Radiographic Imaging of Bronchioloalveolar Carcinoma: Screening, Patterns of Presentation and Response Assessment

David R. Gandara, MD,* Denise Aberle, MD,† Derick Lau, MD, PhD,‡ James Jett, MD,‡ Tim Akhurst, MD, PhD,§ James Mulshine, MD,|| Christine Berg, MD,¶ and Edward F. Patz, Jr, MD#

Abstract: Bronchioloalveolar carcinoma (BAC) is a previously uncommon subset of adenocarcinoma with unique epidemiology, pathology, radiographic presentation, clinical features, and natural history compared with other non-small cell lung cancer (NSCLC) subtypes. Classically, BAC demonstrates a relatively slow growth pattern and indolent clinical course. However, in a subset of patients, rapid growth and death from bilateral diffuse consolidative disease occurs within months of diagnosis or recurrence. Recent data suggest that the incidence of BAC is increasing, notably in younger nonsmoking women. The initial radiographic presentation of BAC varies considerably, from single ground glass opacities (GGOs) or nodules of mixed ground glass and solid attenuation to diffuse consolidative or bilateral multinodular disease. The rising incidence of BAC is also reflected in recent lung cancer screening studies employing helical computed tomography (CT), where the differential diagnosis of GGOs includes not only BAC and overt adenocarcinoma, but inflammatory disease, focal fibrosis, and atypical adenomatous hyperplasia. Because advanced-stage BAC presents as measurable mass lesions in fewer than 50% of cases, determination of radiographic response to therapy by standard criteria is often difficult. Here, we review current data regarding the radiographic imaging of BAC: its radiographic presentations in asymptomatic early-stage and in advanced-stage disease, the functional imaging characteristics of BAC, and challenges of response assessment, including evolving opportunities for computer-assisted image analysis.

(J Thorac Oncol. 2006;1: S20–S26)

Bronchioloalveolar carcinoma (BAC) is a previously rare pathologic subtype of adenocarcinoma that seems to be steadily increasing in incidence. In one report, BAC rose fourfold during the period of 1955 to 1990.1 Compared with other subtypes of non-small cell lung cancer (NSCLC), BAC is characterized by a distinct clinical presentation, radiographic appearance, and natural history.2 Further distinguishing BAC from other types of NSCLC is a higher percentage of women, a younger age distribution, and a higher incidence in never-smokers.2 These differences raise the question of whether BAC represents a separate entity with an epidemiology distinct from that of other NSCLCs. In support of this concept are marked similarities between BAC and ovine pulmonary adenomatosis in sheep, caused by the Jaagsiekte retrovirus.3 Whether the clinical course of BAC is different in the various histologic subsets (pure BAC, mucinous or non-mucinous; BAC with invasion; and adenocarcinoma with BAC features) remains controversial.4 Within the context of this review, the term BAC is used to encompass all histologic subtypes.

OBSERVATIONS OF EARLY-STAGE BAC FROM COMPUTED TOMOGRAPHY SCREENING TRIALS

Data from several observational trials with computed tomography (CT) screening are providing insights into CT screening efficacy as well as reshaping our notions of the morphology of early-stage lung cancer. At prevalence CT, the rate of detection of noncalcified lung nodules of any size varies from 5.1 to 51.4%, with the positive predictive valle varying from 0.02 to 0.12.5–12 The rates of new lung nodule detection decrease at incidence screens. Two observational trials have found that lung cancer detection is increased three- to fourfold with CT relative to chest radiography.6,9 Overall, CT detects smaller and more peripheral lung cancers, with selective oversampling of adenocarcinoma by two- to threefold.6–12 In Japanese population-based screening trials, CT-detected lung cancers have been observed with high or equal frequency in never-smokers relative to current or former smokers, although information about secondhand smoke is incomplete.8,11 Among never-smokers, BAC comprises up to 90% of the cancers.8

*University of California Davis Cancer Center, Sacramento, CA; †David Geffen School of Medicine at UCLA, Los Angeles, CA; ‡Mayo School of Medicine, Rochester, MN; §Memorial Sloan Kettering Cancer Center, New York, NY; ||Rush University Medical Center, Chicago, IL; *National Cancer Institute, Bethesda, MD; and #Duke University Medical Center, Durham, NC.

