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# Phase I/II study of amrubicin, a novel 9-aminoanthracycline, in patients with advanced non-small-cell lung cancer

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*Key words:* amrubicin, advanced non-small-cell lung cancer, anthracycline, chemotherapy

## Summary

*Purpose*: Amrubicin is a novel, totally synthetic 9-aminoanthracycline. The present phase I/II study was performed to define its maximum-tolerated dose (MTD), efficacy and toxicity in the treatment of previously untreated patients with advanced non-small-cell lung cancer (NSCLC). *Patients and Methods*: Chemonaive patients were required to have cytologically or histologically proven measurable NSCLC, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, and adequate organ functions. Amrubicin was administered by daily intravenous injection for 3 consecutive days every 3 weeks. *Results*: In a phase I study, four patients were enrolled at dose level 1 (40 mg/m$^2$/day) and four at dose level 2 (45 mg/m$^2$/day). No dose limiting toxicity (DLT), which was defined as toxicity consisting of grade 4 neutropenia and leukopenia lasting four days or more, and grade 3 or 4 toxicity other than neutropenia, leukopenia, anorexia, nausea/vomiting, and alopecia, was observed at these dose levels. Subsequently, at dose level 3 (50 mg/m$^2$/day), 3 of 5 patients experienced DLTs (leukopenia, neutropenia, thrombocytopenia, or gastrointestinal complications). The MTD and recommended dose (RD) were determined to be 50 mg/m$^2$/day and 45 mg/m$^2$/day, respectively. Three partial responses (PRs) were achieved in 13 patients (response rate, 23.1%) in a phase I study. In a phase II study, 15 patients were assessable for efficacy and toxicity at the RD, and four PRs were obtained (response rate, 26.7%). The major toxicities were leukopenia and neutropenia, while non-hematologic toxicities were mild. The overall response rate in the combined patient population of the phase I/II study was 25.0% (7 PRs in 28 patients), with a 95% confidence interval of 10.7% to 44.9%. *Conclusion*: Amrubicin exerted promising antitumor activity on NSCLC with acceptable toxicity.

## Introduction

Amrubicin is a novel, totally synthetic 9-aminoanthracycline, (+)-(7S, 9S)-9-acetyl-9-amino-7-[(2-deoxy-β-D-erythro-pentopyranosyl)oxy]-7,8,9,10- tetrahydro-6,11-dihydroxy-5,12-naphthacenedione hydrochloride, and is similar to doxorubicin in chemical structure, as shown in Figure 1 [1]. Amrubicin showed more potent antitumor activity than doxorubin on several human tumor xenografts implanted in nude mice [2]. Its toxic profile was qualitatively similar to that of doxorubicin in terms of acute toxicities [3], but amrubicin rarely caused delayed-type toxicity as observed with doxorubicin, especially cardiotoxicity [4, 5]. In an early phase II study of single-dose intravenous injection of 120 mg/m$^2$ every 3 weeks, amrubicin exhibited promising antitumor activity on non-small-cell lung cancer (NSCLC) with a response rate of 25% (95% confidence interval, 8.7% to 49.1%) [6].

A major characteristic of amrubicin that is closely associated with the efficacy and toxicity is that it is converted to an active metabolite, amrubicinol, via reduction of its C-13 ketone group to a hydroxy group. The *in vitro* cytotoxic activity of amrubicinol was almost equipotent to that of doxorubicin, and 20 to 220 times more potent than that of its parent compound, amrubicin [7]. The *in vivo* antitumor activity of amrubicin was closely related to the tumor concentration of amrubicinol [8]. In addition, the experimental data have shown that amrubicin yields greater efficacy in daily treatment for 5 consecutive days than in a single treatment, due to accumulation of greater amounts of amrubicinol in tumor tissues [9].

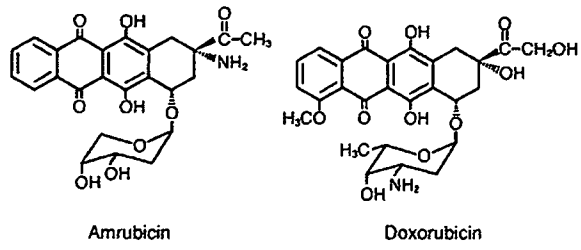


*Figure 1.* Chemical structures of amrubicin and doxorubicin

These data suggest that amrubicin may exert more potent effect against NSCLC in the divided treatment schedule than in the single-dose treatment schedule.

In addition, it has been reported that epirubicin, the same anthracycline derivative as amrubicin, could be administered at higher doses in 3-day consecutive treatment every 3 weeks than in single-dose treatment every 3 weeks, and consequently the high dosage of epirubicin in the former treatment schedule resulted in a higher response rate, compared with standard dosages of epirubicin in the latter treatment schedule, in previously untreated patients with advanced NSCLC [10].

In the present phase I/II study, therefore, daily treatment for 3 consecutive days every 3 weeks was chosen as the divided treatment schedule, and the efficacy and safety of amrubicin were evaluated in previously untreated patients with advanced NSCLC.

## Patients and methods

### *Patient eligibility*

This study involved patients with histologically or cytologically confirmed unresectable NSCLC in stages IIIA, IIIB, and IV. Eligibility criteria included no prior treatment, measurable lesions, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, an estimated life expectancy of at least 2 months, and age less than 75 years. Adequate organ function was required and defined as: white blood cell (WBC) count $\geq$4,000/$\mu$L, platelet count $\geq$100,000/$\mu$L, hemoglobin level $\geq$10 g/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 2 times the upper limit of normal, serum creatinine level $\leq$ normal limit, and electrocardiography (ECG) within normal limits.

The following patients were excluded: those with symptomatic brain metastasis or bone metastasis accompanying pain, those with plural fluid retention requiring treatment like drainage, those with continuous long term treatment with non-steroidal anti-inflammatory agents, glucocorticoids, or morphine derivatives, those with serious complications or other active cancer, and those judged by the investigators to be inappropriate for the study. Patients who were pregnant, breast-feeding, or taking inadequate contraceptive precautions were also ineligible. All eligible patients were required to provide signed informed consent prior to entering this study. The individual investigational review board at each institution approved the treatment protocol.

### *Drug administration*

Amrubicin (Sumitomo Pharmaceuticals Co., Ltd, Osaka, Japan) was supplied as a freeze-dried powder in vials containing 20 mg each, reconstituted in 20 mL of physiological saline or 5% glucose solution, and administered intravenously over 5 minutes on 3 consecutive days every 3 weeks. At least 2 cycles were instituted, except in case of disease progression, unacceptable toxicity or patient refusal.

### *Dose levels*

The phase I study was started at a dosage of 40 mg/m$^2$/day to determine the dose limiting toxicity (DLT), maximum-tolerated dose (MTD) and recommended dose (RD) of amrubicin given on 3 consecutive days (120 mg/m$^2$/course). The starting dosage was set at the same dosage per cycle as that used in the early phase II study for NSCLC in which amrubicin was given once every 3 weeks [6], because experimentally, amrubicin could be administered at a higher total dosage in the divided treatment schedule than in the single treatment schedule [10].

The dosage of amrubicin was escalated by 5 mg/m$^2$/day (15 mg/m$^2$/course). At least four patients were entered at each dose level until the MTD was reached. The dose escalations were determined based on the tolerability observed during the first 3 weeks of treatment as follows. The dose at which none or one patient experienced a DLT was escalated, and the MTD was the dose at which at least two patients developed a DLT, i.e., the dose at which at least 2/4, 2/5 or 2/6 patients experienced a DLT. Dosages were not escalated for individual patients.

The following phase II study was performed at the RD estimated in the phase I study.

### *Definition of DLT, MTD, and RD*

DLT was defined as toxicity consisting of grade 4 neutropenia and leukopenia lasting four days or more, and grade 3 or 4 toxicity other than neutropenia, leukopenia, anorexia, nausea/vomiting, and alopecia. MTD was defined as the dose level at which at least one-third of patients experienced a DLT. The RD was chosen as the dose one-level lower than the MTD.

*Adjustment of dosage and schedule modification*

The treatment was repeated if the WBC count recovered to $\geq$3,000/$\mu$L and the platelet count recovered to $\geq$100,000/$\mu$L. In incomplete recovery, the treatment was delayed until the WBC count recovered to $\geq$3,000/$\mu$L and the platelet count recovered to $\geq$100,000/$\mu$L. If the WBC count and platelet count did not recover within 5 weeks after administration of amrubicin, the trial was discontinued. If the WBC nadir was $<$1,000/$\mu$L for $\leq$3 days, or $\geq$1,000/$\mu$L and the platelet nadir was $\geq$50,000/$\mu$L, the treatment was conducted at the same dosage as the previous course. If the WBC nadir was $<$1,000/$\mu$L for $\geq$4 days and/or the platelet nadir was $<$50,000/$\mu$L, the dosage was reduced by 5 mg/m$^2$/day from the dosage of the previous course.

*Treatment evaluation*

Before treatment, all patients underwent medical history review, physical examination, hematology and serum biochemistry tests, urinalysis, ECG, and baseline tumor measurements (e.g. chest radiography, computed tomography (CT) scan, bone scintigraphy, abdominal CT, brain CT). All measurable and assessable lesions were evaluated within 2 weeks before start of treatment.

