Surgery for Bronchioloalveolar Carcinoma and "Very Early" Adenocarcinoma: An Evolving Standard of Care?

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Abstract: Lobectomy and mediastinal lymph node dissection is the standard surgical management of early stage non-small cell lung cancer (NSCLC) because more limited resections have been associated with a higher risk of local recurrence. Nevertheless, recent lung cancer screening studies have led to the detection of an increasing number of "very early" NSCLC (defined as less than 2 cm in size) and of good-prognosis histologic subtypes, bronchioloalveolar carcinoma (BAC), and adenocarcinoma (AC), mixed subtypes that are potentially appropriate for sublobar resection. The precise indications for sublobar resection remain unclear and are the subject of ongoing clinical trials, but it seems that very early, peripherally located, node-negative AC of a predominantly BAC pattern may be adequately treated in this manner. Multifocal AC and BAC, either synchronous or metachronous, are also effectively treated by complete resection, using limited resections whenever possible. The pneumonic form of BAC, the rarest variant of this disease spectrum, continues to have a poor prognosis despite complete resection. Very limited experience suggests that lung transplantation leads to prolonged survival in highly selected patients with this histologic subtype. To improve our management of very early AC, much more information is needed about the molecular abnormalities of AC and their relationship to clinical outcomes.

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During the past decade, thoracic surgeons have been confronted with demographic and pathological shifts in the group of non-small cell lung cancers (NSCLC) that are potentially resectable.[1] In many countries, adenocarcinoma (AC) has become the most common NSCLC histology. The proportion of women with lung cancer has increased dramatically; in some institutions, half of all patients are female. The number of patients who have never smoked or who have minimal past tobacco exposure is also increasing, especially in North America, because of tobacco control efforts. The widespread use of computed tomography (CT) for lung cancer screening has also led to increased detection of "very early" NSCLC, generally defined as tumors that are 2 cm or less in size, which are usually ACs of mixed subtype or bronchioloalveolar carcinomas (BAC) and which tend to have an indolent clinical behavior.

These epidemiologic shifts have led thoracic surgeons to reexamine the accepted tenets of surgical management of early-stage NSCLC. As part of the November 2004 symposium on BAC, which is the subject of this supplement, a group of thoracic surgeons were asked to review the current management of BAC and very early ACs, focusing especially on the role of sublobar resection. This paper summarizes the discussions held at the symposium and provides updated information on relevant clinical trials.

PATHOLOGICAL CLASSIFICATION OF AC: RELEVANCE TO SURGICAL MANAGEMENT

BAC has long been recognized as a distinct form of AC associated with a favorable prognosis. In 1989, the North American Lung Cancer Study Group (LCSG) reviewed 1635 patients who had undergone resection of AC, 235 of whom had BAC. Resectable BAC occurred more frequently in never-smokers, was diagnosed at an earlier disease stage, and was associated with a better survival rate than invasive AC.[2] During the last 40 years, improved understanding of the pathology of lung AC has prompted substantial changes in the histologic subclassification by the World Health Organization (WHO), which are summarized by Travis et al.[3] in their report from the pathology panel of this symposium (Table 1). From 1967 to 1999, multiple subcategories were added to reflect increasing knowledge about the histologic heterogeneity of AC. Significant changes in the 1999 WHO classification included the addition of atypical adenomatous hyperplasia (AAH) as a preinvasive lesion for lung AC, and the requirement that all BACs demonstrate pure lepidic growth without invasion of stroma, blood vessels, or pleura. In 2004, AC mixed subtype was moved to the top of the list of subcategories in recognition that this is now the most common subtype.[4]

In 1995, Noguchi proposed a six-tier histologic subclassification (types A through F) for small ACs of the lung, recognizing the excellent prognosis associated with BACs (with a purely lepidic growth pattern), the adverse prognostic

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TABLE 1. History of Lung Adenocarcinoma Subclassification According to the World Health Organization

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

From Travis WD, Garg K, Franklin WA, et al. Evolving concepts in the pathology and CT imaging of lung adenocarcinoma and bronchioloalveolar carcinoma. J Clin Oncol 2005;23:3279–3287. Used with permission.

importance of central fibrosis in BACs, and the pathologic heterogeneity of invasive ACs (Table 2).[5] Although the 2004 WHO classification is the internationally accepted system, Noguchi deserves credit for an early attempt to refine the classification and to correlate it with clinical outcomes. As discussed below, the Noguchi system is still used by Japanese investigators to select patients for sublobar resection in ongoing clinical trials. More recently, Noguchi showed that these histologic subtypes have corresponding molecular abnormalities.[6] Areas of histologic types A, B, and C extracted by microdissection from resected ACs were examined by multiplex PCR-LOH and were found to have a progressive rise in the incidence of allelic losses. Deletions of 3p, 17p, 18q, and 22q increased significantly from types A to C, consistent with a model of malignant progression.

Several Japanese studies now confirm that the histologic subtype correlates with CT findings and clinical outcome.[3,7,19] The results of Kodama exemplify these investigations (Table 3). Taken as a whole, these studies suggest that: 1) pure ground-glass opacities (GGO) on CT usually represent BAC without any areas of invasive AC, whereas lesions that show both GGO and solid components on CT (part solid, part nonsolid) are mixtures of BAC and invasive ACs; and 2) small (less than 2 cm in size) tumors with >50% GGO are associated with a 100% chance of being node negative, have an excellent chance of long-term survival after treatment, and probably can be managed by limited resection rather than lobectomy. However, the appropriateness of limited resection for part solid/part nonsolid lesions is unclear and is the subject of clinical trials in Japan. Tumors that are more than 50% GGO on CT seem to have a better prognosis and may potentially be managed by sublobar resection, but preoperative high-resolution CT and intraoperative frozen-section analysis still do not always accurately identify tumors that have a poorer prognosis. Our uncertainties with respect to the optimal surgical management of these lesions reflect the highly variable presentation and behavior of lung ACs, the limitations of CT findings in predicting pathologic findings, and our lack of knowledge of the histologic and molecular features that predict a poor prognosis.

TABLE 2. Noguchi's Histology Typing of Small Adenocarcinoma of the Lung

Type	Description
A	Localized bronchioloalveolar carcinoma
B	Localized bronchioloalveolar carcinoma with foci of collapse of alveolar structure
C	Localized bronchioloalveolar carcinoma with foci of active fibroblastic proliferation
D	Poorly differentiated adenocarcinoma
E	Tubular adenocarcinoma
F	Papillary adenocarcinoma with compressive and destructive growth

From Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. Cancer 1995;75:2844–2852. Used with permission.

TABLE 3. Prognosis in Relationship to Appearance (% GGO)

	GGO < 50%	GGO > 50%	*p*
Patients	52	52	—
Size	13.7	12.3	0.09
Node involvement	8	0	0.01
% local resection	50%	70%	0.001
Relapse	9	0	—
DFS	72%	100%	—

GGO, ground-glass opacity; DFS, disease-free survival.

Adapted from Kodama K, Higashiyama M, Yokouchi H, . Prognostic value of ground-glass opacity found in small lung adenocarcinoma on high-resolution CT scanning. Lung Cancer 2001;33:17–25. Used with permission.

RELATIONSHIP OF TUMOR SIZE TO TUMOR STAGE: SURGICAL IMPLICATIONS

In NSCLC, the size of the primary tumor is known to correlate with the likelihood of lymph node metastases and, therefore, to influence consideration of sublobar resection. The frequency of nodal disease in very early NSCLC has been studied extensively.[20 32] Although lymph node involvement is relatively uncommon in small AC, approximately 10% of tumors that are 1 cm or smaller and 20% of tumors that are 1 to 2 cm in size have nodal metastases (Tables 4 and 5). Relative to AC, squamous cell carcinomas less than 2 cm in size seem to be associated with a lower risk of nodal disease.[20] These findings complicate the selection of patients for limited pulmonary resection because we do not fully understand which patients with very early lung AC may have disease in the intralobar lymphatics or regional nodes. A better understanding of the molecular features in early AC and their relationship to clinical outcome is needed to allow accurate decisions about the use of sublobar resection.

