

Pathology of Lung Cancer

William D. Travis, MD

KEYWORDS

• Pathology • Lung cancer • Pathologic classification

CLASSIFICATION

Worldwide, lung cancer is the most common cause of major cancer incidence and mortality in men, whereas in women it is the third most common cause of cancer incidence and the second most common cause of cancer mortality.¹ In 2010 the American Cancer Society estimated that lung cancer would account for more than 222,520 new cases in the United States during 2010 and 157,300 cancer deaths.² Although lung cancer incidence in the United States began to decline in men in the early 1980s,³ it seems to have plateaued in women.²

Lung cancer can be diagnosed pathologically either by a histologic or cytologic approach.^{4–8} The new International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) Lung Adenocarcinoma Classification has made major changes in how lung adenocarcinoma is diagnosed.^{5,7,9} It will significantly alter the structure of the previous 2004 World Health Organization (WHO) classification of lung tumors (**Box 1**). Not only does it address classification in resection specimens (see **Box 1**), but it also makes recommendations applicable to small biopsies and cytology specimens, for diagnostic terms and criteria for other major histologic subtypes in addition to adenocarcinoma (**Table 1**). The 4 major histologic types of lung cancer are squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and large cell carcinoma.⁶ These major types can be subclassified into more specific subtypes such as lepidic predominant subtype of adenocarcinoma or the basaloid variant of large cell carcinoma.⁶ More detailed reviews of the pathology, cytology, and molecular biology of lung cancer can be found elsewhere.^{5–7,10–18}

Although lung cancer can be divided into many subtypes, historically the most important distinction was between small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC).⁶ This situation is because of the major clinical differences in presentation, metastatic spread, and response to therapy. However, in the past decade, there has been a major transformation in the approach to diagnosis of NSCLC, so now more attention is given to its precise classification in small biopsies and cytology.^{5,7,9,19} Because 70% of lung cancers present in advanced stages, most patients are unresectable and the diagnosis is based on small biopsies and cytology. The main reason for this new importance to classify NSCLC further is because the choice of therapies now is dependent on histology. For example, patients with adenocarcinomas and NSCLC not otherwise specified (NSCLC-NOS) are eligible for *EGFR* tyrosine kinase inhibitors (TKIs) if an *EGFR* mutation is present^{20–24}; they are also eligible for either pemetrexed-based^{25–28} or bevacizumab-based regimens.²⁹ In contrast, if the diagnosis is squamous cell carcinoma, patients are not eligible for these therapies. The implications of these new therapeutic paradigms for lung cancer classification are profound and are outlined in this review.

PREINVASIVE LESIONS

The pathology of preinvasive lesions for lung cancer has attracted increasing interest in recent years because of the growing importance of early detection of lung cancer using screening of high-risk patients by fluorescence bronchoscopy^{30,31} and by spiral or helical computed tomography (CT).^{32,33} In addition, the concepts of preinvasive lesions have evolved over the past several

Department of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA

E-mail address: travisw@mskcc.org

Clin Chest Med 32 (2011) 669–692

doi:10.1016/j.ccm.2011.08.005

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Box 1 Histologic classification of lung cancer^a

- **Preinvasive lesions**
 - Squamous dysplasia/carcinoma in situ (CIS)
 - Atypical adenomatous hyperplasia (AAH)
 - Adenocarcinoma in situ (AIS) (nonmucinous, mucinous, or mixed nonmucinous/mucinous)
 - Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)
- **Squamous cell carcinoma**
 - Variants
 - Papillary
 - Clear cell
 - Small cell (probably should be discontinued)
 - Basaloid
- **Small cell carcinoma**
 - Combined small cell carcinoma
- **Adenocarcinoma**
 - Minimally invasive adenocarcinoma (MIA) (≤ 3 cm lepidic predominant tumor with ≤ 5 mm invasion)
 - nonmucinous, mucinous, mixed mucinous/nonmucinous
 - Invasive adenocarcinoma
 - Lepidic predominant (formerly nonmucinous bronchioloalveolar carcinoma (BAC) pattern, with >5 mm invasion)
 - Acinar predominant
 - Papillary predominant
 - Micropapillary predominant
 - Solid predominant with mucin
 - Variants of invasive adenocarcinoma
 - Invasive mucinous adenocarcinoma (formerly mucinous BAC)
 - Colloid
 - Fetal (low and high grade)
 - Enteric
- **Large cell carcinoma**
 - Variants
 - Large cell neuroendocrine carcinoma (LCNEC)
 - Combined LCNEC
 - Basaloid carcinoma
 - Lymphoepithelioma-like carcinoma

- Clear cell carcinoma
- Large cell carcinoma with rhabdoid phenotype
- **Adenosquamous carcinoma**
- **Sarcomatoid carcinomas**
 - Pleomorphic carcinoma
 - Spindle cell carcinoma
 - Giant cell carcinoma
 - Carcinosarcoma
 - Pulmonary blastoma
 - Other
- **Carcinoid tumor**
 - Typical carcinoid (TC)
 - Atypical carcinoid (AC)
- **Carcinomas of salivary gland type**
 - Mucoepidermoid carcinoma
 - Adenoid cystic carcinoma
 - Epimyoeepithelial carcinoma

^a Modified from the 2004 WHO Classification⁶ and the 2011 IASLC/ATS/ERS Classification of Lung Adenocarcinoma.¹⁰ This classification primarily addresses histology in resected specimens.

decades, with none mentioned in the 1967 WHO classification of lung tumors³⁴ and only bronchial squamous dysplasia and CIS in the 1981 WHO histologic classification of lung tumors.³⁵ In the 1999 WHO classification 2 new lesions were described: AAH and DIPNECH, and these were maintained in the 2004 WHO classification.^{6,36} So in the 1999 and 2004 WHO classification, there were only 3 preinvasive lesions. Now, in the 2011 IASLC/ATS/ERS Classification of Lung Adenocarcinoma, AIS was added as a new preinvasive lesion for adenocarcinoma (see **Box 1**).⁵

Squamous Dysplasia and CIS

Bronchial carcinogenesis is conceptualized as a multistep process involving transformation of the normal bronchial mucosa through a continuous spectrum of lesions, including basal cell hyperplasia, squamous metaplasia, dysplasia, and CIS.^{6,36-38} Associated with the morphologic changes are a series of molecular events that accumulate as the squamous lesions progress through increasing dysplasia to CIS and invasive squamous cell carcinoma. Such changes include allelic loss at the 3p

Table 1
Proposed IASLC/ATS/ERS classification for small biopsies/cytology

2004 WHO Classification	Small Biopsy/Cytology: IASLC/ATS/ERS
Adenocarcinoma Mixed subtype Acinar Papillary Solid	Morphologic adenocarcinoma patterns clearly present: Adenocarcinoma, describe identifiable patterns present (including micropapillary pattern not included in 2004 WHO classification) If pure lepidic growth: mention an invasive component cannot be excluded in this small specimen
No 2004 WHO counterpart: most are solid adenocarcinomas	Morphologic adenocarcinoma patterns not present (supported by special stains): Non-small cell carcinoma, favor adenocarcinoma
BAC (nonmucinous)	Adenocarcinoma with lepidic pattern (if pure, add note: an invasive component cannot be excluded)
BAC (mucinous)	Mucinous adenocarcinoma (describe patterns present)
Fetal	Adenocarcinoma with fetal pattern
Mucinous (colloid)	Adenocarcinoma with colloid pattern
Signet ring	Adenocarcinoma with (describe patterns present) and signet ring features
Clear cell	Adenocarcinoma with (describe patterns present) and clear cell features
Squamous Cell Carcinoma Papillary Clear cell Small cell Basaloid	Morphologic squamous cell patterns clearly present: Squamous cell carcinoma
No 2004 WHO counterpart	Morphologic squamous cell patterns not present (supported by stains): Non-small cell carcinoma, favor squamous cell carcinoma
Small cell carcinoma	Small cell carcinoma
Large cell carcinoma	Non-small cell carcinoma, not otherwise specified (NOS)
LCNEC	Non-small cell carcinoma with NE morphology (positive NE markers), possible LCNEC
Large cell carcinoma with NE morphology	Non-small cell carcinoma with NE morphology (negative NE markers): see comment Comment: This is a non-small cell carcinoma in which LCNEC is suspected, but stains failed to show NE differentiation
Adenosquamous carcinoma	Morphologic squamous cell and adenocarcinoma patterns present: Non-small cell carcinoma, NOS (comment that glandular and squamous components are present) Comment: this could represent adenosquamous carcinoma
No counterpart in 2004 WHO classification	Morphologic squamous cell or adenocarcinoma patterns not present but immunostains favor separate favor glandular and adenocarcinoma component Non-small cell carcinoma, NOS (specify the results of the immunohistochemical stains and the interpretation) Comment: this could represent adenosquamous carcinoma
Sarcomatoid carcinoma	Poorly differentiated NSCLC with spindle or giant cell carcinoma (mention if adenocarcinoma or squamous carcinoma are present)

From Travis WD, Brambilla E, Noguchi M, et al. The new IASLC/ATS/ERS international multidisciplinary lung adenocarcinoma classification. *J Thorac Oncol* 2011;6:247.

region, which is an early event found in 78% of preinvasive bronchial lesions.³⁸ Followed by a series of other molecular events such as loss of heterozygosity at 9p21 (p16), 17p loss (hyperplasia), telomere activation, telomerase

reactivation, retinoic acid receptor (RAR) β loss (mild dysplasia), p53 mutation, vascular endothelial growth factor overexpression (moderate dysplasia), p16 inactivation, Bcl-2 overexpression, and cyclin D1 and E overexpression (CIS).³⁸

Squamous dysplasia may be mild, moderate, or severe depending on the severity of cytologic atypia and the thickness of the abnormality within the bronchial epithelium.^{6,36,37} CIS shows full thickness involvement of the epithelium by marked cytologic atypia. There is a continuum of morphologic changes, but these categories can be separated with good reproducibility.³⁹ Care must be taken not to confuse dysplasia with reactive atypia associated with inflammation or granulation tissue. CIS with involvement of submucosal glands must also be separated from microinvasive squamous cell carcinoma.^{6,36,37}

AAH and AIS

AIS is now added to AAH as a new preinvasive lesion for lung adenocarcinoma.

