European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 03, 2022

ORIGINAL RESEARCH

Spectrum of histopathological lesions in the prostate and their correlation with serum prostate specific antigen levels

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ABSTRACT

Background: Diseases affecting the prostate include benign prostatic hyperplasia (BPH), non-specific inflammatory conditions and malignancy of the prostate, are responsible for significant morbidity and mortality among ageing male patients.This study was done to study the histopathological spectrum of prostatic lesions, classify them and to correlate them with free serum PSA levels.

Material and methods:The sample size was 302. Collected data was analyzed with descriptive statistics followed by chi- square test.Tests were used to analyze the sensitivity, specificity and overall accuracy of serum PSA levels in diagnosing benign and malignant prostatic lesions. p value was calculated and considered statistically significant when p value was less than 0.005.

Results:Majority of the benign lesions had serum PSA in the range of 0-4 ng/ml.About 21% had modest elevation in serum PSA.Majority of the malignant lesions had highly elevated serum PSA levels.BPH-Less than half of the cases showed epithelial and stromal hyperplasia without prostatitis.PIN- 2 had a histology of low grade PIN and 1 had high grade PIN. Adenocarcinoma: Majority of the lesions showed discrete glandular pattern.Gleason score of 7 was the commonest pattern. The sensitivity and specificity of serum PSA in benign lesions was found to be 62% and 95% respectively and in malignant lesions was 95% and 62% respectively.

Conclusion: It was concluded that PSA cut off value >4ng/ml is a diagnostic tool for detection of adenocarcinoma prostate.

Keywords: adenocarcinoma, prostate, PSA levels.

INTRODUCTION

Diseases affecting the prostate include benign prostatic hyperplasia (BPH), non-specific inflammatory conditions and malignancy of the prostate, which are responsible for significant morbidity and mortality among ageing male patients.Histopathological examination (HPE) of the resected or biopsied prostatic tissue is an indispensible modality by which suspected clinical diagnosis of prostatic lesions are confirmed. The measurement of free serum PSA levels coupled with a digital rectal examination (DRE) and HPE has led to improved

detection of prostatic lesions with earlier diagnosis and treatment.[1] Normal levels of PSA are usually less than 4ng/ml, between 4-10ng/mL are borderline and more than10 ng/mL are considered high.[2]Lesions of the prostate such as hyperplasia, non-specific inflammation, infarcts, abscess, premalignant condition and tumors lead to increase in serum PSA levels.[2-5]Multiple other factors like drugs (e.g. Finasteride), urinary tract infections and body mass index also affect serum PSA levels.[5]Gleason's system is now widely being utilized as the histologic grading system for prostatic cancer and is a powerful predictor of cancer behaviour.[3,6]This study was done to study the histopathological spectrum of prostatic lesions, classify them and to correlate them with free serum PSA levels.

MATERIAL AND METHODS

This descriptive study was conducted in the Histopathology section of Department of Pathology, Christian Medical College and Hospital, Ludhiana, done over a period of 3 years which included 2 years of retrospective and 1 year of prospective study. The retrospective period was from 1st January 2012 till 31th December 2013 and prospective study period was from 1st January 2014 till 31st December 2014.The study was done on prostatic tissue obtained either by trucut biopsy, transurethral resection (TURP) or open prostatectomy. The sample size was 302.

INCLUSION CRITERIA

All the prostatic tissue specimens sampled either by trucut biopsies, transurethral resection (TURP) and/or via open prostatectomy procedure and which had serum PSA estimation done.

EXCLUSION CRITERIA

- Prostatic tissue with no serum PSA level.
- Repeat biopsy specimen of the same patient.

The clinical details of all the retrospective and prospective cases were noted down from the histopathology forms available in the Pathology Department and/or from patient's records as per protocol. Free serum PSA level was analyzed by chemiluminescence assay on Roche Hitachi e 411 done in the Department of Biochemistry, Christian Medical College and Hospital, Ludhiana. Kits were procured from Roche.

