Model based on liquid biopsies may predict time to progression in colorectal cancer

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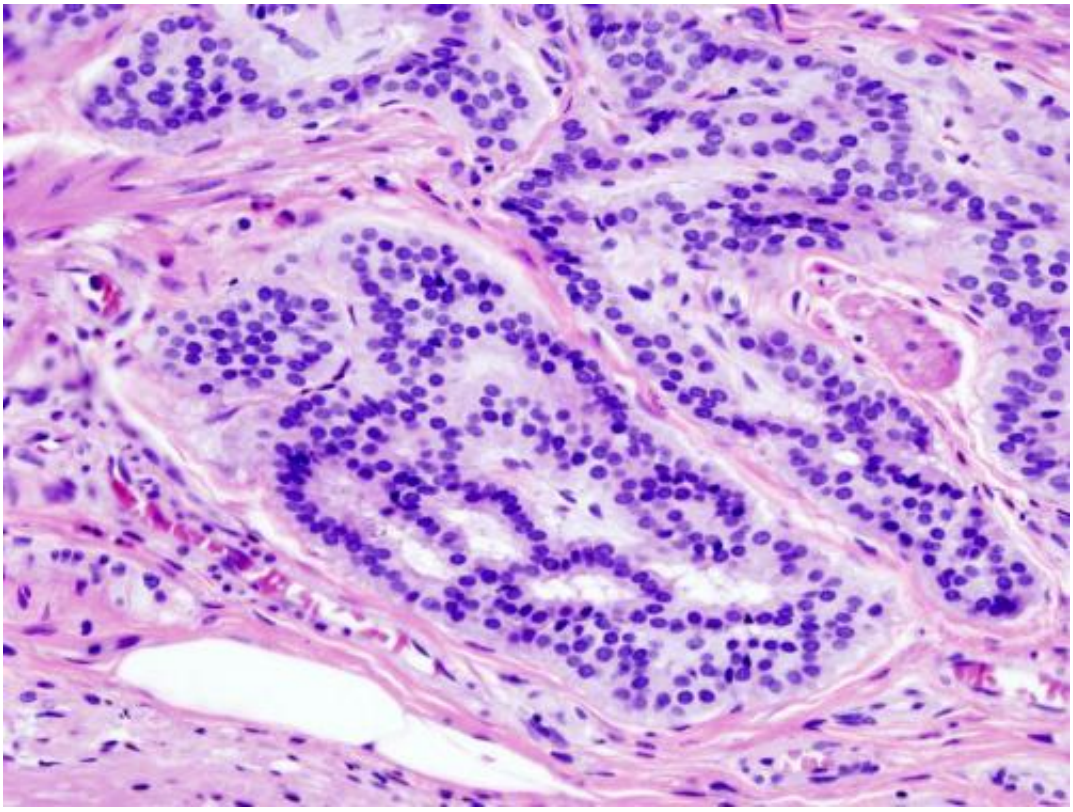

Cancer—Histopathologic image of colonic carcinoid. Credit: Wikipedia/CC BY-SA 3.0

An evolutionary model utilizing serial blood samples from patients with advanced colorectal cancer treated with anti-EGFR therapies in a phase II trial could predict personalized waiting time for progression.

The study is published in *Cancer Discovery*, a journal of the American Association for Cancer Research, by co-senior authors Andrea Sottoriva, Ph.D., MSc, Chris Rokos Fellow in Evolution and Cancer and team leader at The Institute of Cancer Research, London and Nicola Valeri, MD, Ph.D., team leader in Gastrointestinal Cancer Biology and Genomics at The Institute of Cancer Research, London, and consultant medical oncologist at The Royal Marsden NHS Foundation Trust

"By combining frequent longitudinal sampling of cell-free DNA with mathematical modeling of tumor evolution, we were able to make statistical predictions of patients who were at risk of progression," said Sottoriva. "We could also determine when a cancer was going to come back, on a patient-by-patient basis. This is the first time that quantitative forecasting of this sort has been successfully used in cancer."

While clinicians often use tumor biopsies for cancer genotyping, many tumors have intratumor heterogeneity which can drive treatment resistance; therefore, multiple biopsies in time and space are needed to better understand how tumors evolve to resist therapy, explained Valeri.

Liquid biopsies are non-invasive, allowing the collection of circulating tumor DNA at many time points without additional risk to the patient. Furthermore, the analysis of circulating tumor DNA may capture the intratumoral heterogeneity better than a small piece of the tumor, said Valeri.

While much research has focused on the clinical utility of cell-free DNA (cfDNA) for disease monitoring, the use of liquid biopsies as a predictive tool in estimating time to disease progression has not been thoroughly investigated, Sottoriva noted.

The researchers analyzed the results of the PROSPECT-C trial which evaluated biomarkers of both response and resistance to anti-EGFR

therapies in patients with wild-type RAS metastatic colorectal cancer. Tumor biopsies were taken from patients at predefined time points of pre-treatment (baseline) and post-treatment (disease progression), and at partial response in some. Additionally, patients provided plasma samples every four weeks until disease progression.

Even though standard tumor genotyping categorized patients as having metastatic colorectal cancer with wild-type RAS, analysis of baseline cfDNA revealed that many of these patients' tumors had aberrations in RAS proteins, which may explain why they were resistant to cetuximab, an EGFR inhibitor, noted Valeri. Furthermore, ultra-deep sequencing of baseline tumor biopsy cores revealed RAS mutations, further highlighting the limitations of standard methods for tumor genotyping, he added.

Valeri and colleagues generated mathematical models which utilized cfDNA and carcinoembryonic antigen (CEA) levels from individual patients' plasma to predict time to progression. The results were validated using RECIST measurements from radiological imaging data.

The mathematical model utilizing CEA measurements was applied to six patients to predict time to clinical progression. Of these predictions, three were within 10 percent of progression time as measured by RECIST.

Notably, predictions generated with high sensitivity cfDNA profiling allowed for the prediction of progression time several weeks in advance, compared with models utilizing CEA measurements.

With the information garnered from the cfDNA, the researchers could generate multiple models based on the predicted growth of individual subclones driven by different mutations. The accuracy of the models utilizing cfDNA relies on the identification of the dominant subclones in

patients with polyclonal resistance mechanisms, Valeri said.

"Integration of novel monitoring technologies like cfDNA, in combination with mathematical modeling of tumor forecasting, may offer the opportunity to act early, stop therapy, or change treatment to stay one step ahead of the disease," said Valeri. "Our method allows for a more accurate prediction as well as improved monitoring of response to therapy."

Limitations of the study include a small sample size, in addition to focusing on RAS pathway aberrations in the mathematical models, as other genetic and non-genetic determinants will likely cause resistance and disease progression, noted Sottoriva. This model will need to be prospectively validated in future trials, he added.

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