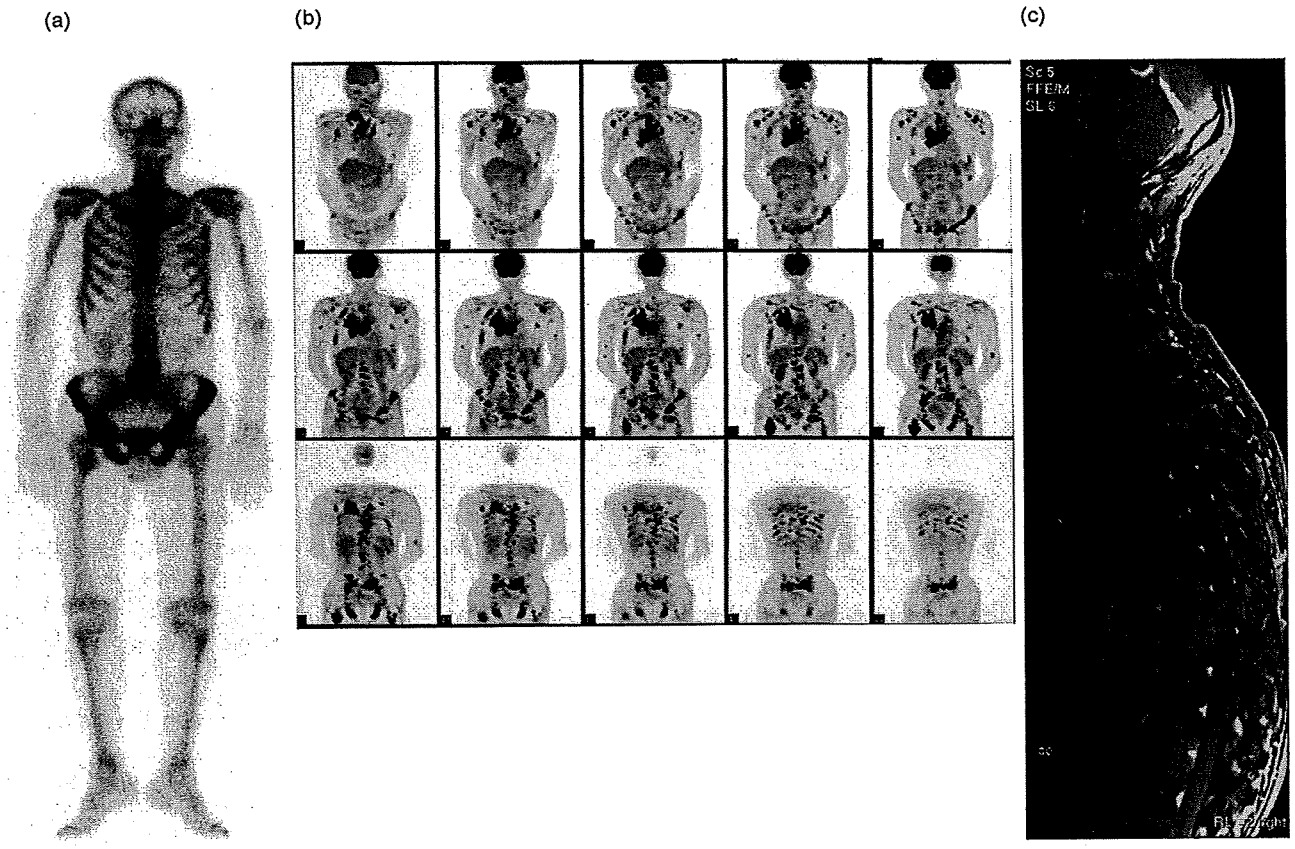

Fig. 1 A 61-year-old man with small-cell lung cancer. Bone scintigraphy was negative for osseous metastasis (a). However, PET scan demonstrated increased FDG uptake in bones throughout the body (b). MRI of the spine confirmed multiple bone metastases (c).

mediastinal lesion showed no change although the primary tumour had decreased in size and atelectasis of the right middle lobe was improved. The mediastinal lymph nodes were considered negative for metastasis (No. 61).

4. Discussion

SCLC tends to disseminate early in the disease course and displays a more aggressive clinical behaviour than NSCLC. Local treatment modalities alone such as radiotherapy or surgery are not effective in prolonging survival beyond a few weeks. Systemic chemotherapy is the mainstay of treatment for patients in all stages of SCLC. A combination of chemotherapy and thoracic irradiation can promote long-term survival for patients diagnosed as having limited disease and recent clinical trials of chemoradiotherapy for LD-SCLC obtained 5-year survival rates of 24–26% [2,3]. However, thoracic irradiation might cause severe radiation pneumonitis, resulting in respiratory failure and/or treatment-related death. Furthermore, thoracic irradiation might also cause oesophagitis which worsens patient quality of life. Accurate clinical staging is important to determine the indications for chemoradiotherapy in SCLC. Our study demonstrated that FDG-PET scan detected unsuspected distant metastases in 8% of patients with LD-SCLC based on conventional staging procedures and that the detection of these new lesions changed their therapeutic strategies. Furthermore, FDG-PET scan detected regional lymph node metastases which had not been visualized on CT scan in 14% of patients. The radiation field could be appropriately set to cover the positive nodes based on the PET study results. Our results reconfirmed those of a previous preliminary study with a smaller number of patients [9].

Is the rate of the detection of unsuspected distant metastases (8%) clinically significant? Previous studies demonstrated that FDG-PET scan detected unsuspected distant metastases in 24% of patients with stage III NSCLC [6,7]. Compared to this result, the impact of FDG-PET on the staging of SCLC seems to be weaker. SCLC tends to have more obvious distant metastases than NSCLC, because of the aggressive biological behaviour of SCLC. Therefore, FDG-PET might detect unsuspected distant metastases at a relatively low rate. The most common region for unsuspected PET-detected metastasis in NSCLC was the abdomen, with 53% of pateints having adrenal, liver, and other lesions [6]. In our study, FDG-PET detected bone metastases in four of five patients who were upstaged from LD to ED. These lesions might reflect metastasis to the bone marrow, although no pathological evidence was obtained, because neither bone marrow biopsy nor aspiration cytology was routinely conducted for the initial clinical staging.

Our retrospective analyses have several limitations. We did not confirm histologically regional lymph node or distant metastases detected by FDG-PET or CT. These lesions were not routinely biopsied and most metastatic lesions were chemosensitive and radiosensitive. Our confirmation was inevitably based on observation of the clinical course.

Table 2 Disagreement between FDG-PET and conventional staging procedures (regional lymph node metastases)

Patient no.	Age (years)	Gender	CT N	PET N	PET M	Interval between CT scan of the chest and FDG-PET (days)	Comments
1	63	Male	3	3	0	8	Contralateral supraclavicular lymph node metastasis (PET)
5	64	Female	1	2	0	34	Subcarinal lymph node metastasis (PET)
16	71	Male	3	3	0	7	Contralateral supraclavicular lymph node metastasis (PET)
20	69	Male	3	3	0	20	Ipsilateral supraclavicular lymph node metastasis (PET)
25	60	Male	3	3	0	27	Ipsilateral supraclavicular lymph node metastasis (PET)
30	66	Male	2	2	0	7	Pretracheal lymph node metastasis (PET)
33	72	Male	3	3	0	13	Ipsilateral supraclavicular lymph node metastasis (PET)
41	49	Female	3	3	0	19	Contralateral supraclavicular lymph node metastasis (PET)
43	73	Male	2	0	0	34	False-positive pretracheal lymph node metastasis (CT)
56	48	Female	3	3	0	11	Ipsilateral supraclavicular lymph node metastasis (PET)
61	74	Male	2	0	0	27	False-positive superior mediastinal and subcarinal lymph nodes (CT).

FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; N, node; M, metastasis.

We employed no special strategies to reduce the bias of PET readers. PET readers might have reported in such a way as to reduce or increase the impact of PET. One-third of patients received FDG-PET after commencement of chemotherapy. However, the median interval between commencement of chemotherapy and FDG-PET was 4 days (range: 1–11 days). We considered the chemotherapy to have had no effects on the findings of FDG-PET in such a short time after the initiation of chemotherapy.

FDG-PET is expected to have the potentially to both up- and downstage patients with SCLC as well as NSCLC. A previous study demonstrated that FDG-PET correctly downstaged ED to LD in three of 120 patients with SCLC [10]. These three patients had adrenal swelling on CT scan, but these lesions were negative on FDG-PET. On the other hand, FDG-PET correctly upstaged LD to ED in 10 of 120 patients with SCLC. It seems that SCLC seldom has a solitary distant metastasis because of its aggressive clinical behaviour. Most ED-SCLC has multiple, not solitary, or obvious distant metastasis. Furthermore, the health insurance system does not allow patients who obviously have metastatic lung cancer to receive FDG-PET in Japan. Therefore, we did not include patients with ED-SCLC in our analysis. Needless to say, FDG-PET is considered to be useful in patients with possible, but not evident, distant metastasis on other imaging tests, such as a solitary adrenal swelling.

According to the VALSG system, LD-SCLC is defined as a tumour confined to one hemithorax and regional lymph nodes [1]. Contralateral hilar or contralateral supraclavicular nodal involvement was classified as ED. According to the International Association for the Study of Lung Cancer (IASLC) consensus report, the classification of LD-SCLC includes bilateral hilar and/or supraclavicular nodal involvement, and ipsilateral pleural effusion [18]. A previous retrospective study demonstrated that the IASLC staging criteria for SCLC patients had a higher prognostic impact than VALSG criteria [19]. Therefore, we adopted the IASLC staging criteria for SCLC in our study.