Complete and differential blood cell counts, platelet counts, and hematocrit values were obtained two times a week as a rule, and biochemical data [AST, ALT, alkaline phosphatase, LDH, total bilirubin, BUN, creatinine, serum bilirubin, albumin, total protein, and electrolytes (Na, K, Cl, and Ca)], and urinalysis findings (protein, glucose, urobilinogen, and occult blood), were recorded weekly. ECG was performed every treatment cycle.

Subjective symptoms and objective signs were checked daily for 5 consecutive days from the start of treatment in each cycle, and thereafter ad libitum.

*Response and toxicity evaluation*

Response was assessed according to the "Criteria for the evaluation of the clinical effects of solid cancer chemotherapy" of the Japan Society for Cancer Therapy [11], which is almost equal to the World Health Organization criteria [12]. A complete response (CR) was defined as the disappearance of all lesions. A partial response (PR) was defined as a reduction by 50% or more in the size of lesions measurable in two dimensions, objective improvement in any evaluable lesions, and no new lesions. CR and PR required response durations of at least four weeks. No change (NC) was defined as lesions unchanged (a reduction of $<$25% or an increase of $<$25% in the size of lesions) for at least four weeks. Progressive disease (PD) was defined as failure, with an increase of $\geq$25% in the size of lesions and appearance of new lesions. The Kaplan-Meier product-limit method was used to estimate the survival time.

Toxicity grading was recorded based on the side effect record form in the "Criteria for the evaluation of the clinical effects of solid cancer chemotherapy" of the Japan Society for Cancer Therapy [11], which is almost equal to the World Health Organization criteria [12]. For toxicity items that were not included on the record form, only their presence or absence was recorded, without grading.

## Results

*Patient characteristics*

Thirteen patients were entered in the phase I study, and subsequently 17 patients in the phase II study, between November 1992 and September 1994. Of the 13 patients entered in the phase I study, 4 were treated at dose level 1 (40 mg/m$^2$/day $\times$ 3), 4 at level 2 (45 mg/m$^2$/day $\times$ 3), and 5 at level 3 (50 mg/m$^2$/day $\times$ 3); all were assessable for efficacy and safety.

In the phase II study, 15 of 17 patients were assessable for efficacy and safety; 2 of them were ineligible because one had suffered from serious complications of pneumonitis and arrhythmia, a deviation against the inclusion criteria in the protocol, and another had been treated without registration prior to the study.

The characteristics of the eligible patients are listed in Table 1.

*Phase I study*

*Toxicity.* Hematologic toxicity is shown in Table 2. Dose-related leukopenia and neutropenia were noted. At dose level 1 (40 mg/m$^2$), one patient experienced grade 4

*Table 1.* Characteristics of eligible patients

| Characteristic | No. of patients | |
|---|---|---|
| | Phase I study | Phase II study |
| No. of patients entered | 13 | 17 |
| No. of eligible patients | 13 | 15 |
| Gender(Male/Female) | 8/5 | 10/5 |
| Median age, years (range) | 69 (45–74) | 65 (29–72) |
| ECOG performance status 0/1/2 | 5/3/5 | 1/12/2 |
| Histology | | |
| Squamous cell carcinoma | 5 | 6 |
| Adenocarcinoma | 7 | 8 |
| Large cell carcinoma | 1 | 1 |
| Stage (IIIA/IIIB/IV) | 2/1/10 | 1/3/11 |

*Table 2.* Hematologic toxicity of amrubicin in phase I study

| | Grade of toxicity (No. of patients) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 40 mg/m² (*n* = 4) | | | | 45 mg/m² (*n* = 4) | | | | 50 mg/m² (*n* = 5) | | | |
| Toxicity | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Hemoglobin, decrease | 1 | 0 | 1 | 0 | 2 | 1 | 1 | 0 | 2 | 1 | 2 | 0 |
| Leukopenia | 1 | 1 | 1 | 1 | 1 | 0 | 3 | 0 | 0 | 0 | 3 | 2 |
| Neutropenia | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 3 | 0 | 0 | 0 | 5 |
| Thrombocytopenia | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 3 | 0 | 1 | 1 |

*Table 4.* Efficacy of amrubicin in phase I study

| | No. of patients | | | | | | |
|---|---|---|---|---|---|---|---|
| Dose | Total | CR | PR | NC | PD | ORR (%) | 95% CI (%) |
| 40 mg/m² | 4 | 0 | 1 | 1 | 2 | 25.0 | |
| 45 mg/m² | 4 | 0 | 2 | 1 | 1 | 50.0 | |
| 50 mg/m² | 5 | 0 | 0 | 5 | 0 | 0.0 | |
| Total | 13 | 0 | 3 | 7 | 3 | 23.1 | 5.0–53.8 |

Abbreviation: CR, complete response; PR, partial response; NC, no change; PD, progressive disease; ORR, overall response rate (CR + PR); 95% CI, 95% confidence interval

neutropenia and leukopenia, which did not last for 4 days or longer. At dose level 2 (45 mg/m²), three of four patients also experienced grade 4 neutropenia, lasted 4 days or longer in only one. At this dose level, no grade 4 leukopenia was observed. Dose-limiting leukopenia and neutropenia lasting for more than 4 days were seen in two and in all five patients at dose level 3 (50 mg/m²), respectively. Grade 3 or 4 hemoglobin decrease and thrombocytopenia each occurred in two patients at the highest dose level. Three patients required blood transfusion or platelet transfusion or both.

As shown in Table 3, non-hematologic toxicities observed frequently in this study were anorexia, nausea/vomiting, fever, diarrhea and alopecia, but no grade 3 or 4 toxicity was seen at dose level 1 or 2. On the contrary, at dose level 3, grade 3 or 4 toxicity was noted in three of five patients; grade 3 nausea/vomiting and melaena and grade 4 hematemesis in one patient each. Because the grade 3 melaena and grade 4 hematemesis were noted in two patients who had received indomethacin or diclofenac sodium over 50 days, these episodes were considered to be associated with the long-term treatment of nonsteroidal anti-inflammatory agents. Therefore, the criteria for entry into the study were revised in the subsequent studies to exclude patients who had been treated with nonsteroidal anti-inflammatory agents for a long period. There was no toxicity to renal or cardiac function but a mild effect on hepatic function was observed. As uncommon toxicities, two episodes of grade 1 vitreous floaters occurred at 40 and 45 mg/m², and one episode of grade 1 eruption occurred at 50 mg/m².

Based on the above results, the MTD and RD of amrubicin in a 3-day consecutive administration were determined as 50 mg/m² (150 mg/m²/course) and 45 mg/m² (135 mg/m²/course), respectively. The DLTs were leukopenia, neutropenia, thrombocytopenia and digestive dysfunction including nausea/vomiting, melaena, and hematemesis.

*Table 3.* Non-hematologic toxicity of amrubicin in phase I study

| | Grade of toxicity (No. of patients) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 40 mg/m² (*n* = 4) | | | | 45 mg/m² (*n* = 4) | | | | 50 mg/m² (*n* = 5) | | | |
| Toxicity | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Stomatitis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Anorexia | 2 | 1 | 0 | –[a] | 1 | 0 | 0 | –[a] | 0 | 2 | 0 | –[a] |
| Nausea/vomiting | 2 | 0 | 0 | –[a] | 3 | 0 | 0 | –[a] | 1 | 1 | 1 | –[a] |
| Diarrhea | 3 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Fever | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 4 | 0 | 0 |
| Alopecia | 1 | 0 | 0 | –[a] | 1 | 3 | 0 | –[a] | 2 | 3 | 0 | –[a] |
| Melaena | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Hematemesis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| AST, increase | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| ALT, increase | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 0 |
| ALP, increase | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| BUN, increase | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |

Abbreviation: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urine nitrogen.
[a]No grading.

*Efficacy.* Antitumor response is shown in Table 4. One of four patients (25.0%) at dose level 1 (40 mg/m²) and two of four patients (50.0%) at dose level 2 (45 mg/m²) showed PR. At dose level 3 (50 mg/m²), three patients discontinued treatment after the first cycle because of toxicity, and none of five patients responded. In total, three of the 13 patients had PR, an overall response rate of 23.1%. One of five patients with squamous cell carcinoma (20.0%) and two of seven with adenocarcinoma (28.6%) responded.

### *Phase II study*

*Efficacy.* In the phase II study, amrubicin was administered daily for 3 consecutive days at 45 mg/m², which was the RD determined in the phase I study. The responses to amrubicin in patients with previously untreated NSCLC are shown in Table 5. Of 15 patients, four (26.7%) achieved PR. Of these responders, one patient (1/6, 16.7%) had a histology result indicating squamous cell carcinoma and three (3/8, 37.5%) had adenocarcinoma.

*Table 5.* Efficacy of amrubicin in phase II study

| Histology | No. of patients | | | | | ORR (%) | 95% CI (%) |
|---|---|---|---|---|---|---|---|
| | Total | CR | PR | NC | PD | | |
| Adenocarcinoma | 8 | 0 | 3 | 3 | 2 | 37.5 | |
| Squamous cell | 6 | 0 | 1 | 5 | 0 | 16.7 | |
| Large cell | 1 | 0 | 0 | 1 | 0 | 0.0 | |
| Total | 15 | 0 | 4 | 9 | 2 | 26.7 | 7.8–55.1 |

Abbreviation: CR, complete response; PR, partial response; NC, no change; PD, progressive disease; ORR, overall response rate (CR + PR); 95% CI, 95% confidence interval.

