Table 3 Thrombocytopenia Incidence

Thrombocytopenia	N	Overall	1/2 Cycles	≥ 3 Cycles
Grade 3/4	31	2/3 (16.2%)	1/1 (6.5%)	1/2 (9.7%)

Nadir platelet counts in 5 cases with grade > 3 thrombocytopenia ($\times 10^4$) were 1.5, 2, 2.5, 3.9, and 4.9.

Table 4 Nonhematologic Toxicities

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	2	1	1	0
Rash	0	2	4	0
Depression	0	0	1	0
Fever (Absence of Neutropenia)	1	0	0	0
Transaminase	3	0	0	0

Among the first 6 patients, 5 had ≥ 3 treatment cycles without treatment delay (4, 3, 2, 8, 4, and 4 cycles for the first, second, third, fourth, fifth, and sixth patients, respectively). Final analysis revealed that 21 of 31 patients received ≥ 3 treatment cycles, but 8 of these patients experienced treatment delay in the first 3 cycles. The treatment completion rate was not sufficiently high at 42%. Ten patients were withdrawn from the study early; the reason for withdrawal was progressive disease for 2 patients, hematologic toxicity for 3 (all were neutropenic but did not have thrombocytopenia), and nonhematologic toxicity for 5 (grade 3 depression in 1 patient and grade 3 rash in 4 patients; 1 was caused by carboplatin, and the others were caused by gemcitabine).

Discussion

Third-generation chemotherapy, consisting of a platinum agent and a third-generation chemotherapeutic agent, including gemcitabine, is considered a standard treatment for advanced-stage NSCLC worldwide. Many studies were carried out to compare the toxicity and efficacy of each regimen of third-generation chemotherapy. According to the ECOG 1594 study, a significant difference in efficacy is difficult to demonstrate among the regimens.[41] In contrast, the profiles of toxicities were demonstrably different among the regimens.

Although platinum compounds, such as cisplatin and carboplatin, are still key drugs in chemotherapy for NSCLC, a recent metaanalysis suggested that treatment with regimens containing gemcitabine showed small but statistically significant improvement in patient survival.[42] With its mild toxicity and easiness in administration, gemcitabine is becoming another key drug in chemotherapy for NSCLC. In a Japanese phase III trial in which gemcitabine/vinorelbine/paclitaxel in combination with a platinum agent were compared with irinotecan/cisplatin, a Japanese standard for NSCLC, gemcitabine/cisplatin exerted the best result; however, the difference was not statistically significant.[35] Recent trials showed that the gemcitabine/carboplatin improved patient survival compared with gemcitabine alone and mitomycin/ifosfamide/cisplatin.[43,44] Taking these results together, gemcitabine/carboplatin is a reasonable combination and becoming widely used for NSCLC.

Early studies of gemcitabine/carboplatin used a 28-day schedule in which gemcitabine was administered on days 1, 8, and 15 and carboplatin was administered on day 1.[23-29] However, because of a high incidence of severe thrombocytopenia, 2 alternate schedules were proposed: one is a 21-day schedule treatment in which gemcitabine is administered on days 1 and 8 with carboplatin administered on day 1,[31] and the other is a 28-day schedule in which gemcitabine is administered on day 1 and 8 with carboplatin on day 8.[30] Obasaju et al conducted a randomized phase II study comparing these 2 schedules.[45] Although the study was not powered to show a statistically significant difference between these 2 regimens, the 21-day schedule seemed to be superior to the 28-day schedule in terms of efficacy. However, grade 3/4 thrombocytopenia was observed in 14% of cycles in the 21-day schedule, higher than that in the 28-day schedule. The 21-day schedule has been used in several other studies, in which thrombocytopenia was still the main problem, accompanied by bleeding episodes, although not frequently.[27,46,47] In the Japanese phase II study described previously, thrombocytopenia was again a major issue, resulting in a high incidence of dose reduction and early withdrawal from the study.[33] Nevertheless, good median survival time of the patients treated with gemcitabine/carboplatin (432 days) and low incidences of nonhematologic toxicities were impressive. Meanwhile, the 28-day schedule in which carboplatin was administered on day 8 appeared to be less myelotoxic than the 21-day schedule but has the problem of low dose intensity.

Our study was designed to evaluate the feasibility and efficacy of gemcitabine/carboplatin in a modified administration schedule. Gemcitabine/carboplatin were administered at 1000 mg/m^2 on days 1 and 8 and at AUC 5 on day 8 of each 21-day cycle, respectively. The main aim of this study was to decrease the severity of thrombocytopenia with minimal effect on dose intensity. The low incidence of grade 3/4 thrombocytopenia was notable, observed in only 2 of 31 patients in the first 2 cycles. This result suggested that the nadir of thrombocytopenia of gemcitabine and carboplatin occur around day 15, and that incidence of severe thrombocytopenia could be decreased even in a 21-day schedule by delaying administration of carboplatin until day 8. We were concerned whether this 3-weekly chemotherapy would become possible by adopting looser criteria (leukocyte count > 2500/μL and platelet count > 75,000/μL) to start new cycles. Other hematologic and nonhematologic toxicities were also mild, and altogether, the treatment was well tolerated. The incidence of stressful toxicities represented by nausea/vomiting, neurologic toxicities, and alopecia was relatively low in the gemcitabine/carboplatin combination.

