Results

Participants

Of the 171 patients who were deemed eligible, 39 refused to participate, and 11 could not be contacted. Of the remaining 121 patients who consented to participate, one refused afterward, and seven did not return the questionnaire by mail. Thus, 70.2% (113/171) of the eligible patients participated in the present study. The psychosocial demographic and medical variables are shown in Table 1. The association between pain and dyspnoea was not shown (χ^2 coefficient = 1.87, p = 0.20).

Table 1. Demographic data (N = 113)

	M ± SD (range)	N	%
Age (years)	67 ± 10 (39–89)		
Sex			
Male		67	59.0
Female		46	41.0
Education (years)	12 ± 3 (6–19)		
≤ 9		14	14.0
> 9		84	72.0
Marital status			
Married		91	81.0
Non-married		22	19.0
Living alone			
Yes		14	12.0
No		99	88.0
Employment			
Yes		44	39.0
No		69	61.0
Type of surgery			
Lobectomy		106	93.8
Pneumonectomy		7	6.2
House income (yen/year)			
< 3,000,000		4	4.0
3,000,000–4,000,000		31	27.0
4,000,000–5,000,000		39	35.0
5,000,000 <		39	35.0
Pathologic disease stage			
IA		69	61.1
IB		24	21.2
IIA		4	3.5
IIB		11	9.7
IIIA		4	3.5
IIIB		1	0.9
Performance status			
0		85	75.2
1 or 2		28	24.8
Pain			
+		62	54.9
−		51	45.1
Dyspnoea			
+		62	54.9
−		50	44.3
Unknown		1	0.8
Smoking status			
Non-smoker		53	46.9
Ex-smoker		20	17.7
Quit smoker		32	28.3
Continued smoker		8	7.1
Recurrent			
+		2	1.8
−		111	99.2
Another cancer			
+		17	15.0
−		96	85.0
Other disease			
+		35	31.0
−		73	64.6
Unknown		5	4.4

Feasibility

Ninety-three percent (113/121) of the participants who had accepted the questionnaire responded. There were no missing data except for item 7 (menstrual changes or fertility) which 15 patients (13.3%) missed out or did not respond to, and who were significantly older than the participants who did respond to this item. The mean age of the former was 72, the latter was 62 (t = 2.36, p = 0.02). There was no significant association with any other demographic variables (e.g. sex, marital status, etc.) and the score of item 7.

Reliability

Table 2 shows the internal consistency using the Cronbach's α coefficients (α = 0.65–0.90) and the individual item to the subscale correlation value. The Cronbach's α coefficients of the social and spiritual well being subscales were less than

Table 2. Internal consistency and item-total correlation

Items to subscale	Cronbach's alpha coefficients	I-T correlation	Mean	SD	Min	Max	Response rate
Physical well being	0.789		65.45	11.17	30	80	87
Fatigue		0.737	6.81	2.35	0	10	100
Appetite		0.761	8.64	2.05	0	10	100
Aches/pain		0.695	8.11	2.09	2	10	100
Sleep		0.781	7.98	2.44	0	10	100
Constipation		0.615	8.24	2.55	0	10	100
Nausea		0.650	9.45	1.60	0	10	100
Menstrual chg/fertility		0.523	8.64	2.72	0	10	87
Overall physical		0.489	6.95	2.36	0	10	100
Psychological well being	0.890		121.46	28.65	36	180	100
Coping		0.517	8.04	2.05	1	10	100
QOL item		0.467	7.78	1.78	2	10	100
Happiness		0.432	7.90	2.02	2	10	100
Control		0.404	7.58	2.21	1	10	100
Satisfaction		0.566	7.80	1.77	3	10	100
Concentration/memory		0.489	6.55	1.92	1	10	100
Usefulness		0.369	7.14	2.38	0	10	100
Appearance		0.448	7.62	2.75	0	10	100
Self concept		0.431	6.89	2.74	0	10	100
Initial dx distress		0.546	3.77	3.31	0	10	100
Ca treatment distress		0.606	5.19	3.53	0	10	100
Time since tx distress		0.660	7.50	2.28	0	10	100
Anxiety		0.766	6.44	2.89	0	10	100
Depression		0.792	7.87	2.40	1	10	100
Fear future test		0.749	7.04	3.03	0	10	100
Fear second ca		0.779	5.21	3.32	0	10	100
Fear recurrent ca		0.784	5.44	3.48	0	10	100
Fear spread ca		0.756	5.69	3.49	0	10	100
Social well being	0.684		59.34	11.55	18	80	100
Family distress		0.384	3.10	2.98	0	10	100
Support/others		0.063	8.12	2.61	0	10	100
Personal relationship		0.689	8.94	1.86	0	10	100
Sexuality		0.614	8.28	2.85	0	10	100
Employment		0.679	7.72	2.91	0	10	100
Home activity		0.714	7.46	2.41	1	10	100
Feel isolate		0.748	8.19	2.41	0	10	100
Financial burden		0.691	7.53	2.49	0	10	100
Spiritual well being	0.652		33.76	11.28	8	70	100
Import relig. activ		0.574	1.88	2.78	0	10	100
Import spiritual activ		0.568	1.90	2.64	0	10	100
Spiritual change		0.537	5.15	2.91	0	10	100
Uncertainty		0.144	6.02	2.78	0	10	100
Positive change		0.685	4.76	3.31	0	10	100
Life purpose		0.748	7.04	2.65	0	10	100
Hopefulness		0.734	7.02	2.69	0	10	100
Overall QOL	0.904						

0.70. Most items indicated a strong to moderate correlation with the subscale. However, items 15 (usefulness), 27 (family distress), 28 (amount of social support received), and 38 (uncertainty about the future) demonstrated a low consistency with the subscale (psychological; $r = 0.37$, social; $r = 0.38$ and $r = 0.06$, and spiritual; $r = 0.14$, respectively). The Cronbach's α coefficients of all subscales were more than 0.70, when these items were excluded from each subscale.

Validity

To confirm the concurrent validity, the Pearson's correlation coefficients between the subscales of SF-36, the fighting spirit and the helplessness/hopelessness subscales of the MAC, and the subscales of the QOL-CS-J were calculated (Table 3). There were moderate correlations between associated subscales including QOL-CS-J physical to SF-36 bodily pain ($r = 0.45$, $p < 0.01$) and vitality ($r = 0.52$, $p < 0.01$); QOL-CS-J psychological to SF-36 mental health ($r = 0.55$, $p < 0.01$); QOL-CS-J social to SF-36 general health perception ($r = 0.31$, $p < 0.01$) and mental health ($r = 0.47, p < 0.01$); QOL-CS-J spiritual to MAC fighting spirit ($r = 0.33, p < 0.01$) and helplessness/hopelessness ($r = -0.32, p < 0.01$); and the QOL-CS-J total to each subscale of SF-36 ($r = 0.25$–$0.64, p < 0.05$).

To test discriminant validity, *t*-tests or χ^2 tests were conducted between grade 0 and more than 1 of performance status, with and without pain, and with and without dyspnoea. Each score of the QOL-CS-J physical and social subscales of patients with good performance status, without pain, and without dyspnoea was significantly higher than each score of patients with poor performance status, with pain, and with dyspnoea.

Discussion

The feasibility was reasonably good because 93% of the participants who received the questionnaire responded, and there were no missing data except for one item. However, 13.3% of the participants apparently refused to respond to the item regarding menstrual changes or fertility. The participants who did not respond to this item were significantly older than the participants who did respond. There are two possible reasons for this: those participants who failed to respond may have already been post menopausal; or the Japanese, especially the elderly, are not accustomed to talk with other people about extremely personal matters such as menstruation or fertility.

A strong to moderate correlation value was indicated for the individual items to the subscale, except for four items; usefulness, family distress, the amount of received social support, and uncertainty about the future. When these items were excluded from each subscale, the internal consistencies of all subscales and total scores were good. There are three possible reasons that these four items showed low associations with each subscale: the participants' characteristics differed from the original QOL-CS validation study, in which 43% of the participants were breast cancer patients and 81% were female [1]; in the current study, the content validity was insufficient, that is, the content of the items was not confirmed by cancer patients; or the cultural differences, that is, the family-centered model of decision making and Buddhism and/or Shintoism as the religious beliefs in Japan. However, these four items had also been

Table 3. Concurrent validity

	QOL-CS				
	Physical	Psychological	Social	Spiritual	Total
QOL-Psychological	0.596**				
QOL-Social	0.569**	0.696**			
QOL-Spiritual	0.101**	0.191*	0.160		
QOL-Total	0.737**	0.934**	0.797**	0.407**	
SF-Physical functioning	0.339**	0.256**	0.273**	0.164	0.315**
SF-Role-Physical	0.267**	0.251**	0.253**	0.129	0.251*
SF-Bodily Pain	0.454**	0.272**	0.208*	0.163	0.384**
SF-General health perception	0.420**	0.554**	0.310**	0.162	0.533**
SF-Vitality	0.520**	0.414**	0.288**	0.235*	0.508**
SF-Social functioning	0.302**	0.265**	0.295**	0.095	0.326**
SF-Role-Emotional	0.440**	0.296**	0.295**	0.180	0.349**
SF-Mental health	0.511**	0.548**	0.474**	0.200*	0.635**
MAC-Fighting spirit	0.161	0.179	0.145	0.329**	0.253*
MAC-Helplessness/hopelessness	−0.356**	−0.418**	−0.328**	−0.321**	−0.473**

*$p < 0.05$, **$p < 0.01$.

suggested to have a weak association with the subscale in the original study [1].

Regarding the concurrent validity, there was correlation between the physical related subscales, the psychological related subscales, and the social related subscales of the QOL-CS-J and the SF-36, and the spiritual well being subscale of the QOL-CS-J and the fighting spirit and helplessness/hopelessness subscales of the MAC. Regarding the discriminant validity, the participants with poor performance status, pain, and dyspnoea demonstrated low scores in the physical and social well being subscale of the QOL-CS-J. These results imply that the validity of the QOL-CS-J is good.

