3. Statistical considerations

Randomization was carried out by a blocked arrangement that balanced the treatment assignments within each institution. All patient data, including clinical, pathological, and outcome measures were entered into a computerized database using a Stat view version 5.0 (SAS Institute Inc. Cary, NC, USA.). The chi-square test and Fischer's test were used to examine the deviation of each patient's characteristics. The Kaplan-Meier method was used to calculate survival analyses. The log-rank test and the generalized Wilcoxon test were used to determine survival differences.

We planned to enter 100 cases into each group. The benefit of adjuvant chemotherapy was assumed to be a 20% increase in the 3-year survival rate (60% in the adjuvant group and 40% in the observation group) [5,6]. Given these assumptions, 154 patients were required, assuming a type 1 error of 0.05 and a type 2 error of 0.20. The primary endpoint was overall survival. The secondary endpoints was disease-free survival. However, the accrual rate was very slow. We abandoned this study in July 1998 after acquiring permission to do so from the JCOG clinical trial review committee. The endpoint was changed to overall survival only. Follow up was done every 6 months by the JCOG data center. The final outcome was confirmed in August 2001.

4. Results

From January 1994 to July 1998, 119 cases were entered from 26 institutes. Of the 119 patients, 59 were randomized to the CDDP + VDS arm and 60 to the surgery alone arm. Only one patient was lost to follow-up.

Forty men and 19 women were included in the adjuvant chemotherapy arm, and 37 men and 23 women were included in the control arm. The median age was 62 in both groups. Pneumonectomy was performed in only six patients in each group. The two groups were well balanced in regard to sex, age, operation performed, preoperative stage, pathological T factors, pattern of combined resection and number of N2 stations (Table 1).

There were no ineligible cases. There were no toxic deaths during adjuvant chemotherapy. Thirty-five of the 59 patients assigned to the chemotherapy arm received three courses of chemotherapy, 55 patients received one or more courses of chemotherapy, and 44 patients received two or more courses. The major cause of

Table 1 Patient characteristics

	Adjuvant chemotherapy	Observation	
Gender (male/female)	40 (68%)/19	37 (62%)/23	0.48
Median age	62 (41–75)	62 (43–74)	0.93
Operation			
Pneumonectomy	6 (10%)	6 (10%)	0.97
Lobectomy	53	54	
Clinical stage			
Stage I–II	44 (75%)	41 (68%)	0.45
Stage III	15 (25%)	19 (32%)	
Pathological T			
T1–/T3	50	55	0.24
Histology			
Adenocarcinoma/squamous cell carcinoma/others	47 (80%)/9/3	40 (67%)/15/5	0.28
Combined resection			
Chest wall	6	3	0.28
Diaphragm	1	1	
Others	9	4	
None	43 (73%)	52 (87%)	
Number of N2 stations			
1	31 (52%)	28 (47%)	0.75
2	24	25	
Unknown	4	6	

Table 2 Compliance of chemotherapy and causes for discontimuation

Chemotherapy	Case no.	Cycles performed			
		0	1	2	3
Fully administered	59	4	11	10	34 (58%)
	34	0	0	0	34
Cause of discontinuation					
Adverse effect	5	0	3	2	–
Patient refusal	18	3	7	8	–
Others	2	1	1	1	–

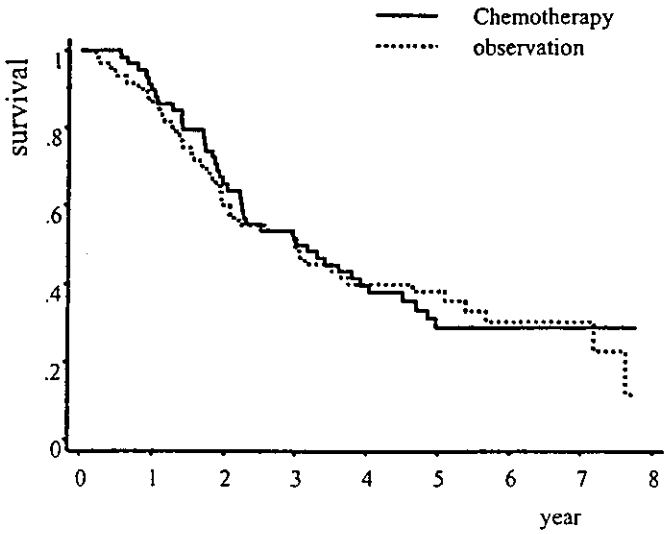
discontinuation of the chemotherapy was patient withdrawal, which accounted for 17 cases (Table 2). There were no grade four adverse effects on hematological data during chemotherapy. The major toxicity was grade 3 neutropenia, which 50% of patients experienced. Only two patients had grade 3 bilirubinemia, and one had grade 3 creatinine elevation.

The 5-year survival was 28.2% in the chemotherapy arm and 36.1% in the control group ($P = 0.89$). The median disease-free survival was 18.3 months in the chemotherapy group and 16.1 months in the control group ($P = 0.66$). There were no statistical differences between the two groups in overall survival by either the log-rank test or the generalized Wilcoxon test (Fig. 1). Almost all deaths were from the original cancer, especially distant metastasis (46%). Lung, bone and brain were frequent sites of relapse in both groups. Lymph node relapses were more frequently seen in the observation group than the adjuvant chemotherapy group ($P = 0.049$) (Tables 3 and 4). Univariate analysis was performed to examine the following factors: treatment arm, age, gender, tumor histology, extent of surgery, existence of combined resection, and number of N2 stations (Table 5). Only an age of 61 or younger was found to be a significant favorable prognostic factor ($P = 0.042$).

5. Discussion

We set out to clarify whether adjuvant chemotherapy is effective in cases of completely resected N2 non-small cell lung cancer.

The first report of adjuvant chemotherapy for completely resected non-small cell lung cancer



Patient at risk

chemotherapy	59	52	38	30	22	12	7	5
Surgery alone	60	52	36	30	22	17	9	4

Fig. 1 Actual survival. The solid line indicates the adjuvant group and dotted line indicates the observation group ($P = 0.89$).

Table 3 Treatment-related adverse effects (WHO grade) by chemotherapy

Adverse effect	Grade 1–2 (%)	Grade 3 (%)	Grade 4 (%)
WBC	44	51	0
Hb	85	7	0
Plt	11	2	0
Bilirubin	11	4	0
SGOT	22	0	0
SGPT	24	0	0
Creatinine	25	1	0
Nausea/vomit	73	9	0
Diarrhea	16	0	0
Infection	5	2	0
Alopecia	78	–	–

Four patients who did not have chemotherapy were excluded from this analysis. $n = 55$.

Table 4 Relapse patterns for each group

Relapse site	Adjuvant chemotherapy	Observation	*P*-value
Bone	10 (2)	8 (1)	0.77
Brain	13 (1)	8	0.31
Lung	13 (2)	10 (4)	0.60
Mediastinal or cervical LN	7	18 (3)	0.049
Others	4 (1)	5	0.99

Data in parentheses represent metastasis found synchronously at another site. All data reflect absolute numbers of patients.

