A Rare Subtype of Non-small Cell Lung Cancer: Report of 159 Resected Stage I-IIIA Pulmonary Lymphoepithelioma-like Carcinoma Cases

Rong-Rong Jiang  
Sun Yat-sen University Cancer Center

Xiao-Meng Dou  
Sun Yat-sen University Cancer Center

Xiao-Li Feng  
Sun Yat-sen University Cancer Center

Wen-Ting Zhu  
Sun Yat-sen University Cancer Center

Man-Xia Guo  
Sun Yat-sen University Cancer Center

Xue-Li Tan  
Sun Yat-sen University Cancer Center

Xiao-Juan Jiang  
Sun Yat-sen University Cancer Center

Jing-Sheng Cai  
Sun Yat-sen University Cancer Center

Li Liu (✉ liuli@sysucc.org.cn)  
Sun Yat-sen University Cancer Center

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Abstract

Background The current study analyzed resected stage I-IIIA pulmonary lymphoepithelioma-like carcinoma (LELC) cases to define the clinical characteristics, prognosis and long-term outcomes of LELC, with the purpose of guiding clinical management for this rare tumor.

Methods Resected stage I-IIIA LELC, adenocarcinoma (ADC), squamous cell carcinoma (SCC) and adenosquamous carcinoma (ASC) cases from our center were enrolled. Propensity score matching (PSM) was applied to minimize the selection bias. Overall survival (OS) and disease-free survival (DFS) were compared between groups. Multivariate analyses were performed to identify the prognostic factors, and a nomogram was developed.

Results A total of 159 LELCs, 2,757 ADCs, 1,331 SCCs and 155 ASCs were included. LELC, dominated among younger patients and nonsmokers, always presented without typical imaging manifestations of lung cancer. LELC was a poorly differentiated disease that lacked driver gene mutations and was positive for immunohistochemistry indicators of squamous cell lineage. Survival analyses revealed that OS was significantly better for LELC than for other common non-small cell lung cancer (NSCLC) both before PSM (all $P < 0.001$) and after PSM (all $P < 0.05$). Further analyses revealed that early pathological node stage and preoperative albumin level $\geq 35$ were identified as independent prognostic factors favoring OS and DFS.

Conclusions LELC, dominated among younger and nonsmoking populations, showed a lower extent of malignancy regarding CT characteristics. It lacked driver gene mutations and was positive for immunohistochemistry indicators of squamous cell lineage. The survival outcome of PSC was better than other common NSCLCs.

Introduction

Primary pulmonary lymphoepithelioma-like carcinoma (LELC), a rare subtype of non-small cell lung cancer (NSCLC), accounts for less than 1% of all lung neoplasms (1) and was first described in 1987 by Begin (2). According to the World Health Organization (WHO) Classification in 2015, it was removed from the subgroup of large cell lung cancer and reclassified as a unique subgroup of NSCLC (3). Owing to the inherent rarity and the lack of prospective clinical trials, the natural course, prognosis and management strategy of LELC requires in-depth investigation.

LELC is an Epstein-Barr virus (EBV)-associated and undifferentiated nasopharyngeal-like carcinoma (2, 4, 5). Previous literature demonstrated that most LELC cases were documented in Southeast Asia including Guangdong Province, Taiwan, Hong Kong and Singapore (6–12). LELC is more prevalent among younger and nonsmoking populations without sexual predilection (6, 9, 11, 12). In addition, several clinical series suggested that LELC has a favorable survival outcome when compared with other lung cancers (6, 8, 11, 12). Although many efforts have been devoted to LELC research in the past few decades, the general
demographics and prognosis remain enigmatic, and larger datasets are warranted to tailor the clinical practice guidelines for this rare disease.

In the current study, we retrospectively reviewed 159 resected stage I-III A LELC cases to sketch an outline of the clinicopathological characteristics of the disease. We also compared the overall survival (OS) of LELC with other common lung cancers both before and after propensity score matching (PSM) with the purpose of helping clinicians estimate individual survival and select a proper treatment strategy.

**Methods**

**Patient Selection**

Consecutive resected patients diagnosed with LELC between 1990 and 2016 from the Sun Yat-sen University Cancer Center (SYSUCC) were retrospectively enrolled. In addition, resected patients diagnosed with adenocarcinoma (ADC), squamous cell carcinoma (SCC) and adenosquamous carcinoma (ASC) from 2001 to 2016 were also included in this study.

All included cases fit the following criteria: [1] pathologically diagnosed as stage I-III A disease and [2] surgical resection was performed. The exclusion criteria were as follows: [1] previous or concurrent other primary cancers; [2] age < 18 years old; [3] underwent neoadjuvant therapy and [4] clinicopathological information was unavailable.

This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. All the included patients signed the informed consent. All methods involved in our article were performed in accordance with the Declaration of Helsinki. The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn), with the approval RDD number as RDDA2020001729. The dataset generated for this study are available on request to the corresponding authors.

**Data Collection**

Clinical, pathological, CT and immunohistochemistry (IHC) data were retrieved from patients’ medical records. Clinical variables included age, sex, main complaint, smoking status, tumor history, preoperative albumin level, preoperative complications, surgical approach, surgical type and adjuvant therapy. In terms of age, LELC cases were assigned to 2 groups (≤ 60 years old and > 60 years old) based on the optimal cutoff value determined by X-tile software (13). The preoperative albumin level was dichotomized according to the lower limit of normal. CT features included tumor diameter, location, morphology, speculation, lobulation, pleural indentation, obstructive pneumonia, cavity, clinical tumor (cT) stage, clinical node (cN) stage and clinical tumor-node-metastasis (cTNM) stage. All the relevant data were collected from imaging reports. TNM staging was performed according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system (14). Pathological characteristics included tumor site, tumor diameter, grade, pleural invasion, lymphovascular invasion, perineural invasion,
examined lymph nodes (ELNs), positive lymph nodes (PLNs), pathological tumor (pT) stage, pathological node (pN) stage and pathological tumor-node-metastasis (pTNM) stage. ELNs and PLNs were also dichotomized according to the cutoff value determined by X-tile software. IHC features included CK, CK5/6, CK7, thyroid transcription factor (TTF)-1, P63, Epstein-Bar virus-encoded RNA (EBER), epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). EGFR testing was performed by the Amplification Refractory Mutation System, and ALK testing was performed by in situ hybridization.

