Table 1. Characteristics of treated patients

No. of entered patients	34
No. of treated patients	33
Sex	
Male	26
Female	7
Age (years)	
Median	77
Range	75–86
PS (ECOG)	
0	7
1	26
Histology	
Adenocarcinoma	20
Squamous-cell carcinoma	9
Large-cell carcinoma	3
Non-small-cell	1
Stage	
IIIA	1
IIIB	9
IIIB with effusion	3
IV	17
Relapse	6
Prior treatment	
None	24
Radiotherapy	4
Surgery	6

PS (ECOG): performance status (Eastern Cooperative Oncology Group).

treatments on only days 1 and 15 of the fifth to fifteenth courses. Between the first and fourth cycles, 77–100% of the patients received treatments on days 8 and 15 treatment (Table 2). Of the 303 planned administrations, 272 (90%) were carried out.

The median actual dose intensities of docetaxel and cisplatin were 13.4 mg/m^2 (range 8.9–16.4) and 16.7 mg/m^2 (range 11.1–20.4) per week, whereas the projected dose intensities were 15.0 and 18.8 mg/m^2 per week for docetaxel and cisplatin, respectively.

Objective tumor response and overall survival

The objective tumor response is shown in Table 3. Two CRs and 15 PRs occurred for an objective response rate of 52% (95% CI 31% to 67%) in 33 treated patients. The overall survival periods of all treated patients are shown in Figure 1. The median survival time of the 33 treated patients was 15.8 months with a median follow-up time for 11 censored patients of 18.1 (15.2–35.5) months. The 1-year and 2-year survival rates were 64% and 26%, respectively.

Table 2. Treatment received

No. of treatment cycles	No. of patients	Treatment received on	
		Day 8	Day 15
1	33	31 (94%)	32 (97%)
2	31	28 (90%)	24 (77%)
3	19	19 (100%)	17 (89%)
4	6	5 (83%)	5 (83%)
5	2	1 (50%)	1 (50%)

Toxicity

The worst grades of hematological and non-hematological toxicities experienced by each patient are listed in Table 4. Both hematological and non-hematological toxicities were relatively mild. No grade 4 hematological or non-hematological toxicities were observed. Only grade 3 leukopenia (6%), neutropenia (12%), anemia (3%), hyponatremia (3%) and nausea/vomiting (3%) were observed. None of the patients received G-CSF. Renal toxicity was also relatively mild: grade 2 renal toxicity was observed in only one of 33 patients.

Discussion

We previously reported that classic standard cisplatin-based chemotherapy regimens cause severe myelotoxicity in elderly patients aged ≥75 years [5]. Based on that previous study of elderly patients with NSCLC, we conducted phase I studies in which cisplatin and docetaxel were administered as three consecutive weekly infusions in both non-elderly and elderly patients with NSCLC using the same eligibility criteria, except for age, and the same definitions of dose-limiting toxicity and maximum-tolerated dose [15]. Our hypothesis was that the recommended dose for elderly patients aged ≥75 years would differ from that for non-elderly patients. In the previous phase I studies, we demonstrated a difference in the recommended dose of docetaxel combined with cisplatin between non-elderly and elderly patients [15]. The recommended doses of docetaxel with 25 mg/m^2 cisplatin were 35 and 20 mg/m^2 on days 1, 8 and 15 for non-elderly and elderly patients, respectively. We also conducted phase II studies for non-elderly and elderly patients with NSCLC using each recommended dose and the same eligibility criteria, except for age. The

Table 3. Response rate

No. of patients	CR	PR	NC	PD	NE	Response rate (95% CI)
33	2	15	13	2	1	52% (31% to 67%)

CI, confidence interval; CR, complete response; NC, no change; NE, not evaluable; PD, progressive disease; PR, partial response.

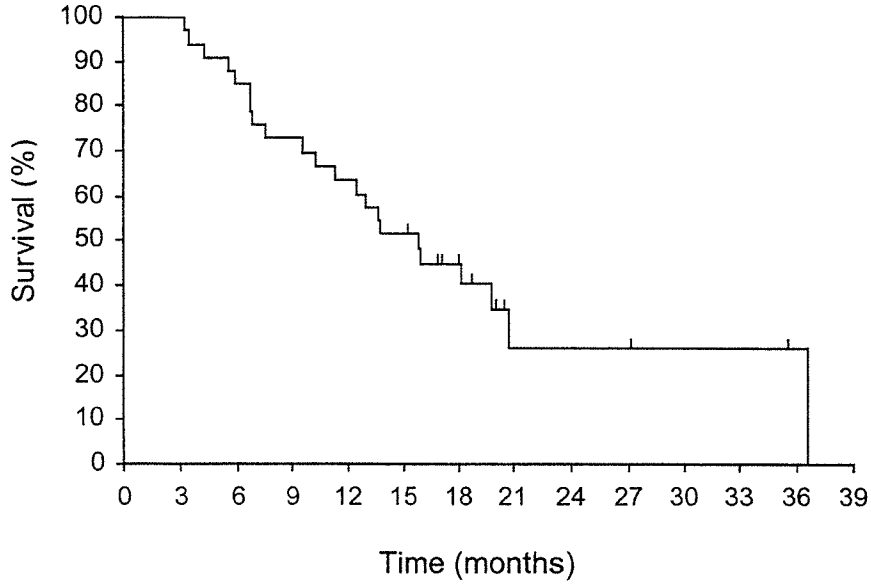

Figure 1. Overall survival time. The median survival time of the 33 treated patients was 15.8 months, and the median follow-up time for 11 censored patients was 18.1 (15.2–35.5) months. The 1-year and 2-year survival rates were 64% and 26%, respectively.

Table 4. Maximum toxicity grades associated with weekly docetaxel and cisplatin in 33 treated patients

	Grade (Japan Clinical Oncology Group)					Grade ≥3
	0	1	2	3	4	
Leukopenia	13	6	12	2	0	6%
Neutropenia	16	5	8	4	0	12%
Anemia	9	8	15	1	–	3%
Thrombocytopenia	30	2	1	0	0	0
Nausea/vomiting	12	10	10	1	–	3%
Hyponatremia	22	8	2	1	0	3%
Diarrhea	23	6	4	0	0	0
Infection	32	1	0	0	0	0
Fever	27	4	2	0	0	0
Bilirubin	25	–	8	0	0	0
Transaminase	25	8	0	0	0	0
Creatinine	28	4	1	0	0	0
Fatigue	26	6	1	0	0	0

results of the phase II study for non-elderly patients with NSCLC have been reported elsewhere [16]. Among the 33 evaluable patients, an objective tumor response of 30% (95% CI 15% to 46%) and a median survival time of 12.8 months were observed [16]. In the current study, we observed an objective tumor response of 52% (95% CI 31% to 67%) and a median survival time of 15.8 months for elderly patients with NSCLC. In spite of the lower dose of docetaxel, the efficacy of the treatment did not seem to be diminished.

