

# Histomorphological Correlation of Prostatic Lesions with Serum Prostate Specific Antigen Levels

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**Abstract:** ***Background:** Prostatic adenocarcinoma is one of the most common cancers occurring in the men above 50 years of age. Serum prostate specific antigen (S.PSA) helps in early diagnosis of prostatic adenocarcinoma. Various benign prostatic diseases may also elevate S.PSA. **Aims and objectives:** 1) To study histopathology of prostatic lesions 2) To correlate histopathological diagnosis with serum prostate specific antigen levels. **Materials and methods:** The study involved histopathological analysis of prostatic lesions of 110 patients admitted in our hospital who had undergone prostatic biopsy or transurethral resection of prostate (TURP) during October 2015 to August 2017. Preoperative S.PSA levels were estimated. The correlation between histopathological findings and S.PSA levels was made. **Results:** Our study included 110 cases, out of which BPH was the commonest disease seen in 81.8% cases, of which BPH without prostatitis constituted 62.7% of the cases. BPH with chronic prostatitis and BPH with acute prostatitis were seen in 13.6% and 5.5% cases respectively. Prostatic carcinoma was seen in 10.9% cases. Other diseases encountered were PIN (4.5%), ASAP (1.8%) and BCG granuloma (0.9%). Adenocarcinoma was the commonest malignancy seen in all 12 cases. Mean S.PSA levels in BPH was 4.41 ng/ml, in BPH with acute prostatitis 11.96 ng/ml, in ASAP 6.05 ng/ml, in PIN 9.88 ng/ml, and in prostatic adenocarcinoma 88.83 ng/ml. **Conclusion:** Our study showed that there was significant correlation between serum PSA levels and various prostatic lesions.*

**Keywords:** Prostate, Hyperplasia, Adenocarcinoma, PSA, Gleason score.

## 1. Introduction

Prostate, an accessory gland of male reproductive system, gives rise to various pathological conditions leading to disease related morbidity in considerable number of males in their late adulthood.<sup>1</sup> Transurethral resection of prostate (TURP) is performed for surgical management of benign prostatic hyperplasia.<sup>2</sup> Normal levels of total serum PSA ranges from 0 to 4 ng/ml. Detection of elevated levels of total serum PSA may help in early detection of prostate carcinoma. Various benign prostatic diseases like BPH and prostatitis and also some iatrogenic manipulations may also elevate total serum PSA levels.<sup>3</sup> Therefore utility of serum PSA as a tumor marker in screening and early detection of carcinoma depends on clear understanding of its levels in neoplastic and non-neoplastic conditions<sup>4</sup>

This study has been undertaken in an effort to study histopathological diagnosis and preoperative total serum PSA levels. This study showed how different prostatic pathologies influence total serum PSA levels and also supported the utility of this tumor marker in diagnosis of carcinoma.

## 2. Aims & Objectives

- 1) To study histopathology of prostatic lesions.
- 2) To correlate histopathological diagnosis with serum prostate specific antigen levels.

