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INVITED COMMENTARY

Newly Proposed Prognostic Grade Group System for Prostate Cancer: Genesis, Utility and its Implications in Clinical Practice

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Abstract We know about the Gleason pattern and Gleason score which are of paramount importance in tailoring the treatment of a prostate cancer. However, there are certain deficiencies in this current scoring system. To simplify the treatment options and have a better idea about the prognosis, a new grade group system has been proposed by ISUP/WHO in 2015. This has been validated in the clinical practice. This commentary takes you through its genesis, utility and its implications on the clinical practice.

Keywords Gleason score · Grade group · Prostate cancer · Active survelliance

Choosing a right treatment in a given case of prostate cancer and its prognosis is influenced by many factors, histological features is one amongst them. These features are aptly expressed in the Gleason pattern and Gleason score in that given case. This scoring system has been updated from time to time by the International Society of Urological Pathology (ISUP), the latest in 2014, and has proposed a new prognostic grade group system [1]. This commentary takes an overview of the deficiencies in the old Gleason scoring system, the new grade groups, its validity and its impact on the clinical practice.

Dr. Donald Gleason and the Veterans Administration Cooperative Urologic Research Group developed the current prostate cancer grading system between 1966–1974 [2]. Five patterns were described (Gleason pattern 1–5), very well differentiated being 1 to very poorly differentiated being 5—adenocarcinoma prostate based on the architectural pattern.

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The aim of that grading system was to have a uniformity in the correct description of that particular prostate cancer. Gleason score is the sum of the most common (primary) and second most common (secondary) grade patterns which ranged from 2–10. The Gleason score was preferred over assigning the worst grade on the histological diagnosis which is usually the case otherwise. In clinical practice, the common Gleason scores seen are 6, 7 or more than 7.

Gleason scoring system has been in the practice for the last four decades. Since we started understanding the nature of the prostate cancer, its biological behaviour and treatment-related outcomes, we could appreciate the fallacies in assigning the Gleason score. The classical example is Gleason score 7 which could be either pattern $3+4=7$ or pattern $4+3=7$. They are grouped under the same score 7, but have different clinical outcomes. Another important aspect was assigning the cribriform pattern, which in the original description was in pattern 3, but it is now reported as pattern 4, this makes a huge difference in decision making and prognosis.

In order to have a uniformity in reporting the Gleason pattern and Gleason score, this system has undergone many revisions by ISUP, first in 2005 and recently in 2014 [1, 3] .The current Gleason grading differs on many fronts to its original description. The silent features of these updates on the Gleason grading consists of cribriform glands and glomeruloid glands be assigned a Gleason pattern 4, grading mucinous carcinoma as pattern 4, small solid cylinders and presence of comedonecrosis be reported as pattern 5. With all cribriform patterns now being reported as pattern 4 than pattern 3 (as per the old system), previously reported Gleason score 6 is now moved to Gleason score 7. It also underlined the fact that Gleason score 2–5 should no longer be assigned on biopsy and only rarely on other specimens. The lowest assigned score therefore is 6, now that we have clarity on the correct description of the histological pattern. ISUP−2015 consensus conference also suggested that

in case of Gleason score 3 + 4 = 7, percentage of pattern 4 be mentioned to help the clinician to prognosticate and choose the right treatment. Though tertiary score finds its place in the consensus conference, it also favoured reporting the worst pattern (even if it is less than 5 %) as the secondary pattern of that score rather than using second most common pattern as a secondary pattern.

Despite these updates, the modified Gleason scoring system still has deficiencies. Interpretation of the Gleason score 6 on the scale of 2–10 is interpreted by patients (and some clinicians) as with intermediate prognosis (as 6 is closer to the highest grade of 10). Many people interpret this score as 6 out of 10 which in their mind is not a good news and needs immediate treatment The lowest score reported on biopsy is 6. In real sense, now we all know that Gleason 3 + 3 = 6 has a favourable outcome and in fact, can be treated with active surveillance (AS) rather than surgical intervention or radiotherapy. There has been a considerable debate on whether Gleason 3 + 3 = 6 should be called cancer at all? [4]. As mentioned earlier, Gleason score 3 + 4 = 7 has a better prognosis than 4 + 3 = 7. Based on the Gleason scores (GS), many risk stratification tables are in the clinical practice; at large, they stratify the patients into low risk (GS less than 7), intermediate risk (GS 7) and high risk (GS 8–10). However, there is enough evidence now to suggest that the patients with Gleason score 8 behave differently than Gleason score 9 and 10, but are put in the same basket.

