

# Advances in lung adenocarcinoma classification: a summary of the new international multidisciplinary classification system (IASLC/ATS/ERS)

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**Abstract:** Due to advances in the understanding of lung adenocarcinoma since the advent of its 2004 World Health System classification, an international multidisciplinary panel [sponsored by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS)] has recently updated the classification system for lung adenocarcinoma, the most common histologic type of lung cancer. Here, we summarize and highlight the new criteria and terminology, certain aspects of its clinical relevance and its potential treatment impact, and future avenues of research related to the new system.

**Keywords:** Adenocarcinoma; lung neoplasms; classification; radiology; pathology

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## Introduction

Lung cancer is the leading cause of cancer death worldwide (1), accounting for 26% of such deaths in women and 28% in men in the USA (2). Of the histologic types of lung cancer, adenocarcinoma is the most common worldwide (3). Recent progress in oncology, radiology, and molecular biology has significantly advanced the understanding of lung adenocarcinoma and its subtypes, which has led to improvements in the paradigm for its clinical management. First, recent progress has highlighted the necessity of distinguishing lung adenocarcinoma from squamous cell carcinoma (SQCC), as several therapies are now available only for adenocarcinoma and certain specific adenocarcinoma mutations (4,5), including: pemetrexed (ineffective in SQCC); bevacizumab (associated with life-threatening hemorrhage in SQCC); crizotinib (targeted to adenocarcinoma with anaplastic lymphoma kinase *ALK* rearrangements); and epidermal growth factor receptor

(EGFR) tyrosine kinase inhibitors (TKIs, first-line therapy for advanced adenocarcinoma with *EGFR* mutations). Further, recent advances in radiologic-pathologic correlation between computed tomography (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 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.

However, the latest World Health Organization

**Table 1** Proposed IASLC/ATS/ERS classification of lung adenocarcinoma in resection specimens

Preinvasive
Atypical adenomatous hyperplasia
Adenocarcinoma <i>in situ</i> *: qualified as nonmucinous, mucinous, or mixed mucinous/nonmucinous
Minimally invasive adenocarcinoma*
Qualified as nonmucinous, mucinous, or mixed mucinous/nonmucinous
Invasive adenocarcinoma <sup>#</sup>
Lepidic predominant*
Acinar predominant
Papillary predominant
Micropapillary predominant
Solid predominant with mucin production
Variants of invasive adenocarcinoma <sup>§</sup>
Invasive mucinous adenocarcinoma*
Colloid (also encompasses former mucinous cystadenocarcinoma category; note of resemblance to the former category can be made if appropriate)
Fetal (low and high grade)
Enteric <sup>+</sup>

\*, formerly part of the bronchioloalveolar carcinoma category; <sup>#</sup>, “mixed” category no longer available, due to IASLC/ATS/ERS proposal to use semiquantitative histologic characterization to discern predominant subtype pattern; <sup>§</sup>, signet ring and clear cell categories no longer available, due to their nonspecific presence in variety of histologic subtypes; <sup>+</sup>, new, rare category which shares characteristics with colorectal adenocarcinoma (which must first be excluded as a potential primary with lung metastases); IASLC, the International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society.

(WHO) classification of lung cancer from 2004 preceded these recent advances in the understanding of lung adenocarcinoma and included only limited relevant genetic and clinical criteria into the 2004 classification system. To accommodate these evolving issues, a multidisciplinary consensus of the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) has sought to accommodate these evolving issues with a new classification system specifically for lung adenocarcinoma, which (I) re-characterizes and expands on certain histologic designations [particularly “mixed” subtype and “bronchioloalveolar carcinoma” (BAC), *Table 1*]; (II) extrapolates the pathologic classification of resected specimens to a new additional classification system for small biopsy and cytology specimens; and (III) addresses immunohistochemical/molecular, radiologic and surgical considerations. The terminology and criteria of the new classification system are intended to better guide routine patient care and to improve accuracy of data collection for clinical trials (6).

### Resection specimens

In the new IASLC/ATS/ERS system, a distinction is made between atypical adenomatous hyperplasia (AAH), adenocarcinoma *in situ* (AIS), minimally invasive adenocarcinoma (MIA), invasive adenocarcinoma, and variants of invasive adenocarcinoma (7) (*Table 1*). The former term BAC, defined as lesions with *in situ* lepidic growth in the WHO classification, is no longer included in the new system, due to widespread confusion in the clinical and research arenas over its application to a broad range of tumors. The IASLC/ATS/ERS classification instead separates resected specimens formerly called BAC into several new pathologic categories/terms, ranging from preinvasive to invasive lesions (*Table 1*), associated with varying prognoses. For greater clarity, it also replaces the former “mixed” subtype with predominant histologic subtype characterization of resected specimens.

