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Efficacy of Prostate Specific Antigen as a Tumor Marker in Differentiating Prostatic Carcinoma from Other Prostatic Lesions

Gautam N. Gole[a], Sheetal G. Gole[b], Dilutpal Sharma[c]

[a]Professor & HOD, Department of General Surgery, Shaheed Hasan Khan Mewati Government Medical College, Nalhar, Nuh, Mewat, Haryana 122107, India. [b]Professor & HOD, Department of Pathology, Employee's State Insurance Corporation Medical College, Faridabad, Haryana 121001, India. [c]Professor, Department of Biochemistry, King George's Medical University, Lucknow, Uttar Pradesh 226003, India.

Abstract

Prostate Specific Antigen has been widely used in diagnosis and management of patients with prostate cancer. It may be elevated in other prostatic diseases. The objective of this study was to evaluate its efficacy to diagnose and differentiate between benign and malignant enlargements. Study also determines relationship between serum prostate specific antigen levels and histopathologic findings in prostatic biopsies. *Materials and Methods:* Study was done at a tertiary care hospital in Telangana over 6 years. A total of 500 patients were included in the present study. Prior to surgery serum prostate specific antigen levels were determined for all the cases and the biopsies were sent for histopathology. *Results:* In the present study mean age of presentation was 64.24 years. Amongst the 500 cases, 451 (90.2%) were of Benign Prostatic Hyperplasia, 32 (6.4%) were of Prostatic Intraepithelial Neoplasia and 17 (3.4%) were of Prostatic Adenocarcinoma. Serum prostate specific antigen levels range distribution was considered into 3 groups as: 0-4 ng/ml included 404 (80.8%) cases, 5-9 ng/ml with 44 (8.8%) cases and 10 ng/ml included 52 (10.4%) cases. Present study revealed sensitivity 70%, specificity 91%, diagnostic accuracy 91%, positive predictive value 23%, and the negative predictive value 98%. *Conclusion:* PSA is specific for prostate but not for prostate cancer. PSA is raised in cancer, prostatic infection, urinary retention & Nodular Prostatic Hyperplasia. There is need of a more reliable and precise serum marker that reflects prostate cancer.

Corresponding Author: Sheetal Gautam Gole, Professor & HOD, Department of Pathology, ESIC Medical College & Hospital, Faridabad, Haryana 121001, India.
E-mail: drsheetalgole@rediffmail.com

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Introduction

In male genital tract the prostatic lesions comprising of non-neoplastic and neoplastic (both benign and malignant tumors) are hormone (androgen) dependent [1,2]. Approach to the diagnosis of prostate cancer has changed radically in the recent years. The emphasis is on an early diagnosis while the process is still localized to the prostate and on radical prostatectomy which is expected to cure the disease. An early diagnosis can be achieved by measuring the serum prostate specific antigen (PSA) levels, ultrasonography (USG) and by doing prostatic biopsies. Incidence of prostate cancer has been reported to be about 6.8/100000 [3] and it has been observed that the incidence is increasing [4].

PSA is a glycoprotein serine protease and was first identified by Wang e*t al*. in 1979. It is a protein manufactured only in the prostate. PSA is the enzyme responsible for liquefaction of semen within a few minutes after it has clotted [6,7]. PSA levels in the blood rise if the barrier between the epithelium and the blood stream is damaged. Three typical sources for damage are: cancer, bacterial infection, and prostate infarction or destruction of part of the prostate by damage to its blood supply [5-7].

PSA is secreted exclusively by the prostatic epithelium. It is not a tumor specific antigen as it reacts with the prostatic material in benign and malignant tissues. It can transiently increase after the manipulation and the irritation of the genitourinary tract. Nevertheless, PSA is expressed by the cancer

tissues at 3 ng/ml in the blood per gram of cancer, as against 0.3 ng/ml/gm of tissue in BPH. Normal level values in healthy males are usually < 4 ng/ml. Serum PSA levels above the reference range have been reported in 50% of the men with stage A prostate cancer, in 80% of the men with stage B disease and in 100% of the men with stage C and D disease.

Serum PSA levels are influenced by the patients' age and prostate size. In a healthy 60 years old man with no evidence of prostatic carcinoma, the serum PSA concentration increases by approximately 3.2% per year (0.04 ng/ml). Chen *et al* [8] study states utilization of age specific ranges has been found to be useful in predicting the survival outcome in Asian men.

Aims and Objectives

i. To study prevalence of distribution of various prostatic lesions.
ii. To evaluate the utility of PSA assay as a method of investigation in diagnosis of prostatic lesions.
iii. To correlate morphological types with Serum PSA levels.
iv. To study the correlation of serum PSA levels and prostatic carcinoma.