In conclusion, FDG-PET scans detected unsuspected distant metastases in five of 63 patients with LD-SCLC (95% CI: 3–18%) and these findings resulted in a change of therapeutic strategies in these five patients. FDG-PET scans also detected contralateral supraclavicular lymph node metastases that had been negative on CT scans in three other

patients. These additional findings facilitated setting appropriate irradiation fields. FDG-PET scan is recommended as an initial staging tool in patients with apparent LD-SCLC.

Conflict of interest

The authors certify that there are no potential conflicts of interest.

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Concurrent Chemoradiotherapy with Cisplatin and Vinorelbine for Stage III Non-small Cell Lung Cancer

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Introduction: Concurrent chemoradiotherapy with full doses of cisplatin-based chemotherapy is standard treatment for inoperable stage III non-small cell lung cancer (NSCLC). Although many platinum-based two drug combinations with third-generation agents are difficult to combine fully with thoracic radiotherapy (TRT), a phase I study reported a full dose of cisplatin (CDDP) plus 80% dose of vinorelbine (VNR) was successfully combined with concurrent TRT.

Methods: Between October 2000 and October 2004, 73 patients with inoperable stage III NSCLC treated with CDDP, VNR, and concurrent TRT were retrospectively analyzed. Patients were treated with CDDP 80 mg/m^2 on day 1 and VNR 20 mg/m^2 on days 1 and 8 every 4 weeks. Radiotherapy was administered concurrently in cycle 1. The total radiation dose was 60 Gy in 30 fractions. Common Terminology Criteria for Adverse Events version 3.0 were used to assess treatment-related adverse events.

Results: Median age was 63 years (40–78). Twenty-nine patients had adenocarcinoma, 63 were male, 47 ECOG PS 1, and 47 stage IIIB. Median chemotherapy cycle was 2.0. Objective response rate was 93% and median survival time was 21 months. Three-year overall survival rate was 33%. Infield control rate was 71%. The most common grade 3 or 4 adverse event was leukocytopenia (67%). Only 3 patients (4%) experienced grade 3 esophagitis. One patient died of radiation pneumonitis 87 days after completion of chemoradiotherapy.

Conclusions: Concurrent chemoradiotherapy with CDDP and VNR was highly active and well-tolerated. This regimen could be used as a control arm in future trial for stage III NSCLC.

Key Words: Concurrent chemoradiotherapy, Non-small cell lung cancer, Cisplatin, Vinorelbine.

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Lung cancer is the leading cause of cancer-related deaths throughout the world, including Japan.[1] Stage III inoperable non-small cell lung cancer (NSCLC) constitutes approximately 30% of all newly diagnosed cases of NSCLC.[2] Historically, patients with stage III NSCLC were treated with thoracic radiotherapy (TRT) alone. Nevertheless, the survival of patients treated with TRT alone was poor, with a 5-year survival rate of approximately 5%.[3] As the treatment option of chemoradiotherapy (CRT) has developed, the survival of patients with stage III NSCLC has improved, with 3-year survival of approximately 15–20% and median survival time (MST) of 15–20 months.[4,5] Several randomized trials have demonstrated that concurrent CRT using full dose of cisplatin-based chemotherapy improves long-term survival compared with sequential CRT.[6–9] Although two-drug combinations with cisplatin (CDDP) and third-generation agents including vinorelbine (VNR), docetaxel, paclitaxel, gemcitabine, and irinotecan are standard chemotherapy regimens for stage IV NSCLC[10–12], it is difficult to deliver full doses of these regimens and concurrent TRT because of excessive toxicity.

Recently a phase I trial of CDDP, VNR, and concurrent RT was reported.[13] The recommended doses were CDDP 80 mg/m^2 on day 1 and VNR 20 mg/m^2 on days 1 and 8. Although this was a phase I study, an encouraging survival rate of 50% at 3 years was reported. On the basis of this result, we have treated inoperable stage III NSCLC patients with CDDP, VNR, and concurrent RT in clinical practice at the National Cancer Center Hospital East, Japan. Herein is our review of the efficacy and tolerability of CRT with CDDP and VNR.

MATERIALS AND METHODS

The objective of this retrospective analysis was to evaluate the efficacy and tolerability of concurrent CRT using CDDP and VNR.

Patient Selection

We reviewed consecutive 106 inoperable stage III NSCLC patients who were treated with CDDP, VNR, and concurrent TRT at the National Cancer Center Hospital East, Japan, between October 2000 and October 2004. Clinically apparent or histologically/cytologically proven N2/N3 disease or T4 otherwise pulmonary metastasis in the same lobe was considered "inoperable." Chest CT, abdominal CT/ultrasonography, bone scintigram or FDG-PET, and brain MRI/CT were performed in all patients. In general, lymph nodes that were larger than 1.0 cm in minor axis were considered as metastatic. Lymph nodes that were involved in multiple stations were considered 'clinically apparent N2/3.' To con-

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firm N2 disease, which was detected in chest CT and considered 'not apparent,' FDG-PET and/or mediastinoscopy was performed. FDG-PET (or PET/CT) was performed in 18 patients. Mediastinoscopy was performed in ten patients. In addition, there were 5 histologically/cytologically confirmed N3 (supraclavicular lymph nodes) diseases. Thirty-three patients were excluded because they participated in a clinical trial that evaluated CDDP plus VNR followed by docetaxel,[14] therefore 73 patients were evaluated in the present analysis. Data of survival, recurrence, and treatments after failure were obtained from medical records. All patients were evaluated at weekly case conference in which radiation oncologists and medical oncologists who had special expertise in thoracic oncology made treatment decisions. Inclusion criteria for CRT in our institution were generally as follows; white blood cell count $>3.0 \times 10^9$/liter, platelet count $>10.0 \times 10^9$/liter, serum creatinine <1.5 mg/dl, total bilirubin <1.5 mg/dl, and transaminase less that twice the upper limit of the normal value. Exclusion criteria were pulmonary fibrosis identified by a chest x-ray, malignant pleural or pericardial effusion, and a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, *severe respiratory failure* and uncontrolled hypertension. All patients gave informed consent before CRT.

Chemotherapy

Chemotherapy consisted of CDDP (80 mg/m^2 on day 1) and VNR (20 mg/m^2 days on 1 and 8). Treatment cycles were repeated every 4 weeks with a maximum of 3 cycles administered. Cisplatin and VNR were administered by intravenous infusion. All patients received prophylactic antiemetic therapy consisting of 5-HT3 antagonist, metoclopramide, and dexamethasone. If a patient experienced excessive adverse events, dose reduction of both drugs was implemented during the subsequent treatment cycle. When leukocyte or platelet counts were inappropriate, or if infection developed at day 8, VNR was withheld.

Radiotherapy

TRT was administered concurrently in cycle 1. A CT-scan based treatment planning was used in all patients. The clinical target volume (CTV) for the primary tumor was defined as the gross tumor volume plus 0.5–0.8 cm margin taking account of subclinical extension. The CTV for metastatic lymph nodes were the same as the gross tumor volume for metastatic lymph nodes. Metastatic lymph nodes were defined as the lymph nodes that were larger than 1.0 cm in minor axis. Regional lymph nodes (mainly #3, #4, #7), excluding the contralateral hilar and supraclavicular lymph nodes, were included in the CTV for elective nodal irradiation. The planning target volume for the primary tumor, the metastatic lymph nodes, and regional lymph nodes was determined as CTVs plus setup margin (0.5 cm) and internal margins according to the respiratory motion on fluoroscopy (circumferential 0.5 cm, cranial 0.5 cm, and caudal 1.0–1.5 cm). Lung heterogeneity corrections were not used, and the doses were prescribed to the center of planning target volume. Principally, the initial radiation field was planned not to exceed 50% of ipsilateral lung volume on chest radiograph, or since August 2003, V20 of the normal lung (the percent volume of normal lung receiving 20 Gy or more) was planned not to exceed 35%. The total radiotherapy dose was 60 Gy in 30 fractions (5 fractions per week) delivered over 6 weeks. Radiation therapy was delivered with megavoltage equipment (6 mV) using parallel opposed fields up to 40 Gy in 20 fractions including primary tumor, the metastatic lymph nodes, and the regional lymph nodes. A booster dose of 20 Gy in 10 fractions was given to the primary tumor and the metastatic lymph nodes according to the CT obtained after initial 40 Gy radiation, using opposed oblique fields to avoid excessive dose to the spinal cord.

Evaluation of Efficacy and Adverse Events

Overall survival was defined as time from start of chemoradiotherapy to death of any cause. Progression-free survival was defined as time from start of chemoradiotherapy to the first documented disease progression or death. Disease progression was subdivided into infield relapse or not. Chest CT was used to asses if the relapse was within the initial radiation field. Response Evaluation Criteria in Solid Tumor criteria were used to assess the best tumor response. Chest CT was reviewed independently by a radiologist. The response rate was calculated as the total percentage of patients with a complete or partial response. In principle, the chest CT was taken 2 and 4 months after starting chemoradiotherapy and as needed to evaluate the response and toxicity. Treatment-related adverse events were evaluated using the Common Terminology Criteria for Adverse Events Version 3.0. Late toxicities were scored according to the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group late radiation morbidity scoring scheme.

Statistical Analyses

Multivariate analyses were performed using Cox regression models. Expected prognostic factors included age (<70 years versus >70), gender (male versus female), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), clinical stage (IIIA versus IIIB), smoking history (<30 pack-year versus >30), histology (adenocarcinoma versus others), tumor size (<5 cm versus >5 cm), stage (IIIA versus IIIB), and weight loss (<5% versus >5%). Kaplan–Meier methods were used to graphically describe the distribution of survival. All statistical analyses were performed using SPSS II for Windows version 11.0.1J.

