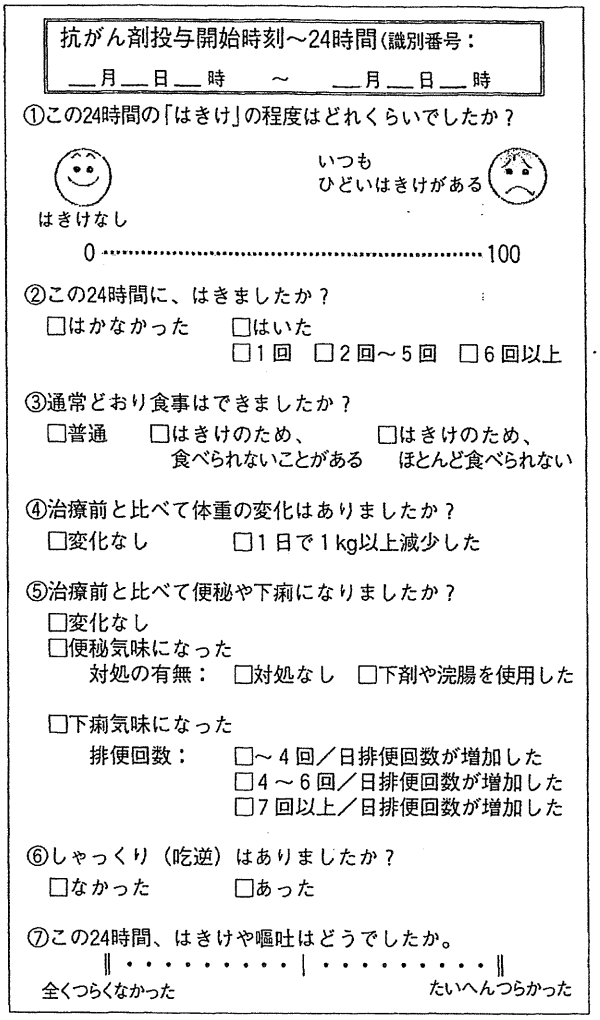
抗がん剤投与開始時刻～24時間(識別番号：
__月__日__時　～　__月__日__時
①この24時間の「はきけ」の程度はどれくらいでしたか？
はきけなし
いつも
ひどいはきけがある
0 100
②この24時間に、はきましたか？
□はかなかった　□はいた
□1回　□2回～5回　□6回以上
③通常どおり食事はできましたか？
□普通　□はきけのため、食べられないことがある　□はきけのため、ほとんど食べられない
④治療前と比べて体重の変化はありましたか？
□変化なし　□1日で1kg以上減少した
⑤治療前と比べて便秘や下痢になりましたか？
□変化なし
□便秘気味になった
対処の有無：□対処なし　□下剤や浣腸を使用した
□下痢気味になった
排便回数：□～4回／日排便回数が増加した
□4～6回／日排便回数が増加した
□7回以上／日排便回数が増加した
⑥しゃっくり（吃逆）はありましたか？
□なかった　□あった
⑦この24時間、はきけや嘔吐はどうでしたか。
全くつらくなかった　たいへんつらかった

図1　患者日誌

対象と方法

2009年4月～2010年1月までに新潟大学医歯学総合病院第二内科を中心とした新潟肺癌治療研究会に属する新潟県下18施設において，術後補助化学療法および進行・再発肺がんにおける化学療法に対する高度および中等度催吐性化学療法を施行した101例を対象とし，プロスペクティブに調査を行った。

本調査の適格基準は，①肺がんに対して初回化学療法を施行する患者，②高度，中等度の催吐性リスクであるCDDPもしくはCBDCAを含む化学療法が計画されている患者，③文書にて本人より本調査への同意が得られた患者とし，除外基準を①化学療法施行前24時間以内に嘔吐を経験した患者，②Day 2以降も高度，中等度催吐性の抗悪性腫瘍薬を使用する患者，③放射線療法を併用する患者とした。

5-HT_3受容体拮抗薬，ステロイドの種類や組合せ，投与期間等に関しては各施設，主治医の判断とした。

悪心・嘔吐実態調査は患者日誌（図1）による調査（患者側）と調査実施医師による化

表1 患者背景

特徴	患者数
年齢（年）	
男性	78
女性	23
中央値	68
年齢幅	46～82
組織型	
小細胞肺癌	23
非小細胞肺癌	78
腺癌	58
扁平上皮癌	18
扁平上皮・腺癌	1
未分化癌	1
PS	
P0	37
P1	61
P2	3

Stage	患者数
Stage 分類	
IIA	1
IIIA	4
IIIB	36
IV	33
術後再発	8
Adj.	19
治療レジメン	
CDDP を含むレジメン	56
CBDCA を含むレジメン	45

表2 化学療法レジメン

	PEM	CPT-11	GEM	VNR	ETP	PAC	DOC	患者数
CDDP	12	4	8	21	5	1	5	56
CBDCA	3	0	2	5	14	21	0	45
計	15	4	10	26	19	22	5	101

PEM：ペメトレキセド ／ VNR：ビノレルビン ／ PAC：パクリタキセル ／ CPT-11：イリノテカン ／ ETP：エトポシド ／ DOC：ドセタキセル ／ GEM：ゲムシタビン

学療法レジメン投与前における催吐予測の評価および化学療法施行後の催吐事象を評価した。

患者日誌より，化学療法施行当日（Day 1）からDay 5（～120時間）まで，24時間ごとの①Visual analog scale（以下，VASと略す）を用いた悪心の程度（100mmのVASで左端が「吐き気なし」に相当する「0」，右端が「いつもひどい吐き気があった」に相当する「100」とした。悪心の有無の評価としては，5 mm未満を悪心なし，5 mm以上を悪心ありとした），②嘔吐性事象の有無，③VASを用いた悪心・嘔吐の全般的印象，満足度（左端が「全くつらくなかった」から右端が「たいへんつらかった」と印字されており，その間を20等分した）を評価した。

調査実施医師より，①化学療法投与前の治療レジメンによる催吐性に関する医師の印象（VASを用い，左端が「軽微」とそれに相当する「0」から右端が「重篤」とそれに相当する「100」が印字されており，その間を等分する「中等度」が入っているアナログスケールを用いた），②化学療法後の催吐事象の有無を評価した。

結　果

本調査の適格基準に該当した101例の患者背景を以下に示す（表1）。年齢中央値は68歳（年齢幅：46～82）であり，男/女比は78/23例，PSの0/1/2は37/61/3例であった。

表3 制吐療法レジメン

制吐療法レジメン	患者数
第一世代5-HT_3受容体拮抗薬＋ステロイド	62
第一世代5-HT_3受容体拮抗薬＋ステロイド＋メトクロプラミド	30
第一世代5-HT_3受容体拮抗薬＋ステロイド＋ドンペリドン	2
第一世代5-HT_3受容体拮抗薬＋ステロイド＋その他	2
第一世代5-HT_3受容体拮抗薬＋メトクロプラミド	1
第一世代5-HT_3受容体拮抗薬のみ	3
メトクロプラミドのみ	1

第一世代5-HT_3受容体拮抗薬の内訳（n=100）	患者数
グラニセトロン（後発品を含む）※	90
ラモセトロン※	32
アザセトロン	1

※1症例で複数薬剤使用例23例

ステロイド投与日数の内訳（n=96）	患者数
Day 1のみ投与	36
Day 2以降も投与	60

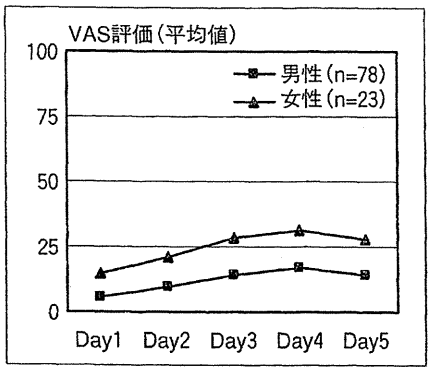

図2 性別による悪心・嘔吐の程度

肺がんの組織型では小細胞癌23例，非小細胞癌78例であった。治療レジメンはCDDPを含むレジメン56例（併用薬：ビノレルビン21例，ペメトレキセド12例等），CBDCAを含むレジメン45例（併用薬：パクリタキセル21例，エトポシド14例等）であった（表2）。制吐療法のレジメンに関しては第一世代5-HT_3受容体拮抗薬とステロイドの2剤のみの併用が62例と最も多く，次いで，これにメトクロプラミドを加えた3剤併用が30例であった（表3）。

1．性別による悪心・嘔吐の程度

悪心・嘔吐の全般的印象，満足度をVASにて評価し，性別毎に解析を行った（図2）。その結果，女性では男性と比べ悪心・嘔吐を「つらく」感じる傾向が認められた。また，男女とも抗悪性腫瘍薬投与後4日目に最も悪心・嘔吐を「つらく」感じることが多く，急性期と比べ遅発期において悪心・嘔吐を「つらく」感じることが多く認められた。

2．レジメン別による悪心・嘔吐の程度

CDDPを含むレジメンおよびCBDCAを含むレジメンでの，嘔吐発現率・摂食障害発現率を評価した。その結果，急性期の嘔吐発現率・摂食障害発現率はCDDPを含むレジメンでそれぞれ5％・16％，CBDCAを含むレジメンでそれぞれ2％・0％である一方，遅発期の嘔吐発現率・摂食障害発現率はCDDP

