Original Article

Treatment options and prognosis of patients with lung squamous cell cancer in situ: a comparative study of lung adenocarcinoma in situ and stage IA lung squamous cell cancer

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Background: Lung squamous cell cancer in situ (LSCIS) is preinvasive squamous tumor and generally overlooked as a potential subtype of pathological and clinical significance, which has seldom been investigated systematically. This study sought to explore the clinical features, prognostic factors, and optimal treatments for LSCIS patients.

Methods: Patients diagnosed with LSCIS (n=449), lung adenocarcinoma in situ (LAIS; n=1,132), stage IA lung squamous cell cancer (LSQCC; n=22,289) and stage IA lung adenocarcinoma (LUAD; n=68,523) were identified in the Surveillance Epidemiology and End Results (SEER) database. Additionally, 512 patients from the Shanghai Pulmonary Hospital diagnosed with LSCIS (n=34), LAIS (n=248), stage IA LSQCC (n=118) and stage IA LUAD (n=112) were included in the study. Kaplan-Meier survival curves were constructed, and Cox proportional hazards regression analyses were performed to examine the overall survival (OS), lung cancer-specific survival (LCSS), and progression-free survival (PFS) of the patients.

Results: The univariate and multivariate analyses showed the patients with LSCIS had significantly worse survival than those with LAIS. Although, the univariate analysis revealed that the LSCIS patients had significantly worse OS and LCSS than the stage IA LSQCC patients, the multivariate analyses showed that the prognosis of the LSCIS was similar to that of the stage IA LSQCC in the SEER cohort. The prognosis of the LSCIS was similar to that of the stage IA LSQCC in the Shanghai Pulmonary Hospital cohort. The univariate and multivariate analyses showed that age (>70 years) and chemotherapy were negative prognostic factors, and surgery was a favorable prognostic factor for the LSCIS patients. The survival of the LSCIS patients who underwent local tumor destruction or excision was similar to that of those who did not receive surgery. Lobectomy was the surgical procedure associated with the highest OS and LCSS in LSCIS patients.

Conclusions: The survivals of the LSCIS were similar to those of the stage IA LSQCC, but significantly worse than those of the LAIS. Surgery was an independent favorable prognostic factor for the LSCIS patients. Lobectomy was a superior choice of surgical procedure, and significantly improved the current outcomes of the LSCIS patients.

Keywords: Lung squamous cell cancer in situ (LSCIS); prognosis; treatment; Surveillance Epidemiology and End Results (SEER)

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Introduction

Lung squamous cell cancer in situ (LSCIS) was formally defined for the first time in the 3rd edition of the World Health Organization (WHO) histology classification of lung tumors, which was published in 2001 (1). Unlike lung adenocarcinoma in situ (LAIS), LSCIS has seldom been systematically investigated and has largely been ignored as a potential subtype of pathological and clinical significance. LAIS is well defined as a neoplasm with dimensions of <3 cm, a lepidic pattern, and a lack of invasion, whereas LSCIS, while thought to be another preinvasive type of non-small cell lung cancer (NSCLC), without any involvement of the basement membrane or metastasis, is not defined by any size criteria for the superficial lesion (2,3), and it can sometimes be difficult to differentiate from high-grade dysplasia even for experienced pathologists (4).

Low-dose computed tomography (LDCT) of the chest has been widely used for early lung cancer screenings for decades (5), and the National Lung Screening Trial has shown that screening the lungs for early parenchymal lesions with LDCT can reduce lung cancer mortality by 20% among high-risk individuals (6). However, as many SCISs arise in the central airways and are initially confined to the epithelial lining of the bronchial wall, LDCT is not an appropriate modality for the detection of such lesions and the clinical features and outcomes of the patients with LSCIS have seldom been investigated because of its relative infrequency.

A few studies have investigated the clinical features and prognosis of LSCIS located in the central airways, which has been treated with local destruction or excision (LDE) using a bronchoscope (7-9). However, the results of these studies showed that LDE might be inadequate in the treatment of LSCIS (10). In addition, because most of these analyses were based on a small number of patients, valid conclusions cannot be drawn.

In the new WHO histology classification published in 2021, LSCIS is defined as a squamous precursor lesion rather than a preinvasive lesion (3), which will affect the treatment strategy for LSCIS. However, very few studies have evaluated the prognosis of LSCIS patients who were treated with various treatments, except LDE. Thus, to improve the management of LSCIS, it is necessary to analyze the clinical features, prognostic factors of survival, and treatment choices for patients with LSCIS.

In this study, we sought to explore the clinical features, prognostic factors, and treatment choices for patients with LSCIS based on a large sample of patients with LSCIS from the population-based Surveillance Epidemiology and End Results (SEER) database and from the Shanghai Pulmonary Hospital in China with a particular focus on the surgical procedures. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-243/rc).

Highlight box

Key findings

- We determined the prognosis characteristics of and preferred treatment for patients with lung squamous cell cancer in situ (LSCIS).

What is known and what is new?

- We identified the prognosis characteristics of LSCIS compared to lung adenocarcinoma in situ and stage IA lung squamous cell cancer. We also found that surgery was an independent favorable prognostic factor of LSCIS.
- We investigated the survival of patients according to the different surgery procedures and found that lobectomy was the most favorable surgical procedure for LSCIS.

What is the implication, and what should change now?

- Our findings are particularly important in the management of LSCIS. We suggest that lobectomy should be the preferred choice of surgical procedure.

Methods

Patient selection

SEER is an authoritative source for cancer statistics in the United States (U.S.). The SEER program provides information on cancer statistics in an effort to reduce the cancer burden among the U.S. population. The data of patients histologically diagnosed with LSCIS, stage IA lung squamous cell cancer (LSQCC), stage IA lung adenocarcinoma (LUAD), or LAIS between 2000 and 2019 were extracted from the SEER database. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had only been diagnosed by autopsy or death certificate; (II) had at least 1 prior lung cancer; and/or (III) had missing information concerning the tumor therapy.

We also followed 512 patients who were diagnosed with LSCIS, stage IA LSQCC, stage IA LUAD, or LAIS and treated at the Shanghai Pulmonary Hospital from 2015 to June 2022. If LSCIS progressing and recurrence

after treated with bronchoscopy, surgical resection would be performed for patients in the Shanghai Pulmonary Hospital cohort. The pathologic diagnosis was confirmed after a surgical resection according to the 2021 WHO's classification. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Shanghai Pulmonary Hospital Institutional Review Board (No. KY2020-1), and the requirement of individual consent for this retrospective analysis was waived.

Study variables

For the SEER cohort, the following clinical information was extracted: age, gender, race/ethnicity, location (upper lobe, lower lobe, middle lobe, main bronchus, or unspecific), tumor staging according to the 8th American Joint Committee on Cancer tumor, node, metastasis (TNM) stage for lung cancer, histologic type, surgery, radiation, reason of non-surgery and chemotherapy. In the Shanghai Pulmonary Hospital cohort, data on patient gender, age, TNM stage, chemotherapy, radiation, and surgical procedures were retrospectively collected.

To capture the survival or disease progression status and survival time, we performed follow-up by examining the patients' medical records or telephone calls. The end date of follow-up for the SEER cohort was December 31, 2019, and that for the Shanghai Pulmonary Hospital cohort was September 1, 2022. Progression-free survival (PFS) was defined as the time from lung cancer diagnosis to the date of disease progression, recurrence, death, or censor. Overall survival (OS) was defined as the time from surgery until death as a result of any cause, and lung cancer-specific survival (LCSS) was defined as the interval from diagnosis until death as a result of lung cancer according to the specific codes provided by SEER.

