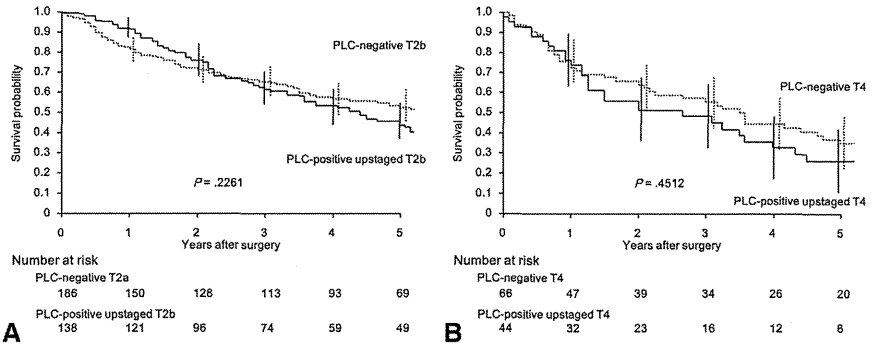

FIGURE 3. Comparisons of survival curves between patients with positive and negative pleural lavage cytology (*PLC*) results according to reevaluations based on International Pleural Lavage Cytology Collaborators recommendations. A, There was no significant difference between PLC-positive upstaged T3 and PLC-negative T3. B, There was no significant difference between PLC-positive upstaged T4 and PLC-negative T4. *Solid lines* indicate patients with positive PLC results and *dashed lines* indicate patients with negative PLC results. The *vertical bars* indicate 95% confidence intervals.

surface immediately after thoracotomy and before lung resection, after which the saline is aspirated and a sample is sent for cytologic screening for malignant cells.[24] In addition, patients with positive PLC results after pulmonary resection have a worse prognosis than those with positive PLC results immediately after thoracotomy.[16,20,21] The finding of a positive PLC result after pulmonary resection is thought to involve human factors associated with surgical manipulation,[11] and the PLC results obtained immediately after thoracotomy may more accurately reflect the biologic malignancy of lung cancer. Second, only 37.3% of NSCLC patients had PLC in this study. One reason for this finding is that the value of PLC has not been recognized in many institutions. In our study, patients who underwent PLC were not compared with the excluded patients. However, 94.8% of patients who underwent PLC were PLC-negative, with clinicopathologic characteristics similar to those of general NSCLC patients. Third, the patients with positive PLC results were significantly different from those with negative PLC results. Matching may equalize this inequality and permit true exploration of the effects of PLC in similar patients. However, we did not match the patients because the aim of our study was to retrospectively examine the clinical significance of the PLC status and illustrate the recommendations of the IPLCC based on an exploratory statistical model using data obtained from a multiinstitution study.[24] Fourth, we did not investigate the incidence of pleural recurrence, although PLC-positive patients had more episodes of recurrence than PLC-negative patients within 5 years after surgery. Patients with positive PLC results have been reported to have a high incidence of pleural recurrence.[19,25,26,33] Other reports have indicated that local intrapleural therapy is effective for local control, although this treatment does not improve survival.[18,34] Because the PLC findings affect all T, N, and M categories, the administration of systemic adjuvant chemotherapy may be effective in patients with positive PLC results. The importance of incorporating PLC results into the TNM classification will be recognized only if the effectiveness of adjuvant chemotherapy is demonstrated prospectively in patients with positive PLC results.

TABLE 4. Comparisons of survival rates between patients with positive and negative pleural lavage cytology (PLC), according to upstaged T categories and reevaluated pathologic stages

	Positive PLC		Negative PLC		
Category or stage	n	5-y survival (%)	n	5-y survival (%)	*P* value
Upstaged T category					
T1a	—	—	1147	88.3	—
T1b	14	76.2	771	79.2	.9417
T2a	12	71.3	1390	67.7	.7518
T2b	138	45.1	186	53.7	.2261
T3	9	25.0	394	46.4	.2568
T4	44	27.6	66	36.2	.4512
Reevaluated pathologic stage					
IA	8	100	1679	88.8	—
IB	7	100	949	77.1	—
IIA	62	61.2	355	62.9	.8223
IIB	21	48.0	250	51.8	.6953
IIIA	70	29.6	629	42.5	.1234
IIIB	20	23.6	34	20.2	.8662
IV	29	27.8	58	30.3	.4962
Total	217	44.5	3954	72.8	<.0001

PLC, Pleural lavage cytology.

CONCLUSIONS

PLC status was an independent prognostic factor in patients with NSCLC who had been surgically treated. Based on the recommendations of the IPLCC, if a single increase in the T category up to a maximum of T4 is assigned to a patient with a positive PLC result, the significant difference in survival disappears between the 2 groups in all T categories and stages. This recommendation appears to be an appropriate method for incorporating PLC findings into the seventh edition of the UICC TNM

classification. The implications of incorporating PLC findings into the TNM classification system is reflected in the treatments for upstaged patients, such as the addition of adjuvant therapy or a change to a more effective adjuvant therapy.

We hope that PLC findings will be incorporated in the next revision of the UICC TNM classification.

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ORIGINAL ARTICLE

The preoperative plasma D-dimer level is an independent prognostic factor in patients with completely resected non-small cell lung cancer

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Abstract
Purpose The plasma D-dimer (D-dimer) level, a marker of hypercoagulation, has been reported to be associated with survival in several types of cancers. This retrospective study was conducted to evaluate the prognostic significance of the preoperative D-dimer level in patients with completely resected non-small cell lung cancer (NSCLC).
Methods A total of 237 completely resected NSCLC patients were included in this study. In addition to age, sex, the smoking status, etc., the association between the preoperative D-dimer level and survival was explored.
Results The patients were divided into three groups according to the D-dimer level: group A (≤0.50 μg/ml, $n = 76$), group B (0.51–0.86 μg/ml, $n = 79$) and group C (>0.86 μg/ml, $n = 82$). The 5-year overall survival rate was 89.6 % (95 % confidence interval (CI) 77.7–95.3) for group A, 75.1 % (95 % CI 62.3–83.6) for group B and 60.1 % (95 % CI 46.8–71.1) for group C ($P_{trend} < 0.001$). A multivariate survival analysis showed that the D-dimer level (group B vs. group A HR 4.25, group C vs. group A HR 4.11) was an independent significant prognostic factor, in addition to age, sex, the pathological stage and the serum carcinoembryonic antigen level.
Conclusions The preoperative D-dimer level is an independent prognostic factor in patients with completely resected NSCLC.

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Keywords Non-small cell lung cancer · Plasma D-dimer level · Prognosis · Surgery

Introduction

Patients with malignant tumors sometimes exhibit a hypercoagulable state, such as venous thromboembolism (VTE) or disseminated intravascular coagulation (DIC). A systemic hypercoagulable state is frequently observed in advanced-stage cancer patients, even in the absence of thrombosis. Trousseau's syndrome is well known to clinicians, partly because Armand Trousseau not only described the relationship between a hypercoagulable state and malignant tumors in 1865 [1] but also diagnosed the syndrome in himself 2 years later, succumbing shortly thereafter to gastric cancer. An analysis conducted by Sack et al. [2] extended the term Trousseau's syndrome to include chronic disseminated intravascular coagulopathy associated with microangiopathy, verrucous endocarditis and arterial emboli in patients with cancer, which often occurs with mucin-positive carcinomas. More recently, the term has been ascribed to various clinical situations, ranging from these classic descriptions to any kind of coagulopathy occurring in the setting of any kind of malignancy [3].

The plasma D-dimer (D-dimer) level is a marker of hypercoagulation, which is usually elevated in patients with thrombosis or DIC. As the D-dimer level is elevated following clot formation, the measurement of the D-dimer level is routinely used for the initial assessment of suspected acute VTE [4]. An elevated D-dimer level can be observed in other clinical settings, such as pregnancy, cancer and infectious disease, or following trauma or surgery. In addition, an elevated D-dimer level has been reported to be associated with the survival in patients with

several types of malignancies, including breast cancer [5, 6], colorectal cancer [7], musculoskeletal sarcoma [8] and so on. However, the relevance of the D-dimer level as a prognostic factor for primary lung cancer has not yet been established. The aim of our study was to clarify the prognostic significance of the preoperative D-dimer level in patients with completely resected primary lung cancer.

Methods

From April 2005 to December 2007, 247 patients with potentially resectable non-small cell lung cancer (NSCLC) underwent measurement of the D-dimer level at Nagoya University Hospital. The D-dimer level was measured within 1 month prior to surgery. One patient who was diagnosed with pulmonary arterial embolism on enhanced computed tomography and nine patients who were unable to undergo complete resection were excluded from this study. All clinical and pathological data were collected using a clinical database and charts. The number of patients with a normal D-dimer level (≤0.50 μg/ml) was 76, almost one-third of the 237 patients. Based on this finding, the patients were divided into three groups according to the D-dimer level to create tertiles: group A (≤0.50 μg/ml, $n = 76$), group B (0.51–0.86 μg/ml, $n = 79$) and group C (>0.86 μg/ml, $n = 82$). Fisher's exact test or an analysis of variance (ANOVA) was used to compare each variable in the three groups, as appropriate. The Kaplan–Meier method was used to calculate the survival rates, and the log-rank test was used to compare the survival curves. A Cox proportional hazard model was used for the univariate and multivariate survival analyses. In addition to the D-dimer level, the other factors examined included the age, sex, smoking status, pathological stage (*p*-stage), histology and the serum carcinoembryonic antigen (CEA) level. *p* values <0.05 were considered to indicate a significant difference. The statistical evaluations were performed using the computer software program, STATA Ver.11 (College Station, TX, USA). The Institutional Review Board of Nagoya University Hospital approved this retrospective study (Approval number: 2012-0162).

