FREE-TO-TOTAL PROSTATE SPECIFIC ANTIGEN RATIO IN CLINICAL STAGING OF PROSTATE CANCER

Hiroshi MAEDA, Yoichi ARAI*, Satoshi ISHITOYA, Kazutoshi OKUBO, Yoshitaka AOKI, Takashi OKADA and Shinya MAEKAWA

From the Department of Urology, Kurashiki Central Hospital, Kurashiki, Japan

The value of the free-to-total serum prostate-specific antigen (f/t PSA) ratio was compared with that of the total prostate specific antigen (tPSA) value for the prediction of clinical stage in patients with prostate cancer. The f/t PSA ratio was obtained from the frozen sera of 56 untreated patients with histologically proven BPH and 78 patients with prostate cancer. The clinical stage was organ-confined in 36, locally advanced in 20 and metastatic in 22 patients. Serum levels of free PSA (fPSA) and tPSA were determined using a chemiluminescent enzyme immunoassay. The f/t PSA ratio was calculated by dividing the fPSA value by the tPSA value and was compared with tPSA and fPSA in the correlation with clinical stage via the Spearman rank correlation test.

Patients with prostate cancer had a significantly lower f/t PSA ratio than patients with BPH. The f/t PSA ratio did not differ between patients with clinically localized and metastatic cancer. tPSA and fPSA reflected the clinical stage and the extent of bone metastasis more accurately than the f/t PSA ratio. The extent of bone metastasis had no effect on the f/t PSA ratio.

The f/t PSA ratio had no additional value in clinical staging compared to tPSA. Our study suggests that the f/t PSA ratio does not reflect tumor load.

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Key words: Prostate specific antigen, Prostate cancer, Free/total, Benign prostatic hyperplasia

INTRODUCTION

Prostate specific antigen (PSA) is a valuable tumor marker in the longitudinal monitoring of prostatic cancer. However, its value is limited in predicting the clinical stage; significant overlap has been obserbed between various stages[1].

Attention has recently been brought to the two different molecular forms of PSA, free and complexed PSA. PSA in serum is bound predominantly to the prostease inhibitors α1-antichymotrypsin and α2-macroglobulin[2] The f/t PSA ratio has been reported to be higher in patients with BPH than in patients with prostate cancer[3], but whether it may improve the prediction of staging in prostate cancer remoins unclear[4]

The present study was undertaken to evaluate the usefulness of f/t PSA ratio for the discrimination of clinical stage and the extent of bone metastasis of prostate cancer.

PATIENTS AND METHODS

Pretreatment sera were obtained from patients referred to the clinical practice for evaluation of prostate disease and were stored in the serum bank of Kurashiki Central Hospital between December 1993 and November 1996. Patient inclusion criteria for this study were as follows: (1) patients had neither previous androgen deprivation therapy nor any previous prostate disease-related surgical intervention, (2) patients had no history of recent urinary tract infection, and (3) histological diagnosis was obtained from transurethral resection of prostate or systematic biopsy performed on 4–6 cores.

The needle biopsy specimen was classified according to the Gleason score[5] Clinical evaluation for cancer staging included digital rectal examination, transrectal ultrasonography (TRUS), chest X-ray, computed tomography of the pelvis, endorectal coil magnetic resonance imaging and bone scintigraphy, supplemented by radiographs if necessary. Clinical staging was basically assigned according to the TNM staging system (1992 revision)[6] Stage T1c was defined as a nonpalpable tumor detected by the PSA test. The case with regional lymph node metastasis was regarded as one with distant metastasis.

Bone metastasis was diagnosed by bone scintigraphy and confirmed by supplementary modalities including plain X-ray, computed tomography and magnetic resonance imaging. The bone scintigraphic results were classified in accordance with extent of disease (EOD) by the method of Soloway et al.[7] The scans were graded according to the following semi-quantitative rating scale: 1) less than 6 bony metastases (a lesion occupying the entire

* AII communication and requests for reprints: Department of Urology, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki 710-8602, Japan.

vertebral body was counted as 2 lesions), 2) 6–20 bone metastases, 3) more than 20 bone metastases but less than a "superscan", and 4) "superscan" (diffuse symmetrical uptake without visualization of the kidneys) or its equivalent (involvement of greater than 75% of the ribs, vertebrae and pelvic bones). These cancer groups were compared with 56 patients with histologically-proven BPH.