Statistical analysis

We used descriptive statistics to summarize the baseline characteristics of the patients. The categorical variables were analyzed by the Chi-squared test and Fisher's exact test. OS, PFS and LCSS survival analyses were performed using the Kaplan-Meier method with the log-rank test. The independent prognostic factors of OS, PFS and LCSS were determined using univariate and multivariate Cox proportional hazards regression models. A full Cox proportional hazards model that included all of the best subsets of predictors determined by a univariate Cox proportional hazards regression model was applied to adjust the baseline variables in the comparison.

A 2-sided P value <0.05 was considered statistically significant. Data analyses were performed using SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA) and the survminer (11) and survival (12) packages of R (13).

Results

Basic characteristics of the patients

A total of 92,393 lung cancer patients from the SEER database were included in the analysis. Of these, the LSCIS, LAIS, LSQCC, and LUAD histology was detected in 449, 1,132, 22,289 and 68,523 patients, respectively (*Table 1*). In the Shanghai Pulmonary Hospital cohort, 512 patients were enrolled, among whom 34, 118, 248 and 112 patients were diagnosed with LSCIS, stage IA LSQCC, LAIS, and stage IA LUAD respectively (*Table 1*). There were more males and more tumors located in the main bronchus in the LSCIS data set than the LAIS, stage IA LSQCC and stage IA LUAD data sets. No tumors in the main bronchus were observed in the patients with LAIS.

In the SEER cohort, only 24.3% of the LSCIS patients underwent surgery, while 68.8% of the LAIS patients, 65.6% of the stage IA LSQCC patients and 78.7% of the stage IA LUAD patients underwent surgery. Surgery was performed for all the patients in the Shanghai Pulmonary Hospital cohort. There were 17.1% of LSCIS patients received chemotherapy, but only 7.3% of the stage IA LUAD patients, 5.6% of the stage IA LSQCC patients and 2.7% of the LAIS patients treated with chemotherapy; 23.6% of the LAIS patients and 28.5% of the stage IA LSQCC patients received radiotherapy, while 16.3% of the stage IA LUAD patients and 15.9% of the LAIS patients received that.

Further analyses were performed in the LSCIS patients in the SEER cohort (Table S1). Of these patients in the SEER cohort, 340 patients treated without surgery and 109 patients underwent resection. In the non-surgery group in the SEER cohort, 45 patients had been recommended to receive surgery. The LSCIS patients receiving surgery were younger than those treated without surgery. In the non-surgery group, 21.8% and 29.1% of the LSCIS patients treated with chemotherapy and radiotherapy, while only 2.8% and 6.4% of the LSCIS patients treated with those in the surgery group.

Table 1 Demographics and clinicopathologic characteristics of the patients with LSCIS, LAIS, stage IA LSQCC and stage IA LUAD in the SEER cohort and the Shanghai Pulmonary Hospital cohort

Characteristics	SEER cohort					Shanghai Pulmonary Hospital cohort				
	LSCIS, N (%)	LAIS, N (%)	LSQCC, N (%)	LUAD, N (%)	P	LSCIS, N (%)	LAIS, N (%)	LSQCC, N (%)	LUAD, N (%)	P
Total	449 (100.0)	1,132 (100.0)	22,289 (100.0)	68,523 (100.0)		34 (100.0)	248 (100.0)	118 (100.0)	112 (100.0)	
Age (years)					<0.001					<0.001
≤60	97 (21.6)	175 (15.5)	2,359 (10.6)	13,813 (20.2)		17 (50.0)	193 (77.8)	43 (36.4)	29 (25.9)	
>60 to 70	154 (34.3)	379 (33.5)	7,309 (32.8)	23,099 (33.7)		12 (35.3)	46 (18.5)	44 (37.3)	44 (39.3)	
>70	198 (44.1)	578 (51.1)	12,621 (56.6)	31,611 (46.1)		5 (14.7)	9 (3.6)	31 (26.3)	39 (34.8)	
Gender					<0.001					<0.001
Male	317 (70.6)	351 (31.0)	12,249 (55.0)	27,676 (40.4)		31 (91.2)	62 (25.0)	100 (84.7)	47 (42.0)	
Female	132 (29.4)	781 (69.0)	10,040 (45.0)	40,847 (59.6)		3 (8.8)	186 (75.0)	18 (15.3)	65 (58.0)	
Race					0.001					1.000
White	371 (82.6)	932 (82.3)	19,682 (88.3)	57,902 (84.5)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Black	55 (12.2)	89 (7.9)	1,765 (7.9)	5,464 (8.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Asian/other	23 (5.1)	111 (9.8)	842 (3.8)	5,157 (7.5)		34 (100.0)	248 (100.0)	118 (100.0)	112 (100.0)	
Primary site					<0.001					<0.001
Main bronchus	46 (10.2)	0 (0.0)	78 (0.3)	247 (0.4)		1 (2.9)	0 (0.0)	3 (2.5)	0 (0.0)	
Upper lobe	237 (52.8)	650 (57.4)	13,544 (60.8)	41,103 (60.0)		25 (73.5)	161 (64.9)	49 (41.5)	68 (60.7)	
Middle lobe	23 (5.1)	68 (6.0)	993 (4.5)	4,472 (6.5)		1 (2.9)	20 (8.1)	13 (11.0)	10 (8.9)	
Lower lobe	120 (26.7)	374 (33.0)	7,314 (32.8)	21,266 (31.0)		7 (20.6)	67 (27.0)	53 (44.9)	34 (30.4)	
Unspecific	23 (5.1)	40 (3.5)	360 (1.6)	1,435 (2.1)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Surgery					<0.001					1.000
No	340 (75.7)	353 (31.2)	7,673 (34.4)	14,626 (21.3)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Yes	109 (24.3)	779 (68.8)	14,616 (65.6)	53,897 (78.7)		34 (100.0)	248 (100.0)	118 (100.0)	112 (100.0)	
Chemotherapy					<0.001					<0.001
No	372 (82.9)	1,102 (97.3)	21,038 (94.4)	63,519 (92.7)		25 (73.5)	248 (100.0)	76 (64.4)	85 (75.9)	
Yes	77 (17.1)	30 (2.7)	1251 (5.6)	5,004 (7.3)		9 (26.5)	0 (0.0)	42 (35.6)	27 (24.1)	
Radiotherapy					<0.001					<0.001
No	343 (76.4)	952 (84.1)	15,942 (71.5)	57,358 (83.7)		33 (97.1)	248 (100.0)	111 (94.1)	108 (96.4)	
Yes	106 (23.6)	180 (15.9)	6,347 (28.5)	11,165 (16.3)		1 (2.9)	0 (0.0)	7 (5.9)	4 (3.6)	

LSCIS, lung squamous cell cancer in situ; LAIS, lung adenocarcinoma in situ; LSQCC, lung squamous cell cancer; LUAD, lung adenocarcinoma; SEER, Surveillance Epidemiology and End Results.

