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Personalized, tumor-informed, circulating tumor DNA assay for detecting minimal residual disease in non-small cell lung cancer patients receiving curative treatments

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Abstract

Background: Circulating tumor DNA (ctDNA) has emerged as a prognostic and predictive biomarker for detection of minimal residual disease (MRD), monitoring treatment response, and early detection of recurrence in cancer patients. In this study, we explored the utility of ctDNA-based MRD detection to predict recurrence in a real-world cohort of primarily early-stage non-small cell lung cancer (NSCLC) patients treated with curative intent.

Methods: Longitudinal plasma samples were collected post curative-intent treatment from 36 patients with stage I–IV NSCLC. A personalized, tumor-informed assay was used to detect and quantify ctDNA in plasma samples.

Results: Of the 24 patients with plasma samples available during the MRD window (within 6 months of curative surgery and before adjuvant therapy), ctDNA was detectable in two patients. Patients with ctDNA-positivity during the MRD window were 15 times more likely to recur compared to ctDNA-negative patients (HR: 15.0, 95% CI: 1.0–253.0, $p = 0.010$). At any time post-curative intent treatment, ctDNA-positivity was associated with significantly poorer recurrence-free survival compared to persistently ctDNA-negative patients ($p < 0.0001$).

Conclusion: Our real-world data indicate that longitudinal, personalized, tumor-informed ctDNA monitoring is a valuable tool in patients with NSCLC receiving curative treatment to identify patients at high risk for recurrence.

KEYWORDS
biomarker, ctDNA, lung cancer, molecular residual disease, prognosis

INTRODUCTION

Lung cancer is the leading cause of cancer-related death among men and women in the USA, estimated to account for ~21% of all cancer deaths in 2023.[1] Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) represent ~85% and ~15% of lung cancer cases, respectively.

Surgery is the foremost curative treatment for patients with resectable NSCLC.[2] Yet, the recurrence rates post-resection remain high at 30%–50%,[3–5] with median time from surgery to local recurrence of ~14 months and median time to distant recurrence of 12.5 months.[5,6] In patients with unresectable NSCLC, definitive radiotherapy or concurrent definitive chemoradiotherapy (CRT) are the preferred treatment choices.[2] However, nodal and distant metastases present a challenge in this patient subpopulation.[7,8] The current

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surveillance protocol to detect recurrence after the completion of definitive treatment relies on computed tomography (CT) scan of the chest with or without contrast every 3–6 months for the first 2–3 years, and then every 6–12 months for the next 2 years, and annually thereafter.[2] Such radiographic imaging surveillance is limited by low sensitivity due to detection of macroscopic disease. Therefore, new tools are needed to detect minimal residual disease (MRD) after curative treatment during surveillance.

Recent literature has demonstrated the utility of circulating tumor DNA (ctDNA) in assessing MRD and detecting recurrence in several tumor types.[9–12] In this study, we evaluated the performance of longitudinal, personalized, tumor-informed ctDNA monitoring to detect MRD and disease progression in a real-world cohort of stage I–IV NSCLC patients receiving curative treatments.

METHODS

Subjects and study design

In this retrospective, real-world study, a total of 116 plasma samples from 36 stage I–IV lung cancer patients treated with curative intent at Northwestern Memorial Hospital were analyzed. Most ($N = 33$, 91.7%) patients received surgery as definitive treatment, of which one patient with stage IV disease had bilateral lung transplantation performed as a curative measure for lung-limited bilateral invasive mucinous adenocarcinoma.[13] The remaining 8.3% ($N = 3$) received definitive CRT. Data on additional clinical interventions after definitive treatment and clinicopathologic features were collected for all patients. Plasma samples were collected after curative-intent treatment either at a single time point or in a longitudinal setting at the discretion of the treating clinician. MRD window was defined as up to 6 months after curative surgery and prior to the start of adjuvant therapy. For MRD analysis, the inclusion criteria were met when patients had at least one plasma time point available during the MRD window and prior to known radiographic recurrence. Recurrence and treatment response were assessed via standard imaging in accordance with RECIST 1.1. The study was performed in accordance with the Declaration of Helsinki and all patients provided written informed consent. Additionally, this study was approved by the Institutional Review Board Committee of Northwestern University, Chicago, USA (STU00207117).