Italian oncology groups have conducted randomized trials for elderly patients aged ≥70 years [21–23]. In these studies, non-platinum-based single or double chemotherapy regimens, such as vinorelbine alone or vinorelbine plus gemcitabine were used for elderly patients with NSCLC [21–23]. These chemotherapy regimens might not be adequate for non-elderly patients with a good PS because the cisplatin plus vinorelbine regimen was significantly superior to vinorelbine alone with regard to both the response rate and the survival [24, 25]. Kubota et al. [26] reported that the frequency of grade 4 leukocytopenia in the elderly (≥70 years of age) group was significantly greater than in the non-elderly group and that no difference in overall survival was observed between the two groups. Langer et al. [27] reported that advanced age alone

Table 5. Chemotherapy for elderly patients with non-small-cell lung cancer

Study	Chemotherapy	Age (years)	No. of patients	PS 2 (%)	Stage III (%)	RR (%)	MST
ELVIS [21]	None	≥70	78	24	28	–	21 weeks
	VNR 30 mg/m^2 days 1, 8 q3 weeks		76	24	26	20	28 weeks
	VNR 30 mg/m^2 days 1, 8 q3 weeks		233	19	29	18	36 weeks
MILES [22]	GEM 1200 mg/m^2 days 1, 8 q3 weeks	≥70	233	18	30	16	28 weeks
	GEM 1000 mg/m^2 + VNR 25 mg/m^2 days 1, 8 q3 weeks		232	19	31	21	30 weeks
SICOG [23]	VNR 30 mg/m^2 days 1, 8 q3 weeks	≥70	60	22	42	15	18 weeks
	GEM 1200 mg/m^2 + VNR 30 mg/m^2 days 1, 8 q3 weeks		60	27	40	22	29 weeks
MPCRN [29]	DTX 36 mg/m^2 weekly × 6 q8 weeks	≥65[a]	39	41	31	18	5 months
Current study	CDDP 25 mg/m^2 + DTX 20 mg/m^2 days 1, 8, 15 q4 weeks	≥75	33	0	29	52	15.8 months (69 weeks)

[a]Or poor candidates for combination chemotherapy due to coexistent medical illness.
ELVIS, The Elderly Lung Cancer Vinorelbine Italian Study; MILES, Multicenter Italian Lung Cancer in the Elderly Study; SICOG; Southern Italy Cooperative Oncology Group; MPCRN, Minnie Pearl Cancer Research Network.
CDDP, cisplatin; DTX, docetaxel; GEM, gemcitabine; VNR, vinorelbine.
MST, median survival time; PS, performance status; RR, response rate.

should not preclude appropriate NSCLC treatment, although elderly patients aged ≥70 years have more co-morbidities and can expect a higher incidence of leukopenia and neuropsychiatric toxicity. In the United States, upper age limits are not included in eligibility criteria to avoid age discrimination. In contrast, most Japanese studies have upper age limits because Japanese government guidelines recommend that elderly patients, >75 years, should not be accrued in common clinical trials [28]. This recommendation was made in concern for the safety of elderly patients. In Japan, most clinical trials include patients aged ≤74 years, and the full-dose chemotherapy is administered. Clinical trials for elderly patients have generally been conducted as specific trials focusing on the treatment of elderly patients in Japan. However, the definition of 'elderly' is still unclear. Thus, the use of platinum-based chemotherapy in elderly patients with NSCLC remains controversial because no randomized phase III studies have been conducted to resolve this question.

Several chemotherapy trials for elderly patients with NSCLC have been reported [21–23, 29] (Table 5). Of the subjects in these trials, 18–41% were PS 2 patients. Eligible patients were 70 or 65 years or older. The response rates of the non-platinum-based single or double chemotherapy regimens ranged from 15% to 22%, and the median survival times ranged from 18 to 36 weeks [21–23, 29]. In the current study, however, PS 2 patients were excluded and only patients aged ≥75 years were included. The objective response rate of 52% (95% CI 31% to 67%) and the median survival time of 15.8 months (69 weeks) in our trial were extremely better than those of previous trials. We considered that the main reason for the better results was the exclusion of PS 2 patients. However, cisplatin chemotherapy might be important not only for non-elderly, but also for elderly patients with NSCLC.

We divided the cisplatin and docetaxel dosages on days 1, 8 and 15 because full-dose cisplatin is too toxic for elderly patients. The weekly administration of docetaxel produces a higher dose intensity and less myelotoxicity [12–14]. Moreover, a weekly schedule may be safer than a 3-weekly schedule because treatment on day 8 and/or day 15 can be omitted if severe toxicity is observed. In the current study, the toxicity, including nausea/vomiting and renal toxicity, was relatively mild, and 90% of the planned administrations were carried out. The dose-limiting toxicities of docetaxel administered in six consecutive weekly infusions were reported to be fatigue and asthenia [12–14]. In the previous phase I study, two out of six patients refused chemotherapy on day 15 because of fatigue and asthenia at level 2: 25 mg/m^2 cisplatin and 25 mg/m^2 docetaxel [15]. However, fatigue and asthenia were relatively mild in the current study because of the relatively low-dose of docetaxel (20 mg/m^2).

We conclude that cisplatin and docetaxel administered as three consecutive weekly infusions is very effective and safe for elderly patients with chemotherapy-naive NSCLC. The JCOG is conducting a phase III study of cisplatin and docetaxel versus docetaxel alone, administered as three consecutive weekly infusions, for elderly patients with NSCLC to examine the role of cisplatin in the treatment of elderly patients with NSCLC.

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Pleural Lavage Cytology Before and After Lung Resection in Non-Small Cell Lung Cancer Patients

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Background. The aim of this study was to analyze on a multivariate basis the prognostic significance of pre-resection and post-resection pleural lavage cytologies in surgically resected primary non-small cell lung cancer (NSCLC) patients, in relation to pathologic TNM factors in a large cohort of almost 1,200 patients.

Methods. From August 1992 through March 2001, pleural lavage cytology (PLC) was performed in 1,214 NSCLC patients without pleural effusion or dissemination undergoing pulmonary resection. The cytologic evaluation was classified into three categories: negative, suggestive, and positive. To investigate the impact on patient survival, PLC results were analyzed with conventional clinicopathologic factors.

Results. Definitive pre-resection PLC result was obtained in 1,194 patients and 38 had a positive result. The 5-year survival rates were 27% if pre-resection PLC was positive and 71% if negative. Of 1,198 patients 54 had a positive post-resection PLC result. The 5-year survival rates were 10% if post-resection PLC was positive and 73% if negative. On multivariate analysis, post-resection PLC was an independent prognostic factor as significant as established clinicopathologic factors.

Conclusions. Pre-resection and post-resection PLC should be recognized as an essential prognostic factor and should be performed in NSCLC patients without pleural effusion and dissemination. Post-PLC, compared with pre-PLC, had a greater and independent impact on survival and needs to be incorporated in the pathologic staging of NSCLC in the future.