LSCIS patients having significantly worse survival than LAIS patients

In the SEER cohort, the survival analysis by the log-rank test showed that the OS [hazards ratio (HR): 0.210; 95% confidence interval (CI): 0.177–0.249; P<0.001; *Figure 1A*] and LCSS (HR: 0.154; 95% CI: 0.121–0.197; P<0.001; *Figure 1B*) of the LSCIS patients were significantly worse than those of the LAIS patients. The survival analyses were also performed in the non-surgery group (OS HR: 0.373; 95% CI: 0.299–0.466; P<0.001; Figure S1A; LCSS HR: 0.296; 95% CI: 0.218–0.401; P<0.001; Figure S1B)

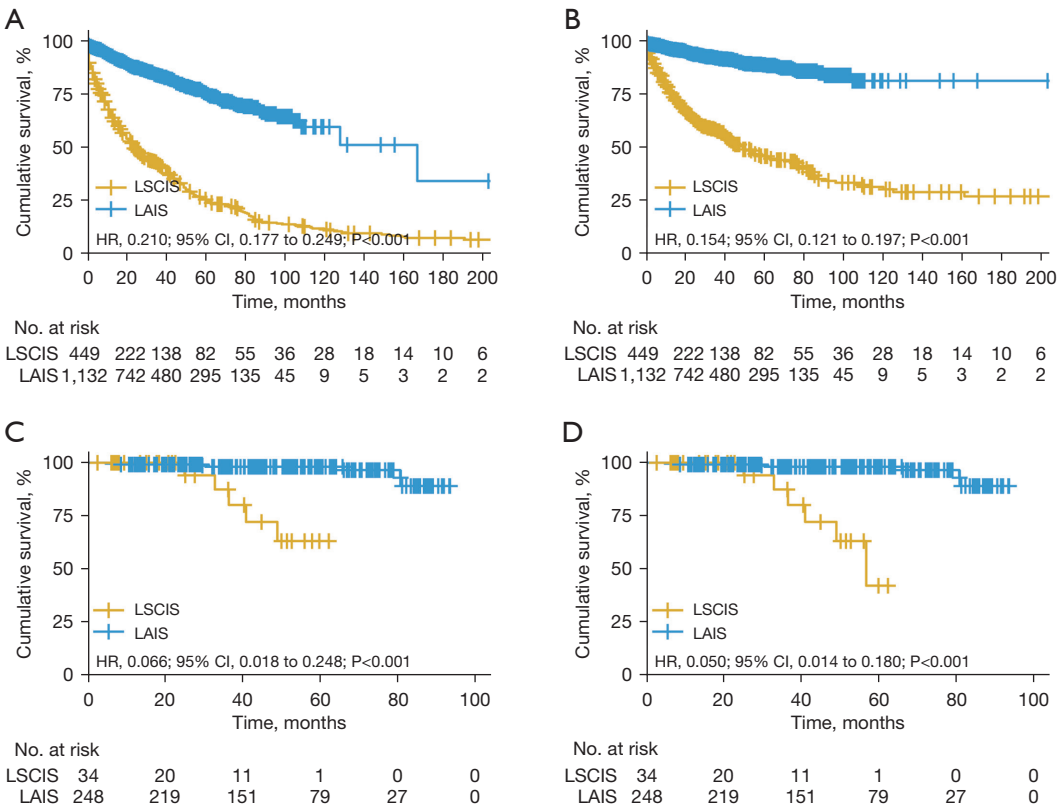

Figure 1 Kaplan-Meier curves of the patients with LSCIS and LAIS. (A,B) OS and LCSS of the patients with LSCIS and LAIS in the SEER cohort; (C,D) OS and PFS of the patients with LSCIS, and LAIS in the Shanghai Pulmonary Hospital cohort. LSCIS, lung squamous cell carcinoma in situ; LAIS, lung adenocarcinoma in situ; OS, overall survival; LCSS, lung cancer-specific survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

and the surgery group (OS HR: 0.256; 95% CI: 0.189–0.348; P<0.001; Figure S1C; LCSS HR: 0.196; 95% CI: 0.123–0.314; P<0.001; Figure S1D) in the LSCIS and LAIS patients in the SEER cohort, and the same trends were observed. In the Shanghai Pulmonary Hospital cohort, the LAIS patients had significantly better survival rates than the LSCIS patients in terms of both OS (HR: 0.066; 95% CI: 0.018–0.248; P<0.001; *Figure 1C*) and PFS (HR: 0.050; 95% CI: 0.014–0.180; P<0.001; *Figure 1D*). Moreover, in order to furtherly investigate the impact of histology on prognosis of lung cancer, survival analysis was performed between stage IA LSQCC and stage IA LUAD. The results showed that stage IA LUAD was associated with significantly better OS (HR: 0.596; 95% CI: 0.584–0.608; P<0.001; Figure S2A) and LCSS (HR: 0.662; 95% CI: 0.643–0.680; P<0.001; Figure S2B) in the SEER cohort and significantly longer OS (HR: 0.491; 95% CI: 0.245–0.983; P=0.045; Figure S2C) and PFS (HR: 0.519; 95% CI: 0.274–0.982; P=0.044; Figure S2D) in the Shanghai Pulmonary Hospital cohort compared with stage IA LSQCC.

After the adjustment of the confounders in the SEER cohort, the multivariate Cox regression model analysis also showed that the survival of the LSCIS patients was significantly worse than that of the LAIS patients in terms of both OS (HR: 0.353; 95% CI: 0.297–0.419; P<0.001; *Table 2*) and LCSS (HR: 0.287; 95% CI: 0.224–0.367; P<0.001; *Table 2*). In the Shanghai Pulmonary Hospital cohort, the LAIS patients had significantly better OS (HR: 0.148; 95% CI: 0.040–0.551; P=0.004; *Table 2*) and PFS (HR: 0.181; 95% CI: 0.053–0.617; P=0.006; *Table 2*) than the LSCIS patients. In the SEER cohort, LSCIS was associated with significantly worse OS (HR, 0.649; 95% CI: 0.582–0.723; P<0.001; *Table 2*) and LCSS (HR, 0.701; 95% CI: 0.608–0.808; P<0.001; *Table 2*) compared with stage IA LUAD. LSCIS patients had significant worse OS (HR, 0.236; 95% CI: 0.074–0.757; P=0.015; *Table 2*) than stage

Table 2 Multivariate Cox analyses of OS, LCSS, and PFS for patients with LSCIS, LAIS, stage IA LSQCC and stage IA LUAD in the SEER cohort and the Shanghai Pulmonary Hospital cohort

Characteristics	SEER cohort				Shanghai Pulmonary Hospital cohort			
	OS		LCSS		OS		PFS	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (years)								
≤60	1.000		1.000		1.000		1.000	
>60 to 70	1.458 (1.415–1.503)	<0.001	1.285 (1.236–1.336)	<0.001	1.924 (0.883–4.193)	0.100	1.562 (0.760–3.212)	0.225
>70	2.224 (2.161–2.289)	<0.001	1.674 (1.612–1.738)	<0.001	3.589 (1.478–8.715)	0.005	2.735 (1.209–6.189)	0.016
Gender								
Male	1.000		1.000		1.000		1.000	
Female	0.726 (0.713–0.740)	<0.001	0.742 (0.724–0.761)	<0.001	1.554 (0.739–3.271)	0.245	0.673 (0.419–1.755)	0.673
Race								
White	1.000		1.000					
Black	1.052 (1.017–1.087)	0.003	1.084 (1.037–1.134)	<0.001				
Asian/other	0.734 (0.704–0.766)	<0.001	0.799 (0.756–0.844)	<0.001				
Primary site								
Main bronchus	1.000		1.000		1.000		1.000	
Upper lobe	1.240 (1.070–1.437)	0.004	1.141 (0.944–1.378)	0.172	0.222 (0.027–1.804)	0.159	0.342 (0.044–2.670)	0.306
Middle lobe	1.186 (1.019–1.381)	0.027	1.138 (0.937–1.384)	0.193	0.187 (0.018–1.930)	0.157	0.162 (0.016–1.685)	0.128
Lower lobe	1.230 (1.061–1.426)	0.006	1.137 (0.941–1.374)	0.185	0.208 (0.024–1.765)	0.150	0.307 (0.038–2.471)	0.267
Unspecific	1.464 (1.250–1.714)	<0.001	1.453 (1.187–1.779)	<0.001				
Surgery								
No	1.000		1.000					
Yes	0.324 (0.314–0.334)	<0.001	0.292 (0.280–0.303)	<0.001				
Chemotherapy								
No	1.000		1.000		1.000		1.000	
Yes	1.396 (1.352–1.442)	<0.001	1.851 (1.781–1.925)	<0.001	3.735 (1.898–7.351)	<0.001	2.664 (1.421–4.997)	0.002
Radiotherapy								
No	1.000		1.000		1.000		1.000	
Yes	0.744 (0.720–0.769)	<0.001	0.717 (0.687–0.747)	<0.001	5.371 (2.120–13.604)	<0.001	7.1661 (3.193–16.061)	<0.001
Histology								
LSCIS	1.000		1.000		1.000		1.000	
LAIS	0.353 (0.297–0.419)	<0.001	0.287 (0.224–0.367)	<0.001	0.148 (0.040–0.551)	0.004	0.181 (0.053–0.617)	0.006
LSQCC	0.900 (0.807–1.004)	0.058	0.895 (0.776–1.003)	0.128	0.475 (0.157–1.433)	0.186	0.704 (0.259–1.913)	0.491
LUAD	0.649 (0.582–0.723)	<0.001	0.701 (0.608–0.808)	<0.001	0.236 (0.074–0.757)	0.015	0.433 (0.152–1.234)	0.117