The planned dose intensities and actual dose intensities were 667 mg/m^2 per week and 638 mg/m^2 per week (95.7% of planned dose intensity) for gemcitabine and 1.67 mg/

minute/mL per week and 1.56 mg × minute/mL per week (93.4% of planned dose intensity) for carboplatin AUC, respectively. Dose intensity for each drug in the 28-day schedule described previously[30,32] was estimated to be 550 mg/m^2 per week for gemcitabine and 1.25 mg × minute/mL per week for carboplatin AUC, respectively. The median cycles of delivery were 3, which was comparable with those of platinum-doublet chemotherapy.[35] Therefore, our main purpose to decrease the incidence of thrombocytopenia and increase dose intensity was achieved, although there are still problems to be solved.

Drug administrations were frequently delayed, treatment time tended to be protracted, and the treatment completion rate we defined was 42%. Unfortunately, early withdrawal from the study was seen in 10 patients (32%). Among these patients, 3 experienced grade > 2 leukopenia (leukocyte count < 3000/μL) on day 8 of the first course, and the other 3 patients developed grade 3 rash after administration of day 1 gemcitabine. For these 6 patients, gemcitabine/carboplatin chemotherapy was considered inappropriate regardless of the schedule. This schedule, which delays carboplatin administration until day 8, would enable early exclusion of the patients who are inappropriate for this combination chemotherapy, avoiding severe hematologic and nonhematologic toxicities. Response rate, median TTP, and median survival time were favorable. However, this might be biased by the small number of patients and the high percentage of patients with good prognostic factors such as female sex and PS of 0 in this study.

Recently, prolonged administration of gemcitabine combined with carboplatin has been tested.[48,49] Because gemcitabine/carboplatin combination chemotherapy has become a widely used regimen, further improvement of this regimen is necessary.

Conclusion

The present study suggests that carboplatin administered on day 8 in a 21-day schedule of gemcitabine/carboplatin reduces severity of thrombocytopenia without having a detrimental effect on efficacy. However, further evaluation is still needed to estimate the efficacy and feasibility of this regimen. The ongoing randomized phase II study compares day-1 and day-8 administration of carboplatin in a 21-day schedule of gemcitabine/carboplatin. In clinical practice, this regimen will be one of the treatment options suitable for outpatients.

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Improved Diagnostic Efficacy by Rapid Cytology Test in Fluoroscopy-Guided Bronchoscopy

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Background: Fluoroscopy-guided bronchoscopy is a safe and routine method used to obtain a histologic or cytologic specimen of peripheral lung nodules, but it has low sensitivity in diagnosing malignant tumors. Although feedback from rapid cytology tests are expected to improve diagnostic rates, the value of the routine use of rapid cytology tests has not been established.

Materials and Methods: We prospectively studied 657 patients with suspected peripheral malignant lung lesions on chest computed tomography who underwent fluoroscopy-guided bronchoscopy between January 2002 and December 2004. Rapid on-site cytopathologic examinations (ROSE) were performed during bronchoscopic examinations. The additional approach to the lesions was performed immediately after conventional bronchoscopic examinations when ROSE was not considered diagnostic.

Results: There were 528 patients diagnosed as having malignant lesions. In 477 of these patients (90.3%), final malignant diagnosis was established by the initial bronchoscopy. Among these, 84 patients (15.9%) were diagnosed only with the additional feedback from ROSE. Of 240 peripheral lesions ≤2 cm, 174 were found to be malignant. Without ROSE, 110 (63.2%) of peripheral malignant lesions were diagnosed by bronchoscopy. The integration of ROSE enabled us to diagnose an additional 40 patients (23.0%) by bronchoscopy. ROSE improved diagnostic yield independent of the site and histology of the lesions and experience of the operators.

Conclusion: ROSE increased the diagnostic yield of bronchoscopy from 74.4% to 90.3% and therefore is an effective reinforcement in bronchoscopic diagnosis of peripheral pulmonary malignancies. The use of ROSE in routine bronchoscopy should be encouraged.

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Examinations used to diagnose pulmonary malignant lesions should be safe, accurate, and optimal for obtaining adequate information. A flexible fiberoptic bronchoscope has become prevalent in obtaining specimen from lung lesions. Although central visible tumors can be diagnosed at high sensitivity, it is reported that the diagnostic rate for peripheral lung lesions is low, from 62% to 86%, even in combination with various techniques.[1–4] Brush, curette, forceps, and aspiration needles have been investigated as tools to obtain diagnostic specimens. Other reports recommend rapid on-site cytopathologic examinations (ROSE) in transbronchial needle aspiration of lymph nodes.[5–7] However, ROSE has not been introduced for diagnosing peripheral lung lesions. Recently, the combination of ultra-fast Papanicolaou staining and multiplanar reconstruction images has been recommended to improve diagnostic accuracy and safety in fluoroscopy-guided transbronchial biopsy.[8] In this prospective study, we integrated ROSE into routine bronchoscopy and evaluated the benefit of bronchoscopy combined with ROSE.

