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Most metastatic colorectal cancers have spread before diagnosis, researchers say

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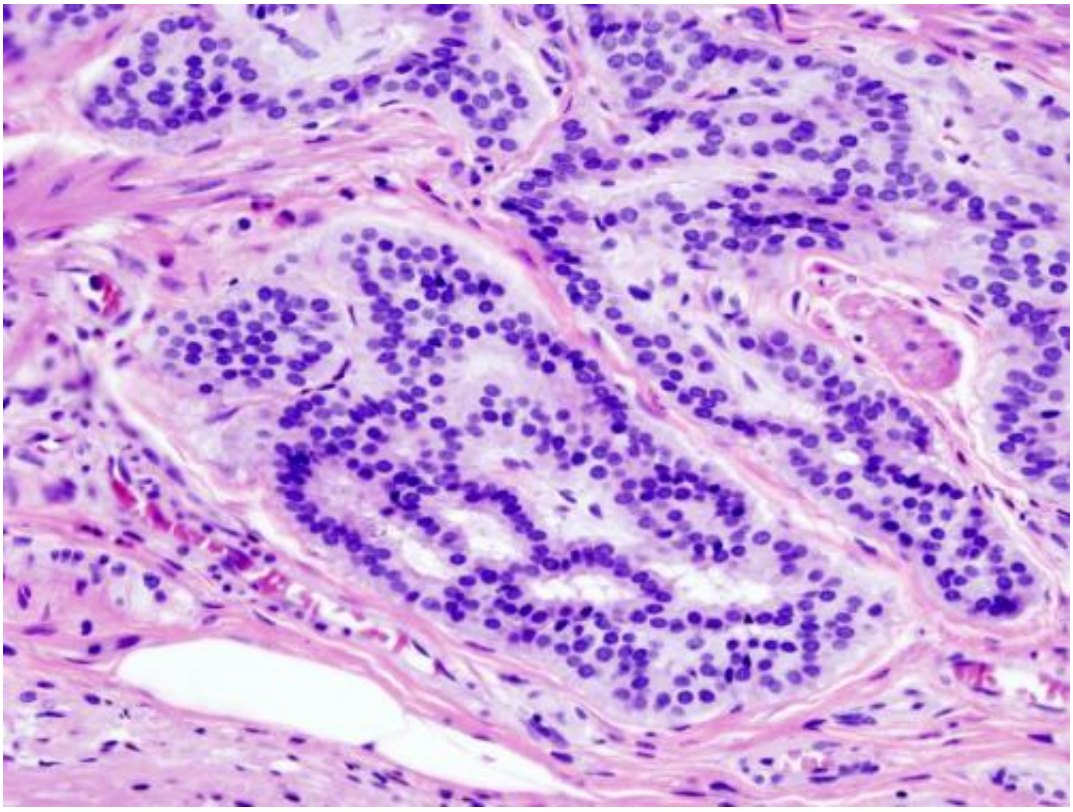

Cancer—Histopathologic image of colonic carcinoid. Credit: Wikipedia/CC BY-SA 3.0

Up to 80% of metastatic colorectal cancers are likely to have spread to distant locations in the body before the original tumor has exceeded the size of a poppy seed, according to a study of nearly 3,000 patients by researchers at the Stanford University School of Medicine.

Identifying patients with early-stage colorectal tumors that are born to be bad may help doctors determine who should receive early treatments, such as systemic chemotherapy, to kill cancer cells lurking far from the tumor's original location.

"This finding was quite surprising," said Christina Curtis, Ph.D., assistant professor of medicine and of genetics at Stanford. "In the majority of metastatic colorectal cancer patients analyzed in this study, the cancer cells had already spread and begun to grow long before the primary tumor was clinically detectable. This indicates that metastatic competence was attained very early after the birth of the cancer. This runs counter to the prevailing assumption that metastasis occurs late in advanced primary tumors and has implications for patient stratification, therapeutic targeting and earlier detection."

