

Long-term results of concurrent chemoradiotherapy using cisplatin and vinorelbine for stage III non-small-cell lung cancer

Hidehito Horinouchi,^{1,6} Ikuro Sekine,¹ Minako Sumi,² Kazumasa Noda,³ Koichi Goto,⁴ Kiyoshi Mori⁵ and Tomohide Tamura¹

¹Division of Internal Medicine and Thoracic Oncology, ²Division of Radiation Oncology, National Cancer Center Hospital, Tokyo; ³Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama; ⁴Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa; ⁵Department of Medical Oncology, Division of Thoracic Oncology, Tochigi Cancer Center, Utsunomiya, Japan

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Concurrent chemoradiotherapy is the standard treatment for unresectable stage III non-small cell lung cancer (NSCLC). The long-term feasibility and efficacy of vinorelbine and cisplatin with concurrent thoracic radiotherapy were investigated. Eighteen patients received cisplatin (80 mg/m²) on day 1 and vinorelbine (20 mg/m² in level 1, and 25 mg/m² in level 2) on days 1 and 8 every 4 weeks for four cycles in a phase I trial. Ninety-three patients received the same chemotherapy regimen except for the fixed vinorelbine (20 mg/m²) dosage and consolidation therapy with docetaxel (60 mg/m², every 3 weeks). The thoracic radiotherapy consisted of a single dose of 2 Gy once daily to a total dose of 60 Gy. A total of 111 patients were analyzed in the present study: male/female, 91/20; median age, 60 years; stage IIIA/IIIB, 50/61; and squamous/non-squamous histology, 26/85. The 3-, 5-, and 7-year overall survival rates (95% CI) were 43.2% (33.9–52.2), 25.2% (17.6–33.5), and 23.2% (15.8–31.4), respectively. The median progression-free survival and median survival time (95% CI) were 13.5 (10.1–16.7) months and 30.0 (24.3–38.8) months, respectively. Four patients (4%) experienced Grade 5 pulmonary toxicities from 4.4 to 9.4 months after the start of treatment. In conclusion, approximately 15% of patients with unresectable stage III NSCLC could be cured with chemoradiotherapy without severe late toxicities after 10 months of follow-up. Although based on the data from highly selected population participated in phase I and phase II trial, this analysis would strengthen and confirm the previous reports concerning concurrent chemoradiotherapy with third generation cytotoxic agents. (*Cancer Sci* 2013; 104: 93–97)

Stage III locally advanced non-small cell lung cancer (NSCLC) accounts for 25–30% of all lung cancer cases.^(1,2) Because of the equal frequency of local and distant recurrences, the combination of systemic chemotherapy and thoracic radiotherapy has been established as a standard of care for patients with stage III NSCLC.⁽³⁾ Concurrent chemoradiotherapy is superior to a sequential approach, as shown by phase III trials in stage III NSCLC.^(4,5)

Ohe *et al.*⁽⁶⁾ reported the long-term follow-up analysis of concurrent chemoradiotherapy with former generation chemotherapy agents (median survival time 16.1 months, and 7-year overall survival rate 12.0%). Few researchers, however, have reported follow-up data of longer than 5 years after concurrent chemoradiotherapy with third-generation chemotherapy. The long-term safety and efficacy of vinorelbine and cisplatin with concurrent thoracic radiotherapy were investigated.

Materials and Methods

Study selection. Two previous studies were included in this analysis. One was a phase I study of concurrent thoracic radiotherapy with cisplatin plus vinorelbine, and the other evaluated docetaxel consolidation therapy following concurrent chemoradiotherapy.^(7,8) These studies were approved by the institutional review board at each institution. Written, informed consent was obtained from all participating patients.

