TABLE 2. Characteristics and Quantitative Characterization of BNS

Patient No.	Age (y)	Sex	Diameter (mm)	Lobe	Linear Discriminant Function			Diagnosis
					Non-Enhanced	2 Min*	4 Min*	
36	51	F	9	RU	−4.24	−12.77	−11.83	Nonspecific†
37	57	F	10	LU	−1.03	−14.41	−10.29	Hamartoma
38	56	F	15	LU	1.82	−7.56	−3.29	Granuloma
39	65	F	8	RM	−4.68	−11.38	−10.45	Nonspecific†
40	52	F	10	LU	−0.64	−6.93	−17.34	Nonspecific†
41	72	F	10	LL	1.25	3.56	−10.7	Granuloma
42	61	M	7	RL	−3.71	−9.15	−16.22	Nonspecific†
43	70	M	9	RU	−1.21	−7.04	−18.99	Organizing/pneumonia
44	68	F	17	LU	0.97	−3.98	−17.41	Pulmonary/infarction
45	47	F	5	RU	−5.3	−18.14	−32.32	Granuloma
46	56	F	12	RU	−0.85	−18.61	−10.88	Tuberculoma
47	59	F	9	LL	−4.81	−9.74	−19.01	Nonspecific†
48	62	F	12	RM	2.14	−5.63	−4.22	Nonspecific†
49	61	F	6	RM	−5.3	−9.09	−23.16	Nonspecific†
50	60	F	8	RU	−3.53	−18.94	−42.75	Nonspecific†
51	68	F	12	RU	0.54	−19.49	−15.17	Nonspecific†
52	67	M	6	RU	−5.3	−12.58	−21.51	Nonspecific†
53	68	M	8	LL	−4.28	−5.13	−27.26	Nonspecific†
54	64	M	8	RM	−3.82	−7.12	−19.13	Hamartoma
55	70	F	15	RM	2.57	−12.02	−38.67	Nonspecific†
56	60	M	15	RL	−0.49	−5.23	−11.81	Nonspecific†
57	53	F	15	RU	1.2	0.83	−7.36	Granuloma
58	73	M	10	LL	−0.08	0.89	−4.16	Pneumonia
59	72	M	17	LL	−3.24	−9.6	−9.89	Nonspecific†
60	58	M	7	RU	−4.94	−14.21	−10.37	Hamartoma
61	45	M	7	LL	−5.3	−11.81	−6.44	Nonspecific†
62	43	F	8	RL	−3.47	−9.39	−14.15	Nonspecific†

*Time after administration of contrast agent.
†The clinical diagnosis of a nonspecific benign lesion was based on no nodule growth for 2 years or longer.
F, female; LLL, left lower lobe; LUL, left upper lobe; M, male; M/d, moderately differentiated; P/d, poorly differentiated; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; W/d, well differentiated.

size during a follow-up observation period of 2 years or more.[4,17]

This study was approved by the ethical committee of our institution. Written informed consent was obtained from the patients.

RESULTS

Receiver operating characteristic curves were used to evaluate the effectiveness of the diagnostic method using the histogram characteristic values of the attenuation, curvedness value, and shape index to differentiate between BNs and MNs. Evaluation was performed for each parameter as well as for values obtained at different time points: before enhancement and 2 and 4 minutes after enhancement.

The areas under the ROC curve for the attenuation before, 2 minutes after, and 4 minutes after contrast enhancement were 0.58 ± 0.07, 0.69 ± 0.07, and 0.57 ± 0.08, respectively (Fig. 4A); those for the curvedness value were 0.78 ± 0.06, 0.83 ± 0.05, and 0.76 ± 0.06, respectively (see Fig. 4B); and those for the shape index were 0.90 ± 0.04, 0.89 ± 0.05, and 0.90 ± 0.04, respectively (see Fig. 4C). The results for evaluation of all 3 parameters combined were 0.91 ± 0.04, 0.99 ± 0.01, and 1.00, respectively (see Fig. 4D).

Evaluation based on all 3 parameters combined gave the best results. The changes in the linear discriminant function scores over time were analyzed for these combined parameters.

The mean scores before enhancement were −2.06 ± 2.70 (range: −5.3–2.57) for BNs and 2.09 ± 1.50 (range: −2.16–5.01) for MNs. Those at 2 and 4 minutes after enhancement were 9.59 ± 5.04 (range: 0.58–23.1) and 15.1 ± 6.50 (range: 1.81–27.1), respectively, for MNs (see Table 1) and −9.43 ± 5.94 (range: −19.5–3.56) and −16.1 ± 9.94 (range: −42.8 to −3.29), respectively, for BNs (see Table 2). The linear discriminant function scores for MNs were significantly higher than those for BNs at all 3 time points: before enhancement ($P < 0.001$), 2 minutes after enhancement ($P < 0.001$), and 4 minutes after enhancement ($P < 0.001$).

When a linear discriminant function score of 0 or higher was considered to indicate malignancy, there were 2 false-negative (FN) findings (cases 28 and 31) and 7 false-positive (FP) findings (cases 38, 41, 44, 48, 51, 55, and 57) before

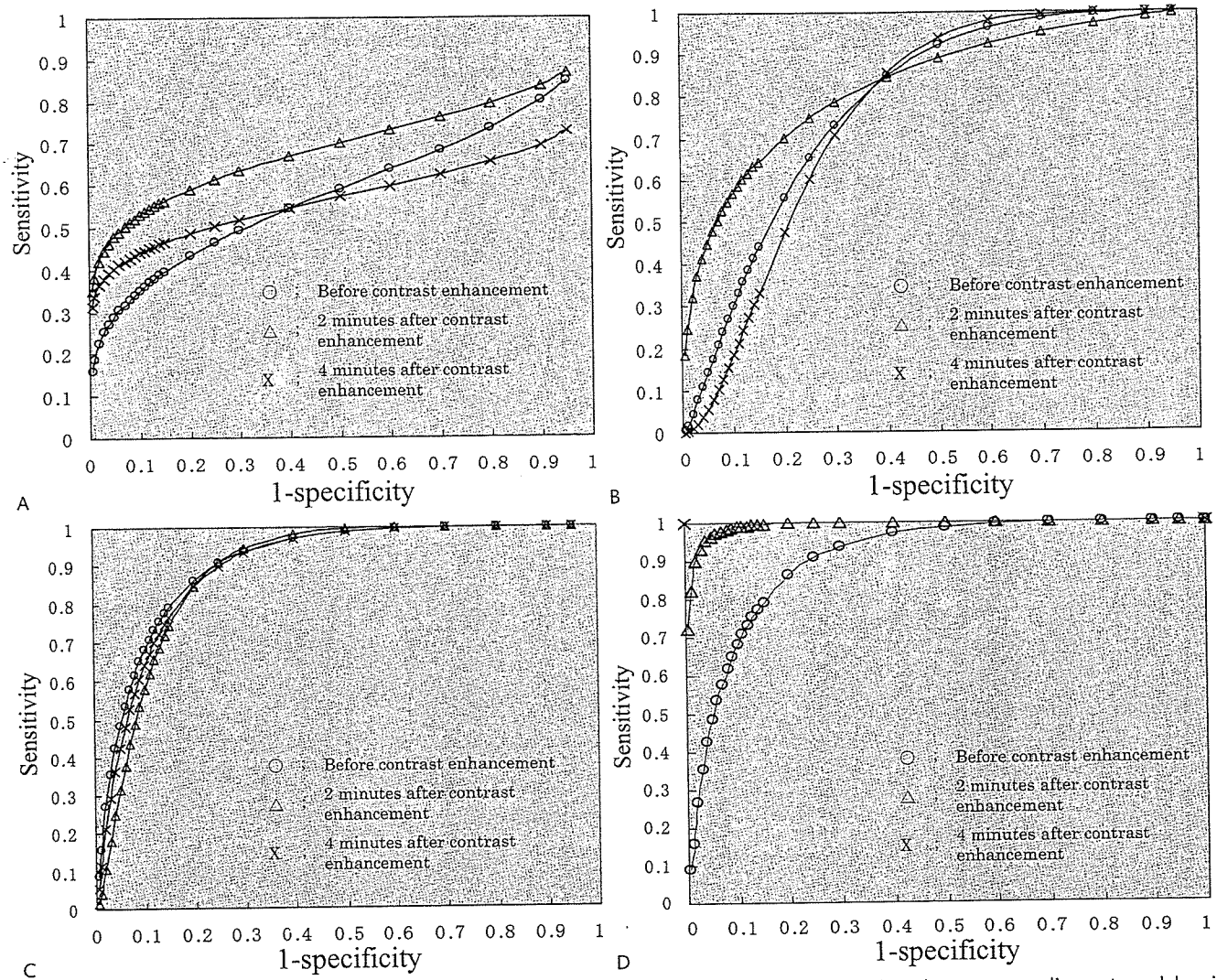

FIGURE 4. Receiver operating characteristic curves for each parameter used to differentiate between malignant and benign nodules. The open circles (○) are before contrast enhancement, and the open triangles (△) and crosses (x) are 2 and 4 minutes after contrast enhancement, respectively. A, Areas under the open circle (○), open triangle (△), and cross (x) curves for attenuation are 0.58 ± 0.07, 0.69 ± 0.07, and 0.57 ± 0.08, respectively. B, Areas under the open circle (○), open triangle (△), and cross (x) curves for curvedness value are 0.78 ± 0.06, 0.83 ± 0.05, and 0.76 ± 0.06, respectively. C, Areas under the open circle (○), open triangle (△), and cross (x) curves for shape index are 0.90 ± 0.04, 0.89 ± 0.05, and 0.90 ± 0.04, respectively. D, Areas under the open circle (○), open triangle (△), and cross (x) curves for the combination of all 3 parameters (attenuation, shape index, and curvedness value) are 0.91 ± 0.04, 0.99 ± 0.01, and 1.00, respectively.

