EDITORIAL

# Is the Patient Cured?

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**After administering a therapy** with curative intent, patients and physicians have 1 key question in mind: is the cancer cured? Unfortunately, because of the limitations of our current standard of surveillance, we can never be sure that all the tumor cells have been eradicated and therefore never be sure of a cure. An implication of this view is that even patients who have responded to treatment still need posttherapy prognostic factors to predict the patient's outcome after treatment.

Related article

In this issue of *JAMA Oncology*, Tie et al[1] hypothesized that circulating tumor DNA (ctDNA) level, measured after surgery and again after chemotherapy, can accurately predict which patients with colon cancer are at high risk for recurrence during a 3-year interval. Their prospective study recruited 100 consecutive patients with newly diagnosed stage III colon cancer who were planned to receive 6 months of adjuvant chemotherapy. The investigators sequenced 15 genes that are commonly mutated in colorectal cancer and identified at least 1 somatic mutation in the tumor tissue of each of the 96 eligible patients. Circulating tumor DNA was identified in 20 of 96 postsurgical patients and 15 of 89 postsurgical and postchemotherapy patients. The presence of ctDNA was an independent factor associated with a poor prognosis in both situations. Their hypothesis that ctDNA could accurately predict which patients were, post therapy, at high risk for a recurrence was not well supported by a receiver operating characteristic (ROC) for postsurgical ctDNA of 0.64 (95% CI, 0.60-0.66). However, the ROC increased with the addition of the pT and pN factors to 0.69 (95% CI, 0.65-0.72). Importantly, the postchemotherapy ctDNA ROC was 0.70 (95% CI, 0.66-0.72), which increased with the addition of pT and pN to 0.78 (95% CI, 0.73-0.81). The addition of ctDNA after surgery to this model did not improve its accuracy, suggesting that the ctDNA status after adjuvant therapy is the more relevant prognostic factor.

To our knowledge, Tie et al[1] have performed the first prospective observational study with ctDNA biomarker as a prespecified primary end point. Although there was no validation cohort in this study, this finding replicates results by Tie et al[2] in patients with stage II disease, demonstrating the performance of ctDNA for assessing prognosis after surgical resection. This work builds on prior publications by evaluating the role of adjuvant chemotherapy and demonstrates the consistency of the assay performance after completion of adjuvant chemotherapy.

To their credit, the investigators assessed the ctDNA level after the primary treatment and after the combination of primary and adjuvant therapy[3] and the clinical and ctDNA prognostic factors individually and in combination.[4,5] The stratification by treatment and by factor allows us to observe a treatment-associated change in a factor that may indicate that the patient responded to the therapy.[3] Because a prognostic factor's predictive power arises from its relationship to the disease, the targets of most new therapies are prognostic factors. Furthermore, additivity is important in prognostic factors, because it suggests that the factors are related to different aspects of the disease and therefore contribute orthogonal information.

We can step back and look at where ctDNA fits into the prognostic process. Cancer treatment can be divided into 3 predictions for patients.[6] The first prediction occurs at the patient's initial diagnosis; we predict whether the tumor's natural history at presentation will allow benefit from treatment. This prediction is classically based on prognostic factors, for example, their extent of disease, including tumor size, lymph node involvement, metastases, and tumor location. In the extremes of prognosis, the effect of treatment with curative intent becomes moot. If the patient's natural history is sufficiently favorable, they may benefit from watchful waiting rather than treatment because we predict that they are unlikely to die of their disease.

An early concern of ctDNA-based prognosis was that the presence of detectable ctDNA after surgery might define a population for which there was no benefit from adjuvant chemotherapy and that the natural history would more closely mirror that of patients with radiographically evident metastatic disease. However, the work of Tie et al[1] increases our understanding that indeed there is a subset of patients with ctDNA detectable after surgery who may obtain long-term disease-free status (and, given enough follow-up, presumably a cure) after adjuvant chemotherapy. This is a valuable piece of information that increases the potential utility of this technology.