Patient selection. The two studies had similar eligibility criteria. They were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; and adequate organ function, including bone marrow, liver, kidney, and lung. Patients were diagnosed to have unresectable disease based on a consensus of thoracic oncologists including surgeons in each institution. The exclusion criteria were reported in previous papers.^(7,8)

Treatment schedule. In the phase I study, treatment consisted of chemotherapy with four cycles of cisplatin and vinorelbine (20 mg/m² in level 1, and 25 mg/m² in level 2) and concurrent thoracic radiotherapy (see below). In the other study, treatment consisted of a chemoradiotherapy portion with three cycles of cisplatin and vinorelbine followed by a consolidation portion with three cycles of docetaxel. Cisplatin (80 mg/m²) was administered every 4 weeks by intravenous infusion for 60 min with 2500–3000 mL of fluid for hydration. Vinorelbine 20 mg/m² diluted in 50 mL of normal saline was administered intravenously on days 1 and 8 every 4 weeks. All patients received prophylactic antiemetic therapy consisting of a 5HT₃-antagonist and a steroid. In the docetaxel (60 mg/m², every 3 weeks) consolidation trial, consolidation therapy was started sequentially in patients whose general condition was acceptable. Follow-up computed tomographies after chemoradiotherapy were scheduled as follows; every 2–4 months during the 1 year, every 6 months in the 2 and 3 years, and every 1 year thereafter.

Thoracic radiotherapy was delivered with megavoltage equipment (≥ 6 MV) using anterior/posterior opposed fields up to 40 Gy in 20 fractions, including the primary tumor, the metastatic lymph nodes, and the regional nodes. A booster dose of 20 Gy in 10 fractions was given to the primary tumor

⁶To whom correspondence should be addressed.
E-mail: hhorinou@ncc.go.jp

and the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique fields. Computed tomography (CT) scan-based treatment planning was used in all patients. The clinical target volume (CTV) for the primary tumor was defined as the gross tumor volume (GTV) plus 1 cm taking into account subclinical extension. CTV and GTV for the metastatic nodes (>1 cm in the shortest dimension) were the same. Regional nodes, excluding the contralateral hilar and supraclavicular nodes, were included in the CTV, but the lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The planning target volumes for the primary tumor, the metastatic lymph nodes, and regional nodes were determined as CTVs plus 0.5–1.0-cm margins laterally and 1.0–2.0-cm margins craniocaudally, taking into account setup variations and internal organ motion. Lung heterogeneity corrections were not used.

Toxicity assessment. Toxicities were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria version 2.0 issued in 1998, and late toxicities associated with thoracic radiotherapy were graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.⁽⁹⁾ Late toxicities were defined as those that occurred or persisted 90 days after completion of radiotherapy. The detailed methods of treatment modification due to toxicity were reported in previous papers.^(7,8)

Response evaluation. In the phase I trial, the objective tumor response was evaluated according to the World Health Organization (WHO) criteria issued in 1979.⁽¹⁰⁾ The Response Evaluation Criteria in Solid Tumors were used to evaluate objective tumor response in the docetaxel consolidation trial.⁽¹¹⁾ Local recurrences were defined as tumor progression in the primary site and in the hilar, mediastinal, and supraclavicular lymph nodes after a partial or complete response; regional recurrence was defined as the development of malignant pleural and pericardial effusions; and distant recurrence was defined as the appearance of distant metastases.

Statistical analyses. Progression-free and overall survival times were estimated by the Kaplan–Meier method, and confidence intervals (CIs) were based on Greenwood's formula.⁽¹²⁾ Progression-free survival time was measured from the date of registration to the date of disease progression, death (from any cause), or the last follow-up. Overall survival time was measured from the date of registration to the date of death (from any cause) or to the last follow-up. Patients who were lost to follow-up without an event were censored at the date of their last known follow-up. A CI for response rate (RR) was calculated using methods for exact binomial CIs. To investigate the association between survival and factors related to patient characteristics, the Cox regression model was used. Potential factors investigated were as follows: age (in 10-year increments), sex, body weight loss ($\leq 5.0\%$ vs $\geq 5.1\%$), histology (squamous cell carcinoma versus non-squamous cell carcinoma), T factor (T1/2 vs T3/4), N factor (N0-2 vs N 3), and stage (IIIA vs IIIB). The STATA 10 for Windows software package (StataCorp LP, College Station, TX, USA) was used for statistical analyses.