Results

The patient characteristics are shown in Table 1. This study included 152 males and 85 females, ranging in age from 31 to 85 years (median 69 years). The mean observation period in the survivors was 51.6 months (range 1–76 months). An elevated CEA level was more frequently

Table 1 The patient characteristics

D-dimer (μg/ml)	Median (range)	Total $n = 237$ 0.7 (0.11–7.58)	Group A $n = 76$ ≤0.50	Group B $n = 79$ 0.51–0.86	Group C $n = 82$ >0.86	*p* value
Age	Years	69 (31–85)	69 (31–84)	69 (33–85)	67 (39–85)	0.857
Sex	Male	152	49	57	46	0.105
	Female	85	27	22	36	
Smoking history	Yes	167	49	54	64	0.154
	No	70	27	25	18	
p-stage	I	152	52	57	43	0.071
	II	37	12	10	15	
	III	48	12	12	24	
Histology	AD	162	54	62	46	0.129
	SQ	51	16	11	24	
	LA	7	2	1	4	
	Others	17	4	6	7	
Surgical procedure	Wedge/Seg	31	11	8	12	0.845
	Lob	192	61	65	66	
	Pn	14	4	6	4	
CEA (ng/ml)	≤5	155	58	56	41	0.005
	>5	81	18	23	40	

Fisher's exact test or an analysis of variance (ANOVA) was used to compare each variable in the three groups

CEA carcinoembryonic antigen, *AD* adenocarcinoma, *SQ* squamous cell carcinoma, *LA* large cell carcinoma, *Wedge* wedge resection, *Seg* segmentectomy, *Lob* lobectomy, *Pn* pneumonectomy

detected in group C than in the other groups ($p = 0.005$). There were more advanced-stage patients in group C, but the difference was not significant ($p = 0.071$).

A univariate analysis showed that the sex (male vs. female: hazard ratio (HR) 2.25; 95 % confidence interval (95 % CI) 1.32–3.85), smoking history (yes vs. no: HR 3.78, 95 % CI 1.62–8.84), pathological stage (stage II vs. stage I HR 3.41, 95 % CI 1.74–6.67, stage III vs. stage I HR 4.19, 95 % CI 2.23–7.89), CEA level (>5 vs. ≤5 HR 1.37; 95 % CI 1.17–1.6) and D-dimer level (group B vs. group A HR 3.43; 95 % CI 1.37–8.62, group C vs. group A HR 5.83; 95 % CI 2.41–14.1) were significant prognostic factors (Table 2).

As shown in Fig. 1, the 5-year overall survival (OS) rate was 89.6 % (95 % CI 77.7–95.3) for group A, 75.1 % (95 % CI 62.3–83.6) for group B and 60.1 % (95 % CI 46.8–71.1) for group C (P_{trend} <0.001). The OS rate of the patients with stage I disease is shown in Fig. 2. The 5-year OS rate was 98.1 % (95 % CI 87.1–99.7) for group A, 80.1 % (95 % CI 66.7–89.2) for group B and 78.2 % (95 % CI 59.8–88.9) for group C ($P_{trend} = 0.0151$). Eight patients with stage I disease (group A 0, group B 4, group C 4) died of recurrence of NSCLC. Eleven patients with stage I disease (group A 1, group B 6, group C 4) died due to other diseases.

A multivariate analysis showed that the age (HR 1.04; 95 % CI 1.01–1.07), sex (male vs. female HR 2.44; 95 % CI 1.15–3.77), pathological stage (stage II vs. stage I HR 2.24; 95 % CI 1.05–4.83, stage III vs. stage I HR 2.68; 95 % CI 1.36–5.29), CEA level (>5 vs. ≤5 HR 2.31; 95 % CI 1.27–4.19) and D-dimer level (group B vs. group A HR 4.25; 95 % CI 1.65–10.91, group C vs. group A HR 4.11; 95 % CI 1.64–10.28) were independent significant prognostic factors (Table 3).

Table 2 The results of the univariate analysis of the overall survival

	HR	95 % CI		*p* value
Age				
Per 1 year	1.03	0.99	1.07	0.061
Sex				
Female	Reference			
Male	2.26	1.32	3.85	0.003
Smoking history				
No	Reference			
Yes	3.78	1.62	8.84	0.002
p-stage				
I	Reference			
II	3.41	1.74	6.67	<0.001
III	4.19	2.23	7.89	<0.001
Histology				
AD	Reference			
Non-AD	1.22	0.69	2.13	0.496
Surgical procedure				
Wedge/Seg	Reference			
Lob	0.59	0.29	1.19	0.14
Pn	0.56	0.15	2.05	0.383
CEA (ng/ml)				
≤5	reference			
>5	1.37	1.17	1.6	<0.001
D-dimer (μg/ml)				
Group A (≤0.50)	Reference			
Group B (0.51–0.86)	3.43	1.37	8.62	0.008
Group C (>0.86)	5.83	2.41	14.1	<0.001

CEA carcinoembryonic antigen, *AD* adenocarcinoma, *Wedge* wedge resection, *Seg* segmentectomy, *Lob* lobectomy, *Pn* pneumonectomy, *HR* hazard ratio, *CI* confidence interval

Discussion

Patients with NSCLC without metastatic disease are considered to be candidates for surgical resection. Although complete resection is often achieved in such patients, with low mortality and morbidity rates [9, 10], some patients experience relapse after surgery. The group of patients at risk is not well characterized; however, some clinicopathological factors, such as a high preoperative CEA level [11], positive results on pleural lavage cytology [12], the presence of intratumoral lymphovascular invasion and a high standardized uptake value on positron emission tomography (PET) [13], have been reported to be associated with recurrence or poor survival after surgery for NSCLC.

D-dimer is a degeneration product of fibrin that is produced when cross-linked fibrin is degraded by plasmin-

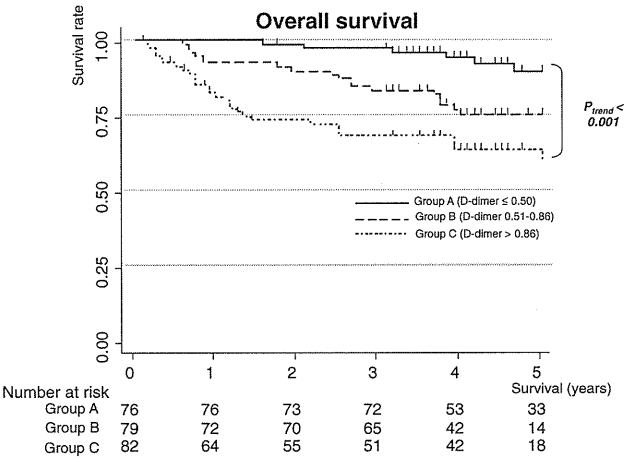

Fig. 1 The overall survival rates of the patients ($n = 237$). The 5-year overall survival rate was 89.6 % (95 % CI 77.7–95.3) for group A, 75.1 % (95 % CI 62.3–83.6) for group B and 60.1 % (95 % CI 46.8–71.1) for group C (P_{trend} <0.001)

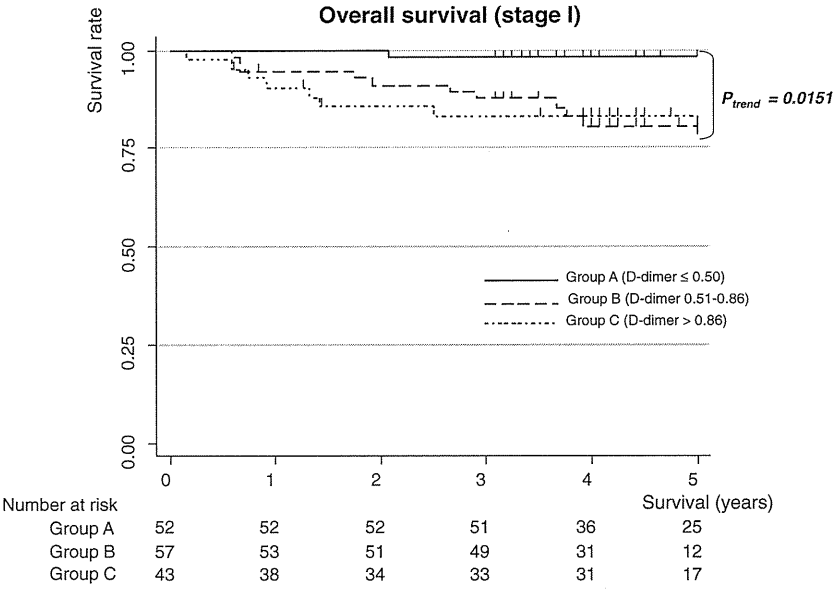

Fig. 2 The overall survival of the patients with pathological stage I disease ($n = 152$). The 5-year OS rate was 98.1 % (95 % CI 87.1–99.7) for group A, 80.1 % (95 % CI 66.7–89.2) for group B and 78.2 % (95 % CI 59.8–88.9) for group C ($P_{trend} = 0.0151$)

Table 3 The results of the multivariate analysis of the overall survival

	HR	95 % CI		*p* value
Age				
Per 1 year	1.04	1.01	1.07	0.025
Sex				
Female	Reference			
Male	2.44	1.15	3.77	0.015
Smoking history				
No	Reference			
Yes	2.27	0.94	5.51	0.069
p-stage				
I	Reference			
II	2.24	1.05	4.83	0.038
III	2.68	1.36	5.29	0.004
Histology				
AD	Reference			
Non-AD	1.26	0.69	2.29	0.459
Surgical procedure				
Wedge/Seg	Reference			
Lob	0.77	0.35	1.71	0.522
Pn	0.92	0.22	3.78	0.908
CEA (ng/ml)				
≤5	Reference			
>5	2.31	1.27	4.19	0.006
D-dimer (μg/ml)				
Group A (≤0.50)	Reference			
Group B (0.51–0.86)	4.25	1.65	10.91	0.003
Group C (>0.86)	4.11	1.64	10.28	0.003

CEA carcinoembryonic antigen, *AD* adenocarcinoma, *Wedge* wedge resection, *Seg* segmentectomy, *Lob* lobectomy, *Pn* pneumonectomy, *NE* not evaluable, *HR* hazard ratio, *CI* confidence interval

induced fibrinolytic activity. The D-dimer level is considered to be a biomarker that globally indicates the activation of hemostasis and fibrinolysis. There are several reports regarding the prognostic significance of the D-dimer level in patients with malignancies [5–8]. For example, Ay et al. [14] analyzed 1,178 prospectively collected cancer patients without VTE who were followed over 2 years until the occurrence of VTE or death. The study included 829 (70.4 %) patients with solid tumors, 148 (12.6 %) with brain tumors and 201 (17 %) with hematological malignancies. The authors divided the patients into quartiles according to the D-dimer level and concluded that a high D-dimer level is associated with a significantly poorer survival in patients with any type of malignancy.

