

# PROSTATE SPECIFIC ANTIGEN DENSITY FOR DISCRIMINATING PROSTATE CANCER FROM BENIGN PROSTATIC HYPERPLASIA IN THE GRAY ZONE OF PROSTATE-SPECIFIC ANTIGEN

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Serum prostate specific antigen (PSA) is currently the best blood marker for prostate cancer. However, low specificity for detection of prostate cancer, especially in the gray zone of PSA, is a problem. We evaluated the clinical significance of PSA density (PSAD) in gray zone PSA cases with conversion of serum PSA to a Stanford reference value.

In a series of histologically confirmed 63 benign prostatic hyperplasia (BPH) patients and 234 prostate cancer patients, 36 BPH patients and 25 prostate cancer patients had gray zone PSA levels. Serum PSA was measured with the Markit-F or Markit-M PA assay. All data were converted to Stanford reference values. We used transabdominal ultrasound to determine prostate volume. PSAD was determined as the serum PSA/prostate volume ratio.

The mean PSA values for BPH and prostate cancer were  $6.42 \pm 1.80$  and  $7.80 \pm 2.15$  ng/ml ( $p = 0.0116$ ), respectively, and prostate volume was  $33.4 \pm 14.1$  ml and  $17.1 \pm 8.2$  ml, respectively ( $p < 0.0001$ ). The mean PSAD for prostate cancer was  $0.572 \pm 0.363$  while that for BPH was  $0.218 \pm 0.085$  ( $p = 0.0001$ ). Cut-off values with sensitivity  $> 90\%$  were 0.218 for PSAD and 30 ml for prostate volume. At these cut-off values, specificity reached 56% for each marker.

In discriminating prostate cancer from BPH in the gray zone of PSA, PSAD demonstrated better performance than PSA.

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**Key words:** Prostate cancer, PSA, PSAD, Cancer screening

## INTRODUCTION

Prostate specific antigen (PSA) is a reliable tumor marker in the diagnosis and management of patients with prostate cancer<sup>1,2)</sup>. Assay systems for detecting serum PSA have adequate sensitivity but have not demonstrated sufficient specificity to be used as a screening test in prostate cancer<sup>3)</sup>. As PSA is organ-specific but not cancer-specific, above-normal serum PSA levels occur in a high proportion of patients with benign prostatic hyperplasia (BPH). PSA is the least specific in Japanese cases when it ranges from 4.0 to 10.0 ng/ml, the so-called gray zone, in the Hybritech assay because a relatively high percentage of patients with BPH have those values<sup>4)</sup>. To enhance the specificity, particularly in the gray zone of PSA, we evaluated PSA density (PSAD) retrospectively. For analyzing data, we converted all serum PSA levels to Stanford reference values to standardize the various PSA assays<sup>4,5)</sup>. Moreover, cases with prostate cancer showing PSAD values less than the cut-off value were examined.

## PATIENTS AND METHODS

Histologically confirmed and untreated 63 BPH

patients and 234 prostate cancer patients visiting urological hospitals were enrolled for evaluation. Histological diagnosis was performed by random systematic needle biopsy or TUR-P. Serum PSA values were obtained before digital rectal examination using the Markit-F or Markit-M<sup>6)</sup> PA assay. All serum data were converted to Stanford reference values according to the literature<sup>4,5)</sup>. Thirty-six BPH patients and 25 prostate cancer patients had gray zone levels of serum PSA, ranging from 4.4 to 11.0 ng/ml (PSA of 4.0 to 10.0 ng/ml in the Hybritech Tandem-R PSA assay was converted to Stanford reference values). Median patient age was 71 years (range 58 to 95) in BPH, and 74 (range 56 to 85) in prostate cancer.

Transabdominal ultrasound was performed using the Aloka SSD-650CL-3.5 MHz, and the entire prostate volume was determined by the following formula: length  $\times$  height  $\times$  width  $\times 0.52$ <sup>7,8)</sup>. The PSAD values were determined as the serum PSA divided by prostate volume.

Student's *t* test was used to determine statistical significance, and *p* values  $< 0.05$  were regarded as significant.

Table 1. Comparison of serum PSA, prostate volume and PSAD in BPH and prostate cancer patients

Disease	No. of cases	Age (years)	PSA (ng/ml)	Prostate volume (ml)	PSAD
BPH	36	71±8	6.4±1.8	33.1±14.1	0.218±0.085
Prostate cancer	25	74±7	7.8±2.2	17.1± 8.2	0.576±0.363
<i>p</i> values		0.123	0.0116	<0.0001	0.0001

### RESULTS

The pathological grade of the 25 prostate cancer patients with gray zone PSA, was well differentiated in 7, moderately differentiated in 11 and poorly differentiated in 7 patients. Of these patients 72% had clinically localized disease, 5 had stage A, 13 had stage B, 3 had stage C, and 4 had stage D disease.