**Follow-up**

In general, postoperative follow-up was carried out every 3 months for the first 2 years, every 6 months for the next 3–5 years, and annually thereafter (15–18). At each follow-up visit, a physical examination and chest and abdominal CT scans were performed (15). If the patient had specific symptoms, the examination was performed as soon as possible for a more careful assessment (15–18). Follow-up information was updated in October 2020 to determine patients' vital status.

**Statistical Analysis**

All statistical analyses were performed using R version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org), IBM SPSS Statistics (version 25.0, IBM Corp, Armonk, NY, USA), X-tile software (13) and GraphPad Prism 8 software. OS was defined as the interval from the date of surgery to the date of death from any cause or the last follow-up. DFS was defined as the time from the date of surgery to the date of tumor recurrence or death from any cause. All survival outcomes were estimated by the Kaplan-Meier method with a log-rank test. Univariate and multivariate Cox analyses were used to identify the prognostic factors, and a nomogram was formulated. The concordance index (C-index) was performed to verify the predicted effect of the nomogram (19). A one to one propensity score matching (PSM) method based on age, sex, smoking status, surgical type, ELNs, pT stage, pN stage, pTNM stage and adjuvant therapy was employed to reduce bias (20). Pearson's χ² test or Fisher's exact test was used to compare categorical variables between groups. X-tile software was used to determine the cutoff value (13). A two-sided \( P < 0.05 \) was considered statistically significant.

**Results**

**Patient characteristics**

Between January 1990 and December 2016, a series of 159 resected stage I-IIIA LELC cases were evaluated. The general characteristics are summarized in Table 1. For clinical features, the median age of the entire cohort was 55 years old (range: 27–75 years old). Males and females were at a comparable proportion (45.3% vs. 54.7%). Nonsmoker (73.6%) accounted for most of the cases, and most patients had normal preoperative albumin levels (88.7%). A substantial number of patients underwent thoracotomy (73.6%) and lobectomy (78.6%). Regarding CT features, most cases were classified as peripheral (73.6%) and irregular (78.0%) tumors. Only a small portion of tumors presented spiculation (25.8%), pleural indentation (12.6%), obstructive pneumonia (17.0%) and cavity (8.2%). Considering
pathological characteristics, almost all were diagnosed as poorly differentiated LELC (96.2%). A small proportion of patients were diagnosed with lymphovascular invasion (10.1%) and perineural invasion (5.7%). Most patients had ELNs > 34 (83.0%). With respect to the IHC characteristics, there were higher expression levels of CK (95.9%), CK5/6 (99.3%), P63 (97.1%) and EBER (99.3%), and lower expression levels of CK7 (96.7%) and TTF-1 (95.1%). Most cases were EGFR-wild (97.0%) and ALK-wild (97.8%).
Table 1
Clinicopathological, CT and immunohistochemistry characteristics of LELC patient.

| Clinical Characteristic               | No. Patients (%) |
|--------------------------------------|-----------------|
| Age                                  | 55 (27–75)      |
| Median (range)                       |                 |
| ≤ 60                                 | 115 (72.3)      |
| > 60                                 | 44 (27.7)       |
| Sex                                  |                 |
| Male                                 | 72 (45.3)       |
| Female                               | 87 (54.7)       |
| Main complaint                       |                 |
| Asymptomatic                         | 63 (39.6)       |
| Cough                                | 47 (29.6)       |
| Haemoptysis                          | 37 (23.3)       |
| Chest pain                           | 9 (5.7)         |
| Othera                               | 3 (1.9)         |
| Smoking                              |                 |
| Non-smoker                           | 117 (73.6)      |
| Smoker                               | 42 (26.4)       |
| Tumor history                        |                 |
| No                                   | 135 (84.9)      |
| Yes                                  | 24 (15.1)       |
| Preoperative albumin level (g/L)     |                 |
| Median (range)                       | 42.7 (28.6–53.3) |
| < 35                                 | 18 (11.3)       |
| ≥ 35                                 | 141 (88.7)      |
| Preoperative complications           |                 |
| None                                 | 116 (73.0)      |
| Hypertension                         | 21 (13.2)       |
| Clinical Characteristic          | No. Patients (%) |
|---------------------------------|------------------|
| Diabetes mellitus               | 5 (3.1)          |
| Hepatitis                       | 9 (5.7)          |
| Other<sup>b</sup>               | 8 (5.0)          |
| Surgical approach               |                  |
| VATS                            | 42 (26.4)        |
| Thoracotomy                     | 117 (73.6)       |
| Surgical type                   |                  |
| Lobectomy                       | 125 (78.6)       |
| Wedge resection                 | 8 (5.0)          |
| Bilobectomy                     | 10 (16.3)        |
| Pneumonectomy                   | 16 (10.1)        |
| Adjuvant therapy                |                  |
| None                            | 79 (49.7)        |
| Chemotherapy                    | 67 (42.1)        |
| Radiotherapy                    | 3 (1.9)          |
| Chemoradiotherapy               | 8 (5.0)          |
| Target therapy                  | 1 (0.6)          |
| Immune therapy                  | 1 (0.6)          |
| Adjuvant chemotherapy regimen (n = 75) |              |
| AP                              | 38 (50.7)        |
| TP                              | 21 (28.0)        |
| GP                              | 9 (12.0)         |
| 5-FU                            | 4 (5.3)          |
| Other<sup>c</sup>               | 3 (4.0)          |

