# A prematurely terminated phase III trial of intraoperative intrapleural hypotonic cisplatin treatment in patients with resected non–small cell lung cancer with positive pleural lavage cytology: The incidence of carcinomatous pleuritis after surgical intervention

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**Background:** The prognosis of patients with resected non–small cell lung cancer without carcinomatous pleuritis whose intrapleural cancer cells were detected by means of a cytologic examination of pleural lavage fluid obtained immediately after a thoracotomy has been reported to be poor.

**Methods:** The Japan Clinical Oncology Group conducted a phase III trial for a 3-year period starting from October 1994 to determine whether intraoperative intrapleural hypotonic cisplatin treatment could effectively control pleural disease and thereby prolong the survival of these patients. The patients were randomized to receive either intraoperative intrapleural hypotonic cisplatin treatment or no treatment before closure of the open thorax. The intraoperative intrapleural hypotonic cisplatin treatment consisted of exposing the entire thorax to cisplatin (50 $\mu$g/mL) in distilled water for 15 minutes.

**Results:** Because of the slow registration pace, the study was prematurely terminated in January 1998. During the 41-month period from the start of the registration, 49 patients were entered into the study, and all were eligible. Twenty-five and 24 patients were randomly assigned to the treatment and control groups, respectively. No statistically significant difference in the overall survival and disease-free survival between the 2 groups was observed. However, the appearance of carcinomatous pleuritis was suppressed by the hypotonic cisplatin treatment (42% of the control group vs 8% of the treatment group, $P = .008$).

**Conclusions:** Although the randomized trial was prematurely terminated, the intraoperative intrapleural hypotonic cisplatin treatment was found to effectively suppress the appearance of carcinomatous pleuritis in resected patients who demonstrated a positive pleural lavage cytology finding.

The presence of cancer cells in the intrapleural space has been reported in a certain percentage of patients with non–small cell lung cancer without carcinomatous pleuritis (malignant pleural effusion, disseminated pleural tumors, or both) who underwent an operation on the basis of the findings of a cytologic examination of intrapleural lavage fluid collected immediately after a thoracotomy.[1-6] On the whole, the prognosis of such patients has been reported to be poor, and the pattern of recurrence has yet to be intensively analyzed. However, considering the site of such cancer cells, the occurrence of carcinomatous pleuritis as a recurrence can be predicted in such patients.

We developed an intraoperative intrapleural treatment regimen in which distilled

water was combined with cisplatin for patients with carcinomatous pleuritis found at thoracotomy. According to our experimental data, the hypotonic cisplatin solution showed a significantly stronger antitumor activity than either the isotonic cisplatin solution or distilled water alone.[7] In a single institutional clinical trial, this treatment modality, which is called *hypotonic cisplatin treatment*, seemed to effectively control carcinomatous pleuritis without any adverse events.[8] As a result, the Surgical Lung Cancer Study Group of the Japan Clinical Oncology Group (JCOG) started a randomized phase III trial to determine whether intraoperative intrapleural hypotonic cisplatin treatment can effectively control pleural disease and thus prolong survival. However, this trial was prematurely terminated because of a poor registration pace. Although the analysis of results from such a failed trial should be limited, the recurrent patterns, including carcinomatous pleuritis, that were prospectively observed are considered worthy of analysis. We therefore focused on that aspect in this study.

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## Methods

### Patients

The patients who were eligible for this study consisted of those with non–small cell lung cancer who had cancer cells detected by means of a cytologic examination of the intrapleural lavage fluid collected immediately after opening the thorax. All such patients had to undergo a macroscopically complete resection of the disease, which ranged from surgical stage I to IIIA. Neither any malignant pleural effusion nor disseminated pleural tumors could be found at thoracotomy. Before operation, all eligible patients were required to be 75 years of age or younger, have an estimated postoperative $FEV_{1.0}$ of greater than 600 mL/m$^2$, have a leukocyte count of 3000/$\mu$L or greater, have a hemoglobin level of 10 g/dL or greater, have a platelet count of 100,000/$\mu$L or greater, have a serum bilirubin level of 1.5 mg/dL or less, have serum glutamic oxaloacetic transaminase-glutamic pyruvic transaminase levels of no more than twice the upper limit of normal, have a serum creatinine level of 1.5 mg/dL or less, and have a blood urea nitrogen level of 25 mg/dL or less. Patients who either underwent a combined resection of the chest wall or pericardium or those with a broad range of pleural adhesion were also excluded from the study.

