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New Pathologic Classification of Lung Cancer: Relevance for Clinical Practice and Clinical Trials

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ABSTRACT

We summarize significant changes in pathologic classification of lung cancer resulting from the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) lung adenocarcinoma classification. The classification was developed by an international core panel of experts representing IASLC, ATS, and ERS with oncologists/pulmonologists, pathologists, radiologists, molecular biologists, and thoracic surgeons. Because 70% of patients with lung cancer present with advanced stages, a new approach to small biopsies and cytology with specific terminology and criteria focused on the need for distinguishing squamous cell carcinoma from adenocarcinoma and on molecular testing for *EGFR* mutations and *ALK* rearrangement. Tumors previously classified as non–small-cell carcinoma, not otherwise specified, because of the lack of clear squamous or adenocarcinoma morphology should be classified further by using a limited immunohistochemical workup to preserve tissue for molecular testing. The terms "bronchioloalveolar carcinoma" and "mixed subtype adenocarcinoma" have been discontinued. For resected adenocarcinomas, new concepts of adenocarcinoma in situ and minimally invasive adenocarcinoma define patients who, if they undergo complete resection, will have 100% disease-free survival. Invasive adenocarcinomas are now classified by predominant pattern after using comprehensive histologic subtyping with lepidic, acinar, papillary, and solid patterns; micropapillary is added as a new histologic subtype with poor prognosis. Former mucinous bronchioloalveolar carcinomas are now called "invasive mucinous adenocarcinoma." Because the lung cancer field is now rapidly evolving with new advances occurring on a frequent basis, particularly in the molecular arena, this classification provides a much needed standard for pathologic diagnosis not only for patient care but also for clinical trials and TNM classification.

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INTRODUCTION

A significant change in pathologic classification of lung cancer occurred with the publication in 2011 of a new lung adenocarcinoma classification under the sponsorship of the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS). The classification outlines many paradigm shifts that affect clinical practice and opens new avenues for research.[1] Pathologists now play an important role in personalized medicine for patients with lung cancer as a result of the newly recognized importance of histologic classification and molecular testing in stratifying patients for specific therapies. This is a central theme of the new classification. Because the lung cancer field is rapidly evolving with new advances occurring on a frequent basis, particularly in the molecular arena, this classification provides a much needed standard for pathologic diagnosis not only for patient care but also for clinical trials.

There are several major differences in this classification compared with those previously published by the WHO. First, this was a multidisciplinary effort with clinicians, radiologists, molecular biologists, and surgeons being involved rather than an effort primarily by pathologists. This led to an emphasis on correlations between pathologic aspects of tumors with clinical, radiologic, and molecular characteristics that allowed for recognition of multiple paradigm shifts in the diagnosis and management of patients with lung cancer. Second, it was recognized that 70% of patients with lung cancer present with advanced-stage disease, which is usually diagnosed on the basis of small biopsies and cytology. Because prior WHO classifications focused on lung cancer diagnosis in resection specimens, which are obtained in only 30% of patients, a major effort was made to define terminology and criteria to be used in small biopsies and cytology. Therefore, this classification is divided into two components based

Table 1. Specific Terminology and Criteria for Adenocarcinoma, Squamous Cell Carcinoma, and NSCLC-NOS in Small Biopsies and Cytology

2004 WHO Classification Including Updated IASLC/ATS/ERS Terminology	Morphology/Stains	IASLC/ATS/ERS Terminology
Adenocarcinoma	Morphologic adenocarcinoma patterns clearly present	Adenocarcinoma (describe identifiable patterns present)
Mixed subtype		
Acinar		
Papillary		
Solid		
Micropapillary		
Lepidic (nonmucinous)		Adenocarcinoma with lepidic pattern (if pure, add note: an invasive component cannot be excluded)
Lepidic (mucinous)		Invasive mucinous adenocarcinoma (describe patterns present; use term "mucinous adenocarcinoma with lepidic pattern" if pure lepidic pattern is present)
No 2004 WHO counterpart; most will be solid adenocarcinomas	Morphologic adenocarcinoma patterns not present (supported by special stains such as TTF-1)	NSCLC-favor adenocarcinoma
Squamous cell carcinoma	Morphologic squamous cell patterns clearly present	Squamous cell carcinoma
No 2004 WHO counterpart	Morphologic squamous cell patterns not present (supported by stains such as p40)	NSCLC-favor squamous cell carcinoma
Large-cell carcinoma	No clear adenocarcinoma, squamous, or neuroendocrine morphology or staining pattern	NSCLC-NOS*

NOTE. Data adapted[1,20] with permission.
Abbreviations: IASLC/ATS/ERS, International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society; NOS, not otherwise specified; NSCLC, non–small-cell carcinoma; TTF-1, thyroid transcription factor 1.
*NSCLC-NOS pattern can be seen not only in large-cell carcinomas but also when the solid poorly differentiated component of adenocarcinomas or squamous cell carcinomas are sampled but do not express immunohistochemical markers or mucin.

on the primary ways lung cancer is diagnosed: (1) small biopsy and cytology specimens for patients with advanced-stage lung cancer (Tables 1 and 2) and (2) resection specimens for early-stage patients who are eligible for surgical resection (Table 3). A major point in this classification is the concept that personalized medicine in advanced lung cancer is determined by histology and genetics and that strategic tissue management of small biopsies is critical not only for diagnosis but also for molecular studies.

