Original Article

Restrictive ventilatory impairment is associated with poor outcome in patients with cT1aN0M0 peripheral squamous cell carcinoma of the lung

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Background: Patients with squamous cell carcinoma (SqCC) of the lung sometimes have a comorbid pulmonary disease such as pulmonary emphysema or an interstitial lung disease (ILD), both of which negatively affect patient outcome. The aim of this study was to determine the outcome of patients in a multicenter database who underwent surgery for cT1aN0M0 peripheral SqCC lung cancer.

Methods: The medical records of a total of 228 eligible patients from seven institutions were reviewed to evaluate the impact of concomitant impaired pulmonary function and other clinicopathological factors on overall survival (OS) and relapse-free survival (RFS).

Results: Six patients with positive or unclear tumor margins were excluded. Of the 222 remaining study patients, 42 (18.9%) and 97 (43.7%) patients were found to have coexisting restrictive or obstructive ventilatory impairment, respectively. Over a median follow-up period of 30.6 months, the 5-year OS and RFS were 69.0% and 62.6%, respectively. By multivariate analysis, ILDs identified on high-resolution computed tomography (HRCT), pulmonary function test results indicating a restrictive ventilatory impairment, and wedge resection were found to be independent risk factors for poor OS. An increased level of serum squamous cell carcinoma antigen (SCC-Ag) (>1.5 ng/mL) and the same risk factors for poor OS were independent risk factors for recurrence. Among patients who underwent anatomical lung resection (lobectomy and segmentectomy, n=173), a restrictive ventilatory impairment was an independent risk factor for poor OS, and increased serum SCC-Ag level, ILDs on HRCT, and restrictive ventilatory impairment were independent risk factors for poor RFS by multivariate analysis. Factors such as visceral pleural invasion, and lymphatic or vascular invasion were not significantly associated with outcome.

Conclusions: A restrictive ventilatory impairment negatively affects the outcome of patients with cT1aN0M0 peripheral SqCC lung cancer.

Keywords: Squamous cell carcinoma of the lung; interstitial lung disease (ILD); restrictive ventilatory impairment

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Introduction

The use of computed tomography (CT) has increased the detection rates of peripheral small non-small cell lung cancers (NSCLCs), the majority of which are adenocarcinomas (1). Patients with these tumors who undergo complete surgical resection are expected to have favorable outcomes (2). Several retrospective (3-5) and prospective (6,7) studies have reported that segmentectomy as an intentional limited resection for patients with early-stage peripheral NSCLC is both oncologically and physiologically beneficial. Squamous cell carcinoma (SqCC) of the lung is the second most common histological subtype of NSCLC after adenocarcinoma. Although both are categorized as NSCLC, lung adenocarcinoma and SqCC manifest different clinical behaviors and outcomes (8,9). For example, lymphatic and vascular invasion predict different outcomes in patients with pathologic stage I lung adenocarcinoma *vs*. pathologic stage I lung SqCC (9). The number of peripheral small lung SqCCs being detected has also increased (10,11); however, the reported prevalence of lung SqCC is low, ranging from 8% to 17% of cT1aN0M0 peripheral NSCLCs (12,13).

In addition to the intrinsic characteristics of lung cancers that indicate biological aggressiveness, a background of pulmonary disease negatively affects patient outcome (14,15). Pulmonary emphysema and interstitial lung diseases (ILDs) are major pulmonary comorbidities that are sometimes seen in patients with lung cancer. Cigarette smoking is a well-established cause of both chronic obstructive pulmonary disease (COPD) and lung cancer, and lung SqCC is strongly associated with smoking (16). ILDs have also been found to be associated with an increased risk of lung cancer (17,18). The prevalence of lung SqCC is increased in patients with ILDs (19,20). Therefore, patients with lung SqCC are more likely to have comorbid pulmonary diseases and impaired pulmonary function.

