

# Lung cancer in connective tissue disease-associated interstitial lung disease: clinical features and impact on outcomes

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**Backgrounds:** Lung cancer (LC) adversely impacts survival in patients with idiopathic pulmonary fibrosis. However, little is known about LC in patients with connective tissue disease-associated interstitial lung disease (CTD-ILD). The aim of this study was to evaluate the prevalence of and risk factors for LC in CTD-ILD, and the clinical characteristics and survival of CTD-ILD patients with LC.

**Methods:** We conducted a single-center, retrospective review of patients with CTD-ILD from 2003 to 2016. Patients with pathologically diagnosed LC were identified. The prevalence, risk factors, and clinical features of LC and the impact of LC on CTD-ILD patient outcomes were observed.

**Results:** Of 266 patients with CTD-ILD, 24 (9.0%) had LC. CTD-ILD with LC was more likely in patients who were older, male, and smokers; had rheumatoid arthritis, a usual interstitial pneumonia pattern, emphysema on chest computed tomography scan, and lower diffusing capacity of the lung carbon monoxide (DLco)% predicted; and were not receiving immunosuppressive therapy. Multivariate analysis indicated that the presence of emphysema [odds ratio (OR), 8.473; 95% confidence interval (CI), 2.241–32.033] and nonuse of immunosuppressive therapy (OR, 8.111; 95% CI, 2.457–26.775) were independent risk factors for LC. CTD-ILD patients with LC had significantly worse survival than patients without LC (10-year survival rate: 28.5% vs. 81.8%,  $P < 0.001$ ).

**Conclusions:** LC is associated with the presence of emphysema and nonuse of immunosuppressive therapy, and contributes to increased mortality in patients with CTD-ILD.

**Keywords:** Interstitial lung disease (ILD); connective tissue disease (CTD); lung cancer (LC); emphysema

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## Introduction

Interstitial lung disease (ILD), particularly idiopathic pulmonary fibrosis (IPF), is associated with an increased risk of developing lung cancer (LC). The incidence of LC among patients with IPF is estimated to range from 4.4% to 48% (1-4). Risk factors for the development of LC in IPF patients include older age, male sex, smoking, and combined pulmonary fibrosis and emphysema (CPFE) (5). The most frequent histological type of LC is squamous cell carcinoma, and LC is often located in peripheral fibrotic areas (6,7). LC is correlated with shorter survival in patients with IPF (6,7).

Connective tissue disease (CTD) represents a group of immunologically-mediated inflammatory disorders that affect a variety of organs. CTD includes rheumatoid arthritis (RA), systemic sclerosis (SSc), polymyositis and dermatomyositis (PM/DM), Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), and mixed CTD. Patients with CTD are highly susceptible to respiratory disorders, particularly, ILD. Like IPF, CTD-associated ILD (CTD-ILD) might be associated with an increased risk of LC. The occurrence of LC is estimated to range from 6.4% to 8.8% in CTD-ILD patients, and risk factors for LC in these patients include heavy smoking and the presence of emphysema (8,9). However, these data are based on a small number of cases, so the relationship between CTD-ILD and LC has not been fully investigated.

Herein, we performed a relatively large-scale, retrospective study to evaluate the prevalence, risk factors and clinical characteristics of LC in CTD-ILD patients and its impact on patient outcome.

## Methods

### *Patients*

This study was approved by our Institutional Review Board (IRB protocol #2105). We reviewed patients with CTD-ILD presenting to the Department of Respiratory Medicine, Kanazawa University Hospital from January 2003 to December 2016. CTD includes RA, SSc, PM/DM, SS, and SLE. Because these diseases overlap with each other in some cases, we expressed them as "components" of CTD. All cases were diagnosed by a rheumatologist, dermatologist or nephrologist using the appropriate classification criteria (10-14). All cases presented with ILD on chest high-resolution computed tomography (HRCT) scan.

Patient baseline data at presentation, including smoking history, occupational exposure, types of CTD, chest HRCT findings, and pulmonary function test results were evaluated. The pattern of ILD on chest HRCT scan was evaluated by two pulmonologists (S Watanabe and K Saeki) in a blindly fashion according to the official ATS/ERS statement (15). The presence of emphysema was observed as well-demarcated areas of decreased attenuation and marked by a thin or no wall, and/or multiple bullae with upper zone predominance. During follow-up, data regarding treatment of CTD and incidence of pathologically proven LC were also collected. In cases with LC, histopathological findings, staging, location of primary lesions, and LC treatment regimens were examined. LC was classified according to the World Health Organization tumor classification, and staging of LC was performed using the 7th edition of the TNM classification of malignant tumors (16).