In the 2004 WHO classification, the preinvasive lesions included only AAH; now, the preinvasive category has

expanded to respect a continuum of morphologic changes between AAH and a new category, AIS, one of the lesions formerly called BAC. AAH is a small (usually  $\leq 0.5$  cm) proliferation of mild to moderate cell atypia in type II pneumocytes and/or Clara cells. AIS, on the other end of the preinvasive spectrum, is defined as a small neoplasia  $\leq 3.0$  cm with pure lepidic growth, along preexisting alveolar structures without stromal, vascular, or pleural invasion, although septal widening with sclerosis is common. AIS is expected to have 100% disease-specific survival when completely resected (8-10).

MIA is another new category of the former BAC lesion and is defined as a predominantly lepidic lesion measuring  $\leq 3.0$  cm with only small foci of invasion, the largest of which must be  $\leq 0.5$  cm. An invasive component in the new classification system is defined as either cells of a histologic subtype other than lepidic, or invasion of malignant cells into myofibroblastic stroma. For the MIA diagnosis, the tumor cannot contain necrosis or invasion into the lymphatics, blood vessels, or pleura (otherwise, the designation is elevated to invasive adenocarcinoma, detailed below). MIA is expected to have nearly 100% disease-specific survival when completely resected (8-10).

Diagnosis of AIS or MIA requires complete histologic sampling of the tumor and therefore cannot be made from small biopsy/cytology sampling. Most cases of AIS and MIA are nonmucinous but when appropriate should be qualified as mucinous, since preliminary findings suggest that such minimally invasive mucinous lesions will also have high survival rates.

As for a solitary resected adenocarcinoma larger than 3.0 cm that otherwise meets MIA/AIS criteria, without evidence of greater than minimal invasion, there is insufficient evidence regarding survival rate. The suggested designation for such a lesion is "lepidic predominant adenocarcinoma, suspect AIS or MIA", with a comment stating that an invasive component cannot be excluded if the specimen cannot be completely sampled.

More than 70% to 90% of resected lung adenocarcinomas fall into the invasive adenocarcinoma category. Most invasive adenocarcinomas show heterogeneous histologic patterns, which pathologists traditionally resisted quantifying due to poor reproducibility and instead classified into the "mixed" subtype. This diluted the clinical and prognostic utility of the "mixed" subtype, which relegated it to a wastebasket category and precluded the study of histologic patterns on prognosis. In the new classification system, histologic patterns are described semiquantitatively in 5% increments, and a

predominant pattern is deliberately chosen and assigned the largest percentage. This approach may ultimately provide a means for grading lung adenocarcinomas. Intraobserver and interobserver variability appears to be low experienced and specifically trained pathologists perform the histologic assessments (11-15). In addition to prognostication, histologic subtyping is useful in comparing multiple tumors to determine common or different patterns and thus determine if tumors are metastases or separate synchronous or metachronous primaries. This is particularly helpful when a previous tumor's slides are not available at the time of evaluation of a new tumor.

The major histologic patterns are lepidic, acinar, papillary, micropapillary, and solid. Lepidic-predominant adenocarcinoma (LPA) is nonmucinous and is another of the former BAC lesions. It demonstrates mostly lepidic growth with: (I) at least one focus of invasive adenocarcinoma measuring  $>0.5$  cm; (II) invasion into lymphatics, blood vessels or pleura; or (III) tumor necrosis. Predominant lepidic growth in the invasive adenocarcinomas is associated with favorable prognosis. Micropapillary is also a new major histologic subtype, introduced because such tumors portend a poor prognosis (16,17) similar to that of predominant solid type adenocarcinoma.

Solid-predominant invasive adenocarcinoma must be distinguished from SQCC and large cell carcinoma. Immunohistochemistry (IHC) may be indicated to make this determination in resection specimens. In fact, by utilizing IHC, large cell carcinoma can often be demonstrated to be poorly differentiated adenocarcinoma or SQCC. The prevalence of the diagnosis of large cell carcinoma is expected to diminish over time, if not disappear, as increasingly sensitive and specific markers of cell lineage become available (18,19).