Results

Characteristics of the patients. From October 1999 to June 2003, 13 patients were registered at dose level 1 and five at dose level 2 of the phase I study, and 93 patients were enrolled in the docetaxel consolidation trial. Thus, a total of 111 patients were analyzed in the present study. The participants' characteristics were as follows (Table 1): male/female 91/20; median age (range) 60 (31–74) years; body weight loss

Table 1. Patients' characteristics

	Clinical trial		
	Phase I trial†	DTX consolidation‡	Total
Number of patients	18	93	111
Age (years)			
Median	58.5	60	60
Range	48–69	31–74	31–74
Sex			
Male	15	76	91
Female	3	17	20
Performance status			
0	4	32	36
1	14	51	65
Unknown	0	10	10
Body weight loss (minus, %)			
0	11	72	83
0.1-5.0	4	9	13
5.1–	3	11	14
Unknown	0	1	1
Clinical stage			
IIIA	9	41	50
IIIB	9	52	61
N factor			
N0	0	6	6
N1	0	3	3
N2	11	58	69
N3	7	26	33
T factor			
T1	1	18	19
T2	6	31	37
T3	7	13	20
T4	4	30	34
Unknown	0	1	1
Histology			
Adenocarcinoma	14	57	71
Squamous cell carcinoma	3	23	26
Adenosquamous	1	0	1
Large cell carcinoma	0	6	6
NOS§	0	6	6
Others	0	1	1

†The phase I study of concurrent thoracic radiotherapy with cisplatin plus vinorelbine. ‡The docetaxel consolidation therapy following concurrent chemoradiotherapy study. §Non-small cell lung cancer not otherwise specified.

$\leq 5.0\%$ / $\geq 5.1\%$ 96/14; stage IIIA/IIIB 50/61; and squamous/non-squamous histology 26/85.

Treatment delivery. Full cycles (four in the phase I trial, three in the docetaxel consolidation trial) of cisplatin and vinorelbine and the full dose (60 Gy) of thoracic radiotherapy were administered in 94 (85%) and 102 (92%) patients, respectively. The delay in radiotherapy was less than 5 days in 74 (67%) patients. In the docetaxel consolidation trial, 59 (63%) patients could enter the consolidation phase, and only 34 (37%) patients completed three cycles of docetaxel chemotherapy, mainly because of toxicities. Of 91 patients with relapses, 27 (30%) received gefitinib as salvage treatments.

Objective tumor response and survival. The objective response rate was 82.0% (95% CI, 74.5–89.1). The 3-, 5-, and 7-year progression-free and overall survival rates (95% CI) were 21.0% (13.9–29.1), 15.7% (9.5–23.4), 14.4% (8.4–22.0), and 43.2% (33.9–52.2), 25.2% (17.6–33.5), and 23.1% (15.7–31.4), respectively (Fig. 1). The median progression-free survival and median survival time (95% CI) were 13.4 (9.8–16.4)

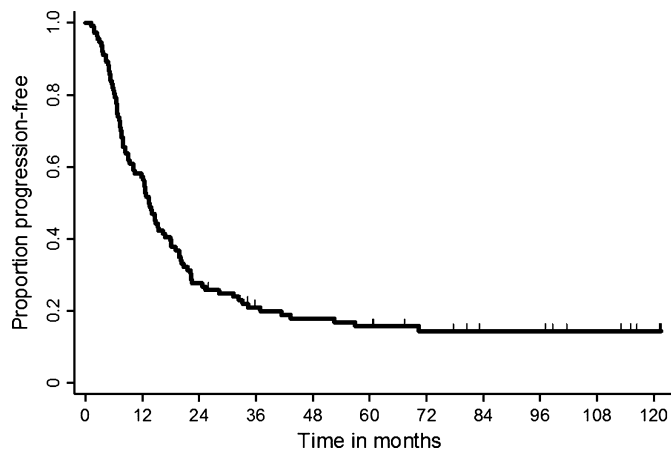


Fig. 1. Progression-free survival ($n = 111$). The median progression-free survival is 13.5 months (95% confidence interval [CI] 10.1–16.7).

months and 30.0 (24.5–38.8) months, respectively (Fig. 2). There was no significant difference in survival results between subgroups; patients with or without docetaxel consolidation and patients with or without gefitinib.

