**Objectives:** To review the current evidence on special issues relating to the diagnosis, imaging, prognosis, and treatment of bronchioloalveolar carcinoma (BAC).

**Methods:** This guideline focuses on aspects of BAC that are unique and ways in which BAC differs importantly from other forms of non-small cell lung cancer (NSCLC). The author reviewed published literature reporting on BAC using key words “histology,” “CT scans,” “fluorodeoxyglucose positron emission tomography scan,” “sensitivity,” “specificity,” “surgical resection,” “sublobar resection,” and “epidermal growth factor receptor tyrosine kinase inhibitor” and selected references from published review articles. Also included was a review of the 1999 World Health Organization (WHO) revised classification system for lung tumors, which established a more restrictive definition of BAC to tumors with a pure lepidic spreading pattern and no evidence of stromal, vascular, or pleural invasion.

**Results:** With the notable exception of a lower likelihood of a positive positron emission tomography finding in the presence of BAC, staging, diagnosis, and treatment are the same as for other histologic subtypes of NSCLC, but additional treatment options that may prove to be equivalent, if not more effective, for more patients exist (eg, epidermal growth factor receptor tyrosine kinase inhibitor therapy, sublobar resection).

**Conclusions:** BAC is a form of adenocarcinoma with unique clinical, radiologic, and epidemiologic features. The diagnosis of BAC should be reserved for tumors that meet the WHO criteria. Additional clinical trials are needed on this population of patients, using strict definitions and enrollment criteria to allow the results to be applied to appropriate patient populations.

(CHEST 2007; 132:306S–313S)

**Key words:** adenocarcinoma; bronchioloalveolar; cancer; epidemiology; guidelines; therapy

**Abbreviations:** BAC = bronchioloalveolar carcinoma; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; FDG = 18-F-deoxyglucose; NSCLC = non-small cell lung cancer; PET = positron emission tomography; PS = performance status; TKI = tyrosine kinase inhibitor; WHO = World Health Organization

Although descriptions of disease consistent with bronchioloalveolar carcinoma (BAC) appeared in the medical literature > 125 years ago,¹ the term *bronchioloalveolar carcinoma* was first applied by Liebow² in 1960 to describe peripheral, well-differentiated lung tumors that grew in a lepidic manner without distortion of the lung architecture. Subsequently, many pathologists and clinicians applied the BAC label in cases of adenocarcinoma with the presence of any significant degree of lepidic growth pattern within the tumor. Perhaps because of this, the apparent incidence of BAC increased dramatically, and some authors³,⁴ cited a prevalence of BAC among cases of non-small...
cell lung cancer (NSCLC) as high as 20 to 24%. Some reports attributed the increased prevalence of adenocarcinomas among all NSCLCs in part to the apparent increased rate of diagnosis of BAC. In 1999, the World Health Organization (WHO) published a revised classification system for lung tumors that established the more restrictive definition of BAC to tumors with a pure lepidic spreading pattern and no evidence of stromal, vascular, or pleural invasion. With this revised criteria, the prevalence of pure BAC among NSCLC case series using the revised classification is < 5%. Despite this lower prevalence, the unique pathologic and radiologic characteristics and unique response profile to targeted therapies make a separate consideration of BAC appropriate for this guidelines update.

**Materials and Methods**

The diagnosis, staging, physiologic evaluation, and treatment of NSCLC are thoroughly covered in other guideline chapters. Therefore, the clinical questions in this guideline were chosen to focus on areas in which there are important differences between BAC and other forms of NSCLC. These guidelines are restricted to patients with known or suspected “pure BAC” as defined in the 1999 WHO revised classification for lung tumors. This classification system requires that the term bronchioloalveolar carcinoma be reserved for a more narrowly defined histologic appearance of cells growing in a lepidic pattern with no stromal, vascular, or pleural invasion. Articles dealing with the prognosis, treatment, and positron emission tomography (PET) characteristics of BAC were chosen from literature searches. Many articles were selected for review on the basis of their presence in the bibliographies of initially selected papers. Meeting abstracts were searched from the last 5 years of meetings of the American Society of Clinical Oncology. Except when needed to illustrate differences over time, articles were chosen preferably when published after 1999 to reflect data using the most current WHO definition of BAC.