There have also been reports regarding the prognostic significance of the D-dimer level in patients with primary lung cancer. Taguchi et al. [15] analyzed 70 primary lung cancer patients (20 treated surgically, 50 treated with chemotherapy or radiotherapy) and concluded that a high D-dimer level is associated with a poor prognosis according to a multivariate survival analysis. Similarly, Altiay et al. [16] reported the prognostic significance of the D-dimer level based on an analysis of 78 non-surgically treated primary lung cancer patients. A recently published study by Zhang et al. [17] also revealed the prognostic importance of the plasma D-dimer level in patients with operable NSCLC. They analyzed 232 patients with resected NSCLC, including 17 patients who developed VTE postoperatively. Although their study question and results somewhat overlapped with our study, we have additionally adjusted for some strong prognostic factors, such as the CEA level and smoking status, in our multivariate survival analysis. Moreover, our study population is considered to

be more homogeneous, because there were no postoperative VTE events in our study subjects.

It is unclear why a high D-dimer level is associated with a poor survival in patients with malignancies, including primary lung cancer. In our study cohort, there were no patients in group A (D-dimer ≤0.5 μg/ml) with *p*-stage I disease who died due to recurrence of NSCLC. In group B (D-dimer 0.5–0.86 μg/ml), which included patients who had *p*-stage I disease, four patients died due to recurrence of NSCLC. In group C (D-dimer >0.86 μg/ml), which included patients with *p*-stage I disease, four patients died due to recurrence of NSCLC. In general, the development of postoperative recurrence is likely due to the establishment of micrometastasis or the presence of circulating tumor cells (CTCs) [18] before treatment, which are considered to be undetectable using current diagnostic modalities, such as computed tomography (CT) and PET-CT. Based on our data, we speculate that a high preoperative D-dimer level may reflect the presence of micrometastasis or CTCs, which lead to the postoperative recurrence of NSCLC. The D-dimer level may, therefore, have the potential power to predict the recurrence of NSCLC, although D-dimer is not released by the tumor itself, unlike CEA.

There are some limitations associated with our retrospective analysis. First, we were unable to conclude whether a high D-dimer level is related to cancer-specific survival, because data regarding the disease-free survival were not available. Second, the number of study subjects was small; however, to our knowledge, the size of the present study cohort is the largest of any report of NSCLC patients. In addition, all patients were confirmed to have no pulmonary arterial emboli on enhanced CT, and were surgically managed.

In conclusion, our multivariate survival analysis showed that the D-dimer level is an independent prognostic factor, in addition to the age, sex, pathological stage and the CEA level. The preoperative D-dimer level is a useful parameter not only for detecting VTE but also for predicting the prognosis of patients with completely resected NSCLC. It may also have the power to predict postoperative recurrence in NSCLC patients. Studies of larger cohorts are needed to confirm the relationship between the preoperative D-dimer level and the prognosis of patients with NSCLC.

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Conflicts of interest None of the authors has any conflict of interest to declare in association with this study.

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Long-term results and predictors of survival after surgical resection of patients with lung cancer and interstitial lung diseases

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Objectives: Patients with interstitial lung diseases have a poor prognosis and are at increased risk of developing lung cancer. We evaluated the survival and predictors of survival after surgical resection in lung cancers in patients with interstitial lung diseases.

Methods: We retrospectively analyzed data from 1763 patients with non–small cell lung cancer with a clinical diagnosis of interstitial lung disease who underwent pulmonary resection between 2000 and 2009 at 61 Japanese institutions.

Results: Male patients (90.4%) and smokers (93.8%) were in the majority. The overall 5-year survival was 40%. The 5-year survivals were 59%, 42%, 43%, 29%, 25%, 17%, and 16% for patients with stage Ia, Ib, IIa, IIb, IIIa, IIIb, and IV, respectively. Patients with stage IA had a 5-year survival of 33.2%, 61.0%, and 68.4% in the wedge resection, segmentectomy, and lobectomy groups, respectively (log-rank test, $P = .0038$). The leading cause of death was cancer recurrence (50.2%), followed by respiratory failure (26.8%). Wedge resection reduced mortality due to respiratory failure when compared with that of lobectomy ($P = .022$). Multivariable analysis revealed that the type of surgical procedure, predicted percent vital capacity, and tumor locations were independent predictors for survival. The 5-year survival was 20% for patients with stage Ia with a predicted percent vital capacity of 80% or less, and 64.3% for patients with a predicted percent vital capacity greater than 80% (log-rank test, $P < .0001$).

Conclusions: In these patients, there are competing risks of death. Wedge resection reduced death caused by respiratory failure but resulted in poorer long-term prognosis than lobectomy. For patients with poor predictors of survival, such as predicted percent vital capacity of 80% or less, surgical resection should be limited. (J Thorac Cardiovasc Surg 2015;149:64-70)

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Supplemental material is available online.

Interstitial lung diseases (ILDs) are associated with an increased risk of lung cancer,[1,2] and the prevalence of lung cancer ranges from 6% to 17% during the course of ILDs. In these patients, Ozawa and colleagues[3] reported that the cumulative incidence rate of lung cancer was approximately 3.3%, 15.4%, and 54.7% at 1, 5, and 10 years, respectively.[3] However, the contribution of anticancer therapies is unclear because these therapies may trigger fatal complications, such as acute exacerbation (AE), and are confounded by the progressive nature and poor prognoses of ILDs. Although the survival of this group of patients was considered to be poorer than that of other

Abbreviations and Acronyms

AE = acute exacerbation
CI = confidence interval
CT = computed tomography
DLCO = carbon monoxide diffusing capacity
FEV1 = forced expiratory volume in 1 second
FVC = forced vital capacity
ILD = interstitial lung disease
IPF = idiopathic pulmonary fibrosis
OR = odds ratio
UIP = usual interstitial pneumonia
%VC = percent vital capacity

patient cohorts with ILDs, no reliable figures based on a large study have been reported to address this problem.

In our previous report using data from 61 institutes in Japan on 1763 patients with lung cancer who had ILDs, we studied the morbidity and mortality rate of patients with pulmonary resection and identified 7 risk factors for postoperative AE of pulmonary fibrosis.[4] By using the same cohort, we have analyzed their long-term survival and the probable factors influencing their survival.

PATIENTS AND METHODS

The patients' basic backgrounds are shown in Table 1. The patient cohort was identical to that used in our previous study. Briefly, the majority of patients were men (90.4%) and ex- or current smokers (93.8%). Usual interstitial pneumonia (UIP) diagnoses were made in 73.7% of the patients by computed tomography (CT) scan. Squamous cell carcinoma was the most common type of lung cancer (46.9%), followed by adenocarcinoma (41.4%). Most of the patients had stage I disease (1028 cases). Lobectomy was the most common surgical procedure (1236 cases, 70.4%), followed by wedge resection (275 cases, 15.7%), segmentectomy (150 cases, 8.6%), bilobectomy (61 cases, 3.4%), and pneumonectomy (33 cases, 1.9%). TNM stages were based on the classification of the malignant tumors by the Union for International Cancer Control (6th edition).[5]

Inclusion criteria for the patients have been described.[4] Patients with ILDs and non–small-cell lung cancer who had undergone pulmonary resection other than surgical biopsy for diagnostic purpose were included. ILDs were confirmed on the basis of a radiologic finding on the chest CT scan according to the clinical criteria proposed by the Japanese Respiratory Society, and these criteria are consistent with the 2011 guidelines of the American Thoracic Society.[6] The cases were categorized into 2 groups according to their radiologic appearance on CT scan: (1) UIP pattern: This group is characterized by the presence of basal-dominant reticular opacities and predominantly basal and subpleural distribution of honeycomb lesions with multiple equal-sized cystic lesions of 2 to 10 mm in diameter with a thick wall; and (2) non-UIP pattern: This group is characterized by the presence of basal-predominant ground glass opacities and infiltrative shadows inconsistent with UIP patterns. The patient data were retrospectively accumulated between January 2000 and December 2009, which is more than the 3 consecutive years at 61 hospitals throughout Japan. The number of patients at each institute varied from 4 to 133; the institutes with a small number patients were the result of more than 3 consecutive years of observation. We were unable to set or investigate the selection criteria for the surgical procedures in each institute.

The study protocol was approved by the institutional review boards of all participating hospitals, including that of the Ethics Committee, Kyoto University Graduate School and Faculty of Medicine (Approval Number: E-982).

The primary end point was overall survival time, defined as the time from surgical procedure to death from any cause. Postoperative patient information, including cancer recurrence site, exacerbation of IP, and cause of death, was also collected until March 2011, the end of data collection.