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Pleural lavage cytology (PLC) has been reported to be a possible prognostic factor in patients with resected non-small cell lung cancer (NSCLC). However, many of the reports are that only PLC immediately after thoracotomy, before lung resection, (pre-PLC) has been studied in detail. The pre-PLC impact on patient outcome has been studied, chiefly, on a univariate basis and has not been studied in relation to the conventional pathologic TNM by multivariate analysis. Although pre-PLC has been reported to be a poor prognosis predictor, a positive result is currently not recognized as equivalent to T4 or a factor indicating incomplete resection. Although PLC after radical NSCLC resection, before chest closure, (post-PLC) has also been studied, significance of post-PLC remains controversial. Higashiyama and associates [1] performed pre-PLC and post-PLC in 325 lung cancer patients, but neither pre-PLC nor post-PLC results were an independent prognostic factor. Dresler and associates [2], who reported the pre-PLC and post-PLC analysis in 137 patients, stated that the 3-year survival rate was significantly better in negative post-PLC patients than in positive patients. We thought further analyses on post-PLC were needed. In the present study, we analyzed both pre-PLC and post-PLC on a multivariate basis, in relation to pathologic TNM factors in a large cohort of almost 1,200 patients.

Material and Methods

From August 1992 through March 2001, a total of 1,387 patients underwent surgical resection for primary NSCLC at the National Cancer Center Hospital East. Intraoperative PLC, which was approved for this observational study by the institutional review board, was prospectively performed in all patients without pleural effusion and dissemination, totaling 1,214 patients, and all were enrolled in this study. As the largest sample size for PLC study was 1,000 before this study, we aimed at accruing well more than 1,000 patients before analysis. Preoperative evaluation included a detailed history, physical examination, bronchoscopy, contrast-enhanced computed tomography (CT) of the chest, and distant metastasis screening (bone, brain, liver, and adrenals). Histologic typing was determined according to the World Health Organization classification [3]. Disease stages were determined based on the TNM classification of the International Union Against Cancer [4]. Immediately after

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thoracotomy, the pleural cavity was carefully washed with 500 mL physiologic saline before any pulmonary parenchyma manipulation. A sample of 50 mL was retrieved for cytologic evaluation (pre-PLC). We performed lung resection (segmentectomy or greater) and complete mediastinal lymph node dissection in 1,199 patients, and lung resection and mediastinal lymph node sampling in 15 patients. Before chest closure, a pleural cavity lavage sample was also retrieved (post-PLC) in the same fashion as pre-PLC. Samples were centrifuged at 1,500 rpm for 5 minutes. The sediment was stained using Papanicolaou's methods. A single cytologist blinded to the clinical-pathologic information evaluated the specimen and classified it into three categories: Papanicolaou classes I and II as negative, class III as suggestive, and classes IV and V as positive. In the survival analyses, we studied only cases with definitive cytologic diagnoses, excluding Papanicolaou class III. To investigate the impact on patient survival, the following conventional clinicopathologic factors were reviewed and analyzed: age, gender, smoking index (< 400 vs ≥ 400), serum carcinoembryonic antigen (CEA) level (< 5.0 mg/mL vs ≥ 5.0 mg/mL), clinical T factor (cT: cT2-4 vs cT1), clinical lymph node status (cN: mediastinal node involvement as cN2 vs less extensive as cN0-1), histologic type of tumor (adenocarcinoma versus others), pleural involvement of surgical (sP0-1 vs sP2-3) and pathologic finding (p0 vs p1-3), lymphatic invasion (positive versus negative), vascular invasion (positive versus negative), pathologic N status (pN: pN2-3 vs pN0-1), degree of fibrotic scarring (scar grade 1-2 vs grade 3-4), nuclear atypia (grade 1 or 2 vs grade 3), mitotic activity (mitotic index 1 or 2 vs 3), and surgical resection completeness (incomplete versus complete). Complete resection was defined as negative surgical margin and no highest mediastinal lymph node involvement. Incomplete resection was defined as positive surgical margin or highest mediastinal lymph node involvement. The smoking index was defined as the product of the number of cigarettes smoked per day and the number of years of smoking. We defined cN2 as mediastinal lymph node(s) greater than 1.0 cm in the shortest dimension on preoperative conventional CT. Pleural involvement was classified according to the Japan Lung Cancer Society criteria: p0; tumor did not extend beyond the elastic pleural layer, p1; tumor invaded the visceral pleura elastic layer but was not exposed on the pleural surface, p2; tumor was exposed on the pleural surface and p3; tumor invaded the parietal pleura or chest wall. Surgeons determined pleural involvement (sP factor) macroscopically before resection. Pathologic pleural involvement (p factor) were diagnosed on the resected specimens by a single pathologist blinded to the surgeons' findings [5]. Lymphatic invasion and vascular invasion indicated tumor cells identifiable in the lymphatic and vascular vessel lumen, respectively. Scar grade was classified into 4 grades: grade 1; tumor had foci of alveolar collapse with resulting condensation of elastic fibers but no or minimal fibroblastic tissue with collagen, grade 2; tumor had fibroblastic tissue with a small amount of collagen fibers, grade 3; tumor had fibroblastic tissue with moderate or abundant amount of collagen fibers, and grade 4; tumor showed hyalinization [6]. Nuclear atypia categorization was based on the most atypical nuclei on sections and divided into 3 grades as follows: grade1; nuclei that were uniform in size and equal to or only slightly larger than those of reactive type II alveolar epithelial

Table 1. Patient Characteristics ($n = 1,214$)

Characteristics	Results	
Gender		
Male	781	(64)
Female	433	(36)
Histology		
Adenocarcinoma	792	(65)
Squamous cell carcinoma	284	(23)
Others	138	(12)
Clinical T factor		
T1	593	(49)
T2	490	(40)
T3	111	(9)
T4	20	(2)
Clinical N factor		
N0	1,005	(83)
N1	116	(10)
N2	92	(8)
N3	1	(<1)
Clinical stage		
IA	550	(45)
IB	376	(31)
IIA	17	(1)
IIB	129	(11)
IIIA	113	(9)
IIIB	24	(2)
IV	5	(<1)
Pathologic T factor		
T1	543	(45)
T2	434	(36)
T3	126	(10)
T4	111	(9)
Pathologic N factor		
N0	801	(66)
N1	204	(17)
N2	202	(17)
N3	7	(1)
Pathologic stage		
IA	438	(36)
IB	256	(21)
IIA	51	(4)
IIB	147	(12)
IIIA	196	(16)
IIIB	113	(9)
IV	13	(1)

(Numbers in parentheses are percentages)

Table 2. Pre-PLC Result and Clinicopathologic Characteristics

Factors	Pre-PLC (n = 1,194)		P Value
	Positive (n = 38)	Negative (n = 1,156)	
Age	63	63	0.740
Gender			
Male	25	746	
Female	13	410	0.873
Treatment modality (resection type)			
Lobectomy	34	1,049	
Pneumonectomy	1	64	0.177
Limited resection	3	43	(limited resection vs others)
Pathologic stage			
I	16	667	
II	3	193	0.056
III	19	283	(stage I vs others)
IV	0	13	
Histology			
Adenocarcinoma	26	751	
Squamous cell carcinoma	6	274	0.660
Large cell carcinoma	3	47	(adenocarcinoma vs others)
Other	3	84	
Pathologic pleural involvement			
p0	11	754	
p1–3	27	402	<0.001
Pathologic N status			
N0	17	774	
N1–3	21	382	0.041
Lymphatic invasion			
Positive	27	481	
Negative	11	675	<0.001
Vascular invasion			
Positive	30	633	
Negative	8	523	0.003
Resection completeness			
Complete	28	1,067	
Incomplete	10	89	<0.001
Scar grade			
1–2	0	191	
3–4	35	844	0.001
NA	3	121	
Nuclear atypia			
1–2	15	432	
3	20	607	0.863
NA	3	117	
Mitotic index			
1–2	26	813	
3	9	226	0.539
NA	3	117	

