Original Article

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Prostate Specific Antigen (PSA) Levels and its Correlation to Prostatic Lesions

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ABSTRACT

Background: To correlate PSA levels with prostatic lesions and grade of Prostatic adenocarcinoma

Methods: The study includes male patients with lower urinary tract complaints, advised to get their PSA levels and Transrectal ultrasound (TRUS) guided prostatic biopsy done. Study design was observational and retrospective. Universal sampling method has been used for selection, during study period May 2015 to September 2016. Ethical clearance has been obtained from Medical Ethical Committee of Saifee Hospital. We received 116 TRUS biopsies in the described time frame. The relevant data for these were collected from the hospital and departmental records.

Results: Out of 116 cases, 57 cases were malignant and 59 cases were benign. Fifty-three (93%) of the malignant cases and 54 (91.5%) of the benign cases had PSA levels above 4 ng/ml. Thus, association of PSA level and type of lesion was found to be statistically insignificant ($p > 0.05$). The mean PSA level was 19.67ng/ml in Grade 1 Prostatic adenocarcinoma, 10.84ng/ml in Grade 2 Prostatic adenocarcinoma, 21.07ng/ml in Grade 3 Prostatic adenocarcinoma, 39.06ng/ml in Grade 4 Prostatic adenocarcinoma and 399.26ng/ml in Grade 5 Prostatic adenocarcinoma. Thus, the mean PSA level increased as the grade increased but it was statistically not significant ($p > 0.05$).

Conclusion: Serum PSA level as tumor marker has limitations. Thus, histopathological examination is more specific for correct diagnosis in clinically suspicious cases.

Keywords: *Prostate Specific Antigen, Prostatitis, Prostatic adenocarcinoma*

Introduction

Benign prostate hyperplasia, prostate carcinoma and prostatitis are three pathologic processes which frequently affect the prostate gland.[1] One of the most interesting aspect of the prostate is that both benign and malignant tumors are hormone (androgen) dependent and are associated with significant morbidity and mortality in man.[2]

Nearly 1 in 10 men in their 70s will have Acute Urinary Retention in the subsequent 5 years. As these disorders are common in elderly men; assessment and management of prostate is the important aspect in geriatrics practice and attracts research in gerontology.[2] Prostate cancer is an important growing health problem, presenting a challenge to urologists, radiologists and pathologist. Currently, many men are identified as having early prostate cancer through the use of prostate specific antigen (PSA) screening.[3] It is known that a raised PSA level can also occur in non-malignant conditions like benign prostatic hyperplasia (BPH), inflammation, diagnostic and surgical procedures. These conditions may mimic cancer and cause confusion in diagnosis.[4] Thus, transrectal ultrasound (TRUS) guided biopsy of the prostate is the major method by which prostate cancer is diagnosed.[5]

Materials and Methods:

The present study was undertaken in Histopathology department of Saifee Hospital, Mumbai.

It includes male patients with lower urinary tract complaints who were advised to get their PSA levels and TRUS guided prostatic biopsy done. Study design was observational and retrospective. Being an observational study, universal sampling method has been used for selection of study participants during study period May 2015 to September 2016. We received 116 TRUS biopsies in the described time frame. The relevant data of these were collected from the hospital and departmental records. Majority of the cases came as 6 core biopsies, each in different containers, 3 from right and 3 from left lobe of prostate.

They were sampled from periurethral zone, peripheral zone and central zone of either lobe of prostate and labelled. Right side of lobe was labelled as I and left side of lobe as II. Periurethral zone was labelled as ‘A’, Peripheral zone as ‘B’ and central zone as ‘C’. Few specimens were sent in a single container.

Special stain (ZN stain) and immunohistochemistry (HMW-CK, p63 and AMACR) were used in granulomatous prostatitis and suspicious lesions respectively.

Ethical clearance has been obtained from Medical Ethical Committee of Saifee Hospital. Data entry was done in Excel and analysed with the help of statistician. Microsoft word and excel have been used to generate tables. Qualitative data is presented with the help of Frequency and Percentage table.

Results

Out of 116 cases, 57 cases were malignant and 59 cases were benign. Age wise, upto 49 years, 2 benign cases (3.4%) and 2 malignant cases (3.5%) were noted. In 50-70 years age range, 30 benign cases (50.8%) and 22 malignant cases (38.6%) were noted. The maximum number of cases belonged to the age group 70 years and above (60 cases ie 51.7%). Of these, 33 were malignant (57.9%) and 27 were benign (45.8%) group.

