Lung adenocarcinoma is the most common histologic subtype of lung cancer worldwide, accounting for almost half of all lung cancers. Reflecting this importance, advances have taken place in oncology, molecular biology, pathology, radiology, and surgery of lung adenocarcinoma during the past few decades. However, the histologic subclassification of lung adenocarcinoma has remained difficult because of the heterogeneous nature of lung adenocarcinomas pathologically, molecularly, clinically, and radiologically. Given this background, in 2011 an international multidisciplinary classification sponsored by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) was proposed1 (Table 1). This new adenocarcinoma classification provides uniform terminology and diagnostic criteria for multidisciplinary strategic management and also provides improved guidelines reflecting the latest understanding of lung adenocarcinomas (Table 2).

### COMPARISON WITH 2004 WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION

#### Major Alteration (1): Discard the Term “Bronchioloalveolar Carcinoma (BAC)”

In this new classification, the term “BAC” is no longer used. “BAC” was originally defined by pathologists as a noninvasive lesion in 1999,2 but since then the term has been used to represent a broad spectrum of tumors, including (a) small noninvasive peripheral adenocarcinomas with 100% 5-year survival, formerly known as nonmucinous BAC; (b) small minimally invasive peripheral adenocarcinomas with approximately 100% 5-year survival; (c) invasive adenocarcinomas of mixed subtype; (d) the mucinous subtype of adenocarcinomas formerly known as mucinous BAC; and (e) advanced-stage IV mucinous adenocarcinomas with a very low survival rate.1,2,8 Consequently, there has been considerable confusion in both clinical and molecular research with regard to this former category.2 To clarify the nomenclature, the term BAC is now referred to as “former BAC” in the new classification. The former BAC concept is applicable to multiple categories in the new classification (Table 3).

#### Major Alteration (2): Adenocarcinoma In Situ (AIS) and Minimally Invasive Adenocarcinoma (MIA)

For resection specimens, new concepts have now been adopted, including adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) for small peripheral adenocarcinomas with either pure lepidic growth (AIS) or predominantly lepidic growth with invasion ≤5 mm (MIA), respectively, to define patients who will have 100% or near 100% disease-specific survival if they undergo complete resection. AIS and MIA are typically nonmucinous but in rare cases may be mucinous.3,4
<table>
<thead>
<tr>
<th>Categories</th>
<th>Alterations</th>
<th>Categories</th>
<th>Alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinvasive lesions</td>
<td></td>
<td>IASLC/ATS/ERS Classification</td>
<td>2004 WHO Classification</td>
</tr>
<tr>
<td>AAH</td>
<td>NC</td>
<td>AAH</td>
<td>NC</td>
</tr>
<tr>
<td>AIS</td>
<td>Reclassified category, formerly BAC, pure lepidic, ≤3 cm with no invasion, usually nonmucinous and rarely mucinous</td>
<td>BAC</td>
<td>Discarded terminology</td>
</tr>
<tr>
<td>MIA</td>
<td>New category, lepidic predominant, ≤3 cm with ≤5 mm invasion, usually nonmucinous and rarely mucinous</td>
<td>Nonmucinous/mucinous/mixed or indeterminate</td>
<td></td>
</tr>
<tr>
<td>Invasive adenocarcinoma</td>
<td></td>
<td>Adenocarcinoma, mixed subtype</td>
<td>Discarded category</td>
</tr>
<tr>
<td>Lepidic predominant</td>
<td>Reclassified category, formerly nonmucinous BAC pattern with &gt;5 mm invasion</td>
<td>Acinar adenocarcinoma</td>
<td>Integrated into acinar predominant adenocarcinoma</td>
</tr>
<tr>
<td>Acinar predominant</td>
<td>Reclassified category</td>
<td>Papillary adenocarcinoma</td>
<td>Integrated into papillary predominant adenocarcinoma</td>
</tr>
<tr>
<td>Papillary predominant</td>
<td>Reclassified category</td>
<td>Micropapillary predominant</td>
<td>New category</td>
</tr>
<tr>
<td>Solid predominant with mucin production</td>
<td>Reclassified category</td>
<td>Solid adenocarcinoma with mucin production</td>
<td>Integrated into solid predominant adenocarcinoma with mucin production</td>
</tr>
<tr>
<td>Variants</td>
<td></td>
<td>Variants</td>
<td></td>
</tr>
<tr>
<td>Invasive mucinous adenocarcinoma</td>
<td>Reclassified category, formerly mucinous BAC</td>
<td>Invasive mucinous adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Colloid variant</td>
<td>NC</td>
<td>Mucinous (colloid) carcinoma</td>
<td>NC</td>
</tr>
<tr>
<td>Fetal variant</td>
<td>NC</td>
<td>Fetal adenocarcinoma</td>
<td>NC</td>
</tr>
<tr>
<td>Enteric variant</td>
<td>New category</td>
<td>Mucinous cystadenocarcinoma</td>
<td>Discarded from histologic subtype, regarded as cytologic change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Signet ring adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clear cell adenocarcinoma</td>
<td></td>
</tr>
</tbody>
</table>