AAH

AAH is a bronchioloalveolar proliferation that resembles but falls short of criteria for BAC, non-mucinous type (Fig. 1).^{5,6,37,38,40-42} AAH is most commonly encountered as an incidental histologic finding in a lung cancer resection specimen.^{36,43,44}

The incidence of AAH varies from 5.7% to 21.4% depending on extent of the search and the criteria used for the diagnosis.⁴⁴⁻⁴⁷ Most lesions of AAH are less than 5 mm in diameter and frequently they are multiple.^{44,45} Histologically AAH consists of a focal proliferation of slightly atypical cuboidal to low columnar epithelial cells along alveoli and respiratory bronchioles (see Fig. 1). Slight thickening of alveolar septa may be present.

AAH must be separated from a variety of lesions, the most important of which is the non-mucinous AIS, MIA, or lepidic predominant

adenocarcinoma (LPA).⁴⁸ This distinction can be difficult because there is considerable overlap in the morphologic features between AAH and the lepidic pattern of adenocarcinoma.^{36,43,49,50} There are currently no data to show that patients with lung cancer and AAH have any different prognosis from those without AAH.⁵¹

AIS

In the new IASLC/ATS/ERS adenocarcinoma classification AIS is defined as a glandular proliferation measuring 3 cm or less that has pure lepidic growth lacking invasion (Fig. 2).⁵ In most cases the tumor cells are nonmucinous, with a proliferation of type II pneumocytes or Clara cells, but rarely are they mucinous consisting of tall columnar goblet cells having abundant apical mucin. If these lesions are completely resected, patients have been reported to have 100% 5-year disease-free survival (DFS).⁵²⁻⁵⁹ By CT these lesions typically consist of a ground-glass nodule if nonmucinous and a solid nodule if mucinous AIS.⁵

DIPNECH

DIPNECH is a rare condition in which the peripheral airways are diffusely involved by neuroendocrine (NE) cell hyperplasia and tumorlets (Box 2, Fig. 3).^{60,61} The clinical presentation resembles interstitial lung disease manifest by airway obstruction caused by bronchiolar fibrosis in approximately half of the patients.^{60,61} The remaining patients typically present with multiple incidentally discovered pulmonary nodules, often found during follow-up for an extrathoracic malignancy. Because carcinoid tumors are frequently found in patients with DIPNECH and the tumors are often multiple, this is believed to represent

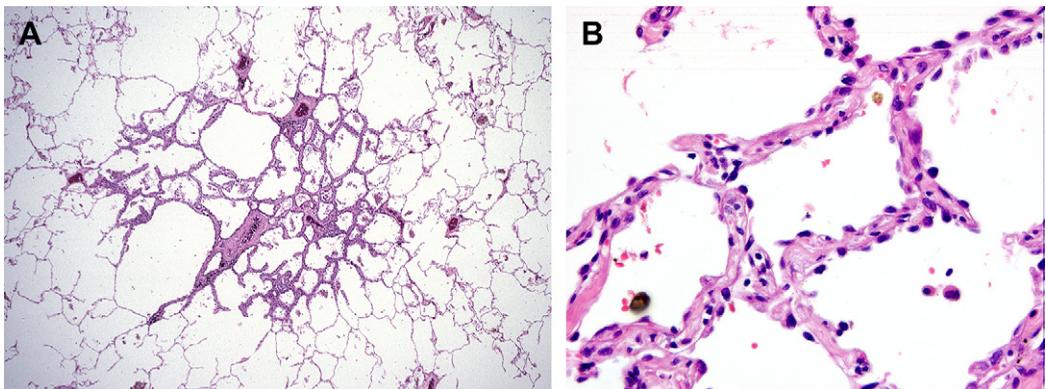


Fig. 1. AAH. (A) This millimeter-sized bronchioloalveolar proliferation is ill defined, with mild thickening of the alveolar walls (hematoxylin-eosin, original magnification $\times 20$). (B) The alveolar walls show mild fibrous thickening and the hyperplastic pneumocytes show minimal atypia and there are gaps between the cells (hematoxylin-eosin, original magnification $\times 400$).

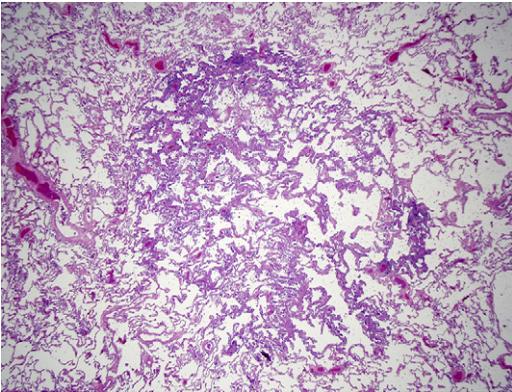


Fig. 2. Nonmucinous AIS. This circumscribed nonmucinous tumor grows purely with a lepidic pattern. No foci of invasion or scarring are seen.

a preinvasive lesion for carcinoid tumors.^{6,61} There is a distinctive CT appearance consisting of centrilobular nodules and pulmonary nodules, which correspond to the tumorlets and carcinoid tumors, respectively. Furthermore, in patients who present with clinical manifestations of interstitial lung disease, the CT can be normal or it can show mosaic perfusion from air trapping, bronchial wall thickening, and bronchiectasis.^{61,62}

SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma accounts for approximately 20% of all lung cancers in the United States.⁶³ Historically, two-thirds of squamous cell carcinomas presented as central lung tumors, whereas many among the remaining third are peripheral.^{64,65} However, recent reports document that an increasing percentage of squamous cell carcinomas are found in the periphery, exceeding 50% in some studies.⁶⁶ The morphologic features that suggest squamous differentiation include intercellular bridging, squamous pearl formation, and individual cell keratinization (**Fig. 4**). In well-differentiated tumors these features are readily apparent; however, in poorly differentiated tumors they are difficult to find.⁶⁷ Squamous cell carcinoma arises most often in segmental bronchi and involvement of lobar and mainstem bronchus occurs by extension.⁶⁸ Squamous cell carcinoma can have papillary, clear cell, small cell,⁶⁹ and basaloid subtypes.³⁶ However, this subtyping needs updating because it does not address well the morphologic spectrum of appearances of lung squamous cell carcinoma and it does not allow for meaningful correlations with clinical, prognostic, or molecular features. For example, the

Box 2

The spectrum of NE lung proliferations and tumors

1. NE cell hyperplasia and tumorlets
 - a. NE cell hyperplasia
 - i. NE cell hyperplasia associated with fibrosis or inflammation
 - ii. NE cell hyperplasia adjacent to carcinoid tumors
 - iii. Diffuse idiopathic NE cell hyperplasia with or without airway fibrosis/obstruction
 - b. Tumorlets (less than 0.5 cm)
2. Tumors with NE morphology
 - a. TC (0.5 cm or larger)
 - b. AC
 - c. LCNEC
 - Combined large cell NE carcinoma^a
 - d. Small cell carcinoma
 - Combined small cell carcinoma^a
3. Non-small cell carcinomas with NE differentiation (NED)
4. Other tumors with NE properties
 - a. Pulmonary blastoma
 - b. Primitive neuroectodermal tumor
 - c. Desmoplastic round cell tumor
 - d. Carcinomas with rhabdoid phenotype
 - e. Paraganglioma

^a The histologic type of the other component of non-small cell carcinoma should be specified.

