and irradiation have managed the residual disease for more than 10 years. From our available data of those patients with the adjuvant therapy, we think that aggressive postsurgical treatment including chemotherapy is useful to cure or control residual lesions in patients with incomplete resection of the primary tumors, effectively maintaining their quality of life for a longer period.

In the multimodality therapy, some complications were noted. With chemotherapy, fatal infection and tumor lysis syndrome were observed in peculiar patients with parathymic syndrome of hypogammaglobulinemia and extensive lymphocytic thymoma associated with peripheral blood T-cell lymphocytosis,[18] respectively. No mortality was encountered in surgical treatment. After radiation therapy, mild cardiac dysfunction was observed in two patients who had whole mediastinal irradiation for malignant pericardial effusion.[19] This complication is probably caused by doxorubicin and radiation affecting the heart muscle synergistically. On the whole, we think that this multimodality therapy is tolerable as long as attention is paid to any peculiar conditions.

For the recurrent tumors in six patients exhibiting CR, we aggressively performed retreatment. Extrapleural pneumonectomy or partial pleurectomy was carried out in three patients with pleural recurrences, pulmonary metastasectomy was carried out in one patient who was in a postpneumonectomy state, and repetitive radiotherapy was carried out in two patients with mediastinal or diaphragmatic local recurrences. All six patients are still in good general condition 37 to 193 months after the initial treatment. From our experience, we consider that aggressive retreatment for recurrences even after the multimodality therapy is very important for controlling disease and maintaining good quality of life, as previous reports have also advocated.[21,22]

The treatment of advanced thymoma is still controversial. However, investigators have recently advocated the necessity of multimodal approaches to therapy that introduce the enhancement of tumor resectability, cure rate, and/or long-term disease control.[10–15] In studies of such multidisciplinary treatment, Shin et al.[12] and Kim et al.[15] have reported excellent results in the survival of patients with stage III or IV thymoma. Their study protocol was considered a precise long-term treatment, which consisted of induction chemotherapy (cisplatin, doxorubicin, cyclophosphamide, and prednisone), surgical resection, postoperative radiotherapy, and consolidation chemotherapy. From our study, we also recognize the importance of postsurgical adjuvant therapy for patients with advanced disease and/or incomplete resection as well as the importance of retreatment for recurrences after the multimodality therapy. Future studies on the treatment of advanced invasive thymoma should follow a meticulous scheme of a primary multidisciplinary approach to therapy and retreatment of recurrences.

In conclusion, CAMP therapy was highly effective for invasive thymomas. Although this study was limited by its small number of patients and its nonrandomized clinical trial design, we believe that the multimodality therapy containing this chemotherapy is justifiable for the initial treatment of patients with advanced thymoma such as stage III disease with major vessel invasion, stage IV disease, and recurrence. Further studies are warranted to determine the optimal treatment strategy.

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ORIGINAL ARTICLE

Phase II study of weekly chemotherapy with paclitaxel and gemcitabine as second-line treatment for advanced non-small cell lung cancer after treatment with platinum-based chemotherapy

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Abstract
Purpose We evaluated the tolerability and activity of the combination of weekly paclitaxel (PTX) and gemcitabine (GEM) in second-line treatment of advanced non-small cell lung cancer (NSCLC) after treatment with platinum-based chemotherapy.
Patients and methods PTX (100 mg/m^2) and GEM (1,000 mg/m^2) were administered to patients with previous treated NSCLC on days 1 and 8 every 3 weeks.
Results A total of 40 patients (performance status 0/1/2, 7/27/6 pts) were enrolled. The response rate was 32.5% (95% confidence interval: 18.0–47.0%). The median survival time was 41.7 weeks (95% confidence interval: 28.5–54.7 weeks). The median time to disease progression was 19 weeks. Hematological toxicities (grade 3 or 4) observed included neutropenia in 60%, anemia in 15%, and thrombocytopenia in 12.5% of patients. Non-hematological toxicities were mild, with the exception of grade 3 diarrhea, pneumonitis, and rash in one patient each. There were no deaths due to toxicity.
Conclusion The combination of weekly PTX and GEM is a feasible, well-tolerated, and active means of second-line treatment of advanced NSCLC.

Keywords Non-small cell lung cancer · Second-line chemotherapy · Weekly chemotherapy · Gemcitabine · Paclitaxel

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Introduction

The clinical usefulness of second-line chemotherapy has been established for cases of advanced non-small cell lung cancer (NSCLC) in which tumor has recurred or exhibits resistance to treatment after first-line chemotherapy. The effectiveness of docetaxel, pemetrexed, and elrotinib for second-line chemotherapy for NSCLC has been demonstrated in phase III clinical studies [13, 23, 24]. Furthermore, paclitaxel (PTX) and gemcitabine (GEM) have been shown to be effective against NSCLC resistant to platinum preparations [5, 16, 20]. There appears to be partial non-cross-resistance between these drugs and platinum preparations.

In previous attempts at second-line chemotherapy for NSCLC, the response rate was 0–38% for patients treated with PTX alone at intervals of 3 weeks [12, 21, 25] and 8–37.5% for patients treated with low-dose weekly PTX therapy [5, 16, 26, 28]. On the other hand, the rate of response to uncombined GEM therapy was 6–21% [7, 11, 17, 20, 22].

In combined PTX and GEM therapy, the two drugs exhibit interactions with each other but no overlap or synergism of adverse reactions. When this combined

regimen was applied to previously untreated patients with NSCLC, the response rate was high, at 29–46% [1, 3, 4, 8, 15, 18]. When a combination of PTX (administered every 3 weeks) and GEM was used for second-line chemotherapy, the response rate was either 18 or 39% [2, 14].

Weekly chemotherapy for lung cancer has recently been attempted at several facilities [3, 9]. Favorable results of weekly chemotherapy have also been reported for recurrent NSCLC [5, 16, 26, 28]. Compared to standard regimens of chemotherapy, with administration of drugs at intervals of 3–4 weeks, weekly chemotherapy has certain advantages. For example, the single dose level of anti-cancer drugs can be reduced with weekly chemotherapy, and the dose level can be adjusted after the start of treatment depending on signs of hematological toxicity of the drugs or the general condition of individual patients. In comparison with treatment at intervals of 3–4 weeks, weekly chemotherapy was of equal efficacy but had fewer side effects [3]. Weekly chemotherapy is thus a promising means of treating cases of recurrent NSCLC in which bone marrow function has been compromised by first-line chemotherapy.

The present study was undertaken to evaluate the effectiveness and safety of weekly chemotherapy using a combination of PTX and GEM in cases of advanced NSCLC in which tumor had recurred or relapsed after platinum-based first-line chemotherapy or platinum-based first-line chemotherapy had failed to exert efficacy.

Patients and methods

Patient selection

Patients were required to have histologically or cytologically confirmed non-resectable or metastatic NSCLC that had progressed during or after one or more chemotherapy regimens. The trial was initiated after a rest period of at least 4 weeks following previous chemotherapy (2 weeks in the case of radiotherapy). Patients were required to have recovered completely from prior therapy, and to have no ongoing toxicity greater than grade 1. Other eligibility criteria were as follows: measurable lesions; life expectancy of at least 12 weeks; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; adequate bone marrow reserve (defined as absolute granulocyte count $\geq$ 2,000/ml and platelet count $\geq$ 100,000/ml); adequate hepatic and renal function (defined as serum creatinine level ≤ 2 mg/dl, AST and ALT ≤ 1.5 times the upper limit of normal, and bilirubin ≤ 1.5 mg/dl). Exclusion criteria included pre-existing motor or sensory neurological signs or symptoms $\geq$ grade 2 (Common Terminology Criteria for Adverse Events version 3.0) and active infections. Asymptomatic treated or untreated patients with brain metastases were not excluded from the study. The Ethics Committee of the Tochigi Cancer Center approved the study protocols. Written informed consent was obtained from every patient stating that the patient was aware of the investigational nature of this treatment regimen.

Treatment

Paclitaxel was administered at a dose of 100 mg/m^2 intravenously during a 1-h infusion on days 1 and 8 of the treatment cycle. Gemcitabine was administered at a dose of 1,000 mg/m^2 intravenously during a 30-min infusion on days 1 and 8 of the treatment cycle. Prior to each treatment, patients were given diphenhydramine 50 mg orally, and an H2 blocker intravenously along with dexamethasone 16 mg 30 min before PTX administration. Granisetron 3 mg was administered intravenously as an antiemetic. The length of each chemotherapy cycle was 21 days. Patients who experienced grade 4 leukopenia or neutropenia that lasted for 3 or more days, or who experienced grade 4 thrombocytopenia or reversible grade 2 neurotoxicity or liver dysfunction, received reduced doses of both PTX and GEM (PTX 80 mg/m^2, GEM 800 mg/m^2) for the next cycle. If non-hematological toxicities of grade 3 or higher occurred, treatment was stopped. Subsequent courses of chemotherapy were started after 3 weeks when the leukocyte count was 3,000/mm^3 or more, the neutrophil count was 1,500/mm^3 or more, the platelet count was 75,000/mm^3 or more, serum creatinine were less than 1.5 mg/dl, GOT and GPT were less than twice the upper limit of the normal range, and neurotoxicity was grade 1 or less. If these variables did not return to adequate levels by the first day of the next course of chemotherapy, treatment was withheld until full recovery. If more than 6 weeks passed from the time of the last treatment before these criteria were met or if change in treatment more significant than reduction of dose was indicated, the patient was removed from the study at that time, but still included in the analysis of its results.

Evaluation of responses and toxicity

Pretreatment evaluation included medical history, physical examination, complete blood count, bone marrow examination, serum biochemical analyses,

chest roentgenogram, electrocardiogram, and urinalysis. All patients underwent radionuclide bone scan, magnetic resonance or computerized tomography (CT) of the brain, and CT of the thorax and abdomen. Complete blood count, biochemical tests, serum electrolytes, urinalysis, and chest roentgenograms were obtained before patients received chemotherapy.

