Original Research

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What is the most appropriate test in detecting prostate cancer in patients with intermediate prostate specific antigen levels?

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Abstract

Background: Regarding the variety of tests present for detecting and also screening prostate cancer and also bearing in mind the advantages and disadvantages of these tests we decided to re-evaluate these tests (total prostate specific antigen and all of its modifications) in detecting prostate cancer in men with intermediate serum PSA levels.

Methods: Following a cross sectional study, 100 consecutive men with intermediate serum PSA levels and normal digital rectal examination (DRE) were incorporated. Total and free PSA levels and TRUS-guided systematic prostate biopsy were performed. PSA density, percent free PSA and percent free PSA density were calculated and compared. Statistical analysis was carried out using STATA 8 SE.

Results: Overall, 27 patients had prostate cancer and 73 had benign prostate pathology. PSA density had the greatest area under the curve (AUC) which was significantly higher than percent free PSA density (0.685 vs. 0.448, p<0.001). The AUC of percent free PSA density was not different between benign and malignant biopsy results nor was significantly higher than the AUC of percent free PSA (0.308) or any other screening tests.

Conclusion: PSA density was the most accurate screening test for prostate cancer in patients with PSA levels of 4-10 ng/ml and normal DRE. The percent free PSA density was not significantly more accurate than percent free PSA and regarding the costs of transrectal ultrasonography, it can be concluded that the percent free PSA is more cost-effective and hence more appropriate than percent free PSA density to screen prostate cancer.

Keywords: prostate cancer, prostate specific antigen, accuracy, PSA density, percent free PSA density.

Introduction

Prostate cancer, the fifth most common cancer in the world and the second most common in men [1], estimated to have an incidence rate of 5.1 per 100,000 person-years in Iranian population [2] and affects multiple health problems and health related quality of life [3,4]. Due to these catastrophic reports multiple investigations have been conducted to evaluate usefulness of different screening tests in the early detection of prostate cancer. Among them are total prostate specific antigen (PSA) and its modifications including PSA density, transition zone PSA density, age-referenced PSA, PSA velocity and percent free PSA [5-7].

Total PSA concentration seems not to be sensitive or specific enough for this purpose and its elevation may originate from digital rectal examination, prostate glandular enlargement

caused by benign prostatic hyperplasia (BPH), prostatic inflammation, sexual activity, infarction, or trauma, as well as from prostate cancer [8,9]. In addition, screening a population of men with total PSA levels in the 'gray zone' (4-10 ng/ml) revealed that 22% had prostate cancer [10]. Other studies have defined the prevalence of prostate cancer in men with total PSA less than 4 ng/ml and recommended a new cut-off point of 2.6 ng/ml that would detect more organ confined tumors [11-12]. Hence, regarding the various circulating forms of PSA, others have examined the usefulness of using multiple refinements in the interpretation of total PSA such as PSA density, transition zone PSA density, age-referenced PSA, PSA velocity and percent free PSA to enhance its precision and acquired invaluable results [10,13,14].

Of all modifications for the total PSA, the free PSA ratio or percent free PSA (free PSA/total PSA) has withstood the most scrutiny and remains a subject of considerable interest [14]. In a study performed by Baltaci et al [10], percent free PSA density was suggested as a new concept to overcome the size-dependency of percent free PSA and introduced it as a superior test to calculate percent free PSA with higher specificity for the detection of prostate cancer in men with intermediate levels of total PSA.

Therefore, regarding the importance of introducing a screening test with higher specificity for detecting prostate cancer in its early stages and the geographic discrepancies in the prevalence of this cancer [1,15], This study was conduced to compare different refinements of total PSA in Iranian men with intermediate total PSA levels.

Methods

By cross-sectional study, 100 men with history of a major referral to uronephrology centers (for various reasons including prostate cancer, screening and voiding symptoms, regardless of whether visits were primary or referred) in Tehran were enrolled. All patients had serum PSA between 4.0 and 10.0 ng/ml, and digital rectal examination findings that were not indicative of cancer. Patients who had previously received hormonal treatment for prostatic disease, with a prior diagnosis of prostate cancer, with an indwelling catheter or previous prostatic surgery of any nature, who had active acute prostatitis, were in active urinary retention, and had recently undergone prostatic manipulation or those who were on the medications that may have altered total PSA, were all excluded.

