



**A STUDY ON CORRELATION OF PSA LEVELS WITH  
GLEASON SCORE AND PERINEURAL INVASION IN CARCINOMA  
PROSTATE**

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**ABSTRACT**

Adenocarcinoma of the prostate is one of the most common form of cancer in men, accounting for 29% of cancer in the Western World. Incidence of carcinoma prostate increases proportionally after 50 years of age. Carcinoma prostate constituted the second commonest group next to BPH (Benign Prostatic Hyperplasia) and it is the second important cause of cancer-related death in men after lung cancer. Prostatic cancer is the sixth underlying reason of mortality due to malignancies worldwide. A Cross-sectional study (both prospective and retrospective) from August 2019 to July 2022 was carried out in the Department of Pathology, MMIMSR, Mullana (Ambala). 50 prostatic resection TURP (Transurethral Resection of prostate) samples were included in this study. All relevant clinical findings were noted and histopathological examination were done. This study concluded that in patients with prostatic adenocarcinoma, there is a statistically significant correlation between increasing serum PSA levels and Gleason score. The mean PSA level was found to have statistically significant correlation with presence of perineural invasion. Based on findings of the current study, Gleason score is a prognostic factor for PNI among cases who undergo prostatic surgery. Hence, further studies involving larger multi-specialty hospitals and large group of population are recommended to validate results of present study. Such studies should also examine other prognostic parameters which can help in a disease free survival for the patients. This will further enhance prognostication and estimation of the risk of disease progression.

**Keywords:** Prostate Cancer, TURP, PSA, Gleason Score

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**Introduction:** Prostatic cancer is the sixth underlying reason of mortality due to malignancies worldwide. [1-3] It is estimated that incidence rates for prostate cancer in India ranged from 5.0 to 9.1 per 100, 000/year. [4] As prostatic adenocarcinoma can cause various complications including severe pain, urinary signs and symptom, genitourinary dysfunction, infertility and decreased quality of life, thus concise attention to signs and symptoms and early diagnosis of this malignancy is necessary.[5]

Prostate cancer is known as an invasive tumor that invades easily to other structures nearby. Perineural invasion (PNI) is defined as the infiltration of cancer cells into the perineural space where they track along or around a nerve [6] and is found in 22.4% to 65.4% of prostate cancer specimens in patients with organ-confined (pT2) disease.[7] Prevalence of PNI in prostatic needle biopsies has been estimated to be up to 40% while this rate was found to be even more in biopsies taken after prostatectomy.[8] It seems that PNI in biopsy specimens is in association with extra-prostatic invasion. In addition, recent studies have presented that maximum diameter of PNI is associated with prostate cancer prognosis.[9]

Serum PSA (Serum Prostate-Specific Antigen), a glycoprotein identified by Wang et al (1979), is produced exclusively by the epithelial cells of benign and malignant prostatic tissue with normal levels of 0-4ng/ml.[10] Increased PSA levels are seen in all prostatic diseases but markedly elevated levels are indicative of carcinoma prostate. Interpretation of prostatic biopsies have been a continuous problem to the practicing pathologists. Histological type, grade & stage of prostate carcinoma is vital in planning treatment strategies & predicting survival rate.

For prognostic correlation, various histological grading systems have been introduced. The Gleason s grading system being the most popular one, based on the architectural pattern of growth.[11] Gleason score of less than 6 are generally low grade cancers and are not aggressive. Advanced carcinomas with regional invasion and metastasis, generally belong to scores 8 and beyond. In contrast to many other carcinomas, prostate cancer can be completely cured if detected in the early stage. The combination of the digital rectal examination (DRE), trans rectal ultrasonography (TRUS), and serum Prostate Specific Antigen (S.PSA) represents a powerful diagnostic triad for the detection of early prostatic carcinoma. [12,13]

Previous studies showed the association of PSA with PNI for the prognosis of prostatic cancer. However, some studies have not found this relationship. [14-16] So the present study was conducted to evaluate the association of PSA serum level and Gleason

score with PNI in prostate cancer subjects. The aim and objectives of the study are as follows:

**Aim:** To evaluate the association of PSA serum level and Gleason score with PNI in prostate cancer subjects.

**Objectives**

1. To grade and score prostate cancers based on Modified Gleason grading system.
2. To analyze and correlate the Modified Gleason score and Serum Prostate Specific Antigen levels (free and total).
3. To correlate and assess relevance of PSA values in carcinoma prostate cases with peri-neural invasion.
4. PSA density with Gleason score if available.