OS, overall survival; LCSS, lung cancer-specific survival; PFS, progression-free survival; LSCIS, lung squamous cell cancer in situ; LAIS, adenocarcinoma in situ; LSQCC, lung squamous cell cancer; LUAD, lung adenocarcinoma; SEER, Surveillance Epidemiology and End Results; HR, hazard ratio; CI, confidence interval.

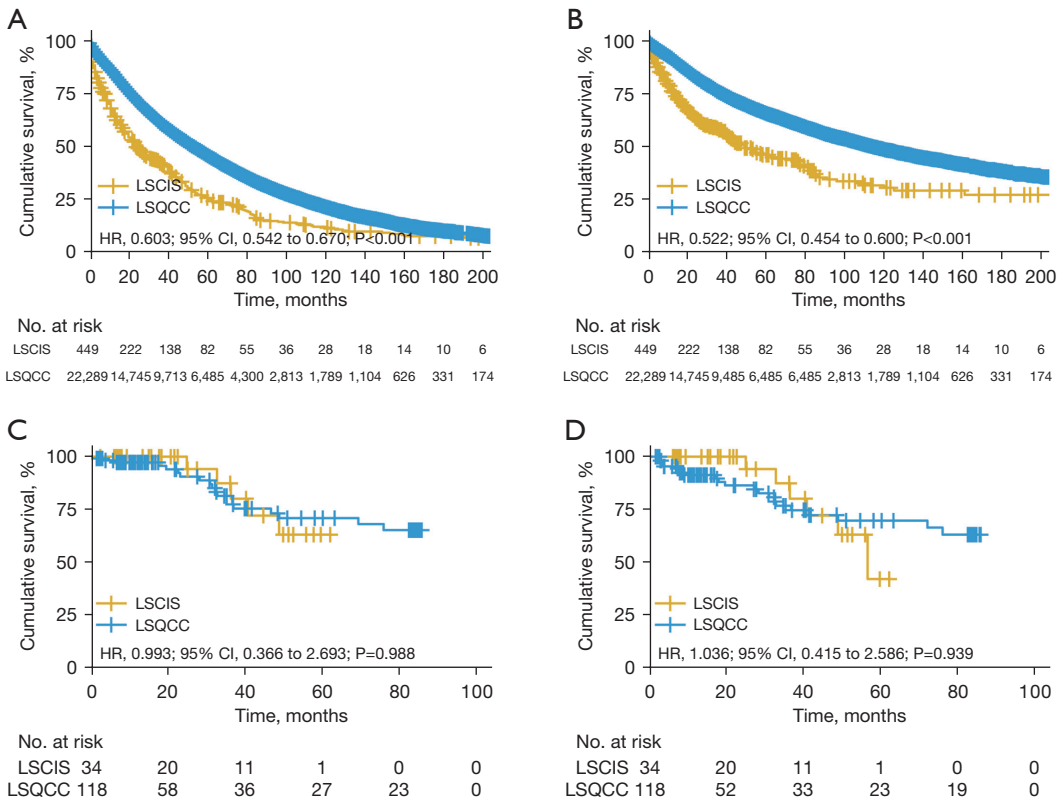

Figure 2 Kaplan-Meier curves of the patients with LSCIS and stage IA LSQCC. (A,B) OS and LCSS of the patients with LSCIS and stage IA LSQCC in the SEER cohort; (C,D) OS and PFS of the patients with LSCIS and stage IA LSQCC in the Shanghai Pulmonary Hospital cohort. LSCIS, lung squamous cell cancer in situ; LSQCC, lung squamous cell cancer; OS, overall survival; LCSS, lung cancer-specific survival; SEER, Surveillance Epidemiology and End Results; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

IA LUAD patients, though no significantly difference was observed between stage IA LUAD and LSCIS in PFS (HR, 0.433; 95% CI: 0.152–1.234; P=0.117; *Table 2*) in Shanghai Pulmonary Hospital cohort.

Unexpectedly, in the SEER cohort, the univariate survival analysis showed the OS and LCSS times of the stage IA LSQCC patients were significantly longer than those of the LSCIS patients (OS HR: 0.603; 95% CI: 0.542–0.670; P<0.001; *Figure 2A*; LCSS HR: 0.522; 95% CI: 0.454–0.600; P<0.001; *Figure 2B*). When patients divided into non-surgery and surgery groups, in non-surgery groups in the SEER cohort, the OS (HR: 0.826; 95% CI: 0.731–0.935; P=0.002; Figure S3A) and LCSS (HR: 0.732; 95% CI: 0.626–0.855; P<0.001; Figure S3B) of LSCIS were significantly worse than those of stage IA LSQCC. However, in the surgery group the survivals were comparable between the LSCIS and stage IA LSQCC patients in the SEER cohort in both OS (HR: 0.933; 95% CI: 0.744–1.169; P=0.544; Figure S3C) and LCSS (HR: 0.942; 95% CI: 0.672–1.321; P=0.730; Figure S3D) and in the Shanghai Pulmonary Hospital cohort (OS HR: 0.993; 95% CI: 0.366–2.693; P=0.988; *Figure 2C*; PFS HR: 1.036; 95% CI: 0.415–2.586; P=0.939; *Figure 2D*).

In the multivariate Cox regression analyses, in the SEER cohort, the OS (HR: 0.900; 95% CI: 0.807–1.004; P=0.058; *Table 2*) and LCSS (HR: 0.895; 95% CI: 0.776–1.003; P=0.128; *Table 2*) of the LSCIS patients were comparable to those of the stage IA LSQCC patients. In the Shanghai Pulmonary Hospital cohort, no significant differences were observed between the LSCIS and stage IA LSQCC patients in terms of OS (HR: 0.475; 95% CI: 0.157–1.433; P=0.186; *Table 2*) and PFS (HR: 0.704; 95% CI: 0.259–1.913; P=0.491; *Table 2*).