Modified from Travis WD, Brambilla E, Müller-Hermelink HK, et al. *Pathology and Genetics: Tumors of the Lung, Pleura, Thymus and Heart*. Lyon (France): IARC, 2004. p. 20; and Travis WD. Lung tumors with neuroendocrine differentiation. *Eur J Cancer* 2009; 45;(Suppl 1):252.

small cell variant probably should be discarded, because most of these cases would better be classified as basaloid variants and the term small cell creates confusion with true small cell carcinoma. Papillary squamous cell carcinomas often show a pattern of exophytic endobronchial growth.^{70,71}

Several articles have proposed alternative approaches to subclassifying pulmonary squamous cell carcinomas.^{66,72,73} These approaches include recognition of an alveolar space-filling

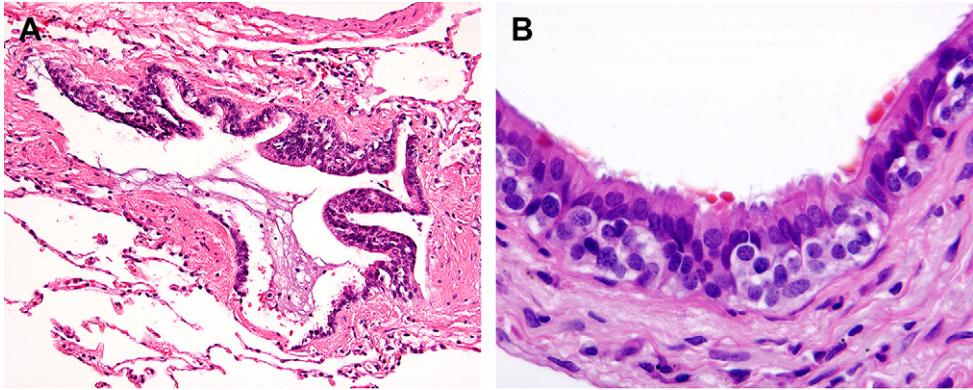


Fig. 3. DIPNECH. (A) This bronchiole shows mild fibrotic thickening of the wall and increased numbers of NE cells in the mucosa (hematoxylin-eosin, original magnification $\times 200$). (B) At the base of the mucosa are numerous round to oval NE cells with small nuclei and clear cytoplasm (hematoxylin-eosin, original magnification $\times 400$).

variant, which corresponds to favorable prognosis.^{66,73} Funai and colleagues⁶⁶ reported 5 cases with 100% disease-free survival, and Watanabe and colleagues⁷³ found that an alveolar space-filling ratio of 70% or more also had a 100% disease-free survival. However, this pattern occurs in only a few cases and is more often seen only focally; in a study from North America prognostic significance could not be shown.⁷⁴ Maeshima and colleagues⁷² defined minimal tumor cell nests as large (>6 tumor cells), small (2–5 cells), and single cell. In this study the single-cell infiltrating tumors had the worst prognosis. Also tumors associated with a background of usual interstitial pneumonia and lymph node metastases had a poor prognosis. Further work is needed to develop a more practical approach

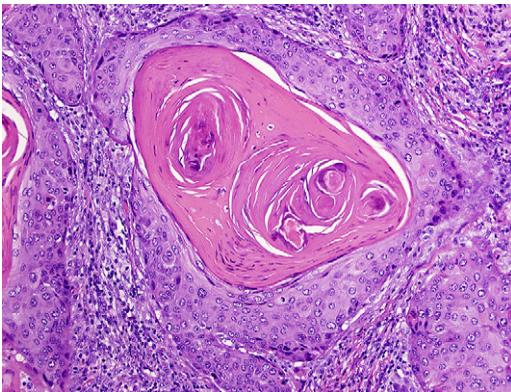


Fig. 4. Squamous cell carcinoma. These tumor cells have abundant eosinophilic keratinized cytoplasm and form nests and keratin pearls characteristic of squamous differentiation (hematoxylin-eosin, original magnification $\times 200$).

to subclassification of squamous cell carcinoma and to identify better histologic predictors of prognosis.

ADENOCARCINOMA

Adenocarcinomas represent 38% of all lung cancers in the United States.^{63,75} The 2011 IASLC/ATS/ERS lung adenocarcinoma classification recommends multiple major changes (see **Box 1**).^{5,7,9,19} First, it is recommended to no longer use the term BAC because the tumors formerly classified under this term are now classified into 5 different tumors. Second, there are new concepts of AIS (see preinvasive lesions) and MIA. Third, it is recommended to no longer use the term mixed subtype, but rather to use comprehensive histologic subtyping to estimate the percentage of histologic patterns in 5% increments within a tumor with final classification according to the predominant subtype. Fourth, tumors with a predominant component formerly called nonmucinous BAC should be classified as LPA. Fifth, micropapillary adenocarcinoma is recognized as a new subtype with a poor prognosis. Sixth, invasive mucinous adenocarcinoma is the term recommended for those tumors formerly classified as mucinous BAC. Sixth, specific terminology and diagnostic criteria are proposed for tumors in small biopsies and cytology specimens along with recommendations for strategic management of tissue and *EGFR* mutation testing in patients with advanced adenocarcinoma.^{5,7,9,19}

ADENOCARCINOMA CLASSIFICATION IN RESECTED SPECIMENS

MIA

MIA was introduced as a lepidic predominant tumor measuring 3 cm or less that has 5 mm or

less of an invasive component (Fig. 5).⁵ Limited data suggest patients with MIA have a near 100% 5-year disease-free survival.^{5,59} Although few articles use the same criteria,^{59,76} multiple studies support this concept.^{77,78} Most of these cases are nonmucinous, but rarely mucinous cases may occur.⁵ By CT nonmucinous MIA typically shows a ground-glass nodule with a solid component measuring 5 mm or less. However, mucinous MIA presents as a solid nodule on CT.⁵

Invasive Adenocarcinoma

Classification of overtly invasive adenocarcinomas is now made according to the predominant subtype. This classification is best determined after using comprehensive histologic subtyping to estimate the percentages of the various histologic subtypes within a tumor in a semiquantitative fashion in 5% to 10% increments. LPA consists of tumors formerly classified as mixed subtype tumors containing a predominant lepidic growth pattern of type II pneumocytes or Clara cells (formerly known as nonmucinous BAC) that have an invasive component greater than 5 mm (Fig. 6A–C). The other major subtypes include acinar (see Fig. 6D), papillary (see Fig. 6E), micropapillary (see Fig. 6F), and solid with mucin-predominant adenocarcinomas (see Fig. 6G, H). The micropapillary predominant subtype is a new addition as a result of the observation in multiple studies that it is associated with poor prognosis in early-stage adenocarcinomas (see Fig. 3).^{5,76,79,80} Signet ring and clear cell carcinoma subtypes are no longer regarded as histologic subtypes, but they are now documented as cytologic features whenever present with a comment about the percentage identified. Although clear and signet ring cell cytologic

changes are seen mostly in the solid subtype, they can also be seen in acinar or papillary patterns as well.^{81,82}

By CT there is a good correlation between amount of the ground-glass component and lepidic growth on biopsy versus the solid component on CT and the invasive components by biopsy.⁷⁶ However, few studies have addressed this issue according to the new classification.

Adenocarcinoma Variants

The variants of lung adenocarcinoma consist of invasive mucinous adenocarcinoma (formerly mucinous BAC), colloid adenocarcinoma, fetal adenocarcinoma, and enteric adenocarcinoma.⁵ Invasive mucinous adenocarcinomas (formerly mucinous BAC) are separated from the nonmucinous invasive adenocarcinomas because of the frequent association with *KRAS* mutation, lack of thyroid transcription factor 1 (TTF-1), and frequent multicentric lung lesions. Histologically these tumors show varying amounts of lepidic, acinar, papillary, or micropapillary growth consisting of columnar cells with abundant apical mucin and small basally oriented nuclei (Fig. 7).⁵ CT findings frequently show localized or multifocal consolidation with air bronchograms forming nodules and lobar consolidation.

Prognosis of Adenocarcinoma Subtypes in Resected Specimens

Few studies have evaluated prognosis of the adenocarcinoma subtypes according to the precise criteria and terminology of the new classification. However, multiple studies have reported 100% 5-year DFS for tumors that

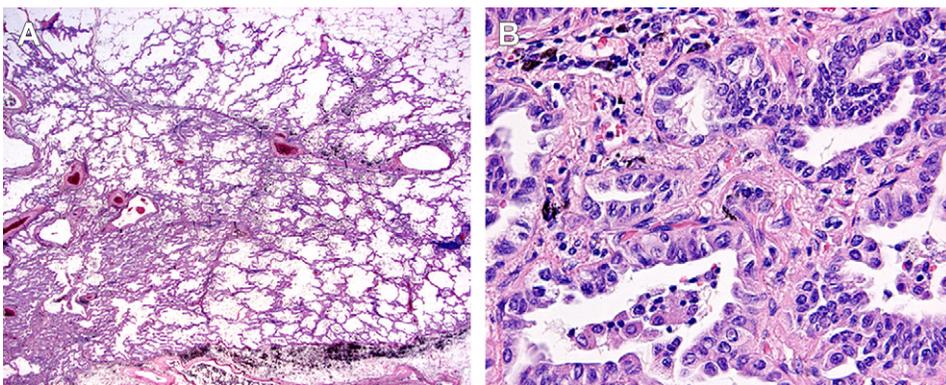


Fig. 5. Nonmucinous MIA. (A) This adenocarcinoma tumor consists primarily of lepidic growth with a small (<0.5 cm) area of invasion (*bottom left*) (hematoxylin-eosin, original magnification $\times 1$). (B) From the area of invasion, these acinar glands are invading in the fibrous stroma (hematoxylin-eosin, original magnification $\times 200$).