Personalized, tumor-informed ctDNA assay using mPCR-NGS workflow

ctDNA was detected and quantified using a personalized, tumor-informed ctDNA assay (Signatera bespoke, multiplex PCR-next generation sequencing [NGS] assay, Natera, Inc.) as previously described.[14] Briefly, a set of up to 16 patient-specific, somatic single nucleotide variants (SNVs) were

TABLE 1 Patient and tumor characteristics of the cohort ($N = 36$).

Patient/tumor characteristics	Number of patients (%)
Stage	
I	18 (50.0)
II	5 (13.9)
III	12 (33.3)
IV[a]	1 (2.8)
Age	
<60	8 (22.2)
≥60	28 (77.8)
Sex	
Male	10 (27.8)
Female	26 (72.2)
Smoking status	
Never	12 (33.3)
Former	21 (58.3)
Current	3 (8.4)
Histology	
Adenocarcinoma	26 (72.2)
Squamous cell carcinoma	10 (27.8)
EGFR status	
Mutant	15 (41.7)
Wild-type	20 (55.6)
Not tested	1 (2.8)
PD-L1	
0%	6 (16.7)
<1%	12 (33.3)
1%–49%	14 (38.9)
≥50%	4 (11.1)
Neo adjuvant therapy	
Chemoimmunotherapy	2 (5.6)
Targeted therapy (osimertinib)	1 (2.8)
Curative-intent treatment	
Surgical resection	33 (91.7)
RT ± chemotherapy	3 (8.3)
Adjuvant therapy (alone or in combination)	21[b] (58.3)
Chemotherapy	9 (25)
Targeted therapy (osimertinib)	12 (33.3)
Immunotherapy	2 (5.6)
ECOG PS[c]	
0	16 (44.4)
1	16 (44.4)
2	2 (5.6)
3	1 (2.8)
4	1 (2.8)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; RT, radiotherapy.

[a]This patient had lung-limited bilateral invasive mucinous adenocarcinoma and was included in this study because he had no evidence of disease after double lung transplantation.

[b]Two patients received adjuvant therapy consisting of chemotherapy and subsequent osimertinib.

[c]PS was measured at the time point of precurative treatment evaluation for each patient. In cases where the data was unavailable, the earliest PS assessment conducted after curative treatment was obtained.

