-ACT in this study ($n = 77$). At the same 4.0 ng/ml for tPSA and 2.8 ng/ml for cPSA and PSA-ACT, cPSA and PSA-ACT missed one less cancer. In addition, a 2.8 ng/ml threshold for cPSA detected 6 fewer false positive cases compared with the same threshold for PSA-ACT.

Figs. 1 and 2 show the receiver operating characteristics (ROC) curves and areas under curves (AUC) with non-volume and volume variables in all 214 cases, respectively. ROC analysis with non-volume variables revealed that the AUC for cPSA (0.736) was greatest, followed by PSA-ACT (0.735), tPSA (0.722), F/T PSA (0.613), C/T PSA (0.591), and ACT/T PSA (0.583). The AUC value for cPSA differed significantly from the values for F/T PSA ($p < 0.005$), C/T PSA ($p < 0.001$) and ACT/T PSA ($p < 0.001$). However, that for cPSA did not differ significantly from PSA-

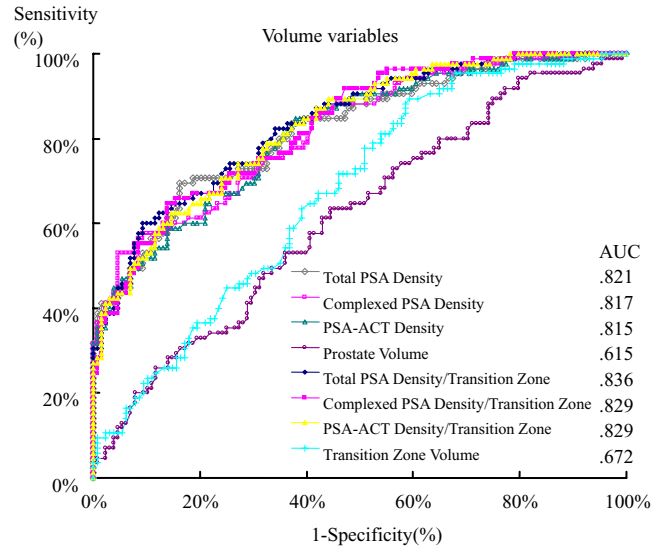


Fig. 2. Comparison of ROC curves with volume referenced variables in 214 samples. The AUC value for PSAD-TZ (0.836) was greatest, followed by cPSAD-TZ (0.829), PSA-ACTD-TZ (0.829), PSAD (0.821), cPSAD (0.817), PSA-ACTD (0.815), TZV (0.672) and TGV (0.615). Despite the significant differences between PSAD-TZ and TZV ($p < 0.001$) and PSAD-TZ and TGV ($p < 0.001$), the AUC value for PSAD-TZ did not differ significantly from the remaining volume variables (cPSAD-TZ, PSA-ACTD-TZ, PSAD, cPSAD, PSA-ACTD).

ACT and tPSA. Comparing the volume variables, the AUC value for PSAD-TZ (0.836) was greatest, followed by cPSAD-TZ (0.829), PSA-ACTD-TZ (0.829), PSAD (0.821), cPSAD (0.817), PSA-ACTD (0.815), TZV (0.672) and TGV (0.615). Despite the significant differences between PSAD-TZ and TZV ($p < 0.001$) and PSAD-TZ and TGV ($p < 0.001$), the AUC value for PSAD-TZ did not differ significantly from the remaining volume variables (cPSAD-TZ, PSA-ACTD-TZ, PSAD, cPSAD, PSA-ACTD). The performance characteristics with respect to sensitivity and specificity targeting to tPSA range from 4.00 to 10.00 ng/ml are summarized in Table 4 (non-volume variables) and Table 5 (volume variables). At sensitivities of 90 to 95%, there were significant differences in the corresponding specificities between cPSA and F/T

Table 4

Specificity of total PSA, PSA-ACT, complexed PSA, free-to-total PSA, ACT-to-total PSA, complexed-to-total PSA at 85%, 90%, and 95% sensitivity targeting to total PSA range from 4.00 to 10.00 ng/ml ($n = 116$)

