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Platinum Opinion

Prostate Adenocarcinoma Grade Group 1: Rationale for Retaining a Cancer Label in the 2022 World Health Organization Classification

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The Gleason system forms the basis for prostate cancer grading worldwide. It has been modified on several occasions, most recently after the International Society of Urological Pathology (ISUP) consensus conferences in 2005, 2014, and 2019, and the 2019 white paper by the Genitourinary Pathology Society [1–4]. At the 2014 ISUP conference the concept of grade groups (GG1–GG5) was introduced, also referred to as ISUP grade, World Health Organization [WHO] grade, or simply grade groups [2,5–7]. Grade groups are based on Gleason scores and have some advantages with respect to communication of results to patients, clinicians, and researchers. Grade groups offer the advantage of appropriately assigning the lowest rank (GG1) to Gleason score (GS) 3 + 3 = 6 cancers to emphasize their generally low risk in the proper clinical context (eg, prostate-specific antigen [PSA] <10 ng/ml and clinical stage ≤cT2a) [2,6]. With the now established shift in management paradigm for low-risk disease (very low and low risk categories

in National Comprehensive Cancer Network [NCCN]) to active surveillance (AS) [8,9], a designation of GG1 of 5 (rather than GS 6 of 10, which may imply a middle-tier grade) is advantageous in helping to alleviate the fear associated with a cancer diagnosis and hence can enhance patient acceptance of active surveillance. The latter has led some authors to question the rationale for keeping the “cancer” label for GS 6 lesions [10,11] against the backdrop of valid concerns regarding overtreatment and the US Preventive Services Task Force recommendation against prostate cancer screening in 2012 [12].

Eggerer et al. [13] recently revisited this decade-old controversy. In their view, “A major contributing factor to overdiagnosis and overtreatment is the designation of a particular pattern of low-grade cellular changes in the prostate as cancer ... A simple terminology change for these lesions and removal of the cancer label would dramatically reduce overdiagnosis and overtreatment and markedly

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change the cost benefit calculus of PSA screening”. This terminology change proposed by Eggener et al. has already been questioned by some experts in the field [14].

Here, as editors of the 2022 edition of the WHO classification of urinary and male genital tumors, we present our rationale for retaining the term *cancer* assigned to GS 6/GG1 prostate adenocarcinoma.

While there is universal agreement among pathologists and clinicians alike that GG1 prostate cancer should not be overtreated and that AS should be the default option for its management, the AS strategy by itself does not equate to benignancy. In fact, the guidelines of numerous American and European cancer organizations (eg, NCCN, American Urological Association, European Society of Medical Oncology, and European Association of Urology) state that a subset of patients with GG2 cancer (GS 3 + 4 = 7) may be offered AS in the appropriate clinical and histologic setting (NCCN low-risk or intermediate-risk category with a small amount of noncribriform Gleason pattern 4). Should the next line of defining benignancy be pushed to such GS 7 tumors? Clearly, no one would argue against the cancerous nature of such GG2 lesions.

Dropping the *cancer* term to facilitate patient adherence to established evidence-based treatment recommendations is counter to our duty as caregivers to fully and transparently inform patients before they opt for an appropriate management choice.

Great strides have been achieved in the interobserver and intraobserver reproducibility of Gleason pattern 4 diagnosis. Application of artificial intelligence in the near future will undoubtedly lead to even greater refinements [15]. Although defined as a stochastic system, all pathologists recognize that prostate cancer grading is on a continuous spectrum of differentiation, and elements of subjectivity remain in distinguishing certain pattern 4 cancer (eg, poorly formed glands) from pattern 3. As a result, the threshold between GG1 and GG2 is not without interobserver variability. Hence, adoption of the GG1/GG2 threshold as the cancer/no cancer divide may raise legal risks related to potential grading disagreements. A grade disagreement that may not ultimately impact an AS recommendation would become a “do I have cancer or not?” from the patient perspective. Faced with such scenario, one can anticipate a significant increase in the proportion of cases for which repeat biopsy is needed because of equivocal diagnoses of “atypical glandular proliferation, rule out adenocarcinoma” reported by concerned pathologists.

One of the strongest rationales for retaining the designation of cancer for GG1 tumors is the fact that Gleason pattern 3 cancer shares many morphologic and canonical molecular alterations associated with higher-grade prostate adenocarcinoma [16,17]. These include nuclear and nucleolar features, lack of basal cells, invasion beyond the confines of the prostate gland proper, overexpression of AMACR, loss of PTEN, GSTP1 downregulation, and *TMPRSS2-ERG* gene fusions [18,19].

