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REVIEW ARTICLE

Evolving Concepts in the Pathology and Computed Tomography Imaging of Lung Adenocarcinoma and Bronchioloalveolar Carcinoma

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ABSTRACT

Purpose
To review recent advances in pathology and computed tomography (CT) of lung adenocarcinoma and bronchioloalveolar carcinoma (BAC).

Methods
A pathology/CT review panel of pathologists and radiologists met during a November 2004 International Association for the Study of Lung Cancer/American Society of Clinical Oncology consensus workshop in New York. The purpose was to determine if existing data was sufficient to propose modification of criteria for adenocarcinoma and BAC as newly published in the 2004 WHO Classification of Lung Tumors, and to address the pathologic/radiologic concept of diffuse/multicentric BAC.

Results
Solitary small, peripheral BACs have an excellent prognosis. Most lung adenocarcinomas with a BAC pattern are not pure BAC, but rather adenocarcinoma, mixed subtype with invasive patterns. This applies to tumors presenting with a diffuse/multinodular as well as solitary nodule pattern. The percent of BAC versus invasive components in lung adenocarcinomas appears to be prognostically important. However, a consensus definition of ''minimally invasive'' BAC with a favorable prognosis could not be achieved. While recognition of a BAC component is possible, the diagnosis of BAC with exclusion of invasive adenocarcinoma cannot be made by small biopsy or cytology specimens.

Conclusion
There is a need to work toward a mutual understanding and consensus between pathologists, clinicians, and researchers with the use of the term BAC versus adenocarcinoma. Future studies should make some attempt to quantitate these components and/or other features such as size of scar, size of invasive component, or pattern of invasion. Hopefully, this work will allow definition of a category of adenocarcinoma, mixed subtype with predominant BAC/minimal invasion and a favorable prognosis.

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INTRODUCTION

We are in the midst of a historic evolution in the study of lung adenocarcinoma, with advances occurring at every level, including pathology, clinical investigation, radiology, molecular biology, and therapy.[1-4] This article reviews the history of the histologic subclassification of lung adenocarcinoma by the WHO and recent developments in our understanding of the computed tomographic (CT) features and pathology of

lung adenocarcinoma. This review also includes the recommendations of a Pathology/Radiology Panel of lung cancer experts developed during a workshop on bronchioloalveolar carcinoma, held November 4 to 6, 2004 in New York City sponsored by the International Association for the Study of Lung Cancer (IASLC) and the American Society of Clinical Oncology. Preparation for this workshop included a meeting of the Pathology Panel held August 20 to 23, 2004 in Washington DC. With the advent of CT screening for lung cancer,[5-10] there has been enormous interest in the CT features and pathology of peripheral lung adenocarcinomas and much has been learned from the correlation of CT images with histology in these tumors. The development of molecular targeted therapies, particularly for epidermal growth factor, has also generated a great deal of interest in correlating the pathology and CT findings of these tumors with molecular and clinical findings.[2-4,11-13]

HISTORY OF LUNG ADENOCARCINOMA HISTOLOGIC SUBCLASSIFICATION BY THE WHO

The evolution in our understanding of the pathology of lung adenocarcinoma is reflected in the substantial changes in histologic subclassification by the WHO from the 1967 to 1981 to the 1999 and 2004 classifications. In the 1967 WHO classification, there were two major subtypes of lung adenocarcinoma (Table 1): Bronchogenic adenocarcinoma and bronchioloalveolar carcinoma (BAC).[14] Bronchogenic adenocarcinoma was then divided into acinar and papillary subtypes. In the 1981 WHO classification, four subtypes of lung adenocarcinoma were recognized including acinar, papillary, BAC and solid carcinoma with mucus formation (Table 1).[15]

However, in the 1999 WHO classification, several major changes were made that were preserved with the 2004 WHO classification (Table 1).[16,17] With the recognition that most lung adenocarcinomas are histologically heterogeneous and consist of more than one subtype, the category of adenocarcinoma with mixed subtypes was added to the four subtypes from the 1981 WHO classification acknowledging that mixed subtype would be the most common histologic type of lung adenocarcinoma.[17] BAC was also modified, formally recognizing three types: nonmucinous (Fig 1), mucinous (Fig 2), and mixed mucinous and nonmucinous. The nonmucinous BACs consist of varying mixtures of type II pneumocytes and Clara cells; however, there is no known clinical significance to determination of these cell types and this is not required to make the diagnosis of BAC.[16,17] The most significant change in the 1999 WHO classification was the requirement that all BACs demonstrate pure lepidic growth without invasion of stroma, blood vessels, or pleura.[16,17] In the previous WHO classifications there was no emphasis on the importance of the amount of BAC component and as a result widely varying histologic criteria were used in publications about this tumor. According to these stricter criteria, most lung adenocarcinomas with a BAC component are now classified as adenocarcinoma, mixed subtype, and the invasive patterns present (acinar, papillary or solid) should be mentioned (Fig 3). The other major change in the 1999 WHO classification was the addition of a group of uncommon variants.

Another major change in the 1999 WHO classification was the addition of atypical adenomatous hyperplasia (AAH) as a preinvasive lesion for lung adenocarcinoma.[16] This was preserved in the 2004 WHO classification.[17] AAH is an atypical bronchioloalveolar proliferation that resembles, but falls short of, criteria for BAC. It consists of a localized proliferation of mild to moderately atypical pneumocytes that usually measure less than 5 mm (Fig 4).[16,17]

In the 2004 WHO classification, the only major change was to move adenocarcinoma, mixed subtype to the top of the list of subtypes, due to its frequency.[17] Importantly, the criteria for BAC were unchanged. A minor change was made to the category of well-differentiated fetal adenocarcinoma, by dropping the "well-differentiated"

Table 1. History of Lung Adenocarcinoma Subclassification According to the WHO

1967[14]	1981[15]	1999[16]	2004[15,17]
Bronchogenic	Acinar adenocarcinoma	Acinar	Adenocarcinoma, mixed subtype
Acinar	Papillary adenocarcinoma	Papillary	Acinar adenocarcinoma
Papillary	Bronchiolo-alveolar carcinoma	Bronchioloalveolar carcinoma	Papillary adenocarcinoma
Bronchioloalveolar	Solid carcinoma with mucus formation	Nonmucinous	Bronchioloalveolar carcinoma
		Mucinous	Nonmucinous
		Mixed mucinous and nonmucinous	Mucinous
		Solid adenocarcinoma with mucin	Mixed nonmucinous and mucinous or indeterminate
		Adenocarcinoma with mixed subtypes	Solid adenocarcinoma with mucin production
		Variants	
		Well-differentiated fetal adenocarcinoma	Fetal adenocarcinoma
		Mucinous (colloid) adenocarcinoma	Mucinous (colloid) adenocarcinoma
		Mucinous cystadenocarcinoma	Mucinous cystadenocarcinoma
		Signet-ring adenocarcinoma	Signet-ring adenocarcinoma
		Clear-cell adenocarcinoma	Clear-cell adenocarcinoma

