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Computational Pathology Predicts Immunotherapy Response and Maps Spatial Biomarkers in Gastric Cancer

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Reliable biomarkers for predicting response to immune checkpoint inhibitors (ICIs) in gastric cancer remain limited. We developed and validated an AI model using whole slide images (WSIs) to predict ICI response and assess its prognostic and biological relevance. The model was trained on 272 slides from 107 patients (development cohort) and externally validated on two independent cohorts (373 slides from 127 patients, 25 slides from 18 patients). We benchmarked three histopathology foundation models and eight multiple-instance learning (MIL) algorithms, identifying the UNI-CLAM combination as the top-performing architecture (AUROC = 0.844). High-attention patch analysis revealed fibrosis and signet ring cells (SRCs) as features enriched in non-responders, while nuclear hyperchromasia and enlargement were more frequent in responders. These features showed distinct spatial distributions on WSIs. The model achieved AUROC values of 0.7151 and 0.7545 in external validation cohorts. Kaplan–Meier analysis confirmed that predicted responders had significantly longer progression-free and overall survival in both internal and external datasets. Gene expression analysis of TCGA-STAD data showed immune pathway activation in predicted responders and increased cell cycle activity in non-responders. Spatial transcriptomics (Xenium 5K) of 14 patients revealed FGFR2 overexpression across multiple cell types in non-responders, while responders showed localized enrichment of immune pathways in tumor-infiltrated regions. These results demonstrate that AI-guided pathology provides a scalable, biologically validated approach for predicting ICI response in gastric cancer.