**Table 1** Toxicities

| | Treatment | | Toxicity grade | | | | |
|---|---|---|---|---|---|---|---|
| | VNR (mg/m$^2$) | Gefitinib (mg per day) | WBC | Neu | Hb | Plt | FN |
| Case 1 | 25 | 250 | G3 | G4 | G3 | G3 | G3 |
| | 20[a] | 250[a] | G3 | G4 | G3 | G0 | G3 |
| Case 2 | 25 | 250 | G4 | G4 | G0 | G0 | – |
| | 20[b] | –[b] | G2 | G2 | G1 | G0 | – |
| Case 3 | 25 | 250 | G4 | G4 | G2 | G4 | G4 |
| Case 4 | 25 | 250 | G3 | G4 | G0 | G0 | G3 |
| | –[b] | 250[b] | G0 | G0 | G0 | G0 | – |

G: NCI-CTC grade; VNR: vinorelbine; FN: febrile neutropenia.
[a] Second course with dose reduction of vinorelbine.
[b] Treatment after combination chemotherapy in the trial.

Toxicities of each case in this combination chemotherapy and in the treatment after the study are summarized in Table 1. One patient (Case 4) continued gefitinib monotherapy after the combination chemotherapy, and experienced no grade 3–4 hematological toxicities. Another patient (Case 2) received two cycles of vinorelbine monotherapy without gefitinib after combination chemotherapy. Vinorelbine alone also induced appreciable neutropenia but to a lesser degree (grade 0 in the first cycle and grade 2 in the second cycle). Case 1 received second cycle of the combination of gefitinib and vinorelbine with a dose reduction of vinorelbine to 20 mg/m$^2$ because the disease showed minor response. Although thrombocytopenia was not occurred in the second cycle, she again underwent severe neutropenia of 33 mm$^{-3}$ in nadir count on 13th day. These results indicate that severe myelotoxicity induced by gefitinib and vinorelbine combination cannot be ascribed to the accidentally high susceptibility of the four patients to one of these drugs, but rather to this combination itself. This toxicity is unique in that it appeared almost selectively to neutrophils. In three patients, the worst neutrophil counts were under 100 mm$^{-3}$. In contrast, lymphocyte counts were stable in all cases. Anemia and thrombocytopenia were also mild. Typical clinical course is shown in Fig. 1.The mechanisms by which gefitinib and vinorelbine combination induces severe neutropenia are not

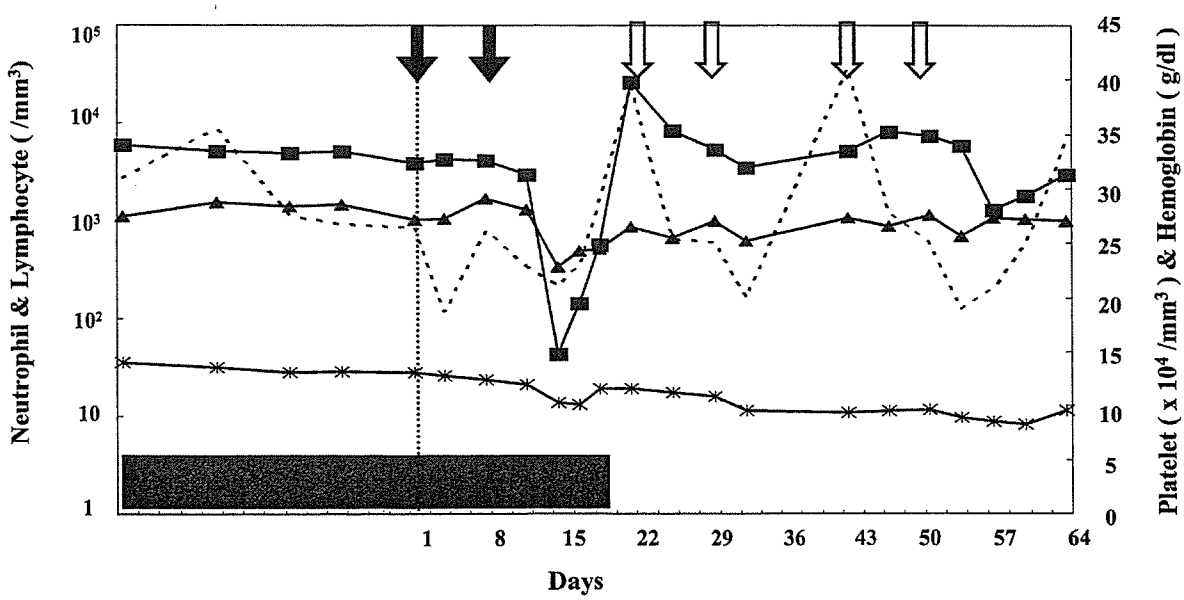


**Fig. 1** Clinical course and hematocyte counts of Case 2 (74-year-old female): (▬) gefitinib 250 mg per day oral administration; (➡) intravenous vinorelbine 25 mg/m$^2$; (⇨) intravenous vinorelbine 20 mg/m$^2$; (■) neutrophil count; (▲) lymphocyte count; (···) platelet count; (✳) hemoglobin value.

known at present. Gefitinib is not myelotoxic even in higher doses in phase I study [7]. When combined with cisplatin and gemcitabine or with carboplatin and paclitaxel, gefitinib did not exert an appreciable increment of myelotoxicity [2,3]. Neutropenia is one of the common toxicities of vinorelbine, but usually well tolerated. Hence, severe myelotoxicity observed in the combination of gefitinib and vinorelbine is beyond the range of the toxicities of each drug. One possible explanation is drug interaction. Vinorelbine is metabolized in liver microsomes in the presence of NADPH-generating systems. The main enzyme involved is CYP3A4 [8]. Because CYP3A4 is also involved in the metabolism of gefitinib (personal communication), the metabolism of each drug may be modulated in the presence of the other. Serum concentration of vinorelbine may have been increased by the presence of gefitinib, resulting in the augmentation of the myelotoxicity of vinorelbine. However, other toxicities of vinorelbine such as decreased intestinal movement or thrombocytopenia did not seem to be intensified in gefitinib and vinorelbine combination. Therefore, the severe and selective neutropenia observed is not explained simply by drug interaction. Another explanation is the synergy of the two drugs on neutrophils alone. For this to happen, the precursor cells of neutrophils have to express EGFR. However, to date there is no supportive evidence for the expression of EGFR on hematocytes. The precursor cells of neutrophils may express unknown target molecules of gefitinib different from EGFR.

Molecular-targeted drugs may exert unpredictable severe toxicities because of their novel mechanisms of action. Life-threatening interstitial lung disease of gefitinib was already reported, for example, in Ref. [9]. In this study, we experienced another unpredictable severe toxicity of gefitinib combined with vinorelbine. Although clinical use of this combination cannot be recommended, analysis of the mechanism of neutropenia induced by gefitinib and vinorelbine combination is crucial for future use of gefitinib and other molecular-targeted drugs.

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13 November 2003

INTERNAL MEDICINE

PICTURES IN CLINICAL MEDICINE

# Metastatic Serous Adenocarcinoma Arising in the Adnexa Uteri and Forming Pleural Cysts on the Diaphragmatic Pleura

Kunimitsu Kawahara[1], Masashi Kobayashi[2], Shinji Sasada[2], Kaoru Matsui[2] and Teruo Iwasaki[3]

**Key words:** pleural cyst, serous adenocarcinoma, adnexa uteri, pleural metastasis

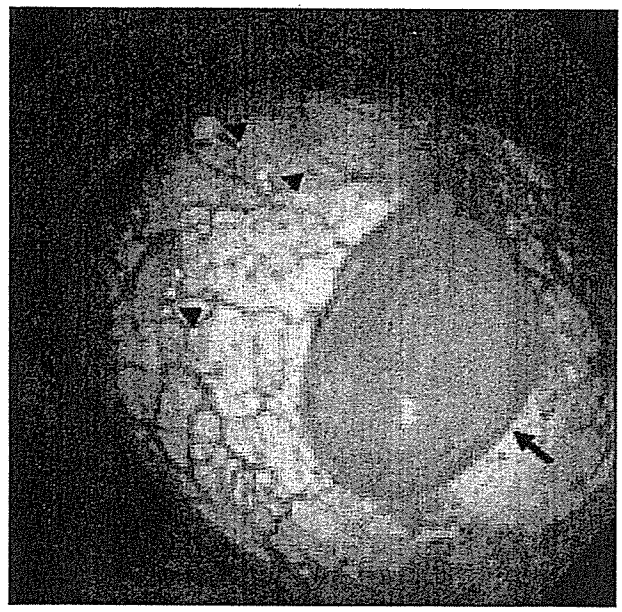

**Figure 1. Left thoracoscopy showed a pleural cyst measuring 1.5cm in diameter (arrow) and adjacent daughter cysts (arrowheads) on the diaphragmatic pleura.**