Responses and toxicity were evaluated on the basis of tumor images obtained by CT and other techniques, laboratory data, and subjective/objective symptoms and signs before, during, and after administration of the study drugs and during the period from completion of treatment to final analysis. Measurable disease parameters were determined every 4 weeks by various means such as computerized tomography. Evaluation was performed in compliance with the Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines for antitumor activity and with Common Terminology Criteria for Adverse Events version 3.0 for safety. Patients were withdrawn from the study if evidence of tumor progression was obtained. The Institutional Ethical Review Committee gave approval to the study.

The primary endpoint of the study was the response rate. Simon's two-stage optimum design was used to determine sample size and decision criteria. It was assumed that a response rate of 30% among eligible patients would indicate potential usefulness while a rate of 10% would be the lower limit of interest, with $\alpha = 0.05$ and $\beta = 0.10$. Using these design parameters, the fist stage of the study was initially to enroll 18 patients, and this regimen was to be rejected if fewer than two patients had an objective response. If two or more patients responded, accrual was to be continued to 36 patients. Considering the percentage of probable dropout cases, 40 patients were required. Secondary endpoints were toxicity and overall survival. Response and survival rates were both calculated on an intent-to-treat basis. Overall survival and time to progression were measured from the start of this treatment up to the time of death or up to the date of the last follow-up clinical assessment. Survival curves were constructed using the Kaplan–Meier method.

Results

Patient characteristics

Forty patients were enrolled in this study from October 2000 to July 2003. All patients were assessable for toxicity, response, and survival. Characteristics of the 40 patients are listed in Table 1. All 40 patients had received a prior platinum-based chemotherapy regimen (Table 1). Two of these patients had received more than one chemotherapy regimen. All 40 patients were eligible for toxicity assessment. Four patients had received prior chemotherapy in the neoadjuvant setting. Of the 40 patients, 15 had initially responded to platinum-based therapy, 24 patients had achieved stable disease (SD), and one had progressive disease (PD).

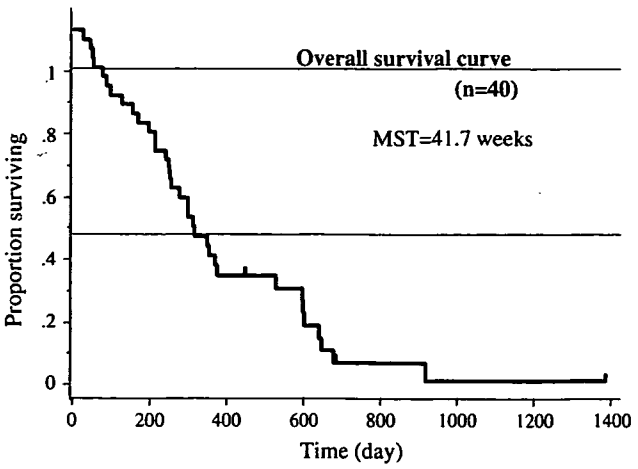

Fig. 1 Kaplan–Meier estimated overall survival curves. Median survival time, 41.7 weeks; 1-year survival rate, 38%

Efficacy of treatment

The mean number of cycles administered per patient was 4, and number of cycles ranged from one to twelve. Three patients required reduction of dose due to neutropenia and thrombocytopenia. Thirteen patients exhibited partial response (PR). Overall response rate was 32.5% (13/40) [95% confidence interval (CI): 18–47%]. SD was achieved in 26 patients (65%), and one (2%) achieved PD. All 40 patients were included in the survival analysis, with a median follow-up time of 82.9 weeks (range 56–263 weeks). The overall median survival time was 41.7 weeks (95% CI: 28.5–54.7 weeks). The 1-year survival rate was 37.5% (15/40) (Fig. 1). The median time to disease progression was 19 weeks.

Toxicities (Table 2)

Table 2 lists toxicities observed during this study. Hematological toxicities included high incidences of leukopenia and neutropenia, with leukopenia and neutropenia of grade 3 or higher occurring in 45 and 60% of patients, respectively. Anemia and thrombocytopenia of grade 3 or higher occurred in 15 and 12.5% of patients, respectively. Non-hematological toxicities

Table 1 Patient characteristics

Eligible patients	40
Gender	
Male	27
Female	13
Age (years)	
Median	59
Range	33–75
Performance status	
0	7
1	27
2	6
Histology	
Adenocarcinoma	30
Squamous cell	8
Large cell	2
Stage III	10
Stage IV	30
Number of metastatic sites	
Median	2
Range	0–3
Location of metastases	
Bone	13
Lung nodules	12
Brain	10
Lymph nodes	7
Liver	5
Adrenals	3
Subcutaneous	1
Prior surgery	4
Prior irradiation	15
Lung only	9
Brain only	4
Lung and bone	2
Prior chemotherapy	40
Cisplatin/vinorelbine	32
Cisplatin/docetaxel	5
Cisplatin/irinotecan	3
Response to prior chemotherapy	
Partial response	15
Stable disease	24
Progressive disease	1

observed included grade 3 pneumonitis in one patient, who exhibited rapid recovery following administration of steroids, grade 3 diarrhea in one, and grade 3 rash in one. Other non-hematological toxicities observed were of grade 2 or less and included nausea in 47.5%, vomiting in 20%, alopecia in 45%, sensory neuropathy in 35%, and fatigue in 32.5% of patients. All of these toxicities disappeared or were improved by symptomatic treatment. There were no deaths due to toxicity.

Discussion

Although a standard regimen of chemotherapy for recurrent NSCLC is being established, it is still important to determine how the outcome of treatment of this cancer can be improved [13, 23, 24]. At this point, the results of large-scale phase III clinical trials indicate single-agent chemotherapy with docetaxel, erlotinib, or pemetrexed as the standard chemotherapy regimen for recurrent NSCLC. In recent years, however, many reports have been published investigating two-drug combined therapy rather than single-agent therapy for recurrent NSCLC, with the objective of further improving therapeutic outcomes [2, 5, 7, 11–14, 20–26, 28].

A large number of reports have been published concerning salvage chemotherapy for recurrent NSCLC. Platinum-based chemotherapy is now used as the first-line chemotherapy at most medical facilities. Reports on second-line chemotherapy for NSCLC published to date have principally concerned uncombined drug therapy or two-drug combined therapy using non-platinum preparations [2, 5, 7, 11, 12, 14, 16, 17, 20–22, 25, 26, 28]. At several facilities, weekly administration chemotherapy has been adopted [5, 16, 26, 28]. Weekly-administration chemotherapy allows single dose levels to be reduced, thus making it possible to adjust the dose levels of anti-cancer agents after the start of treatment depending on adverse reactions or the general condition of individual patients.

Table 3 summarizes the results of two-drug combined therapy for recurrent NSCLC using non-platinum preparations [2, 6, 9, 10, 14, 19, 27]. The studies shown in this table were phase I-II in the case of that reported by Iaffaioli [14], phase III in that by Fossella [9], and phase II in the other studies. The overall response rate varied widely among studies, from 0.8 to 39%. The overall median survival time was 24–47 weeks and the one-year survival rate was 19–46%. Major adverse reactions observed in these studies were signs of hematological toxicity (particularly neutropenia), excluding the studies involving prophylactic G-CSF treatment reported by Androulakis [2] and Wachters [27]. Signs of non-hematological toxicity varied depending on the drugs used, and symptoms and signs unique to each drug were noted.

For combined PTX and GEM therapy for recurrent NSCLC, Androulakis [2] reported an overall response rate of 18%, an overall median survival time of 47 weeks, and a median time to disease progression of 34 weeks. Compared to the present study, the overall response rate reported by Androulakis was lower, while the overall median survival time and median time to disease progression were more favorable in the study by Androulakis. The dosing regimen used by Androulakis involved administration of PTX (175 mg/m^2; day 8), GEM (900 mg/m^2; days 1 and 8), and granulocyte colony-stimulating factor (G-CSF; days

Table 2 Maximum toxicity over 152 cycles (40 patients)

	CTCAE v 3.0 grade (number of patients)					Grade 3 ≤ (%)
	0	1	2	3	4	
Leukopenia	7	4	11	15	3	18 (45)
Neutropenia	6	5	5	17	7	24 (60)
Febrile neutropenia	–	–	–	2	–	2 (5)
Anemia	4	8	22	5	1	6 (15)
Thrombocytopenia	9	21	5	3	2	5 (12.5)
Pneumonitis	36	1	0	1	0	1 (2.5)
Diarrhea	27	9	3	1	0	1 (2.5)
Rash	22	15	2	1	0	1 (2.5)
Nausea	21	19	0	0	0	
Vomiting	32	3	5	0	0	
Fatigue	27	11	2	0	0	
Alopecia	22	17	1	0	0	
Neuropathy-sensory	26	14	0	0	0	
Edema	32	8	0	0	0	
Arthralgia	33	7	0	0	0	

CTCAE v 3.0 Common terminology criteria for adverse events version 3.0

Table 3 Non-platinum regimens used as second-line treatment of non-small cell lung cancer

First author (Ref.)	No. of patients	Regimen and schedule			Response rate (%)	Survival	
						Median (weeks)	1-year (%)
Androulakis [2]	49	P G G-CSF	175 mg/m^2 900 mg/m^2 150 μg/m^2	d 8 q 3w d 1,8 q 3w d 9–15	18	47	37
Iaffaioli [14]	37	P G	90–240 mg/m^2 1,000 mg/m^2	d 1 q 3w d 1,8 q 3w	39	40	46
Fossella [9]	123	FO V	2 g/m^2/day 30 mg/m^2	d 1–3 q 3w d 1,8,15 q 3w	0.8	24	19
Kosmas [19]	43	D G	100 mg/m^2 1,000 mg/m^2	d 8 q 3w d 1,8 q 3w	33	36	28
Cao [6]	33	CPT11 V	300 mg/m^2 30 mg/m^2	d 1 q 4w d 1,14 q 4w	9	25	23
Georgoulias [10]	76	CPT11 G	300 mg/m^2 1,000 mg/m^2	d 8 q 3w d 1,8 q 3w	18.4	38	24.5
Wachters [27]	52	CPT11 D G-CSF	200 mg/m^2 60 mg/m^2 150 μg/m^2	d 1 q 3w d 1 q 3w d 2–12	10	27	30
Present study	40	P G	100 mg/m^2 1,000 mg/m^2	d 1,8 q 3w d 1,8 q 3w	32.5	42	38

P paclitaxel, *G* gem citabine, *F0* infostamide, *V* vinorebine, *D* docetaxel, *CPT-11* irinotecan, *G-CSF* granulocyte colony-stimurating factor, *d* day, *q* every

9–15), with each cycle of treatment lasting for 3 weeks. Because their regimen involved prophylactic administration of G-CSF, the incidence of grade 3 or worse neutropenia was lower than that in the present study (12 vs. 60%). However, the incidence of grade 2 or worse fatigue (a sign of non-hematological toxicity) was lower in the present study (4%) than in that reported by Androulakis (51%).