enhancement, 0 FN findings and 3 FP findings (cases 41, 57, and 58) 2 minutes after enhancement, and 0 FN findings and 0 FP findings 4 minutes after enhancement. Sensitivity values were 94%, 100%, and 100%; specificity values were 74%, 89%, and 100%; and accuracy values were 85%, 92%, and 100%, respectively. Positive predictive values were 83%, 92%, and 100%, and negative predictive values were 91%, 100%, 100%, respectively.

DISCUSSION

The usefulness of diagnostic imaging, focusing mainly on CT, for the evaluation of SPNs has been reported by researchers at a number of medical institutions.[1–4] Several of them have also attempted to differentiate between benign and malignant lesions by using contrast medium and evaluating attenuation within nodules over time.[5–8] These studies were based on attenuation and contrast enhancement patterns obtained for only a few slices in which the nodule was demonstrated, however.

In the present study, the entire nodule was scanned using CE dynamic HCT, and changes in the density and characteristic values (attenuation, shape index, and curvedness value) within the nodule were calculated for 3D quantification with a computer to discriminate between benign and malignant lesions. Contrast-enhanced dynamic HCT in combination with

the computer-aided diagnosis may thus improve the differential diagnosis of BNs and MNs.

With regard to the evaluation and interpretation of the CT data on the lesion, conventional studies have focused only on the 2-dimensional assessment of attenuation and the enhancement patterns in a few slices. The results of these studies were simple and practical, identifying the factors effective for the differential diagnosis to be an observed contrast effect of 20 Hounsfield units (HU) or greater[5,6] or 15 HU or greater,[8] enhancement of the entire lesion,[5] and a high CT value ratio between the nodule and arteries.[7] One problem was that the attenuation was strongly affected by the slice selected or the position of the ROI in the lesion, which was set manually. In the present study, this problem was avoided by automatically extracting the lesion as 3D volume data.[9,12] In addition, the nodule was evaluated by calculating the characteristic values within the nodule using a computer and measuring the density using 3 parameters (attenuation, shape index, and curvedness value).[10] The results showed that evaluation based on the combination of all 3 parameters provided the best results. Using this analysis method, each pixel within a tumor is expressed locally using the attenuation and the shape index and curvedness obtained from the 3D curvature, and the entire lesion is then characterized as benign or malignant using the histogram characteristic values. When these 3 histogram characteristic values were compared with each another, the shape histogram characteristic value was found to be superior to the other 2 values. The combination of these 3 characteristic values provided even better results. It is thought that a more detailed characteristic value for the internal structure of a tumor can be obtained by expressing the internal structure as a combination of attenuation and 3D curvatures.

When a linear discriminant function score not less than 0 at 2 and 4 minutes after enhancement was considered to indicate malignancy, the results showed 0 FN findings and 3 FP findings at 2 minutes after enhancement and no FN or FP findings at 4 minutes. When a linear discriminant function score of 0 or higher was considered to indicate malignancy, benign and malignant lesions were distinguished in all the patients using the data obtained 4 minutes after enhancement. It was considered that the values at 2 minutes were affected by the degree of minute blood vessel density within the nodule and that the values at 4 minutes were affected by the rate of contrast medium flowing into the papillary vessels and interstitial tissues or by the volume of the interstitial tissues.[18] In summary, compared with the techniques used in previous studies, the method described in the present study permits lesions to be extracted with fewer manual operations and higher reproducibility and is based on 3D analysis using 3 parameters (attenuation, shape index, and curvedness value).

The limitations of the present study are as follows. Although the objective of this study was to evaluate the entire nodule, it was difficult to visualize the entire nodule over time, even when an HCT scanner was used. As a result, lesions could not be assessed in 10 patients. It is expected that this problem can be overcome by the introduction of multislice HCT scanners in the near future. In this study, the score was assessed at each time point (before contrast enhancement and 2 and 4 minutes after contrast enhancement). In a strict sense, these scores do not represent the changes in the density of the lesion over time. In the assessment of changes over time, it is important to acquire CT images in exactly the same slice at each time point. The changes over time can then be obtained by performing subtraction between the images before and after contrast enhancement. In practice, however, it is difficult to acquire exactly the same slice at each time point because of the patient's respiratory motion. We are currently working to develop a new algorithm to overcome this problem. When this algorithm is complete, we plan to assess the changes in contrast medium density in lesions over time using subtraction.

In the future, CT-based lung cancer screening is expected to become more widely accepted, resulting in the detection of a larger number of SPNs.[19,20] Therefore, it is likely to become increasingly important to determine whether these lesions are benign or malignant based on evaluation of the images obtained.

Contrast-enhanced dynamic HCT was used for the computer-aided diagnosis of SPNs in the present study. The data obtained using this imaging technique permit the internal structure of lesions to be quantified in a 3D manner and evaluated over time. The results showed that this method is effective for differentiating between BNs and MNs. In the future, further prospective studies should be conducted based on the results reported here and standards for the evaluation of lesions using computer-aided analysis should be established.

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Risk of Pleural Recurrence After Needle Biopsy in Patients With Resected Early Stage Lung Cancer

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Background. Concerning the complications resulting from percutaneous needle biopsy (PNB), although cases of tumor seeding into the needle track have occasionally been reported, there were only two cases of pleural recurrences to date. The aim of this study was to elucidate the real risk of pleural recurrence after needle biopsy in patients with resected early stage lung cancer.

Methods. Between 1986 and 2000, 335 patients with stage I nonsmall cell lung cancer underwent complete resection of the lung tumor. We retrospectively reviewed their medical records and investigated the relationship between the diagnostic methods used and the cancer recurrence patterns.

Results. Preoperative diagnoses were obtained for 290 patients; 220 were diagnosed by bronchoscopy and 66 by PNB. Among the patients without a preoperative diagnosis, 27 were diagnosed by intraoperative needle biopsy and 14 by wedge resection of the lung. Tumors diagnosed by needle biopsy including PNB and intraoperative needle biopsy were smaller and showed less vessel invasion than those diagnosed by other methods ($p < 0.01$). After surgical resection, 9 patients had pleural recurrence and 1 patient, needle track implantation. Seven of these 10 patients were diagnosed by needle biopsy using 18G cutting type needle. Pleural recurrence or needle track implantation was observed for 8.6% of the patients who underwent a needle biopsy, whereas it was 0.9% for patients who were examined using other diagnostic modalities ($p = 0.0009$).

Conclusions. Needle biopsy especially using a cutting-type biopsy needle can cause a pleural recurrence in addition to needle track implantation.

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Percutaneous needle biopsies (PNB) are widely used for the histologic diagnosis of a peripheral indeterminate pulmonary nodule. The overall sensitivity and specificity for diagnosing peripheral lung cancers were 90% and 97% respectively by meta-analysis [1], and even for tumors less than 2 cm in diameter the sensitivity was also as high as 91%.

Although fine-needle aspiration (FNA) is widely used method for performing PNB around the world, automated or semiautomated cutting needles have been tested to increase the diagnostic yield [2–8]. We also previously reported on the usefulness of computed tomographic fluoroscopy-guided transthoracic needle biopsy using an 18G automatic biopsy gun for diagnosing pulmonary lesions, particularly benign lesions [9].

The most frequent complication of PNB is pneumothorax, which occurs for 25% to 30% of patients [10]. For fatal complications of PNB, air embolism and tumor seeding have been previously documented to occur. Cases of needle track implantation accounted for almost all of the cases of tumor seeding, and have been documented to occur at a rate of 0% to 3% [11–13]. Although pleural recurrence due to tumor seeding is a possible adverse event that may occur after PNB [14], only two such cases have been reported [15]. Pleural recurrence after PNB tends to be ascribed to the advanced disease itself a priori, but not to PNB, because malignant pleural effusion or tumor dissemination in the pleural cavity can be seen after usual lung surgery without performing a needle biopsy, especially for patients with locally advanced nonsmall cell lung cancer (NSCLC). Thus, in the present study we investigated the risk of pleural recurrence after needle biopsy for patients with pathologic stage I NSCLC, who were thought unlikely to experience recurrence in the pleural cavity after resection.