## 3. Materials & Methods

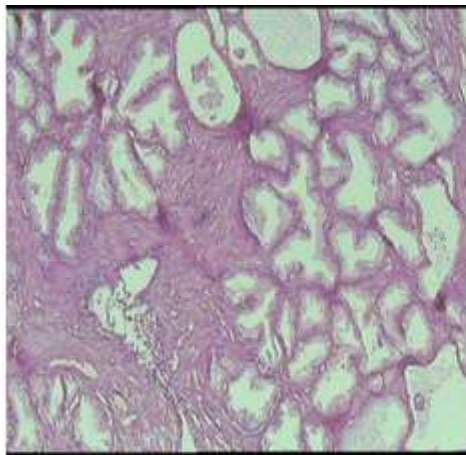
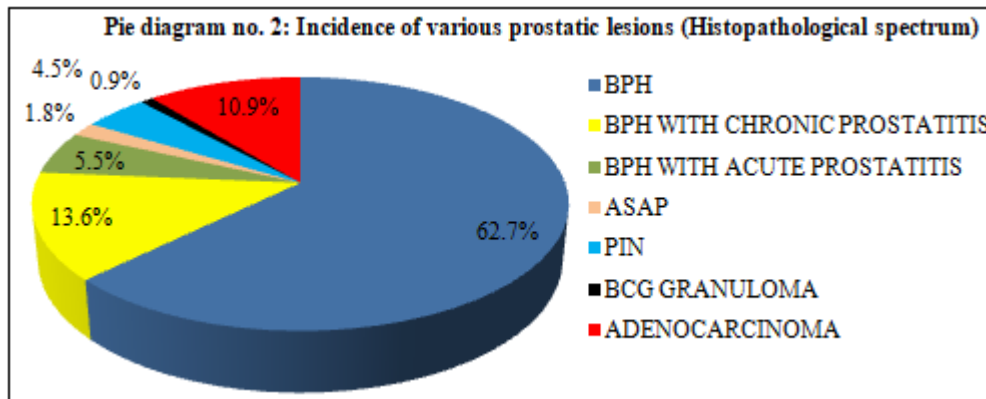
This was the cross sectional study carried out in the department of pathology from October 2015 to August 2017. All patients admitted in department of surgery of our hospital with prostatic complaints who had undergone prostatic biopsy or TURP during October 2015 to August 2017. Inadequate biopsies and patients on therapy for prostatic malignancy were excluded from study. The clinical details, per rectal examination findings, ultrasound findings, laboratory data and relevant past and family history had been taken. Total serum PSA levels estimation was done with Lisa plus micro-plate ELISA reader.

## 4. Results

In the present study we received 110 prostatic samples, amongst them 98 (89.09%) were TURP samples and 12(10.91%) were prostatic biopsies.

### **Incidence of various prostatic lesions:**

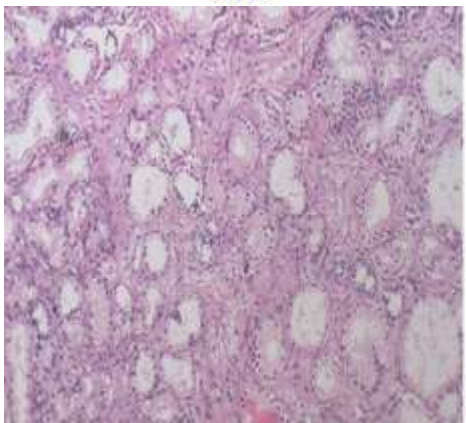
Benign Prostatic Hyperplasia (BPH) was the commonest disease seen in 81.8% cases, of which BPH without prostatitis constituted 62.7% of the cases. BPH with chronic prostatitis and BPH with acute prostatitis were seen in 13.6% and 5.5% cases respectively. Prostatic carcinoma was seen in 10.9% cases. Other diseases encountered were Prostatic Intraepithelial Neoplasia (PIN) in 4.5%, atypical small acinar proliferation (ASAP) in 1.8% and BCG granuloma in 0.9% cases. Adenocarcinoma was the malignancy seen in all 12 cases.



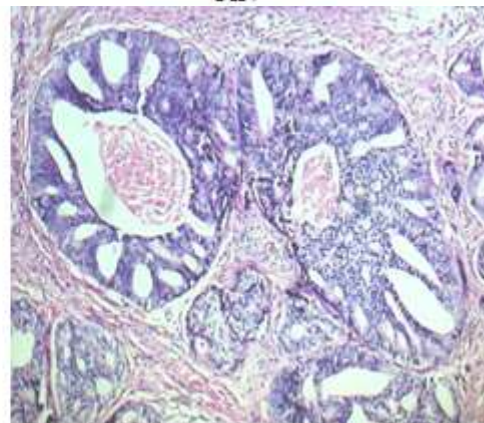
BPH



PIN



Prostatic adenocarcinoma (3+3)



Prostatic adenocarcinoma (4+5)

### Age Specific Distribution of Prostatic lesions

Maximum number of prostatic pathologies including benign and malignant were seen in the age group 60-69 years, followed by 70-79 years. The present study showed overlapping of age groups for the cases of BPH with or without prostatitis and prostatic carcinoma.