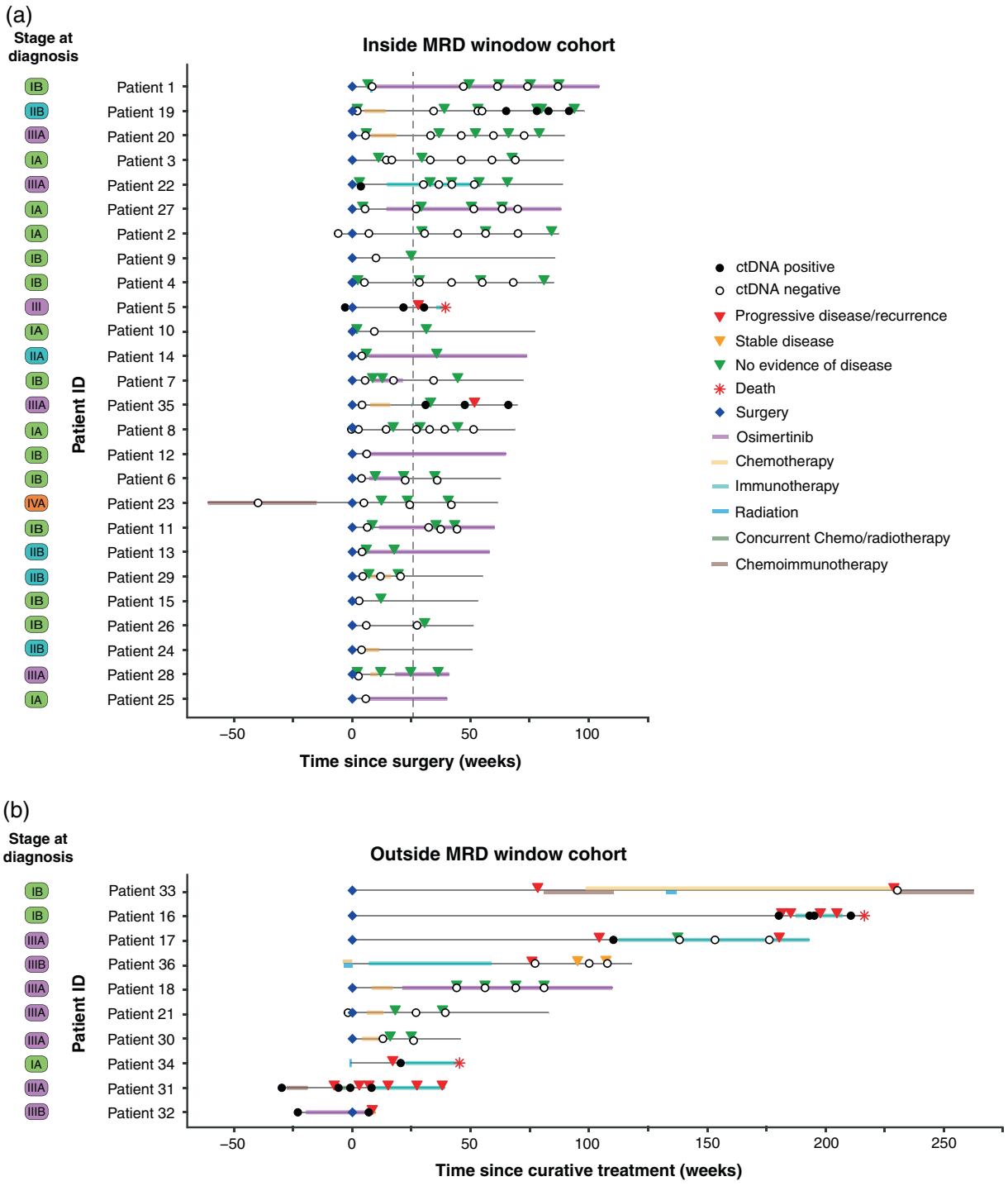

FIGURE 1 Patient overview plots depicting longitudinal ctDNA analysis, treatment regimens, and radiographic imaging results. (a) Cohort within minimal residual disease (MRD) window ($N = 26$). The MRD window, indicated by a dashed line, encompasses the period up to 6 months after curative surgery and before the initiation of adjuvant therapy. (b) Cohort outside MRD window ($N = 10$). Patients in this cohort were analyzed outside the MRD window.

selected from whole exome sequencing (WES) performed on formalin-fixed, paraffin-embedded (FFPE) tumor tissue and matched normal. Primers targeting the patient-specific SNVs were designed, synthesized, and used to detect ctDNA in patients' plasma. Plasma samples with ≥2 SNVs detected above a predefined confidence threshold were considered ctDNA-positive. ctDNA levels were quantified in mean tumor molecules (MTM) per mL of plasma.