Parameter	85% sensitivity		90% sensitivity		95% sensitivity	
	Cutoff	Specificity (%)	Cutoff	Specificity (%)	Cutoff	Specificity (%)
Total PSA	4.55	26.3	4.35	17.0	4.25	13.2
PSA ACT	3.15	27.6	3.05	22.4	2.85	13.2
Complexed PSA	3.00	22.1	2.89	21.3	2.80	14.5
Free-to-total PSA	23.6	23.7	28.3	13.2	35.3	6.6
ACT-to-total PSA	58.0	25.0	54.4	14.5	49.4	5.3
Complexed-to-total PSA	52.6	19.7	49.2	11.8	39.7	5.3

Table 5

Specificity of total PSA density, PSA-ACT density, complexed PSA density, total PSA density/transition zone, PSA ACT density/transition zone, complexed PSA density/transition zone, at 85%, 90%, and 95% sensitivity targeting to total PSA range from 4.00 to 10.00 ng/ml ($n = 116$)

Parameter	85% sensitivity		90% sensitivity		95% sensitivity	
	Cutoff	Specificity (%)	Cutoff	Specificity (%)	Cutoff	Specificity (%)
Total PSA density	0.174	44.7	0.148	27.6	0.137	21.1
PSA ACT density	0.126	48.7	0.102	34.2	0.092	26.3
Complexed PSA density	0.111	47.4	0.099	36.8	0.091	31.6
Total PSA density/transition zone	0.410	53.9	0.344	43.4	0.300	39.5
ACT PSA density/transition zone	0.253	51.3	0.233	48.7	0.195	40.8
Complexed PSA density/transition zone	0.236	52.6	0.218	47.4	0.181	38.2
Prostate volume	33.3	48.0	36.7	38.7	38.3	37.3
Transition zone volume	16.5	49.0	17.3	49.0	20.2	37.3

PSA ($p < 0.05$ and $p < 0.05$). At sensitivities of 85% to 95%, however, there were no significant differences in the corresponding specificities between tPSA and cPSA, or between cPSA and PSA-ACT. At sensitivities of 90% to 95%, the corresponding specificities of PSA-ACTD-TZ revealed best performance (48.7% and 40.8%, respectively). In addition, the specificity of TZV at a sensitivity of 90% (49.0%) was almost equivalent to that of PSA-ACTD-TZ (48.7%). At sensitivities of 90% to 95%, there were significant differences in the corresponding specificities, between PSAD and cPSAD-TZ ($p < 0.05$ and $p < 0.05$, respectively), and between PSAD and PSA-ACTD-TZ ($p < 0.05$ and $p < 0.01$). The performance characteristics with respect to sensitivity and specificity targeting to a tPSA range less than 4.00 ng/ml are summarized in Table 6 (non-volume variables) and Table 7 (volume variables). At sensitivities of 80% to 90%, the corresponding specificities of cPSA performed best (41.7% and 41.3%, respectively), and differed significantly from PSA-ACT ($p < 0.05$ and $p < 0.05$, respectively) and from F/T PSA ($p < 0.05$ and $p < 0.001$). As for the comparison with volume variables, the performances of TZV were almost identical to those of cPSAD-TZ at a sensitivity of 90% although the specificity of

Table 6

Specificity of total PSA, PSA-ACT, complexed PSA, free-to-total PSA, ACT-to-total PSA, complexed-to-total PSA at 80% and 90% sensitivity targeting to total PSA range less than 4.00 ng/ml ($n = 45$)

Parameter	80% sensitivity		90% sensitivity	
	Cutoff	Specificity (%)	Cutoff	Specificity (%)
Total PSA	2.85	38.9	2.45	22.2
PSA-ACT	1.45	27.8	1.45	27.8
Complexed PSA	1.53	41.7	1.53	41.3
Free-to-total PSA	26.0	33.3	36.5	6.0
ACT-to-total PSA	51.5	11.0	37.5	0.0
Complexed-to-total PSA	53.1	33.3	42.6	13.9

Table 7

Specificity of total PSA density, PSA-ACT density, complexed PSA density, total PSA density/transition zone, PSA-ACT density/transition zone, complexed PSA density/transition zone, at 80% and 90% sensitivity targeting to total PSA range less than 4.00 ng/ml ($n = 45$)

Parameter	80% sensitivity		90% sensitivity	
	Cutoff	Specificity (%)	Cutoff	Specificity (%)
Total PSA density	0.119	61.1	0.065	27.8
PSA-ACT density	0.064	52.8	0.034	16.7
Complexed PSA density	0.074	63.9	0.033	25.0
Total PSA density/transition zone	0.232	61.1	0.188	47.2
PSA-ACT density/transition zone	0.126	52.8	0.098	47.2
Complexed PSA density/transition zone	0.146	66.7	0.095	44.4
Prostate volume	26.1	63.9	44.4	16.7
Transition zone volume	15.2	52.8	15.3	52.8

cPSAD-TZ was significantly better than that of TZV at a sensitivity of 80% ($p < 0.05$).