*Table 6.* Hematologic toxicity of amrubicin in phase II study

| Toxicity | No. of pts. | Grade (No. of pts.) | | | | ≥ Grade 3 | |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | No. of pts. | % |
| Hemoglobin, decrease | 15 | 4 | 3 | 3 | 1 | 4 | 26.7 |
| Leukopenia | 15 | 2 | 5 | 5 | 3 | 8 | 53.3 |
| Neutropenia | 15 | 0 | 4 | 3 | 8 | 11 | 73.3 |
| Thrombocytopenia | 15 | 0 | 1 | 3 | 1 | 4 | 26.7 |

*Table 7.* Non-hematologic toxicity in phase II study

| Toxicity | No. of pts. | Grade (No. of pts.) | | | | ≥ Grade 3 | |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | No. of pts. | % |
| Stomatitis | 15 | 3 | 0 | 0 | 0 | 0 | 0.0 |
| Anorexia | 15 | 8 | 3 | 0 | –[a] | 0 | 0.0 |
| Nausea/vomiting | 15 | 9 | 2 | 0 | –[a] | 0 | 0.0 |
| Diarrhea | 15 | 3 | 0 | 0 | 0 | 0 | 0.0 |
| Fever | 15 | 0 | 3 | 1 | 0 | 1 | 6.7 |
| Phlebitis | 15 | 2 | 0 | 0 | 0 | 0 | 0.0 |
| Alopecia | 15 | 4 | 5 | 0 | –[a] | 0 | 0.0 |
| Peripheral neuropathy | 15 | 0 | 1 | 0 | 0 | 0 | 0.0 |
| ECG abnormalities | 12 | 0 | 4 | 0 | 0 | 0 | 0.0 |
| Arrhythmia | 15 | 0 | 1 | 0 | 0 | 0 | 0.0 |
| Palpitation | 15 | 0 | 1 | 0 | 0 | 0 | 0.0 |
| Pneumonia | 15 | 0 | 1 | 0 | 0 | 0 | 0.0 |
| AST, increase | 15 | 3 | 0 | 0 | 0 | 0 | 0.0 |
| ALT, increase | 15 | 3 | 0 | 0 | 0 | 0 | 0.0 |
| Total bilirubin | 15 | 4 | 0 | 0 | 0 | 0 | 0.0 |
| Proteinuria | 15 | 1 | 0 | 0 | 0 | 0 | 0.0 |

Abbreviation: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urine nitrogen.
[a]No grading.

The two studies of phase I and II were combined, and the overall data were analyzed for response. Of 28 patients, seven achieved PR, accounting for an overall response rate of 25% (95% confidence interval, 10.7% to 44.9%). Median survival time was 9.1 months (95% confidence interval, 6.8 months to 12.1 months), and 1-year and 2-year survival rates were 35.7% (95% confidence interval, 18.0% to 53.5%) and 12.1% (0% to 24.6%), respectively.

*Toxicity.* Hematologic toxicity was common, as shown in Table 6. In particular, neutropenia and leukopenia developed in all patients, with grade 3 or 4 leukopenia at 53.3% and neutropenia at 73.3%. Hemoglobin decrease and thrombocytopenia were also frequently noted, but these were less severe, compared with leukopenia and neutropenia. Grade 3 or 4 hemoglobin decrease and thrombocytopenia were each observed in four patients (26.7%). Blood transfusion was required by two patients, and platelet transfusion by one.

Non-hematologic toxicity seen in the phase II study is summarized in Table 7. Stomatitis, anorexia, nausea/vomiting, diarrhea, fever and alopecia were commonly observed, but there were no grade 3 or 4 episodes except for one of grade 3 fever (6.7%). AST, ALT and total bilirubin levels, which were the referenced indices of hepatic function, were slightly increased, but no effect was seen on BUN or serum creatinine levels, the indices of renal function. There were four patients (33.3%) with abnormal ECG, showing nonspecific decreases in T-wave level without ST change. Other effects on cardiac function were palpitation and arrhythmia, occurring in one patient each. No patient had reactions such as abnormal visual system (i.e., myodesopsia), eruption, melaena, or hematemesis, all observed in the phase I study.

## Discussion

The present study was performed as a 3-day consecutive administration every 3 weeks, on the basis of encouraging experimental findings that amrubicin exerted more potent antitumor activity on human tumor xenografts implanted in nude mice in the divided treatment schedule than in the single treatment schedule [9]. When given on 3 consecutive days every 3 weeks, amrubicin achieved an overall response rate of 25% (7PRs in 28 patients) in previously untreated patients with advanced NSCLC. It has been reported that amrubicin also demonstrated an overall response rate of 25% (5 PRs in 20 patients) in an early phase II study which was conducted in chemotherapy-naöve patients by single-dose intravenous injection of 120 mg/m$^2$ every 3 weeks [6]. The data, therefore, indicate that there was no difference in the response rate between two clinical studies conducted under different treatment schedules, but the scales were too small to evaluate which of the two treatment schedules is superior; single-dose treatment or 3-day consecutive treatment, because only 20 or 28 patients were enrolled into each study. Subsequent, larger scale clinical studies are needed for confirmation.

Currently, NSCLC is treated with newer agents such as taxanes, gemcitabine, vinorelbine, and irinotecan, in combination with cisplatin and carboplatin, and these agents have single-agent reproducible response rates of more than 20% for NSCLC [13, 14]. Amrubicin showed response rates of more than 20% in two clinical studies conducted independently and under differing treatment schedules, as described above. These reproducible results strongly suggest that amrubicin is an anticancer agent with promising single-agent activity on NSCLC, comparable to the newer agents for NSCLC in efficacy, and further clinical trials are warranted to evaluate it. In addition, amrubicin is different from other newer agents in mode of action [15], in that it is an potent inhibitor of topoisomerase II, so that amrubicin is expected to play an important role in combination therapy, differently from other agents.

The major toxicity of amrubicin was hematologic, and especially neutropenia and leukopenia were remarkable. In the phase II study, 53.3% and 73.3% of patients experienced grade 3 and 4 leukopenia and neutropenia, respectively. On the other hand, non-hematologic toxicity such as anorexia, nausea and vomiting, diarrhea, fever, and alopecia was frequently observed, but relatively mild; grade 3 or 4 episodes were not seen other than in one patient (6.7%) who experienced grade 3 fever.

As noteworthy toxicity, grade 3 melaena and grade 4 hematemesis were noted in one patient each in the phase I study, although these episodes were not observed in the clinical trials using single-bolus treatment [6, 16]. These toxicities were considered to be associated with the long-term treatment of nonsteroidal anti-inflammatory agents, because these two patients had received indomethacin or diclofenac sodium for more than 50 days. The criteria for entry into the study was therefore revised to exclude patients who had been treated with nonsteroidal anti-inflammatory agents for a long period, and thereafter such episodes have not been experienced. As uncommon toxicity, two episodes of grade 1 myodesopsia and one episode of grade 1 eruption occurred in a phase I study, but these episodes were not observed in the subsequent phase II study.

In a phase II study, 4 patients (33.3%) experienced ECG abnormality, showing nonspecific decreases in T-wave level without ST change. Other effects on cardiac function were palpitation and arrhythmia, which occurred in one patient each. All these effects seemed to be different from cardiomyopathy caused by cumulative doses of doxorubicin, but these data show that amrubicin might affect cardiac function in a different manner from doxorubicin. Therefore, careful observation might be needed concerning the effects of amrubicin on cardiac function in subsequent clinical studies.

## Appendix

Amrubicin has showed reproducible response rates of 18.3% (11/60) and 27.9% (17/61) in two subsequent phase II studies when used as single agents in previously untreated patients with advanced NSCLC. Amrubicin, therefore, is considered to be comparable to newer agents such as paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan in efficacy for NSCLC. The clinical study of amrubicin in combination with other agents, in particular cisplatin, is currently planned.

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General Thoracic Surgery

# Phase II trial of postoperative adjuvant cisplatin and etoposide in patients with completely resected stage I-IIIa small cell lung cancer: The Japan Clinical Oncology Lung Cancer Study Group Trial (JCOG9101)

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**Objective:** Indications for surgical intervention for very limited small cell lung cancer have not yet been determined. The objective of this study is to determine whether resection followed by cisplatin and etoposide is feasible.

**Methods:** From September 1991 through December 1996, 62 patients with completely resected small cell lung cancer who were less than 76 years of age from 17 centers were entered in the trial. Of 62 patients, 61 were eligible, with a median follow-up of 65 months. Chemotherapy consisted of 4 cycles of cisplatin (100 mg/m$^2$, day 1) and etoposide (100 mg/m$^2$, days 1-3). There were 49 (80%) male patients, 44 with clinical stage I disease, 10 with stage II disease, and 6 with stage IIIa disease.

