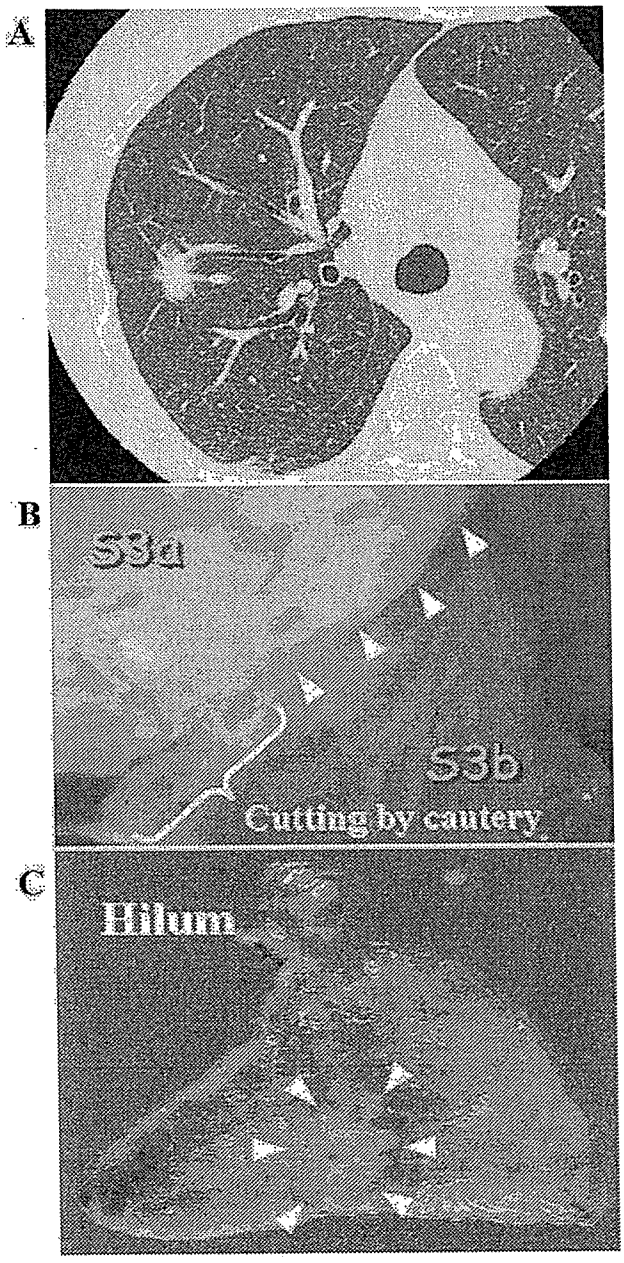

Figure 1. S2b (anterior subsegment of posterior segment) + S3a (posterior subsegment of anterior segment) resection of the right upper lobe, a representative of atypical segmentectomy. A, High-resolution computed tomographic image showing a tumor located at the border between S2b and S3a. B, Intraoperative findings showing the inflation-deflation line *(arrowheads)* between the inflated (resected) S3a and the deflated (preserved) S3b segments. C, Resected surgical specimen showing the tumor *(arrowheads)* with sufficient margin.

TABLE 1. Patient characteristics

No of patients	52
Age (y)	
Range	40-82
Median	65
Sex	
Male	27
Female	25
Size of tumor (mm)	
Range	8-20
Median	18
Histology	
Adenocarcinoma	45
Including bronchioloalveolar carcinoma component	29
Squamous cell	5
Large cell	1
Carcinoid	1
Pathologic	
Stage IA	49
Stage IB	2
Stage IIA	1

System for Lung Cancer.[16] Each patient provided his or her informed written consent based on the protocol approved by the institute's review board before the operation. After the operation, every patient was basically evaluated at 3-month intervals for the first 2 years and at 6-month intervals thereafter.

Results

The characteristics of the patients are listed in Table 1. Among the 52 patients, there were 25 women and 27 men with a median age of 65 (range 40-82) years. Tumor size ranged from 8 to 20 mm (median size 18 mm). Histologically, the vast majority of the patients had an adenocarcinoma (45/52, 86.5%), a high proportion of which contained a bronchioloalveolar carcinoma component (29/45, 64.4%). Pathologic examination showed that curative resections were achieved with free surgical margins in all patients.

Table 2 shows the locations of burdened segments. Upper lobe lesions predominated, with right upper lobe tumors being the most common. Segmentectomy can actually be performed in any lobe, excluding the middle lobe. The operative results are shown in Table 3. The median operative time measured from skin incision to skin closure and median bleeding during the operation were 155 minutes (range 85-225 minutes) and 60 mL (range 10-210 mL), respectively. The median skin incision for the utility access was 65 mm (range 40-120 mm). Postoperative complications occurred in 7 patients (13.5%), the most common one being prolonged air leak. One patient had a late alveolopleural fistula 5 days after the chest tube had been removed on the third postoperative day and required tube drainage for 4 days. Another patient had a minor alveolopleural fistula on the sixth day, which healed without requiring tube

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TABLE 2. Location of burdened lung

No. of patients	52
Lobe	
Upper	29
Lower	23
Resection	
Right	27
S1	3
S1+2a	1
S2	5
S2b+3a	4
S3	3
S6	8
S6+8	1
S7+8	1
S9+10	1
Left	25
S1+2a	1
S1+2+3	7
S4+5	5
S6	7
S8	2
S9+10	3

a, posterior subsegment; *b*, anterior subsegment; *S1*, apical; *S2*, posterior; *S3*, anterior; *S4*, superior; *S5*, inferior; *S6*, superior; *S7*, medial basal; *S8*, anterior basal; *S9*, lateral basal; *S10*, posterior basal.

TABLE 3. Surgical results

No. of patients	52
Operation time (min)	
Range	85-225
Median	155
Bleeding (mL)	
Range	10-210
Median	60
Utility access incision (mm)	
Range	40-120
Median	65
Complication	
Prolonged air leak (>7 d)	4
Late alveolopleural fistula*	2
Supraventricular arrhythmia	1
Air leak duration (d)	
Range	0-11
Median	1
Chest tube duration (d)	
Median	2-13
Range	3

*Occurring after removal of the chest tube.

drainage. In 22 (42.3%) patients no air leak was observed at the time of surgery. The duration of postoperative air leak and chest tube drainage ranged from 0 to 11 days (median, 1 day) and 2 to 13 days (median, 3 days), respectively. There was no case of in-hospital death or 30-day mortality. During the follow-up period (median 16 months; range 2-28 months), we experienced one case of local recurrence in the mediastinal lymph node and another of distant metastasis to the brain, but there was no case of local recurrence in the surgical margin.

Discussion

The development of radiographic devices such as high-resolution computed tomography and the widespread practice of low-dose helical computed tomography for screening[8] have resulted in an amazing increase of early detection of ever-smaller NSCLCs that possibly have a more indolent biologic behavior, such as bronchioloalveolar carcinoma. The trend has rapidly been changing clinical practice in thoracic surgery and, accordingly, many surgeons have without doubt become concerned over the unified treatment with whole lobectomy for these small peripheral cancers. Removing a relatively large volume of healthy lung tissue may result in a poorer quality of postoperative life, a higher frequency of operative morbidity, and fewer possibilities to additionally have a second or even a third NSCLC resected, for which these patients would survive long enough to be at risk. Recently, several authors have reported that sublobar resection was not inferior to lobectomy concerning the prognosis of selected patients with a small-sized NSCLC.[9-12,17-20]

The Lung Cancer Study Group study showed a higher occurrence of local recurrence after sublobar resection,[2] and we noted that their series included a high proportion of wedge resections in the sublobar resection group (32.8%, 40/122) for tumors up to 3 cm in diameter; thus we think that the predominance of wedge resection might have influenced the frequency of local recurrence. In contrast, the percentage of wedge resections was 11.5% (30/260) in our previous report,[12] which targeted tumors up to 2 cm. If the indication had been limited to tumors of 2 cm or smaller and if segmentectomy, which could improve the treated margin, had commonly been used, the frequency of local recurrence could have been lower.[9-12,17,18] Additionally, we are afraid that the more frequent application of wedge resection might lead to a lower assessment of lymph nodes, leading to a potential understaging of the disease, contrary to segmentectomy, which allows the inspection of the status of regional lymph nodes. We believe that segmentectomy is anatomic resection and should be completely distinguished from nonanatomic wedge resection. Nowadays, segmental resections are hardly being performed and the procedure has become unfamiliar to many thoracic surgeons. Particularly when intentionally planning a radical sublobar resection, the surgeon must overcome the great temptation to perform an easier wedge resection. The development of stapling devices has made huge wedge resection without regard to anatomic planes an almost overwhelming alternative to segmen-

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tectomy, despite warnings that the distortion of the stapled residual lobe might lead to pleural complications such as empyema and fistula and loss of lung function. Segmentectomy also allows an optimal resection of suspicious small-sized deep-seated lesions with safe surgical margins, since adopting diagnostic lobectomy for a potential underlying malignancy must be avoided.

In general, segmentectomy is technically trickier than lobectomy, requiring deep 3-dimensional knowledge of the relevant bronchoarterial relationships and possible anomalies of arterial branches. Sharp dissection by scissors accurately and quickly exposes the segmental hilar structures. Habitually, the arterial branches are initially divided, allowing identification of the segmental bronchus, which is the most reliable landmark of a segment because of its rare anomaly. The ligation of segmental vein is best performed last, after the intersegmental plane has been outlined, as the venous drainage might not be actually apparent. Identification of the intersegmental plane, which basically exists in lobes (Figure 2), is performed by differential inflation, in which the diseased segment is selectively inflated by jet ventilation and thus demarcated, quickly producing an inflation–deflation line. It is a great advantage to accurately define the real margin distance provided in an inflated diseased segment and to limit expansion to only the selected segment, not to the entire lobe, for obtaining an appropriate surgical field in this era of VATS. Generally, the reverse procedure is used; occlusion of the segmental bronchus in an airless whole lung is followed by expansion of the lung. Collateral ventilation through Kohn's pores will often fill the diseased segment owing to the positive air pressure used in this method, which accordingly fails to outline the inflation-deflation line. The main cause of the failure is relatively strong positive pressure, which is required to inflate the whole lung. In contrast, the pressure of jet ventilation is absolutely weak to selectively inflate only the targeted segment. During jet ventilation the surgeon can see the gradual inflation of the targeted segment, adjust the pressure of the jet ventilation under his or her direct vision, and stop the jet ventilation at the time of complete inflation before air flows into the collateral ventilation. Intriguingly, the intersegmental plane is approached along the inflation-deflation line at the peripheral site while the intersegmental vein is a landmark at the central portion around the hilum. Although sparing the intersegmental veins that delineate the perimeter of a bronchopulmonary segment and drain contiguous segments, and consequently preserving the venous drainage of adjacent segments, is a requirement of segmental resection to keep the full function of the adjacent segments, the surgeon should not hesitate to remove the intersegmental vein when the margin from the tumor is considered insufficient.

