ultimately those results should be reported in a pathology report or a molecular diagnostic pathology report. These results will need to be integrated in a multidisciplinary manner with clinical and radiologic correlation.

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Diagnosis of Lung Adenocarcinoma in Resected Specimens

Implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society Classification

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• A new lung adenocarcinoma classification has been published by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society. This new classification is needed to provide uniform terminology and diagnostic criteria, most especially for bronchioloalveolar carcinoma. It was developed by an international core panel of experts representing all 3 societies with oncologists/pulmonologists, pathologists, radiologists, molecular biologists, and thoracic surgeons.This summary focuses on the aspects of this classification that address resection specimens. The terms *bronchioloalveolar carcinoma* and *mixed subtype adenocarcinoma* are no longer used. For resection specimens, new concepts are introduced, such as adenocarcinoma in situ and minimally invasive adenocarcinoma for small solitary adenocarcinomas with either pure lepidic growth (adenocarcinoma in situ) and predominant lepidic growth with invasion of 5 mm or less (minimally invasive adenocarcinoma), to define the condition of patients who will have 100% or near 100% disease-specific survival, respectively, if they undergo complete lesion resection. Adenocarcinoma in situ and minimally invasive adenocarcinoma are usually nonmucinous, but rarely may be mucinous. Invasive adenocarcinomas are now classified by predominant pattern after using comprehensive histologic subtyping with lepidic (formerly most mixed subtype tumors with nonmucinous bronchioloalveolar carcinoma), acinar, papillary, and solid patterns; micropapillary is added as a new histologic subtype. Variants include invasive mucinous adenocarcinoma (formerly mucinous bronchioloalveolar carcinoma), colloid, fetal, and enteric adenocarcinoma.It is possible that this classification may impact the next revision of the TNM staging classification, with adjustment of the size T factor according to only the invasive component pathologically in adenocarcinomas with lepidic areas.

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A new lung adenocarcinoma classification has recently been published by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS).[1] This classification outlines multiple paradigm shifts that will impact pathologists in many aspects of the diagnosis and

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Table 1. IASLC/ATS/ERS[a] Classification of Lung Adenocarcinoma in Resection Specimens

Preinvasive lesions
- Atypical adenomatous hyperplasia
- Adenocarcinoma in situ (≤3 cm, formerly BAC)
  - Nonmucinous
  - Mucinous
  - Mixed mucinous/nonmucinous
- Minimally invasive adenocarcinoma (≤3 cm lepidic-predominant tumor with ≤5 mm invasion)
  - Nonmucinous
  - Mucinous
  - Mixed mucinous/nonmucinous

Invasive adenocarcinoma
- Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)
- Acinar predominant
- Papillary predominant
- Micropapillary predominant
- Solid predominant with mucin production

Variants of invasive adenocarcinoma
- Invasive mucinous adenocarcinoma (formerly mucinous BAC)
- Colloid
- Fetal (low and high grade)
- Enteric

Abbreviation: BAC, bronchioloalveolar carcinoma.

[a] *International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society.*

Table 2. Adenocarcinoma In Situ

Diagnostic criteria
- A small tumor ≤3 cm
- A solitary adenocarcinoma
- Pure lepidic growth
- No stromal, vascular, or pleural invasion
- No pattern of invasive adenocarcinoma (such as acinar, papillary, micropapillary, solid, colloid, enteric, fetal,or invasive mucinous adenocarcinoma)
- No intraalveolar tumor cells present
- Cell type mostly nonmucinous (type II pneumocytes or Clara cells), rarely may be mucinous (tall columnar cells with basal nuclei and abundant cytoplasmic mucin, sometimes resembling goblet cells)
- Nuclear atypia is absent or inconspicuous
- Septal widening with sclerosis is common, particularly in nonmucinous adenocarcinoma in situ

Good practice points
- The tumor should be completely sampled. If desired, a small piece may be snap frozen for research if there is no solid component on CT or gross examination and there are no worrisome areas for invasion. This tissue may need to be examined by frozen section if invasion is suspected.
- Size may be underestimated on gross examination, so correlation with CT findings may be necessary to determine tumor size.
- If a solid component is present on CT or on gross examination, the lesion should be evaluated very carefully as this often correlates with an invasive component.
- For adenocarcinoma in situ, particularly mucinous adenocarcinoma in situ, great care must be taken to be sure the lesion is solitary and sharply circumscribed without miliary spread in adjacent lung parenchyma.
- The criteria for adenocarcinoma in situ can be applied in the setting of multiple tumors only if the other tumors are regarded as synchronous primary tumors rather than intrapulmonary metastases.

Abbreviation: CT, computed tomography.

Table 3. Minimally Invasive Adenocarcinoma

Diagnostic criteria
- A small tumor ≤3 cm
- A solitary adenocarcinoma
- Predominantly lepidic growth
- ≤5 mm invasive component in greatest dimension in any 1 focus
- Invasive component to be measured includes (1) any histologic subtype other than a lepidic pattern (such as acinar, papillary, micropapillary, solid, colloid, fetal, or invasive mucinous adenocarcinoma) or (2) tumor cells infiltrating myofibroblastic stroma
- Minimally invasive adenocarcinoma diagnosis is excluded if the tumor (1) invades lymphatics, blood vessels, or pleura or (2) contains tumor necrosis
- Cell type mostly nonmucinous (type II pneumocytes or Clara cells), rarely may be mucinous (tall columnar cells with basal nuclei and abundant cytoplasmic mucin, sometimes resembling goblet cells)

Good practice points
- Same good practice points from Table 1.
- If multiple microinvasive areas are found in 1 tumor, the size of the largest invasive area should be measured in the largest dimension and it should be ≤5 mm. The size of invasion is not the summation of all such foci if more than 1 occurs.
- If the manner of histologic sectioning of the tumor makes it impossible to measure the size of invasion, an estimate of invasive size can be made by multiplying the total percentage of the invasive (nonlepidic) components by the total tumor size.
- As most of the literature on the topic of adenocarcinoma in situ and minimally invasive adenocarcinoma deals with tumors ≤2 or 3 cm, there is insufficient evidence to support the notion that 100% disease-free survival can occur in such tumors >3.0 cm. These tumors should be classified as lepidic-predominant adenocarcinoma, suspect adenocarcinoma in situ, or minimally invasive adenocarcinoma.

classification of lung adenocarcinoma. Unlike previous World Health Organization (WHO) classifications,[2,3] with this effort a new approach to classification of small biopsy and cytology specimens is presented, and this is the topic of a separate article.[4] The present article is focused on resected specimens (Tables 1 through 3) and the impact of the new classification for pathologists in this setting, the topic primarily addressed in prior WHO classifications.

The frequent histologic heterogeneity of lung adenocarcinoma has presented difficult challenges for both pathologists and classification committees in developing a system that is clinically and biologically relevant. This new classification provides an approach to subtyping lung adenocarcinoma that provides a significant advance over previous classifications such as the 2004 WHO[3] and the Noguchi[5] classifications. First, in contrast to these historical classifications, the IASLC/ATS/ERS classification was developed by an international, multidisciplinary panel, allowing for confusing clinical and pathologic aspects of terminology and criteria to be identified and then addressed. For example, the term *bronchioloalveolar carcinoma* (BAC) was very confusing as it was used in several different ways in the revised classification[1] to encompass 5 different types of lung adenocarcinoma with dramatically different clinical and pathologic characteristics. Also, one of the limitations of previous classifications was the large number of tumors that fell into the "mixed subtype" (greater than 90%)[6] and "type C" (50%–60%)[5,7] categories in the 2004 WHO[3] and

Table 4. Summary of Pathology Recommendations Applicable to Resection Specimens

1. We recommend discontinuing the use of the term *bronchioloalveolar carcinoma* (BAC) (strong recommendation, low-quality evidence).
2. For small (≤3 cm), solitary adenocarcinomas with pure lepidic growth, we recommend the term *adenocarcinoma in situ*, which defines patients who should have 100% disease-specific survival if the lesion is completely resected (strong recommendation, moderate-quality evidence). Remark: Most adenocarcinomas in situ are nonmucinous, rarely are they mucinous.
3. For small (≤3 cm), solitary adenocarcinomas with predominant lepidic growth and small foci of invasion measuring ≤0.5 cm, we recommend a new concept of "minimally invasive adenocarcinoma" to define patients who should have near 100% disease-specific survival if the lesion is completely resected (strong recommendation, low-quality evidence). Remark: Most minimally invasive adenocarcinomas are nonmucinous, rarely are they mucinous.
4. For invasive adenocarcinomas, we suggest that comprehensive histologic subtyping be used to assess histologic patterns semiquantitatively in 5% increments, choosing a single predominant pattern. We also suggest that individual tumors be classified according to the predominant pattern and that the percentages of the subtypes be reported (weak recommendations, low-quality evidence).
5. In patients with multiple lung adenocarcinomas, we suggest comprehensive histologic subtyping in the comparison of the complex, heterogeneous mixtures of histologic patterns to determine if the tumors are metastases or separate synchronous or metachronous primary tumors (weak recommendation, low-quality evidence).
6. For nonmucinous adenocarcinomas previously classified as mixed subtype, where the predominant subtype consists of the former nonmucinous BAC, we recommend use of the term *lepidic-predominant adenocarcinoma* and discontinuing the term *mixed subtype* (strong recommendation, low-quality evidence).
7. In patients with early-stage adenocarcinoma, we recommend the addition of "micropapillary-predominant adenocarcinoma," when applicable, as a major histologic subtype owing to its association with poor prognosis (strong recommendation, low-quality evidence).
8. For adenocarcinomas formerly classified as mucinous BAC, we recommend 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 adenocarcinoma in situ, mucinous MIA, or for overtly invasive tumors, as "invasive mucinous adenocarcinoma" (weak recommendation, low-quality evidence).
9. We recommend that the term *non–small cell lung carcinoma* (NSCLC) *not otherwise specified* (NOS) be used as little as possible and we recommend it be applied only when a more specific diagnosis is not possible by morphology and/or special stains (strong recommendation, moderate-quality evidence).

Abbreviations: BAC, bronchioloalveolar carcinoma; MIA, minimally invasive adenocarcinoma.

Noguchi[5] classifications, respectively, which provided little opportunity to stratify patients according to subtypes with clinically and biologically meaningful correlations. Another limitation of these classifications was the understandable lack of recognition of micropapillary adenocarcinoma, which has emerged in recent years as an important poor prognostic subtype of lung adenocarcinoma in early-stage tumors.[8–10] Furthermore, both the 2004 WHO and Noguchi classifications lumped both mucinous and nonmucinous tumors, previously classified as BAC or Noguchi type A or B patterns, together under the same terminology, when these tumors have very different clinical, radiologic, pathologic, and molecular characteristics.[11–17]

This new classification is timely as it has been published in conjunction with 2 major advances in the lung cancer field where it can have a direct impact: (1) the finding by the National Lung Cancer Screening Trial that there is greater than 20% reduction in mortality in high-risk smokers[18] and (2) the concept of personalized medicine whereby histologic classification can determine therapeutic options for patients with lung cancer, although the latter concept is most applicable in the advanced lung adenocarcinoma setting.[19] As applied to resection specimens, this classification shows promise in stratifying patients for adjuvant therapy,[8,20] and it may ultimately impact the next revision of the TNM staging system by providing more accurate staging of multiple lung adenocarcinomas[21,22] and determining the size T factor according to the invasive size rather than total (invasive plus lepidic components) tumor size.[8,20,23] In both of these arenas, application of this new classification will increase the usefulness of information provided in pathology diagnoses, which will impact patient diagnosis and management.

The international multidisciplinary panel that developed this classification included pathologists, oncologists/respiratory physicians, radiologists, molecular biologists, and thoracic surgeons. It also was based on a systematic literature review to weigh evidence and make recommendations (Tables 4 and 5).[1,24] In this article, the evidence-based recommendations are listed with the strength of the recommendation and quality of the evidence according to the GRADE method (Table 4). Some research recommendations are also made in areas of uncertainty where further investigation is needed (Table 5). These tables include the recommendations taken from the main classification publications that are pertinent to the diagnosis of lung cancer in resection specimens.

