gemcitabine, or irinotecan is probably acceptable as the current standard first-line chemotherapy.

First-line single agent with gefitinib is active, but produces unacceptably frequent ILD in the Japanese population. Being female, as well as adenocarcinoma, those who never smoked, and *EGFR* mutation were associated with response to gefitinib. Patients who responded to gefitinib did not experience ILD during gefitinib chemotherapy. Further research via genetics and image analysis is needed to avoid ILD and identify a subgroup of patients that benefit from gefitinib treatment. If this is realized, single agent treatment with gefitinib could be an option as first-line chemotherapy in selected patients with advanced NSCLC. Furthermore, randomized trials are warranted to compare first-line single agent treatment with gefitinib followed by second-line platinum-based chemotherapy with first-line platinum-based chemotherapy followed by second- or third-line gefitinib treatment.

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The authors indicated no potential conflicts of interest.

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A Phase II Study of Docetaxel and Infusional Cisplatin in Advanced Non-Small-Cell Lung Cancer

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Key Words
Non-small-cell lung cancer · Chemotherapy · Cisplatin · Docetaxel · Infusion, continuous

Abstract
Background: To evaluate the efficacy and safety of combination chemotherapy of cisplatin (5-day continuous infusion) and docetaxel for the treatment of previously untreated patients with advanced non-small-cell lung cancer (NSCLC). ***Materials and Methods:*** Eligible patients had an ECOG performance status of 0–2 with measurable NSCLC. Patients received continuous infusion cisplatin 20 mg/m^2/day on 5 days and bolus docetaxel 60 mg/m^2/day (day 1; PiD therapy) at a 4-week interval. ***Results:*** Forty-three patients were enrolled. The mean number of cycles administered per patient was 2, and ranged from 1 to 4. The response rate was 49% (95% confidence interval, 33.9–63.8%). The median survival time was 47 weeks and the 1-year survival rate was 47%. The major toxic effects were grade 3 or 4, neutropenia (88%), leukopenia (81%), thrombocytopenia (14%) and anemia (42%). There were no treatment-related deaths. ***Conclusion:*** PiD therapy was a well-tolerated and active regimen for patients with advanced NSCLC. The major toxicity was neutropenia.

Introduction

Unresectable non-small-cell lung cancer (NSCLC) is known to have an extremely poor prognosis, and its standard treatment remains to be established. The most common chemotherapy for NSCLC is a combination treatment consisting of 2 or 3 drugs including cisplatin (CDDP) as a key drug. The combination treatments have response rates of 30–50%, and have been proven to prolong survival time in clinical stages III [1] and IV [2, 3]; however, the response is only limited.

In recent years, new anticancer drugs have been developed and used for the treatment of NSCLC. Docetaxel is a new hemisynthetic anticancer agent originating from its precursor, 10-deacytylbaccatin III, extracted from the needle leaves of the European yew tree, *Taxus baccata* L. Docetaxel affects microtubules, and shows its cytotoxicity by prematurely stabilizing mitotic microtubules. In phase II clinical studies for the treatment of NSCLC carried out in Europe and the USA, docetaxel showed a response rate of about 30% in previously untreated patients with a better survival time [4, 5]. A major side effect of docetaxel is dose-dependent edema that is proportional to bone marrow suppression. Since hypersensitivity is particularly limiting, it is worth noting that docetaxel can be given by intravenous infusion in a short period of time without any pretreatment.

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In the Japan phase I study, dose-limiting toxicity of docetaxel was found to be leukopenia (neutropenia), and its recommended dose was set at 60 mg/m^2 [6]. In the multicenter phase II clinical study for the treatment of NSCLC carried out in Japan, a response rate of 19% was shown in untreated patients with predominant toxicities of leukopenia and neutropenia [7].

Currently, cisplatin is the active agent for treating NSCLC, and combination chemotherapy consisting of 2 or 3 drugs based on CDDP is a major strategy [8]. CDDP can be administered by short-term intravenous infusion, a divided dosage method, continuous administration, and other methods [9, 10]. CDDP cytotoxicity is enhanced by prolonged exposure to low doses of this drug in in vitro studies [11, 12]. Belliveau et al. [13] reported that the area under the concentration-time curve (AUC) achieved for non-protein-bound CDDP was twice as high after 5-day continuous infusion than that observed when an equivalent dose of CDDP was given by short-term bolus infusion. These findings suggest that continuous infusion of CDDP might improve the therapeutic efficacy as compared with that resulting from conventional short-term bolus infusion. However, compared with short-term intravenous infusion, 5-day continuous infusion makes inpatient hospitalization for at least 5 days necessary, and the duration of confinement for the purpose of infusion is lengthy and therefore onerous for the patient. The efficacy and safety of a continuous infusion lasting 5 days (24 h a day) were confirmed in our facility and some other facilities [10, 14–16]. In addition, combination chemotherapy of infusional CDDP with vindesine or CPT-11 was found to have high response rates in treating NSCLC [17, 18].

Cisplatin and docetaxel show nonsynergistic and additive effects in vitro, no cross-resistance and have a relatively nonoverlapping toxicity profile [19]. Therefore, the development of docetaxel in combination with cisplatin is warranted. We conducted a phase II study of docetaxel and infusional cisplatin, in patients with previously untreated advanced NSCLC, and evaluated antitumor activity and the safety of this therapy.