**Material and methods:**

**Study Area:** 50 prostatic resection TURP (Transurethral Resection of Prostate) samples presenting to the Department of Pathology were diagnosed and also confirmed to have carcinoma prostate were included in the study.

**Study Design:** Prospective cohort study.

**Inclusion Criteria:** All prostatic resection (Transurethral resection of prostate, radical prostatectomies and core needle biopsies) specimens received in the department.

**Exclusion Criteria:**

- Patients already treated/ on follow up for prostate malignancy or those already being managed with Oncological interventions.
- Autolyzed, poorly fixed specimen.

**Case selection:** Patients fulfilling the inclusion criteria and after verifying the exclusion criteria were taken up for the study. Thorough detailed history including supportive investigations were recorded for all the patients on a proforma.

All patients were asked to sign a written consent form (in the language they best understand) prior to commencement of the study. Only those individuals, who volunteer to participate in the study, were included and the data was kept confidential. The study did not impose any burden on the subjects and the Institute; therefore, the study is ethically justified.

**Laboratory assays:**

- Serum PSA levels (free and total)
- Modified Gleason Scoring and presence or absence of peri-neural invasion on histopathology.

- Radiological investigations for co-relation of prostate size and likely metastasis.
- Radiological evidence of metastasis or bone involvement.

**Strategy:**

- Resected Prostate specimens (Prostatectomy) and other biopsies (TURP) received in Department of Pathology were included in the study. Clinical details were obtained from respective Department/patients. Details of any investigations like PSA level, USG, CT and bone scan findings was also recorded.
- All specimens were routinely processed and stained with Hematoxylin and Eosin (H & E stain).
- Gleason score along with presence or absence of peri-neural invasion was assessed in each considered case.

**Statistical Analysis:** Data was analyzed using SPSS V24.0. Suitable statistical tests were applied.

**Results:** Of the total 50 samples of subjects included, 13 subjects (26%) were <65 years of age, 26 (52%) were between 65-75 years of age and 11 subjects (22%) were >75 years of age. The patients' age ranged from 53-92 years. All subjects complained of dribbling of urine, increases in frequency and retention of urine. There were only 4 subjects (8%) with associated complaints of haematuria. (Table 1)

Table 1: Complaints among the study subjects

Complaints	N=50	%
Dribbling Of Urine	50	100
Increases In Frequency	50	100
Retention of urine	50	100
Hematuria	4	8

The median prostate volume was 31 ml (range: 9.8-116.5 ml). The median prebiopsy PSA value was 12.2 ng ml<sup>-1</sup> (range: 3.1—172.8 ng ml<sup>-1</sup>). Median biopsy Gleason score was 8 (range: 6–10). 13 (26%) subjects had prostate volume <30 ml, 28 (56%) patients had prostate volume between 30-60 ml and remaining 9 (18%) patients had prostate volume >60ml. Prostatic specific antigen (PSA) was <10 ng ml<sup>-1</sup> in 14 (28%) subjects, PSA in range of 10-20 ng ml<sup>-1</sup> in 26 (52%) patients and PSA >20 ng ml<sup>-1</sup> in 10 (20%) subjects. According to final pathological evaluation, Gleason score ≤6 (Low) was present in 16 (32%) patients,

Gleason score 7 (Moderate) was present in 23 (46%) subjects and remaining 11 (22%) subjects had Gleason score  $\geq 8$  (High). According to biopsy, perineural invasion was present in only 16 (32%) subjects and was absent in remaining 34 (68%) subjects. (Table 2)

Table 2: Distribution of study subjects according to Prostate volume (ml), PSA ( $\text{ng ml}^{-1}$ ), Gleason score

<b>Prostate Volume (ml)</b>	<b>N</b>	<b>%</b>
<30	13	26
30-60	28	56
>60	9	18
<b>PSA (<math>\text{ng ml}^{-1}</math>)</b>		
<10	14	28
10-20	26	52
>20	10	20
<b>Gleason Score</b>		
$\leq 6$ (Low)	16	32
7 (Moderate)	23	46
$\geq 8$ (High)	11	22
<b>Perineural Invasion</b>		
Absent	34	68
Present	16	32
Total	50	100

The mean serum PSA levels for patients with a Gleason score of  $\leq 6$  (Low) was  $8.61 \pm 6.23 \text{ ng ml}^{-1}$ . The mean serum PSA levels for patients with a Gleason score of 7 (Moderate)  $41.79 \pm 14.62 \text{ ng ml}^{-1}$ . The mean serum PSA levels for patients with a Gleason score of  $\geq 8$  (High)  $60.26 \pm 21.41 \text{ ng ml}^{-1}$ . There was a statistically significant positive correlation between increasing mean serum PSA levels and Gleason score (Anova Test = 13.36,  $p < 0.01$ ). (Table 3)