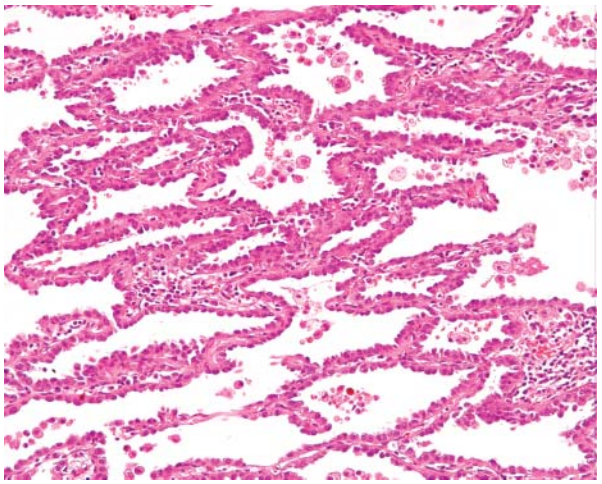

Fig 1. Bronchioloalveolar carcinoma, nonmucinous type. The alveolar walls are lined by a cellular proliferation of atypical pneumocytes that have a hobnail morphology. No invasion is seen.

because it was recognized that there are high-grade fetal adenocarcinomas.

GROSS AND RADIOLOGIC PATTERNS OF BRONCHIOLOALVEOLAR CARCINOMA AND INVASIVE ADENOCARCINOMA

BAC and mixed subtype adenocarcinomas with a BAC component have been recognized to have several gross pathologic and radiologic manifestations in the lung (Table 2). These include: (1) a solitary peripheral nodule (Figs 5-7), (2) multiple nodules (Fig 8), and (3) lobar consolidation (Fig 9).[17-26] When there is a prominent BAC component, the nodules may be ill-defined by gross pathologic exam and mostly ground glass by CT exam (Fig 5).

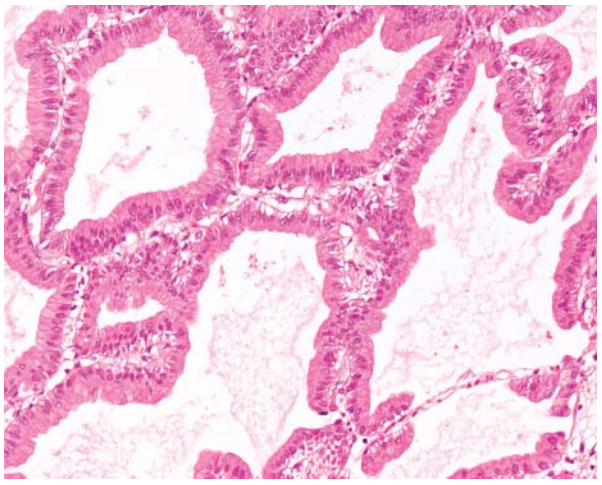

Fig 2. Bronchioloalveolar carcinoma, mucinous type. The alveolar walls are lined by a cellular proliferation of columnar cells with abundant apical mucin and small basally oriented nuclei. No invasion is seen.

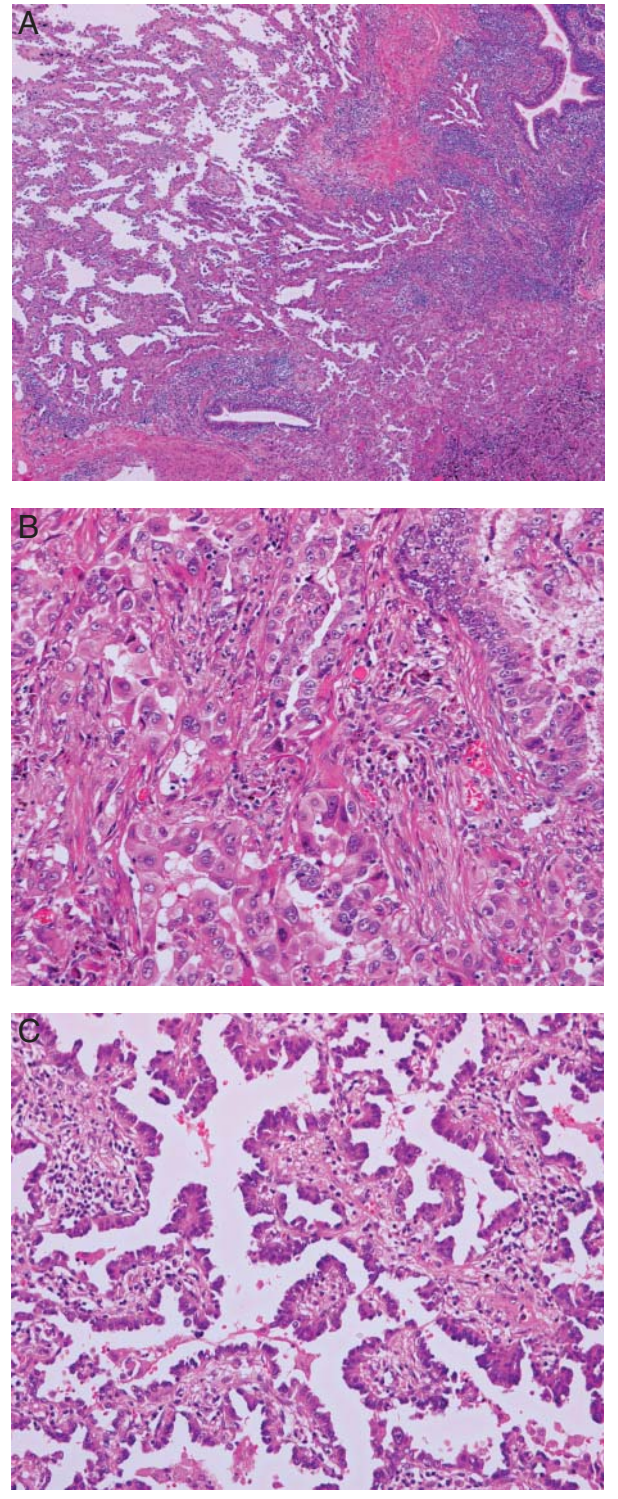

Fig 3. Adenocarcinoma, mixed subtype. (A) A bronchioloalveolar pattern is seen to the left and an invasive component on the right (hematoxylin and eosin X 4). (B) The invasive component consists of acinar glands infiltrating a fibrous stroma (hematoxylin and eosin X 40). (C) Papillary adenocarcinoma is present elsewhere in this tumor. This consists of malignant cuboidal epithelial cells growing along fibrovascular cores in a papillary configuration (hematoxylin and eosin X 10).

