



Bridging histopathology, inferred transcriptomics, and immunotherapy response prediction in head and neck cancer

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Immune checkpoint inhibitors (ICIs) have reshaped the therapeutic landscape of head and neck squamous cell carcinoma (HNSCC); however, durable clinical benefit remains confined to a subset of patients. This ongoing limitation underscores the need for predictive biomarkers that are robust, reproducible, and broadly accessible. In this context, the accompanying study, “Prediction of clinical outcomes of immune checkpoint inhibitors in advanced head and neck cancer directly from histopathology slides using inferred transcriptomics” (1), represents a timely and innovative contribution to translational cancer research.

The authors describe a deep learning-based framework capable of inferring transcriptomic programs directly from digitized hematoxylin and eosin (H&E)-stained histopathology slides and leveraging these features to predict clinical outcomes in patients with advanced HNSCC treated with ICIs. This approach addresses a key limitation of contemporary precision oncology: reliance on molecular assays that may be costly, resource-intensive, and unevenly available. By utilizing routinely acquired pathology material, the proposed strategy offers a scalable avenue for biomarker development with potential global applicability.

Although the reported results are encouraging, they

should be interpreted in light of the relatively limited size of the training and validation cohorts, particularly given the application of deep learning models to high-dimensional inferred transcriptomic features. In such contexts, even well-designed internal validation strategies cannot fully mitigate the risk of overfitting. Accordingly, external validation in larger, independent, and ideally multicenter cohorts will be essential to establish the robustness and generalizability of the proposed framework.

Potential selection bias related to the distribution of responders and non-responders also warrants consideration. In small retrospective cohorts, imbalances in clinical characteristics, prior treatments, or tumor biology between these groups may inadvertently inflate apparent model performance. Transparent reporting of response prevalence and prospective validation in more representative patient populations will therefore be important to mitigate this risk.

The translational relevance of such predictive tools is particularly apparent when viewed in the context of recent advances in immunotherapy for HNSCC. In the recurrent or metastatic setting, pivotal trials such as KEYNOTE-048 and CheckMate-141 established pembrolizumab and nivolumab, respectively, as standards of care, while also

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underscoring the limited predictive accuracy of existing biomarkers, including programmed death-ligand 1 (PD-L1) expression (2,3). More recently, ICIs have expanded into earlier disease stages. The phase III KEYNOTE-689 trial is evaluating perioperative pembrolizumab in combination with standard surgery and radiotherapy, with or without chemotherapy, in patients with resectable locally advanced HNSCC (4). The positive event-free survival signal reported in this study represents a shift toward curative-intent immunotherapy and substantially broadens the population exposed to ICIs, emphasizing the expanding role of ICIs in earlier disease stages (5).

A notable strength of the study is its biologically informed design. Rather than relying exclusively on black-box predictions, the model is grounded in inferred gene expression programs linked to immune activation, tumor microenvironment composition, and immune evasion. This enhances interpretability and supports the biological plausibility of the predictions. Consistent with prior work in computational pathology, the findings further reinforce the concept that morphologic patterns captured on routine H&E slides can reflect underlying molecular and immunologic states (5).

In this evolving therapeutic landscape, the ability to stratify patients according to their likelihood of benefit from immunotherapy is of increasing clinical importance. As ICIs move into neoadjuvant and adjuvant settings, concerns regarding overtreatment and unnecessary toxicity become more prominent. Image-based biomarkers derived from routine histopathology may complement existing markers and offer additional decision support, particularly when molecular profiling is unavailable or inconclusive.

Despite its promise, several challenges must be addressed before the proposed approach can be integrated into routine clinical practice. The retrospective nature of the analysis and the use of relatively limited cohorts raise questions regarding generalizability, particularly given the biological heterogeneity of HNSCC related to human papillomavirus (HPV) status, anatomic subsite, and prior therapies. External validation across multi-institutional cohorts and diverse slide preparation and scanning protocols will be essential.

Moreover, while inferred transcriptomics enhances interpretability, it does not replace direct molecular measurements. Prospective studies comparing inferred gene expression profiles with experimentally generated transcriptomic data will be necessary to establish robustness and reproducibility. Pre-analytical variables, including tissue

fixation, staining variability, and slide quality, also merit careful consideration.

Looking ahead, integrating artificial intelligence (AI)-derived histopathology biomarkers with clinical variables, genomic data, and spatial immune profiling may further improve predictive performance. Prospective clinical trials that incorporate computational pathology models as stratification or decision-support tools will be critical to demonstrate clinical utility, particularly in the perioperative immunotherapy setting exemplified by KEYNOTE-689 (6,7). Recent advances in multimodal deep learning models have demonstrated the potential to predict immunotherapy outcomes by combining histopathologic, transcriptomic, and clinical data (8,9). Prospective clinical trials incorporating computational pathology models as stratification or decision-support tools will be critical to establish clinical utility, particularly in the perioperative immunotherapy setting (5,10).

From a clinical standpoint, the absence of reliable predictive tools carries tangible implications. For instance, in patients with resectable, locally advanced HNSCC—particularly those with HPV-negative disease that may already be amenable to cure with standard surgery and radiotherapy—the routine addition of perioperative immune checkpoint inhibition in the absence of robust biomarkers could lead to unnecessary immune-related toxicity, delays in definitive local therapy, and increased costs without clear benefit.

Beyond individual patient outcomes, this scenario also raises broader ethical and health-economic considerations. Expanding immunotherapy indications without accurate stratification tools may place additional strain on health care systems and exacerbate disparities in resource-limited settings, underscoring the importance of developing predictive strategies that are accessible, biologically grounded, and clinically reliable.

In summary, the authors present a conceptually sound and methodologically innovative approach that bridges routine histopathology, inferred transcriptomics, and immunotherapy response prediction. As immunotherapy continues to expand across disease stages in HNSCC, accessible and biologically informed biomarkers such as those described in this study may play an increasingly important role in advancing precision oncology.

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