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# Peripheral-type small cell lung cancer is associated with better survival and higher frequency of interstitial lung disease

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ABSTRACT

*Objectives:* Small cell lung cancer (SCLC) can be subgrouped into central and peripheral types according to the location of the primary lesion. However, the clinical differences between these two types remain unclear. This study compared their clinical features.

*Materials and methods:* Data on 231 patients with pathologically diagnosed SCLC were retrospectively subgrouped into central or peripheral types. Progression-free survival (PFS), overall survival (OS), treatments, responses to first-line therapy, and frequency of interstitial lung disease (ILD) were compared between the two groups.

*Results:* Of the 231 patients, 101 (44%) had central-type and 130 (56%) had peripheral-type SCLC. Peripheral-type SCLC was associated with a better performance status, higher frequency of ILD, and higher rate of limited disease stage. Patients with peripheral-type SCLC had a significantly longer OS than did those with central-type SCLC (median, 502 vs 370 days, respectively; $p = 0.0186$). Tumor location was not associated with PFS. PFS was poorer in patients with than without ILD (median, 143 vs 213 days, respectively; $p = 0.0038$), as was OS (median, 245 vs 545 days, respectively; $p = 0.0014$). Among patients without ILD, OS was longer in those with peripheral- than central-type tumors (median, 662 vs 421 days, respectively; $p = 0.0074$). Surgical resection was more often chosen for peripheral-type tumors, and this was one reason for the prolonged survival. There was no difference in the response to chemotherapy and/or radiotherapy between central- and peripheral-type SCLC. Multivariate analysis by a Cox proportional hazards model showed that male sex, a poor performance status, extensive disease, the presence of ILD, an elevated serum neuron-specific enolase concentration, and central-type SCLC were poor prognostic factors for OS.

*Conclusion:* Peripheral-type SCLC is associated with better OS and a higher frequency of ILD than is central-type SCLC. The presence of ILD is a poor prognostic factor for both PFS and OS.



## 1. Introduction

Lung cancer can be subgrouped into peripheral and central types according to the location of the primary tumor. Squamous cell cancer and small cell lung cancer (SCLC) have long been believed to be central-type lung cancers because the tumor is usually found in the central area of the lung field or adjacent to the mediastinum at the time of the first diagnosis. In a study performed in 1996, 60% of patients with SCLC had a centrally located tumor [1]. However, recent studies have shown that peripheral-type SCLC is more common [2,3]. In one study, 71 (74%) of 96 patients had a

*Abbreviations:* SCLC, small cell lung cancer; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; TTF-1, thyroid transcription factor-1; UIP, usual interstitial pneumonia; AE, acute exacerbation; PFS, progression-free survival; OS, overall survival; PS, performance status.

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peripheral-type tumor, and only 25 (26%) had a central-type tumor [2]. Another study also reported a higher prevalence of peripheral-type tumors (41 of 69 patients; 59%) [3]. Only a few studies have mentioned the differences in survival between patients with central- and peripheral-type SCLC [1–3]. In two studies (n = 52 and n = 69), no survival difference was observed between the two types [1,3]. Another study (n = 96) reported a poorer prognosis in patients with peripheral-type SCLC [2]. However, no information regarding treatment is available, although the therapeutic strategy influences the prognosis of patients with SCLC.

Interstitial lung disease (ILD) is characterized by diffuse pulmonary interstitial abnormalities that often lead to fibrosis [4]. Recent evidence has shown that preexisting ILD is associated with shorter survival in patients with SCLC [5,6] as well as in patients with advanced non-small cell lung cancer (NSCLC) [7–9]. ILD is known to be a risk factor for the development of various lung cancers, including SCLC [10,11], and peripheral-type lung cancer is often located inside tissues affected by ILD. In addition, thyroid transcription factor-1 (TTF-1) expression is higher in peripheral-type than in central-type SCLC [2]. These findings suggest that SCLC has different characteristics depending on whether its origin is central or peripheral.

Because only limited information is available regarding the clinical differences between central- and peripheral-type SCLC, we retrospectively compared the treatment efficacy, survival, and frequency of ILD in a large number of patients with SCLC.

## 2. Materials and methods

### 2.1. Patients

This study was approved by the Institutional Review Board of Kagawa University and Kagawa Prefectural Central Hospital. Patients with pathologically confirmed SCLC, including combined types, who presented to Kagawa University or Kagawa Prefectural Central Hospital from January 2007 to March 2016 were retrospectively identified, and relevant clinical and laboratory data were collected from their medical records. Patients whose primary tumor location was unknown or undetermined were excluded.