Dissection of the segmental plane by electrocautery is strongly recommended because it offers some advantages

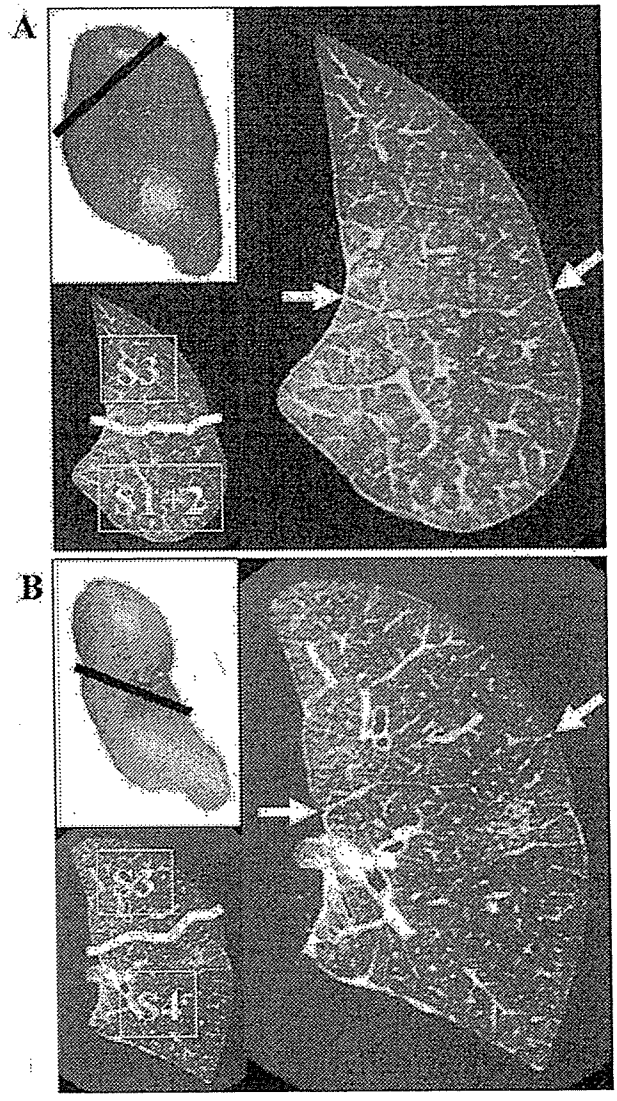

Figure 2. Transaxial (A) and coronal (B) views of specimen computed tomographic image in the left upper lobe, showing the anatomic intersegmental lines between S1+2 (apical and posterior segments) and S3 (anterior segment) (A), as well as between S3 and S4 (superior segment) (B), respectively. These findings are considered evidence of definitely outlined inflation–deflation lines.

over that by staplers: not only can the surgeon extirpate deep-seated tumors or tumors existing in locations where a stapler cannot be applied, but he or she also can freely cut the lung parenchyma to have a sufficient margin, which does not necessarily require afterward checking for residual tumor cells on the cutting planes. If any staple is used, the surgical margin could possibly be more reduced than expected and thus should be investigated. In addition, the

application of stapling devices can often compromise adjacent pulmonary parenchyma, restricting full expansion of the residual segments and thus pulmonary function, a major goal of segmental resection. However, unerring use of staples may be advantageous in patients with emphysema for stringent control of air leak. In the present study, air leak was a delicate issue after segmental resection. Small alveolopleural fistulas may seal, leaving a neutral air space that usually reabsorbs with gradual expansion of the lung because the residual space after segmentectomy is much smaller than that after lobectomy.

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Novel Marker D2-40, Combined With Calretinin, CEA, and TTF-1

An Optimal Set of Immunodiagnostic Markers for Pleural Mesothelioma

Takeshi Mimura, MD[1]
Akihiko Ito, MD, PhD[2]
Toshiko Sakuma, MD, PhD[3]
Chiho Ohbayashi, MD, PhD[2]
Masahiro Yoshimura, MD, PhD[1]
Noriaki Tsubota, MD, PhD[4]
Yutaka Okita, MD, PhD[1]
Morihito Okada, MD, PhD[4]

[1] Department of Cardiothoracic Surgery, Kobe University Medical School, Kobe City, Hyogo, Japan.

[2] Department of Surgical Pathology, Kobe University Medical School, Kobe City, Hyogo, Japan.

[3] Department of Pathology, Hyogo Medical Center for Adults, Akashi City, Hyogo, Japan.

[4] Department of Thoracic Surgery, Hyogo Medical Center for Adults, Akashi City, Hyogo, Japan.

Address for reprints: Morihito Okada, MD, PhD, Department of Thoracic Surgery, Hyogo Medical Center for Adults, Kitaohji-cho 13-70, Akashi City 673-8558, Hyogo, Japan; Fax: (011) 81-78-929-2380; E-mail: morihito1217jp@aol.com

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BACKGROUND. Malignant pleural mesothelioma is a challenging disease with regard to diagnosis and treatment; early and accurate diagnosis would lead to appropriate therapeutic strategies, including extrapleural pneumonectomy. Immunohistochemistry has proven valuable for the diagnosis of the most common epithelioid mesothelioma, although it is often difficult to differentiate it from pulmonary or metastatic adenocarcinoma with absolute certainty if a single antibody is employed. The current study was designed to identify an immunodiagnostic panel for pleural mesothelioma.

METHODS. Large surgical specimens from 66 cases with pleural mesothelioma and 66 with lung adenocarcinoma were immunohistochemically reevaluated under uniform conditions. The antibodies examined were directed against the novel mesothelial marker D2-40, as well as calretinin, CEA, and TTF-1.

RESULTS. For mesothelioma the sensitivities of D2-40 and calretinin were 84.8% and 87.9%, respectively, and their specificities were both 95.5%. For adenocarcinoma, the sensitivities of CEA and TTF-1 were 95.5% and 92.4%, respectively, and their specificities were both 100%. Immunoreactivity to D2-40 and calretinin was observed in most areas of epithelioid differentiation in mesothelioma. Western blots also showed higher levels of D2-40 antigen in pleura invaded by epithelioid mesothelioma as compared with unaffected pleura.

CONCLUSIONS. These data strongly suggest the significant usefulness of D2-40 and calretinin as positive markers, and of CEA and TTF-1 as negative markers, for pleural mesothelioma. The 4-antibody immunohistochemical panel showed high sensitivity and specificity with regard to differentiation of epithelioid mesothelioma from lung adenocarcinoma. ***Cancer* 2007;109:933–8.**

KEYWORDS: pleural mesothelioma, diagnosis, marker, immunohistochemistry, adenocarcinoma.

Malignant pleural mesothelioma (MPM) is an uncommon tumor of difficult diagnosis and wide prognostic implications whose occurrence has been increasing throughout the world. However, the controversy over diagnosis and treatment persists. Few malignancies have such a direct association with exposure to a definite carcinogen as mesothelioma has with asbestos exposure, and the great interest in asbestos has resulted in a level of awareness regarding mesothelioma that people do not have concerning most other cancers of equivalent occurrence, not to mention the social-legal-medical concerns about the disease. Based on the pattern of use of asbestos the occurrence of MPM can be expected to continue to increase in the following decades.

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It is important, albeit not easy, to accurately diagnose MPM for an appropriate clinical management, including curative surgery. One of the most common diagnostic problems is the difficulty in discriminating epithelioid MPM, the most frequent subtype, from lung adenocarcinoma (LAD). Several authors have evaluated the use of various antibodies for the diagnosis of MPM, but the results are still controversial.

D2-40 is a newly monoclonal antibody that reacts with a 40-kD antigen in germ cells and germ cell tumors[1] and recognizes the antigen selectively expressed in lymphatic endothelium. This antibody has proven useful in detecting tumors derived from lymphatic tissue as well as lymphatic involvement by a tumor.[2] Recently, 2 studies suggested that D2-40 might be helpful in differentiating epithelioid mesothelioma from adenocarcinoma because it reacted with epithelioid MPM but not with other cancers.[3,4]

In a clinical setting the diagnosis of MPM is so hard that benign diseases or other cancers could be contaminated with MPM. In this study the diagnosis was strictly based on the histopathologic features of large surgical specimens instead of tiny tissues obtained by needle biopsy or on the cytology of pleural effusion. The purpose of this study was to analyze the potential utility of D2-40 in the diagnosis of MPM, compared with the conventionally used immunohistochemical markers (calretinin, carcinoembryonic antigen [CEA], and thyroid transcription factor-1 [TTF-1]), as well as to define an immunohistochemical panel ideally suited for the definite diagnosis of MPM.

MATERIALS AND METHODS

Paraffin-embedded blocks from pleural specimens obtained by major resection not by biopsy in 66 patients with MPM and 66 with LAD except bronchioloalveolar carcinoma were reviewed by more than 1 pathologist whose specialty is pulmonary oncology. Each case with MPM was definitely diagnosed based on currently accepted histopathologic criteria combined with immunohistochemical findings in addition to clinical and radiographic findings. LAD was diagnosed according to the World Health Organization histologic criteria. The characteristics of the 66 patients with MPM are shown in Table 1. The mean age was 60.6 years (range, 35–78 years) and 56 (84.8%) patients were male. The histology was epithelioid in 48 (72.7%) patients, biphasic in 14 (21.2%), and sarcomatoid in 4 (6.1%). The operative procedure performed was pleurectomy in 33 patients (50%), extrapleural pneumonectomy in 25 (37.9%), and partial resection of the tumor in 8 (12.1%). According to the International Mesothelioma Interest Group (IMIG) staging, there were 8 patients with p-stage I disease (12.1%), 15 with p-stage II (22.7%), 38 with p-stage III (57.6%), and 5 with p-stage IV (7.6%).