RESULTS

Patients' characteristics are shown in Table 1. Median number of chemotherapy cycles were 2.0 (mean 2.4, ranges 1–3). Dose reduction of chemotherapy was implemented in 11 patients mainly due to grade 4 leukocytopenia. Two patients did not receive full dose of radiotherapy. In one patient, radiotherapy was discontinued at the dose of 40 Gy because the tumor was located nearby the spinal cord, and in the other patient because of declined PS.

All 73 patients were assessable for survival, time to progression, response rate, and adverse events. No patient achieved complete response. Partial response, stable disease,

TABLE 1. Patient Characteristics

	Patients (n = 73)	
	No.	%
Age		
Median (range) (yr)	63 (40–78)	
<70 yr	48	66
≥70 yr	25	34
Gender		
Female	10	14
Male	63	86
Histological diagnosis		
Adenocarcinoma	29	40
Squamous cell carcinoma	28	38
Others	16	22
Tumor size		
Median (range) (cm)	5.4 (1.5–12.0)	
<5 cm	33	45
≥5 cm	40	55
ECOG performance status		
0	26	36
1	47	64
Smoking history		
Never smoker	5	7
<30 pack-yr	11	15
≥30 pack-yr	57	78
Stage		
IIIA	26	36
T3N1	3	4
N2	23	32
IIIB	47	64
T4[a]	40	55
N3	12	16
Body weight loss (recent 6 mo)		
<5%	58	79
≥5%	15	21

[a] Six were T4N0, 3 were T4N1, and 5 were T4N3.

TABLE 2. Overall Objective Response

	Number	%
Number of patients evaluated	73	
Complete response (CR)	0	0
Partial response (PR)	68	93.2
Stable disease (SD)	5	7.8
Progressive disease (PD)	0	0
Response rate (95% CI)		93.2 (87.2–99.1)%

CI, confidence interval.

and progressive disease were observed in 68, 5, and 0 patient, respectively (Table 2). The response rate was 93.2% (95% confidence interval; 87.2–99.1%). Median progression free survival time was 12 months and median overall survival time was 21 months with median follow-up of 35 months (ranges 23.7–61.2). Two- and 3-year survival rate was 44 and 33%, respectively. The Kaplan–Meier plots of overall survival are shown in Figure 1; Figure 2 shows progression-free survival. Multivariate analysis showed that no variables significantly affected the overall survival (Table 3).

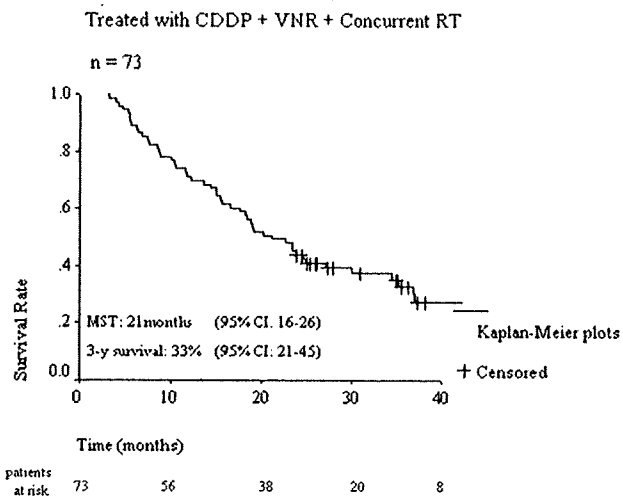

FIGURE 1. Overall survival of patients treated with CDDP + VNR + concurrent RT. CDDP, cisplatin; VNR, vinorelbine; RT, radiotherapy; MST, median survival time; 3-year survival, survival rate at 3 years.

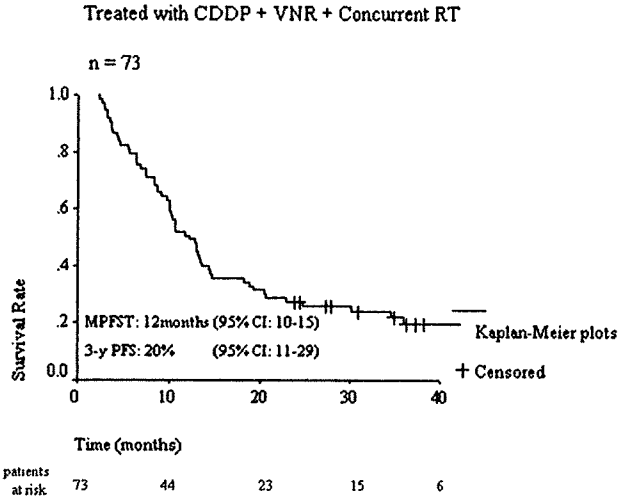

FIGURE 2. Progression-free survival of patients treated with CDDP + VNR + concurrent RT. CDDP, cisplatin; VNR, vinorelbine; RT, radiotherapy; MPFST, median progression-free survival time; 3-year survival, progression-free survival rate at 3 years.

There were 46 disease relapses and 50 deaths. Infield relapses were observed in 21 patients (11 without and 10 with relapse outside of the radiation fields); therefore infield control rate was 71%. Distant metastases were the first sites of the failure in 35 patients; brain (n = 16), bone (n = 10), adrenal gland (n = 5), liver (n = 3), and lung (n = 16). Seventeen patients received docetaxel and 12 received gefitinib as second line treatment. None responded to docetaxel and two patients (16%) responded to gefitinib (and 1 achieved partial response).

TABLE 3. Prognostic Factors Treated with CDDP + VNR + Concurrent TRT (n = 73)

Parameter	Hazard Ratio	95% CI	p
Age (<70 yr vs. ≥70)	1.787	0.941–3.394	0.076
Gender (male vs. female)	1.364	0.490–3.799	0.553
PS (0 vs. 1)	0.818	0.435–1.537	0.533
Clinical Stage (IIIA vs. IIIB)	1.109	0.588–2.093	0.749
Smoking (<30 pack-yr vs. ≥30)	0.698	0.321–1.519	0.365
Tumor size (< 5 cm vs. ≥5)	0.862	0.473–1.569	0.626
Histology (Ad vs. others)	1.565	0.766–3.198	0.219
Body weight loss (<5% vs. ≥5)	1.567	0.786–3.125	0.202

CI, confidence interval; Ad, adenocarcinoma.

The incidence of treatment-related adverse events is listed in Table 4. The most common grade 3 or 4 adverse event was leukocytopenia (67%). Grade 3 or 4 neutropenia was observed in 38 patients (52%). Grade 3 or 4 thrombocytopenia was not observed; grade 3 or 4 anemia occurred in 17 patients (23%). Only 3 patients (4%) experienced grade 3 esophagitis related to radiotherapy. Five patients (7%) developed grade 3 or 4 pneumonitis and one of them died of respiratory failure 87 days after completion of chemoradiotherapy. The autopsy revealed diffuse alveolar damage compatible with radiation pneumonitis and fibrosis. None of the 5 patients with grade 3 or 4 pneumonitis received second line chemotherapy. Another patient of them developed grade 3 pulmonary fibrosis, but no other severe late radiation morbidity was observed.

DISCUSSION

Chemoradiotherapy is standard treatment for patients with inoperable stage III NSCLC. Several trials indicate that concurrent CRT improves long-term survival compared with sequential CRT.[6–9] Nevertheless, the optimal regimen and dose of chemotherapy has not been determined yet. The efficacy of chemoradiotherapy with CDDP and vinca alkaloids or etoposide has been reported, and CDDP plus vindesine with or without mitomycin has been one of the standard chemotherapy regimens.[6,15–17]

VNR is a newer semi-synthetic vinca alkaloid and more active than vindesine against metastatic NSCLC.[18] Zatloukal et al.[8] reported the efficacy of CRT with CDDP and VNR in a randomized phase II trial, which randomized concurrent CRT or sequential. Concurrent arm was favored in overall survival (MST was 16.6 months in the concurrent arm and 12.9 months in the sequential arm). Vokes et al.[19] also reported the efficacy of CRT with CDDP and VNR in randomized phase II trial, which randomized 3 CDDP-based combination chemotherapies with third-generation agents. In this series, MST of all patients were 17 months and 3 year survival of VNR arm was 23%. With these results, concurrent CRT with CDDP and VNR could be considered one of the new standard regimens for stage III NSCLC, although the employed VNR doses in each phase II study were 12.5 mg/m^2 and 15 mg/m^2. Standard doses of CDDP plus VNR for metastatic NSCLC are 80 mg/m^2 of CDDP and 25 mg/m^2 of VNR. The doses of 20 mg/m^2, employed in the present study, are close to the standard. Moreover, 20 mg/m^2 of VNR alone has reported to be active in advanced NSCLC, with response rate of 21.7%.[20]

Results of the present study were encouraging, demonstrating MST of 21 months and a 3-year survival rate of 33%. Our study confirmed clinical usefulness of combination chemotherapy with CDDP, VNR, and simultaneous TRT.

The most common treatment-related adverse events were hematological (grade 3 or 4 leukocytopenia in 67%, neutropenia in 52%, and anemia in 23%), and these were well tolerated. There were 5 patients (7%) who developed grade 3 or more pneumonitis and only one patient (2%) died of radiation pneumonitis. The incidence and mortality of radiation pneumonitis was comparable with other reports.[6,8,9,19,21–24] Recently we have evaluated dose volume histogram and plan V20 not to exceed 35% in CRT, which may contribute to reducing severe radiation pneumonitis.