In this study, we retrospectively reviewed the records from a multicenter database of patients with cT1aN0M0 peripheral lung SqCC who underwent surgery with the aim of evaluating the prognostic impact of relevant clinicopathological factors, including pulmonary function parameters. Since wedge resection even for this clinical tumor stage is considered to be palliative and not curative, we also analyzed the background of patients who underwent wedge resection. Finally, we sought to clarify the outcome of patients who underwent anatomical resection.

Methods

Study population

This study was approved by the ethics board of each institution. The requirement for informed consent was waived because of the retrospective nature of the study. The medical records of a total of 228 patients with cT1aN0M0 peripheral SqCC of the lung who underwent surgery from September 2002 to November 2014 at seven institutions were reviewed retrospectively. Patients were followed at each institution by routine physical and blood examinations and chest or systemic CT scan with or without enhancement every 6 months for the first 2 years, and then plain CT annually. Peripheral tumor was defined as that located within the peripheral two-thirds of the lung parenchyma on CT (21). Tumor-node-metastasis classification stages were revised according to the Seventh Edition of the TNM classification. Patients with lung SqCCs in the tracheobronchial tree and patients with metastatic tumors to the lung were not included in the analysis. Patients who received pre-operative chemotherapy or radiotherapy were excluded. Six patients with positive or unclear tumor margins were excluded from the study, leaving a total of 222 patients for analysis.

Data collection

The following information was collected: age, gender, pulmonary function, tumor location, tumor diameter on high-resolution computed tomography (HRCT) (including size of areas of consolidation), preoperative serum levels of tumor markers [carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC-Ag), and cytokeratin-19 fragments (CYFRA 21-1)], coexisting radiological ILD on HRCT, operative procedure, pathological nodal status, presence/absence of visceral pleural invasion, lymphatic invasion, and vascular invasion. ILD was evaluated by experienced radiologists in chest CT interpretation at each institution, in accordance with the ATS/ERS/Japanese

Respiratory Society/Latin American Thoracic Association Statement (22). Restrictive and obstructive ventilatory impairment were defined as reduced vital capacity of <80% of predicted, and as a ratio of forced expiratory volume in 1 second to forced vital capacity of <70%, respectively. Overall survival (OS) was defined as the time interval from date of operation until date of death or last follow up. Relapse-free survival (RFS) was defined as the time interval from date of operation to date of proven detection of recurrence or metastases. Local relapse was defined as recurrent disease at the primary site or in the lymph nodes either in the hilum or mediastinum within the operated thoracic cavity (7).

Statistical analyses

The relationships between the operative procedures (wedge *vs.* anatomical resection) and clinical factors were analyzed using the chi-square test of independence. The two-sample Student *t*-test was used for continuous variables. The impact of clinicopathological factors on OS and RFS was evaluated by Kaplan-Meier analysis and the log-rank test with 95% confidence intervals (CIs). The Cox proportional hazard regression model was also employed to assess risk factors for survival. All tests of significance were two-sided, and P values less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (version 23; IBM SPSS, Chicago, IL, USA).

Results

Patient characteristics

Patient characteristics (N=222) are shown in *Table 1*. The mean diameters of tumors and areas of consolidation were 15.4 [5–20] and 15.3 [5–20] mm, respectively. The consolidation/tumor ratios ranged from 55.6% to 100%, and 218 (98.2%) of all the tumors appeared as pure solid nodules. Coexisting restrictive and obstructive lung disease on pulmonary function testing was seen in 42 (18.9%) and 97 (43.7%) patients, respectively. Wedge resection was more often conducted for patients who were older, with smaller tumors, and reduced vital capacity. More patients with tumors located in lower pulmonary lobes, ILDs on HRCT, and obstructive pulmonary disease underwent wedge resection, although the data were not statistically significant (*Table 2*).