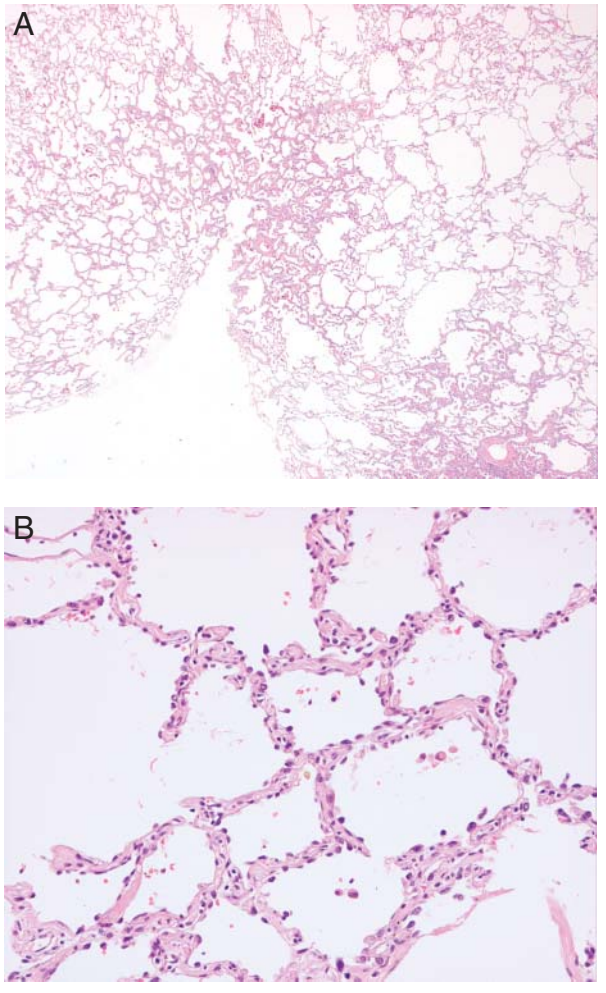

Fig 4. (A) Atypical adenomatous hyperplasia: Two localized nodular areas of atypical adenomatous hyperplasia shows hypercellular alveolar walls (hematoxylin and eosin X 2). (B) The alveolar walls are lined by atypical pneumocytes. There are gaps between the pneumocytes and there is mild thickening of alveolar walls (hematoxylin and eosin X 20).

Adenocarcinomas with an invasive component are more likely to be sharply circumscribed on gross pathologic exam and have a solid appearance by CT (Fig 6). A combination of these gross and CT characteristics may be seen in mixed subtype adenocarcinomas with both BAC and invasive components (Fig 7). When multiple nodules occur, they can be unilateral (Fig 8) or bilateral. They also may consist of a large dominant mass with satellite nodules within the same lobe or multiple nodules in more than one lobe.[17,24,25] The lobar consolidation pattern shows a diffuse parenchymal infiltration that grossly and radiologically is difficult to distinguish from lobar pneumonia (Fig 9).[17,25-27]

Table 2. Bronchioloalveolar Carcinoma: Gross Patterns of Lung Involvement

Solitary nodule
Multiple nodules (unilateral or bilateral)
Dominant nodule with satellites
Multicentric nodules involving one or more lobes
Lobar consolidation

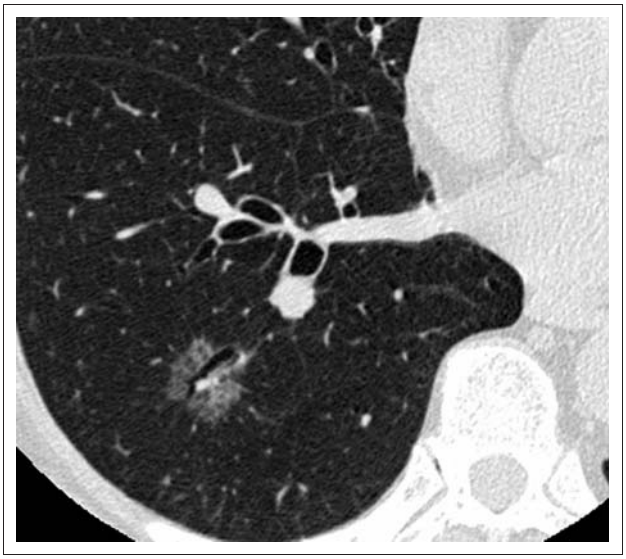

Fig 5. Ground glass density or nonsolid nodule. Chest computed tomography image focused on the right lower lobe shows a 1.5-cm ground-glass density or nonsolid nodule.

Due to significant differences in pathologic, radiologic, and clinical implication among these patterns of presentation by lung adenocarcinoma, the following discussion will be divided into two major categories: (1) solitary, small, peripheral lung adenocarcinomas; and (2) multiple nodules or diffuse consolidation patterns.

