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Loeb, S., Montorsi, F. and Catto, J.W. (2015) Future-proofing Gleason Grading: What to Call Gleason 6 Prostate Cancer? European Urology, 68 (1). 1 - 2. ISSN 0302-2838

https://doi.org/10.1016/j.eururo.2015.02.038

Future-proofing Gleason Grading: What to Call Gleason 6 Prostate Cancer?

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In November 2014, the International Society of Urological Pathology (ISUP) convened a consensus conference on prostate cancer grading in Chicago (IL, USA). Participants included international prostate cancer experts representing pathology, urology, radiation oncology, and medical oncology. The aim was to establish a single vision regarding the future of the Gleason grade system. The timing was in anticipation of the next revision to the TNM classification. Key issues for discussion included the labeling for Gleason 6 prostate cancer and whether it was time to overhaul the terminology used to describe prostate cancer grade.

The Gleason 6 label is perceived as a counseling problem, given that "6" sounds more ominous than "low" grade or "grade 1", which might better reflect the typical natural history of these tumors. A fear is that the labeling might be contributing to overtreatment of this disease. Historically, the vast majority of patients with even low-risk prostate cancer received radical treatment, although the use of active surveillance is increasing globally. In many regions, >40% of men with low-risk disease now receive initial active surveillance [1,2] and these numbers continue to grow. There is also increasing recognition of the role of pathologic reporting in prostate cancer management decisions [3]. Several clinical papers have suggested that cancer is an emotion-laden term and that removing this label could potentially allow for more effective communication with patients and further reduce overtreatment of Gleason 6 disease [4]. Indeed, numerous studies have documented the psychological implications of a prostate cancer diagnosis, including an increased risk of cardiovascular death and suicide within the first few months after diagnosis, even for individuals with well-differentiated cancer [5]. Alternative terminology has been suggested, such as indolent lesion of epithelial origin (IDLE), acinar proliferation with indeterminate malignant potential, and borderline epithelial neoplasm [4,6].

However, there are concerns regarding removal of the label of cancer from Gleason 6 lesions. First, despite its favorable prognosis, Gleason 6 disease does have the hallmarks of cancer from a pathologic perspective. Although distant metastases are extremely uncommon for true Gleason 6 prostate cancers, Haffner et al [7] reported a case in which the lethal clone came from a small, low-grade focus from the primary tumor. Gleason 6 disease also has the ability to invade, which is a necessary and sufficient criterion for distinguishing a malignant neoplasm [8]. In fact, some aggressive cancers such as high-grade glioma brain tumors rarely metastasize but are locally invasive. Second, needle biopsies sample a very small proportion of the prostate. The presence of Gleason 6 cancer can be a surrogate for worse disease elsewhere in the gland that has been

missed by biopsy. A recent literature review found that among men who met the D'Amico low-risk criteria on initial diagnostic biopsy, 42% were reclassified to higher risk on subsequent resampling (rebiopsy or prostatectomy within 6 mo) [9]. Even among men who met the Epstein criteria for insignificant disease on initial biopsy, 34% were reclassified on resampling. Randomized control trial cohorts find similar results when populations are sampled systematically [10]. Had these men been told they did not have cancer on the basis of incomplete information from the initial biopsy, it is unlikely that they would have undergone critical follow-up testing.

Given these conflicting tensions, the ISUP and Epstein and colleagues have proposed a modified classification scheme using prognostic groups that better reflect the true biologic aggressiveness of this cancer (Table 1). Instead of a scale that starts with 6 out of 10, the new prognostic grade groups are on a scale from 1 to 5 with Gleason 6 as group I. Gleason 3 + 4 = 7 and 4 + 3 = 7 will now be split into prognostic groups II and III. Finally, Gleason 8 will be prognostic group IV and Gleason 9–10 is prognostic group V [11]. It was previously shown that these categories predicted prognosis in 7869 men undergoing radical prostatectomy at Johns Hopkins [12]. The 5-yr rates of biochemical progression-free survival were 94.6%, 82.7%, 65.1%, 63.1%, and 34.5% for men assigned to prognostic groups I–V on biopsy, and 96.6%, 88.1%, 69.7%, 63.7%, and 34.5%, respectively, by prostatectomy prognostic groups ($p < 0.001$). At the 2014 meeting, new pooled data on more than 20 000 surgical cases and more than 16 000 biopsies showed similar highly prognostic stratification for the five proposed grade groups.

Although this change in terminology awaits ratification and validation (via long-term use), it is logical and welcome. In our view it will improve counseling of patients and make clearer the choices recommended. That notwithstanding, many factors other than grade are used for management decisions, and decision-making remains heavily based on imperfect information. It is to be hoped that our ability to accurately stage prostate cancer will continue to improve with greater use of multiparametric magnetic resonance imaging and advances in genomic technology. Where this new classification sits among changing methods of diagnosis (eg, shift to image-based targeted biopsy rather than random transurethral ultrasound [13]) remains to be worked through. For now, the consensus was that this new system should be limited to grade, and that other parameters such as the extent of cancer on biopsy should be reported separately. Overall, there was majority support at the meeting to report the new prognostic grade groups alongside the traditional Gleason scores, beginning in 2015.

Conflicts of interest: The authors have nothing to disclose.

Acknowledgments: Stacy Loeb is supported by the NYU Cancer Institute, the Louis Feil Charitable Lead Trust, and the National Institutes of Health under award number K07CA178258. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Table 1 – Prognostic groups

Traditional Gleason score	Prognostic group
6	I
3 + 4 = 7	II
4 + 3 = 7	III
8	IV
9–10	V