Statistical Analyses

Survival curves were estimated using the Kaplan–Meier method. The variables in Table E1 were analyzed for multivariate Cox regression analysis to identify probable predictors of survival. Klebs von Lungen-6, carcinoembryonic antigen, partial pressure of carbon dioxide, partial pressure of oxygen, carbon monoxide diffusing capacity (DLCO), and percent predicted DLCO were not included in the analysis because of missing data more than 5%. Forced expiratory volume in 1 second (liters) was eliminated because it is correlated with predicted percent vital capacity (%VC) (Pearson's correlation coefficient = 0.621). Cox proportional hazards regression analysis was used to estimate the hazard ratio and the 95% confidence interval (CI) of each factor. Multivariate Cox regression analysis with backward elimination was performed to select significant prognostic factors. To examine the relationship between surgical procedures and cause of death, multivariate logistic regression analysis that was adjusted for the significant prognostic factors was used. All reported P values were 2-sided, and a value less than .05 was used for variable selection. Data management and statistical analyses were conducted in the Department of Clinical Trial Design and Management, Translational Research Center, Kyoto University Hospital. All statistical analyses were performed using SAS version 9.3 and JMP version 8.1 (SAS Institute, Inc, Cary, NC).

RESULTS

Cause of Death

Death due to cancer was the main cause of mortality (378/753, 50.2%), and death due to respiratory failure (202/753, 26.8%) was the second most common cause of death. Details of the respiratory failure death were as follows; 72 patients (35.6%) died of AE of interstitial pneumonia within 30 days from the operation, and 117 patients died of AE during the following period (Table 2).

Identification of Prognostic Factors

Cox regression analysis identified that age, sex, pTNM stages, %VC, type of surgical procedure, and tumor location were independent predictors for survival (Table 3). As for surgical procedures, the hazard ratios of the segmentectomy and lobectomy groups versus the wedge resection group were 0.957 (95% CI, 0.698-1.313; $P = .786$) and 0.704 (95% CI, 0.565-0.878; $P = .002$), respectively (Table 3).

Survival

The 5-year survivals were 59%, 42%, 43%, 29%, 25%, 17%, and 17% for pTNM stages Ia, Ib, IIa, IIb, IIIa, IIIb, and IV, respectively (Figure 1, *A*). The 5-year survivals in patients with pathologic stage Ia were estimated to be 33.2% for the wedge resection group, 61% for the segmentectomy group, and 68.4% for the lobectomy group

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TABLE 1. Patients' characteristics

Categories	Cases (%)	Median (range)
Age (y)	1763	71 (36-88)
Sex (male/female)	1593 (90.4)/170 (9.6)	
Smoking history		
Never smoker	109 (6.2)	
Ex/current smoker	1006/632	
Brinkman index*	1742	1000 (0-5760)
Radiologic diagnosis		
UIP/non-UIP pattern	1300 (73.7)/463 (26.3)	
Pathology		
Squamous cell carcinoma	816 (46.9)	
Adenocarcinoma	721 (41.4)	
Large cell carcinoma	64 (3.7)	
Pathologic stage†		
1/2/3/4	1028/311/358/34	
Surgical procedures		
Wedge resection	275 (15.7)	
Segmentectomy	150 (8.6)	
Lobectomy	1236 (70.4)	
Bilobectomy	61 (3.4)	
Pneumonectomy	33 (1.9)	

UIP, Usual interstitial pneumonia. *Brinkman Index: The numbers of cigarettes smoked per day times years. †TNM stages based on the classification of the malignant tumors by the Union for International Cancer Control, 6th edition.[5]

(Figure 1, *B*). Survival of patients with pTNM stage Ia who had wedge resection was poorer than that of the lobectomy group ($P < .0008$) but not significantly different from that of the segmentectomy group ($P < .365$) (Figure 1, *B*).

For all patients, the 5-year survivals of those with lower %VC (≤80%) and normal %VC (>80%) were estimated as 20.8% and 43.8%, respectively (log-rank test, $P < .0001$). For patients with stage IA, the 5-year survivals of those with lower %VC (≤80%) and normal %VC (>80%) were estimated as 20% and 64.3%, respectively (log-rank test, $P < .0001$) (Figure 1, *C* and *D*).

Surgical Procedures and Cause of Death in Patients With Stage IA

Patients with stage IA were selected to evaluate the influence of the types of surgical procedure on the cause of death, using logistic regression analyses that adjusted for age, sex, and %VC. In cases involving death due to cancer, wedge resection and segmentectomy were associated with poor outcome; the odds ratio (OR) of wedge resection versus lobectomy was 2.98 (95% CI, 1.56-5.68; $P = .001$), and the OR of segmentectomy versus lobectomy was 2.56 (95% CI, 1.15-5.67; $P = .021$). In cases involving respiratory failure, the OR of wedge resection versus lobectomy was 0.35 (95% CI, 0.15-0.82; $P = .015$), and the OR of segmentectomy versus lobectomy was 0.80 (95% CI, 0.32-2.01; $P = .641$).

TABLE 2. Cause of death and details of respiratory failure deaths

	Categories	Cases (%)
Cause of death	Lung cancer	378 (50.2)
	Respiratory failure	202 (26.8)
	Other	173 (23.0)
Death due to respiratory failure	Postoperative AE*	72 (35.6)
	Chronic exacerbation†	117 (57.9)
	Other	13 (6.4)

AE, Acute exacerbation. *Interstitial pneumonia within 30 days after surgery. †Exacerbation of interstitial pneumonia occurring ≥31 days after the operation.

TABLE 3. Cox proportional hazards regression analysis for survival

Categories	Cases	Hazard ratio	95% CI	*P* value
Age (y)	1656	1.017	1.005-1.028	.004
Sex				
Male	1497	1.000	—	—
Female	159	0.711	0.535-0.945	.019
Pathologic stage				
Ia	528	1.000	—	—
Ib	469	1.728	1.381-2.163	<.001
IIa	65	2.009	1.352-2.984	<.001
IIb	226	2.497	1.933-3.225	<.001
IIIa	233	3.708	2.884-4.767	<.001
IIIb	102	3.204	2.354-4.361	<.001
IV	33	3.774	2.438-5.841	<.001
%VC	1656	0.980	0.975-0.984	<.001
Procedures				
Wedge resection	250	1.000	—	—
Segmentectomy	137	0.957	0.698-1.313	.786
Lobectomy	1209	0.704	0.565-0.878	.002
Bilobectomy/ pneumonectomy	60	0.745	0.494-1.123	.159
Tumor location				
Upper lobe	649	1.000	—	—
Middle lobe	74	1.421	0.977-2.065	.066
Lower lobe	928	1.409	1.202-1.652	<.001
Multiple	5	0.000	N/A	N/A

CI, Confidence interval; *N/A*, not available; *%VC*, percent vital capacity.

DISCUSSION

Determining the surgical indication for patients with lung cancer with ILDs is difficult. In addition to their impaired pulmonary reserve, it is not clear whether pulmonary resection is beneficial or harmful for each individual. The median survival of the patients with idiopathic pulmonary fibrosis (IPF) reportedly ranges from 2 to 4.2 years from the date of diagnosis.[6-8] Although there is a general understanding that the prognosis of patients with lung cancer with ILDs is poor, existing evidence to support these conclusions was based on a few studies with a comparatively small number of patients (14-56).[9-16] Saito and colleagues[9] reported that the 5-year survival of patients with stage IA lung cancer with IPF was 54.2%, and the propensity-matched analysis confirmed that IPF was the only significant prognostic factor. Watanabe and colleagues[10] reported a 5-year survival of 61.6% after pulmonary resection for patients with stage Ia and stage Ib. Our study elucidated the 5-year survival of this group