DISCONTINUE TERM BRONCHIOLOALVEOLAR CARCINOMA

Many tumors diagnosed as BAC according to the 1999[2] and 2004[3] WHO classifications are now reclassified in the new classification into 5 different entities including (1) adenocarcinoma in situ (AIS) or solitary small noninvasive peripheral lung tumors, associated with a 100% 5-year survival if completely resected[5,8]; (2) minimally invasive adenocarcinomas (MIAs), which are associated with nearly 100% 5-year survival if completely resected[8,25,26]; (3) invasive adenocarcinomas with a lepidic component[27–31]; (4) invasive mucinous adenocarcinoma (former mucinous BAC)[14,27–30]; and (5) widespread advanced-stage adenocarcinomas with a lepidic component, which are associated with a very poor survival rate.[32] Owing to the widespread confusion from the multiple uses of the former *bronchioloalveolar carcinoma* term in the clinical and research arenas, the classification panel concluded that this term was no longer useful and possibly detrimental.[14,33–37]

Pathology Recommendation 1.—We recommend discontinuing the use of the term *bronchioloalveolar carcinoma* (BAC). Strong recommendation, low-quality evidence.

Throughout this article, the term *bronchioloalveolar carcinoma* (applicable in multiple places in the new classification)

Table 5. Pathology Research Recommendations Applicable to Resection Specimens

1. Criteria for minimally invasive adenocarcinoma are based on limited published data and require further validation. Persistent questions include the following: What is the optimal method for measuring the size of the invasive component? Is 0.5 cm the best size cutoff? If multiple areas of invasion are present, should the greatest dimension of the largest invasive focus be used or the total size multiplied by the percentage of the invasive components? What should be the impact of scar size or prominent stromal desmoplasia and stromal inflammation on determining size of the invasive component? Should criteria for MIA be different for mucinous versus nonmucinous tumors?
2. Lepidic growth may also be composed of neoplastic cells with nuclear atypia resembling that of the adjacent invasive patterns. Whether there is any clinical implication is unknown, that is, it is not established if this is lepidic (non-invasive) growth or invasive carcinoma.
3. The level of reproducibility for identifying predominant histologic patterns is untested. In particular, how should the lepidic pattern be distinguished from other invasive patterns such as acinar and papillary?
4. Are tumors that meet criteria for minimally invasive adenocarcinoma associated with 100% disease-free survival if the invasive component is predominantly solid, micropapillary or if they show giant cell and spindle cell components that fail to qualify for a diagnosis of pleomorphic carcinoma?
5. What is the long-term follow-up for completely resected solitary mucinous minimally invasive adenocarcinoma? Can this be the initial presentation for multifocal invasive mucinous adenocarcinoma?
6. Does the micropapillary pattern have a similar poor prognostic significance in advanced stage as well as early stage tumors?
7. Is there any prognostic significance to the aggressive micropapillary or solid components when present in relatively small amounts if they do not represent the predominant pattern? If so, what percentage is needed for such significance?
8. The ability of pathologists to distinguish adenocarcinoma in situ from invasive disease at frozen section is not proven.
9. Currently, we cannot recommend any specific grading system. Further investigation is needed to determine whether the optimal grading system should include architectural versus nuclear assessment or both.

Abbreviation: MIA, minimally invasive adenocarcinoma.

will be referred to as "former BAC." We understand this will be a major adjustment and suggest initially that when the new proposed terms are used, that they be accompanied in parentheses by "(formerly BAC)." This transition will impact, not only clinical practice and research, but also cancer registries' future analyses of registry data.

CLASSIFICATION FOR RESECTION SPECIMENS

The new proposed lung adenocarcinoma classification for resected tumors is summarized in Tables 1 through 3. Major changes include (1) the addition of AIS as a preinvasive lesion to join atypical adenomatous hyperplasia; (2) addition of MIA; (3) classification of invasive adenocarcinomas according to the predominant subtype after comprehensive histologic subtyping by semiquantitatively estimating the percentage of the various subtypes present in 5% increments; (4) use of the term *lepidic* for invasive adenocarcinomas that have a noninvasive component previously classified as BAC; (5) discontinuing the term *mixed subtype*; (6) introducing the term *invasive mucinous adenocarcinoma* for adenocarcinomas formerly classified as mucinous BAC, excluding tumors that meet criteria for AIS or MIA; (7) discontinuing the subtypes of clear cell and signet ring adenocarcinoma and recognizing these as a cytologic feature when any amount is present, however small; and (8) discontinuing the term *mucinous cystadenocarcinoma* and including this entity under the category of colloid adenocarcinoma.

PREINVASIVE LESIONS

In the 1999[2] and 2004[3] WHO classifications, atypical adenomatous hyperplasia was recognized as a preinvasive lesion for lung adenocarcinoma. This was based on multiple studies documenting these lesions as incidental findings in the adjacent lung parenchyma in 5% to 23% of resected lung adenocarcinomas,[38–42] as well as several molecular findings that demonstrated a relationship to lung adenocarcinoma, including clonality,[43,44] *KRAS* (Kirsten rat sarcoma) mutation,[45,46] *KRAS* polymorphism,[47] epidermal growth factor receptor (*EGFR*) mutation,[48,49] p53 expression,[50] loss of heterozygosity,[51] methylation,[52] telomerase overexpression,[53] eukaryotic initiation factor 4E (*eIF4E*) expression,[54] epigenetic alterations in the WNT pathway,[55] and fragile histidine triad (*FHIT*) expression.[56] Depending on the extensiveness of the search, atypical adenomatous hyperplasia lesions may be multiple in up to 7% of resected lung adenocarcinomas.[39,57]

A major change in this classification is the official recognition of adenocarcinoma in situ as a second preinvasive lesion for lung adenocarcinoma in addition to atypical adenomatous hyperplasia. In the category of preinvasive lesions, atypical adenomatous hyperplasia is the counterpart to squamous dysplasia, and adenocarcinoma in situ is the counterpart to squamous cell carcinoma in situ.

Atypical Adenomatous Hyperplasia

Atypical adenomatous hyperplasia is a localized, small (usually 0.5 cm or less) proliferation of mildly to moderately atypical type II pneumocytes and/or Clara cells lining alveolar walls and sometimes, respiratory bronchioles (Figure 1, A and B).[3,58,59] Gaps along the basement membrane are usually seen between the cells, which consist of rounded, cuboidal, low columnar, or "peg" cells with round to oval nuclei (Figure 1, B). There is a continuum of morphologic changes between atypical adenomatous hyperplasia and adenocarcinoma in situ.[3,58,59] A spectrum of cellularity and atypia occurs in atypical adenomatous hyperplasia. Although some have classified atypical adenomatous hyperplasia into low- and high-grade types,[53,60] such grading is not recommended.[3] Distinction between atypical adenomatous hyperplasia that is more cellular and cytologically atypical, and adenocarcinoma in situ, can be difficult histologically and impossible cytologically. The 0.5-cm size is not an absolute criterion; therefore, multiple characteristics, including size and architectural and cytologic features, are needed to separate lesions of atypical adenomatous hyperplasia that are more cellular and atypical from adenocarcinoma in situ.

Adenocarcinoma In Situ, Nonmucinous and/or Mucinous

Adenocarcinoma in situ (one of the lesions formerly known as BAC), is a localized small (≤3 cm) adenocarci-

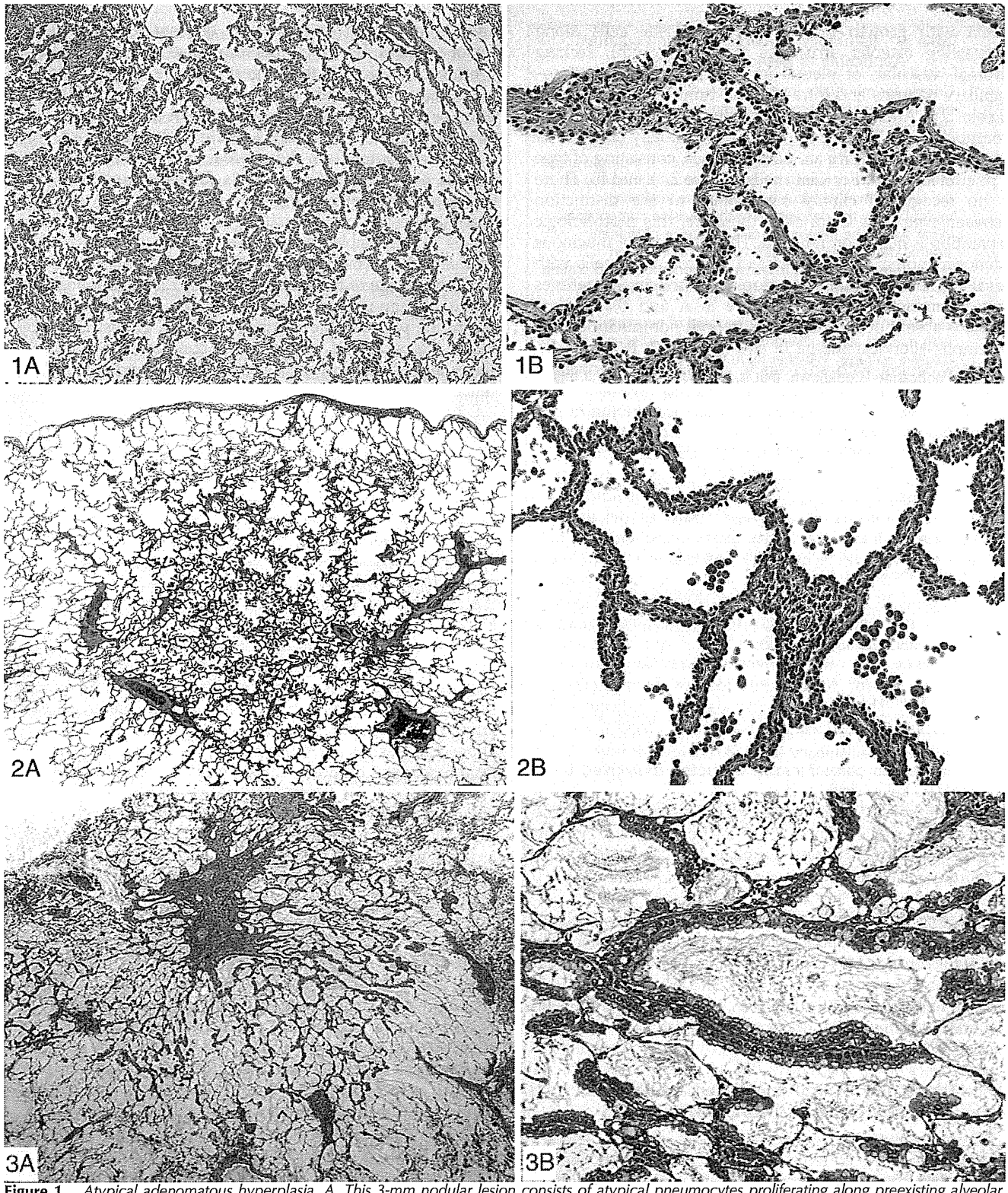

Figure 1. *Atypical adenomatous hyperplasia. A, This 3-mm nodular lesion consists of atypical pneumocytes proliferating along preexisting alveolar walls. There is no invasive component. B, The slightly atypical pneumocytes are cuboidal and show gaps between the cells. Nuclei are hyperchromatic and a few show nuclear enlargement and multinucleation (hematoxylin-eosin, original magnifications ×4 [A] and ×40 [B]).*

Figure 2. *Nonmucinous adenocarcinoma in situ. A, This circumscribed nonmucinous tumor grows purely with a lepidic pattern. No foci of invasion or scarring is seen. B, The tumor shows atypical pneumocytes proliferating along the slightly thickened, but preserved, alveolar walls (hematoxylin-eosin, original magnifications X4 [A] and X40 [B]).*

Figure 3. *Mucinous adenocarcinoma in situ (AIS). A, This mucinous AIS consists of a nodular proliferation of mucinous columnar cells growing in a purely lepidic pattern. Although there is a small central scar, no stromal or vascular invasion is seen. B, The tumor cells consist of cuboidal to columnar cells with abundant apical mucin and small, basally oriented nuclei (hematoxylin-eosin, original magnifications ×4 [A] and ×40 [B]). Reproduced with permission from Travis et al.*[1]

noma with growth restricted to neoplastic cells along preexisting alveolar structures (lepidic growth), lacking stromal, vascular, or pleural invasion. Papillary or micropapillary patterns and intra-alveolar tumor cells are absent (Table 2). Adenocarcinoma in situ is subdivided into nonmucinous and mucinous variants. Virtually all cases of adenocarcinoma in situ are nonmucinous, consisting of type II pneumocytes and/or Clara cells (Figure 2, A and B). There is no recognized clinical significance to the distinction between type II or Clara cells; therefore, this morphologic separation is not recommended. The rare cases of mucinous adenocarcinoma in situ consist of tall columnar cells with basal nuclei and abundant cytoplasmic mucin; sometimes they resemble goblet cells (Figure 3, A and B). Nuclear atypia is absent or inconspicuous in both nonmucinous and mucinous adenocarcinoma in situ (Figures 2, B, and 3, B). Septal widening with sclerosis is common in adenocarcinoma in situ, particularly the nonmucinous variant.