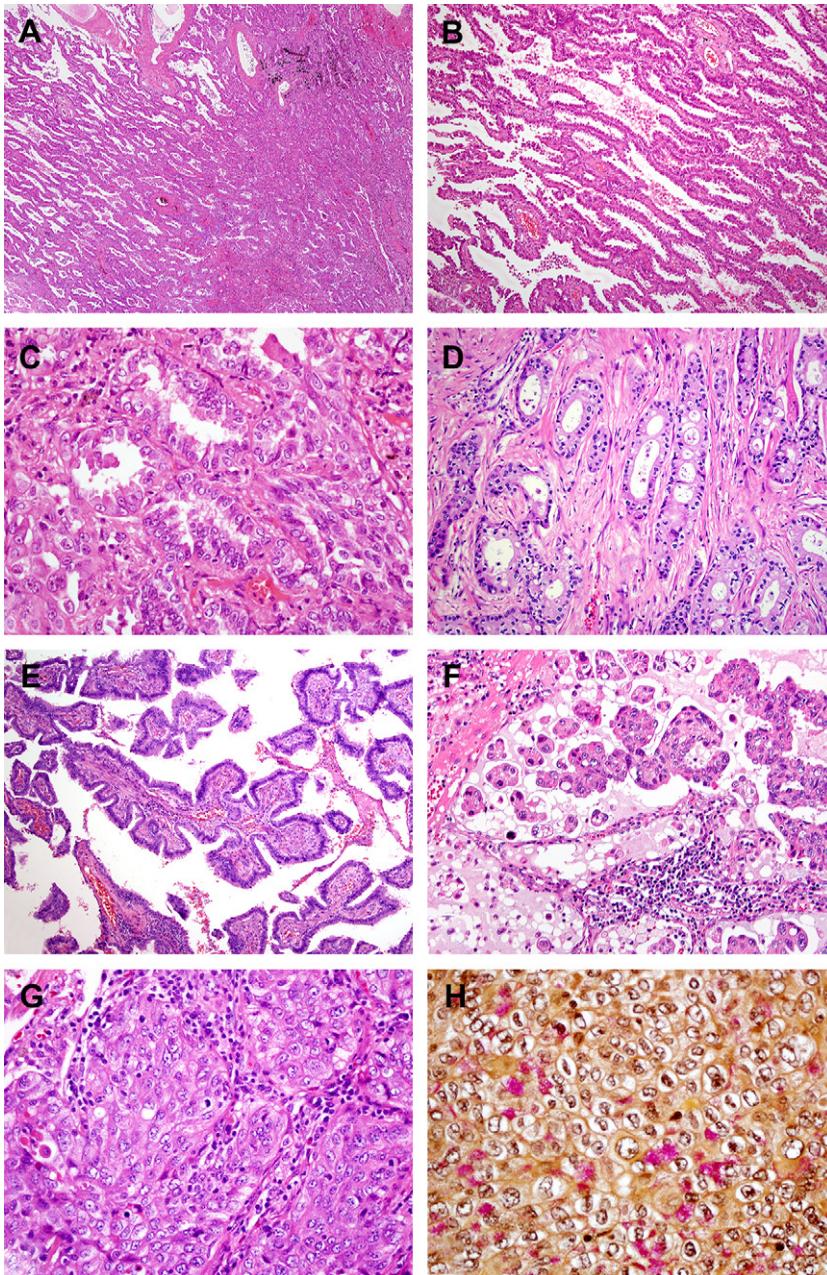


Fig. 6. Major histologic patterns of invasive adenocarcinoma. (A) Lepidic predominant pattern with mostly lepidic growth (*left*) and an area of invasive acinar adenocarcinoma (*right*) (hematoxylin-eosin, original magnification $\times 100$). (B) Lepidic pattern consists of a proliferation type II pneumocytes and Clara cells along the surface alveolar walls (hematoxylin-eosin, original magnification $\times 200$). (C) Area of invasive acinar adenocarcinoma (same tumor as in 6A, B) (hematoxylin-eosin, original magnification $\times 400$). (D) Acinar adenocarcinoma composed of round to oval malignant glands invading a fibrous stroma (hematoxylin-eosin, original magnification $\times 200$). (E) Papillary adenocarcinoma consists of malignant cuboidal to columnar tumor cells growing on the surface of fibrovascular cores (hematoxylin-eosin, original magnification $\times 100$). (F) Micropapillary adenocarcinoma consists of small papillary clusters of glandular cells growing within this airspace, most of which do not show fibrovascular cores (hematoxylin-eosin, original magnification $\times 200$). (G) Solid adenocarcinoma with mucin consisting of sheets of tumor cells with abundant cytoplasm and mostly vesicular nuclei with several conspicuous nucleoli. No acinar, papillary, or lepidic patterns are seen, but multiple cells have intracytoplasmic basophilic globules that suggest intracytoplasmic mucin (hematoxylin-eosin, original magnification $\times 400$). (H) Solid adenocarcinoma with mucin. Numerous intracytoplasmic droplets of mucin are highlighted with this mucicarmine stain (original magnification $\times 400$).

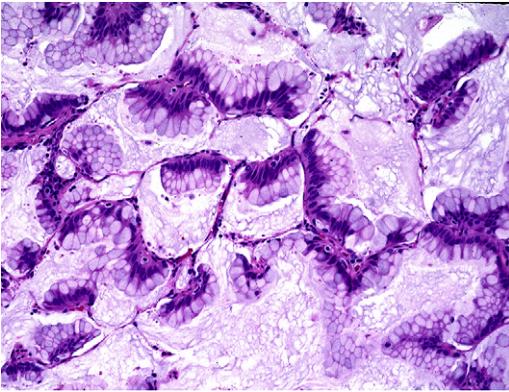


Fig. 7. Invasive mucinous adenocarcinoma. This area of invasive mucinous adenocarcinoma shows a pure lepidic growth. The tumor consists of columnar cells filled with abundant mucin in the apical cytoplasm and small basal oriented nuclei (hematoxylin-eosin, original magnification $\times 200$).

would be classified as AIS in the new classification.^{52–59} Although the specific criteria for MIA proposed in the new classification were not used in previous studies, data from multiple studies suggest that these tumors also have a 100% or near 100% 5-year DFS.^{58,59,78,83}

In a study of 514 stage I adenocarcinomas reported by Yoshizawa and colleagues,⁷⁶ 3 groups of tumors were identified according to grades of clinical behavior: (1) low-grade AIS and MIA with 100% 5-year DFS; (2) intermediate-grade nonmucinous lepidic predominant, papillary predominant, and acinar predominant with 90%, 83%, and 84% 5-year DFS, respectively; and (3) high-grade invasive mucinous adenocarcinoma, colloid predominant, solid predominant, and micropapillary predominant with 75%, 71%, 70%, and 67% 5-year DFS, respectively. Similar results were found in 2 independent datasets.^{84,85}

This finding was confirmed by Kadota and colleagues⁸⁴ in a separate dataset of 540 stage I lung adenocarcinomas in which there was 100% DFS for AIS and MIA, 97% for lepidic predominant, 87% for acinar, 80% for papillary, 59% for micropapillary, and 69% for solid with a 62% 3-year DFS for invasive mucinous and colloid adenocarcinoma. In a Japanese cohort of 432 patients that included some higher stage patients (250 Stage IA, 88 1B, 30 IIA, 13 IIB, 26 IIIA, 4 IIIB, and 15 IV), 5-year DFS was 100% for AIS and MIA, 89% for lepidic predominant, 67% for papillary, 59% for acinar, 61% for solid predominant, and 17% for micropapillary, with 80% for invasive mucinous adenocarcinoma.⁸⁵

Potential Impact of Classification on TNM Staging

There are 2 major ways the new lung adenocarcinoma classification affects TNM staging. First, comprehensive histologic subtyping provides a useful way to compare multiple lung adenocarcinomas by providing a detailed way to assess whether the 2 tumors represent metastasis versus synchronous or metachronous primaries. The distribution of percentages of the histologic components is one of multiple morphologic features in addition to cytologic and stromal characteristics that have been shown to correlate highly with molecular and clinical approaches to making this distinction.^{86–88} Whether or not a second tumor is classified as a separate primary or an intrapulmonary metastasis can significantly alter TNM staging and patient management, particularly for separate lobe or contralateral tumors.

Second, it is possible that in invasive lung adenocarcinomas with a prominent lepidic component comprehensive histologic subtyping may help to determine the size of the invasive component, and this may be more predictive of survival than total tumor size as suggested in several studies reporting that the invasive size is an independent prognostic factor.^{76,77} The invasive tumor size can be estimated by subtracting the percentage of the lepidic component from the total gross size. These data suggest that, similar to breast cancer, the size T factor for early lung adenocarcinomas may be best determined by the size of the invasive component rather than the total tumor size. This finding also needs to be studied by CT to determine if prognosis is best predicted according to the size of the solid component rather than total tumor size including the ground-glass component.⁵ It is hoped that sufficient data can be accumulated before the next TNM revision to address this issue.

ADENOCARCINOMA CLASSIFICATION IN SMALL BIOPSIES AND CYTOLOGY

For the first time in lung cancer classification formal criteria for diagnosis of lung cancer in small biopsies and cytology were proposed by the new IASLC/ATS/ERS lung adenocarcinoma classification (see **Table 1**).⁵ Because 70% of lung cancers present in advanced stages and are unresectable, they are diagnosed in these small specimens. These new criteria were driven by the need to separate adenocarcinoma from squamous cell carcinoma because of the therapeutic implications based on histology. Patients who have either adenocarcinoma, NSCLC, favor adenocarcinoma,

or NSCLC-NOS rather than squamous cell carcinoma are eligible at the moment for 3 therapeutic options. Patients with advanced stage lung adenocarcinoma with 1 of these histologic diagnoses should be tested for *EGFR* mutation, and if the result is positive, *EGFR* TKI therapy has predictive benefit for response rate and progression-free survival.²⁰⁻²³ Furthermore, it has been shown that in patients with adenocarcinoma or NSCLC-NOS, histology is a strong predictor of response to pemetrexed in patients who have advanced lung cancer.²⁵⁻²⁸ In addition patients with squamous cell carcinoma are at risk for life-threatening hemorrhage in contrast to those with adenocarcinoma.²⁹

For tumors that show clear morphologic features of adenocarcinoma or squamous cell carcinoma, these standard terms are used. However, if the tumor shows only a carcinoma with no clear squamous or glandular features (NSCLC-NOS), a minimal immunohistochemical workup is recommended using a single adenocarcinoma marker and squamous marker, which should allow for classification of most tumors. The best markers for adenocarcinoma and squamous cell carcinoma are TTF-1 and p63, respectively.⁵ In a tumor that shows no clear squamous or glandular morphology, but the staining results favor adenocarcinoma (ie, TTF-1 positive, p63 negative), the tumor should be classified as NSCLC, favor adenocarcinoma (**Fig. 8**). Likewise, the stains in such a tumor favor squamous cell carcinoma, the diagnosis would be NSCLC, favor squamous cell carcinoma (**Fig. 9**). Then for tumors for which there is clear differentiation by light microscopy or special stains, or if the results are conflicting, the diagnosis remains NSCLC-NOS. Cytology is another powerful tool in subclassifying

poorly differentiated NSCLC. In some cases, it may be easier to classify the tumor based on cytology than biopsy.^{4,7} It is recommended to avoid use of the term nonsquamous carcinoma and state the specific diagnosis in precise terms as outlined earlier.⁵ Also use of the term NSCLC should be minimized and instead the specific diagnosis of adenocarcinoma or squamous cell carcinoma should be used whenever possible.⁵

The approach to interpretation of small biopsies and cytology must include considerations of diagnoses other than NSCLC, such as NE tumors (carcinoid, small cell carcinoma, or large cell NE carcinoma) as well as metastatic tumors including metastatic malignant melanoma, breast cancer, or prostate cancer.⁷ Therefore if the initial evaluation does not clearly point to adenocarcinoma or squamous cell carcinoma, some of these other diagnoses may need to be considered.