Material and Methods

Patients

Between October 1986 and December 2000, 687 patients with NSCLC underwent surgical resection of the lung at our hospital. Among them, 335 had pathologic stage I disease, and they constituted the study population. Two hundred patients were men, and the median age was 67 years (range, 35 to 85). The majority of the patients underwent a lobectomy with systematic nodal dissection (n = 256, 76%). Histologic types were adenocarcinoma (n = 222), squamous cell carcinoma (n = 89), and others (n = 24), including large cell carcinoma, large cell neuroendocrine carcinoma, adenosquamous carcinoma, carcinoid, and carcinosarcoma. Primary tumors were classified as T1 in 210 patients and T2 in 125 patients.

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Treatment Policy

Our routine diagnostic strategies for patients with an indeterminate pulmonary nodule were as follows. First, we obtained a histologic or cytologic diagnosis using fiberoptic bronchoscopy. If this failed or was difficult, the patients were then scheduled for diagnosis using PNB under computed tomography (CT) guidance. Almost all biopsies have been performed using an 18G, spring-loaded, automatic biopsy gun with a modified Tru-Cut type needle (Monopty; Bard Radiology, Convington, Georgia) since 1994 (n = 37), while the Tokyo Medical College needle (n = 12) and the Sure-Cut needle (n = 8) were frequently used before that time. If the state of the nodule remained undetermined, a diagnostic thoracotomy or thoracoscopy was subsequently performed. Some patients underwent intraoperative needle biopsy (INB) whereas the others underwent wedge resection of the lung. If a tumor was diagnosed as NSCLC by intraoperative pathology, the patient subsequently underwent complete resection of the tumor with curative intent. After surgery, the patients were scheduled for checkups, chest radiography, and measurement of serum tumor markers every 1 to 3 months for the first 2 years and every 6 months thereafter. When recurrence was discovered, intrathoracic and extrathoracic lesions were always surveyed.

Assessment of Recurrence and Clinicopathologic Features

We reviewed the medical records of all patients to confirm that recurrence had developed. Pleural recurrence was defined as pleural nodule or malignant effusion or both in the hemithorax of the operated side at the first relapse. Malignant effusion was diagnosed cytologically and pleural dissemination was diagnosed if multiple enhanced pleural nodules were observed on chest CT. Patients with any other site of recurrence in combination with pleural recurrence at the first relapse were included among the pleural recurrence cases, because we can not determine which recurrence preceded and caused the other recurrence. To elucidate the difference of tumor characteristics in each diagnostic group, we reviewed the CT images if available (n = 298) and classified these tumors into two categories according to their locations. When the center of a tumor shadow fell within the inner half of the lung, the tumor was classified as being central; and when the center of a tumor shadow fell within the outer half of the lung, the tumor was classified as being peripheral. We checked whether the tumor shadow was touching the pleura or not on the CT image and then examined the pathologic tumor characteristics such as tumor size, lymphatic invasion, and vascular invasion in the tumor in relation to the diagnostic method used. Pathologic stages were classified according to the criteria set forth by the International System for Staging Lung Cancer [16], and histologic typing was determined according to the World Health Organization classification [17].

Statistical Analysis

Correlations between the diagnostic methods used and the tumor characteristics were examined using the χ^2 test and Fisher's exact test. The unpaired t test was used to examine the relationship between the diagnostic methods used and the log-transformed tumor sizes because of their skewed distribution. All statistical analyses were carried out using STATA software [18].

Results

Among the 335 patients, 290 were diagnosed as having NSCLC preoperatively. Among them, the definitive diagnostic methods used were bronchoscopy for 220, PNB for 66, and sputum cytology for 4. Among the 45 patients with a pulmonary nodule without definitive preoperative diagnosis, INB was performed on 27, wedge resection of the lung on 14, and lung resection with curative intent without definitive diagnosis on 4.

Tumor Characteristics and Diagnostic Methods

The relationships between the methods used to obtain pathologic diagnoses and tumor characteristics are shown in Table 1. Tumors diagnosed by PNB showed less lymphatic invasion and were smaller than those diagnosed by bronchoscopy, and tumors diagnosed by INB were smaller and less invasive than those diagnosed by PNB. When we divided the tumors into two groups according to whether needle biopsy was conducted or not, we found that the needle biopsy group was associated with peripheral location, a smaller tumor size, and a lower occurrence of lymphatic and vascular invasion. Although tumors in the patients of the needle biopsy group were located in more peripheral areas, the numbers of tumors touching the pleura were almost identical. Furthermore, the incidence of pleural invasion of the tumors, which was thought to be associated with pleural recurrence, was lower for the needle biopsy group.

Recurrence

Two hundred and ninety-seven patients (88.7%) were followed up until February 29, 2004. Among the 38 patients not followed-up, 34 completed their follow-up after the 5-year anniversary of surgery. The median length of the follow-up period was 80 months, and the relationships between the methods used for histologic diagnosis and the recurrence patterns are shown in Table 2. Seventy-three patients were diagnosed as having recurrence, where the recurrence pattern was distant for 53 and local for 23. Among them, 3 had distant and local recurrence. Nine patients died of unknown causes; and as 1 patient was diagnosed with distant recurrence at an other hospital, we did not know whether pleural recurrence had developed. For the patients with local recurrence, 10 had pleural recurrence or needle track implantation. The percentage of cases for which distant recurrence had developed was similar between patients diagnosed by bronchoscopy and those diagnosed by PNB (18.5% versus

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Table 1. Relationships Between Diagnostic Methods Used and Clinicopathologic Tumor Characteristics

	Diagnostic Methods								
	Preoperative			Intraoperative or Postoperative					
	Bronchoscopic	PNB	Sputum	INB	Wedge	Post	Needle	Nonneedle	*p* Value[a]
Total	220	66	4	27	14	4	93	242	
Clinical									
Sex									
Male	137 (62)	37 (56)	3 (75)	12 (44)	8 (57)	3 (75)	49 (53)	151 (62)	0.105
Female	83 (38)	29 (44)	1 (25)	15 (56)	6 (43)	1 (25)	44 (47)	91 (38)	
Age (years)									
<67	90 (41)	39 (59)	1 (25)	19 (70)	10 (71)	2 (50)	58 (62)	103 (43)	0.001
≥67	130 (59)	27 (41)	3 (75)	8 (30)	4 (29)	2 (50)	35 (38)	139 (57)	
Location									
Peripheral	142 (74)	56 (95)	1 (25)	20 (77)	12 (92)	2 (50)	76 (89)	159 (75)	0.005
Central	50 (26)	3 (5)	3 (75)	6 (23)	1 (8)	2 (50)	9 (11)	54 (25)	
Contact with the pleura									
Yes	91 (47)	32 (54)	2 (50)	8 (30)	6 (46)	1 (25)	40 (47)	100 (47)	0.986
No	101 (53)	27 (46)	2 (50)	18 (70)	7 (54)	3 (75)	45 (53)	113 (53)	
Pathologic									
Histology									
Adenocarcinoma	126 (57)	54 (82)	1 (25)	23 (85)	14 (100)	4 (100)	77 (83)	145 (60)	<0.001
Other	94 (43)	12 (18)	3 (75)	4 (15)	0 (0)	0 (0)	16 (17)	97 (40)	
T factor									
T1	121 (55)	45 (68)	0 (0)	26 (96)	14 (100)	4 (100)	71 (76)	139 (57)	0.001
T2	99 (45)	21 (32)	4 (100)	1 (4)	0 (0)	0 (0)	22 (24)	103 (43)	
Lymphatic invasion									
No	179 (81)	62 (94)	4 (100)	27 (100)	14 (100)	4 (100)	89 (96)	201 (83)	0.002
Yes	41 (19)	4 (6)	0 (0)	0 (0)	0 (0)	0 (0)	4 (4)	41 (17)	
Vascular invasion									
No	138 (63)	49 (74)	1 (25)	26 (96)	14 (100)	3 (75)	75 (81)	156 (64)	0.004
Yes	82 (37)	17 (26)	3 (75)	1 (4)	0 (0)	1 (25)	18 (19)	86 (36)	
Pleural invasion									
No	161 (73)	50 (76)	2 (50)	26 (96)	14 (100)	3 (75)	76 (82)	180 (74)	0.156
Yes	59 (27)	16 (24)	2 (50)	1 (4)	0 (0)	1 (25)	17 (18)	62 (26)	
Tumor size (cm)[b]	2.90	2.38	3.95	1.70	1.20	1.91	2.15	2.75	<0.001

[a] The *p* value for the χ^2 test for the association between needle biopsy and clinicopathologic characteristics in Table 1; [b] Geometric mean.

The numbers in parentheses indicate percentages.

