TABLE 1. Histologic subtype and tumor size distribution in resected specimens

Subtype	No. of cases	Range (mm)	Median (mm)	Resection type (W/S/L)
Type A	2	9-10	—	1/1/0
Type B	23	6-21	12	21/2/0
Type C	15	10-19	14	1/0/14
Atypical adenomatous hyperplasia	5	5-14	8	2/3/0
Fibrosis	4	6-15	10	4/0/0
Granuloma	1	6	—	1/0/0

W/S/L, Wedge resection/segmentectomy/lobectomy plus lymph node dissection, in numbers of patients.

enough to directly palpate with one or two fingers through the ports. Initially, because of the nature of GGOs, we were not sure that we would be able to palpate and localize these lesions. However, we found the GGO-containing lung parenchyma to have a different texture than the surrounding normal parenchyma. When it was impossible to determine the tumor location or periphery through the thoracoscopy ports, the procedure was converted to a small thoracotomy. Segmentectomy and lobectomy were done through a muscle-sparing thoracotomy, typically about 12 cm in length.

During the trial, Noguchi classification assessment took about an hour because of the extensive image recording required for study purposes. There were 2 Noguchi type A tumors, 23 Noguchi type B tumors, 15 Noguchi type C tumors, 5 atypical adenomatous hyperplasias (AAH), 4 fibroses and 1 granuloma. Their size distribution is summarized in Table 1. In addition to the intraoperative slides, further postoperative slides were prepared and studied. The postoperative slides did not differ significantly from the intraoperative slides. One initial frozen-section type B diagnosis was revised to type C after postoperative pathologic study. We discussed this with the patient in detail, and he chose not to have any further treatment. He is still alive without any signs of recurrence after more than 5 years.

No morbidity or mortality has been seen. During the follow-up period, with a range of 19 to 68 months (median 50 months), as this is being written (May 2004), there have been no recurrences. Enrollment concluded without a forced quit.

Discussion

The Lung Cancer Study Group conducted a prospective randomized trial to evaluate the role of limited resection versus lobectomy for T1 N0 M0 non–small cell lung carcinomas. They reported significantly increased local recurrence and marginally but not significantly higher cancer death rates in the limited resection group relative to the lobectomy group. On the basis of their observations, they concluded that lobectomy was the surgical treatment of choice for patients with T1 N0 M0 non–small cell lung carcinomas.[1] However, there has been some question whether limited resection is always contraindicated. We reported a retrospective review of peripheral lung cancers of all types less than 1 cm in diameter in 1998.[5] Of the 16 small tumors, 7 displayed an invasive nature. We therefore concluded that tumor size alone is not a sufficient indicator for limited resection. This observation is consistent with a recent report on subcentimeter lung cancers from the Mayo Clinic.[13] However, in patients with impaired respiratory function, limited resection has been tried and has often yielded acceptable outcomes.[14] Several researchers have reported, although in retrospective studies, that limited resection could be an acceptable alternative in patients with T1 N0 M0 disease and insufficient pulmonary reserve.[3,4]

Noguchi and associates[7] conjectured that type A and type B tumors are in situ carcinomas, whereas type C is an advanced stage of types A and B. If Noguchi type A and B peripheral tumors are truly in situ, noninvasive carcinomas, limited resection would be the management of choice for these tumors. As a result, in August 1998 we started this prospective clinical trial with intraoperative frozen-section examination to establish the Noguchi classification and limited resection for probable in situ adenocarcinoma with GGO characteristics in the lung periphery.

As noted, Shimosato and associates[6] evaluated cancer fibrotic focus or scarring and patient prognosis. Increased lymph node metastasis and pleural and blood vessel invasion were present with greater scarring and fibrotic focus. Aoki and colleagues[15] noted the pleural indentation and vascular convergence increased with tumor development in Noguchi type B and C tumors. This information was incorporated into our patient selection criteria.

A concern in our trial was the accuracy of frozen-section examination. The correct classification as atypical adenomatous hyperplasias or Noguchi type A,[16] or as Noguchi type B or type C tumors,[7] has been reported as being difficult, even more so with frozen sections. We think that the equipment developed for this trial and the methods and techniques applied contributed significantly to our outcomes. Finding the GGO "spongelike" structure could be felt in the lung made locating the lesion and ensuring sufficient resection margin much easier. The customized stapling cartridge and negative-pressure specimen inflation were useful in frozen-section preparation. They made it much easier to work with the specimen. Stereoscopic microscopy enabled the pathologist to locate regions of interest for detailed examination. For Noguchi subtype determination, VvG staining proved to be a powerful aid in separating Noguchi type A and B

from type C. These tools, methods, and techniques, together with the expertise of our pathologist, resulted in high frozen-section examination accuracy: only 1 type B lesion in 50 cases was recategorized as type C postoperatively. This patient underwent only a wedge resection and, after being fully informed of the underdiagnosis, potential outcomes, and additional treatment options, decided not to undergo any further treatment. He is still alive after more than 5 years without recurrence.

The other patients with 14 Noguchi type C tumor, whose diagnoses were confirmed by postoperative pathologic study, underwent lobectomy and systematic lymph node dissection after the frozen-section diagnosis. Detailed pathologic study after the operation revealed no nodal involvement, pulmonary metastases, lymphatic permeation, or vascular invasion in the specimens. It is likely that these patients will survive. Kondo and colleagues[17] studied air-containing lesions 2 cm or smaller, including GGO or subsolid tumors. These lesions were of interest if their opacity area decreased by more than 50% on the mediastinum-setting CT from the lung-setting CT. They reported that this patient cohort survived 5 years without recurrences after either standard or limited resection, and most of them had no node metastases or vessel involvement. So although Noguchi type C tumors are invasive, they may well represent an early invasive stage. On the basis of our finding of no nodal involvement, lymphatic permeation, or vascular invasion, and Kondo and colleagues' similar results and survival rates,[17] we conjecture that Noguchi type C tumors in our trial might well also have been curatively treated by limited resection. However, we did not address this issue in our trial.