TABLE 1
Characteristics of Patients With Mesothelioma (N = 66)

Factor	No. (%)
Age, y	
Mean [range]	60.6 [35–78]
Sex	
Men	56 (84.8)
Women	10 (15.2)
Histologic subtype	
Epithelioid	48 (72.7)
Biphasic	14 (21.2)
Sarcomatoid	4 (6.1)
Operation	
Pleurectomy	33 (50.0)
Extrapleural pnemonectomy	25 (37.9)
Incomplete resection	8 (12.1)
IMIG staging	
I	8 (12.1)
II	15 (22.7)
III	38 (57.6)
IV	5 (7.6)

IMIG indicates International Mesothelioma Interest Group.

Over a period of 15 months we prospectively performed pleural biopsy in 15 patients who were clinically suspected of MPM and obtained final diagnoses using D2-40, calretinin, CEA, and TTF-1 antibodies. Our policy for diagnosing MPM is to carry out pleural biopsy by video-assisted thoracoscopic surgery (VATS), which allowed us to collect large specimens under general anesthesia and to examine the tissues using this combination of immunohistochemical markers.

Immunohistochemistry

Tissue sections (4 μm thick) were air-dried overnight at 37°C, deparaffinized in xylene, and rehydrated in a descending ethanol series. Endogenous peroxidase activity was blocked by immersion for 10 minutes in 0.3% hydrogen peroxide in methanol followed by a single wash in phosphate-buffered saline (PBS), pH 7.4. Sections for D2-40 immunodetection were autoclaved for 7 minutes at 105°C in 10 mM citrate buffer solution (pH 6.0). Sections were incubated with D2-40 monoclonal antibody (DakoCytomation, Glostrup, Denmark; 1:50 dilution), calretinin monoclonal antibody (DakoCytomation, 1:50 dilution), CEA monoclo-

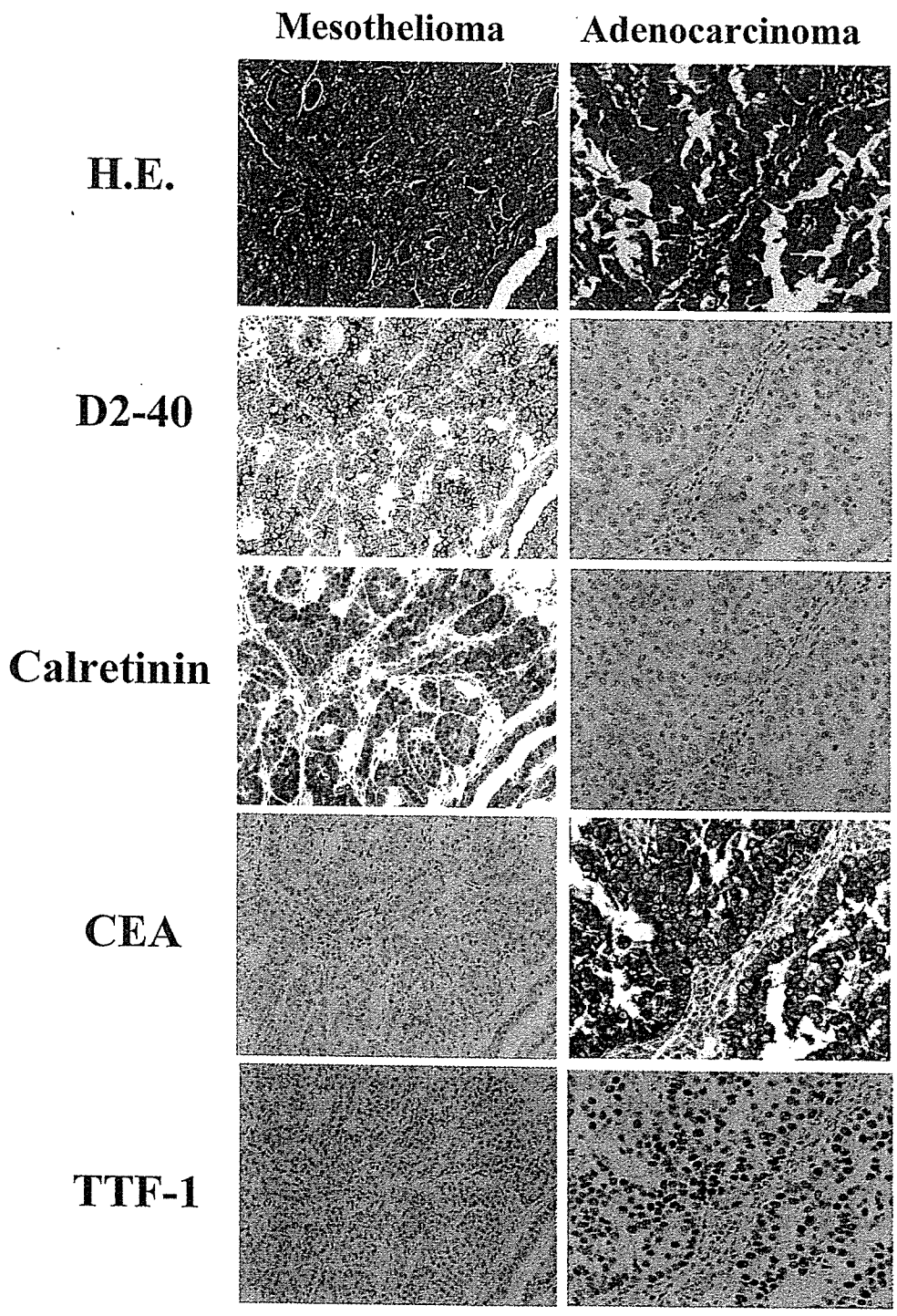

FIGURE 1. Representative images of hematoxylin and eosin staining (H&E) and immunostaining for D2-40, calretinin, CEA, and TTF-1 in adjacent sections of epithelioid mesothelioma (left) and pulmonary adenocarcinoma (right). In mesothelioma, strong D2-40 reactivity was observed along the apical surface of the cell, whereas the nuclei and cytoplasma show strong positive staining for calretinin. In adenocarcinoma the cytoplasma demonstrates positivity for CEA and the nuclei reveals reactivity for TTF-1. In contrast, there is no staining for D2-40 and calretinin in adenocarcinoma, or no reactivity for CEA and TTF-1 in mesothelioma. Original magnification ×200.

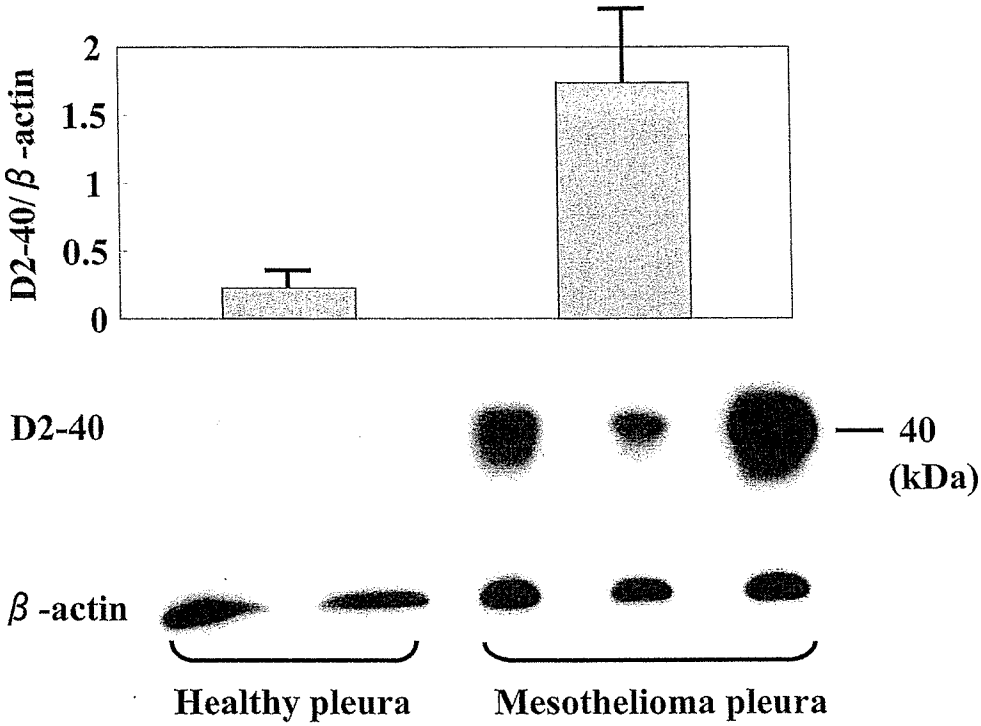

FIGURE 2. D2-40 expression in parietal pleura with and without epithelioid mesothelioma. Representative Western blots are shown. Quantitative densitometric data (expressed as D2-40/β-actin antigen levels, n = 6 for each group) from multiple samples are shown as the mean value ± standard deviation.

nal antibody (DakoCytomation, 1:50 dilution), and TTF-1 monoclonal antibody (DakoCytomation, 1:100 dilution). The color was developed using 3,3′-diaminobenzidine (Sigma Chemical, St. Louis, MO) as the chromogen. The slides were then counterstained with Mayer hematoxylin, dehydrated, and mounted. Negative controls were prepared by substituting the specific primary antibody with nonimmune serum or control mouse IgG.