Table 5 Univariate analyses according to prognostic factors

Factors		*P*-value
Study arm	Adjuvant vs. obsevation	0.840
Age	≤61 vs. >61	0.042
Gender	Female vs. male	0.505
Histology	Adenocarcinoma (ad) vs. non-ad	0.220
Operation	Pneumonectomy vs. lobectomy	0.614
Combined resection	With vs. without	0.116
Number of N2 station	1 vs. 2	0.333

There is no significant difference between any factors.

using a CDDP-based regimen, reported by Holmes et al. [1], included stages II and III, and demonstrated slight effectiveness of adjuvant chemotherapy for large cell and adenocarcinoma cases. LCSG801 [7] also included T2N0 and T2N1 patients, but revealed no effectiveness of adjuvant chemotherapy for non-small cell lung cancer at all. Niiranen et al. reported another randomized trial for completely resected non-small cell lung cancers [8]. Although they demonstrated the efficacy of adjuvant chemotherapy for T1-3N0 patients, the higher number of pneumonectomies included in the observation group might have caused the difference. A meta-analysis of adjuvant chemotherapy by the Non-Small Cell Lung Cancer Collaborative Group reported that the hazards ratio in most trials slightly favored adjuvant chemotherapy but the *P*-value was not significant [9]. The 5-year survival rate for adjuvant chemotherapy patients was 5% better than for surgery alone. A BLT study (ASCO 2003, abstract#2543), which enrolled 381 patients from 56 institutes and included all stages, also could not show the effectiveness of chemotherapy. An 8% 2-year survival advantage was seen with chemotherapy in another meta-analysis for node positive patients [10]. Therefore, the selection of particular stages for perioperative chemotherapy may have been the key to the success seen in that adjuvant chemotherapy trial.

Dautzenberg reported a randomized trial that compared adjuvant radiation versus adjuvant radiation plus chemotherapy [11]. They found no significant difference in overall survival. However, in the subset analyses, patients with N2 disease treated with chemoradiation had a significantly better survival than radiation alone. Keller also reported no difference between survival rates for adjuvant chemo-radiotherapy and adjuvant radiotherapy for stage II and IIIa cancers [12]. Although there have been many clinical trials for non small cell lung cancer, there have been almost no reports on clinical trials of adjuvant chemotherapy for n2 disease. Only Pisters et al. [13] made a report on comparing adjuvant chemo-radiotherapy and adjuvant radiotherapy limited to 71 cases of T1-2 N2 disease including incompletely resected patients. They also did not demonstrate any therapeutic effectiveness. There are several large-scale randomized control studies of adjuvant chemotherapy for patients with completely resected lung cancers. An ALPI study (ASCO 2002, abstract#1157) reported ineffective results, while an IALT study (ASCO 2003, abstract#6) showed slight efficacy of adjuvant chemotherapy. Those two trails included radiation therapy frequently for patients with nodal metastasis. Those reports, mentioned above, aimed to

determine the efficacy of adding chemotherapy to radiation therapy after surgery for patients with nodal metastasis. PORT meta analysis reported that post operative radiation therapy was not useful even in nodal metastasis patients [14], so we aimed to determine the efficacy of adding chemotherapy after surgery for patients with mediastinal nodal metastasis without radiation therapy.

Ohta et al. reported an adjuvant trial for stage IIIa disease conducted by JCOG [3], which also revealed no effectiveness of adjuvant chemotherapy. Although the patients were randomly assigned to each group, the surgery alone group included a higher number of N2 disease patients than the adjuvant chemotherapy group, which may have been related to the negative result. We enrolled only completely resected N2 disease to reduce the heterogeneity of diseases.

Compliance is important in adjuvant chemotherapy. LCSG801 [7] was criticized for low compliance, which was seen as one possible reason for negative data. In our series, 58% of patients received the targeted dose and 75% received two or more courses without serious adverse effects. This appeared sufficient for adjuvant chemotherapy. Although the number of patients accrued was small, the two survival curves were almost identical. Thus, in pathological N2 disease, adjuvant chemotherapy using CDDP and VDS does not improve survival.

The initial target of neoadjuvant chemotherapy was only locally advanced cancer. A few small-sample trials have shown some efficacy of perioperative chemotherapy [15,16]. Recently, a Bimodality Lung Oncology Trial (BLOT) study focused on earlier stages as a target for chemotherapy [13]. The French trial for neoadjuvant chemotherapy also included stages I-IIIa [17]. These two groups hold great expectations for perioperative chemotherapy in earlier stages. Considering these studies, adjuvant chemotherapy is also warranted with new agents for earlier stages of cancer.

6. Conclusion

Patients with N2, NCSLC who had undergone complete resection, were randomized to surgery only or adjuvant chemotherapy (cisplatin 80 mg/m^2 on day 1; vindesine 3 mg/m^2 on days 1 and 8; ×3 courses). This trial was terminated before accumulation of the planned numbers for registration because of a slow accrual rate. A total of 119 patients were randomized (59 patients in the adjuvant arm and 60 with surgery alone). The median survival was 36 months for both groups. There was no significant difference in survival between the adjuvant chemotherapy group and the observation group. The efficacy of adjuvant chemotherapy for completely resected NSCLC with N2 disease might be so small that the number of patients in this study was insufficient to detect the efficacy of this classic regimen.

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Prognosis and histologic features of small pulmonary adenocarcinoma based on serum carcinoembryonic antigen level and computed tomographic findings

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Abstract

Objectives: In 2001, we proposed the criteria for combined evaluation of the serum carcinoembryonic antigen (CEA) level and the tumor shadow disappearance rate (TDR) to predict pathologic N0 (pN0) disease in pulmonary adenocarcinomas. The objective of the present study was to determine the prognosis and histologic features in small-sized pulmonary adenocarcinomas according to serum CEA level and TDR. **Methods**: We reviewed clinical records of 189 consecutive patients with peripheral pulmonary adenocarcinoma 3.0 cm or smaller who underwent major lung resection and systematic lymph node dissection: 50 patients with TDR 0.8 or more and normal CEA level (group I) and 139 patients with TDR < 0.8 and/or elevated CEA level (group II). Among them, we investigated histologic features of 177 adenocarcinomas according to serum CEA level and TDR. **Results**: The 5-year survival rates were 95% for group I and 75% for group II ($P = 0.002$), and for pN0 patients, 97% in group I and 87% in group II ($P = 0.04$). In univariate analyses, TDR, preoperative serum CEA level, and the maximum tumor dimension on computed tomographic (CT) scan were significantly associated with prognosis. Multivariate analysis showed that only preoperative serum CEA level and TDR were significant independent prognostic factors, and the maximum tumor dimension was not significant. Group I patients developed no local recurrence, including lymph node metastases. In 25 group I adenocarcinomas 2.0 cm or smaller, no lymph node involvement, two lymphatic permeation, two vascular invasion, and one pleural involvement tumors were observed. These signs of local invasiveness were less frequent than the remaining adenocarcinomas. CT findings correlated well with histologic findings in small-sized adenocarcinomas. **Conclusions**: Combined evaluation of preoperative serum CEA level and TDR may enable us to identify minimally invasive adenocarcinomas with good prognosis. Candidates for limited lung resection without systematic lymph node dissection could be selected based on these findings.

Keywords: Lung cancer; Limited surgery; Carcinoembryonic antigen; Computerized tomography scan; Adenocarcinoma

1. Introduction

Many small-sized lung cancers, especially peripheral adenocarcinomas, have been found as a result of the introduction of computed tomographic (CT) screening for lung cancer [1]. Among them, bronchioloalveolar carcinoma (BAC) with small invasive foci has been found increasingly. Several investigators reported that these BAC type adenocarcinomas are likely to appear as localized ground glass attenuation (GGA) [2–5]. In the latest edition of World Health Organization (WHO) classification of lung tumors [6], BAC is classified as non-invasive carcinoma. If the relationship between GGA and BAC is conclusive, candidates for limited lung resection could be selected based on CT findings.

We previously reported that pathologic N0 (pN0) status in peripheral pulmonary adenocarcinoma was predictable by the combined evaluation of serum carcinoembryonic antigen (CEA) level and a radiological parameter, tumor shadow disappearance rate (TDR) [7]. TDR is the ratio of a maximum tumor area in mediastinal window setting images to that in

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pulmonary window setting images on conventional CT scans. We speculated that TDR could be interpreted as the extent of both GGA and BAC. However, we did not show in the previous study the data on the correlation between TDR and histologic features and prognostic implication of TDR.

The objective of the present study was to determine the prognosis and histologic features in small-sized pulmonary adenocarcinomas according to serum CEA level and TDR.

