

# Clinicopathological characteristics of lung cancer in patients with systemic sclerosis

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## Abstract

**Background and objectives:** Systemic sclerosis (SSc) is a connective tissue disorder (CTD) associated with an increased risk of malignancy including lung cancer (LC). Our objective was to provide a description of demographics and clinicopathological characteristics of LC patients with SSc.

**Methods:** Lung cancer patients with SSc admitted to Peking Union Medical College Hospital from January 2000 to August 2017 were reviewed. Demographic and clinicopathologic data were collected.

**Results:** Of the 12 cases included in our study, all were female. No patients had a history of smoking. The most common histological type was adenocarcinoma, followed by squamous cell carcinoma and small-cell carcinoma. No driver mutation was identified in the five patients undergoing genetic testing. Eight patients had interstitial lung disease (ILD). Six were manifested as nonspecific interstitial pneumonia (NSIP) and two as usual interstitial pneumonia (UIP). Four (33.3%) patients underwent surgical resection. Among them, two had ILD with a normal preoperative pulmonary function tests (PFT). Eight (66.7%) patients received chemotherapy. Radiotherapy was administered in only one (8.3%) patient. No grade 3/4 adverse events were documented.

**Conclusion:** The predominance of female patients in our study is different from that reported in general lung cancer patients. A high proportion of patients has SSc-ILD, including NSIP and UIP. Surgery or radiotherapy could still be considered in carefully selected patients with ILD.

## KEYWORDS

interstitial lung disease, lung cancer, pulmonary function test, systemic sclerosis, treatment

**Abbreviations:** ATS/ERS, American Thoracic Society/European Respiratory Society; CTD, connective tissue disorder; DNA, deoxyribonucleic acid; ECOG, Eastern cooperative oncology group; EGFR, epidermal growth factor receptor; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; LC, lung cancer; NSIP, nonspecific interstitial pneumonia; PCR, polymerase chain reaction; PFT, pulmonary function tests; PS, performance score; SSc, systemic sclerosis; UIP, usual interstitial pneumonia.

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## 1 | INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disorder characterized by widespread vascular dysfunction and progressive fibrosis of the skin and internal organs. Several population-based SSc cohort studies have reported an increased incidence of malignancy.<sup>1-4</sup> However, a paucity of literature has described the detailed clinicopathological characteristics of lung cancer in patients with SSc and its treatment outcome. In this study, we report the histological type and molecular profile of SSc-associated lung cancer and its stage of lung cancer at presentation and treatment outcome. Additionally, we also provide a description of the chest imaging and information about treatment modality in SSc-associated lung cancer.

## 2 | MATERIALS AND METHODS

Eight hundreds and thirty eight patients with SSc were admitted to Peking Union Medical College Hospital, Chinese Academy of Medical Sciences from January 2000 to August 2017. Among them, 14 SSc patients with LC were identified. After excluding two patients whose medical records could not be retrieved, 12 LC patients were included in this study. The diagnosis of SSc was established according to the American College of Rheumatology criteria for classification of SSc.<sup>5</sup> Lung cancers were confirmed by a pulmonary pathologist. Those patients meeting both the criteria for SSc and lung cancer were included. Data abstracted from the medical record included demographics, gender, age at the time of diagnosis of SSc and LC, smoking history, performance status, disease stage, tumor histology and genetic mutation status, tumor location, high-resolution computed tomography (HRCT) findings, pulmonary function tests (PFT) and serologic markers for SSc.

The mutational analysis was performed on the deoxyribonucleic acid (DNA) samples extracted from surgically resected or biopsied specimens of lung adenocarcinomas. Epidermal growth factor receptor (EGFR) mutation status was tested by qualitative real-time polymerase chain reaction (PCR) using EGFR RGQ PCR Kit. ALK fusion was tested by immunohistochemistry using VENTANA ALK (D5F3) CDx Assay. The clinical stage was determined on the basis of the international tumor, node, metastasis (TNM) criteria for cancer staging. Performance status was assessed according to the Eastern Cooperative Oncology Group (ECOG) performance score (PS). Chest CT scans were reviewed by a pulmonary radiologist and classified based on American Thoracic Society/European Respiratory Society (ATS/ERS) criteria.<sup>6</sup>

### 2.1 | Statistical analysis

This study is a descriptive study. Continuous variables were summarized as mean values (SD) if normally distributed or

as median (range) if skewed. Categorical variables were summarized as frequency and percentage.