INB = intraoperative needle biopsy; PNB = percutaneous needle biopsy.

15.2%). However, the rate of pleural recurrence for the cases diagnosed by PNB was significantly higher than for the cases diagnosed by bronchoscopy (9.1% versus 1.0%, $p < 0.0028$). The rate of distant recurrence for the cases diagnosed by INB was small at 3.7%, but the proportion with pleural recurrence among the cases diagnosed by INB was as high as that for the cases diagnosed by PNB, at 7.4%. Combining the cases diagnosed by PNB with those diagnosed by INB into the needle biopsy group, the percentage of those affected by pleural recurrence for the needle biopsy group was significantly higher than that for the cases diagnosed using other diagnostic modalities (8.6% versus 0.9%, $p = 0.0009$).

The details of these 10 cases are shown in Table 3. All 10 tumors were adenocarcinoma; and the diagnostic methods used were PNB for 6, INB for 2, and fiberoptic bronchoscopy for 2 patients. Two tumors diagnosed by bronchoscopy showed pleural and vessel invasion that may have been related to pleural recurrence. On the other hand, all 5 pleural recurrence cases showing neither pleural invasion nor vessel invasion in the primary tumor were diagnosed by PNB or INB. The average size of the tumors was 2.7 cm with a range from 1.5 cm to 4.8 cm, and the depth from the visceral pleura to the tumor surface on the needle track during needle biopsy ranged from 0 cm to 2.5 cm. Only 1 patient underwent needle biopsy directly through the

Table 2. Number of Cases According to Recurrence Pattern and Diagnostic Methods Used

	Diagnostic Methods							
	Preoperative			Intraoperative or Postoperative				
	Bronchoscopy	PNB	Sputum	INB	Wedge	Post	Needle	Nonneedle
Number of patients	220[a]	66	4	27	14	4	93	242[a]
Recurrence	48 (22.7)	17 (25.8)	3 (75)	3 (11.1)	2 (14.3)	0 (0)	20 (21.5)	53 (22.7)
Distant	39 (18.5)	10 (15.2)	2 (50)	1 (3.7)	1 (7.1)	0 (0)	11 (11.8)	42 (18.0)
Local	11 (5.2)	8 (12.1)	1 (25)	2 (7.4)	1 (7.1)	0 (0)	10 (10.8)	13 (5.6)
Both distant and local	2	1	0	0	0	0	1	2
Pleural recurrence	2 (1.0)[b]	6 (9.1)	0 (0)	2 (7.4)	0 (0)	0 (0)	8 (8.6)	2 (0.9)[b]
Pleural recurrence alone	2 (1.0)[b]	4 (6.1)	0 (0)	1 (3.7)	0 (0)	0 (0)	5 (5.4)	2 (0.9)[b]

[a] Bronchoscopy group includes 9 uninformative cases for recurrence. Recurrence percentages were calculated excluding the uninformative cases. [b] One patient was uninformative for pleural recurrence.

The numbers in parentheses indicate percentages.

INB = intraoperative needle biopsy; PNB = percutaneous needle biopsy.

pleura attached to the tumor, and for only 2 (cases 1 and 4) the distances were less than 1 cm. In regard to surgical procedures carried out in the 10 patients, lobectomy was performed in 7 patients and segmentectomy in 3 patients (cases 3, 7, and 10). Video-assisted thoracic surgery approach was applied in only 1 INB case; however, subsequent resection was carried out under an open thoracotomy. Concerning the pneumothorax and hemothorax after PNB, 2 cases of pneumothoraces were observed among the 6 patients who underwent PNB. Their relapses occurred 12 to 69 months after surgery, and only 2 patients (cases 4 and 8) with a short follow-up period remained alive with the recurrence.

Comment

A number of needle track implantation cases have been reported, and the incidences were reported at 0% to 3% [12, 13, 19–22]. This rate was considered as negligible by some researchers [12, 23, 24] and as important by the others [15, 25, 26]. On the other hand, pleural recurrence after PNB has not been recognized as a real risk of PNB, although it is theoretically possible adverse event. Only two cases of pleural recurrence after PNB were previously reported [15]. Is the real risk of pleural recurrence due to PNB extremely low? We thought that many cases of pleural recurrence due to PNB may have not been reported because of the difficulty in proving its cause. We

Table 3. Clinicopathologic Characteristics of 9 Cases With Pleural Recurrence and Needle Track Implantation

Case No.	Age (years)/Sex	Diagnostic Methods	Pathologic Findings			Concomitant Recurrence	Time to Recurrence (mo)	Outcome
			Histology	Size (cm)	P/Ly/V			
1	67/M	PNB	P/D Ad	2.2	0/−/−	No	20	DOD
2	68/F	INB	M/D Ad	2.8	0/−/−	Lymphadenopathy	13	DOD
3	72/F	INB	W/D Ad	1.5	0/−/−	No	12	DOD
4	58/F	PNB	M/D Ad	1.9	0/−/−	Pulmonary metastasis	36	AWD
5	50/M	PNB	P/D Ad	4.8	1/−/+	Lymphadenopathy	12	DOD
6	81/F	PNB	M/D Ad	2.5	2/−/−	Lymphangitis	28	DOD
7*	80/F	PNB	W/D Ad	2.6	2/−/−	No	24	DOD
8	76/M	PNB	W/D Ad	1.7	0/−/−	No	69	AWD
9	67/F	Br	P/D Ad	3.2	1/−/+	No	18	DOD
10	74/M	Br	M/D Ad	2.4	1/−/+	No	19	DOD

*Needle track implantation case.

Pleural invasion was judged as being P0 when tumor cells did not invade across the visceral elastic layer, P1 when tumor cells invaded across the visceral elastic layer, and P2 when tumor cells were exposed on the pleural surface.

AWD = alive with disease; Br = bronchoscopy; DOD = dead of disease; F = female; INB = intraoperative needle biopsy; Ly = lymphatic invasion; M = male; M/D Ad = moderately differentiated adenocarcinoma; P = visceral pleural invasion; P/D Ad = poorly differentiated adenocarcinoma; PNB = percutaneous needle biopsy; V = vascular invasion; W/D Ad = well-differentiated adenocarcinoma.

therefore conducted this investigation to elucidate the real risk of pleural recurrence after PNB. We hypothesized that pleural recurrence among patients with resected p-stage I NSCLC, especially with no pleural invasion, lymphatic invasion, and vascular invasion, was less likely to occur after surgery. Pleural recurrence, however, was noted in 9 patients. In addition, 1 case of needle track implantation was found. Among them, 5 cases without pleural and vessel invasion were diagnosed by needle biopsy, and for all an 18G cutting-type needle was used. These results suggested that PNB using this type of needle can cause a plural recurrence in addition to needle track implantation.

Another possible explanation for this high rate of pleural recurrence among the patients in the needle group is the difference in tumor biology between the two groups. Some investigators may believe that tumors diagnosed by PNB are in a peripheral location, and that this may be related to the high rate of pleural recurrence. From our results, we actually found that a peripheral location was more frequently observed for patients in the needle biopsy group. However, the numbers of tumors touching the pleura seen by chest CT were similar for both groups, and pathologic pleural invasion was less frequently observed for those in the needle group. We thought that the smaller size of the tumors for the needle biopsy group contributed to these results, which suggested that the differences in the tumor characteristics did not influence the results. However, we can not exclude the possibility that other tumor characteristics that we did not investigate in this study may have influenced the differences we observed.

The type of the needle we used could influence our high incidence of pleural recurrence. Large-bore cutting needles were replaced by FNA to reduce complications. During the 1990s, since the emergence of the automated and semiautomated cutting needle with an 18G to 20G bore, the cutting needle was used again because of its easy handling and its greater harvest of tissue [3–8]. Some studies compared the accuracy of cutting needle biopsy with FNA and concluded that cutting needle biopsy greatly increases the diagnostic accuracy for cases of benign pulmonary disease [4–6, 8]. On the other hand, for malignant lesions, FNA has the same high diagnostic accuracy as a cutting needle when on-site cytopathology is available [8, 27–29]. In our institute, the automated cutting type biopsy needle was conducted from 1994, and we reported its usefulness for benign lesions [9]. However, in the results from our current study, we encountered one case of needle track implantation among the 66 needle biopsy cases. Although, the incidence of needle track implantation at 1.5% was within the range of the reported incidence, it was on the high side. That the highest incidence of needle track implantation was reported by Harrison and coworkers [21], who used cutting type biopsy needle, suggested that cutting type needle usage could contribute to the tumor seeding. Conversely, more than 10 cases of needle track implantation after FNA have been reported [19, 20, 24, 30–34] since the first reported case by Sinner and Zajicek [13]. Ayar and colleagues [35] conducted a questionnaire study to elucidate the predictive factor for needle track implantation. They collected data on more than 60,000 needle biopsy cases. Among the 8 needle track implantation cases discovered in this study, 5 needle track implantations occurred after the use of 19G to 22G needles, and they concluded that they could not find any predictive factor including needle bore size. The thoroughness of our follow-up could have been related to our high incidence of tumor seeding. Our early stage of this study population has also affected the results. Needle track implantation in patients with early stage lung cancer may be more noticeable when compared with those in patients with more advanced disease because other recurrences may precede and obscure the implanted lesions. The occurrence of pneumothorax or hemithorax after PNB might be associated with the development of pleural recurrence. However, the incidence of hemothorax and pneumothorax among the pleural recurrence cases was 0% and 33 % (2 of 6 patients), and these incidences were not higher than the incidences that we previously reported (0% and 42%) [9].

