Pathol. Oncol. Res. (2014) 20:439–443
DOI 10.1007/s12253-013-9714-1

RESEARCH

A new Model Consists of Intravesical Prostatic Protrusion, Prostate Volume and Serum Prostatic-Specific Antigen in the Evaluation of Prostate Cancer

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Received: 5 March 2013 / Accepted: 14 October 2013 / Published online: 1 November 2013

Abstract The Prostate-specific antigen (PSA) level is largely used to diagnose prostate cancer (PCa) in last decades. However, its specificity is low in patients with a PSA level ranging from 4.0 to 10.0 ng/ml. This study aims to define the correlation between intravesical prostatic protrusion (IPP) and PSA and to establish a new model to predict PCa. A total of 339 patients order than 45 years examined between October 2010 and June 2012 were enrolled. Eligible patients were recommended for transrectal ultrasonography (TRUS)-guided prostate biopsies after measuring total prostate volume (TPV), tranzisional zone volume (TZV) and IPP. The levels of total PSA (tPSA), free PSA (fPSA) were analyzed by using Hybritech calibrated Access tPSA and fPSA assays. A new mathematical model, named IPP removed PCa predicting score (IRPPS), consists of tPSA, TZV and IPP was established. The predictive accuracy of IRPPS, PSA density (PSAD), %PSA and tPSA were compared using receiver-operator characteristic (ROC) analysis. Eighty-six patients had PSA levels of 4.0–10.0 ng/ml. Twenty of them were diagnosed as PCa. Using ROC curves, the areas under the curve for IRPPS, PSAD and %PSA and tPSA were 0.786, 0.768 and 0.664 and 0.585, respectively. We suggested IPP grade had a significant relationship with serum tPSA levels. The predictive accuracy of IRPPS was higher than the other 3 indictors.

Keywords Intravesical prostatic protrusion · Prostate specific antigen · Prostate cancer · Diagnostic accuracy

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Introduction

Prostate-specific antigen (PSA) is considered as one of the most remarkable tumor marker in the last decades, which has greatly enhanced the management of prostate cancer (PCa), especially for early detection of this disease [1]. Unfortunately, the serum PSA level is also raised in benign prostatic conditions, such as benign prostate hyperplasia (BPH) and prostatitis [2], which leads to a limited specificity and sensitivity in determining the presence of PCa, especially in the patients with total PSA (tPSA) ranging from 4.0 to 10.0 ng/ml [3].

Intravesical prostatic protrusion (IPP) is a morphological change due to overgrowth of prostatic median and lateral lobes into the bladder [4]. Previous studies have investigated the correlation between IPP and PSA. For example, Lim et al. [5] found good positive correlation between IPP and PSA (r=0.559) in patients with BPH. Lee et al. [6] found that the mean serum PSA level was 2.3 ng/mL, 4.7 ng/mL and 7.4 ng/mL, respectively, for Grade 1 (IPP≤5 mm), Grade 2 (5 mm<IPP≤10 mm) and Grade 3 (IPP>10 mm) IPP cohorts in patients with BPH. However, few studies researched the detailed relationship between PSA and IPP.

In this study, we established a new mathematical model, named IPP removed PCa predicting score (IRPPS) to predict the presence of PCa in patients with tPSA ranging from 4.0 to 10.0 ng/ml. The IRPPS model consists of tPSA, TZV and IPP. The predictive accuracy of IRPPS were compared with several existing indicators, such as tPSA, %PSA, and PSA density (PSAD). Results suggested that the predictive accuracy of IRPPS was higher than the other indicators in predicting the presence of PCa in case of tPSA ranging from 4.0 to 10.0 ng/ml.

Materials and Methods

Patients

Between October 2010 and June 2012, the patients who visited our outpatient department presenting with lower urinary tract symptoms suggestive BPH and elevation of tPSA were enrolled in our study. The study was approved by Shanghai Jiao tong University Xinhua Hospital Ethics Committee and written informed consent was obtained from all patients before enrollment.

Patients were required to receive the examination consisting of serum tPSA level, serum free PSA (fPSA) level, ultrasound measurement of total prostate volume (TPV), tranzisional zone volume (TZV) and IPP. BPH was diagnosed on the basis of history, physical findings and ultrasound. When the value of PSA was over 4.0 ng/ml, a prostate biopsy was done to confirm whether it was benign or not.