4. Discussion

Similar to American and European trials, Japanese research also needs to assess the clinical usefulness of Bayer cPSA in terms of first screening and secondary test in detecting prostate cancer. As is well known, the majority of urologists apply a cutoff value of total PSA with 4.0 ng/ml in the first screening test. Consequently, it is important to analyse whether the optimal cutoff value of Bayer cPSA can increase the number of positive biopsies as well as decreasing the number of cancers missed and the false positive rate, comparing those numbers with the application of a 4.0 ng/ml threshold of total PSA. In this study, the cutoff value of 2.8 ng/ml of cPSA could detect one more positive biopsy patient, decreasing one more cancer missed case and 8 more false positive cases. Furthermore, a

2.8 ng/ml threshold for cPSA detected 6 fewer false positive cases compared with the same threshold for PSA-ACT. This result suggests that Bayer cPSA can replace the first screening test by total PSA and can enhance cancer detection, compared with PSA-ACT. In American studies, the optimal cutoff value for Bayer cPSA (Immuno1) ranged from 3.45 to 3.75 ng/ml [1,12]. An explanation of why the optimal cutoff value for Bayer cPSA between those and this study resulted in some difference is necessary. One possible explanation includes the difference in number of samples and in assay (Immuno1 or Centaur). Currently, only Centaur cPSA can be commercially available in our country. Thus, we need to determine our own cutoff value using Centaur cPSA. To determine optimal cutoff value in Japanese men, further study with a larger number of patients will be necessary. In addition, the result that the correlation of cPSA with PSA-ACT revealed a positive slope ($y = 1.36x - 0.84$) supports the evidence that this novel Bayer cPSA can also detect minor complexed PSA forms such as PSA protease inhibitor (PSA-API), similar to the conventional Bayer cPSA (Immuno1). The comparison of AUC in this study revealed that the value of cPSA (0.736) was almost equivalent to those of PSA-ACT (0.735) and tPSA (0.722). We believe the comparison of AUC as well as of actual number of positive biopsies, cancers missed, and false positive cases is indispensable to determine feasibility of the first screening test.

More importantly, the novel assay also needs to assess whether this is a promising marker to differentiate cancer from non-cancer efficiently in men with total PSA range between 4.00 and 10.00 ng/ml as the secondary test. Comparing the non-volume variables at 80 to 95% sensitivity in this study, the specificity of cPSA was almost equivalent to those of tPSA and PSA-ACT, although cPSA was significantly better than F/T PSA in the total PSA ranges between 4.01 and 10.00 ng/ml. Recently, Djavan et al. [2] conducted a multicenter trial to assess diagnostic performance of Bayer cPSA in European men with a tPSA between 4 and 10 ng/ml. In their study, at 90% sensitivity, specificity of cPSA (20.3%) had a 6% advantage compared with that of tPSA (14.3%) with a 6.6% disadvantage compared with F/T PSA. They concluded that cPSA performs better than tPSA in the differentiation between benign disease and prostate cancer. It is possible to compare the value of specificity between tPSA and cPSA at the same sensitivity with the limited tPSA range. However, comparison between tPSA and cPSA with a tPSA range between 4.0 and 10.0 ng/ml has little value in the clinical perspective because cPSA can not be a tool for obviating prostate biopsy. In terms

of secondary test, comparisons between cPSA and F/T PSA or between C/T PSA and F/T PSA are of great importance. Similar to the previous study [12], cPSA and C/T PSA had no demonstrative diagnostic advantage over F/T PSA to replace prostate biopsy policy in men with a tPSA between 4.00 and 10.00 ng/ml.

