

A COMPARATIVE STUDY OF PROSTATIC SPECIFIC ANTIGEN DENSITY AND ITS CORRELATED HISTOPATHOLOGY IN THE DIAGNOSIS OF BENIGN AND MALIGNANT PROSTATIC DISEASESShravan R. Shanbhag¹, Pradeep Kullal R²**HOW TO CITE THIS ARTICLE:**

Shravan R. Shanbhag, Pradeep Kullal R. "A Comparative Study of Prostatic Specific Antigen Density and its Correlated Histopathology in the Diagnosis of Benign and Malignant Prostatic Diseases". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 58, July 20; Page: 10119-10129, DOI:10.14260/jemds/2015/1460

ABSTRACT: BACKGROUND: Carcinoma of prostate gland is the most common malignancy above 65 yrs of age in men. Most patients with early-stage Ca prostate are asymptomatic. The presence of symptoms often suggests locally advanced or metastatic disease. It is important to detect Ca prostate at an early stage so that mortality due to this malignancy can be minimized. 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 Ca Prostate.

KEYWORDS: Digital Rectal Examination (DRE), PSA, Transabdominal ultrasonography, PSA density, Histopathological examination, BPH, CaP.

INTRODUCTION: Herophilus of Chalcedon in 300 B.C. was the first to use the term –prostate|| because of organ's location-standing before urinary bladder.

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.

Benign prostatic hyperplasia (BPH) is a pathologic process that contributes to, but is not the sole cause of, lower urinary tract symptoms (LUTS) in aging men. Previously held ideas that the clinical symptoms of BPH (Prostatism) are simply due to a mass-related increase in urethral resistance are too simplistic. It is now clear that a significant portion of LUTS is due to age-related detrusor dysfunction and other conditions such as polyuria sleep disorders, and a variety of systemic medical conditions unrelated to the prostate-bladder unit.

BPH is the most common benign tumour in men, and its incidence is age related. The prevalence of histological BPH in autopsy studies rises from approximately 20% in men aged 41–50, to 50% in men aged 51–60, and to >90% men older than 80. Although clinical evidence of disease occurs less commonly, symptoms of prostatic obstruction are also age related. At age 55, approximately 25% of men report obstructive voiding symptoms. At age 75, 50% of men complain of a decrease in the force and calibre of their urinary stream.

Risk factors for the development of BPH are poorly understood. Some studies have suggested a genetic predisposition, and some have noted racial differences. Approximately 50% of men under the age of 60 who undergo surgery for BPH may have a heritable form of the disease. This form is most likely an autosomal dominant trait, and first-degree male relatives of such patients carry an increased relative risk of approximately fourfold.

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Prostate cancer has been the most common non-cutaneous malignancy in U.S. men since 1984, now accounting for one quarter of all such cancers. The estimated lifetime risk of disease is 16.72%, with a lifetime risk of death at 2.57%. Prostate cancer incidence varies by race/ethnicity, with African-Americans at highest risk. For 2008, the American Cancer Society estimated 186,320 new cases of prostate cancer in the United States.

Prostate cancer is rarely diagnosed in men younger than 50 years old, accounting for only 2% of all cases. The median age at diagnosis is 68 years, with 63% diagnosed after age 65. At 85 years of age, the cumulative risk of clinically diagnosed prostate cancer ranges from 0.5% to 20% worldwide, despite autopsy evidence of microscopic lesions in approximately 30% of men in the fourth decade, 50% of men in the sixth decade, and more than 75% of men older than 85 years. PSA- based screening has induced an important age migration effect; the incidence of prostate cancer in men 50 to 59 years of age has increased by 50% between 1989 and 1992, with important implications for deciding on the need for, type of, and complications after therapy.

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 0.12ng/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. Problems with this approach include the facts that⁽¹⁾ epithelial- stromal ratios vary from gland to gland and only the epithelium produces PSA, and⁽²⁾Errors in calculating prostatic volume may approach 25%. The positive predictive value of PSA density is slightly higher than the use of a PSA level >4ng/ml in several series (30–40% versus 20–30%). Instead of adjusting the PSA to total prostate volume, some have advocated adjusting it to transition zone volume (PSA transition zone density).⁽³⁾

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.⁽⁴⁾

In this study the parameters included are PSA (Prostatic specific antigen ng/ml), PSA Density (Serum PSA Concentration divided by the size of the Prostate gland), age specific reference ranges for Serum PSA, ultra sonographically measured Prostatic volume and Direct Rectal Examination.