NA = data not available.

cells, grade 2; nuclei that were uniform in size and up to twice the size of those of reactive type II alveolar epithelial cells, and grade 3; presence of giant tumor cells. Mitotic index was classified into three grades based on the findings of several sections: index 1; up to 5 mitotic cells per 10 high-power fields (HPF), index 2; 6–15 mitotic cells per 10 HPF, and index 3; greater than 15 mitotic cells per 10 HPF [7]. The length of survival was defined as the interval in months between the day of surgical intervention and the date of death due to

Table 3. Post-PLC Results and Clinicopathologic Characteristics

Factors	Post-PLC (n = 1,182)		
	Positive (n = 54)	Negative (n = 1,128)	*p* Value
Age	61	63	0.363
Gender			
Male	37	725	
Female	17	403	0.524
Treatment modality (resection type)			
Lobectomy	48	1,026	
Pneumonectomy	2	63	0.129
Limited resection	4	39	(limited resection vs others)
Pathologic stage			
I	7	673	
II	3	191	<0.001
III	42	253	(stage I vs others)
IV	2	11	
Histology			
Adenocarcinoma	41	731	
Squamous cell carcinoma	4	270	0.094
Large cell carcinoma	4	46	(adenocarcinoma vs others)
Other	5	81	
Pathologic pleural involvement			
p0	26	732	
p1–3	28	396	0.019
Pathologic N status			
N0	10	776	
N1–3	44	352	<0.001
Lymphatic invasion			
Positive	43	463	
Negative	11	665	<0.001
Vascular invasion			
Positive	41	614	
Negative	13	514	0.002
Resection completeness			
Complete	25	1,001	
Incomplete	29	127	<0.001
Scar grade			
1–2	3	186	
3–4	47	821	0.022
NA	4	121	
Nuclear atypia			
1–2	18	423	
3	32	588	0.465
NA	4	117	
Mitotic index			
1–2	42	790	
3	8	221	0.382
NA	4	117	

NA = data not available.

any cause or the last follow-up. An observation was censored at the last follow-up when the patient was alive or lost to follow-up. The survival rates were calculated by the Kaplan-Meier method [8] and univariate analyses were performed by means of the log-rank test. Multivariate analyses were performed using the Cox proportional hazards model [9]. Forward and backward stepwise procedures were used to determine the combination of prognostic factors (StatView: version 5.0; SAS Institute, Inc, Cary, NC). A *p*

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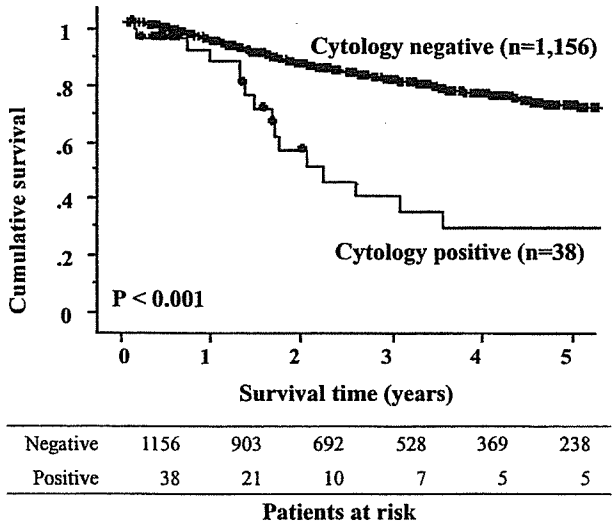
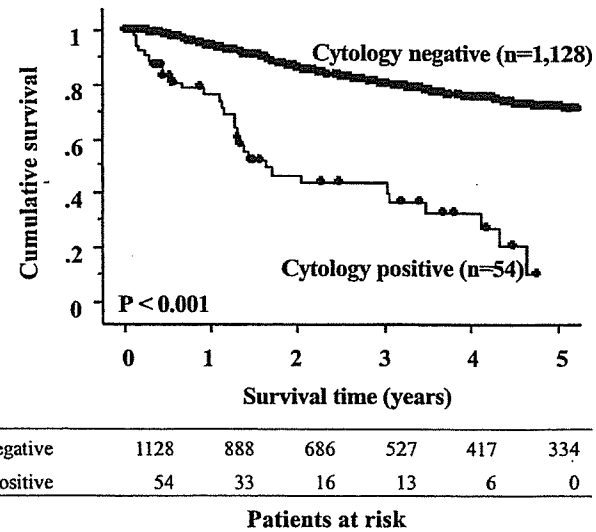


Negative	1156	903	692	528	369	238
Positive	38	21	10	7	5	5

Patients at risk

Fig 1. Survival curves of patients according to pre-PLC results. The 5-year survival rate was 27% for positive pre-PLC patients and was significantly worse (71%) for negative pre-PLC patients. The crosses indicate censored cases at the respective points. (PLC = pleural lavage cytology.)



Negative	1128	888	686	527	417	334
Positive	54	33	16	13	6	0

Patients at risk

Fig 2. Survival curves of patients according to post-PLC results. The 5-year survival rate was 10% for positive post-PLC patients and was significantly worse (73%) for negative post-PLC patients. The crosses indicate censored cases at the respective points. (PLC = pleural lavage cytology.)

value less than 0.05 was taken to indicate a statistical significance.

Results

Patient clinicopathologic characteristics are shown in Table 1. There were 781 men and 433 women. Their ages ranged from 22 to 89, with a median of 65 years. Clinicopathologic characteristics for pre-PLC and post-PLC are shown in Tables 2 and 3, respectively. For pre-PLC, definitive cytologic results were obtained in 1,194 patients, with a positive result in 38 (3.2%). Univariate analyses revealed significant differences between pre-PLC positive and negative patients in pathologic pleural involvement, pathologic N status, lymphatic permeation, vascular invasion, resection completeness, and scar grade. For post-PLC, definitive cytologic result was obtained in 1,182 patients, 54 (4.6%) of which showed a positive result. Significant differences were observed in pathologic stage, pathologic pleural involvement, pathologic N status, lymphatic permeation, vascular invasion, resection completeness, and scar grade between post-PLC positive and negative patients. The 5-year survival rate was 27% for positive pre-PLC patients, which was significantly worse than 71% for negative pre-PLC patients (Fig 1). The 10% 5-year survival rate for positive post-PLC patients was significantly worse 73% for negative post-PLC patients (Fig. 2).