**Results:** Forty-two (69%) patients received 4 cycles of cisplatin and etoposide. No treatment-associated mortality was noted. Median survival time was not reached in patients with pathologic stage I disease, was 449 days in patients with stage II disease, and was 712 days in patients with stage IIIa disease. Three-year survival was 61% overall, 68% in patients with clinical stage I disease, 56% in patients with stage II disease, and 13% in patients with stage IIIa disease ($P$ = .02). Recurrence was noted in 26 (43%) patients overall. Local failure was noted in 6 (10%) patients. Locoregional recurrence tends to be found more frequently in patients with stage IIIA disease. Distant failure was found in 21 (34%) patients overall. Brain metastasis was found in 15% of the patients.

**Conclusion:** Major lung resection followed by postoperative cisplatin and etoposide is feasible, with a favorable survival profile. Because nodal metastasis appears to be a major prognostic factor, preoperative evaluation of nodal status remains a major concern.

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The prognosis of lung cancer remains poor, and this disease is the leading cause of cancer mortality worldwide. Small cell lung cancer (SCLC) comprises approximately 20% of lung cancer cases. Without treatment, SCLC has the most aggressive clinical course of any other type of lung cancer, resulting in a very short median survival time of approximately 2 to 4 months. Although surgical resection is generally indicated for early stage non–small cell lung cancer, this is not always the case with SCLC. This can be explained by the fact that

dissemination to regional lymph nodes or distant organs would be found in most patients with SCLC at the time of initial presentation.[1] Therefore, localized forms of treatment, such as surgical resection or radiation therapy, rarely produce long-term survival, and systemic treatment with current chemotherapy regimens is usually incorporated into the treatment program.

Indications for surgical resection for SCLC have not yet been determined, although several authors have reported that a small minority of patients with limited-stage disease and adequate lung function might benefit from surgical resection.[1-9] According to these reports, the prognosis of resected SCLC was not so poor, especially when no pathologic nodal involvement was observed. The 5-year survival ranged from 26% to 61% in these trials if the tumor was stage I. Because SCLC tends to be disseminated and the results of surgical intervention alone for this disease have been reported to be poor,[1,10] postoperative chemotherapy has been used in most studies. However, the chemotherapy was not standardized, and various chemotherapy protocols were often used. Furthermore, most previous studies were retrospective and thus suffered from the inherent weakness of any retrospective assessment of a given treatment.

Because the combination of cisplatin and etoposide has been considered to be standard in the treatment of SCLC,[11] this combination was selected as a postoperative adjuvant regimen. We conducted a prospective study of surgical resection plus adjuvant chemotherapy for stage I through IIIA SCLC to investigate the efficacy of this treatment strategy.

## Patients and Methods

### Eligibility

Patients who were given postoperative diagnoses of SCLC histologically or cytologically were eligible for enrollment in the study. The patients had to have completely resected pathologic stage I, II, or IIIA disease according to the TNM classification of the International Union Against Cancer.[12] Histologic typing was determined according to the World Health Organization classification.[13] Inclusion criteria included an Eastern Cooperative Oncology Group performance score of 0 or 1, age between 20 and 75 years, no prior treatment for lung cancer, no other concurrent or previous malignancies, a leukocyte count of greater than 3500/$\mu$L, a platelet count of greater than 100,000/$\mu$L, a hemoglobin level of greater than 9.5 g/dL, a serum creatinine level of less than 1.5 mg/dL, and aspartate aminotransferase–alanine aminotransferase values of less than twice the institutional upper limit of normal. Exclusion criteria included a history of myocardial infarction within the past 3 months, hepatic cirrhosis, and/or severe cardiopulmonary dysfunction that required oxygen therapy. The following preoperative investigations were performed before entry into the study: computed tomographic (CT) scanning of the chest, upper abdomen, and brain; bronchoscopy; chest plain film; radionuclide bone scanning; complete blood cell count and serum chemistry; and physical examination. Preoperative mediastinoscopy was performed in some cases. All patients provided written informed consent before entering the study.

### Treatment Schedule

Major lung resection, such as pulmonary lobectomy or pneumonectomy, was required as a surgical procedure for SCLC. Complete hilar and mediastinal lymph node dissections were recommended on the basis of the lymph node map defined by Naruke and colleagues.[14] After confirming complete resection and histologic typing of SCLC histologically, eligible patients were registered in the study.

Chemotherapy consisted of cisplatin (100 mg/m$^2$ on day 1) and etoposide (100 mg/m$^2$ on days 1-3; PE regimen). This regimen was repeated every 4 weeks and was administered in 4 courses. The dose was modified according to the blood cell count and renal function on the day of chemotherapy. Chemotherapy was administered unless the leukocyte count was less than 3000/$\mu$L or the platelet count was less than 75,000/$\mu$L. Chemotherapy was withheld until the counts recovered. If grade 4 hematologic toxicity, according to World Health Organization (WHO) criteria,[15] was seen, the dose of etoposide was reduced to 75%. Chemotherapy was permanently discontinued at any time when the serum creatinine level was 2.0 mg/dL or greater or the blood urea nitrogen level was 30 mg/dL or greater. To assess toxicity, we subjected all patients to complete blood cell counts and blood chemistry evaluations, such as for aspartate aminotransferase–alanine aminotransferase, blood urea nitrogen, and serum creatinine, as well as chest plain film and urinalyses at least once per week during treatment. Toxicity criteria were evaluated on the basis of the WHO criteria.[15]

Patients were followed up at the outpatient department every 3 months postoperatively and underwent CT scans of the chest, upper abdomen, and brain, as well as radionuclide bone scanning every 6 months, even when they were asymptomatic. No postoperative radiotherapy was applied until relapse was apparent.

Sites of relapse were determined by clinical, radiologic, or histologic criteria at initial recurrence. Local failure was defined as recurrence at the primary lung site or hilar-mediastinal lymph nodes. Distant failure was defined as recurrence in the contralateral lung, bone, brain, liver, or other extrathoracic regions.

### Statistical Analysis

The trial was designed as a prospective phase II trial. The primary goal of the study was to estimate the survival. A sample size of 30 was considered to provide a power of 90% for detecting a significant improvement in the 3-year survival (from 20% to 50%) in a 1-sided test with an $\alpha$ value of .025 and a $\beta$ value of .10. The median follow-up period for 35 surviving patients was 65 months. The length of survival was defined as the interval in months between the day of surgical resection of lung cancer and the date of death from any cause or the last follow-up. The survival curves were constructed by using the Kaplan-Meier method,[16] and curves were compared with the log-rank test.

## Results

### Patient Characteristics

Between September 1991 and December 1996, 62 patients were entered in this phase II trial at the 16 institutions that

**TABLE 1. Patient characteristics**

| | |
|---|---|
| Total | 61 |
| Sex | |
| Male | 49 |
| Female | 12 |
| Age (y) | |
| Range | 22-74 |
| Median | 64 |
| Histologic subtype defined by WHO* | |
| Oat cell type | 9 |
| Intermediate type | 45 |
| Combined type | 7 |
| Clinical stage | |
| I | 44 |
| II | 9 |
| IIIA | 8 |
| Side of primary tumor | |
| Right | 32 |
| Left | 29 |
| Operative procedure | |
| Lobectomy | 57 |
| Pneumonectomy | 4 |
| Extent of lymph node dissection† | |
| Complete hilar and mediastinum | 59 |
| Only hilar | 2 |
| Pathologic stage | |
| I | 35 |
| II | 8 |
| IIIA | 18 |
| Performance status | |
| 0 | 32 |
| 1 | 29 |

*Histologic subtyping was determined on the basis of the World Health Organization (WHO) classification. †The extent of lymph node dissection was defined by Naruke and associates.[14]

participated in the study. One patient was excluded because his final histologic category was changed from SCLC to large cell carcinoma. Thus, 61 patients were eligible for assessment of survival data, and their characteristics are shown in Table 1. The median age was 64 years (range, 22-74 years). According to histologic typing defined by the WHO, oat cell, intermediate, and combined types were found in 9, 45, and 7 patients, respectively. Forty-four patients had clinical stage I disease, 9 had stage II disease, and 8 had stage IIIA disease. Pathologically, stage I, II, and IIIA disease was found in 35, 8, and 18 patients, respectively.

### Treatment Administration

As a surgical procedure, pulmonary lobectomy was performed in 57 (93%) patients, and pneumonectomy was performed in the other 4 patients. Among 4 pneumonectomies, 3 were on the left side, and 1 was on the right side. Complete hilar and mediastinal lymph node dissection was performed in 59 (97%) patients.

**TABLE 2. Treatment delivery**

| | |
|---|---|
| Total no. of patients | 61 |
| No. of chemotherapy courses | |
| 0 | 1 (2%) |
| 1 | 5 (8%) |
| 2 | 8 (13%) |
| 3 | 5 (8%) |
| 4 | 42 (69%) |

A total of 204 courses were administered (Table 2). Forty-two (69%) patients underwent a full course of chemotherapy. The other 19 patients did not complete postoperative chemotherapy because of progressive disease in 3 patients, adverse effects in 7 patients, refusal of chemotherapy in 8 patients, and death from pneumonia in 1 patient.

### Treatment-Related Toxicity

No treatment-associated deaths were found. Postoperative bronchopulmonary fistula was found in 1 (2%) patient who underwent pulmonary lobectomy after completion of the first cycle of chemotherapy. Chemotherapy-related toxicity is shown in Table 3. Grade 4 toxicity was found in 9 (15%) patients: leukopenia in 4 patients, thrombocytopenia in 2 patients, nausea in 2 patients, and cardiac failure in 1 patient. One patient died of pneumonia 2 months after the first course of chemotherapy, but this was not considered to be chemotherapy related.