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A 74-year-old woman consulted our hospital complaining of cough that had persisted for the previous 3 months. Chest computed tomographic (CT) scan showed bilateral pleural effusion without any pulmonary lesions. Pleural effusion cytology showed adenocarcinoma. Barium enema, gastroduodenoscopy and abdominal CT did not demonstrate any abnormal findings. Serum CEA, NSE and CYFRA21-1 were 26.8 (cutoff: 5) ng/ml, 43.7 (cutoff: 10) ng/ml and 67.5 (cutoff: 3.5) ng/ml, respectively. After removal of 1,500 ml of pleural effusion, left thoracoscopy showed a few eccentric pleural cysts on the diaphragmatic pleura (Fig. 1). No pleural nodule suggestive of malignancy was recognized. The content of the cyst was clearly serous fluid. Pathologic examination of the cyst showed a small focus of adenocarci-

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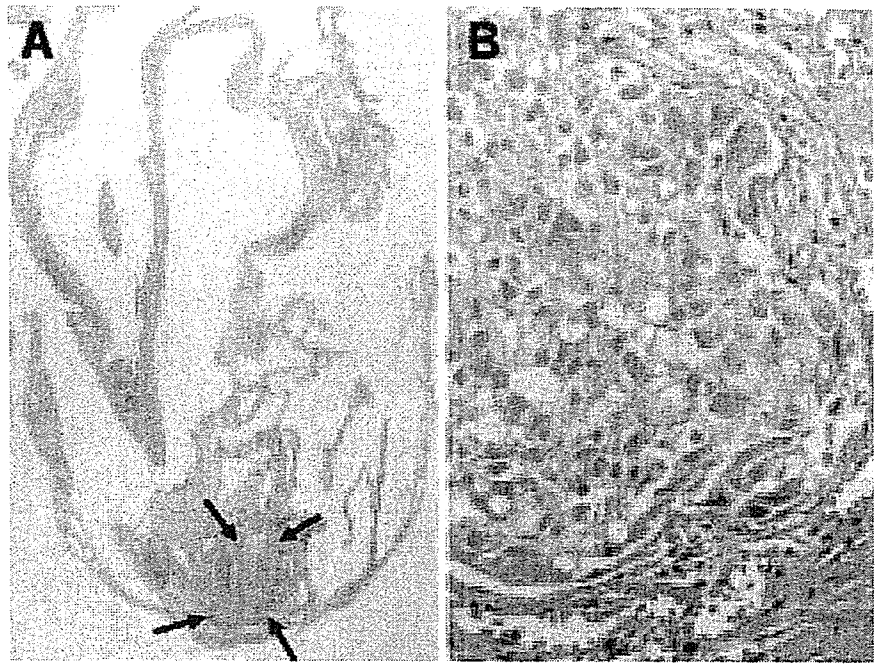


**Figure 2. A: Microscopically, the pleural cyst was unilocular. A small focus of adenocarcinoma was recognized in the cyst wall (arrows). B: Most tumor cells had abundant clear or pale eosinophilic cytoplasm, oval nuclei and inconspicuous nucleoli. Stain: hematoxylin and eosin; magnification A: ×2.5, B: ×100.**

noma (Fig. 2a, b). Immunohistochemical studies showed that these carcinoma cells were positive for AE1/AE3, EMA, CA125 and cytokeratin (CK)-7, but negative for CEA, TTF-1 and CK-20. The tentative diagnosis was Stage IV pulmonary adenocarcinoma. Systemic chemotherapy achieved stable disease. Six months later, the patient underwent surgery for right uterine adnexal tumor with diffuse peritoneal dissemination. Pathologic examination of the resected specimen demonstrated that the tumor was a poorly differentiated serous adenocarcinoma arising in the right adnexa uteri. Conclusively, we diagnosed pleural lesions as distant metastases of uterine adnexal serous adenocarcinoma. To our knowledge, the formation of these pleural cysts by metastatic carcinoma has not yet been reported in the literature. We propose two possible explanations for cyst formation by metastatic lesions: 1) localized edema in the submesothelial space due to carcinomatous obstruction of superficial vessels in the pleura caused pleural cysts; and 2) metastatic cancer cells in the pleura produced serous fluid in the submesothelial space and formed cystic lesions. The elucidation of its etiology, however, requires the accumulation of additional cases. Thoracic oncologists and pathologists should be aware of the varied gross manifestations of metastatic adenocarcinoma to the pleura and should bear in mind the differential diagnoses of pleural cysts.

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ORIGINAL REPORT

# Phase II Study of Etoposide and Cisplatin With Concurrent Twice-Daily Thoracic Radiotherapy Followed by Irinotecan and Cisplatin in Patients With Limited-Disease Small-Cell Lung Cancer: West Japan Thoracic Oncology Group 9902

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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A B S T R A C T

**Purpose**

We initially conducted a randomized phase II study to compare irinotecan and cisplatin (IP) versus irinotecan, cisplatin, and etoposide (IPE) after etoposide and cisplatin (EP) with concurrent twice-daily thoracic radiotherapy (TRT) in limited-disease small-cell lung cancer (LD-SCLC). We amended the protocol to evaluate IP after EP with concurrent twice-daily TRT in a single-arm phase II study because of an unacceptable toxicity in IPE.

**Patients and Methods**

Previously untreated patients with LD-SCLC were treated intravenously with etoposide 100 mg/m$^2$ on days 1 through 3 and cisplatin 80 mg/m$^2$ on day 1 with concurrent twice-daily TRT (1.5 Gy per fraction, a total dose of 45 Gy) beginning on day 2 followed by three cycles of irinotecan 60 mg/m$^2$ on days 1, 8, and 15 and cisplatin 60 mg/m$^2$ on day 1 of a 4-week cycle.

**Results**

Of the 51 patients enrolled, 49 patients were assessable for response and toxicity. The overall response rate and complete response rate were 88% and 41%, respectively. The median survival time for all patients was 23 months. The 2-year and 3-year survival rates were 49% and 29.7%, respectively. The median progression-free survival was 11.8 months. The major toxicities observed were neutropenia (grade 4, 84%), febrile neutropenia (grade 3, 31%), infection (grade 3 to 4, 33%), electrolytes imbalance (grade 3 to 4, 20%), and diarrhea (grade 3 to 4, 14%).

**Conclusion**

EP with concurrent twice-daily TRT followed by the consolidation of IP appears to be an active regimen which deserves further phase III testing in patients with LD-SCLC.

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## INTRODUCTION

Small-cell lung cancer (SCLC), which accounts for approximately 15% of all lung cancer cases, is clinically categorized as the two stages, limited disease and extensive disease. Two meta-analyses have shown the combined modality of chemotherapy and thoracic radiotherapy (TRT) to improve the survival of patients with limited-disease (LD-) SCLC in comparison to chemotherapy alone.[1,2] The schedule, dose, and fractionation of TRT have previously been examined in patients with LD-SCLC in several randomized controlled studies.[3-7] On the basis of the results of these studies, etoposide and cisplatin (EP) with concurrent twice-daily TRT is currently a standard care for the treatment for LD-SCLC. However, the 5-year survival rate is less than 30%, and most patients experience a relapse of the primary tumor or distant metastasis.[3-6] To further improve the therapeutic efficacy, one approach is to develop a new chemoradiotherapy regimen incorporating with a novel active agent.

Irinotecan hydrochloride, a camptothecin derivative, is among the most active chemotherapeutic agents against SCLC with a response rate of 37% as a single agent.[8] A randomized phase III study revealed that irinotecan and cisplatin (IP) was superior to EP in patients with extensive-disease SCLC (ED-SCLC).[9] However, the role of IP in the treatment of LD-SCLC remains to be defined. To clarify the role of this combination regimen in LD-SCLC, we initially conducted a randomized phase II study to

compare two consolidation chemotherapy regimens, IP versus irinotecan, cisplatin and etoposide (IPE), after EP with concurrent twice-daily TRT in LD-SCLC.[10] However, EP with concurrent twice-daily TRT followed by IPE was not feasible because of unacceptable toxicity including grade 4 neutropenia (92%), grade 4 diarrhea (25%), grade 4 infection (25%) and one treatment-related death. We therefore amended the protocol to evaluate EP with concurrent twice-daily TRT followed by consolidation therapy with IP in a single-arm phase II study and herein report the results of this study.

## PATIENTS AND METHODS

### Eligibility Criteria

Patients with histologically or cytologically confirmed LD-SCLC (stage I disease was excluded) were eligible for this study. A limited stage was defined as disease confined to one hemithorax, the mediastinum, and the bilateral supraclavicular area. Cases with a small amount of pleural effusion and a negative cytology were included in the limited-stage group. Other eligibility criteria included the following: no prior chemotherapy or radiotherapy; measurable disease; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; age between 20 and 70 years; life expectancy of at least 3 months; adequate baseline organ function defined as leukocyte count ranging from 4,000 to 12,000/mm$^3$, hemoglobin concentration of at least 9.5 g/dL, platelet count at least 100,000/mm$^3$, AST and ALT 2.0× the upper limit of the normal range (ULN) or less, serum total bilirubin 1.5 mg/dL or less, serum creatinine ULN or less, 24-hour creatinine clearance of at least 60 mL/min, and $Pao_2$ at rest of at least 70 mmHg. The radiation portal should be equal or less than half of one lung.

The patients were ineligible if they had the following criteria: interstitial pneumonitis or pulmonary fibrosis; other respiratory diseases that precluded TRT; malignant pleural effusion or malignant pericardial effusion; active concomitant or a recent (< 3 years) history of any malignancy; uncontrolled angina pectoris, myocardial infarction less than 3 months before the enrollment or congestive heart failure; uncontrolled diabetes mellitus or hypertension; severe infection; intestinal paralysis or obstruction; pregnancy or lactation; or other serious concomitant medical conditions. The study protocol was approved by each institutional review board for clinical use. All patients gave their written informed consent before enrollment.