### Total serum PSA levels in various prostatic lesions

Out of 69 cases of BPH, 73.9% cases had preoperative total serum PSA values in the normal zone (<4 ng/ml), 14.5% had values in the range of 4 to 10 ng/ml, while 11.6% cases had values in the range of 10.1 to 20 ng/ml. Mean total serum PSA level for BPH was 4.41 ng/ml.

Out of 15 cases of BPH with chronic prostatitis, 46.7% cases had total serum PSA values in the normal zone (<4 ng/ml), 40% cases have values in the range of 4 to 10 ng/ml and 13.3% cases in the range of 10.1 to 20 ng/ml. The mean

total serum PSA level for BPH with chronic prostatitis was 4.97 ng/ml.

Out of 6 cases of BPH with acute prostatitis, 33.3% cases had total serum PSA values in the normal zone (<4 ng/ml), whereas 16.7% cases had values in the range of 4 to 10 ng/ml, 16.7% had values in the range of 10.1 to 20 ng/ml, while 33.3% cases had very high values of more than 20 ng/ml. The mean total serum PSA level for BPH with acute prostatitis was 11.96 ng/ml. Statistically significant difference was seen between mean total serum PSA level for BPH alone and BPH with acute prostatitis.

**Table 1:** Histopathological diagnosis with mean total serum PSA levels

Histopathological diagnosis	Mean total serum PSA level (ng/ml)
BPH	4.41
BPH With chronic prostatitis	4.97
BPH With acute prostatitis	11.96
ASAP	6.05
PIN	9.88
BCG granuloma	4.20
Adenocarcinoma	88.83

Both the cases of ASAP had total serum PSA levels in the range of 4 to 10ng/ml. The mean total serum PSA level for ASAP was 6.05 ng/ml. No significant difference is observed between mean total serum PSA values of ASAP and BPH cases. Out of 5 cases of PIN, 20% cases had values of total serum PSA levels in the normal zone (<4ng/ml), 40% have values in between 4-10ng/ml and 40% cases had values in the range of 10.1 to 20 ng/ml. The mean total serum PSA level for PIN cases was 9.88 ng/ml. No statistically significant difference was seen between mean total serum PSA level for PIN and BPH cases. In all 12 cases of prostatic carcinoma were diagnosed, only 1 case (8.3%) had total serum PSA value in the range of 4 to 10 ng/ml, while 11 cases (91.7%) had very high total serum PSA values of more than 20 ng/ml. The mean total serum PSA level for the cases of carcinoma of prostate was very high i.e. 88.83 ng/ml.

#### Association of total serum PSA and Gleason score

Gleason grading of the prostatic adenocarcinoma cases showed, 3 as the most common Gleason primary pattern (dominant grade) seen in 58.33% cases and 7 as the most common Gleason score seen in 33.33% cases.

Gleason score 5 to 9 showed increasing values of mean total serum PSA levels from 8.9 ng/ml to 163.5 ng/ml. The mean total serum PSA levels for Gleason score 10 was dropped to 91.3 ng/ml. Statistically highly significant association was found between Gleason score and mean total serum PSA levels.

**Table 2:** Mean total serum PSA levels in relation with Gleason score

Gleason score	Mean total serum PSA(ng/ml)
5	8.9
6	60.7
7	76.8
8	124.6
9	163.5
10	91.3

(Pearson's correlation coefficient=0.708, p value=0.001)

#### Sensitivity, specificity, PPV and NPV of total serum PSA levels at various cut off values:

At the total serum PSA cut of value of 4 ng/ml, sensitivity was 100% and specificity was 62.3%. At the total serum PSA cut of value of 10 ng/ml, the sensitivity decreased to 91.6% but the specificity increased to 84.7%. Similarly positive predictive value (PPV) for the total serum PSA cut of value of 4 ng/ml was 24.5% and negative predictive value (NPV) was 100%. At the total serum PSA cut of value of 10 ng/ml the PPV increased to 42.3% but the NPV decreased to 98.8%.

