Controversy about Small Peripheral Lung Adenocarcinomas: How Should We Manage Them?

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Abstract: In recent years, the clinical use of high-resolution computed tomography has greatly advanced the diagnosis of small lesions of the peripheral lung. Such small lesions are often associated with ground-glass opacity in computed tomography findings. The noninvasive bronchioloalveolar carcinoma component with a replacement growth pattern of alveolar lining cells manifests as ground-glass opacity. Bronchioloalveolar carcinoma is classified as a subset of lung adenocarcinoma, but has a distinct clinical presentation, tumor biology, and favorable prognosis. Most small peripheral lung lesions including bronchioloalveolar carcinoma putatively originate from the peripheral airway epithelium, in which the epidermal growth factor receptor gene is frequently mutated. As with other subsets of non-small cell lung cancer, surgical resection is a potentially curative treatment. For the ground-glass opacity type of tiny lesions, particularly those less than 1 cm in their greatest dimension, the question has been raised whether lobectomy is really needed. Although several authors in Japan suggest the suitability of limited resection including segmentectomy and wedge resection without any nodal dissections for these small lung adenocarcinomas, this procedure should be validated in future clinical trials.

Key Words: Atypical adenomatous hyperplasia, Bronchioloalveolar carcinoma, Ground-glass opacity.

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The use of recently developed methods of radiographic investigation, particularly low-dose helical computed tomography (CT) for lung cancer, has increased the detection of small lesions in the peripheral lung.[1,2] Ground-glass opacity (GGO) is a finding on CT images of the lung that is usually nonspecific and may be found in many kinds of pulmonary disease, such as inflammation, bleeding, pulmonary lymphoproliferative disorder, atypical adenomatous hyperplasia (AAH), bronchioloalveolar carcinoma (BAC), and well-differentiated adenocarcinoma.[3,4] When focal GGO persists after observation over several months, early adenocarcinoma or BAC is highly suspected.[5] In the revised World Health Organization (WHO) histologic classification, BAC is classified as a noninvasive carcinoma with no evidence of stromal, vascular, or pleural invasion.

Although the therapeutic results for lung cancer are unsatisfactory, good results have been obtained in patients with stage I cancer. Recently, it was reported that annual spiral CT screening can detect lung cancer that is curable in a large collaborative study that screened more than 30,000 asymptomatic persons.[6] The screening resulted in a diagnosis of 412 clinical stage I lung cancer, and the estimated 10-year survival rate was 88%. Although lobectomy with mediastinal lymph node dissection is considered to be appropriate surgical procedure for T1 N0 M0 non-small cell lung cancer (NSCLC), it is not certain whether lobectomy is really needed for the GGO type of such small lesions. Furthermore, it is also not known whether pulmonary resection is really necessary for such small lesions.

To manage and treat this growing entity of small lung adenocarcinoma, it is necessary to understand the features of these tumors. This article reviews the current information on the histopathology, tumor biology, natural history, radiographic findings, and surgical treatment of early-stage peripheral lung adenocarcinomas.

HISTOPATHOLOGY

Most small lesions of the peripheral lung that are not detectable on chest radiographs are diagnosed pathologically as focal BAC or AAH, a precancerous lesion.[5,7] In contrast, small lung lesions detected on chest radiographs include squamous cell carcinomas and poorly differentiated adenocarcinomas, which form solid nodules.

In the study of stage I adenocarcinomas less than 2 cm in diameter by Noguchi et al.,[8] patients with pure BAC (Noguchi type A) and BAC with foci of structural collapse of alveoli (Noguchi type B) had a better 5-year survival rate (100%) than patients with foci of active fibroblastic proliferation (Noguchi type C, 75% survival rate) or pure adenocarcinoma (Noguchi types D–F, 52% survival rate). These findings greatly influenced the 1999 WHO/International Association for the Study of Lung Cancer Classification Panel, which proposed a new, stricter definition of BAC

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that required it to show pure lepidic growth without invasion of stroma, pleura, or blood vessels.[7]

Liebow[9] first reported BAC in 1960, describing the tumor as a well-differentiated adenocarcinoma with neoplastic cells spreading along alveoli, but with little stromal reaction, no invasion, and preservation of alveolar structure. According to the WHO criteria, BAC is a carcinoma in situ, and a tumor cannot be classified as a BAC if it is associated with lymphatic or systemic metastases. BAC is classified further into nonmucinous (60%–80%) and mucinous (20%–40%) types. Nonmucinous BAC is associated with proliferation of Clara cells, nonciliated bronchial epithelium, or type II pneumocytes. Histologic findings in mucinous BAC include goblet cells or mucin-producing columnar tumor cells. Tumors with BAC features and areas of invasion are classified as adenocarcinomas of mixed subtypes, and there is evidence that the presence of any BAC features predicts improved survival compared with pure adenocarcinoma.[7,8,10–13] However, it is still controversial whether a greater proportion of BAC features is a better predictor of survival than is a lower proportion of BAC features

Diagnosing BAC requires histologic examination for the presence or absence of invasion. Cytology is inadequate for the diagnosis of BAC. The sensitivity and specificity of cytology for the diagnosis have not been reported. For similar reasons, frozen section diagnosis of BAC, which involves examining a small portion of the tumor, is probably unreliable. Therefore, diagnosis usually depends on the radiographic findings, which correlate closely with the pathologic diagnosis in the decision of treatment options including surgery.