Western Blot Analysis

Frozen samples of parietal pleura and mesotheliomas were crushed into pieces and vigorously vortexed in a buffer solution containing 50 mM Tris-HCl (pH 8.0), 150 mM NaCl, 1% Triton X-100, and a protease inhibitor cocktail (Sigma Chemical). Impurities were removed by centrifugation. The resulting lysates were separated on 10% SDS-polyacrylamide gels and transferred to immobilon (Millipore, Bedford, MA). The blots were reacted with the D2-40 monoclonal antibody (1:1000 dilution) in a buffer containing 20 mM Tris-HCl (pH 8.0), 150 mM NaCl, 0.05% Tween 20, and 5% skim milk (Difco, Sparks, MD), and then with peroxidase-conjugated antimouse IgG antibody in the same buffer. The color was developed with Western Lighting reagents (PerkinElmer Life Sciences, Boston, MA) before exposure. After stripping, the blots were probed again with an anti-β-actin antibody (Sigma Chemical) according to similar procedures. The chemiluminescent intensity of specific signals was calculated with the FluorChem IS-8000 system (Alpha Innotech, San Leandro, CA). The relative D2-40 signal intensity was obtained by dividing the intensity of D2-40 signals by that of β-actin signals.

RESULTS

As illustrated in Figure 1, immunohistochemical evaluation of epithelioid MPM revealed strong expression of calretinin and D2-40 antigens and a distinct difference in the pattern of staining localization between calretinin (nuclear and cytoplasmic) and D2-40 (membrane). Conversely, both antigens were virtually undetectable in pulmonary adenocarcinoma. The reactivity of CEA and TTF-1 is observed in the cytoplasma and the nuclei of lung adenocarcinoma, respectively. To confirm the role of D2-40 as a potential new marker, we performed Western blot analysis and examined whether there were differences in D2-40 expression between the results of immunohistochemical and Western blot analyses. The latter showed high levels of D2-40 antigen in pleura from patients with MPM compared with low levels of D2-40 antigen in normal pleura (Fig. 2). Also, the level of

TABLE 2
Immunohistochemical Positivity in Mesothelioma and Lung Adenocarcinoma

		D2-40	Calretinin	CEA	TTF-1
	No.	No. (%)	No. (%)	No. (%)	No. (%)
Mesothelioma	66	56 (84.8)	58 (87.9)	0 (0)	0 (0)
Epithelioid	48	43 (89.6)	43 (89.6)	0 (0)	0 (0)
Biphasic	14	11 (78.6)	14 (100)	0 (0)	0 (0)
Sarcomatoid	4	2 (50.0)	1 (25.0)	0 (0)	0 (0)
Adenocarcinoma	66	3 (4.5)	3 (4.5)	63 (95.5)	61 (92.4)

D2-40 determined by immunohistochemical analysis correlated with that estimated by Western blot analysis regardless of the presence of MPM. These data strongly support a participatory role for D2-40 in MPM.

The results of immunohistochemical analyses using D2-40, calretinin, CEA, and TTF-1 are summarized in Table 2. Fifty-six (84.8%) and 58 (87.9%) of the 66 MPM tissue specimens expressed D2-40 and calretinin, respectively, whereas none expressed CEA and TTF-1. Both D2-40 and calretinin were similarly observed in most areas of epithelioid differentiation, although in areas of sarcomatoid differentiation (either biphasic mesothelioma or pure sarcomatoid subtype) they were detected less frequently and the immunoreactivity was less strong. In the cases with LAD, neither D2-40 nor calretinin was detected, except in only 3 cases (4.5%) that showed weak focal staining for both the antibodies. In contrast, CEA and TTF-1 staining was present in 95.5% and 92.4% of LADs, respectively. For mesothelioma, the specificities of D2-40 and calretinin were both 95.5% and the specificities of CEA and TTF-1 for adenocarcinoma were both 100%.

More recently, we prospectively used these 4 antibodies for distinguishing MPM from LAD in 15 patients subjected to VATS biopsy of the pleura for differential diagnosis; the results are shown in Table 3. The final diagnosis was MPM in 8 (53.3%) patients containing 5 epithelioid subtypes and 3 biphasic subtypes, and adenocarcinoma in 7 patients (46.7%) including 5 LADs. In all the patients with MPM the immunoreactivity for D2-40 and calretinin was seen, whereas that for CEA and TTF-1 was never observed. Conversely, there were no adenocarcinomas with positive immunoreactivity for D2-40, positive for calretinin, or negative for CEA. TTF-1 expression is considered to be present only in LAD but not in metastatic adenocarcinoma from other organs, which was supported by our data. Only 1 case with LAD was judged negative for TTF-1, which was very weak focal expression.

TABLE 3
Results of VATS Pleural Biopsy Performed for Suspicious Pleural Mesothelioma During the Last 15-Month Period (N = 15)

			Immunohistochemistry			
Case No.	Age/Sex	Final Pathology	D2-40	Calretinin	CEA	TTF-1
1	66/M	MPM (Bi)	P	P	N	N
2	63/M	MPM (Epi)	P	P	N	N
3	58/M	MPM (Bi)	P	P	N	N
4	68/M	MPM (Epi)	P	P	N	N
5	67/M	MPM (Epi)	P	P	N	N
6	46/F	MPM (Epi)	P	P	N	N
7	62/M	MPM (Epi)	P	P	N	N
8	61/M	MPM (Bi)	P	P	N	N
9	69/F	Adenoca #1	N	N	P	N
10	59/F	Adenoca #2	N	N	P	N
11	67/M	LAd	N	N	P	P
12	69/M	LAd	N	N	P	P
13	63/M	LAd	N	N	P	P
14	69/M	LAd	N	N	P	N*
15	53/M	LAd	N	N	P	P

VATS indicates video-assisted thoracoscopic surgery; M, male; F, female; MPM, malignant pleural mesothelioma; Epi, Epithelioid; Bi, biphasic; LAd, lung adenocarcinoma; Adenoca, adenocarcinoma; P, positive; N, negative.
#1: Pleural metastasis originated from gastric carcinoma.
#2: Metastatic adenocarcinoma with unknown primary lesion.
* Very weak focal reactivity suggesting negative result.

These data powerfully confirm significant function of D2-40 and calretinin as positive markers and CEA and TTF-1 as negative markers in MPM.

DISCUSSION

At present, the diagnosis of MPM depends basically on the histopathology of the lesion and the assessment of clinical and radiological findings. Pleural fluid cytology or pleural needle biopsy seldom provides specimens large enough to perform the immunohistochemical analyses that are crucial for an accurate diagnosis. To confidently obtain an adequate amount of tissue from macroscopically diseased sites we routinely practice VATS biopsy. In the present study, large specimens obtained at the time of major resection of the tumor were reevaluated under uniform conditions by more than 1 pathologist expert in pulmonary oncology.

Immunohistochemistry has proven the most useful method for conclusively diagnosing MPM but it is in general agreed that no single antibody is sufficiently sensitive or specific. In a clinical setting the histologic distinction between epithelioid MPM and adenocarcinoma is often difficult and requires ancillary studies. Therefore, several antibodies must be used for the differential diagnosis of a pleural tumor, and nowadays the use of a panel of antibodies is a

clinically accepted practice. However, the choice of antibodies varies. In this study, a tumor that shows immunoreactivity for D2-40 and calretinin antibodies, but not for CEA and TTF-1 antibodies, is unequivocally MPM, and a tumor negative for D2-40 and calretinin, but positive for CEA and TTF-1, is unquestionably not MPM, but LAD. Of note, D2-40 and calretinin act as positive markers, whereas CEA and TTF-1 function as negative markers in the differential diagnosis of MPM, although great attention should be given to the fact that each antibody has individual deficiencies.

D2-40, a recently developed, commercially available monoclonal antibody could be helpful both in the diagnosis of lymphatic derived tumors and in determining lymphatic invasion by tumors.[1,5] Chu et al[3] demonstrated strong membranous reactivity in 33 of 33 epithelioid mesotheliomas (100%) and in the epithelioid component of 15 of 16 biphasic mesotheliomas (94%). Ordonez[4] also reported positivity for D2-40 in 25 of 29 epithelioid mesotheliomas. The membranous reaction of D2-40 was diffuse and intense in the majority of epithelioid MPM, whereas weak focal membranous positivity was observed in some serous carcinomas and no membranous staining was seen in any of the other carcinomas.[6] In the present study we demonstrated D2-40 protein expression in the pleura invaded by epithelioid MPM through immunohistochemical examinations and Western blotting analyses, and a positive correlation in the level of the protein evaluated by different methods. In addition, our large series showed D2-40 positivity for MPM (56/66, 84.8%), especially for epithelioid MPM (43/48, 89.6%). These findings suggest that D2-40 is one of the most informative markers for the diagnosis of MPM, particularly of the epithelioid subtype.

Among the so-called 'positive' mesothelioma markers, calretinin is one of the most used in the diagnosis of MPM because of its high sensitivity and specificity,[6–8] and is frequently expressed in all histologic types of MPM, in contrast with other highly sensitive mesothelioma markers, which are commonly expressed in the epithelioid component but not in the sarcomatoid component, such as D2-40.[7,8] As well, calretinin is one of the few antibodies that are much more frequently reactive in MPM than in LAD, and thus we included it in the panel of antibodies employed in our series.

CEA is one of the negative mesothelioma markers available for the differential diagnosis of epithelioid MPM and LAD. Approximately 80% of LADs are reported to express CEA, whereas MPMs are typically negative for this marker.[6,8] However, it should be noted that the diagnostic value of CEA immunoreactivity when differentiating between epithelioid MPM and metastatic, nonpulmonary adenocarcinomas depends mainly on the site of origin of the adenocarcinoma. In contrast, TTF-1, which is expressed in adenocarcinomas originating only in the lungs or thyroid, is an important negative marker.[9–12] Previous studies have shown that TTF-1 expression is retained in thyroid carcinomas and in up to 75% of LADs.[9,10] We have never detected CEA nor TTF-1 expression in any of the MPMs investigated so far; therefore, positive staining for either marker should be considered an indication against such a diagnosis.

Therefore, our results show that the use of D2-40, calretinin, CEA, and TTF-1 should allow us to achieve a definite diagnosis in the large majority of suspected cases of MPM. This approach decreases the number of antibodies required in the majority of cases and contributes to the establishment of a more accurate diagnosis of MPM or LAD.