Patients and Methods

Patient Selection

All patients with histologically or cytologically confirmed advanced NSCLC were eligible for this phase II trial. The subjects of this study were patients in clinical stage IV or in stage III with unresectable disease or in whom radiotherapy with curative intent is not possible. Patients with unresectable disease or in whom radiotherapy with curative intent is not possible include those with pleural effusion and dissemination, those with intrapulmonary metastasis within the ipsilateral lobe, those in whom the irradiation field exceeds 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 an expected survival of 12 weeks, age ≤75 years, Eastern Cooperative Oncology Group performance score of 0–2, measurable lesions, adequate hematological function (WBC ≥4,000/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, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase less than twice the normal range). The ethical committee of the Tochigi Cancer Center approved the protocols. Written informed consent was obtained in every case stating that the patient was aware of the investigational nature of this treatment regimen. Pretreatment evaluation included medical history, physical examination, complete blood count, bone marrow examination, serum biochemical analyses, chest roentgenogram, electrocardiogram, and urinalysis. All patients underwent a radionuclide bone scan, and computerized tomography of the brain, thorax and abdomen. Complete blood count, biochemical tests, serum electrolytes, urinalysis, and chest roentgenograms were obtained weekly during this phase II trial. Tests of measurable disease parameters such as computerized tomography were repeated every 4 weeks. Staging was according to the 4th edition of the UICC TNM classification.

Treatment

All patients were admitted to the Tochigi Cancer Center Hospital during this trial. The anticancer drug regimen consisted of a combined administration of docetaxel plus infusional cisplatin. Docetaxel was supplied, in concentrated form, in a sterile vial that contained 80 mg of the drug in 2 ml of polysorbate 80. Docetaxel (Taxotere; Aventis) 60 mg/m^2 was diluted in 250 ml of 5% glucose, and was infused over a 1-hour period on day 1. Three hours after completion of the docetaxel infusion, 20 mg/m^2 of cisplatin was given daily for 5 days by continuous intravenous infusion. One third of the daily dose was administered every 8 h dissolved in 800 ml of physiological saline [14]. The course was repeated every 4 weeks. Antiemetic drugs used were granisetron (3 mg/body/day, bolus infusion for 5 days), metoclopramide (3 mg/kg/day, continuous infusion for 5 days), methylprednisolone (125 mg bolus infusion every 8 h, days 1–5), diphenhydramine (30 mg orally, days 1–7) and alprazolam (1.2 mg orally, days 1–7) [15, 16]. In the first course, no routine premedication was given for hypersensitivity reactions or fluid retention. The reason for this was that the incidence of these events was low at the dose of docetaxel (60 mg/m^2) administered in the present study [7]. However, if hypersensitivity reactions or fluid retention occurred, premedications such as corticosteroids or antiallergic agents were allowed in the subsequent courses. Recombinant human granulocyte colony-stimulating factor was administered when leukopenia/neutropenia of grade 4 occurred.

Patients were treated with at least two cycles of therapy unless disease progression or unacceptable toxicity was encountered or the patients did not wish to continue. Patients who experienced grade 4 leukopenia or neutropenia that lasted for 3 or more days, or who experienced grade 4 thrombocytopenia or reversible grade 2 neurotoxicity or grade 3 liver dysfunction, received reduced doses of

both docetaxel and cisplatin (75% of the previous dose) for the next cycle. Patients who experienced stomatitis of grade 3 or more or renal dysfunction of grade 2 or more received a reduced dose of cisplatin (75% of the previous dose) for the next cycle. If neurotoxicity of grade 3 or more occurred, treatment was stopped. Subsequent courses of chemotherapy were started after day 28 when the leukocyte count was 4,000/mm^3 or more, the neutrophil count was 2,000/mm^3 or more, the platelet count was 100,000/mm^3 or more, serum creatinine was less than the upper limit of the normal range, creatinine clearance was 60 ml/min or more, GOT and GPT were less than twice the upper limit of the normal range, and neurotoxicity was grade 1 or less. If these variables did not return to adequate levels by the first day of the next course of chemotherapy, treatment was withheld until full recovery. If more than 6 weeks passed from the time of the last treatment before these criteria were satisfied, the patient was taken off the study, but still included in the analysis. In the case of stable or progressive disease after two courses of treatment, subsequent therapy was left to the discretion of the physician in charge of the patient.

Assessment of Response to Treatment and Toxicity

The response to treatment was evaluated with WHO criteria. The criteria for response were as follows. Complete response was defined as the complete disappearance of all evidence of tumor for at least 4 weeks. Partial response was defined as a $\geq$50% reduction in the sum of the product of the two greatest perpendicular diameters of all indicator lesions for at least 4 weeks and no appearance of new lesions or progression of any lesion. Progressive disease was defined as a $\geq$25% increase in the tumor area or the appearance of new lesions. All other circumstances were classified as no change. Toxicity was graded according to the common toxicity criteria (version 2).

Statistical Analyses

The primary end point was the objective response rate. The duration of each response was defined as the number of days from the documentation of the response until tumor progression. Survival curves from registration until death were generated by the method of Kaplan and Meier. We chose a 40% response rate as a desirable target level, and a 20% response rate as undesirable. The study design had the power to detect a response of greater than 90%, with less than 5% error. Therefore, we needed 23 assessable patients in first stage and 20 in second stage, according to the mini-max design of Simon. We decided to stop the study if fewer than 5 patients responded in the first stage.

