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Prostate Cancer Grading: Are We Heading Towards Grade Grouping Version 2?

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In this issue of *European Urology*, Dr J.I. Epstein's group [1] report on how Gleason scores (GSs) have been grouped worldwide. They found that only a minority of studies were accurately grouping GSs as grade groups (GGs) [2].

To fully understand the significance and context of this contribution on GGs [1], it is of paramount importance to be fully aware of what preceded this study, what happened soon after proposal of the GGs, how the GG system has been used in routine practice, and what the future holds for prostate cancer (PCa) grading in relation to the GGs.

What preceded the study by Dr. Epstein's group up to 2014?

Uropathologists have used the architectural pattern-based Gleason grading system developed by Dr. D.F. Gleason in the 1960s, and then revised by the International Society of Urological Pathologists in 2005 and 2014 [2,3]. The two successive revisions were needed for several reasons, including: "changes in prostate cancer (PCa) detection and treatment, newer technologies available to better characterize prostatic neoplasms, subsequently described variants of PCa, and further data relating various morphologic patterns to prognosis" [4]. However, we should not forget what happened from 2005 to 2014 between the two revisions.

- There was a so-called 2008–2010 update of the Gleason grading system that addressed "lesions for which the participants could not reach an agreement about their grading, due to lack of clinical data" [2–4] (this refers specifically to the 2005 conference), for which the grading of small cribriform glands and of glomeruloid features was an example [5]. It was suggested that small cribriform glands should be considered as Gleason pattern 4. Glomeruloid structures, an early stage in the formation of cribriform pattern 4, should be all reported as pattern 4. These updates became an integral part of the 2014 revision [2].
- It was also realized that despite modifications to and revision of the Gleason system, there were significant issues. To mention two of them, the grading system ranges from 2 to 10, with 6 being the lowest GS used in routine (the total potential number of separate GSs is 25), and various GSs have been grouped in different ways and combinations with the presumption of a similar prognosis. To deal with the above-mentioned deficiencies, using data for a cohort of 7869 men, in 2013 the Epstein group proposed five GGs, based on the Gleason patterns [6], with each GG including all the GSs with similar prognosis.
- In 2014 there was overwhelming approval from uropathologists and clinicians attending the International Society of Urological Pathologists conference for adoption of the five-GG system [2]. The proposal that the GGs

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should be reported in conjunction with the 2014 modified GSs was also passed [2], with the plan being future use of the GGs only. This quickly became an international standard when it was adopted by the World Health Organization (WHO) and the College of American Pathologists, and in the American Joint Committee on Cancer 2018 TNM revision.

What happened soon after proposal of the five GGs (2014–2016)?

The 2014 proposal generated great enthusiasm among uropathologists. A series of studies based on large numbers of patients were published soon after, giving further strength to the clinical significance of the GGs, and showing that the new PCa grading system reflects prognosis more accurately than the Gleason system, and at the same time is simpler to define [4,7]. For example, one investigation was based on 20 845 men with clinically localized PCa and treated by radical prostatectomy (RP) at the Cleveland Clinic, Memorial Sloan Kettering Cancer Center, Johns Hopkins Hospital, University of Pittsburgh, and Karolinska Institute (Sweden) [8].

What was missing at the time of the 2014 proposal of the GGs was how to fully implement them in routine practice. This issue was addressed and solved in a subsequent publication by Epstein et al. [9].

Current study by the Epstein group

The current paper by the Epstein group [1] follows the initial studies during a time of great enthusiasm for the GGs and the publication on their implementation [9] and addresses the question of how the GG system has been used in routine practice. The study, based on 1576 articles published during 2016–2017, shows that there is still wide variation in how GSs are grouped. We agree with the authors that this could lead to inaccurate results and might thus affect patient care. To avoid this problem, more widespread adoption and understanding of the new PCa grading system composed of the five GGs is of paramount importance.

What the future of prostate cancer GGs could look like

Some adjustments to the GG system could be made to improve its applicability and clinical significance.

GGs and Gleason pattern 4 morphologies

Cribriform, fused, ill-defined, and glomeruloid glands are part of the spectrum of Gleason pattern 4 PCa. Cribriform morphology has a worse prognosis in comparison with the others [10]. When observed on prostate biopsy, cribriform morphology is linked to higher rates of upgrading, upstaging, and positive surgical margins on RP. Investigations using RP specimens have supported the notion that the presence of cribriform morphology is associated with a higher frequency of lymph-node secondary deposits, as well as higher biochemical recurrence; it is also predictive of cancer-specific survival. It has been suggested that the current GG system could be modified to report the presence of cribriform morphology (and/or intraductal carcinoma of the prostate) by adding "C", and its absence without "C" [11]. For instance, GG 2 C could indicate that the tumor is GS 3 + 4, with the pattern 4 showing a cribriform architecture.

GGs and tertiary pattern

Tertiary pattern 5 in 3 + 4 = 7 and 4 + 3 = 7 PCa at RP is recorded as GG 2 and GG 3, respectively, with a minor higher-grade pattern possibly denoted as GG 2+ or GG 3+ in the future [7,12].

Identification of GGs on the basis of tissue quantitation is feasible

Studies have reported on quantitative methods for PCa detection and automated PCa diagnosis, and therefore GG identification is feasible [13]. Diamond et al. [14] explored image analysis of tissue abnormalities in prostate histology. The machine vision system developed in the project highlighted the potential of quantitative methods to provide highly discriminatory information in the automated identification of prostatic lesions. In particular, the system was capable of classifying images with PCa, including the characterization of cribriform glands. Another study by Niazi et al. [15] described the successful identification of visually meaningful histopathological features for automatic grading of PCa. More studies are being published on this topic and will be followed with interest by clinicians. A review of more recent and contemporary studies on tissue quantitation and PCa grading is beyond the scope of this contribution. Readers interested in more information and details on the topic should consult more specialized journals.

GGs supplemented with nuclear morphology

The Gleason system and the GGs are based on the architectural patterns of PCa. The contribution of nuclear morphology to further refinement of the clinical significance of the GSs (and now GGs) has been investigated to a limited extent. It is worth mentioning the proposal by Mostofi in a 1999 WHO-sponsored meeting to supplement the Gleason system with the WHO nuclear grading scheme [16]. For instance, among patients with GS 3 + 3 = 6 (now GG 1) and WHO nuclear grade 3, cancer-specific mortality is significantly higher than among patients with lower grades [16]. This was confirmed in a morphometric study that demonstrated that the nuclear signature is important for better definition of risk groups among PCa patients [17].

Conclusions

To fully understand the significance of the current study on GGs by Epstein et al. [1], it is of paramount importance to be fully aware of the context, bearing in mind that some adjustment to the GG system could be made to improve its applicability and clinical significance.

Conflicts of interest: The authors have nothing to disclose.

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