## 3 | RESULTS

### 3.1 | Demographics

Twelve lung cancers were found among 838 (1.4%) patients with SSc. Of the 12 cases included in our study, all were female. The median age at lung cancer diagnosis was 49.5 years (41-73 years). SSc onset preceded lung cancer in all patients by a median of 13 years (2-22 years). No patients had a history of smoking. However, the history of exposure to firewood fumes was identified in a patient.

### 3.2 | Systemic sclerosis and lung involvement

Results of serologic testing were available for seven of 12 cases: 5/7 antinuclear antibody positive, 3/5 scl-70 antibody positive and 2/5 anticentromere antibody (ACA) positive. Involved organs include lung in eight patients, manifested as interstitial lung disease (ILD) in eight patients and pulmonary artery hypertension (PAH) in one patient; and esophagus in four patients, manifested as esophageal dysmotility. Raynaud syndrome was observed in nine patients, CREST syndrome was observed in two patients. All patients received glucocorticoids. Six patients received methotrexate, four received cyclophosphamide and two received mycophenolate mofetil.

As shown in Table 1, the most common chest imaging findings were nodular opacity ( $n = 12$ ), followed by enlarged lymph node ( $n = 9$ ), reticular opacity ( $n = 9$ ), pleural thickening ( $n = 6$ ), consolidation ( $n = 4$ ), peribronchial thickening ( $n = 4$ ), bronchiectasis ( $n = 3$ ), emphysema ( $n = 3$ ), honeycombing ( $n = 2$ ) and pleural effusions ( $n = 2$ ). Specific CT patterns of ILD were identified in eight patients, including usual interstitial pneumonia (UIP) pattern in two patients and nonspecific interstitial pneumonia (NSIP) pattern in six patients Figure 1. Ten cases had PFT available for review. Two had obstructive dysfunction. Both of them had radiographic emphysema. Four had restrictive dysfunction with decreased diffusing capacity for carbon monoxide (DLco), of whom all had ILD. One had isolated DLco impairment. The remaining patients had normal PFTs.

### 3.3 | Lung cancer

Nine cases presented with an exacerbation of chronic non-productive cough, worsening dyspnea and new-onset weight loss. Two were detected as incidental masses on imaging and

TABLE 1 Imaging findings of SSc-associated lung cancer

Pt no	Nodular opacity	Reticular opacity	Enlarged lymph node	Pleural thickening	Consolidation	Peribronchial thickening	Bronchiectasis	Emphysema	Honeycombing	Pleural effusions	ILD types
1	+	+	+	+	+	+	+	+	+	-	UIP
2	+	+	+	+	-	-	-	-	-	-	NSIP
3	+	+	+	-	-	+	+	-	-	-	NSIP
4	+	+	+	-	-	-	-	-	-	-	None
5	+	-	-	+	+	-	-	+	-	+	None
6	+	+	-	-	-	-	-	-	-	-	NSIP
7	+	-	+	-	+	-	-	-	-	-	NSIP
8	+	+	+	+	-	+	-	-	-	+	NSIP
9	+	+	+	+	-	-	-	-	-	-	None
10	+	+	-	+	-	+	+	+	+	-	UIP
11	+	-	+	-	+	-	-	-	-	-	None
12	+	+	+	-	-	+	-	-	-	-	NSIP

Abbreviations: ILD, interstitial lung disease; UIP, NSIP, nonspecific interstitial pneumonia.



FIGURE 1 Chest computed tomography imaging of a left lower lobe lung mass with NSIP

one was presented with a growing nodule. Clinicopathological characteristics are shown in Table 2. Most of the tumors (83.3%, 10/12) were peripherally located. The frequency of the primary tumor locations was 16.7% (2/12) in the right upper lobe, 25.0% (3/12) in the left upper lobe, 8.3% (1/12) in the right middle lobe and 33.3% (4/12) in the left lower lobe. Three patients were diagnosed at stage II, four at stage III and four at stage IV. One patient with small-cell lung cancer presented at the extensive stage. More than half of patients had an ECOG PS of 0-1. The most common histological type was adenocarcinoma (9/12), followed by squamous cell carcinoma (1/12, shown in Figure 2 and small-cell carcinoma (1/12), in the remaining one case, the histological type was not specified. Five of the nine adenocarcinomas underwent molecular mutational profiling, and no driver mutation was identified.

Among the eight patients with ILD, the most frequent histological type was adenocarcinoma (6/8), followed by squamous cell carcinoma (1/8) and small-cell carcinoma (1/8). As to the location of tumor, four are in the left lower lobe which occurred adjacent to fibrosis site and the remaining two are located near the hilum.

