Lung Cancer: Tumor Subclassification and Use of Predictive Markers

Tumor Subclassification

Non-small cell lung carcinoma (NSCLC) accounts for approximately 80% of lung cancers and for approximately 20% of all cancer-related deaths in North America. Most patients with NSCLC present with advanced disease that is not amenable to surgery; in these situations, chemotherapy can be beneficial.

In the past, patients with all subtypes of NSCLC received the same treatment. However, with the introduction of newer biologically targeted chemotherapies, it has become clear that differentiating between squamous cell carcinoma (SCC) and adenocarcinoma (ADC) within the broad category of NSCLC is important in predicting response to specific chemotherapies and for determining the risk for uncommon but potentially fatal pulmonary hemorrhage in patients with SCC treated with bevacizumab. Moreover, the ADC subtype predicts better response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, although EGFR mutational analysis is required for this identification.

As shown in a 2010 publication from this laboratory (Terry et al. Am J Surg Pathol 34: 1805-1811, 2010), the application of antibodies to p63, TTF-l, CKS, CK7 and NapsinA can be useful in the separation of ADC from SCC. The numbers of antibodies that need to be employed for this distinction range from two to four according to most published studies. Small cell lung carcinomas (SCLC) need to be discriminated from NSCLCs, and the neuroendocrine marker, synaptophysin, is most helpful in this regard.

	p63	TTF-1	CK5	CK7	NapsinA	Synaptophysin
Adenocarcinoma						
Squamous cell carcinoma						
Small cell lung carcinoma (neuroendocrine)						

Heatmap content available in the printed Pathology Reference Guide

Almost always positive	Usually positive	Not helpful	Usually negative	Almost always negative

See introduction to heat maps page 15

Use of Predictive Markers

New molecular-based treatments for NSCLC, particularly the adenocarcinoma subset, have been developed and are largely based on identifying the key molecular pathway that is responsible for driving the growth of a given patient's tumor. According to clinical trial data, these new molecular-based therapies provide for effective treatment options for lung adenocarcinomas and particularly cases with metastatic disease. Examples of relevant pathways targeted by these new therapies include the activated/mutated epidermal growth factor receptor (EGFR) pathway and the EML4-ALK translocation pathway.

The list of new molecular-based therapies with a specific companion predictive molecular test is actively growing. Such new molecular tests allow for a 'personalized' approach to deciding a patient's treatment regimen. Indeed, clinical trial data demonstrate that personalizing treatment as determined by predictive molecular marker testing in lung adenocarcinoma leads to improved patient survival compared to traditional chemotherapy. *See next page for predictive molecular testing currently recommended.*

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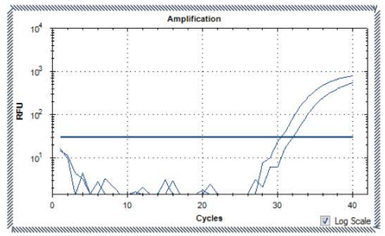
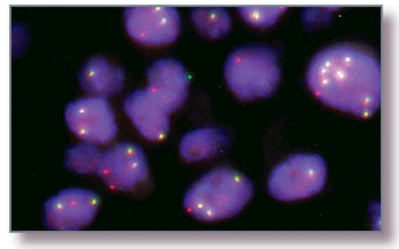
LUNG CANCER MARKERS

EGFR mutation analysis by Real Time PCR

Real-time PCR provides a highly sensitive method to detect activating mutations in the tyrosine kinase domain (exons 18-21) of EGFR in adenocarcinoma specimens. If an activating EGFR mutation is identified, the patient is eligible for treatment with tyrosine kinase inhibitors (TKIs), e.g., erlotinib. Evaluation of tyrosine kinase domain-activating mutations is currently standard of care for determining treatment options in lung adenocarcinoma.



EGFR PCR



ALK Breakapart FISH Positive case

EML4-ALK translocation analysis by FISH

The anaplastic lymphoma kinase (ALK) gene is a tyrosine kinase that is translocated in a number of human tumors. EML4-ALK translocations have been identified in ~5% of all adenocarcinomas and can be readily identified by FISH. When an EML4-ALK translocation is identified, the patient is eligible for treatment with an ALK-inhibitor drug, e.g., crizotinib.

As the presence of an EGFR mutation or an ALK translocation is generally mutually exclusive in adenocarcinoma, the current recommendation is to first test for an EGFR activating mutation. If no EGFR mutation is identified, then the tumor specimen should be tested for an EML4-ALK translocation by FISH. The recommended testing algorithm with relevant treatment option is shown in the diagram.