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GTS

Radical sublobar resection for small-sized non–small cell lung cancer: A multicenter study

Morihito Okada, MD, PhD,[a] Teruaki Koike, MD, PhD,[b] Masahiko Higashiyama, MD, PhD,[c] Yasushi Yamato, MD, PhD,[b] Ken Kodama, MD, PhD,[c] and Noriaki Tsubota, MD, PhD[a]

Objective: At present, even when early-stage, small-sized non–small cell lung cancers are being increasingly detected, lesser resection has not become the treatment of choice. We sought to compare sublobar resection (segmentectomy or wedge resection) with lobar resection to test which one is the appropriate procedure for such lesions.

Methods: From 1992 to 2001, a nonrandomized study was performed in 3 institutes for patients with a peripheral cT1N0M0 non–small cell lung cancer of 2 cm or less who were able to tolerate a lobectomy. The results of the sublobar resection group enrolled preoperatively (n = 305) were compared with those of the lobar resection group (n = 262).

Results: Except for distribution of tumor location, there were no significant differences in any variable, patient characteristics, curability, pathologic stage, morbidity, or recurrence rate. Median follow-up was more than 5 years. Disease-free and overall survivals were similar in both groups with 5-year survivals of 85.9% and 89.6% for the sublobar resection group and 83.4% and 89.1% for the lobar resection group, respectively. Multivariate analysis confirmed that the recurrence rate and prognosis associated with sublobar resection were not inferior to those obtained with lobar resection. Postoperative lung function was significantly better in patients who underwent sublobar resection.

Conclusions: Sublobar resection should be considered as an alternative for stage IA non–small cell lung cancers 2 cm or less, even in low-risk patients. These results could lay the foundation for starting randomized controlled trials anew, which would bring great changes of lung cancer surgery in this era of early detection of lung cancer.

From the Department of Thoracic Surgery, Hyogo Medical Center for Adults,[a] Akashi City, Hyogo, Japan; Department of Chest Surgery, Niigata Cancer Center Hospital,[b] Niigata City, Niigata, Japan; and Department of Thoracic Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases,[c] Osaka City, Osaka, Japan.

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Address for reprints: Morihito Okada, MD, PhD, Department of Thoracic Surgery, Hyogo Medical Center for Adults, Kitaohji-cho13-70, Akashi City 673-8558, Hyogo, Japan (E-mail: morihito1217jp@aol.com).

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In the one and only randomized study to compare lobectomy and sublobar resection for stage IA non–small cell lung cancer (NSCLC) published in 1995, the Lung Cancer Study Group (LCSG) demonstrated a 3-fold increase in the local recurrence rate among patients who underwent sublobar resection,[1] and powerfully supported the indisputable dogma that lobectomy is the standard of care for stage I NSCLC. However, the most broadly referenced report included potentially misleading statements and analyses insufficient to advocate the superiority of lobectomy over sublobar resection as some investigators then and later demonstrated.[2-4]

With the dramatic upsurge in early detection of ever smaller NSCLCs through the development of radiographic tools such as high-resolution computed tomography (CT) and the widespread practice of low-dose helical CT for screening,[5] which is rapidly changing clinical practice, many surgeons have inevitably become concerned over the unified treatment of these small peripheral lesions with whole lobectomy. Generally, patients with a larger tumor have a poorer prognosis and a

Abbreviations and Acronyms

CT = computed tomography
FEV_1 = forced expiratory volume in 1 second
FVC = forced vital capacity
LCSG = Lung Cancer Study Group
NSCLC = non–small cell lung cancer

higher frequency of hematogenous and lymphatic metastases, whereas smaller tumors such as bronchioloalveolar carcinoma usually have a more indolent biologic behavior. Is it uniformly required to extirpate the entire lobe for such tiny peripheral lesions when sufficient margins of resection can be achieved with sublobar resection? Removing a relatively large volume of healthy lung tissue may result in a higher frequency of operative morbidity and poorer quality of postoperative life, reducing the chance for further resections because these patients survive long enough to be at risk for a second or even a third NSCLC. The incidence of second primary lung cancers may be approximately 3% per year[6,7]; thus patients who survive 5 or more years after their first resection would face a significant cumulative danger of second cancers. The larger the amount of the initial resection, the more restricted the surgical options for next resections.

Recently, several reports demonstrated that sublobar resection was not inferior to lobectomy regarding the prognosis of patients with small-sized NSCLC,[8-13] but the number of cases evaluated in those studies was relatively small. The present study, in which we compared the outcome of sublobar resection with that of lobectomy in low-risk noncompromised patients with a T1N0 NSCLC 2 cm or less in size, is the largest series published so far on radical sublobar resection and followed for long-term outcome. The rigid consensus on lobectomy for stage I cancers has never permitted us to carry out a randomized study. In such a situation in which it has been difficult even to plan a randomized trial because of ethical reasons, a well-designed observational trial may function as an effective reference for a future randomized trial. This was a nonrandomized study in which the decision on whether to be assigned to the sublobar resection group or the lobar resection group was taken by the patients themselves. Because the 2 groups were well matched for known prognostic variables, a comparison between the 2 groups was considered scientifically valid.

Methods

Patients

In 3 institutes during a 10-year period, from January 1992 to December 2001, patients were enrolled for entry into this study when they had a clinical T1N0M0 peripheral tumor of 2 cm or less in every dimension located in the outer one third of the lung on CT confirmed to be an NSCLC. Patients included in the study were able to tolerate a lobectomy as evaluated by cardiopulmonary functional tests, had no history of previously treated cancer, and provided his/her informed written consent based on the approved protocol of each institute's review board before registration and surgery. Patients with a tumor located in the right middle lobe were excluded. Radionuclide bone scan and CT examination of the brain, chest, and upper abdomen were routinely required to detect possible metastases. At the time of registration, every patient was assigned to undergo lobectomy or sublobar resection in compliance with his/her decision. In other words, patients were allocated to the sublobar resection group if the patient consented to the sublobar resection, and to the lobectomy group if the patient did not consent to sublobar resection. Patients were invariably scheduled to undergo lobectomy or sublobar resection before the thoracotomy. During the operation, the tumor status was confirmed by the surgeon to be T1N0 on the basis of frozen-section analysis of sampled segmental, lobar, hilar, and mediastinal lymph nodes from the drainage area of the tumor and pleural lavage cytology. In patients assigned to the sublobar resection group, the surgeon cautiously evaluated the appropriateness of a sublobar resection for curative treatment and whether the deliberate procedure would be a segmentectomy or an adequate large wedge resection. Basically, the wedge resection could be used as a sublobar resection for a tumor of 1.5 cm or smaller in diameter and a tumor observed as pure ground-glass opacity by CT, when considered appropriate. Resected specimens were examined histopathologically, and histologic typing was done according to the World Health Organization classification.[14] Surgical–pathologic staging was performed according to the New International Staging System for Lung Cancer.[15]

Surgical Procedure of Segmentectomy

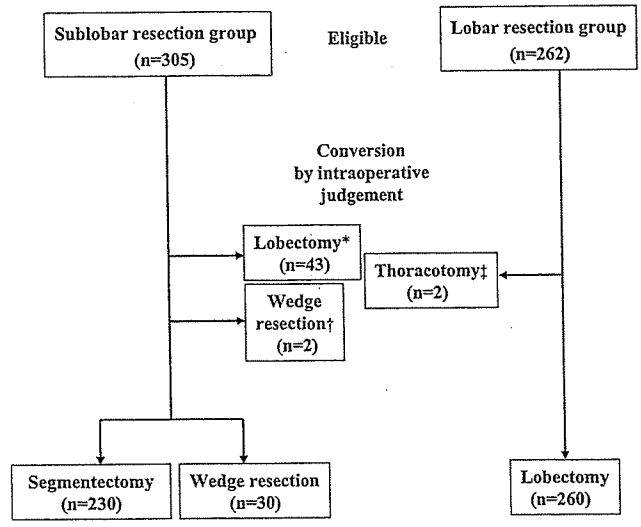
At the hilum, isolation, division, and suture of the suitable segmental bronchus, artery, and vein were required. Intraoperatively, lymph nodes around the hilum and those obtained by mediastinal dissection or sampling were pathologically examined. Surgeons were allowed some latitude regarding the technique to detect and divide the intersegmental plane, including the use of electrocautery, neodymium-yttrium-aluminum garnet laser, or segmental stapling. Because a margin of at least 2 cm of healthy lung tissue was required, the resection line could be placed on the segment adjacent to the affected one or portions of a few adjacent segments or subsegments could be extirpated. After the resection, the surgeon was obliged to corroborate that the tumor and required lymph nodes had been completely removed and proven to be negative for involvement by frozen-section examination. It was specified that when the surgical margin was found to be imperfect or any lymph node was found to be diseased, lobectomy had to be performed instead.

Postoperatively, all complications including minor ones were recorded. Every patient was evaluated at 3-month intervals for the first 2 years, at 6-month intervals for the subsequent 3 years, and yearly thereafter. Follow-up assessment included physical examination, hematologic and biochemical analysis including tumor markers, and chest roentgenograms. Local recurrence was defined as recurrence at the primary site or in lymphatic drainage areas, either hilar or mediastinal within the operated thoracic cavity.

TABLE 1. Base-line characteristics of the patients

Characteristic	Sublobar resection group (n = 305)	Lobar resection group (n = 262)	*P* value
Gender			0.8655
Male	167 (54.8%)	146 (55.7%)	
Female	138 (45.2%)	116 (44.3%)	
Age (years)	35-82	38-84	0.3312
	mean: 63.2	mean: 64.0	
Histology			0.4772
AD	276 (90.5%)	229 (87.4%)	
SQ	27 (8.9%)	30 (11.5%)	
AS	2 (0.7%)	3 (1.1%)	
Size			0.0564
Range	5-20 mm	8-20 mm	
Mean	15.7 mm	16.2 mm	
0-10 mm	36	21	
11-20 mm	269	241	
Location			0.0191
Right upper lobe	101 (33.1%)	112 (42.7%)	
Right lower lobe	54 (17.7%)	54 (20.6%)	
Left upper lobe	106 (34.8%)	63 (24.0%)	
Left lower lobe	44 (14.4%)	33 (12.6%)	

AD, Adenocarcinoma; *SQ*, Squamous cell carcinoma; *AS*, Adenosquamous carcinoma. Fisher's exact test was used to compare categoric variables, and student's *t* test was used for continuous data.



