IOSR Journal Of Pharmacy
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 11, Issue 3 Series. I (March 2021), PP. 46-50
www.iosrphr.org

The Utility of PSA and PSA Density in Assessing the Risk of Prostate Cancer.

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Received 18 March 2021; Accepted 4 April 2021

ABSTRACT
Introduction: The specific threshold of Prostate specific antigen(PSA) to diagnose prostate cancer has been controversial hence Prostate specific antigen density (PSAD) was introduced as better diagnostic tool. Our aim was to identify the sensitivity and specificity of PSA at different cut off values, to assess and compare the utility of PSA and PSAD for diagnosing prostate cancer.
Methods :
A Crossectional study was done on 156 prostatic specimens. Clinical and USG findings and histopathological diagnosis were noted. The PSA and PSAD levels were estimated. Sensitivity, specificity, PPV, NPV and diagnostic accuracy of PSA value at cut off 4ng/ml, and PSAD was compared. Sensitivity and specificity of PSA at 10ng/ml, 20 ng/ml and 50 mg/ml was also compared to predict malignancy.
Results:
Sensitivity, specificity, PPV, NPV and diagnostic accuracy of PSA at cut off 4ng/ml, and PSAD was 93.55%, 52%, 32.58%, 97.01%, 60.26% and 80.65%, 74.40%, 43.86%, 93.240%, 75.64% respectively. Sensitivity of PSA ranged from 93.55% to 45.16% and specificity of 52% to 99.2% with increasing PSA cut off value of 4 ng/ml to 50 ng/ml.
Conclusion:
PSA value at >10ng/ml is better predictor of malignancy as compared at Cut off 4 ng/ml. PSAD is more reliable marker with better diagnostic accuracy in comparison to PSA at 4ng/ml. Histopathology remains the gold standard for diagnosing malignancy.
KEYWORDS: Prostate Pathology, PSA, PSAD

I. INTRODUCTION

Prostatic carcinoma is the sixth most common cause of cancer and the second most common cause of death in men older than 50 years, accounting for 9.7% of cancers in men[1]. Prostate Specific Antigen (PSA) is androgen regulated serine protease secreted by prostatic epithelium. PSA value cut off is 4ng/ml and it varies according to age of patient. PSA values are elevated when normal architecture of prostate is disturbed.[2,3]

PSA is a screening test for early detection of prostate carcinoma thereby decreasing morbidity and mortality[4]. Serum PSA level are significantly raised in prostatic adenocarcinoma(>10ng/dl) however, it is difficult to differentiate prostate carcinoma from BPH when PSA values are intermediate(4-10ng/dl). The role of PSA Density(PSAD) is recommended in various studies with varied results to solve this dilemma.[5] We intend to identify the reliable cut off value of PSA and its sensitivity and specificity in detecting malignancy. This study was conducted to identify the sensitivity and specificity of PSA at different cut off value, to assess and compare the utility of PSA and PSAD as a tumor marker for prostatic malignancy.

II. MATERIAL AND METHODS

The present Descriptive cross-sectional study was carried out in the Department of Pathology at a tertiary care center in western Maharashtra. Total 156 cases were studied which included prostatic biopsies, TURP specimens and radical prostatectomy specimens received from September 2018-August 2020. Inadequate biopsy material, post therapeutic and recurrent tumors were excluded from the study. The study was done after obtaining patient consent and approval from institutional ethical committee. Clinical features, DRE findings and USG findings for volume were recorded.

12 core biopsy specimens were submitted into 4-8 representative paraffin blocks. Transurethral resection specimens weighing 12 grams or less was submitted in their entirety, usually in 6 to 8 cassettes. A radical prostatectomy specimen submitted in its entirety or partially sampled. Tumor and associated periprostatic tissue, all margins along with the bladder neck margins and each seminal vesicle with prostate proper were submitted.[6]

The specimens were inked and fixed routinely in 10% formalin, embedding with paraffin and cutting with microtome at 4 microns. The sections were further stained with hematoxylin and eosin stains. Sections were examined under light microscopy and histopathological diagnosis was made. The PSA & PSAD levels were obtained from central clinical laboratory. Serum PSA was estimated using Chemiluminescent Micro Particle Immunoassay which is two step method and estimates PSA by sandwich assay utilizing Anti-PSA coated paramagnetic micro particles. PSA Density was calculated by using formula:

$$\text{Prostate specific antigen density} = \frac{\text{Serum prostate specific antigen level}}{\text{TRUS Prostate volume in cc}}$$

The PSA and PSAD level were correlated with histopathological diagnosis. Statistical Analysis was done. Specificity, Sensitivity, PPV, NPV and diagnostic accuracy were calculated.