BRONCHOSCOPY

In our hospital, we foremost recommend bronchoscopy with a flexible bronchoscope in the diagnosis of pulmonary nodules because of its safety. If the lesions are not bronchoscopically invisible, procedures to obtain diagnostic materials are performed under fluoroscopic guidance. Transcutaneous fine-needle biopsy (TCNB) is recommended for patients with a negative result of preceding bronchoscopy or with negligible risk of pneumothorax by percutaneous puncture, such as those with lesions invading the thoracic wall. Video-assisted thoracic surgery (VATS) is usually recommended for patients with negative results of bronchoscopy and/or TCNB or lesions unrecognizable under fluoroscopy. For pure GGO, we recommend computed tomographic (CT) follow-up, otherwise VATS.

In bronchoscopy, the specimen for cytology was obtained by curetting or brushing. The material was smeared on two glass slides: one was subjected to ROSE (ROSE sample) and the other to conventional Papanicolaou staining. During ROSE, forceps biopsy was performed to obtain the specimen for histology and cytology. When ROSE was not diagnostic, additional bronchoscopic examinations, such as transbronchial needle aspiration (TBNA), bronchial washing, or ultrathin bronchoscopy, were performed to obtain additional samples just after conventional bronchoscopy. For the analysis, we defined both the material subjected to Papanicolaou staining and the material obtained by biopsy as conventional

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samples. The material obtained by additional bronchoscopic examinations after ROSE was defined as additional samples.

CYTOLOGY AND HISTOLOGY EXAMINATION

We used rapid Shorr stain as a rapid cytology test, which we have recently developed by modifying the Shorr stain.[9] Rapid Shorr stain completes staining very fast (approximately 1 minute) and presents similar coloring to Papanicolaou staining; therefore, it is familiar to the cytoscreeners in our institute. The cytopathologist was able to provide a preliminary diagnosis within a few minutes. Papanicolaou staining was performed after bronchoscopic examination. Tissue specimens obtained by forceps biopsy were fixed in formalin, embedded in paraffin, and stained with hematoxylin-eosin. Additional specific staining was performed when necessary.

PATIENTS

We performed 1900 flexible bronchoscopic examinations between January 2001 and December 2004. Based on the results of chest radiograph and CT, 795 patients were thought to have central lesions and underwent bronchoscopy without fluoroscopy; 1105 patients underwent fluoroscopy-guided bronchoscopy. ROSE was not performed in the examinations to obtain samples for bacterial testing, for visible lesions, or to evaluate lesions diagnosed before, etc. ROSE was not used for the patients entered into another study performed during the same period in which ROSE was not integrated. Other patients' samples were not subjected to ROSE because only a single trial to obtain bronchoscopic material was possible because of patients' stress during bronchoscopy. Excluding these from the 1105 patients who underwent fluoroscopy-guided bronchoscopy, 657 patients received fluoroscopy-guided bronchoscopy with ROSE. ROSE was repeated when we thought it possible and necessary. Despite negative ROSE results, the lesions of very likely malignant or difficulty except for bronchoscopy, we tend to repeat ROSE. If a diagnosis could not be made via bronchoscopy, further work-up for the lesions included surgical procedures, TCNB, follow-up by bronchoscopy, chest radiograph and CT, and sputum investigations.

RESULTS

Bronchoscopic examinations with ROSE were performed under fluoroscopic guidance for 657 peripheral lung lesions. Patient characteristics are listed in Table 1. The final diagnosis of malignant and benign disease was determined in 528 and 117 lesions, respectively. The remaining 12 lesions were not diagnosed and subjected to careful follow-up. Malignant lesions consisted of adenocarcinoma (n = 328), squamous cell carcinoma (n = 87), small cell carcinoma (n = 32), carcinoid (n = 20), large call carcinoma (n = 7), lymphoma (n = 3), metastatic carcinoma (n = 22), and other malignancies (n = 29).

As shown in Table 2, 393 lesions were diagnosed as malignant by using conventional samples alone. ROSE definitively detected malignant cells in 357 malignant lesions but failed to detect atypical cells in 36 malignant lesions. The false-negative rate of ROSE was 9.2% compared with diagnosis based on conventional samples. In ROSE, a limited time period is permitted for screening and diagnosis. However, cancer cells were detected in only one sample with a negative ROSE result by subsequent re-diagnosis with sufficient time. There was no false-positive result in ROSE. However, final diagnosis was obtained with the additional samples in 84 of 135 malignant lesions that were not diagnosed with conventional samples alone. Therefore, the integration of ROSE into bronchoscopic examination improved the diagnostic sensitivity from 74.4% to 90.3% (Figure 1*A*). The improvement of sensitivity was statistically significant ($p < 0.05$) and enabled effective diagnosis for peripheral lung lesions.

TABLE 1. Patient characteristics

Sex	All patients	Patients with malignancy
Male	411	344
Female	246	184
Age (year)		
Range	25–89	27-87
Average	65.7	66.5
Chance of discovery		
Annual screening	250	183
Tests for other diseases	223	176
Subjective symptoms	163	151
Others	21	18
Smoking status		
Smoker	223	190
Ex-smoker	161	136
Non-smoker	210	156
Unknown	63	46

Additional samples for diagnosis were collected by brushing, curetting, forceps biopsy, TBNA, ultra-thin-bronchoscopy, and washing from the same or other bronchi. Sometimes, several methods were combined for obtaining a specimen. The methods to obtain additional specimens were determined based on the bronchoscopic access to the lesions and the condition of patients. We analyzed additional approaches contribute to the improvement of diagnostic accuracy (Table 3). Whereas brushing showed low diagnostic yield, curetting or forceps biopsy from the other branch, TBNA, and forceps biopsy with ultra-thin bronchoscope yielded more than a 65% positive rate in additional approaches. Washing was also useful for diagnosis in additional approaches, but malignant cells were usually detected by the other methods conducted at the same time.