Blood samples were collected and the sera were stored at −70°C until analysis. The laboratory staff were not given any clinical information about the samples. The PSA and fPSA were measured using the Immulyze fully automated random access immunoassay analyzer (Nippon DPC Corporation, Chiba, Japan). The assay performance of the Immulyze analyzer has been reported previously[8]. Immulyze PSA has recently been approved by FDA. Immulyze PSA is a one-step chemiluminescent enzyme immunometric assay. Immulyze fPSA is a two-step chemiluminescent enzyme immunometric assay. The cross-reactivity to the PSA-antichymotrypsin complex of this assay was less than 1%. The functional sensitivities of these assays, defined as 20% below the coefficient variations for samples assayed in duplicate, were 0.04 ng/ml and 0.05 ng/ml for Immulyze PSA and Immulyze Free PSA, respectively. The intraassay and interassay reproducibility was less than 10% for both assays. The f/t PSA ratio was determined by dividing the fPSA value by the total PSA value. The ratio was expressed as a percentage.

Data are expressed as median from 25th to 75th percentile, unless indicated otherwise. Inter-group comparisons were done by the nonparametric test (Mann-Whitney U-test). Box plots were used to illustrate the distribution of various PSA values, including the results of 50% of the participants with the median value plotted inside the box. The middle vertical line represented the 5th and 95th percentiles of all values. As to patients with prostate cancer, the correlation between the stage and the markers was determined by the Spearman rank correlation test by assigning 1, 2, and 3 to T1-2, T3-4 and M1, respectively. Likewise, the correlation between the stage and the markers was determined by assigning 1, 2, and 3 to the Gleason score 2-4, 5-6 and 7-10, respectively. All statistical calculations were made using a computer program; $p<0.05$ was taken as the level of statistical significance.

Table 1. Distribution of Gleason sum and clinical stage in 78 patients with prostate cancer

Gleason sum	Organ-confined (n=36)		locally extended (n=20)		Metastatic (n=22)		Total
	T1	T2	T3	T4	N+	M+	
2– 4	9	10	1	0	1	0	21
5– 6	6	8	11	1	0	3	29
7–10	2	1	7	0	0	18	28
Total	17	19	19	1	1	21	78

Prostate cancer with clinical stages T1, T2, T3, T4 (all N0M0), N+ (T3N2M0), M+ (T1 to T4NXM1). The case with stage N+ is regarded as M+ for calculation in the text.

RESULTS

Patient characteristics

One hundred and thirty four patients who met this inclusion criteria were enrolled in this study; their mean age was 71.3 years. The patient characteristics are shown in Table 1. The mean age of 56 patients with BPH was 68.7 years. Of all 78 cancer patients, the clinical stage was organ-confined (T1-2) in 36, locally advanced (T3-4) in 20, and metastatic in 22 patients. Of 22 patients with metastasis, one had only a regional lymph nodal metastasis and was regarded as M1 for calculation. The other 21 had

Table 2. Total, free and f/t PSA distribution in patients with BPH and prostate cancer

	BPH (n=56)	T1-2N0M0 (n=36)	T3-4N0M0 (n=20)	TxNxM1 (n=22)
Total PSA (ng/ml)				
Median	6.4	12.8	54.5	424
Interquartile	4.1 – 8.7	8.2 –24.7	35.5 – 80.8	119.5–1,912.5
Range	0.8 –71.5	2.9 –54.5	11.9 –927	48.5–5,520
Free PSA (ng/ml)				
Median	1.00	0.98	3.2	25
Interquartile	0.52– 1.2	0.74– 1.43	2.5 – 6.4	9.1– 110.3
Range	0.27–16.1	0.22– 3.9	0.74–165	3.6– 880
f/t PSA (%)				
Median	15.6	7.0	6.4	8.8
Interquartile	11.0 –20.9	5.5 –10.9	5.1 – 9.7	5.4– 10.7
Range	4.4 –67.1	2.6 –19.0	3.0 – 18.8	2.3– 17.1

One case with regional lymph node metastasis is regarded as M1. For total PSA, all comparisons between any groups shows significant difference. For the f/t PSA ratio, no significant difference is seen in any comparison among cancer groups.