LOBECTOMY VERSUS SUBLOBAR RESECTION: CURRENT KNOWLEDGE AND INVESTIGATIONS

A prospective randomized multicenter trial reported by the LCSG in 1995 established lobectomy as the standard approach to resection for T1N0 NSCLC (LCSG trial 821). Sublobar resection, either wedge resection or segmentectomy, for carefully selected patients who had thorough intraoperative evaluation of the extent of the primary tumor and of the N1 and N2 lymph nodes, was associated with a tripling of the local recurrence rate and a 30% increase in the overall death rate. Within the T1 stage category, tumor size did not seem to influence the risk of recurrence, but the numbers of patients who had tumors less than 2 cm in size were small.[33] The increasing incidence of very early NSCLC seen in thoracic surgical practice, primarily via CT screening for lung cancer,[1] has reopened the debate about the use of sublobar resection. This debate is especially relevant to BAC and to some AC of mixed subtype because of their indolent clinical behavior and known propensity for multifocality. Patients with these AC histologic subtypes often have synchronous or metachronous primary tumors that are best managed by resection. Preservation of lung function through the proper use of limited resection can be a critical aspect of achieving prolonged survival and maintaining patients' functional capacity.[34 36] Several retrospective studies and prospective clinical trials suggest that the sublobar resection may be an appropriate operation for very early AC.[11,13,37 40] The parameters that currently seem to allow proper selection of patients for limited resection include tumor size (less than 2 cm and especially 1 cm or less) in combination with tumor histology (BAC or AC, mixed subtype with 50% or greater BAC component or AC, Noguchi types A or B), peripheral tumor location, and absence of N1 or N2 disease based on thorough intraoperative staging. The presence of GGO or of part solid, part nonsolid appearance on CT reflects these tumor characteristics. In ways that are not yet fully understood (aside from the presence of EGFR mutations in some tumors), these clinical and pathologic features represent tumors that most likely have an indolent biological behavior. The adequacy of wedge resection versus anatomical resection via segmentectomy remains undefined, although segmentectomy has been favored in Japanese studies because it provides an optimal deep margin of resection and removes the local lymphatic bed associated with the primary tumor.[39]

Japanese investigators have sought to confirm these selection criteria for sublobar resection through prospective multicenter clinical trials. JCOG trial 0201 (Figure 1), reported at the 2006 meeting of the American Society of Clinical Oncology (ASCO), enrolled patients with clinical

TABLE 4. Prevalence of Nodal Disease in Solid Nodules <2 cm in Size

	n	% Positive Nodes	% N2
Naruke (1993)[25]	287	40	50
Asamura (1996)[24]	174	20	60
Konaka (1998)[25]	171	17.5	66
Takizawa (1998)[26]	157	17	NS
Sugi (1998)[27]	115	19	66
Wu (2001)[28]	136	22	NS
Okada (2003)[29]	265	18	55
Nonaka (2003)[30]	46	28	70
Average		23	

NS, not stated.

TABLE 5. Prevalence of Nodal Disease in Solid Nodules 1 cm or Less in Size

	n	Patients with Positive Nodes (%)
Naruke (1993)[25]	20	8 (16)
Oda (1998)[31]	22	0 (0)
Konaka (1998)[25]	19	0 (0)
Ohta (2001)[20]	11	4 (4)
Miller (2002)[32]	100	7 (7)
Average		9

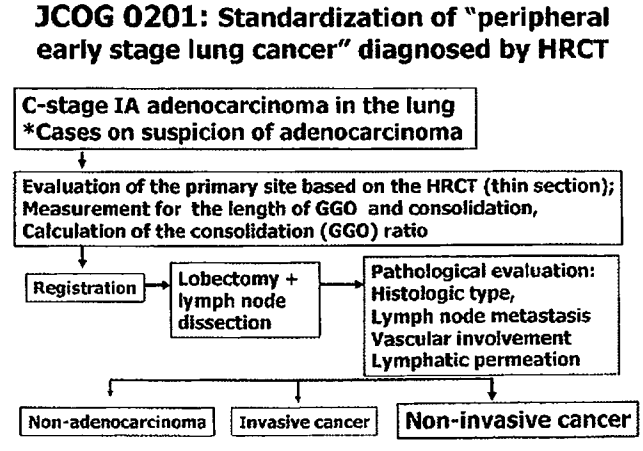

FIGURE 1. Schema for JCOG 0201 trial.

stage IA AC.[41] The primary endpoint was to determine the specificity of high-resolution CT (HRCT) in diagnosing noninvasive AC, using the final pathologic findings as the reference standard. A pathological noninvasive AC was defined as a tumor with no lymph node metastases or lymphatic or vascular invasion. Preoperative evaluation included HRCT to assess the presence of GGO and to calculate the ratio of GGO to solid component of the tumor. Patients then underwent lobectomy and mediastinal lymph node dissection. Final pathological findings were compared with the HRCT features to determine whether the CT could be used to select patients appropriately for sublobar resection. Of the 811 patients enrolled, 545 eligible patients had undergone lobectomy and central data review at the time of the ASCO presentation. Comparison of the CT with the pathological findings showed that HRCT had a specificity of 98.3% but a sensitivity of only 24.7% for the diagnosis of noninvasive AC.

The results of JCOG 0201 have been utilized to develop two new prospective trials. Patients found to have AC 2cm or less in size that are predominantly GGO by HRCT (solid component less than 25% of entire tumor) will be entered on a single arm Phase II trial testing the use of wedge resection for these highly curable indolent tumors. Patients found to have AC 2cm or less in size that have a larger solid component on HRCT (more than 25% but less than 100% of the entire tumor) will be eligible for a prospective randomized comparing lobectomy to limited resection (Figure 2). These trials might also help define which tumors do not require lymph node dissection or sampling, although this is not a planned study endpoint. At the current time lymph node sampling or systematic nodal dissection (SND) remains a key part of accurate tumor staging.[42]

In North America, the Cancer and Leukemia Group B (CALGB), in collaboration with the American College of Surgeons Oncology Group (ACOSOG), is planning a prospective randomized trial comparing lobectomy versus limited resection (wedge or segmentectomy) for patients with AC 2 cm or less in size. This trial does not incorporate the nuanced radiological and histologic selection criteria used in Japanese studies, depending instead on simple size criteria and the basic diagnosis of AC. Designed to reproduce the LCSG 821 trial, but with a focus on smaller tumors, the CALGB trial uses intraoperative assessment of tumor size, tumor location, and nodal involvement, followed by randomization to lobectomy or limited resection. Because of the large numbers of patients and long follow-up time required to identify a survival difference between these two resectional approaches, results from this trial will probably not be available for about 8 years.

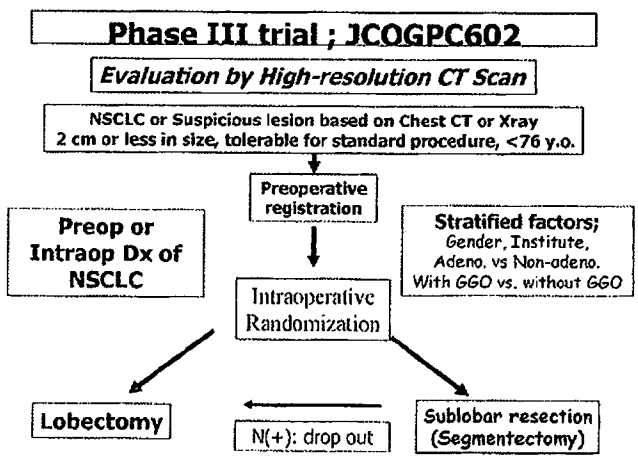

FIGURE 2. Schema for JCOGPC 602 trial.

MANAGEMENT OF THE PNEUMONIC FORM OF BAC: RESECTION, SYSTEMIC THERAPY, OR TRANSPLANTATION?

Most BAC or AC, mixed subtype present as either a single nodule or as multiple lung nodules (synchronous or metachronous) that behave in an indolent manner and are best managed surgically.[34,36,43] The least common variant of this BAC-AC disease spectrum is generally termed the pneumonic form because it presents as a progressive lobar consolidation with mucinous AC filling the alveolar spaces. Resection does not seem to alter the very poor prognosis of this disease, which inevitably progresses to consolidation of both lungs and death from respiratory failure.[34,43] Systemic therapy has also been relatively ineffective in this disease. Thus, most surgeons are reluctant to consider pulmonary resection for this biologically aggressive form of AC. Lung transplantation has been suggested as a potential treatment option. First reported by Zorn et al., lung transplantation in nine patients (single lung in two and bilateral transplants in seven patients) was associated with a poor outcome.[44,45] Only two patients survived long term, whereas the other patients experienced cancer recurrence in the transplanted lungs. More recently, the Toronto group reported their experience with transplantation in 29 patients.[46] Five-year survival was 51%, and recurrence developed in 13 of the transplanted lungs. Although transplantation was performed for advanced multifocal BAC, it is not entirely clear how many of these patients truly had the pneumonic form of mucinous AC. Thus, lung transplantation potentially remains an option for selected patients, but it is associated with a significant risk of recurrent disease and requires further study.

