Original Article

Urology, Nephrology and Andrology International
Volume 1 Number 2, July-December 2016

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Role of PSA in Diagnosing Carcinoma Prostate in India: Is the Situation Same as in Developed Countries

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Abstract

Background: Prostate cancer has become the single most common non-cutaneous malignancy in men. Its incidence has been rising rapidly in most countries including low risk countries like India. Present study deals with the PSA value in patients with prostatic symptoms and its correlation with the prostatic biopsy specimen. *Purpose*: (i) Co-relation of raised PSA in non- carcinoma prostate patients. (ii) At what stage does carcinoma of prostate gets diagnosed in Indian scenario. (iii) What are the treatment options opted by the patients who are diagnosed with carcinoma of prostate for the first time. *Materials and Methods:* First 500 patients that presented with lower urinary tract symptoms and prostatic enlargement through the casualty department, outpatient department and in patient department of the Department of Urology, Ruby Hall Clinic, Pune from March 2012 to February 2014 were included in the present study.Prostatic biopsy was done in cases with either increased serum PSA level and/or palpable nodule and/or suspicious TRUS findings or a combination of two out of these 3 factors. *Results:* Mean PSA value is 8.5ng/ml in BPH patients, indicating higher values in Indian patients, due to prostatitis.Maximum carcinoma prostate patients presented late with metastases. As the limit of PSA value for diagnosis of carcinoma prostate increases from 4ng/ml to 15ng/ml the sensitivity decreases and the specificity and diagnostic accuracy increases.The patients of carcinoma prostate received treatment as per their stage of presentation. *Conclusion:* In Indian context there is an overall baseline elevation of lower minimum level of the normal PSA.This is probably due to association of prostatitis in Indian population.

Keywords: BPH; Carcinoma Prostate in India; Chronic Prostatitis; PSA.

Introduction

Globally, prostate cancer is the second most frequently diagnosed cancer in men (13.6% of the total) and the fifth most common cancer overall. Prostate cancer (PCa) has become the single most common non-cutaneous malignancy in men in the Western world since 1984, and its incidence has been rising rapidly in most countries including low risk countries like India [1].

Majority of the newly detected cases of carcinoma of prostate in developed countries are staged T1c.4. This is attributed to the presence of a comprehensive screening programme with the Prostate specific antigen (PSA) as its screening tool. But the detection of cancer at a stage (T3 and beyond) where a curative procedure is not possible is a major stumbling block in India.

The introduction of PSA in 1980 began a new era in early detection of carcinoma prostate. Prostate cancer one of the commonest malignancy in men in

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developed countries which is known to have a long history before detection. Epidemiological studies have suggested that the period of 10-12 years may elapse between the origin of tumour and its detection with subsequent clinical manifestation or at autopsy.

PSA is organ specific but it is not cancer specific. This results in its inability to differentiate carcinoma of prostate from other benign conditions that lead to rise in PSA levels viz. BPH, infection, etc. Moreover, PSA is not increased in all patients with carcinoma prostate. Also, serum PSA levels are decreased in men with high body mass indices compared to normal weight men. Inspite of all this and false positive and false negative results, its organ specificity has revolutionised the treatment of carcinoma prostate. This has led to a shift in the tumour stage at diagnosis in patients with carcinoma prostate.

Currently the detection strategies for carcinoma prostate include the efficient use of the combination of digital rectal examination, serum PSA levels and the transrectal ultrasonography (TRUS) with systematic biopsy. The normal value for PSA is 0-4ng/ml. Thus, the current three pronged approached has led to increased rate of detection of carcinoma of prostate at an early stage.

Present study deals with the PSA value in patients with prostatic symptoms and its correlation with the prostatic biopsy specimen and the treatment strategies that are followed at that stage of tumour detection in Indian scenario.

Objectives

i. Co-relation of raised PSA in non- carcinoma prostate patients.
ii. At what stage does carcinoma of prostate gets diagnosed in Indian scenario.
iii. What are the treatment options opted by the patients who are diagnosed with carcinoma of prostate for the first time.

Materials and Methods

First 500 patients that presented with lower urinary tract symptoms and prostatic enlargement through the casualty department, outpatient department and in patient department of the Department of Urology at Ruby Hall Clinic Pune, from March 2012 to February 2014 were studied and included in the present study group. All these patients were worked up with detailed history and clinical examination to rule out other causes of LUTS and complications of BPH. PSA assay were done before DRE, catheterisation and TRUS to avoid false elevation in PSA levels. Prostatic biopsy was done in cases with either increased serum PSA level and/or palpable nodule or enlarged prostate on DRE and/or suspicious TRUS findings or a combination of two out of these 3 factors.

