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Platinum Priority – Editorial Reply

Referring to the article published on pp. 413–415 of this issue

Reply re: Murali Varma, Brett Delahunt, Theodorus van der Kwast. Grading Noninvasive Bladder Cancer: World Health Organisation 1973 or 2004 May Be the Wrong Question. Eur Urol 2019;76:413–5

Two Decades of World Health Organisation/International Society of Urological Pathology Bladder Cancer Grading: Time to Reflect on Accomplishments and Plan Refinement in the Molecular Era, Not Regress to Readoption of a 45-year-old Classification

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The Platinum Opinion by Varma et al [1] on grading of noninvasive bladder cancers in 2019 includes a brief historic overview of grading since 1998. In spite of underscoring the well-known weaknesses of the heterogeneous grade 2 group and interobserver reproducibility of the World Health Organisation (WHO) 1973 classification, the authors raise the question of whether the WHO 1973 system should be reported along with the WHO (2016)/International Society of Urological Pathology (ISUP) system for non–muscle-invasive bladder cancer (NIMBC) [2,3]. They outline areas where the WHO/ISUP classification is supposedly clinically deficient (for patients "overtreated" with bacillus Calmette-Guérin) without providing any reference. The statement, "cystectomy might be appropriate for a high-grade recurrence corresponding to WHO 1973 grade 3, but not for a tumour that is the lower end of the high-grade spectrum" also has no references. We would argue respectfully that reverting to a 45-yr-old grading system (WHO 1973) that has been replaced by a criteria-driven system (WHO/ISUP) with proven enhanced reproducibility (confirmed by a European Association of Urology [EAU] panel) and that has been almost universally accepted by pathologists and urologists alike for more than two decades is medically and scientifically inadvisable and without merit.

The two decades since promulgation of the WHO/ISUP system has allowed several significant accomplishments in the classification and management of bladder cancer that were not possible with the WHO 1973 system. These include the following [2]:

(1) Detailed histologic criteria with standardized definitions that have allowed greater reproducibility and the publication of several studies to compare prognosis and treatment results between centers;
(2) Removal of the inevitable and frequent use of diagnostically ambiguous terminology (TCC [transitional cell carcinoma] grade 1–2, TCC 2, TCC grade 2–3);
(3) Promotion of a histologic paradigm for grading bladder lesions that is similar across flat lesions, papillary lesions, and inverted lesions;
(4) Congruence in terminology with urine cytology results (high grade vs non–high grade);
(5) Identification of an expanded group of patients with flat and papillary disease who benefit from intravesical therapy;
(6) Creation of the term *papillary neoplasm of uncertain malignant potential* (PUNLMP), which avoids labeling patients with a carcinoma (outright malignant) diagnosis;
(7) Division of NIMBC into biologically relevant categories (PUNLMP, not associated with invasion or metastasis) and low-grade disease (low risk of progression), and high-grade disease (high risk of invasion and metastasis);
(8) Creation of diagnostic categories that are therapeutically relevant with a focus on prompt intervention for high-grade flat and papillary lesions; and
(9) Correlation of morphology with oncogenic pathways and emerging molecular underpinnings of cancer (that emphasize the stark differences between non–high-grade and high-grade disease).

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On the basis of these accomplishments, the clinical application and value of the WHO/ISUP system has been repeatedly endorsed by WHO in 2004 and 2016 [3,4], the College of American Pathologists (in all its recommendation revisions over two decades) [5], the American Joint Cancer Committee [6], the US Armed Forces Institute of Pathology [7], and the International Collaboration on Cancer Reporting [8]. The only international organization that keeps recommending the 1973 WHO classification, against the opinion of their consulting pathologist, is the EAU [9]. Almost all the major textbooks on pathology, as well as seminars, courses and other educational resources, outline the application of the WHO/ISUP system. An entire generation of pathologists has emerged who only apply the new WHO/ISUP system, and those who have been in practice for longer have forgotten how to use the 1973 system, which has not been in clinical use for decades. An intent of the authors of the Platinum Opinion in promoting the WHO 1973 system is that use of the WHO/ISUP system allegedly groups clinically heterogeneous tumors and is not in keeping with precision medicine initiatives. It is our opinion that recommending use of the 1973 system with its inherent established problems with reproducibility and diagnostic ambiguity is a greater antithesis of precision medicine, which relies on evidence-based objective data.

With the significant achievements over two decades based on a strictly morphologic classification, it is appropriate—as for all classification systems—that we continue to refine the WHO/ISUP system to enhance its clinical value. Refinement has the potential to integrate emerging molecular data and use the transformational power of bioinformatics and computational biology for patient care. In our opinion, efforts in this direction deserve the undivided attention of the pathology, urology, and scientific community. We believe that engaging in a debate on a topic that is not a huge unmet need for urologists (the need for an older classification to supplement the current classification for NIMBC), which would involve relearning a system that has not been in clinical use worldwide (WHO 1973) and with no strong convincing recent data on enhanced clinical utility, is counterproductive.

Conflicts of interest: The authors have nothing to disclose.

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