### *Statistical analysis*

All statistical analyses were performed using SPSS software version 20 (IBM). Categorical variables were represented as counts and percentages, and were compared using the chi-squared test. Continuous variables were reported as median values  $\pm$  standard deviation and interquartile range, and compared using the Mann-Whitney U test. Univariate logistic regression analysis was used to compare CTD-ILD in patients with and without LC. Variables that showed a significant difference were subjected to a multivariate logistic regression. Kaplan-Meier analysis was used to evaluate survival. P values  $<0.05$  were considered statistically significant.

## Results

### *Patient characteristics*

The medical records of 268 patients with CTD-ILD in our hospital from 2003 to 2016 were retrospectively reviewed. Two patients were excluded from the study because they had a lung nodule or mass on chest CT scan without a pathological diagnosis. The remaining 266 patients were included in the present analysis. The median age was 60 years, and the median observation period was 64.0 months. Underlying CTDs included SSc (n=87, 32.7%), PM/DM (n=55, 20.7%), RA (n=53, 19.9%), SS (n=12, 4.5%), and others or overlapping CTDs (n=51, 19.2%).

### Risk factors for LC

Of 266 patients with CTD-ILD, 24 (9.0%) were identified as having LC. Median follow-up was 43.5 months for patients with LC and 66.0 months for patients without LC. Compared to patients without LC, patients with LC were more likely to be male, older, heavy smokers, higher number of cigarettes, have RA, have a usual interstitial pneumonia (UIP) pattern and presence of emphysema on HRCT scan, have a lower predicted diffusing capacity of the lung carbon monoxide (DLco)%, and not be receiving immunosuppressive therapy (Table 1). Immunosuppressive agents included prednisolone, methylprednisolone, cyclophosphamide, cyclosporine, tacrolimus, methotrexate, and biological drugs. Multivariate analysis indicated that the presence of emphysema [odds ratio (OR), 8.473; 95% confidence interval (CI), 2.241–32.033] and nonuse of immunosuppressive therapy (OR, 8.111; 95% CI, 2.457–26.775) were independent risk factors for LC (Table 2).

### Clinical features of LC

The clinical features of the 24 CTD-ILD patients with LC are shown in Table 3; details are provided in Table 4. In 20 patients, LC was diagnosed after the diagnosis of CTD-ILD (median duration, 9 months). The other 4 patients were diagnosed with LC at the time of CTD-ILD diagnosis, and 2 received LC diagnosis before CTD-ILD diagnosis. The primary site of LC was most frequently the peripheral lung area (91.7%). Tumors were located adjacent to fibrotic lesions in 14 (58.3%) cases, and emphysema or bullae were observed in 7 (29.2%) cases (Figure 1). The most common histological type was adenocarcinoma (n=10) followed by squamous cell carcinoma (n=9) and small cell LC (n=3). LC stages were as follows: stage I, 41.7%; stage II, 4.2%; stage III, 25.0%; and stage IV, 25.0%. Treatment of LC was based on staging and guidelines: 12 patients underwent surgery, 2 received chemoradiotherapy, and 10 received chemotherapy. Local recurrence after surgical resection developed in 2 (16.7%) of the 12 patients. Two patients with early-stage LC received best supportive care only because they had severe respiratory symptoms and a low performance status.

### Outcome

Of 266 patients, 41 (15.4%) patients died during the follow-up period. The most frequent cause of death was LC (n=13),

followed by acute exacerbation (n=9), respiratory failure (n=4), infection (n=4), lymphoma (n=3), heart failure (n=3), and other (n=5). Among 24 patients with LC, 16 (66.7%) patients died and the median survival was 68.0 months. Of these 16 patients, 13 patients died from LC (81.3%), 2 from acute exacerbation (12.5%), and 1 from lymphoma (6.3%). One of the acute exacerbation cases occurred after chemotherapy. The survival rate was significantly lower among patients with LC than among those without LC (10-year survival rate: 28.5% vs. 81.8%; log-rank test,  $P<0.001$ ) (Figure 2A). Based on the pathological stage, survival of patients with stage I/II LC or III/IV LC was significantly lower than that of patients without LC ( $P=0.001$  and  $P<0.001$ , respectively). A significant difference was observed between the survival of patients with stage I/II LC and that of patients with stage III/IV LC ( $P=0.013$ ) (Figure 2B).