PATIENTS WITH ADVANCED LUNG CANCER: CLASSIFICATION IN SMALL BIOPSIES AND CYTOLOGY

In the past, non–small-cell lung carcinomas (NSCLCs) were lumped together without attention to more specific histologic typing (ie, adenocarcinoma, squamous cell carcinoma). This was accepted because there was no therapeutic implication to separating histologic subtypes such as adenocarcinoma and squamous cell carcinoma. Recently, this has changed. *EGFR* mutations and *ALK* rearrangements are almost exclusively seen in lung adenocarcinomas and the identification of these molecular abnormalities is clinically relevant. EGFR tyrosine kinase inhibitors are first-line therapy in patients who have advanced lung adenocarcinomas with *EGFR* mutations.[2-6] Crizotinib has been approved by the US Food and Drug Administration (FDA) for advanced adenocarcinomas with *ALK* rearrangements.[7-9] Both *EGFR* mutations and *ALK* rearrangements are almost exclusively seen in lung adenocarcinomas. Among patients treated with pemetrexed, those with adenocarcinoma or NSCLC, not otherwise specified (NSCLC-NOS) fared better than those with squamous cell carcinoma.[10-12] Furthermore, patients with squamous cell

Table 2. IASLC/ATS/ERS Classification for Small Biopsies/Cytology Comparing 2004 WHO Terms With New Terms for Small-Cell Carcinoma, LCNEC, Adenosquamous Carcinoma, and Sarcomatoid Carcinoma

2004 WHO Classification	Small Biopsies/Cytology: IASLC/ATS/ERS
Small-cell carcinoma	Small-cell carcinoma
LCNEC	NSCLC with NE morphology and positive NE markers; possible LCNEC
LCNEM	NSCLC with NE morphology (negative NE markers). Comment: This is an NSCLC in which LCNEC is suspected, but stains failed to demonstrate NE differentiation
Adenosquamous carcinoma	Morphologic squamous cell and adenocarcinoma patterns present: NSCLC-NOS. Comment: Adenocarcinoma and squamous components are present and this could represent adenosquamous carcinoma
No 2004 WHO counterpart classification	Morphologic squamous cell or adenocarcinoma patterns not present but immunostains favor separate glandular and adenocarcinoma components, NSCLC-NOS (specify the results of the immunohistochemical stains and the interpretation). Comment: This could represent adenosquamous carcinoma
Sarcomatoid carcinoma	NSCLC with spindle and/or giant cell carcinoma (mention if adenocarcinoma or squamous carcinoma is present)

NOTE. Data adapted[1,20] with permission.
Abbreviations: IASLC/ATS/ERS, International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society; LCNEC, large-cell neuroendocrine carcinoma; LCNEM, large-cell carcinoma with neuroendocrine morphology; NE, neuroendocrine; NOS, not otherwise specified; NSCLC, non–small-cell carcinoma.

Table 3. IASLC/ATS/ERS Classification of Lung Adenocarcinoma in Resection Specimens

Preinvasive lesions
Atypical adenomatous hyperplasia
Adenocarcinoma in situ (≤ 3 cm; formerly solitary BAC)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Minimally invasive adenocarcinoma (≤ 3 cm lepidic-predominant tumor with ≤ 5 mm invasion)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Invasive adenocarcinoma
Lepidic predominant (formerly nonmucinous BAC pattern with > 5 mm invasion)
Acinar predominant
Papillary predominant
Micropapillary predominant
Solid predominant with mucin production
Variants of invasive adenocarcinoma
Invasive mucinous adenocarcinoma (including formerly mucinous BAC)
Colloid
Fetal (low and high grade)
Enteric

NOTE. Data adapted[1,20] with permission.
Abbreviations: BAC, bronchioloalveolar carcinoma; IASLC/ATS/ERS, International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society.

carcinoma fared better with gemcitabine.[10-12] Finally, squamous cell carcinoma is associated with life-threatening hemorrhage in patients treated with bevacizumab; therefore, it is contraindicated in patients with lung cancer with this histology.[13] These advances have now made it essential for pathologists to make every effort to refine histologic typing of tumors formerly classified as NSCLC.

Role of Pathologists in Personalized Medicine for Patients With Lung Cancer

Pathologists now play a major role in personalized medicine for patients with lung cancer. Therapeutic decisions are heavily dependent on the histologic type of lung cancer (squamous cell *v* adenocarcinoma) and its molecular characteristics (ie, *EGFR* mutation and *ALK* rearrangement status). Based largely on multiple phase III clinical trials,[2-6] the new classification recommends that all patients with advanced lung adenocarcinoma be tested for *EGFR* mutations. Since this classification was written, several studies have demonstrated that crizotinib is effective in patients with advanced lung cancer with *ALK* rearranged tumors.[7,9] In fact, the FDA approved crizotinib for use in advanced NSCLC if the tumor is *ALK* positive as detected by a fluorescent in situ hybridization assay.[14] Therefore testing for *EGFR* mutations and *ALK* rearrangements in patients with advanced lung adenocarcinoma is no longer a research test but should be incorporated into routine clinical practice. Immunohistochemistry appears to be an accurate way to detect *ALK* rearrangements, but this method needs to be tested in clinical trials.[15-17]