Because the diagnosis of NSCLC-NOS was encouraged by previous WHO classifications, because of the lack of any clinical reason to be more precise, in studies of advanced NSCLC, this diagnosis has been made in 20% to 40% of cases, and some data suggest its use has been increasing.^{27,89}

However, with the new IASLC/ATS/ERS criteria and use of immunohistochemistry as well as cytology correlation, the percentage of NSCLC diagnosed as NSCLC-NOS should be less than 5% of cases.^{4,7}

EGFR Mutation Testing

In the new IASLC/ATS/ERS lung adenocarcinoma classification, there is a clinical recommendation that *EGFR* mutation testing be performed in advanced lung adenocarcinomas because of the

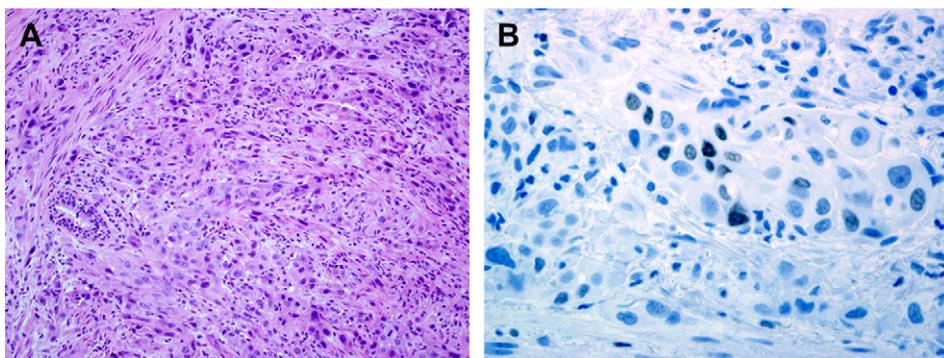


Fig. 8. Non-small cell carcinoma, favor adenocarcinoma. (A) This carcinoma shows no clear squamous or glandular differentiation (hematoxylin-eosin, original magnification $\times 200$). (B) The diffuse positive TTF-1 staining allows for the diagnosis of non-small cell carcinoma, favor adenocarcinoma (hematoxylin-eosin, original magnification $\times 200$).

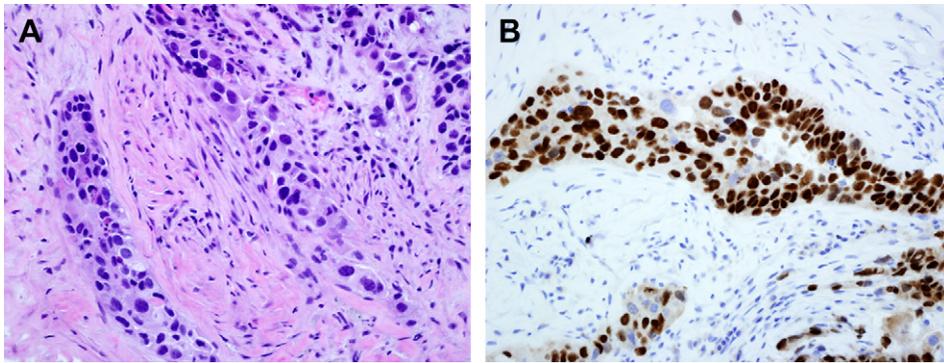


Fig. 9. Non-small cell carcinoma, favor squamous cell carcinoma. (A) This carcinoma shows no clear squamous or glandular differentiation (hematoxylin-eosin, original magnification $\times 200$). (B) The diffuse positive p63 staining and negative TTF-1 staining (*not shown*) allows for the diagnosis of non-small cell carcinoma, favor squamous cell carcinoma (immunohistochemistry for p63, original magnification $\times 200$).

predictive benefit of *EGFR* mutation with treatment by EGFR TKIs as described earlier.⁵ *EGFR* mutation testing should be performed for all patients with a pathologic diagnosis of: (1) adenocarcinoma, (2) NSCLC, favor adenocarcinoma, and (3) NSCLC-NOS. This recommendation has major implications for tissue management and pathologic diagnosis.

Multidisciplinary Strategy Needed to Obtain and Process Small Biopsies and Cytology

Each institution needs to develop a multidisciplinary strategy to manage these small pieces of tissue from (1) obtaining the specimen, (2) processing it in the pathology laboratory, (3) providing material to the molecular diagnostic laboratory, and (4) getting the results back into a pathology report and into the medical record.^{5,7} This process requires ongoing communication between specialists to ensure optimal management of tissues and efficient reporting of results. One of the central aspects of this process that affects radiologists, pulmonologists, or surgeons is the need to obtain sufficient tissue not only for diagnosis but also for molecular studies. To achieve this goal, biopsy procedures should be designed to result either in a core biopsy or a cell block from tissue samples obtained for cytology.^{5,90} Cytology specimens such as pleural fluids should also be processed to generate cell blocks so immunostaining and molecular studies can be performed.

Use Minimal Stains to Maximize Tissue for Molecular Testing

Pathologists should minimize the amount of tissue used for making the diagnosis, including use of as

few special stains as possible.^{5,7} This strategy is necessary to preserve as much tissue as possible for molecular testing. One helpful approach is to cut multiple unstained slides from the block after initial review in cases that are potential candidates for molecular testing, so the block is cut only once and valuable tissue is not lost during the process of facing the block multiple times.⁷ This strategy includes tumors that are either clearly adenocarcinoma or those with NSCLC-NOS patterns on hematoxylin and eosin stain that require special stains. If adenocarcinoma is suspected, by performing only a TTF-1 stain, if the result is positive, it would confirm not only the adenocarcinoma diagnosis but also a pulmonary origin. If by morphology the tumor could be either adenocarcinoma or squamous cell carcinoma, it may be best to perform 1 adenocarcinoma (ie, TTF-1) and 1 squamous (ie, p63) marker as recommended in the new classification.⁵ Limited additional stains may be considered for the small percentage of cases that cannot be classified after this initial panel.^{5,7}

SMALL CELL CARCINOMA

SCLC comprises 14% of all lung cancers, and more than 30,000 new cases are diagnosed per year in the United States.^{63,75} Approximately two-thirds of SCLC present as a perihilar mass. SCLC typically are situated in a peribronchial location with infiltration of the bronchial submucosa and peribronchial tissue. Bronchial obstruction is usually caused by circumferential compression, although rarely endobronchial lesions can occur. Because the diagnosis is usually established on transbronchial biopsy or cytology, is it unusual to encounter SCLC as a surgical specimen.

Extensive lymph node metastases are common. The tumor is white-tan, soft, and friable and frequently shows extensive necrosis. With advanced disease, the bronchial lumen may be obstructed by extrinsic compression. SCLC may present as a solitary coin lesion in up to 5% of cases.^{91,92}

Three subtypes of SCLC were proposed in the 1981 WHO classification: (1) oat cell carcinoma, (2) intermediate cell type, and (3) combined oat cell carcinoma.³⁵ However, in 1988 the IASLC recommended dropping the category of intermediate cell type because expert lung cancer pathologists could not reproduce this subclassification and significant differences in survival could not be shown. They also recommended adding the category of mixed small cell/large cell carcinoma because these patients seemed to have a worse prognosis than other patients with SCLC.⁹³ The category of combined SCLC was retained for SCLC with a mixture of adenocarcinoma or squamous cell carcinoma.⁹³ The 1999 WHO classification discarded the category of mixed small cell/large cell carcinoma because there were data indicating problems in reproducibility for this subtype and lack of confirmation that these patients had a worse prognosis.^{36,94} Therefore in the 2004 WHO classifications there are only 2 types of SCLC: SCLC (with pure SCLC histology) and combined SCLC (with a mixture of any non-small cell type) (see **Box 2**).⁶

SCLC has a distinctive histologic appearance. The tumor cells are small and have a round to fusiform shape, scant cytoplasm, finely granular nuclear chromatin, and absent or inconspicuous nucleoli (**Fig. 10**).⁶ Nuclear molding and smearing

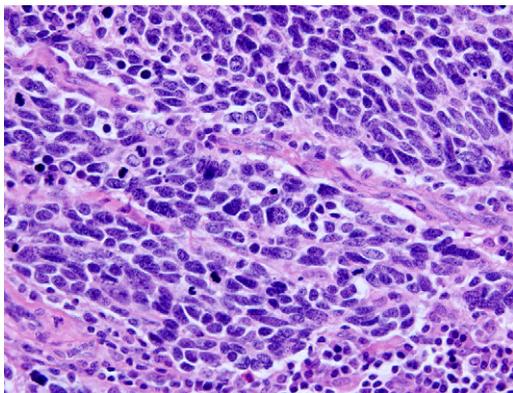


Fig. 10. Small cell carcinoma. This tumor is composed of small cells with scant cytoplasm, finely granular chromatin, and frequent mitoses. Nucleoli are absent (hematoxylin-eosin, original magnification $\times 400$).

of nuclear chromatin as a result of crush artifact may be conspicuous. There is usually extensive necrosis and mitotic rates are high, with an average of 80 mitoses per 2 mm² area.^{6,95,96} The growth pattern usually consists of diffuse sheets, but rosettes, peripheral palisading, organoid nesting, streams, ribbons, and rarely, tubules or ductules may be present.⁹⁷ Basophilic encrustation of vessel walls, also known as the Azzopardi effect, is often seen in necrotic areas.⁹⁷ SCLC is reliably diagnosed in small biopsies and cytology specimens.