During the trial, Noguchi classification assessment took about an hour. This was mostly because we extensively recorded sample images for study purposes. Our pathologist believes that in routine practice, without extensive image recording, the determination can be accomplished in 15 to 20 minutes.

There was no definite difference in size distribution among subtypes. However, all Noguchi type C tumors were 1 cm or larger, whereas other subtypes included subcentimeter tumors. This strengthens the suggestion that limited resection is indicated when a GGO tumor is smaller than 1 cm. Although this contradicts our previous review[5] and a recent report on subcentimeter lung cancers by the Mayo Clinic,[13] that is probably because those series included non-GGO lesions.

In conclusion, Noguchi classification type A and B tumors appear to be in situ, noninvasive carcinomas, and limited resection achieves the goals of local control and survival. With about 5.5 years total on this study, it may be still too early for strong conclusions. Considering the probable slow-growing nature of GGO lesions,[18] 5 years of follow-up is not long enough to conclude that the disease is cured. We will probably have to continue our follow-up for an additional 5 years. However, initial results are encouraging. With the customized stapling cartridges, negative-pressure specimen preparation and inflation, stereoscopic microscopy, VvG staining, and a skilled pathologist, frozen-section classification of Noguchi subtype has been highly accurate. Our results suggest that lung tumors 2 cm or less in diameter with high-resolution CT scan findings of GGO and without evident pleural indentations or vascular convergence may be safely managed with only limited resection.

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REVIEW ARTICLE

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

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ABSTRACT

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

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

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

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

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INTRODUCTION

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

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

HISTORY OF LUNG ADENOCARCINOMA: HISTOLOGIC SUBCLASSIFICATION BY THE WHO

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

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

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

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

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

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

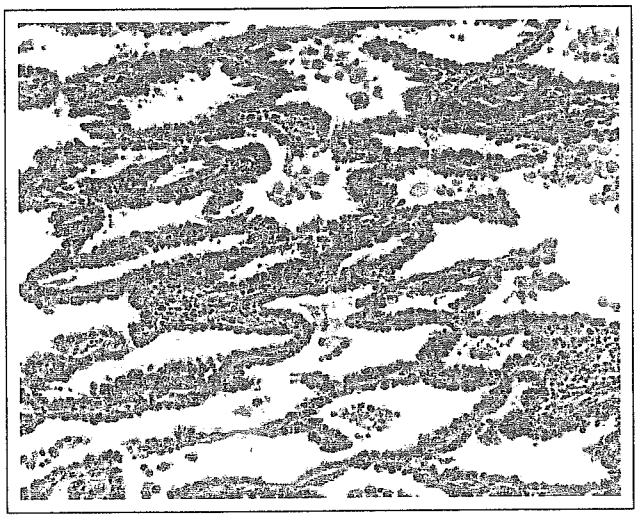

Fig 1. Bronchioloalveolar carcinoma, nonmucinous type. The alveolar walls are lined by a cellular proliferation of atypical pneumocytes that have a hobnail morphology. No invasion is seen.

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

GROSS AND RADIOLOGIC PATTERNS OF BRONCHIOLOALVEOLAR CARCINOMA AND INVASIVE ADENOCARCINOMA

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

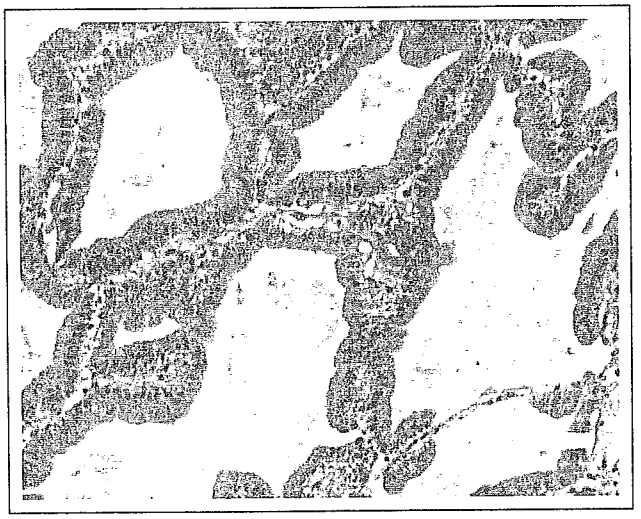

Fig 2. Bronchioloalveolar carcinoma, mucinous type. The alveolar walls are lined by a cellular proliferation of columnar cells with abundant apical mucin and small basally oriented nuclei. No invasion is seen.