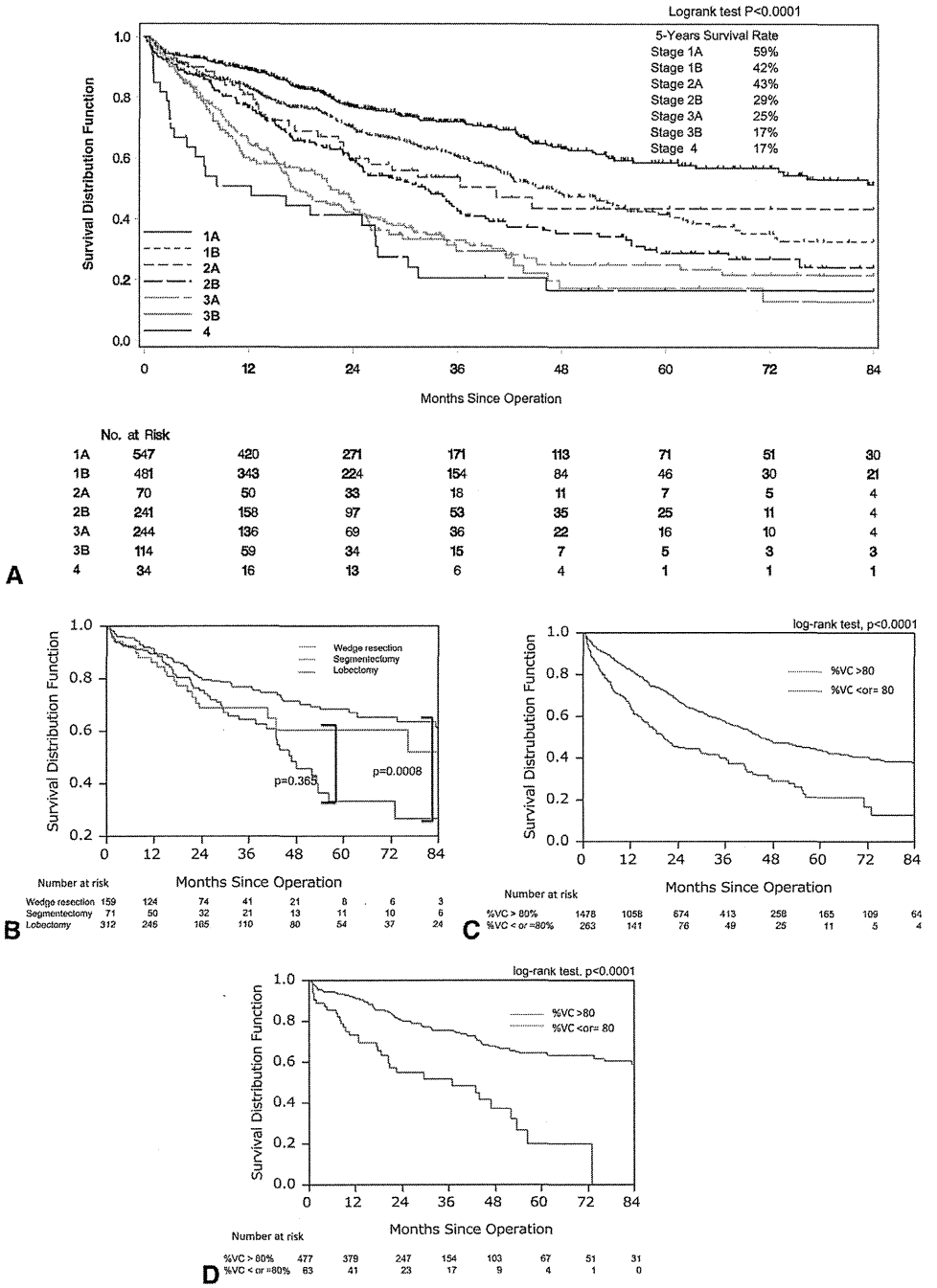

FIGURE 1. A, Overall survival of patients with ILDs who underwent pulmonary resection. B, Survival of the wedge resection, segmentectomy, and lobectomy groups in patients with stage IA; 5-year survival of each group was 29.2%, 60.0%, and 68.6%, respectively. No significant difference was found between the wedge resection and segmentectomy groups (log-rank $P = .365$). C, For all stages, 5-year survival of patients with lower %VC (≤80%) and normal %VC (>80%) was 43.8% and 20.8%, respectively (log-rank test, $P < .0001$). D, For patients with stage IA, 5-year survival of patients with lower % VC (≤80%) and normal %VC (>80%) was 64.3% and 20.0%, respectively (log-rank test, $P < .0001$). *%VC*, Percent vital capacity.

of patients for the various cancer stages and found that the survival was substantially poorer than the recent figures reported by the Japanese Joint Committee for Lung Cancer Registration for overall patients (86.8%, 73.9%, 61.6%, 49.8%, 40.9%, 27.8%, and 27.9% for pathologic stage Ia, Ib, IIa, IIb, IIIa, IIIb, and IV, respectively).[17] This poorer survival is likely due to the high incidence of cancer recurrence, combined with the poor survival of ILD itself. Watanabe and colleagues[9] and Okamoto and colleagues[16] reported an increased cancer recurrence in patients with IPF, but the recurrence rate has not been reported. We determined that recurrence was the main cause of death

TABLE 4. Logistic regression analysis in patients with stage 1A, adjusted for age, sex, and predicted percent of vital capacity

Cause of death	Procedures	Cases (%)	OR	95% CI	*P* value
Cancer	Lobectomy	20/312 (6.4)	1	—	—
	Segmentectomy	12/71 (16.9)	2.56	1.15-5.67	.021
	Wedge resection	26/159 (16.4)	2.98	1.56-5.68	.001
Respiratory failure	Lobectomy	31/312 (9.9)	1	—	—
	Segmentectomy	7/71 (9.9)	0.80	0.32-2.01	.641
	Wedge resection	10/159 (6.3)	0.35	0.15-0.82	.015

CI, Confidence interval; *OR*, odds ratio.

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and was approximately twice as high as that of respiratory failure, indicating the importance of oncologic control for survival.

As for predictors of the patients' survival, multivariable analysis revealed that low %VC was an independent and strong predictor together with the age, sex, pTNM, type of surgical procedure, and tumor location. It is rather appalling that the 5-year survival of the patients with stage IA whose %VC was less than 80% was as poor as 20%. For this group of patients, the decision to perform pulmonary resection should be considered carefully. The natural course of patients with ILDs varies in their disease progression: Some are stable for years, whereas others exhibit more rapid deterioration.[6] Nishiyama and colleagues[18] claimed the median survival of patients with a modified Medical Research Council score of 0 (not troubled with breathlessness except with strenuous exercise) and 1 (troubled by shortness of breath when hurrying on the level or walking up a slight hill) was estimated at 66.7%.[19] Because we showed that cancer was the primary cause of death, lobectomy should be the first choice for those with preserved %VC and good physical status.

Although DLCO is a well-known survival predictor for patients with ILDs, we did not include this in the analysis because of too many missing values, which indicates that DLCO measurement in clinical practice is costly and not common. Impaired right heart function and pulmonary hypertension are known to be associated with the poor prognosis of patients with pulmonary fibrosis.[20] However, preliminary research showed that few patients had the preoperative assessment; thus, we did not include these variables in the study questionnaires.

Patients with lung cancer and ILDs have a high incidence of morbidity and mortality in the perioperative period and a poor long-term prognosis due to both cancer recurrence and deterioration of interstitial pneumonia. To achieve better survival in this group of patients, we propose 2 strategies; one is to decrease the incidence of perioperative fatal complications, namely, AE of IP, and the other is to decrease cancer recurrence. Since Kutlu and colleagues[21] pointed out the high incidence of morbidity and mortality of patients with ILDs in the perioperative periods, AE has begun to be a concern of surgeons.[1,22] Among the problems regarding morbidity, AE is an important issue because it has serious consequences once it occurs. We reported that the incidence of operation-induced AE in this patient group is up to 9.3% and the mortality rate is as high as 43.9%.[4] No effective prophylactics or measures for AE prevention are available so far; only wedge resection may reduce the risk of AE. We reported that segmentectomy and lobectomy increase the risk of AE compared with wedge resection (OR, 3.83; 95% CI, 1.941-7.567; $P = .0005$).[4] However, as we have shown in the present study, long-term survival of patients with stage Ia disease who underwent wedge resections was poorer than that of patients who underwent lobectomy (Figure 1, *B*). The estimated survival curve of the wedge resection group crossed that of the lobectomy group 1 year after the surgery, and the survival of the wedge resection group was significantly poorer than that of the lobectomy group (log-rank test, $P = .0008$). These observations can be explained by the fact that the wedge resection group was less likely to develop AE but had a higher cancer recurrence rate than the lobectomy group. Of note, the curves of the wedge resection group and segmentectomy groups did cross 30 months after the operation, and the survival of both groups showed no significant difference (log-rank test, $P = .365$). Furthermore, multivariate logistic regression analysis on the cause of death (Table 4) showed that the wedge resection and segmentectomy groups had less favorable oncologic outcomes when compared with the lobectomy group. In terms of death caused by respiratory failure, the wedge resection showed a favorable effect when compared with the lobectomy group ($P = .022$), but the segmentectomy group showed no significant effect ($P = .580$). These results implied that segmentectomy seemed to not be beneficial in controlling cancer or reducing respiratory failure. On the other hand, wedge resection may reduce the risk of respiratory failure but resulted in more cancer deaths than in the lobectomy group. Cancer control was shown as the key to achieve better survival; therefore, we believe that lobectomy should be selected except in patients with a high risk of AE. Our former study showed that the patients with a combination of a history of AE of ILDs, preoperative steroid use, UIP pattern on CT, and male gender proved to be at high risk for AE.[4]

Study Limitations

There are study limitations that should be considered in the interpretation of the results. First, this was a retrospective cohort study, which may not necessarily reflect the characteristics of the entire population with this disease. Second, the primary inclusion criterion was the appearance of ILDs on CT. Although radiologic diagnoses were made by each individual institute following criteria based on widely used guidelines, the diagnosis of interstitial pneumonia may vary among institutes. We could not include the assessment of patients' physical status, such as the Borg Scale, 6-minute walk test, and modified Medical Research Council score, which reportedly correlate well with patient survival.[5,17,23]

CONCLUSIONS

In this study, we have investigated the cause of death and the long-term survival of patients with lung cancer concomitant with ILDs who underwent pulmonary resection. We showed that cancer was the primary cause of death, and to achieve better surgical outcomes for this group of patients, lobectomy should be the first choice for those with preserved %VC.

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Discussion

Dr Chukwumere Nwogu *(Buffalo, NY)*. Dr Date, I congratulate you and your colleagues for conducting such a large multi-institutional study. This study provides us with some guidance for decision-making in this difficult group of patients. We typically approach these patients with trepidation as we evaluate them for possible surgical resection. I appreciate the provision of the article and slides before your presentation.

I have 3 questions for you. Before the identification of some risk factors in this study, what specific selection criteria did the surgeons in your consortium use to select the surgical procedures that were offered to your patients, for instance, segmentectomy versus lobectomy? How were those decisions made?

Dr Date. Regarding the selection criteria during this period, this decision was entirely up to the individual institution. This is a retrospective multicenter trial.

Dr Nwogu. In your institution, how did you make that decision?

Dr Date. First, we discussed with the medical oncologists and radiologists whether the patient should be taken to the operating room or not, and then if we decided to perform surgery, we looked at the pulmonary function, quality of life, and so on, and then we decided, but this was probably more of a subjective assessment at that time.

Dr Nwogu. You chose a %VC of 80% as a threshold to decide who should undergo surgery or as a cutoff to decide who would be a favorable candidate, but it seems you did not take into consideration the volume of lung to be resected. Did you look into other parameters, such as the predicted postoperative percent forced vital capacity (FVC) or the predicted postoperative percent DLCO. It seems to me that the risk would be less in a patient in whom you would be able to perform a complete resection with

segmentectomy versus a bilobectomy, for instance. Did you take into consideration the volume of lung to be resected?

Dr Date. That is a great suggestion. We have not looked at our data in that way yet. We will, after your suggestion. I assume that when the postoperative %VC is low, the result is going to be very bad, but we have not done that analysis yet.

