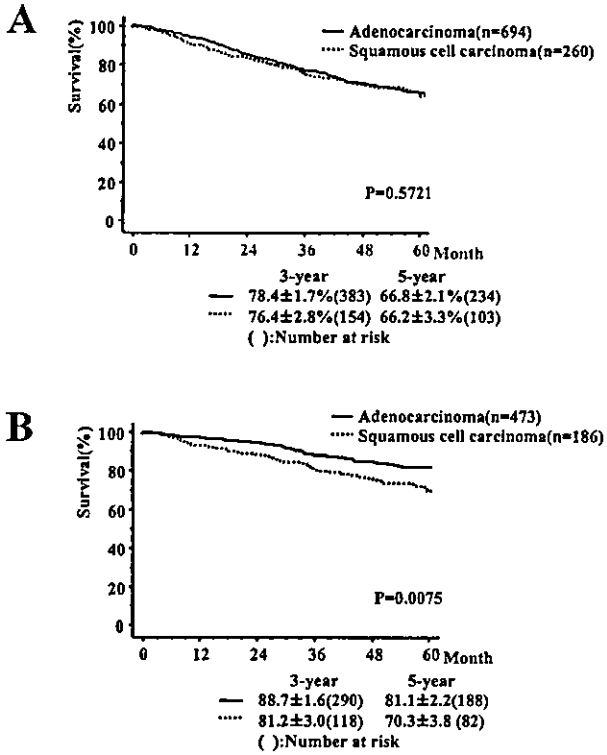

Fig 1. Overall survival curves for patients with clinical (A) and pathologic (B) stage I non-small cell lung cancer distributed according to histologic type.

carcinoma group (41.9% versus 35.3%). The two groups were fairly similar with respect to surgical procedure, resectability of tumor, and pathologic stage.

Overall follow-up ranged from 9 to 225 months, with a median of 62 months for surviving patients. The 5-year survival rates for adenocarcinoma versus squamous cell carcinoma were 66.8% versus 66.2% in patients with clinical stage I disease (Fig 1A). There were no significant differences between the two groups ($p = 0.5721$). In contrast, in patients with pathologic stage I disease, the 5-year survival rates for adenocarcinoma versus squamous cell carcinoma were 81.1% versus 70.3%, respectively (Fig 1B). This difference was significant ($p = 0.0075$). When the disease was diagnosed as proven stage I, patients with adenocarcinoma had better survival than those with squamous cell carcinoma. These data suggested that adenocarcinoma judged preoperatively as clinical stage I disease included more advanced disease compared with squamous cell carcinoma, and that preoperative staging for adenocarcinoma was consequently more difficult.

We then analyzed the effect of preoperative serum CEA level on survival of clinical stage I patients. Among patients with low CEA level (≤2.5 ng/mL), the survival rate was significantly better for those with adenocarcinoma than for those with squamous cell carcinoma ($p = 0.0417$). Among patients with a high CEA level (>5.0 ng/mL), the survival rate of those with adenocarcinoma

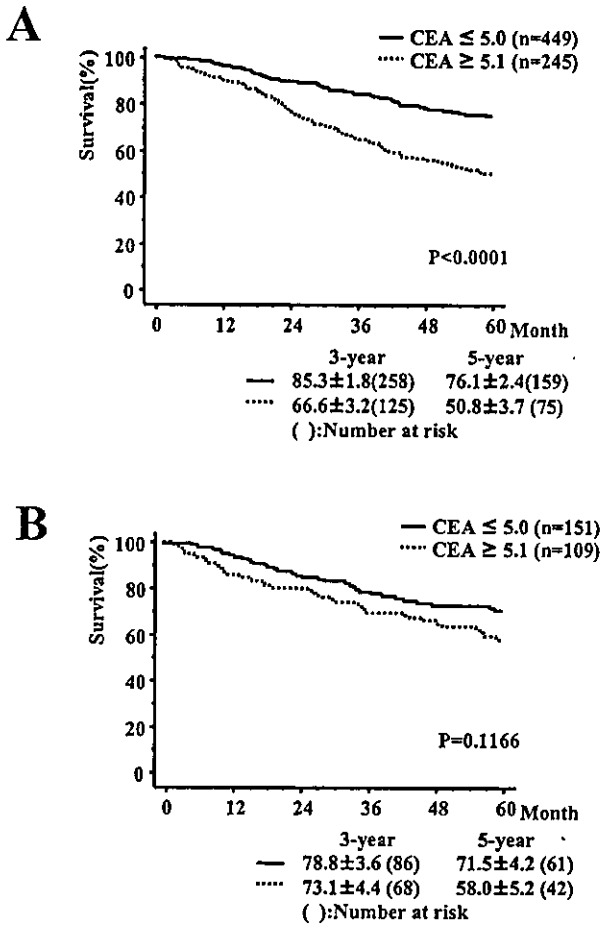

Fig 2. Overall survival curves for patients with clinical stage I adenocarcinoma (A) and squamous cell carcinoma (B) distributed according to preoperative serum carcinoembryonic antigen (CEA) level.

appeared poorer (not significant, $p = 0.1218$), although the survival rates of the two groups were similar ($p = 0.6457$) for those with intermediate CEA levels (2.6 to 5.0 ng/mL). For adenocarcinoma patients, high preoperative CEA levels were associated with a significantly poorer survival ($p < 0.0001$; Fig 2A), the statistical difference of which was definitely reduced in squamous cell carcinoma patients ($p = 0.1166$; Fig 2B). These data indicated the prognostic value of serum CEA before surgery was even more important for adenocarcinoma than for squamous cell carcinoma.

Univariate analyses to identify important preoperative variables for prognosis demonstrated that male sex ($p < 0.0001$), age older than 65 years ($p < 0.0001$), tumor size larger than 30 mm ($p < 0.0001$), current smoker ($p = 0.0022$), and high CEA level ($p < 0.0001$), but not histologic type ($p = 0.5475$), significantly and negatively affected survival of patients with clinical stage I disease. To better evaluate these factors affecting survival, multivariate analysis was performed (Table 2). Male sex ($p = 0.0092$), older age ($p = 0.0001$), and larger size of tumor (p

Table 2. Multivariate Analysis of Preoperative Prognostic Variables (n = 954)

Factors[a]	Unfavorable	Favorable	Risk Ratio	95% CI	*p* Value
Sex	male	female	1.549	1.114–2.153	0.0092
Age	older	younger	1.025	1.012–1.037	0.0001
Size	larger	smaller	1.021	1.015–1.027	<0.0001
Preoperative CEA	higher	lower	1.003	1.000–1.007	0.0401
Histology	AD	SQ	1.307	0.998–1.712	0.0515
Smoking	(+)	(−)	1.047	0.756–1.449	0.7829

[a] Continuous variables for age, size, and CEA level, and categories for sex, histology, and smoking.

AD = adenocarcinoma; CEA = carcinoembryonic antigen; CI = confidence interval; SQ = squamous cell carcinoma.

< 0.0001) strongly predicted failure. Serum CEA status was also an independent significant factor predictive of the outcome ($p = 0.0401$). The multivariate test demonstrated that patients with adenocarcinoma had a marginally (not significant) worse prognosis than those with squamous cell carcinoma ($p = 0.0515$), and that there was no difference in survival between smokers and nonsmokers ($p = 0.07829$).

Next, we examined the effect of postoperative serum CEA level on survival of patients with pathologically confirmed stage I disease. Among patients with either adenocarcinoma or squamous cell carcinoma, those with a high CEA level had a significantly worse prognosis ($p = 0.0003$ and $p = 0.0016$, respectively; Fig 3). The 5-year survival rates of patients with adenocarcinoma and squamous cell carcinoma and a high CEA level were 57.4% and 28.0%, respectively. These data suggested the importance of postoperative serum CEA value even when pathologic examination revealed stage I disease.

To detect the effect of cigarette smoking at the time of diagnosis on CEA tests, the correlation between smoking status and serum CEA values was investigated (Table 3). In patients with adenocarcinoma, smoking is generally believed to play a less vital role in the cause or growth of the tumor compared with other types. Of 694 patients with adenocarcinoma, 345 were smokers (49.7%) and 349 were nonsmokers (50.3%). The ratio of CEA-positive smokers (49.3%, 170 of 345) was significantly higher than that of CEA-positive nonsmokers (21.5%, 75 of 349; $p <$ 0.0001), suggesting that serum CEA level was influenced at least in part by smoking. In addition, 92.3% (240 of 260) of patients with squamous cell carcinoma were smokers, implying that the clinical significance of serum CEA values should be carefully determined, especially in patients with squamous cell carcinoma. Finally, to investigate the influence of smoking on CEA level, we analyzed the survival of smokers and nonsmokers with clinical stage I adenocarcinoma distributed according to their preoperative CEA level (Fig 4). Although nonsmokers with a high CEA value had a significantly worse prognosis than those with a normal CEA value ($p <$ 0.0001), this significant difference disappeared in smokers ($p = 0.1264$). These data suggested the prognosis of nonsmokers with adenocarcinoma was more significantly affected by the CEA level than that of smokers with adenocarcinoma.

