Commentary: ctDNA in Resectable NSCLC: Emerging Canary in the Coal Mine

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Central Message: ctDNA is a promising technology to detect minimal residual disease or early recurrence in resectable NSCLC.

Central Picture Legend: Uma M. Sachdeva, MD, PhD, Assistant Professor of Surgery, Massachusetts General Hospital.

Circulating tumor DNA (ctDNA) is a promising form of blood-based biopsy that can indicate the presence of occult malignant cells in the setting of minimal residual disease (MRD) following curative-intent surgical resection, or for early detection of recurrence after initial clinical or surgical response in multiple cancer types. The use of ctDNA to guide decision-making regarding adjuvant treatment following surgical resection is now standard in colorectal surgery (1). In non-small cell lung cancer (NSCLC), ctDNA has been used to identify actionable mutations and to detect the emergence of resistance in the metastatic setting (2), however its application to earlier stages of disease remains an emerging and important area of investigation.

In the accompanying manuscript, Martin et al. describe the use of a bespoke, tumor-informed ctDNA assay through the commercial company Natera for detection of MRD in an institutional cohort including 108 patients with Stage I or II NSCLC (3). Blood samples were collected and analyzed for ctDNA positivity at 3-month intervals following surgical resection. In this cohort, 4 out of 69 patients had ctDNA detected during the MRD window, within 6 months of surgery, 3 of whom developed confirmed recurrent
disease. Importantly, ctDNA positivity had a median lead time of 28 weeks prior to radiographic detection of disease recurrence. Over the entire follow up period, 10 out of 108 patients demonstrated disease recurrence, 8 of whom demonstrated positive ctDNA, and 7 of whom demonstrated detectable ctDNA prior to radiographic appearance of metastatic disease. All patients with detectable ctDNA underwent earlier PET surveillance, indicating that the presence of ctDNA actively changed surveillance protocols employed.

Taken together, this study provides informative data on the real-world application of ctDNA testing to indicate MRD or predict early recurrence and provides strong data to support further investigation in larger, multi-institutional cohorts with controlled populations. The ongoing TSOG101 trial will provide critical insights, and is currently accruing patients across 29 contributing sites. As the application of ctDNA progresses, the cost of bespoke assays such as the Natera assay will need to be addressed, as this testing is not currently covered by most insurances in this setting. Looking forward, as our knowledge of ctDNA in early NSCLC improves, extensions of this platform will include the use of ctDNA testing as an adjunct to evaluate pulmonary nodules identified on imaging studies, which will be increasingly important in the setting of widespread use of CT scanning and advances in lung cancer screening programs.

References

