Original Article

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Pathology Section

Prognostic Significance of the New Prostatic Carcinoma Grade Grouping System vis-à-vis Biochemical Recurrence: Experience from a Tertiary Care Centre in Dakshina Kannada District, Karnataka, India

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ABSTRACT

Introduction: Prostate cancer is the second leading malignancy in males worldwide with a similar preponderance seen in India. Universally, Prostate Specific Antigen (PSA) is a widely utilised resourceful screening and prognostic marker; however, few patients still present this in advanced stage. Hence, it is crucial to recognise the risk groups with utility of different prognostic parameters like Gleason grade grouping apart from PSA level. Studies have validated the Grade Group (GG) is a prognostic marker for Biochemical Recurrence (BR) as well as disease-specific death of patients.

Aim: To assess the usefulness of the new prostatic GG system as compared to the earlier Gleasons scoring system in prognostication with the post-therapy PSA levels being utilised as evidence of BR.

Materials and Methods: This was a retrospective study conducted on cases received over a duration of three years from January 2017 to December 2019 in the Department of Pathology Yenepoya Medical College, Mangalore. All the prostatic carcinoma slides were reviewed and reported by histopathologists according to modified grade grouping system and College of American Pathologists protocol. All parameters were analysed in SPSS software version 23.

Results: A total of 72 cases (23 prostatectomy and 49 biopsy samples) were included. Majority of prostatectomy cases presented in T3b TNM stage and showed perineural invasion. Significant relationship was found between old Gleason's Scoring (GS) system and new grade grouping with p-value of <0.05. Regression analysis reveals new GG is 15 times better than old GS reporting.

Conclusion: The new grade grouping of prostatic adenocarcinoma is better than GS system in prognostication and compares well with TNM staging and perineural invasion.

Keywords: Gleason score, Malignancy, Prostate specific antigen

INTRODUCTION

Prostate cancer is the second most common malignancy and the sixth leading cause of cancer death in men worldwide. Large variations in the incidence and mortality rate have been observed among countries and racial/ethnic groups, with the lowest incidence seen among Asian men [1]. In India carcinoma prostate is a prominent cancer, and the second leading malignancy in males [2]. Serum PSA is widely used as screening and prognostic biochemical marker to detect the malignancy at an earlier stage; still some patients are diagnosed in advanced stage in India [3]. Hence, it is crucial to recognise the risk groups with utility of prognostic parameters like Gleason grade grouping apart from PSA level [4].

The Gleason system for prostatic adenocarcinoma is the commonly acknowledged grading system. Originally the Gleason system was entirely based on the architectural pattern, distinguishing the acinar adenocarcinoma into five patterns, graded from 1-5; and the total score. However, this was found to have limitations [5]. Over the past several decades since its introduction, the Gleason grading system has undergone several revisions; the major modifications were endeavored in 2005 and 2014 during the International Society of Urological Pathologists (ISUP) consensus conferences [6].

According to various studies, the ISUP 2005 modification was a better predictor of seminal vesicle invasion and lymph node metastases, but did not establish any predictive value, due to lack of universal acceptance of the cribriform glands classification which lead to subjective criteria and was liable to inter observer variability [7]. Other curbs were included in the ISUP 2005 modifications, such as: patterns that Gleason defined as a score of 6 were graded as 7, thus leading to contemporary Gleason score 6 cancers having a better prognosis than historic score 6 cancers [8]. Further, a tertiary grade was added to Transurethral resection of Prostate (TURP) specimens, in the presence of a minor component of a higher grade tumour morphologically dissimilar to primary and secondary grades.

To address the above deficiencies; new grading system was proposed by the ISUP in 2014, which was subsequently integrated into the World Health Organisation (WHO) classification of Tumour of the Urinary System and Male Genital Organs, 2016 edition [1]. The modified new grading system focused toward GGs, defining five distinct GGs based on the Gleason score: GG1=Gleason score ≤6, GG2=Gleason score 3+4=7, GG3=Gleason score 4+3=7, GG4=Gleason score 8, GG5=Gleason scores ≥9, as well as modified morphological criteria for Gleason pattern 4. The new ISUP GGs transpire as more precise and clarified classification to stratify tumours [9].

Several studies have validated the ISUP GGs as prognostic marker for BR as well as disease-specific death of patients [10].

High-risk prostate cancer patients were grouped according to the D'Amico's classification with the following criteria; a patient with PSA >20 ng/mL and/or preoperative Gleason score (GS) of 8-10 and/or clinical disease ≥T2c [11]. Several treatment options are available, including Radical Prostatectomy (RP), Radiation Therapy (RT), and

Androgen Deprivation Therapy (ADT) alone or in combination, but the recurrence rate remains high regardless of the type of treatment [12].