Lesions that meet the criteria for adenocarcinoma in situ have formerly been classified as BAC according to the strict definition of the 1999[2] and 2004[3] WHO classifications and as type A and B adenocarcinoma according to the 1995 Noguchi classification.[5] Multiple observational studies on solitary lung adenocarcinomas with pure lepidic growth, smaller than either 2 or 3 cm, have documented 100% disease-free survival when the lesions are completely resected.[5,61–67] While most of these tumors are nonmucinous, 2 of the 28 tumors reported by Noguchi et al[5] as type A and B in the 1995 study were mucinous. Small size (≤3 cm) and a discrete circumscribed border are important to exclude cases with miliary spread into adjacent lung parenchyma and/or lobar consolidation, particularly for mucinous AIS. This is because the data that indicate 100% 5-year disease-free survival associated with resected AIS are mostly in series of tumors 2 cm or less, with some series including tumors up to 3 cm in diameter; moreover, there are few data regarding mucinous AIS.[5,61–67]

The criteria for AIS as well as MIA can be applied in the setting of multiple tumors only if the other tumors are regarded as synchronous primary tumors rather than intrapulmonary metastases.

Pathology Recommendation 2.—For small (≤3 cm), solitary adenocarcinomas with pure lepidic growth, we recommend the term *adenocarcinoma in situ*, which defines patients who should have 100% disease-specific survival if the lesion is completely resected (strong recommendation, moderate-quality evidence).

Remark: Almost all adenocarcinomas in situ are nonmucinous, rarely are they mucinous.

MINIMALLY INVASIVE ADENOCARCINOMA, NONMUCINOUS AND/OR MUCINOUS

Minimally invasive adenocarcinoma is a small, solitary adenocarcinoma (≤3 cm), with a predominantly lepidic pattern and invasion of 5 mm or less in greatest dimension in any one focus (Table 2).[25,26,68] It is usually nonmucinous (Figure 4, A through C) but rarely may be mucinous (Figure 5, A and B).[8] Minimally invasive adenocarcinoma is, by definition, solitary and discrete.

The invasive component to be measured in MIA is defined as follows: (1) histologic subtypes other than a lepidic pattern (ie, acinar, papillary, micropapillary, and/or solid) or (2) tumor cells infiltrating myofibroblastic stroma. Minimally invasive adenocarcinoma is excluded if the tumor (1) invades lymphatics, blood vessels, or pleura or (2) contains tumor necrosis. If multiple microinvasive areas are found in 1 tumor, the size of the largest invasive area should be measured in its greatest dimension and it should be 5 mm or less in size. The size of invasion is not the summation of all such foci, if more than 1 occurs. This approach was arbitrarily adopted from the approach recommended by the Collage of American Pathologists for measurement of the invasive component of breast cancers that have multiple foci.[69] If the manner of histologic sectioning of the tumor makes it impossible to measure the size of invasion, an estimate of invasive size can be made by multiplying the total percentage of the invasive (nonlepidic) components by the total tumor size. More investigation is needed to determine whether the diagnosis of MIA is best made by using percentage of the invasive component versus the single largest focus of invasion, as recommended in breast cancer.

Evidence for a category of MIA with 100% disease-free survival can be found in the 1995 article by Noguchi et al,[5] in which vascular and/or pleural invasion was found in 10% of the small solitary lung adenocarcinomas that otherwise met the former definition of pure BAC. Even these focally invasive tumors were associated with 100% disease-free survival.[5] Subsequent articles by Sakurai et al[70] and Suzuki et al[71] defined subsets of small lung adenocarcinomas associated with 100% disease-free survival by using scar size less than 5 mm and stromal invasion in the area of bronchioloalveolar growth, respectively. More recently, articles by Borczuk et al,[25] Yim et al,[26] and Maeshima et al[68] have described patients with MIA, defined similarly as in the aforementioned criteria, who have had near 100% disease-specific or very favorable overall survival. There are very limited data regarding mucinous MIA; however, this entity appears to exist. A mucinous MIA with a minor mixture of a nonmucinous component has been reported with no recurrence after 7.4 years.[8] The recent report by Sawada et al[12] of localized mucinous BAC may have included a few cases of mucinous AIS or MIA, but details of the pathology are not specific enough for certainty. A recent series of surgically resected solitary mucinous BACs did not document histologically whether focal invasion was present or not; therefore, AIS versus MIA status cannot be determined, but all 8 patients with tumors measuring 3 cm or less had 100% overall 5-year survival.[72] The diagnosis of AIS or MIA should not be made unless the lesion has a discrete circumscribed border; cases with miliary spread of small foci of tumor into adjacent lung parenchyma and/or with lobar consolidation should be excluded. Mucinous AIS or MIAs are extremely rare and these diagnoses need to be made with caution, as most tumors with this histologic appearance will be invasive mucinous adenocarcinomas (see below).

Also, it remains to be determined if patients with MIA will still have a 100% disease-free survival if the area of invasion shows a poorly differentiated component, such as solid or micropapillary adenocarcinoma, or if there is a giant and spindle cell component that does not meet criteria for pleomorphic carcinoma.

Pathology Recommendation 3.—For small (≤3 cm), solitary adenocarcinomas with predominant lepidic growth and small foci of invasion measuring 0.5 cm or less, we recommend the new concept of "minimally invasive adenocarcinoma (MIA)" to define patients who have near 100% disease-specific survival if

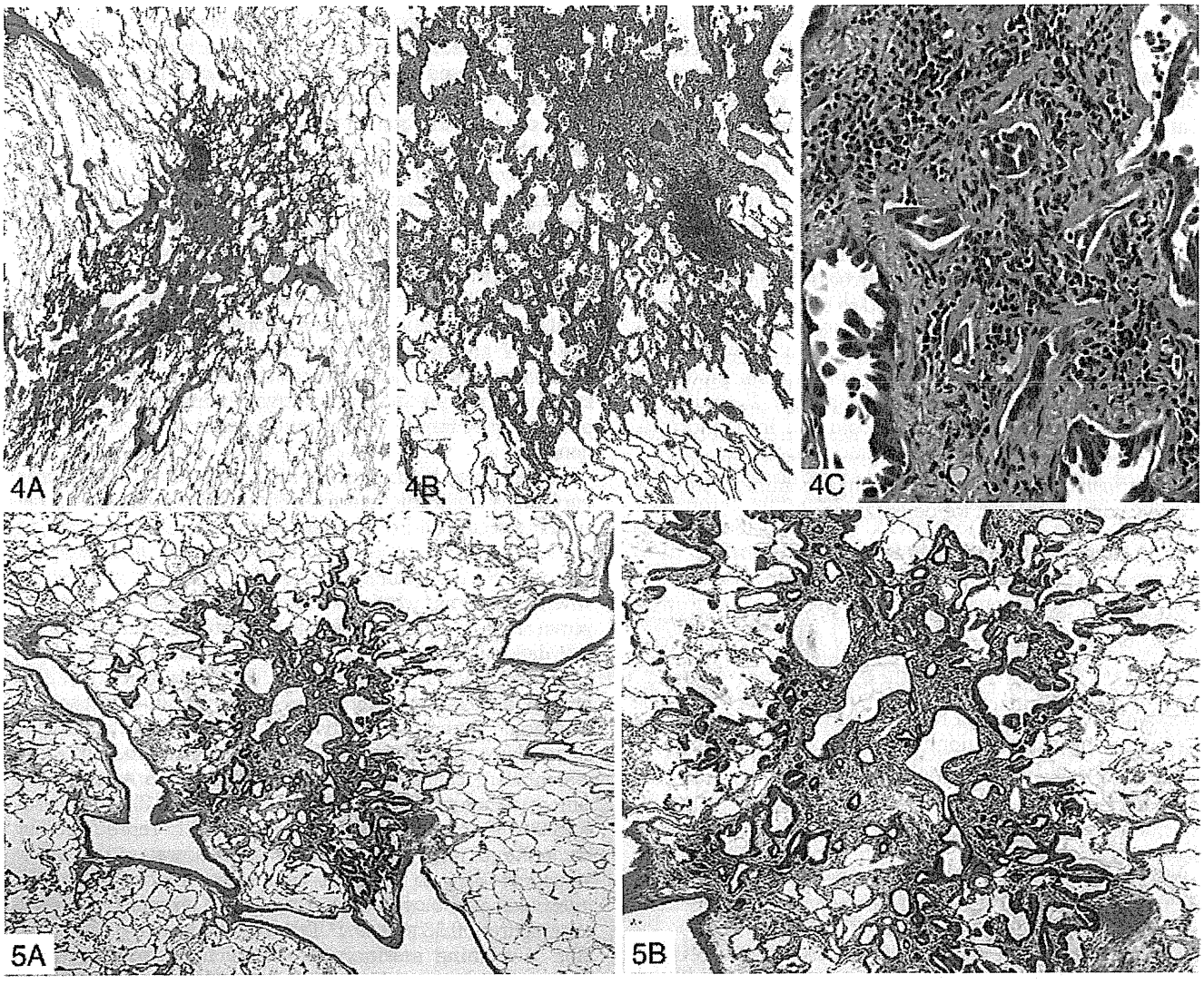

Figure 4. *Nonmucinous minimally invasive adenocarcinoma. A, This subpleural adenocarcinoma tumor consists primarily of lepidic growth with a small (<0.5 cm) central area of invasion. B, To the left is the lepidic pattern and on the right is an area of acinar invasion. C, These acinar glands are invading in the fibrous stroma (hematoxylin-eosin, original magnifications ×4 [A], ×10 [B], and ×40 [C]).*

Figure 5. *Mucinous minimally invasive adenocarcinoma (MIA). A, This mucinous MIA consists of a tumor showing lepidic growth and a small (<0.5 cm) area of invasion. B, The tumor cells consist of mucinous columnar cells growing mostly in a lepidic pattern along the surface of alveolar walls. The tumor invades the areas of stromal fibrosis in an acinar pattern (hematoxylin-eosin, original magnifications ×4 [A] and ×10 [B]). Reproduced with permission from Travis et al.*[1]

the lesion is completely resected (strong recommendation, low-quality evidence).

Remark: Most minimally invasive adenocarcinomas are nonmucinous, rarely are they mucinous.

TUMOR SIZE AND SPECIMEN PROCESSING ISSUES

The Entire Tumor Must Be Sampled for Diagnosis of AIS or MIA

The diagnosis of AIS or MIA cannot be firmly established without histologic sampling of the entire tumor. In a research setting, tissue procurement for frozen tissue banking is encouraged, but in potential AIS and MIA lesions, attention needs to be given to cases for which there is a need to examine the frozen sample histologically. For tumor procurement issues in AIS and MIA, see section on "Molecular-Histologic Correlations."

