Computed tomography-based differentiation of primary pulmonary lymphoepithelioma-like carcinoma and small-cell lung cancer

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Abstract

Background: Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare subtype of lung cancer. Both small-cell lung cancer (SCLC) and LELC often manifest as a centrally located tumor with lymphadenopathy. This retrospective study investigated and compared the initial computed tomography (CT) features and subsequent survival outcomes of LELC and SCLC.

Methods: A total of 50 patients with a confirmed diagnosis of LELC were enrolled and matched at a ratio of 1:1 with patients with SCLC according to the tumor stage. Utilizing a consensus approach, two radiologists reviewed pretreatment CT images. Survival outcomes were analyzed.

Results: Well-defined tumors were significantly more common in the LELC group (LELC: 42% vs SCLC: 24%, $p = 0.005$). Based on the comparisons of the primary tumor with the muscles, LELC tumors exhibited a significantly higher percentage of attenuation on contrast-enhanced CT scans (21.6% ± 29% vs −14.2% ± 37%, $p < 0.001$). The prevalence of vascular or bronchial encasement (18% vs 40%, $p = 0.028$), background emphysematous changes (10% vs 60%, $p < 0.001$), and tumors located in upper lobes (18% vs 64%, $p < 0.001$) was significantly lower in the LELC group. Female gender (70% vs 12%, $p < 0.001$), younger age (57.6 ± 12.0 years vs 68.0 ± 11.0 years, $p < 0.001$), and without a history of smoking (16% vs 88%, $p < 0.001$) were factors more commonly found in the LELC group. The patients with LELC had a better prognosis with significantly longer median survival than did the patients with SCLC (23.4 months vs 17.3 months, $p = 0.01$).

Conclusion: Because SCLC demonstrated a more aggressive disease progression, differentiating LELC from SCLC is crucial. In Epstein–Barr virus-endemic areas, the diagnosis of LELC should be considered when approaching a patient with the above-mentioned CT and clinical features.

Keywords: Lung neoplasms; Small-cell lung cancer; Tomography; X-ray computed

1. INTRODUCTION

Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare subtype of non-small-cell lung cancer (NSCLC), accounting for 0.17% of all lung cancer cases in a study with 24 596 cases,[1] and 0.4% of NSLC[2] in a study with 9851 cases, based on the two largest Chinese studies. Begin et al first reported LELC and noted its association with Epstein–Barr virus (EBV) in 1987.[3] Larger series of LELC have mostly been reported in East Asia, particularly in southern China,[1,4–7] Taiwan,[8,9] Hong Kong,[10] and Singapore.[11] The common manifestations of LELC on computed tomography (CT) scans include a tumor with homogeneous enhancement and the presence of lymphadenopathy, and late-staged lesions of LELC are often centrally situated in the lungs while early-stage tumors are often located peripherally.[2,6,10,12,13] The prognosis of patients with pulmonary LELC is more favorable than that of patients with non-LELC NSCLC.[13,14]

Small-cell lung cancer (SCLC), accounting for approximately 15% of all lung cancer cases, is the most common primary neuroendocrine tumor of the lungs.[15–18] Similar to those of LELC, common CT findings of SCLC include a centrally located tumor with lymphadenopathy.[19–21] However, SCLC is more aggressive than NSCLC and is associated with a poor prognosis.[16,22]

CT is the most widely utilized tool for evaluating lung cancer because of its standardized protocol and accessibility. Differences between the CT features of LELC and SCLC have not been adequately investigated. Moreover, survival outcomes associated with LELC and SCLC have not been thoroughly compared. Therefore, the present study retrospectively investigated and compared the CT features and survival outcomes of patients with LELC and SCLC.

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2. METHODS

2.1. Patients

This study was conducted in accordance with the Declaration of Helsinki and was approved by our institution (VGHIRB No.: 2018-07-020CC). Data for this retrospective study were obtained from the lung cancer registration database of our institution. Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data. Patients who had received a new histopathologically confirmed diagnosis of LELC and had undergone pretreatment contrast-enhanced CT between January 2006 and December 2017 were enrolled. For the control group, the data of patients who had received a new histopathologically confirmed diagnosis of SCLC between January 2006 and December 2017 were retrieved from the same lung cancer registration database, and these patients were matched at a ratio of 1:1 with patients with LELC according to tumor stage. For patients with LELC, the results of in situ hybridization for EBV-encoded small nuclear RNA (EBER) were reported. The survival data of these 100 patients were analyzed.