Surprisingly, ROSE provided more benefit for the diagnosis of small-sized lesions (≤2 cm) (Figure 1*B*). With conventional samples, 110 of 174 small-sized malignant lesions (63.2%) were diagnosed by bronchoscopy. With the help of ROSE, 40 lesions (23.0%) were diagnosed only with an additional sample. Improvement of diagnostic rate for small lesions was significantly greater than that for larger lesions (23.0% versus 12.4%; $p < 0.05$). No significant improvement was observed among the other factors in exam-

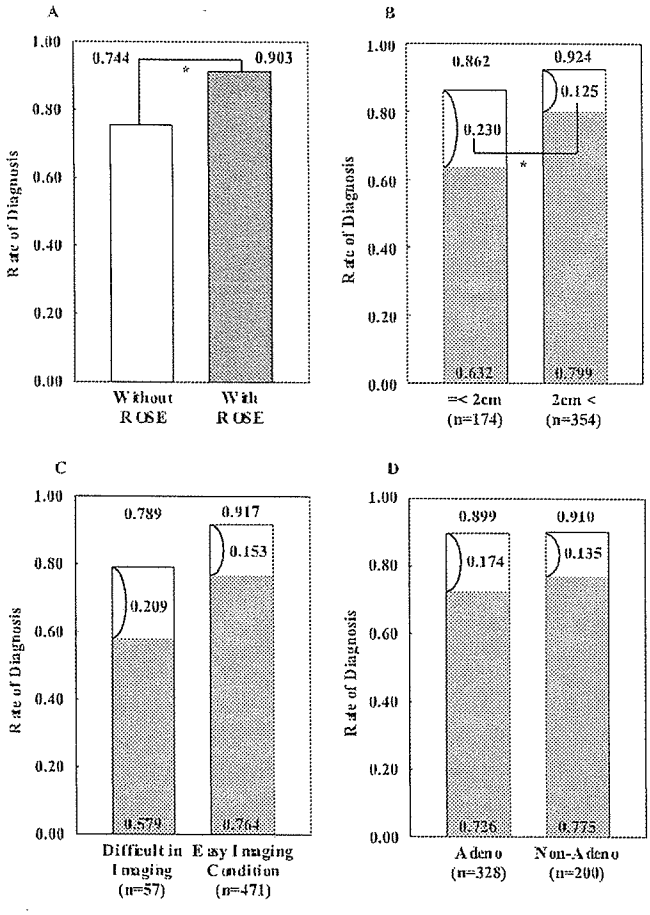

FIGURE 1. ROSE improved diagnostic yield and lesion features. *A*, ROSE improved diagnostic sensitivity. The *gray bar* shows the diagnostic sensitivity of fluoroscopy-guided bronchoscopy with ROSE; the *white bar* shows the diagnostic sensitivity of bronchoscopy without ROSE. The sensitivity is significantly different ($p < 0.05$). *B*, Tumor size and improvement of diagnostic sensitivity by ROSE. The *shaded area* indicates diagnostic sensitivity without ROSE. The improvement in small lesions was better than that in large lesions ($p < 0.05$). *C*, Imaging conditions of the lesions under fluoroscopy revealed diagnostic yield but little difference in improvement by ROSE. The *shaded area* indicates diagnostic sensitivity without ROSE. *D*, Histology type made little difference in diagnostic sensitivity and improvement by ROSE. The *shaded area* indicates diagnostic sensitivity without ROSE.

inations (Figure 1, *C* and *D*). Examination of poorly visible lesions in fluoroscopy had low sensitivity (n = 57, 78.9%) compared with that of clearly visible lesions (n = 471, 91.7%). The improvement by ROSE was slightly higher in examinations for poorly visible lesions (21.1% versus 15.3%), although the difference was not statistically significant. Little improvement by ROSE was shown between histology types of the lesions: adenocarcinoma 52.3%, squamous cell carcinoma 56.3%, small cell carcinoma 50%, and metastatic carcinoma 40.0% of ROSE-negative lesions. Our results also showed the difficulty in diagnosing lesions in the upper lobe and S6, especially in right lung with conventional samples. However, a comparable improvement of diagnostic yield was achieved with ROSE in most areas (from 40% to 60% of ROSE-negative lesions). We calculated the diagnostic yields with conventional samples and additional samples for each examiner to determine the effect of skill level of examiners on usefulness of ROSE. Although the skill level of the examiner tends to correlate to diagnostic yield with conventional samples, improved diagnosis by ROSE was observed similarly in almost all of the examiners (approximately 40% to 52% of ROSE-negative cases).

ROSE was repeated to make a decision for further examinations when access to the lesion was not satisfactory and an additional approach was considered to be possible. We calculated the effect of repeated ROSE on the diagnostic yield of peripheral lung cancer by fluoroscopy-guided bronchoscopy and found that a diagnostic improvement of 89.4% was attained by the first ROSE and 3.2% by the second ROSE (Table 4). Repeated ROSE improved diagnosis in only five of 107 examinations.