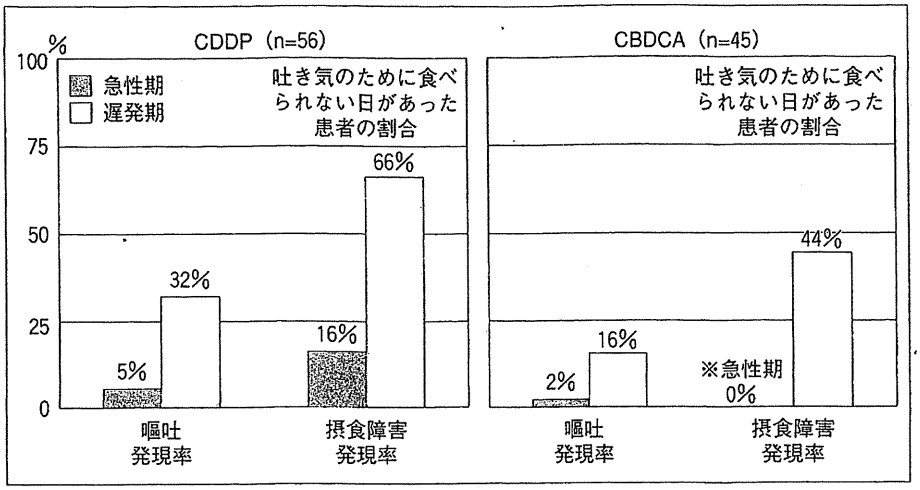

図3 レジメン別化学療法施行時の悪心・嘔吐，摂食障害発現率

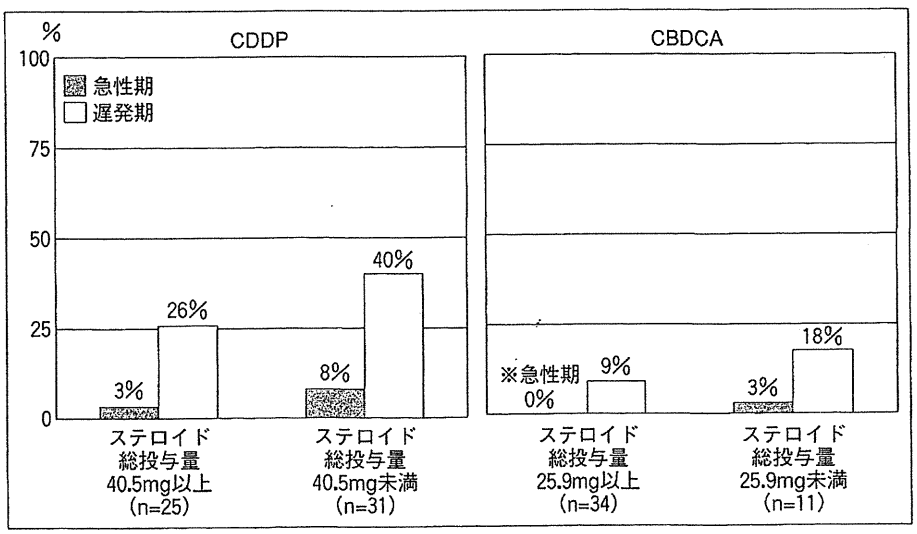

図4 ステロイド使用量と嘔吐発現の関係

を含むレジメンでそれぞれ32%・66%，CBDCAを含むレジメンでそれぞれ16%・44%であり，急性期と比較し遅発期に嘔吐や摂食障害の発現率が高い傾向がみられた（図3）。

3．制吐療法におけるステロイドの総投与量と嘔吐発現の関係

ステロイドの総投与量と嘔吐発現の関係を検討した。ステロイド総投与量のカットオフ値は日本癌治療学会より発刊されている「制吐薬適正使用ガイドライン」で推奨されている用量とした[3]。CDDPを含むレジメンでは1日目16.5mg，2～4日目8mgずつの総投与量40.5mgとし，CBDCAを含むレジメンでは1日目9.9mg，2～3日目8mgずつの総投与量25.9mgとした。その結果，CDDPを含むレジメン，CBDCAを含むレジメンいずれにおいてもガイドライン推奨用量以上のステロイド投与群は推奨用量以下の投与群と比較して嘔吐発現率は低かった。また，ガイドライン推奨用量以上のステロイド投与群においても，急性期と比較して遅発期での嘔吐発現率が高かった（図4）。

4．急性期および遅発期の悪心発現との関係

急性期および遅発期における悪心発現の関係を検討した。その結果，急性期において悪心が認められた患者のうち約96%で遅発期にも悪心が認められた。さらにレジメン別での検討では，CDDPを含むレジメンでは急性期に悪心が認められた場合，すべての患者に遅発期の悪心が認められ，CBDCAを含むレジメンにおいても急性期に悪心が認められた患者の約89%に遅発期の悪心が認められた。また，どちらのレジメンにおいても急性期に悪心が認められた患者は急性期の悪心が認められなかった患者と比較して遅発期の悪心の程度や「つらさ」が強く認められた（図5）。

5．医師と患者の悪心・嘔吐に対する認識の相違

各レジメンによる悪心・嘔吐に対する医師の印象・予測と，調査患者における実際の悪心・嘔吐に対する「つらさ」の認識の相違について検討した（図6）。その結果，CDDPを含むレジメンおよび，CBDCAを含むレジメンの両者において，急性期では医師の悪心・嘔吐の「つらさ」に対する印象と比べ，実際に投与された患者の印象は強くない傾向が認められた。

一方，遅発期では実際に投与された患者の悪心・嘔吐の「つらさ」に対する印象は医師の印象と比べ，ばらつきがあった。

考　察

今回，新潟肺癌治療研究会18施設において肺がん化学療法を実施した101例を対象に悪心・嘔吐の実態調査を実施した。その結果，医師の急性期における悪心・嘔吐の「つらさ」に対する印象はやや過剰であることが認められた。過剰であった理由として，5-HT_3受容体拮抗薬が登場する前から抗悪性腫瘍薬を使用している医師は急性期の強い悪心・嘔吐を経験していることが多く，それらの印象から過剰に認識していることが考えられる。したがって，今回の我々の報告が急性期の悪心・嘔吐に対する適切な判断を行う参考になればと考える。

現状では急性期の悪心・嘔吐において制御率が高いことは明らかであるが，注目すべきは遅発期の悪心・嘔吐である。本調査の結果から，CDDP，CBDCAいずれのレジメンにおいても急性期と比較して遅発期の嘔吐発現率，摂食障害発現率が高いことが認められた。患者の「つらさ」に対する印象は男女共に抗悪性腫瘍薬投与後4日目に最も「つらく」感じており，医師と患者間の認識に乖離があることから，遅発期まで含めた患者の状態の認識と対応が必要と考えられる。また，十分量のステロイド投与群においても急性期と比較して遅発期の嘔吐発現率が高かったことから，従来の第一世代5-HT_3受容体拮抗薬とステロイドだけでは遅発期の悪心・嘔吐のコントロールは不十分であると考えられる。

特に中等度催吐性リスクであるCBDCAレジメンでの悪心・嘔吐は軽視されがちである。MASCCのガイドラインにおいても中等度催吐性リスクの抗悪性腫瘍薬に関して，5-HT_3受容体拮抗薬の中で唯一遅発期に効果があるパロノセトロンとデキサメタゾンの2剤併用療法が推奨されており，パロノセトロンを用いてしっかりと悪心・嘔吐を予防することも重要だと考えられた[4]。

本調査では，新規制吐薬であるパロノセトロンやアプレピタントを使用していない。しかし，新規制吐薬が急速に普及することを考慮すると，従来の制吐薬を用いた肺がん化学療法における悪心・嘔吐の現状を調査した本結果は今後，新薬を含んだ治療法を検討する

