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

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Research Article

Keywords: lymphoepithelioma-like carcinoma, clinical characteristics, survival, prognosis

Posted Date: February 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-214608/v1

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 ≥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-IIIA 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-IIIA 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 $\chi 2$ 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	
Median (range)	55 (27–75)
≤ 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)
Other[a]	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[b]	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[c]	3 (4.0)
CT Characteristic	
Diameter (cm)	
Median (range)	4.2 (1.2–16.0)
Location	

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 ≤ 60, preoperative albumin level ≥ 35, lobectomy surgical type, regular morphology, ELNs ≤ 34, PLNs ≤ 4 and pN0 stage were favorable prognostic factors (Table 2). Multivariate analysis confirmed that age ≤ 60, preoperative albumin level ≥ 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			**0.048**			**0.014**
≤ 60	Ref			Ref		
> 60	2.188	1.008–4.747		2.886	1.235–6.743	
Sex			0.212			
Male	Ref					
Female	1.648	0.753–3.606				
Smoking			0.597			
Non-smoker	Ref					
Smoker	1.250	0.547–2.856				
Tumor history			0.567			
No	Ref					
Yes	0.704	0.212–2.341				
Preoperative albumin level (g/L)			**< 0.001**			**< 0.001**
< 35	Ref			Ref		
≥ 35	0.145	0.066–0.319		0.168	0.072–0.392	
Preoperative complications			0.970			
No	Ref					
Yes	0.984	0.430–2.254				
Surgical approach			0.169			
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[a]		
	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			

[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[a]		
	HR	95% CI	*P*	HR	95%CI	*P*
No	Ref					
Yes	1.514	0.456–5.031				
Site			0.793			
RUL	Ref					
RML	1.067	0.215–5.299				
RLL	1.517	0.294–7.838				
LUL	2.187	0.424–11.291				
LLL	1.448	0.312–6.714				
Grade			0.422			
Poor differentiation	Ref					
Undifferentiation	0.045	0.002–85.872				
Pleural invasion			0.815			
No	Ref					
Yes	1.096	0.509–2.362				
Lymphovascular invasion			0.749			
No	Ref					
Yes	1.217	0.366–4.047				
Perineural invasion			0.944			
No	Ref					
Yes	0.930	0.125–6.904				
Examined lymph nodes			**0.040**			0.218
≤ 34	Ref			Ref		
> 34	2.381	1.039–5.456		1.707	0.586–4.976	

[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[a]		
	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		1.306	0.384–4.450	
pT stage			0.054			
1	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	

[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

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[a]		
	HR	95% CI	*P*	HR	95%CI	*P*
Age			0.102			
≤ 60	Ref					
> 60	1.673	0.904–3.097				
Sex			0.110			
Male	Ref					
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				

[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[a]		
	HR	95% CI	*P*	HR	95%CI	*P*
Surgical type			0.267			
Lobectomy	Ref					
Non-Lobectomy	1.457	0.750–2.832				
Adjuvant therapy			**0.007**			0.063
None	Ref			Ref		
Yes	2.393	1.268–4.517		1.853	0.968–3.546	
Location			0.650			
Central	Ref					
Peripheral	0.861	0.450–1.645				
Morphology			0.071			
Regular	Ref					
Irregular	1.796	0.951–3.390				
Spiculation			0.784			
No	Ref					
Yes	0.906	0.447–1.834				
Lobulation			0.494			
No	Ref					
Yes	0.814	0.450–1.470				
Pleural indentation			0.561			
No	Ref					
Yes	0.737	0.263–2.063				
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[a]		
	HR	95% CI	*P*	HR	95%CI	*P*
Yes	1.552	0.745–3.236				
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				

[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[a]		
	HR	95% CI	*P*	HR	95%CI	*P*
Examined lymph nodes			0.454			
≤ 34	Ref					
> 34	1.324	0.636–2.755				
Positive lymph nodes			**< 0.001**			**0.040**
≤ 4	Ref			Ref		
> 4	4.431	2.339–8.392		2.202	1.035–4.685	
pT stage			0.341			
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			**< 0.001**			**0.026**
0	Ref			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	

[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

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 ≥ 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.

Funding

None

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.

Acknowledgement

We thank Elsevier (http://cn.webshop.elsevier.com) for its language editing assistance.

Disclosure

The authors have no conflict of interest to disclose.