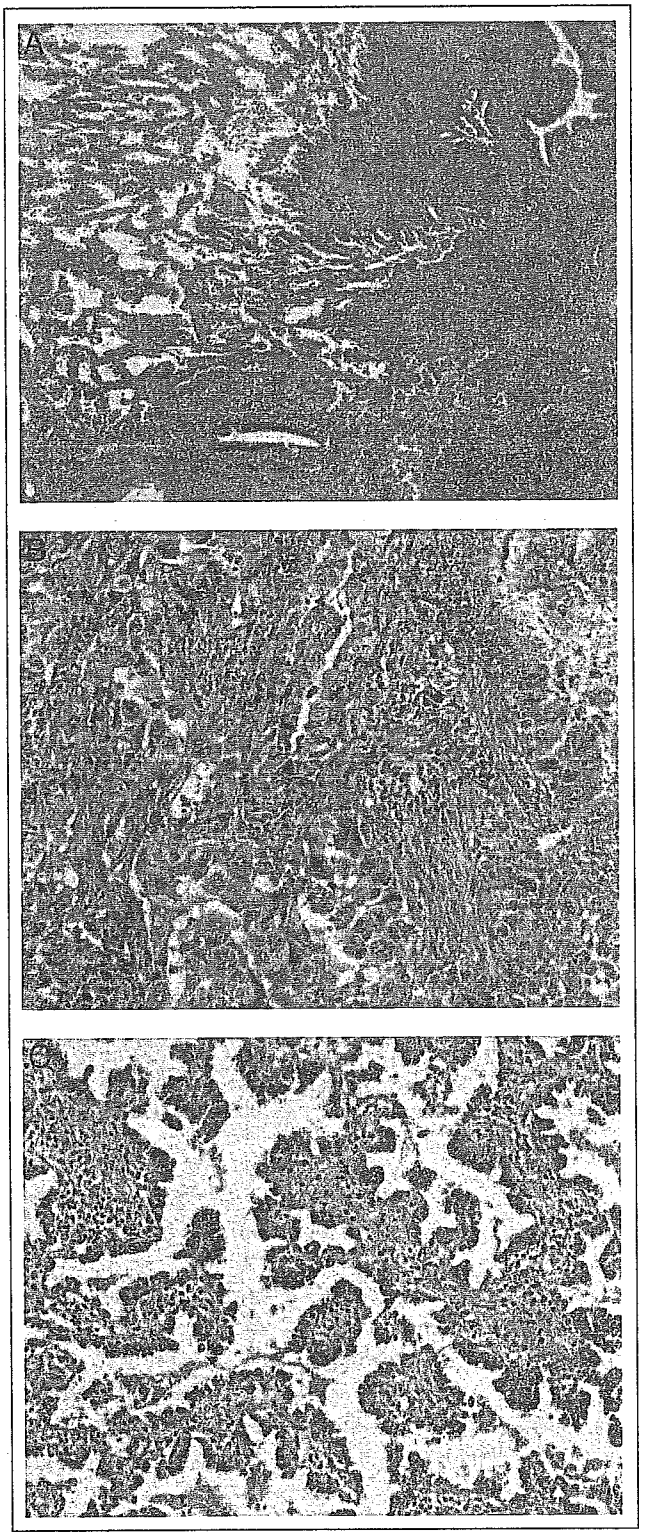

Fig 3. Adenocarcinoma, mixed subtype. (A) A bronchioloalveolar pattern is seen to the left and an invasive component on the right (hematoxylin and eosin X 4). (B) The invasive component consists of acinar glands infiltrating a fibrous stroma (hematoxylin and eosin X 40). (C) Papillary adenocarcinoma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

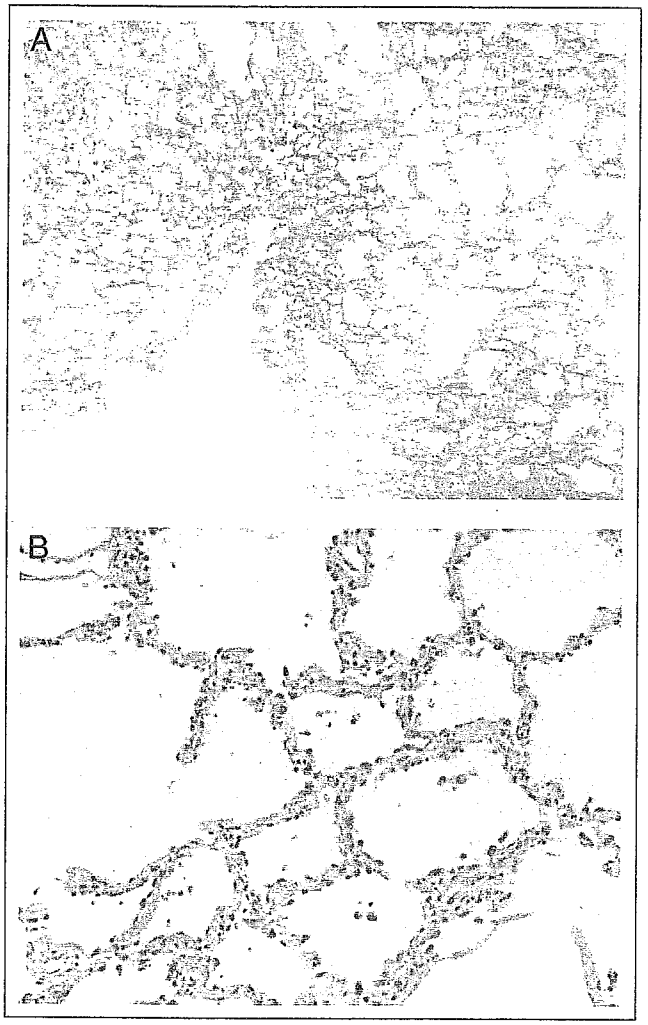

Fig 4. (A) Atypical adenomatous hyperplasia: Two localized nodular areas of atypical adenomatous hyperplasia shows hypercellular alveolar walls (hematoxylin and eosin X 2). (B) The alveolar walls are lined by atypical pneumocytes. There are gaps between the pneumocytes and there is mild thickening of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

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

Table 2. Bronchioloalveolar Carcinoma: Gross Patterns of Lung Involvement

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

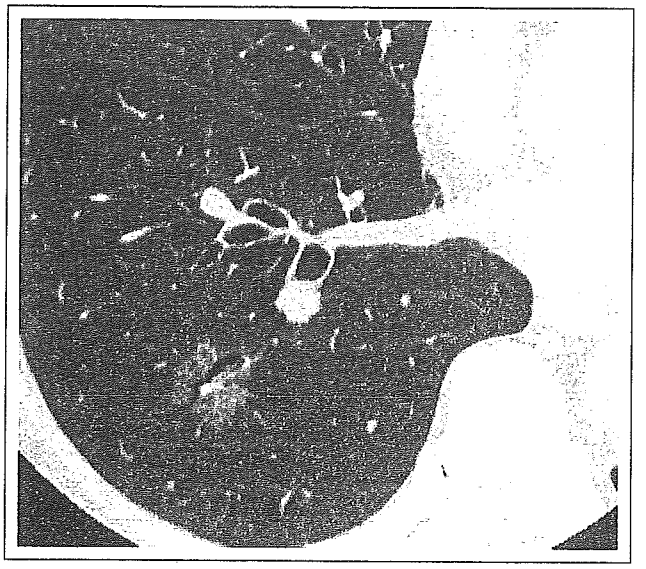

Fig 5. Ground glass density or nonsolid nodule. Chest computed tomography image focused on the right lower lobe shows a 1.5-cm ground-glass density or nonsolid nodule.