DISCUSSION

Bronchoscopic examination with fluoroscopic guidance is often used to obtain a diagnostic specimen of lung nodules. However, most reports have shown relatively low accuracy of diagnosing peripheral lesions by bronchoscopy.[10–12] Bandoh et al.[8] reported refined accuracy up to 91% by combining multiplanar reconstruction images and ultra-fast Papanicolaou staining. They used a historical control for comparison and multiplanar images for another tool. Our study was designed to improve the bronchoscopic diagnosis of peripheral malignant lesions by introducing only ROSE and was performed prospectively in routine bronchoscopic examinations. Therefore, more precise analysis could be performed to estimate ROSE's effectiveness. Our result shows that diagnostic sensitivity of peripheral malignant lesions was improved from 74.4% to 90.3% with ROSE only.

To obtain rapid diagnosis during bronchoscopy, the staining method should be convenient and fast and should present suitable coloring for diagnosis. Several staining methods are applied in ROSE.[8,14,15] We selected rapid Shorr staining for ROSE that we established recently[9] because it is simple, rapid, and similar in coloring to Papanicolaou staining, which is familiar to cytoscreeners and cytopathologists. Additionally, rapid Shorr staining requires only a small area for staining. Rapid Shorr staining is reliable, with low false-positive and false-negative rates.

To improve sensitivity, a method for obtaining additional samples should be carefully determined. When another visible bronchus could be a suitable path to the lesion, we selected this path. When the visible route to the lesion could not be improved, we changed the method for approaching to lesions to TBNA, ultra-thin bronchoscopy, or washing. Comparison among the methods indicates that TBNA and ultra-thin bronchoscopy were most effective in the approach through the same bronchus. In the approach through different bronchi, curetting and biopsy were effective for diagnosis, whereas TBNA was a good alternative (Table 3). Therefore,

TABLE 2. Results of bronchoscopic examinations with ROSE

ROSE	Final diagnosis	Diagnosis by conventional samples	Diagnosis by additional samples	Diagnosis by different examinations
Negative	279			
Malignant	154	26	80	48
Benign	113	13	2	98
Unknown	12	0	0	12
Positive suspected	21			
Malignant	17	10	4	3
Benign	4	1	0	3
Unknown	0	0	0	0
Positive	357			
Malignant	357	357	0	0
Benign	0	0	0	0
Unknown	0	0	0	0

ROSE, rapid on-site cytopathologic examinations.

TABLE 3. Methods of additional sampling for diagnosing malignant lesions

	Tested lesions	Sole positive	Positive
Brushing	16	0 (0.0%)	4 (26.7%)
(from other branch)	4	0 (0.0%)	1 (25.0%)
Curetting and forceps	101	33 (32.7%)	51 (50.5%)
(from other branch)	14	12 (85.7%)	13 (92.9%)
TBNA	35	16 (45.7%)	25 (71.4%)
(from other branch)	7	4 (57.1%)	6 (85.7%)
Washing	29	3 (10.3%)	12 (41.4%)
(from other branch)	4	1 (25.0%)	2 (50.0%)
Forceps with ultra-thin bronchoscope	20	14 (70.0%)	20 (100%)
Washing with ultra-thin bronchoscope	16	0 (0.0%)	11 (68.8%)

TABLE 4. Diagnostic yield of malignant lesions by repeated ROSE

ROSE	Bronchoscopic examinations	Additional examination	Diagnostic yield	Accumulated sensitivity
0	657		393	74.4%
1	657	214	79	89.4%
2	126	94	3	90.0%
3	20	12	2	90.3%
4	1	1	0	90.3%

ROSE, rapid on-site cytopathologic examinations.

alternative routes or methods such as TNBA or ultra-thin bronchoscopy should be considered when ROSE is not diagnostic. We do not recommend brushing and washing.

It has been reported that the size of the lesion has negative correlation to the sensitivity of bronchoscopy. Our results also showed low sensitivity for small lesions (≤2 cm). Surprisingly, however, improvement of diagnostic yield by ROSE was more prominent in diagnosing small lesions (Figure 1*B*). We analyzed the relationship between the size of lesions and the methods by which diagnosis could be made with additional samples. There was no distinct difference in frequency of usage of each method and its ability to yield additional diagnoses between the small and large lesions. Therefore, the reason why diagnostic yield improved more in smaller lesions is not known. One possible explanation is poor fluoroscopic targeting for smaller lesions in bronchoscopy. We used biplane fluoroscopy, but not CT, to determine whether the tip of sampling tools reached the lesions. It is reasonable that the error in targeting by this method is greater for small lesions than for large lesions. ROSE may have improved diagnostic yield partly by correcting the error in targeting.