After chemotherapy, mixtures of large cell, squamous, giant cell, or adenocarcinoma may be seen in 15% to 45% of SCLC.^{98–100}

Combined SCLC

The frequency of combined SCLC depends on the extent of histologic sampling but most studies report this occurs in less than 10% of cases. A combination of SCLC and large cell carcinoma (see **Fig. 8**) is found in about 4% to 6% of cases.⁹³ Approximately 1% to 3% of SCLC may be combined with adenocarcinoma or squamous cell carcinoma.^{93,94,99,101} The amount of the non-small cell component is not important for adenocarcinoma or squamous cell carcinoma so long as the histology is clear. However, for combined small cell and large cell carcinoma at least 10% of large cells is required to make the diagnosis.^{6,95,96} SCLC can also be associated with spindle cell carcinoma,^{102,103} giant cell carcinoma,¹⁰³ and carcinosarcoma.¹⁰⁴ However, there are no consistent data to suggest that there is any significant difference in clinical features, prognosis, and response to therapy compared with patients with pure SCLC.^{94,101}

Although immunohistochemistry is useful in the diagnosis of SCLC, the most important stain is a good-quality hematoxylin and eosin stain that is not too thick or overstained. The diagnosis can be established without immunostains in most cases and it is needed only in problematic cases. A pancytokeratin antibody such as AE1/AE3 is useful to confirm that the tumor is a carcinoma rather than a lymphoid lesion and the most useful NE markers include CD56, chromogranin and synaptophysin, which are best used as a panel. TTF-1 expression is found in 70% to 80% of SCLC.^{6,96,105–109} However, because extrapulmonary small cell carcinomas can express TTF-1, this stain should not be used to determine the primary site of small cell carcinomas.¹¹⁰ The proliferation rate by Ki-67 staining is high, averaging 70% to 90%.¹¹¹

Clinical features and prognosis

SCLC has distinctive clinical properties, with an aggressive clinical course, frequent widespread metastases at presentation, common paraneoplastic syndromes, and responsiveness to chemotherapy.¹¹²

With combination chemotherapy (etoposide/cisplatin) and chest radiotherapy, for patients with limited-stage disease, the median survival is 15 months and 5-year survival is 10%.¹¹²

Differential diagnosis

Separation of SCLC from large cell carcinoma or LCNEC requires the application of a constellation of criteria including cell size, nucleoli, nuclear/cytoplasmic (N/C) ratio, nuclear chromatin, nucleoli, nuclear molding, cell shape (fusiform vs polygonal), and hematoxylin vascular staining (Table 2).^{108,113} There is a continuum of cell size between SCLC and large cell carcinoma,¹¹³ but the cells of SCLC usually are about the diameter of 2 to 3 small resting lymphocytes.⁶ Vollmer¹¹³ showed that the size of cells of SCLC also seems greater in larger biopsy specimens. This finding explains why the tumor cells of SCLC seem larger in well-fixed open biopsies than in transbronchial biopsy specimens.

Disagreement among expert lung cancer pathologists over the distinction between SCLC and NSCLC may occur in up to 5% to 7% of cases.^{114–116} In the study by Roggli and colleagues,¹¹⁵ agreement for the diagnosis of SCLCs for all 5 observers was 93% and for at least 4 of 5

observers it was 98%. In problem cases it can be helpful to try to achieve a consensus approach among other pathology colleagues. If a consensus diagnosis cannot be reached locally, it may be appropriate to refer the case for extramural consultation. For problematic cases in small biopsy specimens, it can be helpful to evaluate any cytology specimens that may have been taken at the time of bronchoscopy because the morphology by cytology may be more diagnostic than in the biopsy specimen.

Crush artifact is common in small biopsy specimens and this can complicate evaluation for diagnosis. Whereas most tumors showing dense sheets of small blue cells turn out to be SCLC, this artifact can also be seen in carcinoid tumors, lymphocytic infiltrates, or poorly differentiated NSCLC. However, even in crushed specimens, some preserved tumor cells with morphology compatible with SCLC should be seen to confirm the diagnosis. Immunohistochemical markers can be of assistance in crushed specimens, because SCLC may show positive staining for cytokeratin, chromogranin, CD56, synaptophysin, TTF-1, and a high proliferation index with Ki-67.^{117,118} Up to 10% of SCLC may be negative for a panel of NE markers if the workup includes CD56. So if all other morphologic features are present the diagnosis of SCLC can be rendered even with negative NE markers.¹¹⁹

If keratin staining is negative in a suspected SCLC, one should be careful to exclude other possibilities such as chronic inflammation,

Table 2
Light microscopic features for distinguishing small cell carcinoma and large cell NE carcinoma

Histologic Feature	Small Cell Carcinoma	LCNEC
Cell size	Smaller (less than diameter of 3 lymphocytes)	Larger
N/C ratio	Higher	Lower
Nuclear chromatin	Finely granular, uniform	Coarsely granular or vesicular Less uniform
Nucleoli	Absent or faint	Often (not always) present May be prominent or faint
Nuclear molding	Characteristic	Less prominent
Fusiform	Common	Uncommon
Polygonal with ample pink cytoplasm	Uncharacteristic	Characteristic
Nuclear smear	Frequent	Uncommon
Basophilic staining of vessels and stroma	Occasional	Rare

Data from Travis WD. Neuroendocrine lung tumors. *Path Case Rev* 2006;11:235–42; and Vollmer RT. The effect of cell size on the pathologic diagnosis of small and large cell carcinomas of the lung. *Cancer* 1982;50:1380–3.

lymphoma, primitive neuroectodermal tumor, or small round cell sarcoma.^{5,7} There is no immunohistochemical or molecular marker that reliably distinguishes SCLC from non-SCLC.^{120,121} However, in a poorly differentiated tumor that is TTF-1–negative and NE-marker–negative but diffusely positive for p63, the diagnosis of basaloid carcinoma or basaloid variant of squamous cell carcinoma is favored.¹²² Nevertheless, the primary criteria for separating SCLC from NSCLC are based on light microscopy (see **Box 2**).⁶

LARGE CELL CARCINOMA

Large cell carcinoma comprised 3% of all lung carcinomas in a recent report of the US National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) data.⁷⁵ This finding is a decrease from 9% reported in the SEER monograph for 1983 to 1987.⁶³ The SEER data include unresectable tumors that would have been diagnosed on small biopsies or cytology as well as resected tumors; other recent surgical series also report a frequency of approximately 3%.^{123,124} These tumors are mostly found in the lung periphery, although they may be centrally located. By gross examination they frequently appear as large necrotic tumors. Large cell carcinoma is a diagnosis of exclusion, where the presence of squamous cell or glandular differentiation needs to be excluded by light microscopy. Histologically the tumors usually consist of sheets and nests of large polygonal cells with vesicular nuclei and prominent nucleoli (**Fig. 11**).⁶ In the separation from solid adenocarcinoma with mucin, there

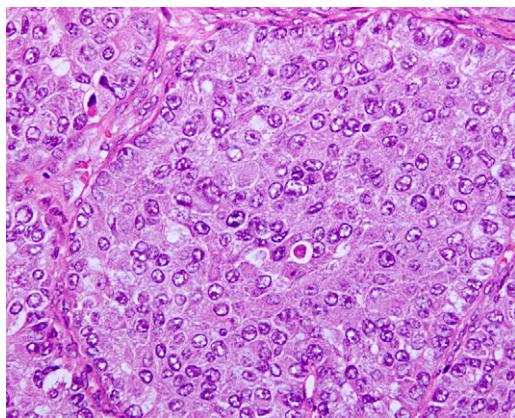


Fig. 11. Large cell carcinoma. This tumor consists of sheets and nests of large cells with abundant cytoplasm and vesicular nuclei with prominent nucleoli (hematoxylin-eosin, original magnification $\times 400$).

