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

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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 resected LELC, with the purpose of guiding clinical management for this rare tumor.

Methods Resected stage I-IIIA LELC, adenocarcinoma (ADC) and squamous cell carcinoma (SCC) 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 and 1,331 SCCs were included. LELC, dominated among younger patients and nonsmokers. 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 cancers (NSCLCs) 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, 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.

Background

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) and squamous cell carcinoma (SCC) from 2001 to 2016 were also included in this study.

All included cases fit the following criteria: (i) pathologically diagnosed as pathological stage I-IIIA disease and (ii) surgical resection was performed. The exclusion criteria were as follows: (i) previous or concurrent other primary cancers; (ii) age < 18 years old; (iii) underwent neoadjuvant therapy and (iiii) clinicopathological information was unavailable.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. All the included patients signed the informed consent. The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit (RDD) 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 and immunohistochemistry (IHC) data were retrieved from patients' medical records. Clinical variables included age, sex, smoking status, tumor history, preoperative albumin level, carcinoembryonic antigen (CEA) level, 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 and CEA level were dichotomized according to the lower limit of normal. Pathological characteristics included tumor site, tumor diameter, grade, examined lymph nodes (ELNs), positive lymph nodes (PLNs), T stage, N stage and TNM stage. ELNs and PLNs were also dichotomized according to the cutoff value determined by X-tile software. IHC features included creatine kinase (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. TNM staging was performed according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system [14].

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, T stage, N stage, TNM 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%) and CEA level (95%). Regarding CT features, most cases were classified as peripheral (73.6%) and irregular (78.0%) tumors. Almost all were diagnosed as poorly differentiated LELC (96.2%). Most patients had ELNs > 34 (83.0%). For 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 characteristics of included 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)
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)
CEA (ug/ml)	
< 5	151 (95.0)
≥ 5	8 (5.0)
Location	
Central	42 (26.4)
Peripheral	117 (73.6)
Morphology	

LELC, lymphoepithelioma-like carcinoma; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe; TTF-1: thyroid transcription factor-1; EBER, Epstein-Bar virus-encoded RNA; CK, creatine kinase; EGFR, epidermal growth factor receptor and ALK, anaplastic lymphoma kinase.

Clinical Characteristic	No. Patients (%)
Regular	35 (22.0)
Irregular	124 (78.0)
Site	
RUL	18 (11.3)
RML	41 (25.8)
RLL	28 (17.6)
LUL	21 (13.2)
LLL	51 (32.1)
Surgical type	
Lobectomy	125 (78.6)
Wedge resection	8 (5.0)
Bilobectomy	10 (16.3)
Pneumonectomy	16 (10.1)
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)
Examined lymph nodes	
Median (range)	22 (1–73)
≤ 34	27 (17.0)
> 34	132 (83.0)
Positive lymph nodes	

LELC, lymphoepithelioma-like carcinoma; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe; TTF-1: thyroid transcription factor-1; EBER, Epstein-Bar virus-encoded RNA; CK, creatine kinase; EGFR, epidermal growth factor receptor and ALK, anaplastic lymphoma kinase.

Clinical Characteristic	No. Patients (%)
Median (range)	1 (0–16)
≤ 4	137 (86.2)
> 4	22 (13.8)
T stage	
1	45 (28.3)
2	75 (47.2)
3	28 (17.6)
4	11 (6.9)
N stage	
0	75 (47.2)
1	31 (19.5)
2	53 (33.3)
TNM stage	
I	52 (32.7)
II	41 (25.8)
III	66 (41.5)
Adjuvant therapy	
No	79 (49.7)
Yes	80 (50.3)
CK (n = 73)	
Positive	70 (95.9)
Negative	3 (4.1)
CK 5/6 (n = 136)	
Positive	135 (99.3)
Negative	1 (0.7)

LELC, lymphoepithelioma-like carcinoma; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe; TTF-1: thyroid transcription factor-1; EBER, Epstein-Bar virus-encoded RNA; CK, creatine kinase; EGFR, epidermal growth factor receptor and ALK, anaplastic lymphoma kinase.