III. RESULTS

We received 156 samples for histopathological evaluation including 96 TURP chips, 44 prostate biopsy, 5 simple prostatectomy and 11 radical prostatectomy specimens. 38.5% (n=60) cases were seen in the age group of 61-70 years. Frequency of micturition followed by urgency were the most common clinical presentation in both benign and malignant lesions. Maximum number of cases had grade II DRE findings (n=86) and volume of 40-60cc(n=65) on USG.

On microscopy, 80% (n=125) cases were benign and 20% (n=31) cases were malignant. 45%(n=20) malignant cases were detected by prostate biopsy while 94.80% (n=91) BPH cases were diagnosed on TURP. Histopathological evaluation revealed 35.89% (n=56) cases of BPH , 37.82% (n=59) cases of BPH with associated lesions, 1.2%(n=2) cases of Basal Cell Hyperplasia, 5.12%(n=8) cases of PIN and 19.87%(n=31) cases of Malignancy. BPH with associated lesions included mainly chronic prostatitis cases along with very few cases of acute prostatitis, granulomatous prostatitis, atrophy and infarct.

In the present study, 64.94%(n=63) BPH cases showed PSA value within normal range i.e. 4ng/ml. Elevated PSA value was observed in BPH with associated Prostatitis cases in the range of 4-20ng/ml due to both architectural and cytological distortion. Majority(75%) of the PIN lesions showed significantly raised PSA value(>20ng/ml) in the range of malignant lesions proving its pre malignant potential. 83.87%(n=26) malignant cases had raised serum level of PSA >10ng/ml and almost half the cases were having value >50ng/ml with maximum value of 435ng/ml which was seen in high grade carcinoma.

Total 31 cases of adenocarcinoma were included in our study. Study showed maximum i.e. 51.60%(n=16) cases were of intermediate risk with Gleason score 7. 29%(n=9) of low risk (Gleason score <7) and remaining 19.30%(n=6) cases were of high risk (Gleason score >7).

83.87%(n=26) malignant cases had raised serum level of PSA >10ng/ml and almost half the malignant cases had PSA value >50ng/ml. There was no linear correlation found between PSA and Gleason grading of malignant lesions.

PSAD was >0.15 ng/ml/cc in 80.64% (n=25) of malignant cases while 74.40% (n=93) benign cases revealed PSAD value within normal range.

Comparative analysis of statistical data for both PSA and PSAD was done to decide the better indicator of prostatic carcinoma as shown in Table no:1

Table 1: Comparative analysis of statistical data for both PSA and PSAD

	SENSITIVITY(%)	SPECIFICITY(%)	PPV(%)	NPV(%)	ACCURACY(%)
PSA(4ng/ml)	93.55	52.00	32.58	97.01	60.26
PSAD(0.15ng/ml/cc)	80.65	74.40	43.86	93.40	75.64

PSAD density showed better specificity and more accuracy than PSA in detecting malignancy.

Comparative analysis of sensitivity and specificity of PSA level using different cut off values of PSA level as >4ng/ml, >10ng/ml, >20ng/ml, >50ng/ml as shown in Table 2. It was noticed that PSA level with cut off >10ng/ml had sensitivity and specificity comparable and closer to sensitivity and specificity of PSAD in diagnosing malignancy.

Table 2. Comparative analysis of sensitivity and specificity of PSA level at different cut off**.**

PSA LEVEL(ng/ml)	SENSITIVITY(%)	SPECIFICITY(%)
>4	93.55	52.00
>10	83.87	77.6
>20	71.88	92.74
>50	45.16	99.2

IV. DISCUSSION

In the present study most of the cases (45.4%) were clustered in age group of 61-70 years, followed by age group 71-80 years (25.4%). These findings were in concordance with the studies done by Hirachand et al[7], Puttaswamy et al[8], Vani et al[9], Jaypradeep et al[10].