Variants of invasive adenocarcinoma now include, among others (*Table 1*), the tumors previously classified as mucinous BAC, which in fact usually have usually demonstrated invasive components and are now termed "invasive mucinous adenocarcinoma". Nonmucinous adenocarcinomas and invasive mucinous adenocarcinoma differ in cell type, in IHC phenotype (*Table 2*), and in radiologic appearance (further details below). Invasive mucinous adenocarcinoma is also strongly correlated (76%) with *KRAS* mutation and almost entirely lack *EGFR* mutation, whereas nonmucinous AIS/MIA/LPA adenocarcinomas demonstrate the converse with 45% positivity for *EGFR* mutation but only 13% for *KRAS* mutation (*Table 2*). Invasive mucinous adenocarcinomas

	Non-mucinous AIS/MIA/LPA	Invasive mucinous adenocarcinoma
<b>Cell type</b>		
Mucin-filled	√	
Columnar	√	
Goblet	√	
Type II pneumocyte		√
Clara cell		√
<b>IHC</b>		
CK7	+++	+++
CK20	+	++
TTF-1	++	+
<b>Genotype</b>		
KRAS mutation	+	+++
EGFR mutation	++	+

AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; LPA, lepidic-predominant adenocarcinoma; EGFR, epidermal growth factor receptor.

may have the same heterogeneous mixture of lepidic, acinar, papillary, micropapillary, and solid patterns as nonmucinous tumors; however, the clinical significance of semiquantitative histologic pattern reporting for invasive mucinous adenocarcinoma is not yet certain and therefore not included in the new classification system. Invasive mucinous adenocarcinomas show a strong tendency for multicentric, multilobar, and bilateral lung involvement, which may reflect aerogenous spread. Mixtures of mucinous and nonmucinous tumors may rarely occur.

Colloid adenocarcinoma is an invasive adenocarcinoma variant that now also encompasses the former mucinous cystadenocarcinoma, a very rare lesion that likely is a part of the colloid adenocarcinoma spectrum. A comment can be made to note a resemblance to the former mucinous cystadenocarcinoma.

Enteric adenocarcinoma is added to the classification system to highlight this rare type of lung adenocarcinoma. While it shares morphologic and IHC features with colorectal adenocarcinoma, it is often histologically heterogeneous with some components that resemble primary lung adenocarcinoma (20). Clinical evaluation is needed to exclude a gastrointestinal primary.

Clear cell and signet ring cell features are now known to occur in the setting of various histologic patterns, without evidence of clinical significance beyond a stronger association with the solid pattern (21). Clear cell and signet ring cell