AIMS AND OBJECTIVE:

1. To evaluate the diagnostic value of PSA Density in pre-operative differentiation of benign and malignant prostatic diseases.
2. To evaluate the correlation of PSA density with histopathological examination reports in Prostatic carcinoma and benign prostatic hyperplasia patients.

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METHODOLOGY:

Study Period: 2yrs.

Study Design: comparative study.

Sample Size: 110 cases.

Source of Data Collection: Both IP and OP patients in Surgery Department, KVG MEDICAL COLLEGE HOSPITAL, SULLIA satisfying the inclusion criteria.

Inclusion Criteria:

- All age groups were included above 35 yrs.
- All patients with various complaints regarding urinary system, bone pain are thoroughly examined clinically by DRE to access the nature of prostate.
- All these patients are subjected to various investigations which included the total serum PSA.
- Trans abdominal USG, FNAC and Tru cut Biopsy of prostate gland.

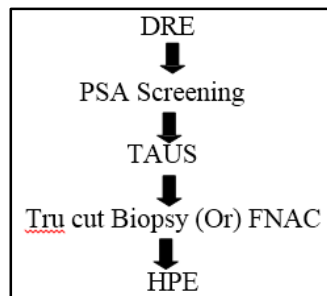
Exclusion Criteria:

- All age groups below 35yrs.

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

Follow up: not applicable,

Mode of Screening the Patients:



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 by ciba corning automated chemiluminescenes's (ACS)⁽⁵⁾ at KVG pathology lab and Transabdominal ultrasound for measuring prostatic volume at Radiology Department.

DRE was not done in patients with neutropenia & acute fissure.

PSA samples were drawn before prostatic manipulation was done or waited at least for 24 hrs after the manipulation

Transabdominal ultrasound was used to measure prostatic volume at Radiology Department. 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 $V = \text{length} \times \text{height} \times \text{width} \times 0.52$.

PSAD is measured using $\text{PSA} / \text{prostatic volume}$.

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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, KVG Medical College for Histopathological evaluation.

METHODS OF DATA ANALYSIS: Collected data was analysed with descriptive statistics followed by Chi-square test and Pearson's Correlation was used 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 $\pm 0.15.7, 2$.

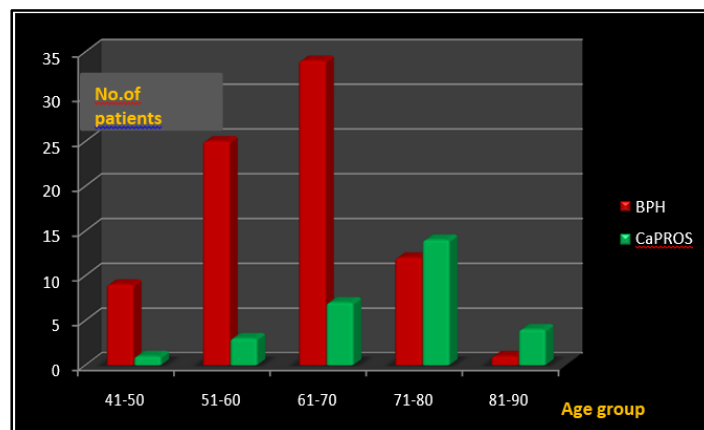
Tests were used to analyse the sensitivity, specificity and overall accuracy of PSAD in diagnosing benign and malignant prostatic diseases.

OBSERVATIONS AND RESULTS: A total number of 110 cases were collected at Surgery department, KVG MEDICAL COLLEGE HOSPITAL, SULLIA. Patients were from both in as well as Out Patient Department, who were residing from Mangalore district, neighbouring districts like Madikere, Mysore and Kasaragod District of Kerala.

In the Table No.1 .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(41.97%) & 71-80(48.27%) respectively.

Age	BPH	% out of total BPH cases	CaP	% out of total CaP cases	Total	BPH (% in that age group)	CaP (% in that age group)
41-50	9	11.11	1	3.44	10	90	10
51-60	25	30.86	3	10.34	28	89.2	10.8
61-70	34	41.97	7	24.13	41	82.9	17.1
71-80	12	14.81	14	48.27	26	46.2	53.8
81-90	1	4.93	4	13.79	5	20	80
Total	81		29	-	110	-	-