2. Patients and methods

2.1. Patients

From August 1992 to April 1997, 189 consecutive patients with peripheral adenocarcinoma 3.0 cm or smaller who underwent major lung resection and systematic lymph node dissection at the National Cancer Center Hospital East were reviewed. One hundred and eighty-five lobectomies, three lobectomies with bronchoplastic procedures, and one pneumonectomy were carried out. There were 89 men and 100 women. The mean age was 63 years, ranging from 33 to 84 years.

2.2. Outcome and patterns of failure

All clinical records were carefully reviewed to examine patterns of failure and outcome. The median follow-up period for the 189 patients was 57 months. The length of survival was defined as the interval in months between the day of surgical intervention and the date of death due to any cause or the last follow-up. The survival rates were calculated by the Kaplan–Meier method, and the curve differences were tested using the log-rank test. Because the median follow-up time was less than 5 years, we calculated 3- and 5-year survival rates separately.

As in our previous report [7], the following tumor dimensions on conventional CT scan was defined: pDmax, the maximum dimension of a tumor on pulmonary window setting images; pDperp, the largest dimension perpendicular

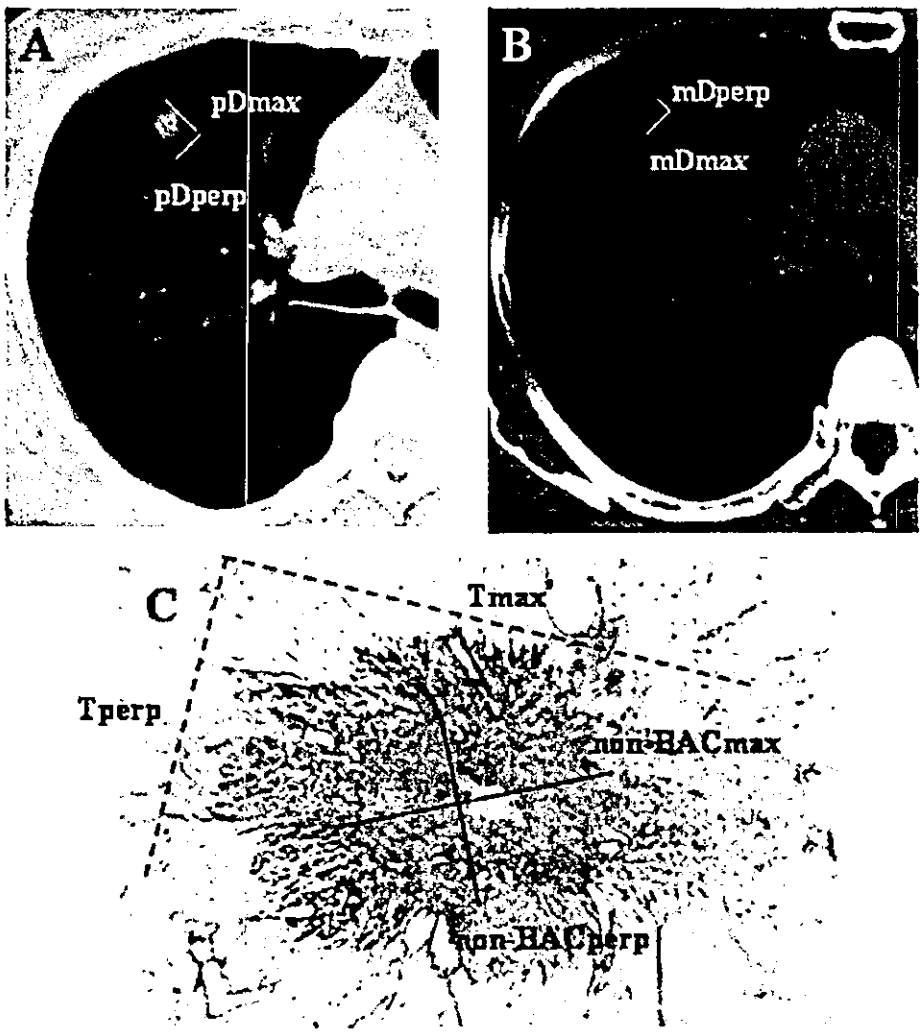

Fig. 1. We measured pDmax and pDperp on pulmonary window setting images (A), and mDmax and mDperp on mediastinal window setting images (B). We also measured Tmax, Tperp, non-BACmax, and non-BACperp at the maximum tumor dimension on low power views (hematoxylin and eosin stain, original magnification 5 ×) as illustrated (C).

to the maximum axis on pulmonary window setting images; mDmax, the maximum dimension of a tumor on mediastinal window setting images; and mDperp, the largest dimension perpendicular to the maximum axis on mediastinal window setting images (Fig. 1A and B). TDR was calculated by the following formula as previously described [7]:

$$TDR = 1 - \frac{(mDmax) \times (mDperp)}{(pDmax) \times (pDperp)}$$

Univariate and multivariate analyses were performed by means of Cox's proportional hazards model on Stat View 5.0 (Abecus Concepts, Inc., Berkeley, CA). In multivariate analysis, forward and backward stepwise procedures were used to determine the combination of preoperatively available factors that were essential in predicting prognosis. The present multivariate analysis included five variables: gender, age, TDR, preoperative serum CEA level, and pDmax. In the statistical analyses, we used continuous variables for age, pDmax, and TDR. Because the distribution of serum CEA values was positively skewed, we used the log-transformed values to normalize the distribution.

2.3. Histologic features

Two authors (K.T. and T.Y.) reviewed 177 of 189 pathologic materials of tumors to investigate histologic features. The resected specimens were fixed with 10% formalin or 99.8% methanol injected directly through the bronchial tree or pleura to be fully expanded. Because material fixation was inappropriate for histologic review, 12 cases were excluded. We studied lymphatic permeation, vascular invasion, pleural involvement, and scar grade [8]. Additionally, we measured the following tumor parameters at the maximum tumor dimension on low power view: Tmax, the maximum tumor dimension; Tperp, the largest tumor dimension perpendicular to the maximum axis; non-BACmax, the maximum dimension of a tumor component other than BAC; and non-BACperp, the largest dimension perpendicular to the maximum axis of the non-BAC component (Fig. 1C). The BAC component was defined as a component of lepidic growth patterns of tumor cells. The non-BAC component was composed of papillary, tubular, and/or solid growth pattern components, with or without fibrotic focus, collapse, necrosis, and/or mucus in a tumor. The size of the non-BAC component was evaluated microscopically on elastica van Gieson as well as standard hematoxylin and eosin staining preparations.

In order to examine the correlation between tumor measurements on CT scans and those on pathologic specimens, we calculated Pearson's correlation coefficient (r). The χ^2-test was used to compare several variables between subgroups according to serum CEA level and TDR. In all statistical analyses, differences were considered statistically significant when $P < 0.05$.

Table 1
Clinicoradiologic characteristics of patients according to TDR and serum CEA level

	TDR ≥ 0.8 and normal CEA level (group I)	TDR < 0.8 and/or elevated CEA level (group II)
No. of patients	50	139
No. of pN0 patients (%)	49 (98)	93 (67)
Age (years, mean ± SD)	64 ± 10	62 ± 10
Gender (male/female)	14/36	75/64
CEA (ng/ml) median	2.3	3.8
(25th, 75th percentile)	(1.8, 3.3)	(2.4, 7.1)
pDmax , mm (mean ± SD)	19 ± 6	23 ± 5
pDperp, mm (mean ± SD)	15 ± 5	18 ± 5
mDmax, mm (mean ± SD)	3 ± 4	16 ± 7
mDperp, mm (mean ± SD)	2 ± 2	12 ± 6
TDR (mean ± SD)	0.96 ± 0.05	0.55 ± 0.22

3. Results

3.1. Patients

The clinical characteristics of the patients are presented in Table 1. There were 49 (98%) pN0 cases and one pathologic N1 (pN1) case in the 50 peripheral adenocarcinoma patients with TDR 0.8 or more and normal preoperative serum CEA level (group I). There were 93 (67%) pN0 cases in the 139 peripheral adenocarcinoma patients with TDR < 0.8 and/or elevated preoperative serum CEA level (group II).