should be less than 5 mucin positive cells in at least 2 high power fields.⁶

The diagnosis of large cell carcinoma cannot be made without a resection specimen.⁶ This situation is because in small biopsies and cytology, the presence of an adenocarcinoma or squamous cell carcinoma component cannot be excluded. There is considerable confusion in the literature on this topic, because tumors have been classified as large cell carcinoma in both pathology as well as clinical publications in which the data were based on small biopsy specimens rather than resections.^{27,125} According to the 2011 IASLC/ATS/ERS lung adenocarcinoma classification, in small biopsy specimens, these tumors would now be classified as NSCLC-NOS if evaluated by light microscopy alone.^{5,6} If immunostains are performed, some of these tumors might be reclassified as NSCLC favor adenocarcinoma or NSCLC favor squamous cell carcinoma and a small percentage would remain as NSCLC-NOS.^{5,6}

It has been known for decades that electron microscopy (EM) of large cell carcinoma frequently reveals features of adenocarcinoma or squamous differentiation.^{126–128} Similar observations are being made using immunohistochemistry, in which studies of large cell carcinomas express adenocarcinoma (TTF-1) or squamous (p63) markers and some have suggested these tumors should now be reclassified.^{125,129} A small percentage of these tumors may also harbor mutations such as KRAS that are associated with adenocarcinoma. However, this information by immunohistochemistry or mutation testing does not add any new information beyond what we have known for decades with EM: (1) tumors classified as large cell carcinoma by light microscopy consist of a heterogeneous group of poorly differentiated tumors most of which share properties (EM, immunohistochemistry, or molecular) of adenocarcinoma, some have squamous features, a smaller percentage have both, and a small subset remains a null phenotype or truly undifferentiated large cell carcinoma. How to resolve this issue needs to be addressed in the upcoming revision of the WHO classification. Regardless of whether the decision is to lump (keep large cell carcinoma close to the current definition) or to split (reclassify most large cell carcinomas according to immunohistochemistry), this decision is arbitrary in the absence of any clinical trial data to compare clinical properties, such as different outcomes or response to therapy, relative to the other major lung cancer histologic subtypes. One option may be to retain the diagnosis of large cell carcinoma based on traditional criteria, but add a comment about the

immunophenotype that may reflect adenocarcinoma or squamous cell carcinoma differentiation.

Several variants of large cell carcinoma are recognized in the 2004 WHO histologic classification of lung cancer (see **Box 1**). These variants include LCNEC,^{6,130,131} basaloid carcinoma,¹³² lymphoepithelial-like carcinoma,^{133,134} clear cell carcinoma,¹³⁵ and large cell carcinoma with rhabdoid phenotype.^{136,137} LCNEC is discussed below.

LCNEC

LCNEC comprises approximately 3% of resected lung cancers.¹⁰⁹ LCNEC is a high-grade non-small cell NE carcinoma that differs from AC and small cell carcinoma (see **Table 2**). Histologic criteria include: (1) NE morphology: organoid, palisading, trabecular, or rosette-like growth patterns (**Fig. 12**); (2) non-small cell cytologic features: large size, polygonal shape, low N/C ratio, coarse or vesicular nuclear chromatin, and frequent nucleoli; (3) high mitotic rate (11 or more per 2 mm²) with a mean of 60 mitoses per 2 mm²; (4) frequent necrosis; and (5) at least 1 positive NE immunohistochemical marker or NE granules by EM (see **Fig. 12B**).^{6,131} It is difficult to diagnose LCNEC based on small biopsy specimens such as needle or bronchoscopic biopsy specimens because it is usually difficult to be certain of the NE morphology without a substantial sampling of the tumor. However, recently criteria were proposed to diagnose LCNEC based on cytology.¹³⁸ The term large cell carcinoma, with NE morphology, can be used for tumors resembling LCNEC by light microscopy but lacking proof of NED by EM or immunohistochemistry.⁶ The term combined LCNEC is used for those tumors

associated with other histologic types of NSCLC such as adenocarcinoma or squamous cell carcinoma (see **Box 1**).⁶ A variety of criteria must be used to separate SCLC from LCNEC (see **Table 2**).

Clinical features

Patients with LCNEC have a median age of 62 years (range 33–87 years) and they are typically heavy cigarette smokers.¹³¹ Patients with LCNEC have a poor prognosis. Travis and colleagues¹³⁰ found the 5-year and 10-year survival for LCNEC is 27% and 11%, respectively, with a significantly worse prognosis than patients with AC. Iyoda and colleagues¹³⁹ found a 35.3% and 31.7% 5-year and 10-year survival, respectively, for LCNEC. Iyoda and colleagues¹³⁹ also found a worse survival for LCNEC compared with classic large cell carcinoma ($P = .031$), whereas Jiang and colleagues¹⁴⁰ found a worse survival for LCNEC compared with non-small cell carcinomas ($P = .046$). However, it has not been possible to show a difference in survival between LCNEC and SCLC.^{130,141} Surgical resection should be performed if possible; however, it remains to be proved whether adjunctive radiation or chemotherapy is effective. Iyoda and colleagues¹³⁹ found no significant difference between the age, sex, smoking history, tumor size, and survival for patients with large cell carcinoma with NE morphology compared with those with LCNEC, although the mitotic rate was higher ($P = .0071$). A recent analysis of the NCI SEER data suggested overall survival and lung cancer specific survival rates for patients with LCNEC after surgical resection without radiation therapy were similar to those for patients who had other large cell carcinoma and better

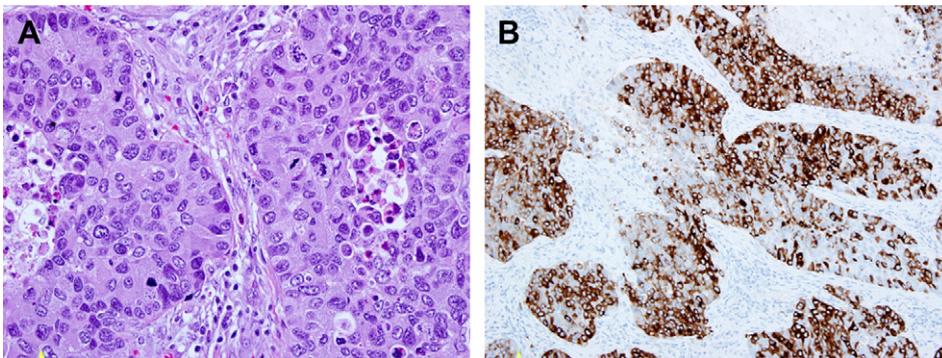


Fig. 12. LCNEC. (A) Peripheral palisading and rosette-like structures give this tumor an NE morphologic appearance. The tumor cells have abundant cytoplasm with large hyperchromatic nuclei. Some of the nuclei show vesicular chromatin or prominent nucleoli. Mitoses are frequent (hematoxylin-eosin, original magnification $\times 400$). (B) The tumor cells are diffusely positive for synaptophysin (immunohistochemistry for synaptophysin, original magnification $\times 200$).

than for those patients with SCLC, although the differences were not significant on multivariate analysis.¹⁴²

If immunohistochemistry is performed on non-small cell carcinomas lacking NE morphology, positive staining can be found in 10% to 20% of cases. Similarly NE granules can be found in up to 10% of cases by EM. Such tumors are called non-small cell carcinomas (adenocarcinoma, squamous cell carcinoma, or large cell carcinoma) with neuroendocrine differentiation (NSCLC-NED).^{36,131} The clinical significance of the diagnosis of NSCLC-NED is not known. Iyoda and colleagues¹³⁹ found that the tumor size of large cell carcinoma with NED (LCC-ND) was larger than that for LCNEC ($P = .0033$), but the survival was not different from patients with LCNEC. Whether these tumors are responsive to SCLC chemotherapy regimens^{143,144} or whether expression of NE markers may be an unfavorable prognostic factor¹⁴⁵⁻¹⁵² remains to be determined.

ADENOSQUAMOUS CARCINOMA

Adenosquamous carcinoma accounts for 0.6% to 2.3% of all lung cancers¹⁵³⁻¹⁵⁷ and it is defined as a lung carcinoma having at least 10% squamous cell and adenocarcinoma by light microscopy.³⁶ Similar to large cell carcinoma enormous confusion has been introduced by use of immunostains. The current WHO definition recognizes this tumor if the 10% of squamous and adenocarcinoma components are diagnosable by light microscopy. This diagnosis should be made only if the adenocarcinoma and squamous components are both recognizable by light microscopy and not purely by immunohistochemistry. This diagnosis may be suspected, but cannot be made by small biopsy or cytology, because a resection specimen is needed.

CARCINOMAS WITH PLEOMORPHIC, SARCOMATOID, OR SARCOMATOUS ELEMENTS

Sarcomatoid carcinomas comprise 0.3% of all invasive lung malignancies.⁶³ This group of lung carcinomas is poorly differentiated and expresses a spectrum of pleomorphic, sarcomatoid, and sarcomatous elements.¹⁵⁸ Pleomorphic carcinomas tend to be large, peripheral tumors that often invade the chest wall and are associated with a poor prognosis.¹⁵⁸ Because of the prominent histologic heterogeneity of this tumor, adequate sampling is important and should consist of at least 1 section per centimeter of the

tumor diameter. Pleomorphic carcinomas should have at least a 10% component of a spindle cell or giant cell component, and frequently other histologic types such as adenocarcinoma or squamous cell carcinoma (Fig. 13) are present.^{6,158}

If the tumor has a pure giant cell or spindle cell pattern the term giant cell or spindle cell carcinoma, respectively, can be used. Giant cell carcinoma consists of huge bizarre pleomorphic and multinucleated tumor giant cells.^{6,158} The cells are often dyscohesive and infiltrated by inflammatory cells, particularly neutrophils. This tumor is defined by light microscopy, but immunohistochemistry, particularly for epithelial markers such as keratin, can be helpful in confirming epithelial differentiation.^{6,158} The diagnosis of pleomorphic carcinoma cannot be made based on small biopsies or cytology; a resection specimen is required to identify the criteria outlined earlier.