This study had two limitations. First, this study examined subjects' responses at only one point in of time. A test–retest reliability needs to be conducted to examine fully the stability of the QOL-CS-J. Second, participants in this study were the survivors of only NSCLC. Further study on cancer survivors of other types and sites needs to be conducted.

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References

1. Ferrell BR, Hassey Dow K, Grant M. Measurement of the quality of life in cancer survivors. Qual Life Res 1995; 4: 523–531.
2. Uchitomi Y, Mikami I, Kugaya A, Nakano T, Okuyama T, Akechi T, Okamura H. Physician support and patient psychologic responses after surgery for nonsmall cell lung carcinoma: A prospective observational study. Cancer 2001; 92: 1926–1935.
3. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. Health Econ 1993; 2: 217–227.
4. Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. J Clin Epidemiol 1998; 51: 1037–1044.
5. Fukuhara S, Ware JE, Kosinski M, Wada S, Gandek B. Psychometric and clinical tests of validity of the Japanese SF-36 Health Survey. J Clin Epidemiol 1998; 51: 1045–1053.
6. Watson M, Greer S, Young J, Inayat Q, Burgess C, Robertson B. Development of a questionnaire measure of adjustment to cancer: The MAC scale. Psychol Med 1998; 18: 203–209.
7. Akechi T, Fukue-Saeki M, Kugaya A, Okamura H, Nishiwaki Y, Yamawaki S, Uchitomi Y. Psychometric properties of the Japanese version of the Mental Adjustment to Cancer (MAC) scale. Psychooncology 2000; 5: 395–401.

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Docetaxel Consolidation Therapy Following Cisplatin, Vinorelbine, and Concurrent Thoracic Radiotherapy in Patients with Unresectable Stage III Non-small Cell Lung Cancer

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Background: To evaluate the feasibility and efficacy of docetaxel consolidation therapy after concurrent chemoradiotherapy for unresectable stage III non–small cell lung cancer (NSCLC).

Patients and Methods: The eligibility criteria included unresectable stage III NSCLC, no previous treatment, age between 20 and 74 years, and performance status 0 or 1. Treatment consisted of cisplatin (80 mg/m^2 on days 1, 29, and 57), vinorelbine (20 mg/m^2 on days 1, 8, 29, 36, 57, and 64), and thoracic radiotherapy (TRT) (60 Gy/30 fractions over 6 weeks starting on day 2), followed by consolidation docetaxel (60 mg/m^2 every 3 to 4 weeks for three cycles).

Results: Of 97 patients who were enrolled in this study between 2001 and 2003, 93 (76 males and 17 females with a median age of 60) could be evaluated. Chemoradiotherapy was well tolerated; three cycles of chemotherapy and 60 Gy of TRT were administered in 80 (86%) and 87 (94%) patients, respectively. Grade 3 or 4 neutropenia, esophagitis, and pneumonitis developed in 62, 11, and 3 patients, respectively. Docetaxel consolidation was administered in 59 (63%) patients, but three cycles were completed in only 34 (37%) patients. The most common reason for discontinuation was pneumonitis, which developed in 14 (24%) of the 59 patients. During consolidation therapy, grade 3 or 4 neutropenia, esophagitis, and pneumonitis developed in 51, 2, and 4 patients, respectively. A total of four patients died of pneumonitis. We calculated a V_{20} (the percent volume of the normal lung receiving 20 Gy or more) on a dose–volume histogram in 25 patients. Of these, five patients developed grade 3 or more severe radiation pneumonitis. A median V_{20} for these five patients was 35% (range, 26–40%), whereas the median V_{20} for the remaining 20 patients was 30% (range, 17–35%) (p = 0.035 by a Mann–Whitney test). The response rate was 81.7% (95% confidence interval [CI], 72.7–88.0%), with 5 complete and 71 partial responses. The median progression-free survival was 12.8 (CI, 10.2–15.4) months, and median survival was 30.4 (CI, 24.5–36.3) months. The 1-, 2-, and 3-year survival rates were 80.7, 60.2, and 42.6%, respectively.

Conclusion: This regimen produced promising overall survival in patients with stage III NSCLC, but the vast majority of patients could not continue with the docetaxel consolidation because of toxicity.

Key Words: Non-small cell lung cancer, Chemoradiotherapy, Consolidation, Docetaxel.

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Locally advanced unresectable non–small cell lung cancer (NSCLC), stage IIIA with bulky N2 and stage IIIB disease without pleural effusion, is characterized by large primary lesions and/or involvement of the mediastinal or supraclavicular lymph nodes and occult systemic micrometastases. A combination of thoracic radiotherapy and chemotherapy is the standard medical treatment for this disease, but the optimal combination has not been established.[1] Although the available data are insufficient to accurately define the size of a potential benefit,[2] concurrent chemoradiotherapy using a platinum doublet has been shown to be superior to the sequential approach in phase III trials of this disease.[3–5] However, third-generation cytotoxic agents, which have provided better patient survival with extrathoracic spread than the old-generation agents, must be reduced when administered concurrently with thoracic radiotherapy.[6] Thus, it has been hypothesized that the addition of systemic dose chemotherapy with a new cytotoxic agent to concurrent chemoradiotherapy, either as induction or as consolidation chemotherapy, might further improve patient survival.[1]

The consolidation chemotherapy with docetaxel was based on the observation that this drug was highly active in the primary treatment of metastatic NSCLC, producing a response rate (RR) as high as 20% after platinum-based chemotherapy failed.[7–9] Highly encouraging results of a me-

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dian survival time (MST) of more than 2 years and a 3-year survival rate of nearly 40% were obtained in a phase II trial of docetaxel consolidation after chemoradiotherapy with cisplatin and etoposide in patients with stage IIIB NSCLC (SWOG study S9504).[10]

We have developed a combination chemotherapy schedule with cisplatin and vinorelbine concurrently administered with thoracic radiotherapy at a total dose of 60 Gy in 30 fractions in patients with unresectable stage III NSCLC. The results of a phase I study in 18 patients were very promising, with a RR of 83%, a MST of 30 months, and a 3-year survival rate of 50%.[6] Thus, addition of docetaxel consolidation to this regimen is a particularly interesting therapeutic strategy. The objectives of the current study were to evaluate the feasibility of docetaxel consolidation therapy after concurrent chemoradiotherapy with cisplatin and vinorelbine and to evaluate the efficacy and safety of the whole treatment regimen including both the chemoradiotherapy and consolidation therapy in patients with unresectable stage IIIA and IIIB NSCLC.

PATIENTS AND METHODS

Patient Selection

The eligibility criteria 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 and 74 years; Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; adequate bone marrow function (12.0×10^9/liter ≥ white blood cell [WBC] count ≥4.0×10^9/liter, neutrophil count ≥2.0×10^9/liter, hemoglobin ≥10.0 g/dl, and platelet count ≥100×10^9/liter), liver function (total bilirubin ≤1.5 mg/dl and transaminase no more than twice the upper limit of the normal value), and renal function (serum creatinine ≤1.5 mg/dl and creatinine clearance ≥60 ml per minute); and a PaO_2 of 70 torr or more under room air conditions. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonia or lung fibrosis identified by a chest x-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or if they were breast feeding. All patients gave their written informed consent.

Pretreatment Evaluation

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest x-rays, chest computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan or ultrasonography, and radionuclide bone scan.

Treatment Schedule

Treatment consisted of a chemoradiotherapy phase with three cycles of cisplatin and vinorelbine followed by a consolidation phase with three cycles of docetaxel (Figure 1). Cisplatin 80 mg/m^2 was administered on days 1, 29, and 57 by intravenous infusion for 60 minutes with 2500 to 3000 ml of fluid for hydration. Vinorelbine diluted in 50 ml of normal saline was administered intravenously on days 1, 8, 29, 36, 57, and 64. All patients received prophylactic antiemetic therapy consisting of a $5HT_3$-antagonist and a steroid.

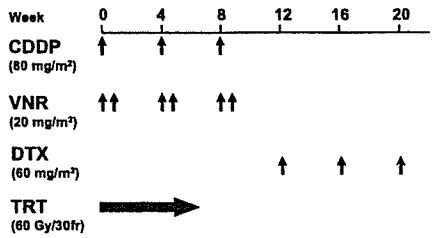

FIGURE 1. Treatment schema. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

Radiation therapy 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 and the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique fields. A 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 account of subclinical extension. CTV and GTV for the metastatic nodes (>1 cm in 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- to 1.0-cm margins laterally and 1.0- to 2.0-cm margins craniocaudally, taking account of setup variations and internal organ motion. Lung heterogeneity corrections were not used.

The criteria for starting consolidation chemotherapy were completion of three cycles of cisplatin and vinorelbine and a full dose of thoracic radiotherapy, the absence of progressive disease, adequate general condition within 6 weeks of the start of the third cycle of cisplatin and vinorelbine (PS 0 or 1, WBC count ≥3.0×10^9/liter, neutrophil count ≥1.5×10^9/liter, hemoglobin ≥9.0 g/dl and platelet count ≥100×10^9/liter, total bilirubin ≤1.5 mg/dl and transaminase no more than twice the upper limit of the normal value, and a PaO_2 of 70 torr or more at room air). Docetaxel (60 mg/m^2) was administered intravenously for 1 hour every 3 to 4 weeks for three cycles.