Biochemical recurrence was defined as an increase in PSA concentration levels >0.2 ng/mL, following RP and increasing on at least two subsequent measurement, or/and >2 ng/mL following RT [13]. No studies of this kind are available targeting the population of this particular District. Hence, it was deemed necessary to research the topic in question in the area under focus.

Objectives

1. To find the association of pTNM stage and Perineural invasion with Gleason scoring system and the new Grade grouping system.
2. To assess the serum pretherapeutic PSA levels and BR with post therapeutic PSA levels where available.
3. To analyse the relationship of serum PSA to the new Grade grouping system.

MATERIALS AND METHODS

This was a retrospective study conducted in the Department of Pathology, Yenepoya Medical College from June 2020 to October 2020 after due ethical clearance approval (protocol no:YEC-1/2020/031). Samples for the study were selected using the convenience sampling technique.

Inclusion criteria: A total of 72 cases of diagnosed prostatic cancer, on both biopsy and RP specimen which were received in the Department of Pathology along with the available pre and postoperative serum PSA levels from January 2017 to December 2019 were included in the study.

Exclusion criteria: Biopsies and prostatectomy specimens which were diagnosed as benign and non neoplastic and cases with no preoperative serum PSA values available were excluded.

The Haematoxylin and Eosin (H&E) stained slides of the selected cases were retrieved from the archives of the Department of Pathology and the Gleason scoring system and Gleason's grade grouping of the cases were reviewed. Comparison with the new grade grouping system was done in the cases where it had not been offered during diagnosis. Association was carried out with the histopathological prognostic factors such as TNM stage, presence/absence of perineural and Lymphovascular Invasion (LVI). Biochemical parameters analysed included serum preoperative PSA levels and BR with postoperative PSA levels.

STATISTICAL ANALYSIS

All parameters were analysed in SPSS software version 23. The findings were tabulated and descriptive statistics and Chi-square test was used; p-value <0.05 was considered as statistically significant.

RESULTS

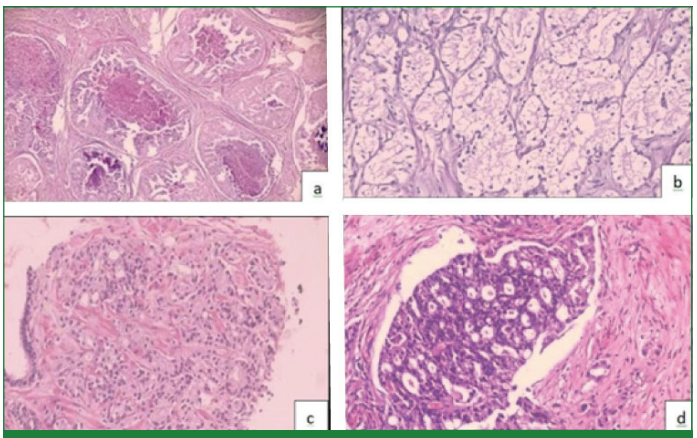
The study included 72 cases of prostate carcinoma, comprising 23 cases of prostatectomy (specimens) and 49 biopsies. All the cases were above 50 years with mean age of 69.2±7.3 years.

As per old GS system, about 22 (30.6%) cases each were in GS7 and GS8 followed by GS9 (14; 19.4% cases), GS6 (8; 11.2% cases) and GS10 (6; 8.3% cases), respectively [Table/Fig-1]. According to new grade grouping system, majority of cases (28; 38.9%) in GG5, followed by GG4 (19; 26.4% cases), GG2 (15; 20.8% cases), GG1 (6; 8.4% cases) and GG3 (4; 5.5% cases), respectively [Table/Fig-1]. The major changes noted in the new grade grouping system were in GS7, which has now been separated into two depending on the volume of each component. If Gleason's pattern 3 is predominating, then a score 7 would be included in GG2, whereas when Gleason pattern 4 was more, the same GS7 would become GG3, with a more ominous prognosis. GG2 (Gleason score 3+4=7) is composed of predominantly well-formed glands with a lesser component of poorly-formed/fused/cribriform glands. GG3 (Gleason score 4+3=7) consists of predominantly poorly-formed/fused/cribriform glands with a lesser component of well-formed glands. The higher GS scores of 9 and 10 have been clubbed together as GG5 (new system), as both are associated with a similar adverse prognosis.