2.2. Analysis of CT images

The pretreatment CT scans of the 100 patients with LELC or SCLC were obtained using multislice CT scanners, namely LightSpeed VCT (GE Healthcare, Waukesha, WI, USA), Brilliance (Philips Medical Systems, Amsterdam, The Netherlands), iCT256 (Philips Medical Systems), Sensation 16 (Siemens Healthineers, Erlangen, Germany), and Aquilion (Toshiba Medical, Tochigi, Japan), with the administration of 70 to 80 mL of an intravenous contrast agent (Iopromide, Ultravist 370, Bayer Schering Pharma, Berlin, Germany or Iohexol, Omnipaque 350, GE health, Chicago, Ilinois) injected at a rate of 1.0 to 1.5 mL/s. Each CT scan was performed 60 seconds after the infusion of the contrast agent. Images were reconstructed at a slice thickness of 3 or 5 mm, and the scan range was from the thoracic inlet to the caudal tip of the liver. All CT images, including those of the lungs, soft tissue, and bone window, were jointly reviewed by two radiologists (L.K. and W.M., with 4 and 28 years of experience, respectively) on the same picture archiving and communication system monitor in a consensus manner. The following CT features were examined: tumor size (defined as the largest transverse diameter of the tumor); location of the epicenter of the tumor, including the involved lobe and tumor site (peripheral or central, where "central" referred to tumors that were located within the inner two-thirds of the lung and were close to the mediastinum, main bronchi, or central pulmonary vessels);[10] tumor borders (classified as well-defined, lobulated, or ill-defined); enhancement patterns of the tumor on contrast-enhanced CT scans (homogeneous or heterogeneous); presence of obstructive pneumonitis, pleural effusion, pericardial effusion, lymphangitic spreading, lung-to-lung metastasis, tumors with vascular or bronchial encasement, or background emphysematous changes in the lungs; and internal characteristics of the tumor, including the presence of calcification and cavities.

Because enhancement was considered, internal control with muscular enhancement was selected to eliminate the effects of variations in cardiac function and contrast infusion protocol as proposed by Ishizumi et al.[23] The percentage difference in the attenuation of the tumor relative to that of the muscle on a contrast-enhanced CT (CECT) image was calculated as follows:

$$\left[\begin{array}{l}(Attenuation\ of\ the\ tumor\ on\ CECT, HU)\\ -\left(\begin{array}{l}Attenuation\ of\ the\ largest\ muscle\ in\ the\ same\\ slice\ on\ the\ CT\ image, HU\end{array}\right)\end{array}\right]\times 100\%]/(Attenuation\ of\ the\ muscle, HU)$$

Besides, the difference of the lesion's HU between noncontrast-enhanced CT (NECT) and CECT was also calculated as follows:

$$(Attenuation\ of\ the\ tumor\ on\ CECT, HU) - (Attenuation\ of\ the\ tumor\ on\ NECT, HU)$$

Lymph nodes larger than 1 cm in the short axis, with clustered distribution, round shape, heterogenous texture, irregular margins or ill-defined border, central necrosis or ring enhancement were included as criteria for lymphadenopathy.[24] The location of the lymph node (ipsilateral peribronchial or hilar, ipsilateral mediastinal or subcarinal, contralateral mediastinal or hilar, or lower neck) was documented according to the regional lymph node classification for lung cancer staging adopted by the 1996 American Joint Committee on Cancer and the Union Internationale Contre le Cancer. Pathological or clinical staging was evaluated according to the seventh edition of the Tumor, Node, and Metastasis classification for lung cancer staging.

2.3. Statistical analyses

Python version 2.7.10 (Python Software Foundation, Delaware, US) was used for data processing. R version 3.4.2 (R Foundation, Vienna, Austria) was used for statistical analyses. Continuous and categorical variables were tested using Student's *t* test and the chi-squared or Fisher's exact test, respectively. The follow-up period was calculated from the date of diagnosis to the patient's latest visit to our hospital until April 2018. The Kaplan–Meier method was used to analyze the overall survival (OS) rate. The log-rank test was utilized to calculate the significance of OS. A *p*-value of less than 0.05 was considered statistically significant.