### Design and Procedure

This trial was initiated by the Lung Cancer Surgical Study Group of the JCOG in October 1994, and the trial was prematurely terminated in January 1998 because of a slow registration pace. Registration was done by fax at the data center of the JCOG during the operations. All patients underwent randomization, and the operator was informed of the randomized result before the end of the operation. The patients were stratified according to surgical stage (I vs II + III A-N0, 1 vs IIIA-N2).[9] The primary endpoint of the study was the incidence of the appearance of clinically detected carcinomatous pleuritis and the overall survival, and the secondary end point was the disease-free survival and safety assessment. The institutional review board or the ethics committee at each site reviewed and approved the protocol. Written informed consent was obtained from all patients.

Immediately after opening the thorax, the pleural cavity was gently washed with 50 mL of saline. To obtain only cancer cells present in the intrapleural space, we avoided touching any of the pleural surfaces on the primary tumor. Next, 20 mL of the lavaged fluid was collected and put into a tube containing ethylenediamine tetraacetic acid. The obtained sediment was stained with Giemsa and the Papanicolaou method and with Alcian blue to determine the presence or absence of cancer cells.

The patients assigned to the control group received no treatment after the tumor was resected, and the open thorax was closed after washing the thorax with saline. Patients randomized to the treatment group received the intraoperative intrapleural hypotonic cisplatin treatment before closure of the open thorax.[7,8] After completing the intrathoracic surgical procedures, the thoracic cavity was washed out with saline to remove any blood, and then it was washed out an additional 2 more times with distilled water to efficiently remove any remaining blood cells by means of hemolysis. Thereafter, the entire thoracic cavity was exposed for 15 minutes to cisplatin in distilled water that had been prewarmed to 38°C to 40°C. The cisplatin concentration used was 50 $\mu$g/mL. After removing the solution by means of suction and washing out the thoracic cavity with saline, 2 chest tubes for patients with a lobectomy and one chest tube for those with a pneumonectomy were inserted, and then the thoracic cavity was closed. Perioperative hydration was not specifically performed.

The performance of postoperative chemotherapy was not allowed until recurrence was identified. Radiotherapy after the operation was performed at the physician's discretion.

All patients were required to undergo bronchoscopy, bone scintigraphy, and a computed tomography (CT) scan of the thorax, including the level of the adrenal glands, before the operation. A follow-up examination was performed every 3 months for 5 years. The examination included a physical examination, measurement of serum tumor markers, and chest radiography every 3 months and a CT scan of the thorax, including the level of the adrenal glands, as well as bone scintigraphy, every 6 months for 5 years. The site of a first recurrence, including carcinomatous pleuritis, was noted obligatorily. Recurrence caused by carcinomatous pleuritis was defined as follows: (1) the appearance of pleural effusion in which the presence of cancer cells was proven by a cytologic examination; (2) the enlargement of an irregular-shaped pleural thickness shadow or pleural mass shadow confirmed by successive CT scans; and (3) cancer in either the pleural thickness or pleural mass detected by means of CT scans and proved by means of a pathologic examination.

### Statistical Analysis

This trial was designed to test the hypothesis that the 3-year survival rate would be 30% in the control group and 50% in the treatment group. The estimated sample size with an $\alpha$ error of .05 and a $\beta$ error of .2 was 100 patients in each group within a 3-year period.

In the present study the overall and disease-free survivals were defined as the time from operation until death from any cause and the time from operation until either death from any cause or a first recurrence. The survival curves were made by using the Kaplan-

**TABLE 1. Patient characteristics**

| | Treatment group (n = 25) | Control group (n = 24) | *P* value |
|---|---|---|---|
| Age (y) | 60.9 ± 9.1 | 58.5 ± 8.0 | .334 |
| Male/female ratio | 10/15 | 8/16 | .628 |
| Histology | | | |
| Adenocarcinoma | 25 | 20 (83%) | .050 |
| Others | 0 | 4 | |
| Pathologic T factor | | | |
| T1 | 6 (24%) | 7 (29%) | .981 |
| T2 | 17 (68%) | 15 (63%) | |
| T3 | 1 | 1 | |
| T4 | 1 | 1 | |
| Pathologic N factor | | | |
| N0 | 14 (56%) | 14 (58%) | .815 |
| N1 | 3 | 4 | |
| N2 | 8 (32%) | 6 (25%) | |
| Pathologic stage | | | |
| I | 12 (48%) | 13 (54%) | .708 |
| II | 3 | 4 | |
| III | 10 (40%) | 7 (29%) | |

Meier method, and a statistical evaluation of the curves was done by means of a log-rank test. Differences between the proportions were evaluated with the $\chi^2$ test.