The second prediction occurs when the patient qualifies for treatment. When the natural history allows the potential for therapeutic intervention, our goal is to predict which therapy will provide the greatest benefit to the patient. To this end, we assess their therapy-specific prognostic factors, which can include demographic, anatomical, and cellular factors and molecular biomarkers. It has been common practice to use natural history prognostic factors to determine patients' primary therapy (surgery and/or radiotherapy) and the need for adjuvant chemotherapy in patients with advanced disease. Since the mid-1970s,[7] biomarker-driven targeted treatments have been added to our clinical armamentarium. For example, in breast cancer, 2 therapy-specific factors are the biomarkers estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2), expression of which predicts a benefit of aromatase inhibitor or antiestrogens or the anti-HER2 antibody trastuzumab. The presence of advanced-stage and microsatellite instability-high/mismatch repair-deficient colorectal cancer predicts which patients will respond to programmed cell death 1 immune checkpoint inhibitor therapy.[8,9] Because ctDNA is a function of tu-

mor bulk but also of other less well-defined variables such as rate of cell turnover and tumor location, it may have properties as a predictive biomarker for disease with differential response to standard adjuvant chemotherapies or experimental therapies not yet defined.[10] Further research is required to define the potential predictive roles of a ctDNA biomarker, which will require larger randomized interventional studies as are currently being planned.

The third prediction occurs once treatment has been administered, either during treatment or on completion of therapy. Circulating tumor DNA has been demonstrated to be an index of treatment response in a number of tumor types, including breast cancer and colorectal cancer. These studies have noted the ability of ctDNA changes to foreshadow radiographic responses, which provide utility for early treatment assessment. Although this possibility was not assessed by Tie et al,[1] one could envision patients with postoperative ctDNA-positive disease being rapidly assessed after 1 or 2 cycles of adjuvant therapy for treatment response, with opportunities to escalate in intensity or planned duration on the basis of suboptimal ctDNA responses.[11] Similarly, we can estimate the patient's prognosis using posttherapy prognostic factors. They include demographic and anatomical or cellular factors and molecular biomarkers. Did a patient respond, and, if he or she did, is there minimal residual disease that requires additional therapy? These posttherapy prognostic factors are becoming an increasingly important therapeutic tool. In addition to this work by Tie et al,[1] ctDNA has been used to assess response to treatment in colorectal cancer[12,13] and in breast cancer.[14]

Time plays an important role in prognosis and treatment. Every prediction and every treatment is associated with an interval; that is, the prediction or treatment is good from the time it is made, or given, until the end of the interval. Furthermore, posttherapy prognostic factors are divided into at least 3 temporal domains, namely, immediate, intermediate, and long-term. For example, prostate-specific antigen is an immediate postsurgical or postradiotherapy prognostic factor, and clinical recurrence is usually a long-term posttherapy prognostic factor. In this context, ctDNA appears to be an immediate posttherapy prognostic factor that can provide a large lead time between detection and clinical recurrence.

Prognostic factors are defined by their use; several factors can be used to predict the same outcome, and a single factor can have several uses. For example, some natural history factors can also predict therapy; patients with ER-positive disease have a good natural history and those with HER2-positive disease have a poor natural history, and both ER and HER2 guide therapeutic decision making. Furthermore, some factors can act as both a therapy-specific and a posttherapy factor. We look for a change in the value of the factor before and after therapy. A change in the factor's value signals a change in the patient's outcome. Finally, therapy-specific and posttherapy prognostic factors can be used in neoadjuvant, primary, and adjuvant settings.

In conclusion, we may be able to use ctDNA to detect the existence of cancer, to determine the cancer site based on cancer-specific mutations, to determine the severity of illness based on the amount of ctDNA, to determine the optimal therapy based on the gene mutations, and, as discussed, to determine response to therapy. In other words, ctDNA is notable for several prognostic uses, and our challenge is to clearly define the utility of the assay in each of these applications, including adjuvant benefit and long-term benefit. Further prospective studies are needed to clearly define the landscape of benefit of this promising biomarker, but the ultimate goal is in sight: answering the age-old question "Is the patient cured?"

## ARTICLE INFORMATION

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