Dr Nwogu. Now that you have this information, how has it affected your practice? How do you balance the tradeoff between higher AE of ILD in the larger resections versus the markedly improved long-term survival in those patients? How do you make that decision now?

Dr Date. Regarding the current practice, the decision is still made on a patient-by-patient basis. However, now that we know the 7 risk factors for AE and 5 independent predictors of survival, we can select the optimal surgical procedure for each patient more objectively than before. Regarding bilobectomy or pneumonectomy, a bigger operation, we looked at the rate of AE, and it was 5 to 7 times more than lobectomy and the long-term survival was disappointing. Therefore, for patients requiring a bigger operation (eg, bilobectomy or pneumonectomy), the surgical option should be limited.

Dr Thomas Egan *(Chapel Hill, NC).* You chose 80% FVC. With such a large number, were you able to look at different thresholds and come up with a suggestion that 80% was an important threshold or was it just chosen as one item to look at?

Dr Date. Honestly, 80% was chosen because 80% is usually used for restrictive disease, and we found that there was a significant difference. That is why we chose that number.

Dr Egan. The reason I ask is because it seems to me that there is probably an FVC threshold where the stage I cases would be better served by another modality, like stereotactic radiosurgery.

Dr Date. That is a good suggestion.

Dr Daniel Miller *(Marietta, Ga).* Were you able to look at the perioperative events that occurred, especially bronchopleural fistula, prolonged air leak, and empyema? We all know that when we operate on patients with ILD, they have a more complicated course. Did that play a major role in the acute respiratory failure during that early recovery period and did that make a difference?

Dr Date. We collected those data and found that the postoperative events, such as prolonged air leak, infection, and so on, can trigger the AE as well, but we wanted to know the preoperative factors that could predict the outcome. Those kind of events occurred after the surgery, and the decision-making is difficult before the surgery.

Dr Miller. Was there a difference between the approach, either video-assisted thoracoscopic surgery or a thoracotomy? Sometimes with these patients, as you know, they are difficult from the standpoint that you have to do a lot of these open.

Dr Date. Approximately 45% of the patients received this operation by video-assisted thoracoscopic surgery and 55% by open thoracotomy. There was no difference between the 2 groups in terms of AE and no difference in survival.

Dr Robert Cerfolio *(Birmingham, Ala).* I have 2 quick questions and a comment. I am surprised you didn't mention pulmonary artery hypertension or assessment of that by echocardiography. Maybe it's different in the United States, but we don't operate in most of these patients because of pulmonary artery hypertension. Did you look at that?

Dr Date. No, we did not look at that because these are the patients who were found to have ILD during the workup phase of lung cancer itself. We believe these are in the very early phase of fibrosis.

Dr Cerfolio. The second question is technical tricks to take the fissure. These fissures are nightmares. They are big and thick. Just quickly tell us some tricks on how you took the thick fissure, especially if you are doing a right upper lobe, the fissure between the upper and the middle.

Dr Date. That is probably a question to my personal experience. We try not to go into the fissure at first. We try to divide the vessels.

Dr Cerfolio. We understand that you do the fissures last.

Dr Date. Yes.

Dr Cerfolio. How do you take them?

Dr Date. We usually use a stapler.

Dr Cerfolio. Which stapler? They are very thick.

Dr Murthy. You're thinking of a different animal. These are patients who have been described on CT scan as having some evidence of ILD.

Dr Cerfolio. So you don't think that they are the real bad ones that we're talking about.

Dr Murthy. Well, you have an FVC greater than 80% predicted in 80% of their study population. The entrance criteria is purely radiographic for this study and appears to be independent of positron emission tomography or functional criteria.

Dr Cerfolio. So they didn't clinically have thick fissures.

Dr Murthy. I doubt it. It's not the type of case you're thinking about of more end-stage disease.

Dr Cerfolio. That's important for us to know in the audience, because those patients don't do well with surgery. The third thing is that I would invite you to look at stereotactic body radiation therapy versus this for the T1As if they really do have significant pulmonary fibrosis.

Dr Sudish Murthy *(Cleveland, Ohio).* Another difference I think the audience has to understand is that when you are looking at percent predicted forced expiratory volume in 1 second (FEV1) and you have a homogeneous population from whom you are getting your norms and you are comparing it with a homogeneous population, it's easy to translate, but in the United States, if you take a standard FEV1 of 80% as being something that is grossly abnormal, it depends on the ethnicity of the person who is getting the spirometry checked. A small East Indian male will have a predicted FVC of 65% or 70%, but he may have totally normal spirometry if he would have had his spirometries done in India. I wouldn't get hung up on the 80% FVC. That is another misleading piece of information.

Dr Ara Vaporciyan *(Houston, Tex).* The decision on the surgical approach was not set in advance because this was a retrospective study, so could a reason for the wedge resection in the patients with high FEV1 be that those patients had a higher disease stage and were being forced into a wedge resection because of concern about their interstitial disease. Likewise, in the lower than 80% group, could those patients have received a wedge resection because they had horrific FEV1, very low, and so the differences in the survival patterns of the wedge resections are due to the bias introduced by the surgeon's decision and differences in stage and FEV1?

Dr Date. That is true, but we did a multivariate analysis that still showed a difference between the 2 groups. I think there is a bias, but that can be overcome by an analysis in a multivariate way.

Dr Vaporciyan. I would warn you that when 2 factors in a multivariable analysis track parallel one another, you can get fooled.

Dr Date. Yes. You may need a randomized prospective trial to prove that.

TABLE E1. Univariate analysis for patients' survival

Factors	Categories	Cases	Hazard ratio	95% CI	*P* value	*P* value of global association
Age		1763	1.013	1.003-1.024	.009	
Sex	Male	1593	1	—	—	
	Female	170	0.659	0.504-0.861	.002	
BMI		1746	0.973	0.951-0.996	.022	
Smoking history	Never smoked	109	1	—	—	.006
	Ex-smoker	1006	1.649	1.170-2.326	.004	
	Current smoker	632	1.428	1.004-2.032	.048	
Brinkman index		1742	1.000	1.000-1.000	.302	
Comorbidities						
Asthma	−	1742	1	—	—	
	+	33	0.838	0.484-1.450	.527	
Emphysema	−	1167	1	—	—	
	+	589	1.084	0.933-1.259	.294	
Collagen disease	−	1654	1	—	—	
	+	102	1.123	0.849-1.485	.416	
KL6* (U/mL)		1043	1.000	1.000-1.000	.002	
	<1000	834	1	—	—	
	>1000	209	1.431	1.157-1.769	<.001	
CEA (ng/mL)		1664	1.001	1.000-1.002	.005	
P_{AO_2} (torr)		1552	0.998	0.991-1.004	.493	
$Paco_2$ (torr)		1547	0.979	0.961-0.998	.030	
%VC		1741	0.977	0.973-0.982	<.001	
	<80	263	1	—	—	
	>80	1478	0.516	0.431-0.617	<.001	
FEV1 (L)		1748	0.739	0.645-0.847	<.001	
FEV1.0%		1749	1.006	1.001-1.012	.024	
	<70	460	1	—	—	
	>70	1289	1.301	1.100-1.539	.002	
%FEV1.0		1742	0.997	0.994-1.001	.122	
DLCO (mL/min/torr)		1121	0.960	0.943-0.978	<.001	
%DLCO		1128	0.993	0.989-0.997	<.001	
Radiologic findings	UIP pattern	1300	1	—	—	
	Non-UIP pattern	463	0.836	0.706-0.988	.036	
Histology	Adenocarcinoma	721	1			<.001
	Squamous cell	816	1.172	1.005-1.366	.042	
	Large cell	64	1.071	0.722-1.587	.734	
	Others	139	1.440	1.107-1.874	.007	
Pathologic stage	Ia	547	1	—	—	
	Ib	481	1.548	1.255-1.909	<.001	
	IIa	70	1.723	1.178-2.521	.005	
	IIb	241	2.203	1.741-2.787	<.001	
	IIIa	244	3.020	2.405-3.791	<.001	
	IIIb	114	3.264	2.464-4.324	<.001	
	IV	34	4.036	2.663-6.116	<.001	
Surgical procedures	Wedge resection	275	1	—	—	<.001
	Segmentectomy/lobectomy	1386	0.840	0.694-1.018	.076	
	Bilobectomy/pneumonectomy	94	1.440	1.056-1.965	.021	
Tumor location	Upper lobe	670	1	—	—	.028
	Middle lobe	77	1.372	0.963-1.953	.080	
	Lower lobe	958	1.249	1.072-1.456	.004	
	Multiple	5	0	N/A	N/A	
VATS	−	964	1	—	—	
	+	798	0.952	0.825-1.099	.500	

(Continued)

TABLE E1. Continued

Factors	Categories	Cases	Hazard ratio	95% CI	*P* value	*P* value of global association
Node dissection	0	311	1	—	—	.680
	1	339	0.919	0.723-1.167	.487	
	2	1104	0.921	0.762-1.113	.394	

BMI, Body mass index; *CEA*, carcinoembryonic antigen; *CI*, confidence interval; *DLCO*, carbon monoxide diffusing capacity; *FEV1*, forced expiratory volume in 1 second; *KL-6*, Klebs von Lungen-6; *N/A*, not available; $Paco_2$, arterial carbon dioxide tension; Pao_2, arterial oxygen tension; *UIP*, usual interstitial pneumonia; *VATS*, video-assisted thoracoscopic surgery; *%VC*, percent vital capacity. *Serum biomarker for pulmonary fibrosis.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Phase III Trial Comparing Weekly Docetaxel Plus Cisplatin Versus Docetaxel Monotherapy Every 3 Weeks in Elderly Patients With Advanced Non–Small-Cell Lung Cancer: The Intergroup Trial JCOG0803/WJOG4307L

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ABSTRACT

Purpose
This phase III trial aimed to confirm the superiority of weekly docetaxel and cisplatin over docetaxel monotherapy in elderly patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Chemotherapy-naïve patients with stage III, stage IV, or recurrent NSCLC age ≥ 70 years with a performance status of 0 or 1 who were considered unsuitable for bolus cisplatin administration were randomly assigned to receive docetaxel 60 mg/m^2 on day 1, every 3 weeks, or docetaxel 20 mg/m^2 plus cisplatin 25 mg/m^2 on days 1, 8, and 15, every 4 weeks. The primary end point was overall survival (OS).