Low incidence of severe radiation-related esophagitis in our study deserves special mention. In the present study grade 3 esophagitis was developed in only 3 patients (4%), which is lower than other studies of concurrent chemoradiotherapy where radiation-related esophagitis was reported to be in the range of 12–46%,[21–23] with the exception of one study using CDDP, vindesine (VDS), and mitomycin.[6] In this report, the incidence of grade 3 or more radiation-related esophagitis was only 3%. The cause of this difference is still unknown; however, low incidence of esophagitis may correlate with the use of vinca alkaloids and Japanese studies. Further examination is warranted. We believe that highly conformal therapy could reduce the rate of esophagitis. Overall, chemoradiotherapy with CDDP and VNR were well tolerated.

Although the collection of toxicity data retrospectively is of concern, most patients were treated as inpatient through-

TABLE 4. Grade 3 or 4 Treatment-Related Adverse Events (NCI-CTC vs. 3.0, n = 73)

Adverse Event	Grade 3 (%)	Grade 4 (%)
Leukocytes	32	36
Neutrophiles/granulocytes	25	27
Hemoglobin	22	1
Platelets	1	0
Febrile neutropenia	14	0
Infection with grade 3 or 4 neutropenia	1	0
Infection without neutropenia	10	0
Pneumonitis/pulmonary infiltrates	5	1[a]
Radiation esophagitis	4	0
Radiation dermatitis	0	0
Anorexia	16	0
Nausea	8	0
Vomiting	5	0
Diarrhea	1	0
Creatinine	0	0
Supraventricular arrhythmia (atrial fibrillation)	1	0

[a] One patient died from radiation pneumonitis 87 d after completion of chemoradiotherapy.

out the treatment course, and toxicity data were recorded on medical records in detail. It should be confirmed by a prospective study.

Taxanes are also investigated widely in patient with unresectable stage III NSCLC. Weekly administration with carboplatin (CBDCA) plus paclitaxel (PTX) and concurrent RT was reported in multiinstitutional phase II study. Reported MST was promising, with 20.5 months.[25] Nevertheless, recently reported phase III trial compared induction chemotherapy plus CRT with CRT alone, which employed weekly CBDCA and PTX, showed disappointing results, with MST of 14 months and 12 months, respectively.[26] The authors concluded that the routine use of weekly CBDCA and PTX with simultaneous TRT should be re-examined. Chemotherapy with docetaxel (DOC) plus CDDP and concurrent TRT was also reported in a phase I/II study.[21] The result was promising, with MST of 23 months, and phase III trial comparing DOC and CDDP to CDDP, VDS, and mitomycin is currently underway.

Local recurrence was observed in 21 patients (29%), and the brain was also a major site of treatment failure (16 patients, 22%). These results are comparable to the literature.[21] On the basis of these observations, other radiation approaches such as hyperfractionated radiotherapy or high-dose thoracic radiation to improve local control should be considered.[27–31] Moreover, whether prophylactic cranial irradiation reduces the incidence of brain metastases should be confirmed.

Advanced age did not correlate with worse prognosis and it is compatible with literature.[32] Gender, tumor size, body weight loss, smoking status did not significantly correlate with shorter overall survival, and it may be due to the small sample size of our study.

We excluded 33 patients who participated in the trial evaluated consolidation docetaxel after concurrent CRT with CDDP and VNR.[14] Sekine and colleagues reported that majority of patients could not continue with consolidation docetaxel after concurrent CRT with CDDP and VNR because of pulmonary toxicity. Although consolidation therapy using docetaxel seems to be highly effective in SWOG phase II study,[33] randomized phase III trial failed to demonstrate that addition of consolidation docetaxel improves survival.[34]

Two patients did not receive full dose of radiotherapy. Nevertheless, these two patients were treated initially with curative intent. Therefore we included these two patients in this analysis. Moreover, exclusion of these two patients did not alter the results (data not shown).

In conclusion, chemoradiotherapy with CDDP and VNR was promising and well tolerated. This regimen could be used as a control arm in future trial for stage III NSCLC.

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Performance Status and Sensitivity to First-line Chemotherapy Are Significant Prognostic Factors in Patients With Recurrent Small Cell Lung Cancer Receiving Second-line Chemotherapy

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BACKGROUND. To the authors' knowledge, the prognostic factors in recurrent small cell lung cancer (SCLC) patients treated with second-line chemotherapy have not yet been clearly identified to date.

METHODS. Between July 1992 and December 2003, 232 of 515 patients who were diagnosed to have SCLC at the National Cancer Center Hospital East were administered second-line chemotherapy for recurrent disease. The authors retrospectively analyzed the relation between clinical factors evaluated at the time of recurrence and the response to second-line chemotherapy or survival in these patients.

RESULTS. The results of univariate analyses revealed that response was significantly associated with the performance status (PS) alone, whereas survival was significantly associated with the PS, disease extent, and sensitivity to first-line chemotherapy. Multivariate analysis identified PS ($P < .0001$) and sensitivity to first-line chemotherapy ($P = .0024$) as the independent prognostic factors for survival. When the patients were grouped according to these 2 significant prognostic factors, the survival of patients with a PS of 0 to 1 was significantly better than that of the patients with a PS of 2 to 4 both among cases that were sensitive and those that were refractory to first-line chemotherapy. Although the survival of sensitive recurrent cases was significantly better than that of the refractory recurrent cases among the patients with a PS of 0 to 1 patients, no survival difference was observed between the sensitive and refractory recurrent cases in the patients with a PS of 2 to 4.

CONCLUSIONS. Both PS and sensitivity to initial chemotherapy were found to be significant prognostic factors for survival in recurrent SCLC patients treated with second-line chemotherapy. These 2 factors should therefore be used as stratification factors in future clinical trials. *Cancer* **2008;113:2518–23.** © *2008 American Cancer Society.*

KEYWORDS: small cell lung cancer, second-line chemotherapy, prognostic factor, performance status, sensitive recurrence, refractory recurrence.

Although the proportion of small cell lung cancer (SCLC) among cases of lung cancer has been decreasing in recent years, it still accounts for 14% of all new lung cancer cases, and the actual number of patients was estimated to be 77,000 in the US and Europe in 2004.[1] In general, SCLC is an exceedingly aggressive cancer, and greater than 66% of patients have clinically obvious metastatic disease at the time of diagnosis.[2] SCLC is also extremely sensitive to chemotherapy; therefore, the main treatment strategy for SCLC is

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systemic chemotherapy. Currently, both cisplatin plus etoposide (PE) and cisplatin plus irinotecan (IP) are considered as standard chemotherapeutic regimens for SCLC.[3,4] Despite the high initial sensitivity to chemotherapy, the majority of patients develop disease recurrence. The prognosis of patients with recurrent SCLC is usually abysmal, and the overall survival time after recurrence is reportedly 2 to 4 months.[5]

In general, second-line chemotherapy is considered for cases with recurrent SCLC, and a few studies have reported on the efficacy of some second-line treatments.[6,7] For example, a prospective randomized trial comparing oral topotecan with best supportive care (BSC) revealed the benefits of treatment with oral topotecan in terms of the survival and quality of life.[7]

Although some studies have shown the importance of both response and the duration of the response to initial chemotherapy in predicting the efficacy of second-line chemotherapy,[8-10] the number of studies conducted to identify the prognostic factors in recurrent SCLC patients is quite limited. In this retrospective study, we investigated the prognostic factors in recurrent SCLC patients administered second-line chemotherapy to determine the factors that need to be used for stratifying the patients in future clinical trials.

MATERIALS AND METHODS

Patient Flow

Between July 1992 and December 2003, 515 patients were diagnosed to have SCLC at the National Cancer Center Hospital East, and 474 of these patients received initial chemotherapy with or without thoracic radiotherapy. Of 474 patients, radiographic response was observed in 409 patients, with 98 demonstrating complete response and 311 demonstrating partial response. An evaluation in April 2007 revealed that among these responders, 322 had developed disease recurrence, 75 had maintained responses, and 12 patients could not be evaluated for disease recurrence. Thus, 387 patients (including the 322 with disease recurrence and the 65 nonresponders) were considered potential candidates for second-line chemotherapy. Of these, 232 received second-line chemotherapy, whereas the remaining 155 did not. There were no distinct eligibility criteria for second-line chemotherapy, and the decision to administer chemotherapy was based on the patient's general condition and willingness to undergo second-line therapy. The patient flow is shown in Figure 1. Among patients who received second-line chemotherapy, those who deemed to have stable disease or not to be evaluable to first-line chemotherapy were treated right after completion of front-line therapy. All patients' data were obtained from our database.

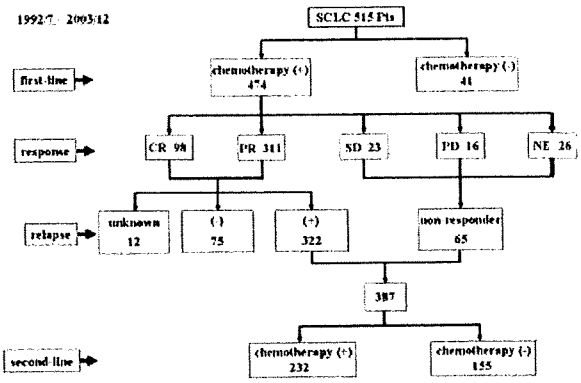

FIGURE 1. Patient flow is depicted. CR indicates complete response; NE, not evaluable; PD, progressive disease; PR, partial response; Pts, patients; SCLC, small-cell lung cancer; SD, stable disease; +, positive; −, negative.