Pattern of relapse. Relapses were noted in 91 (82%) of 111 patients. Initial relapse sites were local alone in 39 (42%) patients, regional alone in 5 (5%), and distant alone in 38 (41%), including 17 (18%) patients with brain metastases as a sole recurrence site. Brain metastases were detected in 19 (21%) patients and were the most frequent sites of distant metastases. Brain metastases were detected within 3 years of initial treatment, and the last brain relapse was observed after 33 months of follow-up (Table 2). Three (3%) patients experienced adrenal metastases as a first relapse site.

Late toxicities. Grade 1, 2, 3, and 5 late pulmonary toxicities were observed in 18 (16%), 15 (13%), 3 (3%), and 4 (4%) patients, respectively. Seventy-two (64%) patients did not experience late pulmonary toxicities (Table 3). Four cases of grade 5 pulmonary toxicity developed at 4.4, 5.9, 9.4, and 9.6 months, respectively, after the treatment started. Late esophageal toxicities were observed in three patients (one grade 1 and two grade 3).

Causes of death in long-term survivors. There were 67 (60%) patients that survived 24 months or more from the initial treatment. Among them, five patients died because of reasons other

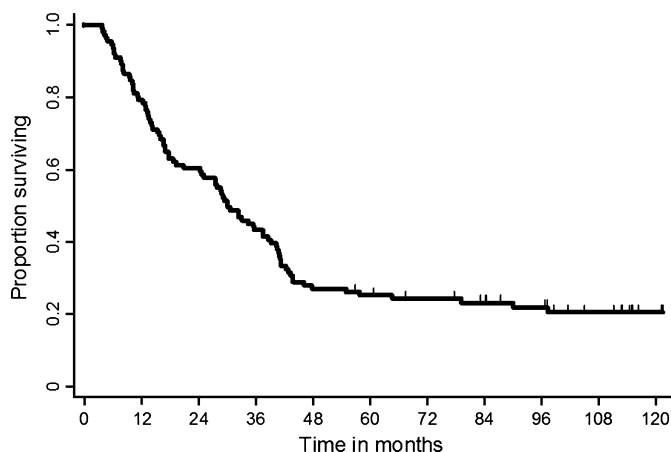


Fig. 2. Overall survival ($n = 111$). The median overall survival is 30.0 months (95% confidence interval [CI] 24.3–38.6).

Table 2. Sites of initial relapse

Site of recurrences	Number of relapses			Total (%)
	<1 year	1–3 years	>3 years	
Local	16	21	2	39 (42)
Distant	23	12	3	38 (41)
Distant without brain	12	4	3	19 (21)
Distant including brain	1	1	0	2 (2)
Brain only	10	7	0	17 (18)
Regional	3	2	0	5 (5)
Others (L/D/R)†	3	5	1	9 (10)
Unknown	–	–	–	2 (2)

†Others includes 2 Local+Regional relapses, 6 Local+Distant relapses, and 1 Local+Regional+Distant relapse.

Table 3. Late pulmonary toxicities§

Toxicity grades	Clinical trial		Total (%)
	Phase I trial†	DTX consolidation‡	
Without late toxicity	10	62	72 (64)
Grade 1	4	14	18 (16)
Grade 2	3	12	15 (13)
Grade 3	1	2	3 (3)
Grade 4	0	0	0
Grade 5¶	0	4	4 (4)

†The phase I study of concurrent thoracic radiotherapy with cisplatin plus vinorelbine. ‡The docetaxel consolidation therapy following concurrent chemoradiotherapy study. §Late toxicities were defined as those that occurred or persisted 90 days after completion of radiotherapy. ¶The Grade 5 pulmonary toxicities developed at 4.4, 5.9, 9.4, and 9.6 months after the treatment started.

than lung cancer. One patient was diagnosed as having pharyngeal cancer at the point of 35 months and died 4 months later. Other than malignancies, community-acquired pneumonia (one patient at 43 months), sudden death due to unknown etiology (two patients at 41 and 42 months) and suicide (one patient at 29 months) were reported, respectively.