Radiologic-Pathologic Correlation for Tumor Size Assessment in Lepidic-Predominant Tumors

It can be difficult to appreciate tumor size on gross examination in lepidic-predominant tumors, and the size recorded by the prosector can underestimate actual tumor size. In such cases, it can be helpful to review computed tomography (CT) scans, which may more accurately demonstrate the size of the tumor, including the ground-glass versus solid components, which usually correspond to the lepidic versus invasive components histologically. If review of the CT reveals a discrepancy with the histologic findings, based on review of initial sections, further sampling of the gross specimen may be needed to make an accurate assessment of the extent of lepidic versus invasive components. An initial pathologic diagnosis of AIS or MIA may need to be reconsidered if the CT shows the tumor to be larger than 3 cm or to have a solid component

larger than 0.5 cm. Adenocarcinoma in situ will typically be a pure ground-glass nodule and MIA will have a predominant ground-glass component with a solid component that will typically be 5 mm or less in size. Both of these tumors should also measure 3 cm or less in total size.[1]

Suspected AIS or MIA Measuring Larger Than 3.0 cm

As most of the literature on the topic of AIS and MIA deals with tumors 2.0 or 3.0 cm or less, there is insufficient evidence to support the notion that 100% disease-free survival can occur with completely resected solitary tumors larger than 3.0 cm that are suspected to be AIS or MIA. Until data validate 100% disease-free survival for completely resected, solitary adenocarcinomas larger than 3.0 cm suspected of being AIS or MIA after complete sampling, the term *lepidic-predominant adenocarcinoma, suspect AIS or MIA* is suggested. If such a tumor larger than 3.0 cm has not been completely sampled, the term *lepidic-predominant adenocarcinoma* is best applied with a comment that an invasive component cannot be excluded.

Number of Sections to Submit for Overtly Invasive Adenocarcinomas

For overtly invasive adenocarcinomas, at least 1 section should be submitted per centimeter of the maximal tumor diameter. Additional sections may be helpful for tumors in which the extent of lepidic versus invasive growth is in question. It can be helpful to sample the interface between the tumor and adjacent nonneoplastic lung parenchyma to identify areas of tumor spread that may not be visible on gross examination.

Optimal Specimen Fixation

No effort was made in this IASLC/ATS/ERS classification to address optimal fixation of specimens for immunohistochemistry or molecular testing. However, it may be reasonable to consider the recommendations of the American Society of Clinical Oncology guidelines for breast cancer regarding estrogen and progesterone receptor testing: (1) specimens should be placed in 10% neutral buffered formalin within 1 hour from tumor removal, (2) resected specimens should be sectioned at 5-mm intervals, and (3) specimens should be fixed for at least 6 hours, but not longer than 48 hours.[73,74] For lung cancer, no data have addressed specimen processing issues for immunohistochemistry or molecular testing as exist for breast cancer, so this is a topic that needs more study before specific recommendations can be made.

INVASIVE ADENOCARCINOMA

As the invasive adenocarcinomas represent more than 70% to 90% of surgically resected lung cases, one of the most important aspects of this classification is to present a practical method to address these tumors, which are often composed of a complex heterogeneous mixture of histologic subtypes. This complex mixture of histologic subtypes has presented one of the greatest challenges to classification of invasive lung adenocarcinomas. In recent years, multiple independent research groups[6,20,21,75–84] have begun to classify lung adenocarcinomas according to the most predominant subtype. This approach provides better stratification of the "mixed subtype" lung adenocarcinomas according to the 1999[2]/2004[3] WHO classifications and has allowed for novel correlations between histologic subtypes and both molecular and clinical features.[6,20,21,75–84]

In the revised classification, the term *predominant* is appended to all categories of invasive adenocarcinoma, as most of these tumors consist of mixtures of the histologic subtypes (Figure 6, A through C). This replaces the use of the term *adenocarcinoma, mixed subtype*. Semiquantitative recording of the patterns in 5% increments encourages the observer to identify all patterns that may be present, rather than focusing on a single pattern (ie, lepidic growth). This comprehensive histologic subtyping should be performed by review of all histologic sections of the tumor. Thus, this method provides a basis for choosing the predominant pattern. While most previous studies on this topic used 10% increments, using 5% increments allows for greater flexibility in choosing a predominant subtype when tumors have 2 patterns of relatively similar percentages; it also avoids the need to use 10% for small amounts of components that potentially may be prognostically important, such as micropapillary or solid patterns. Even though it is possible to have equal percentages of 2 prominent components, a single predominant component should be chosen. Recording of these percentages makes it clear to the reader of a report when a tumor has relatively even mixtures of several patterns versus a clear single predominant pattern. In addition, it provides a way to compare the histologic features of multiple adenocarcinomas (see below).[21] This approach may also provide a basis for architectural grading of lung adenocarcinomas.[78] A reproducibility study of classical and difficult selected images of the major lung adenocarcinoma subtypes, which were circulated among a panel of 26 expert lung cancer pathologists, documented κ values of 0.77 ± 0.07 and 0.38 ± 0.14, respectively.[85] A recent study of reproducibility for predominant pattern[86] showed moderate to good κ values of 0.44 to 0.72 for pulmonary pathologists. For untrained pathologists, κ values were expectedly lower, ranging from 0.38 to 0.47, but these improved to 0.51 to 0.66 after a training session, and reevaluation by the same reviewers led to very high κ values between 0.79 and 0.87.

The histologic subtypes of invasive lung adenocarcinomas encompass a spectrum of histologic patterns that represent a morphologic continuum rather than distinct entities. This concept helps to understand why in some cases it is difficult to distinguish between morphologic patterns, for example, lepidic versus acinar or papillary patterns and papillary versus micropapillary patterns. Nevertheless, since this classification was published, a growing number of studies of resected lung adenocarcinomas[8,20,77,78,84,87–90] have demonstrated its utility in identifying significant prognostic subsets and molecular correlations according to the predominant patterns.

Pathology Recommendation 4.—For invasive adenocarcinomas, we suggest comprehensive histologic subtyping be used to assess histologic patterns semiquantitatively in 5% increments, and then choosing a single predominant pattern Individual tumors are then classified according to the predominant pattern and the percentages of the subtypes are also reported (weak recommendation, low-quality evidence).

Histologic Comparison of Multiple Adenocarcinomas and Impact on Staging

Comprehensive histologic subtyping can be useful in comparing multiple lung adenocarcinomas in a single

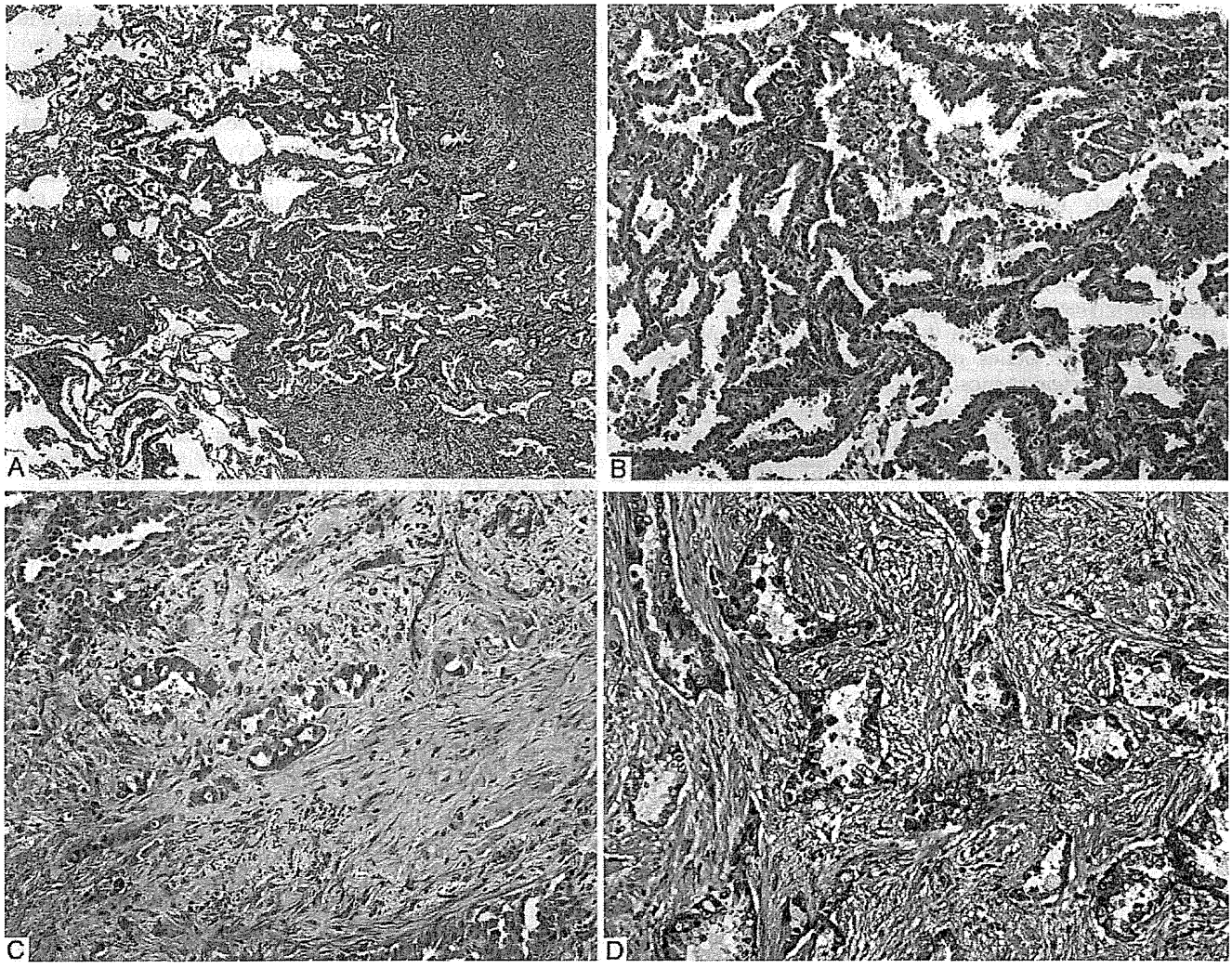

Figure 6. *Lepidic-predominant and acinar adenocarcinoma. A, Lepidic-predominant pattern with mostly lepidic growth (right) and a smaller area of invasive acinar adenocarcinoma (left). B, Lepidic pattern consists of a proliferation of type II pneumocytes and Clara cells along the surface of alveolar walls. C, Area of invasive acinar adenocarcinoma (same tumor as in A and B). D, Acinar adenocarcinoma consists of round to oval malignant glands invading a fibrous stroma (hematoxylin-eosin, original magnifications ×4 [A], ×20 [B and D], and ×10 [C].*

patient in order to distinguish multiple primary tumors from intrapulmonary metastases. This has a great impact on staging for patients with multiple lung adenocarcinomas. Recording the percentages of the various histologic types in 5% increments, not just the most predominant type, allows these data to be used to compare multiple adenocarcinomas, particularly if the slides of a previous tumor are not available at the time of review of the additional lung tumors.[21] In addition to comprehensive histologic subtyping, other histologic features of the tumors, such as cytologic (clear cell or signet ring features) or stromal (desmoplasia or inflammation) characteristics, may be helpful to compare multiple tumors.[21]

Pathology Recommendation 5.—In patients with multiple lung adenocarcinomas, we suggest that comprehensive histologic subtyping may facilitate comparison of the complex, heterogeneous mixtures of histologic patterns for determining if the tumors are metastases or separate synchronous or metachronous primary tumors (weak recommendation, low-quality evidence).