### Survival

Survival data are shown in Table 4. Among the 61 eligible patients, 35 were still alive after a median follow-up of 65

**TABLE 3. Chemotherapy-related toxicity in 60 eligible patients treated for resected stage I to IIIA SCLC**

| | WHO grade | | | | |
|---|---|---|---|---|---|
| Toxicity | 1 | 2 | 3 | 4 | 4 (%) |
| Anemia | 9 | 29 | 16 | 0 | 0 |
| Leukocytopenia | 7 | 17 | 26 | 4 | 6.5 |
| Thrombocytopenia | 11 | 8 | 14 | 2 | 3.2 |
| Infection | 2 | 1 | 0 | 0 | 0 |
| Nausea | 24 | 13 | 13 | 2 | 3.3 |
| Diarrhea | 8 | 2 | 2 | 0 | 0 |
| Azotemia | 35 | 0 | 0 | 0 | 0 |
| Renal failure | 18 | 0 | 0 | 0 | 0 |
| Stomatitis | 14 | 1 | 1 | 0 | 0 |
| Dyspnea | 5 | 0 | 0 | 0 | 0 |
| Fever | 10 | 7 | 0 | 0 | 0 |
| Skin | 4 | 2 | 0 | 0 | 0 |
| Alopecia | 13 | 23 | 11 | 0 | 0 |
| Cardiac dysfunction | 5 | 2 | 1 | 1 | 1.7 |
| CNS | 1 | 1 | 1 | 0 | 0 |
| Peripheral neuropathy | 5 | 1 | 0 | 0 | 0 |

*WHO*, World Health Organization; *CNS*, central nervous system.

**TABLE 4. Survival in patients with resected SCLC who underwent postoperative chemotherapy**

| | Median survival time (d) | Survival 3 y | Survival 5 y |
|---|---|---|---|
| Clinical stage | | | |
| IA | Not reached | 70% | 66% |
| IB | Not reached | 65% | 65% |
| II | Not reached | 56% | 56% |
| IIIA | 530 | 13% | 13% |
| Pathologic stage | | | |
| IA | Not reached | 78% | 73% |
| IB | Not reached | 67% | 67% |
| II | 449 | 38% | 38% |
| IIIA | 712 | 39% | 39% |

months. The overall estimated 3- and 5-year survivals were 61% and 57%, respectively (Figure 1). The 5-year survival was 66%, 56%, and 13% in patients with clinical stage I, II, and IIIA disease, respectively (Figure 2). Among the 44 patients with clinical stage I disease, 27 were classified as having clinical stage IA disease, and the other 17 were classified as having clinical stage IB disease. There was no significant difference in prognosis between clinical stage IA and IB disease. Similar results were obtained regarding the pathologic stage. Pathologic stage I disease showed a significantly better prognosis (Figure 3). The 5-year survivals in the 23 patients with pathologic stage IA disease and the 12 patients with stage IB disease were 73% and 67%, respectively. No significant differences in survival were observed between patients with pathologic stage IA and IB disease.

***Patterns of failure.*** Recurrence was noted in 26 (43%) patients, and the sites of initial relapse at a median follow-up time of 65 months are shown according to the pathologic stage in Table 5. Recurrence was found in 30% of patients with stage IA disease, 25% of patients with stage IB disease, 50% of patients with stage II disease, and 67% of patients with stage IIIA disease.

Local failure was noted in 6 (10%) patients: 4 in the mediastinal lymph nodes and 2 in the bronchial stump. Locoregional recurrence tended to be found more frequently in patients with stage IIIA disease (22%) than in patients with stage I or II disease. Relapse at the bronchial stump was only seen in patients with stage IIIA disease.

Distant failure was found in 22 (36%) patients overall: 6 (26%) with stage IA disease, 2 (17%) with stage IB disease, 4 (50%) with stage II disease, and 9 (50%) with stage IIIA disease. Distant failure was most frequently noted in the brain, followed by the liver. The incidence of brain metastasis was 15% overall, 17% in patients with stage IA disease, and 11% in patients with stage IIIA disease. Bone metastasis was noted exclusively in patients with stage IIIA disease.

***Discrepancy between clinical and pathologic stages.*** Table 6 shows the relationship between the clinical stage and the pathologic stage. Among 44 patients with clinical stage I disease, only 33 (75%) had pathologic stage I disease, and

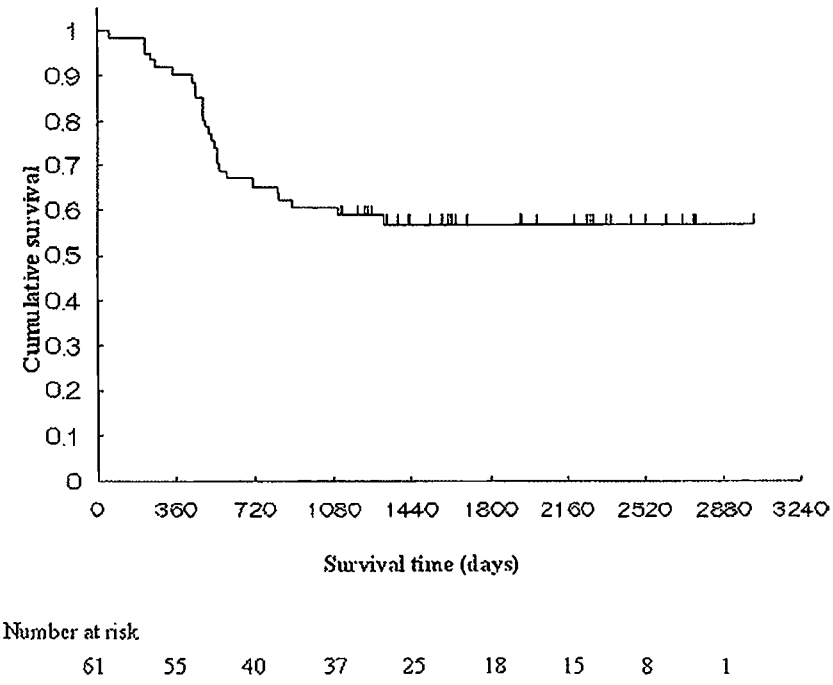


**Figure 1. Survival curve for overall patients with resected SCLC.**

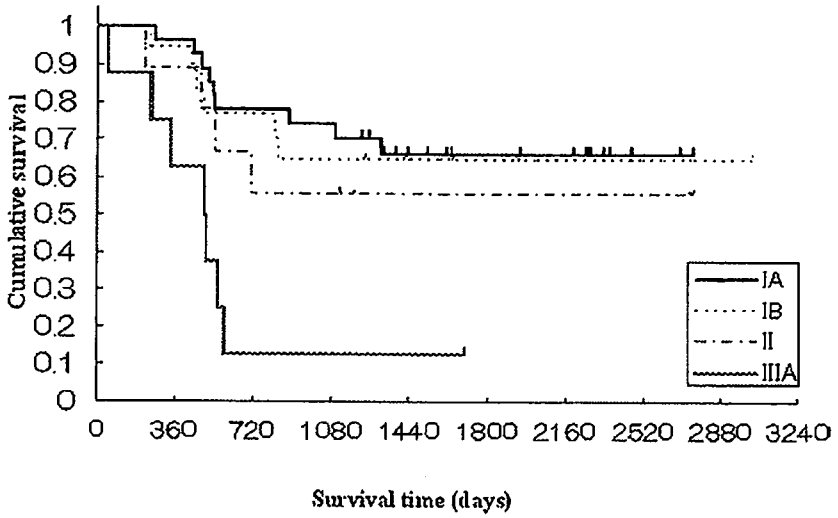


Figure 2. Survival curves for patients with resected SCLC by clinical stages.

6 had stage IIIA disease. Five patients with clinical stage IA disease had mediastinal lymph node metastasis. According to the Bowker test of symmetry, these differences were statistically significant.

## Discussion

This phase II trial showed that postoperative PE for patients who underwent surgical resection of stage I to IIIA SCLC was feasible, and the outcome was acceptable. Survival was excellent in patients with stage I disease and did not appear to be inferior to that with chemoradiotherapy in patients with stage II or IIIa disease.

On the basis of the results of the British Medical Research Council, radical radiotherapy has been preferable to surgical intervention for SCLC,[17,18] and the indications for surgical resection for SCLC are still controversial. An operation would be indicated for limited SCLC because the most common relapse site after radiotherapy was locoregional, and surgical intervention might improve local control.[19] Several authors have reported that a small minority of

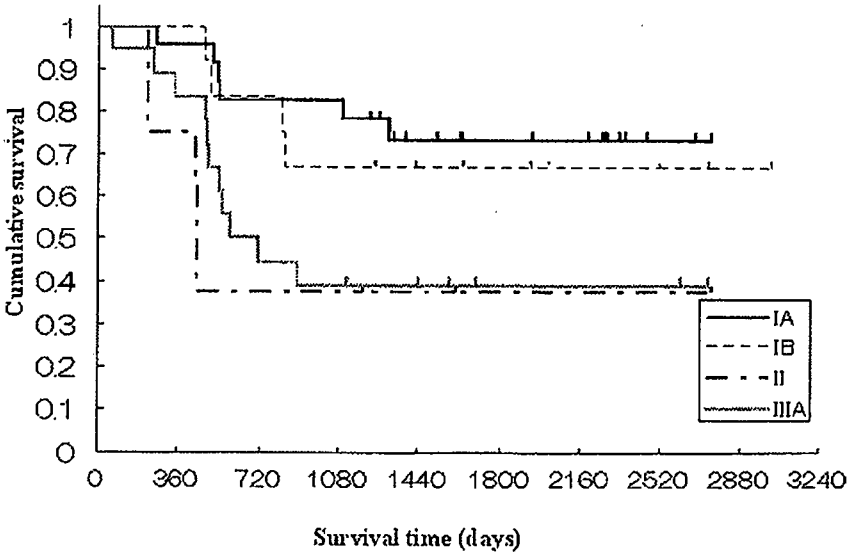


Figure 3. Survival curves for patients with resected SCLC by pathologic stage.