**CT Characteristic**

| Diameter (cm) | Median (range) |
|---------------|---------------|
|               | 4.2 (1.2–16.0) |
| Clinical Characteristic          | No. Patients (%) |
|---------------------------------|------------------|
| Central                         | 42 (26.4)        |
| Peripheral                      | 117 (73.6)       |
| Morphology                      |                  |
| Regular                         | 35 (22.0)        |
| Irregular                       | 124 (78.0)       |
| Spiculation                     |                  |
| Yes                             | 41 (25.8)        |
| No                              | 118 (74.2)       |
| Lobulation                      |                  |
| Yes                             | 85 (53.5)        |
| No                              | 74 (46.5)        |
| Pleural indentation             |                  |
| Yes                             | 20 (12.6)        |
| No                              | 139 (87.4)       |
| Obstructive pneumonia           |                  |
| Yes                             | 27 (17.0)        |
| No                              | 132 (83.0)       |
| Cavity                          |                  |
| Yes                             | 13 (8.2)         |
| No                              | 146 (91.8)       |
| cT stage                        |                  |
| 1                               | 49 (30.8)        |
| 2                               | 64 (40.3)        |
| 3                               | 33 (20.8)        |
| 4                               | 13 (8.2)         |
| cN stage                        |                  |
| 0                               | 73 (45.9)        |
| 1                               | 31 (19.5)        |
### Clinical Characteristic

| No. Patients (%) |
|------------------|
| 2                |
| 49 (30.8)        |
| 3                |
| 6 (3.8)          |

| cTNM stage |
|------------|
| IA1        |
| 0 (0.0)    |
| IA2        |
| 13 (8.2)   |
| IA3        |
| 20 (12.6)  |
| IB         |
| 13 (8.2)   |
| IIA        |
| 15 (9.4)   |
| IIB        |
| 32 (20.1)  |
| IIIA       |
| 37 (23.3)  |
| IIIB       |
| 25 (15.7)  |
| IIIC       |
| 4 (2.5)    |

### Pathological Characteristic

| Site, n (%) |
|-------------|
| RUL         |
| 18 (11.3)   |
| RML         |
| 41 (25.8)   |
| RLL         |
| 28 (17.6)   |
| LUL         |
| 21 (13.2)   |
| LLL         |
| 51 (32.1)   |

| Diameter |
|----------|
| Median (range) |
| 4.0 (0.6–11.0) |

| Grade |
|-------|
| Well differentiation |
| 0 (0.0) |
| Moderately differentiation |
| 0 (0.0) |
| Poor differentiation |
| 153 (96.2) |
| Undifferentiation |
| 6 (3.8) |

| Pleural invasion |
|------------------|
| No               |
| 98 (61.6)        |
| Clinical Characteristic         | No. Patients (%) |
|-------------------------------|------------------|
| Yes                           | 61 (38.4)        |
| Lymphovascular invasion       |                  |
| No                            | 143 (89.9)       |
| Yes                           | 16 (10.1)        |
| Perineural invasion           |                  |
| No                            | 150 (94.3)       |
| Yes                           | 9 (5.7)          |
| Examined lymph nodes          |                  |
| Median (range)                | 22 (1–73)        |
| ≤ 34                          | 27 (17.0)        |
| > 34                          | 132 (83.0)       |
| Positive lymph nodes          |                  |
| Median (range)                | 1 (0–16)         |
| ≤ 4                           | 137 (86.2)       |
| > 4                           | 22 (13.8)        |
| pT stage                      |                  |
| 1                             | 45 (28.3)        |
| 2                             | 75 (47.2)        |
| 3                             | 28 (17.6)        |
| 4                             | 11 (6.9)         |
| pN stage                      |                  |
| 0                             | 75 (47.2)        |
| 1                             | 31 (19.5)        |
| 2                             | 53 (33.3)        |
| pTNM stage                    |                  |
| IA1                           | 1 (0.6)          |
| IA2                           | 9 (5.7)          |
| IA3                           | 17 (10.7)        |
| Clinical Characteristic | No. Patients (%) |
|-------------------------|------------------|
| IB                      | 25 (15.7)        |
| IIA                     | 9 (5.7)          |
| IIB                     | 32 (20.1)        |
| IIIA                    | 66 (41.5)        |
| **Immunohistochemistry Characteristic** |                    |
| CK (n = 73)             |                  |
| Positive                | 70 (95.9)        |
| Negative                | 3 (4.1)          |
| CK 5/6 (n = 136)        |                  |
| Positive                | 135 (99.3)       |
| Negative                | 1 (0.7)          |
| CK 7 (n = 91)           |                  |
| Positive                | 3 (3.3)          |
| Negative                | 88 (96.7)        |
| TTF-1 (n = 103)         |                  |
| Positive                | 5 (4.9)          |
| Negative                | 98 (95.1)        |
| P 63 (n = 139)          |                  |
| Positive                | 135 (97.1)       |
| Negative                | 4 (2.9)          |
| EBER (n = 147)          |                  |
| Positive                | 146 (99.3)       |
| Negative                | 1 (0.7)          |
| EGFR (n = 99)           |                  |
| Mutated                 | 3 (3.0)          |
| Wild                    | 96 (97.0)        |
| ALK (n = 91)            |                  |
| Mutated                 | 2 (2.2)          |
| Clinical Characteristic | No. Patients (%) |
|------------------------|------------------|
| Wild                   | 89 (97.8)        |

\(^a\) other includes 1 patient main complaint for weight loss and 2 patients main complaint for fever.

\(^b\) other includes 1 patient had low limb paralysis, 2 patients had gastric ulcer, 2 patients had asthma and 3 patients had hyperthyroidism.

\(^c\) other includes 1 patient was administered vincristine and 2 patients were administered Adriamycin + cyclophosphamide.