Researchers and clinicians have assumed that cancers acquire the ability to metastasize through the gradual accumulation of molecular changes over time. These changes, the thinking goes, confer specific traits that eventually allow cancer cells to escape the surrounding tissue, enter the bloodstream and take up residence in new locations. In this scenario, metastasis, if it occurs, would be a relatively late event in the evolution of the primary cancer.

Curtis, who co-directs the molecular tumor board at the Stanford Cancer Institute, is the senior author of the study, which will be published online June 17 in *Nature Genetics*. Postdoctoral scholar Zheng Hu, Ph.D., is the lead author.

Second-leading cause of cancer death

Colorectal cancer is the second-leading cause of cancer death in men and women combined in the United States. It metastasizes most often to the liver. Rarely, it metastasizes to the brain, where it is almost always fatal.

The initial changes to the genome that cause cancer are called driver mutations. The driver changes that jumpstart colorectal cancer are well-known, making it a good model to learn more about how and when the disease progresses. Curtis and her colleagues sought to reconstruct when metastasis occurred on a patient-by-patient basis and to identify its drivers by analyzing tumor-genome data.

Studying tumor biopsies, the researchers compared patterns of genetic mutations in the primary tumors of 23 patients with the patterns in their liver or brain metastases. They looked for similarities or differences between primary and metastatic cancers obtained from the same person. They then used those patterns to create a kind of evolutionary tree of each patient's cancer—similar to one a biologist might make to trace the evolution of an animal species from a single ancestor.

The trees the researchers pieced together indicated that in 17 of 21 patients (two of the original patients were excluded from the analysis), the metastatic tumors were started by just one cell, or a small group of genetically similar cells, that broke off from the primary tumor early in its development.

"The cells that formed the metastasis were more closely related to the ancestors of the primary tumor than its present-day relatives," Curtis said. "Moreover, the metastasis shared early drivers present in the 'trunk' of the evolutionary tree, but harbored few additional drivers. This suggested that these cancers acquired metastatic competence very early on during their growth."

To further pinpoint when metastasis occurred, Curtis and her team developed a computer program and statistical method to measure the time of metastatic spread relative to the size of the primary tumor in an individual patient. Their analysis provides the first quantitative evidence for early metastatic spread in human colon cancer—a pattern observed

in virtually all cases they examined. However, Curtis noted that not all colorectal tumors will metastasize and that it will be important to also understand cellular processes that keep the cancer from spreading to other organs.

A culprit: Mutated PTPRT

Curtis and her colleagues then took what they had learned and applied it to 938 people with metastatic and 1,813 people with non-metastatic colorectal cancer whose medical histories were known and whose primary tumors had been profiled to identify genetic changes in known cancer-associated genes.

"We found that specific combinations of mutations were highly predictive of metastasis," Curtis said. For example, mutations in a gene called PTPRT, in combination with mutations in classic colorectal cancer driver genes, were almost exclusively found in patients with metastatic cancers.

Previous studies have shown that the loss of PTPRT function increases the activity of a protein called STAT3, which enhances cellular survival. The researchers speculate that inhibiting STAT3 might thwart tumor growth and metastasis.

Curtis and her colleagues are now working to learn whether specific molecular changes tilt the balance of metastasis in colorectal cancers toward the liver or the brain. They are also applying similar analyses to other types of cancers.

"The concept of early systemic spread has been controversial, due in part to the challenge of quantifying this process in the human system and the reliance on animal models," Curtis said. "These data indicate that metastasis can occur early in human colorectal cancer and highlights the

critical need for the earlier detection of aggressive disease. New biomarkers based on specific combinations of alterations might enable the identification of potentially lethal colorectal tumors at an earlier stage so that they may be intercepted and appropriately treated, potentially with therapies directed against their specific aberrations."

More information: Quantitative evidence for early metastatic seeding in colorectal cancer, *Nature Genetics* (2019). DOI: 10.1038/s41588-019-0423-x , www.nature.com/articles/s41588-019-0423-x

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