Belani [19] reported the results obtained with combined use of PTX and GEM as first-line chemotherapy for NSCLC. In their study, PTX was administered using two regimens and a comparison was made between treatment with PTX on day 1 (200 mg/m^2) and weekly treatment with PTX on days 1 and 8 (100 mg/m^2/dose; identical to the regimen used in the present study). According to their report, the response rate was 45% for the first regimen and 46% for the second regimen, the median survival time was 42 and 39 weeks and the 1-year survival rate 46 and 41% for the first and second regimens, respectively. Efficacy thus did not differ

significantly between the two regimens. Signs of hematological toxicity were the major adverse reactions observed following treatment with both regimens. The incidences of neutropenia and alopecia were lower with the weekly regimen. On the basis of these results, Belani concluded that weekly PTX treatment combined with GEM is also useful as first-line chemotherapy for NSCLC.

In conclusion, weekly chemotherapy with PTX and GEM is a tolerable and active regimen for patients with advanced NSCLC previously treated with platinum-containing chemotherapy regimens. It should be recommended as a candidate regimen in planning a phase III clinical study of NSCLC previously treated with platinum-containing chemotherapy, and will ultimately be evaluated in a phase III clinical study.

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Clinical Studies

Randomised phase III trial of carboplatin plus etoposide *vs* split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702

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We compared the efficacy and the safety of a carboplatin plus etoposide regimen (CE) *vs* split doses of cisplatin plus etoposide (SPE) in elderly or poor-risk patients with extensive disease small-cell lung cancer (ED-SCLC). Eligibility criteria included: untreated ED-SCLC; age $\geqslant 70$ and performance status 0–2, or age <70 and PS 3. The CE arm received carboplatin area under the curve of five intravenously (IV) on day 1 and etoposide 80 mg m^{-2} IV on days 1–3. The SPE arm received cisplatin 25 mg m^{-2} IV on days 1–3 and etoposide 80 mg m^{-2} IV on days 1–3. Both regimens were given with granulocyte colony-stimulating factor support in a 21–28 day cycle for four courses. A total of 220 patients were randomised. Median age was 74 years and 74% had a PS of 0 or 1. Major grade 3–4 toxicities were (%CE/%SPE): leucopenia 54/51, neutropenia 95/90, thrombocytopenia 56/16, infection 7/6. There was no significant difference (CE/SPE) in the response rate (73/73%) and overall survival (median 10.6/9.9 mo; $P=0.54$). Palliation scores were very similar between the arms. Although the SPE regimen is still considered to be the standard treatment in elderly or poor-risk patients with ED-SCLC, the CE regimen can be an alternative for this population considering the risk–benefit balance.
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Keywords: small-cell lung cancer; carboplatin; cisplatin; etoposide; elderly; poor-risk

Approximately half of patients with small-cell lung cancer (SCLC) are older than 70 years, and the proportion of elderly SCLC patients is continuously increasing in Japan (Morita, 2002). However, since many investigators have arbitrarily excluded elderly patients from clinical trials, no standard chemotherapeutic regimen has been established for elderly patients with SCLC. The Japan Clinical Oncology Group (JCOG) has reported that carboplatin plus etoposide (CE) is an active and less toxic regimen in elderly patients with SCLC (Okamoto *et al*, 1999). However, other clinical trials have indicated that the combination chemotherapy of reduced (Souhami *et al*, 1997) or split doses of cisplatin plus etoposide (SPE) (Murray *et al*, 1998; Westeel *et al*, 1998) can be safely and effectively administered in elderly or poor-risk patients with SCLC. Therefore, we conducted a phase III trial comparing CE with SPE in elderly or poor-risk patients with SCLC. Although elderly is not the same as poor-risk, many clinical trials for the elderly have included both types of patients. Therefore, we decided to include both elderly and poor-risk patients with SCLC at the time of proposal for this phase III trial.

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PATIENTS AND METHODS

Patient selection

Eligibility criteria included patients with histologically or cytologically confirmed SCLC who were $\geqslant 70$ years of age and had an Eastern Cooperative Oncology Group performance status (PS) of 0–2, or who were <70 years in age and had a PS of 3. Additional criteria consisted of extensive disease (ED), chemotherapy-naive, evaluable or measurable disease, expected survival $\geqslant 2$ months, adequate organ functions (leucocyte count $\geqslant 4000\,\mathrm{mm}^{-3}$, platelet count $\geqslant 100\,000\,\mathrm{mm}^{-3}$, haemoglobin level $\geqslant 9.0\,\mathrm{g\,dl}^{-1}$, AST/ALT $\leqslant 2\times$ upper limit of normal range, total bilirubin $\leqslant 1.5\,\mathrm{mg\,dl}^{-1}$, creatinine $\leqslant 1.5\,\mathrm{mg\,dl}^{-1}$, 24-h creatinine clearance (Ccr) $\geqslant 50\,\mathrm{ml\,min}^{-1}$, and PaO2 $\geqslant 60$ mmHg), no symptomatic pericardial or pleural effusion requiring drainage, no active concomitant malignancy, no senile dementia, and written informed consent. Exclusion criteria included brain metastases requiring radiotherapy, superior vena cava (SVC) syndrome requiring radiotherapy, serious medical or psychiatric illness, or pregnancy or lactation. Staging procedures included chest X-ray, computed tomography (CT) scan of the chest, CT scan or magnetic resonance

imaging (MRI) of the brain, CT scan or ultrasound of the abdomen, isotope bone scanning, and bone marrow aspiration or biopsy.

Treatment protocol

Patients were randomised to either the CE arm or the SPE arm. The CE regimen consisted of carboplatin area under the curve (AUC) of five intravenously (IV) on day 1 and etoposide 80 mg m^{-2} IV on days 1, 2, and 3. The SPE regimen consisted of cisplatin 25 mg m^{-2} IV on days 1, 2, and 3 and etoposide 80 mg m^{-2} IV on days 1, 2, and 3. Cycles were repeated every 3–4 weeks for up to four courses. In our previous phase II study using the CE regimen for elderly patients with SCLC, carboplatin AUC of 5 on day 1 and etoposide 100 mg m^{-2} on days 1, 2, and 3 were administered every 4 weeks (Okamoto *et al*, 1999). However, because grade 3 or 4 neutropenia occurred in 91% of the patients, in the current phase III trial we decided to reduce the etoposide dosage to 80 mg m^{-2} on days 1, 2, and 3, and repeat the cycle every 3–4 weeks instead of every 4 weeks. Twenty-four-hour Ccr was substituted for glomerular filtration rate (GFR) in Calvert's formula. Antiemetic prophylaxis with 5-HT3 antagonists plus dexamethasone was used at the treating physician's discretion. According to the Japanese approved guideline, prophylactic use of recombinant human granulocyte colony-stimulating factor (G-CSF) was recommended for daily administration after day 4 until the leucocyte (neutrophil) count exceeded 10 000 (5000) mm^{-3}. If the leucocyte (neutrophil) count decreased to less than 3000 (1500) mm^{-3}, then G-CSF was restarted. However, the actual use of G-CSF was left at the discretion of the treating physician. Subsequent courses of chemotherapy were initiated when leucocyte count $\geqslant$3000 mm^{-3}; platelet count $\geqslant$75 000 mm^{-3}; Cr$\leqslant$1.5 mg dl^{-1}; AST/ALT$\leqslant$2.5 $\times$ upper limit of normal range; and either PS$\leqslant$2 and age$\geqslant$70 years, or PS$\leqslant$3 and age$<$70 years were satisfied both after day 21 and two or more days after the discontinuation of G-CSF. If the above criteria were not satisfied by the first day of the next course, treatment was withheld until full recovery. If more than 6 weeks passed from day 1 of the last course, the patient was removed from protocol treatment. Dose modifications were made based only on grade 4 haematologic toxicities. If grade 4 leucopenia or neutropenia lasting 4 days or more was present, or grade 4 thrombocytopenia occurred, the doses for the next course were carboplatin AUC of 4 on day 1, cisplatin 20 mg m^{-2} for 3 days, and etoposide 60 mg m^{-2} for 3 days. If the same haematologic toxicity was observed after dose reduction, the patient was removed from protocol treatment. If grade 3 or 4 non-haematologic toxicities, except for nausea/vomiting and hyponatraemia, occurred, the patient was removed from protocol treatment even if the toxicities improved thereafter.

Responders after four courses were not allowed to receive further chemotherapy until progressive disease (PD) developed. Although post-protocol treatment was left at the discretion of the physician, crossover treatment was prohibited.

Evaluation

Tumour responses were evaluated according to World Health Organization criteria (World Health Organization, 1979). Toxicities were evaluated according to JCOG Toxicity Criteria (Tobinai *et al*, 1993), which are similar to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC ver 1) for the grading of toxicities.