Clinical Characteristic	No. Patients (%)
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)
Wild	89 (97.8)

LELC, lymphoepithelioma-like carcinoma; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe; TTF-1: thyroid transcription factor-1; EBER, Epstein-Bar virus-encoded RNA; CK, creatine kinase; EGFR, epidermal growth factor receptor and ALK, anaplastic lymphoma kinase.

A total of 2,757 ADC cases and 1,331 SCC 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) and Table S2 (SCC vs. LELC). After PSM, all covariates were well balanced among these pairs.

Cox regression analysis and nomogram

Regarding OS, a univariate analysis revealed that age ≤ 60, preoperative albumin level ≥ 35, lobectomy surgical type, regular morphology, ELNs ≤ 34, PLNs ≤ 4 and N0 stage were favorable prognostic factors (Table 2). Multivariate analysis confirmed that age ≤ 60, preoperative albumin level ≥ 35, lobectomy surgical type, regular morphology and N0 stage were independent predictors favoring OS (Table 2). A

nomogram, formulated based on the statistically significant factors from the multivariate analysis, showed that N stage was the strongest predictor, followed by preoperative albumin level and tumor morphology (Figure S1). 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	
CEA (ug/ml)			0.362			
< 5	Ref					
≥ 5	0.980	0.612–1.952				
Location			0.374			
Central	Ref					
Peripheral	0.696	0.312–1.549				
Morphology			**0.005**			**0.006**

[a] Variables with *P* value less than 0.05 were included in the multivariate analysis

HR, hazard ratio; CI, confidence interval; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe

Characteristic	Univariate Analysis			Multivariate Analysis[a]		
	HR	95% CI	*P*	HR	95%CI	*P*
Regular	Ref			Ref		
Irregular	2.953	1.380–6.316		3.802	1.479–9.774	
Surgical type			**0.036**			**0.015**
Lobectomy	Ref			Ref		
Non-Lobectomy	2.312	1.056–5.059		3.136	1.243–7.907	
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				
Examined lymph nodes			**0.040**			0.218
≤ 34	Ref			Ref		
> 34	2.381	1.039–5.456		1.707	0.586–4.976	
Positive lymph nodes			**< 0.001**			0.702
≤ 4	Ref			Ref		
> 4	5.714	2.596–12.579		1.306	0.384–4.450	
T stage			0.054			
1	Ref					

[a] Variables with *P* value less than 0.05 were included in the multivariate analysis

HR, hazard ratio; CI, confidence interval; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe

Characteristic	Univariate Analysis			Multivariate Analysis[a]		
	HR	95% CI	*P*	HR	95%CI	*P*
2	1.171	0.433–3.167				
3	1.319	0.403–4.324				
4	4.482	1.361–14.760				
N 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	
Adjuvant therapy			0.597			
No	Ref					
Yes	1.227	0.574–2.623				
[a] Variables with *P* value less than 0.05 were included in the multivariate analysis						
HR, hazard ratio; CI, confidence interval; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe						

Univariate analysis of DFS demonstrated that albumin level ≥ 35, did not perform adjuvant therapy, PLNs ≤ 4 and N0 stage had favorable impacts on DFS (Table 3). Multivariate analysis confirmed that albumin level ≥ 35, PLNs ≤ 4 and N0 stage were independent favorable prognostic factors (Table 3). A nomogram was also developed, and it revealed that N stage was also the strongest predictor, followed by preoperative albumin level and PLNs (Figure S2). 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	
CEA (ug/ml)			0.482			
< 5	Ref					
≥ 5	0.861	0.775–1.414				
Location			0.650			
Central	Ref					
Peripheral	0.861	0.450–1.645				
Morphology			0.071			

[a] Variables with *P* value less than 0.05 were included in the multivariate analysis

HR, hazard ratio; CI, confidence interval; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe

Characteristic	Univariate Analysis			Multivariate Analysis[a]		
	HR	95% CI	*P*	HR	95%CI	*P*
Regular	Ref					
Irregular	1.796	0.951–3.390				
Surgical type			0.267			
Lobectomy	Ref					
Non-Lobectomy	1.457	0.750–2.832				
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				
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	
T stage			0.341			

[a] Variables with *P* value less than 0.05 were included in the multivariate analysis

HR, hazard ratio; CI, confidence interval; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe

Characteristic	Univariate Analysis			Multivariate Analysis[a]		
	HR	95% CI	*P*	HR	95%CI	*P*
1	Ref					
2	1.395	0.635–3.064				
3	1.791	0.727–4.409				
4	2.578	0.861–7.716				
N 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	
Adjuvant therapy			**0.007**			0.063
No	Ref			Ref		
Yes	2.393	1.268–4.517		1.853	0.968–3.546	

[a] Variables with *P* value less than 0.05 were included in the multivariate analysis

HR, hazard ratio; CI, confidence interval; RUL, right upper lobe; RML, right middle lobe; RLL, right low lobe; LUL, left upper lobe; LLL, left low lobe

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 (LELC vs. ADC, $P < 0.001$; LELC vs. SCC, $P < 0.001$; 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) and SCC (83.0% vs. 58.9%; $P < 0.001$; Fig. 2B).

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. In addition, 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 N 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 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 and SCC 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], which was contradicted with ours. 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 might reduce life expectancy.

The multivariate analysis revealed that N stage and preoperative albumin level were correlated with both OS and DFS 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, T stage and tumor grade, two 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 was also a poorly differentiated disease that 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 ADC and SCC.

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

RDD, Research Data Deposit

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

RUL, right upper lobe

RML, right middle lobe

RLL, right low lobe

LUL, left upper lobe

LLL, left low lobe

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

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. All the included patients signed the informed consent.

Consent for publication

Not application

Availability of data and materials

The dataset supporting the conclusions of this article is available in the Research Data Deposit (RDD) public platform (www.researchdata.org.cn), with the approval RDD number as RDDA2020001729.

Competing interests

The authors have no conflicts of interest to declare.

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None

Authors' contributions

(I) Conception and design: Liu Li and Xiao-Meng Dou
(II) Administrative support: Liu Li
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Figures