Comment

Preoperative serum CEA value had independent prognostic value after adjusting for sex, age, tumor size, and histologic type as evaluated in patients treated surgically for clinical stage I non–small cell lung cancer. Its increase was related to clinically and statistically significant reduction in survival even after intentional curative resection for early-stage disease. Although serum CEA value

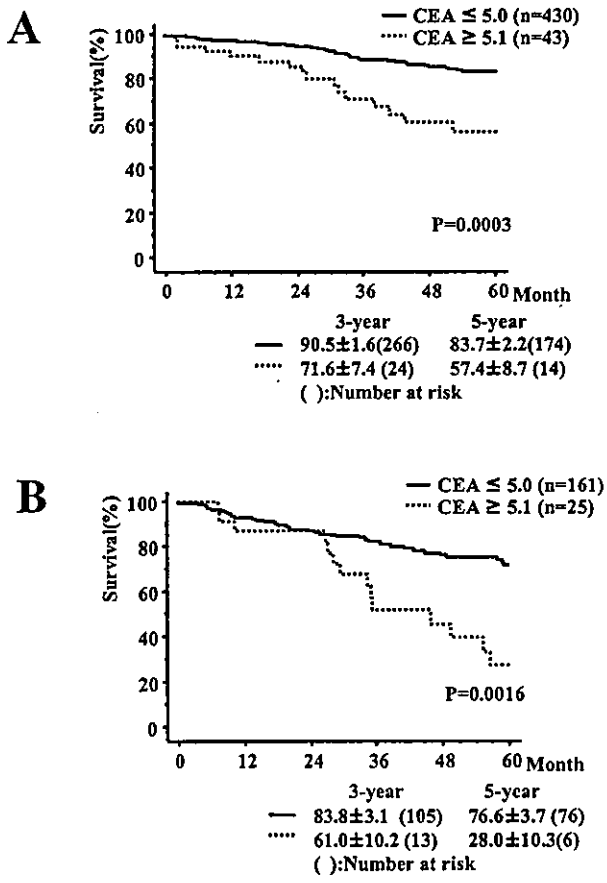

Fig 3. Overall survival curves for patients with pathologic stage I adenocarcinoma (A) and squamous cell carcinoma (B) distributed according to postoperative serum carcinoembryonic antigen (CEA) level.

Table 3. Relationship Between Preoperative Carcinoembryonic Antigen and Smoking Status in Patients With Clinical Stage I Disease

Factors	Total	CEA High	CEA Normal	*p* Value
Adenocarcinoma	694	245	449	<0.0001
Smoking (+)	345	170	175	
Smoking (-)	349	75	274	
Squamous cell carcinoma	260	109	151	<0.0001
Smoking (+)	240	105	135	
Smoking (−)	20	4	16	

CEA = carcinoembryonic antigen.

does not appear to be a specific marker of lung cancer, it is an essential prognostic factor. Thus, our data obtained from a large number of patients verified the importance of preoperative CEA as an adjuvant factor to conventional ones used for preoperative clinical staging despite modern progress in imaging and diagnostic procedures.

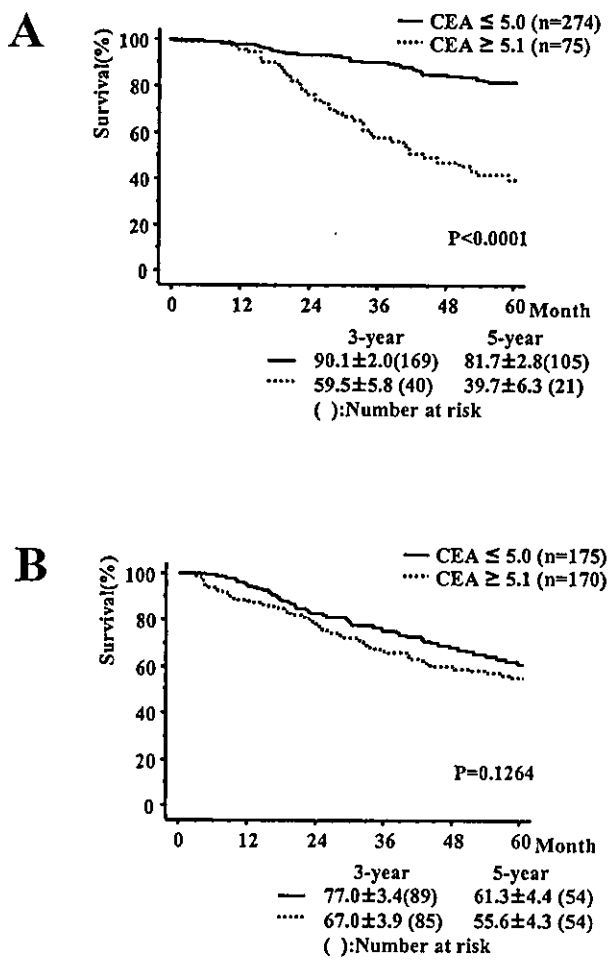

Fig 4. Overall survival curves for nonsmokers (former/never) (A) and current smokers (B) with clinical stage I adenocarcinoma distributed according to preoperative serum carcinoembryonic antigen (CEA) level.

The relationship between serum CEA values and tumor histologic type remains obscure. The most interesting issue examined in this study was whether a histologic difference between adenocarcinoma and squamous cell carcinoma could affect serum CEA value. Interestingly, although serum CEA levels were significantly higher in patients with adenocarcinoma than in those with squamous cell carcinoma, the proportion of CEA-positive patients with adenocarcinoma (35.3%, 245 of 694) was less than that of CEA-positive patients with squamous cell carcinoma (41.9%, 109 of 260). Based on these data, we speculated that the majority of CEA-positive patients with squamous cell carcinoma had marginally positive levels of CEA, and consequently that the specificity of the CEA test was low for squamous cell carcinoma patients. In addition, based on survival analyses (Figs 2, 3), we considered that the CEA test was more accurate and more specific for adenocarcinoma than for squamous cell carcinoma. The difference in specificity of CEA testing between adenocarcinoma and squamous cell carcinoma was thought to depend basically on the biologic nature of each tumor. However, we could not rule out the possibility that other factors might contribute to this difference.

Because the factor most strongly influencing the increase of serum CEA was reported to be cigarette smoking [10, 11], we quantified the effect of smoking on serum CEA level. Among nonsmokers, the rate of CEA-positive patients was 21.5% (75 of 349) for adenocarcinoma and 20.0% (4 of 20) for squamous cell carcinoma. In contrast, among smokers, the rate of CEA-positive patients was 49.3% (170 of 345) for adenocarcinoma and 43.8% (105 of 240) for squamous cell carcinoma. These data suggested that in more than half of CEA-positive smokers, serum CEA was increased by cigarette smoking. On the other hand, although the proportion of smokers among adenocarcinoma patients was 49.7% (345 of 694), that among squamous cell carcinoma patients was 92.3% (240 of 260). That is why the specificity of serum CEA tests was low for squamous cell carcinoma. Besides, the survival analysis showed that the CEA level more significantly influenced the outcome of nonsmokers with adenocarcinoma than that of smokers with adenocarcinoma, confirming that CEA was not necessarily valid in current smokers. These data suggested that the value of CEA as a marker should be considered in relation to the histology of non–small cell lung cancer subtypes and smoking status.

Postoperative serum CEA values, the role of which did not appear to be influenced by the histologic type, provided valuable information regarding patient prognosis after surgery. Even though our analysis was limited to pathologically proven stage I disease, the increase in postoperative serum CEA was associated with poor survival rates, which for 5 years were 57.4% and 28.0% for adenocarcinoma and squamous cell carcinoma, respectively. These data indicated that measurement of postoperative serum CEA, as well as preoperative CEA, provides information useful for detecting patients at high

risk of poor survival; consequently in patients with high serum CEA levels, additional adjuvant therapy might have to be considered.

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INVITED COMMENTARY

Since the early 1970s, several studies have shown that high carcinoembryonic antigen (CEA) levels were a potential marker of poor prognosis in nonsmall cell lung cancer (NSCLC). Abnormally elevated CEA levels were reported in 30% to 70% of patients with NSCLC and were most frequently observed in patients with adenocarcinoma and advanced stage carcinoma. Despite its potential value, CEA was often falsely elevated in smokers and in patients with restrictive or obstructive pulmonary disease. Consequently, the stage of disease and performance status of the patients remained better predictors of survival than CEA, and in 1997, The American Thoracic Society and the European Respiratory Society did not recommend the routine measurement of CEA for patients with NSCLC, because it did not influence the management of these patients.

However, the past decade has been associated with significant changes in the mode of presentation and treatment of NSCLCs. Adenocarcinoma has become more frequent than squamous cell carcinoma in North America and Asia, low-dose chest computed tomography has been popularized, the incidence of bronchioloalveolar carcinoma has been rising (particularly in nonsmokers), and chemotherapy has been proven beneficial in patients with early stage NSCLC.

These changes have brought a whole new set of questions in our current management of patients with stage IA and IB NSCLC. Do all patients with very early stage NSCLC require a lobectomy or would segmentectomy be an appropriate operation in some patients? Do all bronchioloalveolar carcinomas have to be treated similarly to other NSCLCs, or is there a spectrum of disease between bronchioloalveolar carcinoma and adenocarcinoma? Do all patients with early stage NSCLC require chemotherapy in addition to surgery, and should they receive it before or after surgery?

Refinements to our current evaluation of patients with early stage NSCLC is needed to answer some of these questions. The measurement of tumor markers could potentially be part of this evaluation. Carcinoembryonic antigen is an inexpensive and readily available serum marker that has been shown to be one of the few independent preoperative predictors of survival in patients with small adenocarcinoma. High preoperative CEA level has also been shown to be associated with a higher risk of nodal metastasis in patients with NSCLC, and particularly in patients with clinical stage IA adenocarcinoma. The combination of a normal preoperative CEA level with a high tumor disappearance rate, which is determined by the ratio of the tumor area between the mediastinal and the lung windows on chest computed tomography, was recently shown to preoperatively predict the selection of a group of patients with peripheral adenocarcinoma that had no nodal metastasis [1].

This study from Okada and colleagues looking at the role of histology and smoking status on the prognostic value of CEA in patients with clinical stage I NSCLC reiterates the importance of CEA as an independent preoperative prognostic variable along with age, gender, and size of the tumor [2]. The authors eventually demonstrate that elevated preoperative CEA level had a predictive impact on prognosis only in nonsmokers with adenocarcinoma; this group also included previous smokers that had stopped smoking before their diagnosis of NSCLC. This finding may explain some of the discrepancies that were observed in the past and the low accuracy of elevated CEA level to predict outcome when it is indifferently applied to all patients with NSCLC.

