Although molecular studies may be pending, the surgical pathology and/or cytology report should not be delayed until after molecular test results are completed. However, 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 classification of lung adenocarcinoma. Unlike previous

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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.

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 Noguchi[5] classifications, respectively, which provided little

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.

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) will be referred to as "former BAC." We understand this will

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.

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) adenocarcinoma with growth restricted to neoplastic cells along

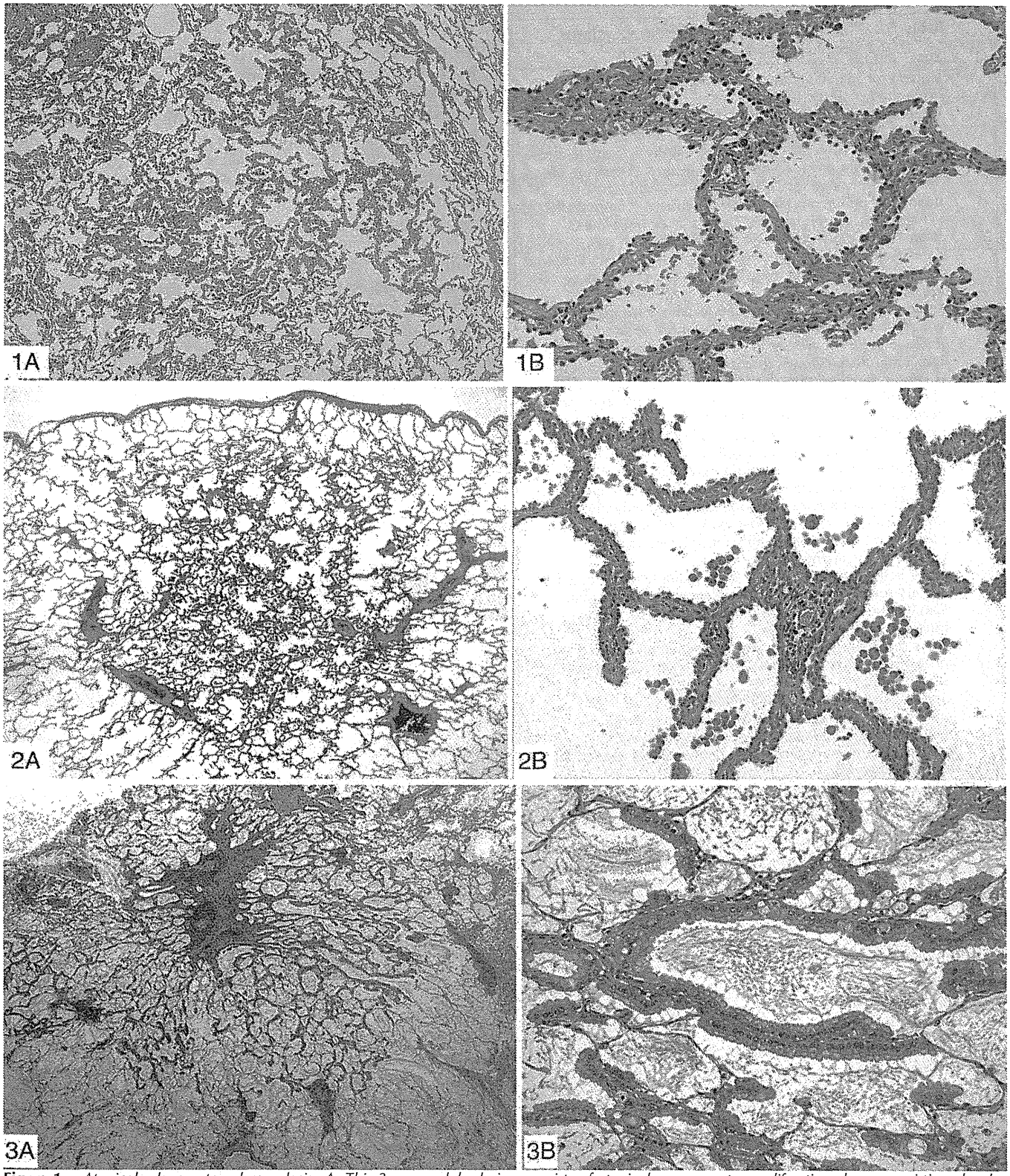

Figure 1. *Atypical adenomatous hyperplasia. A, This 3-mm nodular lesion consists of atypical pneumocytes proliferating along preexisting alveolar walls. There is no invasive component. B, The slightly atypical pneumocytes are cuboidal and show gaps between the cells. Nuclei are hyperchromatic and a 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]

