Analysis of circulating tumor DNA: The next paradigm shift in detection and treatment of lung cancer

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Circulating tumor DNA and recurrence.

Central Message

Circulating tumor DNA provides a noninvasive means of diagnosis and surveillance of lung cancer. This evolving technology represents the next paradigm shift in lung cancer care.

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The discovery that specific activating mutations confer sensitivity of lung cancer cells to tyrosine kinase inhibitors ushered in a new era of precision therapy and constituted the first major paradigm shift in the diagnosis and treatment of lung cancer in several decades.^{1,2} The National Cancer Institute-sponsored randomized trial demonstrating that computed tomographic screening reduces lung cancer-specific mortality prompted the second paradigm shift in lung cancer care.³ US Food and Drug Administration approval of immune checkpoint inhibitors as first- or second-line therapy for non-small cell lung cancer was the third major paradigm shift in lung cancer treatment.⁴ More recently, the rapid development of next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) is promoting the fourth paradigm shift in lung cancer care in less than 15 years.⁵⁻⁷

In this issue of the *Journal*, Isbell and colleagues⁸ review the current status of ctDNA analysis in patients with lung cancer. The review is well balanced and highlights results of several leading publications in this rapidly evolving field. The central themes emerging from these studies are that levels of ctDNA vary among patients with cancer of similar tissue histologic type and stage; however, in any given patient with detectable ctDNA, there appear to be good correlations between ctDNA levels and tumor burden, prognosis, and survival. Current data suggest that patients with detectable ctDNA at diagnosis have worse outcomes than those with no detectable ctDNA. Furthermore, patients whose ctDNA levels persist after definitive treatment of their neoplasms are significantly more likely to have early disease recurrence and death than are patients whose ctDNA levels are undetectable after treatment (Figure 1). Molecular progression appears to precede clinical recurrence and progression.

NGS of ctDNA allows the detection of cancer-associated driver mutations, such as *EGFR* or *RAS*, as well as “passenger” mutations that do not impact growth or metastatic

potential of the cancers but are nonetheless useful for disease surveillance. For example, by using cancer-personalized profiling by deep sequencing techniques to monitor disease status in patients with lung cancer after definitive standard-of-care treatment, Chaudhuri and associates⁶ identified driver mutations in 35%, passenger-only mutations in 35%, and both types of mutations in 30% of patients with detectable ctDNA. The presence of detectable mutations during surveillance preceded clinical recurrence or progression by approximately 5 months.

NGS of ctDNA may also reveal actionable mutations not detected by fine-needle aspiration of heterogeneous solid tumors, as well as clonal evolution in response to therapy. Furthermore, NGS of ctDNA may identify cancers with high mutational burdens with the potential to respond to immune checkpoint inhibitors,⁶ and decreases in ctDNA correlate with and precede clinical regressions in lung cancer patients who receive these agents.⁷

One limitation of the existing technology is that ctDNA is not detected in all patients with lung cancer; another limitation is that the amount of tumor required for reliable detection of ctDNA is approximately 10 cm³ at a threshold of 0.1% variable allele frequency.⁵ As such, ctDNA analysis currently is not applicable for use in lung cancer screening, nor can ctDNA analysis reliably establish or exclude the presence of early invasive cancers in ground glass opacities. Theoretically, whole-genome amplification could increase input DNA levels for NGS, but it could also enhance the potential for false-positive sequencing results due to amplification errors.

FIGURE 1. Circulating tumor (ctDNA) levels reflect disease burden and prognosis in patients with lung cancer. The ctDNA levels increase as occult lung cancer progresses, diagnosis is established, and treatment is initiated. In patient 1 (blue line), circulating tumor DNA levels fall below the detection threshold and remain undetectable until tumor recurs. Molecular recurrence (MR) precedes clinical recurrence (CR). Chemotherapy is initiated, at which point circulating tumor DNA levels fall again, indicating a chemosensitive tumor. In contrast circulating tumor DNA levels fall but remain detectable in patient 2 (yellow line), who has more rapid molecular as well as clinical recurrence of a treatment-resistant cancer in the setting of molecular residual disease (MRD).

Although recent studies in high-tier journals are encouraging,⁵⁻⁷ additional, larger prospective trials are necessary to establish the reliability, reproducibility, and accuracy of ctDNA analysis in lung cancer patients. The American Association for Thoracic Surgery and Thoracic Surgery

Oncology Group-sponsored multicenter trial examining the utility of ctDNA as prognostic and predictive biomarkers in patients with lung cancer undergoing induction therapy before surgery is a big step in the right direction.

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