TRUS was done using real time ultrasound scanner equipped with 7.5MHz (end firing).

Volume of prostate was measured by Prolate ellipsoid formula (volume = 0.52 x L X W X H).

Inclusion Criteria

i. Patients with LUTS (related to prostatism, other causes ruled out by history and relevant investigation)
ii. Palpable nodule or suspected DRE
iii. Raised PSA
iv. Suspected findings on TRUS

Exclusion Criteria

i. H/O prostatic surgery.
ii. H/O urethral manipulation.
iii. Patients with indwelling catheter.
iv. Patients with signs and symptoms of acute prostatitis.

Patients were explained about prostatic biopsy procedure and following informed consent, patients were subjected for Trucut biopsy under local anesthesia under antibiotic cover.

Biopsy specimen were sent to the Department of Pathology, Ruby Hall Clinic, Pune for histopathological evaluation.

Statistical Analysis

Collected data was analyzed with descriptive statistics. Chi-square test and Pearson's Correlation coefficient was used to analyse the association and comparison. Tests were used to analyse the sensitivity, specificity and overall accuracy of PSA in diagnosing benign and malignant prostatic diseases.

Results

Out of the 500 patients included in the study, 125 patients underwent transrectal ultrasound guided

prostate biopsy. Of these, 74 patients were diagnosed with carcinoma of the prostate. They received treatment according to the stage of disease. Rest 51 patients (out of 125 patients) who had negative biopsy and 375 of other raised PSA patients (who did not have biopsy) had a repeat PSA testing after a course of antibiotics after 4 weeks. The PSA in these patients did not regress to normal at the end of 4 weeks. Repeat PSA third time was done after another 2 months only in 105 patients who came for follow up. All these 105 patients had normal PSA values (</= 4ng/ml) at the end of 3 months. Out of these 105 patients, 54 patients had relief of their symptoms after a repeat course of antibiotics. 51 patients were not relieved symptomatically and underwent transurethral resection of prostate. All of these patients on histopathology were found to have non-malignant etiology.

The mean age of the patients with carcinoma prostate was 69.3 years and the mean age of BPH patients was 56.95 years. BPH and Carcinoma prostate manifested clinically between the age group 40-90 years, in which the maximum patients of BPH and Carcinoma prostate presented in the age group 51-80 years (70.19% and 79.93% of BPH and Carcinoma prostate patients respectively). The values are statistically significant. Maximum number of BPH patients had PSA in the range of 2-10 ng/ml while Carcinoma prostate patients are maximum in the range of >40ng/ml. The mean PSA value in BPH patients is 8.5ng/ml and 42.8ng/ml in carcinoma patients. The study shows that there is statistically significant relation between the PSA and the age of the patients i.e. as the age increase the PSA value also increases. In this study, the maximum number of BPH patients had prostate volume upto 40 cc followed by the volume of 40-50 cc. In the Carcinoma prostate group maximum patients had volume of 40-50 cc followed by upto 40 cc group. Table 1shows that in the present study maximum carcinoma prostate patients presented late with metastases, followed by the organ confined disease. The patients of carcinoma prostate received treatment as per their stage of presentation **(Table 2)**. **Table 3, 4 and 5** show that as the limit of PSA value for diagnosis of carcinoma prostate increases from 4ng/ml to 15ng/ml the sensitivity decreases and the specificity and diagnostic accuracy increases. This is statistically significant.

Table 1: Stage of diagnosis of CaP

Stage	No. of Patients	Percentage
Tis N0 M0	1	1.35
T2 N0 M0	19	25.68
T2 N2 M0	2	2.7
T3 N0 M0	9	12.16
T3 N1 M0	2	2.7
Metastatic (Any T, Any N, M1)	41	55.41
Total	74	100

Table 2: Treatment opted by patients of CaP

Treatment opted	No. of Patients	Percentage
Hormonal alone	34	45.95
Radical prostatectomy	16	21.62
Radical radiotherapy + Hormonal	6	8.11
Orchitectomy	6	8.11
Radical radiotherapy	4	5.41
Orchitectomy + Hormonal	2	2.7
Orchitectomy + Channel TURP	2	2.7
Radical radiotherapy + Ochitectomy	1	1.35
Hormonal + Channel TURP	1	1.35
Watchful waiting	1	1.35
Orchitectomy + Abiraterone+ Hormonal	1	1.35
Total	**74**	**100**

Table 3: Sensitivity and specificity of serum PSA(at 4ng/ml)

PSA	No. of patients aged over 45 years	
	CAP	BPH
Test positive (>4ng/ml)	71	374
Test negative (<4ng/ml)	1	0