Material and Methods

The study was done at a tertiary care hospital in Telangana for the duration of 6 years. A total of 500 patients who were clinically and radiologically recognized to have an enlarged prostate were included in the study. Prior to procedure serum PSA levels were determined for all the cases. Relevant clinical data including the provisional diagnosis, age and mode of presentation were documented.

Procedures included Transurethral resection of prostate (TURP), open prostatectomy, and prostatic biopsy. Of these 500 patients, 430 patients underwent TURP, 18 patients underwent open prostatectomy and 52 having preoperative serum PSA of ≥ 10 ng/ml were subjected to prostatic biopsy. All prostatic specimens were sent for histopathology. All the 500 prostate specimens were fixed in 10% neutral buffered formalin and 5µ sections were stained with Hematoxylin and Eosin (H&E) stain. Various histopathological diagnoses were as following: Benign Prostatic Hyperplasia (BPH), BPH with chronic prostatitis, BPH with granulomatous prostatitis, BPH with basal cell hyperplasia, Prostatic intraepithelial neoplasia (PIN) [Low-grade PIN (LGPIN) and High-grade PIN (HGPIN)] and Prostatic adenocarcinoma. Histopathological diagnosis was considered as a gold standard and was compared with PSA levels to determine the sensitivity and specificity of PSA assay. The PSA assay was carried out using the ARCHITECT for total PSA assay by Chemiluminescent microparticle immune assay (MEIA).

Results

A total of 500 prostate cases were studied for serum PSA levels and simultaneous histopathological examination of the biopsies. The youngest patient was 45 years old and the oldest patient was 85 years old with a mean age of presentation being 64.24 years. Peak age incidence for various prostatic lesions was 60-69 years accounting for 402 (80.4%) cases (Table 1). Amongst the 500 cases, 451 (90.2%) were of BPH (Figure 1 & Figure 2A) which included BPH only 394 (87.36%), BPH with Chronic Prostatitis 32 (7.09%), BPH with Granulomatous Prostatitis 10 (2.21%), BPH with Basal Cell Hyperplasia 15 (3.32%). The second common lesion was PIN 32 (6.4%), which constituted LGPIN 22 (68.75%) and HGPIN 10 (31.25). Prostatic Adenocarcinoma (Figure 2B, 2C & 2D) cases were 17 (3.4%) (Table 2). The PSA levels range distribution was considered into 3 groups as: 0-4 ng/ml included 404 (80.8%) cases. Of these BPH were 396 (87.80%), PIN were 6 (18.75%), and Adenocarcinoma were 02 (11.76%). PSA levels 5-9 ng/ml included 44 (8.8%) cases. Amongst this BPH were 32 (7.09%), PIN were 9 (28.125%), and Adenocarcinoma were 3 (17.64%). More than or equal to 10 ng/ml included 52 (10.4%) cases. Amongst this BPH were 23 (5.09%), PIN were

Table 1: Age distribution

Age in Years	No of Patients (%)
40-49	06 (1.2)
50-59	25 (5)
60-69	402 (80.4)
70-79	59 (11.8)
80-89	08 (1.6)
	500 (100)

17 (53.125%), and Adenocarcinoma were 12 (70.58%) (Table 3). Amongst the total 500 total cases, the case distribution was as follow: True positive cases (12); false positives cases (40); true negative cases (443); and false negative cases (5) (Table 4). Present study revealed sensitivity 70%, specificity 91%, diagnostic accuracy 91%, positive predictive value 23%, and the negative predictive value 98%.

Table 2: Lesion Distribution

Histopathological Diagnosis	No. of Patients (%)
BPH [Total]	451 (90.2)
BPH Only	394 (87.36)
BPH with Chronic Prostatitis	32 (7.09)
BPH with Granulomatous Prostatitis	10 (2.21)
BPH with Basal Cell Hyperplasia	15 (3.32)
PIN [Total]	32 (6.4)
LGPIN	22 (68.75)
HGPIN	10 (31.25)
Prostatic Adenocarcinoma	17 (3.4)
	500 (100)

BPH: Benign Prostatic Hyperplasia; PIN: Prostatic Intraepithelial Neoplasia; LGPIN: Grade Prostatic Intraepithelial Neoplasia; HGPIN: High Grade Prostatic Intraepithelial Neoplasia

Table 3: Distribution of different lesions according to Prostate Specific Antigen Levels

PSA range (ng/ml)	Total (%)	BPH (%)	PIN (%)	Adenocarcinoma (%)
0-4	404 (80.8)	396 (87.80)	6 (18.75)	02 (11.76)
5-9	44 (8.8)	32 (7.09)	9 (28.125)	03 (17.64)
≥ 10	52 (10.4)	23 (5.09)	17 (53.125)	12 (70.58)
	500 (100)	451	32	17