Analyzed Clinical Factors

The correlations between clinical factors evaluated at the time of disease recurrence, such as the age (<70/≥70), sex (women/men), Eastern Cooperative Oncology Group performance status (PS) (0-1 or 2-4), disease extent (limited disease [LD]/extensive disease), sensitivity to first-line chemotherapy (sensitive/refractory), and response to second-line chemotherapy or survival after disease recurrence were retrospectively investigated in the 232 patients. In this study, patients who responded to initial chemotherapy and developed disease recurrence more than 3 months after the completion of chemotherapy were defined as sensitive recurrence cases, whereas patients who did not respond to initial chemotherapy or developed disease recurrence within 3 months were defined as refractory recurrence cases.

Tumor Evaluation and Statistical Analysis

Tumor response was re-evaluated by 2 physicians (Y.H.K. and K.G.) using the Response Evaluation Criteria in Solid Tumors (RECIST).[11] The survival time was measured from the date of disease recurrence. The survival curve was estimated by the Kaplan-Meier method, and compared by the log-rank test. Comparison between each clinical factor and response was performed by the chi-square test. Multivariate analysis was conducted according to the Cox proportional hazard model. $P < .05$ was considered to denote statistical significance. All statistical analyses were performed using StatView statistical

TABLE 1
Characteristics of All Patients at the Time of Disease Recurrence (N = 387)

Characteristics	Second-line Chemotherapy (+) (n=232)	(−) (n=155)	P
Age at recurrence, y			<.0001
Median	65	68	
Range	30-80	28-87	
Gender			.9867
Women	38 (16%)	25 (16%)	
Men	194 (84%)	130 (84%)	
PS at recurrence			<.0001
0-1	162 (70%)	43 (28%)	
2-4	70 (30%)	112 (72%)	
Disease extent at recurrence			.0476
LD	65 (28%)	30 (19%)	
ED	167 (72%)	125 (81%)	
Response to first-line chemotherapy			<.0001
CR/PR	216 (93%)	108 (70%)	
SD/PD	16 (7%)	47 (30%)	
Sensitivity to first-line chemotherapy			.1661
Sensitive	146 (63%)	63 (41%)	
Refractory	86 (37%)	92 (59%)	

+ indicates positive; −, negative; PS, performance status; LD, limited disease; ED, extensive disease; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

software (version 5.0; Abacus Concepts, Berkley, Calif).

RESULTS

Patient Characteristics

The characteristics of the 387 patients who were believed to be potential candidates for second-line chemotherapy (of whom only 232 eventually received second-line chemotherapy, designated as the chemotherapy group) are listed in Table 1. The patients in the chemotherapy group were significantly younger ($P < .0001$), had better PS ($P < .0001$), and had a higher frequency of LD ($P = .0476$) than the nonchemotherapy group. Whereas the response to first-line chemotherapy was significantly different ($P < .0001$), the sensitivity to first-line chemotherapy was not significantly different ($P = .1661$) between the 2 groups, and approximately 33% of the patients who received second-line chemotherapy were refractory recurrence cases. As first-line chemotherapy, 156 patients (67%) had received platinum plus etoposide combination chemotherapy, and 24 (10%) had received the IP regimen. The second-line chemotherapy regimens administered to the 232 patients are listed in Table 2. At our hospital, the vast majority of the patients had received some kind of platinum-based combination chemotherapy, such as cisplatin, vincristine, doxorubicin, and etoposide; cisplatin, etoposide, and irinotecan (PEI); IP; PE; or carboplatin plus etoposide. The distribution of these regimens was similar in the sensitive and refractory recurrence patients.

TABLE 2
Second-line Chemotherapy Regimens Administered to 232 Patients

Regimen	No. of Patients	No. Sensitive (%)	No. Refractory (%)
CODE	80	50 (34)	30 (35)
PEI	44	17 (12)	27 (31)
IP	34	28 (19)	6 (7)
PE	19	13 (9)	6 (7)
CE	14	12 (8)	2 (2)
TOP	14	9 (6)	5 (6)
CPT-11	13	9 (6)	4 (5)
AMR	6	5 (4)	1 (1)
Others	8	3 (2)	5 (6)
Total	232	146 (100)	86 (100)

CODE indicates cisplatin, vincristine, doxorubicin, and etoposide; PEI, cisplatin, etoposide, and irinotecan; IP, cisplatin and irinotecan; PE, cisplatin and etoposide; CE, carboplatin and etoposide; TOP, topotecan; CPT-11, irinotecan; AMR, amrubicin.

TABLE 3
Univariate Analysis for Response and Survival

Characteristics	No. of Patients	Response Rate, %	P	MST, Months	P
Age at recurrence, y					
<70	167	56	.5058	9.0	.6347
≥70	65	62		8.8	
Gender					
Women	38	68	.1826	10.0	.5672
Men	194	55		8.7	
PS at recurrence					
0-1	162	63	.0126	11.0	<.0001
2-4	70	44		4.9	
Disease extent at recurrence					
LD	65	62	.5085	12.6	.0043
ED	167	56		7.3	
Sensitivity to first-line chemotherapy					
Sensitive	146	60	.4413	10.6	.0016
Refractory	86	53		6.8	

MST indicates median survival time; PS, performance status; LD, limited disease; ED, extensive disease.

Predictive and Prognostic Factors

According to the results of the univariate analyses, response was significantly associated with the PS alone, whereas survival was significantly associated with the PS, disease extent, and sensitivity to first-line chemotherapy (Table 3). Survival curves drawn according to the PS and sensitivity to first-line chemotherapy are shown in Figure 2 and 3, respectively. Multivariate analysis identified PS ($P < .0001$) and

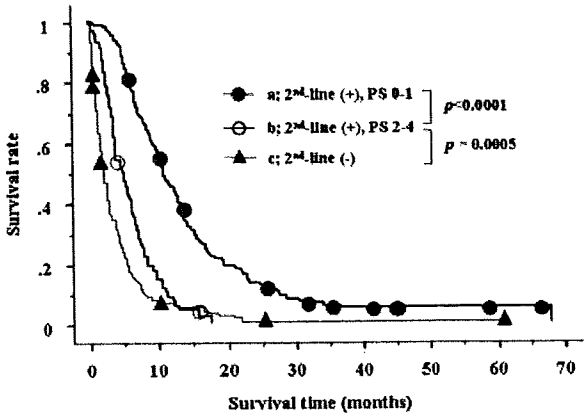

FIGURE 2. Survival curves according to the performance status (PS) at the time of disease recurrence. + indicates positive; −, negative.

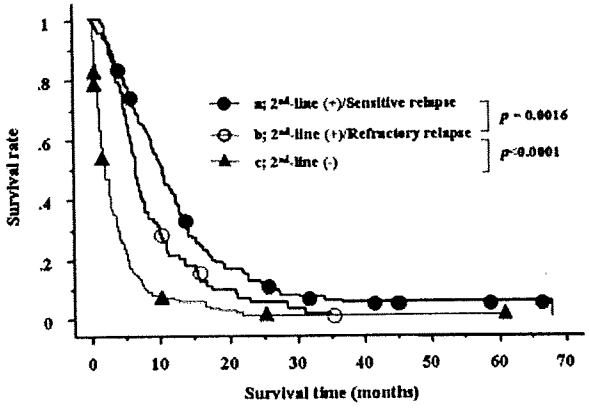

FIGURE 3. Survival curves according to sensitivity to first-line chemotherapy. + indicates positive; −, negative.

sensitivity to first-line chemotherapy ($P = .0024$) as the independent prognostic factors for survival (Table 4). The survival of patients with a PS of 2 to 4 ($P = .005$) (Fig. 2) and refractory disease recurrences ($P < .0001$) (Fig. 3) was significantly better than that of those who did not receive second-line chemotherapy.

In addition, we performed further analysis, in which all patients who received second-line chemotherapy were divided into 4 groups according to the combination of the 2 identified independent prognostic factors for survival: Group A (PS of 0-1/sensitive recurrence), Group B (PS of 0-1/refractory recurrence), Group C (PS of 2-4/sensitive recurrence), and Group D (PS of 2-4/refractory recurrence). The survival curves for each group are shown in Figure 4. The survival of patients with a PS of 0 to 1 was significantly better than that of the patients with a PS of 2 to 4 among both cases with sensitive

TABLE 4
Multivariate Analysis for Survival

Variables	Odds Ratio	95% CI	P
PS at recurrence, 0-1	3.171	2.307-4.357	<.0001
Disease extent at recurrence, LD	1.308	0.956-1.790	.093
Sensitivity to first-line chemotherapy, sensitive	1.544	1.166-2.043	.0024

95% CI indicates 95% confidence interval; PS, performance status; LD, limited disease.

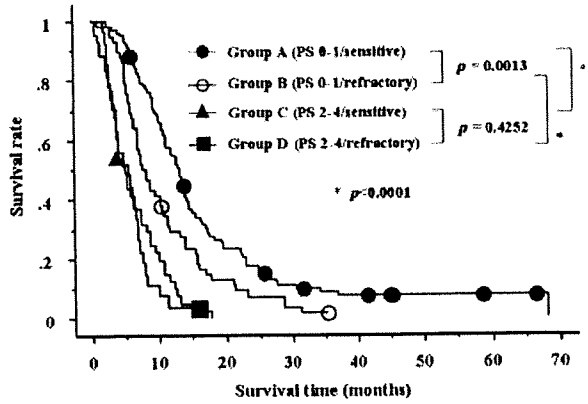

FIGURE 4. Survival curves according to the 2 independent prognostic factors. PS indicates performance status.

(Group A vs Group C; $P < .0001$) and those with refractory recurrence (Group B vs Group D; $P = .0001$). Whereas the survival of the sensitive recurrence cases was significantly better than that of the refractory recurrence cases among the patients with a PS of 0 to 1 (Group A vs Group B; $P = .0013$), no survival difference was observed between the sensitive and refractory recurrence cases among the patients with a PS of 2 to 4 patients (Group C vs Group D; $P = .4252$).

