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Gleason's Grading of Carcinoma Prostate with PSA Correlation

Authors
Dr Lovely Jose[1], Dr Suma M.T.[2], Dr Santha Sadasivan[3], Dr Souda V.M[4]
[1]Assistant Professor, Department of Pathology, Government Medical College Thrissur, Kerala, India
Mobile no : 9349252524 Email: *drlovelybino@gmail.com*
[2]Associate Professor Department of Pathology, Government Medical College, Thrissur Kerala, India
[3]Rtd.Professor of Pathology, Government Medical College, Thiruvananthapuram, Kerala, India
Mobile no.9400854172, Email: *santhasreekumar@gmail.com*
[4]Rtd.Associate Professor of Pathology, Government Medical College, Thiruvananthapuram, Kerala, India
Mobile no.9447763479, Email: *drsoudathaha@gmail.com*
Corresponding Author
Dr Suma MT
Mobile no: 9847678928. Email: *suma1879@gmail.com*

ABSTRACT
Introduction: *Serum PSA levels have been linked directly to a number of important prognosticators in the prostate gland including histologic grade. The present study has been undertaken on cases of carcinoma prostate, whose trucut needle biopsy is evaluated with Gleason grading, scoring and subsequently correlated with pretreatment PSA levels.*
Methods: *The study was conducted in a teritiary health care centre over a span of two years on patients with symptoms of prostatism or that of metastatic prostatic malignancy such as back pain. Digital rectal examination (DRE) and serum PSA estimation followed by transrectal prostatic biopsy was done. Micromorphometric analysis of obtained material was done on standard haematoxylin and eosin (H and E) preparations. Determination of differentiation of tumor was performed using Gleason grading. Statistical analysis of the obtained data was performed using "SPSS package". To assess the correlation and prediction of Gleason's primary grade with PSA and Gleason's total score with PSA, regression and correlation analysis was done*
Results: *The most common pattern seen was Gleason grade 3 and the least common was Gleason grade 1. There is a statistically significant correlation between serum PSA with Gleason's primary grade and score*
Conclusions: *Carcinoma of prostate associated with an elevated serum PSA level is more likely to be of higher grade than carcinoma with normal PSA levels.*
Key words: *Gleasons grading, carcinoma prostate, serum PSA.*

Introduction

Prostate carcinoma is the third most common malignant tumor in men accounting for one third of diagnosed cancers. It is now the second leading cause of cancer death among men, behind lung carcinoma.[1] Disease specific five year survival rate for localized or regional carcinoma remains high at 96%.Generally the incidence and mortality are

higher in Western countries than in developing countries. Since the early 1990's, the incidence has increased in many countries and much of this increase can be correlated with the increased detection of the disease following introduction of widespread Prostate specific antigen (PSA) testing[2]. Prostate cancer is predominantly a disease of the elderly men, with more than 75% of new prostate cancers being diagnosed in men older than 65 years. Prostate cancer exhibits no specific presenting symptoms and is usually clinically silent, although it may cause urinary obstructive symptoms mimicking benign prostatic hyperplasia (BPH). As a consequence, cancer used to be often initially manifested in metastatic sites such as cervical lymph nodes and bone. But the scenario has changed with the introduction of serum PSA as a tumor marker for prostatic adenocarcinoma[3]. Both the American Cancer Society and the American Urological Association recommend digital rectal examination (DRE) with serum PSA as part of the annual physical examination of all men older than 50 years4.Grading has been advocated as a method of improving the pathologist's ability to accurately predict a particular tumor's biologic behaviour. Many systems have been proposed to assess morphologic features of prostatic adenocarcinoma and hence to derive a histological grade that is indicative of the degree of malignancy. However Gleason system has found greatest application worldwide. Serum PSA levels have been linked directly to a number of important prognosticators in the whole prostate gland including tumor volume, histologic grade and positive surgical margins[5,6]. Studies have been reported correlating pretreatment PSA levels and Gleason grade and score. Conflic-ting reports ensued, with a few establishing strong positive correlation between serum PSA and histologic grade. The present study has been undertaken on cases of carcinoma prostate, whose trucut needle biopsy is evaluated with Gleason grading, scoring and subsequently correlated with pre treatment PSA levels. It is a blind study where the grading is done without knowing the PSA level.

