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Precision medicine in non–small cell lung cancer in comparison pathology and biomarker interpretation

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Abstract
Non–small cell lung cancer (NSCLC) has become a prominent example of precision medicine among solid tumor malignancies. Clinical management of NSCLC now depends on surgical, chemotherapeutic, and radiation treatment regimens based on pathologic findings and clinical staging as well as targeted therapies based on molecular profiling. As molecular testing becomes increasingly important, preserving tissue for this purpose while rendering an accurate histological diagnosis becomes a key consideration, particularly in advanced-stage NSCLC, in which small biopsy samples or aspirates are often the only specimen available. Next-generation sequencing panels are a powerful method of providing information relevant for both standard-of-care and investigational treatment options. However, taking advantage of the abundance of information gleaned from these panels requires careful annotation, prioritization, and reporting of molecular findings and their clinical significance. Although molecular profiling has traditionally relied on direct sampling of neoplastic tissue, blood-based diagnostics now offer the potential to provide some clinically useful information noninvasively.

Keywords: cancer, annotation, medicine, diagnostics, pathology

Introduction

Although tissue biopsies play a key role in NSCLC care and have a range of purposes, blood-based diagnostics in some instances offer the potential to noninvasively provide similar, clinically useful information. The management of lung cancer, particularly NSCLC, has evolved tremendously over the last 15 years. Among solid tumor cancers, NSCLC management has become a prominent example of precision medicine. Clinical management of NSCLC now depends on pathologic findings, clinical staging, and molecular profiling. Although early-stage disease is largely treated surgically (with or without adjuvant chemotherapy and/or radiation), targeted therapy based on molecular findings is the preferred treatment option for metastatic NSCLC when a targetable alteration is present. Molecular profiling has traditionally relied on direct sampling of neoplastic tissue. However, blood-based diagnostics may provide similar information by using noninvasive testing. Increasingly, pathologists view the approach to classification of pulmonary lesions as distinct according to the type of sampling procured. The approach to small samplings, such as fine-needle aspiration, bronchoscopic biopsy, and endobronchial ultrasonography–guided fine-needle aspiration, is markedly different from how a pathologist begins to assess a resected specimen [5].For example, the finding of squamous carcinoma on a small biopsy sample does not exclude the possibility that this represents a partial sampling of an adenosquamous carcinoma, which has a probability of targetable alterations similar to that of adenocarcinoma[6] This is of particular and growing importance: Small samplings are often the only tissue specimens procured from patients with advanced-stage NSCLC because they will likely not proceed to surgical resection. Importantly, balancing the needs to fully classify the lesion with the need to preserve material for molecular and other biomarker testing has become a paramount consideration in the daily workflow for pathologists who manage these small specimens.

Classification of Tumors

The overriding goal of pathologists should be to define, whenever possible, the histological type of tumor present in a sample deemed to be malignant. In resection samples, the availability of abundant materials can make this more straightforward; however, in small samplings, extensive characterization by IHC or other modalities can interfere with preserving tissue for molecular characterization for therapeutic decision-making. The WHO classification divides epithelial tumors first and foremost into NSCLC and small cell lung cancer. This is largely a historically derived nomenclature; in 1926 Barnard published findings suggesting that "oat cell carcinoma," as it was then known, should be considered a bronchogenic carcinoma rather than a lymphomatous or sarcomatous lesion as had been previously thought. As the study of lung tumors advanced, it became clear that this type of tumor was distinct from other lung tumors, leading to this classification of "small cell carcinoma" and "non–small cell carcinoma," which remains in use today. NSCLC collectively describes numerous epithelial-derived tumors, of which the two most common histologic types are adenocarcinoma and squamous cell carcinoma. Other histologic types are varied and typically rare, such as large cell carcinoma, pleomorphic carcinoma, and salivary gland–like tumors of the lung. Proper identification of the appropriate histologic type is important because it affects prognosis and,

in many cases, therapy selection as well as considerations for molecular testing. An important change in the reporting of invasive adenocarcinoma is the recommendation to include characterization of the histologic subtypes, which include lepidic, acinar, papillary, solid, and micropapillary and may correlate with histologic grade. The recommendation has been made to characterize lesions according to the predominant subtype and estimate the percentage of various subtypes in 5% increments. There is some evidence that the tumor subtype may be associated with prognosis in patients with early-stage resected disease, with the presence of higher-grade histologic types (micropapillary and solid) being associated with a higher incidence of occult lymph node metastases. In clinical practice, however, the predominant subtype of adenocarcinoma does not currently affect therapy decisions, and the clinical application of determining subtype has not been established in advanced-stage disease.