Table 1: Distribution of BPH and Ca Prostate in different age group



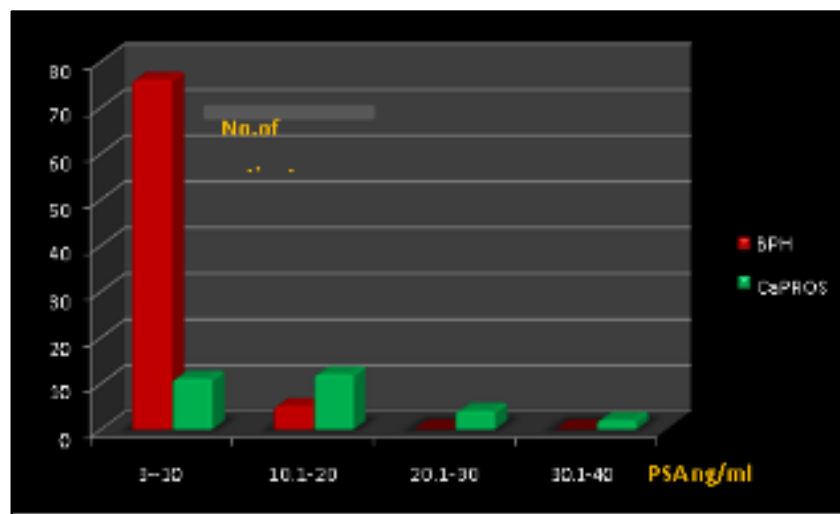
Bar chart No. 1

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PSA ng/ml Range	BPH	CaP	Total	BPH	CaP
3-10	76	11	87	87.4	12.6
10.1-20	5	12	17	29.4	70.6
20.1-30	0	4	4	0	100
30.1-40	0	2	2	0	100

Table 2: Distribution of Range of the PSA in Benign and malignant prostate diseases

In the Table No.2 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- 20ng/ml.



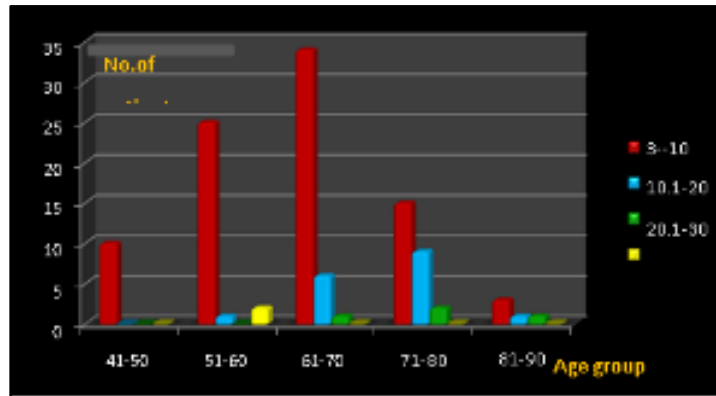
Bar chart No. 2

Age Group	3-10	10.1-20	20.1-30	30.1-40	Total
41-50	10(11.49%)	0(0%)	0(0%)	0(0%)	10
51-60	25(28.73%)	1(5.88%)	0(0%)	2(100%)	28
61-70	34(39.08%)	6(35.29%)	1(25%)	0(0%)	41
71-80	15(17.24%)	9(52.94%)	2(50%)	0(0%)	26
81-90	3(3.44%)	1(5.88%)	1(25%)	0(0%)	5
Total	87	17	4	2	

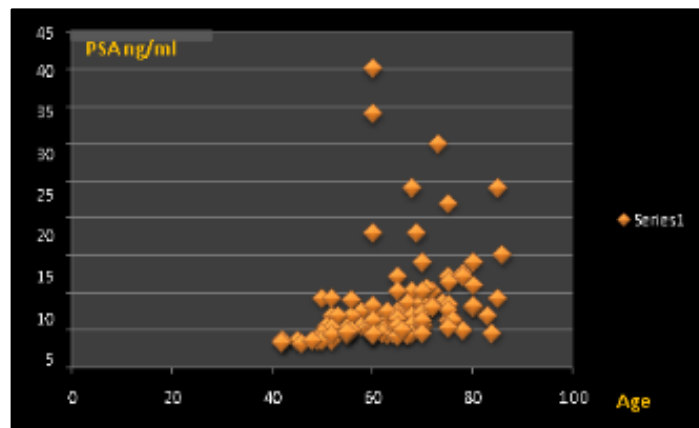
Table 3: Distribution of PSA ng/ml in different age group

In the Table No.3 The maximum number of patients were in the range of 3- 10ng/ml in which, age group 61-70 were having highest (39.08% of the pts in that range) followed by PSA range 10.1- 20ng/ml in which, age group 71-80 have shown maximum number (52.94% of the pts in that range).