BPH: Benign Prostatic Hyperplasia; PIN: Prostatic Intraepithelial Neoplasia

Table 4: Diagnostic accuracy of Prostate Specific Antigen level assay for prostatic malignancy

PSA level	Histopathological Diagnosis		Total
	Positive for carcinoma	Negative for carcinoma	
Positive for carcinoma (≥ 10ng/ml)	True Positive: 12	False Positive: 40	52
Negative for carcinoma (0-9 ng/ml)	False Negative: 5	True Negative: 443	448
Total	17	483	500

Table 5: Comparison of benign and malignant proliferative prostatic lesions with other studies

Lesion	Maru *et al.*[11]	Djavan *et al.*[13]	Shashidhar *et al*[14]	Present Study
BPH	81.53%	83%	90.60%	90.2%
Adenocarcinoma	6.87%	17%	8.28%	3.4%

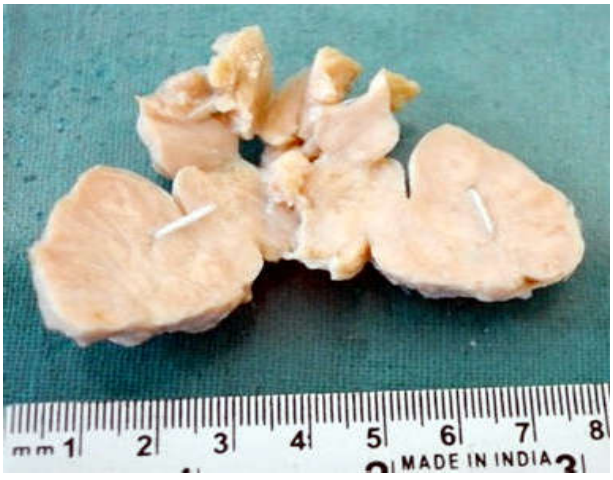

Figure 1: Gross specimen of Benign Prostatic hyperplasia

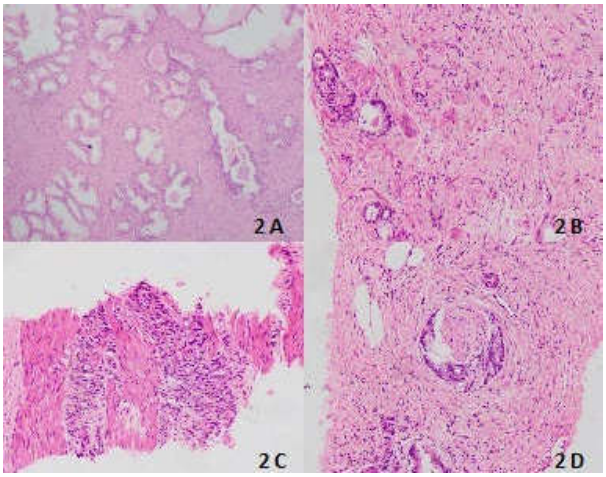

Fig. 2A: Benign Prostatic hyperplasia: Photomicrograph showing glandular enlargement of the prostatic glands with few glands showing intraluminal papillary infolding and corpora amylacea (4X) **2B:** Prostatic Adenocarcinoma (Prostatic biopsy): Photomicrograph showing tumour with fused glands and forming glomeruloid structure. (10X) **2C:** Prostatic Adenocarcinoma (Prostatic biopsy): Photomicrograph showing tumour cells infiltrating into the stroma. (10X). **2D:** Prostatic Adenocarcinoma (Prostatic biopsy): Photomicrograph showing perineural tumour cell invasion. (40X)

Discussion

The early diagnosis and management of BPH and adenocarcinoma prostate could be achieved in the first phase by the combined use of serum PSA estimation, digital rectal examination (DRE) and in the second phase prostate imaging by transrectal ultrasound of prostate gland (TRUS), and ultrasound (USG) guided biopsy of prostate in select cases. Of these, serum PSA played a dominant role because of its highest sensitivity for Carcinoma Prostate compared to other modalities [9].

Diagnostic efficiency of any tumor marker is judged by its specificity and sensitivity. It is well documented in literature that PSA concentration in healthy males varies from one population to other throughout globe. Lowest values of serum PSA in healthy males compared to many other populations in Western as well as Asian Pacific countries have been reported [10].

PSA is produced exclusively by the epithelial cells lining the prostatic acini and ducts of prostatic tissue. Because of its high specificity for prostate tissue, PSA is the preferred serum marker for Prostatic carcinoma. Unfortunately, PSA is specific for prostate tissue but not for prostate cancer. It is also found in abnormal concentrations in normal and benign lesions of the prostate such as BPH and other non-neoplastic lesions [11].