3. RESULTS

3.1. Patient demographics

A total of 62 patients who had received a new histopathologically confirmed diagnosis of LELC between January 2006 and December 2017 were identified. Fifty of these patients had undergone pretreatment contrast-enhanced CT and were thus enrolled in this study. Subsequently, 50 patients who had received a new histopathologically confirmed diagnosis of SCLC between January 2006 and December 2017 were matched at a ratio of 1:1 with the patients in the LELC group according to the tumor stage. The cancer stage was determined as I, II, III, and IV

Table 1

Basic characteristics of 100 patients with LELC or SCLC

	LELC (n = 50)	SCLC (n = 50)	*p*
Age	57.6 ± 12.0 (31-87)	68.0 ± 11.0 (47-87)	<0.001*
Sex			<0.001*
Male	15 (30%)	44 (88%)	
Female	35 (70%)	6 (12%)	
Positive smoking history	8 (16%)	44 (88%)	<0.001*
Positive result of EBV in pathology slide	50 (100%)	-	
Stage			
I	11 (22%)	11 (22%)	1.000
II	8 (16%)	8 (16%)	
III	20 (40%)	20 (40%)	
IV	11 (22%)	11 (22%)	

EBV = Epstein–Barr virus; LELC = lymphoepithelioma-like carcinoma; SCLC = small-cell lung cancer.
* $p < 0.05$.

in 11, 8, 20, and 11 patients, respectively, in both the LELC and SCLC groups (Table 1).

The proportion of male patients was significantly higher in the SCLC group than in the LELC group (88% in the SCLC group vs 30% in the LELC group, $p < 0.001$). The patients in the SCLC group were significantly older than those in the LELC group (68.0 ± 11.0 years in the SCLC group vs 57.6 ± 12.0 years in the LELC group, $p < 0.001$). The proportion of the patients with a history of smoking was significantly higher in the SCLC group than in the LELC group (16% in the LELC group vs 88% in the SCLC group, $p < 0.001$). All specimens obtained from the LELC patients tested positive for EBER.

3.2. Radiological characteristics at diagnosis

Table 2 summarizes all the CT features of LELC and SCLC. No significant difference was observed in the tumor size and tumor site by location (whether the tumor was centrally or peripherally located) between the LELC and SCLC groups (Table 2). SCLC tumors were observed in the upper lobes more frequently than LELC tumors (64.0% in the SCLC group vs 18.0% in the LELC group, $p < 0.001$). Well-defined tumors were significantly more common in the LELC group than in the SCLC group (42% in the LELC group vs 24% in the SCLC group, $p = 0.005$; Figure 1). No statistical difference in lymph node involvement was observed between the LELC and SCLC groups. Lung-to-lung metastasis was slightly more frequent in the LELC group than in the SCLC group, but the difference was nonsignificant (20% in the LELC group vs 8% in the SCLC group, $p = 0.150$). Vascular or bronchial encasement was significantly more prevalent in the SCLC group than in the LELC group (40% in the SCLC group vs 18% in the LELC group, $p = 0.028$). Background emphysematous changes in the lung parenchyma were significantly more prevalent in the SCLC group than in the LELC group (60% in the SCLC group vs 10% in the LELC group, $p < 0.001$; Figures 1 and 2).

Table 2

CT features of 100 patients with primary LELC or SCLC

	LELC (n = 50)	SCLC (n = 50)	*p*
Tumor size (mean ± SD) (cm)	4.5±2.4 (0.9-10.0)	4.3± 3.1 (0.8-12.0)	0.795
Tumor site by lobe			<0.001*
Right	29 (58%)	32 (64%)	
RUL	2 (4%)	20 (40%)	
RML	13 (26%)	3 (6%)	
RLL	14 (28%)	9 (18%)	
Left	21 (42%)	18 (36%)	
LUL	7 (14%)	12 (24%)	
LLL	14 (28%)	6 (12%)	
Tumor site by location			1.000
Central	37 (74%)	36 (72%)	
Peripheral	13 (26%)	14 (28%)	
Tumor border			0.005*
Ill-defined	3 (6%)	15 (30%)	
Lobulated	26 (52%)	23 (46%)	
Well-defined	21 (42%)	12 (24%)	
Lymph node involvement			0.938
N0	13 (26%)	11 (22%)	
N1	11 (22%)	13 (26%)	
N2	12 (24%)	11 (22%)	
N3	14 (28%)	15 (30%)	
Attenuation pattern			1.000
Homogeneous	37 (74%)	38 (76%)	
Heterogeneous	13 (26%)	12 (24%)	
Percentage difference of attenuation of lesion relative to muscle on contrast-enhanced CT (%)	21.6 ± 29 (–42~91)	–14.2 ± 37 (–218~49)	<0.001*
Obstructive pneumonitis	10 (20%)	17 (34%)	0.177
Pleural effusion	10 (20%)	13 (26%)	0.635
Pericardial effusion	3 (6%)	6 (12%)	0.485
Lymphangitic spreading	6 (12%)	7 (14%)	1.000
Lung-to-lung metastasis	10 (20%)	4 (8%)	0.150
Calcification	1 (2%)	2 (4%)	1.000
Cavity	1 (2%)	0 (0%)	1.000
Emphysematous change of lung	5 (10%)	30 (60%)	<0.001*
Vascular and/or bronchial encasement	9 (18%)	20 (40%)	0.028*

CT = computed tomography; EBV = Epstein–Barr virus; LELC = lymphoepithelioma-like carcinoma; LLL = left lower lobe; LUL = left upper lobe; N0 = none; N1 = ipsilateral peribronchial or ipsilateral hilar; N2 = ipsilateral mediastinal or subcarinal; N3 = contralateral mediastinal or contralateral hilar or lower neck; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; SCLC = small-cell lung cancer.
*$p < 0.05$.