Although much progress has been made in identifying validated molecular targets for lung adenocarcinoma, only recently have potential targets been identified for squamous cell carcinoma, including FGFR1 amplification and *DDR2* mutations, which may render these patients sensitive to FGFR inhibition and dasatinib, respectively.[18-20] The Cancer Genome Atlas project sponsored by the National Cancer Institute has identified molecular alterations that may represent molecular targets in the majority of lung squamous cell carcinomas.[20] In the future, this may lead to effective targeted therapies for lung squamous cell carcinomas, which would increase the importance of accurate pathologic classification in small biopsies and cytology.

The necessity for molecular testing is particularly true for patients with advanced lung cancer in which the diagnosis is usually based on small biopsies and cytology. The need for molecular testing in these patients has dramatically changed how pathologists analyze these specimens. Previously their main responsibility was only to make a pathologic diagnosis but now these small tissue specimens need to be managed to preserve as much material as possible for current and future molecular testing.

Special Stains Required for NSCLC-NOS and the Need for a Multidisciplinary Approach

One of the major new proposals in the IASLC/ATS/ERS classification is the development of standardized criteria and terminology for pathologic diagnosis of lung cancer in small biopsies and cytology (Tables 1 and 2). In addition to the criteria and terminology, there are two paradigm shifts for pathologists in tumor classification and management of specimens. The first is the need to perform immunohistochemistry to further classify tumors formerly diagnosed as NSCLC-NOS. Because the distinction between histologic types of lung cancer (particularly adenocarcinoma *v* squamous cell carcinoma) is so important, in the new classification, it is recommended that pathologists use special stains to try to further subtype carcinomas that are difficult to classify by light microscopic evaluation of hematoxylin and eosin sections alone. The second major change is the need for the entire multidisciplinary team involved with the diagnosis and treatment of patients with advanced lung cancer to develop a tissue management strategy, in which, through communications among all members of the team, pathologists not only make a diagnosis but also preserve as much tissue as possible to be submitted for molecular testing. When sufficient material is unavailable from the initial diagnostic procedure to determine the minimal characteristics of a tumor, repeat biopsy may be required. Planning discussions for diagnostic procedures should include all members of the multidisciplinary team.

New Standardized Diagnostic Criteria and Terminology for Small Biopsies and Cytology

In proposing the criteria and terminology for diagnosis of lung adenocarcinoma in small biopsies and cytology, the IASLC/ATS/ERS committee had to make recommendations for terminology and criteria for other major lung cancer histologic types because such criteria are not a part of the current WHO classification (Table 2).

For tumors with classic morphologic features the diagnostic terms "adenocarcinomas" (Fig 1A) and "squamous cell carcinomas" (Fig 1B) can be used (Table 1). The morphologic features of these tumors are described in detail elsewhere.[21-24] If an NSCLC does not show definite glandular or squamous morphology in a small biopsy or cytology specimen, it is classified as NSCLC-NOS.[1,25] Tumors with this morphology should be studied with a limited special stain workup in an attempt to classify them further. Using a single adenocarcinoma marker (ie, thyroid transcription factor-1 [TTF-1] or napsin-A), a