**TABLE 5. Site of the first relapse by pathologic stages***

| Variables | Overall | Stage IA | Stage IB | Stage II | Stage IIIA |
|---|---|---|---|---|---|
| No. of patients | 61 | 23 | 12 | 8 | 18 |
| No. of recurrence | 26 (43%) | 7 (30%) | 3 (25%) | 4 (50%) | 12 (67%) |
| Recurrence | | | | | |
| Local | | | | | |
| Overall | 6 (10%) | 1 (4%) | 1 (8%) | 0 (0%) | 4 (22%) |
| Mediastinum | 4 | 1 | 1 | 0 | 2 |
| Bronchial stump | 2 | 0 | 0 | 0 | 2 |
| Distant | | | | | |
| Overall | 22 (36%) | 6 (26%) | 2 (17%) | 4 (50%) | 9 (50%) |
| Brain | 9 (15%) | 4 (17%) | 0 (0%) | 3 (38%) | 2 (11%) |
| Bone | 3 | 0 | 0 | 0 | 3 |
| Liver | 7 | 1 | 1 | 1 | 4 |
| Lung | 2 | 0 | 1 | 0 | 1 |
| Small intestine | 2 | 1 | 0 | 0 | 1 |

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limited-stage SCLCs could be managed with an operation and postoperative chemotherapy.[1-9] According to those reports, the 5-year survivals were 28% to 36% overall and 26% to 61% in patients with stage I disease. However, most of those reports were retrospective and used various combinations of chemotherapy. Therefore, a prospective trial of adjuvant chemotherapy for patients with resected SCLC using standardized chemotherapy has been needed. Our survival data suggest that postoperative PE after major lung resection and hilar and mediastinal lymph node dissection is a feasible and promising treatment, especially for patients with stage I SCLC. The 3- and 5-year survivals for patients with stage I disease were 78% and 73%, respectively, and the median survival time was not reached. As for patients with stage II or IIIA disease, the results were not definitive, and a further prospective study is needed. This study dealt with postoperatively proved SCLC. As to the indication for surgical intervention for preoperatively diagnosed SCLC, controversies still remain. Our recommendation is as follows. When a patient has SCLC of clinical N1 or N2 status, chemoradiotherapy should be considered because a survival after an operation alone would not be good enough. Surgical intervention should be considered, however, for patients with clinical stage I disease because an operation followed by chemotherapy offers a good prognosis, as shown in this study, and because such SCLC sometimes turns out to be non-SCLC postoperatively. A phase III trial comparing chemoradiotherapy with surgical intervention followed by chemotherapy is interesting. However, the number of patients with SCLC with clinical stage I or II disease is very small, and we do not think it is possible to perform the phase III trial in this population.

**TABLE 6. Relationship between clinical and pathologic stages**

| Clinical stage | Pathologic stage I | II | IIIA | *P* value* |
|---|---|---|---|---|
| I | 33 | 5 | 6 | .011 |
| II | 1 | 3 | 5 | |
| IIIA | 1 | 0 | 7 | |

**P* value in Bowker's test of symmetry.

Because clinical stage and pathologic stage were significant prognostic factors in our trial, preoperative staging, intraoperative staging, or both should be a major concern for the treatment of very limited SCLC. Actually, the following preoperative investigations were performed before entry into the study in this cohort: CT scans of the chest, upper abdomen, and brain; bronchoscopy; chest plain film; radionuclide bone scans; complete blood cell count and serum chemistry; and physical examination. If the diagnosis of SCLC was made preoperatively, we recommend the same preoperative workup as done by us in this study. Furthermore, if swollen lymph nodes are detected on thoracic CT scans, we absolutely recommend mediastinoscopy for such cases. As for positron emission tomography, we have no recommendation thus far because this modality has recently begun to be evaluated, although it could be useful for staging N1 disease. Intraoperatively, hilar and mediastinal lymph node sampling or dissection was performed in 59 (97%) patients. This intraoperative staging is also important for deciding on the treatment strategy.

The site of the first relapse was another fruit of our study. This clinical trial did not use postoperative mediastinal irradiation or prophylactic cranial irradiation (PCI). We should discuss the importance of these strategies for very limited SCLC. As to locoregional recurrence, approximately 10% of the patients showed relapse in the mediastinal lymph nodes, bronchial stump, or both. Five percent of patients with stage I or II disease eventually have locore-

gional recurrence, whereas this is seen in 22% of patients with stage IIIA disease. These results suggest that patients with stage IIIA disease, at least, could benefit from postoperative mediastinal irradiation, whereas those with stage I or II disease might not need to undergo radiotherapy. Thus, postoperative chemoradiotherapy might be used in a future trial for stage IIIA disease.

Auperin and associates[20] reported that PCI improved both overall survival and disease-free survival among patients with SCLC in complete remission. Surgically resected SCLC would be considered SCLC in complete remission, and PCI would be indicated. Overall, 15% of the patients in our study showed brain metastasis. Even among patients with stage IA disease, more than 10% of the patients had brain metastasis. Therefore, PCI might be necessary for all patients with completely resected SCLC, whereas some authors have insisted that patients with pathologic stage IA SCLC can be cured without any adjuvant treatment.[19]

Noda and coworkers[21] reported that combination chemotherapy consisting of irinotecan (CPT-11) and cisplatin was superior to PE for extensive SCLC. Although concurrent radiotherapy with CPT-11 would be harmful, we would use the new regimen for very limited SCLC, especially for stage II or IIIA SCLC.

Major lung resection with complete hilar and mediastinal lymph node dissection followed by postoperative PE is a feasible treatment and results in a favorable survival profile. Survival was especially good for patients with stage I disease. Our strategy could be used as a standard treatment arm in a future trial for very limited SCLC.

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# Pilot Study of Concurrent Etoposide and Cisplatin Plus Accelerated Hyperfractionated Thoracic Radiotherapy Followed by Irinotecan and Cisplatin for Limited-Stage Small Cell Lung Cancer: Japan Clinical Oncology Group 9903

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**Abstract** **Purpose:** Irinotecan and cisplatin (IP) significantly improved survival compared with etoposide and cisplatin (EP), in patients with extensive-stage small cell lung cancer (SCLC) in a previous Japan Clinical Oncology Group (JCOG) randomized trial. JCOG9903 was conducted to evaluate the safety of sequentially given IP following concurrent EP plus twice-daily thoracic irradiation (TRT) for the treatment of limited-stage SCLC (LSCLC).

**Experimental Design:** Between October 1999 and July 2000, 31 patients were accrued from 10 institutions. Thirty patients were assessable for toxicity, response, and survival. Treatment consisted of etoposide 100 mg/m$^2$ on days 1 to 3, cisplatin 80 mg/m$^2$ on day 1, and concurrent twice-daily TRT of 45 Gy beginning on day 2. The IP regimen started on day 29 and consisted of irinotecan 60 mg/m$^2$ on days 1, 8, and 15 and cisplatin 60 mg/m$^2$ on day 1, with three 28-day cycles.

**Results:** There were no treatment-related deaths. The response rate was 97% (complete response, 37%; partial response, 60%). Median overall survival was 20.2 months; 1-, 2-, and 3-year survival rates were 76%, 41%, and 38%, respectively. Of the 24 patients who started the IP regimen, 22 received two or more cycles. Hematologic toxicities of grade 3 or 4 included neutropenia (67%), anemia (50%), and thrombocytopenia (4%). Nonhematologic toxicities of grade 3 or 4 included diarrhea (8%), vomiting (8%), and febrile neutropenia (8%). Of the 20 patients with recurrence, none had local recurrence alone and only two had both local and distant metastasis as the initial sites of disease progression.

**Conclusions:** IP following concurrent EP plus twice-daily TRT is safe with acceptable toxicities. A randomized phase III trial comparing EP with IP following EP plus concurrent TRT for LSCLC is ongoing (JCOG0202).

Despite efforts to curb smoking, lung cancer remains the leading cause of cancer deaths in many industrialized countries. Small cell lung cancer (SCLC) accounts for about 15% of all lung cancer histology. Whereas combination chemotherapy is the cornerstone of SCLC treatment, meta-analyses showed that adding thoracic radiotherapy to combination chemotherapy significantly improves the survival of patients with limited-stage SCLC (LSCLC; i.e., disease confined to the hemithorax; refs. 1, 2). Several randomized trials have shown that early use of concurrent thoracic radiotherapy is superior to sequential or late use when etoposide and platinum are employed as combination chemotherapy (3–5). An intergroup phase III study showed accelerated hyperfractionated radiotherapy with etoposide and cisplatin (EP) to be superior to standard fractionation, with 5-year survival rates of 26% and 16%, respectively (6). Although substantial progress has been made during the past two decades, many LSCLC patients experience tumor recurrence and succumb to the disease, indicating the need for improved LSCLC therapy.