On CECT, the percentage difference in the attenuation of the lesion relative to that of the muscle was significantly higher in the LELC group (21.6% ± 29%) than in the SCLC group (–14.2% ± 37%, $p < 0.001$; Figs. 1–3). In addition, on CECT, homogeneous enhancement was more common than heterogeneous enhancement in both the groups (Table 2). When comparing the attenuation of the lesion on NECT and CECT, LELC was significantly more enhanced (30.4 ± 15.4 HU, n = 40) than SCLC (21.3 ± 12.9, n = 34, $p = 0.008$).

In the LELC group, heterogeneously enhanced tumors were significantly larger than homogeneous enhanced tumors; however, no such significant difference was observed in the SCLC group (Table 3). In addition, centrally located tumors were more prevalent than peripherally located tumors in both the groups, but the difference was nonsignificant. In both groups, centrally located tumors were significantly larger than peripherally located tumors (Table 3). Late-stage tumors were more commonly centrally located, while early-stage tumors could reside both peripherally and centrally (Table 4).

No significant difference was observed between the SCLC and LELC groups in terms of the presence of obstructive pneumonitis, pleural effusion, pericardial effusion, calcification and cavity in the tumor, or lymphangitic spreading (Table 1).

3.3. Survival analysis

The median follow-up periods of the patients in the LELC and SCLC groups were 23.4 (range: 0.9–154.6) months and 17.3 (range: 1.4–89.2) months, respectively. The 2- and 5-year OS rates of the patients with LELC were 0.71 and 0.56, respectively, and those of the patients with SCLC were 0.40 and 0.22, respectively. Figure 4 presents the cumulative survival probabilities of the patients after the initial diagnosis of LELC or SCLC. The results of the log-rank test indicated that the survival outcomes of the patients with LELC were superior to those of the patients with SCLC ($p = 0.01$).

4. DISCUSSION

In our study, among the patients matched by tumor grade, LELC tumors exhibited higher attenuation and well-defined borders on contrast-enhanced CT images more frequently than did SCLC tumors. Background emphysematous changes in the lung vascular or bronchial encasement and tumors located in upper lobes were more common among the patients with SCLC than among those with LELC. Women, young patients, and patients without a history of smoking were factors more commonly found in the LELC group. Primary LELC is strongly associated with EBV infection. The survival outcomes of the patients with LELC were superior to those of the patients with SCLC.