SUMMARY

Lobectomy and lymph node sampling or systematic nodal dissection remain the standard surgical treatment for patients with early stage NSCLC. However, limited resection may be an appropriate option for patients with very early AC and BAC based on tumor size, location, and relative proportion of BAC to AC. Very small BAC are probably appropriately treated by limited resection. Accurate criteria for selecting patients for limited pulmonary resection await the results of ongoing clinical trials and an improved understanding of NSCLC biology in relationship to clinical outcome.

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Systemic Therapy of Bronchioloalveolar Carcinoma: Results of the First IASLC/ASCO Consensus Conference on Bronchioloalveolar Carcinoma

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Introduction: Bronchioloalveolar carcinoma (BAC) is a subtype of adenocarcinoma of the lung with unique pathological, clinical, and molecular characteristics.

Methods: This consensus conference group reviewed studies performed specifically in BAC and data from patients with BAC who were included in clinical trials of all non–small-cell lung cancer (NSCLC) subtypes.

Results: Although BAC as defined by the World Health Organization represents less than 5% of adenocarcinomas, as many as 20% of adenocarcinomas have BAC features. These latter tumors are more likely to have mutations in the epidermal growth factor receptor (EGFR) gene and to be sensitive to the EGFR tyrosine kinase inhibitors gefitinib and erlotinib. Although most patients are men and have a history of smoking cigarettes, proportionally more are women and never smokers. Patients with BAC are routinely treated with drugs and regimens appropriate for patients with all subtypes of adenocarcinoma of the lung; four studies have been performed specifically in this disease.

Conclusions: There is insufficient evidence to confirm or refute the assertion that the sensitivity of BAC to chemotherapy is different from that of other lung cancer histologic types. The unique clinical and molecular characteristics associated with BAC led this panel to conclude that future clinical trials should be designed specifically for persons with BAC. Recommendations for trial design and research questions are proposed.

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Bronchioloalveolar carcinoma (BAC) may be distinguished from other adenocarcinomas of the lung by unique histology, radiology, molecular biology, and clinical course. It is thought that the course of patients with BAC is more indolent than in persons with other non–small-cell lung cancer (NSCLC) histologies. Although "pure" BAC is defined explicitly by the World Health Organization (WHO),[1] there are many more patients whose adenocarcinomas have features of BAC, making the histologic classification of such tumors uncertain.[2] Several clinical trials have been performed specifically in patients with BAC, based on the notion that these tumors may be somewhat less sensitive to standard chemotherapy and that the biology of BAC differs from that of other adenocarcinomas.

MATERIALS AND METHODS

This conference group reviewed results of patients with BAC included in trials studying patients with NSCLC in general and five studies designed specifically for persons with BAC, testing paclitaxel, gefitinib, and erlotinib. Local treatment approaches are also outlined here, including inhalational therapy with investigational anticancer agents. The conference group made recommendations for clinical trial design and further research in BAC.

RESULTS

Results in Patients with BAC Included in ECOG Trial 1594 in Patients with Advanced NSCLC

The Eastern Cooperative Oncology Group (ECOG) studied four platinum-based regimens as initial therapy for patients with NSCLC.[3] This study included 1163 patients, 17 of whom were classified as having BAC by the investigator. The response rate in patients with BAC was 6% compared with 20% for patients with other types of NSCLC. Median

survival for persons with BAC was 12 months compared with 8 months overall.

Trials Conducted Specifically in Patients with BAC

Paclitaxel by 96-hour Infusion for Patients with BAC (SWOG9714)

The Southwest Oncology Group (SWOG) conducted the first prospective trial for patients with BAC.[4] Patients in this trial had ECOG performance status 0 to 2 and stage IIIB/IV BAC as determined by the treating institution. All 58 patients received paclitaxel 35 mg/m^2/day continuously infused for 96 hours every 21 days. The partial response rate was 14%. Median overall survival was 12 months, and the 3-year survival rate was 13%. Because of a high treatment-related death rate (9%, 5/58), this regimen was not pursued. However, this trial demonstrated the feasibility of conducting prospective trials in patients with BAC in a cooperative group setting and established benchmarks for future studies.

Paclitaxel by 3-hour Infusion for Patients with BAC (EORTC 08956)

The European Organization for Research and Treatment of Cancer Lung Cancer Group studied a 3-hour paclitaxel infusion in patients with stage IIIB/IV BAC.[5] Nineteen patients received paclitaxel 200 mg/m^2 every 21 days. Two partial responses were confirmed (response rate of 11% (95% CI, 1 to 35%). The median survival was 9 months, and the 1-year survival rate was 35% (95% CI, 14 to 56%). The study was terminated because of a low response rate.

Gefitinib (Iressa) for Patients with BAC (SWOG 0126)

SWOG S0126 evaluated 500 mg of gefitinib per day.[6] The study was undertaken based on the detection of epidermal growth factor receptor (EGFR) protein in BAC tumors collected from S9714, the activity seen in patients with NSCLC in phase I trials of gefitinib, and reports of rapid and durable responses in patients with BAC.[7,8] This study enrolled 55 patients with eligibility identical to the preceding S9714 trial along with 35 previously treated patients. All had performance status of 0 to 2 and stage IIIB/IV BAC as determined by the treating institution. Approximately one third of patients had a dose reduction to 250 mg based on toxicities, and 11% discontinued therapy. Three patients developed increasing pulmonary infiltrates and hypoxemia requiring treatment with steroids, antibiotics, and supplemental oxygen after discontinuing gefitinib. Each of these patients died of what was possibly treatment-related interstitial lung disease, although disease progression, infection, or other causes may have contributed. Among patients with measurable disease, gefitinib response rates (RECIST) were 19 and 9% for chemo-naïve and chemo-pretreated patients, respectively. Complete responses were seen. The median survival of untreated patients was 12 months, similar to that in SWOG 9714. Several patients had progression-free survival of more than a year, something not observed with paclitaxel. The survival at 2 and 3 years was 38 and 23%, an improvement on the 29 and 13% seen in S9714. Patients with nonmucinous BAC had superior survival on gefitinib compared with those with the same histologic features treated with paclitaxel on protocol S9714 discussed above.[9] Increased EGFR gene copy number detected by fluorescence in situ hybridization was associated with improved survival.[10] Correlations of clinical outcomes with EGFR protein expression measured by immunohistochemistry and EGFR mutations are ongoing.

Erlotinib (Tarceva) for Patients with BAC

During the early testing of erlotinib, dramatic responses were observed in patients with BAC. To follow up on this lead, four centers undertook a phase II trial of erlotinib 150 mg daily in patients with BAC—both "pure BAC" as defined by the WHO and adenocarcinoma with BAC features.[2,11] A total of 159 patients with stage IIIB or IV inoperable NSCLC had central review of biopsy specimens. BAC was identified in 66% of submitted specimens. Like the SWOG studies, pathological eligibility was determined by the reading from the pathology department where the patient was treated, not by central review. One hundred one patients were treated; 67% of the patients were women, and 22% had previously received chemotherapy. Central pathology review showed that 12% were "pure BAC" and that 88% had adenocarcinoma with BAC features. Twenty-five percent of the patients had never been smokers. A final report is planned for the first half of 2006.

Erlotinib treatment led to partial responses (RECIST criteria) in 20 of the 84 patients evaluated at the time of the report (24%; 95% CI, 16 to 34%). The partial response rate was 40% in never smokers and 19% in current or former smokers. The 1-year survival rate rfor all patients was 58%; the median survival rate has not yet been determined. There was one case of interstitial lung disease resulting in treatment-related death. EGFR exons 18 to 24 have been sequenced in 19 tumor specimens to date. Among nine patients with partial responses, six had EGFR mutations, two with deletions in exon 19, and four had substitution mutations in exon 21 (L858R).[12] None of the 10 patients who did not have partial responses had a mutation in EGFR exons 18 to 24. The trial closed to accrual in April 2005. Studies of EGFR protein expression, EGFR copy number, sequencing of EGFR exons 19 and 21, and sequencing of KRAS exon 2 will be obtained from all patients with tumor tissue available. A final report is planned for the first half of 2006.

Trial of gefitinib for patients with Pneumonic-Type Adenocarcinoma

This prospective French Thoracic Oncology Intergroup 30-center phase II study (IFCT 04-01) opened in May 2004 to evaluate gefitinib 250 mg daily as a first-line therapy for patients with nonresectable, pathologically proven, pneumonic-type adenocarcinoma as defined by Wislez et al.[13] This group includes adenocarcinomas with both mixed-invasive and BAC-predominant subtypes. Interim results were reported at the International Association for the Study of Lung Cancer meeting in Barcelona, Spain in July 2005.[14] Objective responses were documented in four of 24 patients reported

(17% observed rate, 95% CI, 5 to 37%). Tissue will be analyzed for expression of EGFR, HER2, P-AKT, and MAPK as well as mutations in KRAS codon 12 and EGFR exons 18 to 21. A final report on 90 patients is planned for the first half of 2006.