PROCESSING OF THE PROSTATIC BIOPSIES

For prospective cases, specimens were received and detailed macroscopic examination was done. The tissue received was fixed in 10% neutral buffered formalin and processed. In case of TURP specimen, tissue was taken in a minimum of four cassettes (each cassette hold approx.2gms) and in case of excess tissue, one additional cassette for each additional 10 gm of tissue was taken. In cases of prostatectomy specimens, multiple sections were made at a distance of 3 to 5 mm. Trucut biopsy specimens were grossed entirely. After grossing, representative tissue sections were processed overnight for 15½ hours in an automated tissue processor (Leica TP 1020) which involved dehydration done by use of graded alcohols beginning with 70% ethanol in water then progressed through 95-100%. This was followed by clearing done by xylene, and later embedding of tissues into paraffin blocks. The sections were cut at 3-5 micron thickness and subsequently stained by haematoxylin and eosin stain.

For retrospective cases, the slides and data were taken out from the pathology records. Clinical and gross details were noted down as per protocol. Microscopic examination of both the retrospective and prospective cases was done personally and classified as BPH, BPH with associated prostatitis, premalignant (adenosis, PIN- low and high grade) and malignant. The malignant lesions were further graded as low, intermediate and high grade based on Gleason's score. Fresh sections were cut from available paraffin blocks if required for

retrospective cases. Immunohistochemistry (CK5/6, P63 and AMACR) was done in doubtful cases to differentiate premalignant from malignant lesions.

MODIFIED GLEASON GRADING SYSTEM[6.7]

SCORE DESCRIPTION

1. Single, separate, uniform glands in closely packed masses with a definite, usually rounded, edge limiting the area of tumor.
2. Single, separate, slightly less uniform glands, loosely packed (separated by small amounts of stroma), with less sharp edge.
3. a. Single, separate, much more variable glands, may be closelypacked but usually irregularly separated; ragged, poorly defined edge.
   b. Like 3a, but very small glands or tiny cell clusters
   c. Sharply and smoothly circumscribed rounded masses ofPapillary or loose cribriform tumor(papillary intraductal tumor)
4. a. Ragged outlined, ragged infiltrating, fused glandular tumor
   b. Like 4a, with large pale cells(hypernephroid)
5. a. Sharply circumscribed, rounded masses of almost solid Cribriform tumor, usually with central necrosis (Comedocarcinoma)
   b. Ragged masses of anaplastic carcinoma with only enough gland formation or vacuoles to identify it as adenocarcinoma.

GLEASON SCORE

Primary grade is assigned to the dominant pattern and secondary to the sub-dominant pattern. The two numeric grades are added to obtain the combined Gleason score. In tumors with one pattern, the number is doubled.

WHO HISTOPATHOLOGICAL GRADING

GX Grade cannot be assessed
G1 Well differentiated tumor (Gleason score 2-5)
G2 Moderately differentiated tumor (Gleason score 6)
G3-4 Poorly differentiated tumor/undifferentiated (Gleason score 7-10).

PROCEDURE FOR HEMATOXYLIN AND EOSIN (H&E) STAINING

a. Sections were dewaxed by placing them on hot plate at a temperature of 60^{o}C and then in xylene for 1-2 minutes.
b. Rehydration through descending grades of alcohol was done and slides were brought to distilled water.
c. Sections were then stained with Mayer hematoxylin (progressive) for 10 to 15 minutes.
d. Washed in running tap water until sections turned “blue” for 5 minutes.
e. Stained with 1% aqueous Eosin Y for 10 minutes.
f. Washed surplus stain in running tap water for 1 to 5 minutes.
g. Sections dehydrated through graded alcohol
h. Cleared in xylene and mounted with DPX (Dibutyl Phthalate Xylene)

STATISTICAL ANALYSIS

Collected data was analyzed with descriptive statistics followed by chi- square test.Tests were used to analyze the sensitivity, specificity and overall accuracy of serum PSA levels in diagnosing benign and malignant prostatic lesions. p value was calculated. Values were considered statistically significant when p value was less than 0.005.

RESULTS

The present study was undertaken to correlate serum PSA levels in various prostatic lesions. The sensitivity and specificity were calculated to evaluate the effectiveness of serum PSA levels.

Out of 302 specimens, 72.5% (n=219) were of BPH, 1% (n=3) of PIN and 26.5% (n=80) were of Adenocarcinoma. Nine cases of adenocarcinoma had foci of PIN.