Five-year survival rates for patients with negative pre-PLC and post-PLC (n = 1,094), positive pre-PLC and negative post-PLC (n = 21), negative pre-PLC and positive post-PLC (n = 37), and positive pre-PLC and positive post-PLC (n = 13) were 81, 50, 12, and 0%, respectively. Multivariate analyses revealed 6 independent prognostic factors when only factors available before lung resection were analyzed (Table 4): age, CEA level, cT factor, cN factor, sP factor, and pre-PLC result. When factors available after postoperative pathologic evaluation were included in multivariate analyses, however, 10 independent prognostic factors were recognized, but pre-PLC result was not (Table 5): Age, CEA level, cT factor, pT factor, pN factor, p factor, lymphatic invasion, vascular invasion, resection completeness, and post-PLC result.

Comment

The first report on PLC was in 1958 by Spjut and associates [10]. They reported the results of post-PLC in 49 patients with lung cancer undergoing surgical resection. The cytologic results were positive for malignant cells in 16 (33%) of them, but outcomes were not analyzed. In 1984, Eagan and colleagues [11] reported positive post-PLC in 12 (8.9%) of 135 patients. Lung cancer recurred in nine of the 12 patients, with only two in the

Table 4. Multivariate Analysis Results for Prognostic Factors Available Before Lung Resection

Variable	Hazard Ratio (95% CI)	*p* Value
Age	1.020 (1.006–1.035)	0.005
Gender	0.958 (0.638–1.436)	0.833
Smoking (S.I > 400)	0.963 (0.648–1.433)	0.853
CEA	1.732 (1.320–2.272)	<0.001
cT factor (2–4 vs 1)	0.624 (0.475–0.814)	0.002
cN factor (1–3 vs 0)	0.512 (0.379–0.691)	<0.001
sP factor (2–3 vs 1–2)	0.621 (0.475–0.814)	<0.001
Pre-PLC	2.980 (1.683–5.277)	<0.001

CEA = serum carcinoembryonic antigen; CI = confidence interval; PLC = pleural lavage cytology; S.I = smoking index.

Table 5. Multivariate Analysis Results Including Factors Available After Lung Resection

Variable	Hazard Ratio (95% CI)	*p* Value
Age	1.021 (1.006–1.037)	0.006
CEA	1.301 (0.970–1.744)	0.079
cT factor (2–4 vs 1)	0.971 (1.411–2.051)	0.071
cN factor (1–3 vs 0)	0.951 (0.652–1.388)	0.796
sP factor (1–3 vs 0)	1.244 (0.834–1.856)	0.284
pT factor (2–4 vs 1)	1.285 (1.181–1.399)	<0.001
pN factor (1–3 vs 0)	0.446 (0.316–0.629)	<0.001
p factor (1–3 vs 0)	0.726 (0.527–1.001)	0.050
Histology (Ad.[a] vs others)	1.100 (0.769–1.573)	0.602
Lymphatic invasion	1.495 (1.058–2.114)	0.023
Vascular invasion	2.161 (1.410–3.311)	<0.001
Scar grade (3–4 vs 1–2)	0.792 (0.453–1.383)	0.412
Nuclear atypia (3 vs 1–2)	0.634 (0.447–0.898)	0.010
Mitotic index (3 vs 1–2)	0.875 (0.617–1.239)	0.452
Resection completeness	0.676 (0.472–0.968)	0.033
Pre-PLC	1.833 (0.949–3.541)	0.071
Post-PLC	1.803 (1.077–3.018)	0.024

Ad.[a] = adenocarcinoma; CEA = serum carcinoembryonic antigen; PLC = pleural lavage cytology.

ipsilateral pleural space. Eight patients died of lung cancer, one recurring locally and seven having distant metastases. They concluded the prognostic role of PLC needed further study. The first report on pre-PLC was by Kondo and associates in 1989 [12], followed by their expanded result analyses in 1993 [13]. They reported that 42 (9.0%) of 467 lung cancer patients undergoing surgery with little or no pleural effusion had a positive pre-PLC result. The 3-year survival rates of the patients with negative and positive cytology results were 68.7% and 22.9%, respectively. The prognosis of the positive cytology group was as poor as that of stage IIIB or IV patients. They concluded that pre-PLC was an important prognostic factor, indicating microscopic cancer cell exfoliation into the pleural cavity and subclinical malignant pleural effusion. Okada and associates [14] reported, based on 1,000 patients in 2003, that 45 (4.5%) patients had positive pre-PLC findings. Positive cytologic findings were observed more frequently in patients with adenocarcinoma, advanced stage, extended lymph node involvement, pleural involvement, lymphatic invasion, vascular invasion, high serum CEA level, and male gender. The survival rate at 5 years was 28% in patients with a positive result and 67% in negative patients ($p < 0.001$). Multivariate analysis demonstrated that pre-PLC was an independent prognostic determinant ($p = 0.0290$). Higashiyama and associates [1] performed pre-PLC and post-PLC in 325 lung cancer patients without malignant pleurisy. Positive post-PLC patients especially with adenocarcinoma resulted in a poor outcome. The survival rate at 5 years was 71% in 250 patients with negative pre-PLC and post-PLC results, while it was 33% in 19 patients with positive results. However, in multivariate analyses, neither pre-PLC nor post-PLC result was an independent prognostic factor in their study. Dresler and associates [3] reported the pre-PLC and post-PLC analysis in 137 patients in 1999. The 3-year survival rates of the patients with negative and positive pre-PLC results were 55% and 0%, respectively ($p = 0.088$). The 3-year survival rates of the patients with negative and positive post-PLC results were 50% and 0%, respectively ($p < 0.04$). In the present study, we analyzed both pre-PLC and post-PLC in almost 1,200 patients, the largest cohort ever studied with regard to PLC. Both pre-PLC and post PLC were analyzed in a multivariable setting, together with conventional significant clinicopathologic prognostic factors we reported previously [15]. Although our study yielded results similar to previous studies and post-PLC proved to be an important prognostic predictor, we found no difference in PLC results in relation to histologic characteristics. There have been a considerable number of reports concluding positive pre-PLC to be a poor prognosis predictor since pre-PLC was first reported by Kondo and associates in 1989 [12]. However, positive pre-PLC is currently not recognized as equivalent to T4 or a factor indicating incomplete resection [16–18]. In our study, pre-PLC was an independent prognostic factor when analyzed with prognostic factors available before lung resection, but not when postoperative pathologic factors and post-PLC results were combined in analyses. Positive pre-PLC patient outcome, when post-PLC was negative, was not very poor, with the 5-year survival rate reaching almost 60%. Therefore, positive pre-PLC result alone does not contraindicate surgical resection. In contrast, post-PLC proved to be an independent prognostic factor as significant as other established prognostic factors, including pathologic TNM status. No positive post-PLC patients survived beyond 4 years. As the patient outcome was extremely poor when pre-PLC was also positive, adjuvant therapy may be needed in these patients. We conclude PLC should be recognized as an essential prognostic factor and should be performed in NSCLC patients without pleural effusion and dissemination. And post-PLC, compared with pre-PLC, had a greater and independent impact on survival and needs to be incorporated in the pathologic staging of NSCLC in the future. As Vicidomini and associates referred to in their recent article on PLC [19], the results of the American College of Surgeons Oncology Group's Z0040 trial, which has completed a 1,200 patient accrual, will further define the potential implications of PLC in the management of lung cancer.