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Bar chart No. 3



Correlation Graph

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.⁽⁷⁾

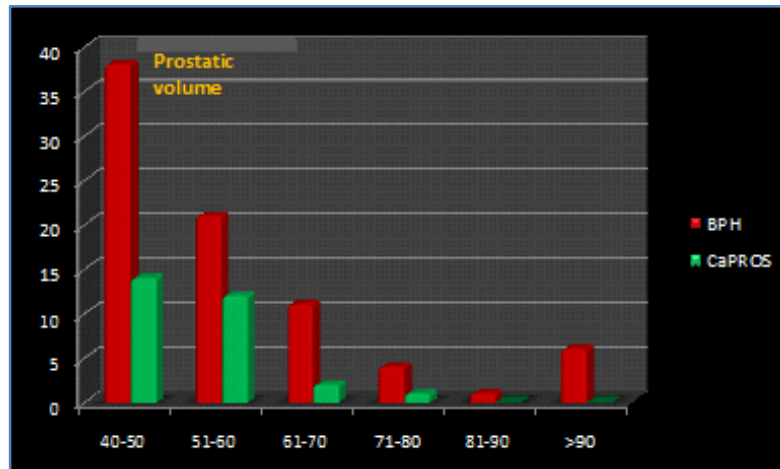
**Pearson correlation=0.353, P<0.01

Volume in cc	BPH	%	CaP	%	Total	BPH (%)	CaP (%)
40-50	38	46.91	14	48.27	52	73.1	26.9
51-60	21	25.92	12	41.37	33	63.6	36.7
61-70	11	13.58	2	6.89	13	84.6	15.4
71-80	4	4.93	1	3.44	5	80	20
81-90	1	1.23	0	0	1	100	0
>90	6	7.40	0	0	6	100	0
Total	81		29		110		

Table 4: Distribution of Prostatic volume in benign and malignant prostatic diseases

In the Table No.4. The maximum number of patients with BPH and CaP are shown the Trans Abdominal Ultrasonogram (TAUS) volume between 40-50cc, in which the CaP patients occupies the maximum of 48.27%, followed by BPH 46.91%.

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Bar chart No. 4

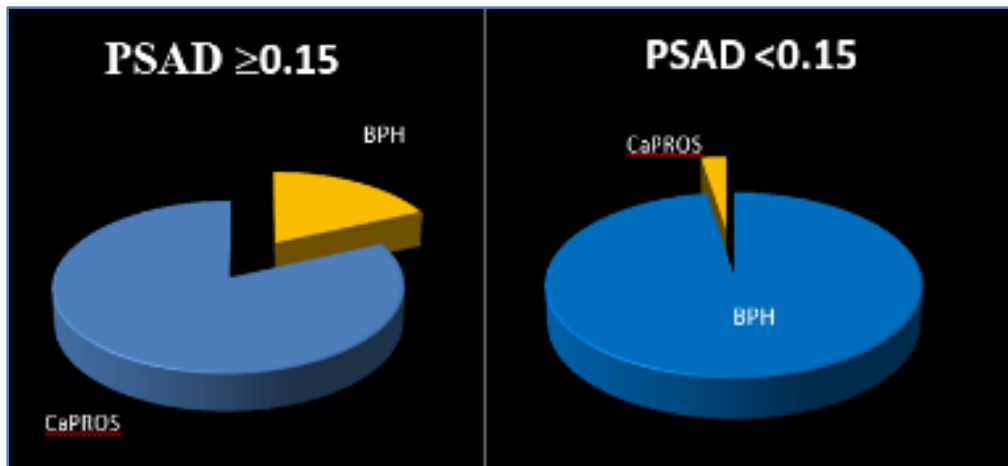
PSAD	BPH	CaP	Total	BPH (%)	CaP (%)
<0.15	75	2	77	97.4	2.6
±0.15	6	27	33	18.2	81.8

Table 5: Distribution of PSA density in benign and malignant prostatic diseases

The Table No.5 subjected to Chi-square statistical test to evaluate the association between the PSAD cut off values and BPH, CaP which is confirmed with HPE, derived value $\chi^2=99.26$ which is statistically significant at the level of 0.05.

$\chi^2=99.26$, $P<0.05$.

The above table explain the strong association of the PSA density with BPH and CaP which is highly significant ($p<0.05$).



Pie Diagram No.1

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	PSA	USGV	PSAD
BPH	5.98±0.23	58.49±1.79	0.1199±0.01
CaP	15.68±1.89	53.58±1.79	0.2852±0.03

Table 6: Mean and SE of PSA, USGV and PSAD in Benign and malignant prostatic diseases

PSAD	+Ve (BPH)	-Ve	Total
±±0.15	75	2	77
> 0.15	6	27	33

Table 7: Tests to analyse the sensitivity, specificity, accuracy of PSAD in diagnosing benign prostatic diseases

Sensitivity: 92.59%, Specificity: 93.1% Predictive value of positive test: 97.4% Predictive value of negative test: 81.81% Percentage of false negative: 7.4% Percentage of false positive: 6.89% Overall accuracy: 92.72%.

