Review Article

The 2011 IASLC/ATS/ERS pulmonary adenocarcinoma classification: a landmark in personalized medicine for lung cancer management

Yong Tang*, Zhe He*, Qihang Zhu, Guibin Qiao

Department of Thoracic Surgery, General Hospital of Guangzhou Military Command of PLA, Guangzhou 510010, China
*These authors contributed equally to this work.
Correspondence to: Guibin Qiao. Department of thoracic surgery, General Hospital of Guangzhou Military Command of P.L.A, Liuhua Road 111, Guangzhou 510010, China. Email: guibinqiao@126.com.

Abstract: In 2011, three authoritative academic communities, International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society (IASLC/ATS/ERS), published a novel lung adenocarcinoma histologic classification. The major modifications of this classification include the abolishment of the term "bronchioloalveolar carcinoma (BAC)", the establishment of new classification systems for resection and small biopsy or cytology specimens, the emphasis of molecular test and comprehensive histologic evaluation for tumor specimens, etc. This new lung adenocarcinoma classification signifies the era of personalized medicine comes to real-world practice in lung cancer field. Here, we introduce the background why the lung adenocarcinoma classification needs to be revised, and what we should consider in clinical practice according to this new classification.

Keywords: Adenocarcinoma; lung neoplasms; classification

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In the past few decades, the incidence of lung adenocarcinoma has been increasing rapidly worldwide. Adenocarcinoma has become the most common histological type of lung cancer, and approximately a half of lung cancer patients are diagnosed with adenocarcinoma type at present (1). Meanwhile, a great progress in oncology, surgery, radiology, and molecular biology has significantly improved the understanding of lung adenocarcinoma (2-9). Therefore, the 2004 WHO lung adenocarcinoma classification cannot perfectly guide current clinical practice.

In 2011, under the lead of a legendary scholar, Dr. Travis, experts from International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society (IASLC/ATS/ERS) reached a consensus on new lung adenocarcinoma classification (10). The new classification stemmed from a multidisciplinary approach with integration of clinical, radiologic, molecular, and imaging features, and it could further improve our diagnostic, prognostic, and predictive capabilities for lung adenocarcinoma. In this review, we introduce the background and main modifications of this reclassification, as well as the modern concepts which should be considered in clinical practice.

The reasons why we need a new classification for lung adenocarcinoma

As a result of advances in the last decade in the understanding of lung adenocarcinoma, particularly in area of medical oncology, molecular biology, and radiology (2-9), there is an urgent need for a new classification. The development of new classification was not based on pathology alone, but rather on an integrated multidisciplinary platform. New classification could provide not only pathologic information, but also predictive and prognostic guide for personalized therapy. The recently new developed three kinds of antitumor agents used in

lung cancer, including epidermal growth factor receptor (EGFR), tyrosine kinase inhibitors (TKI), pemetrexed, and bevacizumab, demanded the good distinction between adenocarcinoma and squamous cell carcinoma. These drugs are now available only for adenocarcinoma and certain specific adenocarcinoma mutations.

Another important reason for this modification of histologic classification was the term of "bronchioloalveolar carcinoma (BAC)" which had been applied for half of century but still remained confusion in clinical practice (11-16). As early as 1876, Professor Louis Malassez found and reported a pathology type, which is different from other lung cancer, not only maintains holding complete alveoli structure, but also has features such as well cancer cellular differentiation, growth by the alveolar wall, and slightly response from basilar membrane. With the accumulation of clinical information and further experiments, in 1960, Professor Liebow came up with the name of BAC (17), then had been approved by public, eventually was listed as one of two subtypes of lung adenocarcinoma in the WHO first lung cancer organization classification in 1967. The definition of BAC got expounded in 1999, strictly required the cancer cellular expanding as squame, complete alveoli structure, basilar membrane, vein and pleura not damaged by cancer cellular. The 2004 lung cancer histologic classification emphasized the strict definition of BAC again, and the term BAC required to be used only for the tumor without invasive component (18). However, this concept was not accepted widely for clinical practice and research communication. Before the 2011 new classification was announced, the term BAC continued to be confusedly used for tumors including BAC component. The former term BAC was used for abroad spectrum of tumors including (I) solitary small noninvasive peripheral lung tumors (pure BAC); (II) adenocarcinomas with minimal invasion (adenocarcinoma, predominantly BAC); (III) adenocarcinomas with BAC component (adenocarcinomas, predominantly invasive adenocarcinoma); (IV) mucinous BAC; and (V) widespread advanced disease with morphologic BAC appearance under the microscope (10). The consequences of confusion from the above uses of the former BAC term in the clinical and research arenas had been the subject in the lung cancer field. Therefore, new lung adenocarcinoma histologic classification recommended discontinuing the use of the term "BAC".

