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ORIGINAL ARTICLE

Significance Of Prostate Specific Antigen And Prostate Volume In The Diagnosis Of Prostatic Diseases

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ABSTRACT

Background and Objectives: Prostate Specific Antigen (PSA) has been used as a screening tool for prostate cancer. Controversies exist with studies showing significant prostate cancer in men with normal PSA. The objective is to study the role of PSA in differentiating benign and malignant diseases of prostate and Prostate Specific Antigen Density (PSA-D) in prostate diseases.

Methods: This is a prospective study of data from 100 patients in our Medical College Hospital from July 2005-May 2007. All patients with lower urinary tract symptoms (LUTS), suggestive of prostate enlargement, were included. Patients with urethral strictures, calculi or with a previous history of surgeries and procedures on the prostate were excluded. All patients underwent digital rectal examination, serum PSA measurement and transrectal ultrasonography to measure prostate volume. Prostatic pathology was confirmed by biopsy in all patients after obtaining informed written consent.

Results: The mean age was 68.05 ± 8.27 (SD) years. 40% of the patients had PSA values between 4-10ng/ml. There was no statistical correlation between age and PSA. Digital rectal examination had a sensitivity of 65.5% for detection of prostate cancer. Prostatic volume, as an independent variable, was not significant in predicting malignancy. Total PSA done in all cases was significant for the detection of cancer at levels >10ng/ml. PSA-D improved the sensitivity to detect malignancy.

Conclusion: PSA is significant in detecting prostate cancer at values >10ngm/ml. Prostate volume is not significant for diagnosis of prostatic diseases but PSA-D has a high sensitivity (96.55%) in detecting prostate cancer.

Key words: Prostate Specific Antigen (PSA); Prostate Volume; Digital rectal Examination (DRE); PSA density (PSA-D)

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Introduction

The burden of prostate diseases on Health Departments throughout the world is on the rise, as a consequence of the improved survival rate of the population. Benign Prostatic Hyperplasia (BPH) accounts for the majority of bladder outflow obstructions in men >50 years of age, with prostate cancer being an important differential diagnosis. Therefore, it is necessary to investigate the patient thoroughly before planning the management.

Prostate Specific Antigen (PSA) has been used as a screening tool for cancer. But controversies exist [1],[2],[3] regarding its usefulness, with studies showing significant prostate cancer in men with normal PSA. PSA and prostate volume have an age dependant log linear relationship [4].Studies have shown that prostate volume with PSA correlation is a better indicator for prostate diseases [5], [6]. This study aims to correlate PSA levels and PSA Density in prostate diseases in our clinical set up, for diagnostic accuracy and for planning further management.

Objectives Of The Study:

1. To study the role of PSA in differentiating benign and malignant diseases of prostate.
2. To study Prostate Specific Antigen Density (PSA-D) in prostate diseases.

Material And Methods

This study consecutively included one hundred patients with symptoms suggestive of prostate diseases, registered at our Medical College Hospital from July 2005 to May 2007. Ethical committee clearance was obtained prior to the study. All patients were admitted and underwent a standard evaluation of digital rectal examination, serum PSA measurement and transrectal ultrasonography (done by a single sonologist) to measure prostate volume. Serum PSA was estimated on the day of admission before any procedures on the prostate or urethra. Patients were prepared with proctoclysis enema in the night and early morning, and a transrectal ultrasound was performed on all patients to measure the prostate volume and to calculate the prostate specific antigen density. Prostatic pathology was confirmed by transrectal biopsy (was done by a single urologist, uniform technique) in all patients after obtaining informed written consent. The histopathology report was confirmed by a single pathologist. Collected data were tabulated and analyzed for possible association using Chi-square Test, along with sensitivity, specificity and predictive values.

Inclusion Criteria

All patients were admitted to our Medical College Hospital with lower urinary tract symptoms (LUTS) suggestive of prostate pathology.

Exclusion Criteria:

1. Patients with other causes of LUTS like urethral strictures or calculi.
2. Previous history of surgeries or procedures on the prostate.

PSA blood test: After the generation of specific anti-PSA antiserum, it is used to identify the presence of PSA in the sera of metastatic prostate cancer patients by rocket-immunoelectrophoresis (IEP). PSA values obtained from the patient's sera and from prostate tissues proved to be immunologically identical. These significant findings provided the basis for the development of an enzyme-linked immunosorbent assay (ELISA).

