

Original Research Article

Role of prostatic specific antigen density and its correlation with histopathology in diagnosis of the carcinoma of prostate

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ABSTRACT

Background: The specific threshold for prostate-specific antigen (PSA) to delineate patients who are at the highest risk has been controversial. It is wiser to refine PSA by its derivative parameter like PSAD (PSA/vol) which can be used as a better diagnostic tool in early detection of carcinoma of prostate. To evaluate sensitivity and specificity of PSAD in diagnosis of carcinoma of prostate.

Methods: A study including 70 patients was done in Pravara Medical College and Rural Hospital, Loni. Patients were screened for prostatic diseases by DRE, blood PSA (ng/ml) estimation, prostatic volume by transabdominal ultrasonography and prostatic biopsy by FNAC or Tru cut Biopsy.

Results: In the present study maximum incidence of BPH and CaP manifested in the age group of 61-70 (i.e., 35.18%) and Ca prostate were in age group of 71-80 (i.e., 50%). The maximum number of patients with BPH were having PSA values between 3-10 ng/ml, where as in CaP the value varied between 10.1-20 ng/ml. The maximum number of patients were in the range of 3-10 ng/ml in which age group 61-70 were having highest (35.71% of the pts in that range) followed by PSA range 10.1-20 ng/ml in which, age group 71-80 have shown maximum number (54.54% of the pts in that range). The sensitivity, specificity, accuracy of PSAD in diagnosing malignant prostatic diseases were analysed and values were as follows: sensitivity: 87.50%, specificity: 92.59%.

Conclusions: It was concluded that patients with PSAD >0.15 can be advised for prostatic biopsy and regular follow so that appropriate treatment is performed and mortality due to prostatic malignancy is reduced.

Keywords: Digital rectal examination, PSA, Transabdominal ultrasonography, PSA density, BPH, CaP

INTRODUCTION

All elderly men will exhibit some enlargement of prostate accompanied by various symptoms of prostatism. The distress caused, demands relief and surgery can bring dramatic improvement in these senior patients. Before attempting surgical treatment it is worth investigating the patient to rule out malignancy.

Prostate - specific antigen (PSA) is a tumour marker of 1990's and it has replaced prostatic acid phosphatase as well as serum acid phosphatase as the prostatic tumour marker of choice. Because PSA is not prostate cancer specific and prostate cancer develops in man at an age when the prevalence of benign prostatic hyperplasia is high, several parameters have been developed and investigated to enhance the sensitivity and specificity of the PSA test.

PSA levels are elevated approximately 0.12 ng/ml/g of BPH tissue. Thus, patients with enlarged glands due to BPH may have elevated PSA levels. The ratio of PSA to gland volume is termed the PSA density. Some investigators advocate prostate biopsy only if the PSA density exceeds 0.1 or 0.15, while others have not found PSA density to be useful.

The concept of PSA density (PSAD) has been described as, the PSA value divided by the prostate volume. This concept emerged from the information that benign prostatic hyperplasia produces 0.3 ng/ml of PSA per gram of prostate tissue and prostate cancer produces 10 folds of this amount.

PSA levels associated with a small prostate may have prostate cancer while the same value of PSA in a man with a large prostate may indicate BPH. It has been suggested that a PSAD greater than 0.15 is associated with 25% incidence of cancer, and a PSAD less than 0.10 is associated with 5% incidence of cancer.¹

Histologically, most lesions are Adenocarcinomas that produce well-defined, readily demonstrable gland patterns. The glands are typically smaller than benign glands and are lined by a single uniform layer of cuboidal or low columnar epithelium. In contrast to benign glands, prostate cancer glands are more crowded, and characteristically lack branching and papillary infolding. The outer basal cell layer typical of benign glands is absent. The cytoplasm of the tumour cells ranges from pale-clear as seen in benign glands to a distinctive amphophilic appearance. Nuclei are large and often contain one or more large nucleoli. There is some variation in nuclear size and shape, but in general pleomorphism is not marked. Mitotic figures are uncommon.²

Objective of this study was to evaluate sensitivity and specificity of PSAD in diagnosis of carcinoma of prostate.

METHODS

A total number of 70 cases were collected at Department of Surgery, Pravara Medical College Hospital, Loni. Patients were from in patient department, who were residing from Mangalore district, neighbouring districts like Rahuri, Sangamner, Shrirampur, Kopargaon, Akole in Maharashtra. Duration of study was 2 years (1 October 2013 to 31 August 2015).

Inclusion criteria

1. All age groups were included above 40 years patients presenting with lower urinary tract symptoms which would include.
2. Incomplete voiding, frequency, intermittency, urgency, weak stream, straining, nocturia.
3. Routinely in male patients aged above 50 yrs.