**Results**

*Are There Distinctive Clinical and Epidemiologic Features of Patients With BAC? Are There Prognostic Differences Between BAC and Other NSCLC Histologic Subtypes?*

Compared with patients who have other forms of lung cancer, patients with BAC are more likely to be nonsmokers (although smokers are at increased risk for all forms of lung cancer, regardless of histology) or have a minimal smoking history. The proportion of patients who have BAC and are female is closer to 50% and is higher than in other histologic types of lung cancer, and the occurrence of nodal spread and extrathoracic metastasis is much less than in other forms of NSCLC. The pathologic features that distinguish BAC from adenocarcinoma are discussed in the “Diagnostic Surgical Pathology in Lung Cancer” chapter and are not reiterated in detail here. Perhaps because of the recent history of the use of CT screening, particularly in Japan, there is a large body of literature emerging on small peripheral adenocarcinomas. One especially important report6 in 1995 subclassified 236 patients with small-diameter (< 2 cm) peripheral adenocarcinomas on the basis of the degree of stromal response or invasiveness associated with the proliferating carcinoma cells. As in most pathologic descriptions of adenocarcinoma since then, the majority of tumors were of a mixed subtype, with areas of lepidic (or bronchioloalveolar) patterns of growth mixed with areas of more solid, invasive tumors and/or a stromal fibrotic response. They found that patients with no or only minimal stromal response and no invasion (Noguchi type A or B, what would now be commonly referred to as pure BAC) had the most favorable prognosis, with a 100% 5-year survival rate among the 34 patients who met these criteria. Since this report, numerous studies7–21 have confirmed a more favorable prognosis for patients whose tumors have more prominent, or purely BAC, growth patterns relative to those with tumors that display a prominent stromal reaction or invasive components. While all these studies have found improved stage-specific survival in patients with BAC as compared with more invasive adenocarcinomas, not all have found a correlation between the percentage of tumor occupied by BAC histology and prognosis.22 Partly as a result of observations such as these, the WHO revised its classification system for lung tumors in 1999 and again in 2004, in each case reserving the BAC classification for tumors that demonstrate only lepidic growth patterns and have no evidence of stromal, vascular, or pleural invasion. Tumors that have a “solid” component but possess some areas of lepidic growth are considered adenocarcinomas with focal bronchoalveolar features and should not be included in series of pure BAC.23,24 Subsequent to the revised classification, Zell et al25 examined the survival of patients with BAC diagnosed before and after the revision (1985 through 2003) and demonstrated that the median survival of patients whose BAC was diagnosed after 1999 (53 months) was significantly greater than those whose BAC was diagnosed before 1999 (32 months). The authors25 concluded that the improved survival reflected the more restrictive definition of BAC, suggesting that the current definition selects patients with a more favorable prognosis compared with stage-matched patients with other histologic types of NSCLC. This same group26 subsequently confirmed the improved stage-specific survival of patients with BAC relative to “non-BAC” adenocarcinomas. These26 and other authors27 have advocated for a revised staging system for patients with BAC, revised criteria for surgical resection, or both.
It is important to note that the pattern of growth that characterizes BAC can be appreciated accurately only in large biopsy specimens. In fact, the 1999 WHO classification of lung tumors advocates that a final diagnosis of BAC can be rendered only on the basis of a surgical specimen. In patients with unresectable BAC, this presents pathologists and clinicians with a dilemma because the diagnosis of BAC may have implications for treatment choice (see recommendation 3). In such cases, the diagnosis should be made with caution or not at all on small biopsy specimens such as those obtained during bronchoscopy. This is especially true when the radiologic pattern of disease on CT scan is not consistent with pure BAC because many invasive adenocarcinomas have a leading edge of lepidic growth pattern that might suggest BAC. That this diagnosis has prognostic implications underscores the importance of patients' being evaluated in a multidisciplinary setting that includes pathologists, radiologists, oncologists, thoracic surgeons, and chest physicians.