Apart from prostatic volume, other factors contributing to increase in PSA in men is age, episodes of subclinical or clinical prostatitis, intermittent bouts of prostatic ischemia, infarction and the presence of prostate cancer that cannot be detected by currently available methods [5]. Furthermore, as men grow older, their prostate glands may become more "leaky". The normal physiological barriers that keep PSA in the prostate duct system may become more permeable and allow serum PSA to enter the general circulation via the capillaries and lymphatics [11].

The need for an accurate marker is driven by the fear of unnecessary biopsies on the one hand and the more danger risk of missing a treatable prostate disease on the other. As PSA is organ specific and not prostate cancer-specific, there is considerable degree of overlap between patients with benign pathologies such as prostatitis, benign hyperplasia or urinary retention [12].

In the present study, patients were aged predominantly between 60-69 years. The mean age at diagnosis in this study was 64.24 years. In patients with BPH, 396 (87.80%) had serum PSA of less than 4 ng/ml, 32 (7.09%) had serum PSA in the range of 5 to 9 ng/ml and 23 (5.09%) patients had serum PSA more than 10 ng/ml. Almost all patients 12 (70.58 %) with adenocarcinoma had raised serum PSA of more than 10 ng/ml, two patients (11.76%) were having a serum PSA of 0-4 ng/ml and three patients (17.64%) were having a serum PSA of 5 - 9 ng/ml. This study revealed a statistically significant correlation between serum PSA and adenocarcinoma. These findings were consistent with the study conducted by Djavan *et al.* and Shashidhar *et al.* [13, 14] (Table 5).

In our study, 32 (7.09%) had serum PSA in the range of 5 to 9 ng/ml and 23 (5.09%) patients had serum PSA more than 10 ng/ml diagnosed as BPH. The above findings i.e. a rise in serum PSA level ≥ 4 ng/ml does not always indicate the presence of prostatic cancer because benign conditions such as hyperplasia and prostatitis can also increase the serum PSA levels [14,15,16].

Ferrero et al. suggested that the results of PSA must be interpreted cautiously, as they could be elevated in cases of prostatitis, prostate infarction, lithiasis and abscess formation [17].

The present study revealed 17 (53.125 %) patients of PIN with PSA ≥10 ng/ml. Study done by Ellis WJ and Brawer MK suggested that patients with PIN may also have elevated PSA concentrations. When PIN is associated with elevated PSA, a high incidence of invasive carcinoma is noted on subsequent biopsy. Further investigation into the associations will further

refine the clinical utility of this powerful tumor marker [18].

In the present study, 2 patients (11.76%) and 3 patients (17.64%) having serum PSA levels (0-4 ng/ml) and (5-9 ng/ml) respectively were diagnosed as adenocarcinoma. This is explained by few cancers that are so poorly differentiated that the epithelial cells lose expression of a PSA encoding gene.[19] Therefore, a proliferating tumour does not reveal increased serum PSA levels and this can practically lead to diagnosis of tumour at later stages and poor prognosis than tumours producing more PSA [14].

In our study, true positive cases were 12, false positives cases were 40, true negative cases were 443 and false negative cases 5. Present study revealed sensitivity 70%, specificity 91%, diagnostic accuracy 91%, positive predictive value 23%, and the negative predictive value 98% considering 10 ng/ml as cut-off value.

In the study done by Vani *et al.* sensitivity and specificity with cut-off PSA value of 4 ng/ml were 100% and 38.1%, respectively. Sensitivity and specificity with cut-off PSA value of 10 ng/ml were 21.4% and 71.4%, respectively. Positive predictive value and negative predictive value with a cut-off of PSA 4 ng/ml were 39.5% and 100%, and with cut-off 10 ng/ml were 55.5% and 93.7%, respectively [20].

Conclusion

PSA can be used as a marker of choice in the primary diagnosis of a prostatic enlargement, when an early diagnosis is required or when invasive methods like biopsy are not possible due to the patients' conditions. It can be used as a marker for a prostatic malignancy in cases of disseminated unknown primary malignancies.

There is high prevalence of adenocarcinoma of prostate in patients with high serum PSA levels, but not all prostate cancers are associated with an elevated serum PSA level. Hence, there is a need of estimation and interpretation of different PSA forms like free PSA levels, prostatic density, PSA velocity, etc. to improve the sensitivity and specificity of PSA. Histopathological evaluation is confirmatory for diagnosis of prostatic lesions.

Thus, PSA is specific for the prostate but not for prostate cancer. PSA is raised in cancer, prostatic infection, urinary retention & Nodular Prostatic Hyperplasia. There is need of a more reliable and precise serum marker that reflects prostate cancer (in the current PSA range of 5 to 9 ng/ml).

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