*Reasons for conversion to lobectomy: surgical N1 disease, n=11; surgical N2 disease, n=9; insufficient margin, n=23.
†‡ Reason for conversion to wedge resection or toracotomy only: pleural dissemination (n=4).

Figure 1. Treatment flow chart.

Distant metastasis was defined as intrapulmonary metastasis or metastasis to other organs. Pulmonary function tests comprising forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1), were administered preoperatively and at 2 months after surgery.

Statistical Methods

Fisher's exact test was used for intergroup comparison of categoric variables, and the Student *t* test was used for continuous data. Survivals were estimated by the Kaplan-Meier method,[16] and differences in survival were determined by log-rank analysis. Multivariate analysis with preoperative prognostic stratification variables was done using Cox proportional hazards regression model.[17] Zero time was the date of pulmonary resection, and the terminal event was death attributable to cancer, non-cancer, or unknown causes for overall survival analysis. Operative mortality defined as a 30-day postoperative death was included in the survival analyses. Disease-free survival was the interval from the date of resection to proven detection of recurrence or metastases. Recurrent disease was defined as the discovery of any new lesion considered to be recurrence of the original lung cancer. All patients were followed until death or study termination, unless lost to follow-up. Analyses of potential survival differences within subgroups and of potential prognostic factors were reported with 2-sided *P* values.

Results

Of the 567 patients preoperatively enrolled, 305 (53.8%) were assigned to the sublobar resection group and 262 (46.2%) were assigned to the lobar resection group. There were no significant differences in gender, age, or histologic type between the 2 groups (Table 1). The mean size of the tumor was a little smaller in the sublobar resection group, although the observed difference was of borderline statistical significance ($P = .0564$). However, location of the tumor was not well balanced ($P = .0191$). Patients with a tumor in the right upper lobe tended to be allocated to the lobar resection group, whereas those with a tumor in the left upper lobe tended to be assigned to the sublobar resection group.

During the operation, the planned procedures were changed for various reasons (Figure 1). Forty-three of the 305 patients in the sublobar resection group underwent lobectomy. Among them, sufficient surgical margins were not obtained in 23 patients, N1 disease was diagnosed in 11 patients, and nodes were judged to be N2 positive intraoperatively in 9 patients. In addition, noncurative wedge resection was carried out in 2 patients because pleural dissemination was found at the time of thoracotomy. Thus, 260 patients in the sublobar resection group underwent operation as planned, 230 patients underwent segmentectomy, and 30 patients underwent curative wedge resection. In contrast, thoracotomy without removal of the tumor was performed in 2 of the 262 patients enrolled in the lobar resection group because of pleural dissemination.

The median follow-up of living patients in the sublobar and lobar resection groups was 72 months (range, 29-155

TABLE 2. Postoperative findings of the patients

Cheracteristic	Sublobar resection group (n = 305)	Lobar resection group (n = 262)	P value
Curability			0.2577
Complete resection	303 (99.3%)	257 (98.1%)	
Incomplete resection	2 (0.7%)	5 (1.9%)	
Pathological stage			0.7819
IA	266 (87.2%)	217 (82.8%)	
IB	7 (2.3%)	10 (3.8%)	
IIA	10 (3.3%)	12 (4.6%)	
IIB	2 (0.7%)	2 (0.8%)	
IIIA	14 (4.6%)	15 (5.7%)	
IIIB	6 (2.0%)	6 (2.3%)	
Postoperative complications	20 (6.6%)	19 (7.3%)	0.7429
Recurrence	43 (14.1%)	45 (17.2%)	0.3524
Distant metastasis	28 (9.2%)	27 (10.3%)	
Local recurrence	15 (4.9%)	18 (6.9%)	

Fisher's exact test was used to compare categoric variables.

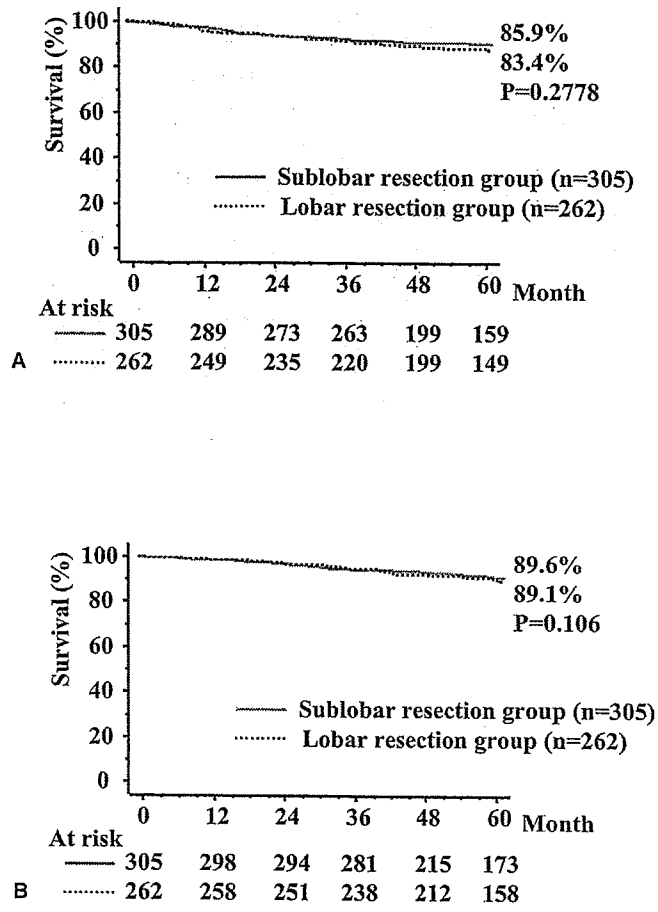


Figure 2. Disease-free survival (A) and overall survival (B). Curves correspond to patients who were initially enrolled for this study (sublobar resection group, *solid line*; lobar resection group, *short-dash line*).

months) and 71 months (range, 22-158 months), respectively. There were no significant differences between the 2 groups in curability, pathologic stage, incidence of postoperative complication, and recurrence (Table 2). It is noteworthy that the rate of local recurrence did not differ significantly between the 2 groups. Particularly, the recurrence in the remaining part of the affected lobe that we had intentionally preserved with sublobar resection was our prime concern. Among the 260 patients who underwent curative sublobar resection, recurrence was detected in the residual part in 3 patients (1.2%). One patient who underwent segmentectomy of the left upper division for squamous cell cancer showed recurrence in the surgical margin 5 months after surgery and is alive at 87 months after left completion pneumonectomy. Another patient presented a pulmonary metastasis just in the remaining portion at 49 months after right S2 segmentectomy for adenocarcinoma and is alive at 16 months after completion lobectomy. The third patient with right S3 segmentectomy for papillary adenocarcinoma had occurrence of bronchioloalveolar carcinoma at 40 months postoperatively and is surviving at 38 months after completion lobectomy. All 3 patients are free of disease at the time of this report. There was only 1 operative death in the sublobar resection group. The patient died of acute myocardial infarction 29 days after surgery, although he had been discharged from the hospital after a quick uneventful recovery.

Survival

Figure 2 shows the disease-free and overall survivals of the sublobar resection group and lobar resection group, demonstrating no significant differences between them ($P = .2778$ and $P = .106$, respectively). Moreover, multivariate analysis using potential preoperative prognostic determinants revealed that irrespective of gender, age, histologic type, tumor size, and tumor location, the disease-free interval and prognosis in the 2 groups were similar (Table 3; hazard ratio, 1.241, $P = .3024$ and hazard ratio, 1.363, $P = .1537$, respectively). Next, we examined the surgical outcome in patients who underwent curative resection for pT1N0M0 disease (Figure 3). Not surprisingly, the survival after curative wedge resection was good because the procedure had been indicated for smaller tumors with possibly indolent biologic behavior. Both the disease-free and overall survivals were comparable in patients in p-stage IA whether treated with segmentectomy or lobectomy.

Pulmonary Function

Because lung function tests were not mandatory for this study, information regarding the testing completed pre-

TABLE 3. Proportional hazard model

Variables	Disease-free survival		Overall survival	
	Relative risk	*P* value	Relative risk	*P* value
Gender				
Male (vs Female)	1.761	0.0105	1.568	0.0531
Age				
Older	1.012	0.2761	1.030	0.0168
Histology				
Non-AD (vs AD)	0.526	0.0909	1.149	0.6360
Size				
Larger	1.098	0.0058	1.022	0.4994
Side				
Left (vs Right)	1.307	0.2004	1.200	0.3976
Lobe				
Upper (vs Lower)	1.483	0.1041	1.576	0.0667
Enrolled group				
Lobar (vs Sublobar)	1.241	0.3024	1.363	0.1537

AD, Adenocarcinoma. Continuous data for age and size, and categories for gender, histology, side, lobe, and enrolled group.