Materials and Methods

The study design was a Retrospective study conducted in the Department of Pathology of a teritiary health care centre in South India. The study duration was two years. Patients who presented to the Department of Urology, with symptoms of prostatism or that of metastatic prostatic malignancy such as back pain were selected for this study. All patients were subjected to standard urological examination according to the modified protocol in keeping with diagnostic protocol for prostatic carcinoma. Digital rectal examination (DRE) and serum PSA estimation followed by transrectal prostatic biopsy was done. The biopsy was performed with trucut needle with transrectal or transperineal approach with previous preparing of the patient with antibiotics and purgation. The biopsy obtained by transurethral resection of prostate (TURP) were also analysed. The indications for biopsy were changes of prostate clinically assigned as adenoma with presence of areas suspicious of malignancy, suspected malignant changes on DRE, clinically clear malignant changes, or intermediary or high serum PSA values. Patients with strong clinical suspicion of malignancy but who were negative on first biopsy underwent a repeat biopsy. In all investigated individuals, the level of PSA was determined in identical way. PSA was estimated from venous blood using fluoro immunometric method based on direct "sandwich" technique. There was no immediate manipulation on prostate, [DRE, prostatic massage, endoscopic examination] before taking the blood sample for PSA. The range of PSA taken as normal is 0-4 nanogram per ml. Micromorphometric analysis of obtained material was done on standard haematoxylin and eosin (H and E) preparations. Fixation of tissue samples has been done in 10% formaldehyde solution for 24 hours. The tissue was prepared routinely, put in paraffin, cut on microtome to the thickness of 4 microns and then the sections were stained by H and E method. All those cases found to be negative for malignancy on biopsy examination were excluded from the study. Determination of differentiation of

tumor was performed using Gleason grading. Both primary (dominant) grade and secondary (the second frequent) grades were determined and Gleason score was obtained by summing up the two grades. Gleason grade ranged from 1 to 5 and the score ranged from 2 to 10. The patients were divided into three groups according to the value of Gleason score as Group 1(score 2-4), Group 2 (score 5-7) and Group 3 (score 8-10). Statistical analysis of the obtained data was performed using "SPSS package". For describing the patients with respect to age, type of biopsy, Gleason's primary grade, secondary grade and Gleason's score, PIN, perineural invasion, we have used percentages, Mean, Median and S.D. To assess the correlation and prediction of Gleason's primary grade with PSA and Gleason's total score with PSA, regression and correlation analysis was done

Observations

During the study period of two years, a total of 620 biopsies of prostate were received in the Department of Pathology. Of these, the majority 528 cases (85.25%) were TURP specimens done for clinical diagnosis of benign prostatic hyperplasia. 92 cases (14.76%) were trucut needle biopsies done with a clinical diagnosis of carcinoma prostate. Of these, 45 cases (7.2%) turned out to be malignant and PSA values were estimated in all these patients before taking the biopsy. Carcinoma was detected in 15 cases of TURP specimens. Thus, in all, 60 cases of carcinoma were analysed

Table 01 Age distribution

Age	Number	Percentage
50 – 59	8	13.3
60 – 69	24	39.9
70 – 79	19	31.7
80 – 89	9	15

In some of the cases of clinically suspected malignancy in whom the initial biopsy was negative, repeat biopsy showed malignancy. This occurred in 4 cases (6.67%).

Histopathological analysis of Carcinoma prostate.

Most of the needle biopsies contained more than one histologically recognizable pattern (35/60) (58%). The most common grade noted was Gleason pattern 3. The least common pattern noted was 1. No cases with Gleason pattern 1 was observed in this study. The second least common pattern observed was grade 2.

Table 02 Distribution according to Gleason grade

Primary Gleason grade	No of patients
1	0
2	1
3	26
4	29
5	4
	Total = 60

Gleason's score 7 was noted in maximum number of cases (25 cases). Gleason's score 6 was the second frequent one (14cases).No cases were observed with a Gleason's score of 2, 3 & 4.

Table 03 Distribution according to Gleason score

Gleason score	No. of patients.
2	0
3	0
4	0
5	3
6	14
7	25
8	12
9	6
10	0

PSA values ranged from 3 to 118ng/ml. The average of PSA for the various age distribution is given below:

Table 04 Distribution according to age and serum PSA level

Age	Average of PSA ng/ml
52-61	35.8
62-71	42.5
72-81	43.0
82-91	52.0

Highest average PSA was found in the age group of 82-91 years. The average PSA in all age group is 43.3 ng/ml.