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Original Article

The Lung Cancer Database Project at the National Cancer Center, Japan: Study Design, *Corresponding Rate* and Profiles of Cohort

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Background: The lung cancer database project was established in 1999 at the National Cancer Center Hospital East, Japan, as an ongoing project to integrate data on various factors in lung cancer patients. The aim of the project was to construct a *large-scale cancer registry* for lung cancer that would contribute to basic research and clinical research in the future.
Methods: Between July 1999 and July 2004, consecutive lung cancer patients were recruited into this project. The baseline survey consisted of self-administered questionnaires concerning various demographic data, health habits and psychological factors. Medical information was obtained from the patients' medical charts. Urine specimens and blood samples were collected, and DNA was extracted from blood lymphocytes.
Results: Out of the 2506 patients who were asked to participate in the project, 2036 (81%) patients with newly diagnosed, untreated primary lung cancer were enrolled. The final analytic cohort consisted of 1995 patients. Virtually all of the 1995 patients (*corresponding rate*, 99%) completed the questionnaires on demographic data and health habits. The corresponding rates for the questionnaires on psychological factors and dietary habits were 99 and 94%, respectively. In a follow-up survey conducted to determine vital status as of December 2004, a total of 1051 patients (53%) had died and 44 patients (2%) were lost to follow-up.
Conclusions: This paper overviews the rationale for initiating the lung cancer database project, Japan. This database should prove useful for researchers examining the pathogenesis of lung cancer and may contribute to the formulation of a framework for cancer treatment.

Key words: follow-up survey – health habits – large-scale cancer registry – lung cancer – psychological factors

INTRODUCTION

Lung cancer is the most common form of cancer and the most common cause of cancer-related deaths throughout the world (1,2). In Japan, lung cancer is the leading cause of death from cancer among men and women, and the incidence of lung cancer has been increasing in recent years (3). In 2003, the number of lung cancer deaths reached 41 615 (22% of all cancer-related deaths) in men and 15 086 deaths (12% of all cancer-related deaths) in women (3). Lung cancer is often resistant to treatment, so research programs designed to share epidemiologic, psychosocial and molecular biology data are needed to improve treatment efficacy and patient outcome. It is difficult to determine the factors associated with lung cancer outcome because of the marked clinical heterogeneity of patients. In earlier reports, various individual characteristics like age, sex, pathologic stage, performance status, co-morbidity, molecular biological markers, marital status, psychological factors and smoking status have all been implicated to contribute to the survival rate in lung cancer (4–7). Further clarification of the factors contributing to survival from lung cancer is needed.

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Approximately 400 newly diagnosed primary lung cancer patients visit the National Cancer Center Hospital East (NCCHE), Japan, for treatment each year. In 1999, the Lung Cancer Database Project was initiated as an ongoing project to integrate information on various factors in lung cancer patients. The aim of the project was to construct a large-scale cancer registry for lung cancer that would contribute to basic research and clinical research in the future. In addition, by investigating the factors that influence the outcome of patients with lung cancer, we hoped to clarify several specific points related to cancer treatment in order to improve patient outcome.

This paper describes the epidemiological background and the study design, the questionnaire corresponding rates, the cohort profile and the survival rates obtained in a follow-up survey of patients in the Lung Cancer Database Project.

METHODS

Study Setting

The NCCHE was founded in the city of Kashiwa in suburban eastern Japan on July 1, 1992. The NCCHE has 425 beds and consists of 9 clinical divisions. As of January 1, 2005, the hospital staff included 73 physicians, 17 pharmacists and 268 nurses. During 2004, this hospital took care of 146 802 outpatients, including 7706 newcomers and 7506 inpatients.

Study Cohort

The project was approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center, Japan (in March, 1999). The Japanese Ministry of Health, Labour and Welfare established the two guidelines that follow ['the Ethical Guidelines Concerning Human Genome and Gene Analysis' (in March, 2001) and 'the Ethical Guidelines Concerning Epidemiologic Study' (in June, 2002)]. (http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/ekigaku/dl/shinkyu.pdf http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/genome/dl/shinkyu.pdf).

When we planned a new study based on this project, the study needed to be approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center, Japan. Moreover, the study followed two guidelines by the Japanese Ministry of Health, Labour and Welfare.

Data from subjects who participated in the Lung Cancer Database Project at the NCCHE and at the National Cancer Center Research Institute East were used in this study. We distributed two self-administered questionnaires to the patients before the start of cancer treatment (at baseline). The first questionnaire included questions on various demographic data, health habits and psychological factors (including the Mental Adjustment to Cancer Scale, the Eysenck Personality Questionnaire-Revised and the Hospital Anxiety and Depression Scale), and the second was on dietary habits (the Food Frequency Questionnaire). Medical information was obtained from the patients' medical charts. After admission but before cancer treatment, urine specimens and blood samples were collected, and DNA was extracted and collected from blood lymphocytes. These samples were stored at 80 C until further use. We previously reported part of the information in a project (8).

The subjects enrolled in this study were all newly diagnosed primary lung cancer patients, who had visited the Division of Thoracic Oncology of the NCCHE, Japan. Patients were included in this database study if they met all of the following criteria: knowledge of their lung cancer diagnosis; new diagnosis of primary lung cancer; physically capable of completing the questionnaires; absence of cognitive impairment (i.e. dementia, delirium); ability to provide written consent; and no problems regarding the patients' participation in this project, as judged by their physicians.

Study Procedure

In the initial study plan, the sample size and accumulation period were decided as 1500 patients and 5 years, respectively. Approximately 400 newly diagnosed patients with primary lung cancer visit the NCCHE each year. We estimated that the rate of ineligible patients and/or patients who would refuse to participate in the project would be 25%.

Between July 1999 and July 2004, consecutive patients eligible for the project were recruited after disclosure of their diagnosis by their attending physician. The patients completed the questionnaires during the waiting period before admission, and the questionnaires were collected after the patients were admitted. All patients provided their written informed consent prior to enrolment in this project.

MEASUREMENTS

Demographic Data And Medical Information

Demographic factors (age at time of cancer diagnosis, sex, education level, marital status, smoking history, past history of cancer and family history of cancer) and medical information (histology, clinical stage, pathologic stage, cancer treatment of first line, performance status and symptoms) were obtained from the self-administered questionnaires and the patients' medical charts. Performance status (PS) was assessed by each attending physician using the Eastern Cooperative Oncology Group criteria (9).

Fagerström Tolerance Questionnaire [FTQ]/ Fagerström Test for Nicotine Dependence

Nicotine dependence was evaluated using the Fagerström Tolerance Questionnaire (FTQ) and the Fagerström Test for Nicotine Dependence (FTND). In 1978, Fagerström developed a self-rating scale (the FTQ) to assess nicotine dependence and used the questionnaire in a smoking cessation clinic (10). As a revised version of the FTQ, the FTND was developed by Heatherton et al. in 1991 (11). The Japanese version of the

FTND is a reliable and valid measure of nicotine dependence in patients with smoking-related cancers (12).

