Expert Perspectives

The Revised NCCN Guidelines for Non-Small Cell Lung Cancer

Expanding Screening Options with Liquid Biopsies

Liquid biopsies represent one of the most exciting recent advances in the screening of non-small cell lung cancer (NSCLC). Many patients have distinct biomarkers that can make them optimal candidates for current and emerging targeted therapies. Tissue biopsies have long represented the standard for diagnosing patients and screening for biomarkers. However, these biopsies can be invasive and clinicians often fail to collect enough tissue to screen patients for biomarkers after the initial diagnosis.

"Get as must tissue as you can," said Philip D. Bonomi, MD, the Alice Pirie Wirtz Professor of Medical Oncology in the Department of Internal Medicine at Rush Medical College. "You did a biopsy and made a diagnosis? That's great, but it isn't enough. You are doing a disservice to the patient because they might miss out of a therapy that could extend their life for a number of years."[1]

Liquid biopsies (also known as plasma biopsies or plasma genotyping) may offer an alternative screening method for some patients. Tumor DNA can be analyzed from a simple, noninvasive blood test instead of taking tissue directly from a patient's tumor. The NCCN Guidelines have recently been updated to encourage the use of liquid biopsies in cases where tissue biopsies may not be feasible. There are a number of current technologies that enable liquid biopsies, including those based on circulating tumor DNA (ctDNA), whole circulating tumor cells (CTCs), and circulating exosomes. The FDA recently approved a technique taking advantage of circulating free DNA (cfDNA) in EGFR mutation analysis that has already been successfully used in clinical studies.[2]

"[Liquid biopsies are] minimally invasive; you can do it on everybody," Bonomi said. "If people have bad performance status, or a difficult area to biopsy where you can't get enough issue, it is useful. Also, it can be done repeatedly so you can follow patients with it. There are many advantages." [1]

Being able to continually monitor patients may be especially important for biomarkers that can change throughout the course of treatment. For example, sudden resistance to EGFR TKI therapy is frequently accompanied by the development of a mutation in exon 20 of the EGFR gene that creates a mutant T790M protein. Monitoring patients for the development of this mutation could help signal when to switch to a new therapy, such as osimertinib, which targets the T790M in addition to more common EGFR mutants.[3]

In fact, the NCCN Guidelines recommend liquid biopsies as a screening option for the EGFR T790M mutation. A recent study found that the noninvasive test had a 70% sensitivity for detecting T790M and successfully detected the

mutation in 31% of 58 patients.[4] Another study found a rapid plasma genotyping method to have a 79% predictive value for the T790M mutation.[5] Additional studies have demonstrated that liquid biopsies can be similarly effective at detecting additional EGFR mutations and unrelated biomarkers in a range of patients.[5-7]

Liquid biopsies may be especially helpful for instances where clinicians need quick results and cannot rely on standard tissue biopsies due to tumor location, size, or even previously collected samples that have deteriorated too far for accurate results.[8]

"I routinely see patients where I need a result today and the tissue I have available is not adequate for getting me genotyping." said Geoffrey R. Oxnard, MD, from Harvard Medical School. "That's where I think of liquid biopsies or noninvasive testing as an alternative."[8]

However, liquid biopsies are not equally accurate across all types of tumors. Existing studies suggest that tests are more effective in more advanced cancer when there may be more evidence of the tumor circulating in the patient's blood stream.[4-5, 8]

"When I'm thinking about who to [conduct] a liquid biopsy on, the question that I am asking for an individual patient is 'does their cancer shed DNA?'" said Oxnard. "We are looking for DNA that is effectively a needle in a haystack. The haystack being all of the patient's [DNA and] the needle being the tumor DNA floating around there."[8]

Consequently, negative liquid biopsy results can sometimes be falsely negative, especially in patients in earlier stages of cancer. The NCCN guidelines therefore still recommend tissue biopsies when feasible after negative liquid biopsy results.[4-5, 9]

The Future of Liquid Biopsies

Liquid biopsies are currently a useful tool in the screening and management of NSCLC patients, and their future potential is very promising. The first major step for improving the technique likely involves increasing their accuracy and effectiveness.

Once these techniques are able to provide accurate readings in earlier stages of cancer and fewer false negative results, their applications are almost limitless. Oxnard along with Sandip Patel, MD, from the UC San Diego Moores Cancer Center recently reflected that the biopsies could be used to select targeted treatment plans for patients, continuously monitor patients for new mutations, monitor for cancer progression after surgical resection, or even diagnose cancer in its earliest stages.[10-11]

“There is potentially even a role for these assays in cancer prevention,” Patel said. “[For example,] early detection of cancer polyps and lung nodules such that we can intervene in a patient’s favor even before these can be detected by imaging.”[10-11]

References

1. Welch A. Standard Biopsies Retain Significant Role in Lung Cancer Care. http://www.onclive.com/web-exclusives/standard-biopsies-retain-significant-role-in-lung-cancer-care. October 3, 2017. Accessed October 31, 2017.
2. Perakis S, Speicher MR. Emerging concepts in liquid biopsies. BMC Med. 2017 Apr 6;15(1):75.
3. ESMO 2017 Press Release. Osimertinib Improves Progression-free Survival in Patients with EGFR Mutated Lung Cancer. http://www.esmo.org/Conferences/ESMO-2017-Congress/Press-Media/Press-Releases/Osimertinib-Improves-Progression-free-Survival-in-Patients-with-EGFR-Mutated-Lung-Cancer. September 9, 2017. Accesssed October 17, 2017.
4. Oxnard GR, Thress KS, Alden RS, et al. Association between plasma genotyping and outcomes of treatment with osimertinib (AZD9291) in advanced non-small-cell lung cancer. J Clin Oncol 2016;34:3375–3382.
5. Sacher AG, Paweletz C, Dahlberg SE, et al. Prospective validation of rapid plasma genotyping for the detection of EGFR and KRAS mutations in advanced lung cancer. JAMA Oncol 2016;2:1014–1022.
6. Gray JE, Okamoto I, Sriuranpong V, et al. Osimertinib vs SoC EGFR-TKI as first-line treatment in patients with EGFRm advanced NSCLC (FLAURA): Plasma ctDNA analysis. Presented at: the IASLC 18th World Conference on Lung Cancer; October 15-18; Yokohama, Japan. Abstract 8978.
7. Nam J. Liquid Biopsies Detect Unknown Driver Mutations in Advanced NSCLC. http://www.cancertherapyadvisor.com/iaslc-2017/lung-cancer-nsclc-liquid-biopsy-unknown-driver-mutation/article/701193/. October 18, 2017. Accessed October 31, 2017.
8. Oxnard GR, Patel S. The Role for Liquid Biopsy in NSCLC. http://www.onclive.com/insights/liquid-biopsy-nsclc/the-role-for-liquid-biopsy-in-nsclc. September 6, 2017. Accessed October 31, 2017.
9. Ettinger DS, Wood DE, Aisner DL, et al. Non-Small Cell Lung Cancer, Version 9.2017, NCCN Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. September 28, 2017. Accessed October 15, 2017.
10. Oxnard GR, Patel S. Future Directions for Liquid Biopsy in NSCLC. http://www.onclive.com/insights/liquid-biopsy-nsclc/future-directions-for-liquid-biopsy-in-nsclc. September 6, 2017. Accessed October 31, 2017.

11. Oxnard GR, Patel S. Liquid Biopsy for NSCLC: Emerging Developments. http://www.onclive.com/insights/liquid-biopsy-nsclc/liquid-biopsy-for-nsclc-emerging-developments. September 6, 2017. Accessed October 31, 2017. .