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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.

Participating Institutions

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Interstitial Shadow on Chest CT is Associated with the Onset of Interstitial Lung Disease Caused by Chemotherapeutic Drugs

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Objective: Pretreatment computerized tomography (CT) films of the chest was studied to clarify the influence of interstitial shadow on developing interstitial lung disease (ILD).
Methods: Eligible patients were those lung cancer patients who started to receive first-line chemotherapy between October 2001 and March 2004. Patients who received thoracic radiotherapy to the primary lesion, mediastinum, spinal or rib metastases were excluded. We reviewed pretreatment conventional CT and plain X-ray films of the chest. Ground-glass opacity, consolidation or reticular shadow without segmental distribution was defined as interstitial shadow, with this event being graded as mild, moderate or severe. If interstitial shadow was detected on CT films of the chest, but not via plain chest X-ray, it was graded as mild. Patients developing ILD were identified from medial records.
Results: A total of 502 patients were eligible. Mild, moderate and severe interstitial shadow was identified in 7, 8 and 5% of patients, respectively. A total of 188 patients (37%) received tyrosine kinase inhibitor (TKI) treatment, namely gefitinib or erlotinib. Twenty-six patients (5.2%) developed ILD either during or after chemotherapy. Multivariate analyses revealed that interstitial shadow on CT films of the chest and treatment history with TKI were associated with the onset of ILD.
Conclusions: It is recommended that patients with interstitial shadow on chest CT are excluded from future clinical trials until this issue is further clarified, as it is anticipated that use of chemotherapeutic agents frequently mediate onset of ILD in this context.

Key words: interstitial lung disease – interstitial shadow – chemotherapy – lung cancer – CT

INTRODUCTION

Interstitial lung disease (ILD) is known to be an adverse event in cancer chemotherapy and radiotherapy. Recently, ILD has attracted considerable attention in Japan since the observation that gefitinib caused ILD (1). Gefitinib is a tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor and is active in patients with recurrent non-small cell lung cancer (NSCLC) after platinum-based chemotherapy (2,3). Gefitinib was first approved for the treatment of advanced NSCLC by the Japanese regulatory agencies on 5 July 2002. From August 2002 to April 2003, ~28 000 patients with NSCLC were given gefitinib in Japan. However, 616 patients suffered from ILD and 246 patients died of ILD, according to a report from AstraZeneca. The West Japan Thoracic Oncology Group conducted a retrospective survey to clarify the risk factors related to ILD (4). Out of 1976 patients with NSCLC who received gefitinib across 84 institutions, 91 patients were suspected of having developed ILD. This group also analyzed the patients' background, together with computerized tomography (CT) films of the chest, before treatment and at the onset of ILD in this subcohort. Five experts in thoracic radiology in these extramural reviews diagnosed ILD in 64 patients. Multivariate analysis indicated that the predictive risk factors for the development of ILD were as follows: male, smoking and existence of idiopathic pulmonary fibrosis. However, this group did not review CT films of the chest in all 1976 patients. How much interstitial shadow on chest CT impacts ILD development remains unknown.

ILD has a high associated risk of death, even if steroid therapy resolves ILD temporarily. Furthermore, ILD affects salvage chemotherapy. In cases where patients are at a high risk of developing ILD, anti-cancer drugs that tend to cause ILD should be avoided. Previous analysis often included only those cases developing ILD, but not all cases undergoing chemotherapy (4,5). The frequency of interstitial shadow in

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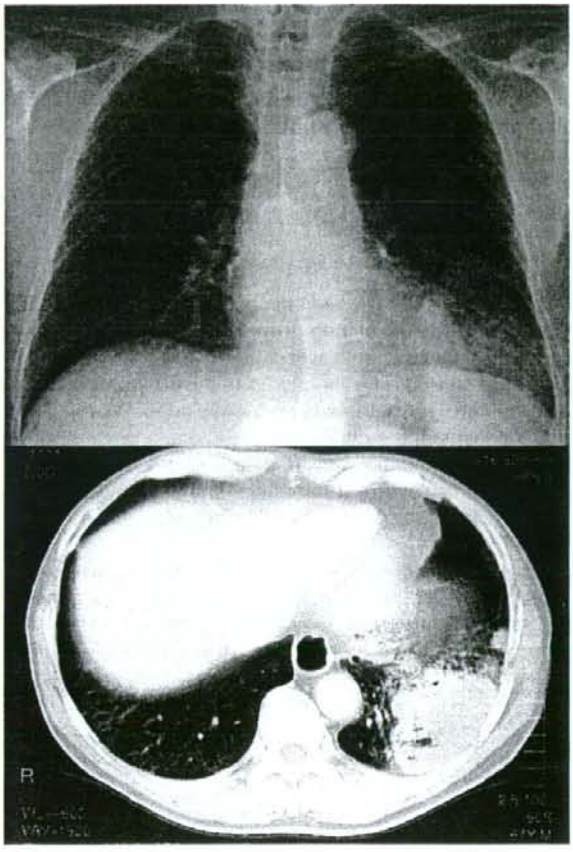