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A rare case of hemangioma arising from the azygos vein: Informative procedure with endobronchial ultrasonography

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Clinical Summary

A 52-year-old woman with a previous history of vasospastic angina presented with an asymptomatic mediastinal mass on her routine follow-up chest roentgenogram. Values shown by means of hematologic and biochemical examinations were within normal range. A computed tomographic scan demonstrated a mass of 40 mm in diameter with a smooth margin adjacent to the trachea, superior vena cava, and ascending aorta. It showed high enhancement, although the degree of enhancement was lower than that of the surrounding vascular structures. Because a vascular tumor was suspected, digital subtraction angiography was performed, but this did not show feeder arteries or other vascular staining. Magnetic resonance imaging suggested high intensity on the T1-weighted image and low intensity on the T2-weighted image. No flow void was demonstrated (Figure 1, *A*). A diagnosis of lymphoadenopathy, such as Castleman disease or a malignancy, was given by radiologists. An ordinary bronchoscopic examination also showed no abnormal lesion. XBF-UC40P, a new prototype bronchofiberscope with an electrical curved linear array method, clearly showed a cystic mass with blood flow by using the power Doppler mode (Figure 1, *B*). No definite findings were detected on abdominal and cardiac echocardiographs.

Because a vascular tumor was strongly suggested on the basis of endobronchial ultrasonography (EBUS), surgical removal of the mass by means of video-assisted thoracotomy was performed. Macroscopically, the mass seemed to be a varix of the azygos vein. No abnormal findings were observed in the superior vena cava and right atrium. The wall of the cyst was very thin, and delicate manipulation was absolutely necessary in dissecting the tumor (Figure 2, *A*). Pathologic examination of the excised tumor showed it to be a hemangioma composed of various cavities separated by fine septa lined with attenuated endothelium not unlike the hemangiomas of other regions. The wall of the tumor was composed of smooth muscle and connective tissues (Figure 2, *B*). The postoperative course was uneventful.

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Discussion

Although many kinds of tumors originate from the mediastinal structures, vascular tumors of the azygos vein are extremely rare. In fact, to the best of our knowledge, there has been only one case report of such a tumor[1] and no reports of hemangioma of the azygos vein. It is very difficult to establish a preoperative diagnosis for this kind of tumor only by means of radiologic examination. On the basis of the findings of digital subtraction angiography, which did not show definite feeder arteries or vascular staining, our radiologists considered the tumor to be a solid tumor, such as a lymphoadenoma. The azygos vein is hardly enhanced in angiography, even by means of phlebography. Also, its slow turbulent flow probably prevents the appearance of a flow void on chest magnetic resonance.[2]

A new prototype, EBUS, however, showed information crucial for understanding the details of the mass. EBUS revealed that the mass contained cystic structures with blood flow, which was detected by using the power Doppler mode. This finding was sufficient for us to avoid the performance of transtracheal needle aspiration biopsy-cytology or percutaneous needle aspiration, which might have led to bleeding. In cases of right paratracheal cystic tumor, we must also be careful because the mass could be a varix of the azygos vein[3-5] or a vascular tumor. EBUS with a power Doppler device provides crucial information for the diagnosis of vascular tumors, especially in this zygous vein area. Although this is the very first EBUS with the power Doppler mode, we are convinced that this procedure is very useful in accurately diagnosing masses in the paratracheal area.

We appreciate the assistance of Olympus Optical, Co, Ltd, in the use of the prototype bronchofiberscope XBF-UC40P.

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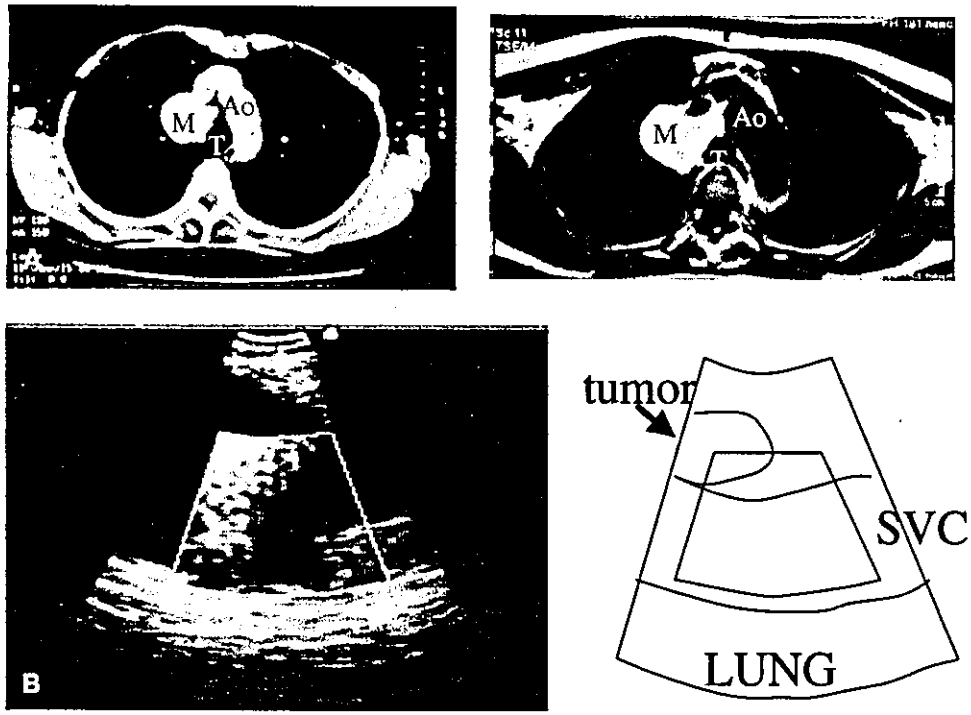

Figure 1. A, A chest computed tomographic scan demonstrated a mass *(M)* with high enhancement adjacent to the right wall of the trachea *(T)*. Magnetic resonance imaging showed a mass with high intensity on the T1-weighted image. No flow void was observed. *Ao,* Aorta. Left, Chest computed tomographic image with mediastinal window. Right, T1-weighted image with magnetic resonance imaging of the chest. B, EBUS revealed the mass to be cystic, with high blood flow by the power Doppler mode. The area surrounded by the *white line* indicates the area subjected to power Doppler analysis.

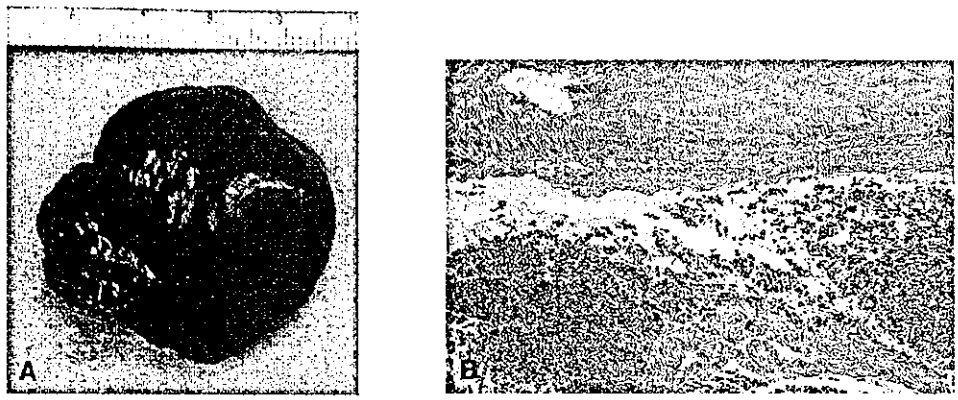

Figure 2. A, Macroscopic findings of the resected specimen. B, Microscopic findings showing various cavities filled with red cells separated by fine septa lined with attenuated endothelium are compatible with the diagnosis of hemangioma.

A New Technique for Endobronchial Ultrasonography and Comparison of Two Ultrasonic Probes*

Analysis With a Plot Profile of the Image Analysis Software NIH Image

Yoshihiro Nakamura, MD; Chiaki Endo, MD; Masami Sato, MD, FCCP; Akira Sakurada, MD; Shun-ichi Watanabe, MD; Ryuzo Sakata, MD; and Takashi Kondo, MD

Study objectives: **Endobronchial ultrasonography (EBUS) is currently the sole clinical method available for delineating the bronchial wall structure; however, the image resolution is inadequate. Thus, an improved image analysis system is needed for both a more accurate and more readily interpretable endobronchial ultrasonogram.**

Materials and methods: **A total of 10 patients underwent pulmonary resection for lung cancer. EBUS was performed on the bronchi of the resected lungs, which had been immersed in physiologic saline solution. The same bronchial lesion in each specimen was imaged with two probes: 20 MHz and 30 MHz. The images were analyzed using the plot profile derived from freeware image analysis software: NIH Image (National Institutes of Health; Bethesda, MD). The measured echo intensity of the bronchial wall was statistically analyzed.**

Results: **A normal bronchial wall image consists of five layers, and the plot profile shows a W-shaped curve. The mean value of the echo intensity of each peak or trough of the W-shaped curve was calculated and compared for both probes. The differences in the mean echo intensity between both the third and fourth layer and the second and fourth layer were found to be significantly greater with the 30-MHz probe than with the 20-MHz probe. The echo intensity curve of a central-type lung cancer was not W shaped, indicating that the bronchial wall was not composed of the normal five layers.**

Conclusion: **We employed image analysis software and drew a plot to obtain a W-shaped curve from the EBUS image data. This enabled us to make an objective assessment of the laminar structure of the bronchial wall. In order to clearly recognize the laminar structure of the bronchial wall, the 30-MHz probe was found to be more useful than the 20-MHz probe.**

(CHEST 2004; 126:192–197)

Key words: bronchial wall invasion; central-type lung cancer; endobronchial ultrasonography; image analysis

Abbreviations: EBUS = endobronchial ultrasonography; PDT = photodynamic therapy

The laminar structure of the bronchial wall as visualized by endobronchial ultrasonography (EBUS) was first described by Hurter and Hanrath[1] in 1992. Subsequently, a number of studies[2–9] have been conducted, suggesting that EBUS might be useful for imaging the laminar structure of the bronchial wall and evaluating the depth of tumor invasion in central-type bronchogenic carcinoma. EBUS is currently the sole method available for delineating the bronchial wall structure in the clinical setting; however, the image resolution is inadequate for the attainment of a clear laminated view of the bronchial wall, which has a maximum thickness of approximately 5 mm. A learning curve is required for the ultrasonic evaluation of the extent of tumor invasion into the bronchial wall. Even experienced interpreters have to rely on their subjective judgment. For more accurate and simpler interpretation,

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we employed an image analysis system for EBUS that enabled us to acquire a clear laminated view of the bronchial wall and make an objective assessment of the feasibility of echo probes and the extent of tumor invasion *ex vivo*.