### 2.2. Definition of central- and peripheral-type SCLC

Based on previous reports [1,2,12], primary tumors involving segmental or more proximal bronchi were defined as central-type tumors. Primary tumors involving subsegmental or more distal bronchi were defined as peripheral-type tumors.

### 2.3. Classification of ILD and diagnosis of idiopathic pulmonary fibrosis and acute exacerbation

ILD was classified into three categories in accordance with the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association statement [13]: ILD with a usual interstitial pneumonia (UIP) pattern, ILD with a possible UIP pattern, and ILD inconsistent with a UIP pattern. A UIP pattern was defined as having all of the following four features: (1) subpleural and basal predominance, (2) reticular abnormality, (3) honeycombing with or without traction bronchiectasis, and (4) absence of features listed as inconsistent with a UIP pattern [13]. If honeycombing was absent but other features met the criteria for UIP, the case was classified as a possible UIP pattern [13].

Diagnoses of acute exacerbation (AE) of ILD were made in accordance with the following criteria detailed in previous studies: (1) worsening of dyspnea within 30 days, (2) new radiologic bilateral ground-glass abnormality and/or consolidation superimposed on a background of reticular shadows or honeycombing, (3) no evidence of pulmonary infection, and (4) exclusion of alternative causes, including left heart failure, pulmonary embolism, and acute lung injury of identifiable cause [7,8,14].

### 2.4. Statistical analysis

Progression-free survival (PFS) was defined as the time between the start of chemotherapy or molecular-targeted therapy and diagnosis of disease progression or death. Overall survival (OS) was defined as the time between the date of diagnosis and date of death from any cause. PFS and OS curves were constructed by the Kaplan–Meier method, and differences in survival were compared using the log-rank test. Fisher's exact test and Student's *t*-test were used to analyze patient characteristics and the significance of the association of AE with ILD. Laboratory and pulmonary function data are presented as mean ± standard deviation. All statistical analyses were conducted using Ekuseru-Toukei 2015 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

## 3. Results

### 3.1. Patient and tumor characteristics

In total, 231 patients with pathologically confirmed SCLC were included in this study. Relevant characteristics of the patients are shown in Table 1. Based on the location of the primary tumor, 101 patients (44%) had central-type SCLC and 130 patients (56%) had peripheral-type SCLC. Peripheral-type SCLC was associated with a better performance status (PS), higher frequency of ILD, and higher rate of limited disease stage. The diagnostic procedures were also different. Diagnosis via pleural effusion was more frequent for central-type SCLC, whereas computed tomography-guided and surgical approaches were more often performed for peripheral-type SCLC. Transbronchial diagnosis was the most common technique in both groups. Among tumor markers, the concentrations of cytokeratin 19 fragment and neuron-specific enolase were statistically higher in central-type SCLC.

### 3.2. Treatment with and response to chemotherapy and/or radiotherapy

Active treatment was conducted in approximately 90% of patients (Table 2). The rates of chemoradiotherapy and chemotherapy were similar between patients with central- and peripheral-type SCLC, whereas the rate of surgery was higher in patients with peripheral- than central-type SCLC (17% vs 4%, respectively; $p = 0.0027$). Of 26 patients who underwent surgery, 20 (77%) received adjuvant chemotherapy (carboplatin and etoposide in 19 of these 20 patients) with or without thoracic radiotherapy (2 and 18 patients, respectively); the remaining 6 (23%) underwent surgery only. There was no difference in the response rate to chemotherapy and/or radiotherapy as evaluated by the RECIST criteria (78% and 83% in central- and peripheral-type SCLC, respectively).

### 3.3. Better survival in patients with peripheral-type tumors

Kaplan–Meier survival curves including all patients showed a significantly longer OS in patients with peripheral- than central-type SCLC (median, 502 vs 370 days, respectively; $p = 0.0186$) (Fig. 1A).

Univariate analysis by the log-rank test revealed that a poor PS, extensive disease stage, no surgery, central-type location, presence of ILD, and elevated serum concentrations of lactate dehydrogenase and tumor markers were associated with poor OS (Table 3). Multivariate analysis by a Cox proportional hazards model showed