Table 3: Distribution of mean PSA (ng ml<sup>-1</sup>) according to Gleason score

Gleason Score	Mean PSA (ng ml <sup>-1</sup> )	SD
≤6 (Low)	8.61	6.23
7 (Moderate)	41.79	14.62
≥8 (High)	60.26	21.41
Anova Test	13.36	
p value	<0.01*	

\*: statistically significant

The correlation between PSA (ng ml<sup>-1</sup>) and Gleason score was statistically significant (p value<0.01). (Table 4)

Table 4: Correlation between PSA (ng ml<sup>-1</sup>) and Gleason score

PSA (ng ml <sup>-1</sup> ) & Gleason Score	Value
r value	0.67
p value	<0.01*

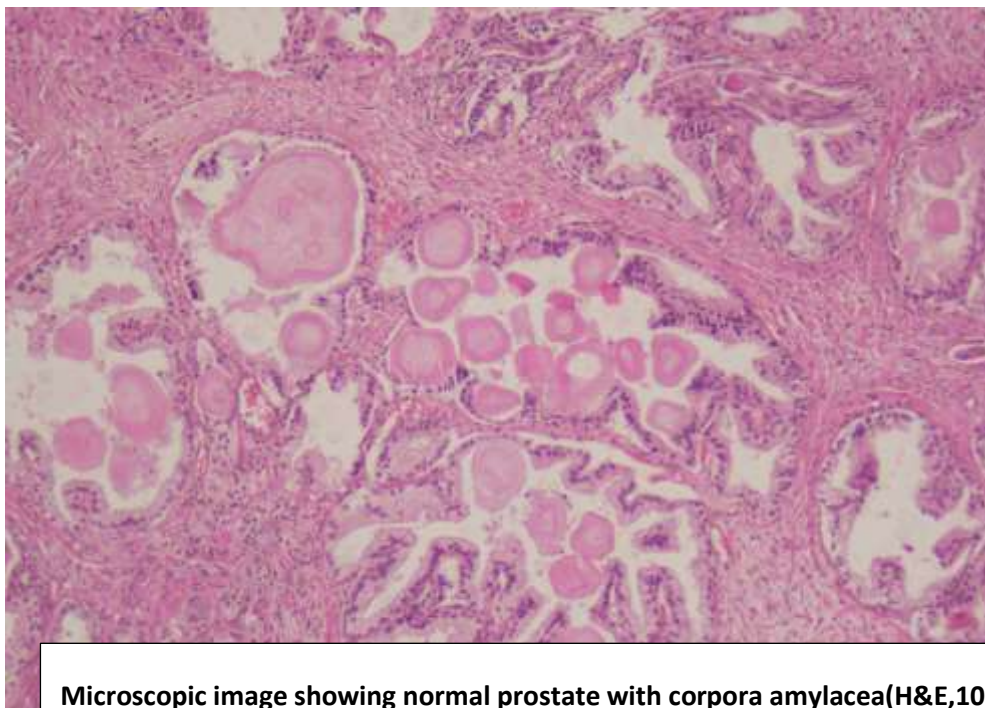
\*: statistically significant

The mean PSA (ng ml<sup>-1</sup>) in cases with Perineural Invasion was 56.39±19.48 and in subjects in whom Perineural Invasion was absent mean PSA (ng ml<sup>-1</sup>) was 8.02±5.59. The mean level of PSA was statistically significant correlated with presence of Perineural Invasion (t Test= 23.52, p value <0.01). (Table 5)