Materials and Methods

Materials

From February through March 2002, 10 patients underwent pulmonary resection for lung cancer. The operative procedure was a pneumonectomy in one case, a sleeve lobectomy in two cases, and a lobectomy in seven cases. The resected lung specimens were used for this study. The specimens were immersed in physiologic saline solution within 1 hour of the resection, in order to prevent autolytic changes and to obtain high-quality ultrasonic images without interference from air. The EBUS system used in this study was manufactured by Olympus (Tokyo, Japan), and had the following specifications: an EU-M 30 processor; a UM-BS20-26R ultrasonic probe (20-MHz radial scanner; rotation rate, 400/s); a XUM-BS30-26R ultrasonic probe (30-MHz radial scanner; rotation rate, 400/s); and a MAJ-643R (latex balloon sheath; outer diameter, 2.6 mm). The balloon sheath of the ultrasonic probe was filled with physiologic saline solution.

EBUS Procedure

EBUS was performed on the bronchus of the resected lung within 1 h of the resection. During the EBUS procedure, the resected lung was immersed in physiologic saline solution. First, the ultrasonic probe with the balloon sheath was inserted into the bronchial lumen. Second, the balloon sheath was expanded with physiologic saline solution until the lumen was obstructed. Third, EBUS images of the bronchus were captured after adjusting the brightness and contrast of the images (Fig 1). The same bronchial lesion in each specimen was observed using two different types of probes: 20 MHz and 30 MHz.

With the use of the balloon sheath, the study conditions were similar to the actual conditions in EBUS. When we perform EBUS in actual patients, the ultrasonic probe is used with the balloon sheath; for this reason, the balloon sheath was used in this study, although clearer images can be obtained if the EBUS is performed without the balloon sheath.

Image Analysis

The captured ultrasonogram was analyzed using freeware image analysis software (NIH Image, Version 1.62; National Institutes of Health; Bethesda, MD).[10] The plot profile of the NIH Image was used, and the echo intensity of the ultrasonogram was measured. When an echo image was pure white (hyperechoic) in the ultrasonogram, the plot profile indicated 256 pixels; when it was pure black (hypoechoic), it indicated 0 pixels.

First, a radial line from the ultrasonic probe was drawn on the ultrasonogram, which perpendicularly intersected the bronchial wall. Second, the echo intensity on the line was plotted, and the plotted data on the total length of the line were obtained. Finally, we obtained the echo intensity curve as shown in Figure 2, *top*. Normally, the bronchial wall consists of five layers in an ultrasonogram: an innermost hyperechoic layer representing the balloon latex sheath and the bronchial epithelium; a hypoechoic second layer representing the submucosal layer; a hyperechoic third layer, which represents the marginal echo of the bronchial cartilaginous layer; a hypoechoic fourth layer representing the bronchial cartilaginous layer; and the outer most hyperechoic fifth layer representing the marginal echo of the outer cartilaginous layer and the outer margin of the bronchial wall. Therefore, the echo intensity curve is W shaped. The longitudinal axis represents the echo intensity, and the horizontal axis represents the distance from the ultrasonic probe.

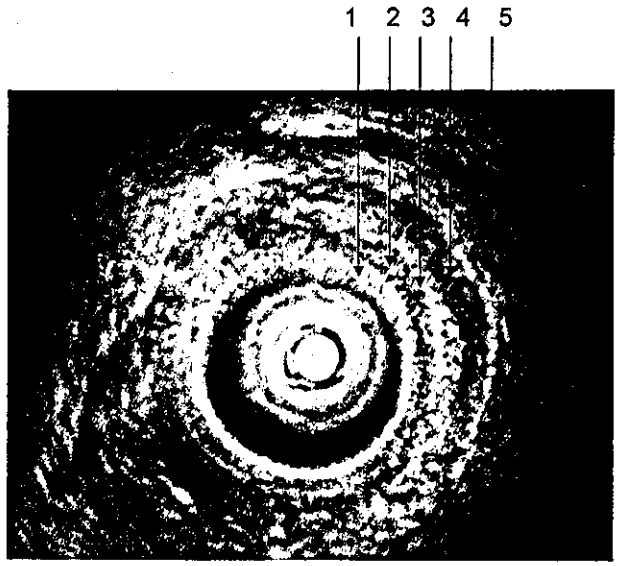

FIGURE 1. Representative endobronchial ultrasonogram showing a laminar structure of the bronchial wall. A central circular lesion is an echo probe, and a five-layer laminar structure is depicted. The first lamina is a hyperechoic layer representing the balloon sheath and the bronchial epithelium; the second lamina is hypoechoic layer representing the submucosal layer and the bronchial smooth-muscle layer; the third lamina is a hyperechoic layer representing the marginal echo of the luminal aspect of the bronchial cartilaginous layer; the fourth lamina is a hypoechoic layer representing the bronchial cartilaginous layer; and the outermost (fifth) lamina is composed of a hyperechoic layer representing the marginal echo of the outer cartilaginous layer and the outer margin of the bronchial wall. Numbered arrows indicate the layers of the bronchial wall as mentioned above.

The analysis was made of the image displayed on the monitor. The pixel values altered when the brightness of the image was changed. However, these alterations did not influence the results of the image analysis. First, each lamina has to be distinguished from the others in order to clearly recognize the laminar structure of the bronchial wall. If the difference of the pixel values between laminae increases, we can more clearly recognize the laminar structure. Accordingly, the most important thing to clearly recognize the laminar structure is not the pixel values of each lamina but the difference in pixel values between laminae. Furthermore, the differences of the pixel values between peaks and troughs did not vary even if the brightness of the image was changed. Because the change of each pixel value was the same as other values, the difference in the pixel values was constant.

Second, if we compare the performance of two ultrasound probes, each ultrasound image had to be obtained under the optimal conditions of that probe; specifically, each image must be obtained by the ultrasound probe, which is in accordance with its performance characteristics. The optimal conditions for one