3.2. Outcome and patterns of failure

The overall 3- and 5-year survival rates were 88 and 80%, respectively. The 3- and 5-year survival rates of group I patients were 98 and 95%, and those of group II patients were 84 and 75%, respectively. The survival curves showed a statistically significant difference between the two groups ($P = 0.002$; Fig. 2). In pN0 patients, the overall 3- and 5-year

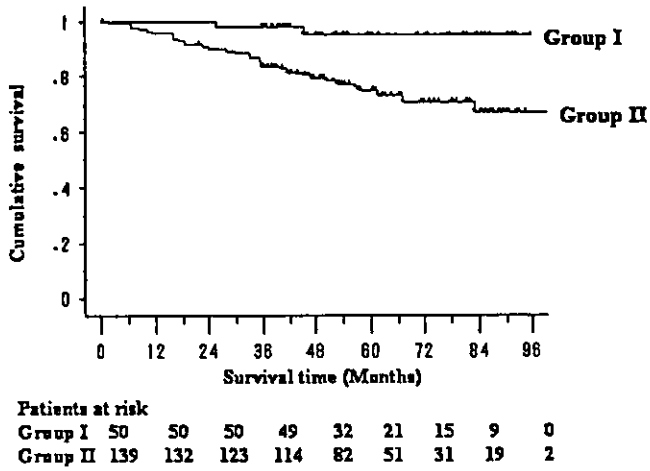

Fig. 2. Survival curves for group I and II patients. A statistically significant difference was observed between the outcomes of group I and II patients (log-rank test, $P = 0.002$).

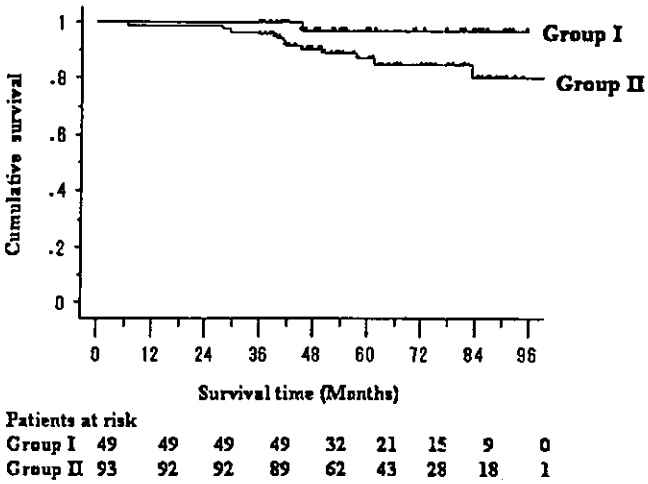

Fig. 3. Survival curves for group I and II pathologic N0 patients. A statistically significant difference was observed between the outcomes of pathologic N0 patients in groups I and II (log-rank test, $P = 0.04$).

survival rates were 97 and 91%, respectively. The 3- and 5-year survival rates of pN0 patients in group I were 100 and 97%, and those in group II were 96 and 87%, respectively. The survival curves also showed a statistically significant difference between the two groups ($P = 0.04$; Fig. 3).

Two patients in group I died during follow-up period. One developed brain and bone metastases 44 months after initial surgical resection, and died of primary lung cancer. The other was the only patient with pN1 disease and died of lower gingival cancer without any signs of primary lung cancer recurrence. No group I patients developed local recurrence including mediastinal lymph node metastases. The other 48 group I patients were alive with no signs of recurrence. Of 139 group II patients, 36 (26%) developed local and/or distant recurrences: 7 (5%) patients showed mediastinal lymph node metastases, 5 (4%) supraclavicular lymph node metastases, and 31 (22%) distant metastases (Table 2).

In univariate analyses (Table 3), TDR ($P = 0.004$), preoperative serum CEA level ($P = 0.002$), and pDmax ($P = 0.008$) were significantly associated with prognosis. In multivariate analysis, TDR ($P = 0.02$) and preoperative serum CEA level ($P = 0.03$) were shown to be independently significant prognostic factors.

Table 2
Patterns of failure in peripheral pulmonary adenocarcinoma according to TDR and serum CEA level

	TDR ≥ 0.8 and normal CEA level (group I, $n = 50$)	TDR < 0.8 and/or elevated CEA level (group II, $n = 139$)
No. of recurrence (%)	1 (2)	36 (26)
Site of recurrence (%)		
Mediastinal lymph node	0 (0)	7 (5)
Supraclavicular lymph node	0 (0)	5 (4)
Distant metastases	1 (2)	31 (22)

Table 3
Univariate analyses of prognostic factors in peripheral pulmonary adenocarcinoma

Variable	Hazard ratio	95% CI	*P*-value
Age	0.996	0.964–1.028	0.8
Gender	0.732	0.379–1.413	0.4
CEA[a]	2.231	1.346–3.696	0.002
pDmax	1.093	1.023–1.168	0.008
TDR	0.158	0.045–0.554	0.004

CI, confidence interval.
[a] Log-transformed serum CEA levels were used.

3.3. Histologic features

The relationship between tumor histologic characteristics and TDR and serum CEA level combined according to tumor size (2.0 cm or smaller versus 2.1–3.0 cm) is shown in Table 4. No lymph node involvement was found in group I tumors 2.0 cm or smaller. Although there was one pN1, no pathologic N2 cases were found in group I tumors 2.1–3.0 cm in size. There were significantly more pN0 tumors in group I than in group II. Group I tumors were more frequently negative for lymphatic permeation and vascular invasion, and there were more lower scar grade tumors (grade 1/2 versus grade 3/4) than group II tumors. Pleural involvement tended to be negative in group I tumors 2.0 cm or smaller ($P = 0.06$) and was significantly more frequently negative in group I tumors 2.1–3.0 cm in size ($P = 0.005$) compared with group II.

Statistical correlation was shown between pDmax and Tmax ($r = 0.63$, $P < 0.0001$), pDperp and Tperp ($r = 0.61$, $P < 0.0001$), mDmax and non-BACmax ($r = 0.56$, $P < 0.0001$), mDperp and non-BACperp ($r = 0.60$, $P < 0.0001$), pDmax × pDperp and Tmax × Tperp ($r = 0.62$, $P < 0.0001$), mDmax × mDperp and non-BACmax × non-BACperp ($r = 0.58$, $P < 0.0001$; Fig. 4). These findings suggested that the measurements of non-BAC component in pathologic specimens correlated well with those of tumor opacity on mediastinal window setting images.

4. Discussion

Adenocarcinoma is the most common histologic type of lung cancer, and its incidence has been increasing [9]. Many small peripheral adenocarcinomas with BAC component have, in particular, been found since helical CT scanning was introduced for lung cancer screening [1]. In the latest edition of WHO classification [6], BAC is clearly defined as an adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular or pleural invasion. Noguchi et al. [10] classified small peripheral adenocarcinomas into six subtypes (types A–F). Type A

Table 4
The relationship between tumor histologic characteristics and TDR and serum CEA level combined according to tumor size

	pDmax 0–20 mm ($n = 69$)			pDmax 21–30 mm ($n = 108$)		
	TDR ≥ 0.8 and normal CEA level (group I) (%)	TDR < 0.8 and/or elevated CEA level (group II) (%)	P^a	TDR ≥ 0.8 and normal CEA level (group I) (%)	TDR < 0.8 and/or elevated CEA level (group II) (%)	P^a
No. of tumors	25	44		21	87	
Lymph node status						
N0	25 (100)	32 (73)		20 (95)	57 (66)	
N1	0 (0)	4 (9)		1 (5)	10 (11)	
N2	0 (0)	8 (18)	0.004	0 (0)	20 (23)	0.007
Lymphatic permeation						
Negative	23 (92)	26 (59)		18 (86)	46 (53)	
Positive	2 (8)	18 (41)	0.004	3 (14)	41 (47)	0.006
Vascular invasion						
Negative	23 (92)	27 (61)		18 (86)	45 (52)	
Positive	2 (8)	17 (39)	0.006	3 (14)	42 (48)	0.005
Pleural involvement						
Negative	24 (96)	35 (80)		21 (100)	62 (71)	
Positive	1 (4)	9 (20)	0.06	0 (0)	25 (29)	0.005
Scar grade						
1 or 2	16 (64)	8 (18)		14 (67)	18 (21)	
3 or 4	9 (36)	36 (82)	0.0001	7 (33)	69 (79)	<.0001

[a] P-value in χ^2-test.