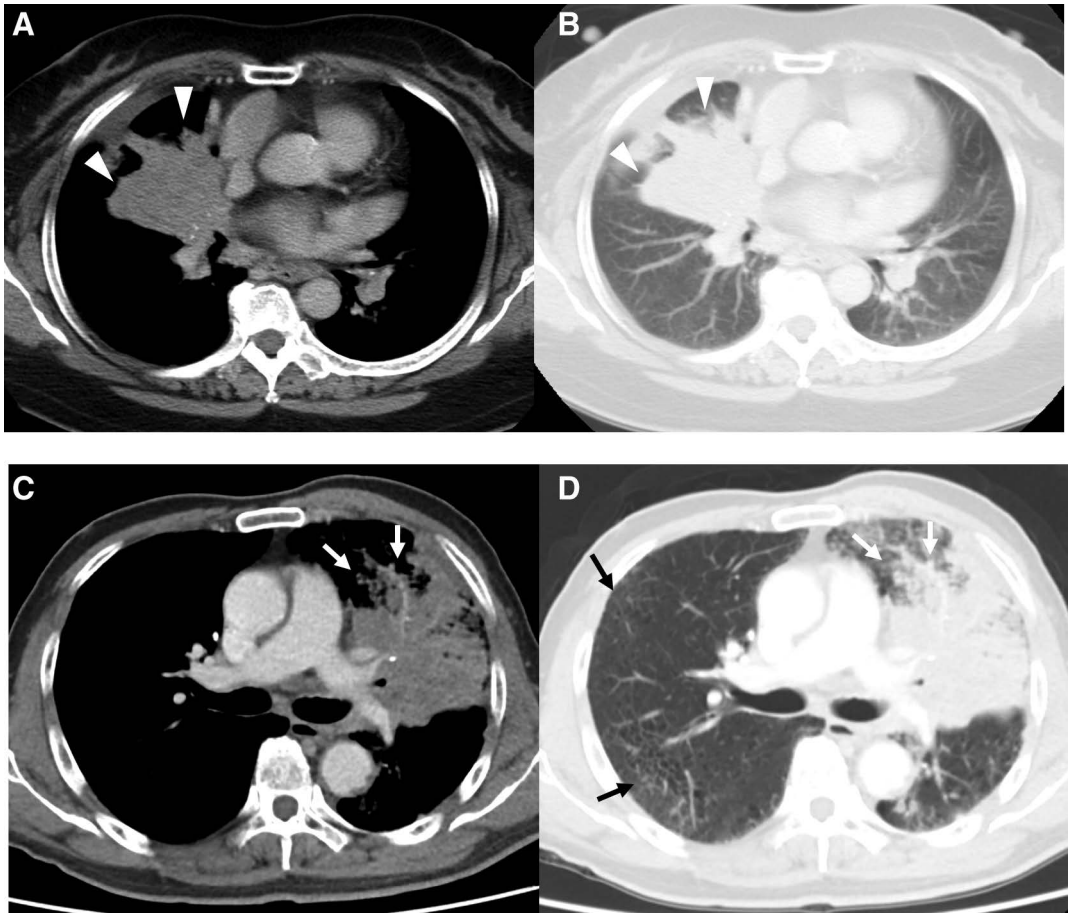

Fig. 1 (A–D) A 58-year-old woman with stage 4 LELC. A CT scan with mediastinal window (A) and lung window (B) demonstrates a tumor situated in the RML. A 63-year-old man with stage 4 SCLC. A CT scan with mediastinal window (C) and lung window (D) demonstrates a tumor situated in the LUL. Both tumors are located centrally. However, the border of LELC is lobulated (white arrowhead) compared to the irregular border of SCLC (white arrows). The LELC shows more prominent enhancement (56 HU and 33% higher than right erector spinae muscles) compared to (C) SCLC (62 HU and 3% lower than right erector spinae muscles). Emphysematous change of the lung fields is conspicuous in the SCLC (black arrows). CT = computed tomography; LELC = lymphoepithelioma-like carcinoma; LUL = left upper lobe; RML = right middle lobe; SCLC = small-cell lung cancer.

Although LELC and SCLC exhibit some similarities in CT features, different CT characteristics were also observed between LELC and SCLC in the present study. First, on contrast-enhanced CT scans, when tumors were compared with the nearby muscles, the attenuation of LELC tumors was more prominent than that of SCLC tumors. In addition, when compared to NECT, CECT of LELC was enhanced significantly more than SCLC was. To our knowledge, no previous study has reported this finding. Microscopically, intense lymphoplasmacytic cells usually infiltrate LELC tumors, and lymphoplasmacytic reactions often correlate with increased vascularity, which may explain why the attenuation of LELC tumors was more obvious than that of SCLC tumors on CECT.[9,25,26] Second, background emphysematous changes in the lung parenchyma were significantly more common in the SCLC group than in the LELC group. Cigarette smoking is responsible for up to 95% of SCLC cases,[15–18] but no such relationship has been reported for LELC.[2,6,10,12,13] Chronic smoking may cause emphysematous changes in the lungs.[27] In addition, SCLC tumors were more frequently observed in the upper lobes of the lungs in our study. The tumors in the patients with a history of smoking were observed to be located in the upper lobes more frequently, which could be explained by the deposition distribution of smoking particles.[28] Therefore, in this study, the findings of a higher prevalence of emphysematous changes in the lung parenchyma and the location of tumors in the upper lobes in the SCLC group than in the LELC group may be reflective of the higher proportion of smokers among the patients with SCLC than among those with LELC. Third, the finding that ill-defined tumors were significantly more common in the SCLC group than in the LELC group is similar to the findings of previous studies.[6,12] Fourth, vascular or bronchial encasement was significantly more common in the SCLC group than in the LELC group, which might contribute to the more aggressive behavior of SCLC.