Other reasons for reclassifying lung adenocarcinoma included the evaluation of small biopsies and cytology specimens and assessment of biomarkers, etc.

What should we learn from new lung adenocarcinoma classification

The 2011 lung adenocarcinoma classification developed by a multidisciplinary approach with integration of clinical, radiologic, molecular, and imaging features. There is a completely new system to provide diagnostic criteria and terminology in small biopsies and cytology, and this was not addressed in previous World Health Organization classifications. In addition, new histologic classification recommends that EGFR mutation and echinoderm microtubule associated protein-like 4 (*EML4*) and anaplastic lymphoma kinase (ALK) gene fusions (*EML4-ALK*) should be assessed for patients with advanced lung adenocarcinoma. Therefore, small biopsy and cytology specimens need to be processed strategically not only for diagnosis but also to preserve tissue for molecular testing. Besides standard hematoxylin and eosin-stained sections, this classification also emphasizes the role of immunohistochemistry in the differential diagnoses between lung adenocarcinoma and other histologic types, particular for small biopsy and cytology specimens. The comprehensive histologic subgrouping and evaluation according to the predominant subtype were introduced for the first time; it has implications for prognosis and clinical prediction that could help to identify patients for adjuvant therapy even with early disease. Among invasive adenocarcinoma, the major change has been the replacement of the confusing mixed subtype adenocarcinoma, 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 improve the diagnostic reproducibility of adenocarcinoma and allow for data sharing and comparability. This adenocarcinoma classification according to the predominant histologic subtypes has prognostic, molecular, and predictive implications; may also help to distinguish multiple lung primaries from metastases; and is robustly correlated with either radiologic imaging counterparts or TNM staging according to the proportion of adenocarcinoma *in situ* (AIS) component and may support an architectural approach to grading based on the growth patterns.

With the discontinue using of BAC term, new classification introduces two concepts of "AIS" and minimally invasive adenocarcinoma (MIA) to define a subgroup of patients who should have a 100% disease-free survival. The survival rate of AIS and MIA can reach 100%,

whereas the widely spread low grade adenocarcinoma has poor prognosis (19-23). Because the same diagnosis caused different prognosis, the application of BAC was questioned. Therefore, the new classification suggested to remove BAC application and used other terms instead, with the result that lung adenocarcinoma was classified to AIS, MIA, Lepidic predominant adenocarcinoma (nonmucinous), Adenocarcinoma, predominantly invasive with some nonmucinous lepidic component; invasive mucinous adenocarcinoma. A distinct subdivision of adenocarcinoma related lesions into preinvasive and invasive growths, the former comprising atypical adenomatous hyperplasia (AAH) and the new concept of AIS to replace the time-honored and often misinterpreted term of BAC, and the latter made of actually invasive tumors classified according to predominant growth patterns and variants by comprehensive histologic evaluation. The sharing of a continuum of morphological changes between AAH 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 assumption that AIS is a cytologically bland lesion without 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 adenocarcinoma, which usually are of higher grade. The 2012 NCCN guide book accepted this suggestion. AIS and MIA are new terms aiming at opacity in the lung adenocarcinoma spectrum meaning either a pure ground glass nodule (GGN) or part-solid nodule with a predominant ground-glass component, and the survival rate can reach or close to 100% after operative removal in 5 years (24).