Up Staging

Key differences between the two versions include an additional tier of early-stage disease (T1c), reclassification of lesions greater than 5 cm but 7 cm or less in greatest dimension as T3 (instead of T2), and reclassification of tumors greater than 7 cm in greatest dimension as T4 (instead of T3). These and other revised staging criteria have become incorporated into routine practice, but some of the changes, particularly in synoptic reporting, may be unfamiliar to practicing oncologists. For example, spread through air spaces is now an optional component of the pathologic staging synoptic report, and its presence portends a higher risk for recurrence in tumors treated with limited resection. Another substantial change in the staging system includes separate measurements of invasive and lepidic components in adenocarcinoma. An additional area addressed directly in the new staging approach is classification of multifocal disease for the consideration of separate primary tumors versus intrapulmonary metastases, using a predominantly histologic-based approach.

Growing evidence suggests that molecular testing can be a useful approach to determining the clonal relationship between multiple tumor nodules.

Specimen Management

Histologic processing of biopsy samples is typically accomplished in 1 business day, allowing for a preliminary assessment of a sample on the following day. IHC staining can add 1 to 3 days or more to total assessment time, particularly if staining is done in stages to minimize tissue use for classification. Often, molecular testing is not initiated until the histologic assessment is complete, in case material is needed for additional IHC. Of particular note in the recently updated guidelines for the testing of NSCLC is the option to use cytopathology specimens other than cell blocks, such as smear preparations or touch preparations [3] Increasingly, molecular laboratories are validating this specimen type to increase patient access, shorten turnaround time, and reduce the need for repeat biopsies to successfully perform molecular studies in patients with NSCLC.

Molecular Biomarkers in NSCLC

Association for the Study of Lung Cancer, and Association for Molecular Pathology recommend evaluation of *EGFR*, *ALK*, and *ROS1* on all patients with lung cancer patients who have metastatic nonsquamous disease, irrespective of clinical characteristics.[3] These guidelines do not recommend other genes, including *BRAF*, *KRAS*, *RET*, *ERBB2* (*HER2*), and *MET*, as routine stand-alone assays outside the context of a clinical trial; however, in the United States a combination therapy is approved for patients with NSCLC who have *BRAF* p.V600E mutation, which may raise the impetus to consider a stand-alone assay for this target. Of note, multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond *EGFR*, *ALK*, and *ROS1*. For laboratories performing next-generation sequencing (NGS), it is recommended that *BRAF*, *KRAS*, *RET*, *ERBB2*, and *MET* be included. Panels often include targets without immediate clinical utility based on the possibility that such information may be useful in the future. As the volume of data from NGS testing grows, so does the challenge of separating findings that are clinically meaningful and prioritizing their clinical utility. Molecular pathologists—in collaboration with their oncology colleagues—are tasked with evaluating this abundance of data, distilling down to what is clinically relevant, and communicating this information in the most cogent and manageable manner possible. A general algorithm for NGS data analysis can be illustrated as in Fig.1.

Biopsy Versus Liquid Biopsy

The fundamental role of pathology in lung cancer care is inherently tied to a fundamental role for tissue biopsies. However, the invasive nature of tissue biopsies has led to interest in noninvasive ways of obtaining the same information. Such noninvasive blood-based diagnostics are sometimes termed “liquid biopsies.” Although a range of blood-based diagnostics are being studied, the best-established and most widely used technologies study free-floating DNA within the plasma (cell-free DNA [cfDNA]) [38]. This represents an intuitive extension of tumor analysis wherein DNA-based biomarkers represent some of the most transformative diagnostics in the care of NSCLC. Here we review the various roles that biopsies play in lung cancer care and the potential for plasma cf DNA genotyping to serve as an alternative.

Diagnostic Biopsy

The initial diagnostic biopsy is essential in that it establishes the diagnosis of malignancy and allows for histologic typing, as discussed previously. Patients and oncologists both rely on the certainty of a pathologic diagnosis when planning cancer care and are reluctant to initiate cancer treatment without it; thus, it is a type of biopsy that noninvasive methods may never come to replace.

It must be acknowledged, however, that there are instances where comorbidities preclude biopsy and treatment must be considered based upon a presumed diagnosis of lung cancer. For example, radiotherapy is at times performed on early-stage lung cancer in the absence of pathologic proof, an approach that comes with some risk for overtreatment. One could similarly envision scenarios where a patient presents with a lung mass and metastases to bone, brain, or liver and

the patient is too ill for a diagnostic biopsy.
If plasma genotyping in that instance detected a mutation that is largely pathognomonic for lung cancer like (e.g., an *EGFR* mutation or *ALK* fusion), one could consider empirical targeted therapy for presumed lung cancer. But in such a case, pathologic confirmation should still be pursued should the patient's condition improve.