Figure 1. Mild interstitial shadow. An X-ray film of the chest shows no obvious interstitial shadow. A CT film of the chest demonstrated ground-glass opacity in the right basal lung. Interstitial shadow is classified as mild in this case.

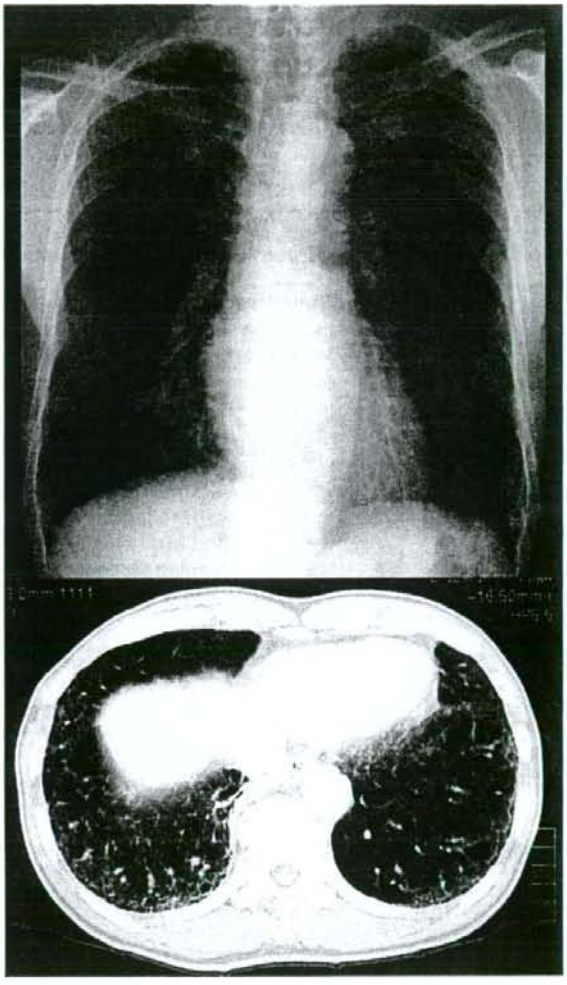

Figure 2. Moderate interstitial shadow. An X-ray film of the chest shows bilateral reticular shadow in the basal area. A CT film of the chest demonstrated bilateral reticular shadow just below the pleura. Interstitial shadow is distributed in 10–30% of the bilateral lower lobes, with this being classified as moderate.

pretreatment CT films of the chest in patients with lung cancer remains unknown, and also how much interstitial shadow confers a risk toward ILD. To further clarify the influence of interstitial shadow on developing ILD, we retrospectively analyzed pretreatment CT films of the chest in consecutive lung cancer patients receiving chemotherapy.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of lung cancer patients who began to receive first-line chemotherapy between October 2001 and March 2004 at the Division of Thoracic Oncology in the National Cancer Center Hospital East. Patients who received thoracic radiotherapy to the primary lesion, mediastinum, spinal or rib metastases were excluded. Plural pulmonologists (S.N., Y.H.K., K.Y., and K.G.) reviewed pretreatment conventional CT and plain X-ray films of the chest. Whether patients had developed ILD or not was blinded to the pulmonologists when they read the films. Conventional spiral CT films were used in our analysis, as high-resolution CT was not routinely conducted. Ground-glass opacity, consolidation or reticular shadow without segmental distribution was defined as interstitial shadow. Localized low attenuation area was defined as emphysema. The grading criteria for interstitial shadow was mild (<10% in bilateral lower lobes), moderate (10–30% in bilateral lower lobes) and severe (>30% in bilateral lower lobes) (Figs 1, 2, and 3). These breakpoints (10 and 30%) were chosen for convenience sake. Interstitial shadow detected on CT films of the chest, but not on plain X-ray, corresponded to mild interstitial shadow. The grading criteria for pulmonary emphysema were mild (<10% in bilateral lungs), moderate (10–30% in bilateral lungs) and severe (>30% in bilateral lungs).