### Study Evaluation

The pretreatment baseline evaluation included a complete medical history and physical examination, a CBC, blood chemistry studies, flexible bronchoscopy, electrocardiography, chest radiography, computed tomography of the chest, computed tomography or ultrasound study of the abdomen, computed tomography or magnetic resonance imaging of the brain, bone scintigraphy and bone marrow aspiration with or without biopsy. A CBC and blood chemistry studies were repeated every week. At the end of the study, all of these studies except for flexible bronchoscopy and bone marrow aspiration were repeated unless the patient had stable or progressive disease.

### Treatment Schedule

The patients initially received induction chemoradiotherapy consisting of etoposide 100 mg/m$^2$ on day 1 through 3 and cisplatin 80 mg/m$^2$ on day 1 with concurrent twice-daily TRT. After the induction chemoradiotherapy, the patients received three cycles of consolidation chemotherapy consisting of irinotecan 60 mg/m$^2$ on days 1, 8, and 15 and cisplatin 60 mg/m$^2$ on days 1. Consolidation chemotherapy was repeated every 4 weeks for three cycles.

The first cycle of consolidation chemotherapy was begun 4 week after the initiation of induction chemoradiotherapy if the leukocyte count was at least 4,000/mm$^3$; the platelet count was at least 100,000/mm$^3$; AST and ALT 2.0× ULN or less; serum bilirubin 1.5 mg/dL or less; serum creatinine of ULN or less; the patient did not have fever (≥ 38°C), diarrhea within the past 24 hours, or intestinal paralysis or obstruction; and $Pao_2$ of at least 70 mmHg. The subsequent cycle of consolidation chemotherapy was repeated if the leukocyte count was at least 3,500/mm$^3$; the platelet count was at least 100,000/mm$^3$; AST and ALT 2.0× ULN or less; serum bilirubin 1.5 mg/dL or less; serum creatinine ULN or less; the patient did not have fever (≥ 38°C), diarrhea within the past 24 hours, or intestinal paralysis or obstruction. The use of granulocyte colony-stimulating factor (GCSF) was recommended after day 4. However, its administration was withheld on the day of administration of irinotecan.

TRT was performed with 6 MV or higher photons from a linear accelerator and began on day 2 of the induction chemoradiotherapy. Patients received 1.5 Gy per fraction twice daily with at least a 4-hour interval (preferably a 6-hour interval or more) between each fraction over a 3-week period (a total dose of 45 Gy). A radiation field included the primary tumor, the bilateral mediastinal and ipsilateral hilar lymph nodes with a margin of 1.5 to 2.0 cm. Radiation to the supraclavicular lymph nodes was administered only if they were involved. The inferior border extended 5 cm below the carina or to a level including ipsilateral hilar structures, whichever was lower. After initial irradiation with a dose of 30 Gy, off-cord (ie, the spinal cord was outside the field) oblique boost fields were used. The radiation field in the afternoon was not different from that in the morning. Computed tomography planning was not required and lung density corrections were not performed. Prophylactic cranial irradiation (PCI) was administered to the patients achieving complete response or good partial response with a total dose of 25 Gy in 10 fractions.

### Dose Modification

Dose modification based on the toxicity of the induction chemoradiotherapy was not allowed at the time of the first administration of IP. In each cycle of IP, irinotecan on day 8 or 15 was withheld if a leukocyte count of less than 2,000/mm$^3$ or a platelet count of less than 50,000/mm$^3$ was determined, or if a patient had fever (≥ 38°C) or grade 2 or higher hepatotoxicity or any diarrhea within the last 24 hours or intestinal paralysis or obstruction. In the second and the third cycle of consolidation chemotherapy, the dose modification was made as follows. If a leukocyte nadir count of less than 1,000/mm$^3$ or a neutrophil nadir count of less than 500/mm$^3$ for 3 or more days or if febrile neutropenia developed or if a platelet nadir count of less than 25,000/mm$^3$ was observed or if grade 2 hepatotoxicity or diarrhea was observed, irinotecan was decreased by 10 mg/m$^2$ in the subsequent cycle, if grade 2 or lower renal toxicity was observed during the previous course of treatment, only cisplatin decreased by 25%, if grade 3 or higher nonhematologic toxicity (excluding nausea, vomiting, and hair loss) developed, then cisplatin decreased by 25% and irinotecan decreased by 10 mg/m$^2$ in the following cycle. The patients were removed from the study if the following toxicities were observed: grade 4 diarrhea; grade 3 or higher renal toxicity or creatinine of at least 2.0 mg/dL; grade 3 or higher hepatotoxicity; grade 2 or higher pulmonary toxicity or $Pao_2$ at rest less than 60 mmHg.

### Evaluation

The Response Evaluation Criteria in Solid Tumors (RECIST) were used for the response assessment.[11] Toxicity was evaluated according to the National Cancer Institute–Common Toxicity Criteria (version 2.0). An extramural review was conducted to validate the eligibility of the patients, staging, and response.

### Statistical Analysis

The primary end point of this study was the 2-year survival rate. We calculated the sample size based on Fleming's single-stage design of the phase II study.[12] We set a 2-year survival rate of 35% as a baseline survival rate and 20% as the high level of interest with a power of 0.9 at a one-sided significance level of .05, requiring an accrual of 53 eligible patients. The study was initially begun as a randomized phase II study to compare two consolidation arms, namely IP versus IPE after concurrent chemoradiotherapy. Because of the unacceptable toxicity in the triplet regimen, the study was modified to a single-arm phase II study to evaluate IP after EP with concurrent TRT and 11 patients in the IP arm were included in the analysis of this study.

The duration of survival was measured from the day of entry onto the study, and the overall survival curve and progression-free survival curve were calculated according to the method of Kaplan and Meier.[13]

### Patients Characteristics

Between February 2000 and November 2002, 51 patients were enrolled onto this study. Table 1 lists the baseline characteristics of the patients. Two patients were considered to be ineligible because a secondary primary tumor was found after the administration of EP with concurrent TRT. Therefore, 49 patients were assessable for response and toxicity.

### Treatment Administration

Seven patients were removed from the study after the administration of EP with concurrent TRT because of treatment delay due to toxicity (six patients) and patient rejection (one patient). Eight patients each discontinued the treatment after each cycle of IP. The major reasons for the discontinuation of IP included treatment delay due to toxicity (three patients), diarrhea (three patients), and ileus (three patients), patient rejection (two patients), and the doctor's judgment (two patients). Overall, 34 patients (69%) received at least two cycles of IP and 26 patients (53%) completed the entire treatment. Irinotecan was omitted in 35 (11%) of 306 cycles. The dose-intensity of irinotecan was 30.5 mg/m$^2$/wk (68% of the planned dose) and cisplatin 11.6 mg/m$^2$/wk (77% of the planned dose) in the consolidation chemotherapy.

### Response and Survival

On an intention-to-treat basis, the overall response rates and the complete response rates were 88% (95% CI, 78.6% to 96.9%) and 41%, respectively. After a median follow-up of 29.9 months, the median survival time for all patients was 23 months (Fig 1). The 2-year and 3-year survival rates were 49% and 29.7%, respectively. The median progression-free survival was 11.8 months (Fig 2).

### Toxicity

Tables 2 and 3 show the major toxicities. Grade 4 neutropenia was observed in 80% of the patients and 10 (20%) patients had febrile neutropenia in concurrent chemoradiotherapy, whereas grade 4 neutropenia was observed in 40% of the patients and seven patients (17%) had febrile neutropenia in consolidation chemotherapy. In contrast, anemia and thrombocytopenia were relatively mild. One patient had grade 4 esophagitis in concurrent chemoradiotherapy. In the consolidation chemotherapy, grade 3 or 4 diarrhea was observed in six patients (14%) and grade 3 or 4 infection was observed in seven patients (17%). Two patients had grade 3 or 4 radiation pneumonitis. Grade 4 adhesive ileus developed in a patient who had a history of abdominal surgery and ileus. The major toxicities observed through the entire course of the treatment were neutropenia (grade 4, 84%), febrile neutropenia (grade 3, 31%), infection (grade 3 to 4, 33%), electrolytes imbalance (grade 3 to 4, 20%) and diarrhea (grade 3 to 4, 14%). There was one treatment-related death caused by radiation pneumonitis.

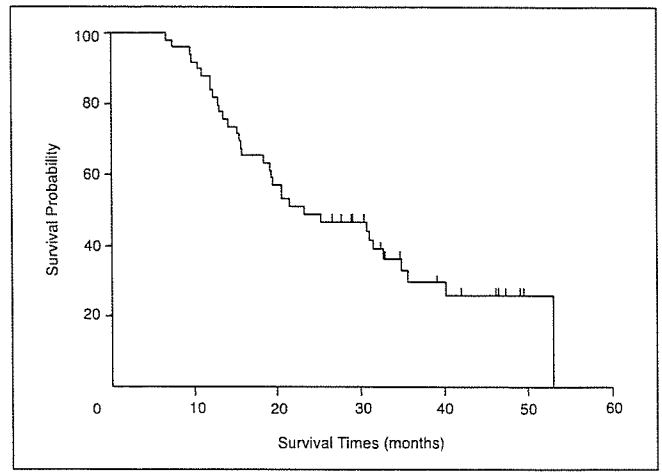


**Fig 1.** Kaplan-Meier survival curve of 49 eligible patients with limited-disease small-cell lung cancer. The median survival time was 23 months, and the 2-year and 3-year survival rates were 49% and 29.7%, respectively.