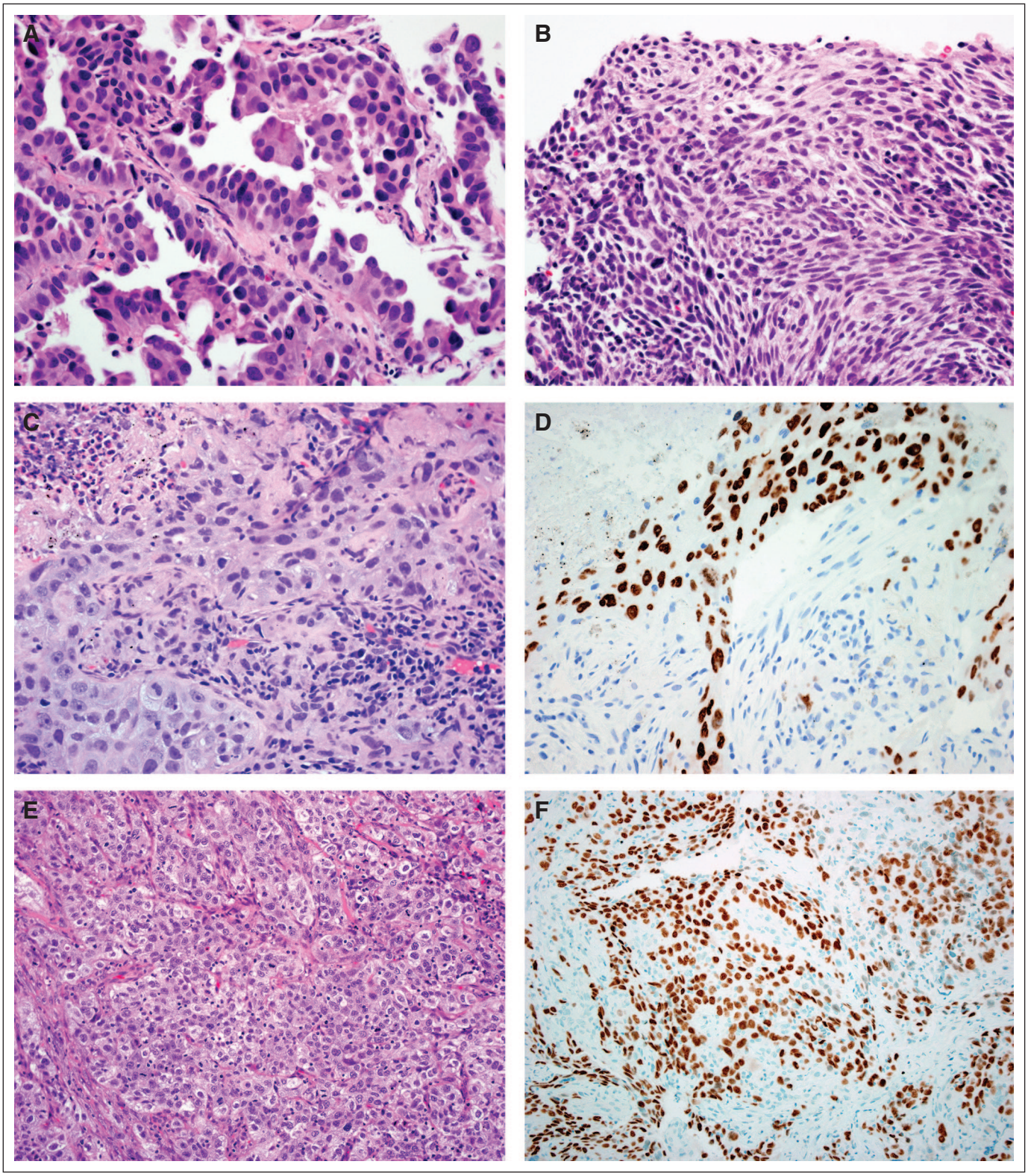

Fig 1. (A) Adenocarcinoma: This small biopsy shows fragments of adenocarcinoma with an acinar and micropapillary configuration (hematoxylin and eosin stain; ×40). (B) Squamous cell carcinoma: This small biopsy shows squamous cell carcinoma with nests of tumor cells that focally have keratinization and intercellular bridges (hematoxylin and eosin stain; ×20); non–small-cell lung cancer-favor adenocarcinoma. (C) This tumor shows a solid pattern of growth with no clear squamous acinar, papillary, or lepidic growth and no intracytoplasmic mucin (hematoxylin and eosin stain; ×20). (D) A thyroid transcription factor-1 stain is positive, favoring an adenocarcinoma (immunohistochemistry for thyroid transcription factor-1; ×40); non–small-cell lung cancer-favor squamous cell carcinoma. (E) This biopsy shows a solid nest of tumor cells with no clear glandular or squamous differentiation (hematoxylin and eosin stain). (F) p40 shows strong nuclear staining (immunohistochemistry for p40).

single squamous marker (ie, p40 or p63), and/or mucin stains is recommended.[21] Tumors that are positive for an adenocarcinoma marker or mucin are classified as NSCLC–favor adenocarcinoma (Figs 1C and 1D). Tumors that are positive for a squamous cell carcinoma marker with negative adenocarcinoma marker(s) are classified as NSCLC–favor squamous cell carcinoma (Figs 1E and 1F). Cytology is a powerful diagnostic tool that can accurately subtype NSCLC in most cases.[26] Tumors that cannot be classified after evaluation of special stains remain classified as NSCLC-NOS. Terminology and criteria are also provided for other tumors in which the small biopsy and cytology may suggest possible diagnoses such as sarcomatoid carcinoma, adenosquamous carcinoma, and large-cell neuroendocrine carcinoma (Table 2).

Clinical Trials: Need for Use of the New Terminology and Criteria

The new terms and criteria should be incorporated into routine patient care and the data collection and reporting of clinical trials. For the problematic cases that were previously classified as NSCLC-NOS, there are several reasons for using more specific criteria and terminology. The terms "NSCLC–favor adenocarcinoma" and "NSCLC–favor squamous cell carcinoma" were helpful to pathologists for communicating with clinicians when the diagnosis was uncertain on morphology alone and that special stains were required to make the diagnosis and for clinical trials to capture the change in diagnosis in the 20% to 40% of NSCLCs that were previously classified as NSCLC-NOS.[10,12,27,28] These cases will now be redistributed by using immunohistochemistry or mucin stains into the categories of NSCLC–favor adenocarcinoma or NSCLC–favor squamous cell carcinoma, and a small percentage (ideally $\leq 5\%$) will remain unclassifiable as NSCLC-NOS. The term "NSCLC-NOS" should be used as little as possible and it should be used only for NSCLC that cannot be further classified by morphology and/or special stains.[1]

The primary approach for histologic classification of lung cancers in the existing clinical trials for EGFR tyrosine kinase inhibitors pemetrexed and bevacizumab was based on review of hematoxylin and eosin slides alone without use of immunohistochemistry.[2-6,12,13] For example, it is recommended that patients with squamous cell carcinoma should not be given bevacizumab. However, there are no data to support that this recommendation can be made for patients with NSCLC–favor squamous cell carcinoma in which the only pathologic evidence for squamous differentiation is based on immunohistochemistry and not on light microscopy. Although there may be an inclination to lump these cases together with squamous cell carcinoma and not give bevacizumab to such patients, in all probability, some of these cases may have been classified as NSCLC-NOS in previous clinical studies. Without testing the impact of immunohistochemistry on reclassification of the patients formerly classified as having NSCLC-NOS in future clinical trials, we will never know the answer to such questions.