Present Study included 80%(n=125) benign and 20% (n=31) malignant cases. Comparative analysis of incidence of benign and malignant lesions in present study was done with studies done by Puttaswamy et al[8], Jaypradeep et al[10] concluded that incidence of both benign and malignant cases increases with increasing age but incidence of benign lesion is more than malignant in all age groups which reflects that hyperplasia is a normal aging process. It is believed that main reason of the hyperplastic process is Dihydro testosterone (DHT) induced growth factors cause increase proliferation of stromal cells and decrease in death of epithelial cells resulting in the accumulation of senescent cells in the process forming nodules.[11]

PSA is an easy and most commonly used marker for screening and diagnosis of adenocarcinoma in patients with obstructive symptoms[11]. Serum PSA value increases depending on the extent of underlying pathology. In our study majority of BPH cases showed PSA value within normal range i.e. 4ng/ml. Malignant cases had raised PSA value > 10ng/ml. The study conducted by Vani et al[9] showed an average PSA of 6.8ng/ml in benign lesions and 107ng/ml in malignant lesion.

Efffect of prostatitis on PSA level was studied separately at PSA value of 4ng/ml. 70% cases of BPH with associated prostatitis showed PSA level >4ng/ml. Schatteman et all[12] conducted a study to see the effect of prostatitis on PSA level which concluded that not the extent of inflammation but the aggressiveness of lesion is responsible for raised PSA level. [15]

Our study included 8 cases of PIN. 75% (n=6) cases had PSA level above 10ng/ml suggesting that premalignant intraepithelial lesions causes rise in PSA level. In the study done by Iqbal B et al[13] 10% cases were found with PIN and all were having increased level of PSA possibly due to breach in the protective layers between prostatic lumen and capillary.

Vani et al[9] concluded that Individuals with PSA level >10ng/ml were showing 18 times more chances of malignancy in comparison to PSA <10ng/dl. Our study had similar conclusion showing 10 times more chances of being positive for malignancy with PSA level >10ng/ml in comparison to individuals with PSA <10ng/ml.

Study done by Shih W J et[14] al included 65 men with prostatic adenocarcinoma and were divided into low and high Gleason score. Out of 65 patients 42 were included in high gleason grade with mean PSA level 134.39 ng/ml and 23 with low gleason grade had mean PSA level of 23.62 ng/ml. Study suggested that PSA level appear to be positively correlated with high grade carcinoma. Above findings were in concordane with our study. All high grade cases (n=6) showed PSA level >10ng/ml and 66.66% (n=4) had level >50ng/ml with highest value of 435ng/ml in grade 5 case suggesting positive correlation with PSA level.

Lojanapiwat et al[15] studied the sensitivity and specificity of PSA level in the diagnosis of prostate cancer.

Table No 3. The comparative study results of Lojanapiwat el al with present study.

PSA LEVEL(NG/ML)	SENSITIVITY(%)		SPECIFICITY(%)	
STUDY TYPE	Lojanapiwat et al	Present	Lojanapiwat	Present
>4	98.5	93.55	32.4	52.00
>10	81.5	83.87	55.5	77.6
>20	65.88	71.88	87.5	92.74
>50	47.8	45.16	98.2	99.2

The study suggested that PSA at level 4ng/ml had better sensitivity but lower specificity and specificity increases with increasing PSA cut off value. The usefulness of PSA is for early diagnosis of malignant lesions but it carries a risk of overdiagnosis and resultant negative biopsies owing to poor specificity.

In view of low specificity, sensitivity and positive predictive value (PPV) of serum PSA, we compared PSAD in our study with PSA levels in detecting malignancy. We found that PSA Density is better marker to detect adenocarcinoma with more specificity and diagnostic accuracy. Out of 31 cases 26 were showing PSAD value > 0.15ng/ml/cc. Majority of benign cases were having value <0.15ng/ml/cc. P value at cut of 0.15 was most significant with increased specificity and had more accuracy i.e. 75.64% in comparison to PSA level.

Choudhary et al[16] studied the sensitivity and specificity of PSAD at cut off value of 0.15ng/ml/cc in prostate cancer patients which was 87.50% and 92.59% respectively. The above value explain the strong association of the PSAD with prostate cancer which is highly significant as compared to PSA value at level 4ng/ml.

V. CONCLUSION

PSA is an early sensitive marker for diagnosing prostate carcinoma. Though it has limitation at cut off value 4ng/ml. We conclude that PSA value of >10ng/ml along with PSAD > 0.15ng/ml are more reliable markers with better diagnostic accuracy. Histopathology still remains the gold standard for diagnosing malignancy.

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Dr. Archana C Buch, et. al. "The Utility of PSA and PSA Density in Assessing the Risk of Prostate Cancer." *IOSR Journal of Pharmacy (IOSRPHR)*, 11(03), 2021, pp. 46-50.