Deep learning reveals valuable clues about kidney cancer in pathology slides

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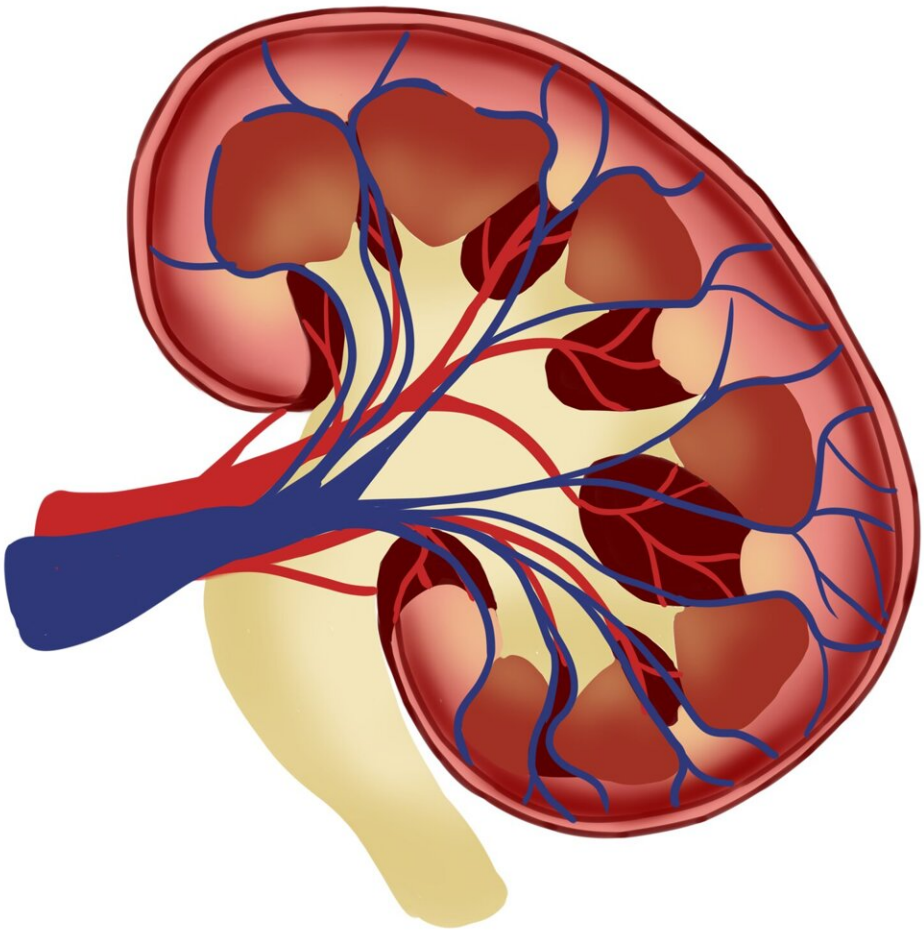

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A team of Dana-Farber researchers has identified a potential new way to assess clinically valuable features of clear cell renal cell carcinoma (ccRCC), a form of kidney cancer, using image processing with deep learning. Their AI-based assessment tool evaluates two-dimensional pictures of a tumor sample on a pathology slide and identifies previously underappreciated features, such as tumor microheterogeneity, that could help predict whether a tumor will respond to immunotherapy.

Their results suggest that pathology slides contain important biological information about ccRCC tumors—and possibly all types of tumors—that could be valuable for understanding more about the biology of the cancer.

The work, which is described in *Cell Reports Medicine*, is part of a broader effort at Dana-Farber to use AI in biologically grounded ways to transform cancer care and cancer discovery.

"This is an example of the growing convergence of AI and cancer biology," says co-senior author Eliezer Van Allen, MD, Chief of the Division of Population Sciences at Dana-Farber. "It represents a major opportunity to measure key features of the tumor and its immune microenvironment at the same time. These measures could help drive not only biological discovery but also potentially guide cancer care."

Renal cell carcinoma is among the 10 most common cancers worldwide. The clear cell subtype (ccRCC) accounts for 75–80% of metastatic cases. Some tumors are sensitive to immune checkpoint inhibitors (ICIs), but so far there are no measures that predict whether a ccRCC tumor will respond to immunotherapy with an ICI.

"We wanted to know what a tumor that responds to immunotherapy looks like," says first author Jackson Nyman, Ph.D., who was a graduate student in Van Allen's lab and is now at PathAI. "Is there anything in the

pathology slide that might give us clues about what is different about the tumors?"

As part of diagnosis, pathologists analyze pathology slides of tumor samples that have been stained to reveal the structures of cells. A routine measure is nuclear grade, which indicates how far tumor cells deviate from normal cells.

Nyman, who collaborated with Van Allen, Dana-Farber pathologist Sabina Signoretti, MD, and Toni Choueiri, MD, Director of the Lank Center for Genitourinary Oncology at Dana-Farber, on the project, first trained an AI model to assess a tumor's nuclear grade. The AI model was not only able to assess nuclear grade, but also to identify differences in grade across a tumor sample.

The finding inspired the team to expand their deep learning model to quantify tumor microheterogeneity and immune properties, such as immune infiltration, across the slide. Tumor microheterogeneity is a measure of how much the nuclear grade varies across the slide. Immune infiltration is a measure of how deeply lymphocytes, the warriors of the immune system, have penetrated the tumor. These measures are possible for pathologists to complete, but far too time-consuming to do routinely.

When they assessed a set of ccRCC pathology slides with their AI model, they saw that some tumors were markedly homogeneous while others had many different nuclear grades in many different patterns. They could also see that in some tumors, lymphocytes were present while others lacked substantial infiltration.

"There was a visual difference in some patient images versus others that had not been obvious before," says Nyman. "We wondered if certain patterns might be predictive of a response to immunotherapy."

To answer this question, the team used the AI-based tool to assess pathology slides of tumors from patients who were part of the CheckMate 025 randomized phase 3 clinical trial. The trial tested monotherapy with an ICI or an mTOR inhibitor in patients with ccRCC who had been previously treated with standard therapy.

They found that features such as tumor microheterogeneity and immune infiltration were associated with improved overall survival among patients taking immune checkpoint inhibitors. The tumors that responded to ICIs had both higher levels of tumor microheterogeneity and denser infiltration of lymphocytes in high-grade regions.

"These signals are hiding in plain sight," says Van Allen. "They are just hard for pathologists to practically measure on individual slides. With AI, we have a scalable way to potentially squeeze a lot more information out of these slides."

The tool is not ready for clinical use, but as a next step, the team is testing it in an ongoing clinical trial involving combination immunotherapy as first-line treatment in patients with ccRCC. The team also plans to explore whether these visual clues in pathology slides are related to molecular features of the tumor, such as alterations in genes.

"The use of deep learning strategies to identify tumor and microenvironmental features from histopathology slides and determine their relationship to molecular and clinical states may have value across tumor types and therapeutic modalities," says Van Allen.

More information: Eliezer M. Van Allen, Spatially aware deep learning reveals tumor heterogeneity patterns that encode distinct kidney cancer states, *Cell Reports Medicine* (2023). DOI: 10.1016/j.xcrm.2023.101189. www.cell.com/cell-reports-medi … 2666-3791(23)00356-7

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