All patients underwent transrectal ultrasound guided (TRUS-guided) laterally directed systematic for 10 to 12 core biopsies of the prostate by the automated biopsy gun and an 18-gauge needle with transverse ultrasound guidance. Biopsy results were classified as benign or malignant. Prostatic intraepithelial neoplasia was not classified as cancer. TRUS was performed by two well trained sonographist using a 7.5-MHz transrectal probe (Esaote Technos MP, Italy). Prostate volume was calculated by TRUS using the ellipsoid formula, volume = $(\pi/6)$ length$\times$ width$\times$ height.

Total and free PSA were measured before any manipulation of the prostate gland and percent free PSA was calculated as the ratio of free PSA to total PSA multiplied by 100. Percent free PSA density was calculated as the percent free PSA divided by the prostate volume. Total and free PSA levels were measured using ELIZA Kit (Dialplus Inc., USA) and CanAg (EIA Sweden) PSA kits, respectively. Blood samples were taken and centrifugated at 1,600g for 15 min at 4 °C. Serum samples were seperated and then frozen at 80 °C within 2 h after venipuncture, and they were not thawed and refrozen before testing.

Statistical analysis and ethical consideration:

Statistical analysis was carried out using STATA&SE (STATA Corp., Texas, USA) and quantitative data were expressed as mean± SD. Benign and malignant subsets were statistically compared using Student's t test. Receiver oper-

Variables	Biopsy-negative (n = 73)		Biopsy-positive (n = 27)		P value
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Age (year)	66.6 ± 8.9	68.0 (23.0-82.0)	66.9 ± 6.8	66.0 (52.0-81.0)	0.856
Total PSA (ng/ml)	6.79 ± 1.84	6.70 (4.0-10.0)	7.33 ± 1.59	7.50 (4.8-10.0)	0.238
Free PSA (ng/ml)	1.43 ± 0.89	1.20 (0.40-6.79)	1.14 ± 0.59	1.0 (0.32-2.50)	0.118
PSA density	14.8 ± 8.7	12.9 (5.0-50.0)	20.5 ± 10.0	19.2 (8.0-46.0)	0.006
Percent free PSA	21 ± 10.1	18.53 (5.0-74.0)	15.3 ± 6.7	14.67 (5.0-31.0)	0.010
Percent free PSA density	0.44 ± 0.25	0.39 (0.08-1.43)	0.38 ± 0.16	0.35 (0.16-0.74)	0.370
Prostate volume (cm^3)	56.0 ± 25.8	50.0 (13.0-147.0)	43.3 ± 17.9	42.0 (12.0-86.0)	0.015

PSA; prostate specific antigen, SD; standard deviation.

Table 1 Clinical and demographic results stratified by biopsy findings.

ating characteristics (ROC) curves with respect to the efficacy of differentiating benign and malignant prostate species for total PSA, free PSA, PSA density, percent free PSA and percent free PSA density were generated. The area under the corresponding curves was calculated and used as an index of accuracy. For all tests, a p value <0.05 was considered significant. The research protocol accommodates to the ethical guidelines of the 1975 Declaration of Helsinki.

Results

A total of 100 consecutive male patients (mean age; 66.7 ± 8.4 years) were studied, with 27 patients having biopsy-proved prostate carcinoma and 73 patients benign prostate hyperplasia (BPH) as their etiology. According to the inclusion criteria, all patients had elevated serum PSA levels in the 'gray zone' (4.0 - 10.0 ng/ml), digital rectal examinations which were not compatible with prostate cancer and no history of recent drug consumption. Clinical and demographic findings of current study are shown in Table 1 stratified by biopsy findings. There were no significant differences in patients age, total PSA, free PSA and percent free

PSA density between patients with benign and malignant prostate diseases. However, PSA density, percent free PSA and prostate volume were significantly different between patients with benign and malignant biopsy results (P value= 0.006, 0.010 and 0.015, respectively).