Among the 232 patients who received second-line chemotherapy, 29 received the same regimen as first-line chemotherapy, and the rest received a regimen different from first-line chemotherapy. However, these differences did not appear to have an impact on either response ($P = .7519$) or survival ($P = .5873$).

DISCUSSION

Some studies have shown the importance of both response and the duration of the response to initial chemotherapy in predicting the survival of recurrent SCLC patients receiving second-line chemotherapy,[8-10] and currently it is widely accepted that recurrent SCLC patients should be classified into 2 groups: cases with sensitive recurrence and those with refrac-

tory recurrence.[12] In contrast, Sundstrom et al, who recently analyzed 19 clinical factors at both the time of initial diagnosis and the time of recurrence, have suggested that the PS at the time of disease recurrence, and not the sensitivity status to first-line chemotherapy, was the only significant prognostic indicator for survival after second-line chemotherapy.[13] In this study, we investigated the relation between clinical factors evaluated at the time of disease recurrence and survival after recurrence, and identified both PS and sensitivity to first-line chemotherapy as being significant prognostic factors for survival.

Some may argue that the survival time of the patients with a PS $\geq$3 in this study was too short, which might have strongly influenced the inferior survival of the patients with a PS of 2 to 4 as compared with that of the patients with a PS of 0 to 1. Although our study included 18 cases with a PS $\geq$3 among the patients administered second-line chemotherapy, the results of the analyses were found to be the same even after exclusion of these patients with a PS $\geq$3 (data not shown). This finding suggests that the prognosis of the patients with a PS of 2 is clearly different from that of the patients with a PS of 0 to 1 patients. The diversity of our second-line regimens may be criticized as well, because the differences in the regimens could have affected the patients' outcomes. However, to our knowledge, there are no comparative studies suggesting the superiority of any particular regimen for second-line chemotherapy. At our hospital, as shown in Table 2, mainly platinum-based combination chemotherapy is used even for second-line chemotherapy, and various agents are combined with platinum agents.

The results of the current study indicate that the prognosis of patients with impaired PS is inevitably poor. In such patients, no survival difference was found between the cases with sensitive and those with refractory recurrence. Does this mean that patients with a PS $\geq$2 should not receive second-line chemotherapy? A phase 3 trial comparing oral topotecan with BSC demonstrated a significant survival advantage of oral topotecan, and such survival benefit was also found to be preserved for patients with a PS of 2 who accounted for approximately 30% of the enrolled patients.[7] Conversely, with regard to the patients with a PS $\geq$3, there is no evidence as yet to suggest the clinical benefit of administering second-line chemotherapy. In our study, however, response rates of 64% in patients with a PS of 3 (n = 14) and 25% in patients with a PS of 4 (n = 4) were observed. These results suggest that second-line chemotherapy might be beneficial for adequately selected patients with a PS of $\geq$2, although the survival benefit is limited as compared with that for the patients with a PS of 0 to 1. Further studies are required for precise selection of criteria for second-line chemotherapy.

In this study, the survival of patients who received second-line chemotherapy with a PS of 2 to 4 or refractory recurrences was still significantly better than that of those who did not receive second-line chemotherapy. However it was not surprising, because the patient selection for second-line chemotherapy was performed pragmatically, and patients who were thought to be unfit for chemotherapy were not administered second-line chemotherapy. The finding that the nonchemotherapy group had more patients with a PS of 2 to 4 and refractory recurrence, the 2 independent prognostic factors identified in this study, suggests that our patient selection was reasonable.

The prognosis of recurrent SCLC patients is generally poor, and to our knowledge no standard treatment has been established for these patients. In addition to the randomized trial comparing oral topotecan with BSC mentioned above, 2 phase 3 trials for recurrent SCLC have been reported to date.[14,15] A trial comparing intravenous topotecan with the combination of cyclophosphamide, doxorubicin, and vincristine demonstrated comparable response rates and survival; however, intravenous topotecan yielded greater symptomatic improvement for 4 of the 8 symptoms evaluated.[14] In the other trial, comparing oral topotecan with intravenous topotecan, no survival difference was observed.[15] Currently, topotecan is the only drug approved by the US Food and Drug Administration for recurrent SCLC. Recently, however, promising results of phase 2 studies have been reported for drugs other than topotecan for recurrent SCLC. In particular, amrubicin[16,17] and PEI[18,19] have been shown to yield excellent response rates and survival in not only sensitive but also refractory recurrent cases. In Japan, a phase 3 randomized trial comparing topotecan with PEI is now ongoing.

In conclusion, we identified PS and sensitivity to initial chemotherapy as being significant prognostic factors for survival in patients with recurrent SCLC treated with second-line chemotherapy. PS was also found to be predictive in terms of response. In future clinical trials of second-line chemotherapy, both PS and sensitivity to initial chemotherapy should be incorporated as stratification factors. The survival benefit of second-line chemotherapy is limited in patients with impaired PS, even among sensitive recurrence cases. Therefore, careful consideration of the potential risks and benefits is required in the treatment of these patients.

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Clinical Outcome of Chemoradiation Therapy in Patients with Limited-Disease Small Cell Lung Cancer with Ipsilateral Pleural Effusion

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Background: The indications for definitive thoracic radiotherapy (TRT) in limited-disease small cell lung cancer (LD-SCLC) and ipsilateral pleural effusion have not been thoroughly investigated. We retrospectively investigated the clinical outcome of LD-SCLC patients with ipsilateral pleural effusion.

Methods: The medical records of SCLC patients who received treatment at the National Cancer Center Hospital East between July 1992 and December 2006 were reviewed. Sixty-three of the 373 LD-SCLC patients (17%) had ipsilateral pleural effusion. Of these, 62 patients received chemotherapy as an initial treatment, and were included in this study. Since about 1998, definitive TRT was routinely performed if the patient's pleural effusion disappeared after induction chemotherapy. The 62 patients were divided into three subgroups: group A included patients who received chemotherapy and TRT (n = 26), group B included patients who did not receive TRT in spite of the disappearance of pleural effusion after first-line chemotherapy (n = 8), and group C included patients who did not receive TRT and whose pleural effusion persisted after first-line chemotherapy (n = 28).

Results: The response rate for first-line chemotherapy was 74%. Ipsilateral pleural effusion disappeared after first-line chemotherapy in 34 patients (55%). The median overall survival time was 11.8 months, and the 2 and 3-year survival rates were 21 and 10%, respectively. In groups A, B, and C, the median survival times were 19.2, 10.5, and 9.2 months, respectively, and the 2-year survival rates were 38, 25, and 7%, respectively.

Conclusion: Long-term survival was achieved by LD-SCLC patients with ipsilateral pleural effusion who successfully underwent chemoradiotherapy.

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Lung cancer is the leading cause of cancer-related deaths worldwide. In Japan, over 56,000 people died of lung cancer in 2003. Small cell lung cancer (SCLC) accounts for about 15% of all forms of lung cancer. SCLC has a more aggressive biologic behavior than non-small cell lung cancer. At the time of presentation, two-thirds of patients exhibit disseminated disease. SCLC is sensitive to chemotherapy, with a response rate of 70 to 80%. A clinical two-stage system proposed by the Veterans Administration Lung Study Group distinguishes limited-disease (LD) and extensive-disease (ED) in SCLC.[1] LD is defined as being limited to one hemithorax, including mediastinal, contralateral hilar, and ipsilateral supraclavicular lymph nodes, whereas ED represents tumor spread beyond these regions. The current standard care for LD-SCLC is a combination of chemotherapy and thoracic radiotherapy (TRT). On the other hand, ED-SCLC is treated with chemotherapy alone. The original definition of LD was a tumor volume that could be encompassed by a reasonable radiotherapy plan. According to the International Association for the Study of Lung Cancer (IASLC)'s consensus report, on the other hand, the classification of LD-SCLC includes bilateral hilar and/or supraclavicular nodal involvement and ipsilateral pleural effusion.[2] However, the indication for definitive TRT in patients with LD-SCLC and ipsilateral pleural effusion have not been thoroughly investigated. Recently, the IASLC proposed the seventh edition of the tumor, node, metastasis (TNM) classification for lung cancer. In the proposals, the presence of a pleural effusion is considered as M1 disease.[3–6]

Definitive TRT is contraindicated in lung cancer patients with malignant pleural effusion. We have sometimes treated SCLC cases in which the ipsilateral pleural effusion disappeared after induction chemotherapy. Should definitive TRT be indicated in SCLC patients if the ipsilateral pleural effusion disappears after induction chemotherapy? Since about 1998, we have routinely performed definitive TRT if the patient's pleural effusion disappeared after induction chemotherapy. In this retrospective study, we investigated the clinical course and outcome of LD-SCLC patients with ipsilateral pleural effusion and exam-

ined the overall survival in patients who received chemotherapy and TRT, comparing with that of ED-SCLC or LD-SCLC patients without ipsilateral pleural effusion. We also applied the proposed seventh edition of the TNM stage to our cohort.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of lung cancer patients who received treatment at the National Cancer Center Hospital East between July 1992 and December 2006. During this period 699 patients were newly diagnosed as having SCLC. Three-hundred and seventy-three patients were diagnosed as having LD-SCLC, and 326 were diagnosed as having ED-SCLC using conventional staging procedures, including a medical history and physical examination, chest radiography, computed tomography (CT) scan of the chest, CT scan or ultrasound of the abdomen, bone scan, and CT scan or magnetic resonance imaging of the brain. In this study, LD-SCLC was defined as disease limited to one hemithorax, including mediastinal, contralateral hilar, and supraclavicular lymph nodes, ipsilateral pleural effusion, and pericardial effusion; ED-SCLC was defined as tumor spread beyond these manifestations.[2] Sixty-three of the 373 LD-SCLC patients (17, 95% confidence interval (CI): 13–21%) had ipsilateral pleural effusion. Thirty-seven SCLC patients underwent surgical resection as an initial treatment, and 13 patients received only TRT and/or best supportive care. Remaining 649 patients received chemotherapy as an initial treatment. Of these, 62 LD-SCLC patients had ipsilateral pleural effusion, and were included in this study. The patient characteristics are shown in Table 1. The breadth of the pleural effusion was measured using a CT scan of the chest (Figure 1). Cytologic examination of the pleural effusion prior to treatment was performed in 26 patients. Eleven patients had cytologically positive effusion. Ten patients also had pericardial effusion. Three patients had solid pleural tumor and pleural effusion detected on CT scan. Twenty-six patients had atelectasis. Of these, 14 patients received cytologic examination of the pleural effusion, and four patients had cytologically positive effusion.