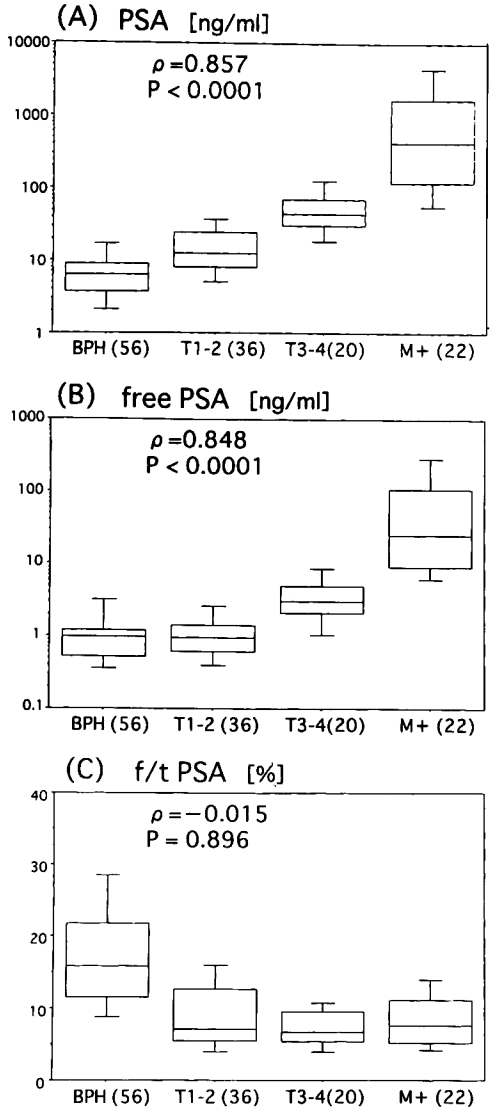

Fig. 1. (A)–(C). Levels of three variables: (A) PSA, (B) free PSA and (C) free to total PSA ratio (f/t PSA), in 56 BPH patients and 78 prostatic cancer patients are shown according to clinical stages T1-2, T3-4 (all N0M0) and M+ (TXN1M0 or TXNXM1). As to patients with prostate cancer, the correlation between the stage and each marker was determined by the Spearman rank correlation test by assigning 1, 2, and 3 to T1-2, T3-4 and M1, respectively. Note that the correlation of f/t PSA with clinical stage is not significant. ρ: Spearman's rank correlation coefficient.

distant metastasis, including 3 with distant lymph nodal metastasis alone and 18 with bone metastasis. The number of patients with an EOD of 1, 2, 3 and 4 was 4, 6, 1 and 7, respectively.

Comparison in BPH, localized and metastatic prostatic cancer.

Table 2 shows the distribution of tPSA, fPSA and f/t PSA. No significant difference was seen in the f/t PSA ratio among the cancer groups, although tPSA and fPSA differed significantly with the cancer group. fPSA did not differ significantly between patients with clinically organ-confined cancer (T1-2N0M0) and those with histologically-proven BPH.

Table 3. Total, free and f/t PSA distribution in patients with metastatic prostate cancer.

	LYMPH NODE (n=4)	EOD 1–2 (n=10)	EOD 3–4 (n=8)
Total PSA (ng/ml)			
Median	876	213*	904.5
Interquartile	66.6–927	89.6–631	443–3,140
Free PSA (ng/ml)			
Median	38.0	15.4*	102
Interquartile	7.5–100	7.85–44.0	23.8–351
f/t PSA (%)			
Median	6.4	7.1	9.8
Interquartile	4.2–11.2	6.1–9.9	4.9–12.6

LYMPH NODE group comprised of one regional and four distant metastatic cases. *Free and total PSA values show significant difference between patients with an EOD of 1–2 and those with an EOD of 3–4. For the f/t PSA ratio, no significant difference is seen between patients with an EOD of 1–2 and an EOD of 3–4.

Figure 1 shows all variables stratified according to clinical stage. By the Spearman rank correlation test, all variables except the f/t PSA ratio showed a significant correlation with cancer progression. tPSA showed the best correlation with clinical stage among all variables (Spearman rank correlation coefficient=0.857, $p<0.0001$). By the Spearman rank correlation test, all variables except the f/t PSA ratio showed a significant correlation with the Gleason score. Spearman's rank correlation coefficient was 0.566 ($p<0.0001$) in tPSA, 0.552 ($p<0.0001$) in fPSA and −0.050 ($p=0.661$) in f/t PSA ratio.