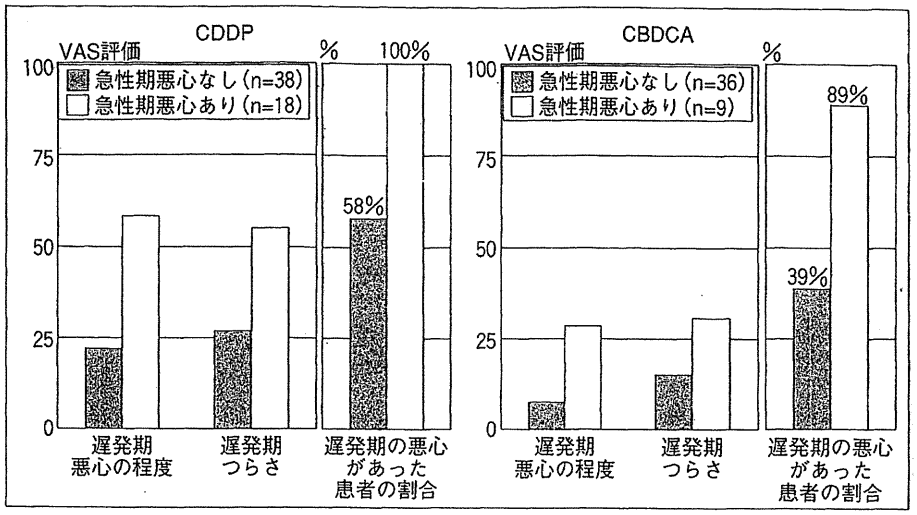

図5　急性期および遅発期の悪心発現の相関

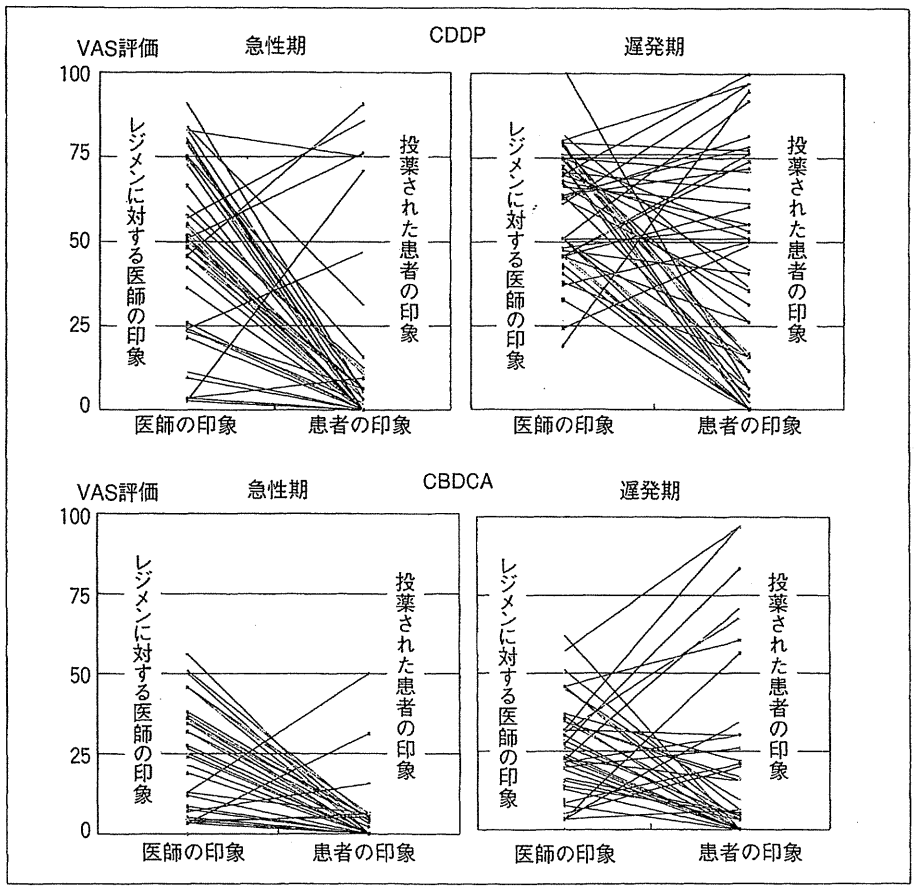

図6　シスプラチン/カルボプラチンレジメン時の医師と患者の認識の相違

上で参考となる。

現在，新潟肺癌治療研究会において本調査をヒストリカルコントロールとした高度催吐性抗悪性腫瘍薬投与に起因する急性及び遅発性の消化器症状に対するパロノセトロン，アプレピタント，デキサメタゾンの三剤併用療法の有効性と安全性を検討する臨床第Ⅱ相試験を実施中である。

また，中等度催吐性抗悪性腫瘍薬投与に起因する急性及び遅発性の消化器症状に対して，パロノセトロン，アプレピタント，デキサメタゾンの三剤併用療法と，従来の二剤併用療法とを比較した臨床第Ⅱ相試験を実施中である。

結　語

制吐薬適正使用ガイドラインでも示されている通り，化学療法に起因する悪心・嘔吐は予防が何よりも重要である。今回調査をした結果，化学療法による悪心・嘔吐に悩まされている患者の実態を把握することが極めて重要であることを改めて認識することができた。また，化学療法による悪心・嘔吐の制御には，さらに改善の余地があることを確認することができた。我々は，上記のような新規制吐薬の評価を通じて，患者がより安心して化学療法を受けられる環境を今後さらに整えていくことが大切であると考える。

深　謝：

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Erlotinib after gefitinib failure in relapsed non-small cell lung cancer: Clinical benefit with optimal patient selection

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ABSTRACT

Background: Recent reports have suggested that erlotinib therapy after gefitinib failure requires optimal patient selection to obtain clinical benefits in relapsed non-small cell lung cancer (NSCLC). However, insufficient evidence exists to determine which clinical factors best identify patients who benefit from erlotinib therapy.

Methods: One hundred twenty-five patients with relapsed NSCLC who had received erlotinib therapy after gefitinib failure were retrospectively evaluated between January 2008 and May 2009.

Results: The response rate (RR), disease control rate (DCR), and median progression-free survival (PFS) for all patients were 9% (95% confidence interval [CI], 5–15%), 44% (95% CI, 35–53%), and 2.0 months (95% CI, 1.4–2.5 months), respectively. The median survival time was estimated to be 11.8 months (95% CI, 6.4–16.0 months). Using multivariate analysis, good performance status (PS), *EGFR* mutation-positive status, and benefit from prior gefitinib therapy were identified as significant predictive factors for disease control. Using a proportional hazards model, benefit from prior gefitinib therapy, good PS, and insertion of cytotoxic chemotherapies between gefitinib and erlotinib therapies emerged as significant predictive factors for longer PFS. Thirty-two patients with concomitant PS 0/1, benefit from prior gefitinib therapy, and insertion of cytotoxic chemotherapies between gefitinib and erlotinib therapies benefitted more from erlotinib therapy: RR, 25% (95% CI, 12–43%); DCR, 72% (95% CI, 53–86%); and median PFS, 3.4 months (95% CI, 2.4–4.9 months).

Conclusions: Higher efficacy of erlotinib after gefitinib failure can be achieved with proper patient selection criteria, including good PS, benefit from prior gefitinib therapy, and insertion of cytotoxic chemotherapies between gefitinib and erlotinib therapies.

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1. Introduction

Erlotinib and gefitinib, both of which belong to the oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) family, have been widely used to treat patients with relapsed advanced non-small cell lung cancer (NSCLC). In the Iressa Survival Evaluation in Lung Cancer (ISEL) study, gefitinib failed to show a survival benefit compared with placebo for recurrent advanced NSCLC [1]. Conversely, erlotinib demonstrated a survival benefit for recurrent advanced NSCLC in a randomized phase III study (BR. 21) [2], which showed that erlotinib was significantly superior to placebo in terms of overall survival. The discrepancy between erlotinib and gefitinib was suggested to be due to differences in the usual dosage. Erlotinib was administered at its maximum tolerated dose (MTD; 150 mg), whereas gefitinib was administered at a dose of 250 mg: approximately one-third of its MTD (700 mg) based on dose-evaluating phase II studies [3,4]. Thus, erlotinib may have a higher biological activity than gefitinib. These findings suggest that salvage treatment with erlotinib may be an option for patients after treatment failure with gefitinib. In fact, some prospective studies were recently conducted to evaluate the efficacy of erlotinib after gefitinib failure [5–7]. These reports have suggested that optimal patient selection is important to obtain clinical benefit. However, insufficient evidence exists to determine which clinical factors contribute to optimal patient selection. The aim of our study was to perform further analysis at the largest scale to date.

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2. Patients and methods

2.1. Patients

Between January 2008 and October 2009, we analyzed 125 patients with relapsed NSCLC who had received erlotinib therapy after gefitinib failure at our institutes. Results were analyzed retrospectively using case records and radiographic records. Patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–3, with no organ dysfunction. Patients who reported never smoking in their lifetime were defined as never smokers, those who had smoked within 1 year of the diagnosis were categorized as current smokers, and the rest were considered to be former smokers.

Written informed consent regarding the administration of erlotinib was obtained from all patients.

2.2. Treatment methods

Patients received erlotinib at a dose of 150 mg/day. Dose reduction to 100, 75, or 50 mg/day and dose interruption were performed when intolerable toxicities were observed. Therapy was continued until disease progression, intolerable toxicity, or patient withdrawal.

2.3. Evaluation of efficacy and toxicity

Baseline evaluations, including medical history, physical examinations, and laboratory tests were performed. Evaluation of treatment response by computed tomography (CT) scan was repeated every 4–8 weeks according to the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [8]. If a patient was documented to demonstrate a complete response (CR) or a partial response (PR), a confirmation was necessary after more than 4 weeks. Disease control was defined as the best tumor response of CR, PR, or stable disease (SD) that was confirmed and sustained for 8 weeks or longer. The response rate (RR) and disease control rate (DCR) were defined as CR + PR and CR + PR + SD ≥ 8 weeks, respectively. Because of the retrospective nature of this study, strict application of RECIST for brain lesions was occasionally impossible. Progression-free survival (PFS) was defined as the period from the start of treatment to the date when disease progression was observed. Overall survival (OS) was defined as the period from the start of erlotinib treatment to the date of death. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). The TKI-free interval was defined as the period between termination of gefitinib therapy and initiation of erlotinib therapy.