(localized BAC) and type B (localized BAC with a focus of collapsed alveolar structure) showed no lymph node metastasis, rare vascular invasion and excellent prognosis of 100% 5-year survival rate. BAC and Noguchi's types A/B could be regarded as minimally invasive, possibly in situ, adenocarcinomas.

Recently, several investigators reported that GGA on high-resolution computed tomography (HRCT) corresponded to lepidic tumor growth in the BAC component [2–5]. A greater extent of GGA in a tumor opacity on HRCT scans correlated with histopathologic lower invasiveness and better outcomes [2,11–13]. Others reported better outcomes in adenocarcinoma with a greater extent of BAC components in pathologic specimens [14,15]. Suzuki et al. [16] reported that in peripheral pulmonary adenocarcinomas 3.0 cm or smaller, a good correlation was demonstrated between the size of central fibrosis in pathologic specimens and outcome. The central fibrosis or non-BAC component in a tumor would appear as consolidation on HRCT scans [3,5].

Based on these previous findings, we can assume that histopathologically minimally invasive adenocarcinomas, possible candidates for limited surgical resection, are predictable based on CT findings: greater extent of GGA or minimal consolidation in a tumor opacity. However, no quantitative analyses comparing the size of GGA or consolidation in tumor opacities on CT scans, with the sizes of BAC or non-BAC components in pathologic specimens have been reported previously. In this study, we showed that the size of non-BAC component

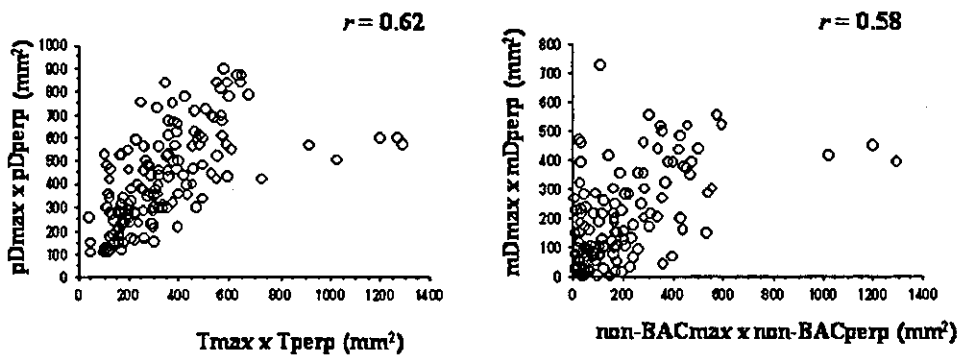

Fig. 4. Statistical correlation was shown between pDmax × pDperp and Tmax × Tperp ($r = 0.62$, $P < 0.0001$), mDmax × mDperp and non-BACmax × non-BACperp ($r = 0.58$, $P < 0.0001$).

correlated well with that of tumor opacity in mediastinal window setting images on conventional CT scans.

The most common definition of GGA is "a hazy increased attenuation of lung, but with preservation of bronchial and vascular structure" [17]. However, it is sometimes difficult to accurately define the edges of GGA when measuring its size. GGA area usually disappears in mediastinal window setting images. Measuring the size of tumor opacity in a mediastinal window-setting image is an easy and reproducible way to evaluate the size of a non-GGA area. Calculating TDR is more objective than quantifying GGA by visual estimation in a pulmonary window setting image as in previous studies [3,11,12]. However, the reproducibility and inter-observer variations in calculating TDR need to be verified in a larger prospective study. Since HRCT should yield more accurate measurements than conventional CT scans, especially in small-sized tumors, we are planning a similar study using HRCT data.

Kondo et al. [13] classified surgically resected pulmonary adenocarcinomas 2.0 cm or smaller into two types: 'air-containing type' and 'solid density type'. The air-containing type was defined as a tumor in which the tumor opacity area on a mediastinal window setting image was half or less of that on a pulmonary window setting image by visual estimation on HRCT. The solid density type, on the other hand, was defined as a tumor in which the tumor opacity area on mediastinal window setting images was more than half of that on a pulmonary window-setting image. Among 66 air-containing type adenocarcinomas, no lymph node involvement, one lymphatic permeation, one vascular invasion, and one pleural involvement tumors were observed histopathologically. The air-containing type adenocarcinoma could be considered minimally invasive. All patients with air-containing type adenocarcinomas were alive and relapse-free after a mean observation period of 851 days following resection. These results were consistent with ours. In our study, no lymph node involvement, two lymphatic permeation, two vascular invasion, and one pleural involvement tumors were observed in 25 adenocarcinomas 2.0 cm or smaller in patients with TDR 0.8 or more and normal preoperative serum CEA level. Shimosato et al. [8] initially reported prognostic impact of fibrotic focus (scar) in patients with adenocarcinomas 3.0 cm or smaller. They proposed scar grade, which correlated well with tumor invasiveness such as lymph node involvement, vascular invasion, and pleural involvement. They suggested that a small peripheral adenocarcinoma <3.0 cm with no or little collagenization (grade 1 or 2) could be considered to be in an 'early stage' of development and could be surgically curable. There were more grade 1/2 tumors in group I patients than in group II in our series. If limited lung resection is curative enough for small-sized adenocarcinomas with no or minimal invasiveness, preoperative combined evaluation of serum CEA level and TDR is useful in selecting candidates for limited lung resection.

Although a number of prognostic factors have been reported for patients with surgically resected non-small cell lung cancer, tumor size and lymph node status are considered to be the most significant prognostic factors. We showed that the outcome of group I patients was excellent (5-year survival rate: 95%) and significantly better than group II patients with completely resected adenocarcinomas 3.0 cm or smaller. Even when the prognostic impact of pathologic lymph node status was excluded, the same result was demonstrated. Multivariate analysis showed that both preoperative serum CEA level and TDR were significant independent prognostic factors. Maximum tumor dimension on CT scan was significant in univariate analysis, but not significant in multivariate analysis. These results indicate that tumor size does not have independently significant impact on prognosis in adenocarcinomas 3.0 cm or smaller.

Patients with an adenocarcinoma 2.0 cm or smaller, if preoperative serum CEA level was normal and TDR was 0.8 or more, showed no lymph node involvement (pN0) and developed no local recurrence including lymph nodes. The results suggest that limited lung resection without systematic mediastinal lymph node dissection might be acceptable for these patients. Because these factors are available preoperatively, they are useful not only to predict outcome but also to determine the extent of resection.

In summary, peripheral small-sized pulmonary adenocarcinomas predicted as pN0 by combining serum CEA level and TDR showed no mediastinal lymph node involvement and resulted in excellent outcomes without local recurrence. CT findings correlated well with histologic findings in small-sized adenocarcinomas. Signs of local invasiveness such as lymphatic permeation, vascular invasion, and pleural involvement, were rare in small-sized adenocarcinomas with normal preoperative serum CEA level and a TDR of 0.8 or more. Combined evaluation of preoperative serum CEA level and TDR may enable us to identify minimally invasive adenocarcinomas with good prognosis.