Results

Patient Characteristics

Forty-three patients were enrolled in this study from July 1997 to June 1999 and received 105 cycles of the regimen. Table 1 shows the patient characteristics. There were 14 women and 29 men with a median age of 61 years (range 34–75). One patient had stage IIIA, 7 patients stage IIIB, and 35 patients stage IV disease. In stage IIIA, 1 patient classified as c-T3N2M0 had lung cancer with a bulky tumor (10 cm), associated with extranodal and N2 involvement. Among the 7 stage IIIB patients, there were three T4 cases in which pleural effusion and pleural dissemination were present, two T4 cases of intrapulmonary metastasis in the ipsilateral lobe, and two T4N3 cases with mediastinal infiltration and supraclavicular fossa lymph node metastasis.

Table 1. Patient characteristics

Patients	43
Sex (M/F)	29/14
Age[1], years	61 (34–75)
Performance status: 0/1/2	9/30/4
Stage: IIIA/IIIB/IV	1/7/35
Histology: Ad/Sq/Other	27/14/2

Ad = Adenocarcinoma; Sq = squamous cell carcinoma.

[1]Value represents median with the range given in parentheses.

Treatments Administered

The mean number of cycles administered per patient was 2, and ranged from 1 to 4. In 99 of 105 cycles (94%), PiD was administered at 4-week intervals. In 5 of 6 cycles, in which cisplatin could not be administered at a 4-week interval, it was given a week later. As for the remaining cycle, it was administered 6 weeks later. The reason for the delay of the administration was the patient's request for 1 cycle and neutropenia in 5 cycles. Dosage was reduced in 7 cycles (7%). Reductions in dosage of docetaxel and cisplatin were made, respectively, in 6 cycles (6%) and 7 cycles (7%). The former reduction was made because 6 cycles showed neutropenia grade 4, and the latter reduction was made because 5 cycles showed neutropenia grade 4, and 1 cycle showed both neutropenia grade 4 and creatinine grade 3, and 1 cycle showed creatinine grade 2.

Response to Treatment and Survival

The response rate was 49% (95% confidence interval, CI, 33.9–63.8%); a complete response was observed in 1 and partial response in 20 patients (table 2). The median duration of the response was 39.2 weeks (range 5–147 weeks). The median survival time was 47 weeks (95% CI, 6–152 weeks) and the 1-year survival rate was 47% (fig. 1). Two patients are still alive.

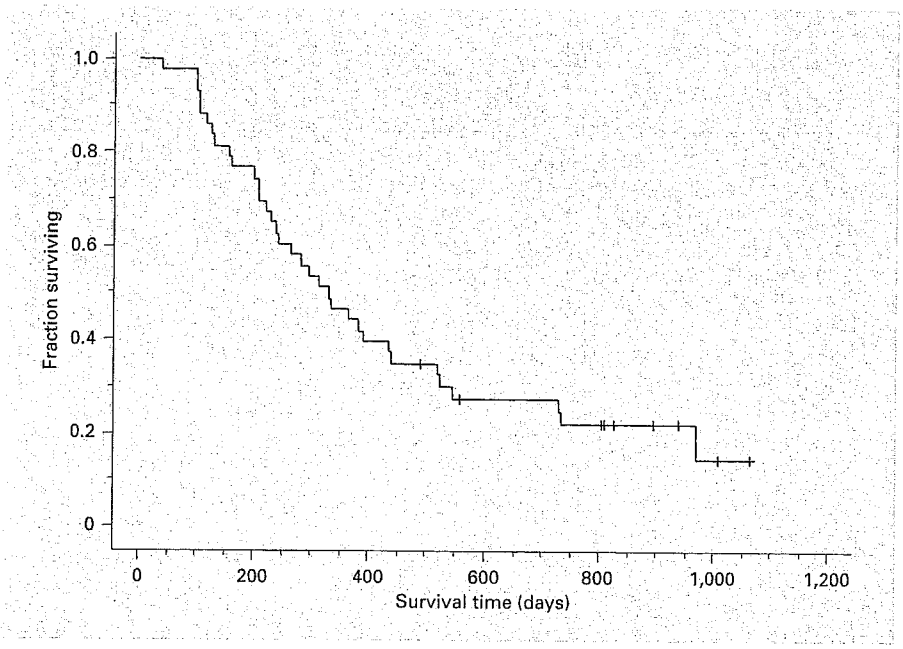

Fig. 1. Kaplan-Meier estimated overall survival curves. Median survival time was 47 weeks; 1-year survival rate was 47%.

Table 2. Chemotherapeutic evaluation (n = 43)

Cycles[1]	2 (1–4)
Response: CR/PR/NC/PD	1/20/20/2
Response rate, %	49
Response duration, weeks	
Average	39.2
Range	5–147
1-year survival rate, %	47

CR = Complete response; PR = partial response; NC = no change; PD = progressive disease.

[1]Value represents average with the range in parentheses.

Table 3. Toxicity (n = 43 patients)

	Maximum toxicity terms of CTC grade					Grade ≥3
	0	1	2	3	4	%
Leukopenia	1	1	6	29	6	81
Neutropenia	1	0	4	13	25	88
Anemia	1	6	18	18	–	42
Thrombocytopenia	25	5	7	6	0	14
Creatinine	23	18	1	1	0	2
SGOT/SGPT	30	12	1	0	0	0
Vomiting	5	7	31	0	–	0
Diarrhea	20	16	7	0	0	0
Alopecia	20	22	1	–	–	
Edema	36	6	1	0	–	0
Neuropathy	40	3	0	0	0	0

Figures represent number of patients. CTC = Common toxicity criteria; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

Toxicity

Table 3 shows the types and grades of toxicities resulting from the treatment, using the common toxicity criteria. All 43 patients could be evaluated for toxic reactions. The major toxicity was myelosuppression. Leukopenia <2,000/mm^3 (grade 3 or 4) was observed in 35 patients (81%), of whom 6 patients showed grade 4. Neutropenia <1,000/mm^3 (grade 3 or 4) was observed in 38 patients (88%), of whom 25 patients showed grade 4. Eight patients developed febrile neutropenia. Thrombocytopenia <5 × 10^4/mm^3 (grade 3 or 4) was observed in 6 patients (14%), and a hemoglobin nadir (grade 3) in 18 patients (42%). There were no episodes of bleeding or fluid overload.