Mental Adjustment to Cancer (MAC) Scale

The patients' psychological response to their cancer diagnosis was measured using the Japanese version of the MAC scale, a 40-item, self-rating scale developed in England (13). The scale consists of five subscales: fighting spirit (16 items), anxious preoccupation (9 items), fatalism (8 items), helplessness/hopelessness (6 items) and avoidance (1 item). The respondents were asked to read a number of statements that might describe their reactions to having cancer and to circle the number indicating the degree to which each statement applied to them. Each item was rated on a scale of 1–4, ranging from 'definitely does not apply to me' to 'definitely applies to me'. Previous studies have revealed that the MAC scale is adequately valid and reliable (14).

Eysenck Personality Questionnaire-Revised

Personality was evaluated using the Eysenck Personality Questionnaire-Revised (EPQ-R). The Japanese translation of the original English version of the EPQ-R Short Form is one of a series of personality inventories developed by Eysenck and colleagues (15). It contains 48 questions with dichotomized responses (yes or no); there are 12 questions for each of the four subscales (extraversion, neuroticism, psychoticism and lie). The scores on each subscale ranged from 0 to 12, with higher scores indicating a greater tendency to possess the personality trait represented by each subscale. Extraversion represents sociability, liveliness and assurgency; neuroticism represents emotional instability and anxiousness; psychoticism represents tough-mindedness, aggressiveness, coldness and egocentricity; and lie represents unsophisticated dissimulation and social naivety or conformity (16). Previous studies have revealed that the EPQ-R is adequately valid and reliable (17).

Hospital Anxiety and Depression Scale

Anxiety and depression symptoms were evaluated using the Hospital Anxiety and Depression Scale (HADS). The HADS (18) consists of a 7-item anxiety subscale and a 7-item depression subscale to assess symptoms of anxiety and depression during the preceding week in medically ill patients. The HADS has been used as a reliable and valid method of screening for depression in patients with cancer. Each item is rated on a scale of 0–3, with higher scores denoting a greater mood disturbance. The reliability and validity of the Japanese version of this questionnaire has been established in Japanese cancer patients (19).

Food Frequency Questionnaire

Dietary habits were assessed using the semiquantitative Food Frequency Questionnaire (FFQ), which was constructed for a population-based prospective study in Japan (20) and contains questions regarding 138 foods. For each food item, the participants reported the usual serving size. When the patient's dietary habits changed following the appearance of symptom(s) resulting in hospitalization, the dietary habits before the appearance of the symptom(s) was reported. Nine responses were possible for each food item, ranging from 'never' to '7 or more times per day'. The average daily intake of nutrients was calculated by multiplying the frequency of the consumption of each item by its nutrient content per serving and totaling the nutrient intake for all food items. The method used to calculate the average daily intake of each food and nutrient based on the FFQ responses has been described elsewhere (21).

Urine Specimens

Urine specimens (20 ml) were collected after admission but before treatment, and stored at 80 C until further use.

Blood Samples

Blood samples (20 ml) were collected after admission but before treatment. After storing the samples for about 2 h at 4 C, the serum was separated by centrifugation (1870 *g*, 10 min) and stored at 80 C until further use.

DNA

Peripheral blood samples (3 ml) were collected after admission. DNA was extracted from the blood lymphocytes *by a specialist at the Division of Thoracic Oncology, NCCHE, Japan*, and strictly stored at 80 C until further use.

Patients' DNA samples were analyzed after deleting their names and addresses. When we analyzed their DNA samples in planning a new study, these samples were labeled again with new identification numbers which could be linked to patients' information only by the specialist. Patients' DNA samples were strictly kept at the NCCHE, Japan. This project created the system concerning DNA sampling and reservation.

Follow-up Method

To assess vital status as part of a follow-up study, survival was confirmed by referring to the medical records, by normal postal mail, or using municipality registration data. Follow-up surveys were conducted once a year between July 1999 and December 2004 by members of our co-medical staff.

In order to protect patients' personal information, we planned a new study based upon this project, which needed to be approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center, Japan. Each patient's information was analyzed after deleting his/her name and address. When we analyzed their information, we labeled again with new identification numbers which could be linked to patients' information. The clinical data included in this project was carefully managed by the researcher and the research secretariat.

RESULTS

Questionnaires concerning psychological factors and dietary habits achieved the target of 1500 participants within 4 years, and the questionnaires were completed in July 2003. The questionnaire on demographic variables was distributed for 5 years, and was completed in July 2004. In total, the project was explained to 2506 patients, of whom 2036 (81.3%) patients with newly diagnosed, untreated primary lung cancer were enlisted during the enrollment phase. A total of 470 cases were ineligible for the following reasons: could not be contacted (49 cases), lung cancer diagnosis not confirmed at time of admission (175 cases), non-lung cancer (120 cases), poor physical symptoms (77 cases), refusal to participate in the project (43 cases), treated for lung cancer at another hospital (5 cases), or not yet informed of their diagnosis (1 case). In 40 of the 2036 patients, written informed consent could not be confirmed, and one patient withdrew consent during the follow-up period. Finally, the analytic cohort consisted of 1995 patients.

For the corresponding rate according to baseline assessments among the patient, virtually all of the 1995 patients (corresponding rate, 99%) completed the questionnaires on demographic data and health habits. The corresponding rates for the questionnaires on psychological factors and dietary habits were 99 and 94%, respectively.

The demographic data and medical information is summarized in Table 1. Most of the patients were in their sixth decade at the time of their lung cancer diagnosis (38%), and there were more men than women (71 versus 29%, respectively). As for clinical stage, most of the patients (27%) had stage IV lesions, followed in descending order by IA (24%), IIIB (18%) and IB (14%). Histological classification revealed adenocarcinoma to be the most common lesion (58%), followed in descending order by squamous cell carcinoma (21%) and small cell carcinoma (11%). Most of the patients (44%) underwent surgery as their first-line treatment, followed in descending order by chemotherapy (37%) and chemotherapy plus radiotherapy (11%). Most of the patients were either PS 1 (50%) or PS 0 (44%).

For the vital status among this patient as of December 2004, out of the 1995 patients, 1051 patients had died (52.7%) and 44 patients had been lost to follow-up (2%). The proportion of patients lost to follow-up was low, ranging from 1 to 17%.

Table 1. Demographic and medical characteristics of the project subjects at the baseline

Variable	No. of subjects	%
Age in years at lung cancer diagnosis		
≤39	24	1
40–49	103	5
50–59	456	23
60–69	751	38
70–79	605	30
≥80	56	3
Sex		
Man	1,426	71
Woman	569	29
Clinical stage*		
IA	483	24
IB	285	14
IIA	20	1
IIB	114	6
IIIA	181	9
IIIB	367	18
IV	545	27
Histologic type		
Adenocarcinoma	1151	58
Squamous cell carcinoma	418	21
Large cell carcinoma	170	9
Cartinoid	10	1
Small cell carcinoma	218	11
Other	28	1
Treatment of first line		
Operation	880	44
Chemotherapy	736	37
Chemotherapy plus radiotherapy	228	11
Palliative care	91	5
Radiotherapy	36	2
Chemotherapy plus operation	13	1
Laser	6	0
Operation plus chemotherapy	3	0
Chemotherapy plus radiotherapy plus operation	2	0
Performance status at pre-treatment†		
0	886	44
1	993	50
≥2	116	6

*Defined by TNM classification: International Union Against Cancer.
†Defined by the Eastern Cooperative Oncology Group.