NC indicates no change.
In the new classification, invasive adenocarcinomas are classified according to their predominant pattern using comprehensive histologic subtyping. The term “predominant” is added to all categories of invasive adenocarcinomas, as most invasive adenocarcinomas are composed of a mixture of several histologic subtypes. This replaces the previous classification of mixed subtype adenocarcinoma, and the term “mixed subtype” is no longer to be used. Recent investigations have indicated that >90% of lung adenocarcinomas correspond to the mixed subtype according to the 2004 WHO classification.

Choosing a single predominant pattern after semiquantitative recording of the patterns in 5% increments is recommended. Semiquantitative recording of the patterns can be carried out in every pathologic slide containing the tumor and can be summed up. Histopathologic classification according to the predominant pattern as well as reporting the percentages of the subtypes is recommended. In this manner, invasive adenocarcinomas are classified as lepidic (formerly “mixed subtype with non-mucinous bronchioloalveolar”), acinar, papillary, and solid predominant invasive adenocarcinomas. Micropapillary predominant adenocarcinoma is added as a new histologic subtype of invasive adenocarcinomas.

In the new classification, invasive mucinous adenocarcinomas (formerly “mucinous BAC”) and colloid, fetal, and enteric adenocarcinoma are included as variants of invasive adenocarcinomas. Enteric adenocarcinoma is added to the variants on the basis of histologic characteristics.

### TABLE 2. Recommendations for Good Practice of Radiologists

<table>
<thead>
<tr>
<th>Radiologic Issues</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology</td>
<td>When a pure GGN or part-solid nodule with a predominant ground-glass component is found, the term BAC should no longer be used. These tumors need to be classified by the new terms of AIS, MIA, and LPA.</td>
</tr>
<tr>
<td>CT protocol</td>
<td>Thin-section CT technique (≤3 mm in reconstruction thickness) is recommended for subsolid lesions to record the size of (a) the solid component and (b) total tumor size, including both solid and ground-glass components.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Changes in shape, size, and attenuation can help determine further strategy between CT follow-up and surgical intervention.</td>
</tr>
<tr>
<td>Biopsy</td>
<td>Radiologists performing biopsies should consider obtaining sufficient tissue not only for traditional histologic analysis but also for molecular and immunohistochemical analysis.</td>
</tr>
<tr>
<td>Change of former BAC concept</td>
<td>Invasive adenocarcinomas previously classified as “mucinous BAC” should be separated from nonmucinous adenocarcinomas and should be classified as “invasive mucinous adenocarcinoma”.</td>
</tr>
</tbody>
</table>