Only one similar investigation that dealt with the risk of pleural recurrence was reported by Sawabata and colleagues [36]. This group studied 239 patients with completely resected NSCLC of less than 3 cm in maximum diameter and reported that no pleural carcinomatosis occurred for 45 patients who underwent PNB by FNA and wedge resection of the lung. The difference between their study and ours was that their study population included only 22 cases diagnosed by needle biopsy and 71 (30%) with stage II or more advanced disease for which other forms of recurrence could have obscured pleural recurrence.

To avoid the tumor seeding, some researchers have used a coaxial method for which aspiration or the cutting needle passes through an outer needle that stick into the normal lung [5, 6, 28, 37]. However, the effectiveness of this method has not been demonstrated.

The retrospective approach of this study is a weak point. Therefore, we can not conclude from this study that needle biopsy should be avoided. However, the results call doctor's attention to the potential risks faced by needle biopsy and suggest the need for further investigations focusing on pleural recurrence after needle biopsy. To elucidate the real risk of needle biopsy concerning the tumor seeding according to the type of needle or needle size, pleural recurrence and needle track implantation have to be investigated prospectively for patients with early stage lung cancer in multi-institutional setting. Randomized control trial is an ideal method, if possible. When the real risks of pleural recurrence and needle track implantation are discovered, this information will be indispensable for patients who would undergo this needle biopsy.

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ORIGINAL ARTICLE

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Phase II study of the combination of vinorelbine and cisplatin in advanced non-small-cell lung cancer

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Abstract *Purpose*: To evaluate the efficacy and safety of combination chemotherapy with cisplatin and vinorelbine for the treatment of previously untreated patients with advanced non-small-cell lung cancer (NSCLC). *Patients and methods*: Eligible patients were those with measurable NSCLC. They were treated with two or more cycles of a regimen consisting of vinorelbine 25 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1 every 3 weeks. *Results*: A total of 45 patients were enrolled. The response rate was 51.1% (23/45; 95% CI 35.8% to 66.3%). The median survival was 286 days with a 1-year survival rate of 40%. The median number of treatment cycles was 2. The major toxic effect was neutropenia of grade 3 or higher (84%). Nonhematological toxicities, including vomiting (62%), were mild (grade 2 or less). There were no treatment-related deaths. *Conclusion*: The high response rate and good tolerability proved this combination therapy to be a safe and effective treatment for advanced NSCLC.

Keywords Non-small-cell lung cancer · Vinorelbine · Cisplatin · Phase II study

Introduction

Vinorelbine ditartrate [1], a vinca alkaloid derivative, shows antitumor activity mainly by inhibiting microtubule polymerization in tumor cells just as other vinca alkaloid drugs do [2, 9]. Clinical studies of vinorelbine (VNR) have shown a good therapeutic outcome in non-small-cell lung cancer (NSCLC) and breast cancer, and a reduction in peripheral neuropathy that occurs frequently with vinca alkaloids [5, 7, 10, 12]. The combination of VNR and cisplatin (CDDP) (VP therapy) has shown a synergistic effect in vitro, while the main side effects are different between the drugs [4]. A phase I-II study has demonstrated efficacy of this combination in NSCLC [3]. VP therapy is considered a promising combination regimen for NSCLC on account of its higher response rate and longer survival compared with VNR or CDDP alone, or CDDP combined with vindesine [8, 17].

In clinical studies performed in Europe and the US, patient compliance rate was as low as 50% or less with regard to VNR when VP therapy, as VNR 25 mg/m^2 weekly and CDDP 80 mg/m^2 on day 1, was repeated every 4 weeks. This indicates the need to reconsider the dosing schedule of VNR [17]. Another dosing schedule for VP therapy (VNR 20 to 30 mg/m^2 on days 1 and 8 and CDDP 80 mg/m^2 on day 1 every 3 weeks) showed almost complete compliance and was found to be beneficial since the response rate was 28.3% to 56.7% and the survival 9.2 to 10.6 months [6, 13, 15, 17].

VP therapy is an effective regimen against advanced NSCLC. A multicenter joint phase III study is being planned in Japan to compare four regimens for advanced NSCLC: CDDP plus irinotecan used as a reference arm, CDDP plus VNR every 3 weeks, CDDP plus gemcitabine and carboplatin plus paclitaxel. A phase II study of VP therapy has not been conducted in Japan. We therefore carried out a phase II study of VNR 25 mg/m^2 on days 1 and 8 plus CDDP 80 mg/m^2 on day 1 given every 3 weeks in advanced NSCLC to evaluate the efficacy and safety of VP therapy.

Patients and methods

Patient selection

Patients eligible for the study were those admitted to our hospital between August 1999 and October 2001 who were histologically or

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cytologically diagnosed as having NSCLC and who were in clinical stage III or IV with unresectable disease, or in whom radiotherapy with curative intent was not possible, including those who had pleural effusion and dissemination, those with intrapulmonary metastasis within the ipsilateral lobe, those in whom the irradiation field exceeded one-half of one lung, those with metastasis to the contralateral hilar lymph nodes, and those with reduced lung function. None of the patients had received prior therapy. Other eligibility criteria included expected survival of 12 weeks, age ≤ 75 years, Eastern Cooperative Oncology Group performance score (PS) of 0–2, measurable lesions, adequate hematological function (WBC ≥4000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥10 g/dl), renal function (serum creatinine ≤ 1.5 mg/dl, creatinine clearance ≥60 ml/min), and hepatic function (total serum bilirubin ≤ 1.5 mg/dl, serum GOT and serum GPT less than twice the upper limit of normal). Written informed consent was obtained from every patient with the statement that the patient was aware of the investigational nature of this treatment regimen. Pretreatment evaluation included medical history, physical examination, complete blood count, serum biochemical analyses, chest roentgenogram, electrocardiogram and urinalysis. All patients underwent radionuclide bone scan and computerized tomography of the brain, thorax, and abdomen.

Treatment

The anticancer drugs were administered via the intravenous route, VNR 25 mg/m^2 (Navelbine, Kyowa Hakko Kogyo) on days 1 and 8 and CDDP 80 mg/m^2 (Randa, Nippon Kayaku) on day 1. This combination therapy repeated every 3 weeks constituted a cycle of treatment. The minimal number of cycles to be evaluated was two. On day 8, the physician examined the patient and evaluated the development of adverse events, and if leukocytes had decreased to below 2000/mm^3, platelets had decreased to below 75,000/mm^3 or fever with infection had occurred, administration of VNR on that day was withheld at the discretion of the physician. To proceed with the second and subsequent cycles, patients were required to have a neutrophil count ≥1500/mm^3 and a platelet count ≥100,000/mm^3. Those patients receiving granulocyte colony-stimulating factor (G-CSF) were observed for 3 days after the final dose of G-CSF to ensure that their neutrophil count was 1500/mm^3 or more. Serum creatinine levels were required to be below the upper limit of normal and serum GOT/GPT levels below twice the upper limit of normal. In the presence of liver dysfunction due to apparent liver metastasis, however, serum GOT and GPT levels were required to be below three times the upper limit of normal. If fever occurred or if the PS advanced to grade 3 or worse, the subsequent cycle was postponed until the temperature fell below 38°C or until the PS returned to 2 or less. In the presence of grade 2 peripheral neuropathy dosing was temporarily postponed; with improvement to grade 1 or less treatment was cautiously resumed, but medication was discontinued if 6 weeks passed without any improvement. Peripheral neuropathy (including transient) grade 3 or higher required discontinuation of treatment. For the third and subsequent cycles, VNR or CDDP was decreased by 25% in accordance with the treatment-related adverse events observed during the preceding cycle. Steroid and HT_3-antagonist were administered to prevent nausea and vomiting.

Target population size and interim analysis

Simon's two-stage minimax design [16] was used to estimate the number of patients required for interim and final analyses at a threshold response rate (P_0) of 0.20, an expected response rate (P_1) of 0.40, $\alpha = 0.05$ and $\beta = 0.10$. If the interim analysis revealed 6 responding patients out of 24, recruitment would be continued until the target population size was achieved. The combination therapy was considered effective if 14 or more of 45 patients showed response in the final analysis.

Since an interim response rate of 48.1% (13/27) [11] was obtained, it was necessary to enroll up to 45 patients for the final analysis.