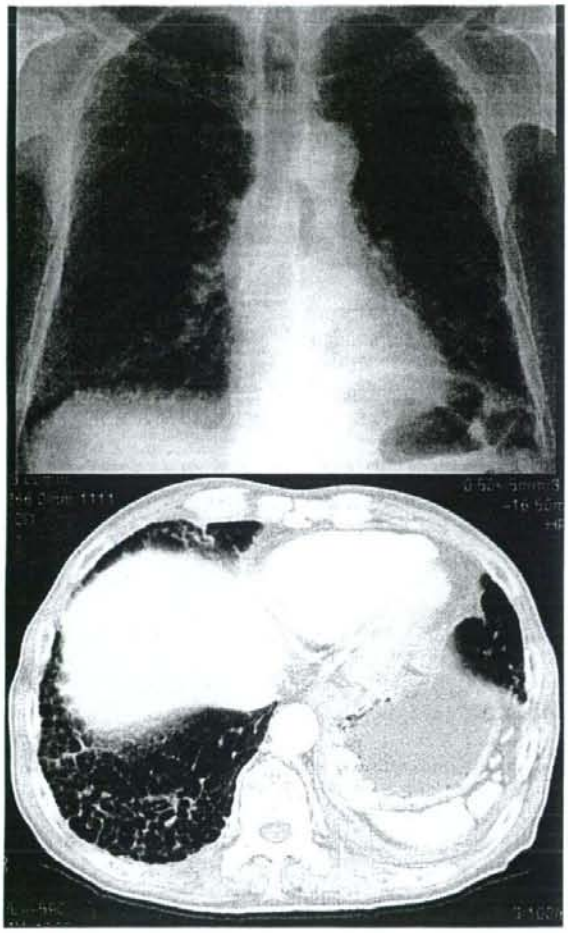

Figure 3. Severe interstitial shadow. An X-ray film of the chest shows bilateral reticular shadow. Reticular shadow is distributed in >30% of the bilateral lower lobes, with this being classified severe.

We identified patients developing ILD, utilizing medical records. ILD was diagnosed on the basis of standard or high-resolution CT findings of the chest (diffuse ground-glass opacity, reticular shadow or consolidation without segmental distribution), elevation of serum levels of lactate dehydrogenase (LDH) and/or KL-6, and lack of response to antibiotics. Bronchoalveolar lavage had not been performed to rule out infections. Most patients diagnosed as ILD were treated with corticosteroids. We compared patients who either had or had not developed ILD in terms of existence and severity of interstitial shadow, emphysema and/or pulmonary bullae on CT films of the chest, as well as patient characteristics including age, gender, smoking history and regimens of received chemotherapy. Comparisons between proportions were performed using a Fisher exact test or a Pearson chi-square test, as appropriate. Multivariate analyses were performed using the logistic regression procedure to determine the relationship between several factors and the onset of ILD.

RESULTS

A total of 502 patients were eligible, with the relevant patient characteristics shown in Table 1. A total of 74% of patients were male and 84% of patients had NSCLC, while the remaining 16% had small cell lung cancer; 79% of the patients were smokers, while 21% never smoked. Platinum-based chemotherapy was performed on 384 patients (76%). A total of 188 patients (37%) received tyrosine kinase inhibitor (TKI) treatment, namely gefitinib or erlotinib. TKI therapy was administered as a first-line ($n = 48$), second-line ($n = 68$), third-line ($n = 62$), fourth-line ($n = 9$) or fifth-line ($n = 1$) regimen. Out of 48 patients treated with TKI as a first-line treatment 41 had been entered into a phase II trial of single agent treatment with gefitinib (6).

Radiological findings on this patient cohort are listed in Table 2. Interstitial shadow was detected on chest X-ray and CT in 13 and 20% of patients, respectively. Mild, moderate or severe interstitial shadow was identified in 7, 8 or 5% of patients. Pulmonary emphysema was detected in 38% of patients. Mild, moderate or severe pulmonary emphysema was detected in 18, 10 or 10% of patients. Pulmonary bullae were detected in 20% of patients.