All these patients are subjected to various investigations which include the total serum PSA, Transabdominal USG (PROSTATE Volume), PSAD, TRUS, urine analysis and culture and sensitivity. Depending upon the above results we can proceed with FNAC or biopsy of prostate gland for further management.

Exclusion criteria

Urinary catheterization within last 15 days, UTI, prostatic biopsy within last 12 weeks, TURP within last 16 weeks, prostatic massage within last 48 hrs.

The qualifying patients are informed of risks and benefits of each operation and are to sign a detailed informed consent in their native language.

Patients were chosen for the study on the basis of clinical history and DRE. Patient with LUTS symptoms and enlarged prostate on DRE were further subjected to PSA screening through blood examination at Pravara pathology lab and transabdominal ultrasound for measuring prostatic volume at Radiology Department.

PSAD is measured using PSA / prostatic volume.

Patients were explained about prostatic biopsy procedure and following consent, patients are subjected for either FNAC or Tru cut biopsy under short general anaesthesia.

Specimen was sent to the Department of Pathology, Pravara Medical College for Histopathological evaluation.

Obstructive symptoms

Hesitancy, poor flow not improving by straining, dribbling even after micturation is complete (subjective), intermittent stream- stops and starts, poor bladder emptying, episodes of near retention.

Irritative symptoms

Frequency, nocturia, urgency, urge incontinence, nocturnal incontinence.

Digital rectal examination (DRE)

It is the mainstay of examination of the prostate. Note its consistency (normal or firm), its surface (smooth or irregular), and estimate its size. (It can be helpful to relate its size to common objects (e.g. fruit or nuts!) The normal bilobed prostate has a groove (the median sulcus) between the two lobes and in prostate cancer this groove may be obscured.

DRE should be avoided in the profoundly neutropenic patient (risk of septicaemia) and in patients with an anal fissure (DRE would be very painful).³

DRE tends to underestimate prostate size up to 40 gm.⁴

Prostatic specific antigen (PSA)

In present study serum PSA level is determined by using the Ciba Corning Automated Chemiluminescences's system (ACS).⁵ The PSA level in a given specimen determined with assays from different manufacturers can vary due to differences in assay methods and reagent specificity.

Serum PSA level was not interpreted as absolute evidence of presence or absence of malignant disease, so it was correlated with other parameters like DRE, Tumour volume, age of patient etc.

Care was taken that PSA samples are drawn before prostatic manipulation was done or waited at least for 24 hrs after the manipulation.

In the present study patients were subjected to TAUS for measurement of volume of prostate gland. It was chosen as modality because:

1. Versatility, relative low cost and lack of side effects.
2. Could detect bladder calculi, diverticula's and other obvious bladder pathology which mimics symptoms of prostate enlargement.
3. Could visualise the contour and echo texture of the prostate gland and lymph nodes involvement in case of prostatic carcinoma.

Prostatic volume was measured using ellipsoid formula under experienced hands. Patients with minimal bladder volume of 100 to 200 ml were subjected to USG for near correct estimation of prostate volume by USG.⁶

Ellipsoid formula, $V = \text{length} \times \text{height} \times \text{width} \times 0.52$.

PSA density (PSAD)

PSA density (PSAD) was calculated by PSA value derived from above described system divided by the prostate volume by TAUS.

Method of specimen collection

In the present study specimen was collected by Transrectal Trucut biopsy or FNAC under aseptic precautions.

Patient is explained about the procedure, its need and complications if any. An informed written consent was taken prior to procedure.

Tru cut biopsy was done with help of Tru cut needle through transrectal route under local or short time GA depending on patient's compliance. Patient was advised to stay for a short period and sent on the same day. Aseptic precautions and utmost care were taken not to injure neighbouring rectal mucosa or haemorrhoidal vein while doing procedure. Short course of antibiotics was advised to prevent septic complications.

True cut biopsy

True cut biopsy done in lithotomy position, using a Biopsy gun and index finger as a guide through the rectum, having 18G calibre used take samples around 8-9 taken and sent immediately to pathology Department in formalin jar containing formalin.

Collected data were used to analyse the sensitivity, specificity and overall accuracy of PSAD in diagnosing benign and malignant prostatic diseases and to analyse the association and comparison between PSAD and Histopathological reports respectively. In this Present study the cut off value for PSAD to differentiate benign and malignant prostatic disease is >0.15 .^{7,4,8}

Formulas

Sensitivity: $A/(A+C) \times 100$; Specificity: $D/(B+D) \times 100$; Predictive positive test: $A/(A+B) \times 100$; Predictive negative value: $D/(C+D) \times 100$; % of false negative: $C/(A+C) \times 100$; % of false positive: $B/(B+D) \times 100$; Overall accuracy: $A+D/(A+B+C+D) \times 100$.