Serum PSA values converted to Stanford reference values, prostate volume, and PSAD were compared in the overall BPH and prostate cancer groups (Table 1). The mean PSA values for BPH and prostate cancer were 6.4±1.8 (range; 4.56 to 10.8) and 7.8±2.2 (range; 4.56 to 12.74) ng/ml, respectively, the difference being significant ( $p=0.0116$ ). Patients with BPH and prostate cancer had a mean prostate volume of 33.4±14.1 (range; 13.2 to 78.9), and 17.1±8.2 ml (range; 5.5 to 42.1), respectively, the difference also being significant ( $p<0.0001$ ). The mean PSAD

for prostate cancer was 0.576±0.363 (range; 0.14 to 1.74) while that for BPH was 0.218±0.085 (range; 0.09 to 0.45) ( $p=0.0001$ )

Using various cut-off values of PSAD, we examined the clinical utility. At a PSAD of 0.218 (mean in BPH cases), 92% sensitivity, 56% specificity, and 71% efficacy were obtained (Table 2). In the same manner, we evaluated the significance of prostate volume. There were no cancer cases with a prostate volume of more than 50 ml in our series; sensitivity was 100% at this level. When a prostate volume of 30 ml was used as a cut-off value, the clinical utility was similar to that of PSAD (Table 3). However, the specificity for maintaining sensitivity of about 90% was only 17% with the use of a cut-off value of PSA of 4.8. The 6 prostate cancer patients with the lowest values of PSAD are presented in Table 4. Two of the 25 patients with prostate cancer showed a PSAD of <0.218 and prostate volume of >30 ml (cases 1 and 2). One patient was diagnosed as T2 by digital rectal examination, the other was identified by core needle biopsy because of elevated serum PSA (6.27 ng/ml, T1c).

Table 2. Clinical utility of PSAD according to various cut-off values

Cut-off values (level in BPH cases)	Utility (%)		
	Sensitivity	Specificity	Efficacy
0.218 (mean)	92	56	71
0.303 (mean+S.D.)	84	86	85
0.388 (mean+2S.D.)	76	92	85
0.473 (mean+3S.D.)	56	100	82

Table 3. Clinical utility of prostate volume according to various cut-off values

Cut-off values (ml)	Utility (%)		
	Sensitivity	Specificity	Efficacy
20	72	83	79
25	88	67	75
30	92	56	71
40	96	36	61
50	100	11	48

Table 4. Prostate cancer cases showing low values of PSAD

No.	PSAD	Age (years)	Clinical stage	Pathological grade	PSA (ng/ml)	Prostate volume (ml)
1	0.14	80	B2	POR	5.70	42.1
2	0.19	79	B0	MOD	6.27	33.7
3	0.22	56	B1	WEL	4.75	21.6
4	0.30	75	A1	WEL	5.89	20.0
5	0.32	70	B1	WEL	6.76	20.9
6	0.34	80	D2	WEL	4.76	14.2

### DISCUSSION

PSA was identified and purified by Wang et al.<sup>9)</sup> in 1979. Kuriyama et al.<sup>10)</sup> developed a highly sensitive enzyme immunoassay. PSA is a 34,000 dalton glycoprotein with kinin-kallikrein-like serine protease activity produced by prostatic ductal epithelial cells. PSA has become the most useful tumor marker in the management of prostate cancer, but the lack of specificity for screening of prostate cancer is a problem<sup>1)</sup> Diagnosis of prostate cancer is uncommon at a PSA of below 4 ng/ml, and common at that above 10 ng/ml. In the gray zone of PSA between 4.0 and 10.0 ng/ml, the diagnosis of prostate cancer is difficult<sup>11)</sup>. Many tools have been proposed to increase the specificity while maintaining

sensitivity in the gray zone of PSA.

Serum PSA is thought to be dependent on the volume of the prostate and the number of epithelial cells within the prostate<sup>12)</sup> From this finding, Benson et al.<sup>13)</sup> introduced the concept of PSAD defined as serum PSA divided by the volume of the prostate, and many studies have been reported<sup>14-16)</sup>. We previously reported the clinical significance of PSAD in distinguishing between BPH and early stages of prostate cancer<sup>15)</sup>, when overlapping serum levels of PSA between BPH and early stages of prostate cancer is a problem. Moreover, Benson et al.<sup>17)</sup> reported that PSAD offers significant advantages over PSA alone in the evaluation of patients with BPH and prostate cancer in the gray zone of PSA. In their report, the stage of prostate cancer was not mentioned, and they did not discuss prostate cancer cases with values lower than the cut-off values. We have compared the stages and grades of prostate cancer patients and discussed cases showing PSAD values lower than the cut-off values. Fortunately, these cases were diagnosed based upon abnormal digital rectal examination and high PSA value. Although a conclusion can not be drawn because of the small number of cases examined, the cases with prostate cancer showing low PSAD may be diagnosed by other diagnostic procedures.