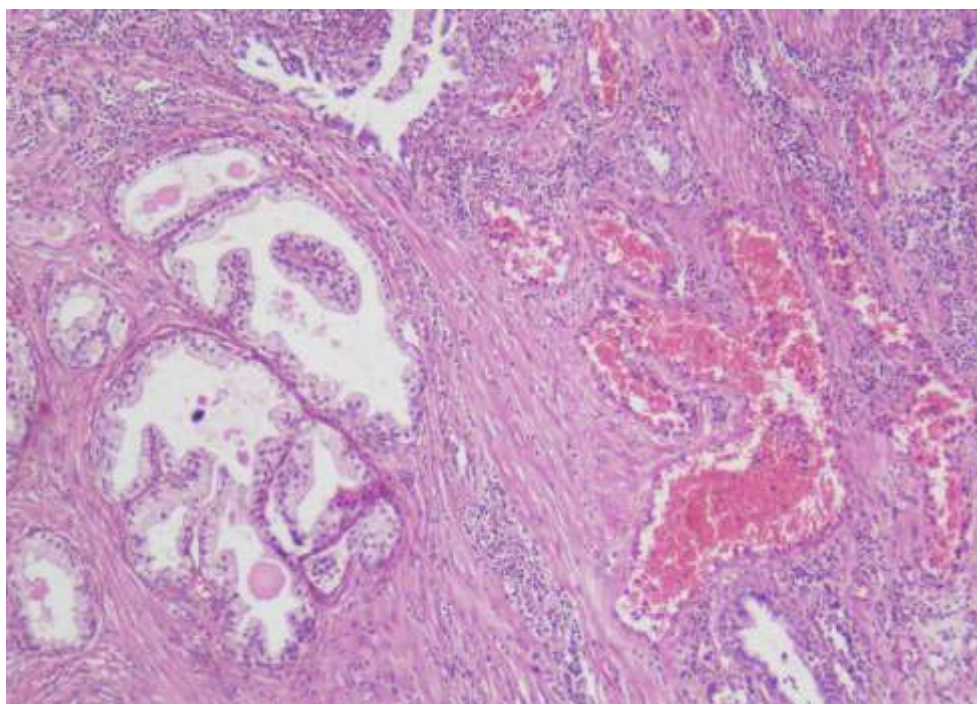
Table 5: Distribution of mean PSA (ng ml<sup>-1</sup>) according to Perineural Invasion

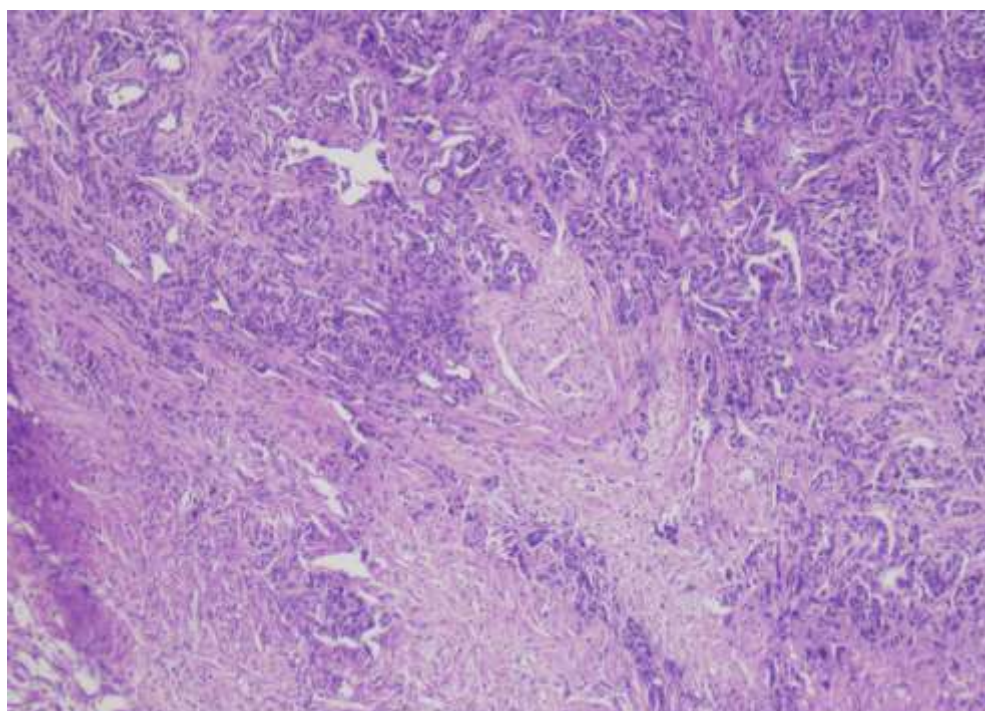
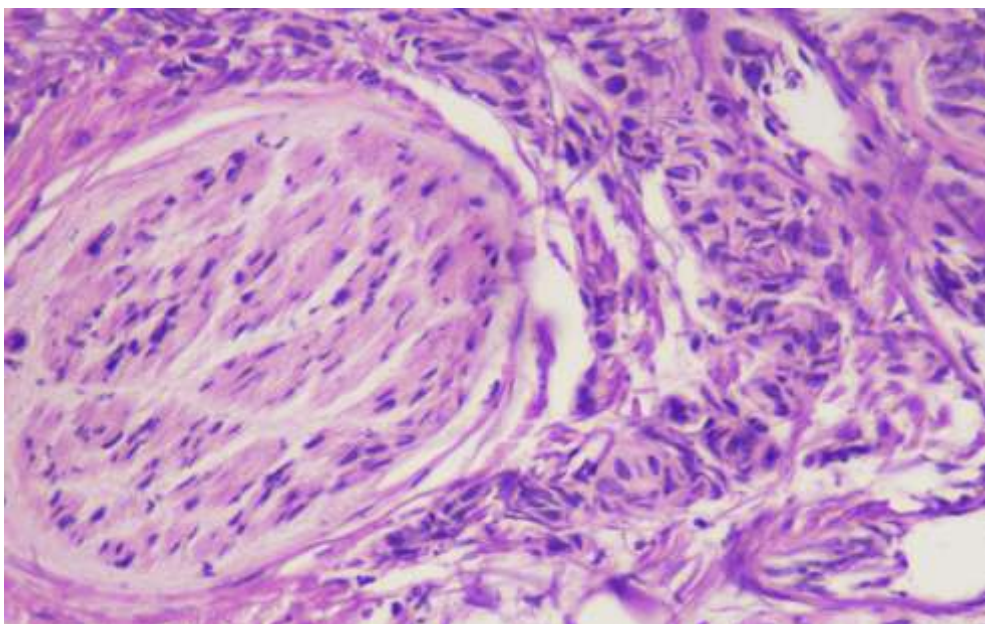
Perineural Invasion	Mean PSA (ng ml <sup>-1</sup> )	SD
Absent	8.02	5.59
Present	56.39	19.48
t Test	23.52	
p value	<0.01*	

