Letter to the Editor

Is machine learning-based assessment of tumor-infiltrating lymphocytes on standard histologic images associated with outcomes of immunotherapy in patients with NSCLC?

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Recent advances in artificial intelligence and slide scanning technology have enabled big data analysis of pathology tissue images. We read with great interest the article by Rakaee and colleagues (1), who developed a machine learning (ML)-based method to count tumor-infiltrating lymphocytes (TILs) on hematoxylin-eosin-stained standard pathologic images of primary or metastatic tumors. The authors demonstrated an association between TIL status based on ML-based assessment and outcomes of immune checkpoint inhibitor (ICI) therapy in patients with non-small cell lung cancer (NSCLC). Specifically, in retrospective cohorts of patients with NSCLC who underwent anti-programmed death-ligand 1 (PD-L1) or anti-programmed death-1 (PD-1) (i.e., anti-CD274 or anti-PDCD1) monotherapy, high-TIL (≥250 cells/mm^2) tumors were associated with more prolonged survival as compared with low-TIL (<250 cells/mm^2) tumors. Particularly for PD-L1-negative tumors, TIL assessment showed good performance in predicting ICI response. Very few patients with PD-L1-negative and low-TIL tumors responded to ICI therapy. We would like to raise three concerns for consideration.

The first concern is whether the ML-based method is more accurate than an experienced pathologist in determining TIL status and predicting ICI response. We note that the ML-based model was developed based on pathologist-derived annotations (1). Counting TILs is easy for artificial intelligence but is labor-intensive for pathologists. However, dichotomizing tumors based on the TIL status is relatively easy for experienced pathologists. Undoubtedly, the ML-based model is capable of dichotomizing tumors with greater speed and reproducibility than pathologists. Nonetheless, the concordance of TIL estimation or the difference in prediction performance between the ML-based and pathologist assessments needs to be examined, as has been done in prior computational TIL assessment research (2).

The second concern is the impact of specimen characteristics on the predictive performance of ML-based assessment. In our practice, we pathologists encounter

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histomorphological variations by specimen type. Compared with resection, biopsy specimens have smaller tumor areas and provide less information about the tumor-immune microenvironment. However, the interval between tumor sampling and ICI treatment is shorter, so the TIL status is more current. In contrast to primary tumors, metastatic tumors reflect the co-evolution of cancer and anticancer immune responses but may be affected by metastatic organ-dependent immune regulation (3). In this study, metastatic liver lesions had fewer TILs compared to primary and other metastatic lesions (e.g., lymph node and pleura) (1). The lower TIL counts in metastatic liver lesions may be explained by the immunoprivileged nature of the liver (4). A single TIL cutoff value was used for different specimen types (e.g., biopsy *vs.* resection, primary *vs.* various metastatic sites) in this study (1), but this could be potentially adjusted for better performance. Moving forward, we need to evaluate the predictive performance of ML-based TIL assessment for each specimen characteristic.

The last concern is the molecular characteristics of the worst-responding PD-L1-negative and low-TIL tumors. We speculate that this tumor subset may be characterized by *CD274* (*PD-L1*) copy number loss (CNL). Using a cohort overlapping with this study, the authors' group previously reported an association between *CD274* CNL and impaired ICI efficacy in nonsquamous NSCLC (5). Additionally, emerging evidence suggests that NSCLCs with CNL have reduced PD-L1 immunostaining and create an immunologically "cold" tumor microenvironment (6). Molecular characteristics may be integrated with pathological images to predict the treatment response more accurately.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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