**Recommendations**

1. **We recommend that the use of the term bronchioloalveolar carcinoma be reserved for lung cancers that meet the criteria established in the revised WHO classification system for lung tumors.** Grade of recommendation, 1B

2. **For patients with suspected BAC, we recommend that a surgical biopsy be used to establish a histopathologic diagnosis.** Grade of recommendation, 1C

*In the Absence of a Surgical Biopsy, Are There Characteristic Radiologic Patterns of Disease That Suggest the Presence of BAC?*

Because many patients with lung cancer are not candidates for surgery and the diagnosis of BAC may have prognostic implications, it is important to determine whether there are radiologic correlates that predict the histologic pattern. In the original description of BAC by Liebow, the characteristic patterns of radiologic disease noted in association with BAC were separated into one of three patterns: (1) a single focus of disease on a CT scan with ground-glass appearance or a nodule/mass containing prominent air-bronchograms, (2) multifocal lesions with the same appearance, or (3) dense pneumonic consolidation. In the context of trials examining low-dose helical CT scans for lung cancer screening and with the increased use of CT scans for diagnosing non-pulmonary disease, a field of literature examining the management of small, peripheral pulmonary nodules is newly emerging, and the Fleischner Society issued recommended guidelines for managing very small pulmonary nodules. One concept that is emerging from this body of literature is that of the nonsolid, “ground-glass” nodule, defined as a focal area of increased lung opacity that does not distort or obscure the underlying lung markings. Yang et al. found a strong correlation between ground-glass attenuation in a nodule and the presence of BAC in the corresponding histology. They examined high-resolution CT morphologic features of 59 small (diameter, 6 to 20 mm), surgically resected peripheral lung adenocarcinomas to determine the correlation between CT features and tumor growth pattern. Sixteen of 17 pure BAC tumors (94%) appeared as ground-glass attenuation. Ten of 14 tumors with a focal solid/invasive component appeared as heterogeneous nodules having both ground-glass and solid components on CT. All four of four entirely solid tumors appeared on CT as homogeneous nodules of soft-tissue attenuation. These authors concluded that CT patterns corresponded to the histopathologic findings of different tumor growth patterns. Two studies examined the prognostic significance of pure ground-glass attenuation in CT scans of a combined 179 patients and found that the presence of a significant ground-glass component is associated with reduced likelihood of lymph node metastasis and increased long-term survival. A second appearance that can be seen is the presence of a pneumonic consolidation. Many times, patients with the latter presentation are treated for presumed pneumonia, and the initial suspicion for BAC is not raised until radiologic follow-up fails to show any resolution. In most series, patients with a pneumonic pattern have a worse prognosis than single-focal or multifocal nodular patterns of BAC and frequently have complaints of bronchorrhea. Given that the current criteria for BAC mandate that the diagnosis be made only on examination of large (surgical) biopsy specimen, the appearance of a CT scan characteristic of BAC has important implications when patients are not surgical candidates. In the absence of a surgical biopsy, the diagnosis of BAC should be made only in patients with a compatible CT radiologic pattern, accompanied by a compatible histopathologic pattern on biopsy.

**Recommendation**

3. **For patients who are unable to undergo surgical biopsy, the diagnosis of BAC should be made only with compatible histopathologic pattern on transbronchial or core needle biopsy and a CT demonstrating a pure ground-glass or pneumonic appearance.** Grade of recommendation, 1C
Are There Important Differences in the Performance Characteristics (Sensitivity, Specificity, and Positive and Negative Predictive Values) of PET Scans Among Patients With BAC?