In our study, the patients with LELC and SCLC exhibited some characteristic clinical features, which are consistent with the findings of previous studies. First, SCLC was significantly more prevalent among male patients,[11,15,22] whereas LELC was significantly more prevalent among nonsmoking and female patients.[4,12,29] Second, compared with patients with SCLC, patients with LELC were frequently diagnosed at younger ages.[2,5,6,10,12–15,22,29,30] Third, in the lung cancer registration database of our institution, the proportion of patients with advanced-stage SCLC was higher than that of patients with early-stage SCLC. In a previous study, only 5% of patients with SCLC received a diagnosis of stage I tumor.[31] Tumor stages among the patients with LELC were more evenly distributed. Moreover, even when the tumor stage was controlled for in our study, prognosis was still poor among the patients with SCLC. And the 2- and 5-year OS rates of the patients with LELC were

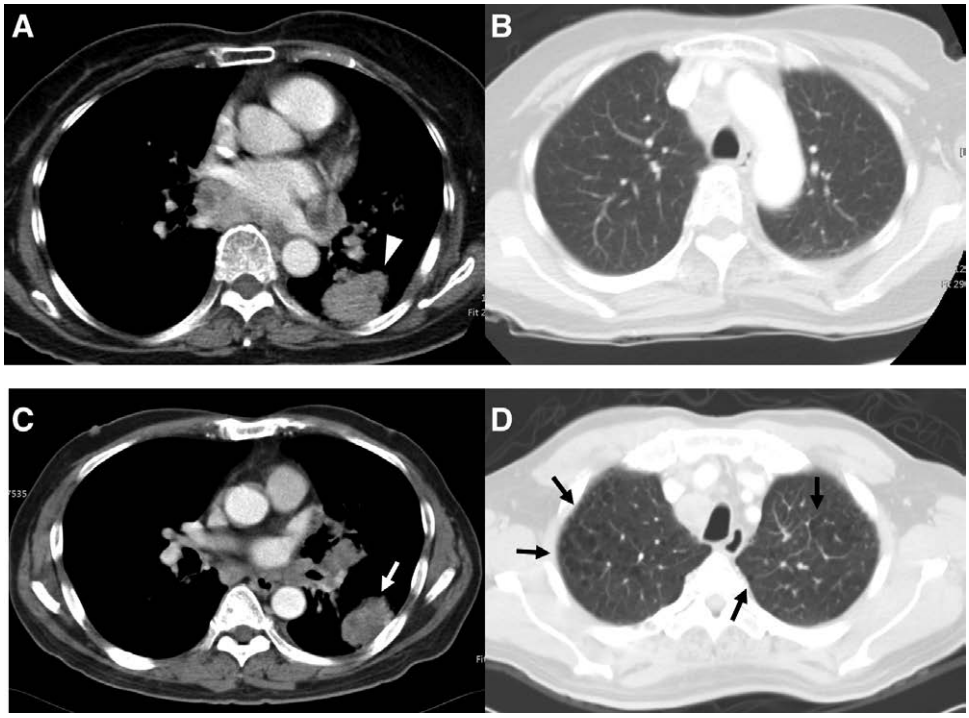

Fig. 2 (A–D) A 64-year-old woman with stage 4 LELC. A CT scan with mediastinal window (A) and lung window of upper lung filed (B) demonstrates a tumor situated in the LLL. A 69-year-old man with stage 4 SCLC. A CT scan with mediastinal window (C) and lung window (D) demonstrates a tumor situated in the LLL. Both tumors are located peripherally with a lobulated border. However, LELC (white arrowhead) shows more prominent (81 HU and 42% higher than right erector spinae muscles) and homogeneous enhancement compared to SCLC (white arrows) with less prominent (60 HU and 2% higher than right erector spinae muscles) and heterogeneous enhancement. Emphysematous change of the upper lung fields is conspicuous in the SCLC (black arrows). CT = computed tomography; LELC = lymphoepithelioma-like carcinoma; LLL = left lower lobe; SCLC = small-cell lung cancer.