### Patterns of Relapse

Table 4 lists first sites of relapse. Of 12 patients (24%) with local relapse (defined as relapse within the radiation portal), only one had a relapse solely at locoregional sites and 11 at both local and distant site including three with brain metastasis. Of 27 patients (55%) with distant relapse only, 13 had brain metastasis. Overall, 16 patients (33%) showed brain metastasis as the initial site of relapse, and eight of them had received PCI.

**Table 1.** Patient Characteristics (N = 51)

| Characteristic | No. | % |
|---|---|---|
| Age, years | | |
| Median | 62 | |
| Range | 45-70 | |
| Sex | | |
| Male | 42 | 82 |
| Female | 9 | 18 |
| ECOG performance status | | |
| 0 | 22 | 43 |
| 1 | 28 | 55 |
| 2 | 1 | 2 |
| Stage | | |
| II | 2 | 4 |
| IIIA | 35 | 69 |
| IIIB | 14 | 27 |

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

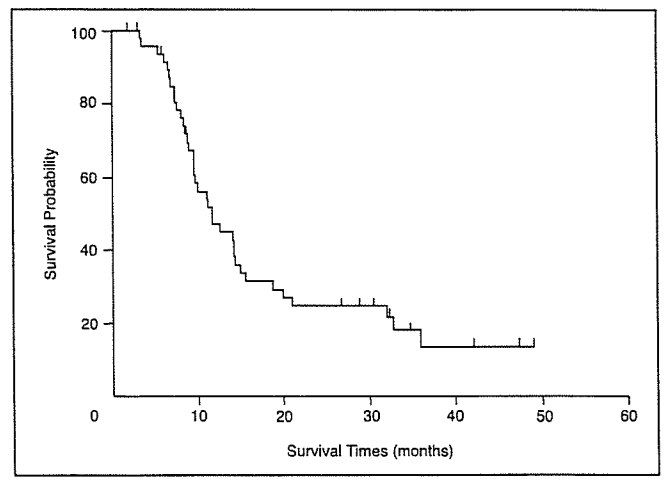


**Fig 2.** Kaplan-Meier progression-free survival curve of 49 eligible patients with limited-disease small-cell lung cancer. The median progression-free survival time was 11.8 months.

**Table 2.** Major Toxicities During Concurrent Chemoradiotherapy (n = 49)

| Toxicity | Grade 3 | | Grade 4 | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Hematologic | | | | |
| Leukopenia | 27 | 55 | 19 | 39 |
| Neutropenia | 8 | 16 | 39 | 80 |
| Anemia | 2 | 4 | 1 | 2 |
| Thrombocytopenia | 10 | 20 | 0 | 0 |
| Febrile neutropenia | 10 | 20 | 0 | 0 |
| Nonhematologic | | | | |
| Nausea/vomiting | 7 | 14 | 0 | 0 |
| Diarrhea | 0 | 0 | 0 | 0 |
| Constipation | 0 | 0 | 0 | 0 |
| Infection | 9 | 18 | 0 | 0 |
| Mucositis | 0 | 0 | 0 | 0 |
| Esophagitis | 0 | 0 | 1 | 2 |
| Dyspnea | 1 | 2 | 0 | 0 |
| Pneumonitis | 0 | 0 | 0 | 0 |
| Hepatic | 0 | 0 | 0 | 0 |
| Electrolytes | 2 | 4 | 2 | 4 |

In this phase II study, we evaluated the consolidation of IP after EP with concurrent twice-daily TRT and thus achieved an overall response rate of 88%, a 2-year-survival rate of 49% and a 3-year-survival rate of 29.7%. Although the number of assessable patients was slightly smaller than the planned sample size, this study confirmed 24 2-year survivors, and the power calculation showed a 97% probability to correctly reject inactive treatment, thus yielding only a 35% or less 2-year-survival rate. These results are comparable to those in phase III studies evaluating EP with concurrent twice-daily TRT.[3-6] Jeremic et al[7] reported a better survival outcome by using daily carboplatin and etoposide with concurrent twice-daily TRT followed by EP. However, this result has rarely been confirmed by other groups. The Japanese Clinical Oncology Group (JCOG) conducted a pilot study to evaluate the feasibility of IP after EP with concurrent TRT (JCOG9903).[14] The doses and schedule of cisplatin, etoposide, and irinotecan and dose, fractionation and schedule of TRT were similar to ours. They reported that this regimen was feasible with a response rate of 97%, a 2-year survival rate of 41% and a 3-year survival rate of 38%, which are similar to those in our study. Although a phase III study conducted in Japan showed the superiority of IP over EP in ED-SCLC,[9] another phase III study conducted in North America failed to confirm the superiority of IP over EP.[15] A randomized phase III study to compare IP versus EP after EP with concurrent TRT is currently ongoing in patients with LD-SCLC in Japan.

**Table 3.** Major Toxicities During Consolidation Chemotherapy (n = 42)

| Toxicity | Grade 3 | | Grade 4 | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Hematologic | | | | |
| Leukopenia | 27 | 64 | 8 | 19 |
| Neutropenia | 18 | 43 | 17 | 40 |
| Anemia | 17 | 40 | 5 | 12 |
| Thrombocytopenia | 8 | 19 | 0 | 0 |
| Febrile neutropenia | 7 | 17 | 0 | 0 |
| Nonhematologic | | | | |
| Nausea/vomiting | 9 | 21 | 0 | 0 |
| Diarrhea | 5 | 12 | 1 | 2 |
| Constipation | 3 | 7 | 2 | 5 |
| Ileus | 2 | 5 | 1 | 2 |
| Infection | 9 | 21 | 1 | 2 |
| Mucositis | 0 | 0 | 0 | 0 |
| Esophagitis | 0 | 0 | 0 | 0 |
| Dyspnea | 2 | 5 | 0 | 0 |
| Pneumonitis | 1 | 2 | 1 | 2 |
| Hepatic | 1 | 2 | 0 | 0 |
| Electrolytes | 4 | 10 | 1 | 2 |

**Table 4.** Site of First Failure (n = 49)

| Site | No. of Patients | % |
|---|---|---|
| Progression free | 10 | 20 |
| Locoregional | 1 | 2 |
| Locoregional and distant | 11 | 22 |
| Distant | 27 | 55 |
| Brain only | 8 | 16 |
| Brain and others | 5 | 10 |
| Others | 14 | 29 |

Although a potential approach is to substitute irinotecan for etoposide in the combination of EP with concurrent TRT, we did not combine IP concurrently with TRT because two phase I studies demonstrated that combining IP with concurrent TRT was not feasible when the full dose of irinotecan was administered on days 1, 8, and 15.[16,17] On the basis of these results, we administered IP as consolidation therapy after EP with concurrent twice-daily TRT. After this article was initially submitted, Langer et al[18] reported phase I study of once every 3 weeks scheduling of IP with concurrent twice-daily TRT (45 Gy) or once-daily TRT (70 Gy) in patients with LD-SCLC, thus concluding that IP with concurrent twice-daily TRT was safe and feasible. A further evaluation of this regimen is thus warranted.

One group evaluated IP administered as an induction followed by EP with concurrent twice-daily TRT.[19] Their results are comparable to those of our study and EP with concurrent twice-daily TRT.[3-6] However, this regimen was highly myelotoxic (grade 4 neutropenia, 91%) with febrile neutropenia in 60% of the patients. Furthermore, early TRT is an important issue to obtain the improved outcome in LD-SCLC. Recent meta-analyses revealed that when platinum-based chemotherapy was concurrent with TRT in LD-SCLC, an improved survival was associated with early TRT.[20-22] Another group evaluated the addition of paclitaxel to EP with concurrent TRT.[23] Although their results are comparable to those of our study and EP with concurrent twice-daily TRT,[3-6] they concluded that the triplet regimen would not further improve the survival outcome in patients with LD-SCLC.

Esophagitis is a toxicity of a particular concern in concurrent chemoradiotherapy. We observed grade 3 or 4 esophagitis in one patient (2%), whereas the JCOG9903 trial reported it in 7% of the patients. These figures contrast with those in the studies evaluating etoposide and a platinum with concurrent twice-daily TRT (9% to 32%).[3-7] The substitution of irinotecan for etoposide may reduce the incidence of grade 3 or 4 esophagitis. Furthermore, a lower incidence of esophagitis has been noted in a Japanese trial.[4] A possible explanation for this includes differences in the

chemotherapy interval (once every 4 weeks *v* once every 3 weeks) and in ethnic background. Neutropenia was the most prominent toxicity in this study and its incidence is higher than that in the Turrisi et al study.[3] However, no toxic death resulting from neutropenia was observed. Diarrhea was the most troublesome nonhematologic toxicity of irinotecan and one of the major causes for treatment discontinuation in this study.