In some of the major clinical trials that included patients with advanced lung cancer, lung cancers were classified as large-cell carcinoma,[10,12,27] but according to the 2004 WHO classification, that diagnosis cannot be established without a resection specimen because of the need for thorough histologic sampling to exclude the presence of any other differentiated component, such as squamous cell carcinoma or adenocarcinoma.[22] The term "non-squamous cell carcinoma" is used in some clinical reports to lump adenocarcinomas with NSCLC-NOS cases in comparison with squamous cell carcinomas, but this term should not be used by pathologists in diagnostic reports.

Molecular Testing According to Histologic Categories

Tumors that are candidates for *EGFR* mutation and *ALK* rearrangement testing are those diagnosed as adenocarcinoma, NSCLC–favor adenocarcinoma, or NSCLC-NOS.[1] Although the only molecular test recommended in patients with these diagnoses in the setting of advanced lung cancer is *EGFR* mutation testing,[1] it is recognized that in many institutions, *EGFR* mutation testing may be performed in patients with early-stage disease, and other molecular analyses will be performed, including *KRAS* mutation testing and testing for *ALK* rearrangements, because these tumors are sensitive to specific agents such as crizotinib.[9]

In the near future, there will be sufficient evidence to recommend testing for molecular alterations characteristics of squamous cell carcinoma. Several molecular targets such as *FGFR1* amplification and *DDR2* mutation are under early stages of investigation for squamous cell carcinoma.[18,29] Tumors diagnosed as squamous cell carcinoma and NSCLC–favor squamous cell carcinoma are appropriate to test for molecular markers that may represent therapeutic targets in squamous cell carcinoma.

Multidisciplinary Strategy to Manage Small Tissue and Cytology Samples

Because of the need for molecular testing, each institution needs to develop a multidisciplinary strategy for obtaining and processing small biopsy and cytology specimens so that sufficient material is available not only for diagnosis but also for molecular studies. Small biopsies, including formalin fixed paraffin embedded tissues (as obtained through a core needle biopsy or transbronchial biopsy) and/or cytologic samples, can be used for many molecular analyses, but the tissue needs to be managed strategically.[30-32] Preparation of cell blocks from cytology specimens such as pleural fluids is helpful because it provides material that can readily be used for both immunohistochemical and molecular studies. This strategy needs to consider the entire process of lung cancer diagnosis beginning with the approach to obtaining biopsies or cytology specimens to how they are processed in the pathology department and then to how they are delivered to the molecular laboratory and processed expeditiously so the results can be documented in a pathology report. As pathologists manage these specimens, they need to minimize the amount of tissue used for diagnostic workup and preserve as much material for molecular testing as possible.[1,25,33] Because there are many local issues that will vary from one institution to another, no specific recommendations are made on how this should be done. Each of the specialists involved with the tissue management process needs to participate in the development of the initial strategy and have an ongoing mechanism for addressing new techniques and assays as well as any problems that arise.

CLASSIFICATION IN RESECTION SPECIMENS

There are several important modifications to the 2004 WHO Classification that apply to resection specimens. Likely the most significant change is the discontinuation of the term "bronchioloalveolar carcinoma (BAC)." This term was previously used for at least five different

entities with disparate clinical and molecular properties, leading to great confusion in routine clinical care and research. To address two of these entities, the concepts of adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) were proposed for small solitary (≤ 3 cm) adenocarcinomas with a lepidic pattern that either lacked invasion or showed only small foci of invasion measuring ≤ 0.5 cm. AIS and MIA should define patients with either 100% or near 100% 5-year disease-free survival if completely resected. Third, the term "mixed subtype" was discontinued, and invasive adenocarcinomas are now classified according to their predominant subtype. By using this approach, the proportions of each of the histologic subtypes are estimated in a semiquantitative manner and a predominant pattern is designated. Fourth, the term "lepidic-predominant adenocarcinoma" is proposed for nonmucinous tumors formerly classified as mixed subtype in which the predominant subtype consists of the former nonmucinous BAC. Fifth, micropapillary adenocarcinoma is introduced as a major histologic subtype since multiple studies have shown that patients with such tumors have a poor prognosis. Sixth, tumors formerly classified as mucinous BAC are now reclassified into mucinous AIS or MIA or invasive mucinous adenocarcinoma; because a high percentage of these tumors have *KRAS* mutations, they often lack TTF-1 expression, and computed tomography (CT) frequently shows nodules of consolidation with air bronchograms that are frequently multinodular and multilobar in distribution. Finally, clear cell and signet ring adenocarcinoma are discontinued as major subtypes because they are cytologic changes that can occur in multiple histologic patterns of adenocarcinoma; however, these features can now be recorded when any amount, however small, is present.[1,34]