The Staging Biopsy
In planning curative therapy for lung cancer, staging biopsies, such as mediastinal lymph node biopsies or biopsies of suspected metastatic sites are routine. Because staging imaging studies (PET, MRI) are imperfect, biopsies are a common supplement. For example, in a patient with an isolated rib lesion on PET, fine-needle aspiration of the bone lesion can confirm metastatic disease and inform prognosis. Plasma genotyping could eventually play a similar orthogonal role in evaluating for the presence of disease spread.

The Biopsy to Assess for Residual Disease
Neoadjuvant therapy is one of several standard management strategies in planning multimodality therapy for locally advanced NSCLC.
One reason neoadjuvant therapy is attractive is that it permits the testing of the resection specimen for degree of pathologic response. Many studies have now shown that a major pathologic response, defined as at least 10% residual viable tumor in resected lung and lymph node tissue, portends a much better postoperative prognosis, whereas the presence of greater than 10% residual tumor confers a higher risk for recurrence. Plasma cfDNA genotyping may also offer an opportunity for detection of residual active cancer, as initially shown in a prospective cohort of 230 patients with resected stage II colon cancer, where the 8% of patients with detectable tumor mutations in plasma cfDNA postoperatively had a dramatically worse recurrence-free survival

The Recurrence Biopsy
Cancer recurrence after attempted curative therapy is a dramatic moment for a patient with lung cancer because recurrence often indicates that their cancer is no longer curable. Given the seriousness of lung cancer recurrence, biopsy to pathologically confirm recurrence is standard for patients more than 6 to 12 months out from curative therapy. As discussed above for diagnostic biopsies, a noninvasive assay in some cases might serve as an alternative in patients with lung cancer too sick to undergo a recurrence biopsy.
This would make the most sense in patients whose definitively treated lung cancer was known to harbor a pathognomonic lung cancer genotype (e.g., an *EGFR* mutation or *ALK* fusion).
If this variant were detected in plasma at time of suspected recurrence, a trial of targeted therapy could serve as an alternative to biopsy, confirming recurrence.
Similarly, if the pretreatment genotype is known, the presence of those markers could serve a similar purpose, although caution is warranted if the alteration is common to multiple malignancies (such as *KRAS* or *TP53* mutations).

The Biopsy for Genotyping
It is well established that diagnostic lung cancer biopsies are frequently inadequate for the range of molecular studies now needed for treatment decisions, such as PD-L1 IHC and NGS. The diagnostic specimen may be small and much of the tissue could be exhausted during the performance of necessary studies to determine the diagnosis and histologic subtype. For this reason, a repeat biopsy is commonly required to permit complete molecular testing. Plasma cfDNA genotyping is an intuitive noninvasive option for such patients who are planning an additional biopsy. In 2016 the FDA approved the first plasma cf DNA genotyping assay for detection of *EGFR* mutations in patients with NSCLC who did not have tumor tissue available for genotyping. Furthermore, broader genotyping of a range of oncogenic drivers in cfDNA is now possible with commercially available plasma NGS technologies. Still, the sensitivity of plasma genotyping for driver mutations present within the tumor is only in the range of 60% to 80%. This means that negative plasma genotyping results must reflex to a biopsy for tumor genotyping. In some cases, it may be worth concurrently scheduling a biopsy procedure while waiting for plasma genotyping results because this shortens the time interval to molecular testing in the event of a negative plasma genotyping report.

Résistance Biopsy
Biopsies for genotyping of lung cancer drug resistance have more recently emerged as a standard of care since the FDA approval of osimertinib for *EGFR*-mutant lung cancer and acquired drug resistance mediated by a specific resistance mutation, *EGFR* p.T790M [54] And yet, such resistance genotyping has long been used for clinical trial enrollment given the range of potentially targetable resistance mechanisms in *EGFR*-mutant lung cancer [55] Furthermore, such resistance biopsies are increasingly common as targetable resistance mechanisms can be seen with other targeted therapies, such as *ALK* and *MET* inhibitors. The convenience of plasma cfDNA genotyping makes it an ideal technology for testing for many of these resistance mechanisms, such that it is now an established standard for *EGFR* p.

Conclusion
Precision medicine is exemplified by NSCLC in which management is tailored based on pathologic findings, clinical staging, and molecular profiling. Next-generation sequencing panels enable molecular profiling that includes information relevant for both standard of care and investigational treatment options. Taking full advantage of this abundance of information requires careful annotation, prioritization, and reporting of molecular data. Preserving tissue for molecular testing while rendering, an accurate histologic diagnosis has also become a key consideration for pathologists and oncologists. Blood-based diagnostics now offer the potential to also provide clinically useful information noninvasively.

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