## 5. Discussion

In the present study majority of the prostatic tissue was obtained by TURP procedure i.e. 89.09%. In the study done by Wadgaonkar et al prostatic tissues obtained by TURP were 86.3% out of 80 prostatic samples received.<sup>5</sup>

#### Incidence of various prostatic lesions:

In the present study benign prostatic hyperplasia (BPH) was seen in 81.8% cases, of which BPH without prostatitis constituted 62.7% of the cases. In the study done by Wadgaonkar et al, majority of the cases (83.8%) were BPH, of which BPH without prostatitis constituted 60% of the cases.<sup>5</sup> Another study done by Kshitij et al<sup>6</sup> showed BPH incidence in 85.8% cases. In the present study PIN was observed in 4.5% cases. The study done by Kshitij et al<sup>6</sup> found incidence of PIN in 4.5% cases. In the present study incidence of ASAP was 2.1%. In the study done by Orhan et al<sup>7</sup> the incidence of ASAP was 4.7%. Carcinoma was identified in 10.9% cases in our study, which was comparable with the studies done by Bhatt et al<sup>8</sup>, Manjit et al<sup>9</sup>, Aslam et al<sup>10</sup> and Rizwan Javed et al.<sup>11</sup>

#### Age Specific Distribution of Prostatic lesions:

Present study showed 69 cases of BPH, which formed the major type of lesion in the study. Maximum cases were seen in the age group of 60-69 years having 43.5% of cases. The study done by Wadgaonkar et al<sup>5</sup> showed 67 cases of BPH and majority were in the age group 60-69 years (43.5%). Shakya et al<sup>12</sup> in their study of 106 BPH cases, found 47.16% of cases between 71-80 years followed by 33.96% cases in 61-70 years.

In the present study, malignant cases showed peak in two age groups, i.e. in 60-69 years and 70-79 years, having 58.3% and 25.0% cases respectively. In the study done by Wadgaonkar et al<sup>5</sup>, malignant cases showed peak incidence in two age groups, i.e. in 60-69 years and 70-79 years, each comprising 41.7% of cases. Anunobi et al<sup>13</sup> showed prostate carcinoma in an age range of 40 to 98 years, with a mean age of 66 years and peak prevalence in the 60-69 year age group.

#### Total serum PSA levels in various prostatic lesions:

In the present study, 73.9% of the BPH cases had total serum PSA < 4 ng/ml. 14.5% cases had modest elevation in total serum PSA, in the range of 4-10 ng/ml and 11.6% had total serum PSA in the range of 10-20 ng/ml. In the study done by Wadgaonkar et al<sup>5</sup>, 40.3% of the BPH cases had total serum PSA < 4 ng/ml and 59.7% of patients with elevated total serum PSA (> 4.0ng/ml). Another study done by Kshitij et al<sup>6</sup> showed 71.6% BPH cases had total serum PSA levels below 4ng/ml.

In present study 11.6% cases of BPH showed total serum PSA level beyond upper limit of gray zone i.e., 10 ng/ml. The PSA values > 10ng/ml were reported in 7% and 14% by Partin et al and Barak et al.<sup>14</sup> These findings were comparable with present study. The mean total serum PSA level for BPH cases was 4.47 ng/ml, which was comparable with study done by Lee F et al.<sup>15</sup>

In the present study, 66.7% cases of BPH with acute prostatitis showed total serum PSA levels >4ng/ml. Mean total serum PSA levels of BPH with acute prostatitis was significantly high as compared to BPH cases in the present study (t value=4.490, p value<0.001). It was concluded that acute prostatitis gives rise to elevation of total serum PSA levels.

Similar observations were made by Robles et al<sup>16</sup> and Yamamoto et al.<sup>17</sup> This might be because of release of PSA stored in epithelial cells into the stromal tissue after apoptosis which leaks into blood circulation as a result of hypervascularity and increased vascular permeability associated with acute prostatitis as suggested by Hasui Y. et al.<sup>18</sup> Also Kiehl et al<sup>19</sup> in their study, concluded that BPH and acute prostatitis is associated with PSA elevation when glandular epithelium is disrupted.