### Discussion

In the present study, we observed that LC was an important prognostic factor in patients with CTD-ILD. The clinical course of CTD-ILD is highly heterogeneous; some patients are stable for long periods, while others experience an accelerated clinical and functional decline (17). Life-threatening complications of ILD include acute exacerbation, respiratory failure, and secondary pulmonary arterial hypertension (18). However, the disease course and cause of death of CTD-ILD patients have not been fully examined. In our study, LC occurred in 9% of all study patients and was the most frequent cause of death among patients with CTD-ILD.

We identified two risk factors for LC in CTD-ILD patients. The first was the presence of emphysema, specifically, CPFE. Cottin *et al.* first characterized CPFE as a syndrome defined by the co-existence of emphysema in the upper lobes and fibrosis in the lower lobes on chest HRCT. All patients with CPFE were current or ex-smokers (19). Sugino *et al.* reported that the prevalence of LC among patients with CPFE is higher than that in patients with IPF alone (20). CPFE is also observed in patients with CTD-ILD and may be associated with an increased risk of LC (9). In the present study, most of the patients with LC with CPFE were current or ex-smokers: of 14 patients, 8 were current-smokers, 5 were ex-smokers, and 1 was a never-smoker. Although smoking is a major cause, CTD itself may also play a role in the development of emphysema (9,21). Another risk factor for LC was nonuse

**Table 1** Characteristics of patients with connective tissue disease-associated interstitial lung disease (CTD-ILD) with or without lung cancer (LC)

Characteristics	CTD-ILD with LC (N=24)	CTD-ILD without LC (N=242)	P value
Male/female (% male)	15/9 (62.5)	73/169 (30.2)	0.002
Age, years	66±10 (61–73)	59±13 (51–67)	0.003
Observation periods, months	43.5±45.4 (12.0–91.5)	66.0±43.6 (30.0–102.5)	0.176
Smoking history			<0.001
Current-smokers	14 (58.3)	44 (18.2)	
Ex-smokers	2 (8.3)	35 (14.5)	
Never-smokers	8 (33.3)	163 (67.4)	
Cigarettes per day			<0.001
Non	8 (33.3)	163 (67.4)	
<20	0 (0.0)	29 (12.0)	
21–30	7 (29.2)	32 (13.2)	
≥30	9 (37.5)	18 (7.4)	
Occupational exposure	4 (16.7)	29 (12.0)	0.527
CTD			
RA component	13 (54.2)	64 (26.4)	0.008
SSc component	7 (29.2)	110 (45.5)	0.137
PM/DM component	2 (8.3)	62 (25.6)	0.078
SS component	3 (12.5)	37 (15.3)	1.000
SLE component	1 (4.2)	16 (6.6)	1.000
Chest HRCT findings			0.001
UIP	10 (41.7)	29 (12.0)	
Not UIP	14 (58.3)	213 (88.0)	
Emphysema	14 (58.3)	19 (7.9)	<0.001
Pulmonary function test			
FVC, % predicted	89.7±33.1 (73.8–95.9)	89.3±29.6 (73.2–103.3)	0.844
FEV <sub>1</sub> , % predicted	91.6±42.1 (63.9–106.7)	90.0±66.9 (75.9–103.1)	0.929
DLco, % predicted	35.2±25.3 (6.3–54.4)	51.8±24.6 (39.0–66.1)	0.009
Treatment of CTD			
Steroids	4 (16.7)	67 (27.7)	0.335
Immunosuppressants	3 (12.5)	6 (2.5)	0.038
Both steroids and immunosuppressants	6 (25.0)	137 (56.6)	0.004
Without steroids or immunosuppressants	11 (45.8)	32 (13.2)	<0.001

Data are presented as n (%) or median ± standard deviation (interquartile range). CTD, connective tissue disease; ILD, interstitial lung disease; RA, rheumatoid arthritis; SSc, systemic sclerosis; PM/DM, polymyositis and dermatomyositis; SS, Sjögren's syndrome; SLE, systemic lupus erythematosus; HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in one second; DLco, diffusing capacity of lung carbon monoxide.

**Table 2** Multivariate analysis: risk factor for lung cancer (LC) in connective tissue disease-associated interstitial lung disease (CTD-ILD)

Variables	Odds ratio	95% CI	P value
Age	1.027	0.970–1.087	0.367
Male gender	1.003	0.232–4.336	0.997
RA component	1.904	0.574–6.316	0.293
Smoking history	1.230	0.545–2.774	0.618
UIP pattern	0.446	0.143–1.392	0.164
Emphysema	8.473	2.241–32.033	0.002
DLco% predicted	0.979	0.959–1.000	0.050
Without steroids or immunosuppressants	8.111	2.457–26.775	0.001

RA, rheumatoid arthritis; UIP, usual interstitial pneumonia; DLco, diffusing capacity of lung carbon monoxide.