Address for correspondence: David R. Gandara, MD, Department of Internal Medicine, Hematology/Oncology Cancer Center UC Davis Medical Center, Sacramento, California 95817. E-mail: david.gandara@ucdmc.ucdavis.edu

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ISSN: 1556-0864/06/0109-0020
Early focal BAC or adenocarcinoma has three morphologic appearances on CT: 1) pure ground glass (GGO)/nonsolid, appearing as hazy increased attenuation that does not obscure the underlying bronchovascular markings; 2) solid, in which the nodule attenuation completely obscures the underlying bronchovascular markings; and 3) mixed/semisolid, having both GGO and solid components.\textsuperscript{13,14} These three appearances on CT correspond roughly to a biological range extending from benign lesions or BAC at one end to invasive adenocarcinoma at the other.

Pure focal GGO can represent both malignant and benign conditions, including focal inflammation, organizing pneumonia, focal fibrosis, aryl hydrocarbon hydroxylase, and adenocarcinoma (Figure 1). When malignant, pure GGOs tend to represent a more biologically indolent neoplasm that corresponds to the lower grades of the Noguchi classification\textsuperscript{15–18} or to atypical adenomatous hyperplasia. Lesion size roughly portends increasing histologic grade and biological aggressiveness. Lesions larger than 1 cm are more commonly malignant,\textsuperscript{19,20} particularly if they persist for several months or increase in size on serial assessment, as discussed below.

Lesions of mixed attenuation, in which there is a solid component within the GGO nodule, suggest increasing biological virulence. BAC exhibits a purely lepidic growth component within the GGO nodule, suggesting increasing biological aggressiveness. Lesions larger than 1 cm are more commonly malignant,\textsuperscript{19,20} particularly if they persist for several months or increase in size on serial assessment, as discussed below.

Lesions of mixed attenuation in which there is a solid component within the GGO nodule, suggest increasing biological virulence. BAC exhibits a purely lepidic growth pattern with proliferation of cells along the alveolar walls absent stromal, vascular, or pleural invasion. Radiographic–pathologic correlations have shown that with pure BAC lesions having mixed attenuation on CT, the solid component corresponds to areas of structural collapse of alveoli.\textsuperscript{21,22} Mixed lesions may also represent BAC with small invasive foci and fibroblastic proliferation (Noguchi type C lesions or mixed adenocarcinoma with BAC component), so the observation of a solid component increases the level of suspicion for invasive adenocarcinoma. The relative size of the solid component, or central fibrosis, seems to be an independent prognostic indicator of tumor biology and correlates with histologic factors of vascular invasion and lymph node involvement as well as survival.\textsuperscript{23,24}

With pure GGO or mixed-attenuation lesions, evolving features on serial CT that suggest malignancy are: (a) an overall increase in size of a GGO, (b) development of a solid component within a GGO, or (c) an increase in the solid component of a mixed-attenuation lesion\textsuperscript{20,25} (Figure 2); these changes should generally prompt histologic sampling. Finally, coarse spiculation is also observed with higher frequency among malignant than benign nodules; in fact, spiculation is reported to portend findings of lymph node metastases and vascular invasion, and significantly predicts worse survival in patients with adenocarcinoma.\textsuperscript{26,27}

Table 1 provides some perspective on the degree of overlap that exists between CT features, the World Health Organization (WHO) classification of lung cancers, and the Noguchi classification of adenocarcinomas.\textsuperscript{15,28} Although CT features demonstrate a logical trend from less to more biologically aggressive, overlap between categories of lung cancer type (and prognosis) exist, and CT alone is insufficient to partition lesions into meaningful biological strata.