There are several factors other than the size of tumors related to diagnostic yields. The experience of the examiners relates to the diagnostic sensitivity of bronchoscopic examinations.[16] The location of the lesion, histology type, and visibility under fluoroscopy can influence the yield. We analyzed the relationship between these factors and diagnostic yield. Experience of examiners, location of the lesion, and fluoroscopic visibility of lesions showed some relation to the diagnostic yield. However, improvement of diagnosis by ROSE was similarly observed for all examiners. Diagnostic yield of the lesions in the upper lobe and S6 was relatively low. However, we did not observe a clear difference of improvement by ROSE by location. Examinations for poorly

visible lesions under fluoroscopy showed low sensitivity compared with clearly visible lesions. The improvement by ROSE was slightly higher in the examinations for poorly visible lesions, although not statistically significant. Comparison among histology types of the lesions showed little difference in sensitivity and improvement by ROSE. We encourage the use of ROSE for diagnosing peripheral lesions, especially those of small size, regardless of their location, fluoroscopic visibility, or experience of the examiners.

We usually performed curetting and forceps biopsy only once before ROSE. Although repeated curetting and biopsy were thought to improve sensitivity, we repeated the collection of specimens only in negative ROSE cases, including false negatives. We performed additional examinations for only 214 cases with ROSE and showed an increased sensitivity by 14.9% instead of performing repeated curetting and biopsy in most of the 657 cases without ROSE. ROSE enabled us to avoid unnecessary examinations, even including false-negative cases. Considering the low effectiveness of repeated ROSE, single ROSE is recommended. Recently, CT screening and positron emission tomography have been experimentally introduced for the early detection of lung cancer.[16–18] We expect to diagnose peripheral lung nodules more safely and accurately in the future. The combination of ROSE with fluoroscopy-guided bronchoscopy is encouraged as a conventional method to enhance its safety and sensitivity.

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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

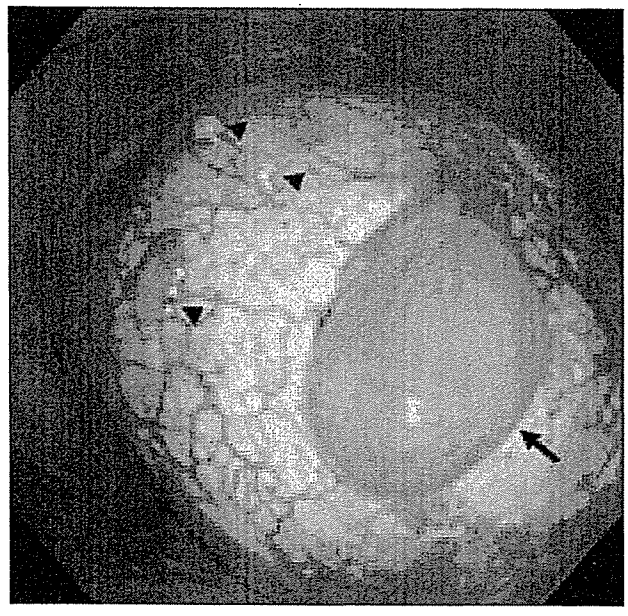

Figure 1. Left thoracoscopy showed a pleural cyst measuring 1.5cm in diameter (arrow) and adjacent daughter cysts (arrowheads) on the diaphragmatic pleura.

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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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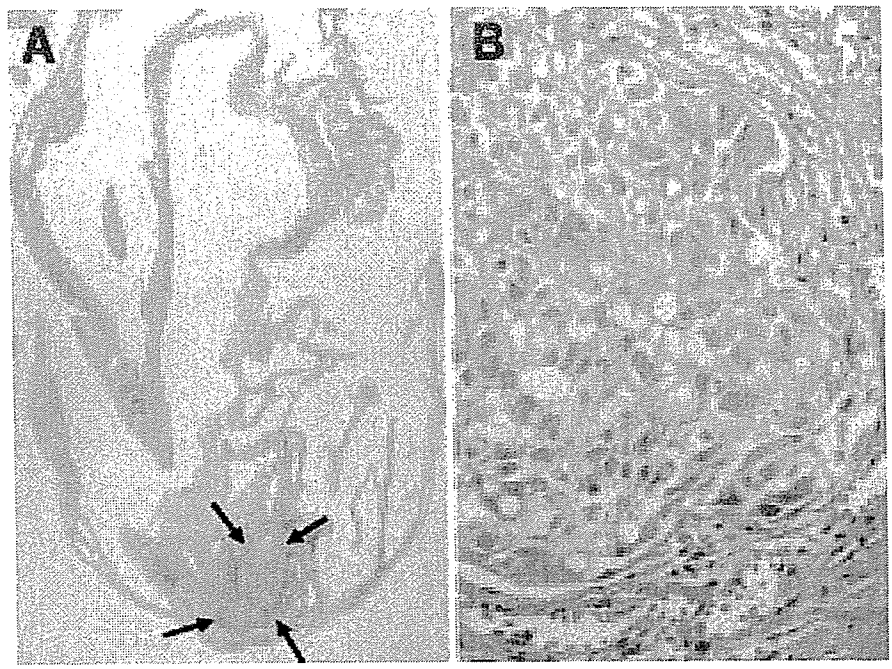

Figure 2. A: Microscopically, the pleural cyst was unilocular. A small focus of adenocarcinoma was recognized in the cyst wall (arrows). B: Most tumor cells had abundant clear or pale eosinophilic cytoplasm, oval nuclei and inconspicuous nucleoli. Stain: hematoxylin and eosin; magnification A: ×2.5,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

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]

RESULTS

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.