It has been observed that when sera from metastatic prostate cancer patients were examined by gel filtration, the reactive antigen or the circulating PSA antigen eluted as a peak at a molecular weight of 96,000, while the antigen isolated from prostate tissues eluted at 34,000. Additional studies with immunoprecipitation and two-dimensional IEP revealed that in addition to PSA, the serum PSA peak contained "normal serum protein contaminants." This was the first report concerning complexed PSA, as it is called today.

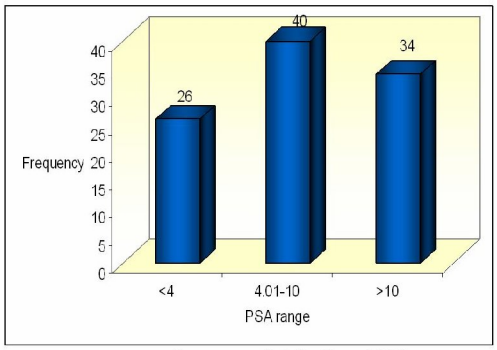
Results

The mean age in our patient group was 68.05 years, with a standard deviation of 8.27 and 81% of the patients were in the age group between 56 to 75 years.[Table/Fig 1]

(Table/Fig1) Age distribution in the study

Age of the patient	No. of the patient (percentage)
<55	5%
56-75	81%
>75	14%

A majority of patients in the study had serum PSA values between 4.01-10ng/ml [Table/Fig 2].



(Table/Fig 2) Frequency distribution of PSA range

P value 0.107

In our study, there was no log linear increase of PSA values with age. The correlation was not significant [Table/Fig 3].

(Table/Fig 3)Correlation between Age and PSA

		PSA range			Total
		0-4	4.01-10	>10	
Age range	<55	4	1	1	6
	56-75	22	31	27	80
	>75	1	7	6	14
Total		27	39	34	100

The correlation between Digital rectal examination and Histopathology, revealed the following: [Table/Fig 4]

Sensitivity for detection of prostate cancer = 65.5%

Specificity for detection of prostate cancer = 91.5%

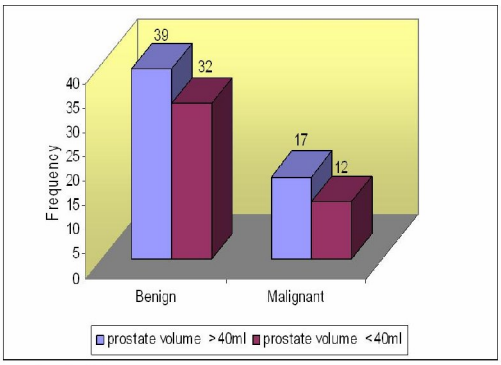
Positive predictive value = 76%

Negative predictive value = 86.7%

(Table/Fig 4)Correlation between Digital rectal examination and Histopathology

		HPE		Total
Clinical imp		Benign	Malignant	
	Benign	65	10	75
	Malignant	6	19	25
Total		71	29	100

In our study, prostate volume was found to be insignificant in differentiating the benign from the malignant disease of the prostate [Table/Fig 5].



p value 0.736

(Table/Fig 5)Correlation between Prostate volume and Histopathology

Twenty nine cases were detected to have prostate cancer, among which 27 patients had a PSA value more than 10 ng/ml and 2 patients had a PSA value within the range of 4.01-10ng/ml. [Table/Fig 6].

(Table/Fig 6) Correlation between PSA range and Histopathology

		HPE		Total
		Benign	Malignant	
PSA range	0-4	27		27
	4.01-10	37	2	39
	>10	7	27	34
Total		71	29	100

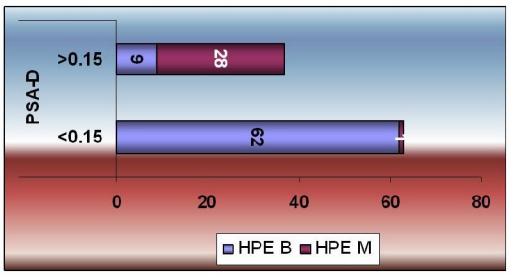
Hence, the correlation of the PSA value range of more than 10ng/ml to the histopathology was done and the cross tabulation result is as shown in [Table/Fig 7].

(Table/Fig 7) Correlation at PSA>10 ng/ml with Histopathology

		HPE		Total
PSA range		Benign	Malignant	
	<10	64	2	66
	>10	7	27	34
Total		71	29	100

When PSA values were more than 10ng/ml, our study was found to have a sensitivity of 93.1%; a specificity of 90.1%; a positive predictive value of 79.41% and a negative predictive value of 96.97% for the detection of prostate cancer.

