RESEARCH ARTICLE

Diagnostic Role of Serum Free-to-Total Prostate Specific Antigen (PSA) Ratio in Prostate Cancer with Serum Total Concentration of PSA below 4 ng/mL

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Abstract

Purpose: To examine the effectiveness of serum free-to-total prostate specific antigen ratio (%fPSA) for the detection of prostate cancer (PCa) in men with different serum total PSA (tPSA) categories. Materials and Methods: From January 2010 to December 2013, a total of 225 patients with lower urinary tract symptoms (LUTS) underwent tPSA and %fPSA measurements. Histological examination with calculation of Gleason score and whole body bone scans were performed in identified cases of PCa. Results: PCa was diagnosed in 44 (19.6%) patients and the remaining 181 patients had benign prostate disease. PCa was detected in 5 (23.8%), 13 (8.7%) and 26 (47.3%) cases with tPSA level ranges ≤4 ng/ml, 4 to 10 ng/ml and >10 ng/ml, respectively. The average Gleason score was 7.2±0.2. Some 6 (13.6%) out of 44 PCa patients had bone metastases. The sensitivity was 80% and specificity was 81.3% at the cut-off %fPSA of 15% in PCa patients with a tPSA level below 4 ng/mL. A lower %fPSA was associated with PCa patients with Gleason score ≥7 than those with Gleason score ≤6 (11.7±0.98 vs. 16.5±2.25%, *P*=0.029). No obvious relation of %fPSA to the incidence of bone metastasis was apparent in this study. Conclusions: The clinical application of %fPSA could help to discriminate PCa from benign prostate disease in men with a tPSA concentration below 4 ng/mL.

Keywords: Benign prostate hyperplasia - free-to-total prostate specific antigen ratio - prostate cancer

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Introduction

Prostate cancer (PCa), accounting for about 14% of male cancers, was recognized as the most frequent malignant cancer among American men (Parkin et al., 2005; Ferlay et al., 2010). In recent years, the prevalence of PCa in Asian countries had also been on the rise because of westernized lifestyle (Akbari, et al., 2008; Matsuda et al., 2009; Van Dong et al., 2014). Prostate specific antigen (PSA), a 27.4 kDa glycoprotein produced by prostate gland, was known to be elevated in the serum of PCa patients. Therefore, it was commonly used in the screening of PCa. However, it was uneasy to discriminate benign prostate hyperplasia (BPH) from PCa in circumstances such as elevated serum PSA concentrations between 4.0 and 10.0 ng/mL. The serum free-to-total PSA ratio (%fPSA), found to be an effective indicator in order to differentiate the diagnosis of BPH from PCa, was therefore, utilized for discriminating between benign and malignant diseases of the prostate gland in order to improve the poor specificity of serum total PSA (tPSA) examination alone (Catalona et al., 1995; Correale et al., 1996). In previous studies, the cut-off levels of %fPSA with the best performance of sensitivity and specificity were calculated on the basis of specific age and tPSA ranges (Miller et al., 2001; Thakur et al., 2004; Erol et al., 2014; Kitagawa et al., 2014). Nevertheless, delayed detection of prostate cancer was still found in patients with initial tPSA concentration less than 4.0 ng/mL (Thompso et al., 2004), in which the laboratory characteristics of %fPSA remained unknown. Hence, a further investigation should be necessitated to establish the diagnostic role of %fPSA in different tPSA ranges.

In this study, we examined the relationship between %fPSA at various cut-off values and different tPSA ranges of patients with PCa and BPH in the Taiwanese population. We also surveyed the association of %fPSA to the Gleason score and incidence of bone metastasis in PCa individuals.

Materials and Methods

The study was conducted on a total of 225 patients with initial chief complain of lower urinary tract symptoms (LUTS) and was regularly followed up at the Far Eastern

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Memorial Hospital (FEHM) in New Taipei city, Taiwan, from January 2010 to December 2013. Clinical data of these patients were retrospectively obtained via the chart review. The blood was sampled for serum PSA measurement. All blood specimens were collected before patients receiving any manipulative procedures in avoidance of possible bias due to unexpected release of PSA from prostate gland. The serum total and free PSA concentrations were determined by Roche E170 automated immunoassay analyzer. The experimental procedure was performed according to the manufacturer's protocol. In addition, digital rectal examination (DRE) was assessed and transrectal sonography (TRUS)-guided biopsy of the prostate gland was performed for pathological verification if the DRE showed abnormal findings. The Gleason score was further calculated and whole body positron emission tomography (PET) scan with fluorodeoxyglucose (FDG) was done for the screening of any bone metastasis in pathologically identified cases of PCa.