Vomiting grade ≥2 occurred in 31 patients (72%). Diarrhea grade ≥2 was observed in 7 patients (16%). Grade 1 or 2 alopecia and edema were observed in 23 and 7 patients, respectively. In the first cycle, creatinine showed grade ≥2 in 2 patients, resulting in transient rises. In the following cycle, the creatinine level was kept at grade 1 by reducing the dosage of cisplatin. Grade 1 or 2 skin rash was observed in 3 patients. Finally, there were no treatment-related deaths.

Discussion

Cisplatin is one of the key drugs for the treatment of NSCLC. Its high response rate of 40% and safety when it was given alone by continuous infusion over 5 days [14] are confirmed.

Docetaxel is also an active agent to treat NSCLC, and docetaxel of 60 mg/m^2/day (day 1), a recommended dose in Japan, showed a response rate of 19% [7]. Docetaxel has no cross-resistance with cisplatin, and in clinical practice, docetaxel was effective in some patients who were resistant to cisplatin [19]. In addition, additive effects are confirmed between cisplatin and docetaxel, and major side effects of the two drugs are different.

This was a phase II study to determine the usefulness and safety of combination chemotherapy of cisplatin (5-day continuous infusion) and docetaxel for the treatment of advanced NSCLC. The response rate in this study was 49%, which is higher than with docetaxel alone. In comparison with other combination therapies, response rates were 39–42% for cisplatin (bolus) and docetaxel [20, 21], and 58.5% for cisplatin (infusion) and irinotecan with G-CSF. In combination with cisplatin (bolus) and newly developed anticancer agents, the response rates were 44% with paclitaxel [22], 31% with gemcitabine [23], and 26% with vinorelbine [24]. Although these studies differed as regards patients' backgrounds, generally, combination therapies showed better response rates than docetaxel alone.

In our study, side effects predominantly involved hematological toxicity (leukopenia, neutropenia, and anemia). Fever associated with neutropenia was observed in 8 (23%) of 43 patients, and they were treated by administering antibiotics. Hematological toxicities were similar to those in other combination therapies [20, 21]. Nonhematological toxicities were mild, with only 1 patient showing an increased creatinine level of grade 3. The increase was transient, and soon returned to normal. Peripheral edema was observed in only 16%, which was markedly lower than the 24–46% found in other studies [5, 25, 26]. When accumulated doses of docetaxel exceeded 500 mg/m^2, the incidence of edema increased, and at a dose of 85 mg/m^2 or less, eruption was not observed [27]. The dosage was 60 mg/m^2 in our study, and no patients received 500 mg/m^2. There were no side effects concerning hypersensitivity or treatment-related deaths.

We carried out a phase II study of combination treatment of cisplatin (5-day continuous infusion) and docetaxel in 43 patients with NSCLC. The response rate was 49%, and median survival time was 47 weeks. A major side effect was neutropenia. A combination treatment of infusional cisplatin and docetaxel is a tolerable and active regimen for patients with advanced NSCLC. It is to be recommended as a candidate regimen in planning a phase III clinical study in advanced NSCLC, and this regimen will ultimately be evaluated in a phase III clinical study.

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Development of a Novel Computer-Aided Diagnosis System for Automatic Discrimination of Malignant From Benign Solitary Pulmonary Nodules on Thin-Section Dynamic Computed Tomography

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Objectives: As an application of the computer-aided diagnosis of solitary pulmonary nodules (SPNs), 3-dimensional contrast-enhanced (CE) dynamic helical computed tomography (HCT) was performed to evaluate temporal changes in the internal structure of nodules to differentiate between benign nodules (BNs) and malignant nodules (MNs).

Methods: There were 62 SPNs (35 MNs and 27 BNs) included in this study. Scanning (2-mm collimation) was performed before and 2 and 4 minutes after CE dynamic HCT. The CT data were sent to a computer, and the pixels inside the nodule were characterized in terms of 3 parameters (attenuation, shape index, and curvedness value).

Results: Based on the CT data at 4 (MN: 1.81–27.1, BN: −42.8 to −3.29) minutes after CE–dynamic HCT, a score of 0 or higher can be assumed to indicate an MN.

Conclusions: Three-dimensional computer-aided diagnosis of the internal structure of SPNs using CE dynamic HCT was found to be effective for differentiating between BNs and MNs.

