The New Taxonomy of Lung Adenocarcinoma Stemming from a Multidisciplinary Integrated Approach

Novel Pathology Concepts and Perspectives

Giuseppe Pelosi, MD, MIAC

Lung cancer is the leading cause of morbidity and death all over the world and a significant burden on healthcare resources of most countries. Among the diverse histologic subtypes, adenocarcinoma (AD) is the most common type of lung cancer in both males and females in most countries, even in young people, and in tumors detected in screening low-dose computed tomography programs. The characteristic mixture of multiple subtypes has been a major source of inconsistency in subclassification in the past, hence the axiom, the more tumor categories, the more difficulties in the diagnosis. Therefore, new diagnostic criteria and uniform and consistent terminology are needed to improve accuracy and permit correlations between pathology and multiple patient characteristics including clinical features, tumor staging, molecular signatures, prognostic and predictive markers, and imaging data. Morphology still remains an agreed-on gold standard for AD, but a global rethinking of its histopathologic basis by exploiting an integrated multidisciplinary approach could really improve our diagnostic, prognostic, and predictive capabilities. The issue of accurate subtyping of poorly differentiated tumors and limited diagnostic material for predictive purposes is strictly intermingled with this scenario and often presents a difficult challenge, because most lung cancer patients are discovered with locally advanced or metastatic disease, so cytology or biopsy samples are the only available material. Therefore, in the past, the term “non-small cell lung cancer, not otherwise specified” has been encouraged mainly due to the lack of a clinical reason to classify more precisely. This situation has led to the uncomfortable feeling that histopathology is a finite and imperfect source of diagnostic, prognostic, or predictive information in lung cancers and that molecular studies are more important than histology for prognosis and prediction. For these reasons, this new multidisciplinary classification of AD that is presented in the Journal under the aegis of three outstanding scientific communities devoted to lung cancer, namely the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society, represents an extraordinary, meritorious, and almost herculean effort by Dr. William D. Travis, which surely will contribute to address many contemporary issues and questions on the subject of pulmonary AD through a close integration of pathologic, clinical, molecular, and radiologic data.

There are several innovative aspects of this classification. First, it relies on a multidisciplinary approach with integration of clinical, radiologic, molecular, and imaging features. Second, there is a completely new proposal to provide diagnostic criteria and terminology in small biopsies and cytology, a problem not addressed in previous World Health Organization classifications. Third, for patients with advanced lung AD, epidermal growth factor receptor mutation assessment is recommended, so small biopsy and cytology specimens need to be processed strategically not only for diagnosis but also to

Department of Pathology and Laboratory Medicine, Fondazione IRCCS National Cancer Institute, and Department of Medicine, Surgery, and Dentistry, University of Milan School of Medicine, Milan, Italy.

Disclosure: The author declares no conflicts of interest.

Address for correspondence: Giuseppe Pelosi, MD, MIAC, Department of Pathology and Laboratory Medicine, Fondazione IRCCS National Cancer Institute, Via G. Venezian, 1, I-20133 Milano, Italy. E-mail: giuseppe.pelosi@istitutotumori.mi.it and giuseppe.pelosi@unimi.it

Copyright © 2011 by the International Association for the Study of Lung Cancer

ISSN: 1556-0864/11/0602-0241

Journal of Thoracic Oncology • Volume 6, Number 2, February 2011

241
preserve tissue for molecular testing. Fourth, for resected ADs, the concepts of AD “in situ” (AIS) and minimally invasive AD (MIA) are introduced to define a subset of patients who should have a 100% disease-free survival. Fifth, in patients with invasive ADs, the introduction of comprehensive histologic subtyping and classification according to the predominant subtype has implications for prognosis and clinical prediction that could help to identify patients for adjuvant therapy even in early stage lung AD. Furthermore, it improves stratification of invasive ADs to allow for molecular and radiologic correlations and ultimately may impact on tumor, node, metastasis (TNM) staging if tumor size may be better predicted by the invasive component size rather than the gross diameter. The dogma that AD classification had to rely exclusively on standard hematoxylin and eosin-stained sections rather than under the guidance of findings stemming from immunohistochemistry or molecular assays has been overcome in the present classification, particularly in small biopsies.