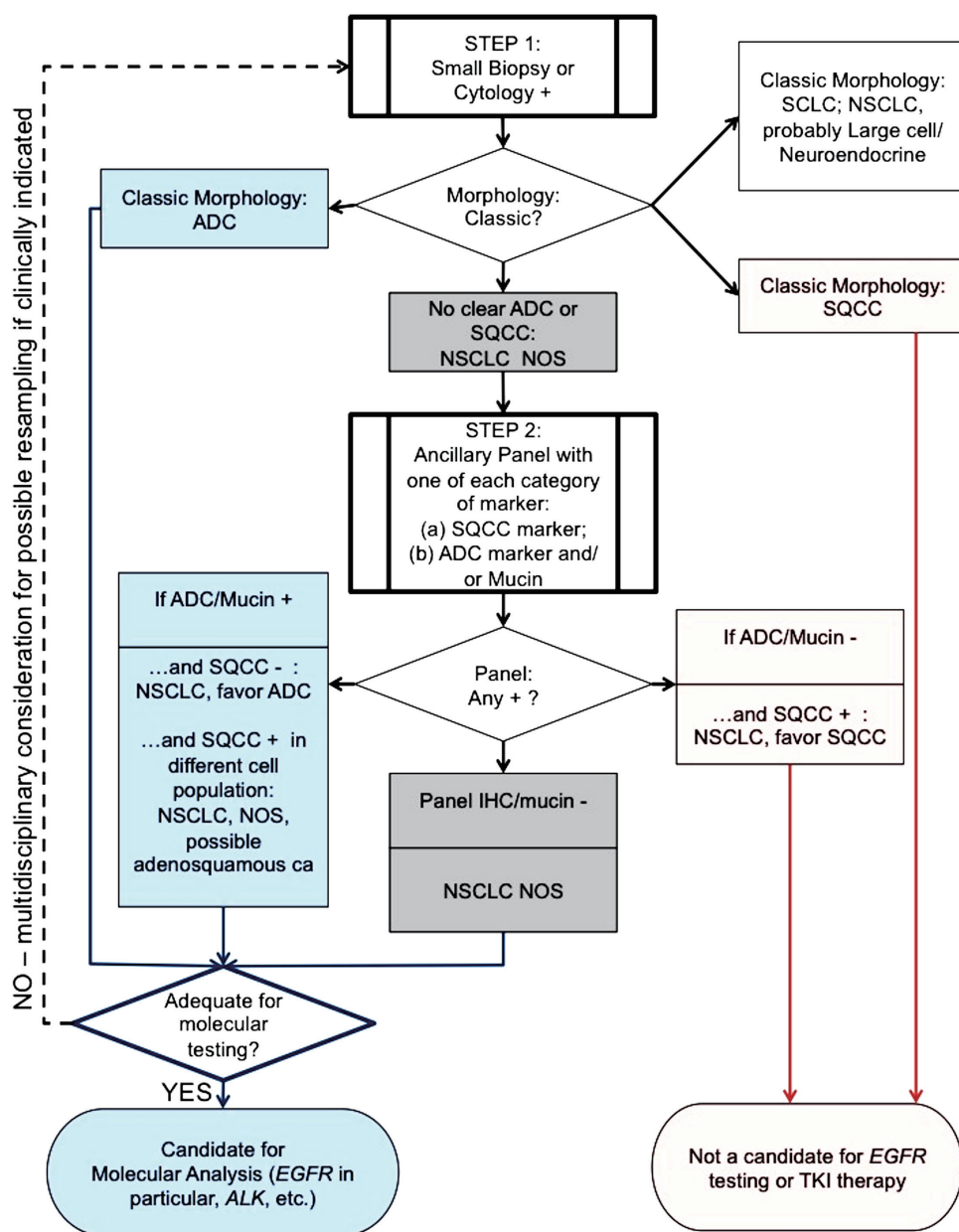
features can be recorded if present, but are no longer their own respective subtypes.

### Diagnosis on small biopsies/cytology

The histologic heterogeneity of lung adenocarcinoma limits the diagnostic accuracy of small biopsy/cytology specimens when compared to resected specimens. Small biopsy and cytologic specimen also precludes the diagnosis of such lesions as pure *in situ* adenocarcinoma and/or large cell carcinoma. However, because most lung cancers are not resected, the terminology used for small biopsy and cytology non-small cell lung cancer (NSCLC) diagnoses need to be adequate for treatment. The IASLC/ATS/ERS classification system is the first to provide standardized terminology for diagnosis in small biopsies and cytology (22) (*Figure 1*).

In many cases, adenocarcinoma and SQCC can be distinguished based solely on standard morphologic criteria: glandular architecture for adenocarcinoma and keratinization and intercellular bridges for SQCC. If adenocarcinoma architectural patterns are recognized, they can be mentioned in the report. Cytology also remains a useful adjunct to small biopsies and IHC in reducing diagnostic ambivalence, even proving on occasion to be more informative.

In NSCLC cases where the morphology is not distinctly



**Figure 1** Algorithm on diagnosis of lung adenocarcinoma by small biopsy (fiberoptic bronchoscopy, transbronchial, core, or surgical biopsy specimen) or cytology (effusion, aspirate, washing, or brushing). If a small biopsy/cytology specimen (Step 1) does not provide a classic morphologic diagnosis of a major histologic lung cancer type, an ancillary panel (Step 2) can potentially further distinguish between adenocarcinoma and squamous cell carcinoma. Usually, a single squamous cell marker and a single adenocarcinoma marker (or mucin) is adequate for this differentiation (please refer to the accompanying article for details). Further molecular characterization may be useful for adenocarcinoma or NSCLC NOS, if the specimen sample is adequate for molecular testing, to clarify the potential for such molecular-targeted therapy as TKI. For adenocarcinoma or NSCLC specimens that are inadequate for molecular testing or diagnostically problematic, a multidisciplinary discussion should be undertaken to consider the clinical utility for resampling. +, positive; -, negative; ADC, adenocarcinoma; SQCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer; NOS, not otherwise specified; IHC, immunohistochemistry; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor.