The ROC curves for PSA density, percent free PSA and percent free PSA density are depicted in figures 1 to 3, respectively. The AUCs for total PSA, free PSA, PSA density, percent free PSA and percent free PSA density and their statistically differences with percent free PSA density are illustrated in Table 2. The AUC for percent free PSA density (0.448) was not significantly higher than the AUC for percent free PSA (0.308), free PSA (0.357) and total PSA (0.576). PSA density was the only test with AUC (0.685) which was significantly greater than percent free PSA density (P value < 0.001).

Discussion

Following this study we found that the ROC curves for total PSA, free PSA, percent free PSA and percent free PSA density were essentially identical and the AUC for percent free PSA density was not significantly higher that

Variable	n	AUC	SE	95% CI	p value*
Total PSA	100	0.576	0.061	0.456-0.696	0.147
Free PSA	100	0.357	0.068	0.224-0.491	0.112
PSA density	100	0.685	0.061	0.564-0.806	<0.001
Percent free PSA	100	0.308	0.066	0.178-0.437	0.096
Percent free PSA density	100	0.448	0.064	0.322-0.575	N/A

n; sample size, AUC; area under the curve, SE; standard error, CI; confidence interval, PSA; prostate specific antigen, NA; not available due to equal values.
*compared with percent free PSA density values.

Table 2. The AUCs for total PSA and their modifications.

the previously mentioned tests. In the study, PSA density yielded the highest AUC (0.685), which was significantly greater than the accuracy of the percent free PSA and percent free PSA density.

A limitation of PSA as a tumor marker is the substantial overlap in values between men with benign prostatic hyperplasia (BPH) and those with prostate cancer [16,17]. In addition, serum PSA level increments may be originated from digital rectal examination, prostatic inflammation, sexual activity, infarction, or trauma, as well as patient`s age and prostate volume [7-9,18,19]. On the other hand, the use of PSA as a screening modality brings clinicians the dilemma of what to do with a patient who has an abnormal value. Currently, many of these patients undergo one or more ultrasound-guided biopsies. Essentially, patients with serum PSA levels of 10 ng/ml require systematic biopsies. However, in a subset of patients with serum PSA of 4.0 to 10 ng/ml and normal digital rectal examinations, recommendation regarding biopsy remains somewhat controversial. Regarding these disadvantages numerous studies introduced multiple refinements in the interpretation of the total PSA such as PSA density, transition zone PSA density, age-referenced PSA, PSA velocity and percent free PSA to enhance its precision and got invaluable but to some extent controversial results[10,13, 14].

Benson et al [19] introduced the term PSA density in 1992 to correct PSA for prostate volume since prostate cancer releases more PSA per volume unit into the circulation than BPH [19,20] PSA density is defined as the total serum PSA level (ng/ml) divided by the transrectal ultrasound determined prostate volume (cc). Ideally PSA density could better differentiate between prostate cancer and BPH in men with intermediate (4 to 10 ng/ml) PSA levels and a normal digital rectal examination [9]. Our findings, although with some controversies [21-23] could not demonstrate any statistical or clinical difference between those with positive
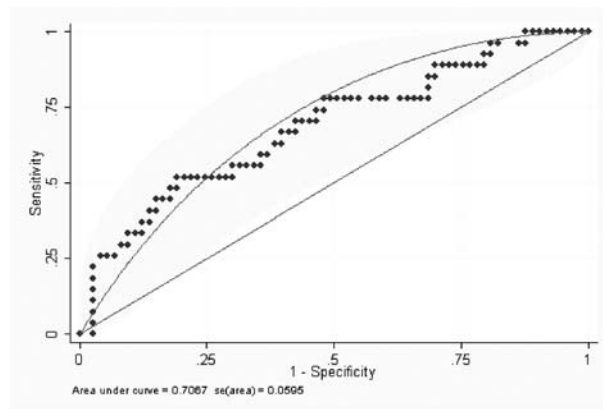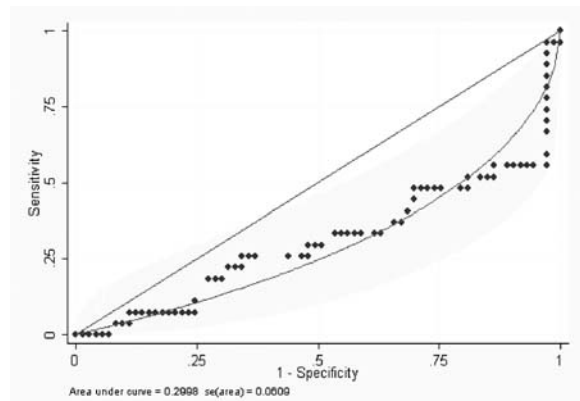

Fig. 1. ROC curve for PSA density.