2.4. EGFR mutational analysis

We isolated tumor DNA from various specimens, and the *EGFR* mutation status was analyzed using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method, as previously reported [9]. Almost all *EGFR* mutational analyses were performed before administration of gefitinib.

2.5. Statistical analysis

The DCR was compared between demographic factors using Fisher's exact test or Spearman's rank correlation. Multivariate analysis on factors to obtain better disease control was performed using logistic regression analysis. The survival distribution was estimated by the Kaplan–Meier method. PFSs were compared between demographics factors using the log-rank test. Multivariate analysis on factors to obtain a longer PFS was performed using a proportional hazards model. A backward stepwise approach was adopted as our variable selection method for multivariate analyses. A *P*-value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using JMP 7 software (SAS Institute Inc., Cary, NC, USA).

Table 1
Patient characteristics.

Characteristics	No. of patients	%
Age		
Median (range)	64 (37–84)	
Prior regimens		
Median (range)	3 (1–11)	
Gender		
Male	49	39
Female	76	61
Smoking history		
Never	70	56
Former	27	22
Current	28	22
Performance status (ECOG)		
0, 1	88	70
2, 3	37	30
Histology		
Adenocarcinoma	117	94
Other	8	6
EGFR mutation status		
Positive	63	50
Negative	28	23
Unknown	34	27
Response to prior gefitinib therapy		
Complete response	3	2
Partial response	68	55
Stable disease	22	18
Progressive disease	28	22
Not evaluable	4	3
Chemotherapy between G and E therapies		
Cytotoxic agent	65	52
None	60	48
PFS of prior G therapy (months)		
Median (range)	7J.6 (0.2–64.3)	
EGFR-TKI-free interval		
Median (range)	2.1 (0–31.7)	

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; G, gefitinib; E, erlotinib; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

3. Results

3.1. Patient characteristics

Between January 2008 and October 2009, 125 patients with relapsed NSCLC who had been treated with erlotinib after gefitinib failure were evaluated retrospectively. Patient characteristics are shown in Table 1. Female patients (61%), never smokers (56%), and patients with PS 0 or 1 (70%) were predominant. The histology of most patients was adenocarcinoma (94%). *EGFR* mutations were investigated in 91 (73%) of 125 patients, and mutations were detected in 63 (50%) patients. In total, 71 (57%) of 125 patients responded to prior gefitinib therapy.

3.2. Tumor response

Out of 125 patients, 11 had a PR and 44 had SD, yielding an overall RR of 9% (95% confidence interval [CI], 5–15%) and a DCR of 44% (95% CI, 35–53%). The characteristics of patients who achieved PR are shown in Table 2. Most patients were female, never smokers, and in good PS. The histology of all these patients was adenocarcinoma, and they responded to prior gefitinib therapy. Eight of 11

Table 2
Characteristics of patients who obtained a partial response.

Age	Gender	Smoking	Histology	PS	*EGFR* mutation	PFS with E (months)	Response of prior G	PFS with G (months)	TKIfree interval (months)	Chemotherapy between G and E
59	F	Never	Ad	1	G719S	2.4	PR	10.6	3.6	CDDP+VNR
75	F	Never	Ad	3	Del-19	6.6	PR	27.8	0	None
83	F	Never	Ad	1	Del-19	4.8[a]	PR	4.2	2.0	GEM
78	M	Never	Ad	1	Del-19	2.5[a]	PR	11.4	0	None
71	F	Never	Ad	1	Del-19	3.6[a]	PR	6.2	1.5	GEM+VNR
54	F	Never	Ad	1	L858R	7.8	PR	24.1	13.6	3 regimens
60	F	Current	Ad	1	L858R	4.2	PR	18.2	0	None
75	F	Never	Ad	0	Unknown	8.2	PR	19.2	5.4	CBDCA+PTX
60	F	Never	Ad	0	Unknown	4.8[a]	PR	12.1	5.6	CDDP+GEM
66	F	Never	Ad	1	Unknown	7.2[a]	PR	26.4	7.7	DOC+S-1
61	F	Never	Ad	1	None	5.0	PR	8.6	15.5	2 regimens

PS, performance status; EGFR, epidermal growth factor receptor; PFS, progression-free survival; E, erlotinib; G, gefitinib; TKI, tyrosine kinase inhibitor; M, male; F, female; Ad, adenocarcinoma; G719S, G719S point mutation in exon 18; Del-19, deletion mutation in exon 19; L858R, L858R point mutation in exon 21; PR, partial response; CDDP, cisplatin; VNR, vinorelbine; GEM, gemcitabine; CBDCA, carboplatin; PTX, paclitaxel; DOC, docetaxel.
[a] Patient is still progression-free.

patients received cytotoxic chemotherapies between gefitinib and erlotinib administration.

3.3. Survival

The median PFS was 2.0 months (95% CI, 1.4–2.5 months; Fig. 1A), and the median overall survival time was 11.8 months (95% CI, 6.4–16.0 months; Fig. 1B).

3.4. Toxicity profile

Frequencies and grades of toxicities are shown in Table 3. The most common side effect was skin rash, which was recorded in 101 patients (81%). Interstitial lung disease was observed in four (3%) of 125 patients. No treatment-related death was observed. Grade 3/4 non-hematological adverse events were observed in 38 (30%) of 125 patients. Particularly, in poor PS (2/3) patients, 16 (43%) of 38 patients experienced grade 3/4 non-hematological toxicities, including fatigue or anorexia. Dose reduction or interruption was performed in 61 (49%) of 125 patients because of adverse events. In poor PS patients, dose modification was performed in 24 (63%) of 38 patients.

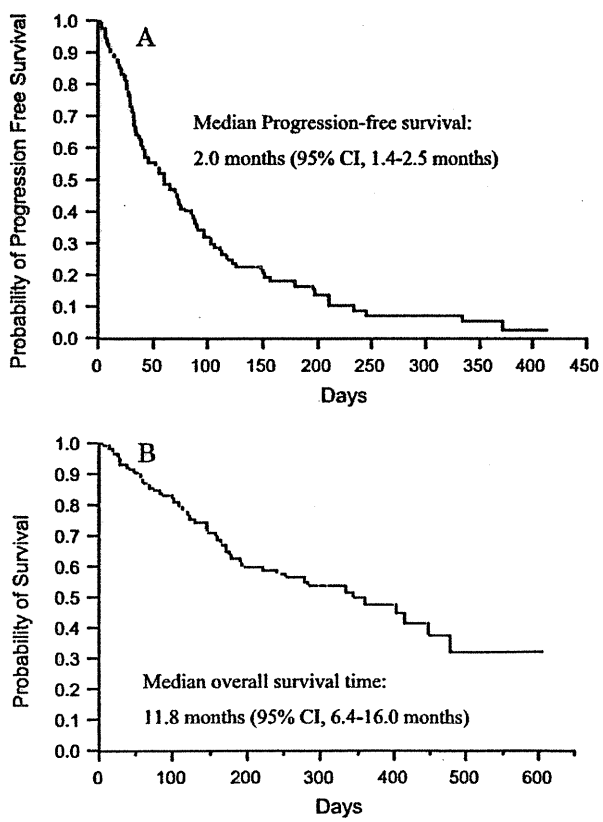

Fig. 1. The curve of progression-free survival (A) and overall survival (B).

3.5. Analysis of disease control and progression-free survival

Analysis of disease control is shown in Table 4. Using univariate analysis, smoking history, PS, *EGFR* mutation status, and response to prior gefitinib therapy were suggested to be predictive factors for better disease control. In multivariate analysis using a logistic regression model, PS 0/1, *EGFR* mutation-positive (or unknown) status, and benefit from prior gefitinib therapy were significant predictive factors to obtain disease control (Table 5).

Analysis of PFS is also shown in Table 4. Using univariate analysis, smoking history, PS, and response to prior gefitinib therapy were suggested to be predictive factors for longer PFS. In multivariate analysis using a proportional hazards model, PS 0/1, benefit from prior gefitinib therapy, and insertion of cytotoxic chemotherapies between gefitinib and erlotinib therapies were significant predictive factors to obtain longer PFS (Table 5).

Thirty-two patients with concomitant PS 0/1, benefit from prior gefitinib therapy, and insertion of cytotoxic chemotherapies between gefitinib and erlotinib therapies benefitted more from erlotinib therapy: RR, 25% (95% CI, 12–43%); DCR, 72% (95% CI, 53–86%); median PFS, 3.4 months (95% CI, 2.4–4.9 months).

Characteristics of patients who achieved the longest three PFSs are shown in Table 6. PD in all three cases was caused by progression of brain metastases, while primary and other lesions remained SD. Gefitinib was directly switched to erlotinib in all three cases.

No correlation was found between skin rash and clinical benefit as evaluated by DCR and PFS.

3.6. Response of central nervous system (CNS) metastases

Brain metastases were confirmed in 62 (50%) of 125 patients in our study. CNS lesions in 21 (34%) of these 62 patients responded to erlotinib after gefitinib failure. Seven (11%) patients were SD, and PD was observed in five (8%) of these 62 patients. Twenty-nine (47%) patients with CNS metastases were not evalu-

Table 3
Frequencies and grades of toxicities.