RESULTS

Majority of the patients belong to lower and middle socio economic strata of mixed occupations. BPH and CaP manifested clinically between the age group of 41-90, in which the Maximum incidence of BPH and CaP manifested in the age group of 61-70 (35.18%) & 71-80 (50%) respectively. The maximum number of patients with BPH is shown the PSA value between 3-10ng/ml, where as in CaP the value varied between 10.1-20 ng/ml (Table 1).

Table 1: Distribution of range of the PSA in benign and malignant prostate diseases.

| PSA ng/ml range | BPH | CaP | Total | BPH (%) | CaP (%) |
|-----------------|-----|-----|-------|---------|---------|
| 3-10 | 50 | 6 | 56 | 89.28 | 10.71 |
| 10.1-20 | 4 | 7 | 11 | 36.36 | 63.63 |
| 20.1-30 | 0 | 2 | 2 | 0 | 100 |
| 30.1-40 | 0 | 1 | 1 | 0 | 100 |

Table 2: Distribution of PSA ng/ml in different age groups.

| Age group | 3-10 | 10.1-20 | 20.1-30 | 30.1-40 | Total |
|---------------|------------|-----------|---------|---------|-------|
| | N (%) | N (%) | N (%) | N (%) | |
| 41-50 | 4 (7.14) | 0 (0) | 0 (0) | 0 (0) | 4 |
| 51-60 | 12 (21.42) | 1 (9.09) | 0 (0) | 0 (0) | 13 |
| 61-70 | 20 (35.71) | 3 (27.27) | 1 (50) | 0 (0) | 24 |
| 71-80 | 14 (25) | 6 (54.54) | 0 (0) | 0 (0) | 20 |
| >80 | 6 (10.71) | 1 (9.09) | 1 (50) | 1 (100) | 9 |
| Total | 56 | 11 | 2 | 1 | 70 |

Table 3: Distribution of PSA density in benign and malignant prostatic diseases.

| PSAD | BPH | CaP | Total | BPH (%) | CaP (%) |
|-----------------|-----|-----|-------|---------|---------|
| <0.15 | 50 | 2 | 52 | 96.15 | 3.75 |
| >0.15 | 4 | 14 | 18 | 22.23 | 77.77 |

The maximum number of patients were in the range of 3-10 ng/ml in which, age group 61-70 were having highest (35.71% of the pts in that range) followed by PSA range 10.1-20 ng/ml in which, age group 71-80 have shown maximum number (54.54% of the pts in that range) (Table 2).

The age of the patient when correlated with serum PSA value in the present study showed there is significant rise in PSA value with age. Pearson correlation 0.43, $P < 0.01$.

The maximum number of patients with BPH and CaP are shown the trans abdominal ultrasonogram (TAUS) volume between 40-50 cc, in which the BPH patients occupies the maximum of 42.59%, followed by CaP 37.50%.

Chi-square statistical test was applied to evaluate the association between the PSAD cut off values and BPH, CaP which is confirmed with HPE, derived value $X=41.44$ which is statistically significant at the level of 0.05. There was strong association of the PSA density with BPH and CaP which is highly significant ($p < 0.05$) (Table 3).

Sensitivity: 92.59%, specificity: 87.50%, predictive value of positive test: 96.15%, predictive value of negative test: 77.78%, overall accuracy: 90.04%.

Accuracy of PSAD in diagnosing benign prostatic diseases: sensitivity: 92.59%, specificity: 87.50% predictive value of positive test: 96.15% predictive value of negative test: 77.78%, overall accuracy: 90.04% (Table 4).

Table 4: Tests to analyse the sensitivity, specificity, accuracy of PSAD in diagnosing benign prostatic diseases.

| PSAD | +Ve (BPH) | -Ve | Total |
|-----------------|-----------|-----|-------|
| <0.15 | 50 | 2 | 52 |
| >0.15 | 4 | 14 | 18 |

Accuracy of PSAD in diagnosing malignant prostatic diseases: sensitivity: 87.50%, specificity: 92.59%, predictive value of positive test: 77.78%, predictive value of negative test: 96.15%, overall accuracy: 90.04% (Table 5).

Table 5: Mean and SE of PSA, USGV and PSAD in benign and malignant prostatic diseases.

| | PSA | USGV | PSAD |
|------------|------------|---------------|-------------|
| BPH | 6.36+2.63 | 59.59.8+20.15 | 0.107+0.075 |
| CaP | 14.78+6.90 | 58.56+13.21 | 0.245+0.073 |

Accuracy of PSAD in diagnosing malignant prostatic diseases in PSA range 3-10ng/ml: sensitivity: 83.33%, specificity: 96.00%, predictive value of positive test: 71.43%, predictive value of negative test: 97.96%.