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

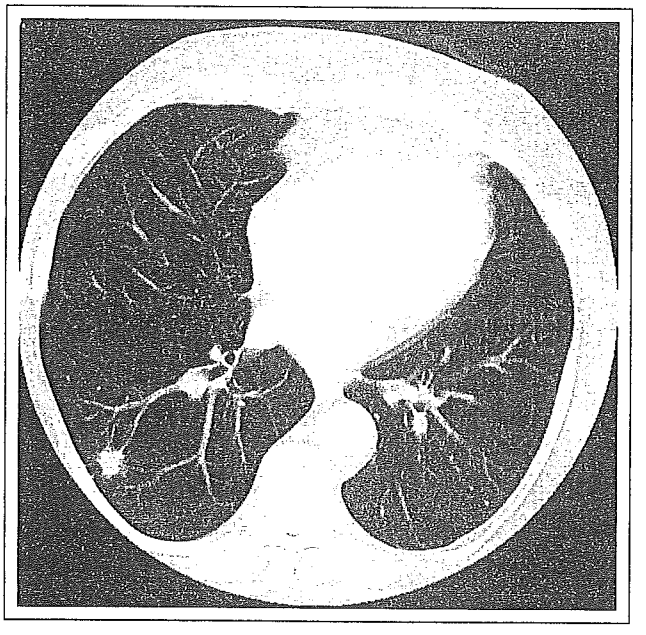

Fig 6. Solid nodule. Chest computed tomography image at the level of right inferior pulmonary vein shows a 1-cm solid nodule with feeding vessels.

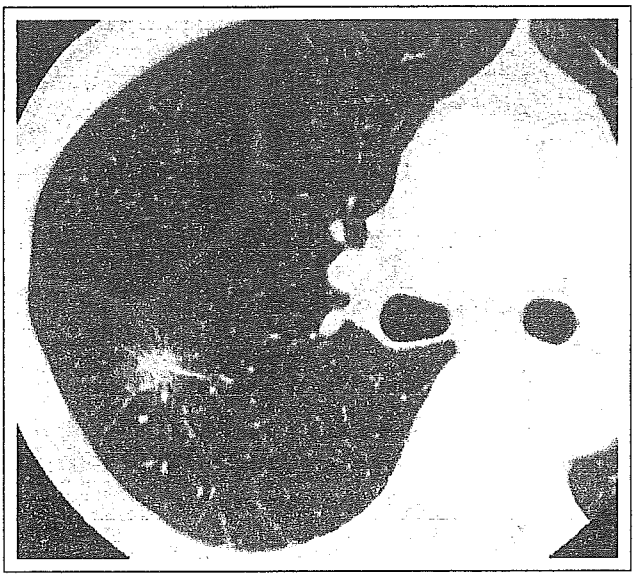

Fig 7. Part-solid nodule. Chest computed tomography image shows a 2-cm spiculated mixed-density nodule with solid central part and nonsolid peripheral portion. The adjacent major fissure is pulled toward the nodule.

Solitary, Small, Peripheral Lung Adenocarcinomas

Pathologic aspects. Over the past 10 years, a series of important articles about solitary, small (2 or 3 cm or less) peripheral nodular lung adenocarcinomas has revolutionized our concept of the pathology of these tumors. This began in 1995 with the work of Noguchi et al,[28] which pointed out that small peripheral lung adenocarcinomas with a pure BAC pattern and no invasion had 100% 5-year survival, and patients with mixed BAC and invasive components had a survival of 75% in contrast to those with a purely invasive growth pattern who had a survival of 52%.[28] These findings greatly influenced the 1999 WHO/IASLC Classification Panel, who proposed a new, stricter definition of BAC that required it to show pure lepidic growth without invasion of stroma, pleura, or

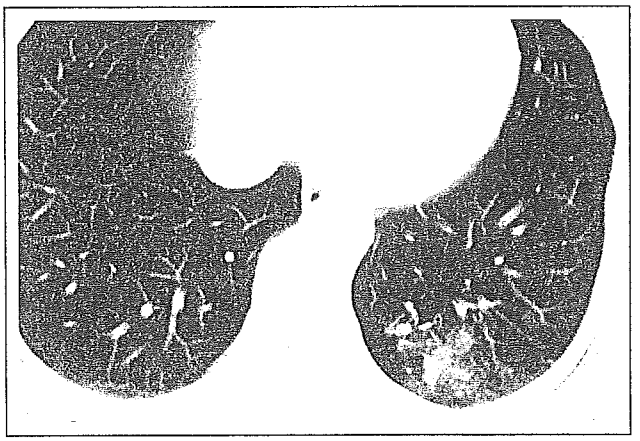

Fig 8. Multicentric bronchioloalveolar carcinoma. Chest computed tomography image shows multiple nodules in the left lower lobe.

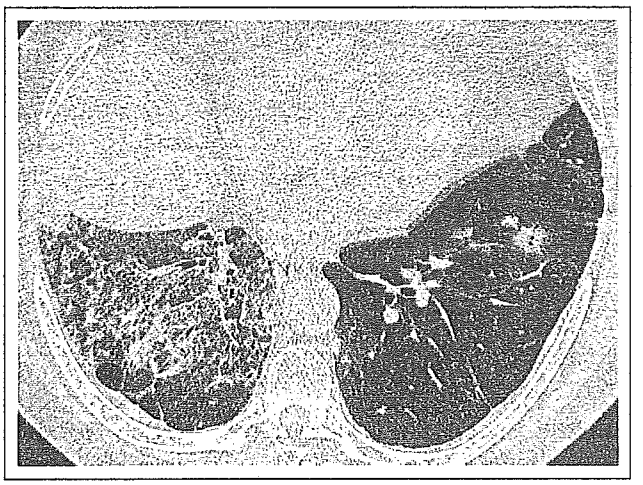

Fig 9. Bilateral multifocal bronchioloalveolar carcinoma with consolidative pattern. Computed tomography image shows large consolidation in the right lower lobe and nodules in the left lower lobe.

blood vessels.[16] The same proposal was also adopted by the 2004 WHO classification.[17] One implication of these criteria is the importance of complete histologic sampling of tumors 3 cm or less in diameter if they have a BAC component, so that focal areas of invasion can be identified.