Carcinosarcoma and Pulmonary Blastoma

Carcinosarcoma is a tumor composed of a mixture of carcinoma and sarcoma that should show heterologous elements such as malignant cartilage, bone, or skeletal muscle according to the 2004 WHO classification.^{6,158} Pulmonary blastomas are composed of a glandular component that resembles well-differentiated fetal adenocarcinoma and a primitive sarcomatous component. Fetal adenocarcinoma is no longer regarded as the epithelial pattern of pulmonary blastoma, but rather as a variant of adenocarcinoma.^{6,158}

TYPICAL AND ATYPICAL CARCINOID

Carcinoid tumors account for 1% to 2% of all invasive lung malignancies.⁶³ Approximately 50%

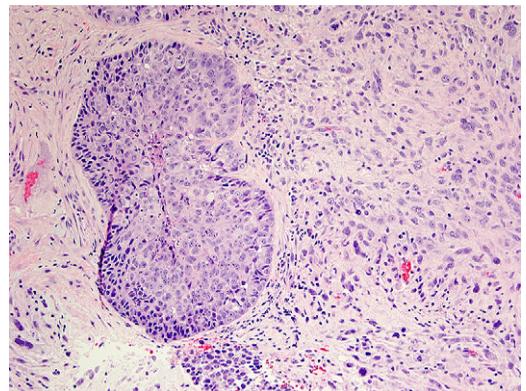


Fig. 13. Pleomorphic carcinoma. This tumor is composed of squamous cell carcinoma (*left*) and an malignant spindle cell proliferation (*right*) (hematoxylin-eosin, original magnification $\times 200$).

of patients are asymptomatic at presentation.^{96,112,159} Typical carcinoid (TC) and atypical carcinoid (AC) occur at any age, with an average of 45 to 55 years, and there is no sex predilection. They are the most common lung tumor in childhood.¹⁶⁰ Symptoms include hemoptysis in 18%, postobstructive pneumonitis in 17%, and dyspnea in 2% of patients. Paraneoplastic syndromes include the carcinoid syndrome, Cushing syndrome.^{96,112}

The primary approach to treatment of pulmonary carcinoids is surgical resection.^{161,162} Patients with TC have an excellent prognosis and rarely die of tumor.^{96,112} The finding of metastases should not be used as a criterion for distinguishing TC from AC because 5% to 20% of TCs have regional lymph node involvement.^{161,162}

Compared with TCs, ACs have a larger tumor size, a higher rate of metastases, and the survival is significantly reduced. The mortality reported in most series is approximately 30%, ranging from 27% to 47%.^{96,112}

Carcinoid tumors may be central, with a frequent polypoid endobronchial component. Peripheral carcinoids are usually found in the subpleural parenchyma. Both TCs and ACs are characterized histologically by an organoid growth pattern and uniform cytologic features consisting of moderate eosinophilic, finely granular cytoplasm with nuclei possessing a finely granular chromatin pattern (Fig. 14, Table 3). Nucleoli are inconspicuous in

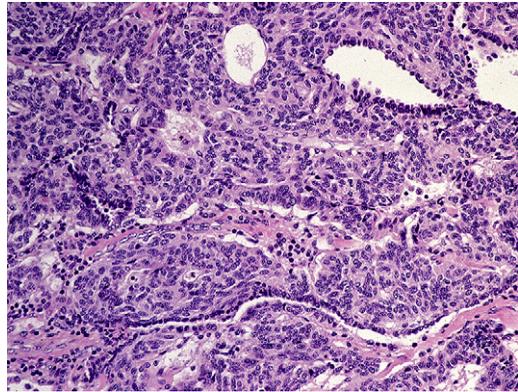


Fig. 14. Typical carcinoid. This tumor is growing in organoid nests and consists of uniform medium-sized cells with a moderate amount of eosinophilic cytoplasm (hematoxylin-eosin, original magnification $\times 200$).

most TCs, but they may be more prominent in ACs. A variety of histologic patterns may occur in both ACs and TCs, including spindle cell, trabecular, palisading, rosette-like, papillary, sclerosing papillary, glandular, and follicular patterns.¹³¹ The tumor cells of pulmonary carcinoid tumors may have oncocytic, acinic cell-like, signet ring, mucin-producing, or melanocytic features.¹³¹

ACs are defined as carcinoid tumors with mitoses between 2 and 10 per 2 mm² area of viable tumor (10 high power fields in certain microscopes) or the presence of necrosis (Fig. 15).¹³⁰

Table 3
Typical and atypical carcinoid: distinguishing features

Histologic or Clinical Feature	Typical Carcinoid	Atypical Carcinoid
Histologic patterns: organoid, trabecular, palisading and spindle cell	Characteristic	Characteristic
Mitoses	Absent or <2 per 2 mm ² area of viable tumor (10 high power fields on some microscopes)	2–10 per 2 mm ² or area of viable tumor (10 high power fields on some microscopes)
Necrosis	Absent	Characteristic, usually focal or punctate
Nuclear pleomorphism, hyperchromatism	Usually absent, not sufficient by itself for diagnosis of AC	Often present
Regional lymph node metastases at presentation (%)	5–15	40–48
Distant metastases at presentation (%)	Rare	20
Survival at 5 years (%)	90–95	50–60
Survival at 10 years (%)	90–95	35

Data from Colby TV, Koss MN, Travis WD. Tumors of the lower respiratory tract; Armed Forces Institute of Pathology fascicle, third series. Washington, DC: Armed Forces Institute of Pathology, 1995. p. 295; and Travis WD. Pathology of lung cancer. Clin Chest Med 2002;23:77.

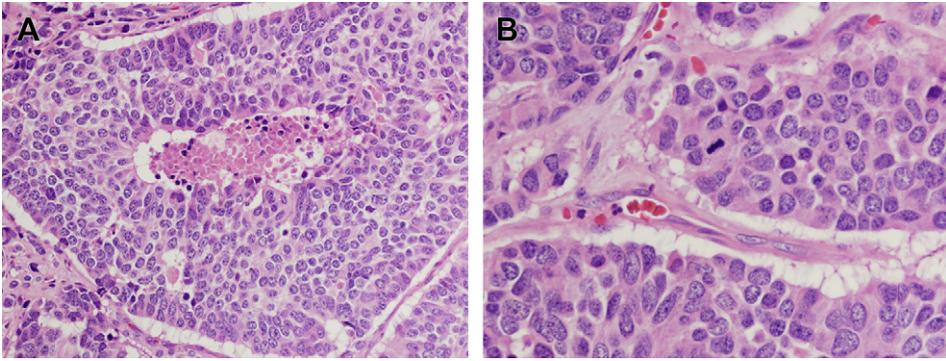


Fig. 15. Atypical carcinoid. (A) Punctate foci of necrosis are present in the center of several organoid nests of uniform tumor cells. This feature is characteristic of atypical carcinoids (hematoxylin-eosin, original magnification $\times 200$). (B) The tumor cells are uniform, with moderate spindle-shaped cytoplasm, and the nuclear chromatin is finely granular. A single mitosis is present (*center*) (hematoxylin-eosin, original magnification $\times 800$).

The presence of features such as pleomorphism, vascular invasion, and increased cellularity is not so helpful in separating TC from AC. In TC necrosis is absent and mitotic figures are rare (<2 per 2 mm^2) (see [Table 3](#)).^{130,131} The necrosis in AC usually consists of small foci centrally located within organoid nests of tumor cells; uncommonly the necrosis may form larger confluent zones.

Carcinoid tumors stain for NE markers such as chromogranin, synaptophysin, and CD56. A low proliferation rate ($\leq 5\%$) is seen in TC by Ki-67 staining compared with AC, in which it is usually between 5% and 20%.^{111,163} In small crushed biopsies Ki-67 staining can be helpful to separate TC or AC from the high-grade LCNEC or SCLC, which have high proliferation rates.^{111,163}

SUMMARY

This article reviews current concepts in pathologic classification of lung cancer based on the 2004 WHO classification of lung tumors and the 2011 IASLC/ATS/ERS classification of lung adenocarcinoma. AIS is now added to the other preinvasive lesions that include squamous dysplasia/CIS, AAH, and DIPNECH. Major changes in lung disease diagnosis have now resulted from the new IASLC/ATS/ERS classification including: (1) the term BAC is no longer used because tumors formerly classified under this term fall into 5 different places in this classification; (2) new concepts of AIS and MIA have been introduced; (3) comprehensive histologic subtyping is recommended for evaluation of invasive lung adenocarcinomas with classification according to the predominant subtype; (4) micropapillary adenocarcinoma is introduced as a new subtype with a poor prognosis; (5) for tumors previously classified as mixed subtype with a predominant

component formerly called nonmucinous BAC, the term LPA is recommended and the term mixed subtype is discontinued; (6) tumors formerly classified as mucinous BAC are now classified as invasive mucinous adenocarcinoma (formerly mucinous BAC). The topic of lung cancer diagnosis in small biopsies and cytology is now addressed for the first time with an official standardized classification in which specific terminology and diagnostic criteria are proposed along with recommendations for strategic management of tissue and *EGFR* mutation testing in patients with advanced adenocarcinoma. The pathology of other lung cancers is also discussed such as large cell carcinoma, sarcomatoid carcinomas, and NE tumors, including small cell carcinoma and large cell NE carcinoma, as well as typical and atypical carcinoid tumors.

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