Toxicity Assessment and Treatment Modification

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest x-ray were performed once a week during the course of treatment. Acute toxicity was graded according to the NCI Common Toxicity Criteria, and late toxicity associated with thoracic radiother-

apy was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Vinorelbine administration on day 8 was omitted if any of the following were noted: WBC count $<3.0 \times 10^9$/liter, neutrophil count $<1.5 \times 10^9$/liter, platelet count $<100 \times 10^9$/liter, elevated hepatic transaminase level or total serum bilirubin of at least grade 2, fever ≥38°C, or PS ≥2. Subsequent cycles of cisplatin and vinorelbine chemotherapy were delayed if any of the following toxicities were noted on day 1: WBC count $<3.0 \times 10^9$/liter, neutrophil count $<1.5 \times 10^9$/liter, platelet count $<100 \times 10^9$/liter, serum creatinine level ≥1.6 mg/dl, elevated hepatic transaminase level or total serum bilirubin of at least grade 2, fever ≥38°C, or PS ≥2. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level rose to 2.0 mg/dl or higher. The dose of vinorelbine or docetaxel was reduced by 25% in all subsequent cycles if any of the following toxicities were noted: WBC count $<1.0 \times 10^9$/liter, platelet count $<10 \times 10^9$/liter, or grade 3 or 4 infection or liver dysfunction. Thoracic radiotherapy was suspended if any of the following were noted: fever ≥38°C, grade 3 esophagitis, PS of 3, or PaO_2 <70 torr. Thoracic radiotherapy was terminated if any of the following were noted: grade 4 esophagitis, grade 3 or 4 pneumonitis, PS of 4, or duration of radiotherapy of over 60 days. The use of granulocyte colony-stimulating factor during radiotherapy was not permitted unless radiotherapy was on hold. The criteria for termination of docetaxel consolidation were not defined in the protocol.

Response Evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumor.[11] Local recurrence was 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 as the development of malignant pleural and pericardial effusions; and distant recurrence as the appearance of a distant metastasis.

Study Design, Data Management, and Statistical Considerations

This study was conducted at three institutions: the National Cancer Center Hospital, National Cancer Center Hospital East, and Tochigi Cancer Center. The protocol and consent form were approved by the institutional review board of each institution. Registration was conducted at the registration center. Data management, periodic monitoring, and the final analysis were performed by the study coordinator.

The primary objective of the current study was to evaluate the feasibility of docetaxel consolidation therapy. The secondary endpoints were toxicity observed during chemoradiotherapy and consolidation therapy, the best response, and overall survival in all patients eligible to participate in this study. Because no standard method to evaluate consolidation chemotherapy after chemoradiotherapy has been established, we arbitrarily defined the primary endpoint of this study as a ratio (R) of the number of patients receiving docetaxel without grade 4 nonhematological toxicity or treatment-related death to the total number of patients receiving docetaxel. The sample size was initially estimated to be 34 patients with a power of 0.80 at a significance level of 0.05, under the assumption that a R of 0.95 would indicate potential usefulness, whereas a R of 0.8 would be the lower limit of interest, and that 85% of patients would move into the consolidation phase. An analysis of the first 13 patients, however, showed that only 8 (61%) patients advanced into the consolidation phase. The reasons for not receiving docetaxel were disease progression in one, delay in completion of chemoradiotherapy in two, grade 3 esophagitis in one, and death due to hemoptysis in one patient. Considering that the SWOG trial S9504 included 83 patients, we decided to revise the number of patients in the current study. According to Simon's two-stage minimax design, the required number of patients was calculated to be 59 with a power of 0.80 at a significance level of 0.05, under the assumption that a R of 0.85 would indicate potential usefulness, whereas a R of 0.7 would be the lower limit of interest.[12] Assuming that 61% of registered patients would move into the consolidation phase, the sample size was determined to be 97 patients.

Overall survival time and progression-free survival time were estimated by the Kaplan–Meier method, and confidence intervals (CI) were based on Greenwood's formula.[13] Overall survival time was measured from the date of registration to the date of death (from any cause) or to the last follow-up. 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. Patients who were lost to follow-up without event were censored at the date of their last known follow-up. A CI for RR was calculated using methods for exact binomial CIs. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for statistical analyses.

RESULTS

Registration and Characteristics of the Patients

A total of 97 patients were enrolled in this study between April 2001 and June 2003. Four patients were excluded from this study before the treatment was started because the radiation treatment planning disclosed that their tumors were too advanced for curative thoracic radiotherapy. Thus, 93 patients who received the protocol-defined treatment were the subjects of this analysis (Figure 2). There were 76 males and 17 females, with a median age of 60 (range 31–74). Body weight loss was less than 5% in 77 patients; adenocarcinoma histology was noted in 57 patients, and stage IIIA disease was noted in 41 patients (Table 1).

Treatment Delivery

Treatment delivery was generally well maintained in the chemoradiotherapy phase (Table 2). Full cycles of cisplatin and vinorelbine and the full dose of thoracic radiotherapy were administered in 80 (86%) and 87 (94%) patients, respectively. Delay in radiotherapy was less than 5 days in 61 (66%) patients. In contrast, the delivery of docetaxel was poor (Table 2). A total of 59 (63%) patients could enter the consolidation phase, and only 34 (37%) patients completed three cycles of docetaxel chemotherapy. The reasons for not

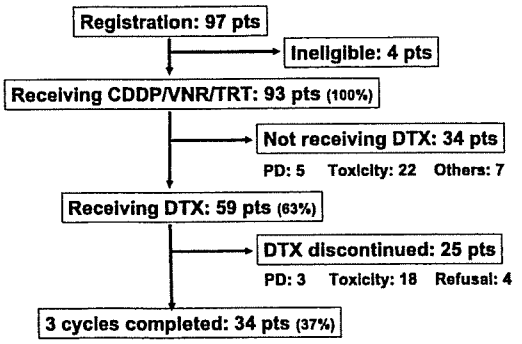

FIGURE 2. Patient registration. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

receiving consolidation were toxicity in 22 (65%) patients including pneumonitis in seven patients, myelosuppression in five patients, esophagitis in four patients, liver dysfunction in two patients, infection in two patients, other toxicity in two patients, progressive disease in five (15%) patients, patient refusal in three (9%) patients, early death due to hemoptysis in one (3%) patient, and other reasons in three (9%) patients. Of the 59 patients, 18 (31%) discontinued docetaxel consolidation because of toxicity, including pneumonitis (n = 14) and esophagitis, infection, gastric ulcer, and allergic reaction (n = 1 each), four (7%) because of patient refusal, and three (5%) because of progressive disease.

Toxicity

Acute severe toxicity in the chemoradiotherapy phase was mainly leukopenia and neutropenia, whereas grade 3 or 4 thrombocytopenia was not noted (Table 3). Severe nonhematological toxicity was sporadic, and grade 3 esophagitis and pneumonitis were observed in only 11 (12%) and 3 (3%) patients, respectively. Acute severe toxicity in the consolidation phase also consisted of neutropenia and associated infection (Table 4). In addition, grade 3 or 4 pneumonitis developed in 4 (7%) patients. The R observed in this study was 0.05 (3 out of 57 patients), which was much lower than the hypothetical value. Grade 3 or 4 late toxicities were included lung toxicity in four patients, esophageal toxicity in two patients, renal toxicity in one patient, and a second esophageal cancer that developed 35.4 months after the start of the chemoradiotherapy in one patient. Treatment-related

TABLE 1. Patient Characteristics

Characteristics	n	%
Gender		
Male	76	82
Female	17	18
Age median (range)	60	31–74
Weight loss		
<5%	76	81
5–9%	12	13
≥10%	3	3
Unknown	2	2
Histology		
Adenocarcinoma	57	61
Squamous cell carcinoma	23	25
Large cell carcinoma	12	13
Others	1	1
Stage		
IIIA	41	44
IIIB	52	56

TABLE 2. Treatment Delivery

Variables	n	%
Cisplatin and vinorelbine chemotherapy		
Total number of cycles		
3	80	86
2	10	11
1	3	3
Number of vinorelbine skips		
0	63	68
1	25	27
2–3	5	5
Thoracic radiotherapy		
Total dose (Gy)		
60	87	94
50–59	4	4
<50	2	2
Delay (days)		
<5	61	66
5–9	20	22
10–16	6	6
Not evaluable (<60 Gy)	6	6
Docetaxel consolidation		
Number of cycles		
3	34	37
2	12	13
1	13	14
0	34	34

TABLE 3. Acute Toxicity in Chemoradiotherapy (n = 93)

	Grade			
Toxicity	3	4	3 + 4	%
Leukopenia	54	18	72	77
Neutropenia	33	29	62	67
Anemia	21	0	21	23
Infection	15	1	16	17
Esophagitis	11	0	11	12
Hyponatremia	11	0	11	12
Anorexia	9	1	10	11
Nausea	5	—	5	5
Pneumonitis	3	0	3	3
Syncope	2	0	2	2
Hyperkalemia	2	0	2	2
Ileus	0	1	1	1
Cardiac ischemia	1	0	1	1

TABLE 4. Acute Toxicity in Consolidation Therapy (n = 57)

Toxicity	Grade 3	Grade 4	Grade 3 + 4	%
Leukopenia	33	11	44	77
Neutropenia	24	26	50	88
Anemia	5	0	5	9
Infection	5	1	6	11
Esophagitis	2	0	2	3
Anorexia	1	0	1	2
Pneumonitis	2	2	4	7

death was observed in four (4%) patients. Of these, three received docetaxel, and one did not. The reason for death was pneumonitis in all patients. We calculated a V_{20} (the percent volume of the normal lung receiving 20 Gy or more) on a dose–volume histogram in 25 patients. Of these, five patients developed grade 3 or severer radiation pneumonitis. A median V_{20} for these five patients was 35% (range, 26–40%), whereas that for the remaining 20 patients was 30% (range, 17–35%) (p = 0.035 by a Mann–Whitney test).

Objective Responses, Relapse Pattern, and Survival

All 93 patients were included in the analyses of tumor response and survival. Complete and partial responses were obtained in 5 (5%) and 71 patients (76%), respectively, for an overall RR of 81.7% (95% CI, 72.7–88.0%). Stable and progressive diseases occurred in 12 (13%) and 5 (5%) patients, respectively. With a median follow-up period of 29.7 months, 38 patients developed locoregional recurrence, 32 developed distant recurrence, 4 developed both locoregional and distant recurrences, and 19 did not. The median progression-free survival time was 12.8 (95% CI, 10.2–15.4) months (Figure 3). Two patients underwent salvage surgery for a recurrent primary tumors. Conventional chemotherapy and gefitinib monotherapy were administered after recurrence in 20 and 25 patients, respectively. The median overall survival time was 30.4 (95% CI, 24.5–36.3) months. The 1-, 2-, and 3-year survival rates were 80.7, 60.2, and 42.6%, respectively. (Figure 4).