Data were presented as the mean ± standard deviation or number and percentage (%). All statistical analyses were performed using the statistical software SPSS (version 15.0; SPSS Inc., Chicago, USA). Student's t test was used for analysis of continuous data and Chi-square test for categorical data. Statistically significance was considered if a *P* value was less than 0.05.

Results

The clinical characteristics of patients with PCa and BPH were listed in Table 1. Among these 225 patients, 44 were identified as PCa with respective Gleason scores and the remaining ones were diagnosed as BPH. The mean age of patients with PCa was significantly higher than those with BPH (71.6±1.2 *vs* 66.9±0.7 years, *P*=0.004). The concentrations of serum total and free PSA were also markedly higher in patients with PCa than those with BPH (178.42±117.86 *vs* 11.85±4.80 ng/mL, *P*=0.005, and 18.07±11.16 *vs* 2.22±0.90 ng/mL, *P*<0.001, respectively). The %fPSA was significantly lower in patients with PCa than those with BPH (13.32±1.05 *vs* 19.40±0.56%, *P*=0.006). The patients were then further categorized into 3 groups according to the tPSA levels for further analysis. In the first group with total serum PSA level of 4 ng/mL or less, 21 cases were identified and 5 of them were diagnosed with PCa (23.8%). In the second group with tPSA level between 4 to 10 ng/mL, 149 cases were identified and 13 of them were diagnosed with PCa (8.7%). In the third group with tPSA level ranges more than 10 ng/mL, 55 cases were identified and 26 of them were diagnosed with PCa (47.3%). The average Gleason score was 7.2±0.2 in patients with PCa and 6 of them had bone metastases (13.6%) according to the report of whole body bone scan.

The sensitivity and specificity of %fPSA at different cut-off levels in various tPSA categories were calculated as shown in Table 2. The sensitivity was 63.6% and specificity was 71.3% at the %fPSA of 15% in all patients with PCa and BPH. For the first group, the sensitivity and specificity were 80% and 81.3% at the cut-off %fPSA of 15%, respectively. The sensitivity and specificity for the second group were 53.9% and 72.1% at the cut-off %fPSA of 15%. For the third group, they were 65.4% and 62.1% at the cut-off %fPSA of 15%, respectively. In general, the sensitivity increased whereas the specificity decreased in company with increased cut-off level of %fPSA.

The relationship of %fPSA to the Gleason score and incidence of bone metastasis in patients with PCa was shown in Table 3. The %fPSA was significantly lower in PCa patients with the Gleason score of 7 or more comparing to those with the Gleason score of 6 or less (11.69±0.98 *vs* 16.47±2.25%, *P*=0.029). The %fPSA was lower in PCa patients with bone metastases than those without, but no statistical significance was shown (11.13±1.96 *vs* 13.66±1.17%, *P*=0.413).

Table 1. The Clinical Characteristics of Patients with Prostate Cancer and Benign Prostate Hyperplasia

	PCa (n=44)	BPH (n=181)	*P* value
Age (year)	71.6±1.2	66.9±0.7	0.004
Total PSA (ng/ml)	178.42±117.86	11.85±4.80	0.005
Free PSA (ng/ml)	18.07±11.16	2.22±0.90	<0.001
Free-to-total PSA ratio (%)	13.32±1.05	19.40±0.56	0.006
Total PSA≤4 (ng/ml)	5 (23.8)	16 (76.2)	
4<Total PSA≤10 (ng/ml)	13 (8.7)	136 (91.3)	
Total PSA>10 (ng/ml)	26 (47.3)	29 (52.7)	
Gleason score	7.2±0.2	-	
Bone metastasis	6 (13.6)	-	

PCa, prostate cancer; BPH, benign prostate hyperplasia; PSA, prostate specific antigen; Data were expressed as mean± standard error or number (percentage)

Table 2. The Sensitivity and Specificity of Free-to-total PSA Ratio at Different Cut-off levels in Various Serum Total PSA Categories in Patients with Prostate Cancer and Benign Prostate Hyperplasia

	All (n=225)	Total PSA≤4 (n=21)	4<Total PSA≤10 (n=149)	Total PSA>10 (n=55)
%fPSA ≤0.20				
Sensitivity (%)	88.6	100	76.9	92.3
Specificity (%)	38.1	68.8	38.2	20.7
%fPSA ≤0.15				
Sensitivity (%)	63.6	80	53.9	65.4
Specificity (%)	71.3	81.3	72.1	62.1
%fPSA ≤0.10				
Sensitivity (%)	38.6	40	23.1	46.2
Specificity (%)	90.6	100	90.4	86.2

PSA, prostate specific antigen; %fPSA, free-to-total PSA ratio

Table 3. The Relationship of free-to-total PSA Ratio to the Gleason Score and Incidence of Bone Metastasis in Patients with Prostate Cancer

	Free-to-total PSA ratio (%)	*P* value
Gleason score		0.029
≥7	11.69±0.98	
≤6	16.47±2.25	
Bone metastasis		0.413
Positive	11.13±1.96	
Negative	13.66±1.17	

PSA, prostate specific antigen; Data were expressed as mean± standard error or number (percentage)

Discussion

The present study investigated the effectiveness of %fPSA in differential diagnosis of benign and malignant prostate diseases. Our study indicated that %fPSA could be utilized as an effective predictor for PCa especially in patients with tPSA level of 4 ng/mL or less. In addition, the low %fPSA was remarkably associated with the Gleason score of 7 or more. There was no apparent association of %fPSA to the incidence of bone metastasis.