Other Strategies

Adenovirus P53 Administered by Bronchioloalveolar Lavage in Patients with BAC

Because BAC is characterized by thin sheets of tumor cells growing along the airways, agents delivered by inhalation should have direct access to the tumor. A phase I study of p53 gene transfer using an adenovirus vector (Ad-p53; RPR/INGN 201) delivered via bronchioloalveolar lavage (BAL) to involved lobes of the lung was conducted at the University of Wisconsin and Vanderbilt University.[15] Treatments consisted of two BAL at the same dose level given 2 weeks apart to a single involved lobe. Additional treatment to all involved lobes was allowed if initial treatments were tolerated. The initial dose was 2×10^9 viral particles per dose, escalated in 10-fold increments. Among 14 patients registered, grade 4 pulmonary toxicity was noted at the 2×10^9 dose level. Two additional patients at this level did not suffer a dose-limiting toxicity. After the completion of two cycles, pathologic response was noted on rebiopsy in two patients, four of nine patients showed improved diffusing capacity, and four of 11 had symptomatic improvement.

Autologous Antitumor Vaccine GVAX (CG8123)

GVAX (CG8123) (Cell Genesys, Inc.) is a GM-CSF gene-modified autologous tumor cell vaccine that has shown antitumor activity in patients with NSCLC and, specifically, BAC.[16,17] Despite these reports, no trials of this construct are planned for patients with BAC.

Inhalational Therapy: Interferon-α, Doxorubicin, Cisplatin, and Indomethacin

A number of phase II trials and case reports of inhaled therapy have been described, with endpoints of tumor control and palliation of bronchorrhea. Ten patients with locally advanced BAC were treated with interferon-alpha as an inhaled aerosol with initial doses from 1 to 10 million units three times weekly and escalated to 20 million units daily.[18] No symptomatic or radiographic responses were seen. Aerosolized doxorubicin has been administered to patients with primary and secondary pulmonary malignancies, including six with NSCLC and at least one with BAC. Efficacy data have not yet been reported.[19]

Bronchorrhea: A Defining Symptom of BAC

Bronchorrhea, defined as the production of sputum of >100 ml/day, is a defining symptom of BAC. Seen in about 5% of patients, bronchorrhea causes substantial discomfort. Successful treatment of BAC eliminates this condition. A variety of treatments directed at this symptom have been studied, including inhaled indomethacin,[20,21] oral and inhaled corticosteroids,[22] and macrolide antibiotics.[23,24] Gefitinib inhibits mucin production[25] and decreases bronchorrhea.[26–29]

Response Assessment in BAC Trials

Because of the diffuse nature of the pulmonary lesions often characteristic of BAC, some investigators have suggested that standard methods for response assessment may be inadequate for phase II trials conducted specifically in patients with BAC. Despite these concerns, the current standard of care includes patients with BAC in trials of NSCLC in general and routinely employs standard bidimensional or unidimensional response assessment. In addition, all four multicenter phase II trials completed exclusively in patients with BAC used standard criteria and reported no difficulties assessing response by both bidimensional[4,5] and unidimensional[6,30] methods of assessment.

DISCUSSION

Consensus Recommendations

- Because BAC represents a subtype of lung adenocarcinomas with unique clinical characteristics and molecular profile, studies specifically designed for this illness are warranted.
- The diagnosis of "pure" BAC requires a *histologic* specimen from the lung.
- A precise histologic classification of all NSCLC is needed.
- For clinical trials testing systemic therapies for activity in BAC, a histologic specimen and confirmation by central pathologic review are mandatory.
- For clinical trials testing systemic therapies for NSCLC in general, although histologic confirmation is favored, the use of either histology or cytology with a mandated central review is an acceptable alternative.
- Any feature of BAC in a pathologic specimen would qualify a patient for BAC-specific treatment or trials.
- If clinical features suggest a diagnosis of BAC (e.g., bronchorrhea, pneumonic consolidation, multifocal disease, visually normal bronchoscopy, etc.), but initial pathological testing is inconclusive, additional histological evaluation is warranted.
- A detailed cigarette-smoking history should be determined in all NSCLC patients. The minimum information necessary would classify people as current, former (stopped more than 1 year ago), or never smokers (fewer than 100 lifetime cigarettes).
- There is insufficient evidence to confirm or refute that the sensitivity of BAC tumors to chemotherapy is different from that of other types of NSCLC.
- Standard bidimensional (WHO, SWOG) or unidimensional (RECIST) methods of response assessment can be used in phase II trials conducted in persons with BAC.

- Phase II trials have demonstrated that gefitinib and erlotinib have activity in BAC patients when given as initial treatment and after chemotherapy.
- In phase II trials of BAC patients receiving systemic therapies, the observed survival appears longer than in studies of NSCLC patients.
- Investigational therapy is acceptable at any point in the course of advanced BAC.
- Bronchorrhea is a defining symptom of BAC. It is best managed by effective treatment of BAC.

Research Areas

- A trial of initial gefitinib or erlotinib, then a platinum-based doublet versus an initial platinum-based doublet, and then gefitinib or erlotinib
- Exploration of the use of gefitinib and erlotinib both before and after surgery
- Trials of BAC-specific targeted therapies must include determination of molecular correlates for the target of interest
- Special areas to be addressed in clinical trials of systemic therapies in BAC:
  - Central pathology review
  - Response assessment
  - Smoking history
  - Prior and comorbid pulmonary diseases.
- Proposed or in-progress studies:
  - Phase II trial of weekly bortezomib (Velcade) as first- or second-line treatment (conducted by the California Cancer Consortium)
  - Phase II trial of twice-weekly bortezomib (Velcade) as first- or greater-line treatment (conducted by Millennium Pharmaceuticals)
  - Phase II trial of pemetrexed (Alimta) as first- or second-line treatment (conducted by SWOG)
  - Phase II trial of cetuximab (Erbitux) as first- or second-line treatment (conducted By ECOG).
  - Phase II IFCT 05-04 trial: effect of an early therapeutic permutation on the tumoral control of patients receiving in the first line a specific inhibitor of tyrosin kinase of EGFR (erlotinib) or a taxane-based chemotherapy (paclitaxel + carboplatin) for the treatment of nonresectable adenocarcinoma with bronchioloalveolar features.

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INTERNAL MEDICINE

□ CASE REPORT □

Three Cases of the Nodular Pulmonary Amyloidosis with A long-term Observation

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Abstract

Long-term observation with chest radiograph and computed tomography (CT) scan was performed for pulmonary amyloidosis. There are few reports of primary pulmonary amyloidosis with a long-term observation. We encountered three cases of nodular pulmonary amyloidosis observed by intermittent chest radiograph or CT for 5 years or more. The patients were a 54-year-old man, and 67- and 68-year old women. For diagnosis, transbronchial biopsy and percutaneous lung biopsy were performed. Amyloid nodules grew slowly and two cases showed findings of cavity and calcification.

Key words: pulmonary amyloidosis, Long-term observation, Bronchofiberscopy

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Introduction

Amyloidosis is defined as an abnormal protein formed by amyloid fibrils that are deposited in the extracellular tissue. Tracheobronchial-pulmonary amyloidosis is cryptogenic and also confined in the respiratory system. Compared with systemic amyloidosis, localized pulmonary amyloidosis usually has a benign course. However, there are few detailed reports regarding the long-term radiographic change. Here, we present three cases of nodular pulmonary amyloidosis that were observed for at least five years.

Case Reports

Case 1

A 68-year-old woman had an abnormal shadow on chest radiograph in a screening survey (Fig. 1). She was a non-smoker and in good health. Her first chest CT scan was performed on February 26, 1999 (Fig. 2a). A single nodule with a calcification of 25 mm in diameter was observed at the right middle lobe. After that, she did not visit the clinic regularly. She came for an examination on September 5, 2003 due to dyspnea on exertion. The chest CT revealed that the nodule was growing (Fig. 2b) and calcification increased. Amyloid deposition was proven by bronchoscopic lung biopsy. Amyloid was not found in the liver or rectum biopsy. The latest CT on March 9, 2005 showed that the nodule size had increased (Fig. 2c). New nodules were observed on the latest CT film.

