ORIGINAL RESEARCH

Evaluation of PSA serum level and Gleason score with PNI in prostate cancer subjects

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ABSTRACT

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

Material and methods: 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.Thorough detailed history including supportive investigations was recorded for all the patients on a proforma.Record 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. **Results**: There was a statistically significantpositive correlation between increasingmean serum PSA levels and Gleason score. The correlation between PSA (ng ml−1) and Gleason score was statistically significant (p value<0.01). The mean PSA (ng ml^{-1}) in cases with Perineural Invasion was 56.39±19.48 and in subjects in whom Perineural Invasion was absent mean PSA (ng ml^{-1}) was 8.02±5.59. **Conclusion:** This study concluded that in patients with prostatic adenocarcinoma, there was a statistically significantpositive correlation between increasingmean serum PSA levels and Gleason scoreof 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 isa prognostic factor of PNI among casesundergone prostate biopsy.

Keywords: Prostate Cancer, TURP, PSA, Gleason Score

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 was 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. Record 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 >75yeras of age. The patients' age ranged from53-92 years. All subjects complained of dribbling of urine, increases in frequency and retention of urine. Patients having associated complain of hematuria were only 4 subjects (8%). (Table 1)

Table 1: Complaints among the study subjects

Complaints	N=50	%
Dribbling Of Urine	50	100
Increases In Frequency	50	100
Retentionof 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−1(range: 3.1—172.8 ng ml−1). 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 <10ng ml^{-1} in 14 (28%) subjects, PSA in range of 10-20ng ml^{-1} in 26 (52%) patients and PSA >20ng ml^{-1} in 10 (20%) subjects. According to final pathological evaluation, Gleason score ≤6 (Low) was present in 16 (32%) patients, Gleason score7 (Moderate)was present in 23 (46%) subjects and remaining 11 (22%) subjects had Gleason score ≥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 (ng ml^{-1}), Gleason score

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

The mean serum PSAlevels for patients with a Gleason score of ≤6 (Low) was 8.61 ± 6.23 ng ml^{-1}. The mean serum PSAlevels for patients with a Gleason score of 7 (Moderate) 41.79 ± 14.62ng ml^{-1}. The mean serum PSAlevels for patients with a Gleason score of ≥8 (High) 60.26 ± 21.41ng ml^{-1}.There was a statistically significantpositive correlation between increasingmean serum PSA levels and Gleason score(Anova Test= 13.36,p <0.01). (Table 3)

Table 3: Distribution of mean PSA (ng ml^{-1}) according to Gleason score

Gleason Score	Mean PSA (ng ml^{-1})	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−1) and Gleason score was statistically significant (p value<0.01). (Table 4)

Table 4: Correlation between PSA (ng ml^{-1}) and Gleason score

PSA (ng ml^{-1})& Gleason Score	Value
r value	0.67
p value	<0.01*

*: statistically significant

The mean PSA (ng ml^{-1}) in cases with Perineural Invasion was 56.39±19.48 and in subjects in whom Perineural Invasion was absent mean PSA (ng ml^{-1}) 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^{-1}) according to Perineural Invasion

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

*: statistically significant

DISCUSSION

In the present study, of the total 50 samples of subjects included, 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 >75yeras of age. The patients' age ranged from 53-92 years. These findings were in accordance to 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, increases in frequency and retentionof 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 wasdribbling of urine, increases in the frequency and retentionof urine constituting 97.3 per cent patients. Associatedhematuria 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−1(range: 3.1to172.8 ng ml−1). Median biopsy Gleason score was 8 (range: 6 to10).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−1, and the medianprostate volume was 32 ml (range: 10.9–123 ml). Median biopsy Gleasonscore was 7 (range: 6–10).Niroomand H et al [2] found in their study that, themeanserum PSA level was 11.4 ± 6.9 ng/mL (ranging from 1.1 to36.6).The pathology results of the biopsies showed a meanGleason 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 10-20ng ml^{-1} i.e., 52% (n=26), followed by PSA <10ng ml^{-1} in 14 (28%)subjects and least number of subjects had PSA >20ng ml^{-1} i.e., only 10 (20%) subjects. These findings were almost similar to findings of Yang R et al [13], who found that 48.3% subjects had PSA in range of 10-20ng ml^{-1}, 30.4% patients had PSA <10ng ml^{-1} and only 21.3% patients had PSA >20ng ml^{-1}.

According to final pathological evaluation, maximum subjects (n=23, 46%) had Gleason score7 (Moderate), followed by Gleason score ≤6 (Low) present in 16 (32%) patients and remaining 11 (22%) subjects had Gleason score ≥8 (High). These findings were almost similar to results of Yang R et al [13], who found that 39.9% subjects had Gleason score7 (Moderate), followed by Gleason score ≤6 (Low) (n=100, 33.8%) and least number of subjects had Gleason score ≥8 (High) (n=78, 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 only 85 (28.7%) patients and was absent in 211 (71.3%) subjects.

The mean serum PSAlevels for patients with a Gleason score of ≤6 (Low) was 8.61 ± 6.23 ng ml^{-1}. The mean serum PSAlevels for patients with a Gleason score of 7 (Moderate) 41.79 ± 14.62ng ml^{-1}. The mean serum PSAlevels for patients with a Gleason score of ≥8 (High) 60.26 ± 21.41ng ml^{-1}.There was a statistically significantpositive correlation between increasingmean 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 PSAlevels for patients with a Gleason score of <6(124.2 ± 147.3 ng ml^{-1}) was significantly lowerthan that of patients with a Gleason score of ≥ 6 (238.6 ± 236.8 ng ml^{-1}) (p = 0.003). There was a statistically significantpositive correlation between increasingmean 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 (ng ml^{-1}) and Gleason score was statistically significant (p value<0.01).The mean PSA (ng ml^{-1}) in cases with Perineural Invasion was 56.39±19.48 and in subjects in whom Perineural Invasion was absent the mean PSA (ng ml^{-1}) 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).

According to findings of Yang R et al [13], thethree predictive factors (Gleason score, Perineural Invasion, and number of positivecores) in biopsy specimens significantly increased the possibility ofcapsular 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

significantpositive correlation between increasingmean serum PSA levels and Gleason scoreof 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 isa prognostic factor of PNI among casesundergone 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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