Lepidic-predominant adenocarcinoma typically consists of bland pneumocytic cells (type II pneumocytes or Clara cells) growing along the surface of alveolar walls with morphology similar to that defined in the above section on AIS and MIA (Figure 6, A and B). Invasive adenocarcinoma is present in at least 1 focus, measuring more than 5 mm in greatest dimension. Invasion is defined as (1) histologic subtypes other than a lepidic pattern (ie, acinar, papillary, micropapillary, and/or solid) and/or (2) myofibroblastic stroma associated with invasive tumor cells (Figure 6, C). The diagnosis of lepidic-predominant adenocarcinoma rather than MIA is made if the cancer (1) invades lymphatics, blood vessels, or pleura or (2) contains tumor necrosis. It is understood that lepidic growth can occur in metastatic tumors as well as in invasive mucinous adenocarcinomas. However, the specific term *lepidic-predominant adenocarcinoma* in this classification defines a nonmucinous adenocarcinoma that has lepidic growth as its predominant component, and these tumors are now separated from invasive mucinous adenocarcinoma. The term *lepidic-predominant adenocarcinoma* should not be used in the

context of invasive mucinous adenocarcinoma with predominant lepidic growth.

Lepidic growth may also be composed of neoplastic cells with nuclear atypia resembling that of the adjacent invasive patterns. Whether there is any clinical implication is unknown, that is, it is not established if this is in situ or invasive carcinoma. This point is made in the classification as a research recommendation to encourage further investigation of this issue (Table 5).

In the categories of mixed subtype in the 1999[2]/2004[3] WHO classifications and of type C in the Noguchi classification,[5] respectively, there was no assessment of the percentage of lepidic growth (former BAC pattern); therefore, in published series diagnosed according to these classification systems, most of the lepidic-predominant adenocarcinomas are buried among a heterogeneous group of tumors that include predominantly invasive adenocarcinomas. However, several studies[25,63,91–93] have shown that lepidic growth is associated with more favorable survival in cases of small solitary resected lung adenocarcinomas with an invasive component. Using this approach, several recent studies of early stage adenocarcinomas[8,20,84] demonstrated excellent outcome for these patients, with as high as 86% to 90% 5-year recurrence-free survival.

Pathology Recommendation 6.—For nonmucinous adenocarcinomas previously classified as mixed subtype, for which the predominant subtype consists of the former nonmucinous BAC, we recommend use of the term *lepidic-predominant adenocarcinoma* and discontinuation of the term *mixed subtype* (strong recommendation, low-quality evidence).

Acinar-predominant adenocarcinoma shows a majority component of glands, which are round to oval with a central luminal space surrounded by tumor cells (Figure 6, D).[3] The neoplastic cells and/or glandular spaces may contain mucin. Acinar structures also may consist of rounded aggregates of tumor cells with peripheral nuclear polarization with central cytoplasm without a clear lumen. Adenocarcinoma in situ with collapse may be difficult to distinguish from the acinar pattern. However, when the alveolar architecture is lost and/or myofibroblastic stroma is present, invasive acinar adenocarcinoma is considered present. Cribriform arrangements are regarded as a pattern of acinar adenocarcinoma.[94]

Papillary-predominant adenocarcinoma shows a major component of a growth of glandular cells along central fibrovascular cores (Figure 7, A and B).[3] This should be distinguished from tangential sectioning of alveolar walls in an area of lepidic adenocarcinoma. If a tumor has lepidic growth, but the alveolar spaces are filled with papillary structures, the tumor is classified as papillary adenocarcinoma. Myofibroblastic stroma is not needed to diagnose this pattern.

Micropapillary-predominant adenocarcinoma has tumor cells growing in papillary tufts (florets that lack fibrovascular cores; Figure 7, C and D).[3] These may appear detached and/or connected to alveolar walls. The tumor cells are usually small and cuboidal with minimal nuclear atypia. Ringlike glandular structures may "float" within alveolar spaces. Vascular and stromal invasion is frequent. Psammoma bodies may be seen.

The micropapillary pattern of lung adenocarcinoma was cited in the 2004 WHO classification[3] in the discussion, but there were too few publications on this topic to introduce it as a formal histologic subtype.[9,10,95] While most of the studies have used a very low threshold for classification of adenocarcinomas as micropapillary, including as low as 1% to 5%,[9,10] recent reports[8,20,84,87] have 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 patients with early-stage disease have reported data indicating this is a poor prognostic subtype.[8–10,75,78,96–103]

Additional evidence for the aggressive behavior of this histologic pattern is the overrepresentation of the micropapillary pattern in metastases compared to the primary tumors, where it sometimes comprises only a small percentage of the overall tumor.[78] The clinical significance of minor micropapillary components in primary lung adenocarcinomas that are not micropapillary predominant needs further study.

Pathology Recommendation 7.—For patients with early-stage adenocarcinoma, we recommend the addition of "micropapillary-predominant adenocarcinoma," when applicable, as a major histologic subtype owing to its association with poor prognosis in early-stage disease (strong recommendation, low-quality evidence).

Solid-predominant adenocarcinoma with mucin production shows a major component of polygonal tumor cells forming sheets that lack recognizable patterns of adenocarcinoma, that is, acinar, papillary, micropapillary, or lepidic growth (Figure 8, A through C).[3] If the tumor is 100% solid, intracellular mucin should be present in at least 5 tumor cells in each of 2 high-power fields, confirmed with histochemical stains for mucin (Figure 8, B).[3] Solid adenocarcinoma must be distinguished from squamous cell carcinomas and large cell carcinomas, both of which may show rare cells with intracellular mucin. Some solid adenocarcinomas have dense eosinophilic cytoplasm that resembles that of squamous cell carcinoma with a "pseudosquamous" morphology. Even in resection specimens, in poorly differentiated tumors that have a suggestion of squamous morphology (Figure 8, A) but lack clear squamous morphology, such as keratinization, pearls, or bridges, immunohistochemistry may be indicated with an adenocarcinoma marker such as thyroid transcription factor-1 (TTF-1) (Figure 8, C) and a squamous marker, such as p63 or the recently described p40, which is an isomer of p63 with greater specificity for squamous cell carcinoma.[104]

Neuroendocrine immunohistochemical markers should only be used in cases for which there is suspected neuroendocrine morphology. If neuroendocrine morphology is not suspected, neuroendocrine markers should not be used.

VARIANTS

Rationale for Changes in Adenocarcinoma Histologic Variants

Rationale for Separation of Invasive Mucinous Adenocarcinoma (Formerly Mucinous BAC) from Nonmucinous Adenocarcinomas.—Multiple studies[11,13–15,17,105–109] indicate that tumors formerly classified as mucinous BAC have major

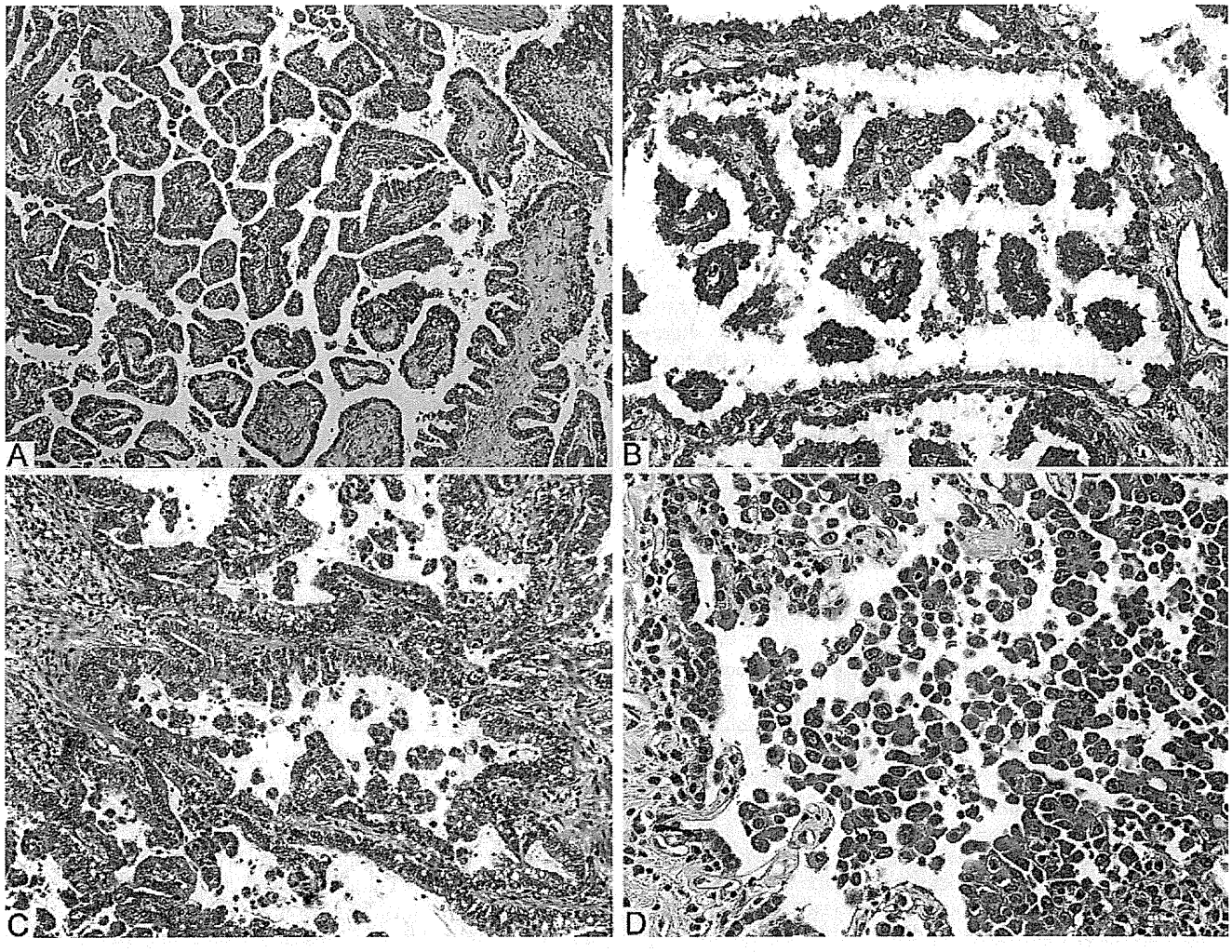

Figure 7. *Papillary and micropapillary adenocarcinoma. A, Papillary adenocarcinoma consists of malignant cuboidal to columnar tumor cells growing on the surface of fibrovascular cores. B, Papillary adenocarcinoma consisting of intra-alveolar papillary structures with fibrovascular cores. Although there is a cuboidal lining of tumor cells around the airspace in a lepidic fashion, this pattern should be classified as papillary adenocarcinoma. C, Micropapillary adenocarcinoma. Within the airspaces the tumor is growing in papillary structures lacking fibrovascular cores. Although there are some true papillary areas with fibrovascular cores, and some tumor cells growing in a lepidic pattern along the surfaces of the airspaces, most of this pattern should be regarded as micropapillary. D, Micropapillary adenocarcinoma. This tumor is spreading through the alveolar space with a spectrum of small papillary structures lacking fibrovascular cores to single dyscohesive cells (hematoxylin-eosin, original magnifications ×4 [A], ×20 [B and C], and ×40 [D]).*

clinical, radiologic, pathologic, and genetic differences from the tumors formerly classified as nonmucinous BAC (Table 6). In particular, these tumors show a very strong correlation with *KRAS* mutation and lack of *EGFR* mutation, while nonmucinous adenocarcinomas are more likely to show *EGFR* mutation and only occasionally *KRAS* mutation (Table 6). Therefore, in the new classification, these tumors are now separated into different categories (Table 1). The neoplasms formerly termed *mucinous bronchioloalveolar carcinoma* (*mucinous BAC*), are now recognized as having invasive components in most cases, and are classified as "invasive mucinous adenocarcinoma (formerly mucinous BAC)," or mucinous AIS or MIA if they meet the criteria outlined in Tables 2 and 3.

Rationale for Including Mucinous Cystadenocarcinoma in Colloid Adenocarcinoma.—Tumors formerly classified as "mucinous cystadenocarcinoma" are very rare and they probably represent part of the spectrum of colloid adenocarcinoma. Therefore, we suggest that these adenocarcinomas, which consist of unilocular or oligolocular cystic structures by imaging and/or gross examination, be included in the category of colloid adenocarcinoma.[110] For such tumors, a comment could be made that the tumor resembles that formerly classified as mucinous cystadenocarcinoma.