Surgery being an independent favorable prognostic factor for LSCIS

To identify the independent favorable prognostic factors

Table 3 Univariate and multivariate Cox analyses of OS and LCSS in the patients with LSCIS in the SEER cohort

Characteristics	OS				LCSS			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (years)								
≤60	1.000		1.000		1.000		1.000	
>60 to 70	1.176 (0.870–1.588)	0.292	1.200 (0.888–1.620)	0.235	1.499 (0.996–2.255)	0.052	1.602 (1.063–2.414)	0.024
>70	1.846 (1.389–2.454)	<0.001	1.794 (1.349–2.386)	<0.001	2.082 (1.404–3.087)	<0.001	2.092 (1.403–3.119)	<0.001
Gender								
Male	1.000				1.000			
Female	0.827 (0.654–1.047)	0.114			0.864 (0.637–1.172)	0.346		
Race								
White	1.000				1.000			
Black	1.317 (0.968–1.792)	0.080			1.310 (0.881–1.949)	0.182		
Other	0.886 (0.484–1.621)	0.695			0.958 (0.449–2.045)	0.912		
Primary site								
Main bronchus	1.000				1.000			
Upper lobe	1.291 (0.902–1.847)	0.163			1.416 (0.870–2.305)	0.162		
Middle lobe	1.430 (0.818–2.501)	0.210			1.333 (0.618–2.874)	0.464		
Lower lobe	1.103 (0.747–1.629)	0.622			1.232 (0.728–2.085)	0.436		
Unspecific	1.230 (0.691–2.191)	0.482			0.957 (0.402–2.278)	0.921		
Surgery								
No	1.000		1.000		1.000		1.000	
Yes	0.454 (0.350–0.588)	<0.001	0.465 (0.358–0.605)	<0.001	0.345 (0.237–0.501)	<0.001	0.371 (0.252–0.546)	<0.001
Chemotherapy								
No	1.000				1.000		1.000	
Yes	1.275 (0.961–1.690)	0.092			1.753 (1.259–2.442)	0.001	1.502 (1.051–2.147)	0.025
Radiotherapy								
No	1.000				1.000		1.000	
Yes	1.228 (0.958–1.575)	0.105			1.474 (1.084–2.003)	0.031	0.941 (0.674–1.315)	0.723

OS, overall survival; LCSS, lung cancer-specific survival; LSCIS, lung squamous cell cancer in situ; SEER, Surveillance Epidemiology and End Results; HR, hazard ratio; CI, confidence interval.

for LSCIS, univariate and multivariate Cox regression analyses for OS and LCSS were performed in the LSCIS data set from the SEER database (*Table 3*). The univariate analyses revealed that age and surgery were significantly correlated with both OS and LCSS, and chemotherapy was significantly correlated with LCSS. These significant factors were selected for further multivariate analyses. The multivariate Cox regression analyses also indicated that age and surgery were significantly correlated with OS and LCSS. Further, being aged >70 years at the time diagnosis had the most negative effect on OS (HR: 1.794; 95% CI: 1.349–2.386; P<0.001; *Table 3*) and LCSS (HR:

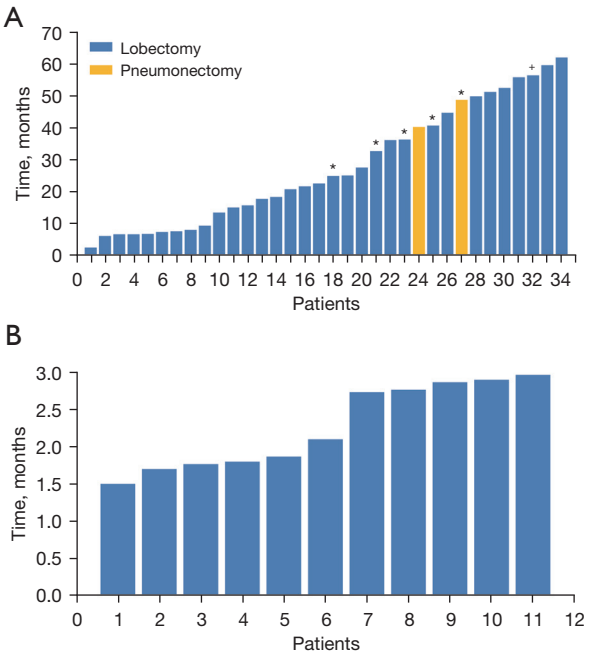

Figure 3 Outcomes of the patients with LSCIS treated with LDE, lobectomy, and pneumonectomy in the Shanghai Pulmonary Hospital cohort. (A) Outcomes of the patients with LSCIS treated with lobectomy and pneumonectomy; (B) outcomes of the patients with LSCIS treated with LDE by bronchoscope before lobectomy and pneumonectomy. *, death; +, recurrence. LSCIS, lung squamous cell carcinoma in situ; LDE, local destructed or excised.

2.092; 95% CI: 1.403–3.119; P<0.001; *Table 3*). Surgery was associated with improved OS (HR: 0.465; 95% CI: 0.358–0.605; P<0.001; *Table 3*) and LCSS (HR: 0.371; 95% CI: 0.252–0.546; P<0.001; *Table 3*). Unexpectedly, compared to patients treated without chemotherapy, those received chemotherapy had significantly worse LCSS (HR: 1.502; 95% CI: 1.051–2.147; P=0.025; *Table 3*).

Lobectomy (rather than LDE) being the most favorable surgical procedure for LSCIS

We also investigated the survival of the LSCIS patients according to the different surgical procedures, including LDE, sublobectomy, lobectomy, and pneumonectomy in the LSCIS patients set. All the LSCIS patients at the Shanghai Pulmonary Hospital underwent surgical resection, and of these patients, 32 underwent lobectomy and 2 underwent pneumectomy (*Figure 3A*). Among the patients, 11 underwent LDE by bronchoscope before the lobectomy or pneumectomy, but these patients underwent surgery because of the progression or recurrence of tumors within 3 months of LDE (*Figure 3B*). Of the 32 patients who underwent lobectomy, a tumor recurred in 1 patient and 4 patients died. Of the 2 patients who underwent pneumectomy, 1 patient died and the tumors recurred in no patients (*Figure 3B*). No significant difference was observed between the patients who underwent lobectomy and pneumonectomy (recurrence OR: 0.969; 95% CI: 0.910–1.031; P=0.941; death OR: 7.000; 95% CI: 0.362–135.517; P=0.276; Table S2).

Survival analyses were also performed in the SEER cohort. The patients in the non-surgery group and those in the LDE group had similar OS (HR: 0.720; 95% CI: 0.412–1.258; P=0.248; *Figure 4A*) and LCSS (HR: 0.814; 95% CI: 0.416–1.595; P=0.549; Figure S4A), while the patients in sublobectomy (OS HR: 0.667; 95% CI: 0.471–0.945; P=0.047; *Figure 4B*; LCSS HR: 0.440; 95% CI: 0.232–0.834; P=0.012; Figure S4B), lobectomy (OS HR: 0.364; 95% CI: 0.251–0.527; P<0.001; *Figure 4C*; LCSS HR: 0.229; 95% CI: 0.127–0.416; P<0.001; Figure S4C), and pneumonectomy (OS HR: 0.282; 95% CI: 0.116–0.687; P=0.005; *Figure 4D*; LCSS HR: 0.287; 95% CI: 0.091–0.904; P=0.033; Figure S4D) groups had significantly better OS and LCSS. No significant difference was observed between the sublobectomy and LDE groups in terms of OS (HR: 0.838; 95% CI: 0.421–1.688; P=0.615; *Figure 5A*) and LCSS (HR: 0.570; 95% CI: 0.231–1.404; P=0.222; *Figure 5B*). Significant decreases in OS and LCSS were observed in the LDE group compared with the lobectomy group (OS HR: 0.433; 95% CI: 0.221–0.850; P=0.015; *Figure 5A*; LCSS HR: 0.226; 95% CI: 0.091–0.564; P=0.011; *Figure 5B*). Lobectomy was associated with significantly better OS (HR: 0.484; 95% CI: 0.284–0.824; P=0.008; *Figure 5A*) and marginally significantly better LCSS (HR: 0.477; 95% CI: 0.203–1.121; P=0.089; *Figure 5B*) than sublobectomy. The LSCIS patients who underwent pneumonectomy had significantly better OS (HR: 0.316; 95% CI: 0.100–0.996; P=0.049; *Figure 6A*) and LCSS (HR: 0.197; 95% CI: 0.041–0.953; P=0.043; *Figure 6B*) than those who underwent LDE. Significantly better OS (HR: 0.365; 95% CI: 0.137–0.967; P=0.043; *Figure 6C*) and comparable LCSS (HR: 0.608; 95% CI: 0.165–2.236; P=0.454; *Figure 6D*) were observed in the patients who underwent pneumonectomy compared with those received sublobectomy. No significant differences in OS (HR: 0.796; 95% CI: 0.310–2.040; P=0.634; *Figure 6E*) and LCSS (HR: 1.343; 95% CI: 0.378–4.768; P=0.648; *Figure 6F*) were