The age of the patients included in the study ranged from 35 to 94 years with a mean age of 70.1 years. Majority (40.1%) of patients were in 7^{th} decade (BPH) followed by in 8^{th} decade (33.4%) in adenocarcinoma. The mean age of presentation for BPH and Carcinoma was 69.4 years and 71.7 years respectively. Of the total cases, majority of the specimens received were of TURP chips (74.8%), followed by trucut biopsy (24.8%); prostatectomy specimens were only 0.3% of the total specimens.Of these, most of the patients had grade II prostatomegaly on clinical examination in benign cases and grade IV in malignant cases. Of the 240 cases, the consistency of the prostate was mentioned in only 124 cases of which 85 were benign and 39 were malignant. Out of 85 benign cases, majority (83 cases) had firm prostate whereas 2 cases had prostate with hard consistency which were associated with inflammation. Of the 39 malignant cases, 33 prostates were hard and 6 were firm in consistency. Hard prostatic nodule was significantly associated with malignant cases in our study. Most of the patients (63.6%) in our study presented with acute and chronic urinary retention, increased frequency, poor urinary stream while 38% had nocturia, burning micturition and incomplete voiding. In our study, serum PSA was done in all 302 cases. Majority of the benign cases [137 cases; 62.5%] had serum PSA in the range of 0-4 ng/ml. About 21% had modest elevation in serum PSA, in the range of 4.1-10 ng/ml whereas 28 of the benign cases (12.7%) had serum PSA in the range of 10.1-20 ng/ml of which 19 cases were associated with inflammation. Eight of the benign cases (3.8%) in the study had very high range of serum PSA elevation with value more than 20 ng/ml of which 5 cases were associated with inflammation. The median serum PSA value in benign cases was 2.9ng/ml. Of the three cases of PIN, two had serum PSA in the range of 10.1-20 ng/ml while one had serum PSA more than 20 ng/ml.

In the present study majority of the malignant cases [62.7% (50/80 cases)] had highly elevated serum PSA levels of more than 20 ng/ml. Twenty six (32.3%) of the malignant cases had serum PSA in the range of 10.1- 20 ng/ml whereas 4 had PSA less than 10ng/ml. The median serum PSA value in malignant cases was 24.7 ng/ml.

Table 1: PSA value in various prostatic lesions

PSA VALUE(ng/ml)	BPH n(%age)	PIN n (%age)	Adenocarcinoma n (%age)
0-4	137(62.5%)	-	02(2.5%)
4.1-10	46(21%)	-	02(2.5%)
10.1-20	28(12.7%)	02(66.7%)	26(32.3%)
20.1-100	06(2.8%)	01(33.3%)	25(31.2%)
>100	02(1%)	-	25(31.5%)
Median PSA value	2.9	16.8	24.7
Range	0.1-101.2	14.6-1448	0.03-2975

PSA VALUE IN BENIGN PROSTATIC HYPERPLASIA (BPH)

Less than half of the cases [n=69 (31.50%)] showed epithelial and stromal hyperplasia without prostatitis**.** Corpora Amylacea was seen in all BPH cases**.** Squamous metaplasia was seen only in 01 case (0.4%)**.** Chronic inflammatory cells of varying degree were found in 35.15% of the cases in our study**.** Acute and chronic inflammation was seen in 66 (30.13%) cases of which one case showed squamous metaplasia and granulomatous prostatitis respectively**.** Seven cases (3.2%) had evidence of granulomatous prostatitis and one case

showed evidence of xanthogranulomatous prostatitis with presence of foamy histiocytes within the glandular lumina and stroma**.**

Table 2: PSA value in Benign Prostatic Hyperplasia (BPH)

Histopathological diagnosis	n (%age)	PSA value range(ng/ml)
BPH	69(31.5%)	0.1-101
BPH with chronic prostatitis	77(35.2%)	0.18-101.2
BPH with acute on chronic prostatitis*	66(30.1%)	0.3-59.2
BPH with granulomatous prostatitis	07(3.2%)	0.5-22
BPH with squamous metaplasia	01(0.4%)	0.72
BPH with xanthogranulomatous prostatitis	01(0.4%)	2.2
Total cases	221(100%)	

***** One case of BPH with acute on chronic prostatitis showed squamous metaplasia and granulomatous prostatitis.

PSA VALUE IN PROSTATIC INTRAEPITHELIAL NEOPLASIA (PIN)

PIN is characterised by intraepithelial proliferation of secretory epithelium that displays a spectrum of cytologic changes culminating in those that are indistinguishable from carcinoma. In our study, prominent histological features viz. Increased cellularity, pseudostratification, intraluminal papillary formation, bridging of lumen and cribriform formation helped us in diagnosing and grading PIN.