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

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

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

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

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

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

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

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

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

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

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

Lung Adenocarcinomas Presenting as Multiple Nodules and Lobar Consolidation

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

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

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

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

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

SMALL BIOPSY SPECIMENS AND CYTOLOGY

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

GLOBAL EPIDEMIOLOGIC DIFFERENCES

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

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

NEED FOR CONSENSUS WITH BAC VERSUS ADENOCARCINOMA TERMINOLOGY

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

NEED FOR FUTURE STUDIES

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

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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特集　肺癌の画像診断法：最近の展開

肺癌のCT画像診断における コンピュータ診断支援システムの現状と展望

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要　旨

肺癌のCT画像診断においてコンピュータ診断支援システム（CAD）に期待されるのは肺結節の存在診断，質的診断などである。研究レベルでは，CAD併用により，存在診断能の向上が報告されている。すでに製品版としていくつかのシステムが提供されているが，実地の臨床現場や検診現場で即戦力となるシステムの開発が今後の課題である。

Key words：低線量CTによる肺癌検診，コンピュータ診断支援システム，ラングイメージデータベース，存在診断，質的診断/Lung cancer screening by low-dose helical CT, computer-aided diagnosis, lung image database consortium, detection and classification of pulmonary nodules

1 はじめに

本項においてはCT画像を用いた肺癌のコンピュータ診断支援（computer-aided diagnosis，以下CAD）について概説する。

2 低線量CTによる肺癌検診の検診CT画像を用いたCAD開発

実際の肺癌CT検診の検診CT画像を用いたCAD開発は，現在のところ，日本で実施されている（された）検診プロジェクトのデータのみで行われている（表1）。低線量CTによる肺癌検診は1993年に東京都予防医学協会の「東京から肺がんをなくす会」[1]により開始された。国立がんセンター，東京都予防医学協会，徳島大学工学部仁木研究室，東芝の共同研究によりCADのプロトタイプが開発された[2]。このCADシステムは，1997年9月より，国立がんセンターの中央病院と東病院において，「東京から肺がんをなくす会」のsingle slice CTを用いた低線量CTによる肺癌検診の画像診断に際し試験運用が開始された。2002年9月より，比較読影機能を有するCADシステム（UNIX版）[3]（図1）に更新され，2003年からは，Windows XP professional上でも作動するシステムとなっ

Current Status and Perspective of Computer-Aided Diagnosis for Lung Cancer
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表 1　低線量CTによる肺癌検診のデータのCADによる解析

著者	仁木*		後藤[5]	Armato[7]	Armato[9]	
CT装置	Single	Multislice	Single	Single	Single	
電圧 (kVp)	120	120	120	120	120	
電流 (mA)	50	30	50	25/50	25/50	
pitch	2	2	2	2	2	
ビーム幅 (mm)	10	2	10	10	10	
再構成間隔 (mm)	10	10	10	10	10	
肺癌結節の数	59	16	80	38	69	
CADの感度 (%)	76	81	98.7	84	83	80
false positive (1被験者あたり)	8.5	5.6	13.2			
false positive (1スライスあたり)				1	1.6	0.85

*未出版データ。[5][7][9] 文献番号。

〔文献5) 後藤良洋, 角村卓是, 中島邦佳, ほか. 肺癌CADシステム及び付加機能の開発. 医用画像情報学会雑誌 2004；21：91-6. 7) Armato SG, Li F, Giger ML, et al. Lung cancer：Performance of automated lung nodule detection applied to cancers missed in a CT screening program. Radiology 2002；225：685-92. 9) Armato SG, Roy AS, MacMahon H, et al. Evaluation of automated lung nodule detection on low-dose computed tomography scans from a lung cancer screening program. Acad Radiol 2005；12：337-46. より引用〕

た。本システムの性能としては，東京から肺がんをなくす会の症例の10 mm再構成検診CT画像を解析した成績としては，single slice　CTの場合では，肺癌検出の感度は79%（45例/59例中），false positiveは1被験者あたり8.5個，multislice CTの場合（2 mm×4列で撮影し10 mm再構成した検診CT画像）では，肺癌検出の感度は81%（13例/16例中），false positiveは1被験者あたり5.6個となっている。使用した装置はsingle slice CTは東芝TCT-900S superhelixで，撮影条件は120 kV，50 mA，X線ビーム幅10 mm，スキャン時間1秒/1回転，寝台移動速度20 mm/秒で画像再構成間隔は10 mmである。Multislice　CTとしては東芝Aquilionで，撮影条件は120 kV，30 mA，X線ビーム幅2mm×4列，スキャン時間0.5秒/1回転，寝台移動速度22 mm/秒で画像再構成間隔は10mm，2mmである。2005年からIBM製の900万画素の液晶モニター上で新規のアルゴリズムによりmultislice CT対応のCADシステムの構築が開始されている。

日立健康管理センターにおいて1998年より総合健康診断の胸部画像診断として肺癌CT検診を開始した[4]。日立健康管理センターと日立メディコ技術研究所と共同で肺癌検診用CADシステム「canPointer™」を開発した[5]。CanPointer™の性能は，日立健康管理センタにおいて1998年4月～2001年3月の間に発見された肺癌78症例80病変に対して解析を実施すると感度は98.7%（80病変中79病変を検出）し，false positiveは1症例あたり13.2個であったと報告している[5]。