Criteria for inclusion were age>45 years old, BPH and PCa patients with PSA ranging from 4.0 to 10.0 ng/ml (confirmed by ultrasound (BPH) or prostate biopsy (PCa)). Criteria for exclusion were age ≤45 years old, previous operation in bladder, prostate or urethral, current history of acute urinary retention (AUR), acute prostatitis or prostate abscess, urethral stricture, bladder stone, neurogenic bladder dysfunction, chronic urinary tract infection and diabetes mellitus.

PSA Assay

Blood samples were obtained before any prostatic manipulations that might cause a transient increase of biomarkers. The serum levels of tPSA and fPSA were analyzed by using Hybritech calibrated Access tPSA and fPSA assays.

Assessment of Prostate Volume (PV) and IPP

The ultrasound machine made by Siemens sequoia 512 (EV8C4-S, frequency 3–8 MHz) was used to estimate PV (ml) and IPP (mm). Transabdominal ultrasound scan was used to assess IPP with the patient in the supine position when bladder volume was 100 to 200 ml [7]. IPP was measured by the vertical distance from the tip of the protrusion to the base of the urinary bladder in the midsagittal plane of transrectal ultrasonography (TRUS). We divided patients into three groups based on the degree of IPP: Grade 1 (IPP≤5 mm), Grade 2 (5 mm<IPP≤10 mm) and Grade 3 (IPP>10 mm). Transrectal ultrasound scan was used to assess PV with the patient in the left decubitus position. The transverse and sagittal sections were recorded after marking the transition zone (TZ). The transverse, anteroposterior, superoinferior diameters of the total prostate as well as those of the TZ were measured from the transverse and sagittal views. Total prostate volume (TPV) and TZ volumes (TZV) were calculated by using the following formula: = π/6×transverse diameter (mm)×anteroposterior diameter (mm)× superoinferior diameter (mm) [8]. All TRUS were done by an experienced radiologist.

Table 1 The basic characteristics of enrolled patients

	BPH patients(n=319)			PCa patients(n=20)		
	mean	SD	median	mean	SD	median
age	72.44	7.88	73	72.05	7.88	69.50
tPSA	6.91	7.49	4.41	7.18	1.58	7.30
fPSA	1.48	2.13	0.95	1.18	0.85	0.13
TPV	69.09	36.29	61.00	51.65	18.33	49.50
TZV	43.11	30.77	37.00	28.10	14.09	27.00
IPP	10.10	8.09	10.00	10.00	4.54	9.50

tPSA total prostate specific antigen, *fPSA* free prostate specific antigen, *TPV* total prostate volume, *TZV* transitional zone volume, *IPP* intravesical prostatic protrusion

Calculation of IRPPS

The IPP may have impact on the tPSA levels. Our model is try to remove the impact of IPP on PSA. IRPPS was calculated by the formula: [tPSA - IPP^(1/3)]/TZV.

Statistical Analysis

Statistical package for social sciences (SPSS), version 19.0 was used for our statistic analysis. The data was presented as the mean ± SD. Kruskal-Wallis H test was used to assess the statistical significance among the three groups. Predictive accuracy of IRPPS was quantified as the area under the ROC curve (AUC), where a value of 100 % indicates perfect prediction and 50 % is equivalent to a toss of a coin. The relationship between IPP and tPSA was tested using the Spearman ρ coefficient analysis. For all statistic tests, a P-value <0.05 was considered to be statistically significant.

Table 2 The serum tPSA level in BPH patients with different IPP grade

		mean	SD	P value
tPSA(ng/ml)	Grade1(n=93)	4.07	5.50	<0.001
	Grade2(n=75)	5.21	3.78	
	Grade3(n=151)	9.49	9.00	

tPSA total prostate-specific antigen

Table 3 Results between BPH group and PCa group($n=86$)