Palliation score

Study-specific eight-item palliation scores were completed by patients before treatment and 3 weeks after the third course of chemotherapy. The attending physicians were not allowed to complete the scores. The items consisted of cough, pain, anorexia, shortness of breath, well-being, nausea, diarrhoea or constipation, and sleep. The items were scored as not at all present (0), a little (1), moderate (2), and very much (3). The sum of the total score for all eight items was compared between the baseline and post-treatment assessments. If the post-treatment score was below the baseline score, the palliation score for that patient was judged as having shown improvement.

Study design and statistics

This trial was designed as a multicentre, prospective, randomised phase III trial. The study protocol was approved by the Clinical Trial Review Committee of JCOG and the institutional review board of each participating institution before the initiation of the study. The primary endpoint was overall survival (OS). In this study, the experimental arm was the CE arm and the control was the SPE arm. The MST of our previous phase II trial for elderly patients with extensive disease small-cell lung cancer (ED-SCLC) using the CE regimen was 10.1 months. The MST of the SPE regimen for a similar population was not available at the time of the study proposal. Although Westeel and co-workers in 1998 and Murray and co-workers in 1998 reported an excellent MST of SPE plus concurrent chest radiotherapy for elderly or frail patients with limited disease (LD)-SCLC, an MST of the SPE regimen for elderly or frail patients with ED-SCLC was not available at that time. The only data available on the CAV/PE regimen for elderly or poor-risk patients with SCLC using reduced cisplatin (60 mg m^{-2} IV on day 1) were reported by Souhami and co-workers in 1997 and the MST of that study was 5.9 months. Therefore, for statistical calculations in the current phase III trial, we used the MST value of the Souhami trial for the control arm instead of the MST of the SPE regimen. In addition, an individualised AUC-based dosing strategy of carboplatin was expected to have greater efficacy and less toxicity compared with the SPE regimen at that time. This trial was designed as a superiority trial and the planned sample size was 110 patients in each arm for 80% power to detect a 0.67 hazard ratio for CE to SPE in OS at an alpha of 0.025 (one sided) (Schoenfeld and Richter, 1982). Patients were randomised to receive either CE or SPE with a minimisation method for balancing centre, PS (0–1 *vs* 2–3) and age ($\geqslant$70 years *vs* $<$70 years).

Survival distributions were compared by unstratified log-rank test. Proportion of improvement in palliation score was evaluated by Fisher's exact test. The change in each symptom score by treatment arm was evaluated by the Wilcoxon rank-sum test. The relationship between the interval of each chemotherapy course and the two regimens was evaluated by the Wilcoxon rank-sum test. Multivariate analysis was performed using Cox's proportional hazards model to evaluate the importance of seven clinically selected variables (treatment arm, PS, age, sex, lactate dehydrogenase level, alkaline phosphatase level, and leucocyte count) as prognostic factors. All *P*-values in this report are two sided, excluding *P*-values for OS and progression-free survival (PFS).

The interim analysis was performed after half of the planned number of patients had been enrolled in March 2002, with adjustment for multiplicity by the alpha-spending function (DeMets and Lan, 1994) with an O'Brien-Fleming type boundary. Because the interim analysis did not meet the prespecified stopping criteria, the study was continued and the planned accrual of 220 patients was randomised in this trial.

RESULTS

Patient characteristics

Between August 1998 and February 2004, a total of 220 patients were registered from 24 institutions. Baseline characteristics were well balanced between the arms. Median age was 74 years, 92% were 70 years or older, 88% were male, and 74% had a PS of 0 or 1 (Table 1). One patient in the CE arm was found to have LD after the completion of protocol chemotherapy due to protocol violation, and this patient was considered ineligible (Figure 1).

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Delivery of treatment

Reasons for termination of treatment are listed in Figure 1, and there were no major differences between the arms. Of the patients, 63% in the CE arm and 67% in the SPE arm completed four courses, and 11% in the CE arm and 8% in the SPE arm did not complete treatment because of toxicity or complications. Treatment-related death (TRD) occurred in four patients; three patients in the CE arm and one in the SPE arm. All TRDs of patients who were ⩾70 years old with a good pretreatment PS (all PS 1) were associated with neutropenic infection, which occurred after the first course of chemotherapy. Although the median interval of chemotherapy was slightly more prolonged in the CE arm than in the SPE arm, total delivered courses were similar between the arms (Table 2). One patient in the SPE arm never received chemotherapy due to the occurrence of delirium after registration. Dose reduction was more frequently observed in the CE arm than in the SPE arm: 29% *vs* 10%, $P<0.01$. Course delay, G-CSF delivery and total courses with G-CSF delivery were similar between the arms.

Toxicity and palliation score

Toxicities are listed in Table 3. Grade 3 or 4 leucopenia and neutropenia occurred in 54 and 95% of the CE arm *vs* 51 and 90% of the SPE arm, respectively. Grade 3 or 4 thrombocytopenia occurred more frequently in the CE arm than in the SPE arm: 56 *vs* 16%, $P<0.01$. Gastrointestinal toxicities including nausea or vomiting and diarrhoea were mild in both arms. There were few grade 3 or 4 toxicities and no remarkable differences between the arms. Other non-haematologic toxicities were similarly distributed between the arms. Grade 3–4 hyponatraemia, mainly caused by syndrome of inappropriate antidiuretic hormone (SIADH) secretion, occurred in 14–16% of the patients. More importantly, thrombocytopenia occurred more frequently in the CE arm, but none of the patients in either arm showed grade 3 or 4 bleeding. Only one patient in the CE arm showed grade 2 bleeding. Because no grading of febrile neutropenia was listed in JCOG toxicity criteria, the rate of the toxicity was not investigated in this study.

Baseline and post-treatment palliation scores were evaluated in 220/220 (100%) and 208/220 (95%) patients, respectively. We handled missing values by imputing the worst score. Improvement was achieved in 69 (63%) patients in the CE arm *vs* 61 (56%) patients in the SPE arm, although the difference was not statistically significant ($P=0.34$). Similarly, there were no statistical differences in the change of each symptom score between the arms (Table 4).

Objective tumour response, PFS and OS

The objective response rate of 73% was quite similar between the arms. Five CRs and 75 PRs were observed in each arm (Table 5). Progression-free survival curves and OS curves are shown in Figure 2A and B. Ninety-seven percent of the patients had progressed or died at the time of final analysis. Progression-free survival was quite similar between the arms ($P=0.20$, one sided).

Table 1 Patient characteristics

	CE ($n=110$)	SPE ($n=110$)	*P*-value
Age (years)			
Median (range)	74 (56–86)	73.5 (55–85)	0.34
⩾70 years old (%)	102 (93)	100 (91)	0.81
Sex (male/female)	95/15	98/12	0.68
ECOG PS, 0–1/2/3	81/21/8	81/19/10	0.80
⩾5% weight loss	26	38	0.18
LN metastasis			
Contralateral mediastinum	71	59	0.13
Supraclavicular	89	79	0.15
Distant metastasis			
Liver	30	30	1.0
Lung	31	30	1.0
Brain	18	18	1.0
Bone	25	17	0.23
Adrenal	13	7	0.24
Bone marrow	12	12	1.0

CE, carboplatin plus etoposide; ECOG, Eastern Cooperative Oncology Group; LN, lymph node; PS, performance status; SPE, split doses of cisplatin plus etoposide.

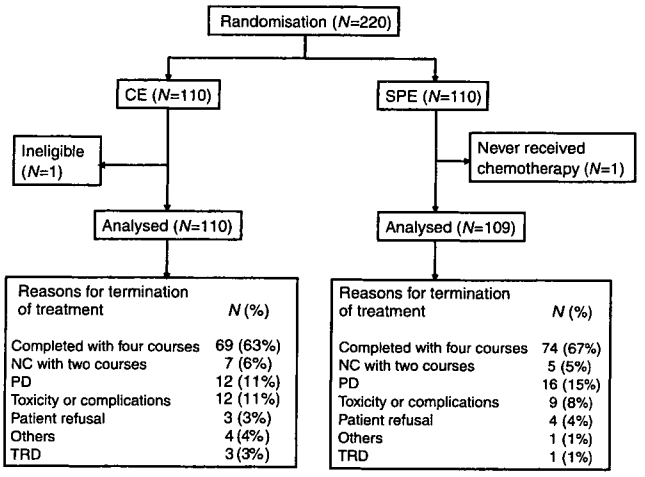

Figure 1 Flow diagram of randomised phase III trial of CE *vs* SPE in elderly or poor-risk patients with extensive disease SCLC.

Table 2 Compliance and drug delivery

	CE ($n=110$)	SPE ($n=109$[a])	*P*-value
Median interval of each chemotherapy (days) (range)			
1–2	27 (14–35)	23 (20–37)	0.02[b]
2–3	25 (21–56)	22 (20–35)	0.07[b]
3–4	27 (21–36)	24 (21–38)	0.05[b]
Total delivered courses/projected courses	353/440 (80%)	360/436 (83%)	
Dose reduction	32 (29%)	11 (10%)	<0.01[c]
Course delay	45 (41%)	40 (37%)	0.58[c]
G-CSF delivery	81 (74%)	84 (77%)	0.64[c]
No. of courses with G-CSF delivery/number of total courses	183/354 (52%)	203/362 (56%)	

CE, carboplatin plus etoposide; G-CSF, granulocyte colony-stimulating factor; SPE, split doses of cisplatin plus etoposide. [a]One patient never received chemotherapy due to delirium after registration. [b]Wilcoxon rank-sum test. [c]Fisher's exact test.

