A randomized trial comparing induction chemotherapy followed by surgery with surgery alone for patients with stage IIIA N2 non-small cell lung cancer (JCOG 9209)

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Objective: We performed a prospective randomized trial in patients with potentially resectable stage IIIA N2 non-small cell lung cancer to confirm the efficacy of induction chemotherapy before surgical resection.

Methods: Patients with stage IIIA N2 non-small cell lung cancer, all with histologically or cytologically confirmed metastases to the ipsilateral mediastinal lymph nodes, were randomly assigned to receive either three cycles of induction chemotherapy (cisplatin at 80 mg/m² on 1 day and vindesine at 3 mg/m² on 2 days) followed by surgery or surgery alone.

Results: This trial was prematurely terminated because the accrual rate was too slow, which lowered the study's statistical power considerably. From June 1993 through April 1998, a total of 62 patients were enrolled, and 31 patients were assigned to each treatment group. The objective clinical response rate of induction chemotherapy was 28%. Complete resection was achieved in 20 patients in the induction chemotherapy group (65%) and 24 in the surgery alone group (77%). Median follow-up was 6.2 years. Median overall survivals were 17 months for the induction group and 16 months for the surgery alone group. The estimated 1-, 3-, and 5-year survivals, respectively, were 68% (95% confidence interval 51%-85%), 23% (95% confidence interval 8%-38%), and 10% (95% confidence interval 0%-20%) for the induction chemotherapy group and 65% (95% confidence interval 48%-82%), 26% (95% confidence interval 11%-41%), and 22% (95% confidence interval 7%-37%) for the surgery alone group. There was no statistically significant difference in survival between the groups ($P = .5274$). Treatment-related death was not observed in either group.

Conclusion: This randomized trial to compare induction chemotherapy (cisplatin and vindesine) followed by surgery with surgery alone for patients with stage IIIA N2 non-small cell lung cancer did not demonstrate a survival difference between the groups, although this may have been because the statistical power was limited.

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The treatment strategy for patients with non-small cell lung cancer (NSCLC) with ipsilateral mediastinal lymph node involvement (N2) remains controversial. Mountain¹ concluded that surgical resection was not indicated for these patients, because most of them were suspected to have occult distant metastasis. In Japan, however, surgical resection has been favored for these patients. Japanese researchers reported that a considerable 5-year survival was obtained for cases with

Figure 1. Treatment schema of JCOG 9209. Induction chemotherapy of three cycles of cisplatin (P) at 80 mg/m² on day 1 and vindesine (V) at 3 mg/m² on days 1 and 8.

direct node involvement by the primary tumor or with a limited number of N2 nodes.^{2,3} Clinical N2 diagnosis that was based on plain chest radiography was reported to result in a very low resection rate.⁴ Even among the patients with resectable disease, survival was poor compared with the patients whose N2 disease was diagnosed only by mediastinoscopic biopsy or by surgical dissection.^{3,4} Trials of postoperative adjuvant chemotherapy for NSCLC have not shown prognostic benefit.⁵⁻⁸ The Japan Clinical Oncology Group (JCOG), performed a phase III trial that compared surgery followed by adjuvant chemotherapy (cisplatin and vindesine) with surgery alone for patients with completely resected stage IIIA NSCLC.⁷ This trial failed to demonstrate therapeutic benefit of the adjuvant chemotherapy. A multi-variable analysis, however, demonstrated that pathologically staged N2 disease was a significant prognostic factor for survival. This result indicated that patients with stage IIIA N2 NSCLC should be studied separately from the other patients with IIIA disease.

Although many phase II trials have suggested benefits for induction chemotherapy or induction chemoradiotherapy for patients with stage III N2 NSCLC,⁹⁻¹³ the efficacy of these modalities is not definitively established by phase II trials. We planned a prospective randomized trial for patients with potentially resectable stage IIIA N2 NSCLC to compare induction chemotherapy followed by surgery with surgery alone. This study was the first randomized trial for this setting. We used combination chemotherapy with cisplatin and vindesine, which was the most popular combination chemotherapy for NSCLC at that time in Japan. Although this phase III trial was designed to enroll 100 patients in each group within 3 years, starting in June 1993, it was stopped in April 1998 because the patient accrual rate was too slow.