Whereas many studies have addressed the performance characteristics (sensitivity, specificity, and positive and negative predictive values) of 18-F-fluorodeoxyglucose (FDG) PET scanning for patients with known or suspected lung cancer, none has prospectively identified patients with BAC to determine separately the accuracy of FDG-PET for this subtype of NSCLC. Nevertheless, available data permit drawing some important conclusions about the utility of FDG-PET in the diagnosis and staging of BAC. In the most widely cited metaanalysis of PET scanning in NSCLC, Gould et al\textsuperscript{33} found a sensitivity of 96.8% and a specificity of 77.8% of FDG-PET for lung cancer. Higashi et al\textsuperscript{34} reported on 29 patients with 30 adenocarcinomas of the lung (7 BAC) using a semiquantitative measure of FDG uptake relative to the mediastinal blood pool. Of the 7 BACs, 4 showed negative results on FDG-PET, whereas only 1 of 23 non-BAC tumors showed a negative result. These authors\textsuperscript{34} also reported on quantitative measures of FDG uptake (standardized uptake value) and showed that the mean standardized uptake value of the patients with BAC (1.36 ± 0.821) was lower than that of well-differentiated adenocarcinomas (2.92 ± 1.28) and moderately differentiated adenocarcinomas (4.63 ± 1.86). Kim et al\textsuperscript{35} performed PET scans in 48 patients with lung cancer, 9 with BAC. The mean peak standardized uptake value for patients with BAC was again significantly lower than for other histologic subtypes (p < 0.001). The authors noted that BAC is a potential cause of false-negative findings of malignancy on FDG-PET scans and cautioned that FDG-PET scans should be interpreted in combination with high-resolution CT findings. Lowe et al\textsuperscript{36} prospectively enrolled 89 patients with solitary pulmonary nodules, 60 of which turned out to be malignant. Of five false-negative PET scan results in their study, one was BAC, three were squamous cell carcinoma, and one was a malignant melanoma.

One more retrospective review of a tumor registry by Heyneman et al\textsuperscript{37} during a 6-year period revealed 15 patients who had pathologically documented BAC and had PET scans. Nine of 15 patients in their study had positive PET scan results. The majority of false-negative results were in patients with focal BAC, as opposed to those with pneumatic pattern of disease, who, in this small study, were more likely to have positive PET scan results. Marom et al\textsuperscript{38} reported on FDG-PET findings of 192 patients with lung cancer ranging in size from 3 to 25 mm in diameter, 9 of whom had negative results on PET scan (ie, demonstrated low FDG uptake). Patients with small tumors, as well as those with carcinoid tumors and BAC, were more likely to have negative PET scan results. This and other studies\textsuperscript{34–36,39,40} confirm that BAC tumors are disproportionately represented in that group of lung cancers in which FDG-PET scan results are negative.

**Recommendation**

4. For patients whose CT scans show ground-glass attenuation or pneumonic consolidation (suggesting BAC), PET scans often show false-negative results, and therefore we recommend that a PET scan with negative results be followed by additional diagnostic testing to exclude the presence of cancer. Grade of recommendation, 1C

Is Lobectomy Necessary for All Patients With BAC?

As with other forms of NSCLC, surgery represents the “gold standard” of treatment in early stage disease. Patients with resected BAC have prolonged survival and a lower recurrence rate after surgical resection than those with other subtypes of NSCLC.\textsuperscript{41,42} The recognition of lower rates of regional lymph node spread in patients with small BAC tumors has led several groups of investigators\textsuperscript{20,43–46} to study the possibility that lesser resection could provide equivalent oncologic outcome in patients with pure BAC (Table 144–46,48,49,63). Ishiwa et al\textsuperscript{47} examined the presence of lymph node micrometastasis (by cytokeratin immunohistochemistry) in 54 patients with small peripheral carcinomas (< 2 cm). Of the 13 patients with pure BAC tumors, none had micrometastasis, as compared with 11 of 30 patients with non-BAC histology.

Several investigators have explored the use of wedge resection vs lobectomy in stage I disease. Koike et al\textsuperscript{48} reported on results of 233 patients with small (< 2 cm) peripheral lesions. All patients were believed to be suitable candidates for lobectomy but were offered limited resection (in a nonrandom manner); 159 patients opted for lobectomy, and 74 patients consented to more limited resection. Sixty patients underwent segmentectomy, and 14 patients underwent a wedge resection. After a mean follow-up of 52 months, there was no difference between the two groups in overall 3-year or 5-year survival rates or in the recurrence of tumor. No information was provided on histologic subtypes. Sakurai et al\textsuperscript{49} retrospectively examined the pathology of 108 patients with T1 adenocarcinomas resected between 1985 and 2002, using the revised WHO classification, and found 25 patients with pure BAC. The remaining patients had invasive adenocarcin-
None of the patients with pure BAC and 30 of 83 patients with adenocarcinoma had lymph node involvement at the time of surgery. The 5-year survival rates of the groups with BAC and adenocarcinoma were 100% and 63.5%, respectively. On the basis of these studies, there seems to be no disadvantage for a more limited resection when compared with lobectomy for patients with stage I BAC (particularly tumors ≤2 cm in size by CT).