### TABLE 3. Categories of New Adenocarcinoma Classification in Which the Former BAC Concept Was Used

<table>
<thead>
<tr>
<th>Categories</th>
<th>Pathologic Findings</th>
<th>CT Findings</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIS</td>
<td>Small (≤3 cm), pure lepidic growth, noninvasive, usually nonmucinous and rarely mucinous</td>
<td>Nonmucinous AIS: typically a pure GGN, sometimes a part-solid or occasionally a solid nodule</td>
<td>100% disease-free survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mucinous AIS: a solid nodule or consolidation</td>
<td></td>
</tr>
<tr>
<td>MIA</td>
<td>Small (≤3 cm), predominantly lepidic growth and ≤5 mm invasion, usually nonmucinous and rarely mucinous</td>
<td>Not fully established</td>
<td>Near 100% disease-free survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonmucinous MIA: a part-solid nodule with a predominant ground-glass component and a 5-mm or smaller central solid component</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mucinous MIA: a solid or part-solid nodule</td>
<td></td>
</tr>
<tr>
<td>LPA</td>
<td>Invasive nonmucinous adenocarcinoma that shows lepidic growth as its predominant component</td>
<td>A part-solid mass with variable proportion of ground-glass component</td>
<td>90% 5-year recurrence-free survival</td>
</tr>
<tr>
<td>Other subtype predominant adenocarcinoma having lepidic component</td>
<td>Invasive nonmucinous adenocarcinoma that is predominantly acinar, papillary, micropapillary, or solid, plus a small proportion of a lepidic component</td>
<td>Not fully established</td>
<td>Variable, relatively poor prognosis in micropapillary and solid predominant subtypes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usually a solid mass</td>
<td></td>
</tr>
<tr>
<td>Invasive mucinous adenocarcinoma</td>
<td>Invasive mucinous adenocarcinoma that has lepidic growth as its predominant component</td>
<td>A spectrum of patterns including solid mass, part-solid mass, or consolidation with CT angiogram sign A strong tendency for multicentric, multilobar, and bilateral lung involvement</td>
<td>Variable</td>
</tr>
</tbody>
</table>
immunohistochemical features that are shared with colorectal adenocarcinoma. For the diagnosis of enteric adenocarcinoma, a primary gastrointestinal origin should be excluded. The rationale for changes in the classification of adenocarcinoma variants is based on 3 new concepts. 1 First, the separation of invasive mucinous adenocarcinoma (formerly "mucinous BAC") is based on many investigations showing that former "mucinous BACs" are significantly different from former "nonmucinous BACs" in terms of major clinical, radiologic, pathologic, and genetic aspects, in particular because of different frequencies of epidermal growth factor receptor (EGFR) and KRAS mutations.7,9–11 EGFR mutations are more frequent in nonmucinous adenocarcinomas, whereas KRAS mutations are more frequent in mucinous adenocarcinomas. Second, the rare mucinous cystadenocarcinoma is now reclassified as colloid adenocarcinoma, as these likely represent a spectrum of colloid adenocarcinoma. Finally, clear cell and signet ring cell features are removed from histologic subtypes and are now regarded as cytologic changes. Their presence and extent will continue to be reported with an association with molecular features. For example, signet ring cell features are present in up to 56% of tumors with echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) gene fusions.1

Major Alteration (5): Classification Guidance for Different Types of Samples

As approximately 70% of lung cancers are detected in advanced stage and are unresectable,12 diagnosis is frequently established on the basis of small biopsies and/or cytology. In the new classification, for the first time in the
history of lung cancer classification, standardized criteria and terminology for the pathologic diagnosis of lung cancer in small biopsies and cytology have been proposed (Fig. 1). This had not been addressed in prior WHO classification systems.1 Recently, 3 major advances have made histologic subclassification important for therapeutic decision making in advanced lung cancer patients, particularly for the distinction between adenocarcinoma and squamous cell carcinoma. First, \(\text{EGFR}\) mutations have been found to be associated with improved responsiveness to first-line \(\text{EGFR}\) tyrosine kinase inhibitors and with improved clinical outcome in advanced lung adenocarcinoma patients.13,14 Second, bevacizumab is contraindicated in patients with advanced squamous cell carcinoma because of increased risk of life-threatening hemorrhage.15 Third, pemetrexed is more effective in patients with adenocarcinoma compared with those with squamous cell carcinoma.16