We collected clinical data on the patients from their medical records; this data included the chemotherapy regimen that was received, the response to first-line chemotherapy, whether pleural effusion disappeared after first-line chemotherapy, and whether the patient underwent definitive TRT. The World Health Organization's response criteria were used.[7]

Overall survival was defined as the interval between the start of treatment and death or the final follow-up visit. Median overall survival was estimated using the Kaplan-Meier analysis method.[8] Survival data was compared among groups using a log-rank test. The breadth of pleural effusion was compared using the Mann-Whitney U test. All reported p values are two-sided.

RESULTS

The induction chemotherapy regimens were shown in Table 2. Most common regimen was cisplatin or carboplatin plus etoposide. In LD patients with ipsilateral pleural effusion, there were three complete responses, 43 partial responses, seven no changes, and six progressive diseases. Response was not evaluated in three patients because of early death. The response rate was 74% (95% CI: 62–84%). Ipsilateral pleural effusion disappeared after first-line chemotherapy in 34 patients (55, 95% CI: 42–68%).

TABLE 1. Patient Characteristics

	LD-SCLC without Ipsilateral Pleural Effusion	LD-SCLC with Ipsilateral Pleural Effusion	ED-SCLC
No. of patients	270	62	317
Sex			
Male	226	50	262
Female	44	12	55
Age, yr			
Median	66	67	66
Range	38–87	46–79	28–85
Performance status			
0	71	2	20
1	178	45	203
2	14	10	59
3	6	5	28
4	1	0	7
Breadth of pleural effusion on CT scan, cm			
Median		2.3	
Range		0.5–9.4	
Cytology of pleural effusion			
Positive		11	
Negative		15	
Not examined		36	

Patients who received chemotherapy as an initial treatment were included.
LD, limited-disease; SCLC, small cell lung cancer; ED, extensive-disease; CT, computed tomography.

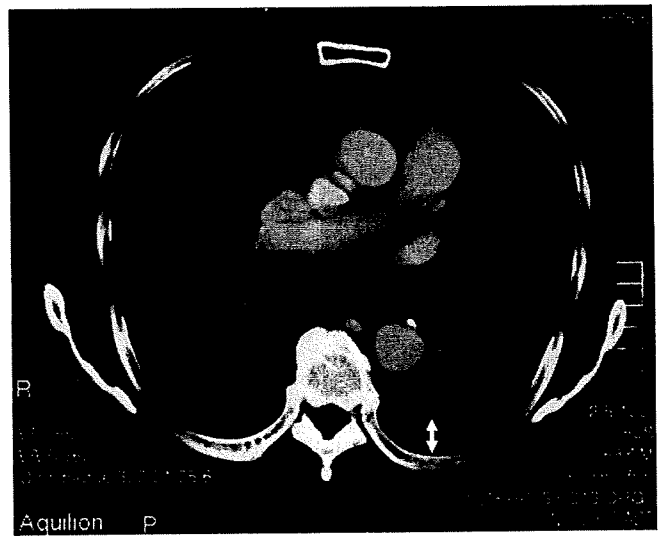

FIGURE 1. Ipsilateral pleural effusion. The arrow indicates the breadth of pleural effusion.

TABLE 2. Induction Chemotherapy Regimens and Response

	LD-SCLC without Ipsilateral Pleural Effusion	LD-SCLC with Ipsilateral Pleural Effusion	ED-SCLC
Chemotherapy regimens			
Platinum + ETP	252	54	154
Cisplatin and irinotecan containing regimens	10	2	92*
CODE	7	5	52
CAV/PE	1	1	11
Other	0	0	8
Response			
CR	64	3	28
PR	189	43	213
NC	8	7	37
PD	5	6	18
NE	4	3	21
Response rate (%) (95% CI)	94 (90–96)	74 (62–84)	76 (71–81)

*Nine patients received chemotherapy of cisplatin and topotecan.

LD, limited-disease; SCLC, small cell lung cancer; ED, extensive-disease; ETP, etoposide; CODE, weekly cisplatin, vincristine, doxorubicin, plus etoposide; CAV/PE, cyclophosphamide, doxorubicin, plus etoposide alternating with cisplatin plus etoposide; CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable; CI, confidence interval.

Since about 1998, definitive TRT to the primary lesion and mediastinum was routinely performed in patients whose pleural effusion disappeared after chemotherapy. We divided the 62 patients in this study into three subgroups: group A included patients who received chemotherapy and TRT (n = 26), group B included patients who did not receive TRT in spite of the disappearance of pleural effusion after first-line chemotherapy (n = 8), and group C included patients who did not receive TRT and whose pleural effusion persisted after first-line chemotherapy (n = 28).

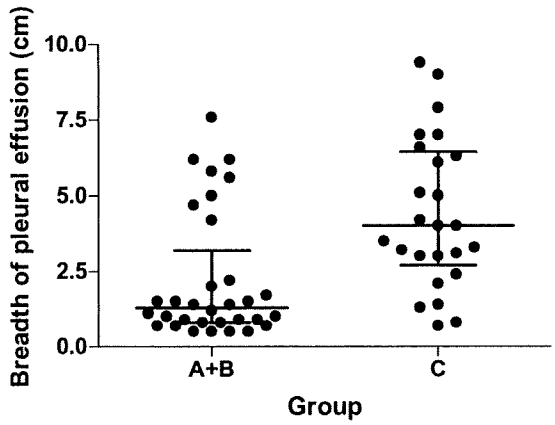

FIGURE 2. Breadth of pleural effusion in subgroup A + B, and C. Group A included patients who underwent chemotherapy and thoracic radiotherapy (TRT) (n = 26), group B included patients who did not undergo TRT in spite of the disappearance of pleural effusion after first-line chemotherapy (n = 8), and group C included patients who did not undergo TRT and whose pleural effusion persisted after first-line chemotherapy (n = 28). The line represents the median with the interquartile range.

The median (range) breadth of pleural effusion was 11.2 cm (0.5–7.6 cm) in group A, 1.8 cm (0.5–5 cm) in group B, and 4 cm (0.7–9 cm) in group C. Combining group A and B, the median breadth of pleural effusion was 1.3 cm, which was significantly lower than that of group C (p = 0.0007) (Figure 2).

In group A, all but two patients received platinum-based chemotherapy. One patient received weekly cisplatin, vincristine, doxorubicin, plus etoposide (PE) therapy, and the other patient received cyclophosphamide, doxorubicin, PE alternating with cisplatin PE therapy. Three of the 26 patients in group A underwent TRT (twice daily, 45 Gy in total) concurrently with the first course of chemotherapy. The breadths of pleural effusion in those three patients were 0.7, 0.8, and 1.0 cm. Two, seven, and one patient underwent TRT (once daily, 50 Gy in total) concurrently with the second, third, and fourth courses of chemotherapy, respectively. Thirteen patients underwent TRT (once daily, 50 Gy in total) sequentially after chemotherapy. Six patients received prophylactic cranial irradiation (PCI) of 25 Gy.

Figure 3*A* showed the survival of the all 699 SCLC patients by the proposed seventh edition of TNM stage. Figure 3*B* showed the survival of the 649 SCLC patients who received chemotherapy as an initial treatment. The survival of LD patients with ipsilateral pleural effusion was intermediate between those of LD patients without effusion and ED patients ($p < 0.0001$). The median survival time in LD patients with ipsilateral pleural effusion was 11.8 months (95% CI: 9.2–16.6), and the 1, 2, 3 and 5-year survival rates were 48, 21, 10 and 8%, respectively. Four patients have survived for over 5 years. One patient had a cytologically negative pleural effusion, and cytologic examinations were not performed for the remaining three patients. Breadth of pleural effusion of these four patients ranged from 1.0 to 1.5 cm. Two of these four patients have not shown any progression for more than 5 years. One patient who received only chemotherapy as an initial treatment developed a local recurrence 3 years after the first-line treatment. This patient received concurrent chemoradiotherapy and achieved a complete response. Unfortunately, he developed brain metastasis 9 years after the first-line chemotherapy and received whole brain radiotherapy. The other patient developed cervicular and inguinal node metastases 8 months after the initiation of first-line chemotherapy and concurrent TRT with three courses of chemotherapy. This patient received second, third, and fourth-line chemotherapy, radiotherapy to the cervicular and inguinal node metastases, and surgical resection of the recurrent inguinal node metastasis. He has not shown any signs of progression for 3 years and 3 months after the final surgical resection of the metastatic inguinal node. All three patients who had solid pleural tumor died within 31 months.