In the new classification, tumors formerly regarded as BAC included a wide spectrum of entities with varied clinical behavior such as AIS, MIA, lepidic-predominant adenocarcinoma, overtly invasive adenocarcinoma with a lepidic component, and invasive mucinous adenocarcinoma. AIS should not be equated with tumors previously classified as BAC, particularly in registry databases such as Surveillance, Epidemiology, and End Results (SEER).[35] Such data could be misleading because AIS is the rarest of lung adenocarcinoma subtypes, representing only 0.2% to 3% of cases in white populations[36,37] and up to 5% in a Japanese series.[38] The vast majority of cases previously classified as BAC represent tumors with invasive components.

Since the publication of the classification, a series of reports have been published that provide validation of various aspects of the classification in resection specimens. Studies from Australia,[37] Europe,[39] Asia,[38] and North America[36,40] have demonstrated that the proposed subtyping has prognostic value.

ADENOCARCINOMA IN SITU

AIS is added to the group of preinvasive lesions along with atypical adenomatous hyperplasia (Table 3).[1,34] AIS is defined as a localized small (≤ 3 cm) adenocarcinoma consisting of neoplastic pneumocytes growing along pre-existing alveolar structures (lepidic growth), lacking stromal, vascular, or pleural invasion (Figs 2A and 2B). There should be no papillary or micropapillary patterns, and intra-alveolar tumor cells are absent. AIS is typically nonmucinous, consisting of type II pneumocytes and/or Clara cells (Fig 2B), but rare cases of mucinous AIS occur.

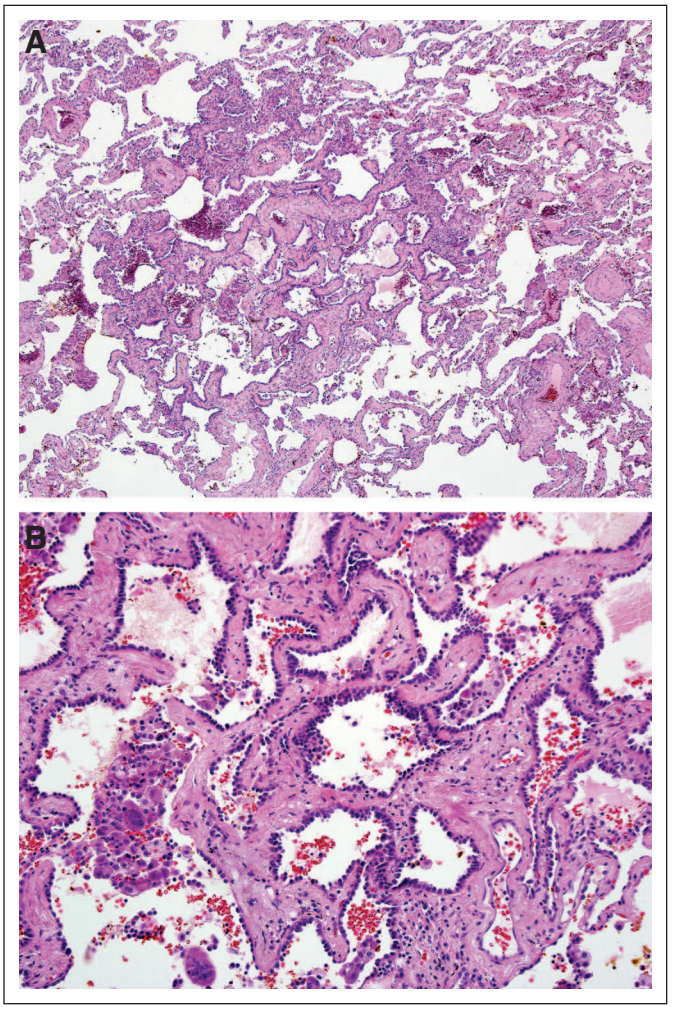

Fig 2. Nonmucinous adenocarcinoma in situ. (A) This circumscribed nonmucinous tumor grows purely with a lepidic pattern. No foci of invasion or scarring are seen (hematoxylin and eosin stain; ×4). (B) The tumor shows atypical pneumocytes proliferating along the slightly thickened but preserved alveolar walls (hematoxylin and eosin stain; ×40).

The concept of AIS was proposed with the intent of defining lesions that should correlate with a 100% disease-free survival if completely resected. This proposal was supported by multiple retrospective observational studies in tumors either ≤ 2 cm or ≤ 3 cm.[1] In the setting of multiple tumors, the criteria for AIS as well as MIA should be applied only if the other tumors are regarded as synchronous primaries rather than intrapulmonary metastases.