Adverse effect	Grade 1/2	Grade 3	Grade 4	Grade 3/4 (%)
Rash	90	11	0	9
Diarrhea	26	2	0	2
Fatigue	24	5	0	4
Anorexia	29	16	0	13
Liver dysfunction	9	2	0	2
Interstitial lung disease	2	2	0	2

Table 4
Univariate analyses of disease control rate and progression-free survival.

Characteristic	Disease control rate	*P*-value of DCR	Progression-free survival (months)	*P*-value of PFS
Age				
<65	46% (30/65)	0.7187	1.8	0.2655
≥65	42% (25/60)		2.5	
Prior regimens				
<5	49% (33/67)	0.2127	2.3	0.4742
≥5	38% (22/58)		2.2	
Gender				
Male	39% (19/49)	0.3447	1.9	0.5184
Female	47% (36/76)		2.3	
Smoking history				
Never	51% (36/70)	0.0181	2.4	0.0482
Former	48% (13/27)		2.5	
Current	21% (6/28)		1.2	
PS (ECOG)				
0, 1	56% (49/88)	<0.0001	2.8	<0.0001
2, 3	16% (6/37)		0.8	
EGFR mutation				
Positive	51% (32/63)	0.0112	2.4	0.2185
Negative	21% (6/28)		1.5	
Unknown	50% (17/34)		3.0	
Response to prior gefitinib				
CR + PR	52% (37/71)	0.0112	2.9	0.0005
SD	50% (11/22)		2.0	
PD	25% (7/28)		1.3	
Chemotherapy between G and E				
Cytotoxic agent	42% (27/65)	0.5639	2.4	0.5794
None	47% (28/60)		2.0	
PFS of prior gefitinib				
<10 months	41% (29/70)	0.5872	2.0	0.4900
≥10 months	47% (26/55)		2.4	
TKI-free interval				
<6 months	46% (28/61)	0.6758	2.4	0.5717
≥6 months	42% (27/64)		2.0	

DCR, disease control rate; PFS, progression-free survival; PS, performance status; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; G, gefitinib; E, erlotinib; TKI, tyrosine kinase inhibitor.

able because brain CT or magnetic resonance imaging (MRI) data were not available, or patients were receiving whole brain radiotherapy or stereotactic radiotherapy around erlotinib administration.

Eight patients simultaneously had leptomeningeal metastases. Of these, five responded to erlotinib, one was PD, and two were not evaluable (response was defined as the improvement of clinical symptoms and/or findings of brain MRI).

Table 5
Multivariate analyses of disease control rate and progression-free survival.

Characteristics	Disease control rate	*P*-value of DCR	OR 95% CI	Progression-free survival (months)	*P*-value of PFS	HR 95% CI
PS (ECOG)						
0, 1	56% (49/88)	<0.0001	11.60	2.8	<0.0001	<0.0001
2, 3	16% (6/37)		0.15–0.50	0.8		0.47–0.73
EGFR mutation						
Positive or unknown	51% (49/97)	0.0045	4.59	2.5	0.075	1.52
Negative	21% (6/28)		0.26–0.79	1.5		0.65–1.02
Response to prior gefitinib						
CR + PR + SD	52% (48/93)	0.0040	0.23	2.5	0.0003	0.41
PD	25% (7/28)		1.26–3.65	1.3		1.24–1.94
Chemotherapy between G and E						
Cytotoxic agent	42% (27/65)	0.0570	0.42	2.4	0.0447	0.67
None	47% (28/60)		0.99–2.52	2.0		1.00–1.49

DCR, disease control rate; PFS, progression-free survival; OR, odds ratio; CI, confidence interval; HR, hazard ratio; PS, performance status; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; G, gefitinib; E, erlotinib.

Table 6
Characteristics of patients who achieved the longest three PFSs.

Age	Sex	Smoking	His	PS	*EGFR* mutation	Response of E	PFS (E)	Response of G	PFS (G)	TKI-free interval	Chemo between G and E
56	F	Never	Ad	1	Del-19+T790M[a]	SD	(13.8)	PR	7.2	1.0	None
61	F	Never	Ad	1	Del-19+L858R	SD	12.4	CR	32.4	0.1	None
65	M	Former	Ad	1	Del-19	SD	(11.6)	PR	9.8	0.6	None

PFS, progression-free survival; His, histology; PS, performance status; EGFR, epidermal growth factor receptor; E, erlotinib; G, gefitinib; TKI, tyrosine kinase inhibitor; F, female; M, male; Ad, adenocarcinoma; Del-19, deletion mutation in exon 19; T790M, T790M point mutation in exon 20; L858R, L858R point mutation in exon 21; SD, stable disease; PR, partial response; CR, complete response.
Numbers in parentheses mean still progression-free.
[a] With gefitinib treatment, progressive disease was assessed by the occurrence of brain metastases despite SD in other lesions. Subsequently, the brain tumor was surgically resected and the T790M mutation was detected in the brain tumor tissue. After surgery, erlotinib was initiated.

4. Discussion

In our study, the RR, DCR, and median PFS were 9%, 44%, and 2.0 months, respectively. These results are similar to those of previous reports regarding erlotinib after gefitinib failure [5–7], which reported RRs less than 10%, DCRs of approximately 30%, and median PFSs of 1.7–2.0 months. Furthermore, two pooled analyses, including prospective and retrospective studies, were performed that revealed the RR and DCR to be approximately 10% and 30%, respectively [10,11].

Using multivariate analysis, we demonstrated that PS 0/1, *EGFR* mutation-positive status (or unknown), and benefit from prior gefitinib therapy were significant predictive factors to obtain better disease control. PS 0/1, benefit from prior gefitinib therapy, and insertion of cytotoxic chemotherapies between gefitinib and erlotinib therapies were also significant predictive factors for longer PFS using multivariate analysis. The results of the two pooled analyses concluded that erlotinib can be an option for highly selected NSCLC patients after gefitinib failure. They suggested that clinical benefit from erlotinib after gefitinib failure was produced more frequently in patients who had responded to prior gefitinib therapy than in those who experienced PD on prior gefitinib therapy. We agree with their suggestion, and as shown by the present multivariate analyses, we propose two additional predictive factors: good PS and insertion of cytotoxic chemotherapies between gefitinib and erlotinib therapies. Thirty-two patients with these three concomitant factors in our study demonstrated the following good results: RR, 25% (95% CI, 12–43%); DCR, 72% (95% CI, 53–86%); and median PFS, 3.4 months (95% CI, 2.4–4.9 months).

Although PS is a common prognostic factor in patients with NSCLC, PS in our study was a significant predictive factor for erlotinib therapy. We considered that the cause may be less feasibility of erlotinib for poor PS patients. In our study, grade 3/4 adverse events were found in 16 (43%) of 38 patients with PS 2/3. Dose reduction or interruption was performed in 24 (63%) of 38 poor PS patients, and we considered that the dose intensity was not sufficiently maintained to promote the benefits of erlotinib. Hotta et al. suggested that discontinuation of erlotinib therapy was frequently observed in poorer PS patients [12]. They concluded poor PS is related to low compliance. A phase II trial evaluating erlotinib for PS 2 patients with NSCLC revealed that grade 3/4 toxicities, including fatigue and anorexia, were found in 40% of 76 patients [13]. For poor PS patients, erlotinib should not be given routinely after gefitinib failure because of the absence of efficacy and high frequency of severe toxicities.

Twenty-one of 62 (34%) patients with brain metastases responded to erlotinib therapy in our study. Additionally, eight patients simultaneously had leptomeningeal metastases, and five of these eight patients responded to erlotinib therapy. Erlotinib therapy after gefitinib failure may be much more effective for brain metastases (with or without leptomeningeal metastases) compared with other lesions. In the clinical course of patients with the longest three PFS (13.8, 12.4, and 11.6 months), gefitinib was directly switched to erlotinib after evaluation of PD (Table 6). PD of these three cases was caused by progression of brain metastases, while primary and other lesions remained SD. In the clinical course of treatment with EGFR-TKIs, CNS metastases were frequently observed as the cause of PD [14,15]. Furthermore, the high efficacy of erlotinib for CNS metastases after gefitinib failure was found in patients who had responded to prior gefitinib therapy [16]. Therefore, patients with PD from progression of brain metastases, despite SD with other lesions, may be good candidates for erlotinib therapy after gefitinib failure.

We confirmed 11 patients who had achieved PR with erlotinib after gefitinib failure. However, the PFS of PR cases with erlotinib was not much longer than the PFS obtained from prior gefitinib therapy (Table 2). The most successful patients were females, were never smokers, had adenocarcinoma histology, were *EGFR* mutation-positive, showed PR to prior gefitinib therapy, and had a "TKI-free interval" consisting of insertion of cytotoxic chemotherapies. In multivariate analysis regarding PFS in our study, the TKI-free interval with the insertion of cytotoxic chemotherapies between gefitinib and erlotinib therapies was associated with longer PFS. This TKI-free interval may contribute to the recovery of sensitivity to EGFR-TKIs. Interestingly, efficacy of re-administration of gefitinib for initial responders was demonstrated [17,18]. This interval also appears to promote erlotinib efficacy as a comparable benefit of EGFR-TKI re-administration.