Comparison in metastatic prostatic cancer according th EOD

Table 3 also shows the results of each variable in accordance with extent of distant metastasis. tPSA and fPSA showed a significant difference between patients with an EOD of 1–2 and those with an EOD of 3–4, but the f/t PSA did not. There were no differences in any variables between the group with lymph node metastasis alone and that with bone metastasis.

DISCUSSION AND CONCLUSIONS

In clinical staging, PSA alone has been proved to have limited value. The combination of PSA and other variables obtained by biopsy also has been shown to be of limited use. In clinical practice, other modalities including physical examination and imaging studies are necessary for clinical staging, since considerable overlap exists between the clinical stages in free PSA or total PSA values.

Recent studies about fPSA have revealed that prostate cancer patients have a lower percentage of fPSA and a higher percentage of complexed PSA than patients without cancer. The clinical significance of f/t PSA for the detection of prostate cancer has been reported previously, especially in patients with intermediate PSA values[3]

Some investigators noted the value of the f/t PSA ratio for predicting extracapsular cancer[9,10], but their results show some discrepancy and the significance of the f/t PSA ratio for the pathological staging remains unknown. Wolff and associates showed that the f/t PSA ratio did not differ significantly between clinically localized and metastatic prostate cancer, although there was a significant difference between them in tPSA and fPSA[11] Bangma and associates also found no significant difference in the f/t PSA ratio between organ-confined and locally extended cancer or between all T categories and systemic metastatic cancer, although a difference was noted for tPSA[4]. Our study confirmed their conclusion that the f/t PSA ratio had no additional value in clinical staging for prostate cancer compared to tPSA. No significant difference in f/t PSA ratio was noted between organ-confined and locally extended cancer, or between any T category and systemic metastatic cancer, whereas a significant difference was noted in tPSA and fPSA among the cancer groups.

In addition, our study revealed that f/t PSA showed no significant difference between patients with an EOD of 1-2 and those with an EOD of 3-4. To our knowledge, no reports mentioned the relation of f/t PSA ratio with the extent of bone metastasis. Although the study population is small, our study showed that the extent of bone metastasis had no effect on the f/t PSA ratio, whereas free and total PSA showed a significant difference between patients with an EOD of 1-2 and those with an EOD of 3-4.

Stages and EOD scores generally reflect tumor load. Patients with a higher stage and higher EOD score have a higher tumor volume. In our study, tPSA and fPSA proved to reflect the stage and to be better parameters of tumor volume than the f/t PSA ratio.

In conclusion, the f/t PSA ratio has no additional value in clinical staging compared to serum tPSA, and the extent of bone metastasis has no effect on the f/t PSA ratio.

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和文抄録

PSA の F/T 比による臨床病期診断

倉敷中央病院泌尿器科（主任：荒井陽一部長）
前田　浩，荒井　陽一，石戸谷　哲，大久保和俊
青木　芳隆，岡田　崇，前川　信也

前立腺癌の臨床病期診断に関して free PSA (fPSA)，total PSA (tPSA) および fPSA と tPSA の比である free-to-total PSA ratio (F/T 比) を比較検討した．

対象は前立腺疾患で精査された組織学的診断を得た134例（癌78例，前立腺肥大症56例）．前立腺癌の臨床病期は前立腺限局癌が36例，局所進行癌が20例，転移癌が22例，治療前保存血清の fPSA と tPSA を chemiluminescent enzyme immunoassay にて測定．骨転移は Soloway の分類にもとづき EOD に分類．臨床病期との相関には Spearman の順位相関を用い検定．

F/T 比は前立腺癌では非癌よりも有意に低値を示した．非転移癌56例と転移癌22例では有意差を認めず　臨床病期との相関は tPSA は fPSA や F/T 比よりも優れていた．骨転移限局群と広範群で F/T 比に有意差は認めなかった．

F/T 比および fPSA は臨床病期診断の精度向上には寄与しなかった．F/T 比は腫瘍体積を反映しないと考えられた．

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