Chi-square = 5.20, P<0.05, Sensitivity = 98.61%, Specificity = 0%, PPV = 15.96%, NPV = 0%, Accuracy = 15.92%, % of False positive = 100%, % of False negative = 1.39%

Table 4: Sensitivity and specificity of serum PSA(at 10ng/ml)

PSA	No. of patients aged over 45 years	
	CAP	BPH
Test positive (>10ng/ml)	63	141
Test negative (<10ng/ml)	9	233

Chi-square = 60.33, P<0.0001
Sensitivity = 87.50%, Specificity = 62.30%, PPV = 30.88%, NPV = 96.28%
Accuracy = 66.37%, % of False positive = 37.70%, % of False negative = 12.50%

Table 5: Sensitivity and specificity of serum PSA(at 15ng/ml)

PSA	No. of patients aged over 45 years	
	CAP	BPH
Test positive (>15ng/ml)	54	69
Test negative (<15ng/ml)	18	305

Chi-square = 96.67, P<0.0001
Sensitivity = 75%, Specificity = 81.55%, PPV = 43.90%, NPV = 94.43%
Accuracy = 80.49%, % of False positive = 18.45%, % of False negative = 25%

Discussion

Prostate specific antigen (PSA) has revolutionized the approach to men with prostatic disease and is the single best marker for prostatic malignancy today. Further the discovery that PSA exists in the serum in several different molecular forms and that the concentration and ratio of these forms vary according to the state of disease of the prostate gland, represents a substantial advancement in prostate cancer screening and management.

The incidence of prostate cancer is lowest in Asian countries [2,3]. In India prostate cancer does not qualify to be categorized to be a major health problem. In India, prostate cancer is identified as the only 10th common malignancy affecting men [4].

The mean age of diagnosis of carcinoma prostate in this study was 69.3 years. The largest percentage of cancer patients were found in the 65-74 years age group. BPH was found to be clustered over a much wider age range of 51-80 years where over 59.80% of the BPH cases were present in this age group. There is no study in literature which has indicated the age clustering due to the large scale prevalence of this condition. It is noteworthy that relatively greater proportion of cases in this group are asymptomatic.

The internationally accepted level of normal PSA range is 0-4.0ng/ml. This value has been determined on the basis of various western population based studies, which have studied PSA level in conjunction with other diagnostic techniques, primarily digital rectal examination (DRE) and transrectal ultrasound (TRUS). Catalona et al, in a prospective multicentric trial, found a positive predictive value (PPV) of 34% for PSA level greater than 4.0ng/ml as compared to 21.4% for an abnormal DRE in detecting prostate cancer [5]. Cooner et al demonstrated a PPV of 35.4% for a PSA cut off of 4.0ng/ml with a sensitivity of 58.7% and specificity of 60.7% in men undergoing biopsy for suspected prostate on ultrasound [6]. In our study only one patient had a PSA level between 2-4ng/ml, and was diagnosed carcinoma prostate. 258 patients in this study had a PSA level between 2-10 ng/ml and this was the gray area where greater number of prostate cancer and BPH cases were interspersed. The PPV in our study is 15.96% at PSA cut off of 4ng/ml.

In the present study the mean PSA in the carcinoma patients was higher being 126ng/ml. This was due to a large number of patients being diagnosed at an advanced stage. The mean PSA in the BPH patients was 11.44ng/ml. The lowest PSA in present study group is 2.04 ng/ml. Various population based studies have quoted different minimum levels for normal range of PSA [7,8,9,10]. In the present study one case was found to have cancer at 2.04ng/ml, it is therefore observed that the lower minimum level of normal PSA in Indian context is probably higher than the screening population of western countries. Therefore it can be inferred that in Indian context there is an overall baseline elevation of lower minimum level of the normal PSA. However this awaits further evaluation and confirmation by future population based studies.

It has been stated that cancer secretes 12 times more serum PSA per volume than BPH [11]. Therefore the volume of prostate with carcinoma prostate is presumed to be smaller than those with BPH. In our study the average size of prostate in BPH patients is 46.9cc and 49.2cc in carcinoma patients.