Evaluation of response and toxicity

Response and toxicity were evaluated on the basis of tumor images obtained by CT and other techniques, laboratory data and subjective/objective symptoms before, during and after administration of the study drugs and during the period from completion of treatment to the final analysis. Measurable disease parameters were determined every 4 weeks by various means such as computerized tomography. Evaluation was made in compliance with Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [14] for antitumor activity and with NCI Common Toxicity Criteria version 2 for safety. The Institutional Ethical Review Committee gave approval to the study.

Results

Patient characteristics

Table 1 gives characteristics of the patients included. Their median age was 59.5 years (range 35 to 75 years). Male, PS 1 and adenocarcinoma predominated. There were 26 patients (58%) with stage IV disease and 19 (42%) with stage IIIB disease.

Treatments administered

The total number of cycles administered was 126 with a median of two per patient (ranging from one to four cycles; Table 2) and 43 patients received two cycles or more. In the two patients who received fewer than two cycles, treatment was discontinued because of CDDP-induced renal dysfunction in one and patient refusal in the other. Patients who completed two cycles or more accounted for 96% of patients (43/45). Except the two patients who received only one cycle, the every-3-week

Table 1 Patient characteristics

Eligible patients (*n*)	45
Age (years)	
Median	59.5
Range	35–75
Sex (*n*)	
Male	34
Female	11
Performance status (*n*)	
0	11
1	32
2	2
Histology (*n*)	
Adenocarcinoma	30
Squamous cell carcinoma	9
Other	6
Stage (*n*)	
IIIB	19
IV	26

Table 2 Efficacy of treatment ($n=45$)

No. of cycles	
Median	2.0
Range	1–4
Response	
Partial response	23
No change	21
Not evaluable	1
Response Rate (%)	51.1
95% CI (%)	35.8–66.3
1-year survival rate (%)	40

dosing schedule was adhered to by 88% of patients (38/43) in the second cycle, 68% (17/25) in the third and 92% (12/13) in the fourth, with a total of 83% (67/81). Only in two cycles was VNR withheld on day 8. The dose of VNR was reduced in 9% of dose administrations (22/250) and the does of CDDP was reduced in 8% (10/126). The planned dose intensities were 16.7 mg/m^2 per week for VNR and 26.7 mg/m^2 per week for CDDP while the actual dose intensities were 16.4 and 24.7 mg/m^2 per week, respectively. The median delivered dose intensity for CDDP (day 1) and VNR (days 1 and 8) of each course together was 90% or more (Table 3).

Efficacy of treatment

Of the 45 patients, 23 showed a partial response, 21 showed no change and 1 was not evaluable (Table 2). The response rate was 51.1% (23/45; 95% CI 35.8% to 66.3%; Table 2). The nonevaluable patient died of sudden hemoptysis on the 22nd day after the start of the second cycle (43rd day after the start of treatment) and could not be evaluated. Ten patients were alive at the time of this report. The time to progressive disease was 172 days and the median survival was 286 days (95% CI 248 to 404 days; Table 2). The 1-year survival rate was 40%.

Table 3 Median delivered dose intensity

	Median dose intensity (%)			
	Course 1	Course 2	Course 3	Course 4
CDDP	100	98.8	96	92.3
VNR				
Day 1	100	98.6	95.5	93.8
Day 8	97.8	98.6	95.5	93.8

Toxicities

Table 4 lists toxicities observed during the study. Hematological and blood biochemical reactions included a high incidence of leukopenia and neutropenia, i.e. leukopenia and neutropenia of grade 3 or higher occurred in 73% of patients (33/45) and 84% (38/45), respectively. Neutropenia-associated fever was limited to two patients. All neutropenic patients recovered upon treatment with G-CSF. Platelets decreased in 4% of patients (2/45). Creatinine was temporarily elevated in 15.6% (7/45).

Subjective and objective symptoms observed were of grade 2 or less and included vomiting in 77.8% of patients (35/45), hiccough in 33.3% (15/45), constipation in 40% (18/45), diarrhea in 22% (10/45), rash in 31.1% (14/45) and injection site reaction in 26.7% (12/45). All of these toxicities disappeared or improved with symptomatic treatment. There were no toxic deaths.

Discussion

As for the VP regimen for advanced NSCLC, the every-3-week dosing schedule has been tried in several medical facilities [6, 13, 15, 17]. Table 5 summarizes the clinical outcomes of every-3-week VP therapy reported in the literature and in this study. Response rates range from 28% to 57% and median survival is approximately 10 months. The results are similar among the studies.

In 96% of patients (43/45), two or more cycles of VP therapy were administered. The every-3-week dosing

Table 4 Toxicities ($n=45$)

Toxicity	Grade (Common Toxicity Criteria)				Grade 3/4 (%)
	1	2	3	4	
Leukopenia	4	3	25	8	33 (73%)
Neutropenia	2	2	13	25	38 (84%)
Anemia	12	3	1	4	5 (11%)
Thrombocytopenia	5	1	2	0	2 (4%)
Creatinine	5	2	0	0	–
Vomiting	29	6	0	0	–
Hiccough	15	0	0	0	–
Constipation	13	5	0	0	–
Diarrhea	9	1	0	0	–
Rash	10	4	0	0	–
Neuropathy	4	0	0	0	–
Injection site reaction	4	8	0	0	–
Alopecia	3	0	0	0	–

Table 5 Outcomes of studies of VP therapy (VNR days 1 and 8, CDDP day 1, every 3 weeks)

Reference	VNR (mg/m^2)	CDDP (mg/m^2)	Response	Median survival time (months)
4	25	80	28.3% (28/99)	9.2
10	25	80	56.7% (42/74)	10
11	20–25	80	46.7% (14/30)	10.6
1	30	80	36.2% (47/130)	–
Present study	25	80	51.1% (23/45)	9.6

schedule was adhered to in 85% of all cycles administered. In cycles in which noncompliance was seen, medication was postponed to the 4th to 5th week because, in most cases, the neutrophil count in the 3rd week failed to meet the criterion for going on to subsequent cycles. The planned dose intensity was almost attained since the actual dose intensity was 16.4 mg/m^2 per week for VNR and 24.7 mg/m^2 per week for CDDP, accounting for 98% and 93% of the planned values, respectively [13].

Most adverse reactions were hematological. In particular, leukopenia and neutropenia of grade 3 or worse occurred in 73% and 84% of 45 patients, respectively. Others have reported the incidence of leukopenia of grade 3 or worse to be 8% to 33% [6, 13, 17]. Although the difference in patient characteristics hinders simple comparison and analysis of these data, it can be said that leukopenia was more frequent in our study. The leukocyte count improved rapidly upon treatment with G-CSF. Nonhematological toxicities were mild and adverse reactions of grade 3 or higher were not noted.

The combination of VNR 25 mg/m^2 on days 1 and 8 and CDDP 80 mg/m^2 on day 1 was administered every 3 weeks to 45 patients with advanced NSCLC in this phase II study. The response rate was 51.1%; the main adverse effect was neutropenia. The high response rate and good tolerability indicate that this combination therapy is a safe and effective treatment for advanced NSCLC. Its usefulness will be further verified in phase III studies.

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Objective definition and measurement method of ground-glass opacity for planning limited resection in patients with clinical stage IA adenocarcinoma of the lung☆

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Abstract

Objective: The standard operation for patients with stage IA lung adenocarcinoma is considered to be a lobectomy. Recently, some researchers have reported that patients with tumors showing greater proportions of ground-glass opacity (GGO) at computed tomography (CT) could be candidates for limited resection, because of its less aggressive nature. However, the lack of a precise definition or standard measuring method of GGO prevents its general use as an index for planning limited resection. Therefore, we attempted to define GGO based on CT number and measured it more objectively. **Methods**: Between 1998 and 2001, 90 patients with clinical stage IA adenocarcinoma, who underwent standard or intentional limited resection and whose images of chest high-resolution CT were preserved in Digital Imaging and Communications in Medicine (DICOM) format, constituted the study population. The tumor shadow seen on the solid window (WL, −160 HU; WW, 2 HU) was regarded as the central solid area of the tumor seen on the lung window, and GGO was defined as the whole tumor area with the exception of the central solid area. Each area was measured using Scion Image (Scion Corp., Frederick, MD). We analyzed the relationship between the proportion of GGO and both of pathologic findings and recurrence. **Results**: Among the 90 tumors, 31 (34.4%) were calculated to have a GGO area greater than or equal to 50%. Of these, 27 (87%) tumors were bronchioloalveolar carcinoma. Lymphatic and vascular invasions, or nodal involvement were found only in patients with a smaller proportion of GGO (<50%) ($P < 0.05$). During the follow-up period (median 36 months), recurrences occurred in eight patients who were diagnosed as having tumors showing smaller proportion of GGO (<50%). **Conclusions**: Tumors with a greater proportion of GGO measured by our method are thought to have a less invasive nature. Our objective measuring method of GGO could be useful for future multicenter trials to elucidate the value of limited resection for clinical stage IA adenocarcinoma based on the proportion of GGO.