On the basis of these observations, the following recommendations for advanced-stage non–small cell lung cancer (NSCLC) were made. First, the \(\text{EGFR}\) mutation test is recommended for patients with advanced lung adenocarcinoma. Second, NSCLC should be further classified into a more specific type, such as adenocarcinoma or squamous cell carcinoma, and the term NSCLC—not otherwise specified (NSCLC—NOS) is to be used as little as possible for small biopsies and cytology samples.1

**CLINICAL, RADIOLOGIC, AND PATHOLOGIC FEATURES OF SUBTYPES**

**Atypical Adenomatous Hyperplasia (AAH)**

AAH is defined as a localized, small (usually \(\leq 5\) mm) proliferation of atypical type II pneumocytes and/or Clara cells lining the alveolar walls and respiratory bronchioles (Fig. 2).17 A continuum of morphologic changes between AAH and nonmucinous AIS has been suggested.17–19 Differentiation between highly cellular and atypical AAH and AIS can be difficult histologically and impossible cytologically. On chest computed tomography (CT), AAH is characteristically shown as a small pure ground-glass nodule (GGN) usually measuring \(< 5\) mm.20 It can be either single or multiple.21,22

**AIS**

AIS (one of the lesions formerly known as BAC) is a localized small (\(\leq 3\) cm) adenocarcinoma in which growth of neoplastic cells is restricted to preexisting alveolar structures (lepidic growth) that lack stromal, vascular, or pleural invasion. Papillary or micropapillary patterns and intra-alveolar tumor cells are absent. Although most AIS lesions are nonmucinous, several cases of mucinous AIS have been reported.3 Nonmucinous AIS consists of type II pneumocytes and/or Clara cells (Fig. 3). The rare cases of mucinous AIS consist of tall columnar cells and abundant cytoplasmic mucin (Fig. 4). Tumors that meet the criteria for AIS have been documented to have 100% disease-free survival.3,23–25 On CT, nonmucinous AIS appears typically as a pure GGN (Fig. 3).10 In contrast, localized BAC and Noguchi type A adenocarcinomas can appear as partly solid nodules because of focal collapsed alveoli or focal thickened alveolar septa.26,27 These articles were published in the early 2000s; thus, the classification scheme of small adenocarcinomas was different from that in the current classification. Therefore, further radiologic-pathologic correlation studies in numerous cases can identify the CT features of nonmucinous AIS. Mucinous AIS can appear as a solid nodule or as a consolidation28 (Fig. 4). The pure GGN of AIS usually appears on thin-section CT as slightly higher attenuation compared with the very faint GGN of AAH.29,30 AIS also can be either single or multiple.29

**MIA**

MIA is a small, solitary adenocarcinoma (\(\leq 3\) cm), with a predominantly lepidic pattern and invasion \(\leq 5\) mm in its greatest dimension.31 MIA is usually nonmucinous (Fig. 5) but in rare cases can be mucinous. The invasive component of MIA is defined as follows: (a) histologic subtype other than a lepidic pattern (ie, acinar, papillary, micropapillary,
or solid); or (b) tumor cells infiltrating myofibroblastic stroma. MIA should be excluded if the tumor (a) invades lymphatics, blood vessels, or pleura or (b) contains tumor necrosis. If multiple microinvasive areas are found in 1 tumor, the largest dimension in the largest invasive area should be measured, and it should be \( \leq 5 \text{ mm} \) in size. The size of invasion is not the summation of all invasive foci, if multiple foci occur. If the measurement of the size of invasion is impossible because of the manner of histologic sectioning, invasive size can be estimated by multiplying the total percentage of the invasive (nonlepidic) components by the total tumor size. Many investigators have demonstrated a near 100% disease-specific or very favorable overall survival in patients diagnosed as having adenocarcinomas meeting the criteria of MIA.\(^3,4,31,32\)

Imaging features of MIA are as yet not fully described. A provisional description of nonmucinous MIA on thin-section CT is a part-solid nodule consisting of a predominant ground-glass component and a small solid component measuring 5 mm or less (Fig. 5).\(^33\) Mucinous MIA can appear as a solid or part-solid nodule.\(^28\) There is an overlap among imaging features of AAH, AIS, and MIA.