LELC, lymphoepithelioma-like carcinoma; VATS, video-assisted thoracic surgery; AP, pemetrexed + platinum; TP, paclitaxel + platinum; GP, gemcitabine + platinum; 5-FU, 5-Fluorouracil; cT stage, clinical tumor stage; cN stage, clinical node stage; cTNM stage, clinical tumor-node-metastasis stage; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe; pT stage, pathological tumor stage; pN stage, pathological node stage; pTNM stage, pathological tumor-node-metastasis stage; TTF-1: thyroid transcription factor-1; EBER, Epstein-Bar virus-encoded RNA; EGFR, epidermal growth factor receptor and ALK, anaplastic lymphoma kinase.

A total of 2,757 ADC cases, 1,331 SCC cases and 155 ASC cases from SYSUCC between January 2001 and December 2016 were also enrolled. The clinicopathological features of these tumors before and after PSM are listed in Table S1 (ADC vs. LELC), Table S2 (SCC vs. LELC) and Table S3 (ASC vs. LELC). Before PSM, there were higher percentages of patients under the age of 60 (LELC vs. ADC vs. SCC vs. ASC = 72.3% vs. 48.4% vs. 42.4% vs. 46.5%) and nonsmokers (LELC vs. ADC vs. SCC vs. ASC = 73.6% vs. 56.7% vs. 17.1% vs. 60.0%) in the LELC cohort than in the other 3 cohorts. After PSM, all covariates were well balanced among these pairs.

**Cox regression analysis**

Regarding OS, a univariate analysis revealed that age \(\leq 60\), preoperative albumin level \(\geq 35\), lobectomy surgical type, regular morphology, ELNs \(\leq 34\), PLNs \(\leq 4\) and pN0 stage were favorable prognostic factors (Table 2). Multivariate analysis confirmed that age \(\leq 60\), preoperative albumin level \(\geq 35\), lobectomy surgical type, regular morphology and pN0 stage were independent predictors favoring OS (Table 2). A nomogram, formulated based on the statistically significant factors from the multivariate analysis, showed that pN stage was the strongest predictor, followed by preoperative albumin level and tumor morphology (Figure S1, online only). The C-index of the nomogram was 0.86 [95% confidence interval (CI): 0.91 – 0.81].
Table 2
Univariate and multivariate COX proportional hazard model analysis for overall survival.

| Characteristic                  | Univariate Analysis |          |          |          | Multivariate Analysis\(^a\) |          |          |
|---------------------------------|---------------------|----------|----------|----------|-----------------------------|----------|----------|
|                                 | HR                  | 95% CI   | P        | HR       | 95% CI                      | P        |
| Age                             |                     |          |          |          |                             |          |          |
| ≤ 60                            | Ref                 |          |          | Ref      |                             |          |          |
| > 60                            | 2.188               | 1.008–4.747 | 0.048   |          | 2.886           | 1.235–6.743 | 0.014   |
| Sex                             |                     |          |          |          |                             |          |          |
| Male                            | Ref                 |          |          |          |                             |          |          |
| Female                          | 1.648               | 0.753–3.606 | 0.212   |          |                             |          |          |
| Smoking                         |                     |          |          |          |                             |          |          |
| Non-smoker                      | Ref                 |          |          |          |                             |          |          |
| Smoker                          | 1.250               | 0.547–2.856 | 0.597   |          |                             |          |          |
| Tumor history                   |                     |          |          |          |                             |          |          |
| No                              | Ref                 |          |          |          |                             |          |          |
| Yes                             | 0.704               | 0.212–2.341 |          |          |                             |          |          |
| Preoperative albumin level (g/L)| < 35                |          |          |          | > 35           |          |          |
| < 35                            | Ref                 |          |          | Ref      |                             |          |          |
| ≥ 35                            | 0.145               | 0.066–0.319 |          |          | 0.168           | 0.072–0.392 |          |
| Preoperative complications      |                     |          |          |          |                             |          |          |
| No                              | Ref                 |          |          |          |                             |          |          |
| Yes                             | 0.984               | 0.430–2.254 |          |          |                             |          |          |
| Surgical approach               |                     |          |          |          |                             |          |          |
| VATS                            | Ref                 |          |          |          |                             |          |          |
| Thoracotomy                     | 1.069               | 0.451–2.531 |          |          |                             |          |          |
| Surgical type                   |                     |          |          |          |                             |          |          |
|                                 | 0.036               |          |          | 0.015    |                             |          |          |

\(^a\) Variables with \(P\) value less than 0.05 were included in the multivariate analysis

HR, hazard ratio; CI, confidence interval; VATS, video-assisted thoracic surgery; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe; pT stage, pathological tumor stage; pN stage, pathological node stage
| Characteristic          | Univariate Analysis |                   |                   | Multivariate Analysis<sup>a</sup> |                   |
|------------------------|---------------------|-------------------|-------------------|-----------------------------------|-------------------|
|                        | HR | 95% CI       | P   | HR | 95% CI       | P   |
| Lobectomy              | Ref |             |     | Ref |             |     |
| Non-Lobectomy          | 2.312 | 1.056–5.059 | 3.136 | 1.243–7.907 |
| Adjuvant therapy       | 0.597 |             |     |     |             |     |
| None                   | Ref |             |     |     |             |     |
| Yes                    | 1.227 | 0.574–2.623 |     |     |             |     |
| Location               | 0.374 |             |     |     |             |     |
| Central                | Ref |             |     |     |             |     |
| Peripheral             | 0.696 | 0.312–1.549 |     |     |             |     |
| Morphology             |     | **0.005**   |     |     | **0.006**   |     |
| Regular                | Ref |             |     | Ref |             |     |
| Irregular              | 2.953 | 1.380–6.316 | 3.802 | 1.479–9.774 |
| Spiculation            | 0.581 |             |     |     |             |     |
| No                     | Ref |             |     |     |             |     |
| Yes                    | 0.761 | 0.288–2.010 |     |     |             |     |
| Lobulation             | 0.764 |             |     |     |             |     |
| No                     | Ref |             |     |     |             |     |
| Yes                    | 0.891 | 0.418–1.896 |     |     |             |     |
| Pleural indentation    | 0.544 |             |     |     |             |     |
| No                     | Ref |             |     |     |             |     |
| Yes                    | 0.640 | 0.151–2.713 |     |     |             |     |
| Obstructive pneumonia  | 0.699 |             |     |     |             |     |
| No                     | Ref |             |     |     |             |     |
| Yes                    | 0.789 | 0.237–2.628 |     |     |             |     |
| Cavity                 | 0.498 |             |     |     |             |     |