DISCUSSION

BPH is more common in 6th and 7th decade while CaP in 7th and 8th decade. This was in favour of study conducted by Collins et al on British population, showing increased incidence of CaP with age with 67% in age grp 80-89 yrs and 40% in age grp 70-79 yrs.⁸

Vesely et al found a statistically significant but weak correlation was found between PSA and age ($r=0.28$, $p=0.0001$).⁸ There is little discrepancy in in R value as there are racial variations in PSA values across different countries as described in study by Shahab et al.⁹ Similarly in favour of study by Basawaraj et al, showing weak but statistically significant correlation between age and PSA ($r=0.189$) p value of <0.05 .¹¹

Serum prostatic specific antigen (tPSA)

Rosette et al formed the European guidelines for BPH management and showed the chance of having prostate cancer is strongly related with the serum value of PSA. For many years the value of 4ng/mL was considered as the upper normal limit of PSA.¹²

This is in favour of study done by Emberton et al in 2008 which showed as PSA value increases chances of malignancy increases. In his study PSA threshold of >1.5 ng/ml should be used to identify patient at risk of BPH and a concentration of >4 ng/ml requires further evaluation and consideration of prostatic biopsy.¹³

However, Botchorishvili et al conducted study in USA and showed the specificity of PSA is most problematic in the range of 2–3 up to 10–15 ng/ml, resulting in a negative biopsy rate of 70–80%.¹⁴

Punglia et al conducted study on 6691 men who underwent PSA-based screening for prostate cancer, stated if threshold PSA value for undergoing biopsy which was set at 4.1 ng/ml, showed that 82 percent of cancers in younger men and 65 percent of cancers in older men would be missed.¹⁵

Thus it was seen that widespread use of PSA in clinical practice led to an increased diagnosis of prostate cancer (PCa), although the specificity of PSA levels less than 10 ng/ml was rather poor.

In another study by Taille et al showed patients f/T PSA ratio increases the specificity of prostatic cancer detection in patients with a total PSA between 4 and 10.0 ng/ml with a non-suspicious digital rectal examination.¹⁶ Thus present study also showed significant correlation as PSA level increases the chances of malignancy also increases which is in favour of the studies mentioned above.

Prostatic volume

Mean and SE of USGV for BPH and CaP is 59.8+20.15 and 58.56+13.21 respectively, which shows CaP patients also have mild to moderate prostatomegaly.

Billebaud et al showed that there is a 15% incidence of P.Ca in the sub-group of patients with normal P.R. and T.R.U. which are only detected by the raised P.S.A. not correlated with the volume of the prostate.¹⁷ Billebaud et al in another study in 1992, in the 186 patients who had never undergone prostate surgery, ultrasound-guided biopsies showed 42 prostate cancers and random systematic ultrasound-guided biopsies showed 75; 14 of the 76 patients with normal digital rectal examination and transrectal ultrasound imaging had a prostate cancer.¹⁸

Shahab et al in 2013 studied, PSA and PSAD cutoff points among Indonesian population suspected for prostate cancer which was 0.15, PSA and PSAD cutoff point for Indonesian men in this series is relatively different from international consensus. The difference might be caused by racial variation of either prostate volume. Furthermore, these data show that PSA and PSAD cutoff point must be adjusted to racial variation to discriminate between malignant and benign disease.¹⁹

Maximum number of BPH patients had the PSAD value <0.15 with sensitivity: 92.59%, specificity: 87.50% predictive value of positive test: 96.15% predictive value of negative test: 77.78%, overall accuracy: 90.04%

Maximum number of CaP patients had the PSAD value >0.15 with a sensitivity: 87.50%, specificity: 92.59%, predictive value of positive test: 77.78%, predictive value of negative test: 96.15%, overall accuracy: 90.04%

Also PSAD studied in pts with PSA range of 3-10ng/ml showed Sensitivity: 83.33%, Specificity: 96.00%, Predictive value of positive test: 71.43%, Predictive value of negative test: 97.96%.

The above values will explain the strong association of the PSA density with BPH and CaP which is highly significant.

This is in favour study done by Bazinet et al which showed sensitivity of 86% and negative predictive value of 91.5%.⁵

Bramhinir et al showed a similar specificity of 87% and negative predictive value of 91.5% at PSAD cutoff 0.15.⁷ Lakshmi et al showed PSA density proved to be very significant ($p<0.001$) in detecting prostate carcinoma in men with PSA levels of 4-10 ng/ml. PSA density cut off value of 0.15 ng/ml² proved to have a sensitivity and specificity of 93.3% & 100% respectively.¹⁴

Thus PSAD >0.15 can aid as a diagnostic tool for early detection of Ca prostate, patients with PSAD>0.15 can be advised for prostatic biopsy and regular follow.

CONCLUSION

It was concluded that PSA and PSAD in DRE positive are very much useful in screening the patients for prostatic carcinoma with cost effectiveness. So, we can hope that further research into molecular and biochemical properties of PSA as well as improvements in measurement techniques no doubt will lead to applications and enhanced clinical use for this important tumor marker.

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