The tPSA concentration between 4 and 10 ng/mL was a "gray zone" for differentiating PCa from BPH. Therefore, the %fPSA was utilized for more accurate detection of PCa. Previous studies indicated that a cut-off value of 15% in %fPSA yielded 94 to 95% sensitivity and 54 to 64% specificity in PCa patients with tPSA level of 4 to 10 ng/mL (Prestigiacomo et al., 1996). For tPSA level of 2 to 4 ng/mL, none of %fPSA was effective in discriminating PCa from BPH (Prestigiacomo et al., 1996). However, accumulating evidence in recent years indicated that serum f/t PSA ratio could not be a good predictor of PCa for tPSA level in such diagnostic gray zone. Agnihotri S et al reported that cut-off values of %fPSA varied from 7% to 15% with increased sensitivity from 58% to 90% and decreased specificity from 63% to 35% (Agnihotri et al., 2014). Lee R et al showed the cut-off levels of %fPSA increased from 7% to 20% with increased sensitivity from 32% to 94% and decreased specificity from 92% to 13%, in company with 61% sensitivity and 57% specificity at the %fPSA of 15% for tPSA concentration of 4 to 10 ng/mL (Lee et al., 2006). These results were compatible with our data, in which 53.9% sensitivity and 72.1% specificity were shown at the %fPSA of 15% in the group with tPSA level from 4 to 10 ng/mL.

Prostate malignancy with low tPSA concentration was not rare. Recently, only few studies examined the effectiveness of %fPSA on later diagnosis of PCa with low tPSA levels. Finne *P* et al reported that approximately 14% of patients with tPSA concentrations below 3 ng/mL were diagnosed as PCa (Finne et al., 2008). Men with %fPSA in the lowest quartile (<14.2%) had a 6.9-fold risk of developing subsequent PCa compared with those with the ratio in the highest quartile (>23.7%) (Finne *P* et al., 2008). Additionally, Ishidoya S reported that 32.7% of patients with tPSA levels arranged from 2 to 4 ng/mL and the %fPSA of 12% or less were found to have PCa (Ishidoya S et al., 2008). Faria EF et al showed that detection rate of PCa was 3.7% in men with tPSA concentrations of 2.5 to 3.9 ng/mL at the %fPSA of 15% (Faria et al., 2012). Sasaki M et al suggested that the lowest quartile of %fPSA (<13.3%) was associated with a 21.2-fold higher risk of having PCa compared with the highest quartile (>22.2%) (Sasaki et al., 2014). Most of the results from previous studies were compatible with our data, in which our results indicated that 23.8% of patients with serum total concentration of 4 ng/mL or less were found to have PCa and the satisfying sensitivity and specificity (80.00 and 81.25%, respectively) were shown in these patients at the %fPSA of 15%. The detection rate could vary with using the %fPSA of 15% in PCa patients with low tPSA concentration, which could be attributed to different countries, living environment and lifestyle.

Masieri L et al reported that lower %fPSA was significantly correlated with higher Gleason score accompanied with tumor extracapsular extension and seminal vesicles involvement (Masieri et al., 2012), which was similar with our results. The incidence of bone metastasis in our patients with PCa included in this study was 13.6%, which was compatible with previous studies (0.8 to 53.6%) (Briganti et al., 2010; Sanjaya et al., 2013). There was no obvious relationship between the %fPSA and incidence of bone metastasis, which was compatible with previous studies (Maeda et al., 1998).

The major limitations of the present study were the small case number and the retrospective study design. Furthermore, the lack of patients' comorbidities and the detailed conditions of prostate gland such as the weight of prostate gland and the existence of extracapsular lesion were not investigated. The variables associated with bone metastases in PCa including bony symptoms and serum alkaline phosphatase levels were not analyzed, either.

In conclusion, the %fPSA could be utilized in the prediction of PCa in tPSA concentration of 4 ng/mL or less. The %fPSA was significantly lower in PCa patients with the Gleason score of 7 or more. The clinical application of %fPSA could help in discrimination of PCa from BPH in men with tPSA concentration below 4 ng/mL.

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