<sup>a</sup> Variables with <i>P</i> value less than 0.05 were included in the multivariate analysis

HR, hazard ratio; CI, confidence interval; VATS, video-assisted thoracic surgery; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe; pT stage, pathological tumor stage; pN stage, pathological node stage
### Characteristic

| Characteristic          | Univariate Analysis | Multivariate Analysis<sup>a</sup> |
|-------------------------|---------------------|-----------------------------------|
|                         | HR  | 95% CI       | P  | HR  | 95% CI       | P  |
| No                      | Ref |               |    | Ref |               |    |
| Yes                     | 1.514 | 0.456–5.031 | 0.793 | 1.514 | 0.456–5.031 |    |
| Site                    |     |               |    |     |               |    |
| RUL                     | Ref |               |    | Ref |               |    |
| RML                     | 1.067 | 0.215–5.299 |    | 1.067 | 0.215–5.299 |    |
| RLL                     | 1.517 | 0.294–7.838  |    | 1.517 | 0.294–7.838  |    |
| LUL                     | 2.187 | 0.424–11.291 |    | 2.187 | 0.424–11.291 |    |
| LLL                     | 1.448 | 0.312–6.714  |    | 1.448 | 0.312–6.714  |    |
| Grade                   |     |               |    |     |               |    |
| Poor differentiation    | Ref |               |    | Ref |               |    |
| Undifferentiation       | 0.045 | 0.002–85.872 | 0.422 | 0.045 | 0.002–85.872 |    |
| Pleural invasion        |     |               |    |     |               |    |
| No                      | Ref |               |    | Ref |               |    |
| Yes                     | 1.096 | 0.509–2.362  |    | 1.096 | 0.509–2.362  |    |
| Lymphovascular invasion |     |               |    |     |               |    |
| No                      | Ref |               |    | Ref |               |    |
| Yes                     | 1.217 | 0.366–4.047  |    | 1.217 | 0.366–4.047  |    |
| Perineural invasion     |     |               |    |     |               |    |
| No                      | Ref |               |    | Ref |               |    |
| Yes                     | 0.930 | 0.125–6.904  |    | 0.930 | 0.125–6.904  |    |
| Examined lymph nodes    |     |               |    |     |               |    |
| ≤ 34                    | Ref |               |    | Ref |               |    |
| > 34                    | 2.381 | 1.039–5.456  | 0.586–4.976 | 1.707 | 0.586–4.976  |    |

<sup>a</sup> Variables with <i>P</i> value less than 0.05 were included in the multivariate analysis.

HR, hazard ratio; CI, confidence interval; VATS, video-assisted thoracic surgery; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe; pT stage, pathological tumor stage; pN stage, pathological node stage
| Characteristic          | Univariate Analysis |                      | Multivariate Analysis<sup>a</sup> |                      |
|------------------------|---------------------|----------------------|-----------------------------------|----------------------|
|                        | HR                  | 95% CI               | P       | HR                  | 95% CI               | P       |
| Positive lymph nodes   |                     | < 0.001              | 0.702  |                     |                      |         |
| ≤ 4                    | Ref                 | Ref                 |         |                     |                      |         |
| > 4                    | 5.714               | 2.596–12.579         | 0.054  | 1.306               | 0.384–4.450          | 0.021   |
| pT stage               |                     |                      |         |                     |                      |         |
| 1                      | Ref                 | Ref                 |         |                     |                      |         |
| 2                      | 1.171               | 0.433–3.167          |         |                     |                      |         |
| 3                      | 1.319               | 0.403–4.324          |         |                     |                      |         |
| 4                      | 4.482               | 1.361–14.760         |         |                     |                      |         |
| pN stage               |                     |                      | 0.001   |                     |                      | 0.021   |
| 0                      | Ref                 | Ref                 |         |                     |                      |         |
| 1                      | 2.041               | 0.548–7.604          |         | 2.139               | 0.524–8.728          |         |
| 2                      | 5.985               | 2.219–16.141         |         | 5.643               | 1.637–19.447         |         |

<sup>a</sup> Variables with <i>P</i> value less than 0.05 were included in the multivariate analysis

HR, hazard ratio; CI, confidence interval; VATS, video-assisted thoracic surgery; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe; pT stage, pathological tumor stage; pN stage, pathological node stage

Univariate analysis of DFS demonstrated that albumin level ≥ 35, did not receive adjuvant therapy, PLNs ≤ 4 and pN0 stage had favorable impacts on DFS (Table 3). Multivariate analysis confirmed that albumin level ≥ 35, PLNs ≤ 4 and pN0 stage were independent favorable prognostic factors (Table 3). A nomogram was also developed, and it revealed that pN stage was also the strongest predictor, followed by preoperative albumin level and PLNs (Figure S2, online only). The C-index of the nomogram was 0.75 (95% CI: 0.68–0.82).
Table 3
Univariate and multivariate COX proportional hazard model analysis for disease-free survival.