Key Words: coin lesion, pulmonary, computer-aided design, lung neoplasms, radiographic image enhancement, tomography, x-ray computed

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The morphologic imaging diagnosis of solitary pulmonary nodules (SPNs) has been performed based on qualitative findings, mainly in computed tomography (CT) images, identified by diagnosticians when evaluating the characteristics of the nodule's margins, internal structure, and relations to surrounding structures.[1–3] The interpretation of these findings tends to differ, however, depending on the person performing the diagnosis, and diagnostic standards for differentiating between benign nodules (BNs) and malignant nodules (MNs) have yet to be established. The quantitative diagnosis of such lesions has been attempted based on the measurement of attenuation in the nodule. Attenuation has been used for the objective assessment of the internal structure of nodules and for the differential diagnosis of BNs and MNs.[4] There have also been reports on the use of contrast medium to evaluate changes in attenuation in nodules over time to differentiate between BNs and MNs.[5–8] In these studies, however, the attenuation in the nodules was measured in only a few slices. Moreover, because the region of interest (ROI) within the lesion was specified manually, the attenuation obtained showed a large degree of variation in different slices.

The use of helical scanning has facilitated the acquisition of volume data for the entire lesion, making it possible to analyze these image data using a computer.[9–11] In the present study, images of the entire lesion were obtained using contrast-enhanced (CE) dynamic helical computed tomography (HCT), and the changes in the density of the lesion over time were calculated with a computer and quantified in a 3-dimensional (3D) perspective for the differential diagnosis of BNs and MNs.

SUBJECTS AND METHODS

CT Imaging Conditions

Computed tomography images were obtained using an Xpress/SX system (Toshiba Corporation, Tokyo, Japan). The scanning parameters were a patient couch-top movement speed of 2 mm/s, a beam width of 2 mm, a tube voltage of 120 kV, a tube current of 200 mA, 1-second scanning, and an ROI of 200 mm. A total of 100 mL nonionic contrast medium (Iopamiron 300 Syringe; Nihon Schering, Tokyo, Japan) was injected at a rate of 2 mL/s using an autoinjector through a peripheral forearm vein. With the patient placed in the supine position and receiving supplemental oxygen via a nasal cannula (2 L/min), helical scanning covering the entire lesion (40–50 mm) was performed 3 times during breath-holding (before enhancement and 2 and 4 minutes after the start of

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contrast injection). Images were reconstructed at 1-mm intervals using a 180° algorithm.

Evaluation of CT Images

CT Image Processing

The tumor lesion was extracted from the thin-section CT images and then reconstructed to obtain a 3D CT image of the tumor.[9] The density was then calculated by characterizing the pixels inside the extracted nodule in terms of 3 parameters (attenuation, shape index, and curvedness value). Based on the calculated density values within each nodule before enhancement and 2 and 4 minutes after the start of injection, a linear discriminant function score was obtained for each time point.

Extraction of Lesions

After the reconstruction of 3D images from the thin-section CT images, ROIs containing the nodules were extracted from these images (Fig. 1). Using a deformable surface model, the nodules were then extracted from these ROIs.[9,12] In some cases, the nodules were located adjacent to the pleura. In such cases, preprocessing was required for extracting the region of the lung fields to separate the pleura from the nodules.[10] The segmentation of the nodule was based on a thresholding technique and selection of object connected components. In the present study, a method based on the deformable surface model proposed by Caselles et al[12] was used for extracting nodular regions with various density distributions.[10] This approach is based on deforming 3D surfaces, represented by level sets, toward the nodule boundary to be extracted in the 3D images. It automatically handles the changes in the surface topology during deformation. In this method, the nodular region is extracted by placing the initial curved surface within the nodule and then transforming the surface to conform to the margins of the nodule using a formula for the curved surface.[12] In this way, excessive overflow of blood vessels and bronchi relative to the curved surface can be prevented by adjusting the end points for curved surface transformation.[10]

Display and Assessment of Characteristic Values Within the Lesion

The pixels in the ROI, including the nodule, were expressed locally using a combination of 3 parameters: the attenuation, shape index, and curvedness value (Figs. 2, 3).[13,14]

The shape index and curvedness value are defined by the 3D curvature of the curved surface. The shape index ranges from 0 to 1. As the shape index approaches 0, the surface becomes increasingly convex (peak surface), and as the shape index approaches 1, the surface becomes more concave (pit surface). Thus, subtle curved surface structures can be expressed in numeric form. The curvedness value reflects the degree of curvature and ranges from 0 to 1. As the curvedness value approaches 0, the surface becomes flatter with less curvature. The concepts of the shape index and curvedness value can be easily understood when these 2 parameters are used for the curved surface of the tumor margins (boundary structures between the periphery of the nodule and the surrounding lung). These parameters, the shape index and curvedness value, obtained from the 3D curvature represent the concavoconvex structure of the curved surface and the degree of curvature of the curved surface, which are both determined from the relations between the target pixels and their adjacent pixels. These parameters can be regarded as indices of the uneven distribution of attenuation within the nodule. The histograms of the shape index, curvedness value, and attenuation within the nodule are obtained, and the scale of each histogram serves as a histogram characteristic value.[14] The Fisher linear discriminant classifier is commonly used in pattern classification and is an optimal classifier when the sample distributions are multivariate normal with equal covariance matrices.[15] The linear discriminant classifier was designed by using the histogram features. A leave-one-out procedure was performed to provide a less biased estimation of the performance of the linear discriminant classifier.[16] In this procedure, 1 nodule image is left out from the classifier design group and a linear discriminant function is formulated using the design group. The discriminant score is computed for the case that is left out by using the linear discriminant function obtained. This process cycles through the data set until every