PSA Density is the ratio of Total Serum PSA (ng/ml) to the Prostatic Gland Volume (ml). PSA-D had a sensitivity of 96.55%; specificity of 87.3%; positive predictive value of 75.67% and negative predictive value of 98.4% [Table/Fig8].



(Table/Fig 8)Correlation between PSA Density (PSA-D) and Histopathology

Discussion

The first tumour marker for prostate cancer was Acid Phosphatase which was described by Gutman and Gutman [7] in 1938, but lost its importance as it was not very prostate specific. The search for a tumour marker which was more sensitive and specific for prostate cancer led to the discovery of several prostate antigens that subsequently came to be known as Prostate Specific Antigen. While many have claimed to be the first to

discover PSA in seminal plasma, most authorities credit Wang and associates who were working at the Roswell Park Cancer Institute in Buffalo, New York, in conjunction with Murphy et al, also at Roswell Park at that time, as having clearly described this protein on gel electropheresis. [8],[9] Prostate-specific antigen testing was introduced into clinical use in the mid-1980s.[10] PSA is a glycoprotein which is secreted by prostatic epithelial cells, and its serine protease activity lyses the clotted ejaculate to enhance sperm motility. It belongs to the Human Kallikrein (HK) family of proteins, i.e., HK3, and is under tight androgen regulation.

The advent and refinement of ultrasound technology has provided a new and important method to examine the prostate. Prostatic volume estimation by transrectal ultrasound is a common clinical procedure. It's uses include the pre-treatment assessment of prostate size and interpretation of elevated prostate specific antigen (PSA) levels. Transrectal ultrasound (TRUS) was initially described as a technique to evaluate rectal pathology. In 1963, Takahashi and Ouchi [11], [12], [13] were the first to describe the use of TRUS to evaluate the prostate. The first clinically applicable images of the prostate obtained with TRUS, were described in 1967 by Watanabe et al.[13].

Prostate growth appears to be related to prostate volume. Numerous studies have confirmed that prostate volume is an important predictor of BPH progression[14],[15]. These studies confirmed that the risk of acute urinary retention increased with increased prostate size, as measured by transrectal ultrasound (a 3-fold increased risk for prostates >30 ml). Roehrborn CG et al.[16] focused on a database of 4627 patients from either BPH or safety trials, for whom baseline data regarding age, prostate volume, and serum prostate-specific antigen (PSA) level were available. Overall, the results suggested that while prostate size increases throughout adulthood, PSA levels do not tend to increase with age until after age 40.

Pauler DK et al [17] investigated the prevalence of prostate cancer among men in the Prostate Cancer Prevention Trial, who had a PSA level of 4.0ng per milliliter or less. They concluded that biopsy-detected prostate cancer including high-grade cancers is not rare among men with PSA levels of 4.0ng per milliliter or less--levels generally thought to be in the normal range.

Sang Eun Lee et al [18] studied 755 patients with a serum PSA level of 2.0–10.0ng/ml, who underwent TRUS guided systematic biopsy. Patients were divided into low (PSA 2.0–4.0ng/ml, *n* = 144) and intermediate (PSA 4.1–10.0ng/ml, *n* = 611) PSA groups. Patients in the low PSA group had significantly smaller prostates and lower PSA density. The rate of cancer detection was 16.7% in the low PSA group and 23.7% (145 of 611) in the intermediate PSA group. In a study

conducted by Babain et al.[19], 151 men who had serum PSA values between 2.5 and 4.0ng/ml, underwent prostate biopsy. Cancer was identified in 24.5% of the patient's biopsies. The median age of the men with cancer was 62 years.

In prostate cancers, a study by Stephen JF[20] concluded that men with smaller prostates had more high-grade cancers and more advanced disease, and suggested that prostate size may be an important prognostic variable that should be evaluated to predict biochemical progression pre- and postoperatively.

PSA Density

It enhances PSA performance. Babain et al [21] were the first to describe the relationship between prostate size and PSA. PSA density is calculated as the ratio of Total Serum PSA (ng/ml) to the Prostatic Gland Volume (ml). Isikay et al[22] studied the role of prostate-specific antigen density in the early detection of prostate cancer and assessed the hypothesis that PSAD offers significant advantages over prostate-specific antigen (PSA) alone in the evaluation of patients with benign (BPH), pre-malignant (PIN) and malignant prostatic diseases. They concluded that the information provided by PSAD is superior to absolute PSA values in the differentiation between BPH and carcinoma prostate, but PSAD was not able to add more information on differentiating BPH from pre-malignant conditions. Klingler et al[23] studied the use of PSAD in enhancing the specificity of PSA in detecting prostate cancer. They studied 77 patients and concluded that PSAD does not significantly identify patients at the risk of prostate cancer, at levels of PSA between 4-10ng/ml.

