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Digital Progesterone Receptor Scoring in Meningiomas: A Step Toward Objectivity or a Supplemental Tool?

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To the Editor,

I have read with great interest the article by Akça and Gökçe titled "Digital Quantification of Progesterone Receptor Expression in Meningiomas: Associations with WHO Grade and Clinicopathological Features" (1). As digital pathology continues to revolutionize our field, the authors' effort to mitigate the inherent subjectivity of manual immunohistochemical (IHC) assessment in meningiomas is highly commendable. By utilizing an FDA-cleared algorithm—originally validated for breast carcinoma but previously shown to be applicable to meningioma tissue through comparative manual scoring (2)—to quantify Progesterone Receptor (PR) expression, this study takes a significant step toward objective diagnostic standards in neuro-oncology. The methodology employed, specifically the calculation of a continuous H-score through digital analysis, successfully confirms the well-established inverse relationship between PR expression and WHO grade. The finding that each 10-point increase in the H-score reduces the odds of a higher WHO grade by 15% is particularly valuable for clinical risk stratification.

However, several points merit discussion. Although the digital H-score improves objectivity, the analysis is based on the manual selection of three representative regions of interest (ROIs). This process may still introduce selection bias, especially in tumors with marked heterogeneity. In contrast, a recent study has employed Whole Slide Imaging (WSI) for PR quantification, allowing assessment of the entire tumor area and potentially providing a more accurate reflection of intra-tumoral heterogeneity (3). Furthermore, while PR was quantified digitally, the Ki-67 index and mitotic counts were assessed manually—a limitation appropriately noted by the authors. Although proliferation markers are integral to WHO grading, the comparative prognostic weight of Ki-67 and PR expression can fluctuate across different clinical cohorts and study designs. In some larger digitally analyzed cohorts, Ki-67 has shown a more consistent association with disease-free survival (DFS) than PR expression, though both markers remain complementary in risk assessment (3, 4). While PR expression serves as a reliable correlate of tumor grade, its independent utility in predicting recurrence appears less robust than digitally quantified Ki-67 hotspot analyses, which offer superior predictive accuracy as demonstrated by Güreşci et al (3).

Critically, cIMPACT-NOW update 8 mandates integrating molecular and copy-number alterations into grading (5). TERT promoter mutations and CDKN2A/B homozygous deletions are established as independent criteria for CNS WHO grade 3, regardless of histology (4). Furthermore, histologically low-grade cases with 1p deletion plus 22q loss and/or NF2 variants are now assigned to CNS WHO grade 2, providing objective stratification for borderline scenarios (5). As acknowledged by the authors, the absence of these molecular data is a limitation, as they are now essential for the standardized grading of aggressive meningiomas. While digital PR and Ki-67 assessment provide useful surrogate data, they cannot fully substitute for molecular testing in borderline or high-grade cases.

Finally, the use of breast-trained algorithms for PR assessment in meningiomas represents a pragmatic and effective application of digital pathology, although biological differences between tumor types should be considered. Future studies integrating automated digital quantification of PR, Ki-67, and mitotic activity within a unified workflow may further reduce inter-observer variability and enhance analytical consistency.

Overall, this study provides a strong basis for the incorporation of digital tools into routine neuropathology practice, supporting the role of PR as a reliable marker of tumor grade and highlighting the value of progressing toward fully automated, whole-slide digital workflows for broader clinical implementation.

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