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

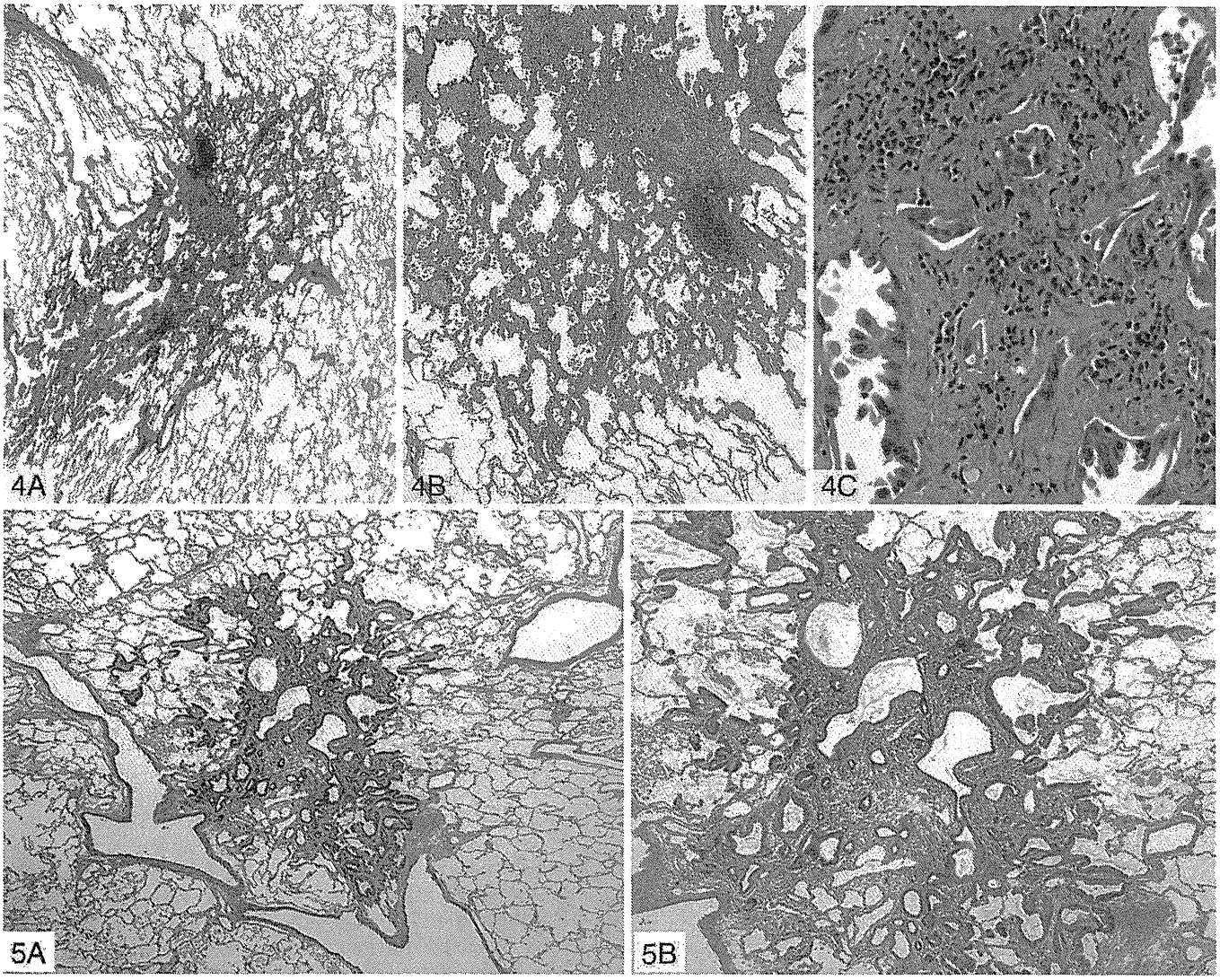

Figure 4. *Nonmucinous minimally invasive adenocarcinoma. A, This subpleural adenocarcinoma tumor consists primarily of lepidic growth with a small (<0.5 cm) central area of invasion. B, To the left is the lepidic pattern and on the right is an area of acinar invasion. C, These acinar glands are invading 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 $0.77 \pm .07$ 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