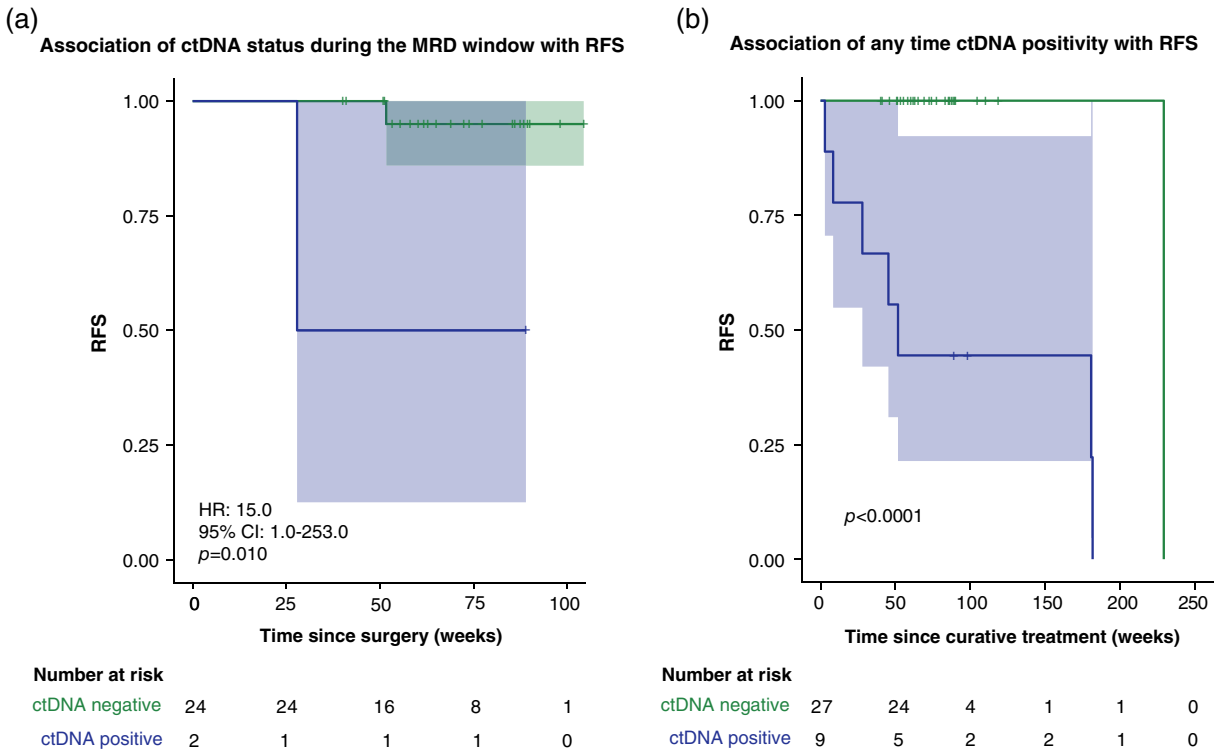

FIGURE 2 Kaplan–Meier analysis of recurrence-free survival (RFS) in stage I–IV lung cancer patients stratified by (a) ctDNA status during minimal residual disease (MRD) window. (b) ctDNA status any time after curative-intent treatment. MRD window was defined as up to 6 months after curative intent treatment and before adjuvant therapy.

Statistical analysis

The primary outcome was recurrence-free survival (RFS), assessed between the date of the completion of curative-intent treatment and the date of radiological findings of recurrence. The Kaplan–Meier method was used to estimate RFS probabilities; a log-rank test was used to estimate *p*-values. Hazard ratios (HR) were obtained from Cox regression analysis. Survival analyses were conducted using R version 4.1.2, with survival, survminer, and coxphf packages.

RESULTS

Patient characteristics

In this cohort of 36 patients with NSCLC, the median patient age was 68.5 years (range: 53–81). Of the 36 patients, 18 (50.0%) patients presented with stage I, 5 (13.9%) with stage II, 12 (33.3%) with stage III, and one (2.8%) with stage IV disease. Tumor histology subtypes included adenocarcinoma ($N = 26$, 72.2%) and squamous cell carcinoma ($N = 10$, 27.8%). The cohort included patients with current ($N = 3$, 8.3%), former ($N = 21$, 58.3%), and no ($N = 12$, 33.3%) history of smoking. Approximately 42% ($N = 15$, 41.7%) of the cohort had epidermal growth factor receptor (*EGFR*) mutations, 55.6% ($N = 20$) were *EGFR* wild-type, and 2.8% ($N = 1$) were not tested. Patient demographics, treatment regimens, and tumor characteristics are summarized in Table 1.