Overall outcomes

The 5-year OS and RFS were 69.0% and 62.6%, respectively [median follow-up period: 30.6 (range, 1–144) months]. Univariate analysis revealed that increased serum level of SCC-Ag, that of CYFRA 21-1, ILDs on HRCT, restrictive ventilatory impairment, and wedge resection were significant risk factors for both poor OS and RFS (data not shown). Multivariate analysis revealed that ILDs on HRCT [hazard ratio (HR) (95% CI) =2.16 (1.15–4.06), P=0.017], restrictive ventilator defect [HR (95% CI) =2.97 (1.57–5.59), P=0.001], and wedge resection [HR (95% CI) =2.03 (1.06–3.89), P=0.034] were independent risk factors for poor OS. An increased level of serum SCC-Ag (>1.5 ng/mL) [HR (95% CI) =1.71 (1.00–2.91), P=0.034] and the same risk factors for poor OS [ILDs on HRCT; HR (95% CI) =2.65 (1.52–4.63), P=0.001, restrictive ventilator defect; HR (95% CI) =2.35 (1.31–4.22), P=0.004, wedge resection; HR (95% CI) =2.85 (1.61–5.05), P<0.001] were independent risk factors for recurrence.

Outcome of patients undergoing anatomical resection

We then further evaluated the patients who underwent anatomical lung resection (segmentectomy and lobectomy, n=173). The characteristics of these patients are shown in *Table 3*. The mean tumor diameter was 15.5 [5–20] mm. The 5-year OS and RFS were 77.5% and 69.8%, respectively. Univariate analysis revealed that increased serum level of SCC-Ag and restrictive ventilatory impairment (*Figure 1A*) were significant risk factors for poor OS. Increased serum level of SCC-Ag, ILDs on HRCT, and restrictive ventilatory impairment (*Figure 1B*) were significant risk factors for recurrence (*Table 4*). Multivariate analysis revealed that restrictive ventilatory impairment was an independent risk factor for OS, and increased serum level of SCC-Ag, ILDs on HRCT, and restrictive ventilatory impairment were independent risk factors for RFS (*Table 5*).

During the median follow-up period of 32.6 [1–144] months, local recurrence was detected in 5 (2.9%) of 173 patients who underwent anatomical resection, as follows: among patients undergoing segmentectomy, 1 patient developed subcarinal lymph node metastasis and 1 patient developed malignant pleural effusion; among patients undergoing lobectomy, 1 patient developed pleural dissemination and 2 patients developed lymph node metastasis in lymphatic drainage areas.

Table 1 Clinicopathological characteristics of all patients

Characteristics	No. (%)
Total cases	222
Age, y (mean ± standard deviation)	72.0±7.7
>70	136 (61.3)
Gender	
Male	189 (85.1)
Smoking status	
Current	70 (31.5)
Former	147 (66.2)
Never	5 (2.3)
Tumor location	
Right upper lobe	57 (25.7)
Right middle lobe	6 (2.7)
Right lower lobe	63 (28.4)
Left upper lobe	49 (22.1)
Left lower lobe	47 (21.2)
Serum CEA (ng/mL)*[1]	
≤5.0	153 (76.5)
>5.0	47 (23.5)
Serum SCC-Ag (ng/mL)*[2]	
≤1.5	111 (74.0)
>1.5	39 (26.0)
Serum CYFRA 21-1 (ng/mL)*[3]	
≤3.5	151 (81.2)
>3.5	35 (18.8)
ILDs on HRCT	
Yes	44 (19.8)
%VC	
<80	42 (18.9)
$FEV_{1.0}$%	
<70	97 (43.7)
Operation	
Wedge resection	49 (22.1)
Segmentectomy	47 (21.2)
Lobectomy	126 (56.8)
Pathological nodal involvement	
pNX	49 (22.1)
pN0	167 (75.2)
pN1	4 (1.8)
pN2	2 (0.9)
Pathological stage	
IA	143 (64.4)
IB	25 (11.3)
IIA	3 (1.3)
IIIA	2 (0.9)
Unclear	49 (22.1)
Visceral pleural invasion	
PL0	192 (87.3)
PL1	28 (8.5)
PL2	2 (4.2)
Lymphatic invasion	
Ly0	152 (68.5)
Ly1	70 (31.5)
Vascular invasion	
V0	156 (70.3)
V1	60 (27.0)
V2	6 (2.7)