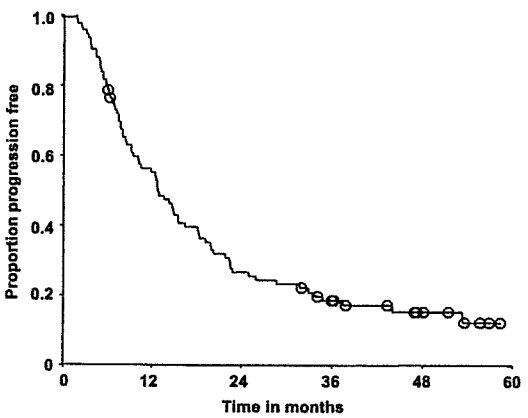

FIGURE 3. Progression-free survival (n = 93). The median progression-free survival time was 12.8 (95% CI, 10.2–15.4) months.

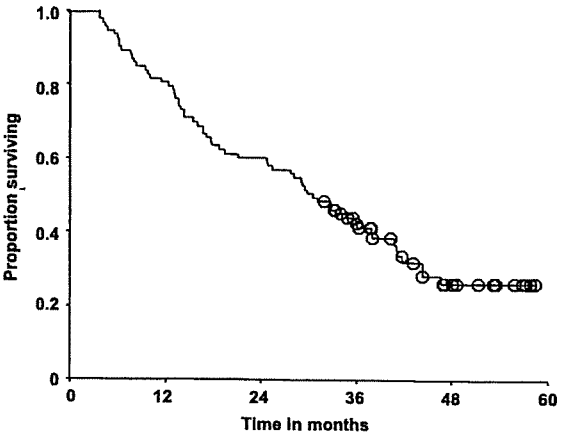

FIGURE 4. Overall survival (n = 93). The median overall survival time was 30.4 (95% CI, 25.4–35.4) months. The 1-, 2-, and 3-year survival rates were 80, 60, and 40%, respectively.

DISCUSSION

This study showed that concurrent chemoradiotherapy with cisplatin, vinorelbine, and standard thoracic radiotherapy was well tolerated, with a high completion rate exceeding 80%. The incidence of acute toxicity, including 67% (62/93) of grade 3 or 4 neutropenia, 12% (11/93) of grade 3 esophagitis, and 3% (3/93) of grade 3 pneumonitis, were comparable with other reports of concurrent chemoradiotherapy.[3,4,10] In contrast, consolidation docetaxel could be administered in only 59 of 93 (63%) patients eligible to participate in this study. Of the remaining 34 patients, 22 (65%) patients did not receive consolidation chemotherapy because of toxicities affecting various organs. Other studies also showed that not all patients proceeded to the consolidation phase after completion of concurrent chemoradiotherapy: 61 to 78% of patients after two cycles of cisplatin and etoposide with radiotherapy,[3,10] and 54 to 75% of patients after weekly carboplatin and paclitaxel with radiotherapy.[14,15] Thus, for 20 to 40% of the patients, concurrent chemoradiotherapy was as much as they could undergo, and the additional chemotherapy was not practical.

Furthermore, the number of patients who fulfilled the three cycles of consolidation docetaxel was only 34 (58%) of the 59 patients, which corresponded to only 37% of those eligible in this study. The reason for the termination of docetaxel in the 25 patients was toxicity in 18 (72%) patients, especially pneumonitis in 14 (56%) patients. The grade of pneumonitis during the consolidation phase was within grade 2 in most cases, and this was probably because docetaxel was discontinued early. Considering that pneumonitis associated with cancer treatment is more common in Japan, docetaxel consolidation is not thought to be feasible in the Japanese population. The MST and the 3-year survival rate in all eligible patients were 33 months and 44% in this study, but docetaxel consolidation was unlikely to contribute to these promising results because only 37% of patients received full cycles of docetaxel. This contrasts clearly with the result of

the SWOG study S9504, a phase II trial of two cycles of cisplatin and etoposide with thoracic radiation followed by three cycles of docetaxel. In this trial, 75% of patients starting consolidation and 59% of those entering the trial received full cycles. In addition, docetaxel consolidation seemed to prolong survival, although this was drawn from a retrospective comparison of the results between the two SWOG studies S9504 and S9019.[10]

There is no widely used definition of consolidation therapy following chemoradiotherapy. Given that consolidation therapy is arbitrarily defined as chemotherapy with three cycles or more after the completion of concurrent chemoradiotherapy, only one randomized trial is available in the literature. The randomized phase III trial of standard chemoradiotherapy with carboplatin and paclitaxel followed by either weekly paclitaxel or observation in patients with stage III NSCLC showed that only 54% of patients proceeded to randomization, and overall survival was worse in the consolidation arm (MST, 16 versus 27 months).[15] Thus, there have been no data supporting the use of consolidation therapy, especially when a third-generation cytotoxic agent such as paclitaxel and vinorelbine is incorporated into concurrent chemoradiation therapy.

The low complete-response rate of 5% in this study may be explained partly by an inability to distinguish between inactive scarring or necrotic tumor and active tumor after radiotherapy. Positron emission tomography (PET) using 18F-fluorodeoxyglucose showed a much higher rate of complete response than conventional CT scanning and provided a better correlation of the response assessment using PET with patterns of failure and patient survival.[16] In addition, the high locoregional relapse rate in this study clearly showed that the conventional total dose of 60 Gy was insufficient. Three-dimensional treatment planning, omission of elective nodal irradiation, and precise evaluation of the gross tumor volume by PET may facilitate the escalation of the total radiation dose without enhanced toxicity.

In conclusion, cisplatin and vinorelbine chemotherapy concurrently combined with standard thoracic radiotherapy and followed by docetaxel consolidation produced promising overall survival in patients with stage III NSCLC, but the vast majority of patients could not continue with the docetaxel consolidation because of toxicity.

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REFERENCES

1. Vokes EE, Crawford J, Bogart J, et al. Concurrent chemoradiotherapy for unresectable stage III non-small cell lung cancer. *Clin Cancer Res* 2006;11:5045s–5050s.
2. Auperin A, Le Pechoux C, Pignon JP, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006;17:473–483.
3. Fournel P, Robinet G, Thomas P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupeqqfrancaisqqqq de Pneumo-Cancerologie NPC 95-01 Study. *J Clin Oncol* 2006;23:5910–5917.
4. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–2699.
5. Curran W, Scott CJ, Langer C, et al. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresected stage III NSCLC: RTOG 9410. *Proc Am Soc Clin Oncol* 2003;22:621 (abstr 2499).
6. Sekine I, Noda K, Oshita F, et al. Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer. *Cancer Sci* 2004;95:691–695.
7. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000;18:2354–2362.
8. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000;18:2095–2103.
9. Fossella FV, Lee JS, Shin DM, et al. Phase II study of docetaxel for advanced or metastatic platinum-refractory non-small-cell lung cancer. *J Clin Oncol* 1995;13:645–651.
10. Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. *J Clin Oncol* 2003; 21:2004–2010.
11. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92: 205–216.
12. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989;10:1–10.
13. Armitage P, Berry G, Matthews J. Survival analysis. In Armitage P, Berry G, Matthews J (eds.), *Statistical Methods in Medical Research* (4th ed.). Oxford: Blackwell Science Ltd, 2002, pp. 568–590.
14. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* 2006;23:5883–5891.
15. Carter D, Keller A, Tolley R, et al. A randomized phase III trial of combined paclitaxel, carboplatin, and radiation therapy followed by either weekly paclitaxel or observation in patients with stage III non-small cell lung cancer. *Proc Am Soc Clin Oncol* 2006;22:635s (abstr 7076).
16. Mac Manus MP, Hicks RJ, Matthews JP, et al. Metabolic (FDG-PET) response after radical radiotherapy/chemoradiotherapy for non-small cell lung cancer correlates with patterns of failure. *Lung Cancer* 2006; 49:95–108.

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LUNG CANCER

Eg5 expression is closely correlated with the response of advanced non-small cell lung cancer to antimitotic agents combined with platinum chemotherapy

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KEYWORDS
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Antimitotic agents;
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Advanced non-small cell lung cancer;
Cyclin B1

Summary
Background: Eg5 is a microtubule motor protein that functions in bipolar spindle assembly. We investigated the relationship between Eg5 expression and the response to chemotherapy of patients with advanced non-small cell lung cancer (NSCLC).
Patients and methods: Eg5 expression was investigated immunohistochemically in 122 formalin-fixed tumor samples from untreated stage IIIB or IV NSCLC patients. We also investigated cyclin B1 expression, which is involved in the G2/M transition. All patients received antimitotic agents combined with platinum chemotherapy. The response to chemotherapy was compared in relation to Eg5 and cyclin B1 expression and in relation to clinicopathological factors.
Results: The response rate to chemotherapy of patients with Eg5-positive tumors was 37%, as opposed to 10% for patients with Eg5-negative tumors, and Eg5 expression was significantly associated with the response to chemotherapy ($P=0.002$). The response rate of patients with cyclin B1-positive tumors (53%) was higher than that of patients with cyclin B1-negative tumors (23%) ($P=0.009$), and Eg5 expression was significantly correlated with cyclin B1 expression ($P=0.005$). A multivariate analysis confirmed Eg5 status to be an independent variable related to response to chemotherapy ($P=0.008$).
Conclusions: Eg5 expression can predict a response to antimitotic agents combined with platinum chemotherapy among patients with advanced NSCLC.