MINIMALLY INVASIVE ADENOCARCINOMA

MIA is defined as a small, solitary adenocarcinoma (≤ 3 cm), with a predominantly lepidic pattern and ≤ 5 mm invasion in greatest dimension in any one focus.[41-43] MIA is usually nonmucinous but it may be mucinous (rare).[36] Measurement of the invasive component of MIA should include the following: histologic subtypes other than a lepidic pattern (ie, acinar, papillary, micropapillary, and/or solid) or tumor cells infiltrating myofibroblastic stroma. MIA should not be diagnosed if the tumor invades lymphatics, blood vessels, or pleura or

if it contains tumor necrosis. More details about measuring invasive size are provided elsewhere.[1,34]

The concept of MIA was introduced to define a population of patients who should have a 100% or near 100% 5-year disease-free survival if the lesion is completely resected. Although there was less evidence to support the concept of MIA compared with AIS,[41-43] all published reports that used these criteria have shown patients with 100% 5-year disease-free survival.[36-38,40]

The diagnosis of AIS or MIA requires that the tumor is completely sampled histologically (ie, the patient has undergone a surgical resection). Both lesions should also have a discrete circumscribed border and be without miliary spread of small foci of tumor into adjacent lung parenchyma and/or have lobar consolidation. Review of CT scans may be helpful in evaluating pathology specimens because the extent of ground glass (usually lepidic) versus solid (usually invasive) patterns can guide pathologists in assessing whether the lesion has been properly measured and/or sampled. For lesions suspected of being AIS or MIA more than 3 cm, the term "lepidic-predominant adenocarcinoma" is best applied with a comment that an invasive component cannot be excluded. This is because there is insufficient data to show that such patients will have 100% 5-year disease-free survival.

INVASIVE ADENOCARCINOMA

Because of the rarity of AIS and MIA, overtly invasive adenocarcinomas represent more than 70% to 90% of surgically resected lung adenocarcinomas. These tumors typically consist of a complex heterogeneous mixture of histologic patterns. The major invasive adenocarcinoma subtypes are now classified according to the predominant component, after performing comprehensive histologic subtyping. This approach is used rather than the former category of adenocarcinoma-mixed subtype. 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 along with the percentages. This approach may also provide a basis for architectural grading of lung adenocarcinomas.[36,44,45] Early reproducibility studies have shown moderate to substantial interobserver agreement among pathologists for the predominant pattern. 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.[46-48] Since this classification was initially published, there have been 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.[36-39,44,49,50]

Lepidic-predominant adenocarcinoma consists of a proliferation of bland pneumocytic cells growing along the surface of alveolar walls similar to the morphology defined in the section on AIS and MIA. Invasive adenocarcinoma is present in at least one focus measuring more than 5 mm in greatest dimension. Invasion is defined as histologic subtypes other than a lepidic pattern (ie, acinar, papillary, micropapillary, and/or solid) and/or myofibroblastic stroma associated with invasive tumor cells. The diagnosis of lepidic-predominant adenocarcinoma rather than MIA is made if the cancer invades lymphatics, blood vessels, or pleura or if it contains tumor necrosis. Several recent studies[36-39] of early-stage adenocarcinomas have shown that lepidic-predominant tumors have favorable prognosis with 86% to 90% 5-year disease-free survival. The term "adenocarcinoma with lepidic pattern" corresponds to some cases previously referred to as "adenocarcinoma with bronchioloalveolar features."

Acinar-predominant adenocarcinoma shows a majority component of glands that are round or oval with a central luminal space surrounded by tumor cells.[22] The neoplastic cells and/or glandular spaces may contain mucin. Papillary-predominant adenocarcinoma shows a major component of a growth of glandular cells along central fibrovascular cores.[22] Micropapillary-predominant adenocarcinoma has tumor cells growing in papillary tufts (florets which lack fibrovascular cores (Fig 3A).[22] These may appear to be detached from and/or connected to alveolar walls. The tumor cells are usually small and cuboidal with minimal nuclear atypia.