Although the majority of these CT data on BAC derive from Japanese screening trials, a higher than anticipated proportion of BAC histology has also been observed in CT screening trials in the United States.\textsuperscript{29,30} For example, the Mayo Spiral CT Screening Trial has detected lung cancer in 66 patients over a 4-year period.\textsuperscript{29} Of these, 12 (18%) were BAC and 26 were adenocarcinoma. Of BAC, seven cases appeared as pure GGOs, three had mixed attenuation, and two were solid. The greater proportion of BAC identified by CT screening in asymptomatic individuals is in variance with findings from the Surveillance, Epidemiology and End Results program administered by the National Cancer Institute, in which review of data collected during two decades (1979–1998) suggests that although BAC is increasing in incidence, it continues to represent only 4% of all NSCLC.\textsuperscript{31} Focal GGOs are not visible on chest radiography by virtue of their low attenuation; as such, CT screening may be identifying a reservoir of preclinical lesions that will force revisions in the prevalence and incidence data on BAC.

**THE POTENTIAL FOR OVERDIAGNOSIS OF BAC**

Overdiagnosis refers to a lung cancer that would not lead to an individual’s death because of slow growth rate and competing age-related risks for death. In the original Mayo Lung Project, Fontana et al\textsuperscript{32} observed 206 lung cancers in the screened group, but only 160 cancers in the control group. They found a significantly better 5-year survival for the screened group compared with the control group; however, there was no difference in lung cancer mortality between the two groups. Accordingly, 46 excess cancers were diagnosed in the screened group compared with the control group, representing a roughly 25% increase. Long-term follow-up studies by Marcus et al\textsuperscript{33} have continued to show a survival...
benefit for the intensely screened group, with no significant mortality benefit. Although controversial, one generally accepted reason for this difference is overdiagnosis of lung cancer. Calculation of average lung cancer volume-doubling times (VDT) may assist in addressing the issue of overdiagnosis. Most reports suggest VDTs in the 100- to 300-day range for NSCLC based on differences in measured tumor diameters over time. In a report by Usuda et al.,34 86 adenocarcinomas had a geometric mean VDT of 163 days. Yankelevitz et al.35 analyzed the results of the Mayo Lung Project and the Memorial Sloan Kettering Cancer Center Screening trial, noting a mean VDT of 101 days in the Mayo study and 144 days in the Memorial study. Only 4 of 87 cancers in those two trials had VDTs of more than 400 days. With a VDT of 400 days, a 3-mm-diameter lesion would require 7.7 years to increase in size to 15 mm in diameter. The authors opined that a VDT of over 400 days would be consistent with overdiagnosis.

Screening CT may potentiate the risk of overdiagnosis, particularly in population-screening programs ongoing in Japan, in which half of the reported lung cancers occur in nonsmoking females and are stage I BAC or well-differentiated adenocarcinomas. These cancers seem to have a distinctively different biological behavior than cancers that are diagnosed in smokers. Recently, 82 lung cancers were detected during a 3-year period in a Japanese mass screening program using helical CT. Serial CT scans in 61 cancers permitted estimates of VDT.36 Cancers were classified into three different types. The mean VDT of GGO lesions was $813 \pm 375$ days, mean VDT of mixed-attenuation lesions was $457 \pm 260$ days, and mean VDT of solid lesions was $149 \pm 125$ days, the latter being more typical of lung cancers detected by earlier chest radiography screening trials. Among the 61 cancers, 31 (50%) had VDTs of more than 340 days, and 90% of these were invisible on chest radiographs, reflecting the high proportion of biologically indolent neoplasms...