Cho et al. reported that erlotinib was effective in patients with wild-type *EGFR* who had SD while receiving gefitinib [5]. In our present study, patients who had SD while receiving gefitinib could achieve a good DCR (50%), but no patients responded to erlotinib. Most of these patients probably had wild-type *EGFR*, and the response rate of erlotinib was considered to be relatively low. Their data suggest that a population exists that can benefit from erlotinib after SD with gefitinib treatment. A high drug concentration with erlotinib may contribute to some patients needing a higher drug concentration than with gefitinib. On the other hand, some mutations such as L747S and D761Y were suggested to have different sensitivities to erlotinib and gefitinib [19,20]. Although these mutations seem to be rare, some patients who respond to erlotinib may have one of these mutations.

Some mechanisms of acquired resistance to EGFR-TKIs after an initial response have been indicated. Documented mechanisms include a T790M point mutation in exon 20 in the EGFR gene that accounts for 50% of resistant cases, amplification of the MET gene (20%), and others (30%) [21–24]. However, neither re-analysis of *EGFR* mutations nor other molecular analyses between administration of gefitinib and erlotinib could be performed in our study. Thus, we could not investigate the cause of sensitivity to erlotinib therapy after gefitinib failure. Further investigations are warranted to clarify the mechanism of sensitivity to erlotinib therapy after gefitinib failure.

Criteria for acquired resistance to EGFR-TKIs in NSCLC have been recently proposed by Jackman et al., and all patients should have the following: (1) previous treatment with a single-agent EGFR-TKI; (2)

either or both of the following: (A) a tumor that harbors an *EGFR* mutation known to be associated with drug sensitivity or (B) objective clinical benefit from treatment with an EGFR-TKI as defined by either: (i) documented PR or CR, or (ii) significant and durable (6 months) clinical benefit (SD) after initiation of EGFR-TKIs; (3) systemic progression of disease while on continuous treatment with EGFR-TKIs within the last 30 days; and (4) no intervening systemic therapy between cessation of EGFR-TKIs and initiation of new therapy [25]. Twenty patients in our study met these criteria, and nine of them obtained clinical benefit (disease control) from erlotinib despite acquired resistance to EGFR-TKIs based on these criteria. Four of nine patients who obtained clinical benefit had CNS progression and responded to erlotinib. Jackman et al. reported that special attention should be paid to patients whose disease progresses only in the CNS [25]. Although patients who meet these criteria rarely respond to erlotinib as an EGFR-TKI re-administration therapy, some patients may obtain clinical benefit in specific situations such as CNS progression and otherwise SD prior to gefitinib therapy.

In conclusion, erlotinib as a re-administration EGFR-TKI therapy may be a good treatment option for a highly selected subset of patients. Optimal patient selection is based on the following factors: benefit from prior gefitinib therapy, good PS, and insertion of cytotoxic chemotherapies between gefitinib and erlotinib therapies.

Conflicts of interest statement

None declared.

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ORIGINAL ARTICLE

The prevalence of pulmonary fibrosis combined with emphysema in patients with lung cancer

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ABSTRACT

Background and objective: **Combined pulmonary fibrosis and emphysema (CPFE) is a unique disorder of the upper lobe, whereas emphysema is usually associated with lower lobe fibrosis. Although CPFE might increase the risk of lung cancer, the prevalence of CPFE in patients with lung cancer and the incidence of lung cancer in patients with CPFE are unknown. The objective of this study was to determine the prevalence of CPFE in lung cancer patients and to assess the clinical features of these patients.**

Methods: **A total of 1143 patients with lung cancer were reviewed. Based on HRCT performed at diagnosis of lung cancer, patients were categorized into four groups: normal, emphysema, fibrosis and CPFE. The clinical characteristics of patients with CPFE were compared with those of the other groups.**

Results: **CPFE, emphysema and fibrosis were identified in 101 (8.9%), 404 (35.3%) and 15 (1.3%) patients with lung cancer, respectively. The median overall survival of CPFE patients ($n = 101$, 10.8 months) was significantly less than that of normal patients ($n = 623$, 53.0 months) or that of patients with emphysema alone ($n = 404$, 21.9 months). Acute lung injury occurred in 20 (19.8%) patients with CPFE.**

Conclusions: **CPFE is more prevalent than fibrosis in patients with lung cancer, and patients with CPFE had a poorer prognosis in the present study. Further investigation is therefore necessary to elucidate whether CPFE is an independent risk factor for lung cancer.**

Key words: combined pulmonary fibrosis and emphysema, interstitial lung disease, lung cancer.

SUMMARY AT A GLANCE

Data for 1143 patients with lung cancer was reviewed to assess the clinical characteristics of patients with lung cancer and CPFE. Patients with lung cancer and CPFE had a poor prognosis and 19.8% of these patients developed severe interstitial lung disease.

INTRODUCTION

Combined pulmonary fibrosis and emphysema (CPFE) is a unique disorder of the upper lobe, whereas emphysema is usually associated with lower lobe fibrosis.[1] Although emphysema and pulmonary fibrosis are entities defined by distinct clinical, functional, radiological and pathological characteristics, both disorders are related to lung cancer, independent of exposure to tobacco smoke. Cross-sectional studies have shown that the prevalence of COPD in subjects diagnosed with lung cancer is 40–70%.[2–4] A population-based cohort study showed that IPF is a risk factor for lung cancer.[5] Based on these studies, CPFE, in which patients present with a combination of pulmonary emphysema and fibrosis, is predicted to be a common disorder in patients with lung cancer. However, the prevalence of CPFE in patients with lung cancer has not been studied, and the clinical characteristics of these patients are not well known. We conducted a retrospective study to examine the prevalence of CPFE in patients with lung cancer, as well as the clinical characteristics of these patients.

METHODS

Patient selection

The medical records for a series of consecutive patients with lung cancer, as confirmed by histological or cytological examination, who were treated in the Division of Respirology and Chest Surgery, NTT Medical Center Tokyo between April 2002 and September 2009, were retrospectively reviewed. Patients with emphysema and fibrosis on HRCT at diagnosis of lung cancer were prospectively identified and the data were recorded before lung cancer treatment, to assess the risk of interstitial lung disease (ILD). Only patients who had a chest HRCT scan, which was performed at diagnosis of lung cancer and was available

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for review, were included in the study. The study protocol was reviewed and approved by the Ethics Committee of NTT Medical Center, Tokyo.

Patients were categorized into four groups: those with normal lungs (except for the presence of the tumour), emphysematous lungs, fibrotic lungs or CPFE lungs, based on chest CT findings. Patients who met the following criteria, as described by Cottin *et al.*,[1] were categorized as having CPFE: (1) The presence of emphysema on CT, defined as well-demarcated areas of decreased attenuation in comparison with contiguous normal lung, and marginated by a very thin (<1 mm) wall or no wall, and/or multiple bullae (>1 cm) with upper zone predominance. (2) The presence of diffuse parenchymal lung disease with significant pulmonary fibrosis on CT, defined as reticular opacities with peripheral and basal predominance, honeycombing, architectural distortion and/or traction bronchiectasis or bronchiolectasis; focal ground-glass opacities and/or areas of alveolar condensation may be associated but should not be prominent. Patients who met criterion 1 were categorized as having emphysema, those who met criterion 2 were categorized as having fibrosis and those who met neither criterion 1 nor criterion 2 were categorized as normal. The electronic medical records were reviewed to obtain clinical and demographic data, including gender, age, smoking history, histology results, route of referral, clinical stage of lung cancer, treatment, treatment-related toxicities and survival.

Response to treatment and treatment-related toxicities

The response of the patients to chemotherapy was assessed using the Response Evaluation Criteria in Solid Tumours criteria. Toxicities related to treatment were assessed according to the National Cancer Institute common toxicities criteria (NCI-CTC version 3.0). Patients were diagnosed as having acute lung injury if the following criteria were met: (i) bilateral infiltration; (ii) PaO_2/fraction of inspired (F_IO_2) <300; (iii) exclusion of other possible causes for (i) and (ii), especially left cardiac failure and progression of cancer.

Statistical analyses

To compare the differences in CT findings between the subgroups, analysis of variance was performed for continuous variables, and the chi-square test or Fisher's exact test was used for categorical variables. Survival time was estimated by the Kaplan–Meier method, and differences in survival time between the subgroups were analysed by the log rank test. Data were analysed using the StatView version 5.0J software package (Statistical Analysis Systems, Cary, NC, USA). A *P*-value of <0.05 was considered significant.

RESULTS

Characteristics of the patients

Data for a total of 1143 patients with lung cancer were reviewed. One hundred and one (8.9%) of these patients showed evidence of CPFE on chest CT performed at diagnosis of lung cancer. Only 15 (1.3%) patients with lung cancer showed evidence of fibrosis without emphysematous features on chest CT. The clinical characteristics of the patients with CPFE are summarized in Table 1. All patients had a history of heavy smoking (mean of 63 pack-years), and 96 of the 101 patients with CPFE (95%) were male.

Histology and clinical stage of lung cancer in patients with CPFE

The distribution of lung cancer histology differed in patients with CPFE compared with those with normal lungs and was similar to that in patients with fibrosis alone or emphysema alone (Table 1). A high prevalence of smoking-related lung cancers, such as small cell lung cancer (SCLC) and squamous cell lung cancer, was observed in patients with CPFE. In total, 57 of the 101 (56.4%) lung cancers in patients with CPFE originated in the lower lobe. This pattern of localization was different from that in the normal and emphysema subgroups, but similar to that in the fibrosis subgroup (39.5%, 35.0% and 60.0%, respectively). Stage IIIB and stage IV lung cancers were defined as advanced stage disease, and 48 of 82 non-small cell lung cancer (NSCLC) patients with CPFE (58.5%) were diagnosed as having advanced stage disease (Table 1). More patients with CPFE than in the other subgroups were diagnosed as having advanced stage disease.