Of the 36 patients, three patients received neoadjuvant therapy (chemoimmunotherapy, $N = 2$, 5.6%; targeted therapy with osimertinib, $N = 1$, 2.8%) and 21 (58.3%) received adjuvant therapy. Adjuvant therapies included chemotherapy ($N = 9$, 25.0%), targeted therapy (osimertinib; $N = 12$, 33.3%), and immunotherapy ($N = 2$, 5.6%). Two patients (5.6%) received chemotherapy followed by targeted therapy with osimertinib as adjuvant therapy. Treatment regimens, longitudinal ctDNA analysis, and radiographic imaging results are depicted in Figure 1.

ctDNA status during MRD window is prognostic of RFS

Of the 36 NSCLC patients, 26 (72.2%) had plasma samples available within the MRD window (MRD cohort; Figure 1a). Compared to patients who were ctDNA-negative ($N = 24$) during the MRD window, those with ctDNA-positivity ($N = 2$) demonstrated inferior RFS and were 15-times more likely to progress (HR: 15.0, 95% CI: 1.0–253.0, $p = 0.010$; Figure 2a). Among the two ctDNA-positive patients, one (Patient 5) recurred 6.3 weeks post ctDNA detection and eventually died (17.8 weeks post ctDNA detection). The other (Patient 22) had ctDNA clearance in response to

atezolizumab and remained disease-free by imaging until the last follow-up (58.9 weeks). Of the 24 ctDNA-negative patients, 23 (95.8%) remained recurrence-free for a median of 67 weeks (range: 40.1–104.4) and one turned ctDNA-positive 20.7 weeks before radiologic progression.

Longitudinal ctDNA status at any time post-curative treatment is prognostic of RFS

In the longitudinal setting ($N = 36$), 9 (25%) patients had detectable ctDNA at any time post-definitive treatment. Compared to patients who were serially ctDNA-negative ($N = 27$), ctDNA-positivity at any time post-curative treatment ($N = 9$) was associated with significantly inferior RFS ($p < 0.0001$; Figure 2b). For example, Patient 16 showed detectable ctDNA approximately 3 years after the curative surgery with consistent increase in ctDNA level during treatment (Figure S1a). The patient had >4-fold increase in ctDNA that correlated with progressive disease by imaging. The patient eventually succumbed to the disease despite receiving immunotherapy and radiotherapy. In four patients who had ctDNA measured prior to imaging, ctDNA detection ranged between 1.2 and 20.7 weeks before radiographic progression.

Of the nine patients with any time ctDNA-positivity, seven patients experienced progression, and one patient underwent ctDNA clearance in response to adjuvant treatment. The remaining patient (Patient 19, Figure 1) was ctDNA-positive at the last four consecutive time points over 28.8 weeks despite showing no evidence of disease on imaging. In this case, ctDNA levels were consistently close to the limit of detection (median: 0.06 MTM/mL, range: 0.04–0.08).

There were two cases where progression was noted via imaging during surveillance, yet no evidence of molecular recurrence was observed. However, one of these patients (Patient 33) had a single time point available immediately after chemotherapy. The other patient (Patient 36) demonstrated radiographic progression after the completion of adjuvant immunotherapy (Figure S1c). However, subsequent scans did not reveal any evidence of progressive disease despite the lack of additional treatment; this case was suspected of pseudoprogression.