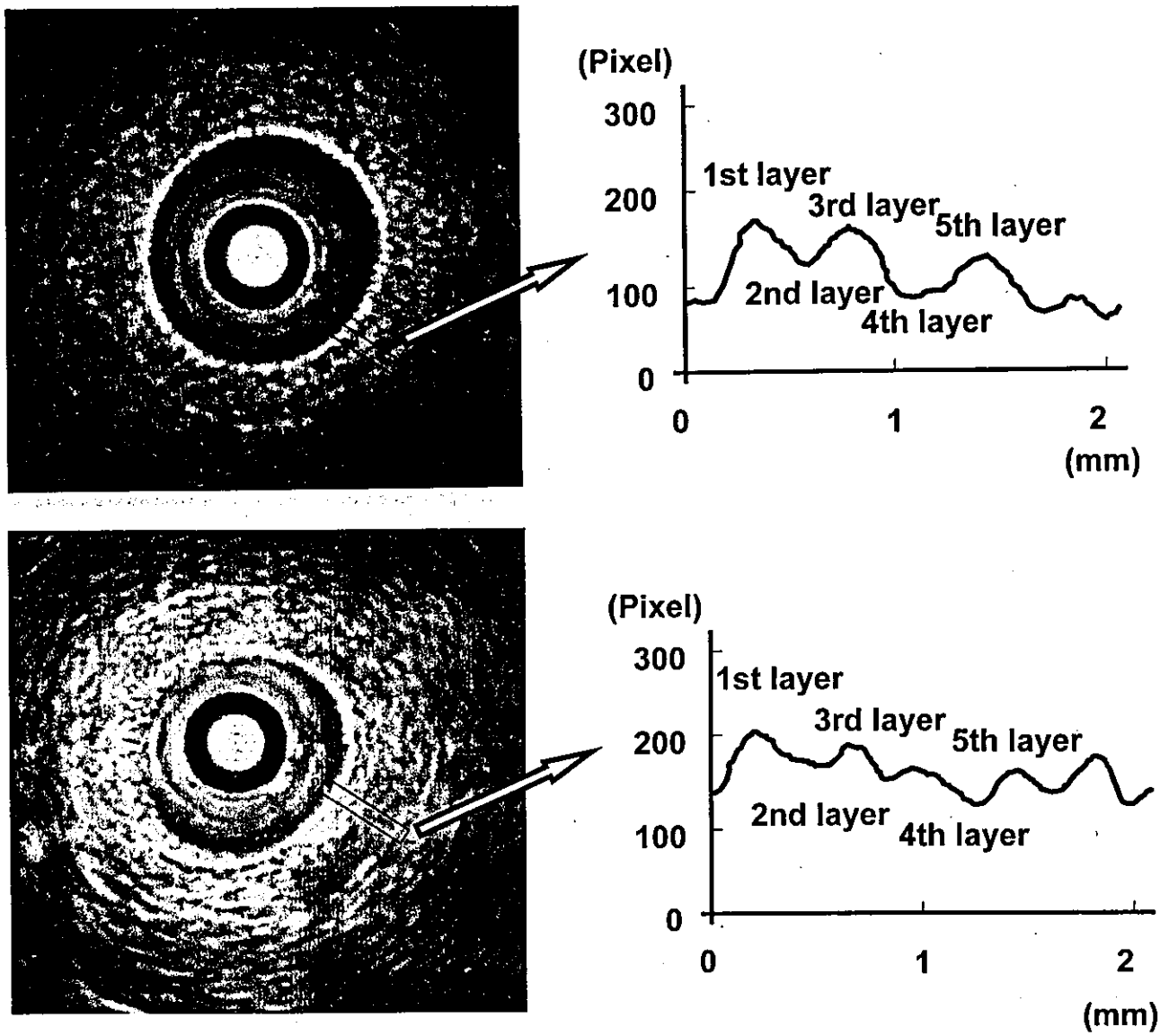

FIGURE 2. EBUS was performed at the same site of the bronchus with two kinds of ultrasonic probes, and ultrasonograms and their accompanying echo intensity curves were obtained (*top*, 30-MHz probe; *bottom*, 20-MHz probe). It would be subjectively understood that the ultrasonogram of the 30-MHz probe (*top*) shows higher resolution than that of the 20-MHz probe (*bottom*). However, the five-layer laminar structure might not be seen easily with the direct evaluation of the ultrasonogram. However, image analysis with NIH Image shows bronchial laminar structure as a W-shaped curve. An open rectangular lesion is analyzed with plot profile of NIH Image, and a certain plot of the rectangle is assigned from 0 to 256 pixels, according to its echo intensity. A W-shaped curve indicates a five-layer laminar structure of the bronchial wall. Echo intensity is plotted on the y-axis, and the distance from the echo probe is shown on the x-axis. Furthermore, the echo intensity curve of the 30-MHz probe shows steeper W-shaped curve than that of the 20-MHz probe. That is, the difference between peak and trough of the echo intensity curve is larger with the 30-MHz probe than the 20-MHz probe, and objectively shows that the 30-MHz probe has higher resolution than the 20-MHz probe.

ultrasound probe may be different than those for the other probe. We had to adjust the brightness of the image each time in order to obtain its optimal conditions.

Statistical Analysis

The measured echo intensity of the bronchial wall was statistically analyzed. The W-shaped echo intensity curve has five peaks and troughs, and each peak or trough represents the echo intensity of the most hyper or hypoechoic lesion in the corresponding layer of the laminar structure of the bronchial wall. The mean value of each peak or trough of the echo intensity curve of all specimens was calculated, and statistical comparison was conducted. The paired t test was used to compare the echo intensities, and $p < 0.05$ was considered as denoting significance. Informed consent was obtained from all patients before they were entered into the study group.

Results

A total of 10 normal bronchi from 10 patients with lung cancer were examined. Figure 2 presents ultrasonograms and echo intensity curves, which were obtained at the same site of the normal bronchus by two different ultrasonic probes: 30 MHz and 20 MHz. It is common knowledge that the ultrasonogram obtained with a 30-MHz probe (Fig 2, *top*) exhibits a higher resolution than that obtained with a 20-MHz probe (Fig 2, *bottom*). However, five layers of laminar structure might not be readily seen by direct assessment of the ultrasonograms. Conversely, the echo intensity curves showed five peaks and troughs, indicating that the normal bronchial wall is a laminar structure consisting of five ultrasonically distinct layers. Moreover, the echo intensity curve of Figure 2, *top*, showed a steeper W-shaped curve than that of Figure 2, *bottom*; specifically, the difference between the peak and trough of the echo intensity curve is greater with the 30-MHz probe than it is with the 20-MHz probe. This finding objectively demonstrates that the 30-MHz probe has a higher resolution than the 20-MHz probe. Figure 3 shows the mean value of the echo intensity of each layer of the laminar structure of the bronchial wall, obtained with different ultrasonic probes: 20 MHz and 30 MHz. Figure 4 shows the difference in the mean echo intensity between the third and fourth layer as well as the second and fourth layer using two different ultrasonic probes. The differences were found to be significantly greater with the 30-MHz probe than with the 20-MHz probe. Figure 5 shows the echo intensity curve of a central-type bronchogenic squamous cell carcinoma. This curve is not W shaped, indicating that the bronchial wall is not composed of the normal five layers and the tumor has invaded beyond the bronchial wall.

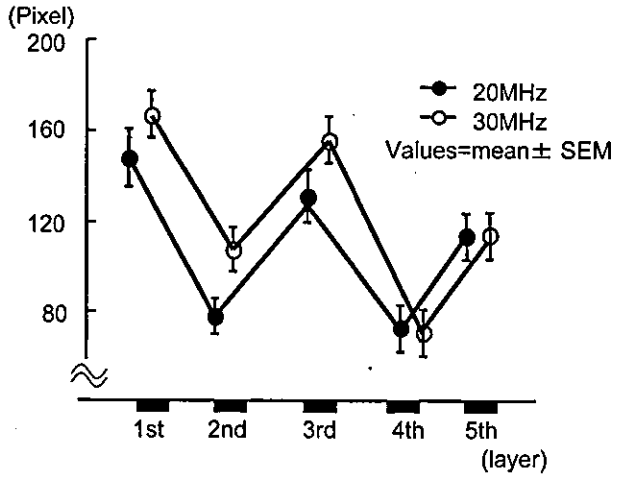

FIGURE 3. Mean value of echo intensity of each layer of the laminar structure of the normal bronchial wall of 10 patients with lung cancer using the 20-MHz (closed circle) and 30-MHz (open circle) echo probes.

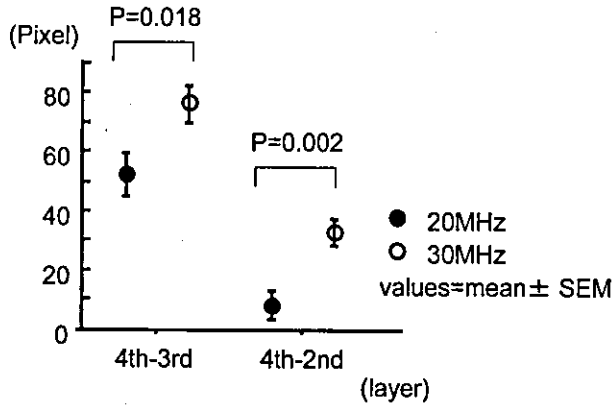

FIGURE 4. The difference in the mean echo intensity between the third and fourth layer and the second and fourth layer using the two types of echo probes. The difference is found to be significantly greater with the 30-MHz probe than with the 20-MHz probe.

Discussion

In almost all reports discussing EBUS, the ultrasound images were compared using subjective evaluation; thus, the results might vary between examiners. For example, when one examiner states that a particular bronchial wall consists of four layers, another may state that it has five layers. When one examiner states that a tumor has invaded beyond the cartilaginous layer, another might state that the tumor is within the cartilaginous layer. When one examiner states that a particular image is clearer than another, a different examiner might state the reverse. These discrepancies are due to inadequate image resolution. If EBUS had a resolution as fine as abdominal ultrasonography, all examiners would arrive at the same conclusion, merely by subjectively evaluating the raw image data.

In cases with early central-type lung cancer, it may be essential for making the appropriate therapeutic decision to know the depth of tumor invasion into the bronchial wall at the laminar level. When a tumor penetrates the cartilaginous layer, photodynamic therapy (PDT) may no longer effective.[8,11–14] To obtain an optimal therapeutic outcome, the physician needs to know whether the lesion has invaded the cartilaginous layer. Currently, EBUS is the only clinically available method for imaging the laminar structure of the bronchial wall; however, the currently available EBUS apparatus does not yield a sharp enough image to permit accurate evaluation of the depth of tumor invasion into the bronchial wall.

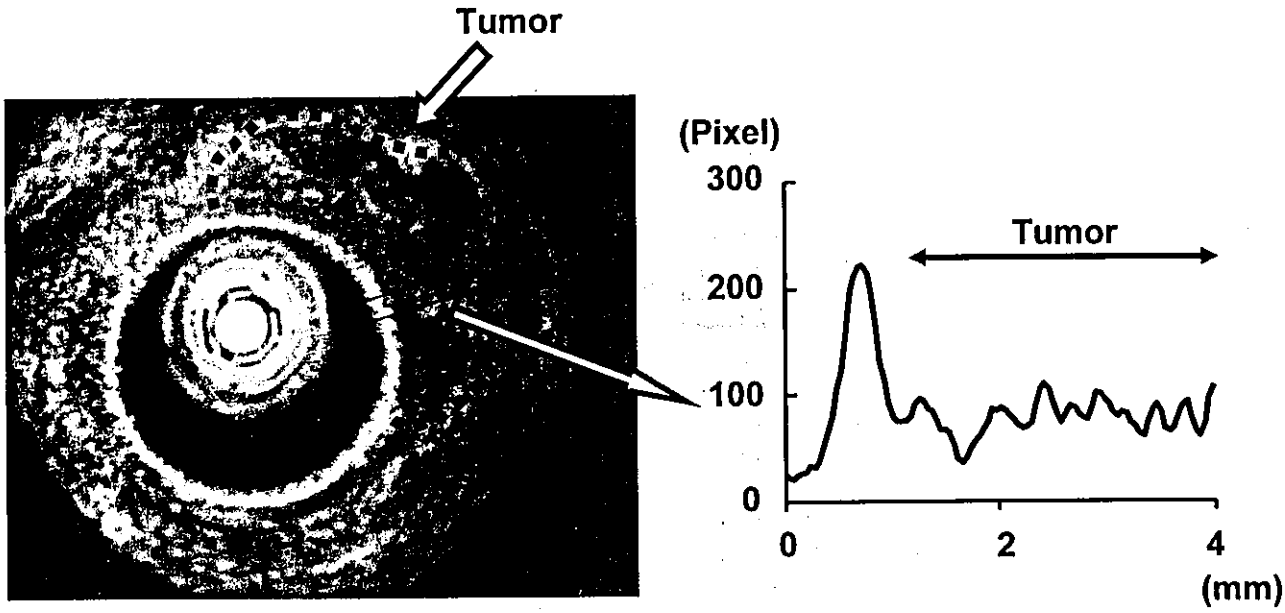

FIGURE 5. Representative endobronchial ultrasonogram showing an endobronchial tumor. A white dotted line shows the margin of the tumor. The image analysis with NIH Image shows a curve that is completely different from the W-shaped curve. This means that the tumor has extrabronchial wall invasion.