The spectrum of lesions in prostatic biopsy seen in our institution were as follows- Prostatic adenocarcinoma- 57 cases (49.14%), Chronic prostatitis- 32 cases (27.59%), Benign prostatic tissue- 15 cases (12.93%), Acute prostatitis and Granulomatous prostatitis- 4 cases each (3.45% each), Chronic prostatitis with microabscess- 2 cases (1.72%), Chronic prostatitis with eosinophilia and chronic prostatitis with sheets of foamy histiocytes-1 case each (0.86% each). ZN stain was carried out on cases of granulomatous prostatitis. All turned out to be negative for tubercle bacilli. Broadly, the lesions can be distributed as- Benign prostatic tissue 15 cases (12.93%), Prostatitis 44 cases (37.93%) and Prostatic adenocarcinoma 57 cases (49.14%).

In the malignant cases, ISUP 2014/ WHO 4th edition (International Society of Urological Pathology 2014/ World Health Organisation 4th edition) Grades 1 to 5 were seen. In few cases, different Gleasons score/Grades were noted in different cores in the same patient. In such cases, the highest Gleasons score/Grade has been considered and statistics have been carried out accordingly. Prostatic adenocarcinoma Grade 5 was present in 26 cases (45.61%), Grade 4 in 11 cases (19.3%), Grade 3 in 7 cases (12.28%), Grade 2 in 4 cases (7.02%) and Grade 1 in 9 cases (15.79%).

Tables 1 and 2, show the association of PSA levels as per type of lesion. 53 (93%) of the malignant cases and 54 (91.5%) of the benign cases had PSA levels above 4 ng/ml. 7% malignant cases had PSA levels upto 4ng/ml. Thus, association of PSA levels and type of lesion is found to be statistically insignificant (p >0.05).

Table 3 shows the distribution PSA level as per grade of Prostatic adenocarcinoma. Pearson Chi Square test was carried out to associate PSA level with Grade of Prostatic adenocarcinoma. Test value was 20.463(a), degree of freedom was 12, P value was 0.059. Thus, association of PSA level with Grade of adenocarcinoma was found to be insignificant (p >0.05).

For Grade 1, the minimum PSA level was 0.18ng/ml, the maximum PSA level was 54.42ng/ml and the mean PSA level was 19.67ng/ml.

For Grade 2, the minimum PSA level was 6.06ng/ml, the maximum PSA level was 18.58ng/ml and mean PSA level was 10.84ng/ml.

For Grade 3, the minimum PSA level was 2.98ng/ml, the maximum PSA level was 70.77ng/ml and mean PSA level was 21.07ng/ml.

For Grade 4, the minimum PSA level was 4.50ng/ml, the maximum PSA level was 102.10ng/ml and mean PSA level was 39.06ng/ml.

For Grade 5, the minimum PSA level was 0.38ng/ml, the maximum PSA level was 2,521.58ng/ml and mean PSA level was 399.26ng/ml.

Discussion

Out of the 116 cases that were studied, 59 cases were benign and 57 were malignant. In present study, 50.86% cases were benign and 49.14% cases were malignant, comparable to 60.91% benign cases and 37.27% malignant cases in the study done by Varsha Khant et al (2017).[6] Another study by Dr. Atchyuta .M et al (2016)[7] had 79.7% benign cases and 20.3% malignant cases. Geographical location and environment may account for this uneven distribution of benign and malignant lesions. The above studies by Varsha Khant et al (2017)[6] and Atchyuta .M et al(2016)[7] included prostatic biopsies as well as prostate

Table 1: PSA level in malignant and benign lesions.

PSA level (nanogram/millilitre)	Type of Lesion		Total
	Malignant	Benign	
Above 4 ng/ml	53 (93.0%)	54 (91.5%)	107 (92.2%)
Upto 4 ng/ml	4 (7.0%)	5 (8.5%)	9 (7.8%)
Total	**57 (100.0%)**	**59 (100.0%)**	**116 (100.0%)**

Table 2: Association of PSA level with benign and malignant lesions

Chi-Square test	Value	df	P Value	Association is
Pearson Chi-Square	0.086	1	0.769	Not Significant
Fisher's Exact Test			1.000	Not Significant

Table 3: Distribution of PSA levels in different Grades of Prostatic adenocarcinoma.