Results
In the first interim analysis, OS of the doublet arm was inferior to that of the monotherapy arm (hazard ratio [HR], 1.56; 95% CI, 0.98 to 2.49), and the predictive probability that the doublet arm would be statistically superior to the monotherapy arm on final analysis was 0.996%, which led to early study termination. In total, 276 patients with a median age of 76 years (range, 70 to 87 years) were enrolled. At the updated analysis, the median survival time was 14.8 months for the monotherapy arm and 13.3 months for the doublet arm (HR, 1.18; 95% CI, 0.83 to 1.69). The rates of grade ≥ 3 neutropenia and febrile neutropenia were higher in the monotherapy arm, and those of anorexia and hyponatremia were higher in the doublet arm.

Conclusion
This study failed to demonstrate any survival advantage of weekly docetaxel plus cisplatin over docetaxel monotherapy as first-line chemotherapy for advanced NSCLC in elderly patients.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related death in most developed countries. Non–small-cell lung cancer (NSCLC) accounts for 85% of all lung cancers, and more than 50% of patients with NSCLC already have advanced disease at diagnosis.[1] The number of elderly patients with lung cancer has also increased, and the median age at diagnosis is 70 years.[2]

The Elderly Lung Cancer Vinorelbine Italian Study, in which single-agent vinorelbine was compared with the best supportive care, first demonstrated the benefits of chemotherapy in elderly patients with advanced NSCLC.[3] In the Multicenter Italian Lung Cancer in the Elderly Study, a combination of vinorelbine plus gemcitabine did not improve survival over vinorelbine or gemcitabine alone and only increased the toxicity frequency.[4] Therefore, single-agent vinorelbine or gemcitabine was established as the standard treatment for elderly patients with NSCLC. We compared docetaxel (every 3 weeks) with vinorelbine in the West Japan Thoracic Oncology Group (the former name of the West Japan Oncology Group [WJOG]) 9904 study, which revealed significantly superior responses and better survival in the docetaxel arm.[5]

However, platinum-doublet chemotherapy has been recommended for patients with NSCLC with a performance status (PS) of 0 or 1,[6-8] and several retrospective subgroup analyses of large phase III trials have shown that the efficacy of platinum-doublet chemotherapy is similar in selected elderly patients and younger patients.[9,10] However, drug excretion or metabolic abilities generally decline because of age-related insufficiencies, especially in renal function. Therefore, modifications of anticancer drug dosages or schedules are recommended in chemotherapy for elderly patients with cancer.[11] In Japan, phase I[12] and II trials of weekly docetaxel plus cisplatin (DP) were conducted in elderly patients with NSCLC. The phase II study revealed a response rate (RR) of 52% (95% CI, 31% to 67%), a median survival time of 15.8 months, and no grade 4 toxicity.[13] On the basis of these promising results, we conducted a randomized phase III trial, the Japan Clinical Oncology Group (JCOG) 0207 trial, to compare DP with single-agent docetaxel. For the control arm, we chose weekly split docetaxel to investigate the effects of added cisplatin. In the second interim analysis, the overall survival (OS) seemed to be more favorable in the DP arm; however, an unexpected large difference was observed in the subgroup of patients age less than 75 years.[14] Therefore, considering the potential disadvantage of single-agent docetaxel therapy in this subgroup, we terminated the study and designed a new phase III trial in which the control arm received bolus infusions of docetaxel every 3 weeks, based on the West Japan Thoracic Oncology Group 9904 study.[5]

PATIENTS AND METHODS

Patients

Patients eligible for this study included chemotherapy-naïve patients with histologically or cytologically confirmed stage III (no indication for definitive radiotherapy), stage IV, or recurrent NSCLC who were age ≥ 70 years, with an Eastern Cooperative Oncology Group PS of 0 or 1 and adequate organ functioning, but who were unsuitable for bolus cisplatin administration. Considering that the age group of 70 to 74 years included those who were suitable and unsuitable for bolus cisplatin administration, we classified the reasons for administration unsuitability in this age group into six categories and examined patients for these conditions before enrollment. The pre-enrollment evaluation is described in the Appendix and Appendix Table A1 (online only). Prior radiotherapy, except for the primary lesion, was permitted if it had been completed at least 2 weeks before enrollment onto the study. Patients with symptomatic brain metastasis, active malignancy within the previous 5 years, superior vena cava syndrome, massive pleural effusion or ascites, critical vertebral metastasis, uncontrolled hypertension or diabetes, severe heart disease, active infection, hepatitis virus B surface antigen seropositivity, pulmonary fibrosis, polysorbate 80 hypersensitivity, or steroid dependence were excluded.

The study protocol was reviewed and approved by the JCOG Protocol Review Committee, WJOG executive board, and institutional review boards of each participating institution before study initiation. All patients provided written informed consent before enrollment.

Study Design and Treatment Plan

Eligible patients were randomly assigned to either the docetaxel arm (docetaxel 60 mg/m^2 infused over 60 minutes on day 1 every 3 weeks) or the DP arm (docetaxel 20 mg/m^2 infused over 60 minutes plus cisplatin 25 mg/m^2 infused over 15 to 20 minutes on days 1, 8, and 15 every 4 weeks). Patients were randomly assigned via the minimization method to balance the arms with the institution, disease stage (III v IV or recurrence), and age (≥ v < 75 years). In the DP arm, treatment was skipped under the following conditions: total leukocyte count less than 2,000/μL, platelet count less than 50,000/μL, creatinine level ≥ 1.5 mg/dL, and presence of fever or grade ≥ 3 nonhematologic toxicity (except constipation, weight loss, cough, hoarseness, and hyponatremia) on day 8 or 15. In both arms, subsequent cycle treatment was administered when the patients met the following conditions: total leukocyte count ≥ 3,000/μL, absolute neutrophil count ≥ 1,500/μL, platelet count ≥ 100,000/μL, serum creatinine level less than 1.5 mg/dL, total bilirubin level less than 2.0 mg/dL, ALT/AST ≤ 100 IU/L, and PS 0 to 2. Administration procedures, dose reduction criteria, and methods are detailed in the Appendix. Both treatments were repeated until the detection of disease progression or appearance of unacceptable toxicity. Radiographic tumor evaluations were performed and assessed, according to RECIST (version 1.0),[15] by each investigator at least every two cycles. Laboratory examinations were performed at least once a week in both arms, and toxicity was assessed before every cycle and classified in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Second-line treatment was administered at the investigator's discretion; however, cross-over to the other treatment arm was not permitted.

Quality-of-Life Assessment

Quality of life (QOL) was assessed by symptom scores, using the seven items of the Lung Cancer subscale of the Functional Assessment of Cancer Therapy–Lung.[16] The patients scored themselves immediately after providing informed consent and after completing the second and third treatment cycles. The proportions of patients with improved scores between the baseline and the end of the third cycle in each arm were compared. Missing data after treatment initiation were considered as indicating no improvement. In addition, we compared least squared means of the total scores from repeated measures analysis of variance with treatment arm, time, and their interaction and the 95% CI at each time point.

Supplementary Ad Hoc Analysis

Additional data collection and ad hoc analysis were performed. Data on the active epidermal growth factor receptor (*EGFR*) mutation status (exon 19 deletion or L858R point mutation) and poststudy treatments were collected because these were considered factors that could potentially affect survival.

Statistical Analysis

OS was the primary trial end point. The secondary end points included RRs, progression-free survival (PFS), symptom scores, and toxicities. The study was designed to provide results with a statistical power of 80%, using a one-sided $\alpha = .05$ to detect a 33% increase in median survival from 10 to 13.3 months. A total of 364 patients was required, accrued over a 4-year period with a 1-year follow-up period. Assuming a 5% rate of ineligible patients and patients lost to follow-up, the study sample size was set at 380 patients. OS, PFS, and responses were assessed in all eligible patients on an intent-to-treat basis. OS and PFS, which are defined in the Appendix, were estimated using the Kaplan-Meier method and were compared using the stratified log-rank test, according to age. Hazard ratios (HRs) of the treatment effects were estimated using the Cox proportional hazards model. RRs were compared using Fisher's exact test.

Two interim analyses were planned, the first after 50% of the patients were enrolled and the second after enrollment was completed. In these interim analyses, the primary end point, OS, was evaluated after adjustment for multiple comparisons, according to the Lan and DeMets method.[17] The O'Brien-Fleming–type α spending function was used. P values presented for the primary analysis were one-sided, in accordance with the trial design, whereas the other analysis values were two-sided. All analyses were performed using SAS software, release 9.1 (SAS Institute, Cary, NC). This study is registered with University Hospital Medical Information Network Clinical Trials Registry (www.umin.ac.jp/ctr/; identification No.: UMIN000001424).