Current reports emphasized that volume referenced indexes using transition zone volume could enhance prostate cancer detection in men with a tPSA between 4.0 and 10.0 ng/ml compared with non-volume referenced indexes [2,13]. In the study of Djavan et al. [2], at 85% sensitivity, the specificity of cPSAD-TZ (32.3%) and PSAD-TZ (30.1%) had an approximately 5% advantage compared with those of cPSA (26.7%), C/T PSA (25.9%) and F/T PSA (26.9%). In 1999, Maeda et al. [13] also determined that the AUC of cPSAD-TZ (0.790) was greatest, followed by cPSAD (0.780), cPSA (0.710), F/T PSA (0.648) and tPSA (0.638) using an enzyme immunoassay for cPSA developed by Chugai Pharmaceuticals (Tokyo, Japan). Similar to our study, the materials in their study were also Japanese, and the authors concluded that cPSAD-TZ performed better than cPSA alone in detecting cancer. In this study, the specificities of PSAD-TZ, cPSAD-TZ and PSA-ACTD-TZ, at 85 to 95% sensitivity, were also better than those of non-volume and total gland volume referenced variables. Interestingly, however, the performance of transition zone volume only in this study was almost equivalent to that of the transition zone referenced serologic indexes. The high performance of transition zone volume alone was also supported by Stamey et al. [14]. They compared the AUCs using three total PSA assays, two F/T PSA assays, and the Bayer cPSA assay (Immuno1) in 170 men (Cancer: 80, BPH: 90). In addition to the serologic assays, similar to our study, they calculated the values of the AUC on total gland volume only and transition zone volume only. They found that the AUC of transition zone volume only (0.857) was highest, compared with total gland volume only (0.838), Bayer C/T PSA (0.827), and two F/T PSA assays (0.821 and 0.813). They concluded that the performance of PSA serum markers, including cPSA, has to be evaluated in terms of the range of the transition zone volume when investigators try to compare novel and conventional assays to each other. On the basis of their and our present results, we believe further multi-institutional prospective studies with respect to transition zone referenced indexes will be needed in the Japanese population.

Several reports focused on whether Bayer cPSA could enhance the detection of prostate cancer in men with a tPSA between 2.0 and 4.0 ng/ml [6] and between 2.5 and 4.0 ng/ml [4,5]. Summarizing from

their reports, around 90% sensitivity, specificities of cPSA related indexes were significantly better than those of F/T PSA. In the comparison between C/T PSA and F/T PSA, around 90% sensitivity, the specificities of C/T PSA provided from 8.5 to 10% improvement compared with F/T PSA [4–6]. Furthermore, at the same sensitivity, those of cPSAD-TZ provided from 2.6 to 49% improvement compared with F/T PSA [4,5]. Despite the small number of cases in this study, targeting men with a tPSA less than 4.00 ng/ml, the specificity of cPSA at 90% sensitivity was significantly better than the remaining non-volume referenced parameters, and was almost equivalent to transition zone referenced indexes. These results suggest that cPSA related index can differentiate cancer from non-cancer more effectively in men with a low tPSA level although the conclusion as to whether Bayer cPSA alone outperforms F/T PSA remains undetermined. However, the cancer detection rate in ethnic studies is of great importance. On the basis of current reports [4,15,16], in American, the cancer detection rate in men with a tPSA between 2.5 (or 2.6) and 4.0 ng/ml ranged from 22 to 27%. In contrast to substantial cancer detection rate in American men, there was scarce data with respect to those rates in Japanese men. Egawa et al. reported [17] that the positive biopsy rate in Japanese men with a tPSA 2.1 to 4.0 ng/ml has been low at between 6% and 9%. They demonstrated that none of the parameters examined by Japanese urologists performed substan-

tially better than tPSA in their consecutive cohort of Japanese men with a tPSA 2.1 to 4 ng/ml. To facilitate the application for cPSA in Japanese men with a low tPSA level, we need to assess whether the cancer detection rate is still low by multi-institutional trials.

5. Conclusion

In this study, the novel Bayer cPSA alone could enhance prostate cancer detection in Japanese men compared with tPSA and PSA-ACT. This study suggested that the diagnostic performance of Bayer cPSA did not provide additional value in men with a tPSA between 4.00 and 10.00 ng/ml. Bayer cPSA is promising in differentiating cancer from non-cancer in men with a tPSA less than 4.0 ng/ml. However, future epidemiological data with respect to prostate cancer detection rate, targeting a low tPSA range, will be indispensable in determining the application of cPSA in Japan.

Disclosure statement

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