## Results

Although a total of 200 patients had been scheduled to be enrolled in this phase III trial during the 3-year period from October 1994, the pace of the patient registration was so slow that the trial was terminated prematurely as of January 1998. During the 41-month period from the start of the registration, only 49 eligible patients were enrolled in the study and randomly assigned to either the hypotonic cisplatin treatment group (25 patients) or the control group (24 patients). All patients underwent a lobectomy. Although performance of postoperative chemotherapy was not allowed until recurrence was observed, 1 patient in the control group did receive chemotherapy. Two patients in the treatment group underwent postoperative radiotherapy. The other patient characteristics are shown in Table 1. The ratio of adenocarcinoma in the treatment group was higher than that in the control group ($P = .0502$), but the proportion of other items was well balanced between the 2 groups.

In the treatment group the dose (mean ± SD) of cisplatin and the volume of distilled water actually used were 78.4 ± 24.9 mg (range, 50-100 mg) and 1488 ± 262 mL (range, 500-2000 mL), respectively. The actual exposure time was 13.2 ± 3.4 minutes (range, 10-20 minutes).

The median time from registration to the last follow-up in the 26 surviving patients was 49 months (range, 29-72 months). As shown in Figures 1 and 2, no statistical difference in the overall survival and the disease-free survival between the treatment and control groups was observed. However, the appearance of the carcinomatous pleuritis was suppressed by the hypotonic cisplatin treatment (Table 2). Carcinomatous pleuritis was observed in 10 (63%) of 16 patients with recurrence in the control group or in 10 (42%) of all 24 patients in the control group, whereas only 2 (17%) of 12 patients with recurrence in the treatment group ($P = .024$) or 2 (8%) of all 25 patients in the treatment group ($P = .008$) had carcinomatous pleuritis. The length of time until the appearance of carcinomatous pleuritis from the operation was 7 and 48 months in 2 patients in the treatment group, respectively, and the same median time in 10 patients in the control group was 18 months (range, 6-38 months), as shown in Figure 2. Among a total of 12 patients with carcinomatous pleuritis, malignant pleural effusion was observed in 8 patients, pleural disseminated tumors in 3 patients, and both in 1 patient. Systemic recurrence was observed in 8 patients in the treatment group and in 7 patients in the control group (Table 2).

Concerning postoperative complications, pneumonia was noted in 2 patients in the treatment group and in 1 patient in the control group. Arrhythmia and prolonged alveolar air leakage was observed in 1 patient each in the treatment group. However, neither any operative deaths nor treatment-related deaths were observed.

## Discussion

When the protocol was approved by the JCOG, approximately 100 patients undergoing resection with non–small cell lung cancer and a positive pleural lavage cytology finding per year were predicted in the Lung Cancer Surgical Group of the JCOG on the basis of a questionnaire survey performed by the group. The main reasons for the failure of this phase III trial are considered to be as follows. Intraoperative intrapleural hypotonic cisplatin treatment was not

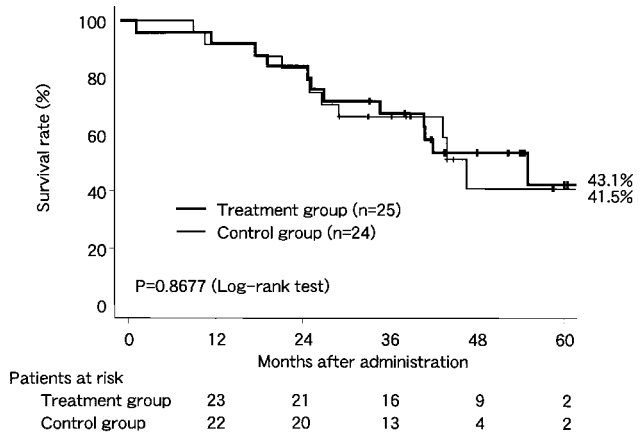


**Figure 1. Overall survival curves of patients in the control and treatment groups.**

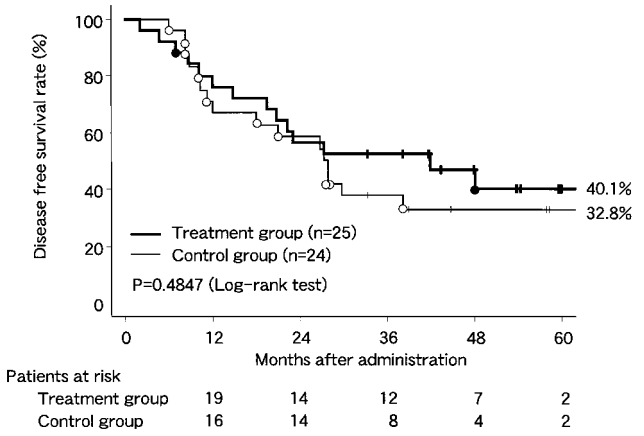


**Figure 2. Disease-free survival curves of the patients in the control and treatment groups. *Filled* and *open circles* represent patients with carcinomatous pleuritis in the treatment and control groups, respectively.**