\*: statistically significant

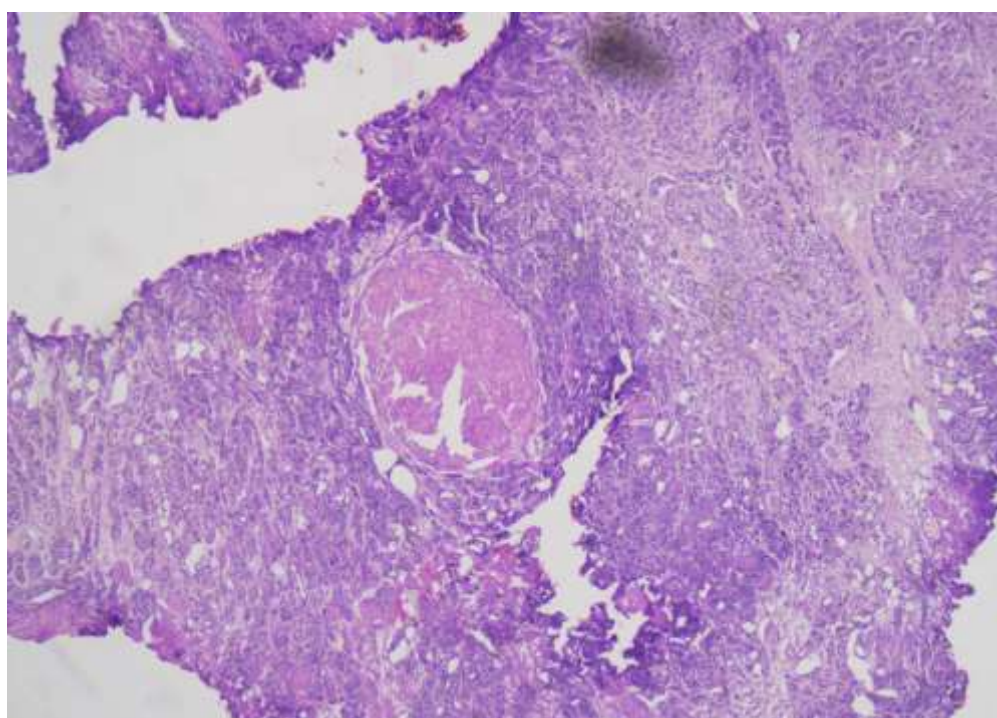
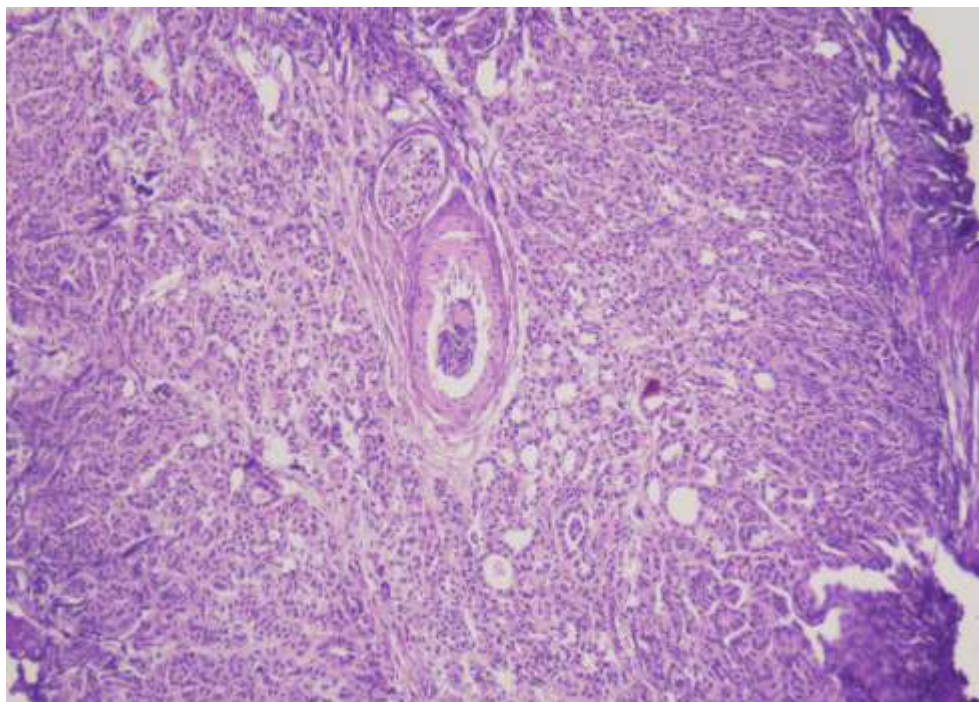