In this study, we employed image analysis software to digitize the EBUS image. This allowed us to draw a plot of the EBUS data from the bronchial wall and perform statistical analysis for an objective assessment. The laminar structure of the normal bronchial wall is represented by a 5-point W-shaped curve, from which the status of each layer can be estimated. When the digitized data did not form a W-shaped curve in this study, the bronchial wall was considered to be abnormal and presence of a tumor or other lesion was assumed. The degree of deviation from W-shaped curve reflected the extent of lesion invasion into the bronchial wall.

Few studies[9,15] have subjectively compared the image quality of the bronchial wall layers using EBUS transducer probes of different frequencies. In this study, we examined the ultrasound images of the bronchial wall structure using both the 20-MHz and 30-MHz transducers. The ultrasound image data were digitized, and the images were statistically compared. The results revealed that the 30-MHz transducer was significantly more useful for delineating the bronchial wall layers than the 20-MHz probe. The 30-MHz transducer achieved excellent results, particularly in regard to the echo contrast between the second and fourth layers as well as between the third and fourth layers. For therapeutic decisions for to use PDT, it is crucial to determine whether the fourth layer is invaded by the tumor; the 30-MHz transducer appeared to be significantly superior to the 20-MHz transducer for the assessment of the extent of tumor invasion into the bronchial wall.

In summary, EBUS has been used commonly in the assessment of tumor invasion in early central-type lung cancers.[2–9] However, it is often difficult to interpret the ultrasound images of the bronchial wall, which has a maximal thickness of 5 mm, and consists of five layers. Although accurate evaluation of tumor invasion of the fourth (cartilaginous) layer is required for a therapeutic decision for PDT or other treatment modalities, raw ultrasound images are often too unclear to distinguish each layer. In this study, we employed image analysis software and drew a plot to obtain a W-shaped curve from the EBUS image data. This enabled us to make an objective assessment of the laminar structure of the bronchial wall. Data distribution also showed a significant difference in the delineation of the bronchial wall structure between the two transducers: 20 MHz and 30 MHz. Our image analysis is an objective evaluation, and any examiner should arrive at the same results. If we cannot clearly image the laminar structure, we cannot accurately evaluate the extent of tumor invasion. For therapeutic decisions for PDT, evaluation of tumor invasion of the fourth layer (the cartilaginous layer) is considered to be crucial. We cannot perform PDT effectively if the tumor has invaded beyond the cartilaginous layer. In this study, we showed the statistically significant superiority of the 30-MHz probe in the imaging of the laminar

structure of the bronchial wall. Specifically, by using the 30-MHz probe, we can more accurately image the cartilaginous layer. Accordingly, the 30-MHz probe was found to be more useful than the 20-MHz probe for recognition of the extent of tumor invasion into the bronchial wall. Until a high-resolution EBUS system permitting direct assessment of an ultrasonogram of the bronchial wall is developed, our approach should remain useful for the detection and evaluation of the laminar structure of the bronchial wall and the extent of tumor invasion. Our image analysis is an objective evaluation, and any examiner should arrive at the same results. Our next goal is to apply this analytical method to EBUS data in clinical practice.

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V. 中心型早期肺癌に対する検査

中心型早期肺癌に対する検査方法として，喀痰細胞診，気管支鏡検査，蛍光内視鏡検査，気管支超音波検査が取り上げられている．それぞれについて決定された推奨を表2に示す．

喀痰細胞診の有効性については，米国において1970年代から80年代にかけて行われた大規模な無作為化比較試験による報告がある．胸部レントゲン写真に喀痰細胞診を加えることによって肺癌死亡が減少するかどうかの検討がなされ，否定的な結論が報告された[5][6]．この結果を受けて，欧米ではスクリーニングとして喀痰細胞診を用いることについては否定的な見解が定着している．しかし，これらの比較試験には様々な問題点が指摘されていること[7][8]，また，我が国においては，複数の症例対照研究によって，胸部レントゲンに喀痰細胞診を併用した検診の有効性が示されていることから[9][10]，こうした形態の肺癌集検が行われている．また，喀痰細胞診が非侵襲的で中心型早期肺癌の発見方法として唯一のものであることなども考慮され，喀痰細胞診を施行することはグレードBとされた．

中心型早期肺癌の内視鏡所見分類，蛍光内視鏡，超音波内視鏡については，有効性が報告されているが，高いレベルのエビデンスが得られているとは言い難いため，これらについての推奨はグレードCとなっている．

表1　内視鏡的早期肺癌の診断基準

臨床的基準	胸部X線写真（断層，およびCT像を含む）が正常像であること
	通常の病期診断に用いられる方法（CTを含む胸部X線写真，腹部CTおよびエコー，脳CT，骨シンチグラムなど）によりリンパ節および遠隔転移がないこと
内視鏡的基準	気管から亜区域支までに限局する
	病巣の末梢縁が内視鏡的に可視できること
	病巣の長径が2 cm以下であること
	組織学的に扁平上皮癌であること

VI. 中心型早期肺癌に対する治療

治療の手段として，外科治療，光線力学的治療（Photodynamic therapy；PDT），気管支腔内照射が取り上げられた（表3）．中心型早期肺癌に対する外科治療について報告されている成績は，5年生存率が80–100%と良好であり，根治的な治療方法としては外科療法が勧められている．縮小手術の治療成績に関しては報告が少なくグレードCとされている．PDTは，治療後の他病死を除いた5年生存率は90%を超え，腫瘍全体にレーザー照射が可能な長径1cm以内かつ深達度が粘膜下層までの症例を対象に行うよう勧められる（グレードB）とされている．気管支腔内照射については，有用性を示唆する報告はあるものの，現時点では十分なエビデンスが存在しないためグレードCとされている．

VII. グレードCの扱い

中心型早期肺癌は，海外における診断治療数が少ないこともあり，エビデンスとなる論文の総数が少ない．そうした事情により，推奨もエビデンスレベルがCにとどまるものが多い結果となっている．よく指摘されることであるが，グレードCは，その推奨の表現が，

表2　検査方法の推奨

検査法	推奨	推奨グレード
喀痰細胞診	喀痰細胞診は中心型早期肺癌の発見法として唯一の検査である．重喫煙者などの高危険群を対象として行うよう勧められる	B
気管支鏡	喀痰細胞診で異型細胞（D，E判定）が得られた場合，気管支鏡による精査を行うよう勧められる	B
	気管支鏡所見による中心型早期肺癌の判定や分類は気管支鏡所見の捉え方に熟練を要すること，観察者間の不一致があること，分類自体が完璧なものでないことに留意する必要があるため，現時点では行うよう勧めるだけの根拠が明確でない	C
蛍光内視鏡	扁平上皮化生を含む気管支の早期病変の診断に有用とする報告が多いが，少なくとも中心型早期肺癌の診断の優位性において確定的な結論は得られていない．また現時点で保険収載されておらず，探索的医療の範疇に入るものである	C
気管支超音波検査	本検査法は中心型早期肺癌の深達度診断に有益であるか否か現在評価中の段階であり行うよう勧めるだけの根拠が明確でない	C

表3 治療方法の推奨

治療方法	推奨	推奨グレード
外科治療	中心型肺癌に対しては標準治療として手術を行うよう強く勧められる．5年生存率は80–100%と良好であるが，合併症や手術関連誌の頻度は他の肺癌手術と同等と考えられる	A
	縮小手術の治療成績に関しては確定的な結論は出ておらず行うよう勧めるだけの根拠が明確でない．適応に関し慎重な患者選択が必要である	C
光線力学的治療	本治療後の他病死を除いた5年生存率は90%を超え，侵襲も手術に比し軽微である．しかし内視鏡的中心型早期肺癌のすべてが本治療の適応ではなく，腫瘍全体にレーザー照射が可能な長径1cm以内かつ深達度が粘膜下層までの症例を対象に行うよう勧められる	B
腔内照射	本治療法の臨床的有用性を示唆する報告はあるものの，現時点では行うよう勧めるだけの根拠が明確でない	C

「…勧めるだけの根拠が明確でない」とされているため，EBMの手法について理解が不十分な読者には，否定的な表現として捉えられることが懸念される．実際には，無作為化比較試験などによる高いレベルのエビデンスが存在しないということを事実として示しているに過ぎず，否定的な意味をもつわけではない．グレードCは，得られるエビデンスを参考にして，患者に治療の選択肢を示し治療を選択していくという，担当医の裁量が期待される性格をもつものである．

VIII. 今後の課題

先に述べたように，我が国においては胸部レントゲンと喀痰細胞診を併用した肺癌集検について有効性が証明されているが，全国的にこのシステムが標準化されているとは必ずしも言えないのが現状である．特に喀痰細胞診は受診者数の地域によるばらつきが非常に大きく，発見肺がん数が極端に少ない地域がある．喀痰細胞診の標準化に向けた関係者のさらなる努力が望まれる．一方，近年，CT検診による驚異的な肺癌発見率が報告され，注目を集めているが，CTによるスクリーニングでは中心型早期肺癌の発見は困難である．CT検診によって末梢型肺癌による肺癌死亡を減少させうるかどうかは重要な課題であるが，中心型早期肺癌発見のための努力がおろそかになることがあってはならない．

本ガイドラインは3年を目途に改訂をおこなう予定で編集されている．その間に，検討が進むことが予想される課題としては，喀痰細胞診の胸部X線写真あるいはCTへの上乗せ効果の証明，中心型早期肺癌発見のためのバイオマーカー，蛍光内視鏡や超音波内視鏡の性能向上，新たな光感受性物質を用いたPDTなどが挙げられる．

IX. おわりに

「EBMの手法による肺癌の診療ガイドライン」の中の，中心型早期肺癌の診療について解説を行った．本ガイドラインの普及により，中心型早期肺癌をふくむ肺癌診療の標準化と，その恩恵に浴する患者が増えることを願って稿を終える．

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MANAGEMENT OF CENTRAL-TYPE EARLY LUNG CANCER: AN EVIDENCE-BASED CLINICAL GUIDELINE

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With the support of the Japan Ministry of Health, Labour and Welfare, clinical guidelines for the management of lung cancer have been completed according to evidence-based methods. In this article, we focus on the guidelines for central-type early lung cancer. Reviewing a total of 3,196 reports that include key words related to central-type early lung cancer, 41 were selected and applied to determine recommendations for diagnostic or therapeutic methods. Among diagnostic methods, sputum cytology for the high-risk group and bronchoscopy for patients with positive sputum cytology were evaluated as recommendable. Among therapeutic methods, surgery and photodynamic therapy were evaluated as recommendable. For some methods, including fluorescence bronchoscopy and endobronchial ultrasonography brachitherapy, there was insufficient evidence to conclude that they are efficacious. At present, efforts to clarify the efficacy of these methods should be continued.

