In Reply.—This letter by Delahunt et al is a rehash of a prior letter that was written to the American Journal of Surgical Pathology (AJSP). We refer the readership to our response in AJSP, rather than repeat our thorough rebuttal.1 However, there are a few new issues that we would like to address.

The authors continue to refer to the new grading system as the International Society of Urological Pathology (ISUP) grading system, despite the fact that the new system was published in 2013 by work at Johns Hopkins Hospital before the 2014 ISUP conference.2 Similarly, the results of the multi-institutional validation study of more than 20 000 patients3 were presented at the 2014 ISUP grading conference and were the driving factor for acceptance to the new grading system both for ISUP and other subsequent organizations, such as the World Health Organization and the College of American Pathologists. Delahunt et al falsely claim, “An early decision of the group was that the grading classification would be known as ISUP grading.” Several of the organizers may have assumed this to be true, but as a coleader of the organizers of Australasia, where the editor, Dr Delahunt, could have fast-tracked their publications to make it appear that our multi-institutional study of more than 20 000 patients was just one of several validation studies, rather than the key one that led to the acceptance of the new grading system and the spawning of subsequent, smaller validation studies in journals with lower impact factors. Delahunt et al also raise a question about whether pattern combinations clature was reached before the 2014 consensus conference. As to the subsequent ISUP Council vote on the nomenclature of the new grade groups, it is merely the opinion of a few individuals who have no mandate to dictate policy for all issues relating to urologic pathology. They have no right to usurp the name of the new grading system, in which the original concept and research, nomenclature, and subsequent critical validation study were done by others.

It is one thing for others to group various grades together for study purposes, and quite another to propose a simple, patient-centric,5 new, 5-group grading system, as was done in 2013.5 The original manuscript in 2013, the subsequent multi-institutional validation study, the AJSP publication on the 2014 ISUP grading conference, and the World Health Organization all avoid referring to the new grading system as ISUP grades, but rather as grade groups 1 to 5. Most recently, the College of American Pathologists adopted the terminology of grade groups 1 to 5, which will be recommended in the latest updates of prostate cancer protocols, which are widely used throughout the United States. In the “Explanatory Notes” of the protocol, it states, “The 9 Gleason scores (2–10) have been vastly lumped into different groups for prognosis and patient management purposes. Epstein et al proposed grouping scores into 5 prognostic categories, prognostic Grade Groups 1–5.9 The validation studies by Delahunt et al and Samaratunga et al from New Zealand and Australia, respectively, cited in the accompanying letter were initiated after the authors of those studies were presented with the findings of the multi-institutional study by Epstein et al at the 2014 ISUP conference. Their studies were published before our validation study was published in European Urology only because they are in Pathology, the journal of the Royal College of Pathologists of Australasia, where the editor, Dr Delahunt, could have fast-tracked their publications to make it appear that our multi-institutional study of more than 20 000 patients was just one of several validation studies, rather than the key one that led to the acceptance of the new grading system and the spawning of subsequent, smaller validation studies in journals with lower impact factors. Delahunt et al also raise a question about whether pattern combinations

References


included in grade group 4 (4+4 = 8, 3 + 5 = 8, and 5 + 3 = 8) are appropriately grouped and have similar clinical behaviors and prognostic significance. In our review article,6 we discussed the limitations of the 2 manuscripts Delahunt et al cite. With contemporary reviews, the clinical outcomes of 3 + 5 = 8 and 4 + 4 = 8 biopsy cases are not different.9 Gleason score 5 + 3 = 8, as the highest grade core at biopsy or nodule at radical prostatectomy, is relatively rare. In our prior multi-institutional study, only 4 of 20,824 radical prostatectomies retrospectively reported as Gleason score 5 + 3 = 8 (O.N.K. and J.I.E., unpublished data, 2016). Of these, only 2 biopsies and 4 radical prostatectomies were contemporarily regraded as Gleason score 5 + 3 = 8. If new, large studies grading 5 + 3 = 8 correctly convincingly show that it belongs to a different grade group, then modifications can be made in the new system to reflect new knowledge generated on cases pathologically graded according to contemporary standards.

Finally, there is the following issue that Delahunt et al bring up, “In effect 2014 ISUP grading cannot be applied to radical prostatectomy specimens as there is no provision for the accommodation of tertiary scores.” There was discussion at the 2014 consensus conference on this issue. It was decided by a large majority that tertiary-grade patterns, also referred to as minor, high-grade patterns, were to be restricted to cases with less than 5% of the higher-grade pattern. Subsequent discussions and voting by the attendees of the consensus conference recommended to record the percentage of pattern 4 for Gleason score 7. Consequently, radical prostatectomy specimens with 98% pattern 3 and 2% pattern 4 would be graded as “3+4 = 7” with less than 5% pattern 4, as opposed to “3+5 = 6” with tertiary pattern 4.10 “Tertiary” higher grade would, therefore, only be used for radical prostatectomy specimens with Gleason scores 3+4 = 7 and 4+3 = 7 with less than 5% pattern 5. It follows that, in cases with more than 5% pattern 5, the higher grade would be included as the secondary pattern within the Gleason score. Otherwise, according to the 2005 grading rules, a tumor with 80% pattern 3 and 20% pattern 5 would be a Gleason score 3 + 5 = 8, and another tumor with 50% pattern 3, 30% pattern 4, and 20% pattern 5 would be graded 3 + 4 = 7, which makes no sense, given that both have the same large amount of Gleason pattern 5 cancer. As noted in the previous AJSP response,1 “Several members of the 2014 organizing committee, instead of incorporating the issue of tertiary patterns and the recommendation to report the percentage of pattern 4 in the 2014 consensus conference published in AJSP in 2016, as I recommended, argued to split these topics into an additional manuscript. There is not even a circulated draft of this additional manuscript over 2 years after the consensus conference. It has led to confusion among pathologists relating to the issue of tertiary grades and recording percent pattern 4.” It is ironic that Delahunt et al criticize the consensus conference for not dealing with tertiary patterns in radical prostatectomy specimens, yet the 3 members of the 2014 consensus conference who argued for splitting off this topic are authors on the accompanying letter from Delahunt et al.

Jonathan I. Epstein, MD; Oleksandr N. Kryvenko, MD


The authors have no relevant financial interest in the products or companies described in this article.