**Table 3** Characteristics of lung cancer (LC) in connective tissue disease-associated interstitial lung disease (CTD-ILD)

Characteristics	N	%
Time of LC diagnosis		
After CTD diagnosis	18	75.0
At the time of CTD diagnosis	4	16.7
Before CTD diagnosis	2	8.3
Localization of LC		
Center of the lung	3	12.5
Periphery of the lung	22	91.7
Emphysema	7	29.2
Interstitial lesions	14	58.3
Normal area	5	20.8
Histology		
ADC	10	41.7
SCC	9	37.5
NSCLC-NOS	1	4.2
SCLC	3	12.5
Multiple cancers	1	4.2
Staging		
I	10	41.7
II	1	4.2
III	6	25.0
IV	6	25.0
I, IV	1	4.2
Treatment		
Surgery	12	50.0
Chemoradiotherapy	2	8.3
Chemotherapy	10	41.7
Palliative care	2	8.3

LC, lung cancer; CTD, connective tissue disease; ADC, adenocarcinoma; SCC, squamous cell carcinoma; NSCLC-NOS, non-small cell lung cancer, not otherwise specified; SCLC, small cell lung cancer

**Table 4** Characteristics of lung cancer (LC) among patients with connective tissue disease-associated interstitial lung disease (CTD-ILD)

Age (years), gender	CTD	Histology	Staging	Treatment
78, M	RA	ADC	I	Surgery
67, F	RA	ADC	I	Surgery
71, M	RA	SCC	I	Surgery
81, M	RA	SCC	I	Surgery
85, F	RA	SCC	I	Surgery, TS-1
69, F	SSc	ADC	I	Surgery
59, M	SSc	SCC	I	Surgery
65, M	SSc	SCC	I	Surgery
61, F	SS	SCC	I	Surgery
65, M	PM/DM	SCC	I	Palliative care
41, F	SSc	ADC	II	Palliative care
74, M	RA	SCC	III	Surgery, CDDP + radiation→DTX
66, M	RA	ADC	III	CBDCA + DTX
76, M	RA	SCLC	III	CBDCA + ETP→NGT
59, F	RA	SCLC	III	CBDCA + ETP
71, F	SSc, SS	ADC	III	Surgery, CDDP + VNR→PEM→GEM
70, F	SS	SCLC	III	CBDCA + ETP→CPT-11→AMR
71, M	RA	ADC	IV	CBDCA + VNR
69, M	RA	SCC	IV	CBDCA + PTX
61, M	RA	ADC	IV	CBDCA + PEM
64, F	RA, SSc	ADC	IV	VNR→TS-1
71, M	SSc	ADC	IV	CBDCA + VNR
76, M	PM/DM	ADC, SCLC	I, IV	Surgery, CBDCA + ETP→CPT-11→AMR
53, M	SLE	NSCLC-NOS	IV	CBDCA + PTX + radiation

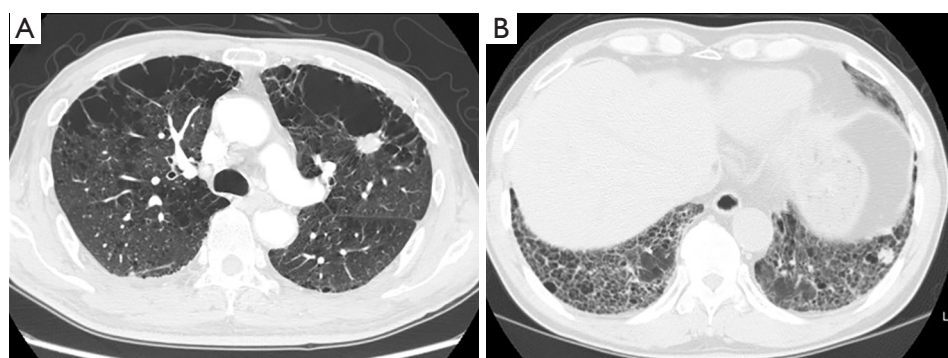
LC, lung cancer; CTD, connective tissue disease; ILD, interstitial lung disease; M, male; F, female; RA, rheumatoid arthritis; SSc, systemic sclerosis; PM/DM, polymyositis and dermatomyositis; SS, Sjögren's syndrome; SLE, systemic lupus erythematosus; ADC, adenocarcinoma; SCC, squamous cell carcinoma; NSCLC-NOS, non-small cell lung cancer, not otherwise specified; SCLC, small cell lung cancer; CDDP, cisplatin; DTX, docetaxel; CBDCA, carboplatin; ETP, etoposide; NGT, nogitecan; VNR, vinorelbine; PEM, pemetrexed; GEM, gemcitabine; CPT-11, camptothecin-11; AMR, amrubicin; PTX, paclitaxel.

of steroids and immunosuppressants. Although there are no proven effective therapies for CTD-ILD, corticosteroids and/or immunosuppressive agents are commonly used as first-line therapy (22). The effects of immunosuppressive therapy on cancer risk remain controversial: some studies have suggested that immunosuppressants such as cyclophosphamide increase the risk of malignancy (23,24); however, other studies have not found this to be true (25,26).