Brain metastasis as an initial site of relapse was observed in 33% of our patients. The JCOG9903 trial reported brain metastasis in 37% of their patients. These rates were higher than those in the studies evaluating etoposide and a platinum with concurrent twice-daily TRT.[4,7] The rate of local recurrence solely was observed in only one patient and none in the JCOG9903 trial. This contrasts with the higher rate of distant failure either with or without local failure in these two studies (77% and 67%, respectively). These increased rates of distant failure including brain metastasis may be partly explained by insufficient administration of IP as consolidation.

A limitation of this study is the treatment feasibility. In this study, 53% of the patients completed the entire treatment and 69% received two or more cycles of IP. The respective values were 58% and 73% in the JCOG9903 trial.[14] In contrast, Takada et al reported that 86% of the patients completed the treatment in EP with concurrent twice-daily TRT.[4] Although the optimal duration of consolidation chemotherapy remains unclear, we consider that at least two cycles of IP is clinically meaningful in view of encouraging survival outcomes in these phase II studies. Whether the relatively low completion rate of IP causes increased distant metastasis and detrimentally affects the outcome will be addressed by the ongoing phase III study. To improve the feasibility, certain supportive measures including the prophylactic GCSF and/or antidiarrheal measures[24] and different dose scheduling (eg, 3-weekly scheduling of IP) should be considered in future studies.

In conclusion, EP with concurrent twice-daily TRT followed by the consolidation of IP appears to be active in patients with LD-SCLC, thus supporting the conduct of the currently ongoing phase III study to compare EP with concurrent twice-daily TRT followed by the consolidation of either EP or IP.


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### Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

### Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Case Reports

# Relapse of Stage I Small Cell Lung Cancer Ten or More Years after the Start of Treatment

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Most patients with small cell lung cancer (SCLC) usually show relapse within 1 or 2 years. Relapses after a 5-year disease-free survival are extremely rare. This report describes two patients with stage I SCLC in whom the disease recurred 10 or more years after the start of initial therapy. Because the recurrence of SCLC was noted in the mediastinal lymph nodes of the same side, we concluded that the patients had a late relapse of SCLC rather than a metachronous lung cancer.

*Key words: 10-year disease-free survival – late relapse – second malignancy – small cell lung cancer*

## INTRODUCTION

Small cell lung cancer (SCLC) is characterized by early and widespread metastases, but good responsiveness to both chemotherapy and radiotherapy. The percentage of long-term disease-free survival was reported in 1983 (1) to be in the range of 15–20% in cases of limited disease (LD) and only a few percent in those with extensive disease, and a recent report suggested an expected 5-year survival rate of ~25% in cases with LD SCLC (2). Previous analyses of long-term disease-free survivors of SCLC (3,4) revealed that relapses usually occurred by 1.5 years after the beginning of combination chemotherapy. However, recent data indicate that as many as one-fourth of the patients who are disease-free at 30 months after the initial therapy develop late relapses (5). Furthermore, in his series, Vogelsang et al. (6) reported that 18 of the 25 long-term survivors (>2 years ) eventually showed relapse, sometimes as late as 8 years after the initial diagnosis. In 1993, we reported the course of a patient with SCLC who showed relapse 9.4 years after the initial treatment (7). In this paper, we report two cases of SCLC in whom relapse occurred after 10 or more years' disease-free survival, along with a review of the total of seven cases of SCLC reported until now, who developed a second SCLC or relapse after 10 years' disease-free survival.

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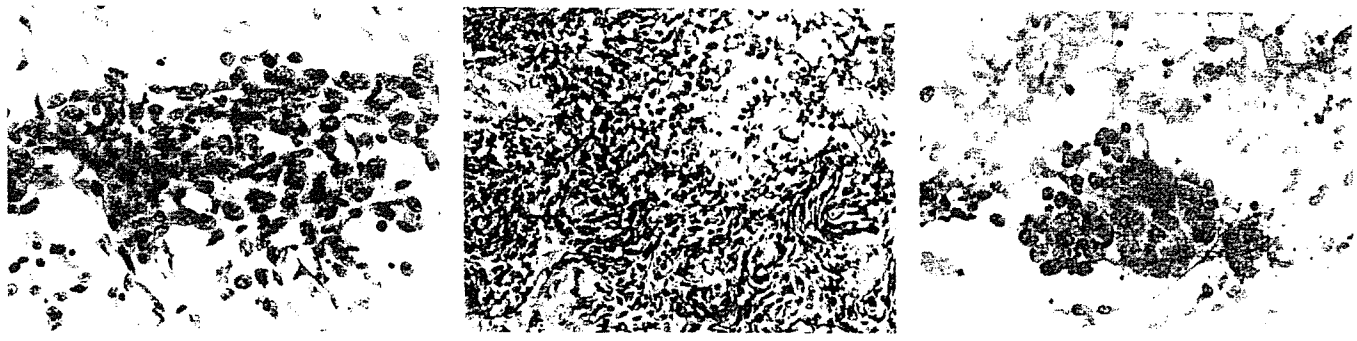
## CASE REPORTS

### CASE 1

A 61-year-old man participated in a mass screening for lung cancer by chest roentgenography (CXR) in June 1994. The Brinkman index was 1200, however, he stopped smoking after the first diagnosis. Fiberoptic bronchoscopy with transbronchial tumor biopsy confirmed the diagnosis of SCLC (Fig. 1a and b). The primary tumor was located in the $B^{1+2}$ segment of the left upper lobe (Fig. 2a). Surgical resection of the left upper lobe was conducted, followed by combination chemotherapy with four cycles of cisplatin and etoposide. Pathologically, the tumor was determined to be stage IA SCLC and had no components of non-SCLC or large cell carcinoma with neuroendocrine properties.

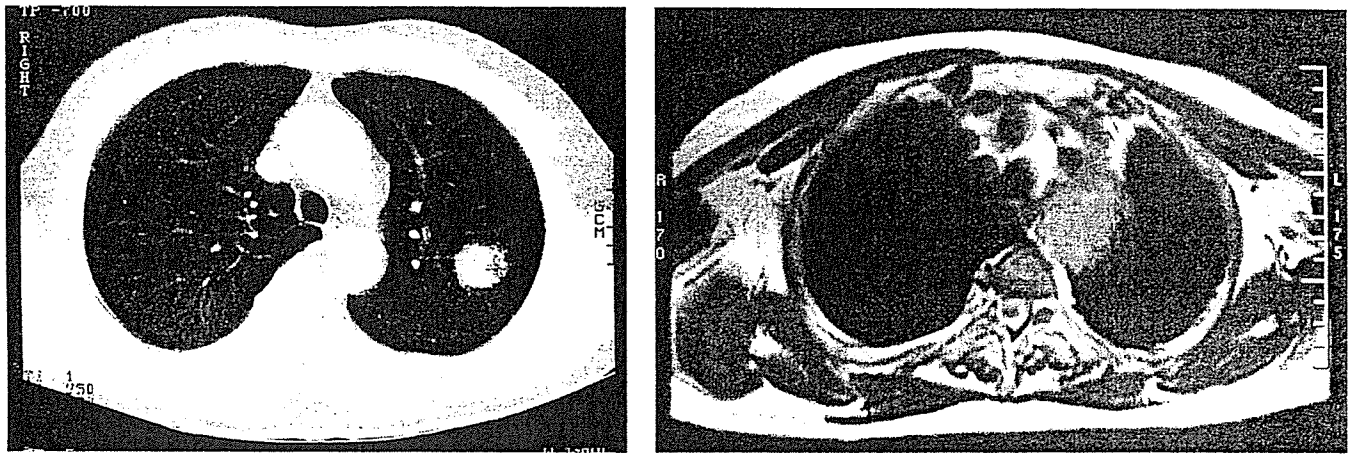
The patient underwent transurethral resection for early-stage bladder cancer (second malignancy) in January 2002 and received radiotherapy (75 Gy) for A2 (early) prostate carcinoma (third malignancy) in March 2004.

In June 2004, when he was 71 years old, a follow-up chest computed tomography (CT) and MRI (Fig. 2b) revealed para-aortic mediastinal lymphadenopathy (40 × 50 mm in size). The serum levels of pro-gastrin-releasing peptide, neuron-specific enolase (NSE) and carcinoembryonic antigen



(a) (b) (c)

**Figure 1.** Cytological (a) and histological (b) appearance of the first tumor in July 1994 and aspiration biopsy (c) of cervical lymph node in September 2005 at relapse in Case 1.