RESULTS

The first interim analysis was performed in September 2010 and included data from 221 patients. Information time, defined as the

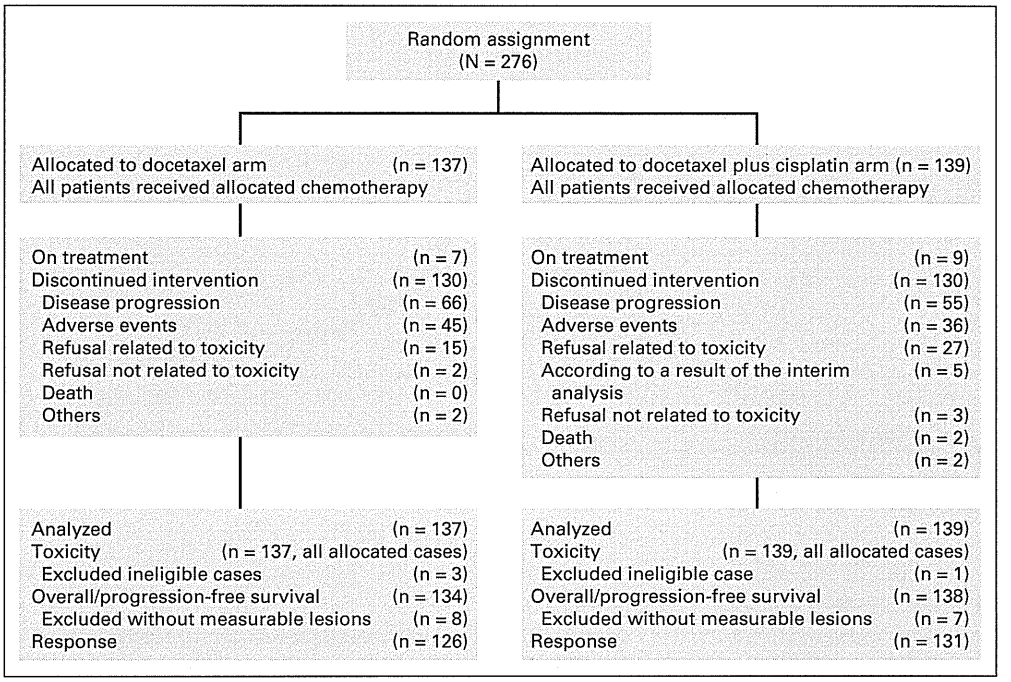

Fig 1. CONSORT diagram.

proportion of the interim events to the planned events, was 0.24 (73 of 304 events). Survival in the DP arm was inferior to that in the docetaxel arm (HR for DP to docetaxel arm, 1.56; 95% CI, 0.98 to 2.49; multiplicity-adjusted 99.99% CI, 0.62 to 3.88; one-sided $P = .97$ and two-sided $P = .06$ by stratified log-rank test), and the predictive probability that DP would be statistically superior to docetaxel on final analysis was 0.996% (< 1%). These results led to early study termination based on the recommendation of the Data and Safety Monitoring Committee, in accordance with the stopping guidelines prespecified in the protocol.

Patient Characteristics

Between October 2008 and September 2010, 276 patients (215 patients from JCOG and 61 patients from WJOG) were enrolled from 56 institutions (36 institutions affiliated with JCOG and 20 institutions affiliated with WJOG). Of these patients, 137 and 139 patients were assigned to the docetaxel and DP arms, respectively. All patients received the study treatments; therefore, all 276 patients were included in the safety analysis set. Three patients in the docetaxel arm and one patient in the DP arm were ineligible because of uncontrolled diabetes (ie, dependence on insulin injections) or previous malignancy. Therefore, these patients were excluded from survival analyses (Fig 1). Although the proportions of female patients and patients with adenocarcinoma were slightly higher in the docetaxel arm than in the DP arm, the patients' baseline characteristics were generally well balanced between the treatment arms (Table 1).

Treatment Delivery

The median number of treatment cycles was four (range, one to 18 cycles) in the docetaxel arm and three (range, one to six cycles) in the DP arm, and the proportion of patients in whom treatment continued for five or more cycles was higher in the docetaxel arm than in the DP arm (31% *v* 8%, respectively). In the docetaxel and DP arms, 37% and 4% of patients required one-step dose reductions, respectively. Furthermore, 19% of patients required two-step dose reductions in the docetaxel arm. In the DP arm, 19% of patients had one or more skipped treatments on day 8 or 15. The major reasons for

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	Docetaxel (n = 137)		Docetaxel/Cisplatin (n = 139)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	76		76	
Range	70-87		70-86	
< 75	31	23	32	23
≥ 75	106	77	107	77
Sex				
Male	95	69	101	73
Female	42	31	38	27
Smoking status*				
Never	38	28	36	26
Smoker	98	72	101	74
ECOG PS				
0	50	36	48	35
1	87	64	91	65
Stage				
III	42	31	43	31
IV or recurrence	95	69	96	69
Histology*				
Adenocarcinoma	91	67	86	63
Squamous	32	24	39	28
Others	13	10	12	9

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.
*Data for one patient in the docetaxel monotherapy arm and two patients in the docetaxel plus cisplatin arm were missing.

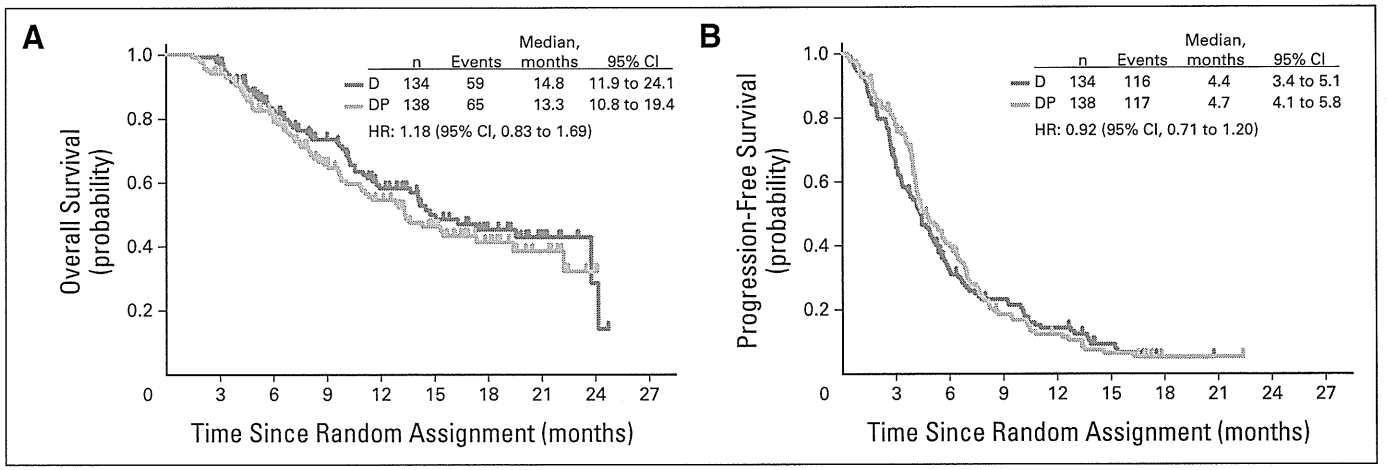

Fig 2. Kaplan-Meier curves for (A) overall survival and (B) progression-free survival. Tick marks indicate censored patients at the data cutoff point (November 2010). D, docetaxel; DP, docetaxel plus cisplatin; HR, hazard ratio.

treatment discontinuation in the docetaxel versus DP arms were disease progression (51% *v* 42%, respectively), adverse events (35% *v* 28%, respectively), and patient refusal to continue treatment as a result of toxicity (12% *v* 21%, respectively).

Efficacy

The overall RRs were 24.6% in the docetaxel arm (95% CI, 17.4% to 33.1%) and 34.4% in the DP arm (95% CI, 26.3% to 43.2%). The difference was not statistically significant ($P = .10$).

By November 22, 2010, 124 (45.6%) of the 272 eligible patients had died (docetaxel arm, n = 59; DP arm, n = 65). The median follow-up time for all eligible patients was 9.6 months. The 1-year survival rates were 58.2% and 54.5% in the docetaxel and DP arms, respectively. The HR for OS was 1.18 (95% CI, 0.83 to 1.69; Fig 2A). The HR for PFS was 0.92 (95% CI, 0.71 to 1.20; Fig 2B).

Toxicity

Hematologic and nonhematologic toxicities are listed in Table 2. Grade ≥ 3 leukopenia and neutropenia occurred more frequently in the docetaxel arm. The incidence of grade 4 neutropenia was 67.9% in the docetaxel arm but only 0.8% in the DP arm. Febrile neutropenia was observed only in the docetaxel arm at an incidence of 15.2%. Grade ≥ 3 anemia, hyponatremia, and anorexia were observed in more than 10% of patients in the DP arm. Four treatment-related deaths occurred, all in the DP arm (2.9%), including three patients who died of pneumonitis and one patient who died of unclassified sudden death.

QOL

Symptom score questionnaire responses were collected from 271 (98.2%) of 276 patients at baseline, 258 patients (93.5%) after the second cycle, and 247 patients (89.5%) after the third cycle. The

Table 2. Toxicities

	Docetaxel (n = 137)			Docetaxel/Cisplatin (n = 139)		
Adverse Event	Grade 3 or 4 (%)	Grade 4 (%)	Missing (No.)	Grade 3 or 4 (%)	Grade 4 (%)	Missing (No.)
Hematologic*						
Leukopenia	62.7	8.2	3	5.4	0	10
Neutropenia	88.8	67.9	3	10.1	0.8	10
Anemia	3.7	0.7	3	16.3	0.8	10
Thrombocytopenia	0	0	3	0.8	0	10
Nonhematologic*						
Febrile neutropenia	15.2	0	5	0	0	8
Hyponatremia	5.2	0.7	3	14.7	0.8	10
Hypoalbuminemia	1.5	—	6	4.7	—	10
Infection	7.6	0	5	8.4	0.8	8
Anorexia	1.5	0	5	10.7	0	8
Nausea	0.8	0	5	3.8	0	8
Diarrhea	3.8	0	5	0.8	0	9
Fatigue	3.0	0	5	5.3	0	8
Pneumonitis	5.3	0	5	2.3	0.8	8

NOTE. There were four treatment-related deaths (2.9%), all in the docetaxel plus cisplatin arm, including three deaths resulting from pneumonitis and one unclassified sudden death.
*Each value was calculated while excluding patients with missing data.