Sl. No.	Old gleasons score	Number of cases	New grade group system	Number of cases	p-value
1	≤6 (3+3,2+3,3+2)	08	1 (3+3)	06	0.001*
2	7 (3+4, 4+3)	22	2 (3+4)	15	
			3 (4+3)	04	
3	8 (4+4,5+3,3+5)	22	4 (4+4,5+3)	19	
4	9 (4+5,5+4)	14	5 (4+5,5+4,5+5)	28	
	10 (5+5)	06			

[Table/Fig-1]: Comparison of old Gleason's score with new Grade Grouping system (n=72).
*p<0.05 as significant

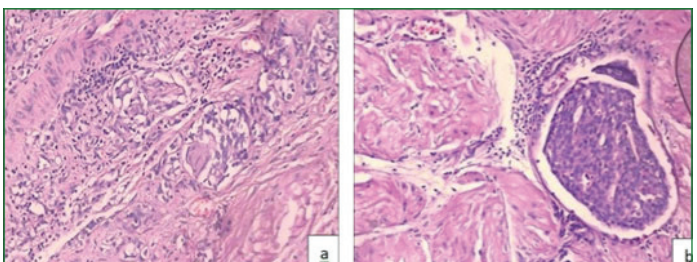
Histomorphological examination showed all the cases as adenocarcinoma of prostate of different Gleason's grade(s), with most having classical acinar pattern microscopically; a few cases having other distinctive patterns were also recorded (13-cribriform, 2-clear cell, 1-comedonecrosis and 1-PIN) [Table/Fig-2a-d]. All the cases were reviewed and graded according to modified new grading system. GS was done by combing the most common (primary) pattern with the second common pattern and later grouped according to (the new grade grouping system.



[Table/Fig-2]: Comedonecrosis of prostate carcinoma (20X; H&E). b) Clear cell pattern of Prostate carcinoma (20X; H&E), c) Adenocarcinoma of prostate (20X; H&E), d) Cribriform pattern of Prostatic Carcinoma (20X; H&E).

Nominal Regression analysis revealed that the new GG system is 15 times better than the old GS reporting. Chi-square test showed considerable association between the new GG system and the old GS system with significant p-value (0.001).

Perineural invasion [Table/Fig-3a] was noted in 36 (50%) of the cases mainly associated with cribriform and clear cell pattern, also seen predominantly high in GG (GG5 followed by GG4). Lymphovascular invasion [Table/Fig-3b] was seen in 17 (23.7%) of cases [Table/Fig-4], with preponderance in (GG5 followed by GG4).



[Table/Fig-3]: a) Perineural invasion (20X; H&E); b) Lymphovascular invasion (LVI) (20X; H&E).

The pTNM staging was applicable for only prostatectomy cases (23); about 52.2% (12) of the cases presented in T3b stage and (2) 8.6% in

N1 status [Table/Fig-4]. Majority of pT3 stage demonstrated perineural invasion. In the current study, we did not find any significant association between pretherapeutic PSA values with the new GG system, perineural invasion and pTNM staging. Out of 23 prostatectomy cases, only 10 cases had postsurgical PSA levels; among which 3 cases had levels >0.2 ng/dL.

Parameters	N=72
Pretherapeutic PSA levels	**Total cases-72**
<10 ng/dL	18
>10 ng/dL	54
Lymphovascular invasion	**Total cases-72 (49 biopsy+23 prostatectomy)**
Positive	17 (7 biopsy+10 prostatectomy)
Negative	55
Perineural invasion	**Total cases-72 (49 biopsy+23 prostatectomy)**
Positive	36 (18 biopsy+18 prostatectomy)
Negative	36
Pathological T stage	**Total cases- 23 (prostatectomy)**
pT2	7
pT3a	4
pT3b	12
pT4	0
Lymph node status	**Total cases 23 (prostatectomy)**
N0	21
N1	2

[Table/Fig-4]: Clinicopathological characteristics of the cases.

As number of cases having recorded postsurgical PSA levels was very few; hence it was not included in the tabulation.

DISCUSSION

Prostate carcinoma is the second most common malignancy in men with a declining mortality rate, presumably due to the utility of screening biomarker such as PSA levels and implementation of modified grading grouping system in reporting. The data in the current study revealed that ISUP new grade grouping system is far superior then the former GS system which was in concordances with Grogan J et al., [7] study and various other studies [14,16]. In the current study, all the cases were aged above 50 years, with mean age of 69.2±73 years which was found to be similar to the finding of Haider N et al., study [14].

The prostatic tumour presenting in GG3 has better prognosis than tumours with GG4, because they are less likely to grow and spread. The present study had various histomorphological patterns/variants of adenocarcinoma prostate with predominance of acinar followed by cribriform pattern. Haider N et al., also found acinar pattern as most common pattern followed by small cell variant [14]. Association of old GS system with the new grade grouping system in the current study was found to be statistically significant (p-value -0.001) [Table/Fig-1], and is comparable to various other studies, as shown in [Table/Fig-5] [14-16].