squamous or adenocarcinoma, an initial histologic/IHC staining panel should be used to refine the diagnosis to “favor adenocarcinoma” or “favor SQCC”, with a comment as to the utilized diagnostic method (light microscopy and/or stain, e.g.). This limited initial workup helps to preserve the remainder of specimen for any necessary molecular studies or further stains (23-29). Limited staining panels can classify the great majority of primary lung carcinomas using only a single marker each for adenocarcinoma [e.g., thyroid transcription factor-1 (TTF-1), mucin, cytokeratin 7] and SQCC (e.g., p63 in particular, cytokeratin 5/6); additional markers are needed in only a small minority of cases. TTF-1 appears to be the best adenocarcinoma marker (excluding for invasive mucinous adenocarcinoma, where cytokeratin 7 may be more useful), providing added value as a confirmatory pneumocyte marker for primary lung origin, in cases of possible metastatic origin (e.g., colon, breast). Clinico-pathologic correlation can also aid the diagnostic process when considerations include metastases or non-carcinoma primary tumors.

As adenocarcinoma and SQCC markers are generally mutually exclusive, “NSCLC-not otherwise specified (NOS)” can be reserved for cases with strong, concomitant features of both adenocarcinoma and SQCC, using comments to describe the relevant morphologic and/or IHC features. If the IHC features of adenocarcinoma (e.g., TTF-1 positive) and SQCC (e.g., p63 positive) present exclusively from each other in separate cell populations within one sample, the possibility of adenosquamous carcinoma can be suggested, although this diagnosis can be reliably made only with demonstration of 10% of each component on a full resection specimen.

The NSCLC-NOS designation should also be reserved for lung carcinoma cases without any definitive morphologic or IHC features of either adenocarcinoma or SQCC (including cases with only weak/equivocal squamous cell IHC staining). In these cases lacking any differentiating features, a multidisciplinary approach may be the best course, to include discussion of the potential diagnostic benefits and therapeutic impact of other characteristics (e.g., imaging features, clinical phenotype, molecular data, and further sampling) on future management.

It is hoped that the use of IHC will reduce the 20-40% of NSCLCs that would have previously been classified as NSCLC-NOS, to 5% or less of NSCLCs. However, of particular clinical import is that the NSCLC-NOS diagnosis should be strongly considered over NSCLC-favor SQCC in cases of truly equivocal morphology and

IHC staining, in order to preserve patient eligibility for further options. A diagnosis of SQCC or NSCLC-favor SQCC currently excludes a patient from histologically driven molecular testing (e.g., *EGFR* mutation, *ALK* rearrangement) and related chemotherapy (TKIs, e.g.), whereas patients with adenocarcinoma, NSCLC-favor adenocarcinoma, or NSCLC-NOS remain candidates for these options. In general, if *EGFR* mutation is present in an NSCLC-NOS tumor, it is more likely an adenocarcinoma than SQCC.

Because previous clinical trials utilized solely H&E slides for histologic classification, the impact of IHC on classification in future clinical trials needs to be further assessed (6). Limitations of small biopsy/cytology include definitive diagnoses such as large cell carcinoma, adenosquamous carcinoma and pleomorphic carcinoma.

### Molecular features/personalized medicine

Histologic molecular correlations for lung adenocarcinoma continue to evolve. The only strong molecular correlation for the predominant histologic subtypes of adenocarcinoma is currently *KRAS* mutation for invasive mucinous adenocarcinoma (10), which is typically also *EGFR* mutation negative, with TTF-1 negativity and MUC 2-5-6 positivity due to its origin of bronchiolar mucinous goblet cells. However, several therapies are available only for treatment of adenocarcinoma with certain molecular features (5). The most important current concepts are: (I) TKIs erlotinib and gefitinib are first-line therapy for patients with advanced lung adenocarcinomas with *EGFR* mutations, which have also been associated with a more indolent course of tumor progression; (II) adenocarcinomas with *ALK* rearrangements are responsive to crizotinib; (III) pemetrexed is contraindicated in SQCC due to a lack of effectiveness; (IV) SQCC is associated with life-threatening hemorrhage when treated with bevacizumab.

In advanced adenocarcinoma, testing for *EGFR* mutations and *ALK* rearrangements is now routine clinical practice. Other molecular targets in adenocarcinoma (for example, *ROS1* mutation) and even in SQCC (*FGFR1* amplification, *DDR2* mutation) will likely also become clinically relevant. Regardless of the target, though further validation is needed, molecular testing offers promise for distinguishing metastases from synchronous primary tumors, even when using small biopsy specimens. Moreover, it may assist in assessing acquired resistance to therapy. For example, *EGFR*-mutated adenocarcinomas treated with

TKIs acquire resistance through *EGFR T790M* mutation, *cMET* amplification, dedifferentiation with epithelial-mesenchymal transition, or development of a small cell carcinoma component. For patients with tumor progression after an initial response to targeted therapy, additional biopsies may be indicated to assess for molecular evolution of the tumor.