**Lepidic Predominant Invasive Adenocarcinoma, Nonmucinous (LPA)**

LPA is defined as nonmucinous adenocarcinomas previously classified as a mixed subtype in which the lepidic component is predominant. A diagnosis of LPA rather than MIA can be made if the tumor (a) contains >5 mm of a histologic subtype other than a lepidic pattern (ie, acinar, papillary, micropapillary, or solid); (b) invades lymphatics, blood vessels, or pleura; or (c) contains tumor necrosis (Fig. 6). The term LPA should not be used in the context of invasive mucinous adenocarcinoma with predominantly lepidic growth (former BAC pattern). Nevertheless, several studies have demonstrated that predominantly lepidic growth is associated with a more favorable survival in small resected lung adenocarcinomas with an invasive component.\(^23,32\) A 90% 5-year recurrence-free survival was reported in a recent study on stage I adenocarcinomas using this approach.\(^34\) On CT, it can be shown as a part-solid opacity with variable proportions of ground-glass and solid components.

**Acinar, Papillary, Micropapillary, and Solid Predominant Adenocarcinomas**

Histopathologically, acinar predominant adenocarcinoma consists mainly of glands with a central luminal space surrounded by tumor cells (Fig. 7).\(^8\) Papillary predominant adenocarcinoma is composed of a growth of glandular cells along central fibrovascular cores (Fig. 8). The new category of micropapillary predominant adenocarcinoma has tumor cells growing in papillary tufts that lack fibrovascular cores (Fig. 9).\(^8\) Solid predominant adenocarcinoma with mucin production reveals a major component of polygonal tumor cells forming sheets and lacks the recognizable patterns of acinar, papillary, micropapillary, or lepidic growth (Fig. 10).\(^8\) If the tumor is 100% solid, intracellular mucin should be found in at least 5 tumor cells in each of 2 high-power fields (Fig. 10).\(^8\) Solid and micropapillary predominant subtypes are associated with a poorer prognosis compared with the other subtypes.\(^34-36\) These subtypes of adenocarcinomas appear as a solid nodule but can also be partly solid if lepidic components are included (Figs. 7–10).

**Invasive Mucinous Adenocarcinoma**

The rationale for separation of invasive mucinous adenocarcinoma (formerly mucinous BAC) from nonmucinous adenocarcinoma is that invasive mucinous adenocarcinoma has different clinical, radiologic, pathologic, and genetic features.\(^7,9-11\) In particular, invasive mucinous adenocarcinomas are usually thyroid transcription factor-1 negative and show a very strong correlation with KRAS

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**FIGURE 3. Preinvasive lesion: nonmucinous AIS.** A, Transverse thin-section CT scan of a 55-year-old woman shows a well-defined round pure GGN in the right lower lobe. B, Tumor shows atypical pneumocytes proliferating along slightly thickened, but preserved, alveolar walls. No foci of invasion or scarring were seen.
mutation. Nonmucinous adenocarcinomas are frequently thyroid transcription factor-1 positive and are more likely to show EGFR mutations. Invasive mucinous adenocarcinomas have a distinctive histologic appearance with goblet or columnar tumor cells with abundant intracytoplasmic mucin. Alveolar spaces often contain mucin. These tumors may show a similar heterogenous mixture of lepidic, acinar, papillary, micropapillary, and solid growth as that in nonmucinous tumors. These tumors differ from mucinous AIS and MIA by 1 or more of the following criteria: size (>3 cm), amount of invasion (>5 mm), multiple nodules, or lack of a discrete border with miliary spread into adjacent lung parenchyma. Multicentric, multilobar, and bilateral lung involvements, which may reflect aerogenous spread, are frequent.

The imaging spectrum of invasive mucinous adenocarcinoma is variable and ranges from nodules to lobar consolidation (Fig. 11). Although these tumors can appear as ground-glass–containing masses, intra-alveolar mucin may make the CT finding solid or nearly solid. On contrast-enhanced CT scans, vessels are well shown to be traversing areas of consolidation (CT angiogram sign). However, the previously described imaging spectrum of invasive mucinous adenocarcinoma could be fraught with problems, as the classification of tumors in the previous literature is inconsistent. Radiologic-pathologic correlation in early and small invasive mucinous adenocarcinomas needs to be performed in numerous cases. In addition, distinctive clinical and radiologic features between small nodular type of invasive mucinous adenocarcinomas and extensive consolidation type of tumors need to be described.