PSA level (nanogram/millilitre)	Grade					Total
	1	2	3	4	5	
Upto 4 ng/dl	2 (22.2%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	1 (3.8%)	4 (7.0%)
4 to 10 ng/ml	3 (33.3%)	2 (50.0%)	2 (28.6%)	3 (27.3%)	1 (3.8%)	11 (19.3%)
10 to 20 ng/ml	1 (11.1%)	2 (50.0%)	2 (28.6%)	1 (9.1%)	5 (19.2%)	11 (19.3%)
Above 20 ng/ml	3 (33.3%)	0 (0.0%)	2 (28.6%)	7 (63.6%)	19 (73.1%)	31 (54.4%)
Total	**9 (100.0%)**	**4 (100.0%)**	**7 (100.0%)**	**11 (100.0%)**	**26 (100.0%)**	**57 (100.0%)**

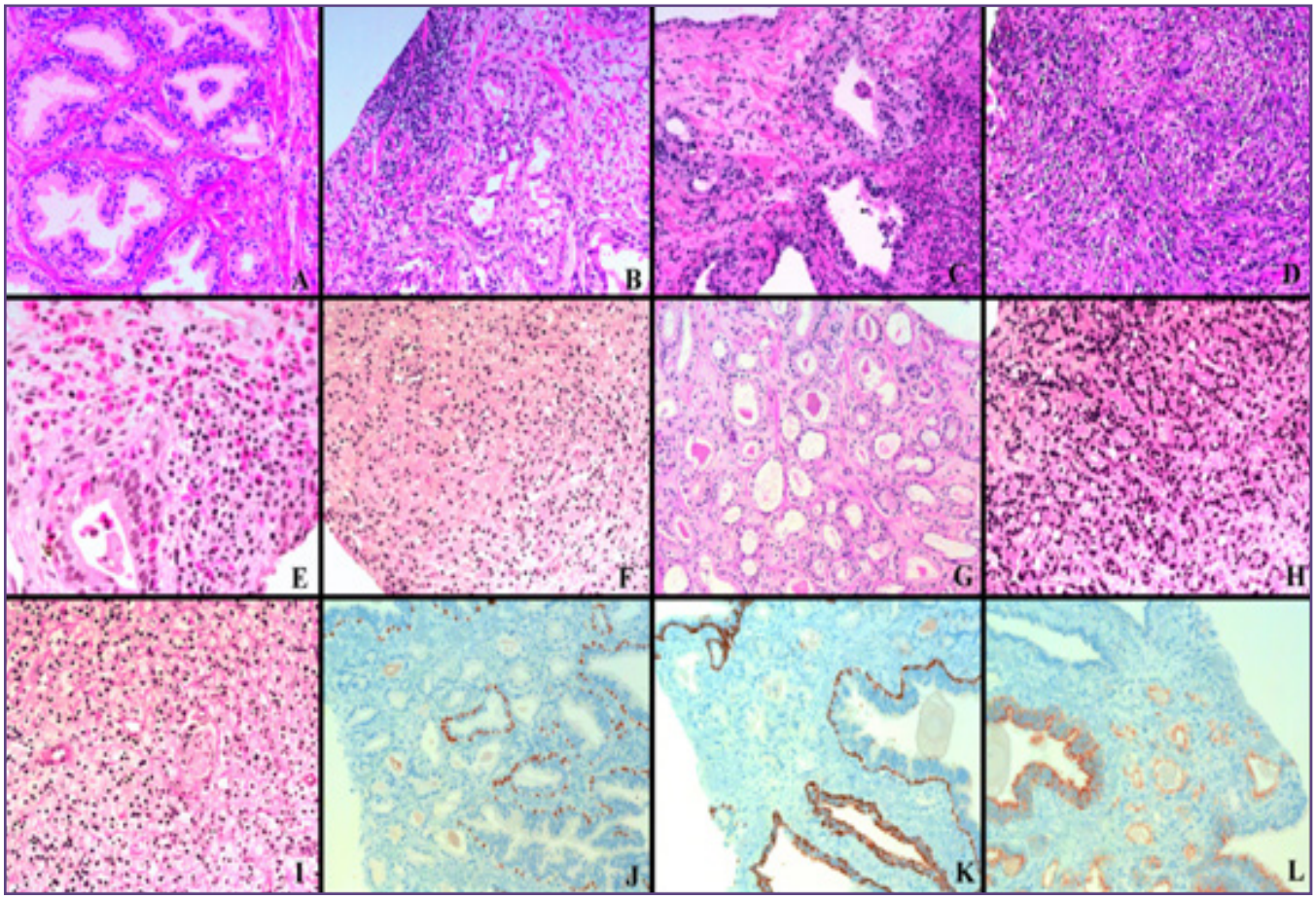

Fig. 4: A- Benign Prostatic tissue (H&E, 20X), B- Chronic prostatitis(H&E, 20X),C-Acute prostatitis (H&E, 20X), D-Granulomatous prostatitis(H&E, 20X), E- Chronic prostatitis with eosinophilia (H&E, 40X), F- Chronic prostatitis with foamy histiocytes (H&E, 20X), G- Prostatic adenocarcinomaGleasons score 3 (H&E, 20X), H- Prostatic adenocarcinomaGleasons score 4 (H&E, 20X), I- Prostatic adenocarcinomaGleasons score 5 (H&E, 20X).On Immunohistochemistry(20X), J- suspicious focus of glands with negative nuclear staining of p63, K- suspicious focus of glands with negative cytoplasmic staining of HMW CK (marker of basal cell), L- AMACR positivity in suspicious malignant glands.

chips(Transrectal Urethral Resection of Prostate chips), whereas we included only TRUS biopsies. This can also account for more benign cases in these studies.

The lesions were classified into three main categories- Benign prostatic tissue, Prostatitis and Prostatic adenocarcinoma. Benign prostatic tissue was seen in 12.93% cases in present study, 85.8% in a study by Kshitij et al (2011),[8] 64.48% in a study by Azmi A. Haroun et al (2011),[9] 56% in a study by Jasani et al (2012)[3] and 38% in a study by Bedarshi Banerjee et al (2016).[10] Prostatic adenocarcinoma was seen in 49.14% cases in present study, 8.35% in a study by Kshitij et al (2011),[8] 27.1% in a study by Azmi A. Haroun et al (2011),[9] 32% in a study by Jasani et al (2012)[3] and 15% in a study by Bedarshi Banerjee et al (2016).[10]