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Table 3 Toxicities (JCOG Toxicity Criteria, Worst Grade of Any Course)

	CE					SPE					
	Grade					Grade					
Toxicity	**1**	**2**	**3**	**4**	**3+4 (%)**	**1**	**2**	**3**	**4**	**3+4 (%)**	***P*-value**
Haematologic											
Leucopenia	5	45	46	13	(54)	8	43	49	7	(51)	0.79
Neutropenia	0	5	46	58	(95)	4	7	41	57	(90)	0.22
Anaemia	9	58	32	—	(29)	20	45	27	—	(25)	0.54
Thrombocytopenia	20	18	29	32	(56)	16	15	12	5	(16)	<.01
Non-haematologic											
Nausea/vomiting	40	24	2	—	(2)	46	28	3	—	(3)	0.68
Diarrhoea	8	9	1	0	(1)	11	3	1	0	(1)	1.0
Bilirubin	—	31	0	0	(0)	—	16	1	0	(1)	0.50
AST	47	9	3	0	(3)	30	8	6	0	(6)	0.33
ALT	40	9	2	0	(2)	38	8	4	0	(4)	0.45
Creatinine	10	2	0	0	(0)	27	3	1	0	(1)	0.50
Hyponatraemia	38	11	7	11	(16)	46	20	6	9	(14)	0.58
PaO2	39	21	7	1	(10)	44	23	2	1	(4)	0.22
Fever	15	15	0	0	(0)	21	16	0	0	(0)	—
Infection	12	15	5	3	(7)	16	7	5	1	(6)	0.78
Bleeding	8	1	0	0	(0)	4	0	0	0	(0)	—
Neurologic-sensory	2	1	0	—	(0)	3	2	0	—	(0)	—
Alopaecia	67	22	—	—		66	15	—	—		

CE, carboplatin plus etoposide; JCOG, Japan Clinical Oncology Group; PaO_2, partial pressure of oxygen; SPE, split doses of cisplatin plus etoposide.

Table 4 Palliation score

	CE		SPE		
	Change from baseline		Change from baseline		
Symptom	**Mean (s.d.)**	**Median (range)**	**Mean (s.d.)**	**Median (range)**	***P*[a]**
Cough	−0.38 (1.16)	0 (−3 to 3)	−0.54 (1.06)	0 (−3 to 3)	0.51
Pain	−0.19 (1.00)	0 (−3 to 3)	−0.19 (0.96)	0 (−3 to 3)	0.96
Anorexia	−0.07 (1.16)	0 (−3 to 3)	0.08 (1.22)	0 (−3 to 3)	0.37
Shortness of breath	−0.05 (1.02)	0 (−2 to 3)	−0.31 (0.95)	0 (−3 to 3)	0.12
Well-being	−0.15 (1.13)	0 (−3 to 3)	−0.02 (1.14)	0 (−3 to 3)	0.48
Nausea	0.16 (0.84)	0 (−2 to 3)	0.26 (0.80)	0 (−1 to 3)	0.21
Diarrhoea or constipation	0.05 (1.07)	0 (−3 to 3)	0.04 (0.99)	0 (−3 to 3)	0.69
Sleep	−0.15 (1.08)	0 (−3 to 3)	−0.04 (0.89)	0 (−3 to 2)	0.10
Total	−0.80 (6.04)	−2 (−12 to 22)	−0.71 (5.35)	−1 (−15 to 21)	0.32

CE, carboplatin plus etoposide; s.d., standard deviation; SPE, split doses of cisplatin plus etoposide. [a]Wilcoxon rank-sum test.

The MST was 5.2 months in the CE arm *vs* 4.7 months in the SPE arm. OS was very similar between the arms ($P = 0.54$, one sided). The MST and 1-year survival rate was 10.6 months and 41% in the CE arm *vs* 9.9 months and 35% in the SPE arm.

Second-line chemotherapy

According to an *ad-hoc* survey (not pre-specified in the protocol), 130 (59%) patients (68 (62%) patients in the CE arm and 62 (56%) in the SPE arm) received second-line chemotherapy after relapse and the regimens were almost equally distributed between the arms. The same regimen as the initial chemotherapy, platinum-based combinations, and irinotecan regimens with or without other agents were administered in 17 (15%), 48 (44%), and 40 (36%) patients in the CE arm *vs* 10 (9%), 44 (40%), and 40 (36%) in

Table 5 Therapeutic response (WHO)

	CE	**SPE**	**Total**
CR	5	5	10
PR	75	75	150
NC	17	11	28
PD	11	16	27
NE	2	3	5
Total	110	110	220
Response rate	73%	73%	
95% CI	63–81%	63–81%	

CE, carboplatin plus etoposide; CI, confidence interval; CR, complete response; NC, no change; NE, not evaluable; PD, progressive disease; PR, partial response; SPE, split doses of cisplatin plus etoposide; WHO, World Health Organization.

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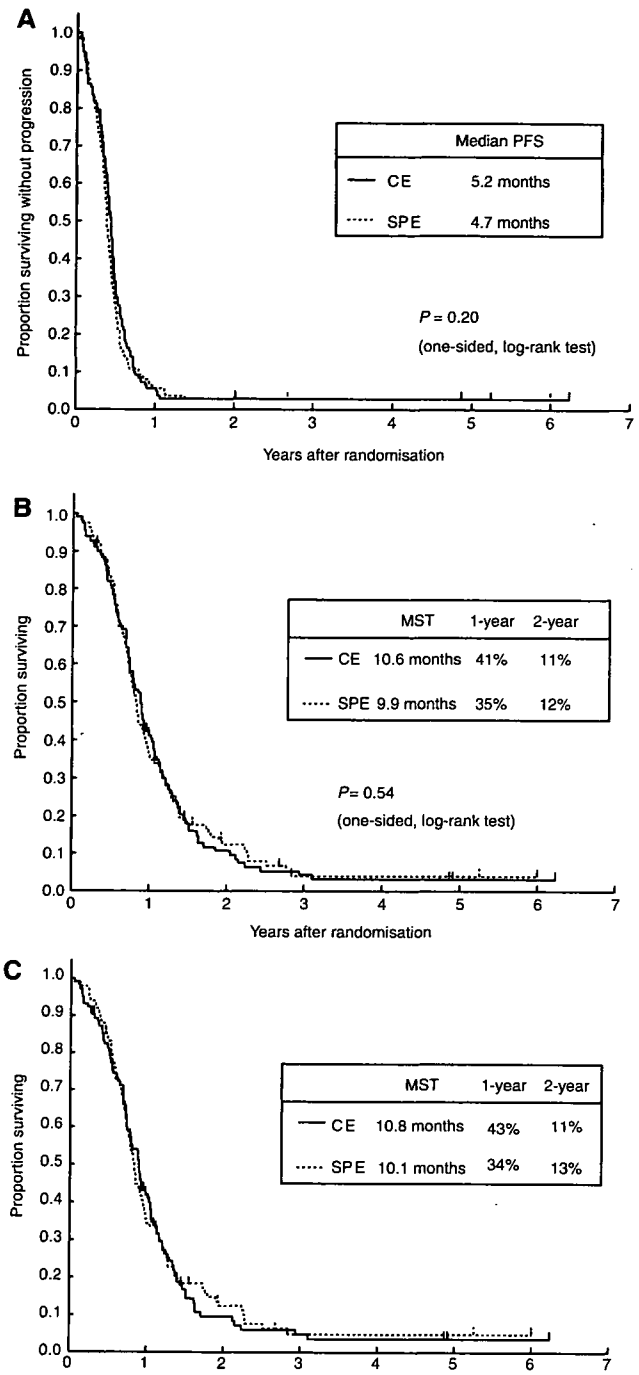

Figure 2 (**A**) PFS curves ($n=220$). (**B**) OS curves ($n=220$). (**C**) Survival curves of the patients ⩾70 years of age with a PS of 0–2 ($n=202$).

the SPE arm. Other chemotherapy regimens included topotecan monotherapy, amrubicin monotherapy, or other regimens.

Subset analysis and multivariate analysis

Subset analysis was performed according to PS and age (Table 6). There were no differences in OS between the arms in any subset; thus, an interaction between treatment and PS is unlikely. The survival curves of the patients ⩾70 years of age with a PS of 0–2 are shown in Figure 2C, and the survival curves were very similar with that of original overall populations. Even in the multivariate analysis with seven selected baseline variables, there was no difference in OS between the arms. High lactate dehydrogenase level was most strongly associated with poor prognosis (Table 7).

Table 6 Subset analysis – overall survival

Subgroup	Number of patients (%)	MST (months) CE	MST (months) SPE
PS 0–1	162 (74)	10.9	10.1
PS 2–3	58 (26)	8.3	8.1
<70 years and PS 3	18 (8)	7.1	6.9
⩾70 years and PS 0–2	202 (92)	10.8	10.0

CE, carboplatin plus etoposide; MST, median survival time; PS, performance status; SPE, split doses of cisplatin plus etoposide.

Table 7 Multivariate analysis with baseline prognostic factors

Variables	*P*-value	Hazard ratio	95% CI
Treatment arm (CE vs. SPE)	0.99	0.99	0.75–1.33
Alkaline phosphatase level (normal *vs* abnormal)	0.97	0.99	0.68–1.46
Lactate dehydrogenase level (⩾ × 1.5 *vs* < × 1.5)	<0.001	1.69	1.23–2.26
Leucocyte count (⩾10 000/mm^3 *vs* <10 000/mm^3)	0.06	1.82	0.99–3.36
Age (⩾75 years *vs* <75 years)	0.77	1.05	0.78–1.41
PS (2–3 *vs* 0–1)	0.41	1.15	0.82–1.61
Sex (female *vs* male)	0.13	0.70	0.45–1.11

CE = carboplatin plus etoposide; SPE = split doses of cisplatin plus etoposide; PS = performance status; CI = confidence interval.