Patients and Methods

Patient Eligibility

Histologic or cytologic diagnosis of NSCLC was obtained by bronchoscopic or transcutaneous needle biopsy before registration. All patients had histologically or cytologically documented ipsi-

lateral mediastinal lymph node metastasis according to a mediastinoscopic specimen and were previously untreated. Preoperative staging included chest radiography, computed tomography (CT) of the chest, CT or ultrasonography of the upper abdomen, CT or magnetic resonance imaging of the brain with contrast media, and bone scintigraphy. Eligibility criteria included a leukocyte count greater than 4000 cells/mm³, a platelet count greater than 100,000 cells/mm³, a hemoglobin count greater than 10 g/dL, and normal renal and hepatic functions. Other criteria were as follows. (1) Clinical N2 disease was observable on plain chest radiography or CT. (2) Patients had to be younger than 76 years. (3) Complete resection had to be deemed possible. (4) Performance status had to be 0 or 1. (5) Patients had to provide written informed consent. (6) Patients with carcinoid tumor, mucoepidermoid carcinoma, or adenoid cystic carcinoma were excluded. (7) Patients with vena cava syndrome, Pancoast syndrome, T3 tumor with rib involvement, or paratracheal lymph node involvement in a left-sided tumor were excluded.

This phase III protocol was inspected and approved by the JCOG ethical committee. Patient registration was done at the JCOG data center.

Treatment Strategy (Figure 1)

All eligible patients were randomly assigned to receive either induction chemotherapy followed by surgery or surgery alone. Induction chemotherapy consisted of cisplatin (80 mg/m² given intravenously on day 1) and vindesine (3 mg/m² given intravenously on days 1 and 8). This treatment cycle was repeated two more times every 4 weeks for patients who had sufficiently recovered from the toxic effects of the previous cycle. Adverse effects of induction chemotherapy were recorded according to the JCOG grade.¹⁴

Surgical resection was performed within 6 weeks after the last chemotherapy. Surgery was either lobectomy, bilobectomy, or pneumonectomy along with systematic mediastinal lymph node dissection. Patients who were found to have unresectable disease at operation or whose resection was found to be incomplete after operation could receive radiation therapy. Patients whose resection was complete were not allowed to undergo any adjuvant therapy. Treatment for recurrence was not restricted.

TABLE 1. Patient characteristics

	Induction chemotherapy	Surgery	p value
No. of patients	31	31	
Age (y)	59 (32-74)	61 (45-74)	.3757
Sex (No.)			.7884
Men	20	21	
Women	11	10	
Histologic type (No.)			.8339
Adenocarcinoma	21	20	
Squamous cell carcinoma	7	8	
Others	3	3	
Clinical T stage (No.)			.0327
T1	2	11	
T2	25	17	
T3	3	3	
Unknown	1	0	

TABLE 2. Induction chemotherapy

Performed cycles	Patients	Reason for halting	
		Progressive disease	Patient refusal
0	2	1	1
1	3	2	1
2	4	3	1
3	22 (71%)		

All figures represent numbers of patients.

Statistical Methods

The number of patients to be enrolled was calculated from the lung cancer survival data at the National Cancer Center in Japan¹⁵ and Memorial Sloan-Kettering Cancer Center.¹⁶ Seventy-five patients in each group were required to provide 80% power to detect a 15% increase (25%-40%) in 3-year survival in the induction chemotherapy group compared with the surgery alone group ($\alpha = .05$, $\beta = .2$). With an expected 10% drop-off among the registered patients, a total of 165 patients would be necessary. We therefore aimed at collecting 200 patients in 3 years. All patients randomly assigned in this trial were followed up to date and included in the analysis. Duration of survival or time to recurrence was calculated from the date of random assignment until the date of death, recurrence, or the last follow-up. The probabilities of overall survival and disease-free survival were calculated with the Kaplan-Meier method. The log-rank test was used to compare survival curves. Statistical differences between proportions were calculated by χ^2 test. All calculations were performed with the StatView (version 5.0; SAS Institute Inc, Cary, NC) software package.

Results

Patient Characteristics

Because the patient accrual rate was too slow, despite the original aim of 200 patients within 3 years, this study was prematurely terminated in almost 5 years. A total of 62 patients were enrolled at 18 JCOG institutions from June

TABLE 3. Clinical response to induction chemotherapy (n = 29)

	No.	%
Complete response	0	0
Partial response	8	28
Stable disease	12	41
Progressive disease	9	31

TABLE 4. Operations

Operation	Induction chemotherapy (n = 31)	Surgery (n = 31)
R0	20	24
Pneumonectomy	2	4
Lobectomy	18	20
R1	1	3
Pneumonectomy	0	1
Lobectomy	1	2
R2	2	2
Pneumonectomy	0	0
Lobectomy	2	2
Exploratory thoracotomy	5	2
Not indicated	3	

All figures represent numbers of patients. A complete resection (R0) was defined as pathologic demonstration of negative tissue margin and an assessment by the surgeon that all detectable disease had been removed. Patients who had a complete gross resection in whom positive margins were found on final pathologic review were classified as having undergone microscopically incomplete resection (R1). Gross residual disease after attempted resection was classified as R2.