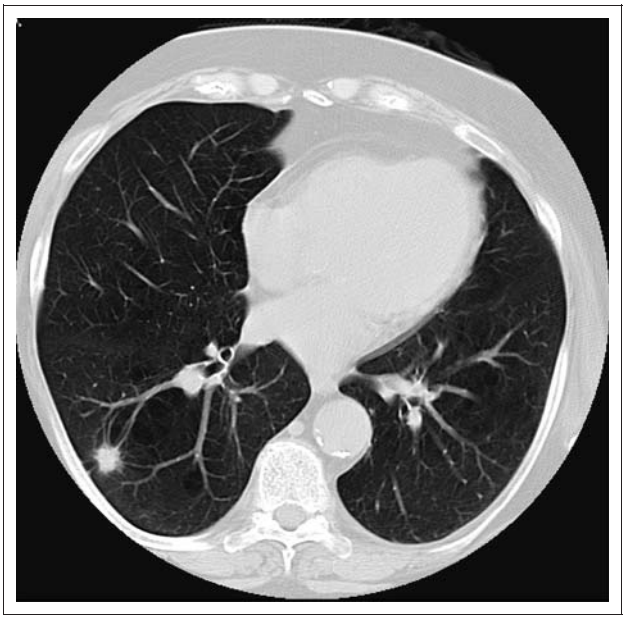

Fig 6. Solid nodule. Chest computed tomography image at the level of right inferior pulmonary vein shows a 1-cm solid nodule with feeding vessels.

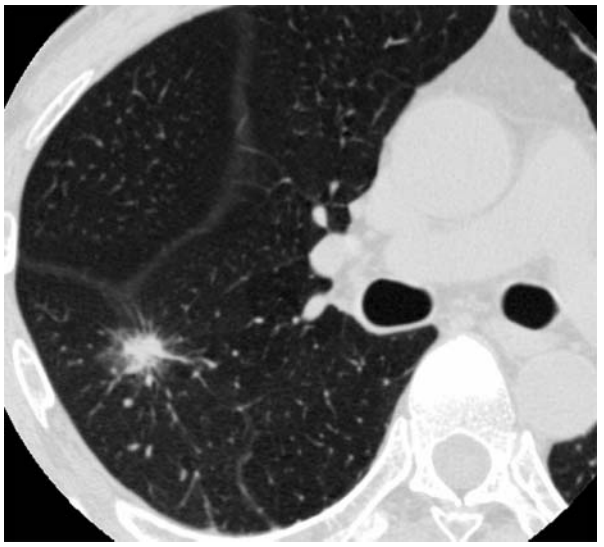

Fig 7. Part-solid nodule. Chest computed tomography image shows a 2-cm spiculated mixed-density nodule with solid central part and nonsolid peripheral portion. The adjacent major fissure is pulled toward the nodule.

Solitary, Small, Peripheral Lung Adenocarcinomas

Pathologic aspects. Over the past 10 years, a series of important articles about solitary, small (2 or 3 cm or less) peripheral nodular lung adenocarcinomas has revolutionized our concept of the pathology of these tumors. This began in 1995 with the work of Noguchi et al,[28] which pointed out that small peripheral lung adenocarcinomas with a pure BAC pattern and no invasion had 100% 5-year survival, and patients with mixed BAC and invasive components had a survival of 75% in contrast to those with a purely invasive growth pattern who had a survival of 52%.[28] These findings greatly influenced the 1999 WHO/IASLC Classification Panel, who proposed a new, stricter definition of BAC that required it to show pure lepidic growth without invasion of stroma, pleura, or blood vessels.[16] The same proposal was also adopted by the 2004 WHO classification.[17] One implication of these criteria is the importance of complete histologic sampling of tumors 3 cm or less in diameter if they have a BAC component, so that focal areas of invasion can be identified.

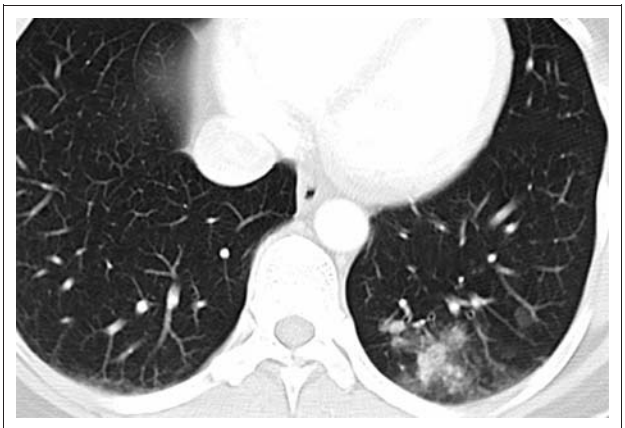

Fig 8. Multicentric bronchioloalveolar carcinoma. Chest computed tomography image shows multiple nodules in the left lower lobe.

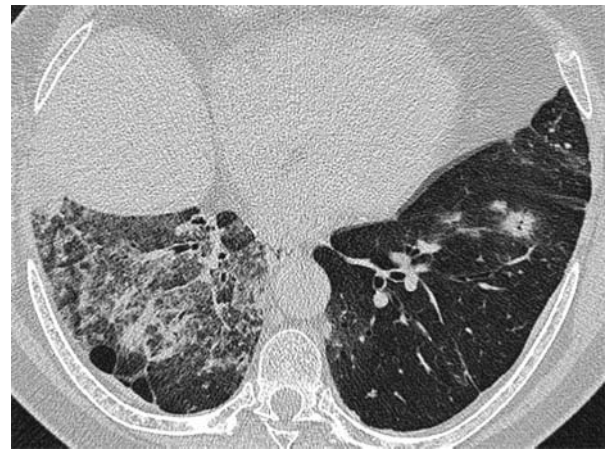

Fig 9. Bilateral multifocal bronchioloalveolar carcinoma with consolidative pattern. Computed tomography image shows large consolidation in the right lower lobe and nodules in the left lower lobe.

Subsequently, multiple other reports have examined solitary, small, peripheral lung adenocarcinomas using different approaches to identify histologic prognostic factors.[8,29-31] Each study identified different histologic features to define a subgroup of mixed subtype adenocarcinomas that have a predominant BAC component and a favorable prognosis. These prognostically important histologic features included size of scar (5 mm or greater; greater than 5 mm to 15 mm; and greater than 15 mm),[8,10] percentage of lepidic growth,[10] percentage of papillary growth,[10] vascular invasion,[10] size of invasive area (5 mm or less versus $>$ 5 mm),[30] and pattern of stromal invasion ([1] within area of BAC growth; [2] localized on periphery of scar; [3] into center of scar).[29]

Suzuki et al[8] demonstrated prognostic importance of the size of scar: 5-year survival of 100% if the scar was 5 mm or smaller; 72% if the scar was more than 5 mm and 15 mm or less in size; and 40% if the scar size was larger than 15 mm. Yokose et al[10] found no deaths in 66 patients whose tumors had more than 75% lepidic growth, a central focus of fibrosis 5 mm or less in diameter, and no elastic fiber framework destruction by tumor cells. Multivariate analysis showed that vascular invasion and $>$ 25% papillary growth were unfavorable prognostic factors.[10] The paper by Terasaki et al[30] had no survival data, but reported a more abnormal immunophenotype for the mixed subtype adenocarcinomas that had a BAC component (group 2) compared with tumors consisting of pure BAC (group 1), and they divided the group 2 cases

into those with invasive areas ≥ 5 mm or compared with invasive areas < 5 mm.