	BPH patients($n=66$)		PCa patients($n=20$)		P value
	mean	SD	mean	SD	
age	68.33	8.85	72.05	7.88	0.096
tPSA	6.77	1.57	7.18	1.58	0.304
fPSA	1.30	0.64	1.18	0.85	0.523
TPV	75.56	26.69	51.65	18.33	<0.001**
TZV	47.24	21.83	28.10	14.09	<0.001**
IPP	13.86	6.91	10.00	4.54	0.005**
%PSA	0.19	0.09	0.16	0.09	0.104
PSAD	0.10	0.05	0.15	0.05	<0.001**
IRPPS	0.12	0.08	0.22	0.13	0.002**

tPSA total prostate specific antigen, *fPSA* free prostate specific antigen, *TPV* total prostate volume, *TZV* transitional zone volume, *TZI* transitional zone index, *IPP* intravesical prostatic protrusion, *%PSA* percent free prostate specific antigen, *PSAD* prostate specific antigen density, *IRPPS* IPP removed prostate predicting score

* P value<0.05

** P value<0.01

Results

A total of 339 patients completed all the required examinations, including 319 BPH patients and 20 PCa patients with IPP. All of the 20 PCa patients with IPP had the tPSA levels ranging from 4.0 to 10.0 ng/ml. Among the 319 BPH patients, only 66 of them with IPP had the tPSA levels ranging from 4.0 to 10.0 ng/ml. The basic characteristics of the study population are presented in Table 1. The median tPSA of BPH patients was 4.41 ng/ml and that of PCa patients was 7.30 ng/ml. The median IPP of BPH patients was 10.00 mm and that of PCa patients was 9.50 mm.

We evaluated the relationship between tPSA level and IPP grade in BPH patients (Table 2). From Table 2, we could find that the mean level of tPSA was raised along with the IPP grade. The mean tPSA level of IPP grade 1 patients was 4.07 ng/ml, and that of IPP grade 2 patients was 5.21 ng/ml. In IPP grade 3 patients, the mean tPSA level raised to 9.49 ng/ml. Statistical analysis showed that the tPSA levels of the three IPP grade were significantly different ($P<0.001$). Therefore, we suggested IPP grade had a significant relationship with serum tPSA levels ($r=0.335$, $P<0.001$).

The patients with IPP who had tPSA levels ranging from 4.0 to 10.0 ng/ml (including 66 BPH patients and 20 PCa patients) were extracted for further analysis (Table 3). From Table 3, we could find that age, tPSA, fPSA and %PSA were not significantly different between PCa patients and BPH patients. The PSAD of PCa patients was significantly higher than that of BPH patients. The IRPPS of PCa patients was also significantly higher than that of BPH group.

Figure 1 shows the sensitivity and specificity for IRPPS, PSAD, %PSA and tPSA in the 4.0–10.0 ng/ml PSA range. From ROC curve, the AUC of IRPPS was 0.786, which was higher than that of PSAD (0.768), %PSA (0.664) and tPSA