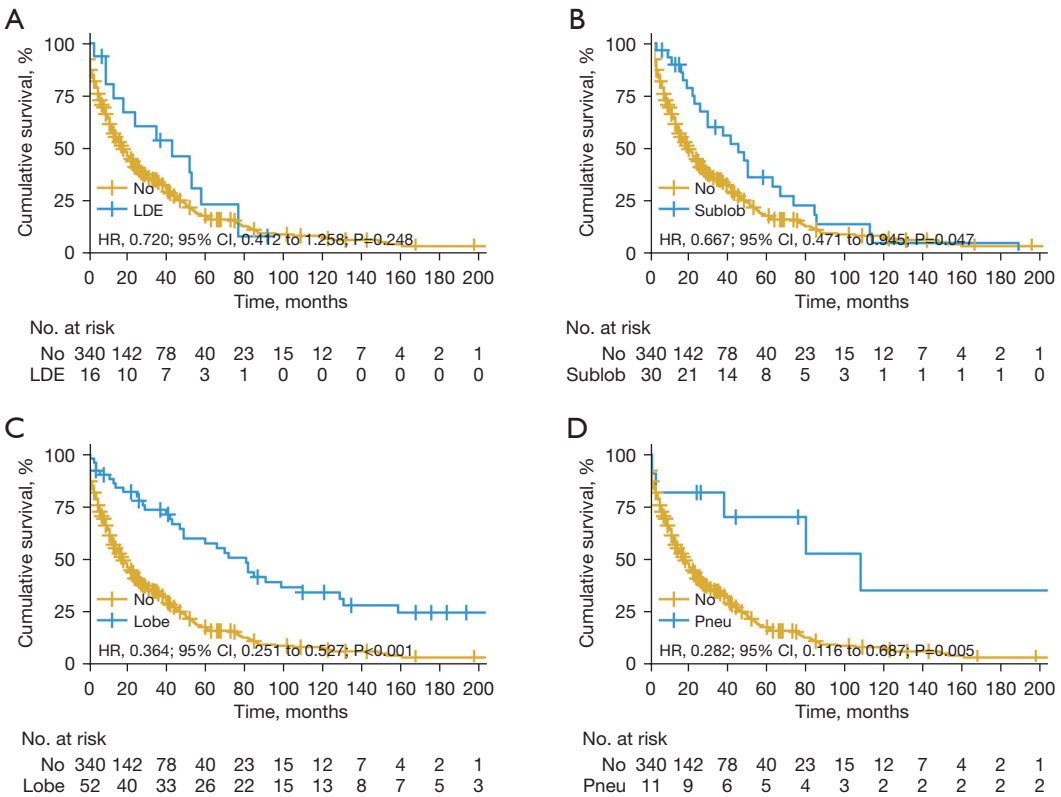

Figure 4 Kaplan-Meier curves of the patients with LSCIS in the SEER cohort according to the surgical procedures. (A-D). OS of the patients with LSCIS in the non-surgery, LDE, sublobectomy, lobectomy, and pneumonectomy groups. No, non-surgery; LDE, local destructed or excised; Sublob, sublobectomy; Lobe, lobectomy; Pneu, pneumonectomy; HR, hazard ratio; CI, confidence interval; LSCIS, lung squamous cell cancer in situ; SEER, Surveillance Epidemiology and End Results; OS, overall survival.

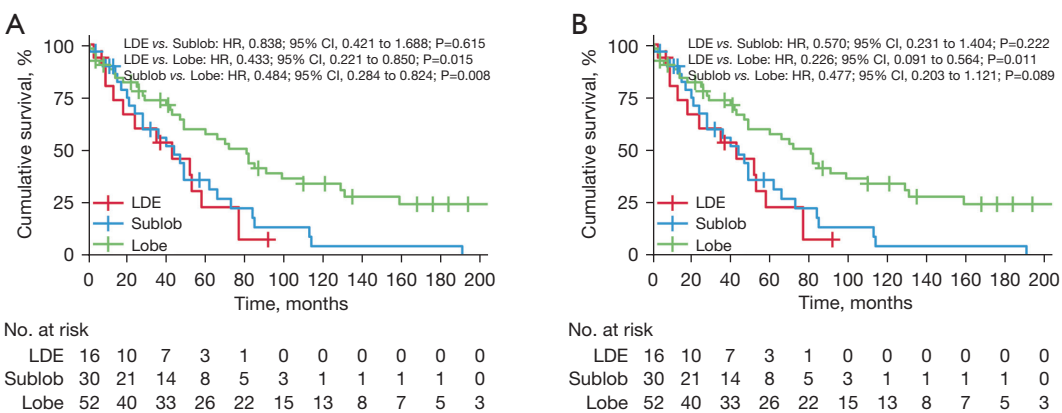

Figure 5 Kaplan-Meier curves of the patients with LSCIS after LDE, sublobectomy, and lobectomy in the SEER cohort. (A,B) OS and LCSS of the patients with LSCIS in the LDE, sublobectomy, and lobectomy groups. LDE, local destructed or excised; Sublob, sublobectomy; Lobe, lobectomy; HR, hazard ratio; CI, confidence interval; LSCIS, lung squamous cell cancer in situ; SEER, Surveillance Epidemiology and End Results; OS, overall survival; LCSS, lung cancer-specific survival.