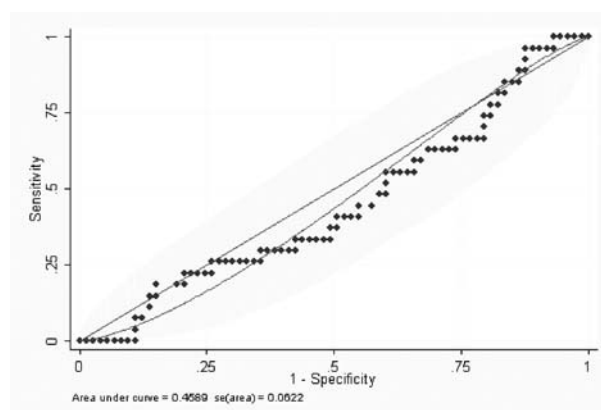

Fig. 2. ROC curve for percent free PSA.

Fig. 3. ROC curve for percent free PSA density.

194

and negative prostate needle biopsies using PSA density, were also in line with some other studies [24]. Limitations of PSA density include its dependence on the examiner to estimate accurately the prostate volume by transrectal ultrasound, and the estimated BPH volume does not necessarily correlate with serum PSA levels since the epithelium-to-stroma ratio varies considerably between individuals, and only the epithelium produces PSA [17-20]. These limitations have led to conflicting results regarding the usefulness of PSA density to detect prostate cancer [21,25].

In 1995 percent free PSA was reported by Catalona et al. as another modality in refining prostate cancer screening [26]. Percent free PSA, another refinement of PSA with an inverse relationship with the probability of having prostate cancer [5,15,27,28], has independently demonstrated an improvement in the specificity of prostate cancer screening [15, 26, 29]. The implication is that approximately 19 to 64% of negative biopsies could be eliminated using percent free PSA [9]. Despite these encouraging results, percent free PSA has the disadvantage of being dependent to the patient's age (18, 30 and 31) and prostate volume [30, 32].

Therefore, with the hypothesis of correcting percent free PSA for prostate volume, Baltaci et al [10] introduced percent free PSA density to improve the specificity of percent free PSA and found that percent free PSA density is more specific than percent free PSA in distinguishing benign from malignant prostate pathology in men with a normal digital rectal examination and an intermediate PSA level. This finding is in contrary with our results which not only did not find any higher specificity for percent free PSA density over percent free PSA, nor did find any statistically significant difference in percent free PSA density in regard to benign and malignant biopsy results. Inasmuch as percent free PSA was significantly different between benign and malignant prostate biopsy results in

our study but not in the study performed by Baltaci et al., this controversy may be secondary to the usage of various diagnostic kits from different manufacturers for the detection of free PSA.

Regarding controversies in the literature, this study may provide information to further clarify the best screening test for the early detection of prostate cancer in patients with total PSA levels within the 'gray zone' of 4-10 ng/ml. Despite several studies performed to assess the usefulness of total PSA and its refinements to detect prostate cancer in patients with intermediate PSA level, the decision on the need of prostate biopsy should not only be based on either of these tests, as they may be affected by different factors such as age and prostate volume. Further studies with larger sample sizes are necessary to evaluate the best screening test for the early detection of prostate cancer in patients with intermediate levels of total PSA levels.

In conclusion, we found that PSA density is the most accurate test for the detection of prostate cancer in patients with intermediate PSA levels of 4-10 ng/ml and normal findings on digital rectal examination. Percent free PSA density was not significantly more accurate than percent free PSA and bearing in mind the costs imposed to perform transrectal ultrasound to determine the volume of prostate. We can conclude that percent free PSA is more cost-effective and hence more appropriate than percent free PSA density to screen prostate cancer.

Acknowledgement

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