**Colloid, Fetal, and Enteric Variants**

Colloid adenocarcinoma shows features similar to those of tumors of the same name seen in the gastrointestinal tract. Abundant pools of extracellular mucin are found with distended alveolar spaces and destruction of alveolar walls. Fetal adenocarcinoma exhibits characteristics that resemble fetal lung tissue and consists of glandular elements with tubules composed of nonciliated cells that resemble fetal lung tubules. Enteric adenocarcinoma shares characteristics with...
colorectal adenocarcinoma, which consists of glandular structures, sometimes with a cribriform pattern, lined by columnar tumor cells with nuclear pseudostratification, luminal necrosis, and prominent nuclear debris.\(^1\)

**IMPLICATIONS FOR T STAGING**

The new seventh edition Union for International Cancer Control/American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system for NSCLC\(^4\) was released recently. There are important implications of the new adenocarcinoma classification for TNM staging. With respect to T staging, although the prognostic impact of tumor size was emphasized in the seventh edition of the staging system, that is, size thresholds of 2, 5, and 7 cm were added to the threshold of 3 cm from the sixth edition,\(^4\) the clinical implication of LPAs needs to be considered for the next revision of TNM classification. LPAs with an extensive ground-glass component are known to be associated with a favorable prognosis.\(^23,34\) In this context, several reports have demonstrated that survival was a function of the diameter of the invasive component and not of the total diameter that includes the lepidic component.\(^32,42\) Therefore, for subsolid adenocarcinomas, measurement of the solid component on CT and of the invasive component on histology as opposed to measurement of the total tumor diameter is suggested.\(^43,44\) If further studies validate this observation, measuring the solid component of subsolid adenocarcinomas should be considered as the appropriate method for size measurement (T staging) in the next revision of TNM classification. AIS and MIA may be classified as Tis (T stage of in situ carcinoma) and T1mi (T1 stage of minimally invasive carcinoma).

**FIGURE 5.** Nonmucinous MIA. A, Thin-section CT scan of a 66-year-old man shows a part-solid nodule in the left upper lobe. B, This tumor consists primarily of lepidic growth of tumor cells (L) with a small (≤5 mm) central area of invasion (I).

**FIGURE 6.** LPA. A, Transverse CT scan of a 60-year-old woman shows a mass composed of peripheral ground-glass opacity and a central solid portion with air bronchogram. B, This tumor consists mostly of lepidic growth of tumor cells (arrows). The central portion of this tumor is an area of invasive acinar adenocarcinoma (asterisks).
in the next TNM classification, respectively, similar to the system of breast cancer.1

IMPLICATIONS FOR MULTIPLE ADENOCARCINOMAS AND M STAGING
Multifocal lung adenocarcinomas are not uncommon. Eighteen percent of adenocarcinomas detected in screening programs23 and 8% to 22% of surgically resected adenocarcinomas have been reported to be multifocal adenocarcinomas.45,46 Pathologically, multiple lung adenocarcinomas can be multiple AAH, AIS, and invasive adenocarcinoma, and they can appear as multiple subsolid nodules.20 Subsolid nodules are reported only very rarely to be metastatic.47 Comprehensive histologic subtyping can be helpful in multiple lung adenocarcinomas to differentiate multiple primary tumors from intrapulmonary metastases. Recording the percentages of each histologic subtype at 5% increments, not just recording the most predominant subtype, allows the data to be utilized to compare multiple adenocarcinomas, particularly if the slides of a previously diagnosed tumor are not available at the time of review of additional lung adenocarcinomas.48 With respect to molecular biomarker expression, DNA mutation sequencing,49,50 immunohistochemistry,51 and gene expression analysis have been tested to distinguish metastases from synchronous primary tumors; however, these approaches need to be prospectively validated. Multiple adenocarcinomas are not a contraindication

FIGURE 7. Acinar predominant adenocarcinoma. A, Transverse thin-section CT scan of a 62-year-old man shows a spiculated solid mass in the right upper lobe. B, Tumor consists of round to oval-shaped malignant glands invading the fibrous stroma.

