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Comment

Letter to the Editor: Spatial proximity of tumor–immune interactions predicts patient outcome in hepatocellular carcinoma

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Abstract
We read with interest the study entitled "Spatial proximity of tumor-immune interactions predicts patient outcome in hepatocellular "in Hepatology (Maestri E, Kedei N, Khatib S, et al. in Hepatology 79(4):768–79, 2024). This study utilized highly multiplexed CODEX imaging to comprehensively analyze the spatial interactions between tumor and immune cells in hepatocellular carcinoma (HCC), yielding several meaningful findings and innovatively proposing the concept of the spatial neighborhood of immune cell infiltration and confirming its association with patient prognosis. After reading the article carefully, we have some suggestions to point out.

To the editor:

We read with interest the study entitled "Spatial proximity of tumor-immune interactions predicts patient outcome in hepatocellular "in *Hepatology*in [1]. This study utilized highly multiplexed CODEX imaging to comprehensively analyze the spatial interactions between tumor and immune cells in hepatocellular carcinoma (HCC), yielding several meaningful findings and innovatively proposing the concept of the spatial neighborhood of immune cell infiltration and confirming its association with patient prognosis. This research meticulously quantifies computational imaging and constructs spatial networks (e.g., Voronoi diagrams) to explore cell–cell spatial interactions, particularly the proximity between CD8 + T cells and tumor cells, which has been less explored in previous studies. This method reveals potential communication networks and niches within the TME that are significant for understanding different immunotherapy responses and overall cancer prognosis. Specifically, the proximity between CD8 + T cells and tumor cells emerges as a strong prognostic indicator for patients, providing a new perspective for stratified treatment of liver cancer patients. We completely agree with these valuable and interesting findings. After reading the article carefully, we have some suggestions to point out.

First, the antibody library for CODEX technology is limited, and some markers of interest (such as FOXP3) were not included, limiting the analysis of regulatory T cells and other cell types. In addition, as the authors note, this test requires multiple antibody combinations and may be expensive [2]. Secondly, the study is limited to a single time point of HCC tissue sections, so more examination of the dynamic changes in the tumor microenvironment is needed. Some studies showed that RNA could reflect the dynamic changes in the tumor's immune environment [3]. By detecting pancreatic cancer tissues, Chen K et al. [4] found that there were significant differences in the tumor immune microenvironment of pancreatic cancer in different clinical stages. Compleme-secreting cancer associated fibroblasts (ssCAF) are significantly correlated with the changes in the tumor immune microenvironment, and the level of ssCAF can reflect the changes in the tumor microenvironment. At present, most studies on RNA mainly focus on tumor tissues. Still, in many cases, patients have not undergone surgical resection or

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biopsy, and detecting RNA without tissue samples is challenging. If circulating RNA can be detected from peripheral blood to predict tumor immune microenvironment, it will have vital clinical significance. Thirdly, cell segmentation and phenotype annotation still require manual adjustment, which may introduce bias. Deep learning algorithms are expected to improve the accuracy and scalability of this process [5]. Radiomics has a high value in evaluating and predicting the tumor microenvironment [6], and it can be assessed after patient imaging at no additional cost. Radiomics can also detect spatial relationships in the microenvironment between tumor cells and immune cells [7]. More exciting results may appear if the authors further compare or combine radiomics with highly multiplexed CODEX imaging.

Despite these limitations, this study demonstrates the potential of multiplexed imaging spatial analysis in revealing the characteristics of the HCC immune microenvironment and discovering new prognostic biomarkers. Multiplexed image analysis applies to quantitative analysis of pathology specimens in immuno-oncology [8]. That will help develop individualized treatment strategies for different HCC subtypes. Future studies may further explore the dynamic changes of the immune microenvironment during immunotherapy to further improve the clinical prognosis of HCC patients.

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Data availability "The datasets used and analysed during the current study available from the corresponding author on reasonable request."

Declarations

Ethics statement Not applicable.

Competing interest The authors declare no competing interests.

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