Keywords: Lung neoplasms; High-resolution computed tomography; Lung neoplasms; Adenocarcinoma; Bronchioloalveolar carcinoma; Limited operation; Ground-glass opacity

1. Introduction

The standard operation for patients with T1N0M0 stage IA non-small cell lung cancer is still lobectomy with systematic nodal dissection, because limited resection for such patients was reported to increase local recurrence and decrease the survival rate compared to lobectomy in a randomized control trial conducted by the Lung Cancer Study Group [1]. Candidates for limited resection, therefore, are thought to be rather a group of patients that have less invasive tumors and a better prognosis than the whole group of stage IA non-small cell lung cancer patients [2]. Much research has been conducted to identify the group of patients with less invasive tumors preoperatively based on the tumor size. However, the tumor size turned out to be less useful, because the incidence of lymph node metastasis in patients with tumors smaller than 2 cm in diameter were reported to be 10–20% [3,4].

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Jang et al. reported that the focal area of ground-glass opacity (GGO) on high-resolution computed tomography (HRCT) could be an early sign of localized bronchioloalveolar carcinoma (BAC) [5]. We demonstrated that in patients with clinical T1N0M0 adenocarcinoma the patients with a higher proportion of GGO area (≥ 50%) on HRCT by visual estimation had neither lymph node metastasis nor lymphatic invasion and were alive without recurrence [6]. From these results, it is considered that such patients may be candidates for limited resection.

However, the lack of a precise definition or standard measuring method of GGO prevents its general use as an index for planning limited resection. To resolve the problems, we characterized the GGO using CT number, and developed more objective measurement methods using Scion Image to quantitate the proportion of GGO area. Then, we tested whether or not this method was useful in predicting less invasive tumors in clinical stage IA adenocarcinoma patients.

2. Materials and methods

Between January 1998 and December 2001, 284 patients with primary lung cancer underwent surgical resection of the lung at our hospital. Of these, 103 patients were given a diagnosis of clinical stage IA lung adenocarcinoma. Among the patients, 90 underwent standard surgical resection or intentional limited resection and their lung images of HRCT were preserved in Digital Imaging and Communications in Medicine (DICOM) format. These patients constituted the study population. For four patients with multiple lung cancer, we investigated the most advanced tumor. Fifty-one patients were men, and the average age was 60.3 years (range 36–78 years). CT scanning was performed on X-Vigor or Aquilion (Toshiba Medical Systems, Tokyo, Japan). HRCT scans were performed over a range of 50 mm, covering the entire lesion. The scanning parameters were a tube voltage of 120 kV, a tube current of 250 mAs for X-Vigor and 150 mAs for Aquilion, 1 or 2 mm collimation, and a reconstruction interval of 1 or 2 mm by using a bone algorithm. The field of view was focused at about 20 cm. GGO was defined as a hazy increase in lung attenuation without obscuring the underlying vascular marking. We tried to define the GGO based on CT number (Hounsfield unit (HU)). When we fixed the window width of CT at 2 HU, the tumor shadow represented the area where the CT value was greater than that of the window level. We changed the window level from 40 to − 320 HU to select the best window level at which the tumor shadow was visually almost identical to the central solid area on the lung window. As a result, we decided the best window level was − 160 HU, and referred to the window setting as 'solid window' (window level − 160 HU; window width 2 HU). The tumor shadow seen on the solid window was thought to represent the central solid area seen on the lung window. Therefore, the GGO area was defined as the tumor shadow on solid window subtracted from tumor shadow on lung window. The areas of the tumor shadows were measured with Scion Image (Scion Corp., Frederic, MD, USA) on one level of each tumor shadow equator on each window settings. Scion Image is an image processing and analysis program for windows computer that is based on the popular NIH Image (NIH, Bethesda, MD, USA) for Macintosh computer. These are freely available for download from their respective website. We used the 'Density slice' command to segment the target area. The details of how to use the Scion Image are also referable to the manual in the website.

Vessels or bronchi in the tumor shadow were erased if the areas were larger than 5% of the tumor shadow. The proportion of GGO was calculated as follows: [(Area on lung window − Area on solid window)/Area on lung window] × 100. A representative case is shown in Fig. 1.

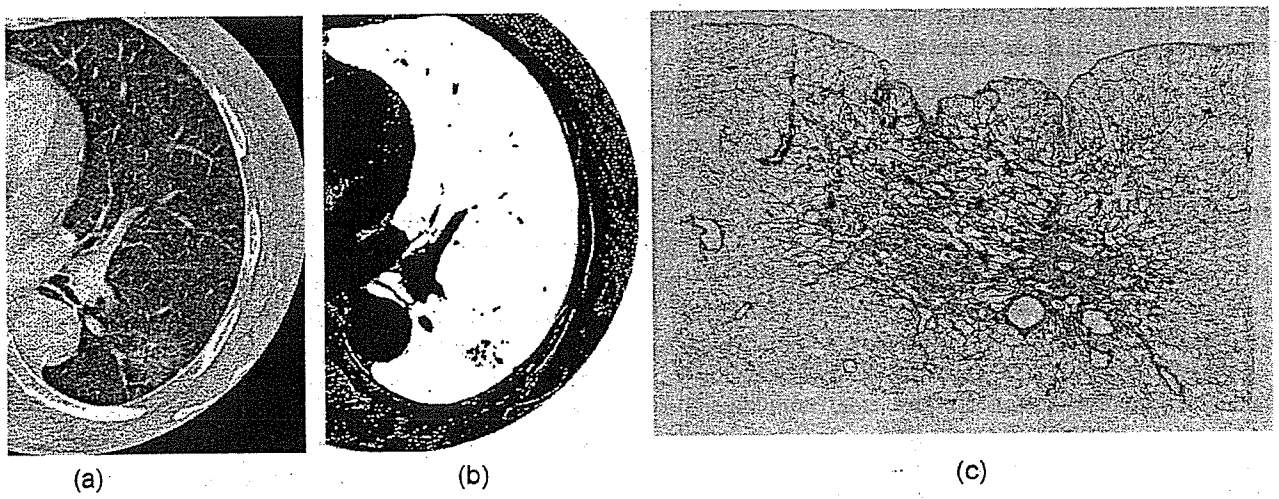

Fig. 1. Seventy-seven-year-old woman with a pulmonary nodule detected by annual screening using chest X-ray examination. Her HRCT images showed a GGO nodule dotted with small solid areas (a). The proportion of GGO was calculated at 86% (b). Pathologic examination revealed that the tumor was BAC. She was alive without any sign of recurrence at 42 months after operation (c).

Table 1
Relationship between proportion of GGO and both pathological findings and recurrence

% GGO	Number of patients	Number of BAC patients	Lymphatic invasion	Vascular invasion	Pleural invasion	Nodal involvement	Recurrence
90–100	14	14	0	0	0	0	0
80–89	8	7	0	0	0	0	0
70–79	4	4	0	0	0	0	0
60–69	3	2	0	0	0	0	0
50–59	2	0	0	0	0	0	0
40–49	10	5	1	0	1	0	0
30–39	7	2	0	1	2	0	1
20–29	8	0	1	1	1	1	0
0–19	34	1	12	9	5	11	7

Four-micrometer sections, including the largest piece cut from the surface of the tumor in each case, were stained with hematoxilin and eosin and elastica van Gieson and examined by means of light microscopy. Intra-tumoral vascular invasion was determined by means of the identification of tumor cells in blood vessels. Lymphatic invasion was also morphologically distinguished from vascular invasion. Pleural invasion was judged as positive if tumor cells invaded across the visceral pleural elastic layer. The tumors were classified into two histologic subtypes according to the classification determined by the World Health Organization (WHO), BAC and other subtypes including acinar, papillary, solid carcinoma with mucin, and adenocarcinoma with mixed subtype [7]. Pathologic stages were classified according to the International System for Staging Lung Cancer criteria [8].

All patients were followed up until death, or the last date of the follow-up (December 31, 2002). The average length of follow-up was 36 months. We investigated the relationship between the proportion of GGO area calculated using our method compared with the pathologic findings and recurrence. The χ^2-test or Fisher's exact test was used to compare several clinical or pathological factors.