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Figures

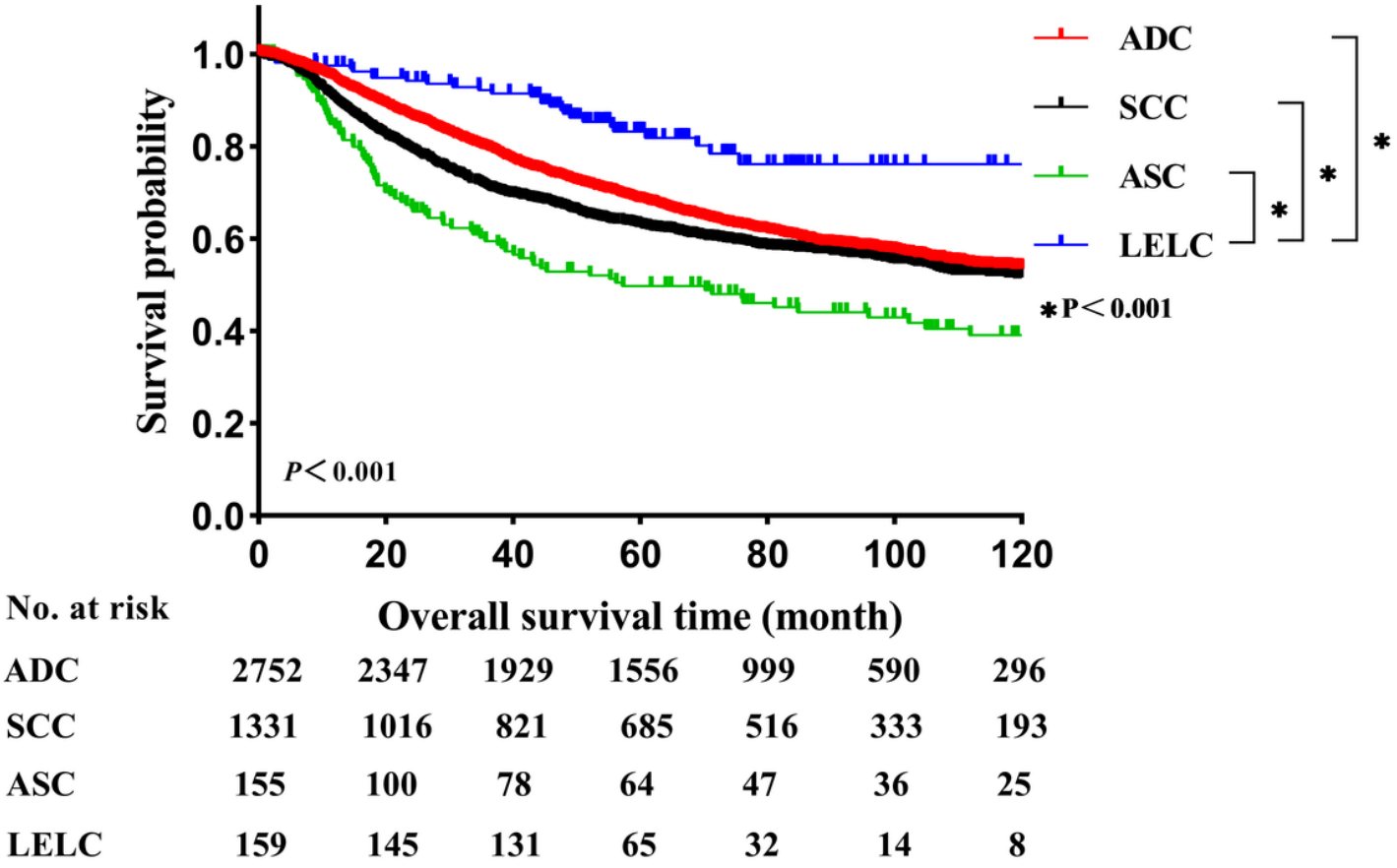

Figure 1

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.

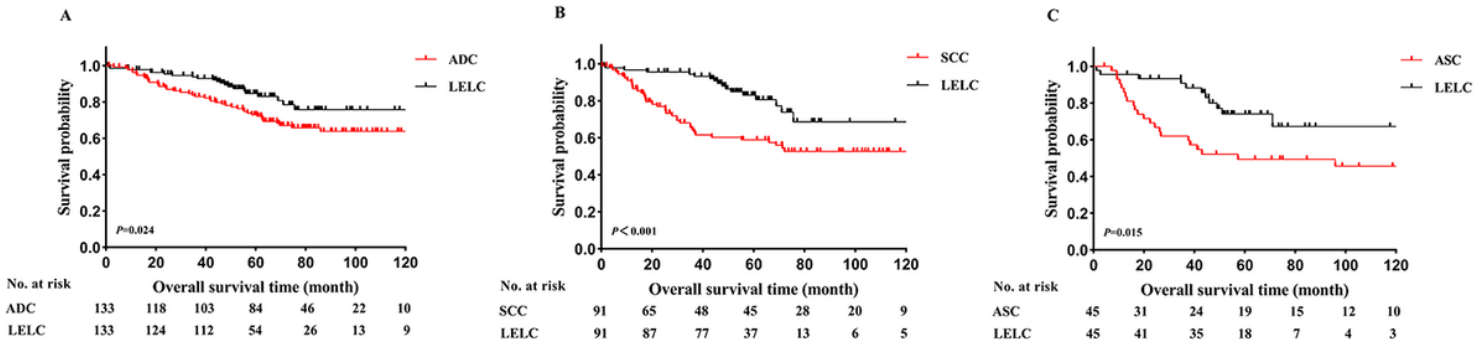

Figure 2

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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