1993 through April 1998. Thirty-one patients were randomly allocated to each treatment group. There were no significant differences between the two groups in age, sex, and histologic distribution (Table 1). There were more patients with clinically staged T1 disease in the surgery alone group than in the induction chemotherapy group.

Induction Chemotherapy

Twenty-two (71%) of 31 patients undergoing chemotherapy received three full-dose cycles of induction chemotherapy (Table 2). The objective response rate was 28% (Table 3). Seven of 8 patients with a partial response underwent three full cycles. Another patient with a partial response received two cycles. Severe toxicity (grade 4) was not observed. Grade 3 toxicities were leukocytopenia in 31%, anemia in 14%, and vomiting in 14%. Three (10%) patients of 31 did not undergo operation because distant metastasis developed in the bone, brain, and contralateral lymph node.

Surgery and Pathologic Examination

Complete resection was achieved in 20 patients (65%) in the induction group and in 24 patients (77%) in the surgery alone group (Table 4). Exploratory thoracotomy was done

Figure 2. Overall Kaplan-Meier survivals in months after random assignment.

in 5 of the induction group (19%) and 2 of the surgery alone group (6%). Pleural dissemination and intrapulmonary metastases were detected in 3 patients each. The other patient had bulky mediastinal node swelling. Complete disappearance of primary tumor in resected specimen occurred in no patients. Four patients had no residual tumor in resected mediastinal lymph nodes according to histologic study, but 1 of them had residual tumor in a hilar lymph node.

Survival Analysis

Median follow-up was 6.2 years (range 3.4-7.8 years). No patient died within 30 days after the operation. Treatment-related death was not observed in either group. Median overall survivals were 17 months for the induction chemotherapy group and 16 months for the surgery alone group. The estimated 1-, 3-, and 5-year survivals, respectively, were 68% (95% confidence interval [CI] 51%-85%), 23% (95% CI 8%-38%), and 10% (95% CI 0%-20%) for the induction group and 65% (95% CI 48%-82%), 26% (95% CI 11%-41%), and 22% (95% CI 7%-37%) for the surgery alone group (Figure 2). There was no statistically significant difference in survival between the groups ($P = .5274$). When only patients with completely resected disease were compared, the median survival and estimated 1-, 3- and 5-year survivals, respectively, were 18 months, 80% (95% CI 63%-97%), 25% (95% CI 6%-44%), and 10% (95% CI 0%-23%) for the induction group and 18 months, 63% (95% CI 44%-82%), 33% (95% CI 14%-52%), and 29% (95% CI 12%-47%) for the surgery alone group ($P = .6066$). According to induction chemotherapy response, the median survival and estimated 3-year survival, respectively, were 30 months and 38% (95% CI 4%-72%) in patients with a

partial response, 18 months and 18% (95% CI 0%-41%) in patients with stable disease, and 12 months and 10% (95% CI 0%-29%) in patients with progressive disease. Statistically significant difference in survival was not observed (partial response vs stable disease $P = .5044$, partial response vs progressive disease $P = .0512$, stable disease versus progressive disease $P = .2304$). When estimated 1-, 3-, and 5-year disease-free survivals, respectively, were compared (Figure 3), they were 57% (95% CI 37%-77%), 10% (95% CI 0%-23%), and 10% (95% CI 0%-23%) for the induction group and 38% (95% CI 20%-56%), 27% (95% CI 11%-43%), and 21% (95% CI 5%-37%) for the surgery alone group ($P = .5964$).

Discussion

Long-term survival after surgical resection of patients with locally advanced NSCLC is poor, especially for those with N2 disease.^{3,4,17,18} The JCOG conducted a phase III trial to compare surgery followed by adjuvant chemotherapy with surgery alone for completely resected stage IIIA NSCLC. This trial failed to demonstrate any therapeutic benefit of adjuvant chemotherapy.⁷ The PORT Meta-analysis Trialists¹⁹ reported that the efficacy of postoperative radiation therapy was not supported. To date postoperative adjuvant therapy has not been proved effective.

Three randomized trials that compared induction chemotherapy followed by surgery with surgery alone or surgery followed by radiation (by Pass and colleagues,²⁰ Rosell and associates^{21,22} and Roth and coworkers^{23,24}) showed significant or marginal survival benefit of induction chemotherapy patients with stage IIIA NSCLC (Table 5). These re-

Probability of Survival

Induction Chemotherapy	31	12	2	0
Surgery	31	13	6	2

Figure 3. Disease-free Kaplan-Meier survivals in months after random assignment.

