1291 A MULTI-TUMOR MACHINE LEARNING MODEL TO IDENTIFY TERTIARY LYMPHOID STRUCTURES IN HISTOPATHOLOGICAL H&E IMAGES AS A POTENTIAL CLINICAL BIOMARKER

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Background Tertiary lymphoid structures (TLS) are ectopic lymphoid structures that develop in benign and tumor tissues with chronic inflammation. TLS are highly organized structures composed of B cells, T cells, and supportive cells within a structural matrix. They are classified as lymphoid aggregates (LA), immature TLS (imTLS), or mature TLS (mTLS) with the presence of a germinal center (GC). The presence and maturity of TLS have been associated with favorable outcomes in multiple tumor indications and with immune-checkpoint inhibitor (ICI) efficacy. We aimed to develop a digital pathology method to quantify TLS presence, prevalence, and localization as a predictive biomarker of ICI clinical outcome We developed a machine-learning (ML) algorithm trained on hematoxylin and eosin (H&E)-stained whole slide images (WSIs) to: (1) accurately and reproducibly identify LAs and TLS; (2) to predict TLS subregions and maturity; and (3) extract TLS model-derived features.

Methods A multi-tumor ML-based TLS detection model was trained by expert pathologists to predict mTLS/GCs, imTLS, and LAs in H&E-stained WSIs (N=2777) from TCGA bladder cancer (BLCA), breast cancer (BRCA), stomach adenocarcinoma (STAD), lung adenocarcinoma (LUAD), and lung squamous cell carcinoma (LUSC). Pre-trained indication-specific tissue segmentation models were applied to distinguish cancer, cancer-associated stroma, and necrosis from normal tissue. Features quantitatively derived from TLS and tissue regions were extracted, and correlations with an RNA-seq-derived TLS-associated gene expression signature were calculated. Log-rank analysis was performed to assess the impact of TLS on prognosis.

Results Our model accurately and reproducibly detected and distinguished LA, imTLS, and mTLS/GC in five indications and performed comparably to manual pathologist-derived annotation. Four model-derived TLS features (proportional area of LA, proportional area of iTLS, proportional area of mTLS, and mean perimeter of imTLS) correlated with a published TLS-gene signature, and three gene-expression clusters were found to be concordant with TLS maturity. The proportional area of mTLS was significantly associated with improved progression-free survival in BRCA ($p=0.01$) and overall survival in LUAD ($p=0.04$).

Conclusions We developed a robust ML-based algorithm that can accurately distinguish and classify TLS structures across five indications. We demonstrated that novel TLS model-derived features correlated with gene expression and survival in several indications. These data highlight the promise of ML-based approaches for the accurate and reproducible evaluation and potential implementation of prognostic TLS biomarker assays in oncology.

Ethics Approval The trial protocols were approved by site institutional review boards or independent ethics committees and conducted according to Good Clinical Practice guidelines, per the International Conference on Harmonisation. Patients provided written informed consent based on Declaration of Helsinki principles.

Consent Patients provided written informed consent based on Declaration of Helsinki principles.

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