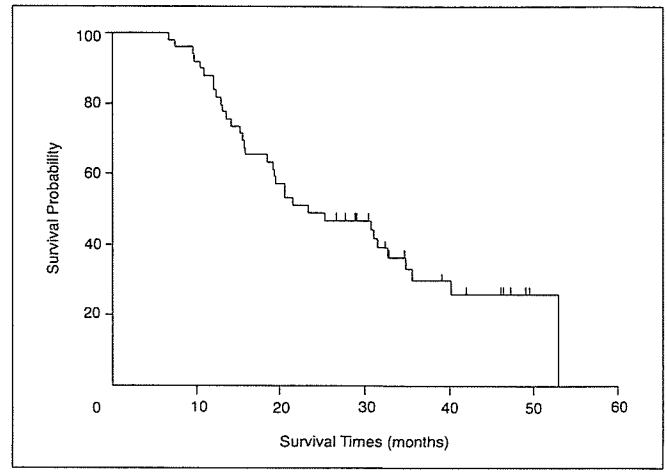

Fig 1. Kaplan-Meier survival curve of 49 eligible patients with limited-disease small-cell lung cancer. The median survival time was 23 months, and the 2-year and 3-year survival rates were 49% and 29.7%, respectively.

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.

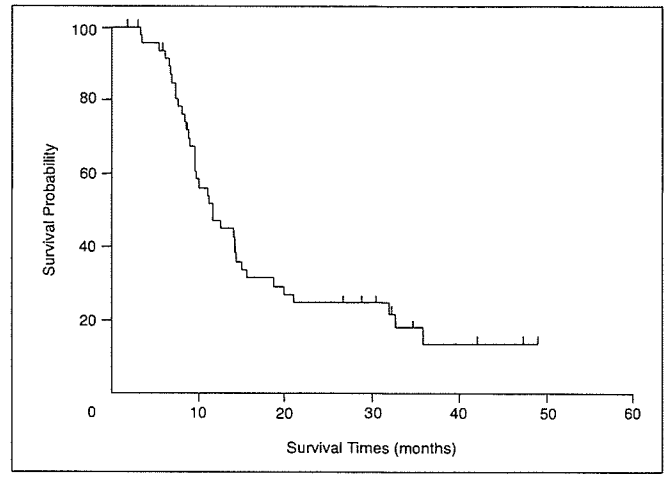

Fig 2. Kaplan-Meier progression-free survival curve of 49 eligible patients with limited-disease small-cell lung cancer. The median progression-free survival time was 11.8 months.

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

DISCUSSION

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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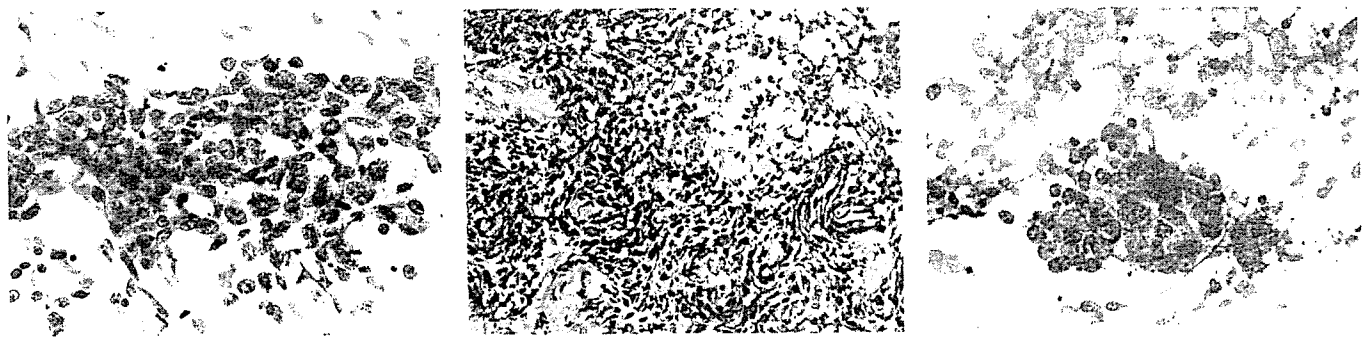
CASE REPORTS

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.