*[1], serum CEA was measured in 200 patients; *[2], serum SCC-Ag was measured in 150 patients; *[3], serum CYFRA 21-1 was measured in 186 patients. CEA, carcinoembryonic antigen; SCC-Ag, squamous cell carcinoma antigen; CYFRA 21-1, cytokeratin-19 fragments; ILD, interstitial lung disease; HRCT, high-resolution computed tomography.

Discussion

In this study, we found that the coexisting restrictive ventilatory impairment was an independent risk factor for unfavorable outcomes in patients undergoing surgery for cT1aN0M0 peripheral SqCC of the lung. Visceral pleural invasion, lymphatic invasion, and vascular invasion, which are known to be unfavorable prognostic indicators for small NSCLCs, were not found to be significant prognostic

Table 2 Operative procedures

Variable	Procedure		P value
	Wedge (n=49)	Anatomical (n=173)	
Age (years)	76.1±6.7	71.5±7.7	<0.001
Gender			
Female	8 (24.2)	25 (75.8)	0.745
Male	41 (21.7)	148 (78.3)	
Tumor location			
Lower lobe	30 (27.3)	80 (72.7)	0.064
Other than lower lobe	19 (17.0)	93 (83.0)	
Tumor size (mm)	12.1±6.6	15.0±4.1	0.004
ILDs on HRCT			
Yes	14 (31.8)	30 (68.2)	0.082
No	35 (19.7)	143 (80.3)	
%VC	85.2±20.9	99.7±18.1	<0.001
$FEV_{1.0}$%	66.9±16.3	71.0±11.5	0.106

ILD, Interstitial lung disease; HRCT, high-resolution computed tomography; VC, vital capacity; $FEV_{1.0}$, forced expiratory volume in 1 s.

indicators in this study.

Among all the study patients, wedge resection was found to be an independent risk factor for both poor OS and RFS. Because the tumors of all the patients in this study manifested solid-dominant or pure-solid appearance on HRCT, we surmise that wedge resection was mainly performed because of the poor condition of the patients, although the reasons for the limited resections were unavailable. However, the procedure was more frequently performed for older patients and those with restrictive ventilatory impairment in this study. Veluswamy and colleagues (23) reported that neither wedge resection nor segmentectomy were equivalent to lobectomy for OS or lung–cancer–specific survival in patients older than 65 years with cT1aN0M0 SqCC of the lung, and concluded that lobectomy should be considered for patients with such tumors. Our results also showed worse outcomes for patients undergoing segmentectomy compared to those undergoing lobectomy, although the results were not statistically significant. Patients with early-stage peripheral lung SqCCs and impaired lung function would more likely receive limited resection; however, lobectomy should be the procedure of choice for patients who are thought sufficiently able to tolerate the procedure.

Lung cancer patients with comorbid ILD have been found to have worse survival than patients without ILD (19,24,25). Sato and colleagues (26) analyzed the surgical outcomes of patients with NSCLC and ILDs who were in a nation-wide database and found that the 5-year OS of patients with stage IA NSCLC and restrictive ventilatory impairment was, surprisingly, as poor as 20%. Our study found radiological evidence of ILDs in almost 20% of patients, and these patients tended to have decreased vital capacity (data not shown). Considering that radiological ILDs could include non-progressive diseases that would exert minimal effect on survival, pulmonary function tests that provide evidence of restrictive ventilatory impairment should reasonably be more predictive of outcome than radiological evidence of ILDs, although their influence upon tumor progression is unknown.

