Background Recent studies suggest that a higher prevalence of stromal composition within tumors is associated with resistance to immune checkpoint inhibitors (ICIs) in various cancer types.1–3 While deep learning models have been used to identify stromal components within tumors at the patch-level with Hematoxylin and Eosin (H&E) stained images, the detection and differentiation of cellular and non-cellular components of the stroma, such as fibroblasts and the extracellular matrix (ECM), remain challenging. Recent studies indicate ECM within Tumor Microenvironments (TMEs) plays pivotal roles in immunotherapy. However, using H&E stained images for detecting and quantifying ECM presents challenges due to its complexity and heterogeneity. Holotomography (HT)4 holds promise for enhanced ECM analysis within TMEs, providing novel insights into therapeutic responses. Here, we aim to develop TME-IS, an innovative computational pipeline that integrates HT with H&E images for enhanced detection and quantification of ECM and cells within TMEs.

Methods Our pipeline contains four major stages: 1) ECM and cell segmentation, 2) Cell type classification, 3) Quantification of ECM components, and 4) Spatial analysis of TMEs. The ECM and cell segmentation is based on deep learning models that achieve comprehensive segmentation via an end-to-end framework in HT images. Next, cell type classification is achieved by exploiting cellular image features. ECM quantification involves the computation of volumetric measurements, length and density to each ECM component within TMEs. Finally, spatial analysis provides an in-depth description of the interplay between cellular components and their adjacent ECM within the TMEs. We apply the pipeline to pre-ICI gastric tumor samples.

Results We demonstrate that computational analysis of ECM in HT images accelerates a comprehensive understanding of TMEs in the context of ICIs. The high-resolution capabilities of HT enable us to detect subtle features within the ECM components, providing valuable insights into its complex and heterogeneous nature. Notably, our framework shows high performance in segmentation of both ECM and cellular structures, providing robustness. The pixel-level results offer valuable insights into the composition and spatial distribution of these components. Our spatial analysis reveals complex patterns in the distribution of the ECM surrounding cells within the TME.

Conclusions We develop TME-IS that facilitates an enhanced insight into the TME based on the integrated segmentation of ECM and cellular structures. Our model is expected to reveal the complex structure of TME, accelerating the interpretation and analysis of TME at subcellular resolution.

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