In the present study, we found 5 cases of isolated PIN. Amongst that 2 cases had total serum PSA more than 4 ng/ml and 2 cases had values >10 ng/ml. The mean total serum PSA level for PIN was 9.88 ng/ml. There was no statistically significant difference between mean total serum PSA level of PIN and mean total serum PSA of BPH cases. (t value=3.281, p value=0.215)

In the study done by Deepak et al<sup>20</sup>, the mean total serum PSA level for PIN was 7.5ng/ml, while in the study done by Brawer and Porter et al<sup>21</sup> it was 7.8 ng/ml. In the present study the mean total serum PSA level for ASAP was 6.05ng/ml. There was no statistically significant difference between mean total serum PSA level for ASAP and BPH cases (t value=0.672, p value =0.163). These findings were comparable with the studies done by Orhan et al<sup>7</sup> and Leone et al.<sup>22</sup> They found mean total serum PSA level 8.75 ng/ml and 6.13 ng/ml respectively.

In the present study, 11 (91.7%) malignant cases had severely elevated total serum PSA levels more than 20 ng/ml. The studies done by Rukhsana et al<sup>23</sup> and Sinha et al<sup>24</sup> also showed elevated total serum PSA levels more than 20 ng/ml in carcinoma cases.

In present study most common primary Gleason grade was 3 seen in 58.33% cases. Most common Gleason score was 7 in 4 (33.33%) cases. Out of these cases, 3 (75%) cases had Gleason grade 3+4. In a study done by Chandanwale et al<sup>25</sup> Gleason grade 3 was the most common primary pattern seen in 64.7% cases. Most common Gleason score was 7 in 9 (52.94%) cases. Out of these 9 cases, 7 (77.77%) cases had Gleason grade 3+4.

#### **Association of total serum PSA and Gleason score:**

In the present study we found that there is increase in the total serum PSA levels with increase in the Gleason score. The study done by Lennox Anderson et al<sup>26</sup> showed mean total serum PSA levels for men with Gleason score of 6 was 50.11ng/ml compared with 70.78 ng/ml in patients with Gleason score of 7, 136.50 ng/ml in patients with Gleason score of 8 and 140.46 ng/ml in patients with Gleason score of 9.

Statistically highly significant association was found between Gleason score and mean total serum PSA levels (p

value =0.001). But as the tumor becomes more poorly differentiated it may not correlate with PSA levels because the tumor cells may not produce PSA as they have lost differentiation<sup>27</sup>

#### **Sensitivity, specificity, PPV and NPV of total serum PSA levels at various cut off values:**

In the present study we observed that at the total serum PSA cut of value of 4 ng/ml, sensitivity was 100% and specificity was 62.3%. At the total serum PSA cut of value of 10ng/ml, the sensitivity decreased to 91.6% but the specificity increased to 84.7%. Similarly positive predictive value (PPV) for the total serum PSA cut of value of 4 ng/ml was 24.5% and negative predictive value (NPV) was 100%.

At the total serum PSA cut of value of 10ng/ml, the PPV increased to 42.3% but the NPV decreased to 98.8%. Similar observation was made by study done by Amayo Obara et al<sup>27</sup>

## **6. Conclusion**

We conclude that the most common pathology encountered in prostate specimens is BPH. Adenocarcinoma is the most common malignancy of the prostate. Most of the diseases of prostate occur in the age group of 60–69 years, followed by 70-79 years. Acute prostatitis gives rise to significant elevation of total serum PSA levels. While BPH, BPH with chronic prostatitis, ASAP and PIN do not cause significant elevation of total serum PSA levels.

Both non-malignant and malignant pathologies can cause an increase in total serum PSA levels, but the chances of finding malignancy increases with rising values of total serum PSA.

More over positive correlation is seen between levels of total serum PSA and Gleason score and Gleason grade groups. But as the tumor becomes more poorly differentiated it may not correlate with PSA levels because the tumor cells may not produce PSA as they have lost differentiation.

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