検診車に搭載した低線量CTによる肺癌検診である信州プロジェクト[6]の検診CT画像を用いてシカゴ大学放射線科グループ[7][8]が

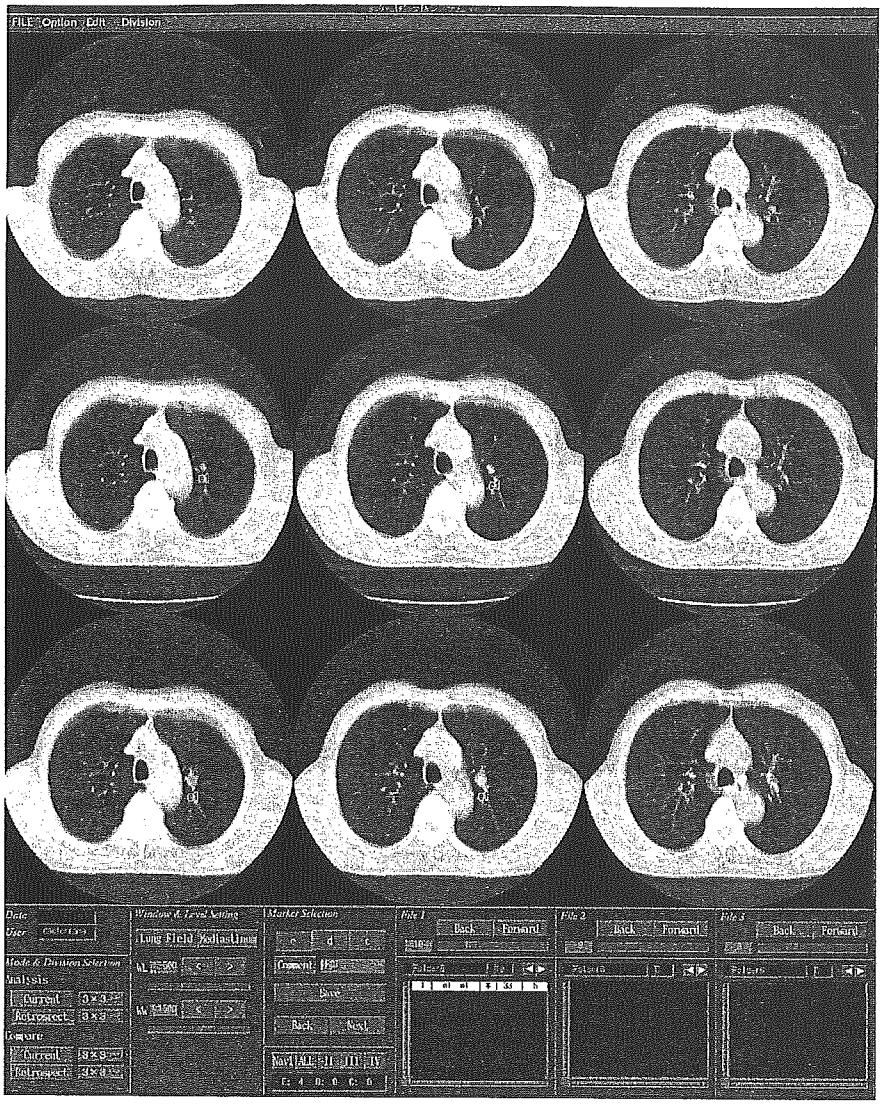

図 1　比較読影機能をもつCADシステムの画面
下段が最新検診CT画像，中段が6カ月前の検診CT画像，上段が1年前のCT画像である。

CADアルゴリズムを開発した。その性能は，信州プロジェクトにおいて見落とされた肺癌の検診CT画像を解析した場合，感度が84%（見落とされた肺癌38例中32例を検出）で，false positiveは1スライスあたり1個であった[7]。実際の検診の際，診断医師が肺結節を発見できなかった肺癌は38例中23個あり，また，肺結節を発見できたが肺癌として疑わなかった肺癌は38例中15個であった。これらの存在診断ができなかった23個の感度は78%（23例中18個を検出）であり，また，質的診断ができなかった15個の感度は93%（15例中14個を検出）であった。その後さらに検討がなされ[9]，66例の肺癌症例を解析した場合，全体では感度は80%であり，性状ごとの感度ではsolid，mixed GGO（GGO：ground-glass opacityのなかにsolid成分を含むもの），pure GGOで，それぞれ90%，80%，56%であり，false positiveは1スライスあたり0.85個であった。

肺結節の視認性の程度による感度では，明瞭に見える結節，不明瞭に見える結節，極めて不明瞭に見える結節で，それぞれ94%，78%，46%であった。

3 Multislice CT 対応の CAD

R2 techonology 社の ImageChecker® CT は2004年に FDA（Food and Drug Administration）の認可を受けた[10]。性能としては，4 mm 以上の solid 結節を80%の感度で検出する[11]。

Medicsight 社の LungCAD™ は，2004年に FDA の認可を受けた CAD で，ユーザー側で検出対象とする肺結節の大きさと感度を設定できるシステムとなっている[12]。

4 肺結節の存在診断に関する研究

読影方法と CAD の併用に関する研究では，低線量 multislice CT の CT 画像を用いて，大きさが1～18 mm（平均3.9 mm）の肺結節457個に対して CAD の診断能の評価が報告されている[13]。結節検出の感度は，1人の放射線科医師による単独読影，CAD の解析，2人の放射線科医師による2重読影では，それぞれ54%，55%，67%であった。放射線科医師による単独読影の後にセカンドオピニオンとして CAD 解析結果を参照すると感度は79%に増加し，2人の放射線科医師による2重読影の感度より優れていた。他の検討でも CAD を併用した放射線科医師の結節検出の感度は，2人の放射線科医師による2重読影の感度より優れていたと報告されている[14]。

Multislice CT 画像上の309個の結節の検出における CAD の役割について検討がなされた[15]。CAD と放射線科医師の感度は，それぞれ81%と85%で有意差がなかったが，5 mm 以下の結節の検出と，他の既存構造に接していない結節の検出の CAD と放射線科医師の感度は，それぞれ83%対75%と，93%対76%で，CAD の方が有意に優れていた。逆に，5 mm より大きい結節の検出と，他の既存構造に接している結節の検出の CAD と放射線科医師の感度は，それぞれ79%対98%と，71%対91%で，放射線科医師の方が有意に優れていた。