Prostatitis was seen in 37.93% cases in present study, 0.64% in a study by Kshitij et al (2011),[8] 2.7% in a study by Jasani et al (2012)[3] and 37% in a study by Bedarshi Banerjee et al (2016).[10] The above mentioned studies included prostate chips (TURP) as well. TURP is the gold standard of surgical treatment for benign prostatic hyperplasia.[11] Thus, more percentage of benign lesions were found in these studies and greater percentage of malignant lesions were found in present study as compared to the above mentioned studies.

Prostatic Intraepithelial Neoplasm (PIN) was reported in few studies like by Bedarshi Banerjee et al (2016),[10] Jasani et al (2012)[3] and Kshitij et al (2011).[8] These studies predominantly included prostate chips (TURP). In TURP specimens, the entire part of gland is sampled and examined under microscope, thus allowing more chances of diagnosing PIN as it may occur in small foci within a gland, which might go unnoticed in a biopsy, hence limiting the usefulness of prostatic biopsy.[10]

The cases of prostatic adenocarcinoma were graded according to the new ISUP/WHO classification 2014 in present study. Nine cases of Grade 1(15.79%), 4 cases of Grade 2(7.02%), 7 cases of Grade 3(12.28%), 11 cases of Grade 4(19.30%) and 26 cases of Grade 5(45.61%) were reported. In the study done by Manjit Singh Bal et al (2013),[12] Gleason score 5-7 were seen in 62.71% cases. The next Gleason score was 2-4, seen in 23.72% cases (Total 86.43%) and in 13.55% cases the Gleason score was 8-10. In the study done by Atchyuta .M et al (2016),[7] Gleason grade 3 was the most common primary pattern in their study. The most common secondary pattern was Gleason grade 4. Thus, the most common Gleason's score was 7 in 43% cases, 5 in 17% of cases, 8 and 9 in 12% of cases each (Total 24%), 6 and 4 in 8 % of cases. However, in present study, Grade 4 and 5 (Gleasons score 8 and 9) were most common, accounting for 64.91% of the malignant cases. Grade 1-3 were seen in 35.09% cases.

Only the cases with PSA levels were included. PSA levels in benign and malignant lesions were compared to other studies. In present study, PSA levels upto 4ng/ml was found in 8.5% of benign cases. Rest 91.5% had PSA level above 4ng/ml. In comparison, study done by Jasani et al (2012),[3] 62.6% of benign cases had PSA upto 4ng/ml while 37.02% benign cases had PSA level above 4ng/ml.

