Brain metastasis is an ominous complication for approximately 50% of patients with advanced NSCLC.\(^1\) Patients with brain metastasis have a poor prognosis, an increased risk of debilitating mental and physical impairment, and a need for local treatment with radiation therapy or surgery. The major obstacle of drug therapy for brain metastasis is the limited penetration through the blood-brain barrier. In recent years, an increase in the incidence of brain metastases has been observed owing to two major factors: (1) the widespread use of magnetic resonance imaging and computed tomography scans in screening the head of patients with advanced cancers and (2) the improvements in local and systemic therapies, particularly for patients with oncogene-driven NSCLCs after receiving effective tyrosine kinase inhibitors (TKIs).

Brain metastases that develop in patients with NSCLC with oncogene-driven tumors, such as gain-of-function EGFR mutations or anaplastic lymphoma kinase (ALK) rearrangements, although receiving first- and second-generation TKIs, such as gefitinib, erlotinib, afatinib, or crizotinib, are less likely to be associated with the development of acquired resistance mutations than the progressive sites of extracranial metastases.\(^2\) This is because first-generation TKIs have a strong extracranial activity but a relatively poor penetration into the central nervous system (CNS). Thus, the tumor cells growing in a “sanctuary site” in the CNS are not exposed to effective concentrations of a TKI and have not gained the acquired resistance to an active dose of that TKI. Isolated intracranial progression is a unique clinical setting in which patients have good extracranial disease control but intracranial tumor progression. For patients who develop isolated intracranial progression on a first- or second-generation EGFR or ALK TKI, switching to a third-generation TKI such as osimertinib or lorlatinib may obviate the need for local therapy and significantly reduce the risk of further CNS progression compared with continuation of the original, earlier generation TKI. With the growing number of effective TKIs, it is important to determine whether the isolated intracranial tumors have specific acquired resistance mechanism(s) or inadequate drug exposure to the molecularly targeted TKI in the “sanctuary” site. In cases in which a more effective TKI is available, the patients can move on to the new treatment and defer the local therapy for brain metastases.\(^3\) As the molecular mutation patterns of brain metastases can be discordant with those of the extracranial primary and metastatic tumors in many patients, it is important to obtain tissue samples from an isolated brain metastasis for assessing molecular resistance mechanism(s). However, it is difficult to perform brain biopsy by means of an invasive procedure.

The clinical application of multiplexed, molecular, biomarker assays has revolutionized cancer diagnosis and treatment, enabling the current era of precision cancer medicine.\(^4\) Currently, broad tumor genomic profiling by next-generation sequencing (NGS) and biomarker-driven cancer treatment have become the standard of care for patients with nonoperable or metastatic NSCLC.\(^5\) Tissue-tumor DNA is the preferred testing material, but these assays have failed in up to 30% of the reported cases, mainly owing to insufficient tumor specimen acquisition.\(^6,7\) Liquid biopsy by
minimally invasive blood draws has emerged as the preferred tissue acquisition method for initial molecular biomarker testing in patients who have insufficient tumor specimens, have inaccessible tumors, or need serial monitoring of biomarker changes and treatment response during their disease course. Genotyping of plasma circulating tumor DNA (ctDNA) has recently received US Food and Drug Administration approval, and genomic profiling of plasma ctDNA has been used increasingly to complement tissue-based genomic assays in precision oncology. The detection of plasma ctDNA in patients with cancer has been associated with high tumor stage, metastasis, and poor prognosis. Alterations in the ctDNA level reflect the dynamic changes of tumor metabolic burden during the disease course. Although the sensitivity of detecting genomic alterations (GAs) and mutation allele frequencies in archived tissue specimens is well known to correlate with the amount and percentage of tumor cells extracted, the sensitivity of detecting GAs in plasma samples is affected by the steady-state level of plasma ctDNA shed by viable tumor cells into the blood, its metabolism in the plasma, and its percentage in relation to the total amount of plasma-cell–free DNA. The sensitivity of different NGS assays using plasma ctDNA at 70% to 82% is similar to that of reverse-transcriptase polymerase chain reaction assays.

In this study, the author determined the clinical utility of liquid biopsy by detecting GAs in plasma ctDNA using an in-house InVisionFirst-Lung NGS assay in patients with oncogene-driven NSCLC and isolated CNS (iCNS) progression. A total of 247 patients with NSCLC with 10 known baseline GAs (EGFR, ALK, BRAF, KRAS, human EGFR2, ROS1, MNNG HOS transforming gene, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, serine or threonine kinase 11, and tumor protein p53) detected on tissue specimens by the NGS assay were selected. Of note, only half of these genes have matched the molecularly targeted therapy. On the basis of the metastatic progression patterns, the patients were divided into three groups, that is, iCNS, extra-CNS only (noCNS), or both (cCNS). iCNS progression was observed in 72%, 23%, and 5% of the patients after the administration of a first-, second-, and third-generation TKI, respectively. ctDNA was found to detect GAs in 52% of the patients with NSCLC having iCNS metastasis, in 84% of the patients with no CNS metastasis, and in 92% of the patients with cCNS metastasis. In 12 patients with NSCLC having iCNS progression, ctDNA was found to detect GAs in six plasma (50%) and 10 cerebrospinal fluid (CSF) (83%) samples. The author also found that there were lower detection rates of driver GAs (37% versus 77% and 73%) and resistance alterations (6% versus 45% and 44%) in patients with iCNS, noCNS, and cCNS, respectively. Serial samples were available for 18 patients in the iCNS group, and seven cases (38.8%) had negative ctDNA at the time iCNS was shifted to positive when the patient had a systemic progression. These data are informative for the management of patients with NSCLC with CNS metastasis and consistent with the author’s knowledge that brain tumors retain EGFR-sensitive mutation sanctuary from extracranial systemic tumor progression and drug treatment.

This study has several clinical implications. First, it confirms that plasma ctDNA assays detect GAs in 50% to 60% of patients with iCNS metastasis and over 80% of patients with extracranial metastasis. Plasma ctDNA level could be used to quantify the systemic tumor burden and assess the prognosis in patients with iCNS progression. Those patients with iCNS disease who have no detectable GA have low or no systemic tumor burden and good prognosis. Plasma ctDNA test might be used to monitor disease progression and select subsequent treatment. Second, CSF ctDNA was an alternative resource for tumor genomic profiling for patients with iCNS metastasis. Of note, only 2 mL of CSF was used in the NGS assay. Currently, most commercially available NGS assays have not been optimized for CSF samples, which might need a smaller volume of CSF and more sensitive ctDNA capture compared with plasma ctDNA assays. Third, iCNS progression was observed in 72%, 23%, and 5% of the patients after administration of a first-, second-, and third-generation TKI, respectively. The frequency of iCNS progression has been decreased by the use of more potent TKIs. Further studies are needed to develop novel drugs with improved CNS penetration to prevent and treat iCNS metastasis.

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