Case 2

A 67-year-old woman had a check-up on January 23, 1995 chiefly for shortness of breath. She was a non-smoker. She had surgical resection of uterine cancer in 1970. Chest radiograph showed multiple nodules of the bilateral lung (Fig. 3a). They were of clear and round form. Bronchoscopy was incomplete for diagnosis. Percutaneous lung biopsy (needle biopsy) was performed and the sample demonstrated AL type amyloid deposition. The echocardiogram was normal and there was no amyloid in the rectum tissue. All nodules were gradually growing and the numbers had increased. A small cavity was noted in 1999 and had disappeared in

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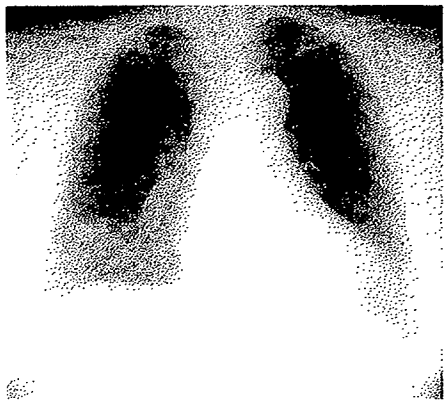

Figure 1. **Chest radiograph findings of a 68-years-old woman (Case 1) on the first visit in 1999. Single nodular shadow size of 22 mm of diameter was noted on the left lower lobe.**

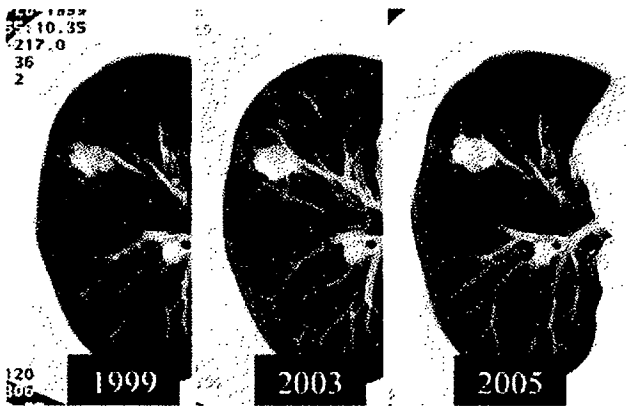

Figure 2a, 2b, 2c. **Chest CT scan of Case 1. Tumor size was 25 × 15 mm on Feb. 26, 1999 (2a), 25 × 20 mm on Sep. 5, 2003 (2b) and 25 × 23 on Mar. 9, 2005 (2c). The size of the nodule became enlarged from 25 × 15 mm to 25 ×23 mm in six years.**

2001 (Figs. 3b, 3c).

Case 3

In a 54-year-old man, an abnormal shadow of chest radiograph was noted in a health examination on August 21, 1991 (Figs. 4, 5a). He had previously been in good health. He worked in the aluminum processing industry for about 20 years. He smoked 1 pack of cigarettes per day for about 34 years. Percutaneous lung biopsy was taken for lesion of the left lower lobe. However, the diagnosis was condensed exudate of the left pleural cavity. Needle biopsy was performed again on June 22, 1992, because the peripheral tumor in the right upper lobe was enlarged. Amyloid deposition was proven in this specimen. No amyloid deposition was observed in the rectum biopsy specimen. Two years later (July 22, 1994), the nodular shadow in the right lower lobe had expanded (Fig. 5b). Two coin lesions newly appeared in the right lung. Bronchoscopic biopsy was performed for the right S^{10} lesion. This sample documented amyloid deposition. The nodule sizes had increased (Fig. 5c) and the latest CT (Fig. 5d) showed a cavitary lesion and calcification.

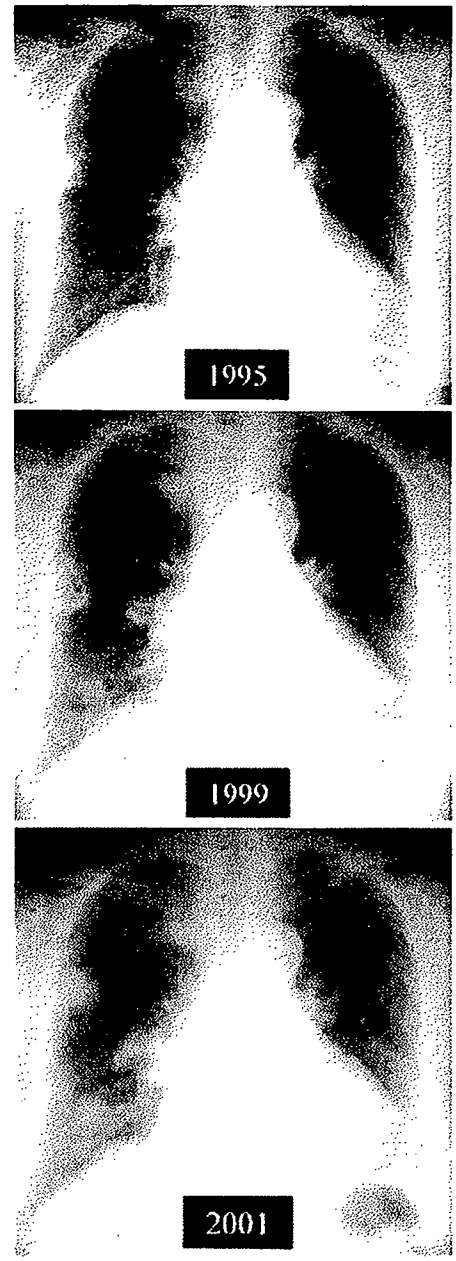

Figure 3a, 3b, 3c. **Chest radiograph of a 57-year-old man (Case 2) in 1995 (3a), 1999 (3b), and 2001 (3c) showed multiple nodular shadows of the right lung. Nodules were gradually growing and calcification and small cavity were noted in 1999, which disappeared in 2001.**

Discussion

Nodular amyloidosis is not associated with systemic disease and is associated with a benign prognosis reticulonodular pattern (1) and many cases of pulmonary localized type

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are reported to be the AL type of amyloid proteins (2, 3). By observing the deposited locus, it can be divided into two types: localized amyloidosis which deposits only in a specific organ and systemic type with deposition in every organ. Gillmore and Hawkins (3) classified laryngeal, tracheobronchial, parenchymal nodular, diffuse alveolar septal and intrathoracic lymphadenopathy in amyloidosis of the respiratory system. The present three cases were regarded as localized parenchymal nodular amyloidosis and long-term survival was expected. Two of the three cases were asymptomatic and were detected by mass screening. Usually, a patient with pulmonary nodular type amyloidosis has no symptom except for the chest radiograph abnormal shadow and an early symptom is dyspnea (4). It is difficult to suppose that the respiratory symptoms are caused only by peripheral nodules, we presumed that the patient was affected by smoking or other complications. However, we could not prove the affect of smoking and or any complicated disease in our cases. On the other hand, the tracheobronchial type can lead to hemoptysis, bloody phlegm (5) and the intrabronchial polyp can be cauterized by YAG laser (1, 4). Generally, systemic amyloidosis is a very poor prognosis. Utz et al (1) reported that the average survival is 16 months after diagnosis.

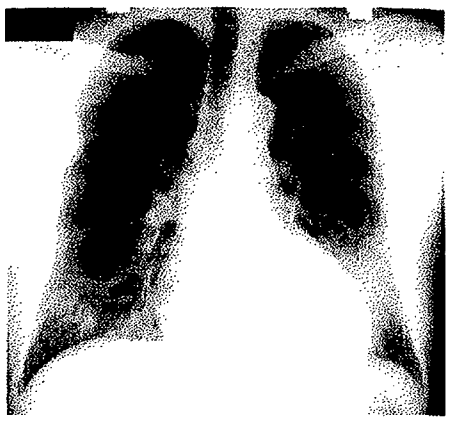

Figure 4. **Chest X-ray of 67-years-old woman (Case 3) on Aug. 21, 1991 revealed multiple bilateral nodules.**

There is insufficient data on pulmonary localized amyloidosis that can take a good course with no treatment; in one report, the nodule gradually became enlarged over 14 years, finally occupying all lung fields (6). Slow continual growth of more than 20 years on chest radiograph and asymptomatic cases has been reported (7). As for the characteristic of pulmonary localized amyloidosis, Gillmore and Hawkins (3) claim that nodules are usually peripheral and subpleural, occurring in the lower lobes, which might be bilateral and range in diameter of 0.4-15 cm. In addition, they grow slowly and frequently had cavities or calcification. These reports did not include chest CT but mainly observation by chest radiograph. In the present cases, the most enlarged nodules (Case 3) were observed from 1 mm to 25 mm in diameter at 13 years and cavitary lesion appeared after 4 years (Case 2), and at 13 years (Case 3) after the first visit. In