TABLE 1. Comparisons Between the World Health Organization and Noguchi Classifications of Lung Cancer and Computed Tomography Appearances

<table>
<thead>
<tr>
<th>World Health Organization 1999</th>
<th>Noguchi</th>
<th>Computed Tomography morphology</th>
<th>Lymph Node involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAH, atypical adenomatous hyperplasia; BAC, bronchioloalveolar cell carcinoma; GGO, ground glass opacity.</td>
<td></td>
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<tr>
<td>Pure BAC, mucinous and nonmucinous</td>
<td>A = Localized</td>
<td>Pure GGO</td>
<td>No</td>
</tr>
<tr>
<td>B = Alveolar collapse</td>
<td>Pure GGO</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Mixed adeno + BAC</td>
<td>C = Fibroblast proliferation</td>
<td>↑ Solid component</td>
<td>Yes</td>
</tr>
<tr>
<td>D = Poorly differentiated</td>
<td>↑↑ Solid component</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>E = Tubular</td>
<td>F = Papillary</td>
<td></td>
<td></td>
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</tbody>
</table>

FIGURE 2. Axial chest CT images from scans obtained 18 months apart in a 70-year-old male with a formerly heavy smoking history. (A) Baseline image shows a poorly circumscribed 18-mm-diameter nodule of mixed attenuation containing GGO with a small, central, solid component (arrow). There is an additional subtle area of pure GGO visible posteriorly. (B) At 18 months, the solid and GGO components of the nodule have increased. A corresponding FDG-PET scan was negative. At resection, this proved to be an adenocarcinoma with mixed bronchioloalveolar and invasive features, well differentiated. The posterior GGO was focal fibrosis. Lymph node dissection was negative for neoplasm.
that are CT detected. Twenty-seven adenocarcinomas had a VDT of more than 450 days, of which 12 had a VDT of more than 730 days. By the standard proposed by Yankelevitz et al., 27 (33%) of these 82 cancers would be considered overdiagnosis. Several low-grade BAC lesions of GGO attenuation have also been observed in the current Mayo CT screening trial during a 3.5- to 4.5-year period, raising the question of whether surgical resection is always the required or appropriate treatment. More data on the biological behavior of these lesions are needed.

**IMAGING FEATURES OF ADVANCED BAC**

In patients presenting outside the setting of lung cancer screening, BAC presents a spectrum of radiographic features, ranging from unifocal to multifocal disease (Figure 3). One classification divides the radiographic spectrum of BAC into three patterns: solitary nodules or masses, localized consolidation, and multicentric or diffuse disease. Roughly 40% of BAC have historically presented as a solitary nodule or mass. These nodules share the features described above for screening-detected BAC, although rarely, cavitation is observed; more commonly, GGO or solid lesions will contain discrete bubble-like luencies or pseudocavitations, corresponding pathologically to patent bronchioles or air-containing spaces within neoplastic glands. About 30% of cases of BAC present with localized consolidation containing air bronchograms that may simulate pneumonia. This pattern is most typical of mucinous BAC. On contrast-enhanced CT, the consolidation is usually of lower attenuation than chest-wall soft tissues because of mucin production, enabling visualization of normally enhancing pulmonary vessels within the consolidation termed the CT angiogram sign. Multicentric disease, consisting of multiple bilateral nodules or consolidations, is observed in about 30% of patients and is associated with a worse prognosis than is localized disease. Associated findings in BAC may include pleural effusions (1–10%), atelectasis (3%), and, rarely, pneumothorax. Hilar or mediastinal lymphadenopathy and distant metastases are features of invasive adenocarcinoma with BAC features.

**METABOLIC IMAGING WITH POSITRON EMISSION TOMOGRAPHY**

Although CT provides inferential information based on exquisite morphologic detail about the biological behavior of BAC, positron emission tomography (PET) using $^{18}$F fluoro-doxy-D-glucose (FDG) has gained wide acceptance as a means of distinguishing benign from malignant lung lesions based on the premise of higher glucose metabolism of malignant tissues. The peak standardized uptake value (SUV) is calculated as a semiquantitative measure of increased FDG uptake within an area of FDG accumulation.