Twenty-six patients (5.2%) developed ILD either during or after chemotherapy. The last regimen of chemotherapy received prior to the onset of ILD included platinum plus vinorelbine or gemcitabine ($n = 4$), platinum plus taxane ($n = 4$), other platinum-based chemotherapy ($n = 2$), vinorelbine plus gemcitabine ($n = 2$), docetaxel plus gemcitabine ($n = 2$), single agent treatment with taxane ($n = 2$) and TKI treatment ($n = 10$). Out of 26 patients who developed ILD, 14 had a history of taking TKI. Four patients developed ILD after first- or second-line chemotherapy with TKI followed by combination chemotherapy of cisplatin plus vinorelbine ($n = 2$) or single agent treatment with docetaxel ($n = 2$).

Univariate analyses demonstrated that male gender ($P = 0.0361$) and interstitial shadow on CT films of the chest ($P = 0.0096$) were significantly associated with the onset of ILD (Tables 1 and 3). Multivariate analyses showed interstitial shadow on CT films of the chest [odds ratio (OR): 3.20, 95% confidence interval (CI): 1.34–7.59] and treatment history with gefitinib or erlotinib (OR: 3.17, 95% CI: 1.36–7.36) were associated with the onset of ILD. Male gender was not a significant risk factor for development of ILD in multivariate analysis (OR: 4.33, 95% CI: 0.97–19.38) (Table 4). Univariate and multivariate analyses demonstrated that neither interstitial shadow on X-ray films nor the number of chemotherapy regimens was associated with the onset of ILD.

DISCUSSION

Pulmonary fibrosis or interstitial pneumonia is considered to be a risk factor for ILD caused by drugs (5). In line with the

Table 1. Patient characteristics (n = 502)

	Total	Developed ILD	No ILD Development	P-value
Gender				
Male	371	24	347	0.0361
Female	131	2	129	
Age				
Median (range)	65 (33–83)	66 (53–77)	65 (33–83)	0.5253
ECOG PS				
0–1	443	26	417	0.0590
2–4	59	0	59	
Pathological type				
Adenocarcinoma	279	14	265	0.8775
Squamous cell carcinoma	84	6	78	
Poorly differentiated carcinoma	56	3	53	
Small cell carcinoma	79	3	76	
Others	4	0	4	
Smoking status				
Current smoker	272	14	258	0.1085
Former smoker	124	10	114	
Never smoked	106	2	104	
Clinical stage				
IB	10	0	10	0.6633
IIB	7	0	7	
IIIA	21	0	21	
IIIB	128	8	120	
IV or recurrence after operation	336	18	318	
Treatment history				
Platinum-based	384	18	366	0.3505
Vinorelbine-containing	295	13	282	0.4145
Gemcitabine-containing	110	7	103	0.4758
Taxane-containing	236	14	222	0.5470
Irinotecan-containing	72	2	70	0.5624
Etoposide-containing	67	2	65	0.5573
TKI	188	14	174	0.0954
Number of chemotherapy regimens				
1	212	9	203	0.7733
2	155	9	146	
3	106	7	99	
4 or 5	29	1	28	

ILD, interstitial lung disease; TKI, tyrosine kinase inhibitor.

Table 2. Radiological findings of plain X-ray and computerized tomography films of the chest

Interstitial shadow on plain X-ray films	65 (13%)
Interstitial shadow on CT films	102 (20%)
Mild	37 (7%)
Moderate	42 (8%)
Severe	23 (5%)
Pulmonary emphysema on CT films	189 (38%)
Mild	92 (18%)
Moderate	49 (10%)
Severe	48 (10%)
Pulmonary bullae	101 (20%)

Table 3. Radiological findings and interstitial lung disease

Radiological findings	Developed ILD	No ILD Development	P-value
Interstitial shadow on plain X-ray films of the chest			
No	23	414	1.000
Yes	3	62	
Interstitial shadow on CT film of the chest			
No	15	385	0.0096
Yes	11	91	
Severity of the interstitial shadow			
No	15	385	<0.0001
Mild	8	29	
Moderate	1	41	
Severe	2	21	
Pulmonary emphysema			
No	14	299	0.4075
Yes	12	177	
Severity of the emphysema			
No	14	299	0.6468
Mild	7	85	
Moderate	2	47	
Severe	3	45	
Pulmonary bullae			
No	18	383	0.2052
Yes	8	93	