FIGURE 8. Papillary predominant adenocarcinoma. A, Transverse thin-section CT scan of a 60-year-old woman shows a solid mass with air bronchogram in the left lower lobe. B, This tumor consists of malignant cuboidal to columnar tumor cells growing on the surface of fibrovascular cores (asterisks).
for surgical exploration\textsuperscript{23,52,53} if there is no evidence of mediastinal lymph node metastasis, although a standard treatment algorithm for multiple adenocarcinomas has not been established yet.

**IMPLICATIONS FOR MANAGEMENT AND QUANTITATIVE ANALYSIS OF SUBSOLID NODULES**

Subsolid nodules are now known to represent the histologic spectrum of peripheral adenocarcinomas that includes AAH, AIS, MIA, LPA, and other subtype predominant adenocarcinomas with a lepidic component.\textsuperscript{1} Recommendations for management of subsolid nodules have not been established yet, but interim guidelines have been proposed by Godoy and Naidich.\textsuperscript{54} As most pure GGNs $<10$ mm are known to be AAH or AIS that may not progress or may very slowly grow without metastasis, the interim guidelines recommend CT follow-up rather than immediate surgical resection for these lesions until definite evidence of malignancy or growth is observed (Table 4).\textsuperscript{54}

Size measurement and growth assessment of subsolid nodules are very important but clinically problematic. In this context, a thin-section CT technique ($\leq3$ mm reconstruction thickness) is helpful for recording the size of both the solid and ground-glass components.\textsuperscript{54} Although volumetric measurements have been suggested as a promising tool for assessing size changes in indeterminate solid nodules,\textsuperscript{55} few attempts have been made to measure the volume of subsolid nodules, especially the separate volumes

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9.png}
\caption{Micropapillary predominant adenocarcinoma. A, Transverse thin-section CT scan of a 55-year-old woman shows a solid mass in the right lower lobe. B, Tumor consists of small papillary tufts floating within alveolar spaces (arrows) and does not show fibrovascular cores. Tumor cells appear detached or connected to alveolar walls (arrowheads).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure10.png}
\caption{Solid predominant adenocarcinoma with mucin production. A, Transverse CT scan of a 58-year-old man shows a large solid mass in the right upper lobe. Heterogenous enhancement in the tumor is seen. B, On fluorodeoxyglucose positron emission tomography scans, high glucose uptake is seen in the tumor. Maximum standardized uptake value was 10.3. C, This tumor consists of solid sheets of tumor cells with abundant cytoplasm and mostly vesicular nuclei with conspicuous nucleoli.}
\end{figure}
of the solid component and ground-glass component. Changes over time in the diameters and/or the volumes of the solid component and of the ground-glass component may possibly provide important prognostic information. Quantitative analysis of CT attenuation and histogram analysis have been recognized as an approach to differentiate AAH and AIS (usually the 1-peak pattern on CT attenuation histogram) from LPA (frequently the 2-peak pattern) (Fig. 12). Differences in CT scanners and interobserver and intraobserver measurement variability are common and may critically impact the performance of CT quantification of subsolid nodules.

**MOLECULAR BIOMARKERS FOR PREDICTING RESPONSE TO CHEMOTHERAPY**

Molecular biomarkers for predicting response to therapy have become prominent after the discovery of EGFR mutations and their association with responsiveness to erlotinib and gefitinib. KRAS mutations are mutually exclusive with EGFR mutations, but their clinical role as predictive and prognostic biomarkers remains controversial. Recent phase 3 trials have demonstrated that patients with EGFR-mutated lung cancers show better treatment outcomes (response rate and progression-free survival) when treated with the EGFR tyrosine kinase inhibitor gefitinib than with conventional platinum-based chemotherapy.