(a) (b)

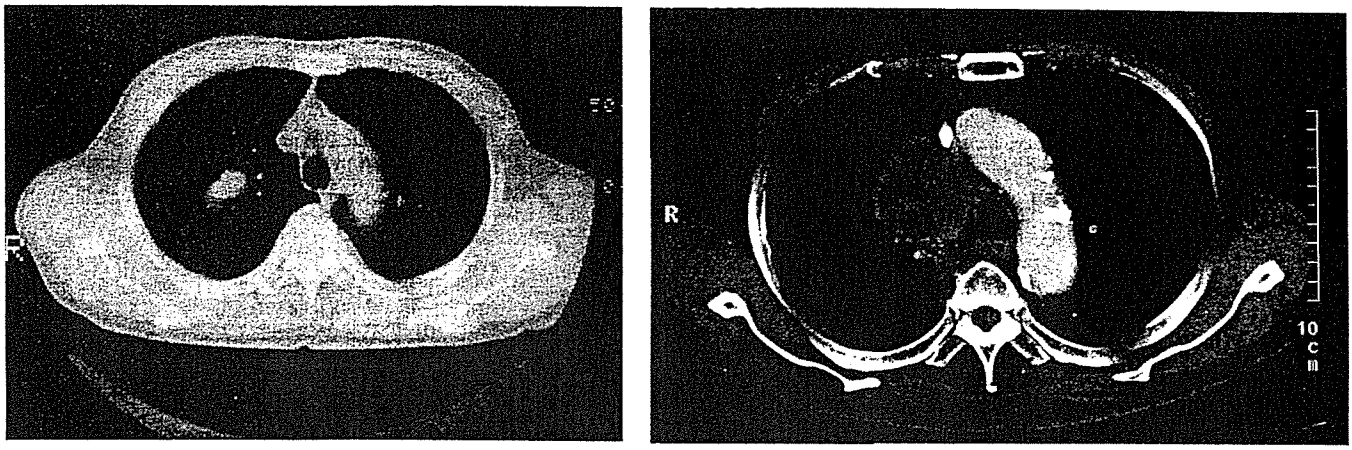
**Figure 2.** Findings on Chest CT (a) at diagnosis in July 1994 in Case 1. Findings on MRI (b) at relapse in 2004. There is mediastinal lymph node enlargement, size, 40 × 50 mm.

(CEA) were 360 pg/ml (normal range <46 pg/ml), 14.9 ng/ml and 1.4 ng/ml, respectively. The performance status on the Eastern Cooperative Oncology Group (ECOG) scale was zero, because he complained only of hoarseness and the serum lactate dehydrogenase (LDH) was normal. The standard staging procedures and upper gastro-intestinal screening by endoscopy revealed no evidence of metastases. Because of the poor pulmonary function of the patient and high metastatic potential of the disease, no surgery or chest irradiation was planned at this time. He was started on combination chemotherapy with irinotecan (CPT-11) at 60 mg/m$^2$ on day 1 and etoposide at 80 mg/m$^2$ on days 1–3, along with granulocyte-colony stimulating factor support on days 4–17 for one cycle, however, he developed severe neutropenia. The tumor regrew within 6 weeks of the treatment-free interval given to allow for his bone marrow recovery. He received CPT-11 at the dose of 50 mg/m$^2$ alone bi-weekly and enjoyed prolonged partial response (PR). In March 2005, multiple bone metastases were observed, along with left cervical adenopathy. Aspiration biopsy of the cervical lymph nodes revealed the typical histologic features of SCLC (Fig. 1c). Brain metastasis occurred in July 2005, and in September 2005, the serum NSE level rose to 245 ng/ml. He died of cancer in October 2005.

## Case 2

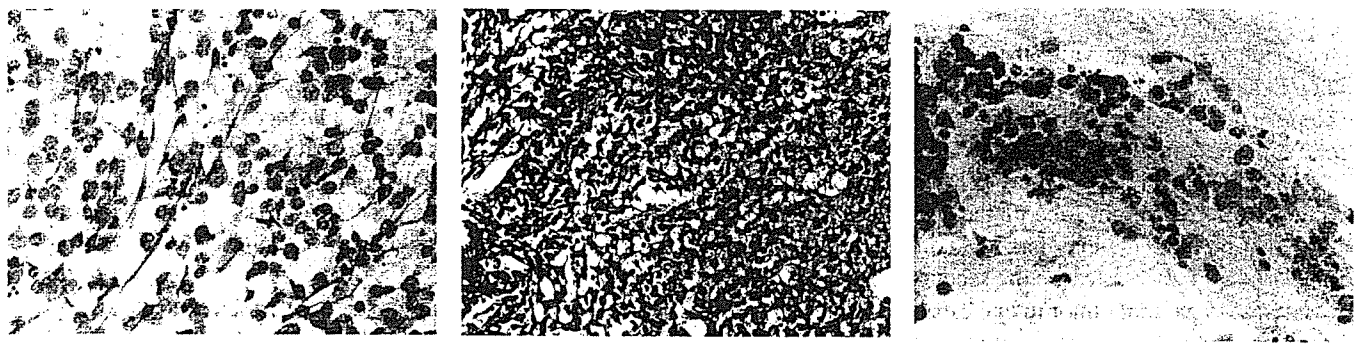
In April 1987, a 72-year-old man visited our hospital with a month's history of productive cough and blood-streaked sputum. He had smoked one packet of cigarettes a day for 52 years; however, he stopped smoking at the first diagnosis of lung cancer. A CXR showed a right upper lobe mass, which was confirmed on chest CT (Fig. 3a). Fiberoptic bronchoscopy with tumor biopsy confirmed the diagnosis of SCLC (Fig. 4a and b). The patient was determined to have stage IB (T2N0M0) SCLC. Chemotherapy was administered with cyclophosphamide, doxorubicin and vincristine alternating with cisplatin-etoposide, for six cycles. Thereafter, sequential chest radiotherapy was administered.

In September 1998, when he was 82 years old and 11.4 years had passed since the initial treatment of SCLC, the patient complained of shortness of breath on walking even as little




(a) (b)

**Figure 3.** Findings on Chest CT (a) in Case 2 at diagnosis in April 1987. A mass measuring 31 × 13 mm in size in the right upper lobe. Chest CT (b) findings at relapse in 1998.



(a) (b) (c)

**Figure 4.** Findings on transbronchial biopsy [cytology (a), and histology (b)] in Case 2 at diagnosis. Sputum cytology (c) at relapse in 1998.

as one block, and hemoptysis. His performance status on the ECOG scale was 3. The serum levels of LDH, NSE and CEA were all within normal range. The sputum cytology result was consistent with the diagnosis of SCLC (Fig. 4c). Chest CT revealed multi-stage mediastinal lymphadenopathy, especially on the ipsilateral side (Fig. 3b). There was no evidence of metastasis elsewhere, as confirmed by brain CT. Because of his poor performance status, the patient received two cycles of monotherapy with oral etoposide (50 mg/body/day for 14 days), with no shrinkage of the tumor. He died of worsened SCLC on 2 May 1999.

Table 1 shows a review of adequately documented cases of recurrence and/or second SCLC after 10 years of disease-free survival. All the patients received systemic combination chemotherapy followed by thoracic irradiation.

## DISCUSSION

Jacobs et al. (8) stated that there were continued relapses of disease until 39 months. Jacoulet et al. (5) reported that the risk of recurrence was <30% beyond 3 years and <10% beyond 5 years. In the treatment of SCLC, 5-year disease-free survival has usually been considered as a benchmark of cure (9,10). However, Niiranen (11) described a case with relapse at the primary site, in the central nervous system and in the skin 11 years after the diagnosis of SCLC.

Brigham et al. (12) estimated that the clinical doubling time of SCLC ranged from 25 to 160 days (median, 77 days; log mean, 81 days; arithmetic mean, 91 days) on the basis of chest radiographic findings. He suggested that highly effective therapy which reduces the residual tumor burden level to that approaching a single cell can be followed by disease-free intervals of more than 6 years before apparent clinical recurrence (>30 doublings). If the longer doubling time of 160 days were used for the calculation, potential relapse of SCLC may not be expected until 13 years after successful induction therapy with complete response as suggested by Al-Ajam et al. (10). It is usually difficult to ascertain whether a second SCLC is a late relapse of the first SCLC or a second primary tumor after a long disease-free survival. Some authors (9,13) suggested that the second diagnosis of SCLC after a long period of survival following the first diagnosis of SCLC should be considered as representing a second primary SCLC, whereas others (14,15) interpret it as representing a relapse of the first SCLC. The

Table 1. Patients of SCLC with 10 years or greater disease-free survival before the second diagnosis of SCLC

| Author | Year of publication | Age/ Sex | Stage | Location of initial tumor | Initial therapy | DFI (years) | First relapse site | Treatment after relapse | Survival after relapse (months) |
|---|---|---|---|---|---|---|---|---|---|
| Niiranen[12] | 1988 | 60/M | LD (I) | NR | RT (60 Gy) | 11 | Lung, Brain, Skin | NR | 2 dead |
| Lassen[15] | 1995 | 65/F | NR | NR | NR | 10.9 | Lung, Brain, Kidney | NR | 2 dead |
| Johnson[16] | 1995 | 69/M | LD | LLL | CT+RT | 12.2 | LLL, LH, L-pl, ML | NR | NR |
| Kitamoto[13] | 2002 | 56/M | LD (IIIB) | LLL | CT+RT* | 10.4 | LUL, LH | CT+RT*** | 10 live |
| Al-Ajam[11] | 2005 | 52/M | LD | RUL | CT+RT** | 10 | RUL, Brain | Whole brain RT, CT$^{\$}$ | 17 alive |
| Present case 1 | | 61/M | LD (IA) | LUL | OP+CT$^{\#}$ | 10 | ML | CT$^{\$\$}$ | 14 dead |
| Present case 2 | | 72/M | LD (IB) | RUL | CT +RT$^{\#\#}$ | 11.4 | ML | CT$^{\$\$\$}$ | 8 dead |

DFI, disease-free interval; NR, not reported; LLL, left lower lobe; LUL, left upper lobe; RUL, right upper lobe; LD, limited disease; ED, extensive disease; ML, mediastinal lymph node; L-pl, left pleural effusion; LH, left hilum lymph node; CT, chemotherapy; RT, chest irradiation; *chemotherapy with cisplatin, etoposide and doxorubicin, and concurrent chest irradiation at 40 Gy in 20 fractions; **CAV (cyclophosphamide + adriamycine + vincristine) and sequential chest irradiation, $^{\#}$Left upper lobectomy and adjuvant chemotherapy with PE (cisplatin + etoposide), $^{\#\#}$chemotherapy with CAV alternating with PE and sequential chest irradiation (45 Gy twice daily), ***PE sequential RT, $^{\$}$PE, $^{\$\$}$etoposide + CPT and CPT alone, $^{\$\$\$}$oral etoposide.

latter contention may be valid if the tumor arose at the same anatomic site as the initial SCLC, although the possibility of a new second primary tumor can still not be completely excluded. Kitamoto et al. (13) considered the second diagnosis of SCLC as a second malignancy, because the primary tumor was located in a different lobe of the lung in his patient. We believe that our patients may have had a relapse rather than a second primary tumor, because the second SCLC developed at the same site as the first tumor in one case, and in the ipsilateral mediastinal nodes in the other, and the specimens at diagnosis and at relapse showed an identical cytological or histological appearance in our patients (Figs 1 and 4).