PSAD	+Ve (CaP)	-Ve	Total
±±0.15	27	6	33
<0.15	2	75	77

Table 8: Tests to analyse the sensitivity, specificity, accuracy of PSAD in diagnosing malignant prostatic diseases

Sensitivity: 93.1%, Specificity: 92.59% Predictive value of positive test: 81.81% Predictive value of negative test: 97.4% Percentage of false negative: 6.89% Percentage of false positive: 7.4% Overall accuracy: 92.72%.

DISCUSSION: AGE: 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 (Ref correlation graph). This is in favour to the study done by Collins GN et al in 1993,⁽⁸⁾ Vesely S et al in 2003,⁽⁹⁾ Uygur MC et al in 2010⁽¹⁰⁾ and contrary to Basawaraj NG et al in 2012.⁽¹¹⁾

Glandular dynamics among aging men suggest that regular PSA monitoring could assist in the assessment of malignant potential and with decisions on appropriate clinical interventions. But on contrary regular prostate cancer screening with PSA, with values indexed by age may ultimately allow greater refinement in choice of when to conduct follow up diagnostic procedures and how to treat the disease when diagnosed.

SERUM PROSTATIC SPECIFIC ANTIGEN (PSA): The present study showed significant correlation as PSA level increases the chances of malignancy also increases.

This is in favour of study done by M Emberton, et al in 2008⁽¹²⁾ which showed as PSA value increases chances of malignancy increases. In his study PSA threshold of ≥ 1.5 ng/ml should be used to

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identify patient at risk of BPH and a concentration of >4ng/ml requires further evaluation and consideration of prostatic biopsy.

PROSTATIC VOLUME AND PSA DENSITY: The measurement of prostatic volume using ellipsoid formula is accurate and detailed method employed in this study is reproducible in experienced hands. Minimal bladder volume of 100 to 200 ml is essential for near correct estimation of prostate volume by USG.6 Ellipsoid formula $V = \text{length} \times \text{height} \times \text{width} \times 0.52$.

The present study showed that there are more chances for malignancy in smaller size prostate.

PSAD ASSOCIATION WITH HPE OF PROSTATE: The present study showed (As explained in observation & results) strong association of the PSA density with BPH and CaP which is highly significant.

In present study patients were above 35 yrs who had enlarged prostate by DRE without any specific range of PSA (3ng/ml and above) when compared with other studies done among patients within range PSA (4-10ng/dl) .

The present study had sensitivity -93.1%, specificity -92.59%, overall accuracy-92.72%, PPV-81.8% & NPV-94.93%.

Other studies Naoki segawa et al⁽¹³⁾ & M Lofti et al⁽⁴⁾ showed sensitivity% - 83.3 & 55.2, specificity% - 61.3 & 67.7, overall accuracy% 51.1, PPV% - 45.5 & 27.6, NPV% - 90.5 & 87.1 respectively.

PPV: Positive predictive value; **NPV:** negative predictive value.

CONCLUSION: DRE can be used as screening method which can be aided by PSAD cut off value ≥ 0.15 as a diagnostic tool for early detection of ca prostate, especially patients with PSA in range of 3-10ng/ml. 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.

ABBREVIATIONS:

- AP - Antero posterior.
- ACS - Automated Chemiluminescences system.
- BPE - Benign Prostatic Enlargement.
- BPH - Benign Prostatic Hyperplasia.
- BPO - Benign Prostatic Obstruction.
- CaP - Carcinoma Prostate.
- DRE - Digital Rectal Examination.
- FNAC - Fine Needle Aspiration Cytology.
- GA - General Anaesthesia.
- HPE - Histopathological Examination.
- IP - In Patient.
- LUTS - Lower Urinary Tract symptoms.
- NGV - Negative Predictive Value.
- OP - Out Patient.
- PPV - Positive predictive value.

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PSA - Prostate Specific Antigen.
 PSAD - Prostate Specific Antigen Density.
 PV - Prostate Volume.
 TAUS - Transabdominal Ultrasonography.
 TRUS - Transrectal Ultrasonography.
 TRUP- transurethral resection of prostate.
 TURP - Trans Urethral Resection of Prostate.
 TZ - Transition Zone.

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