Other molecular predictors such as EGFR gene copy number have also been explored. Data from a phase 3 randomized, placebo-controlled trial of erlotinib in advanced NSCLC demonstrated that EGFR copy number (but not EGFR mutation status) was associated with a better response to erlotinib and with worse survival. Very recently, a new predictive biomarker, the transforming fusion gene EML4-ALK, was identified. This fusion gene is prevalent in approximately 5% of lung adenocarcinomas and is usually found in EGFR/KRAS mutation-negative cases. Younger age, male sex, and never or light smokers may harbor this aberration. A recent study demonstrated a 57% overall response and a 72% 6-month PFS for crizotinib, an inhibitor of ALK, in tumors harboring ALK fusion.

**TABLE 4. Interim Guidelines for Management of Persistent Subsolid Pulmonary Nodules**

<table>
<thead>
<tr>
<th>Number</th>
<th>Size (mm)</th>
<th>Solid Component</th>
<th>Management Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary</td>
<td>&lt; 5</td>
<td>Pure GGN*</td>
<td>No follow-up, usually represents AAH</td>
</tr>
<tr>
<td>≥ 5, &lt; 10</td>
<td>Pure GGN*</td>
<td>Follow-up of at least 3 consecutive annual CTs</td>
<td></td>
</tr>
<tr>
<td>≥ 10</td>
<td>Pure GGN*</td>
<td>Surgical resection, represents malignancy</td>
<td></td>
</tr>
<tr>
<td>Any size</td>
<td>Part-solid nodule*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>&lt; 5</td>
<td>Pure GGN*†</td>
<td>At least 1-y CT follow-up, most likely represents multiple AAH or respiratory bronchiolitis</td>
</tr>
<tr>
<td>≥ 5, &lt; 10</td>
<td>Pure GGN*†</td>
<td>Follow-up CT</td>
<td></td>
</tr>
<tr>
<td>≥ 10</td>
<td>Pure GGN*†</td>
<td>Surgical resection, represents malignancy</td>
<td></td>
</tr>
<tr>
<td>Any size</td>
<td>Part-solid nodule††</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The management strategy in this table is only for persistent subsolid nodules confirmed on initial follow-up CT of 3 to 6 months to evaluate spontaneous resolution.
†For multiple subsolid nodules, the management strategy should be considered according to characteristics of the dominant lesion.

**FIGURE 11.** Invasive mucinous adenocarcinoma. A, Transverse CT scan of a 59-year-old woman shows heterogeneously enhanced consolidation in both lungs. This patient underwent left lower lobectomy and right upper lobe wedge resection due to invasive mucinous adenocarcinoma 3 years ago. This CT scan was performed for the diagnosis of disease recurrence. B, On lung window image of the CT scan, dense consolidation and ground-glass opacities in the right upper lobe and left upper lobe are seen. C, On fluorodeoxyglucose positron emission tomography scans, high glucose uptake is seen in the right upper lobe. Maximum standardized uptake value of right upper lobe consolidation was 5.5. Maximum standardized uptake value of the left upper lobe consolidation was 1.9.
RADIOLOGIC FINDINGS—MOLECULAR BIOMARKER CORRELATION

Several reports have correlated imaging features with 
EGFR mutation, although not many studies have attempted to do so. As the original biological character of the tumor can be preserved before progression to advanced stages or metastasis, these studies were performed in surgically resected adenocarcinomas. A Japanese group reported that a high ratio of ground-glass component and a smaller diameter, especially tumors ≤ 3 cm with ≥ 50% ground-glass components, may predict the presence of EGFR mutations. Another study demonstrated that 27.5% of adenocarcinomas presented as a solid mass on CT and 38.5% of adenocarcinomas presented as a ground-glass-containing mass showing EGFR mutation. Correlation studies with other molecular biomarkers have been performed. High EGFR gene copy number was reported as correlating with adenocarcinomas that show high glucose metabolism at positron emission tomography and a low ground-glass proportion. More correlative series are needed to assess the possible association of molecular and imaging findings.

CONCLUSIONS

The new IASLC/ATS/ERS classification based on a multidisciplinary approach incorporating the latest clinical, molecular, radiologic, and surgical findings offers promise to assist in improving clinical management in the rapidly progressing field of lung adenocarcinoma.

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