Worldwide, lung cancer is the most common cause of major cancer mortality in men and the second most common in women. Recent therapeutic advances have led to a revolution in the lung cancer field in discovering therapeutically tractable oncogene dependency, that have major implications for patient evaluation and approach to diagnosis. The 2011 IASLC/ATS/ERS Classification of Lung Adenocarcinoma addresses these issues. This classification was developed based on an evidence-based approach by an international multidisciplinary panel including pathologists, oncologists/respiratory physicians, radiologists, molecular biologists, and thoracic surgeons. Multiple paradigm shifts are outlined that have a major impact on clinical practice for pathologists as well as the entire multidisciplinary team caring for lung cancer patients. Two review articles one on small biopsies/cytology specimens and the other on resection specimens addressed primarily to pathologists are about to be published and are currently available online.

Since 70% of lung cancer patients present in advanced stages, their diagnosis is usually established based on small biopsies and/or cytology specimens and the primary therapy is chemotherapy; the remaining patients are usually resectable and surgery is the primary treatment. In order to address all types of cancer patients, there are two major components to the classification based on the type of specimen: 1) small biopsies and cytology or 2) resection. Because previous WHO classifications did not provide specific criteria and terminology for pathologic diagnosis of lung cancer in small biopsies and cytology, this new classification is more clinically relevant as it addresses these small specimens and addresses molecular testing.

In recent years, three therapeutic advances for advanced NSCLC have made accurate histologic diagnosis a critical step in developing a personalized approach to management. The first, relates to tyrosine kinase inhibitors as first line therapy in patients with advanced lung adenocarcinoma with \textit{EGFR} mutations. For this reason, in the new classification \textit{EGFR} mutation testing is recommended for advanced lung cancer patients with a histologic diagnosis of adenocarcinoma. Second, patients with adenocarcinoma or NSCLC, not otherwise specified (NSCLC-NOS) are more responsive to pemetrexed than those squamous cell carcinoma. Third, squamous cell carcinoma is associated with life threatening hemorrhage in patients treated with bevacizumab therefore it is contraindicated in lung cancer patients with this histology. Fourth, crizotinib is an FDA-approved therapy for advanced adenocarcinomas with \textit{ALK} rearrangements. Both \textit{EGFR} mutations and \textit{ALK} rearrangements are almost exclusively seen in lung adenocarcinomas. So a pathologic diagnosis of adenocarcinoma or squamous cell carcinoma will determine patient eligibility for \textit{EGFR} mutation testing and for specific therapies. In all of these clinical trials the pathologic diagnoses were based on light microscopy with or without mucin stains but not on the basis of immunohistochemical stains.

While much progress has been made in identifying validated molecular targets for lung adenocarcinoma, only recently have potential targets been identified for squamous cell carcinoma
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including FGFR1 amplification and DDR2 mutations which may render these patients sensitive to FGFR inhibition and dasatinib respectively.11, 12, 13 The Cancer Genome Atlas (TCGA) project sponsored by the National Cancer Institute has identified molecular alterations that may represent molecular targets in the majority of lung squamous cell carcinomas.13 In the future this may lead to effective targeted therapies for lung squamous cell carcinomas, which would only increase the importance of accurate pathologic classification in small biopsies and cytology.

CLASSIFICATION BASED ON SMALL BIOPSIES AND CYTOLOGY

Now that lung cancer therapy is personalized for individual patients based on the histologic type of lung cancer and molecular status, the pathologist’s role and approach to lung cancer diagnosis in small biopsies and cytology have been affected dramatically. The need to classify non-small cell carcinoma (NSCLC) further to distinguish squamous cell carcinoma from adenocarcinoma has not existed until recently so the frequency of NSCLC-not otherwise specified (NOS) has been increasing up to 20-40%. Now pathologists need to make an effort to make a more specific diagnosis using special stains.

Tumors that show morphologic squamous or adenocarcinoma differentiation can be classified as squamous cell carcinoma or adenocarcinoma, respectively. However, for those tumors that lack clear differentiation by morphology and would be classified as NSCLC-NOS in the past, now need to be evaluated by immunohistochemistry. The recommendation is to use a single adenocarcinoma marker such as TTF-1 and a single squamous marker such as the recently described p40 antibody.14 If a NSCLC-NOS by light microscopy shows a staining pattern that clearly points to adenocarcinoma (TTF-1 positive, p40 negative), the tumor can be classified as NSCLC, favor adenocarcinoma. If such a tumor stains with a squamous pattern (p40 positive, TTF-1 negative), then it can be called NSCLC, favor squamous cell carcinoma. If the tumor does not show clear differentiation by immunohistochemistry, it should remain as NSCLC-NOS. These terms and criteria will help track the former NOS tumors that are being reclassified with the addition of special stains for future clinical trials. Advanced stage tumors classified as adenocarcinoma, NSCLC, favor adenocarcinoma or NSCLC-NOS should be tested for EGFR mutation; mutation positive patients are eligible for tyrosine kinase inhibitor therapy. If there is no EGFR mutation, recent data suggests these patients are candidates for EML4-ALK fusion testing and if positive they can receive the FDA approved drug crizotinib,10 and if negative these patients are eligible for pemetrexed or bevacizumab based chemotherapeutic regimens.