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1. Introduction

Lung cancer is a major cause of death from cancer worldwide, and non-small cell lung cancer (NSCLC) accounts for ~85% of all cases of lung cancer. More than half of patients with NSCLC have advanced stage IIIB or IV disease at presentation, and patients with advanced NSCLC are candidates for systemic chemotherapy [1]. Meta-analyses have demonstrated that cisplatin-based chemotherapy for metastatic NSCLC statistically improves patient survival, compared with supportive care alone [2]. However, the response rate to chemotherapy has been poor, and very few patients survive for 5 years [3]. During the 1990s, five new drugs became available for the treatment of metastatic NSCLC: paclitaxel, docetaxel, vinorelbine, gemcitabine, and irinotecan. Each of these drugs has since been evaluated in combination regimens with cisplatin or carboplatin and has produced responses in 20–30% of patients [1]. Unfortunately, despite the increasing number of active chemotherapeutic agents, none of these chemotherapeutic regimens has offered a significant advantage over the others in the treatment of advanced NSCLC in randomized studies [4,5], and advanced NSCLC patients still have a median survival time of <1 year. Several reasons have been offered to explain the response to chemotherapy, such as the presence of drug-resistant tumor cells [6] and the redistribution of tumor cells within the cell cycle after chemotherapy. However, the molecular basis of the response to chemotherapy remains to be explored.

A network of microtrabecular filaments forms the cytoplasmic matrix, giving rise to the concept of the cytoskeleton, which comprises microtubules, actin, and intermediate filaments. Microtubules display a remarkable versatility of function and are involved in multiple biologic phenomena, including mitosis, cell shape determination, cell locomotion, and the movement of intracellular organelles [7]. Microtubule-polymerizing agents, including paclitaxel and docetaxel, and microtubule-depolymerizing agents, including vinorelbine, target preliminary tubulin and can induce disrupting kinetic stabilization of microtubules' polymerization–depolymerization, thus blocking the cell cycle in the mitotic phase [8].

Microtubule motors bind to and move unidirectionally on microtubules, and they have been proposed to generate the force required for spindle assembly and maintenance, attachment of the chromosomes to the spindle, and movement of chromosomes toward opposite poles. The microtubule motor proteins, which are members of the kinesin, dynein, or myosin families, can account for many of the movements of the spindle and chromosomes in dividing cells. Kinesin motors have been shown to be necessary to establish spindle bipolarity, position chromosomes on the metaphase plate, and maintain forces in the spindle [9]. Evidence that kinesin motors facilitate microtubule depolymerization also exists, raising the possibility that the motors modulate microtubule dynamics during mitosis. Eg5, which is a part of the kinesin-5 molecule (a member of the kinesin superfamily), is a microtubule motor protein. Eg5 accounts for many of the movements of the spindle and chromosomes in dividing cells and localizes to the spindle in mitotically dividing cells. It has been implicated in spindle function by both its cellular localization and the effects of mutations. Eg5 function in centrosome or spindle pole body separation is necessary for bipolar spindle assembly [10]. The latest antimitotic agent, named monastrol, is an inhibitor of mitotic kinesin Eg5 [11,12]. Monastrol arrests mitosis by reversibly inhibiting mitotic kinesin Eg5 and impairing bipolar mitotic spindle formation. Prolonged mitotic arrest leads to apoptosis in tumor cells and to senescence or apoptosis in primary cells, and the inhibition of mitotic kinesin Eg5 results in the formation of monoaster spindles leading to mitotic arrest [13].

Cyclin and cyclin-dependent kinase complexes play an important role in the control of the cell cycle [14], and the cyclin B1/cdc2 complex has a role as a maturation/mitosis-promoting factor in the G2–M phase transition during the cell cycle [15]. Thus, lack of regulation of cyclin B1 expression may be involved in uncontrolled cell growth and malignant transformation. Overexpression of cyclin B1 has been reported in various malignant tumors and has been shown to predict a poor outcome in NSCLC, esophageal carcinoma, and head and neck cancer [16–18].

In this retrospective study, we investigated the level of expression of Eg5, in addition to cyclin B1—a molecule involved in the G2/M transition, in clinical samples from patients with advanced NSCLC who were subsequently treated with antimitotic agents and investigated whether its expression predicts response to chemotherapy and outcome.

2. Materials and methods

2.1. Subjects

A total of 122 stage IIIB or IV NSCLC patients received platinum-based combination chemotherapy combined with docetaxel, paclitaxel or vinorelbine at the National Cancer Center Hospital East between August 1997 and July 2004 because of PS 0 or 1 on the Eastern Cooperative Oncology Group scale. Adequate tumor biopsy specimens were obtained from all 122 of these patients before chemotherapy and were analyzed in this study. All of the tumor specimens were obtained before chemotherapy, by bronchoscopy in 83 patients, by percutaneous needle biopsy in 31 patients, by thoracotomy in five patients, and by mediastinoscopy in three patients. The histological classification was based on the third edition of the WHO classification. Clinical staging was based on an initial evaluation consisting of a clinical assessment, chest radiography, computed tomography of the chest and abdomen, computed tomography or magnetic resonance imaging of the brain, and bone scintigraphy. The current international staging system was used for clinical disease staging [19]. The clinicopathological characteristics of all the patients are listed in Table 1. Their median age at diagnosis was 62 years (range, 42–78 years). Seven of the 43 stage IIIB patients were women, and 32 of the 79 stage IV patients were women. All of the patients were treated with antimitotic agents combined with platinum chemotherapeutic regimens in what were considered standard regimens for patients with metastatic NSCLC [20]. Nine of the 43 stage IIIB patients received thoracic radiotherapy after the completion of chemotherapy; three of these patients were women. The median follow-up time of the 122 patients was 26 months (range, 18–54 months).

Table 1 Characteristics of 122 patients with advanced NSCLC

Characteristics	No. of patients
Total no. of patients	122
Gender	
Male	83
Female	39
Age (years)	
Median	62
Range	42–78
Histology	
Adenocarcinoma	80
Squamous cell carcinoma	28
Large cell carcinoma	13
Others	1
Stage	
IIIB	43
IV	79
Performance status	
0	32
1	90
Chemotherapeutic regimen	
Cisplatin + vinorelbine	76
Cisplatin + docetaxel	20
Carboplatin + paclitaxel	26
Smoking history	
Positive	91
Negative	31

NSCLC: non-small cell lung cancer.

After obtaining informed consent in accordance with our institution's guidelines, all of the patients underwent a tumor biopsy and chemotherapy.

2.2. Chemotherapy

The platinum-based regimens were vinorelbine (25 mg/m^2) on days 1 and 8 plus cisplatin (80 mg/m^2) on day 1 of a 21-day cycle (76 patients), docetaxel (60 mg/m^2) on day 1 plus cisplatin (80 mg/m^2) on day 1 of a 21-day cycle (20 patients), and paclitaxel (200 mg/m^2 administered over 3 h) on day 1 plus carboplatin (dosed with an area under the curve of 6) on day 1 of a 21-day cycle (26 patients). All of the patients received two or more courses of chemotherapy before the appearance of progressive disease. We used the RECIST guidelines [21] to evaluate the response to chemotherapy. A complete response was defined as the disappearance of all clinically detectable lesions for at least 4 weeks. A partial response required a minimum of a 30% reduction in the greatest diameter of all of the measurable lesions for a minimum of 4 weeks. Progressive disease was defined as the appearance of new lesions or an increase in disease of >20% measured in the same manner as for partial response. All other results were classified as "no change". The response rate was defined as the total of the complete response cases and partial response cases expressed as a percentage of all cases. PFS (progression-free survival) was measured from the start of chemotherapy until the documentation of progressive disease or death.

2.3. Immunohistochemistry

Immunostaining was performed on 4-μm formalin-fixed, paraffin-embedded tissue sections. The slides were deparaffinized in xylene and dehydrated in a graded ethanol series. For antigen retrieval, the slides for cyclin B1 were immersed in 10 mM citric buffer solution (pH 6.0) and the slides for Eg5 were immersed in 1 mM EDTA retrieval fluid (pH 8.0). All of the slides were heated to 95 °C by exposure to microwave irradiation for 20 min. The slides were then cooled for 1 h at room temperature and washed in water and PBS. Endogenous peroxidase was blocked with 0.3% H_2O_2 in methanol for 15 min. Non-specific binding was blocked by preincubation with 2% BSA plus 0.1% NaN_3 for 30 min; after draining off the blocking serum, the slides were incubated overnight at 4 °C with anti-Eg5 monoclonal antibody (Clone, 20; Dilution, 1:50; BD Biosciences, NJ, USA) or with anti-cyclin B1 monoclonal antibody (Clone, 7A9; Dilution, 1:20; Novocastra Laboratories, Newcastle upon Tyne, UK). The slides were then washed three times in PBS and incubated with a labeled polymer Envision+ (DAKO, Glostup, Denmark) for 60 min. The chromogen used was 2% 3,3′-diaminobenzidine in 50 mM Tris buffer (pH 7.6) containing 0.3% hydrogen. Slides were counterstained with hematoxylin [22,23]. Normal human lung tissue was used as a positive control.

Eg5 staining was considered positive if the cytoplasm of >10% of the tumor cells stained positive. Cyclin B1 staining was considered positive if the nuclei of >10% of the tumor cells stained positive, because the cyclin B1/cdc2 complex translocates from the cytoplasm into the nucleus during the G2/M transition [24–26]. Thus, the criteria for cyclin B1 positivity used in the present report differed from those used in other reports on non-small cell lung cancer, esophageal carcinoma and head and neck cancer. All of the slides were examined and scored independently by two observers (T.S. and G.I.) who had no knowledge of the patients' clinical data. When the antibody evaluations differed between the observers, the observers discussed the results, with or without re-evaluating the slides, until an agreement was reached.