Predictive factors for survival. The associations between overall survival and patients' characteristics (age [in 10-year increments], sex, body weight loss [$\leq 5.0\%$ vs $\geq 5.1\%$], histology [squamous cell carcinoma versus non-squamous cell carcinoma], T factor [T1/2 vs T3/4], N factor [N0-2 vs N 3], and stage [IIIA vs IIIB]) were also examined using Cox regression analysis. Age was significantly associated with survival (hazard ratio [HR] 1.34, 95% CI 1.02–1.75, Table 4).

Discussion

Concurrent chemoradiotherapy has been established as a standard treatment for patients with unresectable locally advanced NSCLC. The long-term feasibility and efficacy of vinorelbine and cisplatin chemotherapy with concurrent thoracic radiotherapy were investigated. The 3-, 5-, and 7-year overall survival rates (95% CI) were 43.2% (33.9–52.2), 25.2% (17.6–33.5), and 23.1% (15.7–31.4), respectively. Older age was associated with poor survival on multivariate analysis (HR 1.34, 95% CI 1.02–1.75).

Two phase III trial examined the efficacy and safety of newer generation cytotoxic agents in concurrent chemoradiotherapy for patients with locally advanced NSCLC.^(13,14) The 5-year survival rates (around 20%) were comparable to cur-

Table 4. Cox proportional hazard model for assessment of overall survival

Factors	Hazard ratio	95% CI	P value
Age			
10-year increment	1		
	1.34	1.02–1.75	0.03
Sex			
Female	1		
Male	1.23	0.69–2.31	0.46
Body Weight Loss			
<5.0%	1		
>5.1%	1.19	0.69–2.11	0.51
Histology			
Non-squamous	1		
Squamous	1.31	0.80–2.19	0.28
T factor			
T1/2	1		
T3/4	0.91	0.53–1.61	0.77
N factor			
N 0–2	1		
N 3	1.05	0.55–2.08	0.85
Stage			
IIIA	1		
IIIB	0.97	0.52–1.83	0.93

rent analysis. To date, the present report (median survival time 30 months and 7-year overall survival rate 23.1%) is one of the longest observation periods after concurrent chemoradiotherapy using third-generation agents for locally advanced NSCLC. Recently, Tokuda *et al.*⁽¹⁵⁾ reported a favorable long-term survival data (median survival time 2.1 years and 5-year survival rate 31%) of concurrent thoracic radiotherapy with docetaxel and cisplatin in a phase II trial conducted by Okayama Lung Cancer Study Group (OLCSG). It seems that the result of these analyses were about twice better than that of the previous long-term report of chemoradiotherapy with former generation agents by Ohe *et al.*⁽⁶⁾ (median survival time 16.1 months and 7-year overall survival rate 12.0%) and others.⁽¹⁶⁾

Of the 91 patients with relapses, 85 (93%) experienced recurrence within 3 years after initial treatment. Local relapses (37 patients, 41%) and distant relapses (35 patients, 38%) were equally frequent. After 3 years of follow-up, two local, three distant (without brain), and one mixed-site recurrence was observed. Considering the proportion of local recurrence was similar to the OLCSG 0007 trial, a better strategy to control local relapse is a key to improving survival in locally advanced NSCLC.⁽¹³⁾ To gain a better local control, the radiation therapy oncology group (RTOG) conducted a phase III trial (RTOG 0617) to examine a higher dose (74 Gy) of radiotherapy with concurrent chemotherapy. However, the experimental arms of higher radiotherapy were terminated early because of survival futility.⁽¹⁷⁾ We recently reported early termination of a multicenter phase II trial of high-dose thoracic radiotherapy (72 Gy) because of slow accrual and pulmonary toxicities.⁽¹⁸⁾ Based on these results, development of another strategy such as surgery followed by induction therapy might offer a better local control in selected patients.⁽¹⁹⁾ On the other hand, 11 of 20 brain relapses as a first recurrence were found within a year of initial treatment. Several authors reported that brain metastases were frequent early in the course after the initial treatment of stage III NSCLC.^(20,21) According to our findings and previous reports, intensive brain surveys might be

indicated for such patients no longer than 3 years from initial chemoradiotherapy.