Lymphovascular invasion was noted in only 24% of cases in the current study and was not of prognostic significance, as opposed to Mitsuzuka K et al., who noted that LVI was a significant predictor for Biochemical Relapse (BCR) after RP in all prostate carcinoma patients [17]. According to Park YH et al., LVI and pathological Gleason's score were considered as first degree associates of BCR, while PSA level, perineural invasion, seminal vesicle invasion and high-grade Prostatic intraepithelial Neoplasia (PIN) were considered as second-degree associates and demonstrated that LVI has a significant risk of BCR [Table/Fig-4] [18].

Perineural invasion in the current study was demonstrated mainly in GG5 followed by GG4 and in pT3 stage. Haider N et al., study demonstrated perineural invasion in 30 cases of prostatic adenocarcinoma and most of the cases presented in GG5 [Table/Fig-6] [14,18].

Sl. No.	Studies	Percentage of cases in old Gleason's Score (GS*) system	Percentage of cases in new modified Grade Group (GG*) system
1	Current study in 2020	GS6-11.2	GG1-8.4
		GS7-30.6	GG2-20.8
		GS8-30.6	GG3-5.5
		GS9-19.4	GG4-26.4
		GS10-8.3	GG5-38.9
2	Haider N et al., study in 2019 (n*=27) [14]	GS6-19.2	GG1-12.7
		GS7-12.7	GG2-10.7
		GS8-17.0	GG3-8.5
		GS9-38.3	GG4-8.5
		GS10-6.4	GG5-53.2
3	Rai NN et al., study in 2019 (n*=109) [15]	GS6-48.0	GG1-54.12
		GS7-29.0	GG2-21.10
		GS8-13.0	GG3 -7.33
		GS9-3.0	GG4-0.0
		GS10-0	GG5-6 cases
4	Gupta S et al., study in 2019 (n*=60 cases) [16]	GS6-5	GG1-5
		GS7-45	GG2-20
		GS8-30	GG3-25
		GS9-15	GG4-31

[Table/Fig-5]: Comparison of old Gleason's scoring (GS) system with new grade grouping system; among various studies [14-16].
*n: Number of cases; *GS: Gleasons score; *GG: Grade group

Sl. No.	Studies	PNI* in various Grade group (GG*)	LVI* in various Grade group (GG*)
1	Current study (n*=72) in 2020	GG1-2 (2.7%)cases	GG1-1 (1.3%) cases
		GG2-5 (6.9%) cases	GG2-1 (1.3%)cases
		GG3-2 (2.7%) cases	GG3-2 (2.7%) cases
		GG4-11 (15.2%) cases	GG4-6 (8.3%) cases
		GG5-16 (22.2%) cases	GG5-7 (9.7%)cases
2	Haider N et al., (n*=47) in 2019 [14]	GG1-2 (4.2%) cases	GG1-0 (0%) cases
		GG2-5 (10.6%) cases	GG2-1 (2.1%) cases
		GG3-2 (4.2%) cases	GG3-0 (0%) cases
		GG4-11 (23.4%) cases	GG4-0 (0%) cases
		GG5-16 (34%) cases	GG5-7 (14.8%) cases
3	Park YH et al., (n*=1210) in 2016 [18]	Over all in 1103 cases out of 1210 cases showed perineural invasion.	GG1-4 (1.5%) cases
			GG2-52 (20.1%) cases
			GG3-95 (36.7%) cases
			GG4 and 5-108 (14.7%) cases

[Table/Fig-6]: Distribution of PNI and LVI in various Grade Group (GG) among different studies [14,18].
n*: Number of cases; GG*: Grade group; PNI*: Perineural invasion; LVI*: Lymphovascular invasion

Pretherapeutic PSA levels with >10 ng/dL in current study was found in 54 cases of which 11 cases presented with levels >100 ng/dL, which was similar to Haider N et al., study [14]; with majority of cases (38) with >10 ng/dL and 11 cases presented with >100 ng/dL. However the Offermann A et al., had contradictory findings in their study, where most of the cases had <10 ng/dL (70.9% of cases) [4]. Post therapeutic PSA values in the present study was available only in 10 cases; among which 3 cases had >0.2 ng/dL; hence BR could not be analysed. While Beauval JB et al., demonstrated that men with one high risk factor had a better BCR-free survival rate than men with two or more high risk factors [3].

Limitation(s)

Absence of significant sampling; more than 50% of the patients did not have postsurgical PSA levels: hence BR could not be assessed in these patients.

CONCLUSION(S)

This study demonstrates that the new GG system of prostatic adenocarcinoma is better than GS system in prognostication and compares well with pTNM staging and perineural invasion. Perineural invasion was associated with a higher GG, while the role of lymphovascular invasion as a prognostic marker is questionable.

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