2.4. Statistical analysis

The correlations between immunohistochemical expression and the clinical variables and response to chemotherapy were evaluated by the χ^2-test or Fisher exact test, as appropriate. PFS was used as a clinical marker for duration of response to chemotherapy. Overall survival was measured from the start of chemotherapy to the date of death from any cause or the date the patient was last known to be alive. Survival curves were estimated using the Kaplan–Meier method, and any differences in PFS and survival between the subgroups were compared by using the log-rank test. The Cox proportional hazards model was used for a multivariate analysis. A multivariate analysis examining the correlation between variables and response to chemotherapy was performed by using logistic regression. P values <0.05 were

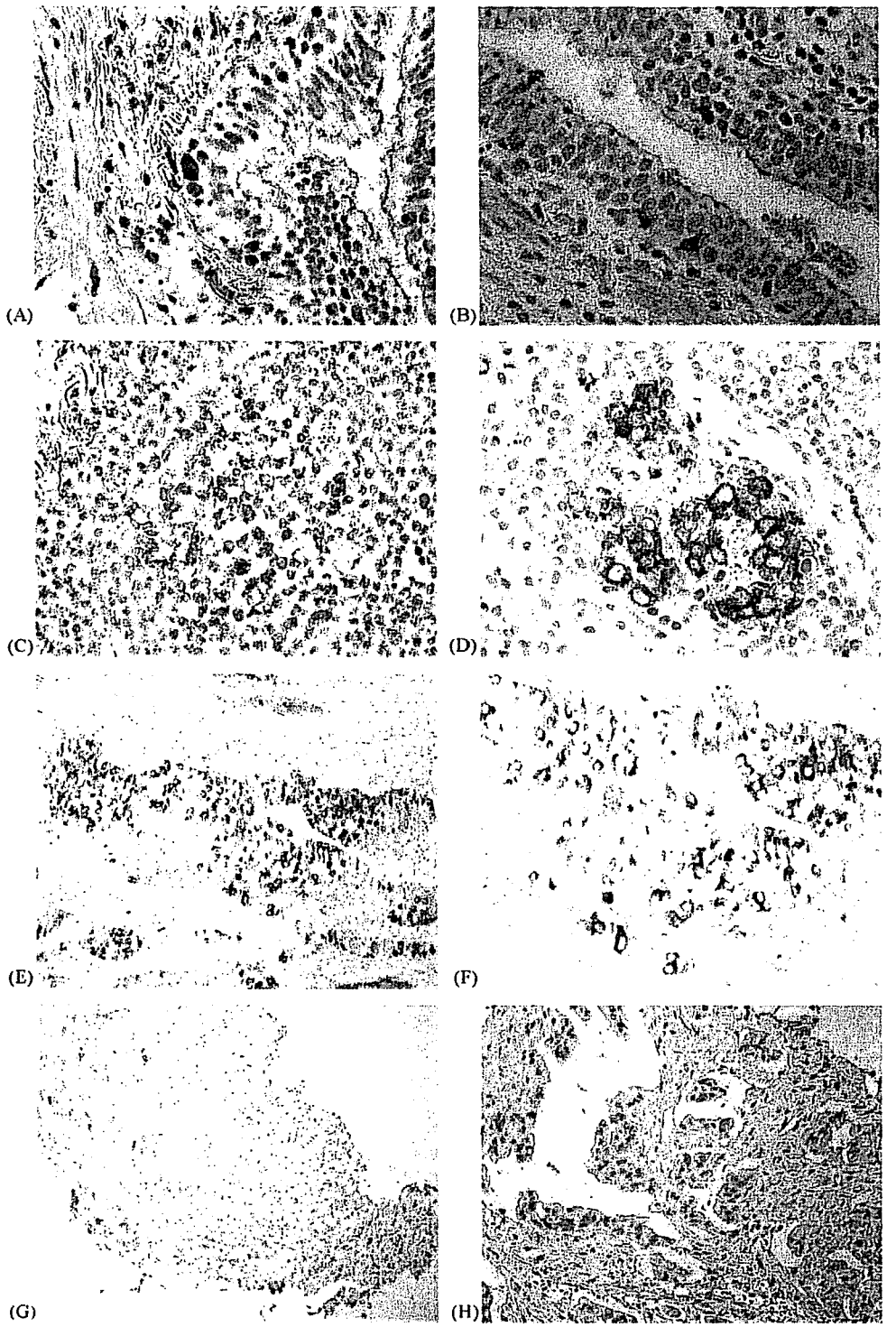

Fig. 1 (A–D) Immunohistochemical staining of Eg5 in normal lung tissue (A), Eg5 is present in part of the basal layer of the bronchial epithelium in this frozen section of normal lung tissue (400×). (B) Eg5 is also present in parts of the basal layer of the bronchial epithelium in this formalin-fixed, paraffin-embedded section of normal lung tissue (400×). (C) Eg5 expression is visible in germinal center lymphocytes giving rise to follicular hyperplasia in this frozen section of normal lung tissue (400×). (D) Eg5 expression is also visible in germinal center lymphocytes giving rise to follicular hyperplasia in this formalin-fixed, paraffin-embedded section of normal lung tissue (400×). (E–H) Immunohistochemical staining of Eg5 in NSCLC (E), low magnification (100×) of squamous cell carcinoma of the lung showing Eg5 immunoreactivity (F), high magnification (200×) of squamous cell carcinoma of the lung showing Eg5 immunoreactivity (G), Eg5 staining was considered to be negative in this adenocarcinoma of the lung: the cytoplasm of <10% of the tumor cells were stained (low magnification; 100×). (H) Eg5 staining was considered to be negative in this adenocarcinoma of the lung: the cytoplasm of <10% of the tumor cells were stained (high magnification; 200×).

considered significant. Two-sided statistical tests were used in all of the analyses. Statistical analysis software (StatView-J Ver. 5.0, Windows) was used for the analyses.

3. Results

3.1. Expression of Eg5 in normal lung tissue

To investigate the validation of immunostaining in the present experiment, we first evaluated Eg5 immunostaining in frozen sections and paraffin-embedded tissue sections of surgical specimens and confirmed that the staining intensity and specificity in the paraffin-embedded tissue sections were almost the same as in the frozen sections. Next, to choose the criteria for immunohistochemical positivity, normal lung tissue was used for Eg5 immunohistochemical staining. Representative immunohistochemical Eg5 staining in normal lung tissue is shown in Fig. 1A–D. In normal lung tissue, Eg5 expression was observed in some of the cells in the basal layer of the bronchial epithelium (Fig. 1A and B) and in germinal center lymphocytes exhibiting follicular hyperplasia (Fig. 1C and D). The frequency of positivity for bronchial epithelial cells and lymphoid germinal center lymphocytes were roughly more than 50% and 90%, respectively. We used these tissues as positive controls. Eg5 immunoreactivity was not detected in the pulmonary parenchyma.

3.2. Expression of Eg5 in NSCLC

The tumors of 82 (67%) of the 122 patients were Eg5 positive. Cytoplasmic staining was observed in most of the Eg5-positive tumors, but some tumors also showed nuclear staining. The median of the percentage staining of the lung cancer cells for Eg5 was 35% (range, 0–100%). Representative immunohistochemical Eg5 staining in NSCLC is shown in Fig. 1E–H. Fig. 1E and F shows the staining results for an Eg5-positive squamous cell carcinoma of the lung. The cytoplasm of almost 80% of the cancer cells stained positive for Eg5. Fig. 1G and H shows an Eg5-negative adenocarcinoma of the lung; this adenocarcinoma of the lung was judged to be negative for Eg5 because the cytoplasm of <10% of the tumor cells showed evidence of staining.

The relationships between the expression of Eg5 and clinical variables are shown in Table 2. Eg5 expression was significantly higher in males than in females ($P=0.03$), in squamous cell carcinoma than in non-squamous cell carcinoma ($P=0.02$), and in current and former smokers than in non-smokers ($P=0.03$).

The tumors of 18 (95%) of the 19 patients with cyclin B1-positive tumors were Eg5 positive, and the tumors of 39 (98%) of the 40 patients with Eg5-negative tumors were cyclin B1-negative (data not shown). Eg5 expression was significantly correlated with cyclin B1 expression ($P=0.005$; data not shown).

3.3. Expression of Eg5 and clinical outcome

All 122 patients were assessed for response to chemotherapy and survival. The relationships between clinical variables, Eg5 expression, and cyclin B1 expression, and the response to chemotherapy and survival in this study are shown in Table 3.

The chemotherapy response rate of patients with Eg5-positive tumors was 37%, as opposed to 10% for patients with Eg5-negative tumors. Eg5 expression was significantly associated with response to chemotherapy ($P=0.002$). The chemotherapy response rate of patients with cyclin B1-positive tumors was 53%, as opposed to 23% for patients

Table 2 Relationship between clinical variables and expression of primary antibodies

	n	Eg5-positive (%) patients	Cyclin B1-positive (%) patients
Total	122	82 (67)	19 (16)
Gender			
Male	83	61 (73)*	15 (18)
Female	39	21 (54)	4 (10)
Histology			
Sq	28	24 (86)**	6 (21)
Non-sq	94	58 (62)	13 (14)
Stage			
IIIB	43	30 (70)	8 19)
IV	79	52 (66)	11 (14)
PS			
0	32	20 (63)	1 (3)
1	90	62 (69)	18 (20)**
Smoking history			
Positive	91	66 (73)*	17 (19)
Negative	31	16 (52)	2 (6)

Sq: squamous; PS: performance status.
* $P=0.03$.
** $P=0.02$.

Table 3 Summary of the relationships between clinical variables and response to chemotherapy and survival

	n	Response rate (%)	P	PFS (months)	P	MST (months)	P
Total	122	28		5.0		12.0	
Gender							
Male	83	28	0.95	5.0	0.43	10.0	0.046
Female	39	28		7.0		15.0	
Histology							
Sq	28	32	0.57	5.0	0.72	9.0	0.64
Non-sq	94	27		5.0		13.0	
Stage							
IIIB	43	33	0.39	6.0	0.01	17.0	0.07
IV	79	25		5.0		11.0	
PS							
0	32	25	0.67	5.0	0.21	14.0	0.16
1	90	29		5.0		10.0	
Smoking history							
Positive	91	27	0.87	5.0	0.23	10.0	0.035
Negative	31	29		6.0		15.0	
Eg5							
Positive	82	37	0.002	5.0	0.08	10.0	0.006
Negative	40	10		6.0		13.0	
Cyclin B1							
Positive	19	53	0.009	5.0	0.77	8.0	0.31
Negative	103	23		5.0		13.0	

PFS: progression-free survival; MST: median survival time.

with cyclin B1-negative tumors, and cyclin B1 expression was also significantly associated with response to chemotherapy ($P = 0.009$).