Although this classification of AD still uses a rather traditional language, there are significant improvements in comparison with the previous schemes. First, a clear subdivision of AD-related lesions into preinvasive and invasive growths, the former comprising atypical adenomatous hyperplasia and the new concept of AIS (nonmucinous and mucinous types) to replace the time-honored and often misinterpreted term of bronchioloalveolar carcinoma (BAC), and the latter made of actually invasive tumors classified according to predominant growth patterns and variants. The sharing of a continuum of morphological changes between adenomatous hyperplasia and nonmucinous AIS, a cytologically low-grade lesion composed of Clara cells and/or type II pneumocytes growing along preexisting alveolar/bronchiolar structures (lepidic pattern) but lacking pleural, stromal, or vascular invasion, makes an unifying concept of preinvasive neoplastic lesions possible with associated risk of progression to invasive tumors. The nosologic position of mucinous AIS still remains debated, and this term should be limited to rare, small-sized, circumscribed, and solitary lesions featuring bland mucinous cells sometimes resembling bronchial goblet cells. The assumption that AIS is a cytologically bland lesion devoid of any invasion but capable of further molecular changes and progression to eventual invasive AD helps us to distinguish this event from lepidic growths of invasive primary or even metastatic AD, which usually are of higher grade. The strict definition of AIS, however, should avoid continuing the improper use of the term BAC abused until recently to indicate both noninvasive and invasive AD with different histologic features and clinical behavior. The upper limit of 3 cm for AIS should allow for complete histologic sampling and avoiding confusion with larger tumors for which there is insufficient evidence that they will have a 100% disease-free survival. When the next TNM revision is developed, AIS should belong to “pTis” category in keeping with the general rules of TNM staging. Invasive mucinous AD (formerly known as mucinous BAC), and enteric AD with intestinal differentiation. Signet ring cell clear cell AD disappear as individual entities because they are regarded as cytological changes occurring in multiple histologic patterns, but when these features are identified even in small amounts, they should be recorded in the diagnosis preferably quantifying them, so the presence of these cytologic features will be reported more often than in prior classifications. This AD classification according to the predominant histologic subtypes has prognostic, molecular, and predictive implications; may also assist to distinguish multiple lung primaries from metastases; and is robustly correlated with either radiologic imaging counterparts or TNM staging according to the proportion of AIS component and may support an architectural approach to grading based on the growth patterns.

Another innovation of the present classification is the introduction of the category of MIA for indicating a usually nonmucinous, lepidic predominant, and low-grade tumor, measuring 3 cm or less, with invasion being limited up to a maximum 5 mm (either showing subtypes other than a lepidic pattern or myofibroblastic stroma). The lack of vascular or pleural invasion or tumor necrosis justifies the excellent prognosis of this tumor type close to 100% just like AIS. In the next TNM revision, MIA may be classified as “pTmi.” In invasive AD where the invasion focus is >5 mm, the approach of this new classification raises the consideration that the size of the invasive components on histologic slides or the solid component on computed tomography scan may be appropriate for sizing T factor, if validated by additional studies.

Among invasive AD, quite wise has been the replacement of the confusing mixed subtype AD, by the new approach of classification according to the predominant growth patterns and variants by semiquantitative assessments in 5 to 10% increments to reflect the spectrum of diverse histologic subtypes in these tumors and different molecular properties. This approach could ameliorate the diagnostic reproducibility of AD and allow for data sharing and comparability. Among growth patterns, a new category of invasive AD with predominant nonmucinous lepidic component resembling AIS/MIA has been devised to replace the confusing term AD with BAC features. Other new entries include AD with a predominant micropapillary pattern (similar to analogous life-threatening tumors arising in breast, urinary bladder, or ovary), invasive mucinous AD (formerly known as mucinous BAC), and enteric AD with intestinal differentiation. Signet ring cell and clear cell AD disappear as individual entities because they are regarded as cytological changes occurring in multiple histologic patterns, but when these features are identified even in small amounts, they should be recorded in the diagnosis preferably quantifying them, so the presence of these cytologic features will be reported more often than in prior classifications. This AD classification according to the predominant histologic subtypes has prognostic, molecular, and predictive implications; may also assist to distinguish multiple lung primaries from metastases; and is robustly correlated with either radiologic imaging counterparts or TNM staging according to the proportion of AIS component and may support an architectural approach to grading based on the growth patterns.

Commendable is the recommendation to assess any advanced lung AD for epidermal growth factor receptor mutations and the encouragement to be aware of the importance of molecular studies. This is a rapidly evolving field, and hopefully, in the near future, additional molecular biomarkers will be validated in clinical trials testing new target therapies (e.g., crizotinib for anaplastic lymphoma kinase translocation). So, managing appropriately small biopsy and cytology specimens should thus become a strategic goal not only for rendering final diagnoses but also to preserve tissue for further molecular testing. A true paradigm shift of the traditional morphology-based approach and an authentic revolution of this classification regards the recommendation of relying on ancillary tools (immunohistochemistry and multi-
disciplinary setting) when rendering different diagnoses in small cytology and biopsy specimens,\textsuperscript{10} to limit the category of non-small cell lung cancer—not otherwise specified to only those cases in which morphology, immunohistochemistry, and multidisciplinary setting are not contributory.

Summing up, I feel that the present classification by Dr. Travis is a valuable global rethinking of lung AD, which finds its strength and innovation in a close integration of improved morphology, clinical and imaging data, immunohistochemistry use, and molecular assays. Thus, this classification is likely to become a common language and denominator among pathologists worldwide, especially those who are engaged with the patient care by moving beyond diagnostics.\textsuperscript{21}

ACKNOWLEDGMENTS
This editorial is dedicated to the memory of Carlotta, an extraordinarily lively girl who untimely died of cancer in the prime of life.

REFERENCES