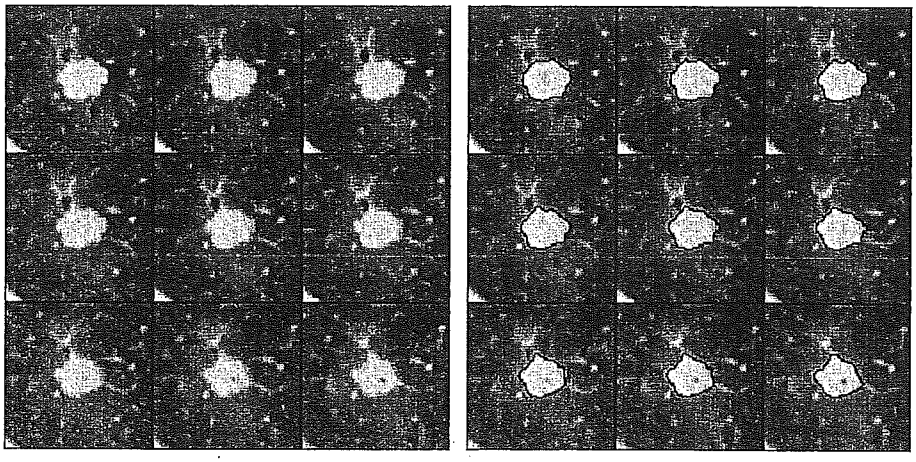

FIGURE 1. Extraction of a pulmonary nodule (case 8).

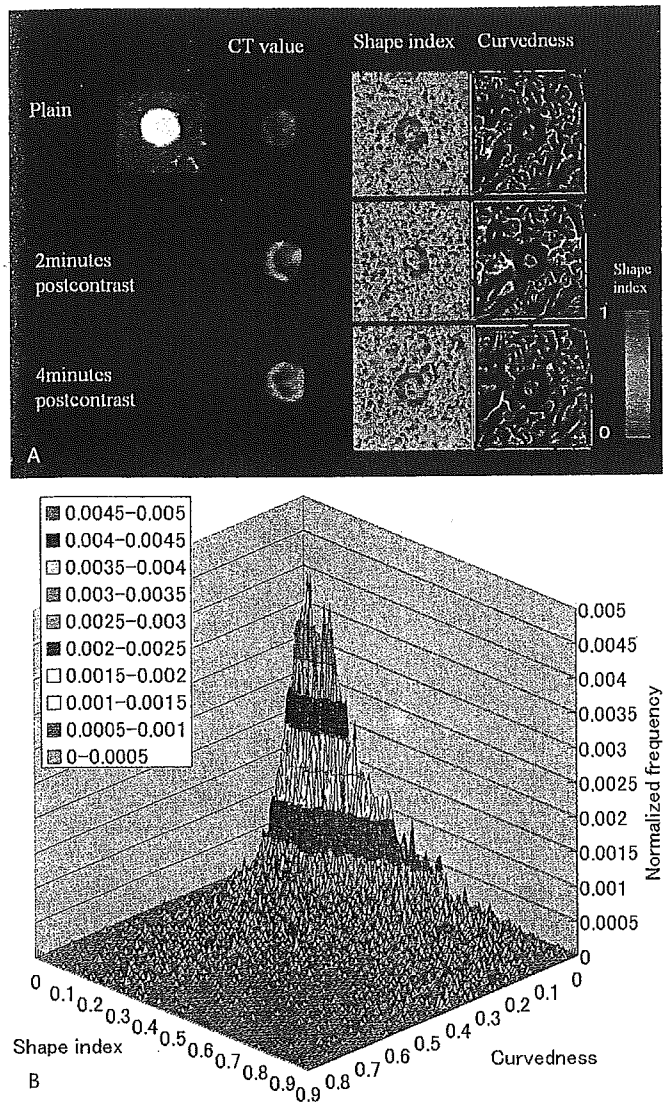

FIGURE 2. A, Characteristic values for a benign nodule (BN; case 37). B, Shape spectra showing a combination of the shape index and curvedness value 4 minutes after contrast enhancement. The *z* axis shows frequency. Most pixels inside a BN have a shape index close to 0 and a low curvedness value. This indicates that pixels inside a BN are mainly of the peak surface type with a smoothly curved surface.

nodule image is used. The overall evaluation time was approximately 4 minutes, including selection of the ROI from the CT images, extraction of the nodule, characterization of the pixels inside the nodule, and calculation of the linear discriminant function scores.

In the present study, each linear discriminant function score was computed from the shape index, curvedness value, and attenuation at each time point: before contrast enhancement and 2 and 4 minutes after the start of enhancement. The malignancy of SPNs was then retrospectively analyzed based on the scores obtained.

In addition, receiver operating characteristic curves were used to evaluate the effectiveness of the linear discriminant score in differentiating between BNs and MNs. Statistical significance was assessed using the unpaired Student *t* test.

Subjects

The subjects in this study were 72 consecutive patients who had undergone chest CT for the detailed examination of SPNs at our department from February 1998 to April 2000. They had only 1 target nodule by CT. Ten patients were not included in the assessment in this study, because CT images of the entire lesion could not be obtained over time (before contrast enhancement and 2 and 4 minutes after contrast enhancement) in these patients because of patient respiratory motion. The remaining 62 patients were evaluated. The mean