Although data for BAC are limited to small series, a number of independent investigators have shown a high false-negative rate of FDG-PET for identifying pure BAC, particularly when focal, relating to relatively slow proliferation rates and the well-differentiated nature of the tumor. Higashi et al. observed negative FDG-PET scans in four (57%) of seven patients with BAC. Similarly, significantly lower peak SUVs were found in nine patients with solitary BAC relative to the SUVs of 39 patients with other types of lung cancer. Heyneman and Patz studied 15 patients with BAC, eight with solitary disease, and seven with multifocal disease. Only 38% of patients with solitary BAC had a positive PET scan, whereas 86% of patients with multifocal disease had a positive scan. FDG uptake has also been shown to correlate with prognosis, especially in adenocarcinoma, in which a high SUV correlates with poorer survival.

Limited data regarding incorporating FDG-PET into lung cancer screening suggest that patients with a focal pulmonary abnormality by conventional imaging studies and a negative PET scan can be observed closely to determine interval growth or resolution of the lesion. BAC should be considered in focal lesions that persist on follow-up CT scans, independent of FDG-PET scan results, and histologic sampling should be considered. Malignant neoplasms (including BAC) that are negative on PET are likely to be well differentiated, exhibit an indolent biology, and have little propensity for regional lymphadenopathy or metastases. The ultimate impact of surveillance of these lesions with CT to determine growth rate is unknown.

**RESPONSE ASSESSMENT TO THERAPY AND COMPUTER-ASSISTED IMAGE ANALYSIS**

Response rate is one of the most important endpoints for assessing the efficacy of antineoplastic treatments. Standardized methods for assessing response, such as those developed by the WHO, have been in place for many years and are typically applied in clinical trials evaluating new therapeutic agents.
agents, as well as in daily oncologic practice. These systems classify cancer lesions as measurable, nonmeasurable, or evaluable based on their imaging appearances. Until recently, the greatest perpendicular bidimensional measurements of a lesion had been considered optimal for basing determination of response. In 1999, the National Cancer Institute (NCI) proposed a modified system known as Response Evaluation Criteria for Solid Tumors (RECIST), which requires only the longest unidimensional diameter of tumor size. Although this system simplifies response assessment and has been shown to correlate equally well with patient outcomes in comparison with bidimensional measurements, there remains a high degree of observer variability. In one study of 33 patients in which lung cancers more than 1.5 cm were independently evaluated by five radiologists, bidimensional and unidimensional measurements were determined on CT scans according to WHO and RECIST criteria. Analysis of variance showed a significant difference among the readers in the measurements of lung nodules. In this study, the probability of misclassifying a tumor as progression ranged from 30 to 43%.

Another shortcoming of RECIST is that treatment response by anatomic criteria may not accurately reflect the positive impact of therapy in some cancers, either for reasons of nonmeasurable disease or because therapy may induce growth arrest, which does not necessarily translate into diminished lesion size. Thus, in some cases, there may be a divergence of response rate by RECIST or WHO criteria from survival benefit. The former problem is particularly applicable to multifocal BAC presenting as pneumonic consolidations or micronodular lesions. A recent clinical trial conducted by the South West Oncology Group (SWOG), S0126, evaluated the efficacy of gefitinib, an epidermal growth factor receptor inhibitor, in patients with advanced-stage BAC. Approximately 50% of the patients presented on chest CT with diffuse lesions that were not measurable by RECIST criteria (Table 2).

Computer-assisted image analysis (CAIA) offers considerable potential for overcoming the limitations of RECIST in analyzing CT image data of patients with BAC and other hard-to-measure cancers; investigations of such systems by several research teams are underway. Here, we summarize results achieved to date by Lau et al evaluating CAIA in patients in the S0126 SWOG trial. As described above, BAC is a good clinical model for testing CAIA because of the high incidence of nonmeasurable lesions. To the extent possible, CAIA was compared with RECIST for the endpoints of response and was also correlated with progression-free and overall survival.

The methodology for this first-generation CAIA, based on the principles of measuring optical density or grayscale attenuation in pixels has been presented elsewhere and is summarized briefly here. CT scans from 78 patients were submitted as high-quality films, digitized with a laser film digitizer, processed by an algorithm, and submitted to mathematical calculation of two- and three-dimensional size.