| Characteristic                  | Univariate Analysis |                      | Multivariate Analysis<sup>a</sup> |                      |
|--------------------------------|---------------------|----------------------|-----------------------------------|----------------------|
|                                | HR                  | 95% CI               | P       | HR                  | 95% CI               | P       |
| Age                            | 0.102               |                      |        |                     |                      |        |
| ≤ 60                           | Ref                 |                      |        |                     |                      |        |
| > 60                           | 1.673               | 0.904–3.097          |        | 0.110               |                      |        |
| Sex                            | 0.110               |                      |        | 0.272               |                      |        |
| Female                         | 1.653               | 0.893–3.061          |        |                     |                      |        |
| Smoking                        | 0.272               |                      |        |                     |                      |        |
| Non-smoker                     | Ref                 |                      |        |                     |                      |        |
| Smoker                         | 1.427               | 0.756–2.693          |        |                     |                      |        |
| Tumor history                  | 0.450               |                      |        |                     |                      |        |
| No                             | Ref                 |                      |        |                     |                      |        |
| Yes                            | 0.698               | 0.275–1.773          |        |                     |                      |        |
| Preoperative albumin level (g/L)| < 0.001             |                      |        | 0.008               |                      |        |
| < 35                           | Ref                 |                      |        | Ref                 |                      |        |
| ≥ 35                           | 0.278               | 0.140–0.554          |        | 0.382               | 0.187–0.781          |        |
| Preoperative complications     | 0.503               |                      |        |                     |                      |        |
| No                             | Ref                 |                      |        |                     |                      |        |
| Yes                            | 1.243               | 0.658–2.347          |        |                     |                      |        |
| Surgical approach              | 0.496               |                      |        |                     |                      |        |
| VATS                           | Ref                 |                      |        |                     |                      |        |
| Thoracotomy                    | 1.278               | 0.631–2.590          |        |                     |                      |        |

<sup>a</sup> Variables with P value less than 0.05 were included in the multivariate analysis

HR, hazard ratio; CI, confidence interval; VATS, video-assisted thoracic surgery; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe; pT stage, pathological tumor stage; pN stage, pathological node stage
| Characteristic          | Univariate Analysis | Multivariate Analysis\(^a\) |
|------------------------|---------------------|-----------------------------|
|                        | HR  | 95% CI | \(P\) | HR  | 95% CI | \(P\) |
| Surgical type          | 0.267|        |       |      |        |       |
| Lobectomy              | Ref |        |       |      |        |       |
| Non-Lobectomy          | 1.457| 0.750–2.832| 0.007| 0.750–2.832| 1.457| 0.750–2.832| 0.063|
| Adjuvant therapy       | 0.007|        |       |      |        |       |
| None                   | Ref |        |       |      | Ref   |       |
| Yes                    | 2.393| 1.268–4.517| 1.853| 0.968–3.546| 1.853| 0.968–3.546| 0.063|
| Location               | 0.650|        |       |      |        |       |
| Central                | Ref |        |       |      |        |       |
| Peripheral             | 0.861| 0.450–1.645| 0.861| 0.450–1.645| 0.861| 0.450–1.645| 0.071|
| Morphology             | 0.071|        |       |      |        |       |
| Regular                | Ref |        |       |      |        |       |
| Irregular              | 1.796| 0.951–3.390| 1.796| 0.951–3.390| 1.796| 0.951–3.390|       |
| Spiculation            | 0.784|        |       |      |        |       |
| No                     | Ref |        |       |      |        |       |
| Yes                    | 0.906| 0.447–1.834| 0.906| 0.447–1.834| 0.906| 0.447–1.834|       |
| Lobulation             | 0.494|        |       |      |        |       |
| No                     | Ref |        |       |      |        |       |
| Yes                    | 0.814| 0.450–1.470| 0.814| 0.450–1.470| 0.814| 0.450–1.470|       |
| Pleural indentation    | 0.561|        |       |      |        |       |
| No                     | Ref |        |       |      |        |       |
| Yes                    | 0.737| 0.263–2.063| 0.737| 0.263–2.063| 0.737| 0.263–2.063| 0.241|
| Obstructive pneumonia  | 0.241|        |       |      |        |       |
| No                     | Ref |        |       |      |        |       |

\(^a\) Variables with \(P\) value less than 0.05 were included in the multivariate analysis

HR, hazard ratio; CI, confidence interval; VATS, video-assisted thoracic surgery; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe; pT stage, pathological tumor stage; pN stage, pathological node stage
| Characteristic         | Univariate Analysis |           |           |           | Multivariate Analysis<sup>a</sup> |         |         |         |
|-----------------------|---------------------|-----------|-----------|-----------|-----------------------------------|---------|---------|---------|
|                       | HR                  | 95% CI    | P         | HR        | 95% CI                            | P       |         |         |
| Yes                   | 1.552               | 0.745–3.236| 0.281     |           |                                   |         |         |         |
| Cavity                | 0.281               |            |           |           |                                   |         |         |         |
| No                    | Ref                 |           |           |           |                                   |         |         |         |
| Yes                   | 1.669               | 0.657–4.236|           |           |                                   |         |         |         |
| Site                  | 0.376               |            |           |           |                                   |         |         |         |
| RUL                   | Ref                 |           |           |           |                                   |         |         |         |
| RML                   | 2.160               | 0.478–9.754|           |           |                                   |         |         |         |
| RLL                   | 2.163               | 0.449–10.418|          |           |                                   |         |         |         |
| LUL                   | 4.071               | 0.879–18.849|          |           |                                   |         |         |         |
| LLL                   | 2.628               | 0.601–11.499|          |           |                                   |         |         |         |
| Grade                 | 0.310               |            |           |           |                                   |         |         |         |
| Poor differentiation  | Ref                 |           |           |           |                                   |         |         |         |
| Undifferentiation     | 0.046               | 0.005–17.781|          |           |                                   |         |         |         |
| Pleural invasion      | 0.399               |            |           |           |                                   |         |         |         |
| No                    | Ref                 |           |           |           |                                   |         |         |         |
| Yes                   | 1.293               | 0.712–2.348|           |           |                                   |         |         |         |
| Lymphovascular invasion| 0.167            |            |           |           |                                   |         |         |         |
| No                    | Ref                 |           |           |           |                                   |         |         |         |
| Yes                   | 1.769               | 0.788–3.973|           |           |                                   |         |         |         |
| Perineural invasion   | 0.991               |            |           |           |                                   |         |         |         |
| No                    | Ref                 |           |           |           |                                   |         |         |         |
| Yes                   | 1.008               | 0.243–4.183|           |           |                                   |         |         |         |