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Risk factors for interstitial lung disease and predictive factors for tumor response in patients with advanced non-small cell lung cancer treated with gefitinib

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Summary A high incidence of interstitial lung disease (ILD) has been reported in patients with non-small cell lung cancer (NSCLC) treated with gefitinib in Japan. We retrospectively analyzed 112 patients with advanced NSCLC who received gefitinib monotherapy. Univariate and multivariate analyses were used to identify risk factors for gefitinib-related ILD and predictive factors for tumor response to gefitinib. The incidence of ILD was 5.4%, and it was higher in the patients with pre-existing pulmonary fibrosis (33% versus 2%; $P < 0.001$). The results of a multivariate analysis showed that pulmonary fibrosis was a significant risk factor for ILD (odds ratio: 177, 95% confidence interval: 4.53–6927, $P = 0.006$). The response rate was 33% in the 98 evaluable patients and higher in women (53% versus 23%; $P = 0.003$), patients with adenocarcinoma (38% versus 6%; $P = 0.010$), never-smokers (63% versus 18%; $P < 0.001$), and the patients with no history of thoracic radiotherapy (39% versus 13%; $P = 0.015$). The results of a multivariate analysis showed that the predictors of tumor response were "no history of smoking" and "no history of thoracic radiotherapy". Never-smokers had a significantly longer survival time than smokers ($P = 0.007$). Although gefitinib therapy confers a clinical benefit on patients with advanced NSCLC, especially on women, patients with adenocarcinoma, never-smokers, and patients with no history of thoracic radiotherapy, it also poses a high risk of ILD, especially to patients with pulmonary fibrosis. The risk-benefit ratio must be carefully considered.

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1. Introduction

Gefitinib (Iressa®; AstraZeneca, Osaka, Japan) is an orally available, selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that displays antitumor activity in patients with previously treated advanced non-small cell lung cancer (NSCLC). The safety and tolerability of gefitinib was established in four open-labeled, multicenter, phase I dose-escalation studies [1–4]. Although diarrhea, skin rash/acne, and nausea were common adverse effects, most of them were mild. Two large-scale, multicenter, randomized phase II studies (IDEAL 1 and 2; Iressa® Dose Evaluation in Advanced Lung Cancer) have demonstrated clinically significant antitumor activity of gefitinib monotherapy in patients with advanced NSCLC who had previously received platinum-based chemotherapy [5,6]. The response rate for gefitinib 250 mg per day in the IDEAL 1 and 2 trials was 18.4 and 11.8%, respectively. These studies also showed that gefitinib monotherapy significantly improved disease-related symptoms and quality of life.

Based on the results of the IDEAL trials, gefitinib was approved in Japan for the treatment of inoperable or recurrent NSCLC on 5 July 2002, and an estimated 28,300 patients had been treated with gefitinib as of April 2003. During the first few months after its approval, many patients demanded to be treated with gefitinib as a "magic bullet" cure; however, when the incidence of interstitial lung disease (ILD) came to light in October 2002, the media reported it in a sensational manner, and as a result patients have become confused by excessive expectations and fear of ILD. The Ministry of Health, Labour and Welfare of Japan reported that the number of gefitinib-related cases of ILD had reached 616 as of 22 April 2003 and that 246 of the patients had died of it. The incidence of ILD and mortality rate from it has been calculated at 2.2 and 0.87%, respectively. Some case reports also suggested a high incidence of gefitinib-related ILD in Japan [7]. In view of this situation, an evidence-based assessment of the risk-benefit of gefitinib for the treatment of NSCLC was urgently needed. However, many questions regarding gefitinib administration remained unanswered, particularly in regard to the risk factors associated with ILD complications. We therefore analyzed a series of cases treated with gefitinib at the National Cancer Center Hospital (NCCH) in Tokyo.

2. Patients and methods

Between July and December 2002, 115 NSCLC patients at the NCCH began taking gefitinib and the 112 of these patients who were followed at the NCCH were retrospectively analyzed in this study. The other three patients were excluded from the analysis because they were followed-up at other hospitals after the first prescription of gefitinib. All the 112 patients had histologically or cytologically confirmed NSCLC. Their disease was locally advanced, recurrent, and/or metastatic. They all received gefitinib monotherapy at a dose of 250 mg per day.

Two independent board-certified diagnostic radiologists (M.K. and U.T.) diagnosed pre-existing pulmonary fibrosis (PF) on the basis of the findings on chest X-rays taken within 1 week of the start of gefitinib therapy. The radiologists had no knowledge of the patients' outcome. The diagnostic criteria for PF were a diffuse linear or honey-comb pattern on chest X-rays that was predominant in the lower zone of the lung.

If a patient had measurable disease, the World Health Organization criteria were used to assess the tumor response. The response rate was calculated as the total percentage of patients with a complete or partial response. Drug-related adverse events were evaluated using the National Cancer Institute-Common Toxicity Criteria (Version 2.0). Chest X-rays were performed periodically to evaluate response and detect pulmonary toxicity, and computed tomography scans of the chest were performed as needed to confirm the response or diagnose ILD. The extent of patients' smoking history was evaluated by using pack-years, which are defined as the average number of cigarettes smoked per day multiplied by the total duration of smoking in years divided by 20. Patients who had smoked for 0, 1–39, and ≥40 pack-years were categorized as "never-smokers", "moderate smokers", and "heavy smokers", respectively.

Univariate and multivariate analyses were performed to identify risk factors for ILD and predictive factors for tumor response to gefitinib. The patient characteristics tested as potential risk factors for ILD and predictive factors for tumor response were age (<70 versus ≥70 years in the univariate analysis and as a continuous variable in the multivariate analysis), sex (female versus male), histological diagnosis (adenocarcinoma versus non-adenocarcinoma), smoking history (never-smokers versus moderate/heavy smokers), performance status (PS 0–1 versus PS 2–3), prior surgery (yes versus no), prior chemotherapy (yes versus no), prior thoracic radiotherapy (yes versus no), and PF (yes versus no). These factors were compared by using a chi-square test in the univariate analysis. Logistic regression analyses were also performed to adjust for each factor. Differences

in time to treatment failure (TTF) and overall survival (OS) among the subgroups were compared by using Kaplan–Meier curves and log-rank tests. TTF was defined as the interval between the start of gefitinib administration and discontinuation of treatment for any reason, confirmed disease progression, or death. All analyses were performed using SPSS statistical package (SPSS version 11.0 for Windows, SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

The patient characteristics are listed in Table 1. All patients were Japanese. Twenty-eight patients (25%) received gefitinib as a first-line treatment; 19 were considered unfit for platinum-based chemotherapy because of poor PS (10 patients) or advanced age (9 patients), and 9 refused platinum-based chemotherapy. The diagnosis of pre-existing PF was almost the same between two radiologists. Although discordance occurred in three cases, 12 patients were finally diagnosed as PF by consensus. All of the 12 patients had computed tomography findings consistent with idiopathic pulmonary fibrosis/usual interstitial pneumonia.

3.2. Interstitial lung disease (ILD) and other toxicities

Among the 112 patients reviewed, ILD developed in 6 (5.4%) during the course of gefitinib therapy, and 4 patients (3.6%) died from ILD. The characteristics of the six patients with ILD are listed in Table 2. All of them had acute onset or exacerbation of respiratory symptoms. In five patients, chest computed tomography scanning revealed new diffuse interstitial changes in both lungs with ground-glass appearances. Because bronchoalveolar lavage or lung biopsy was not performed, we cannot completely exclude lymphangiosis carcinomatosa or other diseases, but the clinical courses and imaging appearances were consistent with drug-induced ILD. Although the other patient (patient 3) died before imaging diagnosis, the autopsy revealed diffuse alveolar damage, and we concluded she died from gefitinib-related ILD.