To demonstrate the applicability of this CAIA program, an example of patient response to gefitinib is shown in pre- and posttreatment CT scans (Figure 4). The two-dimensional tumor size before treatment was 123 (Figure 4A); after treatment, it was 86 (Figure 4B), representing a 30% decrease. Using this method, treatment response to gefitinib in 78 advanced-stage BAC patients enrolled in S0126 was determined (Table 3). Whereas these preliminary data provide the basis for further evaluation of CAIA in response assessment of BAC and other solid tumors, this first-generation methodology involves multiple manual steps, and there are technical hurdles in standardization of

<table>
<thead>
<tr>
<th>Radiographic Features</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidations</td>
<td>45 (40%)</td>
</tr>
<tr>
<td>Mass/consolidations</td>
<td>32 (32%)</td>
</tr>
<tr>
<td>Nodule ≥1 cm</td>
<td>22 (20%)</td>
</tr>
<tr>
<td>Nodule &lt;1 cm</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Total</td>
<td>111 (100%)</td>
</tr>
</tbody>
</table>

FIGURE 4. CT images showing pretreatment (A) and posttreatment (B) responses to gefitinib in a patient in the S0126 SWOG trial using the CAIA program. The two-dimensional tumor size before treatment was 123; after treatment, it was 86, representing a 30% decrease. Using this method, treatment response to gefitinib in 78 advanced-stage BAC patients enrolled in S0126 was determined (Table 3). Whereas these preliminary data provide the basis for further evaluation of CAIA in response assessment of BAC and other solid tumors, this first-generation methodology involves multiple manual steps, and there are technical hurdles in standardization of
Table 3. Response by CAIA in Patients on the SWOG S0126 Trial

<table>
<thead>
<tr>
<th>Responses</th>
<th>Number of Patients</th>
<th>Percentage of Total Patients</th>
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<tbody>
<tr>
<td>Complete response</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Partial response</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Complete response + partial response</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>Stable disease</td>
<td>27</td>
<td>35</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>34</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>78</td>
<td>100</td>
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</table>

FUTURE DIRECTIONS

Although FDG-PET complements conventional noninvasive imaging, FDG remains a relatively nonsel ective imaging agent for lung cancer and, specifically, BAC. However, PET does provide a paradigm for tumor imaging by transcending traditional anatomic approaches. It therefore has the potential to elucidate specific metabolic properties of the tumor. Several experimental studies in this area are just beginning to demonstrate the potential of molecular imaging in the classification of tumors by exploiting imaging patterns to produce a noninvasive tumor profile. This molecular imaging description of a cancer can provide significant diagnostic and prognostic information, enabling better prediction of tumor biology and determination of the appropriate therapeutic regimen. As we gain greater sophistication with targeted imaging agents for PET and other modalities such as magnetic resonance imaging, multimodality imaging that integrates morphologic- and physiologic-feature analysis will become a mainstay in oncologic diagnosis and response assessment.

Additional progress in response assessment will necessarily entail close coordination between all participants in the multidisciplinary arena of oncology: basic scientists, informaticians, clinician scientists, and radiologists. The ability to compare data across trials will require greater standardization of the vocabulary of radiographic response assessment, reporting guidelines, and agreement on the standards for image acquisition, storage, and transmission. These standards are predicated on the specific interpretation tasks, including the determination of metabolic alterations, contrast uptake characteristics, texture analyses, and how advanced CT, magnetic resonance, and PET instrumentation can best provide that data. In addition, the necessary resources for imaging research must be created and maintained, including the development of imaging data repositories enriched with clinico-pathologic and molecular data to support prospective research in the rapidly evolving field of oncology pharmacogenetics.

ACKNOWLEDGMENTS

Supported in part by the International Association for the Study of Lung Cancer (IASLC).

REFERENCES