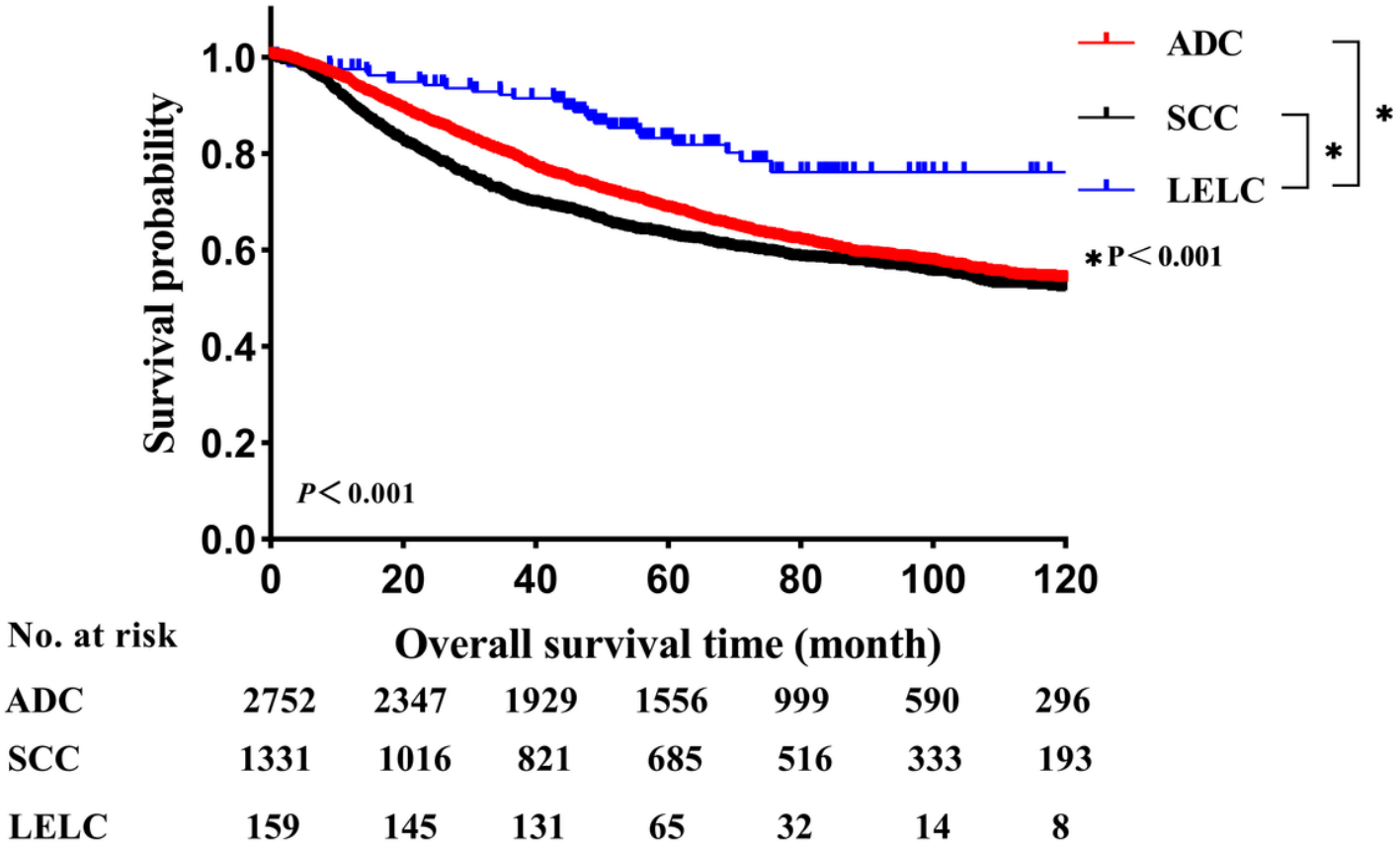

Figure 1

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

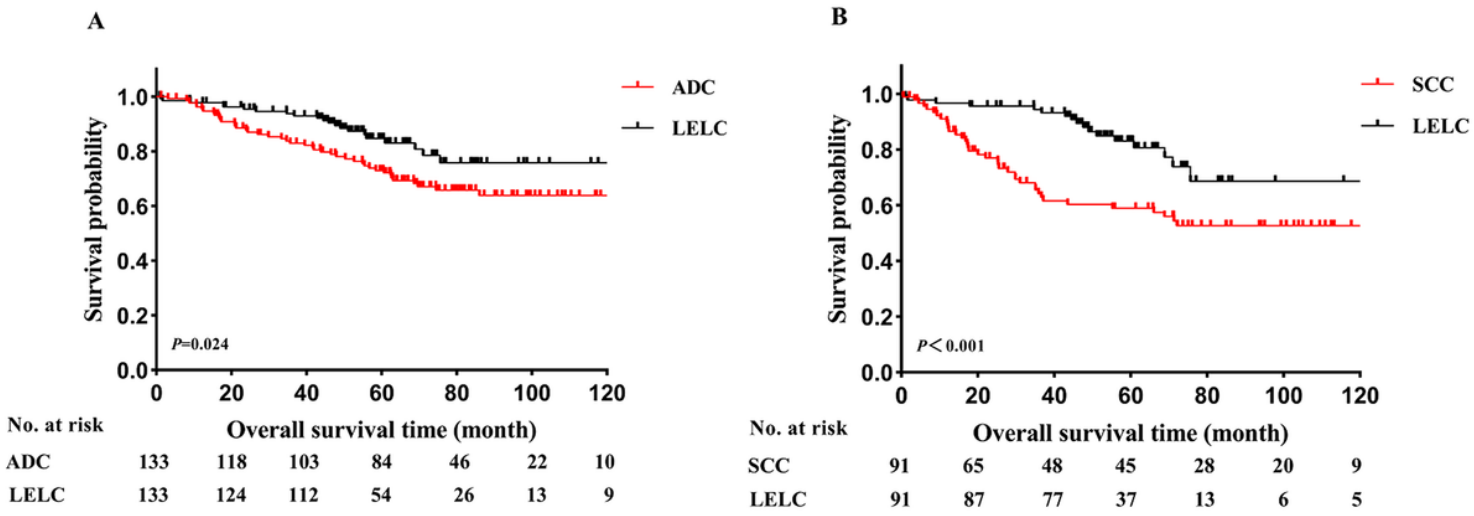

Figure 2

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

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