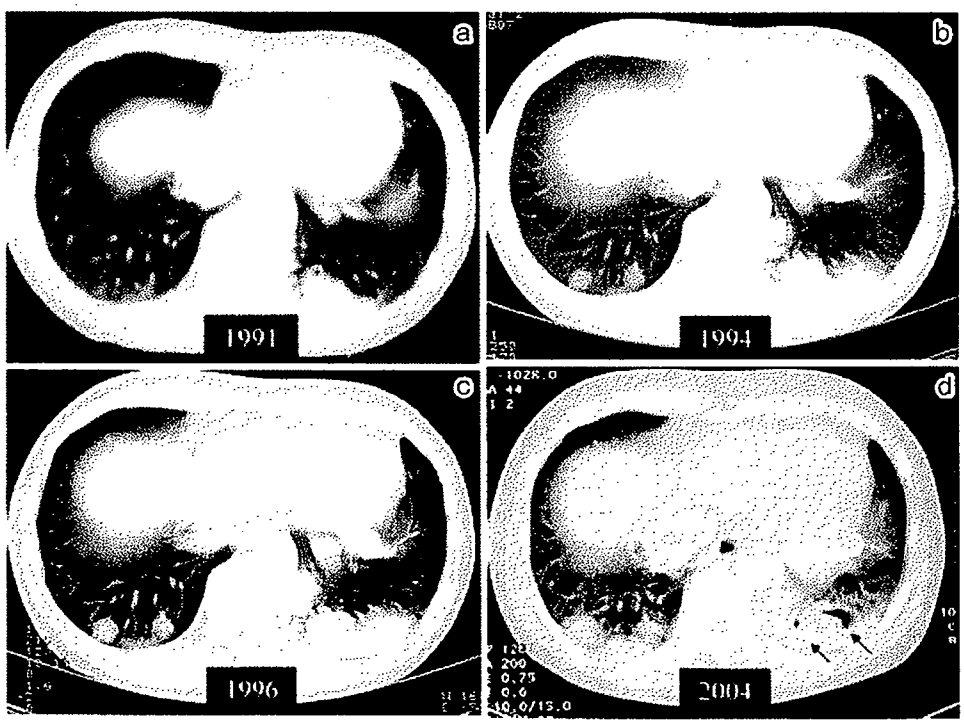

Figure 5a, 5b, 5c, 5d. **The changes in the chest CT findings of Case 3 shown in 5a (1991), 5b (1994) and 5c (1996). The tumor shadows were larger and increased. The mass of the left lower lobe revealed cavity lesions and calcification (arrows) in 2004 (5d).**

case 2, the cavitary lesion disappeared and shrank in 2001. We supposed that the tumor wall became thinner and was crushed by pressure. On chest radiograph, the findings are somewhat limited. In case 3, there was a lesion like a fungus ball. There was a possibility that this change was modified by fungal infection.

The deposition of amyloid protein in limited areas was due to low pH and neighboring proliferation of monoclonal plasma cells and interaction of glycoaminoglycan (8). Hiroshima et al (9) reported one case in which a significant amount of asbestos was observed around the pulmonary amyloid nodule. They suggest that asbestos inhalation is an etiological factor in amyloidosis.

Bronchoscopic diagnosis was attempted in most cases in Japanese case reports from 1985, but the success rate is low. The common diagnostic means was a surgical technique such as open lung biopsy or resection. There was a successful report for accurate diagnosis with CT-guided bronchoscopy for small lesions (10). In addition, there is the question of serious possible bleeding with amyloidosis. Two of 3 patients in the present paper were proved as amyloidosis by bronchoscopy. Strange et al (11) reported a fatal complication of pulmonary hemorrhage and arterial air embolism after transbronchial biopsy. They proposed that biopsy is a potential risk for amyloidosis. In a Mayo Clinic report, 2 of 11 patients lost approximately 100 mL of blood by bronchoscopic lung biopsy (1). Because amyloid deposition exists in the peri-vascular area with wall thickness or destruction, it may bleed easier than other neoplastic lesions. We think that the examination, when amyloidosis is doubtful, should be cautious. In addition, even if we initially diagnose as amyloidosis, careful follow-up is necessary.

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ORIGINAL ARTICLE

Transbronchial needle aspiration cytology of subcarinal lymph nodes for the staging procedure in the diagnosis of lung cancer

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Transbronchial needle aspiration cytology of subcarinal lymph nodes for the staging procedure in the diagnosis of lung cancer
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Objective and background: The aim of this study was to improve the staging of lung cancer with or without lymphadenopathy on chest CT by using transbronchial aspiration cytology (TBAC).

Methods: TBAC of the subcarinal lymph nodes was performed on 153 consecutive patients with lung cancer, with or without subcarinal lymphadenopathy on chest CT.

Results: Thirty-four patients had enlargement of the subcarinal lymph nodes (>1 cm). Eighteen of these had TBAC confirmation of metastases. Another seven patients with no mediastinal involvement on CT were positive for metastases on TBAC. TBAC was the only way to confirm lung cancer in two patients. Therefore, routinely performed subcarinal TBAC contributed to an improved non-operative staging of the patients and diagnosis in 16% (25/153) of the patients with lung cancer. Forty-nine patients with NSCLC had surgical resection of the tumour. Surgical procedure revealed metastases to the subcarinal lymph nodes in three patients in whom the preoperative TBAC diagnosis was normal. No significant complications due to TBAC occurred in any of the patients.

Conclusion: TBAC of the subcarinal lymph nodes is a minimally invasive technique for staging of lung cancer and can provide useful information for the diagnosis of metastases to the subcarinal lymph nodes.

Key words: chest computed tomography, lung cancer, staging, subcarinal lymph node, transbronchial aspiration cytology.

INTRODUCTION

The efficacy of flexible bronchoscopy used in combination with transbronchial needle aspiration (TBNA) has been studied since the early 1980s. TBNA is also known as Wang needle aspiration, and can be performed safely with little morbidity.[1,2] TBNA is most frequently used for cytological diagnosis not only of the parenchymal nodules but also of the mediastinal lymph nodes. Shure and Fedullo reported that TBNA, when used to obtain diagnostic and staging information for mediastinal and subcarinal lymphadenopathy, showed a lower complication rate than mediastinoscopic examination.[3,4] TBNA has become a standard evaluation technique for suspected metastases involving the mediastinal nodes.

Transbronchial aspiration cytology (TBAC) of the subcarinal nodes was performed routinely so as to improve the staging procedure in lung cancer, with or without lymphadenopathy on chest CT. Cytological proof of metastases in the mediastinal lymph nodes and more accurate staging by TBAC.[5] Routinely performed TBAC for subcarinal lymph nodes and optional TBAC of other swollen mediastinal lymph nodes can result in a more correct staging and diagnosis in 25% of patients with lung cancer.[5] In the present study, we analyse how TBAC of subcarinal nodes using flexible bronchoscopy contributes to a

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more accurate staging by proving whether N2 disease, according to International Union Against Cancer (UICC) staging,[6] exists or not.

METHODS

Patients

Transbronchial aspiration cytology was performed on 153 consecutive patients with suspected lung cancer during initial diagnostic bronchofibrescopy over an 18-month period. All patients had histological or cytological confirmation of lung cancer after flexible bronchoscopy. Twenty-six patients had small cell lung cancer (SCLC) and 127 had non-small cell lung cancer (NSCLC).

Equipment

The flexible bronchoscope used in the present study was an Olympus (Tokyo, Japan) 1P10 type. The disposable cytology needle used for TBAC was an Olympus 21-gauge, with a length of 15 mm.

Procedure of bronchoscopic examination

As pre-medication, the patients received a 4% solution of nebulized lidocaine and the larynx was anaesthetized with a 2% solution of lidocaine. They were also administered an i.m. injection of atropine sulphate to reduce bronchial secretion. In all cases, a flexible bronchoscope was passed through an endotracheal tube. Prior to oral intubation, the patients were sedated with i.v. administration of diazepam and fentanyl citrate. During these procedures, patients were supplied with oxygen through an endotracheal tube, and fentanyl citrate was administered every 20 min. N-allylnoroxymorphone was given after the procedure was completed.

Transbronchial aspiration cytology was routinely performed on all patients who were suspected of having lung cancer. In order to avoid contamination, TBAC was performed before endobronchial observation and peripheral sampling. Triple punctures in each of the anterior, central and posterior portions of the carina were done to improve diagnostic accuracy with real time X-ray guidance. Once inserted, the needle was moved up and down while syringe suction was maintained.[7] Specimens were sprayed onto glass slides with a 20-mL syringe including air and fixed with 95% ethyl alcohol. We did not perform subcarinal TBAC on patients who had severe chronic pulmonary emphysema or enlargement of the left atrium of the heart, or who were on anticoagulant therapy.

RESULTS

The histological subtypes of the 153 patients enrolled in the study are listed in Table 1. The number of patients who had subcarinal node enlargement >1 cm in short axis diameter on CT (CT-positive) and who had cytological confirmation of metastases by TBAC (TBAC-positive) was 34 (nine SCLC and 25 NSCLC) and 25 (10 SCLC and 15 NSCLC), respectively (Table 2).