DISCUSSION

In this study, we investigated the performance of a personalized, tumor-informed ctDNA assay to detect MRD and disease progression in a real-world cohort of NSCLC patients receiving curative treatments. We demonstrate that ctDNA status during the MRD window as well as at any time point after curative-intent treatment is predictive of patient outcomes.

ctDNA detection post curative-intent treatment has previously been shown to be associated with unfavorable outcomes in NSCLC patients.[15–20] A recent study reported the findings of the LUCID study, wherein, serial ctDNA monitoring was performed in 88 patients with early-stage NSCLC treated with curative-intent surgery ($N = 69$, 78%) or CRT ($N = 19$, 22%).[15] That study reported that ctDNA detection within 2 weeks to 4 months after treatment was associated with shorter RFS (HR: 14.8, $p < 0.00001$) and overall survival (OS, HR: 5.48, $p < 0.0003$), though with a low sensitivity in the longitudinal setting (64%). Another retrospective study performed ctDNA analysis in 40 patients with localized lung cancer (NSCLC, $N = 37$; SCLC, $N = 3$) treated with curative intent (surgery or stereotactic body radiation therapy for node-negative patients; CRT for node-positive patients).[16] That study reported that ctDNA-positivity at the first post-treatment time point within 4 months of curative treatment was associated with worse progression-free survival (HR: 43.4, $p < 0.001$) and disease-specific survival ($p < -0.001$). Further studies have reported similar findings in NSCLC patients receiving either curative surgery,[17,18,21–23] or curative RT/CRT.[19,20] In the present study, we found that MRD detection assessed as ctDNA-positivity within 6 months from the curative surgery in the absence of adjuvant therapy was associated with 15-fold higher risk of disease progression. Additionally, anytime ctDNA detection during surveillance correlated with significantly shorter RFS.

As discussed above, multiple studies have examined the use of ctDNA monitoring as a tool for assessing the risk of recurrence after curative intent treatment for NSCLC. However, no established consensus exists on the ideal timing and frequency of ctDNA testing. The half-life of ctDNA has been reported to range from 16 min to 2.5 h, with a median half-life of 35 min after tumor resection.[17,24] Other studies in lung cancer have evaluated the timing of postoperative MRD monitoring as: 3 days or 1 month in LUNGCA study,[22] from 2 weeks to 4 months in LUCID study,[15] and 6 months in a real-world study in early-stage NSCLC.[25] The MRD assessment window of an ongoing phase 3, interventional trial (MERMAID-2), which aims to evaluate the efficacy of adjuvant durvalumab in patients with NSCLC who are MRD-positive after curative-intent treatment, is 12 ± 1 weeks after surgery.[26] In our study, we considered MRD window as 6 months, which is representative of the real world setting. Our findings demonstrate that monitoring MRD can effectively assess early recurrence in stage I to IV NSCLC patients receiving curative treatments, even at the 6-month time frame or beyond. However, further research is needed to establish the most optimal monitoring interval or timing.

Previous studies reported median lead times from ctDNA detection to radiological recurrence range from 5.2 to 12.6 months among patients with NSCLC treated with curative intent.[18,21] In our study, we found that ctDNA detection in select cases preceded radiographic progression by up to 20.7 weeks. Early detection of recurrence may be crucial for improving prognosis, and ctDNA monitoring could potentially lead to early therapeutic intervention.

Prospective studies will assess the benefit of treatment in ctDNA-positive patients.[26–31] Specifically, the Indiana Trial (NCT05757843) is a phase 2 study designed to investigate the potential of ctDNA testing in personalizing the duration of consolidation durvalumab in patients with stage III NSCLC.[27] Durvalumab will be discontinued after two consecutive negative ctDNA analyses performed ~4 weeks apart, potentially sparing patients from undergoing unnecessary immunotherapy. The phase 2 ctDNA Lung RCT study (NCT04966663) is investigating the efficacy of adjuvant therapy in NSCLC patients with positive ctDNA after curative-intet surgery.[28] Additionally, BESPOKE study (NCT04761783) is a prospective study aiming to evaluate the utility of the personalized, tumor-informed ctDNA assay in guiding immunotherapy in solid tumors such as NSCLC.[29]