Sakurai et al[29] approached the problem by dividing the pattern of stromal invasion into three categories: grade 0, pure BAC with no invasion; grade 1, invasion in the area of BAC growth; grade 2, stromal invasion on the periphery of a fibrotic focus; and grade 3, stromal invasion into the center of a fibrotic focus. These authors found that tumors with grade 1 and 2 invasion had an excellent prognosis similar to pure BACs (grade 0). They proposed that tumors with grade 1 or grade 2 invasion could be regarded as "minimally invasive" or "early" adenocarcinomas.[29] Since the term "grade" is already used for assessing the degree of histologic differentiation, it would be better to refer to these as "patterns" of invasion rather than "grades."

At the November 2004 BAC meeting in New York, a pathology panel was organized, consisting of the IASLC Pathology Panel supplemented by additional experts from several institutions who had a dedicated interest in BAC. This pathology panel evaluated each of these papers and concluded that it was premature at the present time to generate a definition of minimally invasive adenocarcinoma with a predominant BAC component and the current data are insufficient to make a change in the 2004 WHO classification of BAC and adenocarcinoma. Nevertheless, these studies strongly suggest that such a category can be defined and future studies will need to determine the optimal pathologic criteria.

Radiologic aspects. Due to the strong correlation between CT and pathologic features, as well as the numerous radiologic studies on solitary, peripheral, small lung adenocarcinomas, a CT review panel of expert radiologists was assembled to supplement the pathology panel at the New York BAC meeting. While a variety of different terms have been used for the radiologic appearance of adenocarcinoma nodules, the following terms were recognized by the CT Review Panel: (1) ground glass opacity (GGO) or nonsolid; (2) mixed density or mixed-ground glass opacity; and (3) solid. There are many CT studies that have made detailed correlations with pathology, survival, and/or surgical approach. A few of these studies are summarized in the following paragraphs to illustrate some important radiology-pathology correlations. Not all GGOs represent BAC or adenocarcinomas, but criteria for separating benign from malignant solitary pulmonary nodules is addressed in detail elsewhere.[23,32-40]

Prognostic factors by CT have been shown in several studies. Takashima et al[41] found that lesion size of < 15 mm, GGO areas greater than 57%, and BAC histology correlated with a favorable prognosis by univariate analysis; the percentage of GGO areas was the only independent prognostic factor by multivariate analysis. They demonstrated that air bronchograms and histologic grade were of prognostic importance in multivariate analysis of 52 patients with mixed subtype lung adenocarcinomas with a BAC component.[18] Aoki et al[42] found that small peripheral lung adenocarcinomas with more than 50% GGO by thin-section CT had significantly less lymph node metastases or vascular invasion than those with less than 10% GGO. Survival was significantly better for patients with tumors having greater than 50% GGO compared to those with less than 50% GGO.[42] Coarse spiculation and thickening of bronchovascular bundles around the tumors was associated with lymph node metastases or vascular invasion.[42]

Yang et al[43] found that 94% of pure BAC without alveolar wall collapse demonstrated pure GGO by CT, while 71% of BAC with some alveolar wall collapse appeared as heterogeneous, low-attenuation nodules. They also found that 50% of mixed subtype adenocarcinomas with a BAC component were homogeneous nodules with a soft-tissue density and 29% appeared as nodules with ground-glass attenuation in the periphery and a high-density central zone. Among tumors with a BAC component, the size and CT values of mixed subtype adenocarcinomas were larger than those of pure BACs ($P < .05$). Conversely, the percentage of ground-glass attenuation and retained air space in mixed subtype adenocarcinomas was smaller than those in pure BACs ($P < .01$). All tumors that were completely invasive with no BAC component were homogeneous nodules with soft-tissue density.[43]

One of the clinical implications of identifying a pure GGO pattern in a small peripheral lung adenocarcinoma is the potential for limited wedge resection rather than standard lobectomy. This approach has been suggested in the study by Nakamura et al[44] where no intrathoracic recurrence or distant metastases could be found in 27 patients with tumors that showed a pure GGO pattern. Asamura et al[45] also studied 48 lung carcinomas measuring ≤ 1 cm that had three high-resolution CT patterns: nonsolid GGO type (n = 19); part-solid GGO type (n = 9); and solid type (n = 20). They found no recurrences and BAC histologic type for all 28 GGO (nonsolid and part-solid) lesions, a finding they felt supported use of limited resection for GGO lesions.[45] However, not all pure GGO lesions are pure BACs histologically; they can have a component of invasive adenocarcinoma. Nakata et al[46] found mixed subtype adenocarcinomas with invasive adenocarcinoma as well as BAC in 7% of tumors measuring ≤ 1 cm with a pure GGO pattern by CT and in 38.5% of tumors with a similar CT appearance that were between 1 and 2 cm in size. Watanabe et al[47] reported 17 patients with localized BAC showing pure ground glass attenuation who had a pure BAC pattern on pathology and demonstrated no deaths or relapses with a median of 32 months follow-up.

Serial CT studies with follow-up have demonstrated progression of lung adenocarcinomas with GGO components.

Takashima at al[48] demonstrated lung adenocarcinomas that initially presented as ground-glass opacity subsequently increased in size in 75% of cases, and developed solid components within the nodule in 17%. The solid portions increased in 23%, and in 6% there was appearance of spiculation. Kakinuma et al[49] reported three types of progression of BAC with (1) increasing size in BAC, (2) decreasing size with the appearance of a solid component in one BAC and one adenocarcinoma with mixed subtype, and (3) stable size and increasing density in BAC. This study documents a little recognized finding that not all adenocarcinomas grow, but by CT they may decrease in size over time. All but one of the follow-up cases of lung cancer were noninvasive, whereas the remaining tumor showing GGO with a solid component was minimally invasive.[49]

Lung Adenocarcinomas Presenting as Multiple Nodules and Lobar Consolidation

While lung adenocarcinomas presenting with multicentric nodules and lobar consolidation may present a different clinical problem because they have a more advanced stage, the histologic patterns encountered are the same. Diffuse or multicentric growth patterns can be seen with both nonmucinous and mucinous BAC, but this is more characteristic of mucinous tumors.