The Japan Clinical Oncology Group (JCOG) previously conducted a randomized phase III trial comparing irinotecan and cisplatin (IP) with EP in patients with extensive-stage SCLC. The response rate and overall median survival were significantly better for IP (i.e., 84.4% and 12.8 months with IP versus 67.5% and 9.4 months with EP, respectively). The 2-year

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survival rates were 19.5% for IP and 5.2% for EP (7). These encouraging results prompted us to explore the use of IP in LSCLC. We therefore undertook a pilot study to evaluate the safety of IP following concurrent EP plus twice-daily thoracic irradiation (TRT) for LSCLC.

## Experimental design

*Eligibility criteria.* Patients with histologically or cytologically documented LSCLC, defined as disease confined to one hemithorax including bilateral supraclavicular nodes, were enrolled in this study. Additional eligibility criteria consisted of measurable or assessable disease, age <75 years, Eastern Cooperative Oncology Group performance status of 0 to 2, no previous treatment, leukocyte count $\geq 4{,}000/mm^3$, platelet count $\geq 10^5/mm^3$, hemoglobin $\geq 9.5$ g/d, serum creatinine $\leq 1.5$ mg/d, creatinine clearance $\geq 60$ mL/min, serum bilirubin $\leq 1.5$ mg/d, serum transaminase $\leq 2 \times$ ULN, and $PaO_2 \geq 70$ mm Hg. Exclusion criteria included active infection, uncontrolled heart disease or a history of myocardial infarction within the previous 3 months, interstitial pneumonia/active lung fibrosis on chest X-ray, peripheral neuropathy, malignant pleural or pericardial effusion, diarrhea, intestinal obstruction or paralysis, and active concomitant malignancy. The TRT portal should be no more than half of the hemithorax. No prior chemotherapy or radiotherapy was permitted. Pregnant or lactating women were excluded. Before enrollment in the study, each patient provided a complete medical history and underwent physical examination, blood cell count determinations, arterial blood gas, biochemical laboratory examinations, chest X-ray, electrocardiogram, chest computed tomographic scan, and whole-brain computed tomographic or magnetic resonance imaging, abdominal ultrasound and/or computed tomographic, and isotope bone scans. Blood cell counts, differential white counts, and other laboratory data were obtained weekly during each course of chemotherapy. All patients were reassessed at the end of treatment in the same manner as at the time of enrollment.

*Treatment plan.* Induction chemotherapy consisted of cisplatin 80 $mg/m^2$ on day 1 and etoposide 100 $mg/m^2$ on days 1 to 3. TRT was begun on day 2 of the induction chemotherapy and given twice daily (1.5 Gy per fraction, with $\geq 6$ hours between fractions) and directed to the primary tumor for a total dose of 45 Gy in 3 weeks. The initial field included the primary disease site with a 1.5-cm margin around the mass, the ipsilateral hilum, the entire width of the mediastinum, and the supraclavicular lymph nodes (only if there was nodal tumor involvement). TRT was done with linear accelerators and the energy was 6 to 10 MV photons. After the administration of 30 to 36 Gy, the radiation field was reduced around the primary tumor and involved lymph nodes using parallel opposed oblique fields to limit the dose to the spinal cord and protect the uninvolved lung field. Following chemoradiotherapy, patients were treated with three cycles of IP. The IP regimen started on day 29 and consisted of irinotecan 60 $mg/m^2$ on days 1, 8, and 15 and cisplatin 60 $mg/m^2$ on day 1, with three 28-day cycles. If the leukocyte count decreased to $<3{,}000/mm^3$ or the platelet count fell below $100{,}000/mm^3$ on the first day of IP, chemotherapy was withhold until the counts recovered to $\geq 3{,}000/mm^3$ and $\geq 100{,}000/mm^3$, respectively. Administration of irinotecan was skipped on day 8 and/or 15 if the leukocyte count was $\leq 2{,}000/mm^3$, the platelet count was $\leq 50{,}000/mm^3$, or there was any diarrhea regardless of grade, or a fever of $\geq 37.5°C$. The dose of irinotecan in subsequent cycles was reduced by 10 $mg/m^2$ from the planned dose if grade 4 hematologic toxic effects or grade 2 or 3 diarrhea developed. Administration of granulocyte colony-stimulating factor was prohibited on the days of chemotherapy or radiotherapy. Primary prophylactic granulocyte colony-stimulating factor was not given. For patients who had developed grade 4 neutropenia during the previous cycles of chemotherapy, secondary prophylactic granulocyte colony-stimulating factor administration was allowed. Prophylactic antibiotics were not given.

Treatment was discontinued in patients with grade 4 nonhematologic toxicity. Prophylactic cranial irradiation (25 Gy in 10 fractions) was conducted for patients showing a complete response or near complete response defined as a reduction of >90% in the sum of the products of the greatest perpendicular dimensions of bidimensional lesions. Tumor responses were assessed radiographically. Standard WHO response criteria (8) were used, and all responses were confirmed $\geq 28$ days after initial documentation of the response. JCOG criteria were used to assess toxicity (9). JCOG criteria are similar to those of the National Cancer Institute Common Toxicity Criteria (10). Esophageal toxicity was graded as follows: grade 3, moderate to severe ulceration and edema, cannot eat, requires narcotic drugs; grade 4, serious ulceration and edema, resulting in complete obstruction or perforation.

*Statistical consideration.* The primary objective of this study was to evaluate the safety and feasibility of sequential administration of IP following EP plus concurrent twice-daily TRT. Simon's optimal two-stage design was used to determine the sample size and decision criteria (11). The regimen would be considered feasible if two cycles or more of IP were completed without grade 4 nonhematologic toxicity or treatment related death in at least 90% of patients and not feasible if the completion rate was $\leq 70\%$. The required number of patients was estimated to be 27, with $\alpha = 0.05$ and $\beta = 0.80$. We determined the planned sample size for the study to be 30 patients accrued over 12 months, with 36 months of additional follow-up.

Time-to-progression was calculated from the date of entry into study until the date of documented progression or death (in the absence of progression). Survival was calculated from the protocol treatment start date until the date of death. Both intervals were determined by the Kaplan-Meier method.

The protocol was approved by the Clinical Trial Review Committee of JCOG and the Institutional Review Board of the participating institutions. All patients provided written informed consent.

## Results

*Patient characteristics.* Between October 1999 and July 2000, 31 patients were accrued from 10 institutions. Patient characteristics are detailed in Table 1. Although eligible, no patients with a performance status of 2 were actually enrolled in this trial. Thirty-one patients ultimately participated. One patient did not receive the protocol treatment because of a problem with the radiation equipment in the institution providing treatment. Thus, this patient was not evaluable.

*Adherence to treatment plan.* All patients completed concurrent chemoradiotherapy. Six patients did not receive the IP regimen, because of disease progression, septic shock

**Table 1.** Patient characteristics

| | |
|---|---|
| Patient registered | 31 |
| Assessable | 30 |
| Not assessable (not treated) | 1 |
| Median age (range) | 64 (43-74) |
| Gender | |
| Male | 27 |
| Female | 4 |
| Performance status 0/1 | 8/23 |

during chemoradiotherapy, renal dysfunction, or leukocytopenia, and two refused IP. Of the 24 patients given the IP regimen, 22 received two cycles or more of IP. The reasons for terminating IP before the second treatment cycle were grade 4 diarrhea in one patient and refusal, not significant toxicity, in one patient. Of the 22 patients who received two cycles or more of IP, nine received the original planned dose. In five patients, dose reductions in the second cycle of IP were necessary, 11 patients skipped day 8 and/or 15 irinotecan, and one patient had a minor protocol violation. Fifteen patients required that the second cycle of IP be delayed for 1 to 14 days. Of 17 patients (58%) who received the entire treatment, the median time delay from the planned protocol was 4 days (range, 0-21 days). Six patients were able to start the third cycle of IP without delay, relative to the first cycle of IP.

*Toxicity.* Toxicities associated with concurrent chemoradiotherapy are summarized in Table 2. The major toxicity was neutropenia. One patient had febrile neutropenia and septic shock. The same patient experienced grade 3 fatigue and anterior chest pain. IP was well tolerated (Table 3), despite diarrhea, vomiting, and hematologic toxicities. One patient, who had grade 2 nausea/vomiting, refused further treatment after the first cycle of IP. Another patient, who refused days 8 and 15 irinotecan during the second cycle, had grade 2 diarrhea and nausea/vomiting. No grade 3 or 4 pulmonary toxicity was observed. There were no treatment-related deaths.