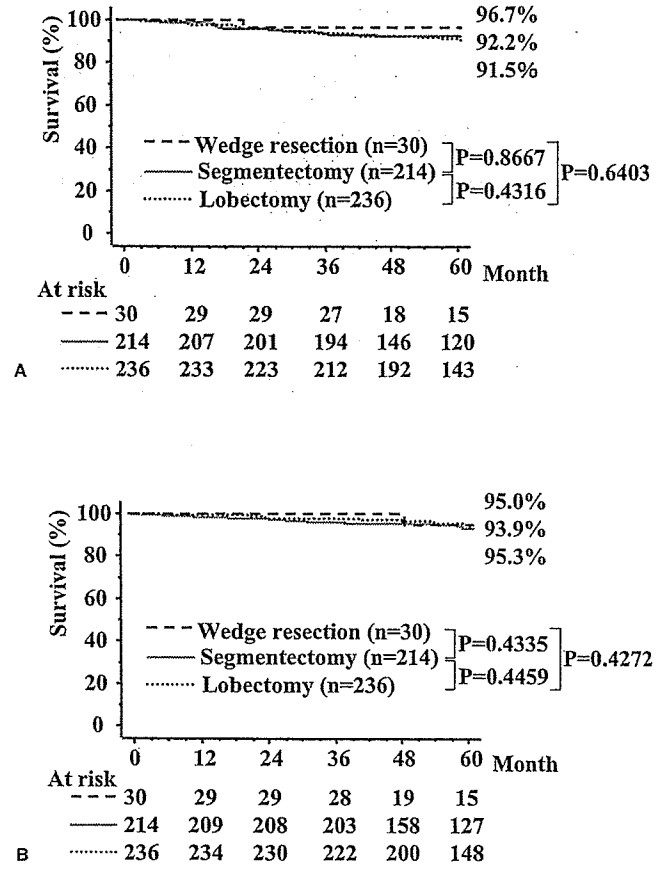


Figure 3. Disease-free survival (A) and overall survival (B). Curves correspond to patients who underwent curative resection for pT1N0M0 tumor (wedge resection, *long-dash line*; segmentectomy, *solid line*; lobectomy, *short-dash line*).

operatively and postoperatively was available on 354 patients (62.4%). We analyzed the data according to the procedure actually executed. Preoperative functional values were similar among the groups who underwent wedge resection (n = 18), segmentectomy (n = 168), and lobectomy (n = 168), confirming that patients in the sublobar resection group could have functionally tolerated a lobectomy (Table 4). In regard to both FVC and FEV_1, the extent of resection seemed to correlate with the reduction of lung function. Next, we directly compared functional changes between the 3 groups. Figure 4 clearly demonstrates that the greater the resected amount of tissue, the more reduced the postoperative pulmonary function. Statistically significant differences in the ratio of postoperative to preoperative FVC and FEV_1 were observed among the 3 groups, although a marginal difference in FVC was seen between the segmentectomy group and the wedge resection group.

Discussion

It is of utmost importance to adequately resolve a controversial issue concerning the choice of resection for peripheral small early-stage NSCLCs, because the detection rate of these lesions potentially amenable to effective treatment with lesser resection has dramatically increased in recent years. In 1995, the LCSG reported 1 randomized study concluding that lobectomy was the standard of care for stage IA NSCLCs,[1] which made a great impact on the following advance of lesser resection, although most recent studies comparing lesser resection with lobectomy for stage IA NSCLC demonstrated equivalent survival.[8-13] Patel and colleagues[4] raised several doubts about the analysis and interpretation of the results of the LCSG study. Their review of the LCSG trial outcome suggested that patients with lesser resections may be at a higher risk of developing local recurrence, lower rate of perioperative lung morbidity, similar cancer-related mortality rate, and better preservation of lung function compared with lobectomy for stage IA NSCLC. Table 5 shows a review of the literature regarding the survivals after resection of stage IA (T1N0M0) NSCLC.[1,8,9,12,18,19]

The LCSG study showed a high incidence of local recurrence after sublobar resection, which we did not find in our series, although the methods of follow-up such as serial CT have been rapidly evolved year after year to identify local recurrence. We are focusing on the high rate of wedge resection in the sublobar resection group (32.8%), although the LCSG study involved stage IA cancers including tumors up to 3 cm in diameter. The predominance of wedge resection might affect the frequency of local recurrence. In our

TABLE 4. Changes of lung function

Procedure	Preoperative values	→	Postoperative values
Wedge resection (n = 18)			
FVC (L)	3.30 ± 0.81	→	3.10 ± 0.69
FEV1.0 (L)	2.29 ± 0.59	→	2.21 ± 0.84
FEV1.0/FVC (%)	70.2 ± 12.1	→	71.9 ± 11.5
Segmentectomy (n = 168)			
FVC (L)	3.16 ± 0.84	→	2.83 ± 0.80
FEV1.0 (L)	2.32 ± 0.64	→	2.10 ± 0.62
FEV1.0/FVC (%)	73.7 ± 9.2	→	74.8 ± 10.0
Lobectomy (n = 168)			
FVC (L)	3.19 ± 0.80	→	2.68 ± 0.77
FEV1.0 (L)	2.32 ± 0.58	→	1.93 ± 0.58
FEV1.0/FVC (%)	73.2 ± 8.3	→	72.5 ± 10.2

FVC, forced volume capacity; *FEV1.0*, forced expiratory volume in 1 second.

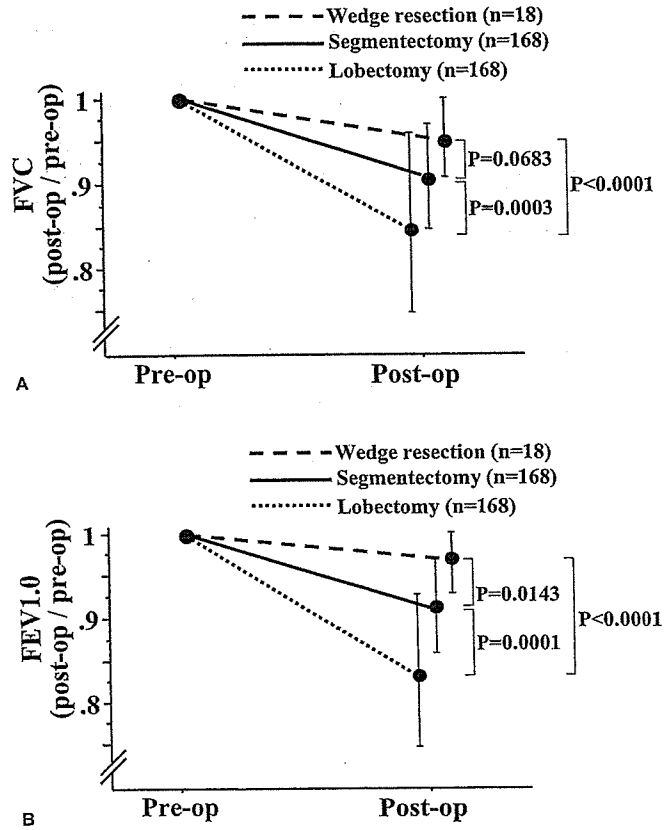


Figure 4. FVC (A) and FEV_1 (B) measured preoperatively and postoperatively (wedge resection, *long-dash line*; segmentectomy, *solid line*; lobectomy, *short-dash line*). Y-axis shows the ratio of the postoperative value to the preoperative one. Values are presented as the mean ± standard error. *FVC*, Forced vital capacity; *FEV_1*, forced expiratory volume in 1 second.

series, which included tumors up to 2 cm, the ratio of wedge resection was 9.8%. The frequency of local recurrence after sublobar resection could have been lower if the indication had been limited to tumors of 2 cm or smaller. In addition, the reasons for the differences in the occurrence of local recurrence may be associated with our preference to favor extended segmentectomy, which can improve the treated margin.[8,9,12,13] The intraoperative lavage cytology of surgical margins may be useful to check whether resection was complete.[20] On the other hand, frequent application of wedge resection can result in less-extensive intraoperative nodal surveillance, leading to a potential understaging of patients, in contrast with segmentectomy, which allows the assessment of nodal status. We are convinced that nodal assessment is obligatory for tumors larger than 2 cm.[21] We, under strict policy, especially when planning a sublobar resection, must resist the great temptation to perform an easier operation such as wedge resection. Many proficient surgeons have emphasized that segmentectomy must be essential and should not be forgotten by current-generation thoracic surgeons.[22-26]

The LCSG also reported that respiratory failure developed in 6 patients requiring postoperative ventilation for more than 24 hours in the lobectomy group, whereas no patient in the sublobar resection group required ventilatory assistance.[1] Longer ago, the LCSG found that the operative mortality was 6.2% after pneumonectomy, 2.9% after lobectomy, and 1.4% after sublobar resections in a universe of 2220 resections for lung cancer.[27] Preserving lung parenchyma can contribute to a lower occurrence of lung dysfunction, complications, and operative deaths, which suggests that perioperative morbidity and mortality rates would be improved with a lesser resection.

An important positive result overlooked in the LCSG trial is the advantage of sublobar resection concerning pulmonary function.[1] The FVC, FEV_1, and maximum voluntary ventilation were all significantly better in patients who underwent sublobar resection at 6 months after surgery. At 12 months the FEV_1 was still significantly better. Recent studies have shown superior lung function after lesser resection,[10-12] and more recently Harada and colleagues[28] demonstrated that the extent of removed lung parenchyma by the segment affected that of postoperative functional loss even at 6 months after segmentectomy or lobectomy for lung cancer. Our series revealed that sublobar resection provided better preservation of both FVC and FEV_1 compared with lobar resection at 2 months after surgery. These findings support that sublobar resection obviously offers a functional merit and constitute a more compelling reason to consider sublobar resection as identification of small cancers increases.

Possibly, not only a diseased margin but also intrapulmonary metastases or involved intralobar nodes might develop in the intentionally preserved lobe after sublobar resection. Under careful follow-up, in our series we identi-

TABLE 5. Summary of literature in prognosis following sublobar and lobar resection for stage IA(T1N0M0)NSCLC

Author	Sublobar resection		Lobar resection	
	Number	5-year survival (%)	Number	5-year survival (%)
Read et al., 1990[18]	113	84	131	74
LCSG 1995[1]	122	44*	125	65*
Kodama et al., 1997[8]	46	93	77	88
Landreneau et al., 1997[19]	102	62	117	70
Okada et al., 2001[12]	68	87	104	87
Koike et al., 2003[9]	74	89	159	90
The present study	305	89.6	262	89.1

NSCLC, non-small cell lung cancer. *statistically significant.

fied 3 patients with local recurrence in the remaining part of the diseased lobe after segmentectomy. At the time of this report all these patients are alive without disease after completion lobectomy (n = 2) or pneumonectomy (n = 1). In our study, as a result of careful selection of patients and strict procedures, sublobar resection offered no survival demerit over lobectomy. Despite the nonrandomized nature of our study, our data force us to suggest that sublobar resection with sufficient margin and nodal assessment should provide appropriate treatment for stage I NSCLC of 2 cm or smaller in lieu of lobectomy in this era of increasing early discovery of small-sized lung cancer. We hereafter might consider the correlation between CT findings and bronchioloalveolar carcinoma component in the selection of patients for radical sublobar resection.[29] At present, the time is ripe for a large randomized trial, which would greatly change the standards of surgical treatment for lung cancer in the near future.