The proportion of free PSA to total PSA in the serum is higher in BPH than in prostate cancer<sup>18)</sup> Luderer et al.<sup>19)</sup> and Van Cangh et al.<sup>20)</sup> have reported that the proportion of free to total PSA ratio (F/T) enhances the ability to distinguish BPH from cancer in the gray zone. However, the advantage of F/T determination is apparent in the higher PSA region of the gray zone<sup>18,24)</sup> Catalona et al.<sup>18)</sup> reported that F/T showed 90% sensitivity and 31.3% specificity in the PSA range of 4–10 ng/ml (Tandem-R PSA). In the range of 2.6–4.0 ng/ml, specificity was only 18% while maintaining the same sensitivity<sup>24)</sup> In Japan, a few clinical studies about the significance of the F/T PSA ratio in the gray zone have been reported and its utility is controversial. Since we did not examine the clinical utility of the F/T PSA ratio, it cannot be compared directly with that of PSAD. However, our PSAD data showed a relatively high clinical utility.

Serum PSA concentration changes in correlation with age<sup>21)</sup>, and the rate of change in PSA is greater in men with prostate cancer compared with men without symptoms of prostatic disease<sup>22)</sup> Brawer et al.<sup>23)</sup> reported that an annual change in the PSA level of 20% is a significant risk for prostate cancer (PSA velocity). From the point of mass screening, PSA velocity is less useful in the differential diagnosis of BPH and prostate cancer because subjects must be examined annually to determine the need for biopsy.

International standardization of PSA has been

pointed out because of the various assay kits available. Stamey organized an International Conference for PSA Standardization at Stanford in 1992 and 1994<sup>5)</sup>. When analyzing data, calculation of serum PSA values according to the conversion rate for each assay is recommended<sup>4)</sup>

We determined prostate volume using transabdominal ultrasound. Transrectal ultrasound is agreed as the best procedure to detect prostate cancer, but transabdominal ultrasound is thought to be useful in determining prostate volume<sup>8)</sup> Transrectal ultrasound is an important diagnostic procedure, but subjects in a mass screening test may feel inconvenience and discomfort.

### CONCLUSIONS

In conclusion, we examined PSA, prostate volume and PSAD in 36 BPH and 25 prostate cancer patients who had gray zone PSA, and found a significant difference in prostate volume and PSAD. Cut-off values with sensitivity of 92% were 0.218 for PSAD, and 30 ml for prostate volume, and the specificity was 56%. Therefore, the determination of PSAD and prostate volume are useful tools for differential diagnosis of BPH and prostate cancer in the gray zone of PSA. Moreover, if the patients were missed by these strategies, other methods for the diagnosis of prostate cancer such as digital rectal examination, transrectal ultrasound, and total PSA determination may help determine the patients needing a biopsy.

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## 和文抄録

PSA gray zone の前立腺肥大症と前立腺癌の  
鑑別における PSAD の臨床的意義

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前立腺特異抗原 (PSA) は特異性が低いため, 特に gray zone における前立腺癌の診断には問題がある。われわれは PSA 値を Stanford reference value で換算し, gray zone 症例における PSA density (PSAD) の臨床的意義を検討した。

組織学的に診断された前立腺肥大症 (BPH) 63例と前立腺癌 (PC) 234例のうち, PSA が gray zone を呈する BPH 36例と PC 25例を対象とした。PSA 値は Markit-F または MPA で測定し Stanford reference value を従い換算した。前立腺は経腹的に外腺を含めて計測し, PSAD 値は PSA 値/前立腺体積で計算した。

PSA 値は BPH で  $6.42 \pm 1.80$ , PC で  $7.80 \pm 2.15$ と

なり, BPH との間を  $p=0.0116$  の有意差を認めた。前立腺体積は BPH で  $33.4 \pm 14.1$ , PC で  $17.1 \pm 8.2$  となり, BPH との間に  $p < 0.0001$  の有意差を認めた。一方 PSAD 値は BPH で  $0.218 \pm 0.085$ , PC で  $0.576 \pm 0.363$  となり BPH との間に  $p=0.0001$  の有意差を認めた。PSAD および前立腺体積の cut-off 値を各々の  $0.218$ ,  $30 \text{ ml}$  とした場合, 90% 以上の感度を維持しながら特異性はともに 56% と良好な結果が得られた。

Gray zone における PSAD 値の測定は, PSA 単独に比較して PC と BPH の鑑別診断に有用である可能性を示唆した結果であった。

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