DISCUSSION

Until recently, there was no standard chemotherapeutic regimen for elderly SCLC patients. Two phase III (Medical Research Council Lung Cancer Working Party, 1996; Souhami *et al*, 1997) and two randomised phase II trials (Pfeiffer *et al*, 1997; Ardizzoni *et al*, 2005) have shown that suboptimal chemotherapies, such as oral etoposide monotherapy or attenuated doses of combination chemotherapy, may lead to reduced survival in elderly or poor-risk SCLC patients when compared with standard doses of combination chemotherapies. The CE regimen, which has acceptable toxicities and reproducible efficacy, has been used in elderly or poor-risk patients with SCLC worldwide, although there have been substantial differences in toxicities and efficacy between the reported phase II trials. Four trials demonstrated both favourable toxicities and efficacy (Carney, 1995; Evans *et al*, 1995; Matsui *et al*, 1998; Okamoto *et al*, 1999) and three showed somewhat disappointing results because of suboptimal doses of oral etoposide (Larive *et al*, 2002), greater inclusion of patients with poor prognostic factors (Samantas *et al*, 1999), and deterioration of comorbidities as a result of chemotherapy (Quoix *et al*, 2001). No phase III trial evaluating the role of the CE regimen in this population has been reported until now.

This is the first phase III trial comparing carboplatin-based CE and cisplatin-based SPE regimens in elderly or poor-risk patients with ED-SCLC. In addition, this is also the largest randomised trial specifically designed for elderly or poor-risk SCLC patients. Although there was no significant difference in the palliation scores, response rate, and OS between the arms, the efficacy of

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both regimens was promising, as this study included only elderly or poor-risk patients with SCLC. Most toxicities were tolerable and the treatment compliance was also favourable in both arms. Approximately two-thirds of the patients received all four cycles of treatment. The CE arm in the current trial had more pronounced thrombocytopenia, which was considered manageable because none of the patients in the CE arm showed grade 3 or 4 bleeding, and the CE arm had a slightly prolonged course interval and a slightly greater incidence of dose reduction. However, in our opinion, these toxicities are less meaningful in clinical practice. More importantly, the CE regimen does not require hydration and can be given in an outpatient setting. Based on the results of this study, many JCOG members prefer the CE regimen to the SPE regimen and consider it to be more suitable for the control arm of future phase III trials.

The MST of each regimen (10.6 months for CE *vs* 9.9 months for SPE) was promising considering that this study included only elderly or frail patients with ED-SCLC. However, some retrospective studies have shown that fit elderly patients who have adequate organ functions, a good PS, and no comorbidity are able to tolerate intensive chemotherapy well and show a similar therapeutic response and survival rate as younger patients (Siu *et al*, 1996; Yuen *et al*, 2000). In fact, in this trial the MST of fit elderly patients $\geqslant$70 years of age with a PS of 0–1 was 10.9 months for the CE arm and 10.1 months for the SPE arm. In contrast, the MST of patients with a PS of 3 was only approximately 7 months. Furthermore, the group of fit elderly patients comprised 74% of the patients in this study. Therefore, the favourable survival rates in our trial may be attributable to patient selection. In other words, one limitation of this study is that the results of this trial cannot be extrapolated to frail elderly with a poor PS and/or comorbid illness because of the likelihood of greater inclusion of fit elderly patients in this trial.

Although the total dose in both the CE and SPE arms was slightly lower than the standard regimen, 92% of the patients showed grade 3 or 4 neutropenia, and dose reduction and course delay occurred frequently. However, the MST of both regimens was comparable with that of non-elderly or non-selected patients with ED-SCLC in historical reports (Noda *et al*, 2002; Niell *et al*, 2005). These findings suggest that both regimens are not suboptimal, but are near-full and effective doses for elderly or poor-risk patients with ED-SCLC. The CE arm in the current trial had a slightly prolonged course interval and a slightly greater incidence of dose reduction when compared to the SPE regimen. However, 95% of the patients showed grade 3 or 4 neutropenia and 56% showed grade 3 or 4 thrombocytopenia. Therefore, we believe that the dose escalation of the CE regimen may be difficult in this trial.

It remains unclear whether the elderly are able to tolerate a single modest dose of cisplatin (60–80 mg m^{-2} IV) on day 1. We feel that a fit elderly person who passes strict eligibility criteria can receive a modest dose of cisplatin IV on day 1. However, the more common situation is of elderly patients who have comorbidity and a poor PS, and cannot tolerate a standard single dose of cisplatin. Westeel *et al* (1998) and Murray *et al* (1998) reported that split doses of cisplatin were safely and effectively administered in elderly or frail patients with LD-SCLC. The SPE regimen appeared to be an appropriate treatment for elderly patients with SCLC who cannot tolerate a standard single dose of cisplatin. However, it remains unclear whether fit elderly patients in our trial can tolerate a standard single dose of cisplatin, and if so, it also remains unclear whether fit elderly patients who receive a standard single dose of cisplatin are able to achieve a more improved survival than those who receive SPE. Unfortunately, no randomised study comparing a single standard dose of cisplatin with SPE has been reported in fit elderly patients with SCLC.

There are some problems with the design in this study. The hypothesis was that carboplatin would improve survival, and the design of the trial was a superiority design with survival as the primary end point. However, this hypothesis was based on two possible misconceptions. First, carboplatin could be better dosed and might be more efficacious than cisplatin in SCLC. Unfortunately, this hypothesis could not be sustained on the basis of the available literatures. A number of clinical trials have indicated that carboplatin-based combination chemotherapy has a similar or slightly reduced efficacy compared with cisplatin-based combination chemotherapy against various tumours (Go and Adjei, 1999; Hotta *et al*, 2004). Therefore, our trial should have been designed as a non-inferiority trial. However, if this trial were planned as a non-inferiority trial, a total sample size would be about 500 to 1000 patients, with equal expected survival and a non-inferiority margin for hazard ratio ranging from 1.2 to 1.3. Second, the cisplatin dose in the control arm was an attenuated dose. Souhami *et al* (1997) used reduced dose of cisplatin (60 mg m^{-2} IV on day 1) and Murray *et al* (1998) used a single course of a split cisplatin dose in their studies. These regimens were completely different from the control arm in the present study. A standard dose of cisplatin given in 3 days is the best way of giving standard cisplatin (30 mg m^{-2} IV on days 1–3) with etoposide (130 mg m^{-2} IV on days 1–3), according the North Central Cancer Treatment Group (Maksmiuk *et al*, 1994). Had standard SPE been used for the control arm, better survival might have been achieved with increased toxicities. Another problem with the design was the inclusion of patients with a PS of 3, even if they were less than 70 years old. This made the target population heterogeneous. The number of such patients actually recruited was quite small, so emphasising the inappropriateness of their inclusion. A further limitation of this study may be a long accrual period of five-and-a-half years. Because our oncologists might have been afraid of the risk of TRD or increased toxicities in frail elderly with a poor PS and/or comorbid illness, more fit elderly patients were selectively registered and consequently the accrual rate was very slow.

In our trial, although both regimens were well-tolerated and efficacy was promising, over 90% of the patients in both arms showed grade 3 or 4 neutropenia, which may be justified and acceptable for a clinical trial involving elderly or poor risk patients with ED-SCLC, because only 6% of the patients showed grade 3 or 4 infection and TRD occurred in only four (1.8%) patients. Because all TRD occurred after the first course of chemotherapy, careful monitoring and management is necessary, particularly in the first course, if CE or SPE are administered to elderly or frail patients. Several retrospective analyses (Findlay *et al*, 1991; Radford *et al*, 1992) and a prospective study (Timmer-Bonte *et al*, 2005) have shown that standard-dose chemotherapy without G-CSF support causes more risk of early death and sepsis in the older population. Moreover, the American Society of Clinical Oncology (ASCO) guideline recommends the use of prophylactic G-CSF in patients at higher risk for chemotherapy-induced infection, such as those having a poor PS, older age, or comorbid illness (Smith *et al*, 2006). In this trial, the prophylactic use of G-CSF was recommended, but the actual use was left to the discretion of the treating physician because the use of G-CSF leads to increased drug cost. Although G-CSF was administered in only 54% of the total courses, we believe that the prophylactic use of G-CSF with CE regimen should be recommended in a new trial or clinical practice.

In conclusion, although the SPE regimen is still considered to be the standard treatment for elderly or poor-risk patients with ED-SCLC, the CE regimen can be an alternative for this population considering the risk-benefit balance. Based on the results of our trial, a phase III trial of the CE regimen *vs* amrubicin monotherapy, supported by a pharmaceutical company, is now ongoing in elderly patients with ED-SCLC in Japan, and a comparative trial of the CE regimen *vs* carboplatin plus irinotecan regimen (Okamoto *et al*, 2006) is being discussed for a future trial in our group.

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Appendix

This study was coordinated by the Japan Clinical Oncology Group (N Saijo, Chairperson) and was performed with the cooperation of the following institutions and investigators: Tochigi Cancer Center Hospital, Tochigi (K Mori, M Noda, T Kondo, and Y Kamiyama); National Nishi-Gunma Hospital, Gunma (S Tsuchiya, Y Koike, K Satoh, A Tohi, and K Kaira); Gunma Cancer Center Hospital, Gunma (K Minato); Saitama Cancer Center Hospital, Saitama (H Sakai, K Kobayashi, and R Kuroki); National Cancer Center, Central Hospital, Tokyo (T Tamura, Y Ohe, H Kunitoh, I Sekine, H Nokihara, and H Murakami); National Cancer Center Hospital East, Chiba (R Kakinuma, K Kubota, H Ohmatsu, K Gotoh, and S Niho); National International Medical Center, Tokyo (Y Takeda, S Izumi, A Kawana, M Kamimura, and M Iikura); Toranomon Hospital, Tokyo (K Kishi, and M Kawabata); Kanagawa Cancer Center Hospital, Kanagawa (K Yamada, I Nomura, F Oshita, and M Ikehara), Yokohama Municipal Citizen's Hospital, Kanagawa (K Watanabe, H Kunikane, H Okamoto, A Nagatomo, and H Aono); Niigata Cancer Center Hospital, Niigata (A Yokoyama, H Tsukada, M Makino, T Shinbo, S Kinebuchi, J Tanaka, M Tango, and T Ohara); Gifu City Hospital, Gifu (T Sawa, M Miwa, T Ishiguro, M Sawada, and T Yoshida); Aichi Cancer Center Central Hospital, Aichi (K Yoshida, and T Hida); Aichi Cancer Center Aichi Hospital, Aichi (H Saitoh, and M Okuno); Osaka City University Medical School, Osaka (S Kudoh, S Kyoh, H Kamoi, N Yoshimura, T Kodama, K Ohtani, S Shiraishi, S Nomura, S Enomoto, H Matsuura, and R Wake); Kinki University Medical School, Osaka (T Nogami, N Yamamoto, S Sakai, K Kodama, K Akiyama, J Tsurutani, K Tamura); Osaka Prefectural Adult Disease Center, Osaka (S Nakamura, F Imamura, M Yoshimura, S Yamamoto, K Ueno, H Ohmiya, H Matsuoka, and H Uda); Osaka Prefectural Respiratory and Allergy Medical Center, Osaka (M Furukawa, T Yamadori, T Takimoto, and T Hirashima); National Kinki Central Thoracic Disease Center, Osaka (S Minami, N Naka, T Kawaguchi, and H Ishikawa); National Toneyama Hospital, Osaka (Y Okano); Osaka City General Medical Center, Osaka (N Takifuji, and M Miyazaki); Kobe City Central Hospital, Kobe (T Nishimura, Y Okazaki, D Kinose, H Fujii, S Takakura, and M Hayashi); Sasebo City General Hospital, Nagasaki (J Araki); Kumamoto Regional Medical Center, Kumamoto (H Senba, T Seto, and S Fujii).