TABLE 5. Reported phase III trials, with or without induction therapy, in other studies of patients with stage IIIA NSCLC and our own

Reference	Stage	Therapy	Patients	MST (m)	P value
Pass and colleagues ²⁰	IIIA (N2)	Preoperative and postoperative etoposide and cisplatin	13	29	.095
Rosell and associates ^{21,22}	IIIA	Postoperative radiotherapy	14	16	.005
		Preoperative and postoperative cisplatin, ifosfamide, and mitomycin	30	22	
Roth and coworkers ^{23,24}	IIIA	Postoperative radiotherapy	30	10	.056
		Preoperative and postoperative cyclophosphamide, etoposide, and cisplatin	28	21	
Current data	IIIA (N2)	Surgery alone	32	14	.527
		Preoperative vindesine and cisplatin	31	17	
		Surgery alone	31	16	

ports revealed high clinical response rates (35%-62%) among patients receiving induction chemotherapy. However, these three trials used different treatment strategies, and Rosell and associates' and Roth and coworkers' study populations included patients with N0 and N1 disease.²¹⁻²⁴ We planned to study induction therapy efficacy in the more homogeneous cohort of patients with potentially resectable stage IIIA N2 NSCLC and performed a prospective randomized trial to compare induction chemotherapy followed by surgery with surgery alone.

Although this trial was designed to enroll 100 patients in each group within 3 years, the recruitment was too slow and the trial was discontinued, resulting in a total of only 62

patients in almost 5 years. Sixty-two patients (31 patients in each group) is calculated to provide 24% power to detect a 15% increase in 3-year survival in the induction chemotherapy group ($\alpha = .05$, $\beta = .76$). The possibility of a type II error is so high that it may invalidate our data. The greatest contributor to the slow rate was failure to obtain informed consent. The reasons for consent refusal were the lack of rewarding compensation to the patients, prolonged hospitalization in the induction chemotherapy group, and wide reports in the domestic media of the ineffectiveness of chemotherapy for NSCLC. Under the circumstances this trial was prematurely terminated in April 1998.

Unlike previous induction chemotherapy studies, our

trial population showed poor response to induction chemotherapy (complete resection rate 0%, partial response rate 28%), and no survival difference was observed between induction and surgery alone groups. We think that this was because all our eligible patients had N2 disease, unlike previous studies that included patients with N0 or N1 disease.

Chemotherapy regimens with new agents, including paclitaxel, docetaxel, vinorelbine, and gemcitabine, have recently been reported to be effective for advanced NSCLC with fewer, less severe effects.²⁵⁻²⁹ Sandler and associates²⁶ reported that as the first-line treatment for NSCLC the regimen of gemcitabine plus cisplatin was superior to cisplatin alone in terms of response rate, time to disease progression, and overall survival. Comella and associates²⁷ reported that a cisplatin, gemcitabine, and vinorelbine regimen was associated with a substantial survival gain when compared with a cisplatin and vinorelbine combination for advanced NSCLC. Although a survival benefit conferred by induction chemotherapy before surgical resection for stage IIIA N2 NSCLC was not demonstrated in our trial, these new agent combinations may prove beneficial for locally advanced NSCLC in future trials.

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Appendix

The study was carried out as a trial by the Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group, chairperson Professor Harubumi Kato, Tokyo Medical University.

The cases in this study were collected from the National Cancer Center Hospital East (Kanji Nagai); National Cancer Center Hospital (Ryosuke Tsuchiya); National Kinki Chuo Hospital (Takashi Mori); Osaka City General Hospital (Hiroto Tada); National Kyushu Cancer Center (Yukito Ichinose); Niigata Cancer Center Hospital (Teruaki Koike); Toho University School of Medicine (Keigo Takagi); Yokohama Municipal Citizen's Hospital (Masa-hiro Kase); Institute of Aging, Development, and Cancer, Tohoku University (Takashi Kondo); Kanagawa Cancer Center Hospital (Haruhiko Nakayama); Tochigi Cancer Center (Kohei Yokoi); Osaka Prefectural Habikino Hospital (Tsutomu Yasumitsu); Yamagata Prefectural Central Hospital (Toru Sato); National Defense Medical College (Yuichi Ozeki); Toyama Prefectural Central Hospital (Hideki Miyazawa); National Toneyama Hospital (Osamu Kuwabara); National Kure Hospital (Kenji Nakamura); and Shikoku Cancer Center Hospital (Hideyuki Saeki).

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