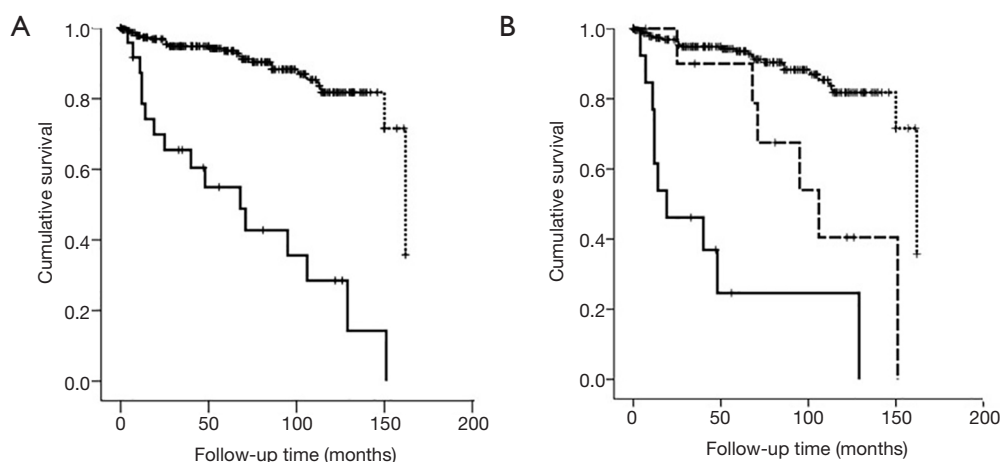
The present study is the first report to show that nonuse of immunosuppressant therapy may be associated with an increased risk of LC.

Although the pathogenic mechanisms underlying LC development in CTD-ILD remain unknown, chronic inflammation and a fibrotic environment are thought to contribute to tumorigenesis (27,28). The results of several studies have indicated that chronic inflammation can





**Figure 1** Representative chest computed tomography findings in connective tissue disease-associated interstitial lung disease (CTD-ILD) with lung cancer (LC). Lung tumor is located adjacent to emphysema (A) and fibrotic lesions (B).



**Figure 2** Kaplan-Meier survival curves. (A) Survival of patients with connective tissue disease-associated interstitial lung disease (CTD-ILD) without lung cancer (LC) (n=242, dotted line) and CTD-ILD with LC (n=24, solid line); (B) survival of CTD-ILD patients with non-LC (n=242, dotted line), stage I/II LC (n=11, dashed line), and stage III/IV LC (n=13, solid line).

initiate tumor development by causing DNA damage or making cell susceptible to mutagens (29). Furthermore, inflammatory mediators, such as tumor necrosis factor, interleukin-1, interleukin-6, growth factors, chemokines, and proteases, can promote the development of cancer via proliferative, anti-apoptotic, and pro-angiogenic effects on the epithelium (30). Although just speculation, it is possible that a lack of immunosuppressive therapy might prolong inflammation, leading to repeated epithelial injury and promotion of the destruction, repair, and remodeling of lung tissue, resulting in the development of LC (31). The present results cannot demonstrate whether immunosuppressant therapy leads to improvement or

stabilization of ILD resulting in the prevention of LC. Further prospective, long-term, observational studies are required to confirm this.

This study had some limitations. First, it was a retrospective single-institution study. Second, although the sample size was relatively large, the numbers of patients with RA and SS were smaller than those with SSc and PM/DM. This may have affected the prevalence of LC in CTD-ILD. Finally, patients presented to our hospital based on a diagnosis of LC. Thus, our study may have been affected by referral or selection bias.

In summary, LC occurs in 9% of patients with CTD-ILD. CPFE and nonuse of immunosuppressive therapy

may be risk factors for LC. Uncontrolled inflammation as well as destruction of lung parenchyma, including fibrosis and emphysema, might contribute to an increased risk of LC. LC significantly impacts survival in patients with CTD-ILD.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* This study was approved by the Institutional Review Board of Kanazawa University Graduate School of Medicine Ethical Committee (ID: 2105) and we waived the requirement for patient consent because of the retrospective nature of this study.

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