Out of the 3 patients diagnosed as PIN, 2 had a histology of low grade PIN (LGPIN) and 1 had high grade PIN (HGPIN)**.**

Table 3: PSA value in Prostatic Intraepithelial Neoplasia (PIN)

PIN	No. of cases(%age)	PSA value range (ng/ml)
Low grade PIN	02 (66.7%)	15.6-30.6
High grade PIN	01 (33.3%)	16.8
Total	03(100%)	

PSA VALUE IN ADENOCARCINOMA

Various morphological patterns were seen with majority of the cases showing one or more than one of the different growth patterns. The tumour was categorized depending on the predominant growth pattern. Majority of the lesions showed discrete glandular pattern. In addition to this, other patterns seen were fused glands, cribriform glands, sheets, cords and tumour with central necrosis pattern. Fifty three cases had showed discrete glandular pattern **.** Fused glandular pattern was seen in 36 cases**.** Cribriform glandular pattern were found in 17 cases. Very few cases showed histology of sheets and cribriform glandular pattern with central necrosis. Perineural invasion were seen in 53 cases of which 2 cases showed presence of ganglion cells**.**Lymphovascular invasion and squamous metaplasia were seen in 2 cases respectively**.** Brisk mitotic activity with abnormal mitotic figures are also seen in high grade tumor**.**

Table 4: Case distribution on the basis of microscopic finding in adenocarcinoma prostate

Sr no.	Microscopic finding	No.of cases
1	Discrete glands	53
2	Fused glands	36
3	Cribriform glands	17
4	Cords	35
5	Sheets	13
6	Cribriform glands with central necrosis	10

7	Perineural invasion	53
8	Lymphovascular invasion	02
9	Squamous metaplasia	02

Nine cases of adenocarcinoma showed foci of PIN. Four cases of adenocarcinoma showed features of LGPIN whereas 5 showed HGPIN. Low grade PIN with adenocarcinoma showed crowding pattern whereas high grade PIN with adenocarcinoma showed epithelial stratification, nuclear pleomorphism, presence of nucleoli and intact basement membrane.

Table 5- PIN with reference to PSA value range

PIN	No. of cases(%age)	PSA value range (ng/ml)
Low grade PIN with carcinoma	04 (44.4%)	14.6-39.8
High grade PIN with carcinoma	05 (55.6%)	16.5-1448
Total	09(100%)	

GLEASON SCORE

All of the 80 malignant cases were graded using Gleason's scoring system. Primary grade was assigned to dominant pattern and secondary grade to subdominant pattern. The two numeric grades are added to obtain the Gleason's score. Lowest Gleason score was 5 and highest score was 9 in the present study.

Most common Gleason score in our study was 7(33.7% cases). We also found 11 cases (13.7%) with Gleason score of 8 and 14 cases (17.5%) with Gleason score of 9**.** All these cases (Grade 7,8& 9) fell under poorly differentiated adenocarcinoma category according to WHO classification. Twenty four cases (30%) were categorised under moderately differentiated adenocarcinoma by WHO with Gleason score of 6 and 4(5%) were described as well differentiated adenocarcinoma with Gleason score of 5**.** PSA value did not show any correlation with increased or decreased Gleason score.

Table 6: Adenocarcinoma cases with reference to Gleason score

Gleason score	No, of cases (%age)	PSA value range (ng/ml)
5	04(5%)	11.86-1448
6	24(30%)	0.03-196
7	27(33.7%)	11-2975
8	11(13.7%)	0.12-1052
9	14(17.5%)	4.5-152.7
10	-	-
TOTAL	80(100%)	

Immunohistochemistry was done in 8 cases to differentiate between Prostatic intraepithelial neoplasia (PIN) and Adenocarcinoma prostate. Eight cases had P63 & CK5/6 negative and AMACR positive and were diagnosed as adenocarcinoma.

