Using Circulating Tumor DNA for Colon Cancer Adjuvant Therapy: To Be or Not to Be?

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SUMMARY

Detection of circulating tumor DNA (ctDNA) postoperatively is prognostic for recurrence for patients with stage III colon cancer. Those with sustained undetectable ctDNA will likely be cured. Eradication of minimal residual disease (per ctDNA clearance) with chemotherapy did not occur in most ctDNA-positive patients and led to eventual disease relapse.

See related article by Henriksen et al., p. 507

In this issue of *Clinical Cancer Research*, Henriksen and colleagues use a highly sensitive methodology for circulating tumor DNA (ctDNA) detection, customized at a $N = 1$ level according to a patient-specific somatic mutation profile, to characterize clinical outcomes for patients with stage III colon cancer who completed curative-intent therapies (1). Their findings contribute important insight as oncologists and patients alike consider how best to incorporate this promising technology as a surrogate for identifying minimal residual disease after resection into the routine clinical management of patients with colorectal cancer.

In short, the goal of multimodality therapies for stage III colon cancer should be to cure as many patients as possible while minimizing or avoiding otherwise unnecessary treatment-related toxicities. Population-based studies have suggested that, while many patients with stage III colon cancer may be cured by surgery alone, adjuvant chemotherapy decreases the risk for cancer-related death and death from any cause (2). While many patients with early-stage colon cancer do achieve cure, the decisions by oncologists for (1) administration of cytotoxic chemotherapy regimens and (2) duration of therapy are often based upon stage of disease and other "high-risk" clinical and pathologic features. Ideally, a validated positive biomarker that is both prognostic (reliably identifies patients at high risk for recurrence) and predictive (reliably identifies those who benefit from adjuvant systemic therapies) could simultaneously spare patients at low risk the otherwise unnecessary toxicity of chemotherapy and remains an unmet need for tailoring treatments for those with locoregional colon cancer.

Here, the authors report retrospectively determined associations between ctDNA profiles and clinical outcomes from 160 patients with resected stage III colon cancer. Use of a multigene ctDNA technique robustly constructed around whole-exome sequencing of the primary colon tumor supports the critical sensitivity for calling detection of minimal residual disease according to ctDNA status. Indeed, in their multivariate analysis, a postoperative ctDNA-positive result outperformed all other examined parameters, including degree of nodal involvement and carcinoembryonic antigen elevation, in prognostication for recurrence risk after surgery. These findings from the authors are consistent with prior series using various ctDNA assays and reinforce the now-accepted notion that risk stratification in identifying those patients with resected colon cancer at the highest likelihood for recurrence is (at present) most reliably determined by a ctDNA-positive status (3, 4).

While patients without detectable ctDNA postoperatively fared better in this series, it is noteworthy that nearly 20% of patients classified as "ctDNA-negative" at the time of their initial postoperative assessment nonetheless recurred. When seeking to detect low absolute ctDNA levels in such patients in accordance with their microscopic foci of remnant tumor deposits, such a false-negative report may have been confounded by higher levels of (nontumor) circulating cell-free DNA, which in turn lowers the variant allele fraction of remnant ctDNA below the current limits of detection (**Fig. 1**).

Indeed, Parikh and colleagues examined a similar population of 70 patients with locoregional colon cancer using a plasma-only ctDNA assay which incorporates profiling of colorectal cancer–specific, multigene somatic mutations and epigenome for determination of ctDNA status (5). In that series, a similar percentage of patients (24%) recurred despite an initial "ctDNA-negative" postoperative result. A consistent theme here is that serial testing for ctDNA in surveillance strategies may improve sensitivity in identifying eventual recurrences. Eventual development of a ctDNA-positive status during long-term follow-up appears to precede the inevitability of clinical and/or radiographic disease relapse.

It is most striking in this retrospective observational series that over 80% of patients with an initial ctDNA-positive postoperative status ultimately developed disease recurrence and were not cured following adjuvant chemotherapy. While sustained clearance of ctDNA in this subgroup (albeit in small numbers) appeared for some patients who remained disease-free, a ctDNA-positive to negative status change was transiently observed (and later reversed) in numerous patients treated with adjuvant chemotherapy who yet still recurred. While the authors do not detail the patterns for recurrence (i.e., local or distant) in these ctDNA-positive patients, it is statistically reasonable to assume they most likely reflect distant metastatic recurrence due to clinically occult, micrometastatic disease dissemination present at the time of initial diagnosis.

On the basis of the authors' findings and given the inherent limitations of the retrospective analysis and observational nature of nonrandomized treatments applied, we cannot assume that all patients