Four patients underwent surgical resection, three submitted to lobectomy and one to wedge resection. Among them, two had ILD with a normal preoperative PFT, the remaining two have normal PFT without presentation of ILD. Eight patients received chemotherapy using pemetrexed, vinorelbine, gemcitabine, taxanes, etoposide and platinum; three in the adjuvant setting, while five in the metastasis setting. Radiotherapy was administered in only one patient. No grade 3/4 adverse events were documented.

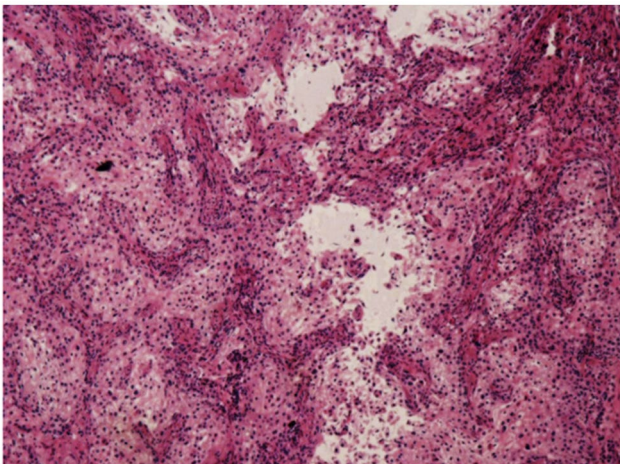
## 4 | DISCUSSION

Several studies indicated an increased risk of lung cancer in patients with SSc.<sup>1-4</sup> In our study, 12 lung cancers were found among 838 (1.4%) patients with SSc, clearly higher than

**TABLE 2** Clinicopathological characteristics of SSc-associated lung cancer

Pt no	Gender	Age	Smoking history	Tumor location	Stage	ECOG PS	Pathology	Molecular profiles	Treatment approaches
1	F	73	None	LH	IV	3	C-nos	NA	None
2	F	67	None	RML	III	2	AC	NA	NA
3	F	63	None	RUL	II	1	AC	EGFR/ALK (-)	Surgery
4	F	62	None	LLL	IV	1	AC	EGFR/ALK (-)	Chemo
5	F	62	None	LLL	III	1	SqCC	EGFR/ALK (-)	Surgery+Chemo
6	F	50	None	LUL	IV	2	AC	NA	NA
7	F	49	None	LLL	II	2	AC	NA	None
8	F	49	None	LLL	III	1	AC	NA	Radio+Chemo
9	F	46	None	RH	ED	1	SCLC	NA	Chemo
10	F	44	None	LUL	IV	1	AC	EGFR/ALK (-)	Chemo
11	F	42	None	RUL	III	1	AC	EGFR/ALK (-)	Surgery+Chemo
12	F	41	None	LUL	II	0	AC	NA	Surgery

Abbreviations: AC, adenocarcinoma; C-nos, carcinoma not otherwise specified; Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance score; ED, extensive disease; LH, left hilum; LLL, left lower lobe; LUL, left upper lobe; NA, not available; No, number; Pt, patients; Radio, radiotherapy; RH, right hilum; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SCLC, small cell lung cancer; SqCC, squamous cell carcinoma.



**FIGURE 2** Specimen stained with hematoxylin and eosin staining showing squamous cell carcinoma with lymphocytes infiltration and fibrosis

the reported prevalence in the general Chinese population.<sup>7</sup> Compared with the higher proportion of male patients in the general lung cancer population,<sup>7</sup> the female predominance in our cases likely reflects the high proportion of female patients in the SSc cohort. In contrast with the high smoking rate reported in the previous epidemiological study,<sup>8</sup> none of our cases had a smoking history. Similarly, Roumm and Medsger<sup>9</sup> reported that lung cancer occurred in the SSc patients was not associated with cigarette smoking. The high prevalence of lung cancer in SSc and the absence of tobacco exposure suggest SSc per se, independent of tobacco exposure, as a risk factor for lung cancer.

The distribution of cancer histology types in our cohort is similar to that in the general population, of which the

majority is adenocarcinoma, followed by squamous carcinoma and small-cell cancer. This is in consistent with the reported histological pattern of the SSc-associated lung cancer.<sup>10-12</sup> Noteworthy, of the nine patients with adenocarcinoma, all are female lifelong nonsmoker, and unexpectedly, did not harbor EGFR mutation or ALK-EML4 fusion gene. The reported prevalence of EGFR mutations is approximately 50% in Asian population<sup>13,14</sup> and even higher (75%) in female never-smokers.<sup>15</sup> The lack of common driver mutations further supports that the chronic autoimmune inflammation may play a role in the carcinogenesis of SSc-associated lung cancer.