Treatment of lung cancer and outcomes in patients with CPFE

The treatment modalities used for the patients with CPFE are summarized in Table 1. Sixteen patients received best supportive care. Nine patients received thoracic radiotherapy. Thirty-three patients underwent surgery, including lobectomies in 26, a segmentectomy in one, and partial resection in six. Sixty patients received chemotherapy; 44 with NSCLC and 16 with SCLC. Six patients (5 NSCLC, 1 SCLC) were treated with radiotherapy, but not concurrently with chemotherapy. The objective rates of response to chemotherapy were 52.4% (95% CI: 36.9–67.6) and 93.7% (95% CI: 80.4–99) for patients with NSCLC and SCLC, respectively.

The median overall survival time (OS) of patients with CPFE was 10.8 months from commencement of treatment (Fig. 1). The median OS in patients with CPFE was significantly different from that in normal patients (53.0 months) or patients with emphysema alone (21.9 months) ($P < 0.001$, Fig. 1). The 5-year survival rates and median OS in patients with stage IA NSCLC treated by surgery were 86.7% and not reached

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Table 1 Characteristics of normal patients and those with combined pulmonary fibrosis and emphysema (CPFE), emphysema alone or fibrosis alone

	CPFE ($n = 101$)	Normal ($n = 623$)	Emphysema ($n = 404$)	Fibrosis ($n = 15$)	*P*-value
Age, years					
Median	70	66	70	70	<0.0001
Range	50–94	17–97	36–100	57–91	
Gender, *n* (%)					
Female	5 (5.0)	302 (48.5)	57 (14.1)	2 (13.3)	<0.0001
Male	96 (95.0)	321 (51.5)	347 (85.9)	13 (86.7)	
Smoking status, *n* (%)					
Ex/current	101 (100)	290 (46.6)	382 (94.6)	14 (93.3)	<0.0001
Smoking history, pack-years					
Median	51.5	5.3	46	50	<0.0001
Range	8–236	0–240	0–100	0–280	
Histology, *n* (%)					
Adenocarcinoma	46 (45.5)	517 (83.0)	196 (48.5)	7 (6.7)	<0.0001
Squamous cell carcinoma	31 (30.7)	60 (9.6)	125 (30.9)	2 (13.3)	<0.0001
Large cell carcinoma	2 (2.0)	6 (1.0)	5 (1.2)	0 (0)	0.8036
Other non-small cell carcinoma	6 (6.0)	18 (2.9)	29 (7.2)	5 (33.3)	<0.0001
Small cell carcinoma	19 (18.8)	25 (4.0)	53 (13.1)	1 (6.7)	<0.0001
Clinical stage of non-small cell lung cancer, *n* (%)					
IA	9 (11.0)	269 (45.0)	82 (23.4)	6 (42.9)	<0.0001
IB	10 (12.2)	55 (9.2)	54 (15.4)	1 (7.1)	0.0338
IIA	1 (1.2)	1 (0.2)	4 (1.1)	0 (0)	0.2362
IIB	2 (2.4)	14 (2.3)	20 (5.7)	0 (0)	0.0356
IIIA	12 (14.6)	40 (6.7)	36 (10.3)	0 (0)	0.0514
IIIB	19 (23.1)	49 (8.2)	53 (15.1)	6 (42.9)	<0.0001
IV	29 (35.4)	170 (28.4)	102 (29.1)	1 (7.1)	0.2654
Advanced stage (IIIB, IV)	48 (58.5)	219 (36.6)	155 (44.2)	7 (50.0)	0.0007
Clinical stage of small cell lung cancer, *n* (%)					
Limited disease	2 (10.5)	3 (12.0)	5 (9.4)	1 (100)	0.5824
Extensive disease	17 (89.5)	22 (88.0)	48 (90.6)	0 (0)	
Primary site, *n* (%)					
Lower lobe	57 (56.4)	236 (37.8)	139 (34.4)	9 (60.0)	0.0002
Route of diagnosis, *n* (%)					
Screening, incidental	45 (46.4)	371 (77.0)	184 (47.7)	10 (76.9)	<0.0001
Symptoms	52 (53.6)	111 (23.0)	202 (52.3)	3 (23.1)	
Treatment, *n* (%)					
Surgery	33 (32.7)	357 (57.3)	169 (41.8)	8 (53.5)	<0.0001
Chemotherapy	60 (59.4)	306 (49.1)	234 (57.9)	10 (66.7)	0.0152
Radiation	6 (5.9)	53 (8.5)	79 (19.6)	0 (0)	<0.0001
Best supportive care only	16 (15.8)	56 (9.0)	41 (10.1)	2 (13.3)	0.1873

in patients with normal lungs ($n = 269$), 79.2% and 79.3 months in patients with emphysema ($n = 82$), and 40% and 29.3 months in patients with CPFE ($n = 9$) ($P < 0.001$, Fig. 1b). The median OS in patients with stage IV NSCLC treated with chemotherapy was 12.3 months, 9.0 months and 7.1 months in patients with normal lungs ($n = 131$), emphysema ($n = 77$) or CPFE ($n = 22$), respectively (Fig. 1c, $P = 0.01$). The presence of CPFE indicated a poor prognosis in patients with early, as well as advanced NSCLC.

Acute lung injury in patients with CPFE

Severe acute lung injury was diagnosed in 20 of the 101 patients with CPFE. The incidence of acute lung injury according to type of treatment is summarized in Table 2. There were no statistically significant differences in the incidence rates for acute lung injury between treatment modalities and surgical procedures. Even among those who received best supportive care only, two of 16 patients (12.5%) with acute lung injury died. Twelve of the 60 patients (20%) with CPFE, who received chemotherapy, experienced acute lung injury. There was a tendency for the incidence of acute lung injury to increase as the number of chemotherapeutic agents increased ($P = 0.0378$, Table 2). The prognosis of CPFE patients with acute lung injury was poor; the mortality rate and median survival time from onset of acute lung injury were 75% and 22 days, respectively.

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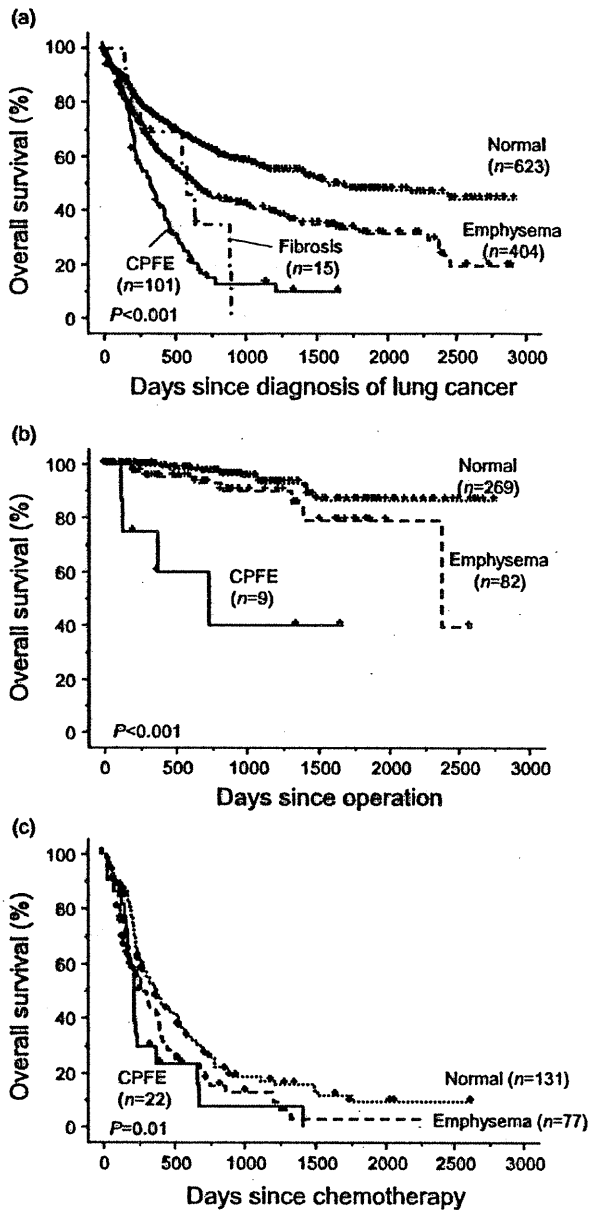

Figure 1 Overall survival in patients with primary lung cancer, according to underlying pulmonary disease (normal: dotted line; emphysema: dashed line; CPFE: solid line; fibrosis: dotted/dashed line), (a) for the overall population, (b) in patients with stage IA non-small cell lung cancer (NSCLC) treated by surgery, and (c) in patients with stage IV NSCLC treated with chemotherapy. CPFE, combined pulmonary fibrosis and emphysema.