KRAS mutations are also frequently found in tumors with solid or micropapillary growth. EGFR mutations are most often seen in nonmucinous adenocarcinomas with lepidic, papillary, and possibly micropapillary growth (30-33). For *EGFR*-mutated tumors, the predominant histologic pattern may predict response to EGFR-TKI therapy (34). *ALK* rearrangement is associated with acinar growth, cribriform morphology, signet ring cell features, and TTF-1 and p63 co-expression (35,36). Despite imperfect correlation, these histologic-molecular associations emphasize the need for histologic subtyping in clinical practice and for the purposes of clinical trials. Questions surrounding intratumoral heterogeneity of phenotype and genotype require further study.

It is anticipated that molecular testing will be recommended for SQCCs in the near future; molecular targets under investigation include FGFR1 amplifications and DDR2 mutations.

Each institution needs a multidisciplinary strategy for obtaining and processing small biopsy/cytology specimens (37,38). Sufficient tumor must be present for diagnosis and for molecular studies. Most critical molecular studies can be performed using formalin-fixed, paraffin-embedded tissue. Preparation of cell blocks from cytology specimens, including pleural fluids, allows for both IHC and molecular studies. A defined biopsy/cytology protocol established in a multidisciplinary manner provides the best means to tailor lung cancer therapy to individual patients.

### Prognostic impact of architectural grading

There is no established grading system for lung adenocarcinoma in resection specimens, and the next revision of TNM staging will likely benefit from consideration of these new classification categories (e.g., AIS, MIA, LPA), as they are unique to adenocarcinoma among the other histologic types of lung cancer and appear to reflect prognosis. Although some studies have addressed architectural grading (39-41), nuclear grading (42-45), or both (46), prognosis for adenocarcinoma is overall probably best predicted by the size of the invasive component, rather

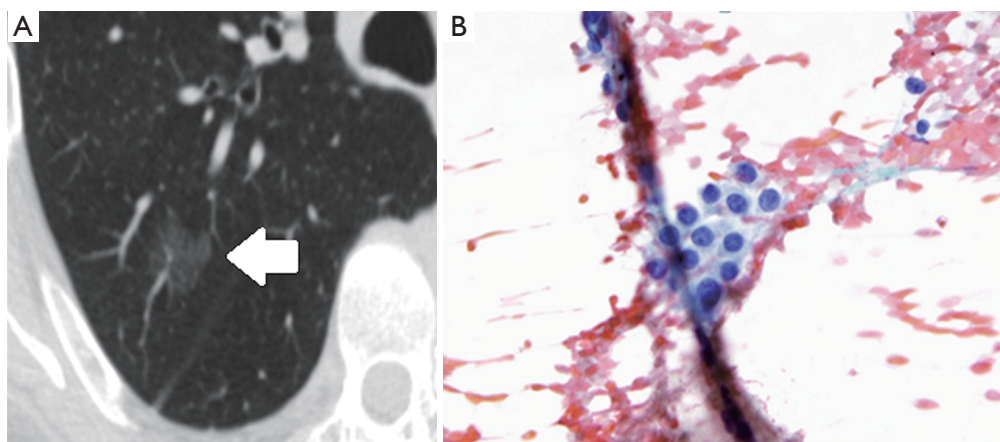
than by total tumor size that combines invasive and lepidic components (39,47). Therefore, the best determining factor for T status might be the size of the invasive component, which is addressed by the new classification criteria; for example, AIS might be classified as Tis, and MIA might be classified as Tmi.

Additionally, histologic subtype may help stratify patients; in early stage disease, the lepidic pattern has a favorable prognosis, papillary and acinar patterns have an intermediate prognosis, and a poorer prognosis is associated with micropapillary, mucinous/colloid, and solid patterns (40,48-56). The implications of other patterns (cribriform, fused glands) are also being investigated (13,57,58). Histologic subtyping may eventually help determine which early stage patients should receive adjuvant therapy, as well as who is best suited for limited resection or completion lobectomy (59). Also, its role in distinguishing intrapulmonary metastasis versus synchronous/metachronous primaries holds promise in TNM staging of adenocarcinoma, although a standard surgical algorithm for multiple nodules without mediastinal lymph node invasion has not yet been established. In advanced-stage disease, the prognostic significance of histologic subtyping is unclear (60-63). Further study is needed.