It has repeatedly been shown that in a significant proportion of cases, GS on needle biopsy may significantly underestimate the final grade and fail to accurately reflect the extent (stage) of disease. More than one-third of tumors

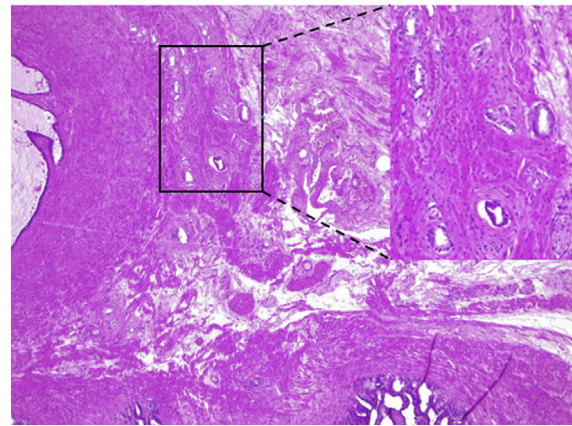


Fig. 1 – Grade group 1, Gleason score 3 + 3 = 6 prostate adenocarcinoma invading seminal vesicle tissue. Hematoxylin and eosin staining, 100× magnification (200× magnification in the inset).

that are graded as GG1 on needle biopsy will be upgraded to GG2 or higher on radical prostatectomy (RP) [20]. Importantly, one-fifth of these patients have non-organ-confined disease (Fig. 1). The use of multiparametric magnetic resonance imaging (mpMRI)/ultrasound fusion guided biopsy has certainly led to great refinement in identifying the best candidates for AS [21]. The fact remains that even in academic high-volume centers, targeted biopsies miss clinically significant cancers and upstaging continues to be encountered in patients who ultimately choose to drop out of AS and undergo RP [22–24]. The likelihood of upgrading and upstaging due to unsampled clinically significant cancer is bound to be higher in a low-volume community practice setting.

It should be recognized that the benign versus malignant paradigm in oncologic pathology is far from perfect [25]. None of the definitional attributes of malignancy is a sufficient or absolute requirement. The rarity of metastasis for GG1 tumors should not be equated with benignancy. For example, basal cell carcinoma and glioblastoma are malignant neoplasms that rarely if ever metastasize. The WHO classification of tumors has frequently embraced changes in nomenclature for malignant neoplasms when deemed appropriate and based on evidence. Examples include the use of *low malignant potential* and *borderline* terminology for several organ systems (eg, multilocular cystic renal neoplasm of low malignant potential and borderline ovarian tumors) and the acceptance of entities such as noninvasive follicular thyroid neoplasm with papillary-like nuclear features. The natural history of each tumor type and grade needs to be considered separately rather than on a simplistic binary system.

In one of the largest prospective trials to date investigating long-term outcomes among patients with GG1 prostate cancer managed with AS following mpMRI/ultrasound fusion targeted biopsy, the risk of metastasis or death from prostate cancer was <1%. Importantly, the trial afforded patients intensive monitoring of their cancer, and as a result almost half of the patients switched to definitive treatment during the course of the trial. These findings support the safety of AS in most men with GG1 prostate cancer, but

specific outcomes may differ in programs with less intensive monitoring [8]. If one were to drop the cancer label from patients enrolled in the trial, adherence to intensive monitoring and the option to choose definitive therapy could be jeopardized. The excellent outcomes attained for patients with GG1 disease who are managed according to current guidelines for their cancerous lesions may not be achieved if these lesions were designated as benign tumors.

In summary, it is our opinion that the rationales for maintaining GS 6/GG1 as the lowest tier for prostate adenocarcinoma grade outweigh the potential benefits that a benign designation may bring. Education for surgeons and patients of the vital role of AS and avoidance of overtreatment should be mainstays of future developments rather than unleashing the dangers of such a drastic change in nomenclature.

Conflicts of interest: Mahul B. Amin has scientific advisory or consultancy roles for and/or stock ownership in LabCorp, Precipio, Ibex Analytics, Cell Max, and Verily. The remaining authors have nothing to disclose.

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Appendix A. Peer Review Summary

Peer Review Summary to this article can be found online at <https://doi.org/10.1016/j.eururo.2022.09.015>.

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