A major clinical challenge affecting physicians using ctDNA to complement recurrence surveillance is the interpretation of positive ctDNA results in patients who have not developed radiographic signs of relapse. In our cohort, one patient (Patient 19) was initially serially ctDNA-negative at four consecutive time points, followed by persistent ctDNA-positive at subsequent four-time points over a period of 28.8 weeks. The detected ctDNA levels were consistently close to the limit of detection despite showing no evidence of disease on imaging. We considered the following possible clinical scenarios to explain this case: residual disease suppressed by immune surveillance, or a low-volume or slow-growing residual disease not yet detectable by imaging. Regarding the possibility of immune surveillance, tumor immune surveillance refers to the body's ability to recognize and eliminate cancer or precancerous cells before they can cause harm.[32] After the surgery and adjuvant chemotherapy, the body may establish a more functional immune surveillance system that can effectively suppress any residual or new tumors, resulting in only small amounts of ctDNA being shed. Alternatively, the patient could have a low volume, slow growing tumor, potentially in a location that is difficult to assess via imaging. This could explain the lead intervals of >12 months for postoperative ctDNA detection over radiographic findings that have previously been reported in NSCLC patients.[23] Therefore, the clinical outcome for the patient remains to be determined. The patient is currently receiving active surveillance with multiple imaging modalities.

When progression on immunotherapy is suspected, it is important to distinguish pseudoprogression from true progression. Pseudoprogression is defined as the initial progression followed by a complete or partial response, or stable disease that lasted for more than 6 months.[33] In our study, we had a patient with suspected progression, which was later confirmed as pseudoprogression. The patient initially had radiographic progression after the completion of adjuvant immunotherapy and subsequently showed no evidence of progressive disease on follow-up imaging for 40 weeks, even though no additional treatment was provided. The patient was persistently ctDNA negative, which is consistent with the classification of this case as pseudoprogression rather than true progression.

There are several strengths of this study. Our study illustrated the utility of ctDNA in a real-world setting for MRD detection and surveillance in early/locally advanced NSCLC patients receiving curative treatment. Although the ctDNA data in lung cancer is emerging, our data builds on the existing evidence and highlights the utility of ctDNA testing in a real-world setting, particularly demonstrating its prognostic value during the MRD window and longitudinally post-curative treatment. We also utilized a tumor-informed approach, wherein patient-specific, somatic SNVs were tracked. Limitations of our study include small cohort size, short follow-up, variability in treatment regimens, and variations in the frequency of radiographic scans and ctDNA testing.

In conclusion, this real-world study found that longitudinal, personalized, tumor-informed ctDNA monitoring may be of value in identifying patients with stage I–III NSCLC receiving curative treatments at high risk for recurrence. Prospective studies are warranted to assess whether ctDNA-based MRD status can help clinicians make an informed decision making in early-stage lung cancer management.

AUTHOR CONTRIBUTIONS

Conception and design: Young Kwang Chae, Sumedha Sudhaman, Timothy Riddell, Michael Krainock and Minetta C. Liu. Financial support: N/A. Administrative support: Charuta C. Palsuledesai and Youjin Oh. Provision of study materials or patients: Young Kwang Chae. Collection and assembly of data: Youjin Oh, Sungmi Yoon, Jeeyeon Lee, Joo Hee Park, Soowon Lee, Timothy Hong, Liam Il-young Chung, Sumedha Sudhaman and Timothy Riddell. Data analysis and interpretation: Young Kwang Chae, Youjin Oh, Sung Mi Yoon, Jeeyeon Lee, Sumedha Sudhaman, Timothy Riddell, Charuta C. Palsuledesai, Michael Krainock and Minetta C. Liu.

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CONFLICT OF INTEREST STATEMENT

The authors confirm there are no conflicts of interest.

DISCLOSURES

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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