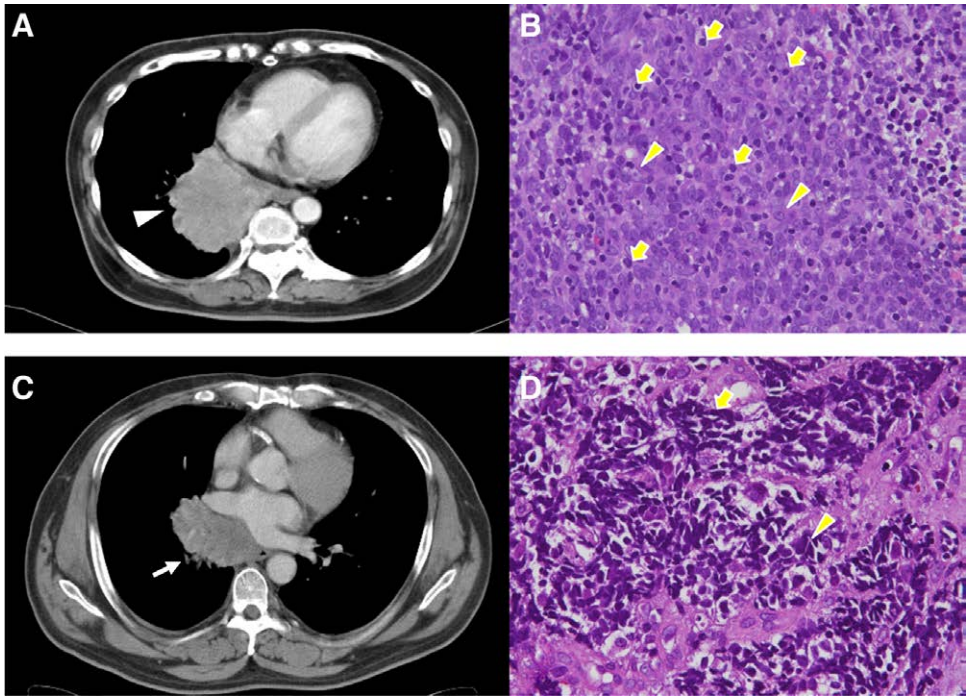

Fig. 3 (A–D) A 68-year-old woman with stage 3A LELC. (A) A CT scan shows a lobulated mass centered in the central right lower lobe (white arrowhead). (B) The tumor cells have vesicular nuclei and prominent nucleoli (yellow arrowhead), and is presented in a syncytial pattern. Prominent lymphocytes infiltration is present (yellow arrow) (H&E stain, 400×). (C, D) A 53-year-old man with stage 3A SCLC. (C) A CT scan shows an ill-defined mass centered in the central right lower lobe (white arrow). (D) The tumor cells have hyperchromatic nuclei, fine chromatin, and scanty cytoplasm (yellow arrowheads). Nuclear molding (yellow arrows) is evident (H&E stain, 400×). LELC shows more prominent enhancement (77 HU and 54% higher than right erector spinae muscles) compared to SCLC (26 HU and 21% lower than right erector spinae muscles). CT = computed tomography; LELC = lymphoepithelioma-like carcinoma; SCLC = small-cell lung cancer.

Table 3

Comparison of tumor size by tumor location and attenuation pattern on contrast-enhanced CT scans of LELC and SCLC

	Homogeneous attenuation	Heterogeneous attenuation	*p*
LELC	3.8 ± 2.0 cm (n = 37) (0.9-7.3)	6.4 ± 2.6 cm (n = 13) (1.6-10.0)	<0.004*
SCLC	4.0 ± 3.0 cm (n = 38) (0.8-12.0)	5.4 ± 3.0 cm (n = 12) (1.3-11.3)	0.184
	Central	**Peripheral**	***P***
LELC	5.0 ± 2.2 cm (n = 37) (0.9-9.7)	2.9 ± 2.5 cm (n = 13) (0.9-10.0)	0.012*
SCLC	5.0 ± 3.3 cm (n = 36) (0.8-12.0)	2.6 ± 1.3 cm (n = 14) (1.2-5.0)	<0.001*

CT = computed tomography; EBV = Epstein–Barr virus; LELC = lymphoepithelioma-like carcinoma; SCLC = small-cell lung cancer.
*$p < 0.05$.

Table 4

Comparison of tumor stage by tumor location in LELC and SCLC

	Early-stage	Late-stage	*p*
LELC			
Central	10	26	0.017*
Peripheral	9	5	
SCLC			
Central	12	25	0.171
Peripheral	7	6	

LELC = lymphoepithelioma-like carcinoma; SCLC = small-cell lung cancer.
*$p < 0.05$.

significantly longer vs SCLC patients (0.71 and 0.56 vs 0.40 and 0.22, respectively). Previous reports have indicated that LELC corresponds with a more favorable prognosis than do other types of NSCLC.[14] By contrast, the prognosis of SCLC is poorer than that of NSCLC.[16,22] Therefore, the finding of the present study that the prognosis of SCLC was poorer than that of LELC is reasonable. Fourth, previous studies have reported that pulmonary LELC is strongly associated with EBV infection, and approximately two-thirds of patients with LELC reside in Taiwan, Hong Kong, or southern China.[25,26,32] In our study, all 50 patients with LELC were Taiwanese, and all were positive for EBER. This finding may support the assumption that EBV infection plays a role in the development of LELC in Asian populations.

The CT features of SCLC and especially of LELC have not been sufficiently reported.[2,6,10,12,13] LELC and SCLC tumors of a relatively large size are situated centrally more frequently, and they are often characterized by the encasement or involvement of vessels and bronchi.[2,6,10,12,13,19–21] Regarding SCLC, less than 5% of patients analyzed in previous studies had peripheral nodules with well-defined margins and homogeneous enhancement without associated lymphadenopathy on contrast-enhanced CT images, and most of these tumors were of an early stage.[20,33] In the present study, we matched the patients with SCLC to the patients with LELC based on the tumor stage of LELC, and a greater proportion of the patients with SCLC were in the early stage; accordingly, the proportion of peripherally located SCLC (28.0%) was also larger in our study as compared with real practice.