Recent Results of Postoperative Mortality for Surgical Resections in Lung Cancer

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Background. Changes in the postoperative mortality rates and causes of death for lung cancer surgery at the specialized hospital for cancer in Tokyo, Japan during the last 16 years were investigated.

Methods. Data on 3,270 consecutive patients who underwent pulmonary resection for primary lung cancer between January 1987 and December 2002 at the National Cancer Center Hospital were retrospectively analyzed. The postoperative 30-day and in-hospital mortality rates and causes of death after pulmonary resection for lung cancer were investigated. Patients were divided into two period groups of almost equal number, the early (1,615 patients from 1987 to 1996) and the late (1,655 patients from 1997 to 2002) periods.

Results. Fifty-eight operative and postoperative deaths occurred during the last 16 years. Thirty-day and in-hospital mortality were 0.6% (21/3,270) and 1.6% (58/3,270), respectively. During the last 6-year period, 30-day and in-hospital mortality were 0.5% (8/1,655) and 0.8% (21/1,655), respectively. The difference was significant between the 30-day/in-hospital mortality for pneumonectomy (3.1%/5.9%) and lobectomy (0.3%/1.3%) ($p < 0.0001$/$p < 0.0001$). The difference in mortality between lobectomy and segmentectomy or a lesser resection was not significant. The 58 deaths were caused by pneumonia/acute respiratory distress syndrome (ARDS) (36%, n = 21), bronchopleural fistula (BPF)/empyema (33%, n = 19), cerebrovascular accident (10%, n = 6), cardiac-related event (7%, n = 4), and others (14%, n = 8). The most frequent cause of death in the early period was BPF/empyema (18/45, 40%), while that in the late period was pneumonia/ARDS (6/13, 46%). Among the pneumonia/ARDS deaths in the late period (n = 6), 5 (83%) were due to acute deterioration of interstitial lung disease after lobectomy.

Conclusions. Recent postoperative mortality rates (30-day, 0.5%; in-hospital, 0.8%) in the treatment of lung cancer are quite acceptable. Special care must be taken for the patient after pneumonectomy, as reported by others. Furthermore, even after lobectomy, proper management of the patient with acute deterioration of interstitial lung disease will be required to improve the future outcome.

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A limited number of reports describe postoperative mortality rates in recent decades, and most reports have defined a postoperative death as one that occurs within 30 days after the procedure. However, with the recent developments in postoperative management, many complicated patients survive more than 30 days, and their deaths can be lost in such studies. This study analyzed the change in mortality rates, including both 30-day and in-hospital mortality, after pulmonary resection for lung cancer in the specialized institution for cancer in Tokyo, Japan during the last 16 years.

Patients and Methods

A total of 3,270 pulmonary resections for lung cancer between January 1989 and December 2002 at the National Cancer Center Hospital, Tokyo, were studied. The postoperative mortality rates, including 30-day and in-hospital mortality, and causes of death were investigated. Thirty-day mortality was defined as a fatality that occurred within 30 days after pulmonary resection, and in-hospital mortality was defined as a fatality occurring at anytime in a postoperative hospital stay.

The 3,270 patients were divided into two period groups of almost equal number, the early (1,615 patients from 1987 to 1996) and the late (1,655 patients from 1997 to 2002) periods. A variety of analyses were performed to determine the changes in postoperative mortality in the last 16 years and to evaluate the risk factor for surgical resection for lung cancer. The result was compared with results from previous reports describing postoperative mortality in lung cancer surgery.

We normally perform the anatomic pulmonary resection for lung cancer through a standard posterolateral thoracotomy. In pneumonectomy cases, after closure of the main bronchial stump by suturing or stapling, we infold the stump with the membranous portion inside and oversew it with interrupted sutures, as we previously reported [1]. Then we prefer to cover the stump with a pericardial fat pad, especially for a right pneumonec-

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Table 1. Number of Lung Resections and Mortality Rates in the Last 16 Years

Years	No. of resections	30-day mortality		In-hospital mortality	
		No. of deaths	Mortality (%)	No. of deaths	Mortality (%)
1987–1996	1,615	13	0.8	45	2.8
1997–2002	1,655	8	0.5	13	0.8
Total	3,270	21	0.6	58	1.8

tomy. We have basically not used neoadjuvant preoperative therapy except for recent superior sulcus tumor cases.

Statistical analyses using the χ^2 test was performed to evaluate the differences in mortality according to the type of resection.

Results

Fifty-eight operative and postoperative deaths occurred during this period. Thirty-day and in-hospital mortality was 0.5% (21/3,270) and 1.6% (58/3,270), respectively. Among the recent 1,655 patients during the last 6-year period, 30-day and in-hospital mortality was 0.5% (n = 8) and 0.8% (n = 21), respectively (Table 1).

Of the 3,270 resections, there were 355 pneumonectomies, 2594 lobectomies, and 321 segmentectomies or lesser resections. The 30-day/in-hospital mortality for pneumonectomy, lobectomy, and segmentectomy or lesser resections was 3.1%/5.9%, 0.3%/1.3%, and 0.3%/0.9%, respectively (Table 2). The difference in the 30-day/in-hospital mortality between the pneumonectomy and lobectomy group ($p < 0.0001/p < 0.0001$) was significant. The difference in the 30-day/in-hospital mortality between lobectomy and segmentectomy or lesser resection group ($p = 0.8641/p = 0.5701$) was not significant. The incidence of pneumonectomy cases decreased from 16.2% (262/1,615) in the early period to 5.6% (93/1,655) in the late period, although the in-hospital mortality of pneumonectomy has not improved between the early and late periods (6.1% vs 5.4%, $p = 0.7975$) (Table 3).

The 58 deaths were caused by pneumonia/acute respiratory distress syndrome (ARDS) (36%, n = 21), bronchopleural fistula (BPF)/empyema (33%, n = 19), cerebrovascular accident (10%, n = 6), cardiac-related event (7%, n = 4), and others (14%, n = 8). The most frequent cause of death in the early period was BPF/empyema (18/45, 40%), while that in the late period was pneumonia/ARDS (6/13, 46%) (Table 4). Death that was due to BPF/empyema in the late period was only 8%. Among the six deaths due to pneumonia/ARDS in the late period, five (83%) were caused by acute deterioration of interstitial lung disease (ILD).

Comment

Lung cancer has been a major cause of death in many developed countries. Surgical resection continues to play an important roll, especially in the earlier stage lung cancer. The detection of early cancer is increasing with the development of computed tomography (CT); therefore, it is important for surgeons to collect precise data on causes of postoperative deaths and try to improve the surgical mortality.

A limited number of previous reports describe postoperative mortality rates in recent decades, and most reports have defined a postoperative death as one occurring within 30 days after the procedure, as shown in Table 5 [2–8]. However, with the development of postoperative management techniques, complicated patients tend to survive more than 30 days and their deaths can be lost in such studies. We addressed this point by collecting all postoperative in-hospital deaths beyond the 30-day limit.

In 1983 Ginsberg and the Lung Cancer Study Group (LCSG) [2] determined the current standards for operative mortality associated with lung cancer resection. They reported that 81 postoperative deaths occurred among 2,220 resections, and the 30-day mortality was 3.7%. In 1999 Harpole and colleagues reported a large series with a 30-day mortality of 5.2% [4]. Our overall 30-day and in-hospital mortality was 0.6% and 1.6%, respectively. During the last 6-year period, 30-day and in-hospital mortality was 0.5% and 0.8%, respectively. These results were better than those noted by others, as shown in Table 5.

We believe this may be due to following reasons:

- The detection of early stage cancer is increasing in Japan with the development of CT scanners;

Table 2. Mortality Rates According to Type of Pulmonary Resections

Type of resections	No. of resections	30-day mortality		In-hospital mortality	
		No. of deaths	Mortality (%)	No. of deaths	Mortality (%)
Pneumonectomy	355	11	3.1[a]	21	5.9[a]
Lobectomy	2,594	9	0.3[b]	34	1.3[b]
Segmentectomy or less	321	1	0.3	3	0.9
Total	3,270	21	0.6	58	1.8

[a] $p < 0.0001$ versus segmentectomy or less group; [b] p = NS versus segmentectomy or less group.

Table 3. Changes in Number of Lung Resections and In-Hospital Mortality According to the Type of Operation

		Pneumonectomy		Lobectomy		Segmentectomy or less	
Years	No. of resections	No. of operation	In-hospital Mortality	No. of operation	In-hospital Mortality	No. of operation	In-hospital Mortality
1987–1996	1,615	262 (16.2%)	16 (6.1%)	1,265 (78.3%)	27 (2.1%)	88 (5.4%)	3 (3.4%)
1997–2002	1,655	93 (5.6%)	5 (5.4%)	1,329 (80.3%)	7 (0.5%)	233 (14.1%)	0
Total	3,270	355 (10.9%)	21 (5.9%)	2,594 (79.3%)	34 (1.3%)	321 (9.8%)	3 (0.9%)

- The percentage of pneumonectomy cases markedly decreased;
- Perioperative management, including anesthesia, surgical techniques, and cardio-respiratory management, has improved;
- Many of our outpatients with a smoking history undergo detailed pulmonary function tests to decide the proper treatment;
- A perfusion scan is performed to estimate postoperative pulmonary function in borderline cases;
- The preoperative evaluation, such as stress echocardiography, is shared with a medical cardiac consultant to reduce the cardiac complications; and
- Great care is taken for diabetic patients not to develop severe complications. The preoperative hospital stay of patients is normally 1 or 2 days; that of diabetic patients is 4 to 7 days, because we strictly control the diabetic status not only after surgery but also before surgery.