The each of PFS and overall survival curves calculated using the Kaplan–Meier method according to Eg5 expression was shown in Fig. 2. The median PFS time for the Eg5-negative group was 6.0 months, as opposed to 5.0 months for the Eg5-positive group (Fig. 2A). The median survival time for the Eg5-negative group was 13.0 months, as opposed to 10.0 months for the Eg5-positive group (Fig. 2B). According to the overall survival data, the Eg5-positive group had a significantly poorer outcome than the Eg5-negative group ($P = 0.006$).

The median PFS time in both the cyclin B1-negative and the cyclin B1-positive group was 5.0 months (Fig. 2C). The median survival time in the cyclin B1-negative group was 13.0 months, as opposed to 8.0 months in the cyclin B1-positive group (Fig. 2D). Cyclin B1 expression was not associated with PFS or overall survival. Among the clinical variables, gender and smoking history were significantly associated with overall survival, and disease stage was significantly associated with PFS, also.

3.4. Multivariate analysis for response to chemotherapy, PFS, and overall survival

Following the univariate analyses for response to chemotherapy, PFS, and overall survival, we performed multivariate analyses. Table 4 shows the results of the multivariate analysis for response to chemotherapy, PFS, and overall survival. The multivariate analysis for response to chemotherapy was performed using logistic regression to determine the prognostic value of Eg5 when other prognostic factors were considered. A multivariate analysis that included gender, histology, stage, PS, smoking history, Eg5 expression and cyclin B1 expression, showed that Eg5 expression was the only significant independent variable correlated with response to chemotherapy ($P = 0.008$).

A multivariate analysis using the Cox proportional hazards model for PFS and overall survival was performed, using gender, histology, stage, PS, smoking history, Eg5 expression and cyclin B1 expression, as variables. No correlation between variables and PFS was found in the multivariate analysis. Stage was the only independent variable significantly correlated with overall survival ($P = 0.036$).

4. Discussion

This is the study to investigate the relationship between the level of expression of Eg5 and the clinical response to chemotherapy and outcome of previously untreated patients with advanced NSCLC. Eg5, a kinesin motor, accounts for many of the movements of the spindle and chromosomes in dividing cells. It localizes to the spindle in mitotically dividing cells and has been implicated in spindle function by both its cellular localization and the effects of mutations.

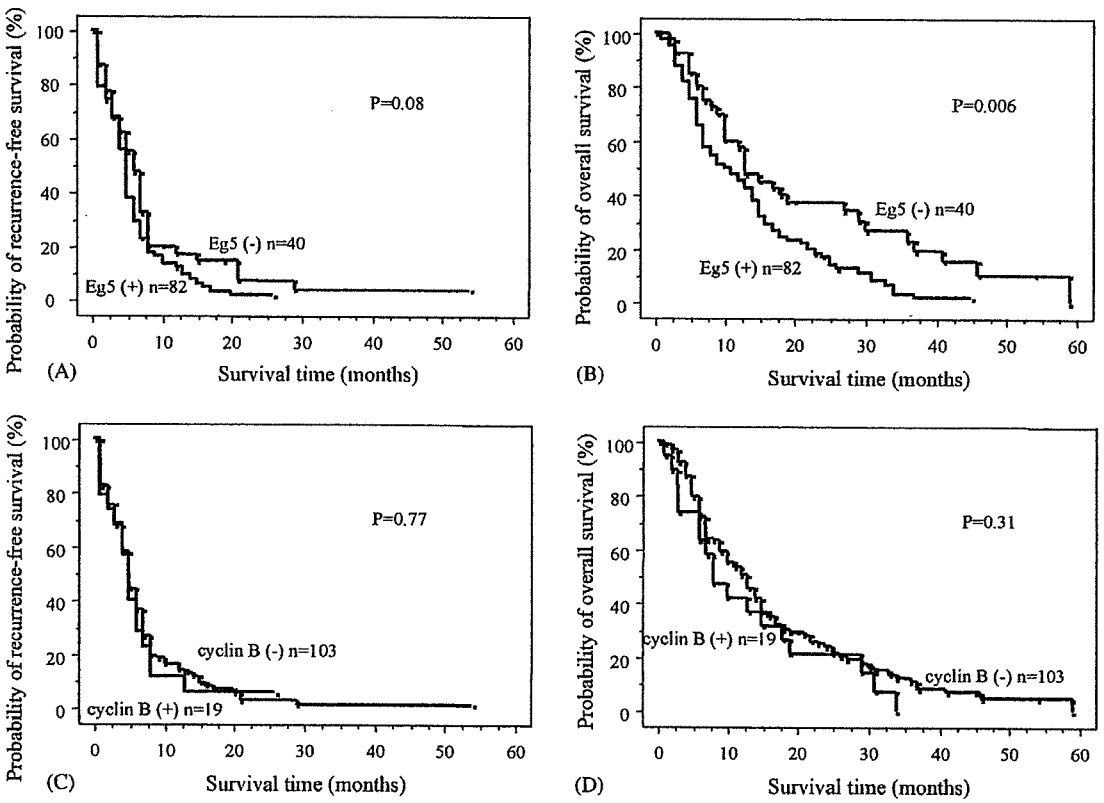

Fig. 2 (A) Progression-free survival curves of 122 patients with advanced non-small cell lung cancer, according to Eg5 expression. The median progression-free survival periods of Eg5-negative and -positive patients were 6.0 and 5.0 months, respectively. (B) Overall survival curves for 122 patients with advanced non-small cell lung cancer, according to Eg5 expression. The median survival periods for Eg5-negative and -positive patients were 13.0 and 10.0 months, respectively. (C) Progression-free survival curves of 122 patients with advanced non-small cell lung cancer, according to cyclin B expression. The median progression-free survival periods of Eg5-negative and -positive patients were 5.0 and 5.0 months, respectively. (D) Overall survival curves for 122 patients with advanced non-small cell lung cancer, according to cyclin B1 expression. The median survival periods for cyclin B1-negative and -positive patients were 13.0 and 8.0 months, respectively.

Eg5 function in centrosome or spindle pole body separation is necessary for bipolar spindle assembly [10].

In normal lung tissue, Eg5 expression was found to be present in some of the cells in the basal bronchial layer of the bronchial epithelium, but its expression in this region was not as strong as in lung cancer tissue. The overexpression of cyclin B1 has been reported in various malignant tumors and has been shown to predict a poor outcome in patients with NSCLC, esophageal carcinoma, and head and neck cancer [16–18]. It has been postulated that the overexpression of cyclin B1 is involved in uncontrolled cell growth and the malignant potential of carcinoma cells. Since the expression of Eg5 in lung cancer tissue has been found to be correlated with the expression of cyclin B1, lung cancer tissue that overexpresses Eg5 in comparison with normal lung tissue is assumed to have greater malignant potential than lung cancer tissue that does not.

Eg5 expression before chemotherapy was correlated with response to chemotherapy and Eg5 status was found to be an independent prognostic factor of response to chemotherapy in a multivariate analysis. Further investigation showed that Eg5 expression was correlated with the response to each type of regimen: the taxan regimens (CDDP + docetaxel: $n = 20$; CBDCA + paclitaxel: $n = 26$; $P = 0.046$), and the vinca alcaroid regimen (CDDP + vinorelbine: $n = 76$; $P = 0.02$) (data not shown). The mechanisms by which Eg5 overexpression affects chemotherapy have not been fully elucidated; nevertheless, Marcus et al. [27] recently reported that mitotic kinesin Eg5 inhibitors induce mitotic arrest and cell death in both paclitaxel-resistant and paclitaxel-sensitive cancer cells and that Eg5 was required for paclitaxel-induced microtubule aster formation (multi-polar spindle configuration) in an *in vitro* assay. They suggested that Eg5 functionality is necessary for paclitaxel-induced mitotic arrest and cell death. These findings may explain our result that Eg5 overexpression before chemotherapy was significantly correlated with response to chemotherapy. The results for docetaxel can be explained in the same manner as for paclitaxel because their modes of action are the same. On the other hand, vinorelbine inhibits the polymerization of tubulin. We suspect that some unknown interaction between tubulin and Eg5 may be modified by vinca alcaloids.

Although Eg5 expression was significantly correlated with response to chemotherapy, the Eg5-positive cases tended to have a poorer outcome in terms of overall survival than the Eg5-negative cases. The reason why the Eg5-positive cases had a poorer outcome remains unclear; despite their higher response to antimitotic agents, Eg5-positive cells may have

Table 4 Multivariate analysis

Variables	Category	Risk ratio	95% CI	P
Multivariate analysis for response of advanced NSCLC patients				
Gender	Male vs. female	0.77	0.245–2.42	0.66
Histology	Sq vs. non-sq	0.89	0.31–2.57	0.83
Stage	IIIB vs. IV	0.64	0.25–1.65	0.35
PS	0 vs. 1	0.98	0.34–2.82	0.97
Smoking history	(−) vs. (+)	0.59	0.18–1.95	0.39
Eg5	(−) vs. (+)	5.16	1.54–17.29	0.008
Cyclin B1	(−) vs. (+)	2.82	0.94–8.45	0.06
Multivariate analysis for PFS of advanced NSCLC patients				
Gender	Male vs. female	0.90	0.56–1.45	0.67
Histology	Sq vs. non-sq	0.89	0.55–1.43	0.63
Stage	IIIB vs. IV	0.60	0.39–0.93	0.02
PS	0 vs. 1	0.92	0.59–1.45	0.72
Smoking history	(−) vs. (+)	0.84	0.51–1.39	0.50
Eg5	(−) vs. (+)	0.77	0.50–1.19	0.24
Cyclin B1	(−) vs. (+)	1.09	0.62–1.89	0.77
Multivariate analysis for OS of advanced NSCLC patients				
Gender	Male vs. female	0.74	0.44–1.26	0.27
Histology	Sq vs. non-sq	1.03	0.63–1.67	0.92
Stage	IIIB vs. IV	0.63	0.41–0.98	0.04
PS	0 vs. 1	0.76	0.47–1.22	0.25
Smoking history	(−) vs. (+)	0.74	0.43–1.30	0.30
Eg5	(−) vs. (+)	0.62	0.39–0.97	0.04
Cyclin B1	(−) vs. (+)	1.03	0.59–1.78	0.93

PFS: progression-free survival; NSCLC: non-small cell lung cancer; PS: performance status; CI: confidence interval; OS: overall survival.

a higher malignant potential, contributing to a poor clinical outcome. This appears to be consistent with the expression of Eg5 being significantly correlated with the expression of cyclin B1, which may be involved in uncontrolled cell growth and the malignant potential of cancer cells.