Since cigarette smoking is strongly associated with the development of lung SqCC (16) and emphysema, patients with lung SqCC often have coexisting emphysema. The negative prognostic impact of emphysema on patients with lung cancer has been shown in several studies (27); however, whether or not coexisting emphysema affects the outcome of patients with early-stage lung SqCC remains unclear. A meta-analysis found a strong association between COPD and worse OS in patients with early-stage lung cancer (27). On the other hand, Lee and colleagues (28)

Table 3 Clinicopathological characteristics of the patients who received anatomical resection

Characteristics	No. (%)
Total cases	173
Age, y (mean ± standard deviation)	71.5±7.7
>70	97 (56.1)
Gender	
Male	148 (85.5)
Smoking status	
Current	60 (34.7)
Former	109 (63.0)
Never	4 (2.3)
Tumor location	
Right upper lobe	44 (25.4)
Right middle lobe	6 (3.4)
Right lower lobe	43 (24.9)
Left upper lobe	43 (24.9)
Left lower lobe	37 (21.4)
Serum CEA (ng/mL)*1	
≤5.0	121 (77.6)
>5.0	35 (22.4)
Serum SCC-Ag (ng/mL)*2	
≤1.5	89 (77.4)
>1.5	26 (22.6)
Serum CYFRA 21-1 (ng/mL)*3	
≤3.5	119 (83.8)
>3.5	23 (16.2)
ILDs on HRCT	
Yes	30 (17.3)
%VC	
<80	22 (12.7)
$FEV_{1.0}$%	
<70	71 (41.0)
Operation	
Segmentectomy	47 (27.2)
Lobectomy	126 (72.8)
Pathological nodal involvement	
pN0	167 (96.5)
pN1	4 (2.3)
pN2	2 (1.2)
Pathological stage	
IA	143 (82.7)
IB	25 (14.5)
IIA	3 (1.7)
IIIA	2 (1.1)
Visceral pleural invasion	
PL0	148 (85.5)
PL1	23 (13.3)
PL2	2 (1.2)
Lymphatic invasion	
Ly0	110 (63.6)
Ly1	63 (36.4)
Vascular invasion	
V0	115 (66.5)
V1	52 (30.1)
V2	6 (3.4)

*1, serum CEA was measured in 156 patients; *2, serum SCC-Ag was measured in 115 patients; *3, serum CYFRA 21-1 was measured in 142 patients; CEA, carcinoembryonic antigen; SCC-Ag, squamous cell carcinoma antigen; CYFRA 21-1, cytokeratin-19 fragments; ILD, interstitial lung disease; HRCT, high-resolution computed tomography.

recently reported that COPD had no impact on the mortality of smokers with NSCLC. We surmise that among the patients we analyzed, of whom more than 97% had a history of smoking and more than 40% had obstructive pulmonary disease, the prognostic impact of COPD would be weakened.

Increased serum levels of tumor markers can be indicators of worse outcomes. In the published literature, high serum levels of CEA (29) and SCC-Ag (9,30) have been found to indicate poor outcomes in patients with early-stage lung SqCC. We also found that a high serum SCC-Ag level was an independent risk factor for

