Utility of Reporting the Percentage of High-grade Prostate Cancer

Lars Egevad,*, Brett Delahunt, Hemamali Samaratunga, John R. Srigley

Gleason score has long been considered the most powerful tissue-based predictor of outcome for prostate cancer. One of the strengths of this system is that it factors in the multiple grades that are often present in a single tumor. However, there is growing awareness of the limitations of Gleason grading. Specifically, few of the original Gleason criteria are currently used and cancers tend to aggregate in the middle of the grade range. Furthermore, it is unclear how cases with multiple Gleason patterns and with different Gleason scores for different biopsy cores should be reported.

The International Society of Urological Pathology (ISUP) has recently addressed a number of these issues. In 2005, several modifications of pattern interpretation were made and rules for reporting of biopsies were modified to include the highest grade in the score, even when this was <5%. In 2014, further changes were proposed, focusing on the reporting of cribriform and glomeruloid architecture and the diagnostic criteria for poorly formed glands[1]. Furthermore, it was decided to group Gleason scores into five grade groups, now known as ISUP grades. Emerging issues were also discussed, such as reporting of the percentage Gleason pattern 4 present in biopsy cores. In the upcoming fourth edition of the World Health Organization classification, due for publication in 2016, reporting of grade groups will be recommended, as well as reporting of the percentage of Gleason pattern 4 for Gleason score 7 tumors. The reporting of percentage Gleason grade 4 tumor tissue has the advantage that this highlights if a cancer is at the lower or higher end of a grade. This is particularly significant, as Sauter et al demonstrate in this issue of European Urology that there is a biological continuum within Gleason score 3 + 4 = 7 and 4 + 3 = 7 tumors that is reflected in clinical outcome [2]. In some jurisdictions, selected patients with Gleason 7 tumors with minimal pattern 4 (≤10%) are eligible for active surveillance [3].

Reporting of percentage Gleason grade 4/5 was first proposed by McNeal et al [4]. The same group later showed that this parameter was an independent predictor of recurrence after radical prostatectomy [5]. In a watchful waiting cohort with long-term follow-up, percentage Gleason grade 4/5 was an independent predictor of disease-specific survival [6].

Percentage Gleason grade 4/5 is theoretically attractive as a prognostic parameter as it emphasizes that the presence of a high-grade component, as well as its quantity, has prognostic significance. In a study assessing the prognostic impact of ploidy heterogeneity using flow cytometry, we showed that the volume of nondiploid cancer could be estimated by combining ploidy heterogeneity with planimetric measurements, and that there was a threshold of 0.9 ml of nondiploid cancer that had to be exceeded for extraprostatic extension or seminal vesicle invasion [7]. Similarly, McNeal et al reported that lymph node metastases were only seen in men with ≥3.2 ml of Gleason grade 4/5 tumor [4].

Despite several publications supporting the role of percentage Gleason grade 4/5 as a prognostic factor, this parameter has not been adopted for general use. One criticism relates to its reproducibility. However, in studies on needle biopsies and prostatectomy specimens we found that the inter- and intraobserver reproducibility among urologic pathologists was as good as for Gleason score [8,9]. The interobserver reproducibility for percentage
Gleason grade 4/5 reached a mean weighted $\kappa$ of 0.60 and 0.66 for biopsy and prostatectomy specimens, respectively, compared to 0.51 and 0.56 for the Gleason score.

Previous studies have used the combined percentages of Gleason patterns 4 and 5, thus including all high-grade cancer [4–6]. In their paper, Sauter et al propose separate reporting of percentages of Gleason patterns 3, 4, and 5 tumor for each biopsy core [2]. This raises questions regarding the workload of general pathologists with a busy practice. Thus, it is desirable to identify a simple and user-friendly method for quantitative grade reporting.

Another contentious area is whether grading should utilize the highest Gleason score for a single core or a global Gleason score based on all cancer present in a biopsy set. In Europe, 77% of pathologists use a global Gleason score, while only 17% report the highest score [10]. In North America, it is often noted that reporting of the highest Gleason score is more common, although to the best of our knowledge this has never been surveyed. An argument in favor of reporting the highest Gleason score is that there is a general tendency for biopsies to undergrade cancers. In view of this, an increase in the average biopsy grade is likely to improve the correlation with prostatectomy specimens. However, for an individual patient with a minute focus of, for example, Gleason 4 + 4 = 8 and multiple biopsies with Gleason 3 + 4 = 7, it is still very unlikely that a prostatectomy specimen would show Gleason 4 + 4 = 8. In a recent study of heterogeneous tumors, composite Gleason scores for biopsies showed greater correlation than worst Gleason scores with radical prostatectomy Gleason scores [11]. Similarly, in a series of hormonally treated prostate cancers, global Gleason score, but not worst Gleason score, was an independent predictor of outcome [12]. Interestingly, the findings of Sauter et al support the use of a global Gleason score for prediction of prostatectomy grade.

A number of problems remain, in particular how to measure percentages. If the linear extent of the grades is estimated on needle biopsies, this does not necessarily reflect the number of cancer cells present in the biopsy specimen. Low-grade cancer glands are often dispersed among benign glands, while high-grade cancer tends to have higher cellularity. What is biologically most relevant, the linear extent or the number of tumor cells? Even more complex is the estimation of grade components in cases in which grades are intermingled, which is a common occurrence.

In conclusion, the findings of Sauter et al add important evidence that the percentages of grade components of prostate cancer have clinical relevance, but considerable work remains to be done regarding incorporation of this information into clinical practice.

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References