Pathologic aspects. Most of the recent detailed pathologic studies of lung adenocarcinoma have focused on the solitary peripheral lung tumors. Accordingly, there have been few detailed pathologic studies of the multicentric adenocarcinomas with BAC components that present as multicentric nodules or lobar consolidation. Most of the recent publications on this subject have been primarily in the clinical literature without incorporation of recent pathologic concepts.[3,50-59] Detailed pathologic study of these tumors is more problematic because they are unresectable and often they are diagnosed only by small biopsy or cytology specimens. Due to the limited sampling, it is difficult to make a complete pathologic assessment of the extent of BAC versus invasive patterns of adenocarcinoma that may be present. Review of biopsy material from multicentric lung adenocarcinomas at the 2004 New York BAC meeting suggested that the spectrum of histologic findings in multicentric lung adenocarcinomas is similar to that in the solitary peripheral tumors; most of these tumors are adenocarcinoma, mixed subtype with a varying spectrum of BAC, acinar, papillary, and solid patterns.

With the many current investigations of the molecular changes and chemotherapeutic agents targeting the human epidermal growth factor receptor (epidermal growth factor receptor, ie, HER-1), such as gefitinib, cetuximab, and erlotinib,[11,60,61] it will be important to carefully define the pathology of the patients involved in these studies as clearly as possible according to 2004 WHO concepts, and to specify what types of specimens have been used to establish the diagnosis. This will allow for more valid comparison of data from different studies because of the prognostically significant implications of the extent of BAC versus invasive components in lung adenocarcinomas.

There is a problem with the current staging system with regard to the prognostic implications for some multicentric lung adenocarcinomas. The presence of a satellite tumor with the same histology in the same lobe is a T4 lesion, thus qualifying as stage 3B.[62] Also, if a tumor with the same histology is found in a separate lobe, then it is classified as M1 and the patient has stage 4 disease.[62] Recent surgical data suggests that this may be inappropriate, particularly with some cases of multiple small peripheral adenocarcinomas or BAC presenting as multifocal disease. Studies by Battafarano et al[50] and Roberts et al[63] indicate that such tumors may be amenable to surgical resection with prolonged survival.

Radiologic aspects. When lung adenocarcinomas with or without BAC present with multiple nodules, the CT features of each of the nodules may have the same spectrum of findings described above in the solitary nodules. The diffuse consolidation pattern may show air-bronchograms and be indistinguishable from pneumonia (Fig 9). Akira et al[27] reported high-resolution CT findings in 38 patients with diffuse BAC and found a spectrum of findings including ground-glass opacity (n = 29), consolidation (n = 29), nodules (n = 28), centrilobular nodules (n = 26), peripheral distribution (n = 19), and air bronchograms (n = 18). They observed three major high-resolution CT patterns: predominantly ground glass (n = 4), consolidative (n = 22), and multinodular (n = 12). While not specific, the characteristic appearance of diffuse BAC consisted of a combination of consolidation and nodules and the coexistence of centrilobular nodules and remote areas of ground-glass attenuation.[27]

SMALL BIOPSY SPECIMENS AND CYTOLOGY

Given the requirement for BAC to show pure lepidic growth without invasion and the knowledge that most lung adenocarcinomas with a BAC component also have areas of invasion, it is impossible to make an unequivocal diagnosis of BAC in small biopsy specimens (needle or bronchoscopic specimens). Similarly with cytology specimens, while there are features that suggest the presence of BAC, this diagnosis cannot be made with certainty because it is not possible to exclude the presence of an invasive adenocarcinoma.

GLOBAL EPIDEMIOLOGIC DIFFERENCES

From the literature and discussions at the 2004 New York BAC meeting, it is apparent that solitary, peripheral BACs as defined by the 2004 WHO classification are much more

common in Japan than in other parts of the world such as the United States and Europe.[8,10,28,30,64,65] It also appears that the mixed subtype adenocarcinomas with predominant BAC components are also much more common in Japan than in other countries.[8,10,28,30,64,65] Whether this is due to the longer history of CT screening in Japan resulting in earlier detection or genetic/environmental differences is not known. This is one of the reasons that our Japanese colleagues have been at the cutting edge of advances in our understanding of lung adenocarcinoma pathology, publishing the majority of important papers on this topic. There also may be differences in interpretation of diagnostic criteria for BAC by pathologists from various countries. The lack of similar detailed pathologic studies from investigators in other countries on the topic of BAC and mixed subtype adenocarcinomas with predominant BAC components presented a problem for the WHO panel in 2004, because it was difficult to propose modifications in a classification to be recommended for the world when the data are mostly from a single country.

NEED FOR CONSENSUS WITH BAC VERSUS ADENOCARCINOMA TERMINOLOGY

Another major problem is the need to work toward a mutual understanding and consensus between pathologists, clinicians, and researchers with the use of the term BAC versus adenocarcinoma. There is a tendency by clinicians to emphasize the term BAC when referring to lung adenocarcinomas, sometimes without acknowledgment of the other invasive subtypes.[55,58,66,67] Given the major shift in pathologic definition of BAC, with recognition of the striking survival significance in separating BAC from invasive adenocarcinoma, pathologists following the 2004 WHO classification are stricter about use of the term BAC. In most of the world, except for Japan, virtually all lung adenocarcinomas with a BAC component are of mixed subtype with an invasive component. Thus, a major cultural change is needed in the lung oncology community to recognize this fact. The recent pathologic studies from Japan (summarized above) indicate that the amount of BAC versus invasive subtypes (acinar, papillary, and solid) components of lung adenocarcinomas is of prognostic significance.[8,10,29,30] Thus, future studies should make some attempt to quantitate these components and/or other features such as size of scar, size of invasive component, or pattern of invasion.