3. Results

The distribution of pathologic BAC, nodal status, lymphatic, vascular and pleural invasions, and recurrence by proportion of GGO were shown in Table 1. Among the 90 tumors, 31 (34.4%) were calculated to have a GGO area greater than or equal to 50%. Among the 31 tumors showing a greater GGO proportion ($\geq$ 50%), 27 (87%) tumors were BACs, and no tumors accompanied vessel invasion, pleural invasion, or lymph node metastasis. On the other hand, among the 34 tumors with a GGO area smaller than 20%, 12 (35%) had lymphatic invasion and 11 (32%) accompanied lymph node metastasis. Lymphatic and vascular invasions, or nodal involvement was found more frequently in patients with a smaller proportion of GGO ($<50\%$) than patients with a greater proportion of GGO ($\geq 50\%$) ($P < 0.05$). During the follow-up period, eight patients had tumor recurrences. Of the patients, six were diagnosed as having mediastinal nodal involvement after surgery. There were three local recurrence cases, three distant recurrence cases, and two both local and distant recurrence cases. Seven patients had tumors showing less than 20% of GGO, and one patient had a tumor showing 33% of GGO.

4. Discussion

Detections of nodules showing greater proportion of GGO had increased strikingly since lung cancer screening with low dose CT began [9]. Higashiyama and colleagues investigated the relation between the proportion of BAC component and prognosis. They documented that the greater degree of BAC involvement might reflect the less frequent nodal involvement and good prognosis [10]. We reported the relation between the proportion of GGO and both clinicopathologic characteristics and recurrence in patients with clinical T1N0M0 adenocarcinoma [6]. In this study,

Table 2
Measurement methods of GGO in article

Source	Year	Slice	Method	Parameter	Window setting
Kuriyama et al.	1999	One	Visual	Area	Lung window
Kim et al.	2001	One	Visual	Area	Lung window
Kodama et al.	2001	One	Visual	Area	Lung window
Aoki et al.	2001	One	Measure	Diameter	Lung window
Kondo et al.	2002	One	Visual	Area	Lung /mediastinal window
Matsuguma et al.	2002	All	Visual	Area	Lung window
Takashima et al.	2002	One	Measure	Area	Lung window

the GGO was estimated using visual estimation on all slices in which the tumor appeared. The patients with a higher proportion of GGO area (≥50%) on HRCT had neither lymph node metastasis nor lymphatic invasion and were alive without recurrence. Besides our study, several studies focusing on GGO have been reported to date (Table 2) [11–16]. In many studies including ours, proportions of GGO were semiquantitated by visual estimation. In one study, diameters of nodules and central solid portions were measured instead of area [14]. And in only one study, GGO area was measured using transparent overlay with crossing points of vertical and transverse lines [16]. We think that calculating the area is better than focusing on dimensions because the shape of the central solid portions are often irregular, and sometimes separate as can be seen in our case in Fig. 1.

Standardization for dealing with GGO in selecting candidates for limited resection is urgently needed so that the data from many studies can be compared. Below, we have listed some problems regarding our former published method of measuring GGO. First, visual estimation is somewhat vague and less reproducible. Second, the definition of GGO itself is determined by visual judgment and can result in inter-observer difference. Third, there is a question as to whether the cut-off value of 50% of GGO is or is not the most valuable point in identifying a candidate for limited resection. This is because the cut-off value of 50% was fixed in order to simplify visual judgment. To resolve these problems, we characterized GGO with a CT number, and the proportion of GGO is quantitated more objectively using software. As a result, we obtained almost the same results as our previous study. Furthermore, it has become much clearer that the tumor shows more invasiveness as its proportion of GGO decreases. From our results, the most useful cut-off value for area of GGO may be around 50%, even when using our method. However, future prospective studies are needed to evaluate the effectiveness of limited resection for patients in the early stages of lung cancer based on the objective measurement of GGO. As mentioned above, NIH Image and Scion Image are now freely available. If the images are saved only on the hard-copy film, not as digital data as we have done, you only have to save a few additional images on solid window on hard copy film in addition to the standard lung and mediastinal window images, and transform them into digital data using a scanner. We believe that our methods could be useful and easily available throughout the world.

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Appendix A. Conference discussion

Dr Hyun-Sung Lee (South Korea): Regarding the proportion of GGO, you measured only the area of tumor and GGO, in other words, a two-dimensional evaluation, but I think the proportions of GGO should be

evaluated by the volume, not the area. With the hypothesis that the shape of tumor and GGO is a sphere, the area is proportional to the square of the diameter, but volume is proportional to the squared 3 of the diameter. By its volume or three-dimensional evaluation, the proportion of GGO will lead the different results. I think this is more reliable. What do you think?

Dr Matsuguma: In our previous study we measured the GGO on all slices and in this study we measured on one slice. One slice is two-dimensional and all slices is three-dimensional, so I cannot directly compare these results. We measured the GGO proportion using the software, so we precisely measured GGO. GGO is not equally distributed around the central solid portion, but we measured on both slices of the maximum shadow of the nodule and maximum shadow of the central solid portion. I thought it might almost represent the nature of the GGO tumor.

Dr P. De Leyn (*Leuven, Belgium*): This entity will gain importance also in West Europe when we will have screening programs. We will see more of these patients than we see now.

When you talk about limited resection, do you mean for nodal dissection, or would you also perform wedge resections for these types of lesions?

Dr Matsuguma: In this study?

Dr De Leyn: Not only in this study, but in your country you see more of these patients and you have a lot of experience. Would you perform wedge resections for these kinds of lesions instead of lobectomy?

Dr Matsuguma: Our limited resection included segmentectomy and wedge resection. In this study there were 10 patients who underwent wedge resection and 7 patients who underwent segmentectomy, that were based on the GGO proportion. Usually we carried out the standard operation for a solid nodule.

Dr F. Rea (*Padova, Italy*): I don't understand. Do you know the histology before planning your operation? Do you do frozen section? Do you decide, using a frozen section?

Dr Matsuguma: Preoperatively?

Dr Rea: Yes, preoperatively. Do you know preoperatively the diagnosis?

Dr Matsuguma: In many cases we diagnosed preoperatively, but in some cases, such as pure GGO or small nodule, were not diagnosed preoperatively.

Dr Rea: And then you decide with the frozen section!

Dr Matsuguma: Yes.

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ORIGINAL ARTICLE

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Schedule-dependent synergism and antagonism between pemetrexed and paclitaxel in human carcinoma cell lines in vitro

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Abstract Pemetrexed is a novel multitargeted antifolate with significant clinical activity against a variety of tumors. We studied the schedule-dependent cytotoxic effects of pemetrexed in combination with paclitaxel in vitro to improve our understanding of how this combination might be used clinically. Human lung cancer A549 cells, breast cancer MCF7, ovarian cancer PA1, and colon cancer WiDr cells were exposed to both pemetrexed and paclitaxel in vitro. Cell growth inhibition after 5 days was determined and the effects of drug combinations were analyzed by the isobologram method (Steel and Peckham). Simultaneous exposure to pemetrexed and paclitaxel for 24 h produced antagonistic effects in A549 and PA1 cells, additive/antagonistic effects in MCF7 cells, and additive effects in WiDr cells. Pemetrexed for 24 h followed by paclitaxel for 24 h produced synergistic effects in A549 and MCF7 cells and additive effects in PA1 and WiDr cells, while the reverse sequence produced additive effects in all four cell lines. Cell cycle analysis supported these observations. Our findings suggest that the simultaneous administration of pemetrexed and paclitaxel is suboptimal. The optimal schedule of pemetrexed in combination with paclitaxel is the sequential administration of pemetrexed followed by paclitaxel, and this schedule should be assessed in clinical trials for the treatment of solid tumors.

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Keywords Pemetrexed · Paclitaxel · Isobologram · Synergism · Antagonism

Introduction

The development of several new antifolates with distinctive chemical features and target enzymes has provided new opportunities to expand the role of antifolates in cancer chemotherapy. Multitargeted antifolate (MTA, pemetrexed) is a pyrrole-pyrimidine analogue of folate [33] currently in broad clinical evaluation. Pemetrexed is transported into cells mainly through the reduced folate carrier system and metabolized to polyglutamated forms [7] which inhibit thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase [30, 31], and has antithymidylate and antipurine effects [5]. Preclinical studies of pemetrexed have demonstrated its antitumor activity against a variety of human cancer cells [2, 29].

Phase I studies have shown that the dose-limiting toxicity includes neutropenia and thrombocytopenia, and other toxicities which are manageable, such as mucositis, skin rashes and transient elevations of transaminases [18, 23–25]. Daily and weekly schedules are associated with severe toxicity and 500 mg/m^2 of pemetrexed every 3 weeks was selected as the optimal schedule and dose for the further development of pemetrexed. Patients with a folate-deficient state showed severe toxicity. In preclinical models, folate supplementation reduced toxicity while maintaining antitumor activity. Based on these observations, folate and cobalamin administration before pemetrexed has been routine in recent clinical trials of pemetrexed [9, 26]. Pharmacokinetic studies have shown that pemetrexed undergoes biphasic plasma clearance with a terminal half-life of 1.1–3.1 h, depending on the schedule of administration [23]. The findings from the phase II trial results are encouraging: clear responses were observed in colorectal cancer, pancreatic cancer, lung cancer, breast cancer, mesothelioma, etc. [3, 4, 8, 10, 19–21, 26, 37]. A recent