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Methods: Patients in a randomized phase III study conducted in western patients (Study-W1) received PEM 500mgm^2 or 900mg/m^2 once every 3 weeks. Patients enrolled in a randomized phase II study conducted in Japan (Study-J1) received PEM 500mg/m^2 or 1000mg/m^2 once every 3 weeks. Eligible patients in each of the studies had a histologic or cytologic diagnosis of NSCLC and had been previously treated. An established pharmacokinetic model was used to estimate AUCs from CrCL for patients in Study-W0 that received PEM 500mg/m^2 (N=265) and for patients in Study-J1. AUC was evaluated as a predictor of clinical efficacy (survival, TTPD, PFS) to identify ERRs. The models included previously identified prognostic factors and inverse of mean daily AUC over the treatment period as covariates.

Results: Study-W1 did not show a survival advantage for the 900mg/m^2 (N=293) dose over the 500mg/m^2 (N=295) dose. Study-J1 showed PEM 500mg/m^2 (N=108) and 1000mg/m^2 (N=108) to have similar efficacy for Japanese patients with previously treated NSCLC. Of the efficacy ERRs evaluated for Study-W0 and Study-J1, AUC was independently significant only for TTPD in Study-W0 and was not significant for other ERRs in either study (ERRs were not evaluated for Study-W1). There is internal consistency between the Study-J1 clinical results and the lack of ERRs for that study and external consistency between the Study-W1 clinical results and the lack of survival ERR for Study-W0.

Conclusion: Based on results available from two large randomized clinical trials and the evaluation of exposure-response relationships from a third trial, high dose PEM (900mg/mm^2 or 1000mg/m^2) does not offer an efficacy advantage over the currently approved 500mg/m^2 dose for either western or Japanese patient populations.

PD4-3-5 Cytotoxic Chemotherapy II, Tue, 16:00 - 17:30

Phase I/II study of oral TS-1 and gemcitabine in elderly patients with advanced non-small-cell-lung cancer (NSCLC): Thoracic Oncology Research Group Study 0502

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Background: Optimal treatment for elderly patients with NSCLC has been under active investigation. This study evaluated the safety and initial efficacy of a novel combination regimen of oral fluoropyrimidine TS-1 plus gemcitabine (GEM) for elderly patients (pts) with advanced NSCLC.

Methods: A phase I/II trial in 11 centers examined TS-1 and GEM in pts with age ≥ 70, stage IIIB/IV previously untreated NSCLC. The starting dose was 60 mg/day (day 1-14) for TS-1 and 800 mg/m^2 for GEM (day 8, 15). GEM was increased to 1000 mg/m^2 at dose level 2 and TS-1 was increased to 80 mg/day at dose level 3. Phase II portion of the study assessed the efficacy and tolerability of the combination regimen at the dose determined in the phase I portion. The primary endpoint was objective response rate.

Results: Twenty two pts were enrolled in the phase I portion: 6 pts on dose level 1, 10 on dose level 2 and 6 on dose level 3. Median age of this group was 75 yrs (range 70-85). Dose limiting toxicities included Gr. 4 neutropenia (2 pts) and Gr.3 skin toxicity (4 pts). The recommended dose (RD) was TS-1 60 mg/day and GEM 1000 mg/m^2, with which 20 pts were subsequently treated in the phase II portion. The median age of 30 pts treated with the RD was 76 yrs (range 70-85). Grade (Gr) 3/4 toxicities include neutropenia (12 pts; 7 with Gr 4), thrombocytopenia (4 pts; 0 with Gr 4), skin toxicity (8 pts), thrombus (1 pt) and peumonitis (2 pts). Nine patients (30%, 95% confidence interval [CI] = 14 to 46%) had partial responses and 16 (53%, 95% CI = 35 to 71%) had stable disease.

Conclusion: Encouraging antitumor activity and safety of TS-1 plus gemcitabine support further development of this combination therapy for elderly patients with advanced NSCLC.

PD4-3-6 Cytotoxic Chemotherapy II, Tue, 16:00 - 17:30

A randomised phase II study comparing two schedules of the 21-day regimen of Gemcitabine and Carboplatin in advanced NSCLC

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Background: Carboplatin AUC 5 d1-Gemcitabine 1250 mg/m^2 d1, 8 is an approved standard regimen in advanced NSCLC. Hematologic toxicity is however frequent; thrombocytopenia is found in more than 40 % of cases, neutropenia in 20%.

Aim: to investigate in two equally dose-dense regimens, whether the toxicity of the Gemcitabine-Carboplatin combination could be reduced by administering Carboplatin on day 8 instead of day 1 and without change in response rate.

Methods: Patients in arm A are treated with Gemcitabine (1250 mg/m^2 days 1,8) and Carboplatin (AUC 5 day 1) Patients in arm B are treated with Gemcitabine (1250 mg/m^2 days 1,8) and Carboplatin (AUC 5 day 8.) Drugs are administered over a 21-day cycle, on an outpatient basis. Toxicity and response are evaluated weekly and every second cycle, respectively.

Statistics: The hypothesis of the study protocol is that regimen B shows a decrease in toxicity of 50% without loss of response rates. Toxicity is defined as a thrombocytopenia and/or neutropenia grade 1. The Bryan and Day design allows to consider both response and toxicity as primary endpoint. With an alpha of 0.10 and a power of 90% the sample size was estimated to be 67 patients in each arm. An interim analysis was performed after 54 included patients, 27 in each arm.

Results: A total of 71 patients were enrolled between April 2004 and March 2006, before the study was prematurely stopped because data showed a statistical significant difference in toxicity. Patient and disease characteristics for the 69 eligible patients are summarized in Table 1. Toxicity and response are reported in Table 2.

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Sublobar Resection for Patients With Peripheral Small Adenocarcinomas of the Lung: Surgical Outcome is Associated With Features on Computed Tomographic Imaging

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Background. Sublobar resection for peripheral small adenocarcinomas of the lung remains controversial. We studied the feasibility of deciding whether to perform limited pulmonary resection on the basis of preoperative images obtained by high-resolution computed tomography.

Methods. A total of 123 patients with adenocarcinoma of the lung underwent sublobar resection of clinical T1N0M0 tumors measuring 2 cm or less in diameter on high-resolution computed tomography. Patients with multiple lung cancers or a history of lung cancer or other malignancies were excluded. The remaining 63 patients were studied. All tumors were classified as "air-containing type" or "solid-density type" according to the tumor shadow disappearance rate on high-resolution computed tomography. We evaluated the surgical outcomes of sublobar resection with respect to findings on high-resolution computed tomography images.

Results. Forty-six patients had air-containing type tumors (tumor shadow disappearance rate ≥50%), and 17 had solid-density type tumors (tumor shadow disappearance rate <50%). Forty-nine wedge resections and 14 segmentectomies were performed. Wedge resection was the most common procedure in patients with air-containing type tumors. Pathologically, air-containing type tumors comprised 38 bronchioloalveolar carcinomas and 8 nonbronchioloalveolar carcinomas. No patient with air-containing type tumors had recurrence after a median follow-up of 70 months (range, 21 to 133 months). Overall and relapse-free survival rates at 5 years were 95% and 100%, respectively, in patients with air-containing type tumors, as compared with 69% and 57%, respectively, in those with solid-density type tumors.

Conclusions. Sublobar resection might be an acceptable procedure for the treatment of small air-containing type adenocarcinomas of the lung on preoperative high-resolution computed tomography. However, our findings must be confirmed in larger, multicenter studies.

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Lobectomy has been established as the procedure of choice for most peripheral, clinical T1 N0 M0 lung cancers. This recommendation was based on the results of a randomized trial performed by the Lung Cancer Study Group, showing that sublobar resections, ie, segmental or wedge resections, had a significantly higher risk of locoregional recurrence [1]. However, increased use of computed tomography (CT) and improved scanning techniques after the 1980s, when the Lung Cancer Study Group trial was performed, have enhanced the detection rate of small cancers, leading thoracic surgeons to reassess the potential benefits of sublobar resection for small peripheral lung cancers [2–4]. Important advances have also been made in pathologic and CT evaluations of adenocarcinoma of the lung, especially bronchioloalveolar carcinoma (BAC) [5, 6].

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We previously reported that the tumor shadow disappearance rate (TDR) on high-resolution CT (HRCT), defined as the ratio of the tumor area of the mediastinal window to that of the lung window, closely reflected the biologic characteristics of small peripheral adenocarcinomas of the lung. Tumors with a TDR of 50% or higher showed no lymph node involvement and rarely had microscopic invasion. Such tumors might therefore be appropriate candidates for limited pulmonary resection [7, 8]. In this study, we analyzed follow-up data in patients in whom sublobar resection was performed on the basis of HRCT findings. We focused on the outcomes of limited pulmonary resection in patients with early adenocarcinomas of the lung on radiologic evaluation.