Sensitivity, specificity and accuracy of serum PSA levels in diagnosing benign prostatic diseases (Table 7)-

PSA level	BPH		Total
	Positive	Negative	
<4 ng/ml	137	4	141
>4 ng/ml	84	77	161

The study showed 137 true positives and 4 false positive cases.

True negatives were 77 whereas 84 cases were false negatives.

The sensitivity of serum PSA was found to be 62% and the specificity was 95%.

Positive predictive value was 97% whereas negative predictive value was 47% Likelihood ratio calculated was 12.55 (95%CI: 0.87 to 0.98).
Serum PSA value in the range of 0-4 ng/ml showed statistical significant (p value < 0.001) when associated with benign lesions.

Sensitivity, specificity and accuracy of serum PSA levels in diagnosing malignant prostatic diseases (Table 8)-

PSA level	Carcinoma		Total
	Positive	Negative	
>4 ng/ml	77	84	161
<4 ng/ml	4	137	141

In malignant cases, True positive cases were 77 and false positive cases were 84.
True negative were 137 whereas false negative cases were 4.
The sensitivity of serum PSA was found to be 95% and the specificity was 62%.
Positive predictive value was 47.8% whereas negative predictive value was 97% Likelihood ratio calculated was 2.50.
Serum PSA value of >4 ng/ml showed statistical significance (P value < 0.001) in relation to malignant prostatic diseases.

DISCUSSION

n our study majority of the patients of BPH presented in the age group of 61-70 years of age and adenocarcinoma in the age group of 71-80 years. The mean age of presentation for BPH and Carcinoma was 69.4 years and 71.7 years respectively**.** Majority of the patients were found to be 7^{th} (BPH) and 8^{th} (adenocarcinoma) decade. TURP chips formed bulk of the specimens in our study accounting for 74.8% of total specimens.
Most commonest lesion in our study was BPH (72.5%) followed by adenocarcinoma prostate (26.5%) which was in concordance with studies done by **Aroraet al[8], Shirish et al[9]**. Out of 80 cases of adenocarcinoma, 9 were associated with PIN which was also documented in the studies done by **Lakhey et al[3]**however the incidence of PIN in these studies were much higher compared to the present study.
Most common clinical presentation (63.6%) in our study was urinary retention, increased frequency and poor urinary stream while 37.9% had nocturia, burning micturition and incomplete voiding.
BPH is a heterogenous disease that is characterised histologically by a variable degree of stromal and epithelial hyperplasia. Less than half of the cases [31.5% (n=69)] showed epithelial and stromal hyperplasia without prostatitis. Similar findings were noticed by **Lakheyet al[3]** and **Akhter et al[10]**.
The serum PSA was done in all 302 cases in our study. Maximum [137(62.5%)] of benign cases had serum PSA value in the range of 0-4ng/ml. The value of PSA in benign lesions in various other studies were also comparable with the present study.[3,10]
Forty six cases (21.0%) had modest elevation in serum PSA ranging from 4.1-10ng/ml. **Goswami et al[2]** showed much higher incidence of PSA elevation in the range of 4-10ng/ml whereas **Lakhey et al[3]** showed lower incidence of modest elevation in PSA level.
Twenty eight of the benign cases (12.7%) had serum PSA in the range of 10.1-20 ng/ml of which 19 cases were associated with inflammation. Similar findings was also noticed by **Goswamiet al[2]andShirish et al[9]**.
Eight (3.8%) cases had serum PSA value more than 20ng/ml of which 5 cases were associated with inflammation. High serum PSA value in BPH was also noticed by **Akhter et al[10], Murthy[12]**and**Anushree et al[11]**.
The median serum PSA value in BPH was 2.9ng/ml.

Squamous metaplasia was only seen in 01 case (0.4%) in the present study. A study conducted by **Shirishet al**[9] found higher incidence (9.6%) of BPH showing squamous metaplasia.
Chronic inflammatory cells of varying degree were found in 35.2%(n=77) of the cases in our study which was comparable with studies done by **Lakhey et al**[3] whereas it was much lower when compared to study done by **Shirish et al** (87.9%)[9].
In our study, acute and chronic inflammation was much higher (30.1%) when compared to other studies**.** One case of acute and chronic inflammation in our study showed presence of squamous metaplasia and granulomatous inflammation.
Seven cases (3.2%) of granulomatous prostatitis were found in our study. **Barazkai etal**[13] in their study showed 7.1% cases of granulomatous prostatitis.