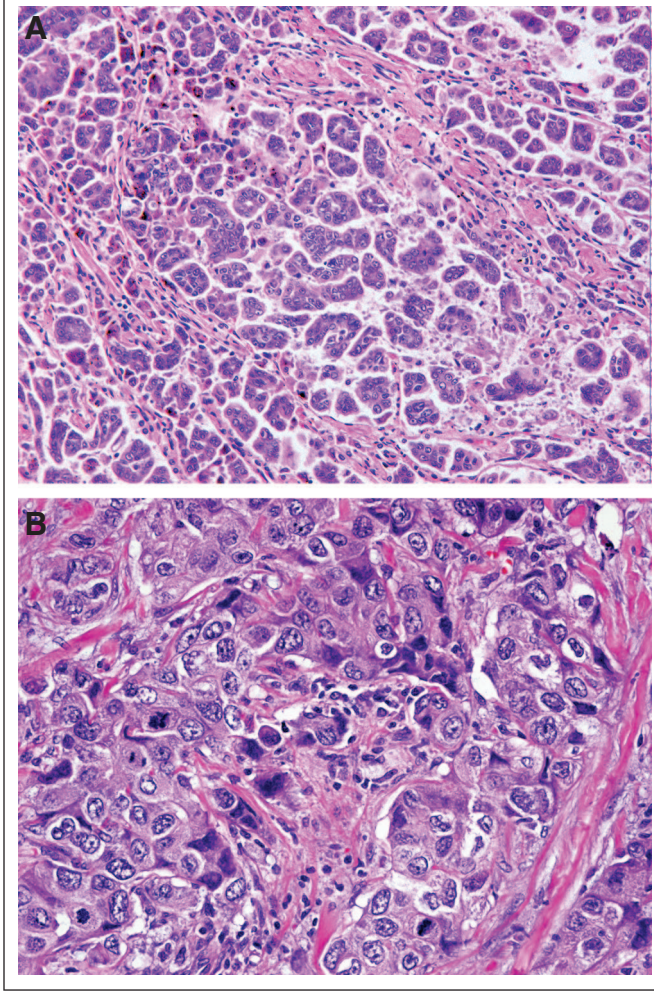

Fig 3. (A) Micropapillary adenocarcinoma. Within the airspaces, the tumor is growing in papillary structures lacking fibrovascular cores (hematoxylin and eosin stain; ×20). (B) Solid adenocarcinoma. This tumor consists of sheets of tumor cells with abundant cytoplasm and mostly vesicular nuclei with several conspicuous nucleoli (hematoxylin and eosin stain ×40).

Solid-predominant adenocarcinoma with mucin production consists of a major component of polygonal tumor cells forming sheets but without any clear acinar, papillary, micropapillary, or lepidic growth (Fig 3B).[22] These tumors must be distinguished from poorly differentiated squamous cell carcinomas and large-cell carcinomas. Immunostains for neuroendocrine markers should be performed only if neuroendocrine morphology is present.

Subtyping of early-stage invasive adenocarcinomas according to predominant subtype has shown prognostic value in multiple studies that generally show favorable prognosis for lepidic-predominant tumors, poor prognosis for micropapillary- and solid-predominant tumors, and an intermediate survival for acinar- and papillary-predominant adenocarcinomas.[36,37,39] The prognostic impact of these different subtypes may be helpful in designing clinical trials to stratify early-stage patients according to histology to determine who should receive adjuvant therapy. Clinical trials of limited resection should also stratify patients according to these histologic/prognostic subtypes, because patients with micropapillary and/or solid subtype may be suited for completion lobectomy in contrast to those with lepidic-predominant tumors.

INVASIVE MUCINOUS ADENOCARCINOMA

Multiple studies show major clinical, radiologic, pathologic, and genetic differences from the tumors formerly classified as nonmucinous BAC.[51-60] Invasive mucinous adenocarcinomas have tumor cells with a goblet or columnar cell morphology with abundant intracytoplasmic mucin. Similar to nonmucinous tumors, they may show the same heterogeneous mixture of lepidic, acinar, papillary, micropapillary, and solid growth. These tumors show a strong correlation with *KRAS* mutation and lack of *EGFR* mutations, although nonmucinous adenocarcinomas are more likely to show *EGFR* mutation. For these reasons, these tumors are now separated into different categories. The neoplasms have invasive components in the majority of cases and are classified as invasive mucinous adenocarcinoma, or rarely, if they meet the diagnostic criteria they may be mucinous AIS or MIA.

Invasive mucinous adenocarcinomas have a propensity for multicentric, multilobar, and bilateral lung involvement. Identical morphology may be seen in metastatic mucinous adenocarcinomas from sites such as the pancreas and ovary. For this reason, clinical and radiologic correlation should be made to exclude primary tumors in these locations.

HISTOLOGIC-MOLECULAR CORRELATIONS

There are no specific histologic-molecular correlations in lung adenocarcinomas in contrast to sarcomas and lymphomas. The frequent finding of *KRAS* mutation and lack of *EGFR* mutation in invasive mucinous adenocarcinoma is the strongest histologic molecular correlation. Most adenocarcinoma subtypes can harbor *EGFR* and *KRAS* mutations, as well as *ALK* rearrangement. *EGFR* mutations are encountered most frequently in nonmucinous adenocarcinomas with a lepidic- or papillary-predominant pattern. There is a tendency for solid-predominant adenocarcinomas to have *KRAS* mutations. *ALK* rearrangement has been mostly associated with an acinar pattern, including a cribriform morphology, and with signet-ring cell features, particularly those with TTF-1 and p63 coexpression.[17,61-63]

POTENTIAL IMPACT ON TNM STAGING

There are several ways the 2011 IASLC/ATS/ERS adenocarcinoma classification can have an impact on TNM staging. First, it may help in comparing histologic characteristics of multiple lung adenocarcinomas to determine whether they are intrapulmonary metastases versus separate primaries. Use of comprehensive histologic subtyping along with other histologic characteristics has been shown to have good correlation with molecular analyses and clinical behavior.[64-66] Second, as with breast cancer staging, it may be more meaningful clinically to measure tumor size in lung adenocarcinomas that have a lepidic component by using invasive size rather than total size to determine the size T factor. Existing data already suggest that this can be applied to CT as well as pathologic assessment of these tumors.[36,41,67,68] It is possible that in the next edition of the TNM, AIS may be regarded as Tis (adenocarcinoma) and MIA may be regarded as Tmi (adenocarcinoma). Hopefully, sufficient data can be published to provide sufficient validation of these concepts to allow the TNM committee to consider these changes.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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