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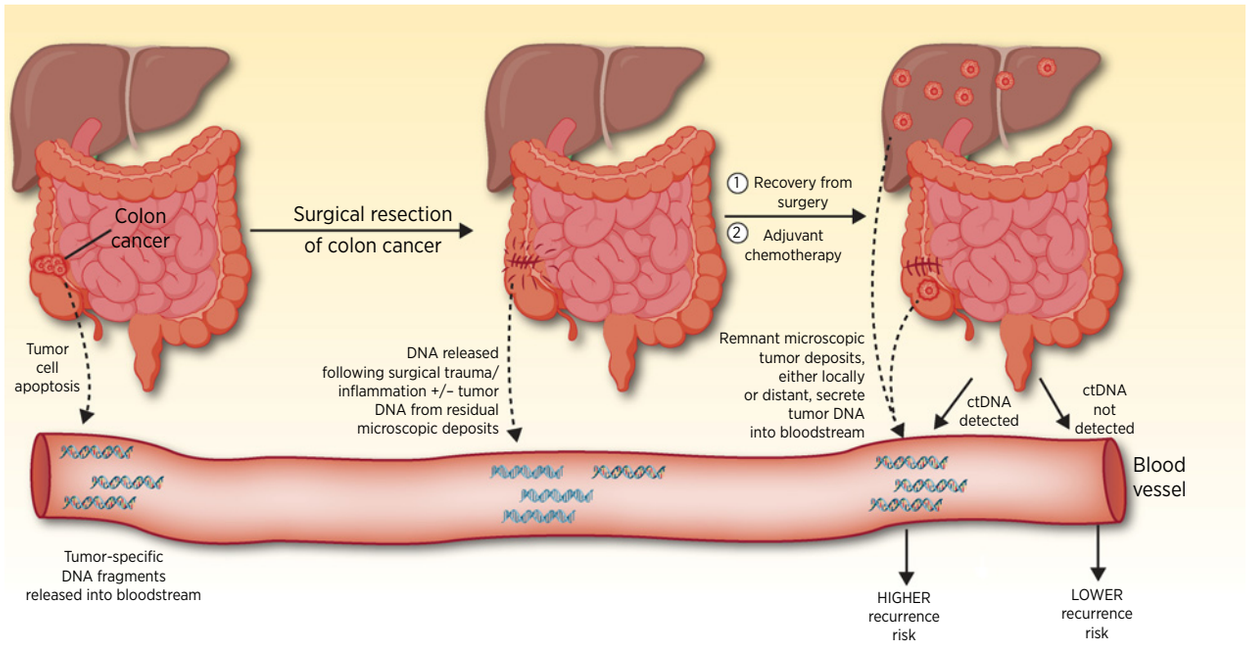

Figure 1.

Sensitivity for detection of low levels of tumor DNA in the bloodstream may be confounded by physiologic processes associated with surgical recovery. When detected, ctDNA is a biomarker prognostic for recurrence and highlights an opportunity for evaluation of novel therapeutic approaches.

with colon cancer at high risk for recurrence following resection, as defined by a ctDNA-positive result postoperatively, definitively or exclusively benefit from receipt of adjuvant chemotherapy. Oncologists must weigh the physical toxicity of chemotherapy on quality of life, the financial toxicities of chemotherapy (on patients and the healthcare system), and the psychological toxicity of a ctDNA-positive result (and the associated knowledge of a nearly inevitable recurrence) in applying ctDNA results toward the decision of adjuvant cytotoxic chemotherapy until more substantiated results justifying its use become available.

While the prognostic power of postoperative ctDNA is now well established, only prospective, randomized phase III clinical trials can provide the much needed level 1 evidence that validates use of ctDNA as a predictive biomarker in patients with early-stage colon cancer. In North America, the NRG-GI005 trial (NCT04068103) is currently enrolling patients with low-risk stage IIA colon cancer and examining ctDNA as a predictive biomarker for both clearance of ctDNA and improvement in recurrence-free survival with use of a fluoropyrimidine/oxaliplatin combination. Likewise, the soon-to-be-activated NRG-GI008 trial will evaluate adjuvant treatment escalation (doublet versus triplet cytotoxic chemotherapy) and deescalation (chemotherapy vs. serial ctDNA surveillance) in patients with stage IIB or stage III colon cancer on the basis of postoperative ctDNA status. Without the necessary data from prospective randomized trials like these and others being conducted around the globe, the utility for ctDNA to predict clinical benefit, counterbalanced by the associated toxicity of treatment, remains unproven and unclear at this point in time.

Another interesting finding reported by the authors includes the heterogeneity in clinical outcomes among the postoperative ctDNA-positive patients according to "slow" and "fast" ctDNA growth-curve kinetics. Here, the authors imply an important point that there may be associated differing tumor biologics among patients with micrometastatic, ctDNA-positive colon cancer. Efforts to better understand the unique biological drivers of micrometastatic colorectal cancer (as defined by a ctDNA-positive status in the absence of otherwise clinically undetectable disease), perhaps distinguished biologically from more evolved, radiographically detectable colon macrometastases, must be applied toward the next generations of clinical trials in this setting.

With their findings, Henriksen and colleagues have contributed substantially to the field and strengthened the need for close monitoring for recurrence through serial evaluation of the ctDNA and for biologically informed trials which account for the diversity of ctDNA-positive patients at high risk for colon cancer recurrence. With impressive performance for ctDNA in prognosticating risk for recurrence, results from prospective trials which validate this technology as a predictive biomarker in informing whether or not patients can be better selected for cure with systemic therapies remain eagerly awaited.

Authors' Disclosures

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References

1. Henriksen TV, Tarazona N, Frydendahl A, Reinert T, Gimeno-Valiente F, Carbonell-Asins JA, et al. Circulating tumor DNA in stage III colorectal cancer, beyond minimal residual disease detection, towards assessment of adjuvant therapy efficacy and clinical behavior of recurrences. Clin Cancer Res 2022;28:507–17.
2. Booth CM, Nanji S, Wei X, Peng Y, Biagi JJ, Hanna TP, et al. Use and effectiveness of adjuvant chemotherapy for stage III colon cancer: a population-based study. J Natl Compr Canc Netw 2016;14:47–56.
3. Tie J, Wang Y, Tomasetti C, Li L, Springer S, Kinde I, et al. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. Sci Transl Med 2016;8:346ra392.
4. Reinert T, Henriksen TV, Christensen E, Sharma S, Salari R, Sethi H, et al. Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer. JAMA Oncol 2019;5:1124–31.
5. Parikh AR, Van Seventer EE, Siravegna G, Hartwig AV, Jaimovich A, He Y, et al. Minimal residual disease detection using a plasma-only circulating tumor DNA assay in patients with colorectal cancer. Clin Cancer Res 2021;27:5586–94.

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