Wistuba et al. (16) reported of observing genetic damage in the adjacent normal and hyperplastic bronchial epithelium in cases of SCLC. Tucker et al. (17) reported that continued smoking increased the risk of second primary cancers in patients treated for SCLC, and the cumulative risk of development of a second primary lung cancer made this cancer a common cause of death. Despite the decreasing incidence of recurrent SCLC with time, the longevity of long-term disease-free survivors continues to be compromised by increasing incidence of second primary smoking-related cancers. Since cigarette smoking cessation after successful therapy is associated with a decreased risk for a second smoking-related primary cancer, the simplest and most important intervention should be to encourage patients to quit smoking (18).

Although the standard therapy for late recurrent disease has not been established, retreatment with chemotherapy similar to the initial treatment (reinduction therapy) is reported to often achieve second responses up to 1 year or longer (19). Sekine et al. (20) also reported a relative good prognosis of patients after late relapse. The median survival time after relapse in their 13 patients was 7.4 months. This may be explained in part by good response to reinduction treatment in these patients or by very sluggish growth in these tumor cells.

Although only seven cases of late relapses after a 10-year disease-free survival have been reported until now, including our two patients, there is still a chance of such rare recurrence occurring beyond this interval. Therefore, careful follow-up is necessary to detect malignant lesions as early as possible in these long-term survivors.

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ORIGINAL ARTICLE

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# Phase I study of weekly cisplatin, vinorelbine, and concurrent thoracic radiation therapy in patients with locally advanced non-small-cell lung cancer

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**Abstract**

***Background.*** The combination of chemotherapy and thoracic radiation therapy (TRT) is considered as a standard treatment for locally advanced non-small-cell lung cancer (NSCLC). Although the frequent interaction of anticancer agents and irradiation may produce stronger radio-sensitizing effects, the daily administration of these agents is complicated. We therefore used weekly administration of these agents, and conducted a phase I study of weekly cisplatin, vinorelbine, and concurrent TRT. The purpose of this study was to identify the maximum tolerated dose (MTD), the dose-limiting toxicity (DLT), and the recommended dose of this treatment.

***Methods.*** Patients with locally advanced NSCLC were enrolled in this study. Both cisplatin and vinorelbine were given intravenously on a weekly schedule for 6 weeks, starting on the first day of TRT, i.e., on days 1, 8, 15, 22, 29, and 36. The total dose of TRT was 60 Gy. The dose of cisplatin was fixed at 20 mg/m$^2$ per week. The starting dose of vinorelbine was 15 mg/m$^2$ per week (dose level 1).

***Results.*** Nine patients were enrolled in this study. All three patients at dose level 1 experienced DLTs. We decreased the dose of vinorelbine to 10 mg/m$^2$ per week (dose level 0). Two of the six patients at dose level 0 experienced DLTs. Therefore, dose level 1 was considered as the MTD, and dose level 0 as the recommended dose. The DLTs of this treatment were esophagitis, fatigue, infection, and hyponatremia.

***Conclusion.*** The recommended dose of cisplatin is 20 mg/m$^2$ per week and that of vinorelbine is 10 mg/m$^2$ per week with standard TRT. A phase II study of this treatment is warranted.

**Key words** Cisplatin · Vinorelbine · Chemoradiotherapy · Non-small-cell lung cancer

## Introduction

Lung cancer is a leading cause of cancer mortality in Western industrialized countries.[1] Approximately 80% of lung cancer is of the non-small-cell histologic type, such as squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Surgery, if possible, is the mainstay of treatment for patients with non-small-cell lung cancer (NSCLC); however, the majority of NSCLC is considered as unresectable due to the local or systemic spread of the cancer. Approximately 30% of NSCLC is locally advanced, unresectable stage IIIA or IIIB disease. The American Society of Clinical Oncology (ASCO) published their guideline (update 2003) for the treatment of unresectable NSCLC.[2] This guideline recommends the following treatment for locally advanced NSCLC: chemotherapy in association with definitive thoracic irradiation is appropriate for selected patients with unresectable, locally advanced NSCLC; radiation therapy should be included as part of the treatment for selected patients with unresectable locally advanced NSCLC; and chemotherapy given to

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NSCLC patients should be a platinum-based combination regimen.

The combination of cisplatin and vinorelbine is more effective than single-agent cisplatin, or cisplatin plus vindesine, for advanced NSCLC.[3,4] Furthermore, some randomized trials have shown that cisplatin plus vinorelbine is as effective as carboplatin plus paclitaxel, cisplatin plus gemcitabine, or cisplatin plus irinotecan.[5–7] Therefore, the cisplatin plus vinorelbine combination is considered as one of the standard platinum-based chemotherapy regimens.

There are two possible advantages of the combination of chemotherapy and radiation therapy. One is spatial cooperation (which means that radiation is effective against the loco-regional tumor, and chemotherapy eradicates micrometastases independently) and the other is the radiosensitizing effects.[8–10] Cisplatin is one of the anticancer agents whose radio-sensitizing effects have been studied extensively, and many preclinical studies have shown that cisplatin enhanced the cytotoxic effects of irradiation.[11] The European Organization for Research and Treatment of Cancer (EORTC) performed a randomized trial comparing the following three arms: thoracic radiation therapy (TRT) alone, TRT combined with weekly cisplatin, and TRT combined with daily cisplatin, for locally advanced NSCLC.[12] The survival rate was 54% at 1 year, 26% at 2 years, and 16% at 3 years for the TRT+daily-cisplatin group, as compared with 44%, 19%, and 13% for the TRT+weekly-cisplatin group, and 46%, 13%, and 2% for the TRT-alone group, respectively. The EORTC concluded that TRT+daily cisplatin had the greatest survival benefit of the three treatment arms and this benefit was due to the improvement of local control. On the other hand, some preclinical studies have shown that vinorelbine also had radio-sensitizing effects.[13–15] Vinorelbine is a potent inhibitor of mitotic microtubule polymerization, and this effect synchronizes cells at the G2/M phase of the cell cycle. This phase is considered as the most radio-sensitive phase; thus, vinorelbine can exhibit radio-sensitizing effects.

Although the frequent interaction of anticancer agents and irradiation may produce stronger radio-sensitizing effects, daily administration of these agents is complicated. Weekly administration is more convenient than daily administration. Therefore, we conducted a phase I study of weekly cisplatin, vinorelbine, and concurrent TRT for locally advanced NSCLC. The purpose of this study was to identify the maximum tolerated dose (MTD), the dose-limiting toxicity (DLT), and the recommended dose of this treatment.

## Patients and methods

### Eligibility criteria

Patients with histologically or cytologically confirmed locally advanced NSCLC were enrolled in this study. All patients were deemed suitable for definitive TRT by a radiation oncologist (T.T.). Other eligibility criteria included the following: age, 20 years or older; Eastern Cooperative Oncology Group (ECOG) performance status, 0 or 1; unresectable stage IIIA or IIIB; absence of malignant pleural or pericardial effusion; absence of involvement of contralateral hilar lymph nodes; no prior chemotherapy or TRT; adequate bone marrow function (leukocyte count ≥4000/μl, neutrophil count ≥2000/μl, hemoglobin level ≥10 g/dl, and platelet count ≥100000/μl), renal function (creatinine level ≤ upper limit of normal and creatinine clearance ≥50 ml/min), hepatic function (aspartate aminotransferase/alanine aminotransferase [AST/ALT] ≤ twice upper limit of normal and bilirubin level ≤ upper limit of normal), and pulmonary function (arterial partial pressure of oxygen [$PaO_2$] ≥70 mmHg); absence of interstitial pneumonitis or pulmonary fibrosis, or other serious illnesses; and no pregnancy or lactation. Written informed consent was obtained from all patients. This protocol was approved by the institutional review board of Osaka Prefectural Medical Center for Respiratory and Allergic Diseases. All patients received the protocol treatment at the same institution.