この研究で開発された CAD システムは放射線科医師の診断を補完する役割を果たす可能性が示唆されたと報告している。以上の検討とほぼ同じ結論が他の検討でも報告されている[16]。

Multislice CT で撮影された胸部 CT の raw data より異なるスライス厚と再構成間隔の画像を retrospective に作成し，CAD の性能評価が検討されている[17]。

スライス厚と再構成間隔は，thin 群1 mm/1 mm（スライス厚/再構成間隔），overlap 群5 mm/1 mm，thick 群5 mm/5 mm の3種類が作成された。それぞれの群において指摘された肺結節数は，それぞれ，thin 群126個，overlap 群121個，thick 群114個であった。CAD の感度と1被験者あたりの false positive は，thin 群95%/5.4個，overlap 群94%/9.7個，thick 群89%/23.6個であった。以上の結果より，CAD の感度はスライス厚が大きくなると減少するが，再構成間隔が小さくなれば向上すると結論している。異なるスライス厚による CAD の性能評

価は，4mm，2mm，0.75mmでも検討されている[18]。0.75 mmのスライス厚の画像で評価する時に，とりわけ肺結節の大きさが10 mm未満の際，CADの性能は放射線科医師の診断能より優れており，第2読影者としての役割が示唆されている。

Multislice CT画像を用いたCADの肺結節の存在診断に関する研究結果の一部を**表2**にまとめた。

5 肺結節の質的診断に関する研究

発見した肺結節の良悪性の質的診断については，CT画像上の結節内部のvoxel間の曲率情報を用いて鑑別するアルゴリズムが開発された。鑑別実験の結果をROC曲線で解析すると，ROC曲線下の面積Azで診断能を評価するとコンピュータが0.97，放射線科医師のなかで専門医では0.90，0.86であり，レジデントでは0.72でありCADの鑑別能が優れていた[19]。他の実験では，6～20 mmの肺癌28例と，大きさと性状が肺癌と一致した良性結節28例を用いて16人の放射線医師が，CADの支援なしで最初に読影し，次にCADの支援ありで読影した。ROC曲線にて解析するとAzはCADが0.83であり，放射線医師の平均AzはCADの支援なしで0.79であったが，CADの支援ありで0.85に有意に増加した。この際，CADの支援を受けると放射線科医師のAzがCAD単独のAzより有意に増加したと報告している[20]。

そのほか，良性と悪性の類似画像を表示し，未確診結節の良悪性の鑑別を支援する手法も提案され[21][22]，造影剤を使用したthin-section CT画像を用いて肺結節の内部構造を解析することにより良悪性の鑑別の可能性が報告されている[23]。

6 CADシステムの評価上の問題点

以上，CT画像を用いたCADシステムに関して概説したが，一番の問題点は個々のシステムはそれぞれの開発グループの画像データベースのみを解析した結果しかもっていないことである。共通の画像データベースを解析した結果でないので，システム間の性能の比較評価が厳密な意味において不可能な現状である。この問題を打破するために，アメリカにおいてはNational Cancer Institute (NCI) 主導で以下に述べる共通の画像データベース作りが進行中である。

7 Lung Image Database Consortium

Lung Image Database Consortium (LIDC)[24][25]とは，アメリカのNCIが予算を出してアメリカの5つの大学が協力して，胸部CT上の肺結節を解析するCAD研究，すなわち，CADの開発，性能向上，評価を促進するために共有できる画像データベースを作成し，インターネットを通じて世界中の研究者に公開しようという目的で設立された研究母体である。このデータベースにより，解剖学的，病理学的な正確な情報に基づいた肺結節の存在診断や質的診断に関わるCADシステムの性能評価が可能となる。2005年11月の北米放射線学会までに300例の肺癌症例のCT画像データが公開予定となっている[26]。

表 2　Multislice CT を用いた CAD の性能

Author	Wormanns[13]	Rubin[14]	Lee[15]		Marten[16]	Kim[17]		
CT scanner	VolumeZoom	VolumeZoom	M×8000	LightSpeed Ultra	Sensation 16	Volume Zoom		
detector	4	4		8	16	4		
tube voltage (kVp)	120	120	120	120	120	120		
tube current (mA)		200～300	350	250～400				
tube current (mAs)	20				80	120		
pitch	1.75	1.5～1.75						
table feed (mm/rot)					19.2			
slice thickenss (mm)	1.25	1.25	2	1.25	0.75	1	5	5
reconstruction increment (mm)	0.8	0.6	1	1.25	0.6	1	1	5
number of nodules	457	195	309		135	126	121	114
nodule size (mm)	1～18		2～30		1～29.6			
mean size of nodule (mm)	3.9		5.8		4.4			
sensitivity of radiologist (%) (single reading)	54	50	85		53			
sensitivity of radiologists (%) (double reading)	67	63						
sensitivity of CAD (%)	55	65	81		76	95	94	89
sensitivity of radiologist+CAD (%)	79	76			93			
false positive (per scan) of CAD		3	28.8		0.55	5.4	9.7	23.6

[13)～17)] 文献番号

〔文献 13) Wormanns D, Beyer F, Diederich S, et al. Diagnostic performance of a commercially available computer-aided diagnosis system for automatic detection of pulmonary nodules : Comparison with single and double reading. Fortschr Rontgenostr 2004 ; 176 : 953-8. 14) Rubin GD, Lyo JK, Paik DS, et al. Pulmonary nodules on multi-detector row CT scans : Performance comparison of radiologists and computer-aided detection. Radiology 2005 ; 234 : 274-83. 15) Lee JW, Goo JM, Lee HJ, et al. The potential contribution of a computer-aided detection system for lung nodule detection in multidetector row computed tomography. Invest Radiol 2004 ; 39 : 649-55. 16) Marten K, Engelke C, Seyfarth T, et al. Computer-aided detection of pulmonary nodules : Influence of nodule characteristics on detection performance. Clin Radiol 2005 ; 60 : 196-206. 17) Kim JS, Kim JH, Cho G, et al. Automated detection of pulmonary nodules on CT images : Effect of section thickness and reconstruction interval-initial results. Radiology 2005 ; 236 : 295-9. より引用〕