Survival analyses for the subgroups in LD patients with ipsilateral pleural effusion are shown in Figures 4, 5 and Table 3. In group A, the median survival time was 19.2 months (95% CI: 16.7–27.9) and the 1 and 2-year survival rates were 81 and

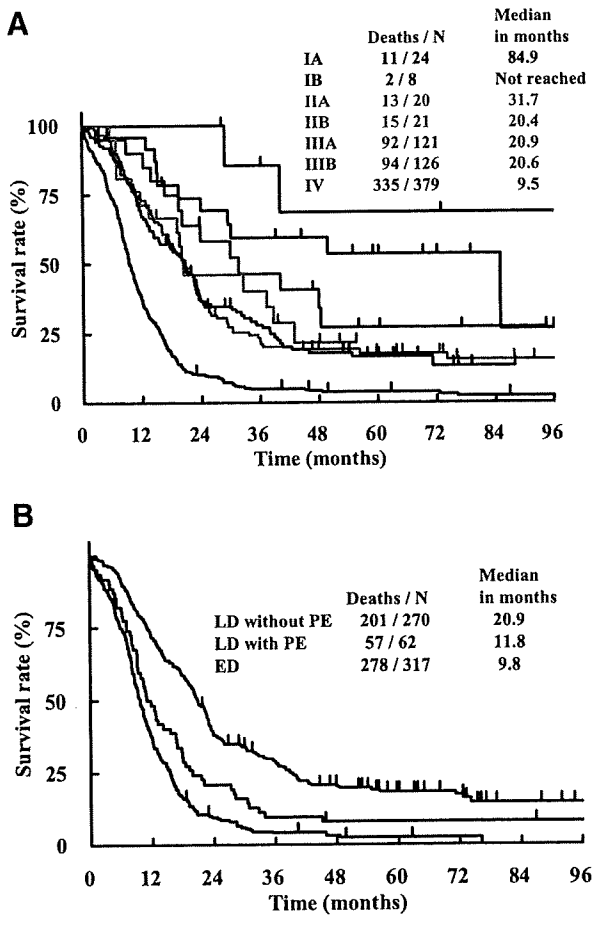

FIGURE 3. *A*, Overall survival in the all 699 patients with small cell lung cancer by the proposed seventh edition of the tumor, node, metastasis stage. *B*, Overall survival in the 649 patients who received chemotherapy as an initial treatment. LD, limited-disease; SCLC, small cell lung cancer; ED, extensive-disease.

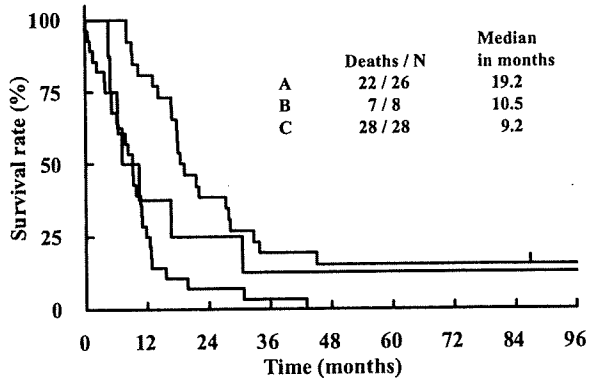

FIGURE 4. Overall survival in subgroups A, B, and C.

38%, respectively. The median survival time of patients with cytologically positive and negative pleural effusion were 9.3 months (95% CI: 3.8–14.2) and 12.7 months (95% CI: 5.1–17.9), respectively. The median survival time of those patients

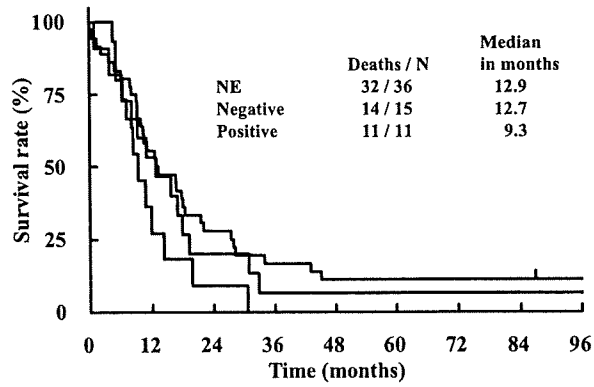

FIGURE 5. Overall survival according to the results of cytologic examination for ipsilateral pleural effusion. NE, not examined.

whose pleural effusions were not examined cytologically was 12.9 months (95% CI: 9.2–18.4). This difference was not statistically significant ($p = 0.1959$).

Disease progression was confirmed in 21 of the 26 patients in group A. The sites of first disease progression included the brain ($n = 10$), regional lymph nodes ($n = 5$), primary lesion ($n = 3$), distal lymph nodes ($n = 2$), liver ($n = 1$), adrenal gland ($n = 1$), and bone ($n = 1$). Twelve (57%) were distant, seven (33%) were local-regional, and two (10%) were both local-regional and distant. Brain metastasis was the only site of recurrence in nine patients. These nine patients had not received PCI. At the time of disease progression, ipsilateral pleural effusion recurred in 10 of the 18 patients.

DISCUSSION

LD-SCLC with ipsilateral pleural effusion accounted for 9% of all the patients with SCLC (63 of 669 patients) and 17% of all the patients with LD-SCLC (63 of 373 patients). Twenty-six (41%) of the LD-SCLC patients with ipsilateral pleural effusion received chemotherapy and definitive TRT. The median survival time of these patients was 19.2 months (95% CI: 16.7–27.9), and the 1 and 2-year survival rates were 81 and 38%, respectively. This overall survival time was comparable to that of LD patients without ipsilateral pleural effusion.

Among the LD-SCLC patients with ipsilateral pleural effusion, the median survival time was 11.8 months (95% CI: 9.2–16.6), and the 1 and 2-year survival rates were 48 and 21%, respectively. This survival was intermediate between those of LD patients without ipsilateral pleural effusion and ED patients. An analysis of 2,580 patients treated in the Southwest Oncology Group trials demonstrated that the survival of patients with LD-SCLC and ipsilateral pleural effusion was not significantly different from that of patients with ED-SCLC and a single metastatic lesion. The median survival times were 13.0 and 12.0 months ($p = 0.85$), respectively.[9] Thus, our data was compatible with that of the Southwest Oncology Group trials. Another analysis of 5,758 patients with SCLC from the IASLC database also demonstrated consistent results.[10]

According to the proposed seventh edition of the TNM classification for lung cancer, LD patients with ipsilateral

TABLE 3. Survival Data

Subgroup	No. of Patients	Median Survival Time (mo) (95%CI)	1-yr Survival Rate (%)	2-yr Survival Rate (%)	3-yr Survival Rate (%)
ED	317	9.8 (8.8–10.6)	37	10	4
LD without ipsilateral pleural effusion	270	20.9 (19.1–22.7)	72	38	29
LD with ipsilateral pleural effusion	62	11.8 (9.2–16.6)	48	21	10
Receiving TRT	26	19.2 (16.7–27.9)	81	38	19
Not receiving TRT	36	9.1 (6.0–10.8)	28	11	6
Not receiving TRT in spite of disappearance of pleural effusion	8	10.5 (4.5–30.6)	38	25	13
Not receiving TRT and persistent pleural effusion after chemotherapy	28	9.2 (5.1–10.8)	25	7	4
Cytologically positive pleural effusion	11	9.3 (3.8–14.2)	27	9	0
Cytologically negative pleural effusion	15	12.7 (5.1–17.9)	53	20	7
Without cytological examination	36	12.9 (9.2–18.4)	56	28	17

CI, confidence interval; ED, extensive-disease; SCLC, small cell lung cancer; LD, limited-disease; TRT, thoracic radiotherapy.

pleural effusion will be classified as stage IV.[3–6] However, prognosis of LD patients with ipsilateral effusion is better than that of ED patients with distant metastasis. If surgical cases such as clinical stage I cases were excluded, the simple staging system, LD or ED, seemed to be sufficient to select treatment strategy.

In our study, four LD patients with ipsilateral pleural effusion have survived for more than 5 years. Three patients received chemotherapy and TRT as an initial treatment. The remaining one patient received only chemotherapy as an initial treatment but received chemotherapy and TRT after a local recurrence. TRT probably contributed to local control and long-term survival in those LD-SCLC patients with ipsilateral pleural effusion. A previous systematic review demonstrated that an early timing of TRT contributed to a significant improvement in long-term survival, compared with a late timing.[11] In patients whose ipsilateral pleural effusion disappears after chemotherapy, definitive TRT should be considered as early as possible.

Disease progression was confirmed in 21 out 26 patients (81%) who received chemotherapy and definitive TRT. The most common site of first failure was the brain. Nine of the 10 patients had not received PCI. In these nine patients, brain metastasis was the only site of recurrence. In LD-SCLC patients with ipsilateral pleural effusion who undergo chemotherapy and definitive TRT, PCI may further improve treatment outcome.

Cytologic examinations of the pleural effusion before treatment were only performed in 26 patients (42%). These cytologic results did not significantly affect overall survival. However, all nine patients with cytologically positive pleural effusion died within 31 months. A similar observation was reported in a cohort of IASLC database.[10]

Chemotherapy regimens were heterogeneous between LD and ED patients. More patients with ED received cisplatin and irinotecan containing regimens. However, response rates were similar between LD with ipsilateral pleural effusion and ED patients (74 and 76%).

In conclusion, long-term survival was achieved by LD-SCLC patients who underwent definitive TRT after their ipsilateral pleural effusion disappeared after induction chemotherapy. A prospective randomized trial is warranted to compare chemotherapy alone with chemoradiotherapy in LD-SCLC patients with ipsilateral pleural effusion. This work was supported in part by a Grant from the Ministry of Health, Labor, and Welfare for the 3rd term Comprehensive Strategy for Cancer Control and a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor, and Welfare, Japan.

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