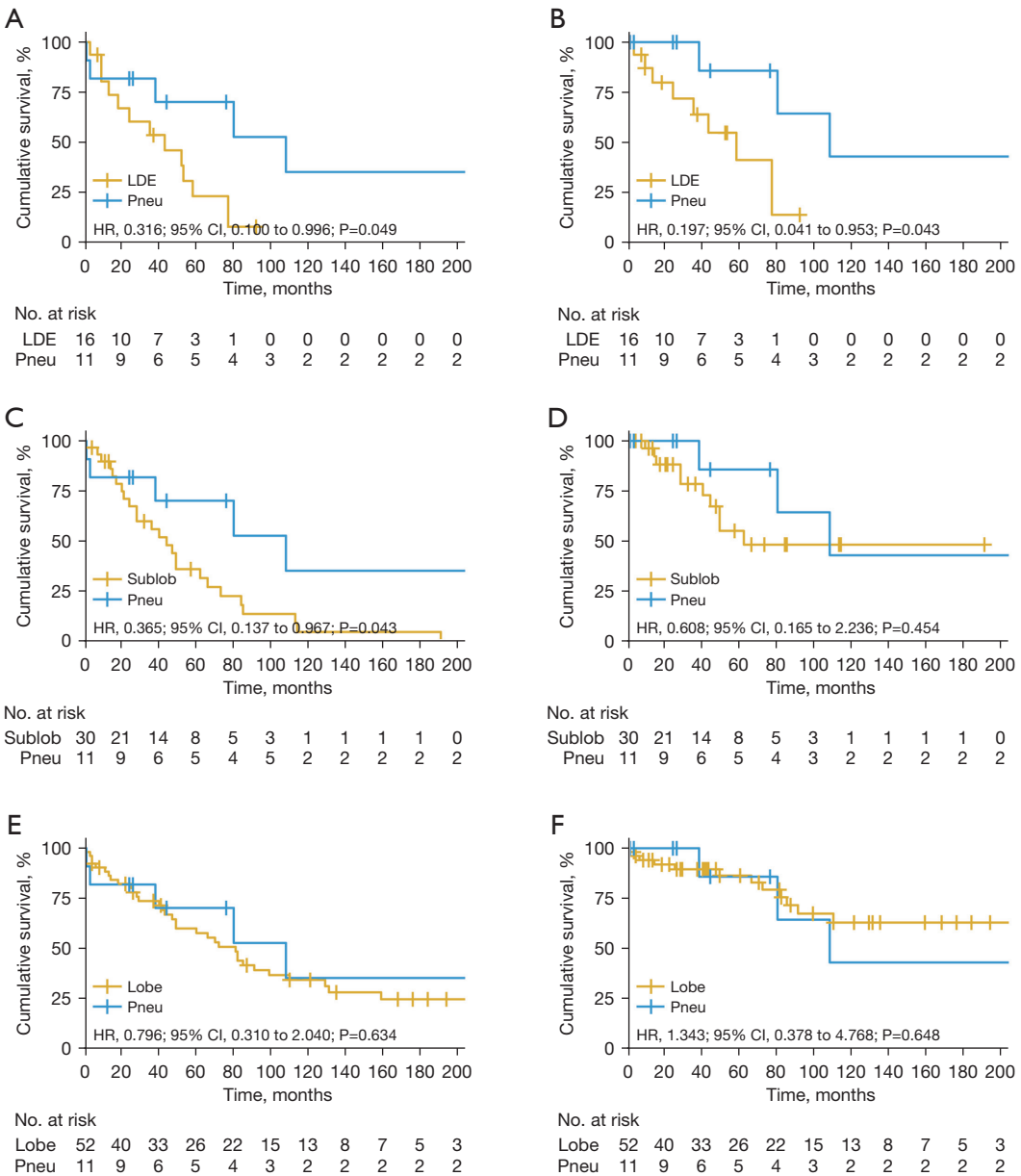

Figure 6 Kaplan-Meier curves of the patients with LSCIS after LDE, sublobectomy, lobectomy, and pneumonectomy in the SEER cohort. (A,C,E) OS of the patients with LSCIS in the LDE, sublobectomy, and lobectomy groups; (B,D,F) LCSS of the patients with LSCIS in the LDE, sublobectomy, and lobectomy groups. LDE, local destructed or excised; Sublob, sublobectomy; Lobe, lobectomy; Pneu, pneumonectomy; HR, hazard ratio; CI, confidence interval; LSCIS, lung squamous cell cancer in situ; OS, overall survival; LCSS, lung cancer-specific survival.

observed between the pneumonectomy and lobectomy groups.

The Cox proportional hazards regression model was applied to furtherly study the use of surgery after controlling for the potential confounding factors (*Tables 4,5*). The results showed that patients' OS and LCSS improved as the extent of lung resected was extend. The patients treated with non-surgery and LDE had similar OS (HR: 0.698; 95% CI: 0.398–1.223; P=0.209 *Table 4*) and LCSS (HR: 0.826; 95% CI: 0.419–1.628; P=0.581;

Table 4 Multivariate Cox analyses of OS and LCSS in the patients with LSCIS in the SEER cohort according to the surgical procedures

Characteristics	OS		LCSS	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)				
≤60	1.000		1.000	
>60 to 70	1.217 (0.899–1.647)	0.203	1.571 (1.041–2.370)	0.031
>70	1.752 (1.310–2.345)	<0.001	1.979 (1.327–2.953)	0.001
Surgery				
Non-surgery	1.000		1.000	
LDE	0.698 (0.398–1.223)	0.209	0.826 (0.419–1.628)	0.581
Sublobectomy	0.606 (0.400–0.918)	0.018	0.420 (0.221–0.801)	0.008
Lobectomy	0.394 (0.271–0.575)	<0.001	0.261 (0.143–0.476)	<0.001
Pneumonectomy	0.253 (0.103–0.618)	0.003	0.274 (0.086–0.866)	0.028
Chemotherapy				
No	1.000		1.000	
Yes	1.089 (0.817–1.450)	0.561	1.482 (1.057–2.077)	0.022

OS, overall survival; LCSS, lung cancer-specific survival; LSCIS, lung squamous cell cancer in situ; SEER, Surveillance Epidemiology and End Results; HR, hazard ratio; CI, confidence interval; LDE, local destructed or excised.

Table 5 Multivariate Cox analyses of OS and LCSS in the patients with LSCIS undergoing surgery in the SEER cohort

Characteristics	OS		LCSS	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)				
≤60	1.000		1.000	
>60 to 70	1.173 (0.652–2.109)	0.595	1.116 (0.466–2.672)	0.805
>70	1.069 (0.550–2.079)	0.844	0.584 (0.213–1.596)	0.294
Surgery				
LDE *vs.* sublobectomy	0.890 (0.451–1.755)	0.736	0.532 (0.212–1.332)	0.178
LDE *vs.* lobectomy	0.422 (0.209–0.854)	0.016	0.179 (0.069–0.467)	<0.001
LDE *vs.* pneumonectomy	0.306 (0.106–0.878)	0.028	0.266 (0.069–1.022)	0.054
Sublobectomy *vs.* lobectomy	0.474 (0.262–0.860)	0.014	0.337 (0.133–0.853)	0.022
Sublobectomy *vs.* pneumonectomy	0.344 (0.128–0.924)	0.034	0.501 (0.130–1.922)	0.314
Lobectomy *vs.* pneumonectomy	0.724 (0.273–1.919)	0.516	1.486 (0.397–5.564)	0.557
Chemotherapy				
No	1.000		1.000	
Yes	0.442 (0.059–3.324)	0.428	1.848 (0.224–15.211)	0.568

OS, overall survival; LCSS, lung cancer-specific survival; LSCIS, lung squamous cell cancer in situ; SEER, Surveillance Epidemiology and End Results; HR, hazard ratio; CI, confidence interval; LDE, local destructed or excised.