Normal levels of serum PSA vary according to the age of the patient, in several disease processes like prostate cancer, prostatic intraepithelial neoplasia and prostatitis.[10] Serum PSA levels are slightly elevated in cases of Benign Prostatic Hyperplasia (BPH) because of prostate tissue specific protease property of PSA.[13] Kiehl and associates (2001)[14] in their study also concluded that BPH and prostatitis is associated with PSA elevation when glandular epithelium is disrupted.[14]

Thus, such high percentage of benign cases with PSA level above 4ng/ml in our study can be attributed to more number of (acute, chronic and granulomatous) prostatitis cases. As high PSA levels can be found in benign conditions also, histopathology is necessary to confirm the diagnosis. In the malignant lesions, in present study 93% cases had PSA level above 4ng/ml comparable to other studies, Sladana et al (2004)[13] and Jasani et al (2012)[3] had 97.5% cases and 98.2% cases with PSA level above 4ng/ml. In a study by Dr. Nirav Hingrajia(2015),[15] 26.5% patients had PSA levels of ≥ 20ng/ml, of which 70% patients had adenocarcinoma, 30% patients had hyperplasia; one of the later had active prostatitis. It showed that patients with markedly elevated serum PSA levels are more likely to harbor adenocarcinoma in their biopsies than benign changes.

Likewise, majority of the malignant cases in present study had PSA level above 4ng/ml. However, a small percent, 7% (4 out of total 57 malignant cases) of the malignant cases had PSA level below 4ng/ml. The lowest PSA level of 0.18ng/ml was seen in Grade 1 prostatic adenocarcinoma.

As a significant number of malignant cases (7%) had low PSA levels (upto 4ng/ml), it is imperative to carry out a TRUS biopsy whenever a clinician palpates a suspicious nodule on per rectal examination. This will enable an accurate diagnosis and early carcinomas will be detected. Thus, serum PSA determination alone, has certain limitations for the diagnosis of prostate cancer.

Association of Gleasons grade and PSA level- The study done by Atchyuta .M et al (2016)[7] showed that there is

strong positive correlation between Gleason score given in prostatic adenocarcinomas and serum PSA values. The results were similar to the studies done by Karazanashvili G et al (2003) [16] and Wei -Jen Shih et al (1992).[17]

In a study by Dr. Nirav Hingrajia (2015),[15] it was observed that the levels of serum PSA increased with increasing Gleason grade and score of the tumor. In their study, majority of cancers (76%) belonged to intermediate to high grade category. Similarly, scores were also moderate to high in majority of cases. Most of the patients having grade 3 or above showed markedly high levels of PSA.

In present study, 73.1% of Grade 5 Prostatic adenocarcinoma,63.6% of Grade 4 Prostatic adenocarcinoma, 28.6% of Grade 3 Prostatic adenocarcinoma, 0% of Grade 2 Prostatic adenocarcinoma and 33.3% of Grade 1 Prostatic adenocarcinoma had PSA level > 20ng/ml.

The minimum PSA level of 0.18ng/ml and maximum PSA level of 2,521.58ng/ml was seen in Grade 1 and Grade 5 Prostatic adenocarcinoma respectively. The mean PSA level was 19.67ng/ml in Grade 1 Prostatic adenocarcinoma, 10.84ng/ml in Grade 2 Prostatic adenocarcinoma, 21.07ng/ml in Grade 3 Prostatic adenocarcinoma, 39.06ng/ml in Grade 4 Prostatic adenocarcinoma and 399.26ng/ml in Grade 5 Prostatic adenocarcinoma. Thus, the mean PSA levels increased as the grade increased but it was statistically not significant (p>0.05).

Conclusion

The study proves that histopathology is essential for detecting prostatic adenocarcinoma. Digital rectal examination findings and PSA levels alone cannot be depended upon. Hence, it is essential to carry out TRUS biopsy and do a histopathological analysis whenever a clinician palpates a hard nodule on per rectal examination. This will enable early diagnosis and treatment. Thus, improving the 5 year survival rate of the patient.

Abbrevations

ng/ml- nanogram/milliliter

SD/ StdDev- Standard Deviation

IHC- Immunohistochemistry

HMW CK- High Molecular Weight Cytokeratin

CK- Cytokeratin

AMACR- Alpha Methyl Acyl coARacemase

ZN stain- ZiehlNeelsen stain

H&E- Haematoxylin& eosin stain

No.- Number

df- Degrees of freedom

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