The relationship between the size of the subcarinal nodes and result of TBAC is shown in Table 3. Out of 34 CT-positive patients, 18 had confirmed metastases by TBAC. Patients with SCLC had increased TBAC-detection of metastases when they had enlargement

Table 1 Histology of lung cancer in 153 patients who had TBAC

SCLC	26
NSCLC	127
Adenocarcinoma	72
Squamous cell carcinoma	33
Large cell carcinoma	11
Others	11

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; TBAC, transbronchial aspiration cytology.

Table 2 Number of patients who had enlargement of subcarinal nodes (CT-positive) and cytological confirmation of metastasis by TBAC (TBAC-positive)

	CT-positive	TBAC-positive
SCLC	9/26 (35%)	10/26 (38%)
NSCLC	25/127 (20%)	15/127 (12%)
Total	34/153 (22%)	25/153 (16%)

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; TBAC, transbronchial aspiration cytology.

Table 3 Relationship between enlargement of the subcarinal nodes and result of TBAC

	CT-positive	CT-negative
SCLC ($n = 26$)		
TBAC-positive	7	3
TBAC-negative	2	14
NSCLC ($n = 127$)		
TBAC-positive	11	4
TBAC-negative	14	98
Total ($n = 153$)		
TBAC-positive	18	7
TBAC-negative	16	112

CT-negative, patients without enlargement of the subcarinal nodes; CT-positive, patients with enlargement of the subcarinal nodes; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; TBAC, transbronchial aspiration cytology; TBAC-negative, patients who did not have confirmation of metastasis to the subcarinal nodes by TBAC; TBAC-positive, patients who had confirmation of metastasis to the subcarinal nodes by TBAC.

Table 4 Relationship between the site of primary tumour and CT findings or results of TBAC (n=153)

Primary site	No. patients	CT-positive	CT-negative	TBAC-positive	TBAC-negative
LUL	42	9	33	5	37
LLL	17	7	10	4	13
LMB	4	1	3	2	2
RUL	34	8	26	3	31
RML	11	3	8	3	8
RLL	35	3	32	4	31
RMB	1	1	0	1	0
Intermedius	5	2	3	2	3
Unknown	4	0	4	1	0
Total	153	34	119	25	128

LLL, left lower lobe; LMB, left main bronchus; LUL, left upper lobe; RLL, right lower lobe; RMB, right main bronchus; RML, right middle lobe; RUL, right upper lobe; TBAC, transbronchial aspiration cytology.

of the nodes (7/9) than ones with NSCLC (11/25). Out of 119 patients without enlargement of the subcarinal nodes (CT-negative), TBAC did not reveal metastases (TBLB-negative) in 112, but seven patients had confirmed metastases by TBAC. The lymphoid cells of TBAC samples were obtained in 112 (79%) of 153 cases.

Forty-nine patients with NSCLC had surgical resection of the tumour. There were no resected cases who were TBAC-positive. In our hospital, pathologically confirmed N2 disease was considered inoperable even though there was no enlargement of mediastinal lymph node on chest CT scan. Furthermore, during the study period, no clinical trials such as neoadjuvant chemotherapy followed by surgery or surgery after adjuvant chemotherapy were available for pathological confirmed N2 disease in our hospital. Therefore, seven patients with pathologically confirmed N2 were treated with radiotherapy with/without chemotherapy. The surgical procedure revealed metastases to the subcarinal nodes in three patients, although preoperative TBAC diagnosis did not show any metastases. All three p-N2 patients who had negative TBAC showed an absence of subcarinal lymph nodes swelling on preoperative chest CT scan. The other 46 patients who had negative subcarinal nodes biopsy by TBAC showed no metastases in resected specimens. The accuracy of TBAC for diagnosing metastases was 94% in the 49 patients. The relationship of the site of primary tumour and CT findings or results of TBAC is listed in Table 4. No exact correlation was observed between the site of primary tumour and the results of TBAC. Summary of the patients in which subcarinal TBAC contributed to the staging or diagnosis are as follows. Radiological N2 was positively confirmed by subcarinal TBAC in 18 patients. N2 was confirmed by subcarinal TBAC in the absence of subcarinal lymph nodes swelling in seven patients. Subcarinal TBAC was the only way to confirm lung cancer in two patients. Therefore, routinely performed subcarinal TBAC contributed to more correct staging and diagnosis in 16% of the patients with lung cancer. No severe complications occurred in any of the cases who received routinely performed subcarinal TBAC.

DISCUSSION

Accurate diagnosis of metastases to the mediastinal lymph nodes influences the treatment plan and prognosis of patients with lung cancer.[8] As approximately 30–40% of patients with lung cancer already have mediastinal metastases at the time of initial diagnosis,[9] and histological or cytological evaluation of metastases to the mediastinal nodes is essential.

Generally, diagnosis of metastases to the mediastinal lymph nodes is based upon imaging and histological information. Commonly used imaging equipment includes positron emission tomography (PET), magnetic resonance imaging and CT. In most clinical settings, contrast-enhanced CT is the investigation of choice, and the size of lymph nodes provides a standard for the diagnosis of metastases by CT.[9] However, micrometastases could be present in lymph nodes without node enlargement and equally enlarged nodes may be due entirely to inflammation.[10] The relationship between size of lymph nodes and presence of malignancy is highly variable. The diagnosis of mediastinal lymph node metastases by CT is based solely on size with the cut-off value being >1.0 cm on the short axis diameter. Mediastinoscopy, video-assisted thoracoscopic surgery and TBAC are used as invasive diagnostic procedures for the sampling of lymph node cells, but TBAC can be performed with relatively simple anaesthesia in a bronchoscopic examination.

Our study showed that TBAC confirmed metastases in 42% of cases with enlargement of the subcarinal nodes. This detection rate was lower than in previous reports, although a high detection (7/9) rate was achieved in patients with SCLC, consistent with previous reports.[7,8] One of the possible reasons for this low rate was that TBAC was performed only on subcarinal nodes, while TBAC was performed at multiple sites in other reports.[7,8] Accuracy of TBAC could not be assessed in the present study because metastases was not finally diagnosed in the TBAC-negative cases, and this is one of the study's limitations. Another limitation is that TBAC is a blind technique with guidance limited to a few endobronchial landmarks and mental reconstruction of the CT scan. We operated on 49

patients with NSCLC and subcarinal metastases was found in three patients by postoperative pathological assessment. The accuracy of TBAC was 94% in the operated patients, which showed the limit of TBAC in establishing a diagnosis. It is possible that the TBAC needle used in this study may not collect enough cells for assessment and would suggest our method might be less useful for identifying micrometastases of lymph nodes. Furthermore, lymphoid cells were obtained in only 112 (79%) of 153 cases. In other words, TBAC could not adequately sample the target lymph nodes in 21% of patients.

In operable cases, right upper lobe tumours might be more likely to spread to the paratracheal region than to the subcarinal region. However, as shown in Table 4, no exact correlation was observed between the site of primary tumour and the TBAC results. This may be due to the fact that more patients with advanced stage tumour were included and only 49 of 153 patients had surgery in our study.

Recent studies for the diagnosis of lung cancer have shown that the highest detection rate of metastases to lymph nodes is achieved by PET,[10] but the role of PET in the treatment plan remains controversial. Mediastinoscopy is usually the best choice for proof of metastases to mediastinal nodes, but it is unable to assess all lymph nodes. TBAC should be performed in combination with other diagnostic procedures. In order to improve the diagnosis by TBAC, TBAC under the guide of CT or endoscopic ultrasound has been developed,[10] although these procedures are still experimental. Metastases to the subcarinal nodes was demonstrated following TBAC in some patients without nodal enlargement. Few studies have been undertaken to assess the presence of metastases in mediastinal lymph nodes that are not enlarged, and TBAC may have diagnostic value in these cases. The potential contribution of the present study is to ask what a blind TBAC in normal sized nodes adds to preoperative staging. Of 119 patients with normal sized nodes there were seven with positive cytology on TBAC. Conversely there were three patients, which were not detected preoperatively in 49 operable patients. Based on the results of the present study, it might be difficult to recommend routine TBAC preoperatively. It was anticipated that analysis of the site of primary tumour might suggest which patients a clinician should have a blind TBAC but the data were not discriminatory as shown in Table 4.

Positron emission tomography is more accurate than CT for detecting mediastinal metastases. However, it should be noted that even PET scan frequently shows false-positive and false-negative in mediastinal staging in the range of 11–16%.[11] Because the detection rate of TBAC using our method was not very high, mediastinoscopy should still be considered the gold standard to confirm N2 disease. Toloza *et al.* reported a meta-analysis of invasive staging consisting of TBAC (TBNA), transtracheal needle aspiration, endoscopic ultrasound-guided needle aspiration and mediastinoscopy. They reported that TBAC has the worst sensitivity and negative predictive value among the invasive procedures.[9] However, considering that TBAC is an easy additional procedure during routine bronchofibreoscopy, the diagnostic yields of TBAC are comparable with other procedures. Furthermore, patients may avoid mediastinoscopy if TBAC is positive, therefore this is useful even if the yield is lower than mediastinoscopy.