As radiologic imaging continues to improve and gains wider use, detection of incidental BACs will increase. Wedge resection provides an ability to remove these lesions while maximally preserving lung function. Watanabe et al\(^{45,49}\) studied the role of wedge resection for patients with ground-glass opacities < 2 cm in diameter. When preoperative CT scans demonstrated a pure ground-glass nodule < 2 cm and intraoperative histology demonstrated pure BAC without evidence of stromal invasion, the patient underwent wedge resection (n = 48). Patients without pure BAC received “extended segmentectomy” with lymph node dissection (n = 20). During the same period, they performed lobectomy on 57 patients with stage IA NSCLC and tumors < 2 cm. There was no difference in clinical outcomes after a mean follow-up period of > 3 years.\(^{49}\)

Although these studies all were well done and provide a compelling rationale for sublobar resections of small peripheral ground-glass lesions, there are important limitations to the routine application of this practice. First, none of these studies reported on a prospectively randomized series of patients. Second, many (although not all) of these studies were conducted in the context of a systematic program of screening using low-dose helical CT, something that is yet to be proved effective in randomized studies and that is still controversial in most health systems. Finally, most of these data come from literature from a single country. Studies\(^{50}\) of the use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have raised the possibility of ethnic differences in the biology of lung cancer. These potential differences suggest the need to prove these results in more ethnically diverse populations before accepting lesser resections as a global standard of care.

**Recommendation**

5. In patients who have suspected BAC and are good surgical candidates, a sublobar resection may be appropriate, provided that the CT scan shows a pure ground-glass appearance, intraoperative pathologic consultation confirms pure BAC without evidence of invasion, and surgical margins are free of disease. Grade of recommendation, 1B

Is First-Line Therapy With EGFR-Targeted Agents Appropriate for Patients With Confirmed BAC?

The widely held view that BAC is less responsive to traditional cytotoxic chemotherapy derives largely from anecdotal experience. Although this may be true, it is not well documented in prospective series, partly because of the differing criteria used to define BAC in older series of patients. Older studies\(^{51,52}\) that examined the response rates of patients with
BAC to standard chemotherapy suggested similar response rates but longer overall survival, comparing BAC with other histologic subtypes. These studies\(^5\)\(^-\)\(^5\)\(^2\) predated both modern chemotherapy regimens and the revised WHO classification, raising questions about the applicability of these studies to present-day lung cancer management. Breathnach et al\(^5\)\(^2\) reported on 52 patients with stage IIIB and IV NSCLC, 28 of whom were designated as having BAC (by pre-1999 criteria) and reported longer survival times for patients with BAC as compared with non-BAC histologic types of NSCLC. However, they did not report chemotherapy response rates by histologic pattern, so no conclusions can be drawn about the relative response rates from this study.