NEED FOR FUTURE STUDIES

More studies are needed to better define a ''minimally invasive'' category, to see how reproducibly pathologists can interpret the various histologic features of prognostic importance. It is particularly important that careful pathologic and radiology/pathology correlation studies are published from multiple countries around the world to help validate or modify the existing pathologic criteria. Correlation of these detailed pathologic studies with CT images will be especially important with the unresectable, multicentric adenocarcinomas. These studies also need to address the issue of reproducibility between pathologists as well as between radiologists. Hopefully, such efforts will promote consistency throughout the world in the approach to diagnosis of BAC and lung adenocarcinoma.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Janne PA, Gurubhagavatula S, Yeap BY, et al: Outcomes of patients with advanced non-small cell lung cancer treated with gefitinib (ZD1839, ''Iressa'') on an expanded access study. Lung Cancer 44:221-230, 2004

2. Lynch TJ, Bell DW, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350:2129-2139, 2004

3. Miller VA, Kris MG, Shah N, et al: Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer. J Clin Oncol 22:1103-1109, 2004

4. Paez JG, Janne PA, Lee JC, et al: EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 304:1497-1500, 2004

5. Henschke CI, Yankelevitz DF, Mirtcheva R, et al: CT screening for lung cancer: Frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol 178:1053-1057, 2002

6. Kaneko M, Kusumoto M, Kobayashi T, et al: Computed tomography screening for lung carcinoma in Japan. Cancer 89:2485-2488, 2000

7. Sone S, Li F, Yang ZG, et al: Characteristics of small lung cancers invisible on conventional chest radiography and detected by population based screening using spiral CT. Br J Radiol 73:137-145, 2000

8. Suzuki K, Yokose T, Yoshida J, et al: Prognostic significance of the size of central fibrosis in peripheral adenocarcinoma of the lung. Ann Thorac Surg 69:893-897, 2000

9. Swensen SJ, Jett JR, Hartman TE, et al: Lung cancer screening with CT: Mayo Clinic experience. Radiology 226:756-761, 2003

10. Yokose T, Suzuki K, Nagai K, et al: Favorable and unfavorable morphological prognostic factors in peripheral adenocarcinoma of the lung 3 cm or less in diameter. Lung Cancer 29:179-188, 2000

11. Pao W, Wang TY, Riely GJ, et al. KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. PLoS Med 2:e17, 2005

12. Kosaka T, Yatabe Y, Endoh H, et al: Mutations of the epidermal growth factor receptor gene in lung cancer: Biological and clinical implications. Cancer Res 64:8919-8923, 2004

13. Pao W, Miller V, Zakowski M, et al: EGF receptor gene mutations are common in lung cancers from ''never smokers'' and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci USA 101:13306-13311, 2004

14. World Health Organization: Histological Typing of Lung Tumours, 1st ed. Geneva, World Health Organization, 1967

15. World Health Organization: Histological Typing of Lung Tumours. 2nd ed. Geneva, World Health Organization, 1981

16. Travis WD, Colby TV, Corrin B, et al: Histological Typing of Lung and Pleural Tumours, 3rd ed. Berlin, Springer, 1999

17. Travis WD, Brambilla E, Müller-Hermelink HK, et al: Pathology and Genetics: Tumours of

the Lung, Pleura, Thymus and Heart. Lyon, IARC, 2004

18. Takashima S, Maruyama Y, Hasegawa M, et al: High-resolution CT features: Prognostic significance in peripheral lung adenocarcinoma with bronchioloalveolar carcinoma components. Respiration 70:36-42, 2003

19. Mirtcheva RM, Vazquez M, Yankelevitz DF, et al: Bronchioloalveolar carcinoma and adenocarcinoma with bronchioloalveolar features presenting as ground-glass opacities on CT. Clin Imaging 26:95-100, 2002

20. Takashima S, Li F, Maruyama Y, et al: Discrimination of subtypes of small adenocarcinoma in the lung with thin-section CT. Lung Cancer 36:175-182, 2002

21. Kodama K, Higashiyama M, Yokouchi H, et al: Prognostic value of ground-glass opacity found in small lung adenocarcinoma on high-resolution CT scanning. Lung Cancer 33:17-25, 2001

22. Zwirewich CV, Miller RR, Müller NL: Multicentric adenocarcinoma of the lung: CT-pathologic correlation. Radiology 176:185-190, 1990

23. Kuhlman JE, Fishman EK, Kuhajda FP, et al: Solitary bronchioloalveolar carcinoma: CT criteria. Radiology 167:379-382, 1988

24. Clayton F: Bronchioloalveolar carcinomas. Cell types, patterns of growth, and prognostic correlates. Cancer 57:1555-1564, 1986

25. 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

26. Thompson WH: Bronchioloalveolar carcinoma masquerading as pneumonia. Respir Care 49:1349-1353, 2004

27. Akira M, Atagi S, Kawahara M, et al: High-resolution CT findings of diffuse bronchioloalveolar carcinoma in 38 patients. AJR Am J Roentgenol 173:1623-1629, 1999

28. Noguchi M, Morikawa A, Kawasaki M, et al: Small adenocarcinoma of the lung. Histologic characteristics and prognosis. Cancer 75: 2844-2852, 1995

29. Sakurai H, Maeshima A, Watanabe S, et al: Grade of stromal invasion in small adenocarcinoma of the lung: Histopathological minimal invasion and prognosis. Am J Surg Pathol 28: 198-206, 2004

30. Terasaki H, Niki T, Matsuno Y, et al: Lung adenocarcinoma with mixed bronchioloalveolar and invasive components: Clinicopathological features, subclassification by extent of invasive foci, and immunohistochemical characterization. Am J Surg Pathol 27:937-951, 2003

31. Yokose T, Suzuki K, Nagai K, et al: Favorable and unfavorable morphological prognostic factors in peripheral adenocarcinoma of the lung 3 cm or less in diameter. Lung Cancer 29:179-188, 2000

32. George CJ, Tazelaar HD, Swensen SJ, et al: Clinicoradiological features of pulmonary infarctions mimicking lung cancer. Mayo Clin Proc 79:895-898, 2004

33. Takashima S, Sone S, Li F, et al: Indeterminate solitary pulmonary nodules revealed at population-based CT screening of the lung: Using first follow-up diagnostic CT to differentiate benign and malignant lesions. AJR Am J Roentgenol 180:1255-1263, 2003

34. Takashima S, Sone S, Li F, et al: Small solitary pulmonary nodules (< or = 1 cm) detected at population-based CT screening for lung cancer. Reliable high-resolutions CT features of benign lesions. AJR Am J Roentgenol 180:955-964, 2003

35. Erasmus JJ, Connolly JE, McAdams HP, et al: Solitary pulmonary nodules: Part I. Morphologic evaluation for differentiation of benign and malignant lesions. Radiographics 20:43-58, 2000