Another major change in the WHO classification in 1999 was the addition of AAH as a precursor lesion for lung adenocarcinoma. This was preserved in the 2004 WHO classification. AAH is a solitary alveolar lesion, usually less than 5 mm in diameter, accompanied by proliferation of type II pneumocyte-like or Clara cell-like cells with varied cellular atypia.[7] Some lesions may exhibit foci of increased atypia that may warrant a diagnosis of BAC. Moreover, AAH lesions are seen occasionally in the periphery of indisputable adenocarcinoma. Miller et al.[14] suggested that AAH might be analogous to adenomatous lesion of the colon, and subsequent studies have supported this hypothesis.[15,16]

TUMOR BIOLOGY

Compared with other subtypes of NSCLC, little is known about the biology of AAH and BAC. According to the adenoma–carcinoma sequence, originally proposed in colon cancer, at least one type of lung adenocarcinoma is supposed to develop from AAH through BAC to adenocarcinoma. This hypothesis is based on the findings that foci of AAH and BAC are found frequently in association with adenocarcinoma and that genetic mutations and chromosomal abnormalities accumulate sequentially in samples of AAH, BAC, mixed BAC, and adenocarcinomas.[17,18]

Although *p53* is altered frequently in lung adenocarcinoma, this gene is mutated infrequently in BAC. Only less than 14% of BAC tumors harbor *p53* mutations, compared with 53% of non-BAC adenocarcinomas.[12,19,20] Nakanishi et al.[21] found that survivin was expressed in all 40 BAC tumors examined, compared with just 9% of low-grade AAHs. This implies a resistance to apoptotic signaling in BAC compared with AAH. Overexpression of *HER2* is common in BAC and non-BAC adenocarcinomas.

Epidermal growth factor receptor (EGFR) is frequently overexpressed and aberrantly activated in NSCLC. Originally, *EGFR* mutations were predominantly found in females, nonsmokers, adenocarcinomas, and Asian patients.[22,23] In terms of morphologic and pathologic features, we found that the *EGFR* gene mutations predominantly occur in adenocarcinomas originated from the peripheral airway epithelium.[24,25] Interestingly, some AAH occasionally harbor *EGFR* mutations, suggesting that *EGFR* mutations occur relatively early in pathogenesis.[24]

Activating *K-ras* mutations were the most extensively investigated genetic alterations in AAH, and the frequency of *K-ras* mutations was 15% to 50%.[15] A series of analysis in AAH, BAC, and adenocarcinoma detected *K-ras* mutations in 27% of AAH, 17% of BAC, and 10% of invasive adenocarcinomas,[26] suggesting that this is an initiating event in lung tumorigenesis. In agreement with other reports, *EGFR* mutations never occur in tumors with *K-ras* mutations.

At present, although genetic alterations of *p53*, *EGFR*, and *K-ras* seem to be associated with the progression from AAH through BAC to adenocarcinoma in the lung, they may not be indicators of treatment strategy for lung cancer. It would be a desirable goal to determine the molecular lesions that could serve as an indication for limited pulmonary resection.

Patients with NSCLC sometimes show a dramatic response to EGFR tyrosine kinase inhibitors such as gefitinib and erlotinib. Investigators have found that mutations in the tyrosine kinase domain of the *EGFR* gene correlate with the response to EGFR tyrosine kinase inhibitors.[22,23] Amino acid substitutions or deletions in exons 18, 19, and 21 were found in 80% of responders to gefitinib compared with 12% of nonresponders.[27] The observation that *EGFR* mutations seem to occur relatively early in pathogenesis is closely associated with reports that gefitinib sensitivity is high in patients with adenocarcinomas with BAC features.[28] In clinical trials evaluating the use of gefitinib in advanced-stage chemotherapy-refractory NSCLC, objective clinical responses were seen in 38% of patients with BAC compared with 8% of patients with non-BAC adenocarcinomas.[28]

NATURAL HISTORY OF SMALL LUNG LESIONS WITH GGO

An important issue is the management of small cancers, especially those showing pure GGO as the dormant lesion. Among patients diagnosed as Noguchi type A, which has a 100% 5-year survival rate, those who did not need resection might be included in the subgroup. Although it has been suggested that the adenoma–carcinoma sequence also applies to tumorigenesis in adenocarcinoma of the lung, no persuasive data have been presented on the percentage of the