The results of univariate and multivariate analyses on risk factors for ILD are shown in Table 3. The incidence of ILD was 33% (4/12) among patients with PF and 2.0% (2/100) among the other patients. PF was the only significant risk factor for ILD in the univariate analysis (odds ratio [OR]: 16.7, 95% confidence interval [95% CI]: 3.40–83.3, $P < 0.001$), and this finding was supported by the results of the multivariate analysis (OR: 177, 95% CI: 4.53–6927, $P = 0.006$). Since all of the patients with ILD were smokers, pack-years were analyzed as a continuous variable in the multivariate analysis, and the results of it suggested the association between increased pack-years and a higher risk of ILD ($P = 0.062$). Since all of the ILD cases had a PS score of 1 and had never undergone thoracic radiotherapy, it was impossible to assess the association between poor PS or prior thoracic radiotherapy and ILD in the multivariate analysis.

Table 1 Patient characteristics

	Patients ($n = 112$)	
	No.	%
Age		
Median (range) (years)	63 (29–83)	
<70 years	80	71
≥70 years	32	29
Sex		
Female	35	31
Male	77	69
Histological diagnosis		
Adenocarcinoma	93	83
Squamous cell carcinoma	12	11
Non-small cell carcinoma (not specified)	6	5
Large cell neuroendocrine carcinoma	1	1
Smoking history (pack-years)		
Never-smokers (0)	34	30
Moderate smokers (1–39)	30	27
Heavy smokers (≥40)	48	43
ECOG performance status		
0–1	92	82
2–3	20	18
Stage		
IIIA/IIIB	21	19
IV	58	52
Recurrence after surgery	33	29
Prior chemotherapy		
Yes	84	75
No	28	25
Prior thoracic radiotherapy		
Yes	26	23
No	86	77
Pre-existing pulmonary fibrosis		
Yes	12	11
No	100	89

Table 2 Characteristics of patients who developed interstitial lung disease

	Age (years)	Sex	Histological diagnosis	PS	PY	Stage	Prior chemotherapy		Thoracic radiotherapy	Pre-existing lung disease	Length of treatment (days)	Survival (days)
							First	Second				
1	66	M	Ad	1	44	IIIB	CDDP+VNR	DTX	No	PF	10	22[a]
2	69	M	Ad	1	28	IV	CBDCA+PTX	–	No	PF	32	67[a]
3	52	F	Ad	1	48	IV	CDDP+GEM	–	No	None	42	42[a]
4	71	M	Ad	1	51	IIIB	UFT	–	No	PF	47	123[a]
5	64	M	Sq	1	129	IV	CBDCA+PTX	DTX	No	None	18	237[b]
6	74	M	Ad	1	64	Rec	CBDCA+PTX	–	No	PF	39	400[b]

Ad: adenocarcinoma, Sq: squamous cell carcinoma, PS: performance status, PY: pack-years smoked, Rec: recurrence after surgery, CDDP: cisplatin, CBDCA: carboplatin, VNR: vinorelbine, DTX: docetaxel, PTX: paclitaxel, GEM: gemcitabine, PF: pulmonary fibrosis.

[a] Treatment-related death.

[b] Death from lung cancer.

Table 3 Risk factors for interstitial lung disease ($n = 112$)

	No. of patients	Incidence of ILD (%)	Univariate analysis		Multivariate analysis	
			Odds ratio (95% CI)	P-values	Odds ratio (95% CI)	P-values
Total	112	5.4				
Age						
<70 years	80	5.0	0.80 (0.15–4.18)	0.791	2.05 (0.46–9.17)	0.347[a]
≥70 years	32	6.3	1			
Sex						
Female	35	2.9	0.44 (0.053–3.62)	0.428	19.1 (0.44–837)	0.126
Male	77	6.5	1		1	
Histological diagnosis						
Adenocarcinoma	93	5.4	1.02 (0.13–8.26)	0.984	0.26 (0.012–5.46)	0.383
Non-adenocarcinoma	19	5.3	1		1	
Smoking history (pack-years)						
Heavy smokers (≥40)	48	10.4	–	0.096[b]	1.50 (0.98–2.29)	0.062[c]
Moderate smokers (1–39)	30	3.3	–			
Never-smokers (0)	34	0.0	1			
PS						
2–3	20	0.0	0	0.240		
0–1	92	6.5	1			
Prior surgery						
Yes (recurrence)	33	3.0	0.48 (0.056–3.94)	0.480	2.48 (0.14–43.2)	0.534
No (advanced disease)	79	6.3	1		1	
Prior chemotherapy						
Yes	84	7.1	–	0.146		
No	28	0.0	1			
Prior thoracic radiotherapy						
Yes	26	0.0	0	0.166		
No	86	7.0	1			
Pulmonary fibrosis						
Yes	12	33	16.7 (3.40–83.3)	<0.001	177 (4.53–6927)	0.006
No	100	2.0	1		1	

CI: confidence interval.
[a] Age was analyzed as a continuous variable in the multivariate analysis. Odds ratio was calculated per 10-year decrease.
[b] Smoking history was analyzed by comparing never-smokers and moderate/heavy smokers in the univariate analysis.
[c] Smoking history (pack-years) was analyzed as a continuous variable in the multivariate analysis. Odds ratio was calculated per 10-pack-year increase.

The incidence of drug-related adverse events is listed in Table 4. Grade 1 or 2 skin rash (81%) and diarrhea (56%) were the most frequent adverse events. Grades 1–3 elevation in glutamic-oxaloacetic transaminase (GOT) and/or glutamic-pyruvic transaminase (GPT) levels was observed in 46% of the patients.

3.3. Efficacy

Of the 112 patients, 98 had measurable disease. Four patients were not evaluated due to early discontinuation. Complete response, partial response, stable disease, and progressive disease were observed in 2, 30, 29, and 33 patients,

Table 4 Toxicity

	No. of patients evaluated	Grade			
		1	2	3	4
Skin rash	109	59	29	0	0
Diarrhea	109	57	4	0	0
GOT/GPT	106	31	8	10	0
Nausea	109	21	5	0	0
Interstitial lung disease (ILD)	112	0	1	1	4[a]

[a] Treatment-related death.

respectively. The response rate was 33% (32/98). The response rates in each subgroup of patients are listed in Table 5. According to the results of the univariate analysis, female gender ($P = 0.003$), adenocarcinoma ($P = 0.010$), no history of smoking ($P < 0.001$), and no history of thoracic radiotherapy ($P = 0.015$) were significant predictors of tumor response to gefitinib. The response rate of male smokers was 14% (8/56), which was lower than both that of female smokers (40%, $P = 0.052$) and that of male never-smokers (70%, $P < 0.001$). When pack-years were analyzed as a continuous variable among the smokers, the association between

Table 5 Response rates among subgroups of patients ($n = 98$)

	No. of patients	Response rate (%)	Univariate analysis		Multivariate analysis	
			Odds ratio (95% CI)	P-values	Odds ratio (95% CI)	P values
Total	98	33				
Age						
<70 years	69	36	1.50 (0.76–2.97)	0.244	1.57 (0.96–2.56)	0.071[a]
≥70 years	29	24	1			
Sex						
Female	32	53	2.34 (1.34–4.06)	0.003	1.84 (0.51–6.56)	0.349
Male	66	23	1		1	
Histological diagnosis						
Adenocarcinoma	81	38	6.51 (1.58–26.8)	0.010	4.27 (0.48–37.0)	0.191
Non-adenocarcinoma	17	6	1		1	
Smoking history (pack-years)						
Never-smokers (0)	32	63	3.44 (1.98–5.97)	<0.001[b]	3.92 (1.03–14.9)	0.045[b]
Moderate smokers (1–49)	22	23	1		1	
Heavy smokers (≥50)	44	16				
PS						
0–1	83	31	0.78 (0.38–1.62)	0.510	0.46 (0.10–2.09)	0.314
2–3	15	40	1		1	
Prior surgery						
No (advanced disease)	68	28	0.64 (0.36–1.14)	0.134	1.25 (0.35–4.41)	0.732
Yes (recurrence)	30	43	1		1	
Prior chemotherapy						
No	24	42	1.40 (0.76–2.58)	0.279	1.32 (0.35–4.95)	0.678
Yes	74	30	1		1	
Prior thoracic radiotherapy						
No	74	39	3.14 (1.24–7.90)	0.015	6.76 (1.30–35.7)	0.023
Yes	24	13	1		1	

CI: confidence interval.