36. Yankelevitz DF, Henschke CI: Small solitary pulmonary nodules. Radiol Clin North Am 38:471-478, 2000

37. Khouri NF, Meziane MA, Zerhouni EA, et al: The solitary pulmonary nodule. Assessment, diagnosis, and management. Chest 91: 128-133, 1987

38. Metzger RA, Mulhern CB Jr, Arger PH, et al: CT differentiation of solitary from diffuse bronchioloalveolar carcinoma. J Comput Assist Tomogr 5:830-833, 1981

39. Nakajima R, Yokose T, Kakinuma R, et al: Localized pure ground-glass opacity on high-resolution CT: histologic characteristics. J Comput Assist Tomogr 26:323-329, 2002

40. Nakata M, Saeki H, Takata I, et al: Focal ground-glass opacity detected by low-dose helical CT. Chest 121:1464-1467, 2002

41. Takashima S, Maruyama Y, Hasegawa M, et al: Prognostic significance of high-resolution CT findings in small peripheral adenocarcinoma of the lung: A retrospective study on 64 patients. Lung Cancer 36:289-295, 2002

42. Aoki T, Tomoda Y, Watanabe H, et al: Peripheral lung adenocarcinoma: Correlation of thin-section CT findings with histologic prognostic factors and survival. Radiology 220:803-809, 2001

43. Yang ZG, Sone S, Takashima S, et al: High-resolution CT analysis of small peripheral lung adenocarcinomas revealed on screening helical CT. AJR Am J Roentgenol 176:1399-1407, 2001

44. Nakamura H, Saji H, Ogata A, et al: Lung cancer patients showing pure ground-glass opacity on computed tomography are good candidates for wedge resection. Lung Cancer 44:61-68, 2004

45. Asamura H, Suzuki K, Watanabe S, et al: A clinicopathological study of resected subcentimeter lung cancers: A favorable prognosis for ground glass opacity lesions. Ann Thorac Surg 76:1016-1022, 2003

46. Nakata M, Sawada S, Saeki H, et al: Prospective study of thoracoscopic limited resection for ground-glass opacity selected by computed tomography. Ann Thorac Surg 75:1601-1605, 2003

47. Watanabe S, Watanabe T, Arai K, et al: Results of wedge resection for focal bronchioloalveolar carcinoma showing pure ground-glass attenuation on computed tomography. Ann Thorac Surg 73:1071-1075, 2002

48. Takashima S, Maruyama Y, Hasegawa M, et al: CT findings and progression of small peripheral lung neoplasms having a replacement growth pattern. AJR Am J Roentgenol 180:817-826, 2003

49. Kakinuma R, Ohmatsu H, Kaneko M, et al: Progression of focal pure ground-glass opacity detected by low-dose helical computed tomography screening for lung cancer. J Comput Assist Tomogr 28:17-23, 2004

50. Battafarano RJ, Meyers BF, Guthrie TJ, et al: Surgical resection of multifocal non-small cell lung cancer is associated with prolonged survival. Ann Thorac Surg 74:988-993, 2002

51. Daly RC, Trastek VF, Pairolero PC, et al: Bronchoalveolar carcinoma: Factors affecting survival. Ann Thorac Surg 51:368-376, 1991

52. McElvaney G, Miller RR, Muller NL, et al: Multicentricity of adenocarcinoma of the lung. Chest 95:151-154, 1989

53. Nadav Y, Pastorino U, Nicholson AG: Multiple synchronous lung cancers and atypical adenomatous hyperplasia in Li-Fraumeni syndrome. Histopathology 33:52-54, 1998

54. Sabloff BS, Truong MT, Wistuba II, et al: Bronchioalveolar cell carcinoma: Radiologic appearance and dilemmas in the assessment of response. Clin Lung Cancer 6:108-112, 2004

55. Volpino P, D'Andrea N, Cangemi R, et al: Bronchioloalveolar carcinoma: Clinical, radiographic, and pathological findings. Surgical results. J Cardiovasc Surg (Torino) 42:261-267, 2001

56. Volpino P, Cavallaro A, Cangemi R, et al: Comparative analysis of clinical features and prognostic factors in resected bronchioloalveolar carcinoma and adenocarcinoma of the lung. Anticancer Res 23:4959-4965, 2003

57. Ebright MI, Zakowski MF, Martin J, et al: Clinical pattern and pathologic stage but not histologic features predict outcome for bronchioloalveolar carcinoma. Ann Thorac Surg 74: 1640-1646, 2002

58. Fujimoto N, Segawa Y, Takigawa N, et al: Clinical investigation of bronchioloalveolar carcinoma: A retrospective analysis of 53 patients in a single institution. Anticancer Res 19:1369-1373, 1999

59. Tosi P, Sforza V, Santopietro R, et al: Bronchiolo-alveolar carcinoma: An analysis of survival predictors. Eur J Cancer 28A:1365-1370, 1992

60. Herbst RS, Sandler AB: Overview of the current status of human epidermal growth factor receptor inhibitors in lung cancer. Clin Lung Cancer 6:S7-S19, 2004 (suppl 1)

61. Perez-Soler R, Chachoua A, Hammond LA, et al: Determinants of tumor response and survival with erlotinib in patients with non–small-cell lung cancer. J Clin Oncol 22:3238-3247, 2004

62. Rusch VW, Appelman HD, Byhardt R, et al: Lung, in Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual. 6th ed. New York, Springer-Verlag, 2002, pp 167-181

63. Roberts PF, Straznicka M, Lara PN, et al: Resection of multifocal non-small cell lung cancer when the bronchioloalveolar subtype is involved. J Thorac Cardiovasc Surg 126:1597-1602, 2003

64. Goldstein NS, Mani A, Chmielewski G, et al: Prognostic factors in T1 NO MO adenocarcinomas and bronchioloalveolar carcinomas of the lung. Am J Clin Pathol 112:391-402, 1999

65. Sakurai H, Dobashi Y, Mizutani E, et al: Bronchioloalveolar carcinoma of the lung 3 centimeters or less in diameter: A prognostic assessment. Ann Thorac Surg 78:1728-1733, 2004

66. Furak J, Trojan I, Szoke T, et al: Bronchioloalveolar lung cancer: Occurrence, surgical treatment and survival. Eur J Cardiothorac Surg 23:818-823, 2003

67. Breathnach OS, Kwiatkowski DJ, Finkelstein DM, et al: Bronchioloalveolar carcinoma of the lung: Recurrences and survival in patients with stage I disease. J Thorac Cardiovasc Surg 121:42-47, 2001