The frequency and control of late toxicities, especially lung injury, have been emphasized along with the improvement of survival by concurrent chemoradiotherapy in stage III NSCLC. In the present analysis, four patients (4%) in the docetaxel consolidation trial experienced grade 5 pulmonary toxicities 4.4–9.6 months from initial treatments. On the other hand, life-threatening pulmonary toxicities were not reported in phase I trial. (Table 3) This difference in the frequency of severe pulmonary toxicities might be related to consolidation docetaxel because the dose of cisplatin (80 mg/m²), vinorelbine (20 mg/m²) and thoracic radiotherapy (60 Gy) were the same in these two trials except for five patients who received 25 mg/m² of vinorelbine in the phase I trial.^(7,8) A relatively higher frequency of pulmonary complications was also reported in the experimental arm of the previous phase III trial that examined docetaxel as a consolidation therapy after concurrent chemoradiotherapy.^(22,23) Although a note of caution might be indicated with docetaxel, the present result suggests that severe pulmonary toxicities were rare after 10 months from concurrent chemoradiotherapy.

According to recent trials, about half of Japanese patients with locally advanced lung cancer survive more than 2 years after concurrent chemoradiotherapy.^(13,14) In those who survived more than 2 years, mortalities due to second primary malignancies and etiologies other than lung cancer were reported by several authors.^(15,24) Five patients (4.5%) died without recurrence of lung cancer and whose causes of death were as follows: second primary malignancy (pharyngeal cancer, one patient), community-acquired pneumonia (one patient), sudden death due to unknown etiology (two patients) and suicide (one patient), respectively. With an even greater proportion of patients cured by modern therapies including combined modality treatments, it would be increasingly important to consider and evaluate an appropriate care and monitoring for survivors.

In the present analysis, older age was significantly associated with poor survival (HR 1.34, 95% CI 1.02–1.75) after adjusting for sex, degree of weight loss, histology, T factor, N factor, and stage. In the previous literature on concurrent chemoradiotherapy with cisplatin and vinorelbine, age (≥ 70 years) was marginally associated with poor survival (HR 1.79, 95% CI 0.94–3.39).⁽²⁵⁾ Several investigators reported higher incidences of adverse events in elderly patients with locally advanced NSCLC, even though they had a similar survival benefit.^(26–28) Furthermore, better clinical outcomes were reported in elderly patients (>70 years) by thoracic radiotherapy rather than chemoradiotherapy with a similar regimen for younger patients.^(29,30) Based on these reports, it is necessary to develop an optimal treatment strategy, especially to find the best chemotherapy regimen combined with thoracic radiotherapy, for elderly patients with stage III NSCLC.

This study had several limitations. First, the proportion of patients with stage IIIA disease was relatively high compared to previous phase III trials, which might have a favorable effect on overall survival.^(13,14) Second, the population included in this analysis was relatively younger than those reported by Segawa *et al.*⁽¹³⁾ and had better prognosis than real world patients. As discussed in this article, younger age might be a better prognostic factor in concurrent chemoradiotherapy (Table 3). The third limitation is potential selection bias in a highly selected population suitable for early phase clinical trials. To enable to follow clinical and prognostic information with the least missing data, however, we selected the patients that participated in the current phase I and feasibility trial of docetaxel consolidation.

In conclusion, approximately 15% of patients with unresectable stage III NSCLC could be cured with chemoradiotherapy without severe late toxicities after 10 months of follow-up. Although based on the data from a highly selected population participated in phase I and phase II trial, this analysis would strengthen and confirm the previous reports concerning concurrent chemoradiotherapy with third generation cytotoxic agents.

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Disclosure Statement

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