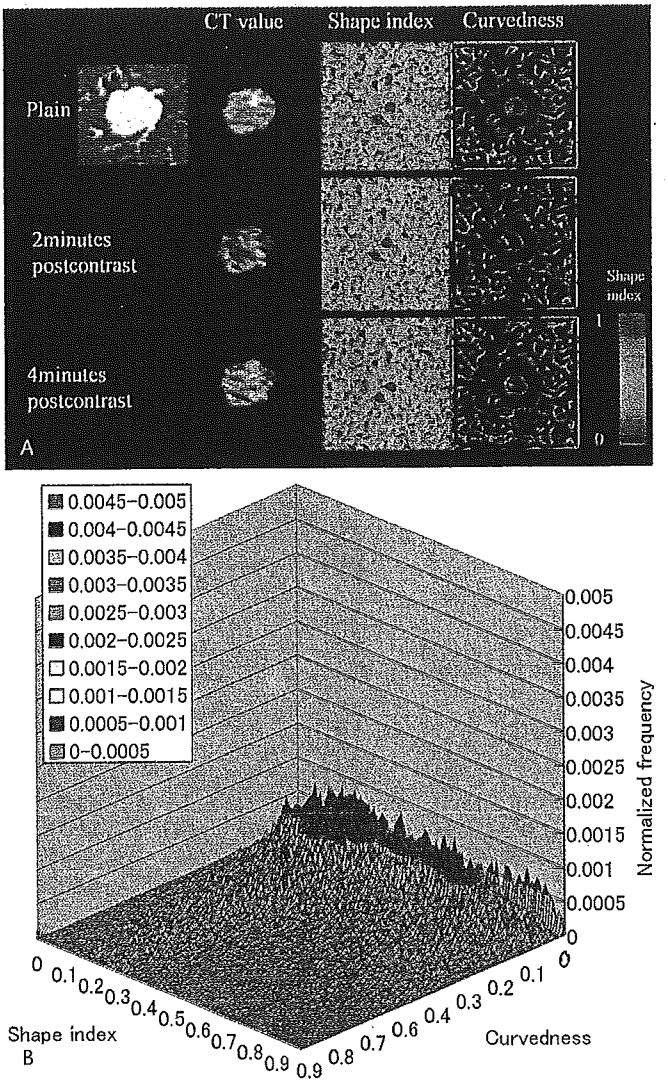

FIGURE 3. A, Characteristic values for a malignant nodule (MN; case 8). B, Shape spectra showing a combination of the shape index and curvedness value 4 minutes after contrast enhancement. Compared with a benign nodule (BN), pixels inside an MN show a wide distribution of shape index values, ranging from 0 to 1, and a high curvedness value. This indicates that pixels inside an MN tend to have pixels other than the peak surface type compared with a BN.

diameter of all nodules was 14 mm (range: 5–25 mm), with a mean diameter of 17 mm (range: 8–25 mm) for MNs and 10 mm (range: 5–17 mm) for BNs. These nodules were classified as 35 malignant lesions (primary lung carcinoma in 33 patients [adenocarcinoma in 31 patients and squamous cell carcinoma in 2 patients] and metastatic pulmonary tumor in 2 patients [breast cancer and colon cancer in 1 patient each]; Table 1) and 27 benign lesions (nonspecific benign lesion in 16 patients, granuloma in 4 patients, hamartoma in 3 patients, organized pneumonia in 1 patient, tuberculoma in 1 patient, pulmonary infarction in 1 patient, and pneumonia in 1 patient; Table 2). The primary lung carcinomas were surgically resected in 29 patients, with the exception of 4 patients with adenocarcinoma. The pathologic stage of the resected tumor was histopathologically graded as stage I in 24 patients, stage II in 1 patient, and stage III in 4 patients. The degree of differentiation of the adenocarcinomas in 27 patients was highly differentiated in 11 patients, moderately differentiated in 14 patients, and poorly differentiated in 2 patients. Metastatic lung tumors were found in these 2 patients based on CT fluoroscopy-guided biopsy. Benign lesions were surgically resected in 4 patients (granuloma, organized pneumonia, tuberculoma, and pulmonary infarction) and identified based on CT fluoroscopy-guided biopsy in 6 patients (hamartoma in 3 patients and granuloma in 3 patients). The nodule disappeared in 1 patient with pneumonia, whereas the remaining 16 patients were diagnosed with a nonspecific benign lesion based on the shape of the lesion and changes in

TABLE 1. Characteristics and Quantitative Characterization of MNS

Patient No.	Age (y)	Sex	Diameter (mm)	Lobe	Linear Discriminant Function			Diagnosis
					Non-Enhanced	2 Min*	4 Min*	
1	5	F	18	RU	1.49	4.42	17.42	W/d AD
2	48	F	18	LU	1.64	10.92	16.95	W/d AD
3	77	M	12	LU	2.4	7.14	24.9	AD
4	68	F	22	RL	4.01	15.77	21.8	M/d AD
5	68	M	11	LU	0.85	6.77	8.18	M/d AD
6	54	F	22	LL	1.96	13.29	14.84	Breast matastasis
7	63	M	12	RU	1.41	9.72	14.77	W/d AD
8	63	M	17	RL	2.25	2.65	9.38	M/d AD
9	55	F	18	LU	3.07	12.34	19.49	M/d AD
10	44	M	15	RU	4.65	4.97	11.71	M/d AD
11	61	F	20	RL	3.21	10.01	17.65	W/d AD
12	84	M	19	LU	3.24	11.07	13.36	AD
13	57	M	15	RU	1.88	9.82	21.61	M/d AD
14	71	M	20	LU	1.11	9.83	13.27	AD
15	61	M	13	RM	1.99	14.51	12.78	Colon matastasis
16	51	F	8	LU	0.93	1.58	9.09	W/d AD
17	51	M	18	LU	3.29	13.02	9.37	P/d AD
18	67	M	15	RU	0.89	12.23	14.58	M/d AD
19	62	F	11	RU	0.87	2.39	22.01	W/d AD
20	61	F	25	RM	1.58	9.56	8.77	W/d AD
21	49	F	19	RM	3.16	13.22	22.45	M/d AD
22	63	F	14	LU	1.32	11.5	9.56	W/d AD
23	45	M	12	RU	1.25	0.58	5.44	M/d AD
24	52	M	18	LU	3.4	9.82	13.59	M/d AD
25	56	F	13	RU	0.28	8.12	17.16	W/d AD
26	53	M	24	RU	2.77	14.89	22.35	M/d AD
27	65	F	23	LU	4.28	16.62	27.11	M/d AD
28	71	F	10	RU	−2.16	5.13	5.27	W/d AD
29	66	F	19	LU	2.68	6.95	18.72	P/d AD
30	40	F	19	RL	2.56	5.87	17.62	M/d AD
31	77	F	16	RU	−0.48	5.56	1.81	M/d AD
32	66	M	15	LL	2.26	23.14	2.95	AD
33	80	M	11	RL	0.13	2.19	22.44	M/d AD
34	68	F	19	RU	5.01	14.78	20.36	W/d AD
35	58	F	24	RL	3.25	15.25	22.56	M/d AD