Transbronchial aspiration cytology of the subcarinal nodes is a minimally invasive technique for staging lung cancer. It can provide useful information for diagnosis of metastases to subcarinal nodes.

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局所進行非小細胞がん治療におけるチロシン・キナーゼEGFR阻害薬：胸部放射線治療との併用療法

大江裕一郎[1]

要旨——切除不能局所進行非小細胞がんに対する標準的治療は化学療法と同時放射線治療であることがほぼコンセンサスとなっているが，治療成績向上のために新たなstrategyが必要と考えられる．Epidermal growth factor receptor (EGFR) を標的とする分子標的治療薬，ゲフィチニブは進行非小細胞肺がん，特に腺がん，非喫煙者，女性，東洋人などには高い効果を示すことが知られており，基礎研究では放射線治療との相乗効果も報告されている．Japan Clinical Oncology Group（JCOG）ではゲフィチニブ併用の意義を検証する放射線化学療法の第III相試験を念頭に置き，シスプラチン＋ビノレルビンによる化学療法後にイレッサと放射線治療を同時併用する臨床試験(JCOG0402MF)が進行中である．欧米で実施されたINTACT，ISEL，S0023などの第III相試験でゲフィチニブの延命効果が示されなかったが，ゲフィチニブをはじめとするチロシン・キナーゼEGFR阻害薬の導入は局所進行非小細胞がんの治療成績を向上させるための最も期待できるstrategyであることに変わりはない．(肺癌．2006;46:261-265)

索引用語——局所進行非小細胞肺がん，化学放射線治療，EGFR阻害薬，ゲフィチニブ

Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor Combined with Chemoradiotherapy for the Treatment of Unresectable Locally Advanced Non-small Cell Lung Cancer

Yuichiro Ohe[1]

ABSTRACT——Chemoradiotherapy is considered to be a standard treatment for unresectable locally advanced non-small cell lung cancer, but new strategies are essential to improve the treatment outcome. Gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor is a promising target-based agent for non-small cell lung cancer, especially in, non-smoking oriental female case of adenocarcinoma. Strong preclinical evidence indicates that the effects of epidermal growth factor receptor inhibition are additive to or synergistic with radiotherapy. The Japan Clinical Oncology Group has started a safety and efficacy trial of induction chemotherapy with cisplatin and vinorelbine followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced non-small cell lung cancer (JCOG 0402-MF). S0023 is a large, phase III, randomized trial comparing concurrent chemoradiotherapy and consolidation docetaxel with or without maintenance therapy with gefitinib. Unfortunately, S0023 was closed based on the interim analysis, which showed that the continuation of S0023 would not have shown a survival benefit for gefitinib. These results may indicate that the maintenance use of gefitinib after induction chemoradiotherapy does not improve the survival of patients with locally advanced non-small cell lung cancer. However, the incorporation of epidermal growth factor receptor tyrosine kinase inhibitors in chemoradiotherapy is still an attractive strategy for locally advanced non-small cell lung cancer. (*JJLC.* 2006;46:261-265)

KEY WORDS——Locally advanced non-small cell lung cancer, Chemoradiotherapy, EGFR inhibitor, Gefitinib

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はじめに

わが国では年間約6万人が肺がんで死亡している．肺がんはがんによる死亡原因の第1位となっており，今後さらに肺がんの発生および死亡が増加すると予測されている．しかし，肺がん全体の治癒率は20%以下といわれ，予後は極めて不良である．

局所進行非小細胞肺がんの標準的治療は胸部放射線治療とされていたが，meta-analysesの結果によりシスプラチンを含む化学療法と胸部放射線治療の併用が標準的治療と考えられるようになった．[1-3] さらに，現在では切除不能局所進行非小細胞がん治療に対する標準的治療は化学療法と同時放射線治療であることがほぼコンセンサスとなっている．[4,5]

Japan Clinical Oncology Group（JCOG）肺がん内科グループで実施した切除不能局所進行非小細胞がんに対する放射線化学療法の6試験に登録された240例の解析では，全症例の生存期間中央値（MST）は16.1月，5年生存率は14.4%であった(Figure 1)．[6] しかし，1日2回照射法，総線量増量，イリノテカンの併用などにより治療成績が向上する可能性は示唆されず治療成績向上のために新たなstrategyが必要と考えられる．[6]

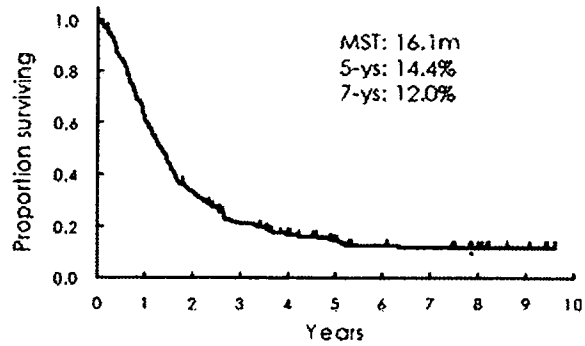

Figure 1. Survival of patients with locally advanced NSCLC treated with chemoradiotherapy in JCOG studies (n=240).

局所進行非小細胞肺がんに対する標準的治療

局所進行非小細胞肺がんの標準的治療は化学療法と同時放射線治療であることがほぼコンセンサスとなっているが，標準的な化学療法レジメンは確立していない．現在，化学療法単独での治療が適応となるIV期非小細胞肺がんに対してはmeta-analysesなどの結果により，プラチナ製剤と1990年代に開発されたいわゆる新規抗がん剤の2剤併用が標準的と考えられている．ただし，新規抗がん剤を含む4つの併用化学療法レジメンを比較検討する第III相試験をはじめとして，新規抗がん剤を含む様々な併用化学療法を含む試験が実施されているものの，どのレジメンが生存期間延長に最も有効なのかの結論は得られていない．局所進行非小細胞肺がんに化学療法と放射線治療を併用する場合の化学療法に関しても同様で，新規抗がん剤を含むレジメンと放射線治療の併用が標準的に使用されてはいるが，具体的な化学療法レジメンが標準的治療として確立しているわけではない．放射線治療と同時併用した場合の化学療法の効果を比較した第III相試験は実施されておらず，僅かにCancer and Leukemia Group B（CALGB）が実施した無作為化第II相試験の結果が報告されているのみである．[7] また，一括投与の化学療法と週1回程度に分割した低用量の化学療法を比較した第III相試験の結果も報告されていない．[5]

国立がんセンター中央病院を中心に実施されたシスプラチン＋ビノレルビンと同時胸部放射線治療の第I相試験では3年生存率50%の成績が報告されている．[8] Southwest Oncology Group（SWOG）で実施されたシスプラチン＋エトポシドと同時胸部放射線治療後に地固め療法としてドセタキセルを実施した試験（S9504）で，MST 26月，5年生存率29%の良好な成績が報告されたことを受け，シスプラチン＋ビノレルビンと同時胸部放射線治療にドセタキセルによる地固め療法を実施するpilot studyが実施された．[9-11] この試験では評価可能症例93例が登録され，奏効率82%，MST 32.8月と良好な成績が得られたものの3コースのドセタキセルが完遂できたのは34例（37%）のみで，34例には全くドセタキセルの投与が行われていなかった．[11] また，4例の治療関連死を認めており，シスプラチン＋ビノレルビンと同時胸部放射線治療後のドセタキセルによる地固め療法をわが国で実施するのは難しいと判断された．しかし，シスプラチン＋ビノレルビンと同時胸部放射線治療はわが国で比較的多く行われているレジメンの1つと思われる．

チロシンキナーゼEGFR阻害薬と放射線治療の併用

Epidermal growth factor receptor (EGFR)のチロシンキナーゼ阻害薬であるゲフィチニブ(イレッサ，ZD1839)は，既治療非小細胞肺がんを対象とした第II相試験で日本人に対しては27.5%の奏効率が報告されている．また，有効例に対しては劇的な腫瘍縮小効果と既存の抗がん剤と比較すると極めて長い効果持続期間を示すことが知られている．

がん細胞株を用いた実験ではEGFRの発現量と放射線感受性が逆相関することが報告されている．また，*in vivo*の実験ではEGFRチロシンキナーゼ阻害薬であるゲフィチニブ，エルロチニブと放射線の相乗効果が報告されている．[12] また，頭頸部がんに対しては，EGFRに対