**Microscopic image showing normal prostate with corpora amylacea(H&E,10X magnification)**

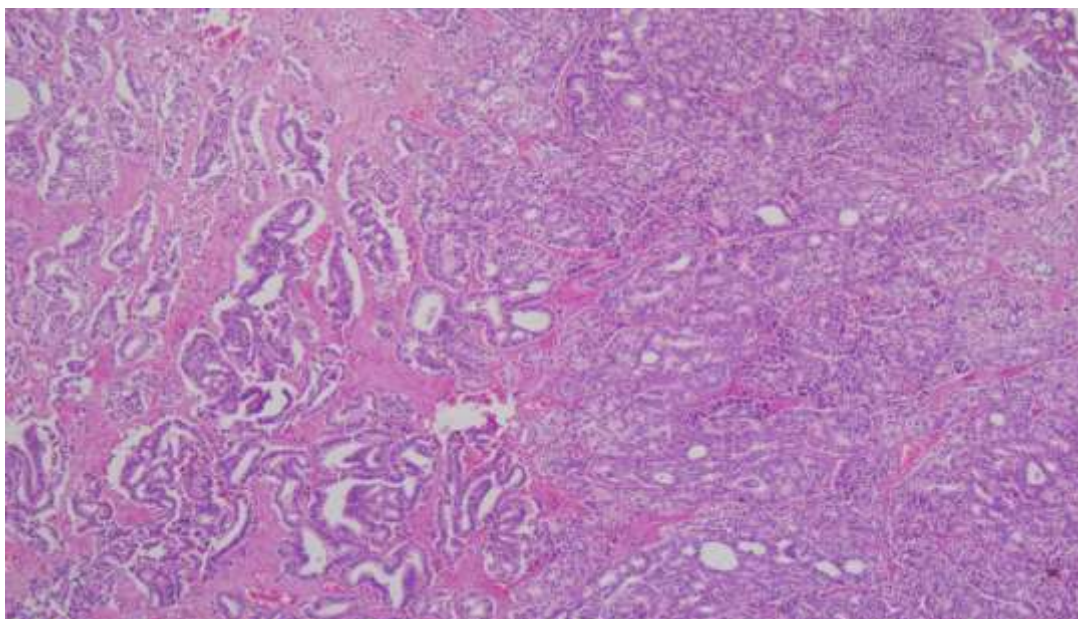




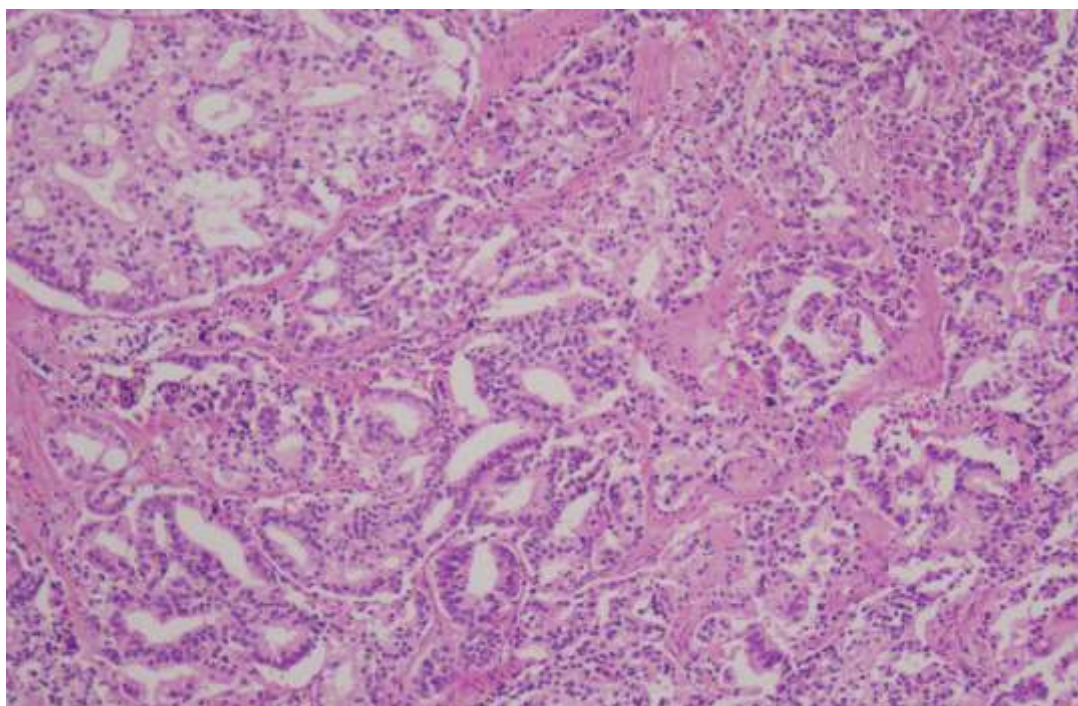




**Microscopic image showing high grade acinar adenocarcinoma with necrosis(H&E,10X magnification)**



**Microscopic image showing low grade acinar adenocarcinoma( Gleason grade 4+3).  
H&E,4X magnification**



**Microscopic image showing low grade acinar adenocarcinoma( Gleason grade 3+4).  
H&E,10X magnification**

**Discussion:** In the present study, of the total 50 samples of subjects included in age range from 53-92 years, maximum subjects i.e., 26 (52%) were between 65-75 years of age, followed by 13 subjects (26%) who were <65 years of age, and 11 subjects (22%) were >75 years of age. The patients' age ranged from 53-92 years. These findings were in accordance with result of Okolo CA et al [17]; Abubakar M et al [18]; Kumari K et al [19].

All 50 subjects (100%) complained of dribbling of urine, increase in frequency and retention of urine. Associated complain of hematuria was present in only 4 subjects (8%). These findings were in accordance to result of Kumari K et al [19], who found that most common presenting complaint in their study was dribbling of urine, increase in the frequency and retention of urine constituting 97.3 per cent patients. Associated hematuria was seen in 7 patients out of 100 subjects.

The median prostate volume was 31 ml (range: 9.8 to 116.5 ml), the median prebiopsy PSA value was 12.2 ng ml<sup>-1</sup> (range: 3.1 to 172.8 ng ml<sup>-1</sup>) and median biopsy Gleason score was 8 (range: 6 to 10). These findings were in accordance with results of Yang R et al., [13], who found that median prebiopsy PSA value was 12.6 ng ml<sup>-1</sup>, and the median prostate volume was 32 ml (range: 10.9–123 ml). Median biopsy Gleason score was 7 (range: 6–10). Niroomand H et al [2] found in their study that, the mean serum PSA level was 11.4 ± 6.9 ng/mL (ranging from 1.1 to 36.6). The pathology results of the biopsies showed a mean Gleason score of 6.2 ± 1.4 (ranging from 4 to 10).

In present study, maximum subjects had prostate volume between 30-60 ml i.e., 28 (56%) patients, followed by 13 (26%) subjects who had prostate volume <30 ml, and only 9 (18%) patients had prostate volume >60 ml. These findings were almost similar to findings of Yang R et al [13], who found that 46.6% subjects had prostate volume <30 ml, 42.9% patients had prostate volume between 30-60 ml and only 10.5% patients had prostate volume >60 ml.