<sup>a</sup> Variables with P value less than 0.05 were included in the multivariate analysis

HR, hazard ratio; CI, confidence interval; VATS, video-assisted thoracic surgery; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; pT stage, pathological tumor stage; pN stage, pathological node stage
| Characteristic          | Univariate Analysis |                      | Multivariate Analysis |                      |
|------------------------|---------------------|----------------------|-----------------------|----------------------|
|                        | HR                  | 95% CI               | P                     | HR                  | 95% CI               | P                     |
| Examined lymph nodes   |                     |                      |                       |                     |                      |                       |
| ≤ 34                   | Ref                 |                      |                       |                     |                      |                       |
| > 34                   | 1.324               | 0.636–2.755          | 0.454                 |                     |                      |                       |
| Positive lymph nodes   |                     |                      |                       |                     |                      |                       |
| ≤ 4                    | Ref                 |                      |                       |                     |                      |                       |
| > 4                    | 4.431               | 2.339–8.392          | < 0.001               | 2.202               | 1.035–4.685          | 0.040                 |
| pT stage               |                     |                      |                       |                     |                      |                       |
| 1                      | Ref                 |                      |                       |                     |                      |                       |
| 2                      | 1.395               | 0.635–3.064          |                       |                     |                      |                       |
| 3                      | 1.791               | 0.727–4.409          |                       |                     |                      |                       |
| 4                      | 2.578               | 0.861–7.716          |                       |                     |                      |                       |
| pN stage               |                     |                      |                       |                     |                      |                       |
| 0                      | Ref                 |                      |                       |                     |                      |                       |
| 1                      | 2.329               | 0.898–6.040          |                       | 2.150               | 0.819–5.639          |                       |
| 2                      | 5.483               | 2.572–11.688         |                       | 3.272               | 1.380–7.758          |                       |

Variables with P value less than 0.05 were included in the multivariate analysis

Survival

In the LELC cohort, the median follow-up time was 55.6 months (range: 0.9-209.9 months). The 3-, 5- and 10-year OS rates were 92.1%, 83.1% and 76.1%, respectively. The 3-, 5- and 10-year DFS rates were 81.1%, 72.7% and 66.1%, respectively.
Before PSM, LELC had the best OS outcomes, followed by ADC and SCC, and ASC had the worst prognosis (LELC vs. ADC, \( P < 0.001 \); LELC vs. SCC, \( P < 0.001 \); LELC vs. ASC, \( P < 0.001 \); Fig. 1). After PSM, the 5-year OS rate of LELC was superior to those of ADC (84.7% vs. 73.0%; \( P = 0.024 \); Fig. 2A), SCC (83.0% vs. 58.9%; \( P < 0.001 \); Fig. 2B) and ASC (74.0% vs. 49.4%; \( P = 0.015 \); Fig. 2C).

**Discussion**

In the present study, the patient characteristics, survival and prognosis of resected stage I-IIIA LELC were retrospectively investigated. Our data demonstrated that LELC was more prevalent in younger patients and nonsmokers, with no obvious gender predisposition. LELC often presents as a peripheral irregular lung mass without typical imaging manifestations of lung cancer. Moreover, LELC is a poorly differentiated disease that lacks typical driver gene mutations and is positive for IHC indicators of squamous cell lineage. In further analyses, LELC had a better survival outcome than other common lung cancers both before and after PSM. Finally, multivariate analyses revealed that both early pN stage and preoperative albumin level \( \geq 35 \) were prognostic factors favoring OS and DFS.

In previous study, several clinical series suggested that LELC is often identified in younger nonsmokers (4, 12, 21), and there was no sexual predilection (4, 21, 22), which was akin to our findings. The abovementioned result suggested that unlike SCC, smoking might not be the main etiology of LELC (7, 12). Most tumors in our cohort were peripheral and had irregular morphology, echoing previous reports (23, 24), but conflicting with Qin et al.'s study (7). In line with our study, Chen et al. reviewed 42 LELC and 134 SCC cases and demonstrated that LELC lacks typical imaging manifestations of lung cancer such as cavity, calcification and vascular convergence (8). In our study, CT characteristics indicated that LELC had a lower extent of malignancies. We proposed that if the CT imaging presented as a peripheral irregular mass without typical manifestations of lung cancer, malignancies such as LELC should be suspected.

In our study, almost all the cases were diagnosed as poorly differentiated disease, which was in accordance with previous findings that LELC is characterized by poorly differentiated tumor cells with prominent nucleoli and large vesicular nuclei (24, 25). IHC data showed that our results were similar to those of Jiang et al, where the authors investigated 43 resected LELC patients and concluded that the tumor is typically positive for CK, CK5/6 and P63, which suggests squamous cell lineage, but is negative for TTF-1 and CK7 (26). Similar scenarios were also seen in Qin et al’s study (7) and Liang et al’s study (4). Owing to the similar morphology and IHC indicators, LELC is often misdiagnosed as SCC (27). Previous reports demonstrated that the presence of EBV in the nuclei of LELC tumor cells is critical for diagnosis. This can be confirmed by EBER in situ hybridization testing (8, 28). In our research, EBER was positive in 99.3% of all the tested patients. From our perspective, if the patient originated from an area with a prevalence of EBV infection and presented with a peripheral lung mass, EBER testing was preferred in the pretreatment examination.

In our study, molecular testing revealed that LELC lacked target agent-sensitive mutations (EGFR and ALK). In the study by Hong et al, the authors explored the genetic landscape of LELC and demonstrated a
low percentage of typical driver mutations, such as EGFR, BRAF and KRAS (29). The same scenarios were also observed in Wang et al’s study (30) and Chang et al’s study (31). The results above indicated that typical driver gene mutations, the main etiology of other common NSCLCs, might not play a critical role in the carcinogenesis of LELC (32). Furthermore, EGFR or ALK-targeted agents might not be suitable in the neoadjuvant or adjuvant therapy of advanced LELC.