Iwaki et al[24] studied the predictive value of prostate specific antigen density in the detection of prostate cancer in patients with elevated prostate specific antigen levels and normal digital rectal findings. For all patients with PSA levels of 4.1-10.0 ng/ml, a PSAD cutoff value of 0.1 reduced the number of biopsies 22.5% (16 of 71 cases). These results suggested that by the measurement of PSAD, some patients with benign disease could be spared a biopsy which would have been performed, based on the PSA results alone.

Modification of the PSA-D is the PSA transition zone density, defined as the serum PSA that is divided by the volume of the transition zone. But the effectiveness of the latter has yet to be proved [25],[26]. Substantial cost is added to early detection by using PSA density instead of the raw PSA level, and measuring PSA density is not practical in primary care settings[27].

Total serum PSA and Prostate volume were the two main indices taken into consideration in our study. A majority of patients were in the age group of 56-75 years in our study, which corresponds to extensive studies done by other researchers [28],[29].The relatively higher percentage of patients in the

PSA range between 4-10ng/ml, when compared to larger studies [30], may be attributed to the other associated features like urinary tract infection and acute retention of urine, as many patients presented to the emergency set up with the above complaints. In the present study, there was no significant rise in serum PSA values with age. This is in contrary to the findings in other larger study populations [28], [29] and may be attributed to the relatively small sample size.

The first clue to a malignant prostate disease is digital rectal examination. In our study, DRE had a sensitivity of 65.5% in detecting prostate cancer [31]. In a rare study that reported long-term outcome, Gerber et al. [32] and Chodak et al [33] found that men who had cancer that was discovered on a serial digital rectal examination, seemed to have a more favourable stage shift than men who had cancer that was discovered on initial examination. So, in spite of being a subjective finding in the diagnosis of prostate diseases, it gives the examiner a useful insight to the pathology that he is dealing with.

Prostate volume as an independent modality for diagnosing prostate diseases, has no statistically significant role, as is indicated in this study, which is in concurrence of the observations made by Mcconnel et al [34].Total serum PSA has a significant role to play in prostate cancer detection, as shown in our study, that at PSA levels of more than 10 ng/ml, sensitivity was 93.1%; specificity was 90.1%; positive predictive value was 79.41% and negative predictive value was 96.97%. These results are comparable to the studies of Cooner et al [13, 35] (sensitivity 65.7% and specificity 82%) and Brawer et al [25] (sensitivity 75% and specificity 94.1%). While correlating PSA levels >4 and cancer, our study had a positive predictive value of 40.8% and is in concurrence with other larger study series as shown in the table [Table/Fig 9].

The PSA density had a high sensitivity (96.55%) and specificity (87.3%) in our study. This is comparable to the larger study done by Van Iersel et al. [37], who had a sensitivity of 92% for the detection of prostatic malignancy at PSAD values >0.15.

(Table/Fig 9) Comparison of positive predictive value (PPV) of PSA>4 ng/ml with other studies

Author	Year	No of biopsies	PPV
Bazinet et al.[36]	1994	565	37
Catalona et al.[30]	1994	1,325	37.1
Cooner et al.[35]	1990	436	35
Rommel et al [37]	1994	2,020	41
Our Study	2006	100	40.8%

Limitations Of The Study:

Our study includes patients with acute retention of urine. This causes elevation of PSA, which might have changed our results. We have taken biopsies from all patients, including those with a PSA value of less than 4 and normal DRE. We could have avoided biopsies in these patients. However, we have obtained informed written consent and ethical committee clearance. A similar study has been reported by Pauler DK et al [17]. It would have been

good if we had analyzed the sensitivity and specificity of both DRE and PSA values of less than 4, 4-10 and more than 10 alone and in combination.

Conclusion

Undiagnosed prostate cancer is highly prevalent, especially among older men. Although many of these cancers may be considered incidental, evidence suggests that consideration of screening is warranted, because earlier diagnosis of clinically significant cancers often has the potential to improve outcome. [39] Serum PSA estimation is a useful tool to detect prostate cancer at values >10ngm/ml. Prostate volume, as an independent entity, is not significant for the diagnosis of prostate diseases. When prostate specific antigen density is calculated, it has a high sensitivity (96.55%) for the diagnosis of prostate cancer. But undoubtedly, new approaches to interpreting PSA values in individual patients will be discovered and new markers will be identified to aid clinicians who deal with one of the most common neoplasm in men.

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