In this study maximum subjects had Prostatic specific antigen (PSA) in range of 10-20 ng ml<sup>-1</sup> (52%), followed by PSA <10 ng ml<sup>-1</sup> in 14 (28%) subjects and, only 10 (20%) subjects had PSA >20 ng ml<sup>-1</sup>. These findings were almost similar to findings of Yang R et al [13], who also found that majority of subjects had PSA in range of 10-20 ng ml<sup>-1</sup>.

According to final pathological evaluation, maximum subjects (n=23, 46%) had Gleason score 7 (Moderate), followed by Gleason score ≤6 in 16 (32%) and Gleason score ≥8 in 11 (22%) cases. These findings were almost similar to results of Yang R et al [13], who

found that 39.9% subjects had Gleason score 7 (Moderate), followed by Gleason score  $\leq 6$  in 33.8% and Gleason score  $\geq 8$  in 26.3%.

According to biopsy, perineural invasion was present in only 16 (32%) subjects and was absent in remaining 34 (68%) subjects. This finding was same as result of Yang R et al [13], who found that in biopsy perineural invasion was present in 28.7% patients and was absent in 71.3% subjects.

The mean serum PSA levels for patients with a Gleason score of  $\leq 6$  (Low) was  $8.61 \pm 6.23 \text{ ng ml}^{-1}$ . The mean serum PSA levels for patients with a Gleason score of 7 (Moderate)  $41.79 \pm 14.62 \text{ ng ml}^{-1}$ . The mean serum PSA levels for patients with a Gleason score of  $\geq 8$  (High)  $60.26 \pm 21.41 \text{ ng ml}^{-1}$ . There was a statistically significant positive correlation between increasing mean serum PSA levels and Gleason score (Anova Test = 13.36,  $p < 0.01$ ). According to findings of Okolo CA et al [17] the mean serum PSA levels for patients with a Gleason score of  $< 6$  ( $124.2 \pm 147.3 \text{ ng ml}^{-1}$ ) was significantly lower than that of patients with a Gleason score of  $\geq 6$  ( $238.6 \pm 236.8 \text{ ng ml}^{-1}$ ) ( $p = 0.003$ ) and there was a statistically significant positive correlation between increasing mean serum PSA levels and Gleason score (Spearman's correlation coefficient = 0.40,  $p = 0.001$ ). Abubakar M et al [18] found in their study that the ANOVA revealed a statistically significant relationship between the serum PSA concentration and the Gleason grade group of cancer ( $P = 0.00$ ).

In the present study the correlation between PSA ( $\text{ng ml}^{-1}$ ) and Gleason score was statistically significant ( $p \text{ value} < 0.01$ ). The mean PSA ( $\text{ng ml}^{-1}$ ) in cases with Perineural Invasion was  $56.39 \pm 19.48$  and in subjects in whom Perineural Invasion was absent the mean PSA ( $\text{ng ml}^{-1}$ ) was  $8.02 \pm 5.59$ . The mean level of PSA was statistically significant correlated with presence of Perineural Invasion ( $t \text{ Test} = 23.52$ ,  $p \text{ value} < 0.01$ ).

According to findings of Yang R et al [13], the three predictive factors (Gleason score, Perineural Invasion, and number of positive cores) in biopsy specimens significantly increased the possibility of capsular invasion in the final pathological results ( $P < 0.05$ ). They also found that prostate size, biopsy Gleason score, number of positive cores, biopsy Perineural Invasion, and biopsy tumor laterality were all significant risk factors of positive surgical margin (PSM) using univariate analysis.

**Limitations:** There were some shortcomings of the present study which includes, 1) smaller sample size, 2) single center study, 3) lack of follow-up of subjects. Therefore, more studies

with larger sample size involving multiple hospitals and long duration follow-up of subjects are required.

**Conclusion:** This study concluded that in patients with prostatic adenocarcinoma, there was a statistically significant positive correlation between increasing mean serum PSA levels and Gleason score of prostatic carcinoma. The mean level of PSA was statistically significant correlated with presence of perineural invasion. Based on findings of the current study, Gleason score is a prognostic factor of PNI among cases undergone prostate biopsy. So further studies involving multiple hospitals and large group of population are recommended to validate results of present study. Such studies should also examine the relationship between the Gleason grade group and stage of cancer. This will further enhance prognostication and estimation of the risk of disease progression.

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