Rationale for Removing Clear Cell and Signet Ring Carcinoma as Adenocarcinoma Subtypes.—Clear cell and signet ring cell features are now regarded as cytologic changes that may occur in association with multiple histologic patterns.[111,112] Thus, their presence and extent should be recorded, but data are not available that show a clinical significance beyond a strong association with the solid subtype. They are not considered to be specific histologic subtypes, although associations with molecular features are possible, such as the recent observation of a solid pattern with greater than 10% signet ring cell features in up to 56% of tumors from patients with echinoderm microtubule-associated protein-like 4 (*EML4*) and anaplastic lymphoma kinase (*ALK*) gene fusions

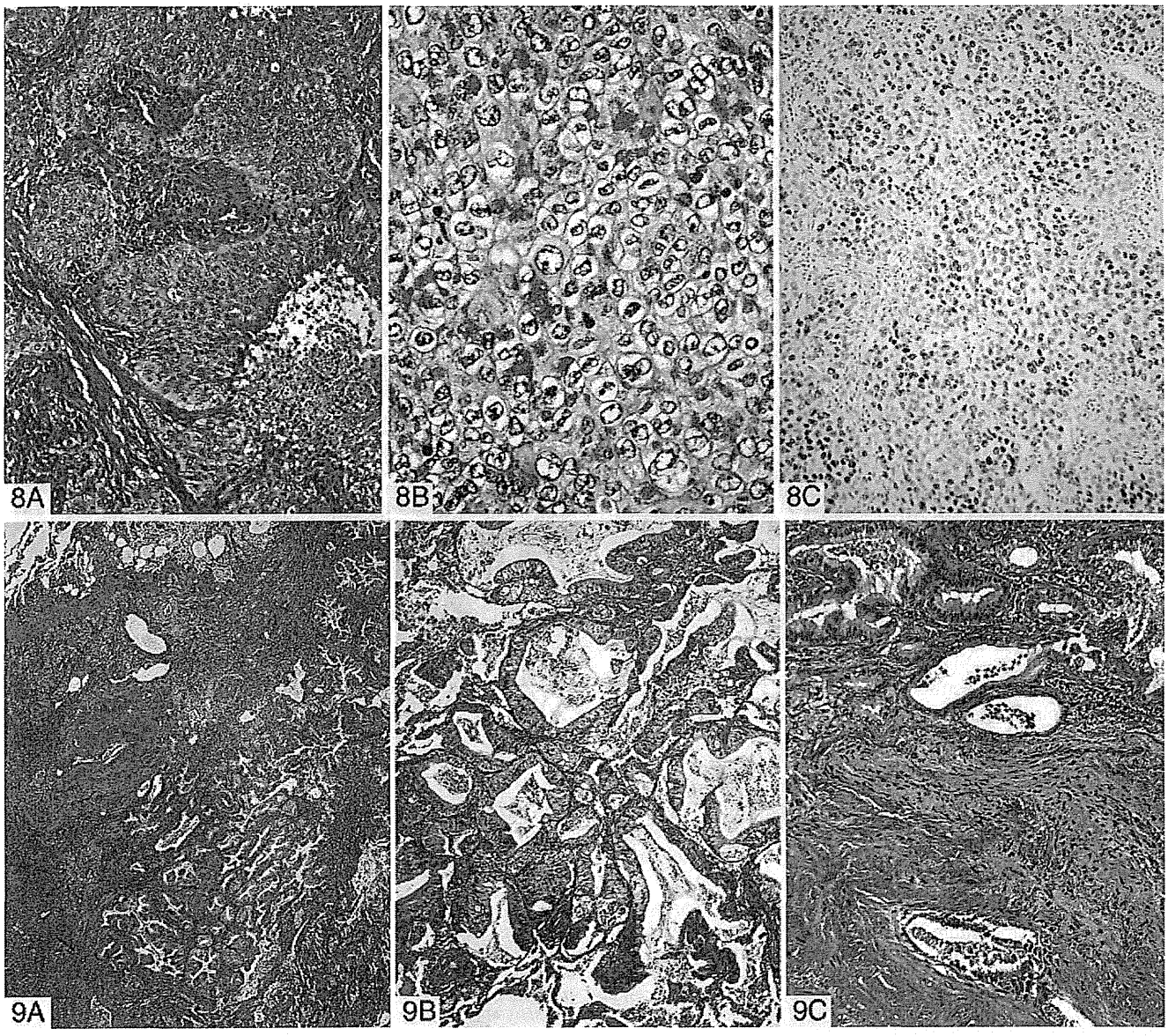

Figure 8. *Solid adenocarcinoma with mucin and pseudosquamous morphology. A, This tumor consists of sheets of tumor cells with abundant cytoplasm and mostly vesicular nuclei with several conspicuous nucleoli. Because this tumor had prominent eosinophilic cytoplasm, it was originally classified as squamous cell carcinoma. No acinar, papillary, or lepidic patterns are seen and there was no suggestion of mucin in tumor cell cytoplasm. B, The tumor showed foci of strong staining for intracytoplasmic mucin in numerous tumor cells. C, Thyroid transcription factor-1 (TTF-1) was diffusely and strongly positive. This tumor had an EGFR exon 19 deletion (hematoxylin-eosin, original magnification ×10 [A]; mucicarmine, original magnification ×40 [B]; TTF-1, original magnification ×20 [C]).*

Figure 9. *Invasive mucinous adenocarcinoma. A, This area of invasive mucinous adenocarcinoma demonstrates areas with lepidic, acinar, and papillary patterns. In addition, there is a fibrotic focus that contains invasive tumor with a desmoplastic stroma. B, The tumor consists of columnar cells filled with abundant mucin in the apical cytoplasm and shows small, basally oriented nuclei. This area shows mostly lepidic growth but also areas suggesting an acinar pattern. C, This photomicrograph highlights a focus of invasion with desmoplastic stroma from A. The invasive area shows an acinar pattern and the tumor cells show less cytoplasmic mucin (hematoxylin-eosin, original magnifications ×4 [A], ×10 [B], and ×20 [C]).*

(EML4-ALK).[113] Rather than diminishing the recognition of these features, this approach will now record any percentage (even <5%) of clear cell or signet ring features, whereas in the previous WHO classifications, the amount needed to be substantial, at the level of a histologic subtype, before it would be included in the diagnosis.

Rationale for Adding Enteric Adenocarcinoma.—Enteric adenocarcinoma is added to the classification to draw attention to this rare histologic type of primary lung adenocarcinoma, which can share some morphologic and immunohistochemical features with colorectal adenocarcinoma.[114] Owing to these similarities, clinical evaluation is needed to exclude a gastrointestinal primary tumor. It is not known if there are any distinctive clinical or molecular features.

Rationale for Maintaining Fetal Adenocarcinoma.—Fetal adenocarcinomas are maintained in this classification with the recognition that low-grade fetal adenocarcinomas are most commonly seen in the fourth decade of life with a slight female

Table 6. Difference Between Invasive Mucinous Adenocarcinoma and Nonmucinous Adenocarcinoma In Situ (AIS)/ Minimally Invasive Adenocarcinoma (MIA)/Lepidic-Predominant Adenocarcinoma (LPA)

Characteristics	Invasive Mucinous Adenocarcinoma (Formerly Mucinous BAC)	Nonmucinous AIS/MIA/LPA (Formerly Nonmucinous BAC)
Female, No. (%)	49/84 (58)[11,17,30,142,143]	101/140 (72)[11,17,30,142,143]
Smoker, No. (%)	39/87 (45)[11,17,30,142,144]	75/164 (46)[11,17,30,142,144]
Radiographic appearance	Majority consolidation; air bronchogram;[13] frequent multifocal and multilobar presentation[12–14,106,108,145,146]	Majority ground-glass attenuation[13,14,37,147–151]
Cell type	Mucin filled, columnar, and/or goblet[13,27,28,30,152]	Type II pneumocyte and/or Clara cell[13,27,28,30,152]
Immunophenotype		
CK7	Mostly positive[a] (+, ≈88%)[14,16,153–156]	Positive[a] (+, ≈98%)[14,16,153–156]
CK20	Positive[a] (+, ≈54%)[14,16,153–156]	Mostly negative[a] (+, ≈5%)[14,16,153–156]
TTF-1	Mostly negative[a] (+, ≈17%)[14,16,17,153,154,156,157]	Positive[a] (+, ≈67%)[14,16,17,153,154,156,157]
Genotype		
KRAS mutation	Frequent[a] (+, ≈76%)[14,15,106,158–160]	Uncommon[a] (+, ≈13%)[11,14,15,106,158–161]
EGFR mutation	Almost none[a] (+, ≈3%)[11,14,15,106,158–161]	Frequent[a] (+, ≈45%)[11,14,15,106,158–161]

Abbreviations: BAC, bronchioloalveolar carcinoma; CK, cytokeratin; TTF-1, thyroid transcription factor-1.

[a] Numbers represent the percentage of cases that are reported to be positive.

preponderance, whereas high-grade fetal adenocarcinomas are most commonly seen in elderly males, suggesting the 2 subtypes may have different oncogenic pathways.[115–117]

Histologic Features of Variant Subtypes

Invasive mucinous adenocarcinoma (formerly mucinous BAC) has a distinctive histologic appearance in which the tumor cells have a goblet or columnar cell morphology with abundant intracytoplasmic mucin (Figure 9, A through C). Nuclear atypia is usually inconspicuous or absent. Alveolar spaces often contain mucin. These tumors may show the same heterogeneous mixture of lepidic, acinar, papillary, micropapillary, and solid growth as in nonmucinous tumors (Figure 9, B and C). The clinical significance of reporting semiquantitative estimates of subtype percentages and the predominant histologic subtype, similar to nonmucinous adenocarcinomas, is not certain. When stromal invasion is seen, the malignant cells may show less cytoplasmic mucin and more atypia (Figure 9, C). These tumors differ from mucinous AIS and MIA by 1 or more of the following criteria: size (>3 cm), amount of invasion (>0.5 cm), multiple nodules, or lack of a circumscribed border with miliary spread into adjacent lung parenchyma.

There is a strong tendency for multicentric, multilobar, and bilateral lung involvement, which may reflect aerogenous spread. Mixtures of mucinous and nonmucinous tumors may rarely occur; if so, the percentage of invasive mucinous adenocarcinoma should be recorded in a comment. If there is at least 10% of each component, it should be classified as "mixed invasive mucinous and nonmucinous adenocarcinoma" with a description of the various components that comprise the tumor.

Invasive mucinous adenocarcinomas (formerly mucinous BAC) need to be distinguished from adenocarcinomas that produce mucin but lack the characteristic goblet cell or columnar cell morphology of the tumors that have historically been classified as mucinous BAC. When mucin is identified by light microscopy or mucin stains in adenocarcinomas that do not meet the above criteria, this feature should be reported in a comment after classifying the tumor according to the appropriate terminology and criteria proposed in this classification. This can be done by adding a descriptive phrase such as "with mucin production" or "with mucinous features," rather than the term *invasive mucinous adenocarcinoma*. Because of the multiple ways mucin can be expressed in lung adenocarcinomas, the specific wording "invasive mucinous adenocarcinoma" is important for this diagnosis.

Metastatic mucinous adenocarcinomas from sites such as the pancreas and ovary can appear morphologically identical to pulmonary invasive mucinous adenocarcinomas; therefore, clinical and radiologic correlation should be made to exclude primary tumors in these locations. Pancreatic mucinous adenocarcinomas are more likely to express cytokeratin (CK) 20 and mucin 2 (MUC2).[118] Metastatic colorectal adenocarcinomas often express caudal-related homeobox 2 (CDX-2) and CK20 with lack of CK7.

Pathology Recommendation 8.—For adenocarcinomas formerly classified as mucinous BAC, we recommend 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, as "invasive mucinous adenocarcinoma" (weak recommendation, low-quality evidence).