A serum PSA threshold of 4ng/ml is usually an indication for prostate biopsy, and PSA levels between 4-10ng/ml, which is considered a grey zone,

are shown to have a low sensitivity, but values above 10ng/ml have a high sensitivity for prostate cancer. The sensitivity reaches even 100% if we consider values higher than 15ng/ml [12]. In the present study 51.60% of the patients had PSA value in the range of 2-10ng/ml, out of which 49.6% were diagnosed with BPH with prostatitis and only 2% were diagnosed with carcinoma prostate. In the range of 10-20ng/ml, 28.2% of patients were present. Out of these, only 2.4% of the patients were diagnosed with carcinoma prostate. Maximum 8.8% of the patients had PSA value >40ng/ml and only 1.20% of patients of BPH had PSA in >40 range and rest 7.60% were carcinoma prostate patients. This is because in the present study out of 14.80% (74/500) of total cancer patients, 7.6% of the patients had PSA in the > 40ng/ml range.

In our study a lower cut off point of 4ng/ml had a sensitivity of 98.61% and specificity of 0%. At PSA level of >10ng/ml the sensitivity decreases to 87.5% and the specificity increases to 62.30%.

There are a few studies [3] in Asian population which showed that the PSA levels were higher due to the presence of prostatitis in these subjects. This was verified in our study as many of the patients with BPH had higher PSA. In the present study 28.2% of patients had PSA in the range of 10-20ng/ml, 7.20% had PSA in the range of 20-30ng/ml, 4.20% in the range of 30-40ng/ml and 8.80% patients had PSA >40ng/ml.

The application of PSA for staging prostate cancer has been the focus of numerous investigations. The use of PSA alone as a tumour marker is not sufficiently sensitive or specific for staging [13]. Although PSA directly correlates with clinical and pathological tumour stage, studies have revealed that this marker cannot accurately predict the final pathological stage for the individual patients [14,15]. In our study, most of the carcinoma prostate patients were diagnosed in the organ confined (27.03%, n=74) or metastasis (55.41%, n=74) stage. This is because our hospital is a tertiary center and large number of patients are referred with diagnosed carcinoma prostate.

In our study, higher PSA values (7.60% cases) before treatment are associated with higher pathological stage of disease at the time of diagnosis. This was correlated with the study by Doughlas et al in which they concluded that higher PSA and free PSA levels are likely to be associated with more locally advanced disease and total PSA was the best marker [16].

The patients of carcinoma prostate received treatment as per their stage of presentation **(Table 2)**. All the available options for treatment were utilized. Organ confined disease was approached with radical treatment and metastatic disease with medical or surgical castration. More patients opted for surgical castration because of financial constraints.

Prostate volume also influence PSA independently. In our study there was overall positive correlation between PSA and prostate volume. But in carcinoma prostate patients it is not significant. Agrawal MS et al in their study on cancer prostate patients also found no correlation between PSA and the prostate volume in their study [17].

Histopathologically, out of 125 patients who underwent biopsy 74 (59.20%) were diagnosed with carcinoma prostate and 51(40.80%) were diagnosed with BPH. Additionally prostatitis was diagnosed in 68.63% of the BPH patients. Morote R.J. also found cancer in 42.6%, BPH in 67.4% and chronic prostatitis in 47.3% of the biopsies done on the basis of abnormal DRE and PSA levels [18].

Conclusion

i. Serum PSA is useful in the routine evaluation of patients with lower urinary tract symptoms for diagnosis of prostatic diseases viz. BPH, prostatitis and carcinoma of prostate .

ii. As the PSA value increases the chances of malignancy increases. But in the present study, in the Indian context as most of the patients has prostatitis, consideration must be given for diagnosis of BPH with associated chronic prostatitis as raised PSA values are not always associated with carcinoma prostate.

iii. The prostate volume correlates well with PSA levels, as prostate volume increases PSA value also increases. But in case of carcinoma prostate PSA and prostate volume showed no statistical correlation.

iv. In this study most of the patients diagnosed with carcinoma prostate are in the advanced stage.

v. Increased PSA in non-carcinoma patients is well correlated with the presence of prostatitis.

vi. As most of the patients were diagnosed in advanced stage, the treatment opted by the patients was medical/surgical castration. Those diagnosed with organ confined disease opted for radical surgery.

vii. It can be inferred that in Indian context there is an overall baseline elevation of lower minimum level of the normal PSA. However this awaits

further evaluation and confirmation by future population based studies.

At the last this study provides information regarding increased PSA values and association of prostatitis in cases of raised PSA values in Indian population. So, we can hope that further research and population based studies in Indian population will add to the final words about increased PSA values.

Limitations

This is a single institute non-randomised clinical study to evaluate the results. The availability of necessary equipments and expertise made the study feasible. However, comparative studies and randomised trials would be of worth before making recommendations. A longer follow up and more number of patients from all over the country are needed.

Acknowledgement

Many many thanks to Mr. Pradeep Borule (Statistician) for contribution in statistical analysis. We have not taken any funds.

Financial support and sponsorship: Nil

Conflicts of interest: None

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