**Table 2.** Major toxicities concurrent EP/TRT ($n = 30$)

| Toxicity | Grade 3, no. patients (%) | Grade 4, no. patients (%) |
|---|---|---|
| Hematologic | | |
| Anemia | 0 | 0 |
| Leucopenia | 13 (43) | 15 (50) |
| Neutropenia | 9 (30) | 19 (63) |
| Thrombocytopenia | 2 (7) | 1 (3) |
| Nonhematologic | | |
| Esophagitis | 2 (7) | 0 |
| Infection | 1 (3) | 0 |
| Hypotension* | 0 | 1 (3) |
| Fatigue* | 1 (3) | 0 |
| Anterior chest pain* | 1 (3) | 0 |
| Febrile neutropenia | 2 (7) | |

*These events occurred in the same patient.

**Table 3.** Major toxicities irinotecan and cisplatin (IP), ($n = 24$)

| Toxicity | Grade 2, no. patients (%) | Grade 3, no. patients (%) | Grade 4, no. patients (%) |
|---|---|---|---|
| Hematologic | | | |
| Anemia | 6 (25) | 12 (50) | 0 |
| Leucopenia | 6 (25) | 12 (50) | 5 (21) |
| Neutropenia | 5 (21) | 12 (50) | 5 (21) |
| Thrombocytopenia | 5 (21) | 1 (4) | 0 |
| Nonhematologic | | | |
| Diarrhea | 4 (17) | 1 (4) | 1 (4) |
| Vomiting | 3 (13) | 2 (8) | 0 |
| Febrile neutropenia | — | 2 (8) | 0 |
| Fever | 2 (8) | 0 | 0 |
| Infection | 4 (17) | 0 | 0 |

Neither grade 2, or more severe, late radiation toxicities nor radiation recall reactions were reported.

*Response and survival.* The overall response rate was 97% (complete response, 37%; partial response, 60%). Overall and progression-free survivals are depicted in Figs. 1 and 2 The median follow-up time of all patients was 20 months and that for surviving patients 40 months. The median progression-free survival was 9 months, and the median overall survival was 20 months. The 24- and 36-month overall survivals were 41% and 38%, the 24- and 36- month progression-free survivals 30% and 26%, respectively.

*Pattern of relapse.* First sites of disease progression are presented in Table 4. Of the 18 patients who have died to date, all died of progressive disease. Surprisingly, no patient showed relapse solely at the local-regional site (within TRT field). Only two patients had both local and distant involvement. There were 11 patients whose initial site of relapse was the brain. Of these, six had relapses solely in the brain. Whereas two patients had complete response and received prophylactic cranial irradiation, four had partial remission and did not receive prophylactic cranial irradiation.

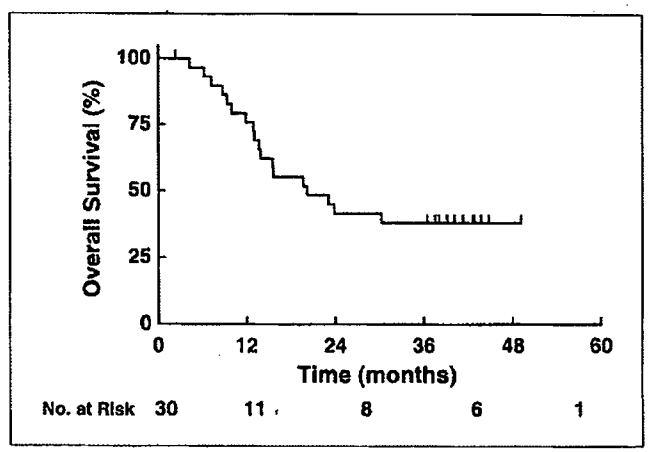


Fig. 1. Overall survival.

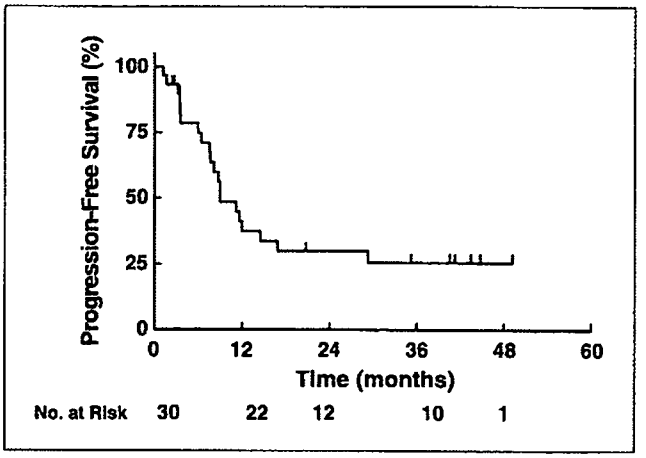


Fig. 2. Progression-free survival.

Other relapse sites included the liver in four patients, bone in three, pleural effusion in three, and supraclavicular lymph nodes in two.

## Discussion

Irinotecan is one of the most active agents against SCLC (12). A phase II study of irinotecan and cisplatin yielded a response rate of 86% and median survival of 13.2 months in patients with extensive SCLC (13). A phase III study confirmed excellent results and showed IP to be more effective than etoposide and cisplatin in extensive SCLC (7). Three confirmatory trials, comparing IP with EP for extensive SCLC are ongoing in Europe and the United States. Although dose-finding studies to explore integrating irinotecan into the early concurrent phase of chemoradiation for LSCLC are also currently being conducted by the Radiation Therapy Oncology Group and other U.S. groups. The dose-finding JCOG study of concurrent use of IP with TRT in stage III non-small cell lung cancer showed that the full dose of irinotecan could not be given due to neutropenia, diarrhea, and pulmonary toxicity (14). Thus, we employed IP as a sequential treatment following EP plus concurrent TRT.

The present trial showed IP following concurrent EP plus twice-daily TRT to be safe, with acceptable toxicities. Hematologic toxicities and diarrhea, while on the IP regimen following concurrent chemoradiotherapy, are similar to those of a previous phase III trial conducted by JCOG (JCOG9503; ref. 7). Neither grade 3 or 4 pulmonary toxicity nor treatment related deaths were observed. The West Japan Thoracic Oncology Group conducted a similar phase II study of EP plus twice-daily TRT followed by IP for LSCLC (15). Promising response (88%) and 2-year survival (51%) rates were reported, with acceptable toxicities.

**Table 4. Sites of first failure ($n = 20$)**

| Site | No. patient (%) |
|---|---|
| Isolated local-regional failure | 0 (0) |
| Local-regional and distant | 2 (10) |
| Distant | 18 (90) |
| Brain only | 6 (30) |
| Other sites of failure* | 12 (60) |

*Recurrence at sites other than the primary tumor or brain only.

Local failure is an important problem in the treatment of LSCLC. Turrisi et al. showed the rate of local failure to be reduced in the twice-daily TRT plus EP group as compared with the once-daily TRT plus EP group: the rate was 52% in the group receiving once-daily therapy and 36% in that receiving twice-daily therapy (6). Eighteen percent of patients who received EP plus concurrent twice-daily TRT had first progression within the thorax in the previous JCOG phase III trial (5). It is noteworthy that no patient relapsed solely at the local-regional site and only two patients had both local and distant involvement in the present trial. There may be an interaction between TRT and IP even given sequentially. Another possibility relates to recent improvements in radiotherapeutic techniques with better imaging of the target volume by chest computed tomographic. This possibility should be assessed in a future randomized trial.

It is important to integrate new active anticancer agents to the combined modality treatments for LSCLC. Irinotecan has been clearly shown to have clinical activity in a randomized trial, against extensive-stage SCLC. Several other new agents including targeted therapies have failed to show clinical activity against SCLC. Based on these considerations, we conducted a randomized phase III trial comparing EP with IP following EP plus concurrent TRT for the treatment of LSCLC (JCOG0202). In the JCOG0202, eligible patients were randomized after the completion of induction chemoradiotherapy. Although feasibility may be a limitation of the present study, improvements are anticipated with appropriate use of granulocyte colony-stimulating factor, antibiotics, and patient education.

In summary, irinotecan and cisplatin following EP plus concurrent twice-daily TRT is a safe and active regimen for LSCLC. The observed low rate of local recurrence is encouraging. A randomized phase III trial comparing EP with IP following EP plus concurrent TRT for the treatment of LSCLC is currently under way.

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# Pitfalls in lymph node staging with positron emission tomography in non-small cell lung cancer patients

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**Summary**
*Background:* The evidence of clinical value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose (FDG) in lymph node (LN) staging in non-small cell lung cancer (NSCLC) has been shown in numerous papers. However, few studies have assessed its limitations. The aim of the present study is to clarify clinicopathologic factors responsible for false PET results.
*Methods:* From July 2000 through December 2001, 71 NSCLC patients underwent both FDG PET and surgical intervention at the National Cancer Center Hospital East, Chiba. Clinical records, computed tomographic (CT) scan findings, PET findings, and histologic findings were retrospectively reviewed.
*Results:* Sensitivity, specificity, accuracy in nodal staging for CT were 29, 83, and 65% and for PET were 39, 79, and 66%, respectively. There were 10 (14%) false-positive PET scans and 14 (20%) false-negative PET scans. The causative factors for false-positive PET scan were: (1) inflammatory conditions in seven patients; (2) PET mis-localization of an interlobar LN as a mediastinal LN in one patient; (3) inability to distinguish the endobronchial polypoid growth of a primary tumor from a lobar LN in one patient; (4) unknown in one patient. All false-positive LNs due to inflammatory conditions showed reactive lymphoid hyperplasia histologically. The causative factors for false-negative PET scan were: (1) limitation of spatial resolution

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