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# The New Prostate Cancer Grading System in High-risk Disease: A Big Step Forward?

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In this issue of *European Urology*, Ham et al [1] report on a study of the newly proposed five-tiered prostate cancer (PCa) grading system in predicting long-term survival outcomes after radical prostatectomy (RP). The question of how to improve prognostic substratification of high-risk disease is highly relevant. To provide an answer, they analyzed a large cohort of men who underwent RP with biopsy or pathologic Gleason score (GS) 8–10 at a single institution over a 30-yr period. With median follow-up ranging from 4 to 6 yr, the data show higher cancer-specific mortality for biopsy and RP GS 9–10 when compared to GS 8. This association remained significant after adjusting for possible known confounders in both the preoperative and postoperative phases.

The authors should be commended for their efforts to test the new five-tiered grading system using a "hard" outcome such as PCa-specific mortality. Many previous studies on this topic, in fact, relied on only biochemical recurrence (BCR)–free survival to define the utility of the new system, with all the known limitations of this approach. In particular, Epstein et al [2] assessed the predictive ability of the system for median follow-up of 3 yr, and found only a slight increase in overall accuracy for BCR prediction when compared to the traditional Gleason grading system (0.008 and 0.012 increase in overall accuracy in the pre- and post-treatment models, respectively). Subsequently, Loeb et al [3] extended follow-up to a median of 4.6 yr and concluded that the increase in C-index between the five-tier Gleason grading system and the three-tier GS system ranged from 0 to 0.01. As we know from previous works, prostate-specific antigen–only recurrence risk is not fully reliable in risk-adapting strategies [4], and use of stronger survival outcomes is recommended.

Substantial heterogeneity has been reported within the high-risk group in contemporary series, prompting several authors to assess the potential benefit of further substratification in predicting long-term outcomes and helping in the choice of adjuvant therapies, especially in the post-surgical phase [5,6]. Despite good predictive results, these tools considered GS 8–10 cancers together, thus precluding definite conclusions about the role of GS or a Gleason grade (ie, 5) as a single predictor. For this reason, the present work by Ham et al centered on high-risk disease. In spite of this, some aspects should be borne in mind when interpreting these results or designing further studies on the same topic. First, the absence of detailed information on the use of adjuvant or salvage treatment(s) is a clear limitation. Even though the authors state that adjuvant therapy use did not exceed 5% among the patients, approximately one third received salvage therapy, and the potential role of these treatments as confounders has not been fully evaluated. The assessment of survival status and cause of death is another potential source of uncertainty; as stated by the authors, PCa-specific mortality was designated when PCa was the underlying cause of death or the patient had a previous diagnosis of castration-resistant PCa at the time of death. However, the latter definition might be somewhat equivocal, especially after the introduction of newer systemic treatments, as it is not uncommon for a patient with asymptomatic castration-resistant PCa to survive for years and die of potential unrelated causes. For this reason, more precise definitions should be used in future studies. Finally, while the number of patients is large, longer follow-up could be advocated to confirm or contradict the findings of the present study, given the long natural history of PCa

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recurrence, especially when survival outcomes are being assessed. On the same issue, Loeb et al [3] clearly acknowledged that their median follow-up of 4.6 yr precluded the ability to draw conclusions regarding long-term survival outcomes.

The last point regarding the real utility of the new classification in clinical practice is perhaps better answered by another recent study. The findings by Dell'Oglio et al [7], while supporting the separation between GS 3 + 4 and 4 + 3, and GS 8 and 9–10, question the overall difference in clinical recurrence–free survival prediction between the three-grade system based on the traditional risk classification and the new five-tiered classification. According to this work, involving 9728 patients in two large-volume centers, use of the new system in the overall population led to only a minimal increase in the C-index.

In conclusion, the results presented by Ham et al underscore the huge heterogeneity within high-risk PCa, confirming what we have known: GS is a stronger predictor of clinical outcome in RP-treated PCa. The new system might certainly be handier and easier to understand for new patients. In our opinion, a big question remains open: if all the other prognostic factors are similar, should GS 8 and 9–10 be treated differently in the postoperative setting, based only on this Gleason score? Well-designed and detailed retrospective studies, as well as prospective trials on adjuvant strategies, are expected to add more granular evidence in this setting. Perhaps the combination of clinical and pathologic information with newer tools providing better insights on PCa biology (such as genome-based tests and biomarkers) could take the prediction models a step further.

***Conflicts of interest:*** The authors have nothing to disclose.

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