[a] Age was analyzed as a continuous variable in the multivariate analysis. The odds ratio was calculated per 10-year decrease.

[b] Smoking history was analyzed by comparing never-smokers and moderate/heavy smokers.

increased pack-years and a lower response rate was also shown (OR per 10-pack-year increase: 0.74, 95% CI: 0.56–0.99, $P = 0.041$).

The results of a multivariate analysis showed that "no history of smoking" ($P = 0.045$) and "no history of thoracic radiotherapy" ($P = 0.023$) were significant predictors of response. It was also suggested that younger patients tended to obtain a higher response rate ($P = 0.071$). Although female gender and adenocarcinoma were not found to be predictive factors in the multivariate analysis, sex and histological diagnosis were significantly associated with smoking history, and these variables may have canceled each other's effect on the dependent variable. The proportion of never-smokers was 69% (22/32) among the women versus 15% (10/66) among the men (correlation coefficient [r] = 0.536, $P < 0.001$), and 67% (54/81) among the patients with adenocarcinoma versus 0% (0/17) among those with non-adenocarcinoma ($r = 0.319$, $P = 0.001$). When a multivariate analysis was performed excluding smoking history as a factor, the OR of the females and patients with adenocarcinoma was 3.81 (95% CI: 1.36–10.7, $P = 0.011$) and 6.45 (95% CI: 0.76–55.6, $P = 0.087$), respectively.

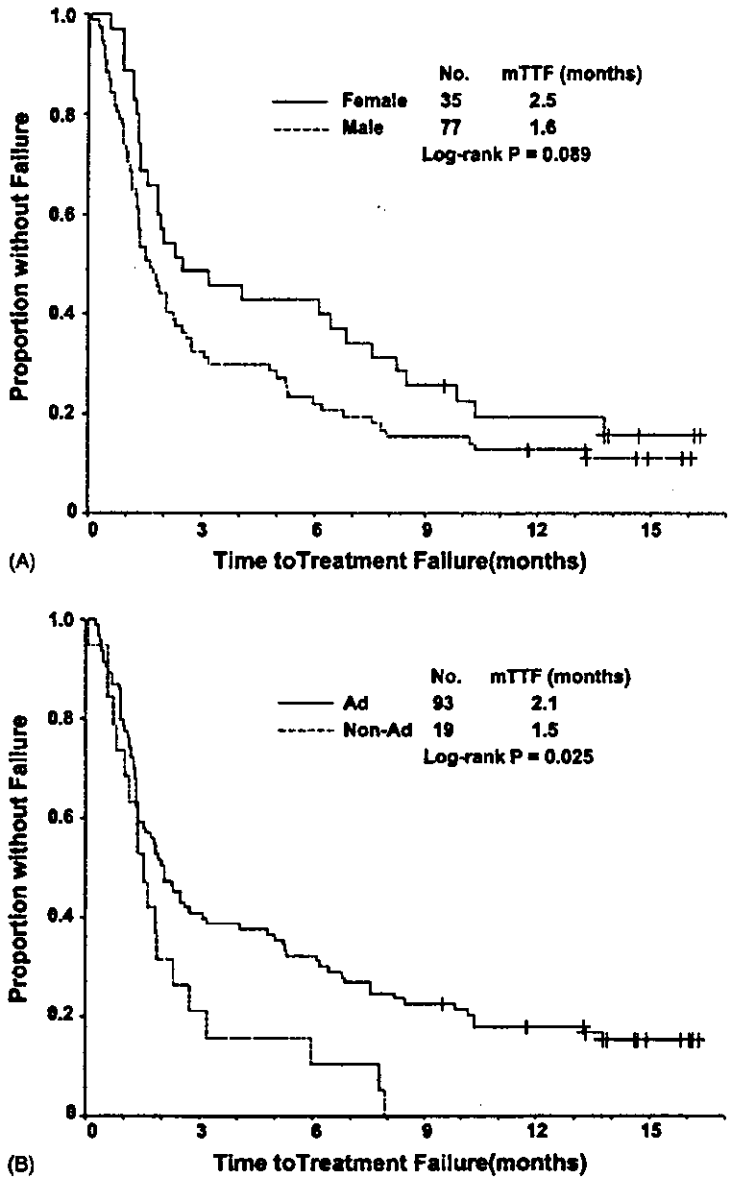

Fig. 1 Kaplan–Meier plot of time to treatment failure according to subgroups: (A) female versus male; (B) adenocarcinoma versus non-adenocarcinoma; (C) never-smokers versus moderate/heavy smokers. mTTF: median time to treatment failure, Ad: adenocarcinoma.

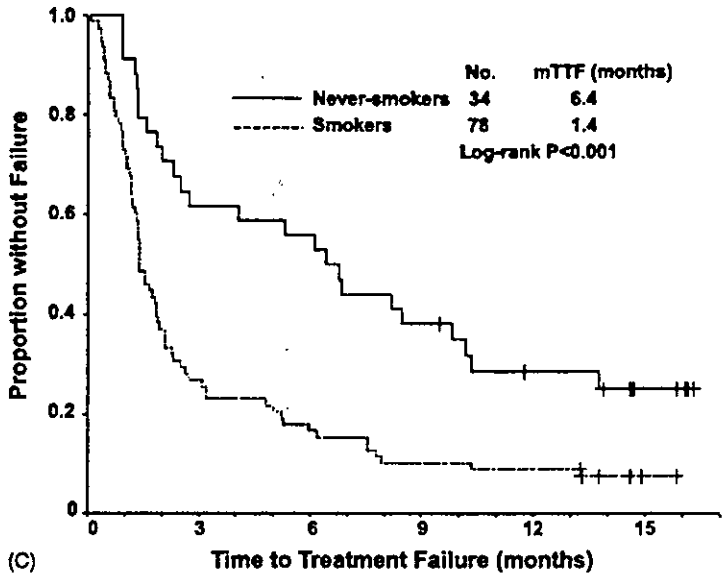

Fig. 1 (*Continued*).

The median follow-up time for survivors was 14.7 months, and ranged from 11.0 to 16.8 months. Sixty-nine patients (62%) died: 65 of disease progression and 4 of toxicity. Gefitinib treatment was terminated in 97 patients (87%) because of disease progression (68 patients), no tumor shrinkage (7 patients), toxicity (19 patients), or at the patients' request (3 patients). The median TTF and the median survival time (MST) for all patients were 1.9 and 10.7 months, respectively. The 1-year survival rate was 45%. The Kaplan–Meier plots of TTF and OS in each subgroup are shown in Figs. 1 and 2. The women had a longer TTF and OS than the men, but the difference was not significant. Patients with adenocarcinoma had a significantly longer TTF than those with non-adenocarcinoma, and "adenocarcinoma" was a marginally significant predictor of longer survival. "No history of smoking" was a highly significant predictor of longer TTF ($P < 0.001$) and longer survival ($P = 0.007$); the MST was 15.3 months in never-smokers and 8.8 months in moderate/heavy smokers.

We observed an association between efficacy and toxicity. As shown in Table 6, those who experienced skin rash or elevation in GOT/GPT levels tended to

Table 6 Association between efficacy and toxicity

	No. of patients	Response rate (%)	P-values*	Median survival (months)	1-year survival (%)	P-values†
Skin rash						
Grade 0	21	12	0.043	3.0	24	0.011
Grade 1	59	33		10.6	44	
Grade 2	29	46		15.3	66	
Diarrhea						
Grade 0	48	33	0.903	9.3	35	0.037
Grade 1–2	61	32		13.6	54	
GOT/GPT						
Grade 0	57	21	0.004	7.8	31	0.006
Grade 1	31	48		15.1	55	
Grade 2–3	18	50		Not reached	83	

* *P*-values for chi-square test between grade 0 and 1–3.
† *P*-values for log-rank test.