Colloid adenocarcinoma shows abundant extracellular mucin in pools, which distend alveolar spaces and destroy their walls (Figure 10, A and B). The mucin pools contain clusters of mucin-secreting tumor cells, which may comprise only a small percentage of the total tumor volume (or area) and thus be inconspicuous (Figure 10, A).[119,120] The tumor cells may consist of goblet cells or other mucin-secreting cells and may form a single layer along fibrous septa (Figure 10, B). Colloid adenocarcinoma is found more often as a mixture with other adenocarcinoma histologic subtypes rather than as a pure pattern. A tumor is classified as a colloid adenocarcinoma when it is the predominant component; the percentages of other components should be recorded.[110] Cystic gross and or histologic features are included in the spectrum of colloid adenocarcinoma, but in most cases this is a focal feature. Cases previously reported as mucinous cystadenocarcinoma are extremely rare and now these should be classified as colloid adenocarcinoma with cystic changes. The cysts are filled with mucin, and lined by goblet or other mucin-secreting cells. The lining epithelium may be discontinuous and replaced with inflammation including a granulomatous reaction or gran-

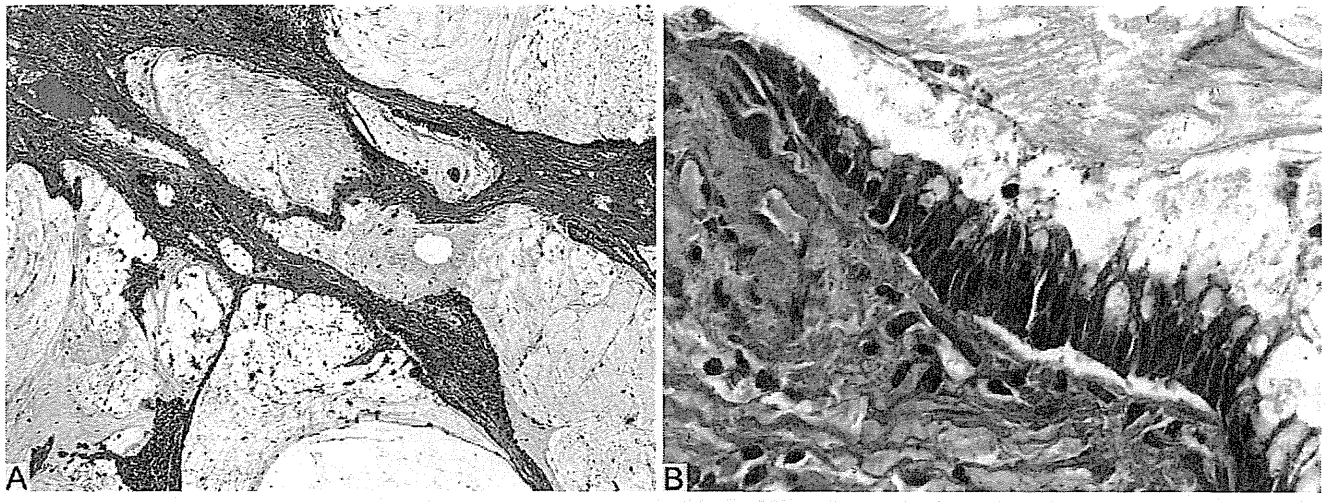

Figure 10. *Colloid adenocarcinoma. A,This tumor consists of abundant pools of mucin growing within and distending airspaces. Focally well-differentiated mucinous glandular epithelium grows along the surface of fibrous septa and within the pools of mucin. Tumor cells may be very inconspicuous. B, The surface of the fibrous wall is lined by well-differentiated cuboidal or columnar mucinous epithelium (hematoxylin-eosin, original magnifications ×10 [A] and ×40 [B]).*

ulation tissue. Nuclear atypia of the neoplastic epithelium is usually minimal.[121] Morphologically, this tumor may be fully indistinguishable from metastases from the appendix; clinical history should be very helpful.[122]

Fetal adenocarcinoma consists of glandular elements with tubules composed of glycogen-rich, nonciliated cells that resemble fetal lung tubules (Figure 11).[3] Subnuclear vacuoles are common and characteristic. Squamoid morules may be in the lumens. Most are low grade with a favorable outcome; high-grade tumors occur. When mixtures occur with other histologic subtypes, a feature that occurs more often in the high-grade tumors, the tumor should be classified according to the predominant component.[115] This tumor typically occurs in younger patients than do other adenocarcinomas. Uniquely, the low-grade fetal adenocarcinomas appear to be driven by mutations in the β-catenin gene and the epithelial cells express aberrant nuclear and cytoplasmic staining with this antibody by immunohistochemistry.[116,117,123] Nakatani et al[116,117] and Sekine et al[123] have suggested that upregulation of components in the WNT signaling pathway, such as β-catenin, are important in low-grade fetal adenocarcinomas, as well as in biphasic pulmonary blastomas. This is in contrast to the high-grade fetal adenocarcinomas, which appear to be distinct from the low-grade tumors.[116,117,123]

Enteric differentiation can occur in lung adenocarcinoma and when this component exceeds 50%, the tumor is classified as pulmonary adenocarcinoma with enteric differentiation. The enteric pattern shares morphologic and immunohistochemical features with colorectal adenocarcinoma.[114] In contrast to metastatic colorectal adenocarcinoma, these tumors are histologically heterogeneous with some component that resembles primary lung adenocarcinoma such as lepidic growth. Recording of the percentages of these other components may be useful. The enteric pattern consists of glandular and/or papillary structures, sometimes with a cribriform pattern (Figure 12, A), lined by tumor cells that are mostly tall columnar with nuclear pseudostratification, luminal necrosis, and prominent nuclear debris.[114] Poorly differentiated tumors may have a more solid pattern. These tumors show at least 1 immunohistologic marker of enteric differentiation (CDX-2, CK20, or MUC2) (Figure 12, B). Consistent positivity for CK7 and expression of TTF-1 in approximately half the cases help in the distinction from metastatic colorectal adenocarcinoma.[114,124] Cytokeratin 7–negative cases may occur.[125] CDX-2 is reduced or absent in most poorly differentiated colorectal carcinomas and more than half show the high-frequency microsatellite instability phenotype.[126] Although this type of tumor will rarely metastasize to the lung, since immunohistochemical detection of mismatch repair protein

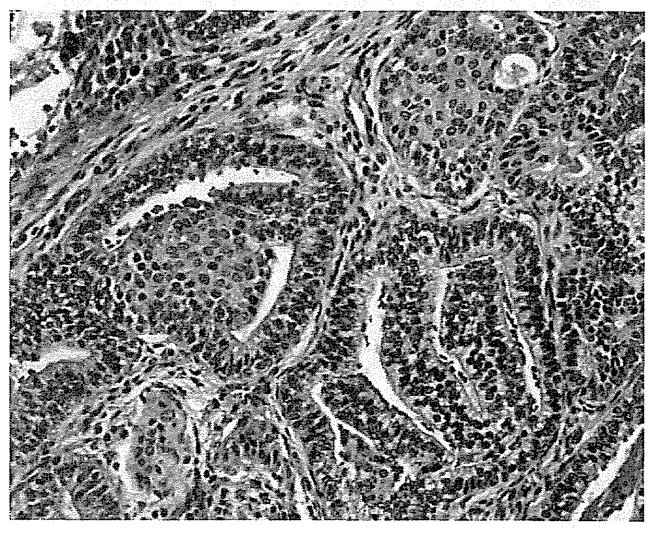

Figure 11. *Fetal adenocarcinoma consists of malignant glandular cells growing in tubules and papillary structures with endometrioid morphology. Some tumor cells have prominent clear cytoplasm, and squamoid morules are present (hematoxylin-eosin, original magnification ×20).*

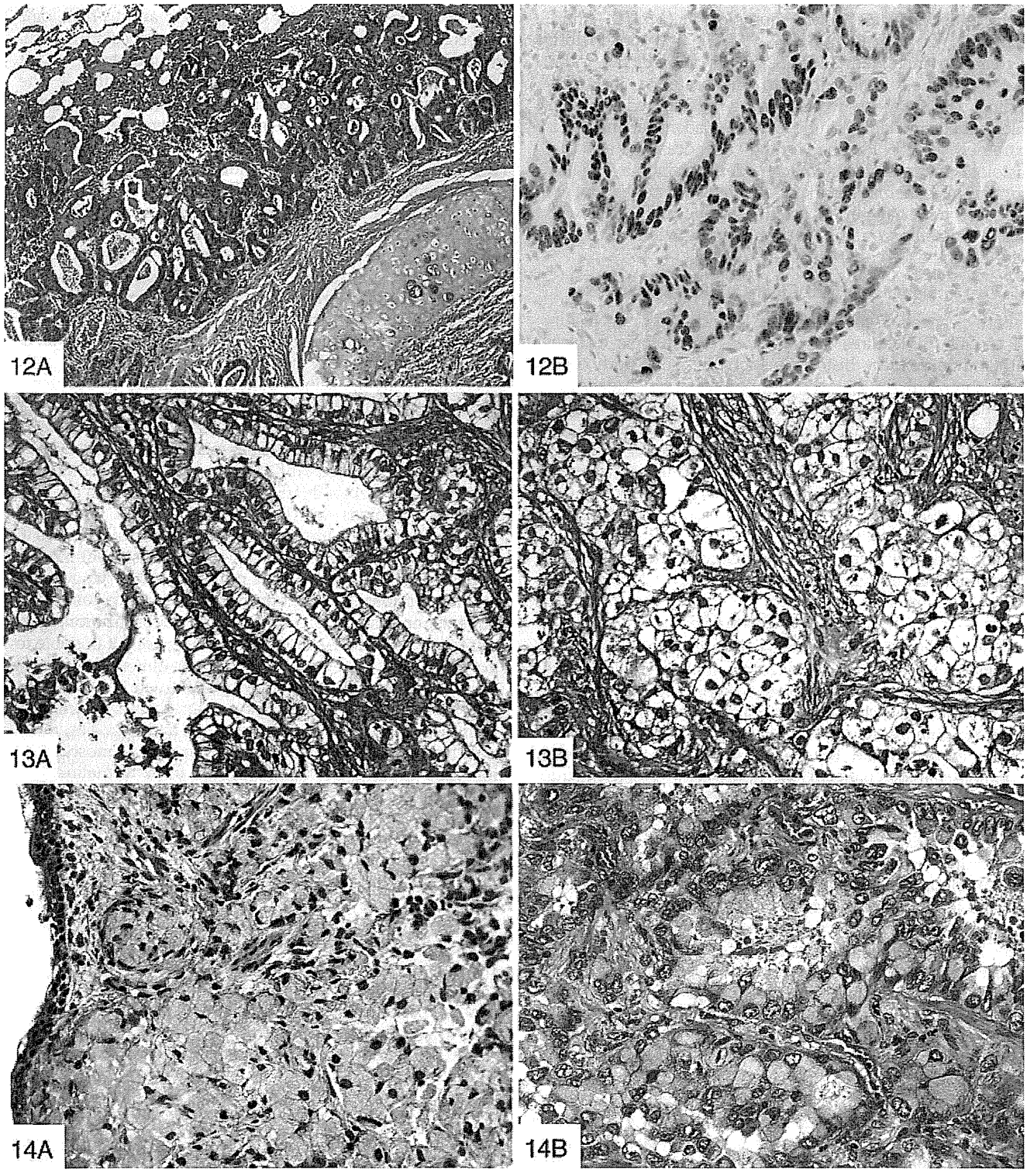

Figure 12. *Enteric adenocarcinoma. A, This tumor consists of an adenocarcinoma that morphologically resembles colonic adenocarcinoma with back-to-back angulated acinar structures. The tumor cells are cuboidal to columnar with nuclear pseudostratification. B, The tumor stains strongly for CDX-2 (hematoxylin-eosin, original magnification ×10 [A]; original magnification ×40 [B].*

Figure 13. *A, Acinar adenocarcinoma with clear cells. The cytoplasm in these tumor cells shows prominent clear cell features. B, Solid adenocarcinoma with clear cell features. The tumor cells in these solid nests have abundant clear cytoplasm (hematoxylin-eosin, original magnifications ×40 [A and B]).*

Figure 14. *Clear cell features: Signet ring features. A, Solid adenocarcinoma with signet ring features. This tumor consists of a uniform population of tumor cells with cytoplasm distended with abundant mucin, with many showing signet ring features. B, Acinar adenocarcinoma with signet ring features. Many tumor cells in this acinar pattern of adenocarcinoma have signet ring morphology (hematoxylin-eosin, original magnifications ×40 [A and B]).*

with antibodies for mutL homolog-1 (*MLH1*), mutS homologs 2 and 6 (*MSH2*, *MSH6*), and postmeiotic segregation increased 2 (*PMS2*) gives a predictive value that is virtually equivalent to microsatellite instability testing, this may be worth testing in selected cases as microsatellite instability in primary lung adenocarcinomas is extremely rare.[127] Primary lung adenocarcinomas that histologically resemble colorectal adenocarcinoma, but lack immunohistochemical markers of enteric differentiation, are probably better regarded as lung adenocarcinomas with *enteric morphology* rather than pulmonary adenocarcinoma with enteric differentiation.[128]

Signet Ring and Clear Cell Features

Both clear cell (Figure 13, A and B) and signet ring (Figure 14, A and B) features are regarded as cytologic features rather than primary histologic subtypes. They both occur most commonly in the solid component of lung adenocarcinomas (Figures 13, B, and 14, A), but they can also be seen in other patterns such as acinar (Figures 13, A, and 14, B), papillary, and micropapillary adenocarcinoma.[111,112] Therefore, these features should not be included in predominant subtype or the summary of percentages for comprehensive histologic subtyping, but rather they can be mentioned at the end of the diagnosis as "with signet ring features" or "with clear cell features," along with the estimated percentage of this cytologic change.