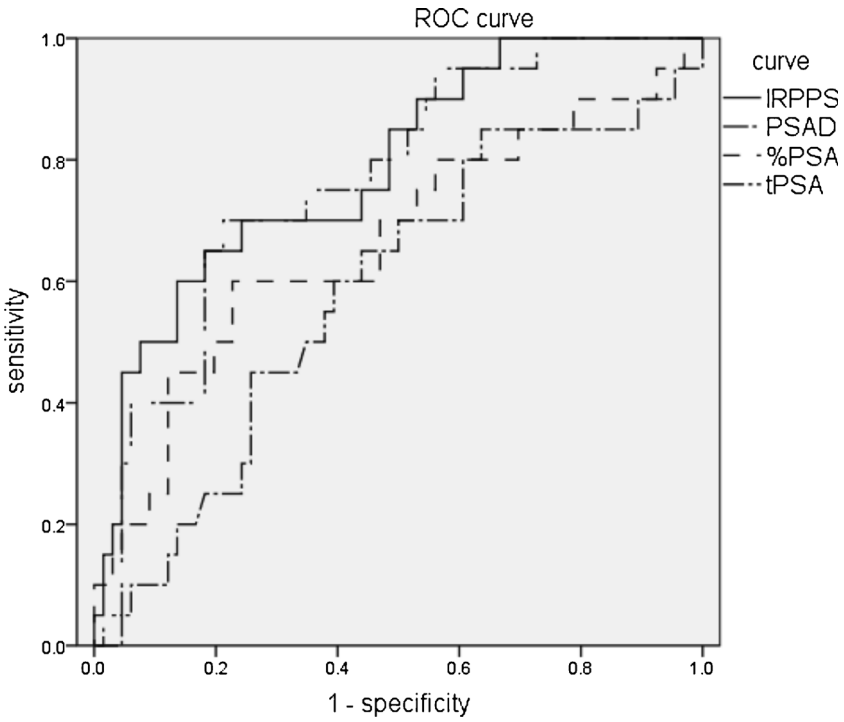

Fig. 1 The sensitivity and specificity for IRPPS, PSAD, %PSA and tPSA in the 4.0–10.0 ng/ml PSA range

(0.585). When IRPPS>0.09, the sensitivity would raise to 90.00 % and the specificity would raise to 47.00 %. This result suggested that the predictive accuracy of IRPPS was higher than the other indicators. A total of 32 patients (37.21 %) could be diagnosed as BPH by IRPPS. This result was confirmed by biopsy.

Discussion

The diagnosis of PCa in patients with tPSA ranging from 4.0 to 10.0 ng/ml, a diagnostic 'grey zone' is difficult because cancer is present in 25 % of patients with a palpably enlarged benign prostate gland [9]. The lack of specificity of tPSA is one of the limitations of its use. The value of IPP in diagnosing PCa has not been fully characterized before. From the current study, IPP was proved to have an impact on the elevation of tPSA.

Lim et al. [5] first found tPSA is correlate well with IPP. Patients with higher PSA is likely to have a higher IPP grade. Our result is consistent with their study. In addition, the tPSA levels among 3 groups divided by IPP grade were significantly different. This result further demonstrated that tPSA had a certain relationship with IPP grade.

In the 86 patients with IPP whose tPSA level ranging from 4.0 to 10.0 ng/ml, 20 patients were diagnosed as PCa. The diagnostic accuracy was 23.26 %, which was similar than other study [10]. In this group, TPV, TZV and IPP of PCa patients were significantly lower than those of BPH patients while tPSA had no significantly difference (Table 3). This result indicated that the increase of PV and IPP may play an important role in elevation of tPSA ranging from 4.0 to 10.0 ng/ml.

Several studies have demonstrated that IPP is a useful predictor for evaluating bladder outlet obstruction (BOO) [5, 11–14]. Laniado et al. [15] and van Renterghem et al. [16] had also shown that patients with high tPSA are significantly associated with BOO. We know that IPP represents the median and lateral lobes of the prostate protruding into the bladder, causing a ball-valve type of obstruction and disrupting the funneling effect of the bladder neck, which increases urethral resistance. In addition, the presence of median lobe enlargement causes dyskinetic movement during micturition [17]. These would cause more obstruction in the group with IPP than that in the group without IPP. As a result, a strong bladder contraction is required to open a channel between the lobes, which tended to lead more PSA leakage from prostate to serum. Additionally, Hammerer et al. [18] confirmed that most PSA leakage from the prostate into the serum comes from the TZ and BPH results almost exclusively from hyperplasia of the TZ. Therefore, the predictive accuracy of IRPPS, which consists of tPSA, TZV and IPP, was higher than that of PSAD, %PSA and tPSA, indicating that IRPPS would be a valid predictor of PCa when the patient had the PSA of 4.0–10.0 ng/ml and IPP measured from transabdominal ultrasound.

The main limitation of current study is the relatively lower sample size, especially in the group with PSA 4.0–10.0 ng/ml. We will collect more patients in the following study. Moreover, not all the patients participated in the urodynamic studies because it was a invasive examination and cost a lot.

Conclusion

From our study, we concluded that tPSA had positive correlation with IPP. For the patient with IPP has the PSA of 4.0–10.0 ng/ml, IRPPS could improve the accuracy in predicting the presence of PCa at prostate biopsy. Threshold value 0.09 of IRPPS had a high sensitivity and considerable specificity.

Acknowledgments The authors wish to thank all patients for their ongoing participation in this study. This study was funded by a grant from Science and Technology Commission of Shanghai Municipality (No.09411950100 & No.1041195200)

Competing Interests All authors of this article had no conflict of interest.

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