Patients and Methods

Our ethics committee was informed of this retrospective study and gave their approval for publication. Individual patient consent was waived by the chairman

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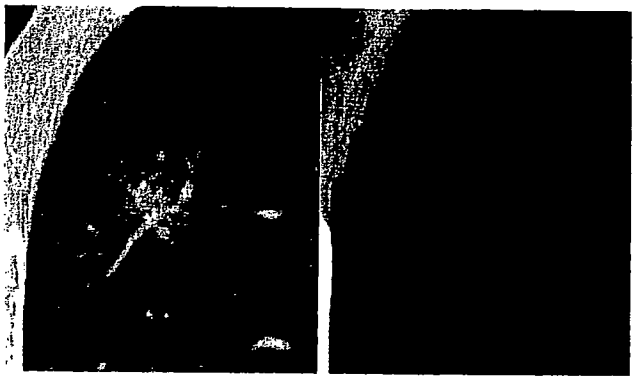


Fig 1. High-resolution computed tomographic image of air-containing type adenocarcinoma (tumor shadow disappearance rate ≥50%).

of the ethics committee. Between July 1992 and October 2004, 329 patients with adenocarcinoma of the lung underwent complete resection of clinical T1 N0 M0 tumors measuring 2 cm or less in diameter on HRCT at our hospital. Preoperative evaluation included a detailed history and physical examination, chest radiography, CT of the chest and upper abdomen, and bone scintigraphy for staging and assessment of resectability.

Chest images were acquired with a model TCT 900S Super HELIX or X-Vigor/Real CT scanner (Toshiba Medical Systems, Tokyo, Japan). High-resolution images targeted to the tumor were obtained continuously at 120 kVp and 200 mAs, with 2-mm section thickness, pitch 1, 1- to 2-mm section spacing, 512 × 512 pixel resolution, 1-second scanning time, and a high spatial reconstruction algorithm with a 20-cm field of view. Images were photographed onto each sheet of film using the mediastinal (level, 40 HU; width, 400 HU) and lung (level, −600 HU; width, 1,600 HU) window settings. As previously reported [7, 8], we classified tumors into two types according to the TDR. Tumor shadow disappearance rate was defined as follows:

$$\text{TDR} = 1 - (\text{tumor area of the mediastinal windows} / \text{tumor area of the lung windows})$$

Fig 2. High-resolution computed tomographic image of solid-density type adenocarcinoma (tumor shadow disappearance rate <50%).

Table 1. Clinical and Pathologic Characteristics of Patients

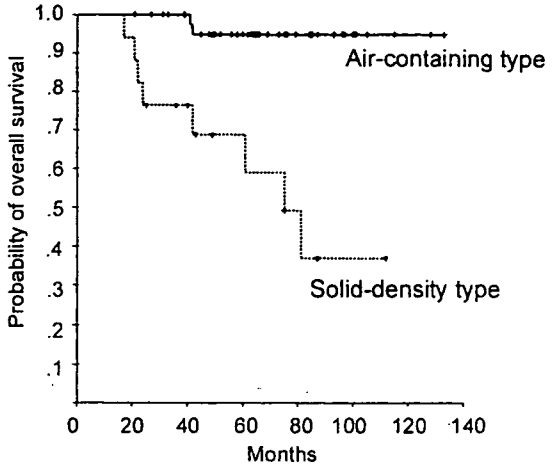
Characteristic	Type of Lesion on HRCT: Air-Containing Type (n = 46)	Type of Lesion on HRCT: Solid-Density Type (n = 17)	p Value
Age			0.7985
Range (years)	43–84	46–79	
Mean (years)	63	64	
Sex			0.5896
Male	19	9	
Female	27	8	
Operative mode			0.2397
Wedge resection	38	11	
Segmentectomy	8	6	
Size (mm)[a]			<0.0001
Range	3–20	7–20	
Mean	10.5	15.6	
Pathologic stage			0.0243
T1	46	14	
T2[b]	0	3	
Histologic subtype			<0.0001
BAC	38	0	
Non-BAC	8	17	
Pleural involvement			0.0001
p0/p1/p2	46/0/0	11/3/3	
Blood vessel invasion			<0.0001
Present/absent	0/46	7/10	
Lymphatic invasion			0.0048
Present/absent	0/46	4/13	

[a] Size of resected specimen was measured grossly. [b] Visceral pleural invasion discovered.

BAC = bronchioloalveolar carcinoma; HRCT = high-resolution computed tomography.

A TDR of 50% or greater was defined as "air-containing type" (Fig 1), and a TDR of less than 50% was defined as "solid-density type" (Fig 2).

Among the 329 patients who underwent complete resection of small adenocarcinomas, lobectomy was performed in 206 (92 with air-containing type, 114 with solid-density type), and sublobar resection was performed in 123 (78 with air-containing type, 45 with solid-density type). Fifty-one patients who underwent sublobar resection were considered unsuitable candidates for lobectomy because of limited pulmonary function or other comorbidities. These patients were considered to have undergone compromised resections. Based on the results of lobectomy with lymph node dissection for the air-containing type tumors, which showed no lymph node involvement and rarely had microscopic invasion [7, 8], we started to perform intentional sublobar resection in patients with air-containing type tumors in 1995 after obtaining complete, written informed consent from each patient. Intentional sublobar resection was defined as wedge resection or segmentectomy for patients who were considered suitable candidates for lobectomy. Intentional sublobar resections were performed for



Patients at risk

Months	0	12	24	36	48	60
Air-containing type	46	46	45	42	36	30
Solid-density type	17	17	14	12	8	7

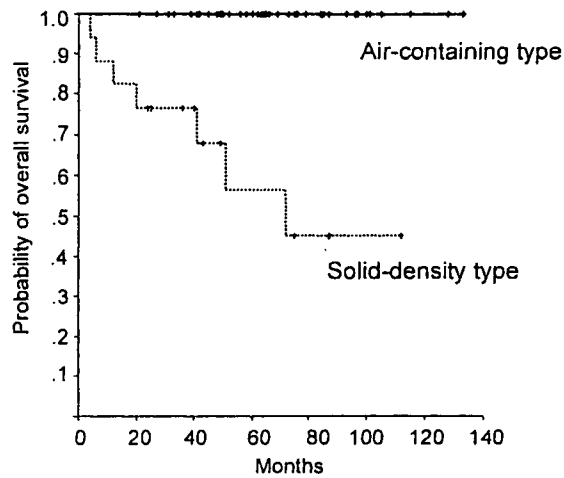
Fig 3. Overall survival curve for patients with air-containing type (solid line; n = 46) and solid-density type (dotted line; n = 17) tumors.

air-containing type tumor on CT images, provided they were located in the outer third of the lung parenchyma. Wedge or segmental resection was performed on the basis of only lesion location and size, and the procedure was selected to achieve adequate resection margins. Sixty-eight patients underwent intentional sublobar resection. The other 4 patients with solid-density type tumors on HRCT underwent sublobar resection because metastatic lung cancer or low-grade malignant tumors were diagnosed on frozen section analysis during operation. Among 123 patients who underwent sublobar resection, a total of 60 patients were excluded because they had a history of previously treated cancer or malignancy of other organs (21 patients), multiple lung cancers (27 patients), or second lung cancers detected during follow-up after resection of their primary lung cancers (12 patients). The remaining 63 patients were studied retrospectively.

Tumor types on HRCT were compared with respect to pathologic findings and surgical outcomes. Pathologic findings included pathologic TNM stage, histologic type of adenocarcinoma, pleural involvement, vessel invasion, and lymphatic invasion. The histologic type of adenocarcinoma and TNM stage were determined according to the World Health Organization classification [9] and UICC staging system [10]. Pleural involvement was defined according to the Japanese Lung Cancer Society classification [11]: p0, visceral pleura is not involved by tumor; p1, tumor has reached but not invaded the visceral pleura; and p2, tumor has invaded the visceral pleura but does not involve the parietal pleura. Briefly, p0 and p1 are classified as T1 disease, and p2 as T2 disease. Survival was calculated by the Kaplan–Meier method, and differences in survival were determined by the log-rank test. Unpaired two-tailed Student's t tests were used to compare mean values. The χ^2 test was used to compare observed percentages. Differences with probability values of less than 0.05 were considered statistically significant.

Results

The 63 patients ranged in age from 43 to 84 years (median, 67 years) and comprised 28 men and 35 women. The clinical and pathologic findings of the patients according to tumor type on HRCT are summarized in Table 1. Eleven air-containing type tumors showed pure ground-glass opacity (GGO), defined as a hazy increase in lung attenuation without obscuring the underlying vascular markings on HRCT. Among the patients with air-containing type tumors, intentional sublobar resection was performed in 39 (85%) and compromised resection in 7. On the other hand, 15 (88%) of the 17 patients with solid-density type tumors underwent compromised sublobar resection; in the other 2 patients low-grade malignant tumors were diagnosed on frozen section analysis during operation. As for the type of surgical resection, 49 wedge resections (78%) and 14 segmentectomies (22%) were performed. Most (83%) of the patients with air-containing type tumors underwent wedge resections. Because most of the sublobar resections in the patients with solid-density type tumors were compromised procedures, wedge resection was more common than segmental resection in these patients. Lymph-node sampling was done in 8 patients with air-containing type tumors. As for the patients with solid-density type tumors, lymph-node sampling was done in 6 patients and dissection in 2. The other 9 patients (53%) with solid-



Patients at risk

Months	0	12	24	36	48	60
Air-containing type	46	46	45	42	36	30
Solid-density type	17	15	13	11	7	5

Fig 4. Relapse-free survival curve for patients with air-containing type (solid line; n = 46) and solid-density type (dotted line; n = 17) tumors.