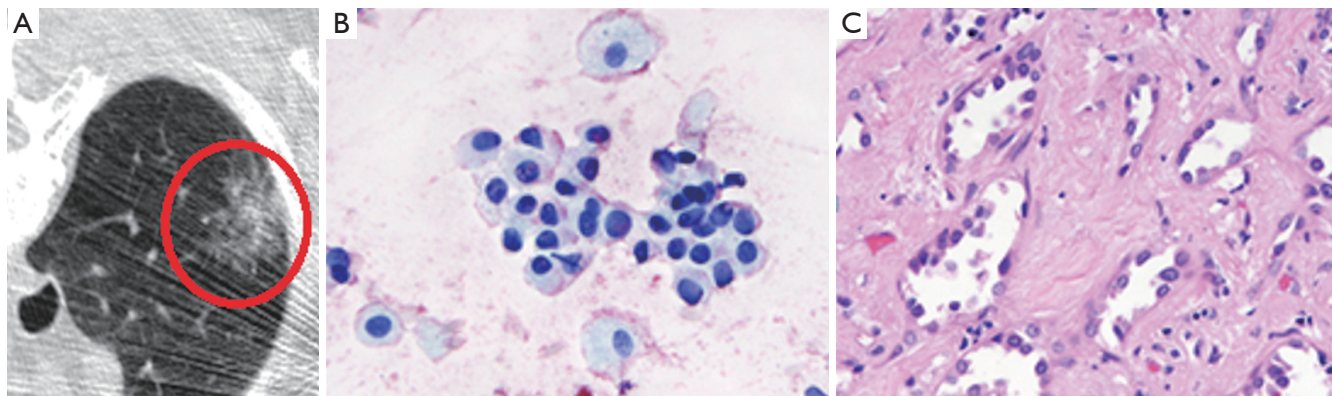
### Correlation with imaging

CT can assist treatment planning, particularly when considering sublobar resection, as CT can demonstrate such tumor characteristics as location, appearance and size. CT may be especially useful in cases diagnosed by small biopsy specimens, when pathology alone cannot estimate the tumor size or its degree of total invasion. CT scanning, optimally with thin sections ( $\leq 3$  mm), can help to further characterize subsolid/semisolid lesions (those containing groundglass and/or a portion of solid component). Similar to the pathologic size cutoff for MIA and AIS, the size threshold for nodule by CT criteria is 3 cm; a larger lesion is radiologically termed a mass. For the spectrum of adenocarcinoma categories, from preinvasive AAH to invasive adenocarcinoma, ground-glass opacity (GGO) on CT scan characteristically corresponds to lepidic tumor growth (Figure 2), while a solid component typically corresponds to invasion (64) (Figure 3), although overlap exists (65-68).

A pure GGO  $\leq 5$  mm therefore may represent AAH, while one  $\leq 3$  cm in diameter is likely to be AIS (Figure 2). MIA is more variable and has not been fully described on



**Figure 2** Radiologic-pathologic correlation for a preinvasive lesion in the adenocarcinoma spectrum. On CT (A), the lesion consists of a purely ground-glass opacity (white arrow), through which vascular structures can still be distinguished. Atypical cells are seen on pathology (B). Given its ground-glass appearance and size of between 5 mm and 3 cm as seen on CT, this lesion likely represents adenocarcinoma *in situ*, although this diagnosis can only be confirmed after no invasive component is demonstrated upon examination of a fully resected surgical specimen. (B, magnification 40 $\times$ ). CT, computed tomography.



**Figure 3** Radiologic-pathologic correlation for an invasive adenocarcinoma. CT evaluation (A) of the right lung shows a subsolid nodule at the periphery, which is greater than 5 mm in size, with a partial solid component (circled). Cytology (B) from the lesion demonstrates atypical bronchioloalveolar cells, with focal stromal invasion demonstrated on surgical biopsy specimen (C), confirming an invasive, T4N0 adenocarcinoma. (B, magnification 40 $\times$ ; C, magnification 20 $\times$ ). CT, computed tomography.

imaging, but in general is expected to contain a small solid component, though predominantly GGO if nonmucinous and more solid if mucinous.