Our study demonstrated that similar to those in other types of lung cancer, tumors with heterogeneous enhancement, albeit without statistical significance in the SCLC group, were larger than those with homogeneous enhancement on CECT. This finding is in agreement with those of previous studies.[6,13,34]

Our study has some limitations. First, a selection bias probably existed. Only patients who had undergone pretreatment contrast-enhanced CT were enrolled. In total, 12 patients diagnosed with LELC were excluded. Because LELC is a rare type of lung cancer, if CT scans of these 12 patients were available and included in the statistical comparison, the results of enhancement patterns might have differed. Second, five different CT apparatuses were used for imaging the patients. The heterogeneity of images may have resulted from different pieces of CT equipment and may have resulted in biased results despite our efforts to eliminate this bias by comparing the lesion with chest wall muscle as internal control. More studies should be conducted to clarify the CT findings of LELC and SCLC by using a single CT scanner. However, as aforementioned, most of our CT findings for both the groups are consistent with the findings of previous studies, and these biases probably would not affect our conclusions. Third, the gender and age predilection probably could not be based on our study because the case selection algorithm of SCLC might have been biased. Hence, the image discrepancy of age and gender proportions could be confounded.

In conclusion, considering that the survival outcomes of the patients with LELC were superior to those of the patients with SCLC even in the setting of similar TNM stage, in

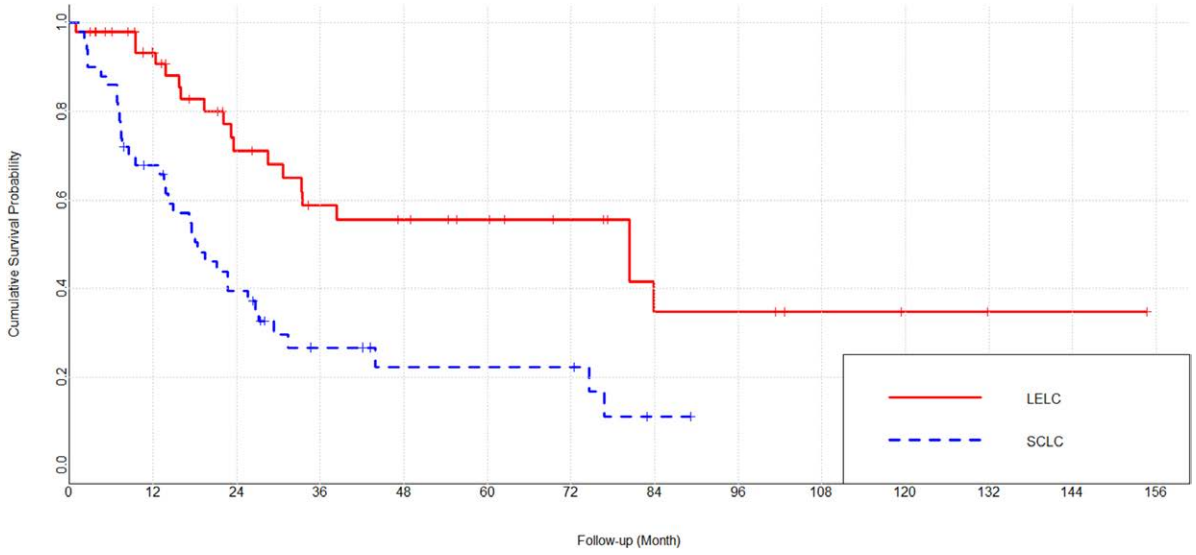

Fig. 4 Cumulative survival probabilities of patients after initial diagnosis with LELC and SCLC ($p = 0.01$). LELC = lymphoepithelioma-like carcinoma; SCLC = small-cell lung cancer.

EBV-endemic areas, differentiating between LELC and SCLC is critical. In spite of the fact that tissue biopsy remains the golden standard for diagnosis, we specifically attained differentials according to clinical, radiological, and pathological evidence for a relatively noninvasive approach. Background emphysematous changes in the lung, vascular or bronchial encasement, and tumors located in upper lobes were less common among the patients with LELC than among those with SCLC. In conclusion, in a younger female nonsmoker with postcontrast-enhanced CT features of higher attenuation and well-defined borders in the central lungs and positive test of EBER, LELC should be considered in the differential diagnosis.

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