### Chemotherapy

Both cisplatin and vinorelbine were given intravenously on a weekly schedule for 6 weeks, starting on the first day of TRT, i.e., on days 1, 8, 15, 22, 29, and 36 (Fig. 1). The doses of cisplatin and vinorelbine are described later. Cisplatin was administered as a 60-min infusion with adequate hydration (at least 1000 ml of fluid). Antiemetic drugs, such as 5-hydroxytryptamine type 3 (5-$HT_3$) receptor antagonists and dexamethasone 8 mg, were given intravenously before the administration of cisplatin. Vinorelbine was administered as a 5-min infusion. The minimum requirements for the administration of cisplatin and vinorelbine were as follows: leukocyte count 2000/μl or more, neutrophil count 1000/μl or more, platelet count 50000/μl or more, nonhematological toxicity grade 2 or less, and no suspension of TRT.

Subsequently, consolidation chemotherapy was given, starting 1 week after the completion of irradiation. If creatinine clearance was 60 ml/min or greater, cisplatin 80 mg/$m^2$ was given intravenously as a 60-min infusion on day 1 and vinorelbine 20 mg/$m^2$ was given intravenously as a 5-min infusion on days 1 and 8 of a 3-week cycle. Standard hydration and antiemetics were also given. If creatinine clearance was less than 60 ml/min, vinorelbine 25 mg/$m^2$ was given intravenously as a 5-min infusion on days 1, 8, and 15 of a 4-

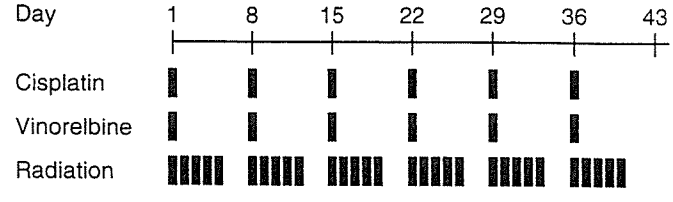


**Fig. 1.** Treatment schedule of weekly cisplatin, vinorelbine, and concurrent thoracic radiation therapy

## Discussion

Some randomized trials and meta-analyses have shown that the combination of chemotherapy and TRT has survival benefits compared with TRT alone for locally advanced NSCLC.[12,19–26] However, long-term survival was rare, with a median survival of 12 to 13.7 months and a 5-year survival rate of only 8% to 17%.

The West Japan Lung Cancer Group conducted a phase III study to compare concurrent chemoradiotherapy with sequential therapy.[27] The chemotherapy consisted of cisplatin, vindesine, and mitomycin, and TRT delivered a total of 56 Gy. The median survival in the concurrent arm was significantly longer than that in the sequential arm (16.5 versus 13.3 months). The Radiation Therapy Oncology Group (RTOG) and a Czech group conducted similar randomized trials and confirmed the superiority of the concurrent therapy over the sequential therapy.[28,29] Furthermore, Choy et al.[30] conducted a randomized phase II study of three regimens: sequential chemoradiotherapy versus induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy followed by consolidation chemotherapy; this was the so-called locally advanced multimodality protocol (LAMP) study. They used the combination of paclitaxel, carboplatin, and TRT. The median survival was 12.5 months for the sequential arm, 11 months for the induction/concurrent arm, and 16.1 months for the concurrent/consolidation arm. These results suggested that concurrent chemoradiotherapy, or possibly concurrent chemoradiotherapy followed by consolidation chemotherapy, was the most effective treatment in patients with locally advanced NSCLC. However, it is undetermined what regimen or what schedule is optimal for chemoradiotherapy.

Several schedules and doses of cisplatin, vinorelbine, and concurrent TRT have been reported. Masters et al.[31] recommended that cisplatin should be administered at 80 mg/m$^2$ on day 1 and vinorelbine at 15 mg/m$^2$ on days 1 and 8 every 3 weeks with standard TRT. After that, the Cancer and Leukemia Group B (CALGB) performed a randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy.[32] In the cisplatin-vinorelbine arm, the doses reported by Masters et al.[31] were used, and the CALGB concluded that induction chemotherapy followed by concomitant chemoradiotherapy was feasible, with the observed survival rates exceeding those of previous CALGB trials for all treatment arms. Sekine et al.[33] conducted a phase I study and reported that the recommended dose of cisplatin was 80 mg/m$^2$ on day 1 and that of vinorelbine was 20 mg/m$^2$ on days 1 and 8 every 4 weeks with TRT including a 4-day interval. The Czech group[29] used the following schedule and dose: cisplatin 80 mg/m$^2$ on day 1 and vinorelbine 12.5 mg/m$^2$ on days 1, 8, and 15 every 4 weeks with standard TRT starting on day 4.

Although the frequent interaction of anticancer agents and irradiation may produce stronger radio-sensitizing effects, there has been no report of a weekly schedule to date. Therefore we conducted a phase I study of weekly cisplatin and vinorelbine with standard TRT. The studies described above[29,31–33] reported that esophagitis and neutropenia were the major toxicities. The present study showed that the DLTs of our regimen were esophagitis, fatigue, infection, and hyponatremia. All patients at dose level 1 experienced grade 3 esophagitis, so this dose was considered an overdose. The strong radio-sensitizing effects may have resulted in the severe esophagitis. On the other hand, no severe neutropenia was observed. The recommended dose of cisplatin is 20 mg/m$^2$ per week and that of vinorelbine is 10 mg/m$^2$ per week in the present study.

The response rate and the median overall survival in this study were 56% and 11.9 months, respectively. Some concurrent chemoradiotherapy studies have reported better results, with response rates of 63% to 85% and median overall survivals of 11 to 18.3 months.[12,27–30,32] As our study had a very small sample size, of only nine patients, we cannot draw conclusions on the efficacy of this treatment from our present results.

In conclusion, our phase I study of weekly cisplatin, vinorelbine, and concurrent TRT showed that the DLTs of this treatment were esophagitis, fatigue, infection, and hyponatremia. The recommended dose of cisplatin is 20 mg/m$^2$ per week and that of vinorelbine is 10 mg/m$^2$ per week, i.e., on days 1, 8, 15, 22, 29, and 36, with standard TRT. We believe a phase II study of this treatment is warranted.

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# Angled Forceps Used for Transbronchial Biopsy in Which Standard Forceps Are Difficult To Manipulate*

## A Comparative Study

*Shinji Sasada, MD; Yoshitaka Ogata, MD; Masashi Kobayashi, MD; Tomonori Hirashima, MD; Kunimitsu Kawahara, MD, PhD; Kaoru Matsui, MD; and Ichiro Kawase, MD*

***Objectives:*** **To evaluate the usefulness of the Sasada transbronchial angled forceps (STAF) in patients with peripheral pulmonary lesions (PPLs), which are difficult to manipulate with standard forceps.**

***Methods:*** **We have invented the STAF, a forceps with an angled tip. One hundred ten patients with PPLs that were difficult to reach with standard forceps were retrospectively evaluated. The patients first underwent bronchoscopy with a standard forceps and then with the STAF. The specimens obtained with standard forceps and those obtained with STAF were separately fixed and analyzed histologically. We compared the histologic diagnosis of the specimens obtained by STAF with that obtained by the specimens obtained with standard forceps. Statistical significance was calculated with the McNemar $\chi^2$ statistic.**

***Results:*** **The diagnostic yield of all lesions from the specimens obtained with STAF (86 of 110 lesions; 78.2%) was significantly higher than that of lesions from the specimens obtained with standard forceps (43 of 110 lesions; 39.1%; $p < 0.001$). Among malignant lesions, the yield obtained with STAF (60 of 72 lesions; 83.3%) was significantly higher than that obtained with standard forceps (32 of 72 lesions; 44.4%; $p < 0.001$). Among benign lesions, the yield obtained with STAF (26 of 38 lesions; 68.4%) was also significantly higher than that obtained with standard forceps (11 of 38 lesions; 28.9%; $p < 0.001$). Among the different lesion areas, the right upper lobe plus the left upper division gave the greatest difference in yield (STAF, 46 of 60 lesions; 76.7%; standard forceps, 22 of 60 lesions; 36.7%; $p < 0.001$). Among the different size ranges, the diagnostic yields obtained with STAF were significantly higher than that obtained with standard forceps except for the size range of ≤ 10 mm. There were two complications, pneumothorax and bronchial bleeding, both of which were controlled easily.**

***Conclusions:*** **The STAF was shown to be useful for obtaining specimens that were sufficient for histologic diagnosis from PPLs that were difficult to manipulate with standard forceps.**

***(CHEST 2006; 129:725–733)***

**Key words:** angled forceps; peripheral pulmonary lesions; transbronchial biopsy

**Abbreviations:** CS = curve-shaped; CTGNB = CT scan-guided needle biopsy; NSCLC = non-small cell lung cancer; PPL = peripheral pulmonary lesion; STAF = Sasada transbronchial angled forceps; TBB = transbronchial biopsy; VATS = video-assisted thoracic surgery

Since the 1970s, transbronchial biopsy (TBB) of the lung performed through a flexible bronchoscope has gained wide acceptance and has become the most common method of performing lung tissue biopsy.[1–4] The numbers of patients with peripheral pulmonary lesions (PPLs) have increased along with the incidence of lung adenocarcinoma.[5,6] Patients in whom a diagnosis cannot be made by flexible fiberoptic bronchoscopy need to undergo CT scan-guided needle biopsy (CTGNB) or video-assisted thoracic surgery (VATS).[7,8] However, CTGNB is associated with critical complications, including air embolism