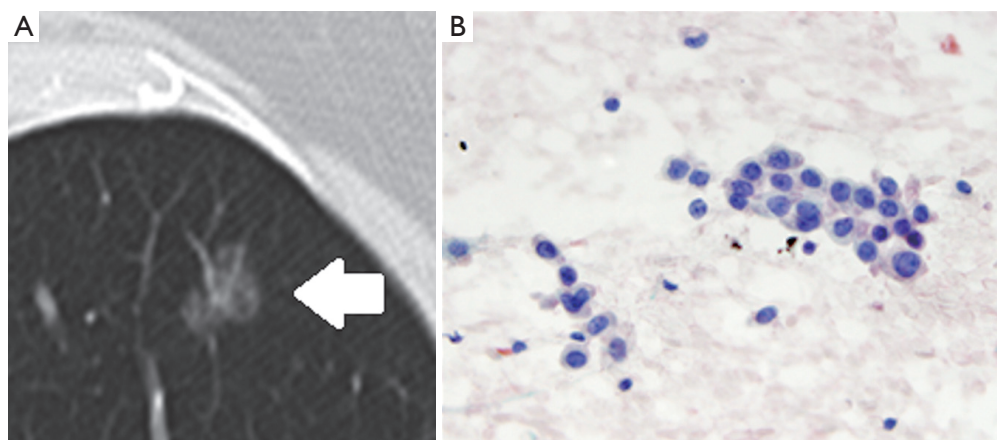
For invasive adenocarcinoma, favorable imaging features include cystic or bubble-like lucencies (*Figure 4*), intratumoral air bronchogram, extensive ground-glass component, and absence of pleural retraction, which are associated with favorable prognosis, well-differentiated tumor, and/or slow growth in stage IA adenocarcinoma. Thick coarse spiculation, on the other hand, has been associated with lymphovascular involvement and lower

post-resection survival. In solid adenocarcinoma, poor outcome and tumor differentiation has been associated with notches/concave cuts within a lesion on imaging.

Invasive mucinous adenocarcinoma, formerly mucinous BAC, possesses a characteristic imaging appearance, often predominantly/entirely solid, with air bronchograms, lobar/multilobar distribution, and potentially multiple scattered opacities (formerly known as multicentric BAC).

Radiology-pathology correlation is also useful in regard to assessment of resection specimens. For lepidic-predominant tumors, multiple tumors, or tumors removed





**Figure 4** Radiologic-pathologic correlation for intralesional lucency within a subsolid nodule. On CT (A), a partially ground-glass, partially solid nodule, suspicious for invasive adenocarcinoma, also demonstrates a subtle pseudocavitation at its posterior aspect (arrow), which is associated with a favorable prognosis. Cytology (B) from the specimen demonstrates atypical bronchioloalveolar cells. (B, magnification 40 $\times$ ). CT, computed tomography.

in multiple pieces, gross pathologic examination may misinterpret actual tumor size or number. CT may give a more accurate impression of gross findings and help ensure that each nodule is identified and sampled thoroughly. If there is a discrepancy between CT findings and initial histology, further specimen sampling may be needed for accurate histologic assessment.

Radiology has an expanding role in determination of prognosis, and imaging studies have the potential to influence clinical decision making in new ways. For example, a small GGO (<500 mm<sup>3</sup>) on CT scan has very little chance of rapid progression and might be considered for close follow-up rather than immediate resection (69). In regard to staging, Murakawa *et al.* showed that the maximum diameter of a solid tumor component measured in the mediastinal window is a better predictor of survival than the combined solid and ground-glass diameter measured in the lung window (70). This suggests that T status measured by the CT size of the solid component may be more prognostically accurate. Additionally, there is a growing recognition that various histologic features can be predicted by positron emission tomography (PET) (71-76). For example, a high SUV<sub>max</sub> is associated with high-grade histology and higher risk of recurrence in stage 1 lung adenocarcinoma (77,78).

## Conclusions

Recent advances in the understanding of lung adenocarcinoma

have highlighted the clinical significance of histologic subtype, tumor invasion, and immunohistochemical and molecular markers in the prognosis and treatment options for this most common lung cancer type. The new IASLC/ATC/ERS multidisciplinary classification system for this cancer allows for greater diagnostic, clinical and research clarity, by incorporating these advances, addressing small biopsy/cytology specimens, and by eliminating previously confusing terminology. The application of this new classification system will likely improve strategic use of tissue samples and increase diagnostic specificity for clinical and research uses. As it becomes more universally applied, the classification system may provide the groundwork for a dedicated TNM staging criteria for this unique lung cancer type, which will further clarify the paradigm for the best treatment of lung adenocarcinoma.

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