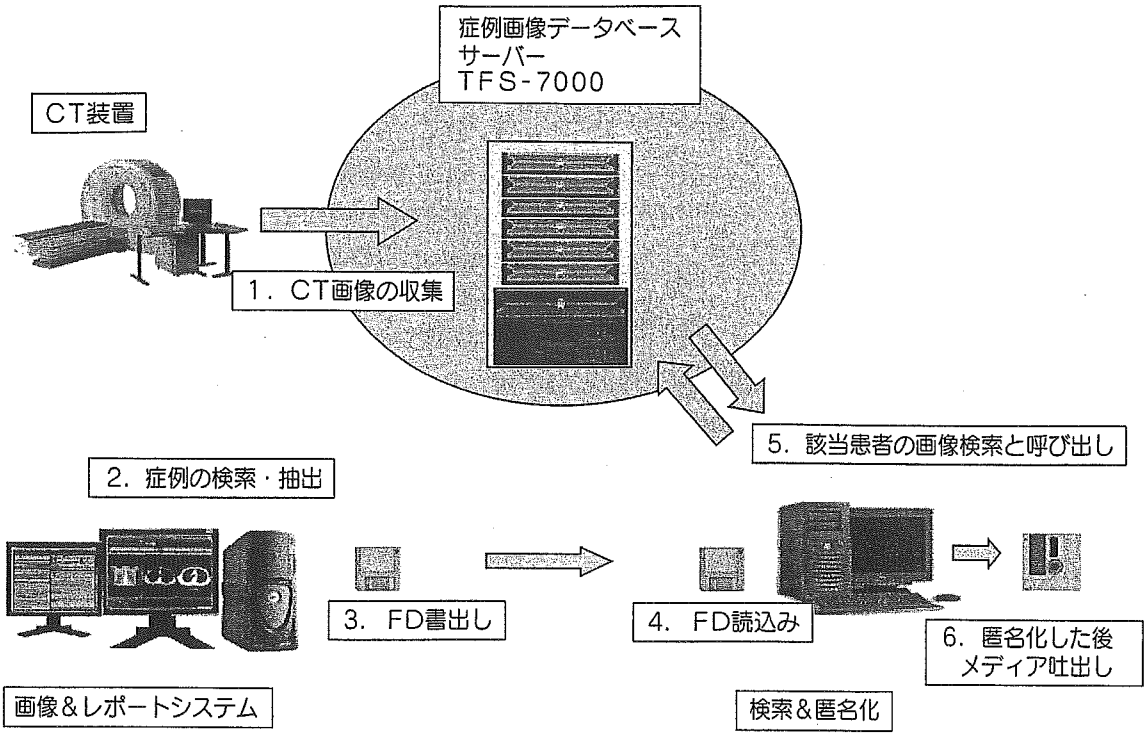

図 2　がん予防・検診研究センターの画像データベースシステム

8 国立がんセンターがん予防・検診研究センターの肺癌検診の画像データベース

がん予防・検診研究センターにおいて，2004年2月より総合検診あるいは単独検診として肺癌検診が開始となった。5 mm以上10 mm未満の肺結節を指摘された受診者は，検診肺外来にてlow-doseの全体の肺の撮影と肺結節部位を通常のthin-section CT撮影を実施している。検診の受診者のCT画像と検診肺外来受診時点でのCT画像はすべてraw dataを保存するとともに，CAD開発のため専用のサーバーに再構成されて蓄積されている（図2）。国立がんセンターの倫理委員会，および個人情報保護小部会の承認を経て，これらのCT画像は匿名化のうえ，医用画像工学を専門とする大学工学部および企業とのCAD開発の共同研究に提供される予定である。

9 期待されるCAD

Multislice CTが肺癌検診に導入されるようになり医師が読影しなければならない画像枚数はsingle slice CTによる肺癌検診と比較して飛躍的に増加している。当がん予防検診研究センターにおいては，1 mm×16列で撮影し，2 mmと5 mmの再構成間隔の画像で読影している。1日あたりの検査数としては，総合検診枠のなかの肺癌検診が25件，そのほかに肺癌単独検診枠が10件で，合計35件である。35件すべての検診を実施したと仮定すると，1日あたりに発生するスライス枚数はスキャン範囲を30 cm幅で7,350枚である。10 mmごとの再構成間隔の画像での読影であれば1,050枚ですむところが，

7倍の画像を読影しなければならない。発見される肺結節の数は，single slice CTを用いた肺癌検診であれば20～40%[27)~30)]であるが，multislice CTでは74%[31)]と約2倍にもなる。その結果として，経年受診や精査の外来における比較読影に関しては，複数個の結節が存在する場合，医師がそれぞれの撮影時点でのCT画像を並べて一つ一つ増大の有無を確認しなければならないことも極めて煩雑な読影業務となってきている。読影量のみならず，処理しなければならない診断結果の情報量の増加の中で，医師がさらにCADの少なからぬfalse positiveを含めた結果を参照するために多数の画像シリーズを再読影しなければならないシステムでは，CADを併用しない場合と比べて診断能が向上し，かつ本当に業務改善につながるのか十分検討がなされなければならない。研究室レベルや少数例の読影実験での有効性評価の結果のみで，CADに過度の期待をかけるのは避けなければならない。CADを導入することによって医師の負担を軽減するためには，検診および臨床現場の現実を十分理解したうえで，新たな発想でのアルゴリズムの開発およびシステム作りが必須であろう。医療側と工学側の共同研究のなかで，真に日常業務に有用なシステムが構築されることを期待する。

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