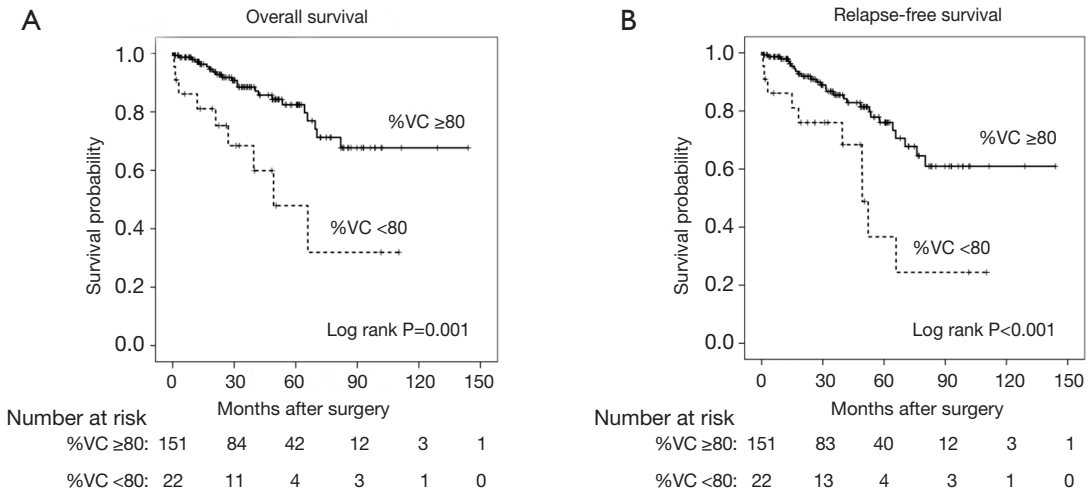

Figure 1 Kaplan-Meier estimates for overall (A) and relapse-free (B) survival by %VC in patients who received anatomical lung resection (n=173).

recurrence after anatomical resection; however, a major limitation of this study was that the serum SCC-Ag level was only measured in 150 (67.6%) of all 222 study patients, and 115 (66.5%) of 173 patients who underwent anatomical resection. The low serum SCC-Ag assessment rate might have been due to the fact that preoperative histological confirmation of lung SqCC was not always performed for these small tumors, and therefore tumor markers were not always assessed. The low assessment rate of serum SCC-Ag level might lead to biased results. Therefore, the prognostic impact of increased serum SCC-Ag in this study should be considered with caution. In addition, we note that coexisting pulmonary diseases such as idiopathic pulmonary fibrosis (31) can lead to increased serum SCC-Ag levels.

Patients with cT1aN0M0 peripheral SqCC of the lung can be candidates for segmentectomy, either intentional or passive. In order to reduce the postoperative risk for local recurrence, the preoperative risk factors for local recurrence after segmentectomy for NSCLC have been studied and identified (32-34). To date, positive tumor margins, visceral pleural involvement, lymphatic invasion, vascular invasion, and tumor grade have been identified as risk factors for local recurrence (33,35). In patients with SqCC of the lung, visceral pleural invasion (30), lymphatic invasion (36) and vascular invasion (9,30) have been found to be risk factors for poor outcomes in several studies that did not assess the effects of pulmonary function parameters in detail. In our study, visceral pleural invasion and lymphatic invasion were not found to be significantly prognostic, although they tended to show worse outcomes. In addition, the presence of vascular invasion did not appear to affect survival in our study. These conflicting study results on the prognostic effects of lymphatic and vascular invasion suggest that their prognostic effects remain unclear. The differences also indicate that accurate identification of these features may be difficult even when employing specific materials such as D2-40. The histopathological criteria for definitively identifying these factors require additional study.

Local recurrence after anatomical resection was seen in 5 (2.9%) of 173 study patients during a median-follow up period of 32.6 months. When limited to segmentectomy, local recurrence developed in 2 (4.3%) of 47 patients. Three of the 5 patients in whom pathological nodal involvement was absent, developed lymph node metastasis. Tsutani *et al.* (36) found that metastasis to locoregional or distant lymph nodes could occur in patients with pathological stage I lung SqCCs after anatomical resection combined with systematic lymphadenectomy. A multicenter phase III trial (JCOG0802/WJOG4607L) that compares segmentectomy with lobectomy for patients with cT1aN0M0 peripheral NSCLC (37), which is now ongoing in Japan, should provide new information about this issue.