PROSTATIC INTRAEPITHELIAL NEOPLASIA (PIN)
PIN is characterised by intraepithelial proliferation of secretory epithelium that displays a spectrum of cytologic changes culminating in those that are indistinguishable from carcinoma. In our study, prominent histological features viz. Increased cellularity, pseudostratification, intraluminal papillary formation, bridging of lumen and cribriform formation helped us in diagnosing and grading PIN.
The study showed 3 patients diagnosed as PIN, 2 had LGPIN and 1 was diagnosed as HGPIN. Two cases of PIN had serum PSA in the range of 10.1-20ng/ml while one case of PIN had serum PSA more than 20ng/ml. Our findings were in concordance with studies done by **Lakhey et al**[3]**, Jasani et al**[14].

ADENOCARCINOMA
Various morphological patterns were seen in malignant cases. All of them showed one or more of the different growth patterns and were categorized depending on the predominant growth pattern. Majority showed discrete glandular pattern. In addition to this, other patterns seen were fused glands, cribriform glands, sheets, cords and with central necrosis pattern.
In the present study, most [62.7% (50/80) cases] of the malignant cases had highly elevated serum PSA levels of more than 20ng/ml. Twenty six (32.3%) of the malignant cases had serum PSA in the range of 10.1-20ng/ml whereas 4 had PSA less than 10ng/ml. Similar observation were made by various other studies[10-12] who found maximum cases of adenocarcinoma with serum PSA levels of more than 20ng/ml. However few other studies done by **Goswamiet al**[2]**, Lakhey et al**[3]**, Arora et al**[8]**, Jasani et al**[14]found serum PSA level to be in the range of 10.1-20 ng/ml.
Nine cases of adenocarcinoma had foci of PIN. Similar findings were also noticed by **Lakheyet al**[3]**, Jasani et al**[14].

GLEASON SCORE
Most common Gleason score in our study was 7(33.7% cases). We also found 11 cases (13.7%) with Gleason score of 8 and 14 cases (17.5%) with Gleason score of 9. All these cases fell under poorly differentiated adenocarcinoma category as per WHO classification. Our findings were almost similar with various other studies.[9,11]while in the study done by **Barakzai et al**[13]most common Gleason score was found to be 8.
The sensitivity and specificity of serum PSA in benign lesions was found to be 62% and 95% respectively in the present study. No studies has been done to compare sensitivity and specificity of the benign cases.
The sensitivity and specificity of serum PSA in malignant lesions was found to be 95% and 62% respectively in the present study. A study done by **Goswami et al**[2] also found sensitivity of serum PSA to be more than specificity in malignant lesions (sensitivity- 86.7% and

specificity -37%).Whereas **lakhey M et al**[3] found specificity to be more than sensitivity in malignant lesions (sensitivity- 78% and specificity- 90%).

CONCLUSION

Out of 302 prostatic specimens studied, benign lesions were common, accounting for 72.5% and malignant lesions accounted for 26.5%. Maximum incidence of BPH and adenocarcinoma manifested in the age group of 61-70 years (41.6%) and 71-80 years(41.3%) respectively. The common presenting symptoms wasacute and chronic urinary retention, increased frequency and poor urinary stream. Majority of the patients with BPH had PSA level <4ng/ml (62.5%); whereas in adenocarcinomawas>20ng/ml (62.7%). The study showed that as the PSA levels increases the chances of malignancy increases. Higher PSA levels were also seen in benign lesions associated with inflammation. The sensitivity, specificity and accuracy of PSA in diagnosing malignant prostatic lesions were analyzed and showing sensitivity of 95%, specificity of 62%, PPV of 47.8% and NPV of 97% .When serum PSA levels in malignant cases were compared, serum PSA >4 ng/ml was significantly associated with malignant lesions, p value < 0.001. It was concluded that PSA cut off value >4ng/ml is a diagnostic tool for detection of adenocarcinoma prostate.

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