At last, the 2011 classification improves stratification of invasive lung adenocarcinoma to allow for molecular and radiologic correlations and ultimately may impact on TNM staging if tumor size may be better predicted by the invasive component size rather than the gross diameter. 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 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 system. In the next TNM revision, MIA may be classified as "pTmi".

The 2011 lung adenocarcinoma classification makes multiple recommendations in pathological, clinical, molecular research and surgical perspectives. The main recommendations are listed below (10).

Pathology recommendations

(I) New classification recommends discontinuing the use of the term "BAC" (strong recommendation, low-quality evidence);

(II) For small (<3 cm), solitary adenocarcinomas with pure lepidic growth, new classification recommends the term "AIS" that defines patients who should have 100% disease-specific survival, if the lesion is completely resected (strong recommendation, moderate quality evidence). Remark: Most AIS are nonmucinous, rarely are they mucinous;

(III) For small (<3 cm), solitary, adenocarcinomas with predominant lepidic growth and small foci of invasion measuring ≤0.5 cm, new classification recommends a new concept of "MIA" to define patients who should have near 100%, disease-specific survival, if completely resected (strong recommendation, low-quality evidence). Remark: Most MIA are nonmucinous, rarely are they mucinous;

(IV) For invasive adenocarcinomas, new classification suggests comprehensive histologic subtyping be used to assess histologic patterns semiquantitatively in 5% increments, choosing a single predominant pattern. New classification also suggests that individual tumors be classified according to the predominant pattern and that the percentages of the subtypes be reported (weak recommendations and low-quality evidence);

(V) In patients with multiple lung adenocarcinomas, new classification suggests comprehensive histologic subtyping in the comparison of the complex, heterogeneous mixtures of histologic patterns to determine whether the tumors are metastases or separate synchronous or metachronous primaries (weak recommendation, low-quality evidence);

(VI) For nonmucinous adenocarcinomas previously classified as mixed subtype where the predominant subtype consists of the former nonmucinous BAC, new classification recommends use of the term LPA and discontinuing the term "mixed subtype" (strong recommendation, low-quality evidence);

(VII) In patients with early-stage adenocarcinoma, new classification recommends the addition of

"micropapillary predominant adenocarcinoma", when applicable, as a major histologic subtype due to its association with poor prognosis (strong recommendation, low-quality evidence);

(VIII) For adenocarcinomas formerly classified as mucinous BAC, new classification recommends that they be separated from the adenocarcinomas formerly classified as nonmucinous BAC and depending on the extent of lepidic versus invasive growth that they be classified as mucinous AIS, mucinous MIA, or for overtly invasive tumors "invasive mucinous adenocarcinoma" (weak recommendation, low-quality evidence);

(IX) For small biopsies and cytology, new classification recommends that NSCLC be further classified into a more specific type, such as adenocarcinoma or squamous cell carcinoma, whenever possible (strong recommendation, moderate quality evidence);

(X) New classification recommends that the term NSCLC-NOS be used as little as possible, and be applied only when a more specific diagnosis is not possible by morphology and/or special stains (strong recommendation, moderate quality evidence).

Clinical recommendation

In patients with advanced lung adenocarcinoma, new classification recommends testing for *EGFR* mutation (strong recommendation, moderate quality evidence).

Remarks: This is a strong recommendation because potential benefits clearly outweigh harms. This recommendation assumes that correct classification by *EGFR* mutation status is associated with important benefit based on randomized phase 3 clinical trials of EGFR-TKI therapy, which demonstrates a predictive benefit for response rate and PFS, but not overall survival, and subset analyses of multiple additional studies.

Molecular research recommendations

(I) More investigation is needed of copy number variation, genomic, and proteomic markers for their relationship to clinical and pathologic variables;

(II) EML4-ALK fusion gene needs further study, particularly in EGFR/KRAS-negative cases;

(III) New classification recommends that research studies of molecular markers be based on well-annotated clinical and pathologic datasets, with adenocarcinomas diagnosed according to this classification;

(IV) MicroRNAs need further evaluation to determine whether they can be helpful in lung adenocarcinoma risk stratification and outcome prediction. There is limited information regarding correlation with adenocarcinoma subtype classification;

(V) Investigations combining both genomic and proteomic studies are needed to determine whether they can provide more accurate subclassification of NSCLC and adenocarcinoma, and more precise information regarding the risk stratification, outcome prediction, and treatment selection for different subtypes of adenocarcinoma.