*Time after administration of contrast agent.

AD indicates adenocarcinoma; 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; SQ, squamous cell carcinoma; W/d, well differentiated.

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

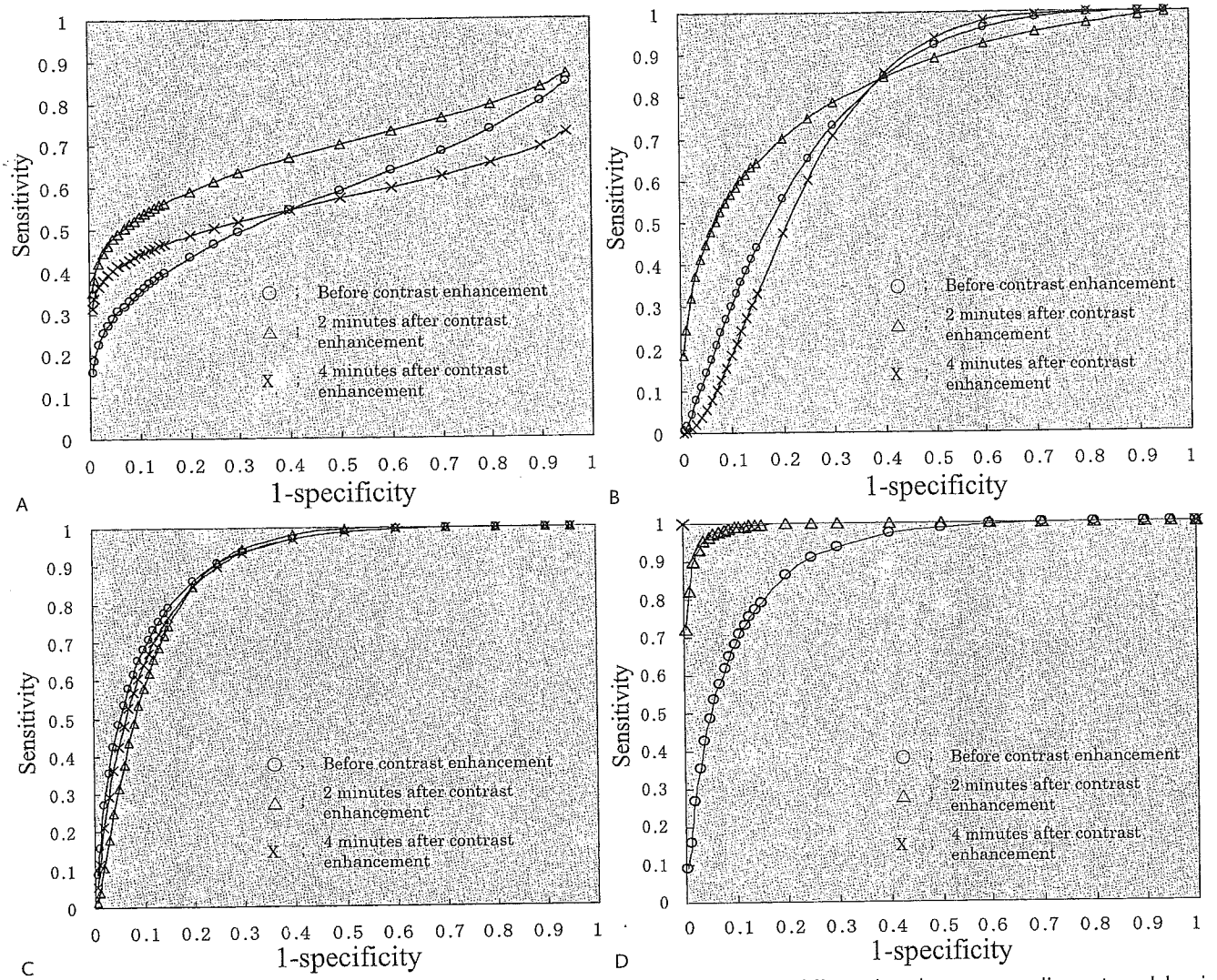

FIGURE 4. Receiver operating characteristic curves for each parameter used to differentiate between malignant and benign nodules. The open circles (○) are before contrast enhancement, and the open triangles (△) and crosses (x) are 2 and 4 minutes after contrast enhancement, respectively. A, Areas under 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

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

[a]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.