More recently,\(^5\)\(^3\)\(^,\)\(^5\)\(^4\) agents that target the EGFR have entered clinical practice, and the results of these trials have improved our knowledge of the biology of lung cancer. One consistent feature of studies\(^5\)\(^5\)\(^-\)\(^5\)\(^7\) that use small-molecule TKI-targeting EGFR is that patients with BAC are disproportionately represented among those who respond to these agents, with some patients demonstrating profound and rapid responses.\(^5\)\(^6\) Therefore, an appropriate question is whether patients with unresectable BAC should be treated primarily with an EGFR-TKI as first-line therapy. One study\(^5\)\(^9\) examined gefitinib in the first-line setting for 37 nonsmokers with stage IIIB or IV adenocarcinomas (7 with pure BAC) and performance status (PS) of 0 to 2 (Eastern Cooperative Oncology Group [ECOG]). They observed a partial response in 25 patients (69%) and stable disease in 4 more (11%) but did not report on response by subtype. Another small study\(^6\)\(^0\) that examined gefitinib as first-line therapy for advanced NSCLC found response rates that varied by PS regardless of histology. Two of the 4 responders (of 22 total patients) had BAC, and the other 2 had adenocarcinoma. This study also found that the response rates were greater in patients with better ECOG PS. The largest study, by Shepherd et al\(^6\)\(^1\)\(^,\)\(^6\)\(^2\) enrolled 731 patients with stage IIIB or IV NSCLC and ECOG PS from 0 to 3. These patients had received one or two previous chemotherapy regimens and were randomly assigned to receive either erlotinib or placebo. The response rates were 8.9% in the erlotinib group and <1% in the placebo group (p < 0.001). Only nonsmoking status, adenocarcinoma histology, and EGFR expression were independent predictors of survival. There was no separate report of BAC subtype.\(^6\)\(^1\)\(^,\)\(^6\)\(^2\) Overall, although the high response rate of patients with BAC to EGFR-targeted TKIs raises the hope that this is an appropriate alternative to standard chemotherapy, there is little experimental proof of its superiority in patients with good PS. In addition, although it is tempting to conclude that patients with poorer PS should be treated with first-line EGFR-TKIs, we must recognize that these patients also have a lesser response to these agents.

**Recommendation**

6. For patients with good PS and unresectable BAC, we recommend the use of standard chemotherapy. The use of first-line EGFR-targeted agents should be reserved for patients with poor PS or those who are enrolled in clinical trials. Grade of recommendation, 2C

**Gaps in Research**

Is Primary Treatment With an EGFR Inhibitor More Effective and Less Toxic Than Standard Chemotherapy or Chemoradiation for Patients With Unresectable Disease? Randomized trials to compare first-line standard chemotherapy with first-line EGFR inhibitors for patients with good PS are needed.

Is Wedge Resection Sufficient for Patients With Small Peripheral BAC? Preliminary data from non-randomized studies in Japan are very encouraging. However, to be generalized, these should be the rationale for prospective studies that enroll highly selected patients who have pure ground-glass opacities of small size and are randomly assigned to lobectomy vs lesser resections if intraoperative pathology documents a pure BAC pattern.

**Conclusions**

BAC is a form of adenocarcinoma with unique clinical, radiologic, and epidemiologic features. Hints that the presence of BAC should be considered frequently come from findings of a pure ground-glass nodule or nodules on a CT scan. Alternatively, the presence of a pneumonic consolidation that does not respond to pneumonia therapy should raise BAC in the differential diagnosis. With the notable exception of a lower likelihood of positive PET scan results in the presence of BAC, staging, diagnosis, and treatment are the same as for other histologic subtypes of NSCLC, but some additional options that may prove to be equivalent, if not more effective, for more patients exist. Additional clinical trials that use strict definitions and enrollment criteria to allow the results to be applied to appropriate patient populations are needed.
SUMMARY OF RECOMMENDATIONS

1. We recommend that the use of the term bronchioloalveolar carcinoma be reserved for lung cancers that meet the criteria established in the revised WHO classification system for lung tumors. Grade of recommendation, 1B

2. For patients with suspected BAC, we recommend that a surgical biopsy be used to establish a histopathologic diagnosis. Grade of recommendation, 1C

3. For patients who are unable to undergo surgical biopsy, the diagnosis of BAC should be made only with compatible histopathologic pattern on transbronchial or core needle biopsy and a CT demonstrating a pure ground-glass or pneumonic appearance. Grade of recommendation, 1C

4. For patients whose CT scans show ground-glass attenuation or pneumonic consolidation (suggesting BAC), PET scans often have false-negative results, and therefore we recommend that a PET scan with negative results be followed by additional diagnostic testing to exclude the presence of cancer. Grade of recommendation, 1C

5. In patients who have suspected BAC and are good surgical candidates, a sublobar resection may be appropriate, provided that the CT scan shows a pure ground-glass appearance, intraoperative pathologic consultation confirms pure BAC without evidence of invasion, and surgical margins are free of disease. Grade of recommendation, 1B

6. For patients with good PS and unresectable BAC, we recommend the use of standard chemotherapy. The use of first-line EGFR-targeted agents should be reserved for patients with poor PS or those who are enrolled in clinical trials. Grade of recommendation, 2C

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