The inhibition of Eg5 has recently been exploited as an aid to cancer treatment [12–14,27–32], and small cell-permeable molecules that inhibit mitotic kinesin Eg5 and do not target tubulin arrest cells in mitosis with monoastral spindles. Chromosomes in Eg5 inhibitor-treated cells frequently have both sister kinetochores attached to microtubules extending to the center of the monoaster. The mitotic kinesin Eg5 inhibitor also induces apoptosis and is effective in inhibiting the proliferation of cancer cells through mitotic arrest. The first small molecule inhibitor of Eg5 was monastrol [11,12], and second-generation Eg5 inhibitors like CK0106023 [29] and HR22C16 [27], which are specific allosteric inhibitors of Eg5 and exhibit antitumor activity *in vivo* or *in vitro*, have been discovered by drug screens. Therapeutic intervention with Eg5-specific inhibitors has also been reported, and SB-715992 has been shown to be a potent inhibitor of mitotic kinesin Eg5. Eg5 inhibitors may be used as new antimitotic agents to treat advanced NSCLC in the future.

In conclusion, our findings indicated that the expression of the mitotic kinesin Eg5 can predict a response to antimitotic agents combined with platinum chemotherapy among patients with advanced NSCLC. Our results have important implications for the treatment of NSCLC because Eg5 inhibitors, which cause tumor cell apoptosis, may be effective in patients with advanced NSCLC.

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References

[1] Bunn Jr PA, Kelly K. New combinations in the treatment of lung cancer: a time for optimism. Chest 2000;117:138S–43S.
[2] Non Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. BMJ 1995;311:899–909.
[3] Bunn Jr PA. Chemotherapy for advanced non-small-cell lung cancer: who, what, when, why? J Clin Oncol 2002;20:23S–33S.
[4] Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92–8.
[5] Kelly K, Crowley J, Bunn Jr PA, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 2001;19:3210–8.
[6] Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997;111:1710–7.

[7] Long BH, Fairchild CR. Paclitaxel inhibits progression of mitotic cells to G1 phase by interference with spindle formation without affecting other microtubule functions during anaphase and telophase. Cancer Res 1994;54:4355–61.
[8] Milross CG, Mason KA, Hunter NR, et al. Relationship of mitotic arrest and apoptosis to antitumor effect of paclitaxel. J Natl Cancer Inst 1996;88:1308–14.
[9] Tsurutani J, Komiya T, Uejima H, et al. Mutational analysis of the beta-tubulin gene in lung cancer. Lung Cancer 2002;35:11–6.
[10] Anne B, Heldi AL, Pierre D, et al. Phosphorylation by p34cdc2 regulates spindle association of human Eg5, a kinesin-related motor essential for bipolar spindle formation in vitro. Cell 1995;83:1159–69.
[11] Heald R. Motor function in the mitotic spindle. Cell 2000;102: 399–402.
[12] Mayer TU, Kapoor TM, Haggarty SJ, et al. Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen. Science 1999;286:971–4.
[13] Youwei Y, Vinod S, Bei X, et al. Inhibition of a mitotic motor protein: where, how, and conformational consequences. J Mol Biol 2004;335:547–54.
[14] Kapoor TM, Mayer TU, Coughlin ML, et al. Probing spindle assembly mechanisms with monastrol, a small molecule inhibitor of the mitotic kinesin, Eg5. J Cell Biol 2000;150: 975–88.
[15] Doree M, Garas S. The cyclin-dependent protein kinases and the control of cell division. FASEB J 1994;8:1114–21.
[16] Takeno S, Noguchi T, Kikuchi R, et al. Prognostic value of cyclin B1 in patients with esophageal squamous cell carcinoma. Cancer 2002;94:2874–81.
[17] Hassan KA, El-Nagaar AK, Soria JC, et al. Clinical significance of cyclin B1 protein expression in squamous cell carcinoma of the tongue. Clin Cancer Res 2001;7:2458–62.
[18] Soria JC, Jang SJ, Khuri FR, et al. Overexpression of cyclin B1 in early stage non-small cell lung cancer and its clinical implication. Cancer Res 2000;60:4000–4.
[19] Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997;111:1710–7.
[20] Bunn Jr PA, Kelly K. New combinations in the treatment of lung cancer: a time for optimism. Chest 2000;117:138S–43S.
[21] Patrick T, Susan GA, Elizabeth AE, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.
[22] Yoh K, Ishii G, Yokose T, et al. Breast cancer resistant protein impacts clinical outcome in platinum-based chemotherapy for advanced non-small cell lung cancer. Clin Cancer Res 2004;10:1691–7.
[23] Kim YH, Ishii G, Goto K, et al. Dominant papillary subtype is a significant predictor of the response to gefitinib in adenocarcinoma of the lung. Clin Cancer Res 2004;10: 7311–7.
[24] Haque SA, Hasaka TP, Brooks AD, et al. Monastrol, a prototype anti-cancer drug that inhibits a mitotic kinesin, induces rapid bursts of axonal outgrowth from cultured post mitotic neurons. Cell Motil Cytoskel 2004;58:10–6.
[25] Toyoshima F, Moriguchi T, Wada A, et al. Nuclear export of cyclin B1 and its possible role in the DNA damage-induced G2 checkpoint. EMBO J 1998;17:2728–35.
[26] Pines J, Hunter T. The differential localization of human cyclins A and B is due to a cytoplasmic retention signal in cyclin B. EMBO J 1994;13:3772–81.
[27] Marcus AI, Peters U, Thomas SL, et al. Mitotic kinesin inhibitors induce mitotic arrest and cell death in taxol-resistant and -sensitive cancer cells. J Biol Chem 2005;280: 11569–77.
[28] Leizerman I, Avunie-Masala R, Elkabets M, et al. Differential effects of monastrol in two human cell lines. Cell Mol Life Sci 2004;61:2060–70.
[29] Roman S, Jeffery TF, Christophe B, et al. Antitumor activity of kinesin inhibitor. Cancer Res 2004;64:3276–80.
[30] John BM, Colette M, John WF. Transient exposure to the Eg5 kinesin inhibitor monastrol leads to syntelic orientation of chromosomes and aneuroploidy in mouse oocytes. Mutat Res 2004;559:153–67.
[31] Maliga Z, Kapoor TM, Mitchinson TJ. Evidence that monastrol is an allosteric inhibitor of the mitotic kinesin Eg5. Chem Biol 2002;9:989–96.
[32] Kapoor TM, Mayer TU, Coughlin ML, et al. Probing spindle assembly mechanisms with monastrol, a small molecule inhibitor of the mitotic kinesin Eg5. J Cell Biol 2000;150: 975–88.

Is surgical resection indicated for a solitary non–small cell lung cancer recurrence?

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Objectives: Some investigators have reported long-term survival after surgical resection of a solitary non–small cell lung cancer recurrence in various sites. However, the role and indications of the second operation remain unclear.

Methods: We reviewed 28 patients with a solitary recurrence after successful initial resection of primary non–small cell lung cancer who underwent resection of the recurrent lesion. The clinicopathologic factors associated with outcome were analyzed.

Results: There were 17 men and 11 women. Recurrence resection was performed for the following sites: 16 in the lung, 5 in the brain, 2 in the adrenal gland, and 1 each in the chest wall, stomach, skin, pelvic lymph node, and malar bone. The median survival time was 25 months, and the 1-, 2-, and 5-year survival rates after recurrence were 89%, 59%, and 32%, respectively. Advanced p-stage (p-stage II and III, n = 14) of the primary tumor was the significant negative prognostic factor. Patients with p-stage II or III had survival equivalent to that of those who had multiple recurrences or were unfit for further surgical intervention.

Conclusions: Resection of a solitary non–small cell lung cancer recurrence might provide long-term survival in highly selected patients. However, surgical resection might be contraindicated if the primary tumor is stage II or III.

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Five-year survival rates of patients with non–small cell lung cancer (NSCLC) have been disappointing, even after successful complete resection, with about 50% of patients eventually experiencing recurrence and death from the disease.[1] Recurrent lesions are generally multiple and disseminated, and additional surgical intervention is usually not indicated. Some investigators have reported long-term survivals after solitary recurrence resection of the brain, adrenal gland, spleen, liver, and bone.[2-10] However, the role and indication of surgical intervention remain unclear. The aim of this study is to investigate clinicopathologic characteristics of patients with NSCLC who underwent resection of a solitary recurrent lesion and to identify prognostic factors.

Patients and Methods

Patients

We retrospectively reviewed the clinical and pathologic files of 1698 consecutive patients with NSCLC who had undergone complete surgical resection at the National Cancer Center Hospital East from 1989 through 2002. Data collection and analyses were approved, and the need for obtaining informed consent from each patient was waived by the institutional review board in January 2004. Patients with synchronous metastasis (M1) were excluded. Among them, we identified 592 (35%) patients with locoregional or distant recurrence in 2003 or earlier. We excluded patients with second pulmonary lesions that were not clearly distinguished from metachronous second primary NSCLC on the basis of the criteria of Martini and Melamed.[11] Our follow-up procedures included physical examination, chest roentgenogra-