Radiology recommendations

(I) When opacity in the lung adenocarcinoma spectrum is either a pure GGN or part-solid nodule with a predominant ground-glass component, new classification recommends that the term BAC no longer be used. These tumors should be classified by the new terms: AIS, MIA, and LPA (strong recommendation, low-quality evidence);

(II) For overtly invasive adenocarcinomas previously classified as mucinous BAC, new classification recommends they be separated from nonmucinous adenocarcinomas and be classified as invasive mucinous adenocarcinoma (strong recommendation, moderate quality evidence).

Remark: At computed tomography (CT), this entity is usually solid or mostly solid, has frequent air bronchograms, shows a lobar or multilobar distribution, and frequently consists of multiple nodular or consolidative opacities (former term multicentric BAC).

Surgery research recommendations

(I) The precise role of limited resection has not been determined yet because of a lack of randomized prospective trials;

(II) The extent of lymph node dissection remains controversial;

(III) The accuracy of frozen section in assessing the presence of invasive adenocarcinoma and the accuracy of frozen section or cytology of resection margins in sublobar resections need to be investigated further, and specific guidelines for frozen section analysis should be developed to guide intraoperative decisions;

(IV) Treatment of multiple lesions has not been standardized.

How should we practice under the guide of new classification

The 2011 IASLC/ATS/ERS lung adenocarcinoma classification is a result of recent revolutionary advances in the field of lung cancer. It was developed through a multidisciplinary approach with close integration of improved morphology, clinical and imaging data, immunohistochemistry use, and molecular assays. Therefore, the pathologists play an important and expanding role in the diagnosis and treatment of lung cancer. In addition, this new classification marks the management of lung cancer truly comes to the era of personalized medicine in the real-world practice. Physicians involved in the care of lung cancer should be aware of several concepts of modern medicine, including the concept of personalized medicine, the concept of integrated medicine and the concept of medical resources protection, to provide the best medical care for patients with lung adenocarcinoma.

The concept of medical resources protection

Because the majority of lung adenocarcinoma patients are presented as advanced or metastatic disease, small biopsy and cytology specimens are critical issue for the personalized treatment. For small biopsy and cytology specimens of lung tumors, best distinction between adenocarcinoma and squamous cell carcinoma is recommended for specific therapies. Furthermore, for patients with advanced lung adenocarcinoma, EGFR and ALK assessments are recommended, so small biopsy and cytology specimens need to be processed strategically not only for diagnosis but also to preserve tissue for molecular testing. Patients with lung adenocarcinoma are eligible for pemetrexed or bevacizumab-based chemotherapy regimens. Patients with adenocarcinoma should also be tested for *EGFR* mutations because patients with *EGFR* mutation-positive tumors may be eligible for first-line TKI therapy.