Our data demonstrated that the OS of LELC was better than those of ADC, SCC and ASC both before and after PSM. Consistent with our results, He et al. assessed 62 LELC patients and suggested that LELC patients enjoy a higher level of survival when compared with ADC, SCC and large cell lung cancer (23). However, their conclusions might be impaired by the relatively small cohort size. In line with our findings, Chen et al. also reviewed 42 LELCs and 132 SCCs and concluded that LELC patients present longer progression-free survival than SCC patients. Nevertheless, OS, the gold standard of evaluating the efficacy of treatment modality, was lacking in their research. In the study by Zhou et al. the authors compared the OS of LELC with ADC, SCC and neuroendocrine tumors (6). Their data suggested that the OS of LELC is superior to those of SCC and neuroendocrine tumors but comparable to that of ADC (6). However, the PSM method was not used in their research, which may confer bias. One plausible explanation for the results observed in our study is that compared with other common NSCLCs, LELC was dominant in younger and nonsmoker patients. Smoking leads to more preoperative complications such as hypertension (33), coronary heart disease (34) and respiratory diseases (35), which may reduce life expectancy.

The multivariate analysis revealed that pN stage and preoperative albumin level were correlated with OS and DFS of resected stage I-IIIA LELC in our study. It is evidenced that nodal stage is an important influencing factor for LELC patient survival (8, 12, 14). For albumin level, Liang et al investigated the outcomes of 52 resected LELCs and demonstrated that the serum albumin level was an independent prognostic factor (4), which was similar to our findings. Surprisingly, pT stage, pleural invasion, lymphovascular invasion and tumor grade, four important prognosis predictors in other NSCLCs, were not correlated with OS and DFS in our study, suggesting that the natural course and biology of LELC might be different from those of other common NSCLCs.

To the best of our knowledge, this study represents the first comprehensive and concurrent analysis of resected stage I-IIIA LELC. In addition, the virtues of this study were that it included the largest cohort size and had a long-term follow-up. Additionally, the evaluation of a wide range of clinicopathological variables allowed us to better understand the demographic trends and prognosis of the disease.

However, our study also had some limitations. First, in the era of precision therapy, molecular indicators such as PD-1, PD-L1, KRAS and BRAF were not involved in our study. Second, despite the significant advantages provided by a larger case number than has ever been reported before, the cohort size was still limited. Finally, the retrospective nature may have contributed to selection bias. Further efforts on prospective data collection and incorporation of the abovementioned factors are warranted.
Conclusions

In conclusion, LELC is a rare distinct subtype of NSCLC, that prevails in young nonsmokers. It often presents as a peripheral lung mass without typical imaging manifestations of lung cancer. Pathological and IHC findings confirmed that LELC, a poorly differentiated diseases, lacked typical driver gene mutations and was positive for squamous cell lineage IHC indicators. Further analyses revealed that LELC had a better survival outcome than other common lung cancers.

Abbreviations

LELC, lymphoepithelioma-like carcinoma
NSCLC, non-small cell lung cancer
WHO, World Health Organization
EBV, Epstein-Barr virus
OS, overall survival
DFS, disease-free survival
ADC, adenocarcinoma
SCC, squamous cell carcinoma
ASC, adenosquamous carcinoma
IHC, immunohistochemistry
PSM, propensity score matching
SYSUCC, Sun Yat-sen University Cancer Center
AJCC, American Joint Committee on Cancer
ELNs, examined lymph nodes
PLNs, positive lymph nodes
C-index, concordance index
VATS, video-assisted thoracic surgery
AP, pemetrexed + platinum
TP, paclitaxel + platinum
GP, gemcitabine + platinum
5-FU, 5-Fluorouracil
cT stage, clinical tumor stage
cN stage, clinical node stage
cTNM stage, clinical tumor-node-metastasis stage
RUL, right upper lobe
RML, right middle lobe
RLL, right low lobe
LUL, left upper lobe
LLL, left low lobe
pT stage, pathological tumor stage
pN stage, pathological node stage
pTNM stage, pathological tumor-node-metastasis stage
TTF-1: thyroid transcription factor-1
EBER, Epstein-Bar virus-encoded RNA
EGFR, epidermal growth factor receptor
ALK, anaplastic lymphoma kinase
CI, confidence interval
HR, hazard ratio

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. All the included patients signed the informed consent. All methods involved in our article were performed in accordance with the Declaration of Helsinki.
Consent for publication
Not applicable

Availability of data and materials
The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn), with the approval RDD number as RDDA2020001729. The dataset generated for this study are available on request to the corresponding authors.

Competing interests
The authors declare that they have no competing interests.

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Author Contributions
Liu Li and Jing-Sheng Cai Conceived and designed this article. Rong-Rong Jiang, Xiao-Li Feng, Wen-Ting Zhu, Man-Xia Guo, Xiao-Juan Jiang and Xue-Li Tan collected and assembled the data. Xiao-Meng Dou and Jing-Sheng Cai analyzed the data. All authors read and approved the final manuscript.

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Figures

Figure 1

Kaplan-Meier estimates of overall survival in LELC versus other NSCLCs before PSM. LELC, lymphoepithelioma-like carcinoma; ADC, adenocarcinoma; SCC, squamous cell carcinoma; ASC, adenosquamous carcinoma; NSCLC, non-small cell lung cancer; PSM, propensity score matching.

Figure 2
Kaplan-Meier estimates of overall survival in LELC versus other NSCLCs after PSM. (A) LELC versus ADC, (B) LELC versus SCC and (C) LELC versus ASC. LELC, lymphoepithelioma-like carcinoma; ADC, adenocarcinoma; SCC, squamous cell carcinoma; ASC, adenosquamous carcinoma; NSCLC, non-small cell lung cancer; PSM, propensity score matching.

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