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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, Illinois. 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. 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 this labeling might be contributing to the overtreatment of this disease. Historically, the vast majority of patients with even low-risk prostate cancer received radical treatment, although recently 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 with well-differentiated cancer.[5] Alternate terminology has been suggested such as Indolent Lesion of Epithelial Origin (IDLE), acinar proliferation with indeterminate malignant potential, or borderline epithelial neoplasm.[4, 6]

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However, there are concerns with removing the label of “cancer” from Gleason 6 lesions. Firstly, despite its favorable prognosis, from a pathological perspective Gleason 6 disease does have the hallmarks of cancer. Although distant metastases are extremely uncommon for true Gleason 6 prostate cancers, Haffner et al. recently reported a case in which the lethal clone came from a small, low-grade focus from the primary tumor [7]. Gleason 6 disease also has the ability to invade, which is a necessary and sufficient criteria to distinguish a malignant neoplasm.[8] In fact, some aggressive cancers like high-grade glioma brain tumors rarely metastasize but are locally invasive. Secondly, 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, which has been missed by biopsy. A recent literature review found that among men who met the D’Amico low-risk criteria at their initial diagnostic biopsy, 42% were reclassified to higher risk at subsequent resampling (rebiopsy or prostatectomy within ≤6 months).[9] Even among men who met the Epstein criteria for insignificant disease at the initial biopsy, 34% were reclassified upon resampling. RCT cohorts find similar results when populations are sampled systematically.[10] Had these men been told they did not have cancer based on incomplete information from the initial biopsy, it is unlikely that they would have undergone critical follow-up testing.

Given these conflicting tensions, the ISUP, Epstein and colleagues have proposed a modified classification scheme using prognostic groups that better reflect 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 of 1 to 5 with Gleason 6 as group 1. 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] These categories were previously shown to predict prognosis in 7,869 men undergoing radical prostatectomy at Johns Hopkins.[12] The 5-year rates of biochemical progression-free survival were 94.6%, 82.7%, 65.1%, 63.1% and 34.5% for men with prognostic groups I–V on biopsy, and 96.6%, 88.1%, 69.7%, 63.7%, and 34.5% by prostatectomy prognostic groups, respectively ($p<0.001$). At the 2014 meeting, new pooled data on over 20,000 surgical cases and over 16,000 biopsies showed similar highly prognostic stratification for the five proposed grade groups.

Whilst this change in terminology awaits ratification and validation (by 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. Hopefully our ability to accurately stage prostate cancer will continue to improve with greater use of multiparametric MRI and advances in genomic technology. Where this new classification sits amongst changing methods of diagnosis (e.g. shift to image-based targeted biopsy rather than random TRUS[13]) remains to be worked through. For now, the consensus was that this new system should be limited to grade, and that other parameters like 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.

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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