There is greater clinical interest in application of additional pathology tools to improve the diagnosis in small biopsies (bronchoscopic, needle, or core biopsies) and cytology specimens from patients with advanced lung cancer, when morphologic features are not clear. In those cases where a specimen shows NSCLC lacking either definite squamous or adenocarcinoma morphology, immunohistochemistry may refine diagnosis. To preserve as much tissue as possible for molecular testing in small biopsies, the workup should be minimal. New classification suggests the initial evaluation use as only one adenocarcinoma marker and one squamous marker. At present, TTF-1 seems to be the single best marker for adenocarcinoma (25). TTF-1 provides the added value of serving as a pneumocyte marker that can help confirm a primary lung origin in 75% to 85% of lung adenocarcinomas. This can be very helpful in addressing the question of metastatic adenocarcinoma from other sites such as the colon or breast. Diastase periodic acid Schiff or mucicarmine mucin stains may also be of value. P63 is consistently reported as a reliable marker for squamous histology and CK5/6 also can be useful. Cytokeratin 7 also tends to stain adenocarcinoma more often than squamous cell carcinoma (26). It is possible that cocktails of nuclear and cytoplasmic markers (TTF-1/CK5/6 or p63/napsin-A) may allow for use of fewer immunohistochemical studies of multiple antibodies. Cases positive for an adenocarcinoma marker (i.e., TTF-1) and/or mucin with a negative squamous marker (i.e., p63) should be classified as "NSCLC favor adenocarcinoma" and those that are positive for a squamous marker, with at least moderate, diffuse staining, and a negative adenocarcinoma marker and/or mucin stains, should be classified as "NSCLC favor squamous cell carcinoma", with a comment specifying whether the differentiation was detected by light microscopy and/or by special stains. These two small staining panels are generally mutually exclusive. If an adenocarcinoma marker such as TTF-1 is positive, the tumor should be classified as NSCLC, favor adenocarcinoma despite any expression of squamous markers. If the reactivity for adenocarcinoma versus squamous markers is positive in a different population of tumor cells, this may suggest adenosquamous carcinoma. If tumor tissue is inadequate for molecular testing, there may be a need to rebiopsy the patient to perform testing that will guide therapy. Cytology is a powerful tool in the diagnosis of lung cancer, in particular in the distinction of adenocarcinoma from squamous cell carcinoma. Whenever possible, cytology should be used in conjunction with histology in small biopsies. Material derived from aspirates or effusions may have more tumor cells than a small biopsy obtained at the same time, so any positive cytology samples should be preserved as cell blocks, so that tumor is archived for immunohistochemical and molecular studies. Furthermore, these materials should be used judiciously in making the diagnosis to preserve as much material as possible for potential molecular studies.

The concept of integrated medicine

Because of the recent advances in the understanding

of lung adenocarcinoma, the 2011 classification was developed from a multidisciplinary approach with close integration of pathology, radiology, molecular biology and clinical research. In clinical practice, physicians should keep in mind that integrated knowledge and skills could provide the best care for patients with advanced lung adenocarcinoma. Recent advances in radiologic-pathologic correlation between CT and histologic assessments of lung adenocarcinoma have allowed for improved preoperative prediction of its histologic subtype, associated patient prognosis, and multidisciplinary treatment planning. Since the majority of lung cancer patients present at advanced and unresectable stages, the determination of therapy for adenocarcinoma often depends on such a radiologic-pathologic correlation and on limited characterization from small biopsy and cytology specimens. Balancing the clinical need for more specific histologic/molecular characterization of adenocarcinoma with the increased use of limited specimens has elevated the level of sophistication in the description and handling of lung adenocarcinoma specimens. There may be cases where multidisciplinary correlation can help guide a pathologist in their evaluation of small biopsies and/or cytology specimens from lung adenocarcinomas. For example, if a biopsy showing NSCLC-NOS is obtained from an Asian, female, never smoker with GGNs on CT scan, the pathologist should know this information as the tumor is more likely to be adenocarcinoma and harbours an *EGFR* mutation (10).

The concept of personalized medicine

The 2011 lung adenocarcinoma classification stemmed from a multidisciplinary with integration of clinical, radiologic, molecular biologic and pathologic data. The introduction of this classification is called a revolutionary event in the field of lung cancer, and is now being hailed as a landmark in personalized medicine for lung cancer management. Before a decade, the treatment strategy for lung cancer had been made only depending on distinction between NSCLC and SCLC histology. However, at the present time, the treatment strategy for lung cancer is made not according to histologic subtype of tumor alone, but the radiologic presentation, the tumor marker status and clinical features also should be considered.