HISTOLOGIC GRADING

Unlike carcinomas of organs such as the breast, prostate, and kidney, there is no established grading system for lung adenocarcinoma in resection specimens. Since the effort to develop this new classification was begun, several studies have examined both architectural and nuclear approaches. While certain histologic subtypes are associated with favorable (lepidic pattern)[5] or unfavorable (solid, micropapillary)[6,9,10,129] prognosis, few articles have addressed grading across all histologic subtypes. Two major studies have addressed architectural grading using the single most predominant pattern[8] or the 2 most prominent patterns.[78] Both approaches have identified prognostically important subsets of lung adenocarcinoma. Nuclear grading has been evaluated in 3 studies, with two suggesting that nuclear size[130,131] and the other that cytologic atypia[129] were predictive of survival. A recent study[132] evaluated both nuclear and architectural grading in stage I lung adenocarcinomas. Although nuclear diameter, nuclear atypia, mitotic count, and atypical mitoses were significant predictors of recurrence in univariate analysis, in multivariate analysis only mitotic count had a significant independent association with risk of recurrence. Increased risk of recurrence was best predicted by a combined high architectural/mitotic grade after adjusting for clinical factors.[132] The impact of adding mitotic counts was greatest in tumors with intermediate architectural grade.[132] While these studies are promising, more validation studies are needed before a final grading system can be recommended for lung adenocarcinoma.

MOLECULAR-HISTOLOGIC CORRELATIONS

The molecular issues in lung adenocarcinoma are addressed in detail in the master classification document.[1] However, because of the importance of molecular histologic correlations, a few brief comments will be addressed. Unlike the specific genetic alterations seen in sarcomas, lymphomas, and leukemias, in lung cancer there are no histologic molecular correlations that are totally specific. Overall molecular, radiologic, and gene pathway correlations with adenocarcinoma subtypes are summarized in Table 7. The most robust histologic molecular correlation is with invasive mucinous adenocarcinoma, since a high percentage of these tumors have *KRAS* mutations and lack of *EGFR* mutations (Table 6). *EGFR* and *KRAS* mutations, as well as *ALK* rearrangement, can be seen in most of the invasive adenocarcinoma histologic subtypes. However, *EGFR* mutations are most often seen in association with nonmucinous adenocarcinomas that are lepidic or papillary predominant, and some report an association with a micropapillary pattern (Table 7). *KRAS* mutations are reported most often in tumors with a solid or micropapillary pattern and can be present in tumors producing extracellular mucin (Table 7). *ALK* rearrangement has been mostly associated with an acinar pattern, including a cribriform morphology, and with signet ring cell features, particularly those with TTF-1 and p63 coexpression.[133–136] Another point of interest is that nonsmoker-associated gene mutations, including *EGFR, EML4-ALK, BRAF*, and human epidermal growth factor receptor 2 (*HER2/neu*), are involved in a subset of adenocarcinomas with TTF-1 expression.[137]

With the emerging importance of molecular diagnostics to guide therapy, a multidisciplinary approach is needed to set a consistent strategy for obtaining and preserving tissue samples optimized to perform studies such as DNA sequence analysis, fluorescence in situ hybridization, and, in some settings, RNA-based studies. It is not yet possible to provide specific guidelines on how to do this in the current document because of the wide variation in infrastructure and expertise from one institution to another. If a portion of a sampled tumor is snap frozen for molecular studies, a few considerations exist for resection specimens. As most critical molecular studies can be performed from formalin-fixed, paraffin-embedded tissue, there is a need for frozen samples only for certain techniques such as comparative genomic hybridization and gene expression profiling. If frozen tissue is being obtained from tumors with lepidic-predominant tumors, for which AIS or MIA is in the differential diagnosis, efforts should be made to ascertain whether this frozen piece has an invasive component. The CT and gross appearance of the lesion should be considered to ensure a solid component is sampled in a tumor that appears part solid on CT. One approach is to perform a frozen section from the tissue saved for storage in a freezer. It is important to have a pathologist confirm the presence of tumor cells before performing molecular studies in the frozen tumor tissue samples.

RADIOLOGIC-HISTOLOGIC CORRELATIONS

There are settings in which pathologic assessment of lung adenocarcinomas can be greatly improved by correlation with radiologic findings. While review of CT reports may be informative, it is also helpful to have access to primary CT images in the frozen section and gross rooms, where pathology specimens are initially processed, and also at the time of review of histologic sections. Review of CT images may be valuable because they may give a better impression about the gross pathologic findings, which can be difficult to appreciate if tumors are removed by the surgeon in several pieces or if the tumor is difficult to identify on gross examination. In this sense, the CT is an extension of the

Table 7. Adenocarcinoma Histologic Subtypes, Molecular and Radiologic Associations

Histologic Subtype Predominant	Molecular Features	CT Scan Appearance	Gene Pathways Associated	Sources
Nonmucinous adenocarcinoma in situ and minimally invasive adenocarcinoma	TTF-1+ (100%); *EGFR* mutation never-smokers: 10%–30%; *KRAS* mutation smokers: 10%–30%	Ground-glass nodule, part-solid nodule	Not known	160, 162, 163, 164, 165
Lepidic (nonmucinous)	TTF-1+ (100%); *EGFR* mutation never-smokers: 10%–30%; *EGFR* amplification: 20%–50%; *KRAS* mutation smokers: 10%; *BRAF* mutations: 5%	Part-solid nodule; ground-glass nodule or solid nodule	Low cell cycle stimulatory; high *WNT*	6, 163, 164, 165, 166, 167, 168, 169, 170, 171
Papillary	TTF-1+ (90%–100%); *EGFR* mutation: 10%–30%; *EGFR* amplification: 20%–50%; *KRAS* mutation: 3% (lack of KRAS); *ERBB2* mutations: 3%; *TP53* mutations: 30%; *BRAF* mutations: 5%	Solid nodule	Low cell cycle stimulatory; high *EGFR*; high Notch	6, 79, 163, 166, 167, 168, 170, 172, 173, 174, 175
Acinar	TTF-1+ or –; *KRAS* mutation in smokers: 20%; *EGFR* mutations: <10% nonsmokers; *EGFR* amplification: 10%; *EML4/ALK* translocation: >5%; *TP53* mutations: 40%	Solid nodule	High *PDGF*; low *EGFR*; low angiogenesis	6, 79, 166, 176, 177
Micropapillary	*KRAS* mutations: 33%; *EGFR* mutations: 20%; *BRAF* mutations: 20%	Unknown	Unknown	6, 75, 171
Solid	TTF-1 (70%); MUC1 positive; *KRAS* mutation smokers: 10%–30%; *EGFR* mutation never-smokers: 10%–30%; *EGFR* amplification: 20%–50%; *EML4/ALK* translocation: >5%; *TP53* mutation: 50%; *LRP1B* mutations; *INHBA* mutations	Solid	High cell cycle stimulatory; high angiogenesis; high *JAK-STAT*; low Notch	6, 79, 166, 176, 177, 178, 179
Invasive mucinous adenocarcinoma	TTF-1 (0%–33% positive); *KRAS* mutation: 80%–100%; no *EGFR* mutation; MUC5+ MUC6+ MUC2+	Consolidation, air bronchograms; less often, ground-glass opacity	Not known	15, 91, 105, 153, 157, 159, 160, 175, 178, 180, 181

Abbreviations: CT, computed tomography; TTF-1, thyroid transcription factor-1.

gross pathologic assessment. There are 2 primary settings in which radiologic pathologic correlation is helpful: (1) in lepidic-predominant tumors (see "Radiologic-Pathologic Correlation for Tumor Size Assessment" above) and (2) if there are multiple tumors. In processing specimens with multiple nodules, review of the CT scan can also be helpful to be sure that each nodule is sampled.

IMPLICATIONS OF THIS CLASSIFICATION FOR TNM STAGING

There are several important implications of this new adenocarcinoma classification for staging that need to be considered for the next revision of the TNM classification. Importantly, we are not making official recommendations, as this can only be done by the International Union Against Cancer/American Joint Committee on Cancer TNM committees. However, we hope to stimulate investigators to study their case material with the intention of providing data that will allow these committees to determine whether official changes should be made in the 8th edition of the TNM classification. The changes relating to the concepts of AIS, MIA, and lepidic-predominant adenocarcinoma parallel classification criteria and terminology currently used in breast cancer,[138] but they would not be applicable to other histologic types of lung cancer. In addition, the comprehensive histologic subtyping approach to assessing invasive adenocarcinomas in this classification provides a useful approach to staging multiple adenocarcinomas.

Adenocarcinoma in situ would be classified as Tis. However, because carcinoma in situ (CIS) can occur with both lung squamous cell carcinoma and adenocarcinoma, these should be specified as Tis (squamous) or Tis (adenocarcinoma), similar to breast cancer where there is Tis (DCIS) for ductal CIS and Tis (LCIS) for lobular CIS.

Minimally invasive adenocarcinoma would be classified as T1mi, similar to microinvasive breast cancer, which is defined as an invasive carcinoma with no focus measuring greater than 1 mm; however, the size for MIA is not greater than 5 mm.

Also, similar to breast cancer, the size T factor for adenocarcinomas with an in situ or lepidic component may best predict prognosis according to the size of the invasive component only rather than the way it is currently practiced by including total tumor size inclusive of both the invasive and the lepidic or in situ components. In early-stage tumors, the tumor size T factor may need to be adjusted from total tumor size to the size of the invasive component only. Several publications in the literature[8,20,23] suggest invasive tumor size is an independent prognostic factor, and it may be a better predictor of prognosis than overall tumor size in lepidic predominant tumors. This needs to be tested radiologically and pathologically by comparing survival according to analysis of total tumor size (ground-glass opacity plus solid components by CT and invasive versus in situ/lepidic components by pathology) compared to only by the size of the solid or invasive component by CT and pathology examinations, respectively.

In addition, for multiple lung adenocarcinomas, comprehensive histologic subtyping can help in distinguishing intrapulmonary metastasis from synchronous or metachro-

nous primary tumors.[21] However, comprehensive histologic subtyping is only 1 tool that should be used to compare tumors, because valuable information can be obtained to address this problem from tumor cytologic characteristics and tumor stroma.[21] The role of molecular testing in this setting is promising, but needs further study.[22,139–141]

These concepts need to be tested vigorously in the next 5 years in both early- and advanced-stage lung adenocarcinoma to determine whether they are sufficiently robust to warrant changes in the 8th edition TNM classification.

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