Eight cases (66.7%) in our cohort have ILD. It was reported that 48% of patients with diffuse cutaneous SSc and 26% with limited cutaneous SSc had radiological ILD.<sup>16</sup> However, the prevalence of ILD was higher in SSc patients with lung cancer. In a retrospective review of 248 SSc patients in an Ontario population, pulmonary fibrosis was observed in all seven cases of lung cancer.<sup>17</sup> Similarly, another epidemiologic study found that lung cancer only occurred in the setting of long-standing pulmonary fibrosis.<sup>9</sup> The aforementioned findings suggested a role of ILD in the development of lung cancer. The proposed mechanism is that the fibrotic process may cause repeated cycles of injury and repair of the respiratory epithelium, which in turn, leads to the accumulation of genetic alterations that drives tumorigenesis forward through sequential cellular morphologic changes.<sup>18-20</sup> This proposition is bolstered by the increase in metaplastic epithelial cells observed in anatomic correlation with lung inflammation and fibrosis.<sup>21</sup> Thus, the excess risk of lung cancer with SSc could be explained, at least in part, by the high prevalence of ILD in SSc patients.

However, the association of this malignancy with interstitial fibrosis was not constant in our cohort. Notably, ILD was not present in four cases. This suggested that pulmonary fibrosis is not a precondition for cancer development. An alternative hypothesis is that shared environmental and genetic risk factors exist between SSc and lung cancer. Several lines of evidence lend support to this hypothesis. First, vitamin D deficiencies have been found both in SSc and lung cancer.<sup>22</sup> Moreover, there is an increased risk of cancer among first-degree relatives of patients with scleroderma.<sup>23</sup> Besides, there may be a predisposition to lung cancer secondary to the use of immunosuppressive agents.<sup>24</sup> All patients in our study had the history of immunosuppressants exposure, which may also contribute to the development of lung cancer.

With regard to treatment approaches for lung cancer in SSc patients, the present study demonstrated that the presence of SSc-associated ILD may pose a challenge for an effective multidisciplinary treatment. One patient with early-stage LC was unable to receive any curative treatment because of the poor respiratory function caused by ILD and another patient with locally advanced LC was treated with chemotherapy alone out of concern over potential exacerbation of ILD after radiotherapy. However, curative resection without major complications was achieved in two patients with ILD. Notably, both patients had a normal preoperative PFT. ILD has been shown to be associated with an increased risk of postoperative morbidity and mortality in lung cancer patients undergoing thoracic surgery.<sup>25,26</sup> Nonetheless, a subgroup of patients has a good long-term outcome, especially those with a lower preoperative carbon monoxide diffusion capacity and a higher preoperative composite physiological index.<sup>27</sup> Similarly, prior studies have identified the preexisting ILD as a significant risk factor for severe radiation pneumonitis.<sup>28-30</sup> Thus, the risk of fatal morbidity should be carefully weighed against the benefits of radiotherapy or surgery in lung cancer patients with SSc and the baseline pulmonary function test results should be factored into patient selection.

This study has several limitations. First, its retrospective nature and limited number of patients may introduce case selection bias and hamper the generalizability of the results. Besides, survival analysis should be performed, and an identification of risk factors would be of value. However, survival data cannot be attained in several patients in the study. Another concern is the lack of a control cohort, which will make the clinicopathological distinctions between SSc-associated lung cancer and the general lung cancer difficult to identify.

## 5 | CONCLUSION

SSc is associated with an increased risk of lung cancer. The predominance of female patients and the absence of smoking

history in our cohort suggested an independent role of SSc itself in the development of lung cancer. This is further supported by the lack of common driver mutations in the female patients without smoking history. As to the treatment for SSc-associated lung cancer, surgery or radiotherapy could still be considered in carefully selected patients even with ILD.

## AUTHOR CONTRIBUTION

*Performed study; collected data; analyzed data; wrote the paper:* Chen, Liu and Wang

*Collected data; analyzed data:* Xu and Zhou

*Analyzed data:* Shi

*Collected data:* Zhang, Liang, Zhao, Zhong

## Ethics

The current study was conducted in accordance with the guidelines of the Declaration of Helsinki and the ethical guidelines for epidemiological research and approved by the Institutional Review Board of Peking Union Medical Hospital.

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