DISCUSSION

The prevalence of CPFE was 8.9% in the consecutive patients with primary lung cancer, who were included in the study. The patients with CPFE were current, heavy smokers and were predominantly males, as described previously.[1] Of interest, 76% of lung cancers

Table 2 Incidence of acute lung injury in patients with combined pulmonary fibrosis and emphysema according to treatment

	Total, *n*	Acute lung injury, *n* (%)	*P*-value
Treatment			
Chemotherapy	60	12 (20.0)	0.6617
Surgery	33	9 (27.3)	
Radiation	6	1 (16.7)	
Best supportive care	16	2 (12.5)	
Surgery			
Total	33	9 (27.3)	0.9307
Lobectomy	26	7 (26.9)	
Partial resection/ segmentectomy	7	2 (28.6)	
Chemotherapy			
Total	60	12 (20.0)	0.0378
First line	60	3 (5.0)	
Second line	35	4 (11.4)	
Third or greater line	17	5 (29.4)	

in patients with CPFE were diagnosed at an advanced stage. The overall survival of lung cancer patients with CPFE was poor, with a median survival time of 10.8 months. Fatal severe acute lung injury occurred more frequently in those with CPFE, irrespective of the treatment modality.

In patients with lung cancer, CPFE based on CT findings was more prevalent than pulmonary fibrosis without emphysema (8.9% vs 1.3% of patients with lung cancer). Previous studies showed that the incidence of lung cancer was higher in patients with IPF than in the general population.[5] Kawasaki *et al.* reported that IPF was diagnosed in 7.5% of patients with surgically resected lung cancers.[6] The present study showed that the prevalence of pulmonary fibrosis without emphysema that could be categorized as IPF was only 1.3% (15 of 1143) among the patients with lung cancer.

Combined pulmonary fibrosis and emphysema may be a risk factor for lung cancer. Kitaguchi *et al.* retrospectively reviewed the records of 47 patients with CPFE and found that 22 of those patients (46.8%) had lung cancer.[7] Katzenstein *et al.* reported the presence of interstitial fibrosis in smokers with no clinical evidence of ILD, and these patients met the criteria for CPFE.[8] Although the present retrospective study was performed at a single institution and has some limitations, the results suggest that patients with CPFE have a higher prevalence of lung cancer, and that CPFE in patients with lung cancer may be underrecognized or misdiagnosed as IPF.

All the patients with CPFE were heavy smokers. The high prevalence of CPFE in patients with lung cancer in this study reflects not only this high smoking exposure, but is also likely to reflect an association in genetic susceptibility to chronic smoking-induced inflammation, as shown in other studies on the relationship between COPD or IPF and lung cancer.[2–5] Genome-wide association studies have identified

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variants in the nicotinic acetylcholine receptor (nAchR) gene on chromosome 15q24/25 as risk factors for nicotine dependence, lung cancer and COPD.[9–11] Lambrechts *et al.* showed that the 15q24/25 nAchR locus was associated with the presence and severity of emphysema as assessed by chest CT.[12] A genome-wide association study identified an association between a common variant of the telomerase-related TERT gene and susceptibility to IPF.[13] Heterozygous mutations in the hTERT or hTR genes have been detected in families with IPF.[14] Shortened telomeres are another risk factor for IPF, including familial, as well as sporadic forms of the disease.[15] Shortened telomeres are also associated with COPD and lung cancer.[16,17] It is not known which genetic variants increase the risk of occurrence of CPFE, or its association with lung cancer. However, Cottin *et al.* speculated that common genetic factor(s), in combination with smoking exposure, play a central role in the pathogenesis of CPFE.[1] Pathological changes consistent with CPFE have been shown in transgenic mice overexpressing the cytokine, TNF-α.[18] Further investigations are necessary to elucidate whether CPFE is an independent risk factor for lung cancer, its role in susceptibility to lung cancer, and whether CPFE might result from overlapping or associated genetic variants implicated in smoking-related inflammation.

Patients with CPFE had a poor prognosis and a high incidence of acute lung injury. Postoperative lung injury occurred in nine of 33 patients with CPFE (27.3%), and two of these nine patients died. Although it was expected that the extent of resection might be related to the incidence of postoperative lung injury, the rate of CPFE exacerbation was not related to the extent of resection or the surgical method. Kawasaki *et al.* reported that patients with ILD had a pulmonary morbidity of 26% and mortality of 8%.[6] Chiyo *et al.* showed that the incidence of postoperative pneumonia and acute exacerbation of ILD was higher in patients with ILD than in those without ILD.[19] The present results suggest that CPFE is a risk factor for severe ILD in patients with lung cancer who are treated by surgery. A strategy for preventing exacerbations of CPFE should therefore be established, in order to improve the survival of lung cancer patients with CPFE.

A standard chemotherapy regimen for patients with lung cancer and CPFE has not been established. Most clinical trials in patients with lung cancer have excluded those with lung fibrosis because of the high incidence of pulmonary toxicity and poor prognosis. Kudoh *et al.* reported that ILD that was induced and/or exacerbated by chemotherapy was relatively common among Japanese patients with NSCLC, and that ILD-related death occurred in about 30% of these patients.[20] They showed that the risk factors for ILD were older age, poor World Health Organization performance status, reduced normal lung area on CT, pre-existing chronic ILD and concurrent cardiac disease.[20] The present findings suggest that CPFE should be included as one of the risk factors for fatal ILD.

The present study had several limitations, including the fact that it was observational and uncontrolled in design, and was performed at a single institution, with retrospective collection of data. The results may have been subject to selection and treatment bias. The indications for therapy and the selection of treatment were not uniform for all patients, thereby limiting evaluation of the effects of treatment. The data presented here should not be interpreted as providing an appropriate evaluation of the efficacy of treatment, which will require randomized prospective studies. Multivariate analysis could not be performed due to the small sample size, and it was not possible to evaluate the potential confounding effects of various other variables related to survival time. However, the existence of emphysema and fibrosis on chest CT were prospectively identified at the diagnosis of lung cancer. Data on the demographic characteristics and survival of patients were unlikely to be affected by the study design.

In summary, there was a high prevalence of CPFE in patients with lung cancer. Patients with CPFE and lung cancer had a history of heavy smoking and a poor prognosis. Acute lung injury was more frequent in patients with CPFE than in those with fibrosis or emphysema alone, irrespective of treatment modalities. A prospective study is necessary to elucidate the association between lung cancer and CPFE, and whether CPFE is an independent prognostic factor for severe acute lung injury.

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Clinical Study

The Frequency of Epidermal Growth Factor Receptor Mutation of Nonsmall Cell Lung Cancer according to the Underlying Pulmonary Diseases

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Background. Although epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are effective in patients with nonsmall cell lung cancer with epidermal growth factor receptor (EGFR) mutation, EGFR-TKIs have a risk of inducing fatal interstitial lung disease (ILD). The selection of chemotherapy based on the EGFR mutation status is recommended, however, the frequency of EGFR mutation in patients with ILD and the efficacy and safety of EGFR-TKI in patients with ILD and EGFR mutation are unknown. *Methods.* We retrospectively reviewed the association of the EGFR mutation status of nonsmall cell lung cancer and pulmonary diseases. Based on high-resolution computed tomography (HRCT) performed at diagnosis of lung cancer, patients were categorized into three groups: normal, emphysema, and fibrosis. *Results.* Of 198 patients with nonsmall cell lung cancer, we identified 52 (26.3%) patients with an EGFR mutation. EGFR mutations were identified in 43 (35.2%) of 122 patients with normal lungs, 8 (13.6%) of 59 with emphysema, and 1 (5.9%) of 17 with pulmonary fibrosis. Of the 52 patients with EGFR mutation, 43 patients received gefitinib. One patient with an EGFR mutation and fibrosis developed fatal ILD. There was not a significant difference in median overall survival from gefitinib treatment between never-smokers and smokers (797 days versus not reached; $P = 0.96$). *Conclusions.* Patients with sensitive EGFR mutation and normal lungs may benefit from an EGFR-TKI treatment even if they have smoking history.

1. Introduction

Gefitinib is a reversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) used for the treatment of nonsmall cell lung cancer patients [1]. Although demographic and clinical factors such as East-Asian race, female gender, nonsmoking status, and adenocarcinoma were shown to be predictive of the efficacy of gefitinib, two pivotal studies showed that the presence of somatic mutations in the kinase domain of epidermal growth factor receptor (EGFR) strongly correlates with increased responsiveness to EGFR-TKIs in patients with nonsmall cell lung cancer [2, 3]. It was later found that the subgroups of patients with nonsmall cell lung cancer who had sensitivity to gefitinib had a high incidence of EGFR mutations [4, 5]. Selecting patients on the basis of EGFR mutations, rather than clinical factors, would likely result in a population with a greater sensitivity to gefitinib. First-line gefitinib for patients with advanced nonsmall cell lung cancer who are selected on the basis of EGFR mutations improves progression-free survival, with acceptable toxicity, compared with standard chemotherapy, although it failed to prolong overall survival [6, 7].

However, EGFR-TKI increases the risk of developing life-threatening interstitial lung diseases (ILDs). The estimated incidence of ILD is low in many countries (e.g., 0.3% in the United States) [8] but is relatively high (4 to 6%) in Japan [9, 10]. An older age, poor World Health Organization performance status, reduced normal lung area on computed