For patients with advanced lung adenocarcinoma, the best choice of anti-tumor drug for treatment is pemetrexed therapy. Advent of successful TKI targeted therapy, directed at specific cell types and subtypes of lung cancer, has increased the need for a more specific cell-type diagnosis. Lung adenocarcinoma may respond to bevacizumab therapy, but severe, even life-threatening, hemorrhage has been reported in patients with squamous cell carcinoma who receive bevacizumab therapy. Although the latter may be related to the bulky size of centrally located squamous cell carcinomas, this observation has been considered particularly urgent for patient care (27). For the first time, two different systems have been developed in this classification, resection specimens and small biopsy and/or cytology specimens, to facilitate the personalized treatment for patients. Even for small biopsy and cytology specimens, EGFR and ALK status assessments are strongly recommended to make the possibility for receiving first line molecular targeted therapy.

For the early stage lung adenocarcinoma, traditionally standard lobectomy plus systematic lymph node dissection has been questioning widely. The new terms of AIS and MIA developed in this classification raise the questions whether these diagnoses can be anticipated by a GGN appearance on CT when presenting as a small, solitary lesion and whether limited resection may be effective therapy for such lesions. Lobectomy is still considered to be standard surgical treatment even for tumors 2 cm or less in size, which have a solid appearance on CT, because such tumors are invasive carcinomas. Whether there can be any change in this standard care for lesions that present with a GGN appearance on CT awaits the results of three randomized trials (JCOG0804 and JCOG0802 in Japan and CALGB 140503 in North America) that randomize such patients to either lobectomy or sublobar resection. Recently, there have been numerous retrospective studies that have suggested that sublobar (limited) resection for early lung cancers may be adequate surgical treatment (9); however, these are not randomized trials. Most reports showed no difference in survival or in locoregional recurrence between lobectomy and sublobar resection for tumors 2 cm or less in size. Tumors with a GGN appearance on CT are reported to have 100% disease-free survival at 5 years after sublobar resection.

For patients with stage I lung cancer, adjuvant chemotherapy is not recommended by NCCN and other authoritative guidelines. However, the limitation of 5-year overall survival of stage I patients, about 70%, raises the interesting in which subgroup of stage I could benefit from chemotherapy after complete resection.

There are numerous studies aimed at seeking the tumor markers to predict patients who can benefit from adjuvant chemotherapy, but the preliminary results are not promising. For the first time, this new lung adenocarcinoma classification introduced a new subtype of micropapillary predominant adenocarcinoma for early-stage patients. The micropapillary pattern of lung adenocarcinoma was described in the 2004 WHO classification in the discussion, but there were too few publications on this topic to introduce it as a formal histologic subtype (28). Although most of the studies have used a very low threshold for classification of adenocarcinomas as micropapillary, including as low as 1% to 5%, it has recently been demonstrated that tumors classified as micropapillary according to the predominant subtype also have a poor prognosis similar to adenocarcinomas with a predominant solid subtype. All articles on the topic of micropapillary lung adenocarcinoma in early-stage patients have reported data indicating that this is a poor prognostic subtype (29). Additional evidence for the aggressive behavior of this histologic pattern is the overrepresentation of the micropapillary pattern in metastases compared with the primary tumors, where it sometimes comprises only a small percentage of the overall tumor (30). Therefore, clinicians should consider adjuvant chemotherapy for stage I patients with micropapillary predominant adenocarcinoma.

The management of multiple pulmonary nodules becomes a common presentation but a Gordian knot (31). In patients with multiple lung adenocarcinomas, the new classification suggests comprehensive histologic subtyping may facilitate in the comparison of the complex, heterogeneous mixtures of histologic patterns to determine whether the tumors are metastases or separate synchronous or metachronous primaries (32). In the setting of multifocal lung adenocarcinomas, when there is no evidence of mediastinal lymph node invasion, multiple nodules are not a contraindication for surgical exploration. A standard treatment algorithm for multiple lesions has not yet been established. Several factors have to be taken into consideration: number and size of the different nodules, synchronous versus metachronous lesions, ipsilateral versus contralateral, primary versus metastatic lesions, and specific nature (AAH, AIS, and MIA) (33).

In conclusion, the 2011 IASLC/ATS/ERS lung adenocarcinoma classification is a revolutionary landmark in the field of lung cancer. In order to provide the best care for lung cancer patients, physicians should realize the rational for reclassification and the modifications recommended by this classification.

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