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Resected well-differentiated fetal pulmonary adenocarcinoma and summary of 25 cases reported in Japan

Shuichi Sato, MD · Teruaki Koike, MD · Yasushi Yamato, MD · Katsuo Yoshiya, MD

Division of Chest Surgery, Niigata Cancer Center Hospital, Niigata, Japan

Keiichi Honma, MD

Division of Pathology, Niigata Cancer Hospital, Niigata, Japan

Hiroko Tsukada, MD

Division of Internal Medicine, Niigata Cancer Hospital, Niigata, Japan

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CASE REPORT

Resected well-differentiated fetal pulmonary adenocarcinoma and summary of 25 cases reported in Japan

Shuichi Sato, MD · Teruaki Koike, MD
Yasushi Yamato, MD · Katsuo Yoshiya, MD
Keiichi Honma, MD · Hiroko Tsukada, MD

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Abstract We report a case of well-differentiated fetal adenocarcinoma (WDFA), which is a variant of pulmonary blastoma. A 36-year-old man was found to have a tumor shadow in the right middle field of a chest radiograph as part of a mass screening examination, and chest computed tomography (CT) showed a 4.5-cm pulmonary mass in the right lower lobe. A diagnosis of adenocarcinoma of the lung was made based on a CT-guided needle biopsy, and right middle and lower lobectomy and lymph node dissection were performed. The postoperative pathological diagnosis was well-differentiated fetal adenocarcinoma. WDFA has a better prognosis than conventional pulmonary blastoma (biphasic pulmonary blastoma). We summarize the cases of WDFA reported in Japan and review the literature.

Key words Well-differentiated fetal adenocarcinoma · Pulmonary blastoma · Prognosis

Introduction

Pulmonary blastoma is a rare lung tumor that consists of primitive epithelial and stromal components that morphologically resemble fetal lung. Well-differentiated fetal adenocarcinoma (WDFA) is defined as a monophasic tumor consisting of an epithelial component that lacks the sarcomatous component of pulmonary blastomas. We describe a case of WDFA and summarize and review the clinical features of WDFA reported in Japan.

S. Sato · T. Koike (✉) · Y. Yamato · K. Yoshiya
Division of Chest Surgery, Niigata Cancer Center Hospital,
2-15-3 Kawagishi-cho, Niigata 951-8566, Japan
Tel. +81-25-266-5111; Fax +81-25-233-3649
e-mail: koike@niigata-cc.jp

K. Honma
Division of Pathology, Niigata Cancer Hospital, Niigata, Japan

H. Tsukada
Division of Internal Medicine, Niigata Cancer Hospital, Niigata, Japan

Case

A 36-year-old man was found to have a tumor shadow in the right middle field of a chest radiograph as part of a mass screening examination. Chest computed tomography (CT) revealed a 4.5-cm pulmonary mass in the right lower lobe, but no lymph node enlargement was observed in the mediastinal space (Fig. 1). Although bronchoscopy did not reveal any tumor lesions, a segmental bronchus (B^7) was compressed and distorted by a mass lesion. A transbronchial biopsy specimen from B^7 was not diagnostic, but a specimen obtained by CT-guided needle biopsy showed glandular or tubular structures, and we made a diagnosis of adenocarcinoma of the lung. There were no distant metastases (clinical T2N0M0).

Posterolateral thoracotomy revealed a tumor in the lower lobe that had invaded the middle lobe, and we performed right middle and lower lobectomy and mediastinal lymph node dissection (ND2a). Grossly, the tumor measured 41 × 39 × 40 mm, had a smooth surface, and consisted of whitish, firm homogeneous tissue with small areas of necrosis and hemorrhage (Fig. 2). Histological sections showed primitive glandular or tubular structures resembling fetal lung, and there were morules consisting of solid nests of epithelial cells. Although a

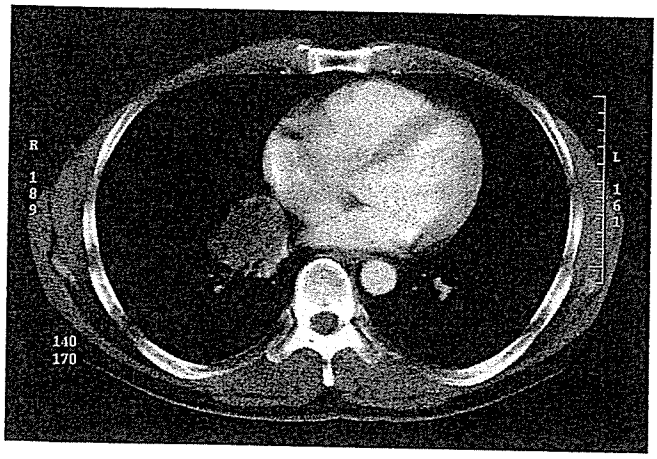

Fig. 1 Chest computed tomography scan showing a mass in the middle and lower lobe that is partly necrotic

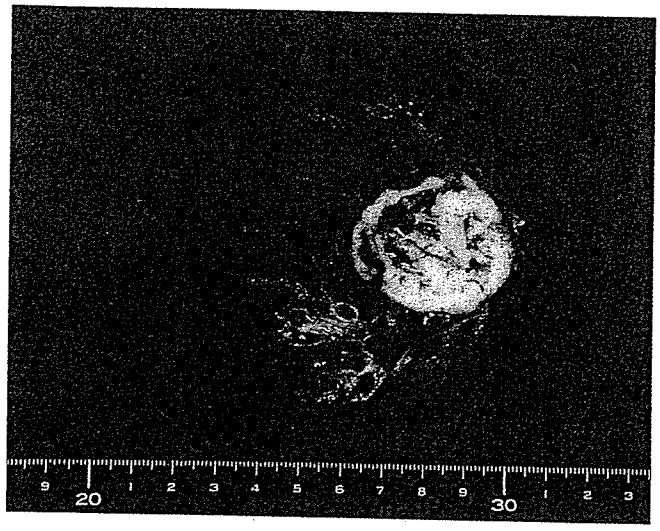

Fig. 2 On the cut surface, the well-circumscribed tumor measured 41 mm in diameter, was homogeneously white with small areas of necrosis and hemorrhage

small stromal component and spindle cells were observed in some areas, no sarcomatous structures, such as cartilage cells, smooth muscle, or striated muscle, were detected; and there was no evidence of a "biphasic" pattern (Fig. 3). The epithelial cells are immunohistochemically positive for several neuroendocrine markers, such as anti-NSE and anti-NCAM antibodies, and the Grimelius stain (Fig. 4).

Based on the above histopathological findings, we made a diagnosis of well-differentiated fetal adenocarcinoma that lacked the sarcomatous component of pulmonary blastoma. No regional lymph node metastases were detected. The pathological diagnosis was T2N0M0 and stage IB. The patient made an uneventful postoperative recovery, and there has been no evidence of recurrence as of 38 months postoperatively.

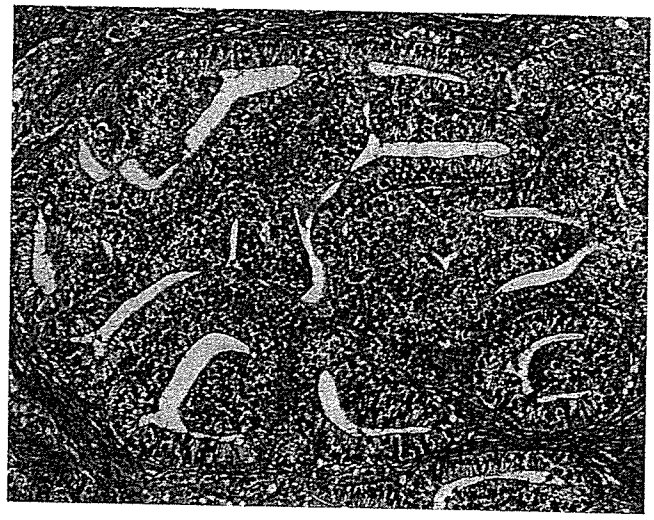

Fig. 3 Histological section showed neoplastic glandular structures, typically lined by pseudostratified columnar epithelium, resembling fetal lung. Note morules (*arrows*) consisted of small solid nests of tumor cells

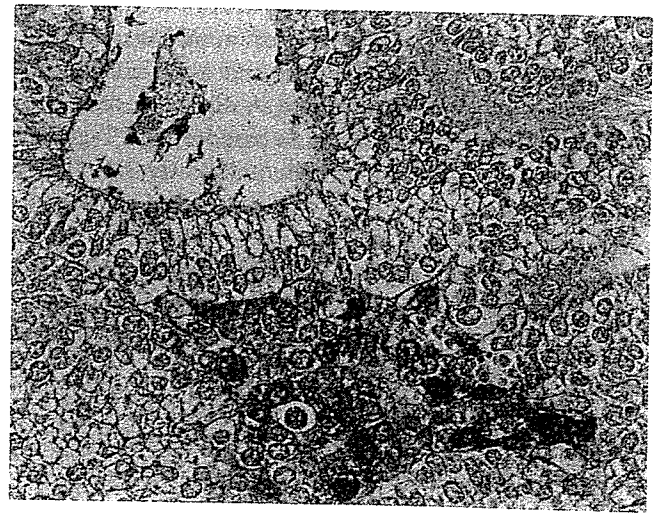

Fig. 4 Immunohistochemically, the epithelial cells were positive for anti-NSE antibody

Discussion

Pulmonary blastoma is defined in the histological classification of lung neoplasms as a tumor consisting of primitive epithelium or mesenchyme that resembles fetal lung. It is a rare lung tumor and is estimated to account for only 0.5% of all pulmonary neoplasms.[1] Zaidai et al.[1] reported that 0.2% (n = 6) of 2720 lung cancers were pulmonary blastomas and that half of the cases of pulmonary blastoma (n = 3, 0.1%) were WDFAs.[2] This rare lung tumor was first described by Barnard in 1952 and called "embryoma of lung" because morphologically it