Table 05 Distribution according to PSA value

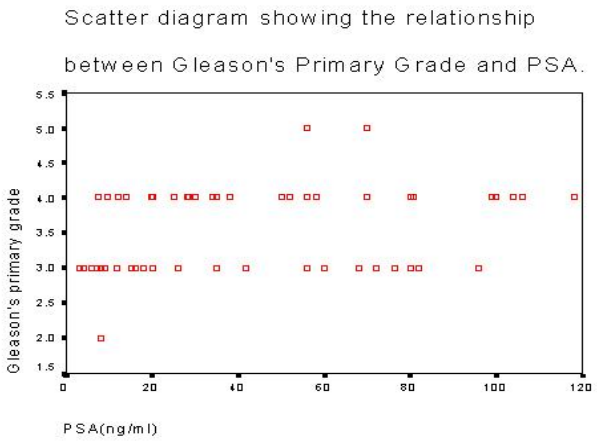
PSA ng/ml	CA Prostate	
	Number	Percentage
0.01 – 4.0	2	3.6
4.01 – 10.00	8	13.3
10.01 - 20.00	10	16.6
> 20.00	40	66.5

In 2 patients (3.6 %), the PSA values were within the reference range of 0.01-4.0 ng/ ml, while in 13.3% (8 cases) it was in the intermediary range of 4.01-10.0 ng/ml. 83.04% (93 cases) were having high values of PSA ranging above 10ng/ml.

Gleason grade and PSA

To investigate the possible relation between Gleason grade and PSA levels, the coefficient of linear correlation was calculated and the regression line was constructed.

Figure 01: Scatter diagram



Gleason score and serum PSA values

Intermediary score of 5-7 were seen with maximum frequency among the study group comprising 70% (42 cases). In this patient subset, the PSA values ranged from 3 to 118 ng/ml. 30 % (18 cases) had a high Gleason score of 8-10 with corresponding PSA values in the range of 7.3-100 ng/ml. Low Gleason score of 2-4 was not encountered in this study

Two cases of Ca prostate were identified in men with PSA levels of 4ng/ml or less. In both the cases Gleason score was 6.To investigate the possible relation between Gleason score and PSA concentration, the coefficient of linear correlation was calculated and regression line was constructed.

Table 06 a. Model summary

Model	R	R2	Adjusted R2	Std. error of estimate
1	0.279(a)	0.078	0.062	0.99
a Predictors; (Constant), PSA(ng/ml)				

Table 06 b. Model summary

Change statistics				
R square change	F Change	df1	df2	Sig.F change
0.078	4.895	1	58	0.031

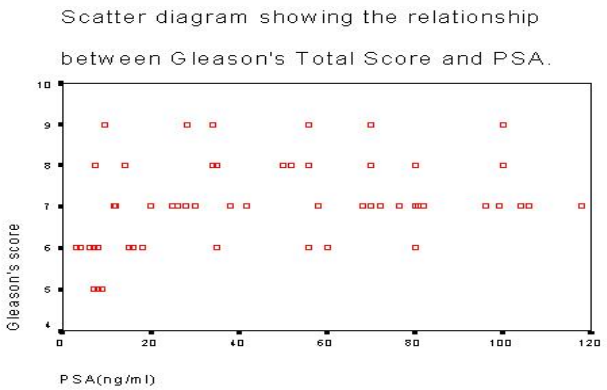
Table 07

ANOVA(b)						
Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	4.804	1	4.804	4.895	.031(a)
	Residual	56.929	58	.982		
	Total	61.733	59			
a Predictors: (Constant), PSA(ng/ml)						
b Dependent Variable: Gleason's score						

Table 08

Coefficients(a)						
		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
Model		B	Std. Error	Beta		
1	(Constant)	6.663	.223		29.904	.000
	PSA(ng/ml)	8.828E-03	.004	.279	2.212	.031
a Dependent Variable: Gleason's score						

Figure 02



There is a statistically significant correlation between serum PSA with Gleason's primary grade and score. Gleason's grade & score influence serum

PSA concentrations and its part is 7.4% & 7.8% respectively

Table 09

Variables	Correlation	Prediction	P value	Significance
Gleason's primary grade vs. PSA	0.272	7.4%	0.035	Significant
Gleason's total score vs. PSA	0.279	7.8%	0.031	Significant

Discussion

The study group included 52 to 87 years. Peak age incidence of Ca prostate was found in the 7th decade (i.e. 38%, 23 cases). This is in concordance with the study of B.G. Matapurkar and O.P. Taneja7. In their study they have reported a peak incidence in the 7th decade which was 33.67%.

The least common pattern encountered was Grade[1]. This correlates well with the observation by others[8,9]. The reason proposed is that in needle biopsy the peripherally located prostatic carcinoma is being sampled which is usually of intermediate or higher grade. It is not infrequent to find a Gleason 1+1 score in radical prostatectomies.

The most common grade noted was Gleason pattern 3. Many studies have also reported the same observation[10,11]. Gleason scores 6 and 7 accounted for the maximum number of cases in this study which is slightly different from the Sladana Zivkovic study11, in which scores 5& 6 accounted in maximum no. of cases

3.6% patients with Ca prostate had PSA values in the referent range (0.01-4), 13.3% had PSA values in the intermediary range (4.01-10), 16.6% had PSA values between 10-20ng/ml and 66.5% had values above 20ng/ml. Comparable values obtained in a similar study by Sladana Zivkovic75 were 2.5%, 27.5%, 17.5% and 52.5% respectively.