**TABLE 2. Site of first recurrence**

| | Treatment group (n = 25) | | Control group (n = 24) | |
|---|---|---|---|---|
| Local recurrence only | 4 | | 9 | |
| Carcinomatous pleuritis | | 2 | | 9 |
| Others | | 2 | | 0 |
| Systemic recurrence only | 8 | | 6 | |
| Bone | | 3 | | 2 |
| Brain | | 1 | | 1 |
| Lung | | 4 | | 2 |
| Lung + liver | | 0 | | 1 |
| Local + systemic | 0 | | 1 | |
| Carcinomatous pleuritis + bone | | 0 | | 1 |
| Total | 12 | (48%) | 16 | (67%) |

well known by doctors in the trial group. In addition, it was difficult to obtain informed consent from patients to join the intraoperative randomized trial.

Although the number of patients analyzed in the present study was small because of the prematurely terminated trial, the number of patients who underwent intraoperative pleural lavage cytology for this trial was estimated to be several hundred. The frequency of a positive cytology finding in patients without carcinomatous pleuritis who underwent a cytologic examination of pleural lavage fluid collected immediately after a thoracotomy has been reported to be 9% (14/158 patients),[2] 9% (42/467 patients),[3] and 14% (11/78 patients).[4] Buhr and colleagues[5] reported an extraordinarily high frequency of 39% (132/342 patients). We have recently reported the results of 1890 patients who underwent pleural lavage cytology immediately after a thoracotomy in JCOG[6]; 142 (8%) of them were found to have intrapleural cancer cells detected by means of a cytologic examination. On the basis of the above findings, and excluding the exceptional findings of Buhr and colleagues, a positive rate of approximately 10% is considered to be most likely. Because the total number of patients analyzed in the present study was 49, about 500 patients were thus considered to have undergone a cytologic examination for the trial.

Although the long-term survival rate was not determined in the present study, the 3-year survival rate was relatively reliable because the median time of follow-up in 26 surviving patients was 49 months. As shown in Figure 1, the 3-year survival rate was 68% in the treatment group and 67% in the control group. These survival rates appeared to be higher than those of other series. According to the results of the 3 reports, the 3-year survival rates ranged from 23% to 44%.[2,3,5,6] In a previous study we observed that the prognosis of patients with pathologic stage I disease was significantly better than that of other patients, even in patients with intrapleural cancer cells detected by means of a cytologic examination.[6] In this study the proportion of patients with pathologic stage I disease was 48% in the treatment group and 54% in the control group, whereas the same proportions in the other series mentioned above ranged from 17% to 43%. Therefore the difference in the proportion of stage I disease might influence the differences in the 3-year survivals to some extent.

Because cancer cells are present in the intrapleural space in those patients, they are expected to have carcinomatous pleuritis postoperatively. However, the recurrent patterns of such patients are still not well known. In retrospective studies the appearance of carcinomatous pleuritis after an operation has been reported to be observed in 2 (9%) of 23 patients[2] and in 11 (26%) of 42 patients.[3] In this prospective study 10 (42%) of 24 patients in the control group were found to have carcinomatous pleuritis. This also means that recurrence caused by carcinomatous pleuritis was observed

in 63% of patients with recurrence in the control group. On the other hand, the appearance of carcinomatous pleuritis was significantly suppressed by the intraoperative intrapleural hypotonic cisplatin treatment. Only 2 (8%) of 25 patients in the treatment group had carcinomatous pleuritis, and this was equal to the 17% of the patients with recurrence in this group. On the basis of these findings, we are now planning to perform a prospective registry by using this intraoperative intrapleural hypotonic cisplatin treatment on patients with a positive pleural lavage cytology finding to obtain further information on survival, the recurrence patterns and adverse events from numerous treated patients, and also to familiarize doctors in this trial group with the hypotonic cisplatin treatment modality.

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## Appendix

Additional participating institutions and principal investigations were the National Shikoku Cancer Center (Hideyuki Saeki, MD), Hiroshima City Hospital (Noritomo Seno, MD), Toneyama National Hospital (Osamu Kuwahara, MD), and Tohoh University (Shiroh Yamazaki, MD).

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