In the new classification, a limited use of special stains is recommended for NSCLC-NOS by light microscopy in order to try to classify these tumors further. Minimizing special stains is helpful to maximize the amount of tissue available for molecular testing.1 A new responsibility for pathologists, in addition to making a correct diagnosis, is to manage these small biopsies and cytology specimens strategically so there is sufficient tissue preserved for molecular studies.

A new emphasis is made on the need for a multidisciplinary approach to lung cancer diagnosis. One of the central proposals in this classification is that each institution needs to have a multidisciplinary strategy that addresses how to obtain these small specimens, how to process them in the pathology laboratory, how to preserve material for molecular testing, sending specimens to the molecular laboratory for expedited testing and the reporting the results in a pathology report. It may be useful to have a multidisciplinary committee to develop this strategy and to monitor issues in an ongoing fashion.
CLASSIFICATION BASED ON RESECTION SPECIMENS

Major changes are also recommended for adenocarcinomas diagnosed in resection specimens:1 1) the term bronchioloalveolar carcinoma (BAC) should not be used anymore, because tumors previously classified under as BAC are represented by five different tumors in this classification; 2) for solitary tumors measuring ≤3cm, new concepts of adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) have been introduced for lesions that have no invasion or ≤5mm invasion, respectively; these patients should have 100% or near 100% disease free survival (DFS); 3) for invasive adenocarcinomas, comprehensive histologic subtyping is recommended for evaluation with classification according to the predominant subtype; 4) micropapillary adenocarcinoma is proposed as a new subtype with a poor prognosis; 5) the term lepidic replaces BAC for tumors with a predominant component formerly called non-mucinous BAC, and the term lepidic predominant adenocarcinoma is recommended along with discontinuing the term “mixed subtype”; 6) invasive mucinous adenocarcinoma (IMA) is the term used to replace those formerly classified as mucinous BAC. IMA are strongly correlated with KRAS mutation Recently strong survival correlations were demonstrated using this classification in Stage I adenocarcinomas with the following 5-year DFS: AIS and MIA (100%), lepidic (90%), acinar (84%), papillary (83%), and there was a poor prognostic group: micropapillary (67%), solid (70%), colloid (71%) predominant tumors as well as invasive mucinous adenocarcinoma (75%).15 Comprehensive histologic subtyping is performed by making semiquantitative estimation of each of the patterns in 5% increments. A deliberate choice needs to be made to give one pattern the largest percentage. It is useful to record in diagnostic reports each adenocarcinoma subtype that is present with the percentages. This approach may also provide a basis for architectural grading of lung adenocarcinomas.15-17 Early reproducibility studies have shown moderate to substantial inter-observer agreement among pathologists for the predominant pattern. A reproducibility study of classical and difficult selected images of the major lung adenocarcinoma subtypes circulated among a panel of 26 expert lung cancer pathologists documented kappa values of 0.77 +/- 0.07 and 0.38 +/- 0.14, respectively.18 A recent study of reproducibility for predominant pattern showed moderate to good κ-values of 0.44 to 0.72 for pulmonary pathologists. For untrained pathologists κ-values were expectedly lower ranging from 0.38 to 0.47, but these improved after a training session to 0.51 to 0.66 and re-evaluation by the same reviewers led to very high κ-values between 0.79-0.87.19 Reproducibility improves after training sessions. However, work is needed to improve separation of difficult problems such as lepidic versus acinar or papillary and micropapillary versus papillary patterns.18, 20 21 Since this classification was initially published, there are a growing number of studies of resected lung adenocarcinomas that have demonstrated its utility in identifying significant prognostic subsets and molecular correlations according to the predominant patterns.15, 16, 22-26

In summary this classification outlines many paradigm shifts in lung cancer diagnosis that crystalize the importance of histology and genetics in personalized medicine for lung cancer patients. Evidence-based recommendations are made that will transform the clinical practice of all physicians involved with lung cancer diagnosis.

Reference List