ILD, interstitial lung disease.

information for prescription, patients with obvious interstitial shadow on chest X-ray should avoid gemcitabine or irinotecan. Although patients with interstitial shadow on chest X-ray were excluded in previous clinical trials in Japan, unexpectedly frequent ILD has been reported, as in the case of combination chemotherapy with docetaxel and gemcitabine (7). Is interstitial shadow on chest X-ray an appropriate criterion to detect interstitial pneumonia or pulmonary fibrosis and avoid ILD? Generally, chest CT can detect interstitial shadow more clearly than chest X-ray. Specifically, high-resolution CT of the chest is essential in diagnosing interstitial pneumonia. However, it has not been determined exactly how much more interstitial shadow detected by CT reveals the onset of ILD. We analyzed CT films of consecutive lung cancer patients who underwent

Table 4. Multivariate analysis of risk factors associated with the onset of interstitial lung disease

Variable	Odds ratio	95% CI	*P*-value
Interstitial shadow on CT films of the chest	3.20	1.34–7.59	0.0086
Treatment history with TKI	3.17	1.36–7.36	0.0073
Male gender	4.33	0.970–19.38	0.0551

CI, confidence interval; TKI, tyrosine kinase inhibitor.

chemotherapy without thoracic radiation therapy. Retrospective review of medical records identified that 26 out of 502 patients developed ILD. We found that interstitial shadow on CT films was associated with onset of ILD, but that interstitial shadow on X-ray was not. We divided interstitial shadow into three classes: mild, moderate and severe. Interstitial shadow on X-ray means moderate to severe interstitial pneumonia. Eight out of 37 patients (22%) with mild interstitial shadow not detected on chest X-ray developed ILD. The reason for the high rate of ILD in patients with mild interstitial shadow is unknown. The criteria of no interstitial shadow on chest X-ray did not sufficiently reduce the risk of ILD. Treatment history with TKI, either gefitinib or erlotinib, was also associated with onset of ILD in multivariate analysis. Conversely, treatment with gemcitabine or irinotecan was not associated with onset of ILD.

Our retrospective analyses have several limitations. We avoided treatment with gemcitabine, irinotecan or TKI in the case of patients with moderate to severe interstitial shadow detectable on chest X-ray films. Some patients who were transferred to another hospital just after chemotherapy may have developed ILD, but detailed clinical courses after transfer were not available. Early death after chemotherapy due to disease progression might conceal the onset of ILD. Although these biases may exist, our analyses were made with an extensive cohort of patients, and therefore the results obtained are of significance.

The frequency of ILD in Japanese patients was reported to range between 3 and 15% in previous clinical trials (6–8). This rate appears to be higher than that observed in the rest of the world. Explanations include the possibility that ILD may be more prevalent among the Japanese or, alternatively, that a greater awareness of the disease could lead to more frequent diagnosis. Furthermore, there may be an increased genetic susceptibility to ILD specifically among the Japanese population (5).

Patients with interstitial shadow on chest X-ray have been excluded in previous clinical trials to avoid ILD caused by chemotherapeutic agents. However, this criterion alone is considered insufficient. It is recommended that patients with interstitial shadow on chest CT are excluded from future clinical trials until this issue is clarified, as it is anticipated that use of chemotherapeutic agents frequently mediate onset of ILD in this context. Therefore, physicians need to understand the associated risk of ILD in patients with interstitial shadow on chest CT and obtain informed consent from patients before administering chemotherapy in clinical practice.

Acknowledgments

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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.

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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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.

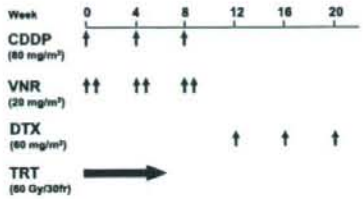

FIGURE 1. Treatment schema. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

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

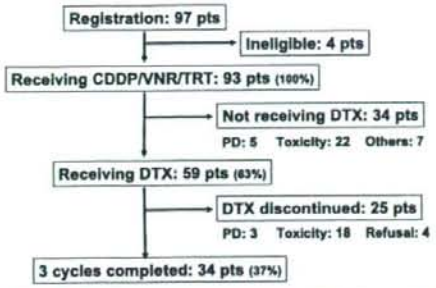

FIGURE 2. Patient registration. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

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