Prostate cancer grading: recent developments and future directions

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The development of the Gleason grading system for prostate cancer grading has provided a powerful tool both for outcome prediction and for informing appropriate treatment. Despite the longevity of Gleason scoring (GS), it has been apparent that the clinical context of prostate cancer, as well as our understanding of the natural history of the disease has evolved since the publication of Gleason’s first paper in 1966 [1]. While a number of studies have made recommendations relating to modification of the Gleason grading system over the past 40+ years, it was not until 2005 that this was formally addressed as a consensus conference held under the auspices of the ISUP [2]. At the conference it was agreed that, for needle biopsies, GS 2–4 should be avoided and GS 5 rarely diagnosed – if ever. This has effectively meant that GS 3 + 3 = 6 is the lowest score reportable for needle biopsies. It was also agreed that cribriform glands were a feature of pattern 4, although small rounded cribriform structures were classified as pattern 3. Poorly formed glands were also included in pattern 4 criteria. Changes were recommended with respect to the Gleason scoring of needle biopsies. Specifically it was accepted that lower grade secondary patterns consisting of < 5% tumour area should be ignored, while higher grade patterns < 5% of tumour area should be reported. Importantly, it was also agreed that if a higher tertiary pattern is present, this should be scored as the secondary pattern. (e.g. 4 + 3 = 7 [3° = 5], becomes 4 + 5 = 9). There was no agreement that this should be applied to radical prostatectomy specimens, where it was recommended that the tertiary pattern continue to be reported. For needle biopsies this has resulted in the upgrading of a significant number of GS 3 + 3, 3 + 4 and 4 + 3 tumours.

In 2014 the ISUP convened a further consensus conference to consider evidence-based advances in our understanding of Gleason grading and to propose further modifications to Gleason grading and the establishment of a new grading system, with grades based upon Gleason scores [3]. At the conference it was agreed that all tumours with cribriform glands should be classified as Gleason pattern 4, while tumours with a mucinous component should be graded according to the underlying architectural pattern. (Fig. 1) Five score groups were proposed (ISUP Grades) i.e. Grade 1 – GS ≤ 6 (≤ 3 + 3); Grade 2 – GS 3 + 4; Grade 3 – GS 4 + 3; Grade 4 – GS 8; Grade 5 – GS 9–10. The ISUP grading system has the advantage of classifying GS 6 tumour – the lowest possible score for needle biopsies - as grade 1 and further, it distinguishes between pattern 3 and pattern 4 dominant GS 7 tumours.

Validation of this new grading had been provided by an analysis of 20845 radical prostatectomies from five institutions and 5510 men treated by radiotherapy from two institutions [3]. These data; however, were based upon 2005 Modified Gleason criteria. More importantly part of the series was non-reviewed and being collected from 2005 means that, especially for earlier cases, classical rather than modified Gleason grading criteria may have been utilized. Furthermore, outcome was based upon PSA failure using different criteria, rather than survival. More recently, two studies have provided some validating data for ISUP grading based upon a variety of outcomes [1].

Despite the apparent advances of the new grading system, there are a number of issues that require further refinement. In particular it has been shown that the interobserver reproducibility of poorly formed glands amongst expert uropathologists was only ‘fair’ [4]. This was most notable in tumours where few poorly formed glands were present or were admixed with other glands. This is of particular significance as poorly formed glands constitute one of the most common subtypes of pattern 4. Also, it has recently been shown that GS 3 + 5 and 5 + 3 tumours have a less favourable outcome that GS 4 + 4 tumours [5], which in the new grading system are all classified under ISUP grade 4. This suggests that any tumours containing pattern 5 should be reclassified either separately or as ISUP grade 5. Additionally issues exist regarding the grading of tumours containing both pattern 3 and pattern 4 (GS 7). Previous reports have indicated that the percentage of pattern 4 in GS 7 tumours is of prognostic significance. A recent detailed study has demonstrated that rather than being dichotomous (i.e. 3 + 4 v 4 + 3), the percentage of pattern 4 is a continuous variable for GS 7 tumours, with low proportions...
It has been suggested for the grading needle biopsies, that in multiple cores showing variable GS, the overall GS of the case should be based upon the core showing the highest score [2]. This means that for a series of cases where one core is 4 + 4 = 8 and the others 3 + 3 = 6 and 3 + 4 = 7, the overall score would be 4 + 4 = 8 (ISUP grade 4), while in reality the pattern 4 tumour may constitute approximately 10% of the tumour volume. The observation that percentage pattern 4 is of prognostic significance raises questions of the validity of case scoring based upon these criteria.

In the initial validation study of ISUP grading based upon needle biopsy scores obtained from patients treated with radiotherapy, as well as in the two subsequent validation studies, there is overlap between some of the individual grades with respect to outcomes [1,3]. In particular this involves grades 1 and 2 tumours, as well as grades 3 and 4 tumours. This raises the question as to whether or not division of cases into grades 1 and 2 is of real clinical utility, as the outcome is not materially different. The situation is similar for grade 3 and 4 tumours and this may become more pronounced once tumours showing 3 + 5 and 5 + 3 morphology are separated from those which are pure pattern 4 (4 + 4).

While advances in Gleason grading have been made with the establishment of ISUP grading, there are clearly nuances of the “new system” that need to be further clarified and refined as we enter the implementation phase.

**Conflict of Interest**

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

**References**


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**Abbreviations:** GS, Gleason score; ISUP, International Society of Urological Pathology.