DISCUSSION

This paper overviews the rationale for initiating the Lung Cancer Database Project at the National Cancer Center, Japan. Few previous studies have analyzed such a wide variety of factors among lung cancer patients, making this a valuable clinical observation project.

The advantages of this cohort study were as follows: (1) as the corresponding rates to the baseline questionnaires on demographics, health habits, psychological factors and dietary habits were satisfactorily high, the data can be regarded as being representative of the subject; (2) because not only medical information but a variety of health habits and psychological factors were assessed using standardized questionnaires, valid evaluations of associations in the pathogenesis

of lung cancer can be made; (3) urine specimens, blood samples and DNA were collected from all patients so that when important new biomarkers are discovered, studies utilizing the database will be able to be promptly performed, hopefully leading to greater treatment efficacy in the future; and (4) the follow-up rate was satisfactorily high. The corresponding rate was high, despite the numerous questions on demographic data, health habits and psychological factors that were asked. For this reason, the research assistants reinvestigated patients who did not completely respond to the questionnaires.

The project had some limitations. First, a sampling bias existed because the project was conducted from only one institution, a teaching cancer center hospital in Japan. Care should be taken when generalizing the results of this project and applying them to other oncology settings. Second, we distributed the questionnaire on psychological variables and health habits only once before the patients underwent cancer treatment. Therefore, possible changes in these variables after cancer treatment remain unclear.

In summary, this project constructed a large-scale cancer registry containing data on the demographics, health habits, psychological factors and medical information on lung cancer patients. This database should prove useful for researchers examining the pathogenesis of lung cancer, and may contribute to the formulation of a framework for cancer treatment.

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Brief Communication

Psychometric properties of the Japanese version of the quality of life-Cancer Survivors Instrument

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Abstract

The purpose of this study was to describe the psychometric properties of the Japanese version of the Quality of Life-Cancer Survivors Instrument (QOL-CS-J) developed in the U.S. This study was conducted as a mail survey to survivors of more than 5 years post curative resection for non-small-cell lung cancer (NSCLC) and who had participated in an earlier survey. This survey included the medical and demographic factors, the QOL-CS scores, and the Medical Outcome Study 36-Item Short Form (SF-36). A total of 113 survivors completed the survey. To confirm the reliability, the Cronbach's α coefficient of each subscale was calculated as an internal consistency (α = 0.65–0.89). To confirm the validity of the trial as conducted, Pearson's correlation coefficients between the subscales of the QOL-CS and the subscales of the SF-36 were calculated. There were moderate correlations between associated subscales including QOL-CS physical to SF-36 bodily pain (r = 0.45) and vitality (r = 0.52), QOL-CS psychological to SF-36 mental health (r = 0.55), QOL-CS social to SF-36 general health perception (r = 0.31) and mental health (r = 0.47), and QOL-CS total to each subscale of SF-36 (r = 0.25–0.64). Findings demonstrated that the QOL-CS-J adequately measured the QOL in long-term NSCLC survivors.

Key words: Japan, Non-small-cell lung cancer, Reliability, The Quality of Life-Cancer Survivors Instrument, Validity

Introduction

The Quality of Life-Cancer Survivors Instrument (QOL-CS) was developed to evaluate the long-term QOL of cancer survivors, to identify enduring problems in adjustment after treatment, and to identify potential areas for support [1]. The QOL-CS has been widely used, although not the case in Japan. The purpose of this study was to evaluate the psychometric properties of the Japanese version of the QOL-CS (QOL-CS-J) tool in Japanese survivors of non-small-cell lung cancer (NSCLC).

Methods

Sample

The sample of survivors of NSCLC was derived from the database of an earlier study [2]. The initial study eligibility criteria required patients to

be of 18 years of age or older; to be aware of the diagnosis of cancer; to be able to speak Japanese; to have undergone a predetermined standard surgical procedure (lobectomy or pneumonectomy with mediastinal lymph node dissection); to have no evidence of brain tumor on computerized tomography or magnetic resonance images of the head; to have no history of or current use of chemotherapy, immunotherapy, or radiation therapy; to have no active concomitant cancer; to have undergone a curative resective procedure; and to have no other medical conditions. Detailed of the original study design and recruitment procedures have been published elsewhere [2]. An additional eligibility criterion of the current study required a survival period of the participants of five years and three months or more since the original curative surgical treatment.

Instruments

QOL Questionnaires

The QOL-CS includes 41 items representing the four domains (physical, social, psychological, and spiritual well-being) of cancer-specific quality of life [1]. The instructions for the survey include the statement "How your experience of having cancer affects your quality of life." The QOL total score (average across items) and the four QOL subscale scores were used as outcomes. Transformations were performed such that higher scores indicated a better QOL for all of the subscales. To create a QOL-CS-J, we obtained copyright permission from Dr. Ferrell who developed the original QOL-CS, and translated the QOL-CS into Japanese, then back-translated the scale into English using a native English speaker who was both conversant with the appropriate terminology and was fluent in Japanese. After that, two trained attending psychiatrists who were on the cancer center staffs, and five healthy volunteers confirmed the content of each item.

The SF-36 is a generic QOL instrument that assesses eight health concepts (physical functioning, role limitations caused by physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations caused by emotional problems, and mental health) [3]. Each scale is scored from 0 to 100. Higher scores indicate a better QOL. The validity and reliability of the Japanese version of SF-36 have been well established [4, 5].

Psychosocial demographic and medical background information

Medical information was assessed regarding the pathologic disease stage, performance status (0–4, defined by the Eastern Cooperative Oncology Group), and the presence or absence of pain and dyspnoea. Furthermore, the fighting spirit and helplessness/hopelessness as cognitive and behavior adjustment to cancer were assessed using the subscales of Mental Adjustment to Cancer scale (MAC) [6]. The validity and reliability of the Japanese version of the MAC have been confirmed [7]. Patients provided demographic information, including age, sex, occupation, and marital status.

Procedure

The Institutional Review Board and the Ethics Committee of the NCC, Japan approved this study, and each patient provided informed written consent.

All eligible outpatients were invited to participate in the study after their follow-up medical visit. The patients completed a series of questionnaires, and mailed them back. If the questionnaires contained any blanks and the patients had agreed to the terms of the study at the time of first contact, a single attempt was made to obtain the missing information by telephone.

Analysis

The Cronbach's α and the item-total correlation of each subscale of the QOL-CS-J were calculated to assess internal consistency reliability.

The Pearson's correlation coefficients between each subscale of the QOL-CS-J and SF-36 were computed to assess the concurrent validity. To test discriminant validity, *t*-tests or χ^2 tests were conducted with the medical background information as the independent variable and each subscale of QOL-CS-J as the dependent variable.

Data analyses were carried out with SPSS 12.0 statistical software. A significant difference was defined as $p < 0.05$.

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.