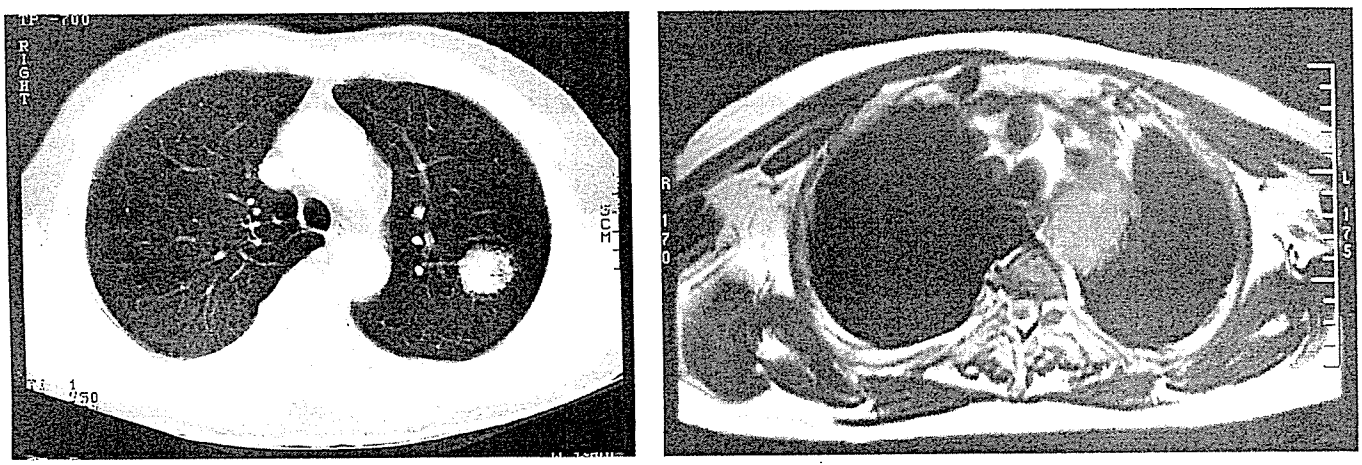
The patient underwent transurethral resection for early-stage bladder cancer (second malignancy) in January 2002 and received radiotherapy (75 Gy) for A2 (early) prostate carcinoma (third malignancy) in March 2004.

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)

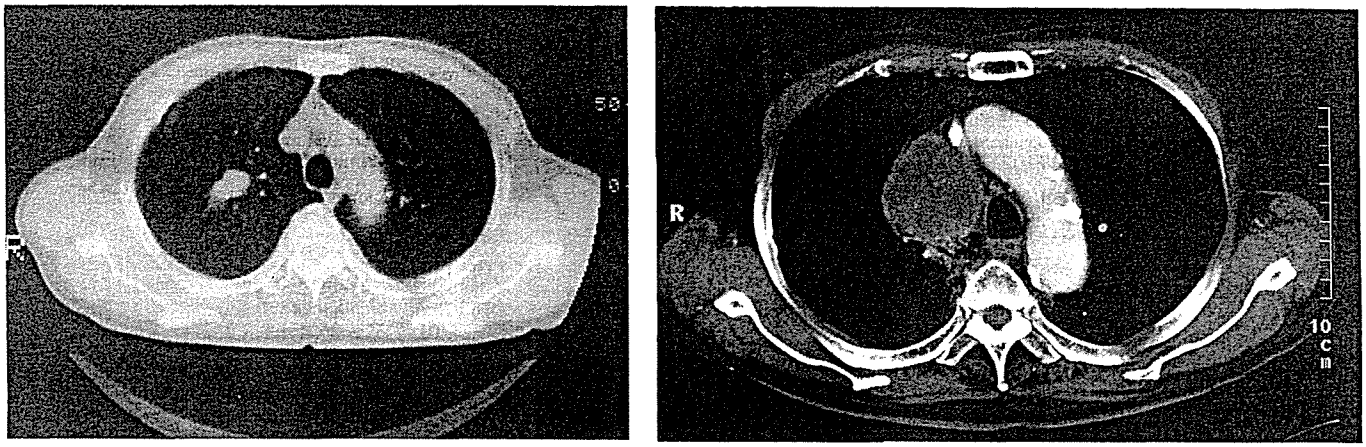
Figure 2. Findings on Chest CT (a) at diagnosis in July 1994 in Case 1. Findings on MRI (b) at relapse in 2004. There is mediastinal lymph node enlargement: size, 40 × 50 mm.

(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

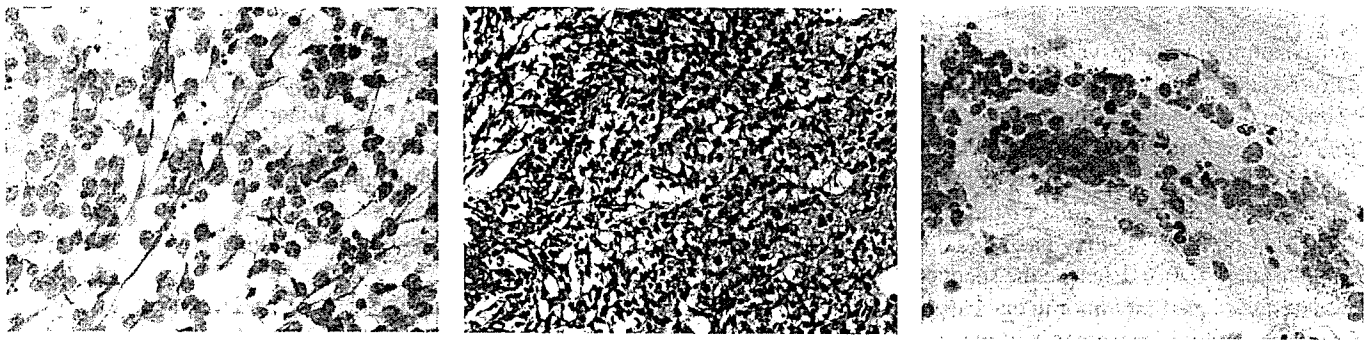
In April 1987, a 72-year-old man visited our hospital with a month's history of productive cough and blood-streaked sputum. He had smoked one packet of cigarettes a day for 52 years; however, he stopped smoking at the first diagnosis of lung cancer. A CXR showed a right upper lobe mass, which was confirmed 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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