Based on the data from Johns Hopkins Hospital, Pierorazia et al. proposed a new grading system in 2013 [5]. The authors proposed a new grading system based on the prognosis and termed it as prognostic grade grouping—grade group I to V (Table 1): grade group 1 (GS ≤ 6), grade group 2 (GS 3 + 4 = 7), grade group 3 (GS 4 + 3 = 7), grade group 4 (GS 4 + 4, 3 + 5, 5 + 3) and grade group 5 (GS 9–10). The prognostic grade group system is based on the modified Gleason scores and has not eliminated the basic concepts of Gleason pattern and score, but has grouped them according the prognosis.

These findings needed validation in the clinical practice, and this was done by Epstein and his colleagues in 2016 [6] .In this study, 20,845 men treated by radical prostatectomy at five academic institutions and 5501 men treated with radiotherapy at two academic institutions between 2005–2014 were studied to assess the validity of the new grade group system. The study confirmed excellent correlation between the grade groups and

Table 1   Newly proposed grade groups in prostate cancer

Grade group	Description
Grade group 1	Gleason score ≤ 6
Grade group 2	Gleason score 3 + 4 = 7
Grade group 3	Gleason score 4 + 3 = 7
Grade group 4	Gleason score 8 (4 + 4, 3 + 5, 5 + 3)
Grade group 5	Gleason score 9–10 (4 + 5, 5 + 4, 5 + 5)

the prognosis, based on PSA recurrence .The authors felt that this simplified grade group system is helpful in prognosticating the patients and could potentially avoid the overtreatment.

Based on these findings, a consensus meeting of genitourinary pathologists, urologists, oncologists and other clinicians was convened by the ISUP, and they proposed that this new grade group system be incorporated in the new 2016 World Health Organisation (WHO) prostate cancer reporting guidelines. The new WHO guidelines in 2016 have adopted these grade groups and have justified its use in the biopsy reporting and its role in the clinical practice [7]. WHO guidelines recommend reporting these grade groups in conjunction with WHO/ISUP modified Gleason score in the histopathology report.

Since these grade groups have appeared in the WHO guidelines, editorial teams of many international journals (*BJUI, European Urology, J Urol*) have also suggested its use in the reporting of prostate cancer in their publications [8].

With these new grade groups, the counselling of the patients would be much simpler. If a patient has a Gleason score of 3 + 3 = 6, it would be grade group 1, the lowest on the scale indicating that patient has favourable outcome. Similarly, a patient with Gleason score 4 + 3 = 7, would be grade group 3 (on the scale of 5) would certainly understand that he is a candidate for a treatment rather than surveillance.

Despite being simple, useful in counselling and prognosticating, it has few deficiencies. In grade group 4 (Gleason score 4 + 4 = 8, 3 + 5 = 8, 5 + 3 = 8), there is now enough evidence to suggest that the prognosis of 4 + 4 = 8 is better than 3 + 5 = 8 and 5 + 3 = 8, but are still clubbed together. It is perfectly understandable that for each permutation and combination of Gleason score, one could not have a separate prognostic group, but it is a point worth considering for the future. Some of the recent evidence suggests that prognosis of Gleason score 5 + 3 = 8 is similar to GS 9. Tertiary pattern, percentage of the worse pattern in a given Gleason pattern, does play a significant role in the prognosis; maybe further guidelines on this aspect would be of great help especially when we call these grade groups as prognostic grade groups. It is also important to note that the PSA biochemical recurrence was used to determine the levels of risk in the grade group system, which might be challenged by some who do not support PSA recurrence as a surrogate of disease progression.

It is heartening to see that these grade groups have been studied in the clinical practice, population based cohort and in the research laboratory recently. Loeb et al. have evaluated Gleason grade groups in a nationwide population based cohort. In this study from the National Prostate Cancer Register of Sweden, 5880 patients with prostate cancer (4325—radical prostatectomy and 1555—radical radiotherapy) were studied to evaluate the performance of new grade groups. The authors concluded that this new grade group system is simple, user friendly in counselling and showed similar predictive accuracy in terms of oncological outcomes compared to the older

staging system [9]. Rubin et al. have found that genomic events in prostate cancer correlate well with the new grade groups especially in grade group 1 with all favourable genomic features; however, in their study, grade groups 4 and 5 did not differ significantly from each other [10].

In conclusion, the new grade group system is simple, easy to adopt and useful in counselling the patients. Treatment options can be tailored according to the grade groups. It has the potential to avoid the fear in grade group 1 patients who will be in a position to choose wisely; it would also help in avoiding the overtreatment.

Compliance with Ethical Standards

Conflict of Interest   Makarand Khochikar declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent   This article does not contain any studies with human or animal subjects performed by any of the authors.

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