Recent improved preoperative and postoperative care as described above could allow more patients to undergo surgery safely.

Others have noted the high operative risk of pneumonectomy. Ginsberg and the LCSG reported a high 30-day mortality of 6.2% for pneumonectomy [2]. We observed a 30-day mortality of 3.1% and an in-hospital mortality of 5.9% for pneumonectomy, which were also significantly higher than for lobectomy. As shown in Table 3, although the mortality of pneumonectomy has not changed, the percentage of pneumonectomy in our resected cases markedly decreased from 16.2% to 5.6%, which contributed to the improvement of our mortality rates. This resulted mainly because of the increasing detection of early stage lung cancer with the development of CT scanners and the aggressive employment of bronchoplasty to avoid pneumonectomy.

As shown in Table 4, the main cause of death shifted from BPF/empyema to pneumonia/ARDS. The decreased incidence of death because of BPF/empyema, which greatly contributed to the improvement of the mortality rate, was the result of two factors. First, as described above, the incidence of pneumonectomy cases is decreasing and consequently, the number of postpneumonectomy BPF has been reduced. Second, we have improved our treatment of BPF/empyema in the late period. We make a chest wall window immediately after BPF develops, even after lobectomy, in order to completely control the infection of the intrathoracic cavity, because massive bleeding from the great vessels due to empyema easily leads to a fatal situation.

Many previous reports have described respiratory complications as a leading cause of death after pulmonary resection [2–5, 9], although none of these have described the detail of the respiratory failure. Among the deaths due to pneumonia/ARDS in our study during the late period, 83% were due to acute deterioration of ILD. All patients who developed ILD exhibited a small interstitial change on preoperative chest CT; therefore, the surgeon should check a preoperative CT to see if the patient has interstitial change and if so, should present the potential risks of acute deterioration of ILD to the patient and his or her family, and special care must be taken on postoperative management. When acute deterioration of ILD develops in the patient, the high-dose administration of steroids may be effective, as reported by Murray and colleagues [10]. Although the effect of this pharmacologic therapy is still controversial [11], an early diagnosis of interstitial pneumonia and the initiation of steroid therapy with mechanical ventilation will be mandatory to ensure survival.

In summary, recent postoperative mortality rates (30-day, 0.5%; in-hospital, 0.8%) in the treatment of lung cancer are quite acceptable. Patients after pneumonectomy showed significant high mortality as previously reported by others. Furthermore, even after lobectomy, proper management of the patient developing acute deterioration of ILD is required to improve the future outcome.

Table 4. Causes of Postoperative Deaths

	No. of cases (%)		
Causes of deaths	Total	Early period (1987–1996)	Late period (1997–2002)
Pneumonia/ARDS	21 (36)	15 (33)	6 (46)
BPF/empyema	19 (33)	18 (40)	1 (8)
Cerebrovascular accident	6 (10)	5 (11)	1 (8)
Cardiac event	4 (7)	4 (9)	0
Others	8 (14)	3 (7)	5 (38)
Total	58 (100)	45 (100)	13 (100)

ARDS = acute respiratory distress syndrome; BPF = bronchopleural fistula.

Table 5. List of Literature Describing Postoperative Mortality for Surgical Resections in Lung Cancer

Authors	Year	Years analyzed	No. of resections	30-day mortality	In-hospital mortality	30-day mortality according to the type of resection		
						Pneumonectomy	Lobectomy	Segmentectomy or less
Fryjordet et al [6]	1971	1949–1976	277	-	13.5%	-	-	-
Weiss [7]	1974	1961–1965	364	14.0%	-	17.0%	10.1%	0%
Ginsberg et al [2]	1983	1979–1981	2,200	3.7%	-	6.2%	2.9%	1.4%
Romano et al [8]	1992	1983–1986	12,439	4.1%	5.0%	11.6%	4.2%	3.8%
Deslauriers et al [3]	1994	1988–1989	783	3.8%	-	-	-	-
Wada et al [5]	1998	1994	7,099	1.3%	-	3.2%	1.2%	0.8%
Harpole et al [4]	1999	1991–1995	3,516	5.2%	-	11.5%	4.0%	-
Present report	2004	1987–2002	3,270	0.6%	1.8%	3.1%	0.3%	0.3%

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INVITED COMMENTARY

Two large North American series have assessed death associated with lung cancer. In 1983, the Lung Cancer Study Group (LCSG) published results of surgical resection for lung cancer [1]. These results are easy to remember, and I quote them closely to patients: 1.5% for wedge or segmental resection, 3% for lobectomy, and 6% for pneumonectomy—a doubling of risk per magnitude of the procedure. Despite concern quoting figures published 20 years ago, these figures are similar to my own personal results. Another, more recent large series published in 1995 included data from part of the prospective, multi-institutional National Veterans Affairs Surgical Quality Improvement Program [2]. In this series, a total of 3,516 patients (mean age, 64.9 years) underwent either lobectomy (n = 2,949) or pneumonectomy (n = 567). Thirty-day mortality was 4.0% for lobectomy (119 of 2,949) and 11.5% for pneumonectomy (65 of 567).

In Japan, a large series of 7,099 patients from the Japanese Association for Chest Surgery, which presumably included some of the current patients, had an overall 30-day operative mortality rate of 1.3%. By operative procedure, the mortality rates were 3.2% for pneumonectomy, 1.2% for lobectomy, and 0.8% for a lesser operation [3].

The current paper, also a large series, has results that will be envied by all thoracic surgeons. In addition to usual 30-day mortality, they additionally analyzed patients who lingered in hospital and died beyond the 30-day cut-off—in-hospital mortality. Thirty-day and in-hospital mortality rates for segmentectomy or wedge, lobectomy, and pneumonectomy were, respectively, 0.3% and 0.9%; 0.3% and 1.3%; and 3.1% and 5.9%. These mortality statistics are currently the lowest published.

The authors split the 3,270 patients into two time groups of almost equal number and analyzed those results. The more recent group had 30-day and in-hospital mortality rates of 0.5% and 0.8%, respectively. Comparison of the two time periods indicates an almost threefold decrease in the percentage of pneumonectomies and an almost threefold increase in the percentage of wedges and segmental resections. To explain the change in practice, the authors have commented on increased detection of early stage lung cancer by the use of computed tomography scanners. Another possible

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Combined Resection of Superior Vena Cava for Lung Carcinoma: Prognostic Significance of Patterns of Superior Vena Cava Invasion

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Background. Combined resection of the superior vena cava (SVC) for lung carcinoma remains challenging in terms of technical aspect and prognosis. We attempted to clarify the surgical outcome of combined resection and reconstruction of the SVC for lung carcinoma.

Methods. Between March 1980 and May 2001, among 3,499 lung resections, 40 (1.1%) patients underwent combined resection of the SVC. Thirty-four were men and 6 were women. Ages ranged from 37 to 77 years, with median of 64 years. Lobectomy and pneumonectomy was performed in 19 and 21 patients, respectively. The SVC system was totally resected and reconstructed with grafts in 11 patients, and partially resected in 29 patients. For the latter patients, autologous pericardial patches were used in 8 patients, and a running direct suture was performed in 21 patients. The survival curves were constructed by the method of Kaplan-Meier, and the curves were compared using the log-rank test.

Results. Thirty-day mortality was 10%. The 5-year survival rate was 24%, with the median follow-up period for living patients 67 months (actual 5-year survivors were 7). The prognoses were compared between patients with SVC invasion by metastatic nodes (n = 15) and those with SVC invasion by a direct tumor extension (n = 25), and the survival difference was statistically significant (5-year survival rate, 6.6% versus 36%; $p = 0.05$).

Conclusions. The pattern of SVC invasion was considered to be a significant prognostic factor, and this factor should be taken into consideration for evaluating the outcome of clinical trials for T4 lung cancer.

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Several authors have reported the feasibility of combined resection of the superior vena cava (SVC) for lung cancer, although invasion of the SVC by lung cancer is usually considered to be inoperable [1–7]. Surgical procedures for resection and reconstruction of the SVC system are complex and technically difficult. Lung cancer infiltrating the SVC frequently involves the bronchial tree, especially the carina, and lobectomy with bronchoplasty or pneumonectomy is often necessary to resect such lung tumors. Therefore surgical morbidity and mortality is not negligible. Some reports insist that the degree of SVC involvement by lung cancer was one of the major prognostic factors. Complete resection is also reported to be a significant prognostic factor. However, even for patients with completely resected lung cancer, the prognosis is not acceptable in this population [7]. Thus, to operate on patients with lung cancer infiltrating the SVC, the selection of surgical candidates is quite important, and we attempted to investigate prognostic factors in patients with resected lung cancer who needed combined resection of the SVC system.

Patients and Methods

Selected Patients

Between March 1980 and May 2001, 3,499 patients with lung cancer underwent surgical intervention at our institute, and 40 patients (1.1%) eventually underwent combined resection of the SVC. There were 34 men and 6 women, a male to female ratio of 5.6:1. Age ranged from 37 to 77 years, with a median of 64 years. All lung cancers were located on the right side. Preoperative workup included a plain chest roentgenogram, thoracic and abdominal computed tomographies, or ultrasonography for abdomen, a brain computed tomography or magnetic resonance imaging, and a bone scan. Disease stages were determined based on the TNM classification of the International Union Against Cancer, 5th edition [8]. Clinical stage was as follows: 3 for stage I, 5 for stage II, 13 for stage IIIA, 12 for stage IIIB, and 6 for stage IV. Preoperative treatment was performed in 6 patients: preoperative chemotherapy for 2, radiotherapy for 1, and chemoradiotherapy for 3, and none of them underwent the multimo-

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