We note that peripheral small lung SqCCs, even solitary tumors, can be metastatic. In this study, we excluded patients with a past history of possible SqCC, such as head and neck cancers, and those patients who died of such cancers. Nevertheless, we cannot completely discard the possibility that we included patients with subclinical SqCC of another organ that metastasized to the lung, which is

Table 4 Outcome of patients undergoing anatomical resection (n=173)

Variable	5-y OS rate (%)	P	5-y RFS rate (%)	P
All	77.5		69.8	
Age (years)				
≤70	80.9	0.235	71.9	0.538
>70	74.5		66.7	
Gender				
Female	82.3	0.493	64.8	0.737
Male	88.6		70.2	
Tumor location				
Lower lobe	78.5	0.953	74.6	0.265
Other than lower lobe	73.4		63.3	
Consolidation size (mm)				
≤10	69.5	0.912	63.8	0.445
>10	79.9		71.1	
Serum CEA (ng/mL)*[1]				
≤5.0	79.8	0.489	72.6	0.186
>5.0	60.9		57.4	
Serum SCC-Ag (ng/mL)*[1]				
≤1.5	79.2	0.039	75.3	0.002
>1.5	62.2		47.3	
Serum CYFRA 21-1 (ng/mL)*[1]				
≤3.5	75.3	0.902	68.8	0.860
>3.5	81.7		79.5	
ILDs on HRCT				
Yes	66.4	0.162	39.3	0.001
No	77.6		76.0	
%VC				
<80	47.9	0.001	29.4	<0.001
≥80	79.9		76.3	
$FEV_{1.0}$%				
<70	77.0	0.700	69.9	0.833
≥70	75.0		70.0	
Operation				
Segmentectomy	57.2	0.127	55.7	0.273
Lobectomy	81.1		74.2	

Table 4 *(continued)*

Table 4 *(continued)*

Variable	5-y OS rate (%)	P	5-y RFS rate (%)	P
Pathological nodal involvement				
Negative	75.5	0.708	70.0	0.481
Positive	83.3		66.7	
Pathological stage				
IA	77.8	0.129	73.3	0.194
Other than IA	65.0		54.9	
Visceral pleural invasion				
Negative	77.0	0.303	71.9	0.267
Positive	68.5		57.3	
Lymphatic invasion				
Negative	80.0	0.232	73.6	0.450
Positive	67.8		63.0	
Vascular invasion				
Negative	73.8	0.525	67.2	0.276
Positive	79.4		75.0	

*[1], missing values were imputed using expectation-maximization algorithm; CEA, carcinoembryonic antigen; SCC-Ag, squamous cell carcinoma antigen; CYFRA 21-1, cytokeratin-19 fragments; ILD, interstitial lung disease; HRCT, high-resolution computed tomography; VC, vital capacity; $FEV_{1.0}$, forced expiratory volume in 1 s; OS, overall survival; RFS, relapse-free survival.

Table 5 Multivariate analysis for survival (n=173)

Risk factor	OS		RFS	
	HR (95% CI)	P	HR (95% CI)	P
SCC-Ag high	–	–	2.73 (1.37–5.45)	0.004
ILDs on HRCT	–	–	1.60 (1.12–2.29)	0.009
%VC <80	3.29 (1.52–7.09)	0.002	2.97 (1.44–6.10)	0.003

HR, hazard ratio; CI, confidence interval; SCC-Ag, squamous cell carcinoma antigen; ILD, interstitial lung disease; HRCT, high-resolution computed tomography; VC, vital capacity; OS, overall survival; RFS, relapse-free survival.

another limitation of this study.

In conclusion, the coexistence of restrictive ventilatory impairment was an independent risk factor for both poor OS and RFS in patients with cT1aN0M0 peripheral SqCC of the lung. Lobectomy, if possible, should offer better outcomes for patients with such tumors. The coexistence of restrictive rather than obstructive pulmonary disease in patients with cT1aN0M0 peripheral lung SqCC should be taken into account during surgical planning.

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None.

Footnote

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

Ethical Statement: This study was approved by the ethics board of Okayama University Hospital (approval number: 1054),

in which all the data was collected. Data collection and analysis was approved by the ethics board of each institution.

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