There was considerable overlap in the distribution of PSA levels among various grades. 2 cases (3.6%) of Ca prostate were seen in men with serum PSA levels of < 4ng/ml. Ian Thompson et al and several others have also reported comparable observations[12]. In his study Thompson noted that high grade cancers were observed throughout this range of PSA values and had an overall prevalence of 2.3%. Also he noted that the majority of cancers identified in men with a PSA level of 4ng/ml or less had a Gleason score of 6, a value that is reported to be associated with increased risk of disease progression in the absence of treatment[12]. These data indicate that although the risk of finding the cancer on biopsy is directly related to PSA levels in the range of 0.0 to 4ng/ml, there is no PSA value below which a man can be assumed that he has no risk of prostate cancer.

Gleason score and PSA values showed a positive linear correlation in our study which is in agreement with the earlier study by Blackwell13. Blackwell and coworkers found a significant positive correlation between serum PSA and primary Gleason grade, in a large series of completely embedded prostatectomy specimens. Ferro and associates15 who evaluated 60 men with prostatic carcinoma found, a poor but yet positive correlation between histological grade and preoperative serum PSA levels. But this is contradicted by Partin and colleagues14. In their study they found negative correlation between PSA and Gleason score which they attributed to the decrease in production of PSA by higher grade tumors. However this finding is not supported by others15. The explanation given is that although poorly differentiated cancer cells produce less PSA than do cells in well to moderately differentiated cancer, they are usually present in large numbers (greater tumor volume) and replace more of the prostate resulting in higher serum PSA levels.

Conclusion

There is positive linear correlation between primary Gleason grade and serum PSA. There is significant positive correlation between Gleason score and PSA concentrations as well. Thus in conclusion, carcinoma of prostate associated with an elevated serum PSA level is more likely to be of higher grade than carcinoma with normal PSA levels. In this era of advanced technology apart from grade and stage of the disease demonstration of molecular markers

also play a pivotal role in the prognostication of renal cell carcinoma.

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References

1. Medscape CME, prostate carcinoma screening with DRE, PSA 2004.
2. American Cancer Society, Cancer Facts & Figures 2004, November 2004
3. Barwer MK: Prostate – specific antigen: current status. CA Cancer J Clin. 1999 Sep-Oct; 49 (5): 264-81.
4. Newcomer, LM, Stanford JL et al: Temporal trends in rates of prostate cancer: Declining Incidence of advanced stage disease, 1974 to 1994. J. Urol 1997; 158: 1927
5. Cheny T, Luderer AA, Thiel RP et al: Using proportions of free to total prostate specific antigen, age and total PSA to predict the probability of prostate cancer. Urology 1996 Apr. 47 (4). 518-24.
6. Polascik TJ, Oesterling JE, Partin AW: Prostate specific antigen: a decade of discovery what we have learned and where we are going. J. Urol 1999 Aug; 162 (2): 293-306.
7. Matapurakar BG, Taneja OP. Incidence of CA prostate – A 5 year survey; The Ind. J. Cancer, Sept. 1969. P 173-183
8. Gleason DF: Histologic grading of prostate cancer. A perspective. Hum Pathol 23: 273-279, 1992.
9. Bostwick DG: Gleason grading of prostatic needle biopsies: Correlation with grade in 316 matched prostatectomies. Am J. Surg Pathol 18: 796-803, 1994.
10. Schroder FH. Blom JHM. Hop WCJ. et al.: Grading of prostatic cancer: 1. An analysis of the prognostic significance of single characteristics. Prostate 6: 81-100, 1985.
11. Correlation between prostate specific Antigen and histopathological difference of CA prostate; Sladana Zovic et al. Arch Oncol. 2004; 12 (3): 148-151.
12. Jan M. Thompson, Danne K. Pauler, Catherine M et al. Prevalence of prostate cancer among men with a PSA level < 4 ng/ml, NEJM 2004; 350: (2239-2245).
13. Blackwell KL, Bostwick DG, Myers RA et al.: Combining PSA with cancer & gland volume to predict more reliably pathological stage. The influence of prostate specific antigen cancer density. J Urol 151: 1565-1570, 1994.
14. Partin AW, Carter HB, Chan DW, et al.: Prostate specific antigen in the staging of localized prostate cancer. Influence of tumor differentiation, tumor volume, and benign hyperplasia. J Urol. 143: 747-752, 1990.
15. Ferro, M.A., Barnes, I.., Roberts, J.B.M. and Smith, P.J.B.: Tumour markers in prostatic carcinoma. A comparison of prostate – specific antigen with acid phosphatase. Brit. J. Urol., 60: 69, 1987