Table 4). However, compared with the LSCIS patients did not received surgery, the OS and LCSS of those who underwent sublobectomy (OS HR: 0.606; 95% CI: 0.400–0.918; P=0.018; LCSS HR: 0.420; 95% CI: 0.221–0.801; P=0.008; *Table 4*), lobectomy (OS HR: 0.394; 95% CI: 0.271–0.575; P<0.001; LCSS HR: 0.261; 95% CI: 0.143–0.476; P<0.001; *Table 4*), and pneumonectomy (OS HR: 0.253; 95% CI: 0.103–0.618; P=0.003; LCSS HR: 0.274; 95% CI: 0.086–0.866; P=0.028; *Table 4*) were significantly improved. Sublobectomy was superior to non-surgery, but not associated with significantly better survival than LDE (OS HR: 0.890; 95% CI: 0.451–1.755; P=0.736; LCSS HR: 0.532; 95% CI: 0.212–1.332; P=0.178; *Table 5*). Lobectomy was significantly superior to LDE (OS HR: 0.422; 95% CI: 0.209–0.854; P=0.016; LCSS HR: 0.179; 95% CI: 0.069–0.467; P<0.001; *Table 5*) and sublobectomy (OS HR: 0.474; 95% CI: 0.262–0.860; P=0.014; LCSS HR: 0.337; 95% CI: 0.133–0.853; P=0.022; *Table 5*) in terms of both OS and LCSS. Pneumonectomy was associated with significantly better OS but not correlated with significantly better LCSS compared with LDE (OS HR: 0.306; 95% CI: 0.106–0.878; P=0.028; LCSS HR: 0.266; 95% CI: 0.069–1.022; P=0.054; *Table 5*) and sublobectomy (OS HR: 0.344; 95% CI: 0.128–0.924; P=0.034; LCSS HR: 0.501; 95% CI: 0.130–1.922; P=0.314; *Table 5*). There were no significant differences between lobectomy and pneumonectomy in terms of OS (HR: 0.724; 95% CI: 0.273–1.919; P=0.516; *Table 5*) and LCSS (HR: 1.486; 95% CI: 0.397–5.564; P=0.557; *Table 5*).

Discussion

Due to the infrequent detection of LSCIS histology in the pathological diagnosis of lung cancer, this subtype has only received limited attention by the scientific community; however, a few controversial results have been published on the prognosis and treatment of these patients (8,9,14,15). However, most of the relevant studies relied on small and unbalanced statistical sample sizes, which limits the reliability of these findings to some extent.

Excellent outcomes for lung cancer *in situ* have been reported (9,16,17). To the best of our knowledge, no previous studies had examined the difference in the prognosis of LSCIS and LAIS patients; however, several studies have reported differences in the prognosis of early stage LSQCC and stage IA LUAD, and concluded that patients with LSQCC had significantly worse outcomes than those with lung adenocarcinoma (18,19). Results in our study also showed that stage IA LUAD patients had significantly better survivals than stage IA LSQCC patients.

This was the first study to describe the long-term survival outcomes of LSCIS and LAIS patients. We found that LSCIS patients had significantly worse survival outcomes than LAIS patients. Furthermore, we found LSCIS patients had worse prognosis than stage IA LUAD patients. These findings strongly indicate that squamous histology is correlated with worse outcomes than adenocarcinoma histology for patients with NSCLC, even in the preinvasive stage.

It is a reasonable assumption that early stage LSQCC patients have a better prognosis than late stage LSQCC patients. However, the evidence of our retrospective study contradicts this logic. Notably, we found no significant difference between the prognosis of LSCIS and that of stage IA LSQCC in both the SEER cohort and the Shanghai Pulmonary Hospital cohort. LSCIS has been considered one of the precursors to LSQCC (3). The outcomes of early LSQCC have been widely reported (18-23). A few studies have reported the survival outcomes of LSCIS patients (7,9,14,15,24,25). However, the quality of evidence from these studies is low, as the number of LSCIS patients was too small for valid conclusions to be drawn. These studies also failed to compare LSCIS and stage IA LSQCC patients in survivals. Thus, the differences in the survival outcomes of the LSCIS and stage IA LSQCC patients remain unclear.

The high risk of progression from LSCIS to invasive LSQCC has been reported in previous studies (8,9,14), which may account for the small difference in survival between the LSCIS and stage IA LSQCC patients in the SEER cohort. These findings indicate that the therapeutic strategy of LSCIS should be similar to that of stage IA LSQCC because of the similar survival of the LSCIS and stage IA LSQCC, and LSCIS having high risk of developing into invasive disease, though LSCIS is classified as a squamous precursor lesion under the 2021 WHO's classification of lung tumors (3).

Chemotherapy is generally recommended for NSCLC patients have advanced stage diseases or cannot tolerate surgery (26,27). For NSCLC patients who cannot tolerate surgery in the absence of evidence, it is not yet known whether the use of chemotherapy will improve the survival of patients with preinvasive NSCLC. In the SEER cohort, in the 77 LSCIS patients receiving chemotherapy, 74 cases did not undergo surgery and the results of our study showed that chemotherapy is associated with poor LCSS. Some studies have reported that chemotherapy cannot prevent the progression of preinvasive squamous cell carcinoma

(28-30). Moreover, chemotherapy is not recommended for preinvasive NSCLC patients, even for those cannot tolerate surgery (31). In the patients having chemotherapy, LSCIS might be treated with chemotherapy which is the preferred treatment for NSCLC patients who cannot undergo surgery when LSCIS developed into an invasive disease. This may be the reason why chemotherapy correlating with worse LCSS in LSCIS patients.

The benefits of radiotherapy have been demonstrated for early stage NSCLC patients (32). Radiotherapy is considered a curative treatment for patients with stage I NSCLC who are unfit for surgery, with the results of population-based studies providing the strongest supporting evidence (33,34). However, our study showed that radiotherapy may not improve the OS and LCSS of LSCIS patients.

Surgical resection plays a significant role in the treatment of NSCLC patients (26-27), and it has been widely reported that surgery improves the survival of lung cancer patients (35,36). However, in relation to the outcomes of LSCIS patients, conflicting results have been reported by different studies (15,37). Kutlu reported that LSCIS at the bronchial resection margin regressed without further treatment (15), while Pasic *et al.* found that the presence of LSCIS in the bronchial resection margin was associated with stump recurrences (37). We found that surgery is superior to non-surgery in the treatment of LSCIS, as the patients who underwent surgery had significantly better OS and LCSS than those treated without surgery in our study.

Since 1995, lobectomy with lymph node dissection has been considered the standard surgical procedure for patients with early stage NSCLC (38). However, it has been suggested that LDE by endobronchial therapies may be effective in treating preinvasive tumors when the LSCIS lesions are located in the bronchus (21,39), as LSCISs are often small and may be completely destroyed and excised by bronchoscopy. However, in the terms of progression of lesions, the proportion of LSCIS lesions treated with bronchoscope is similar to those untreated (10). Our study also showed that a high proportion of lesions treated with bronchoscope progressed in the Shanghai Pulmonary Hospital cohort. We found that LDE was not superior to non-surgery in terms of both OS and LCSS in the SEER cohort. These findings suggest that LDE may be inadequate in the treatment of LSCIS, as it may not prevent progression to invasive cancer or improve the survival of LSCIS patients compared to no surgery.

Some studies have reported that sublobectomy is equivalent to lobectomy in treating early stage lung cancer (40-42). However, we found that sublobectomy is inferior to lobectomy in the treatment of LSCIS patients. Sublobectomy is mainly recommended for patients with peripheral small lesions of NSCLC. However, most LSCISs arise in the central airways, where the tumors show both endobronchial and invasive growth into the peribranchial tissue, and lung parenchyma (7,43). In addition, cancer has been observed to develop elsewhere in the lungs of patients with LSCIS (21,44,45). Some studies reported that prognosis of multiple primary lung cancer is determined by the highest clinical TNM stage and number of lesions in the multiple tumors (46,47). Because of the smaller resection range, sublobectomy may be associated with a lower resection rate of incident tumors elsewhere in the lungs in LSCIS patients than lobectomy.

In certain cases, if a complete oncologic resection cannot be obtained by lobectomy, pneumonectomy is considered the resection of choice. However, pneumonectomy is associated with higher postoperative morbidity and mortality rates than less extensive resections and is an individual predictor of these negative outcomes (48-51). Recently, Chen *et al.* reported that sleeve lobectomy is associated with lower 30- and 90-day mortality, postoperative morbidity, and improved OS and DFS than pneumonectomy in NSCLC patients (52). We found that pneumonectomy may be superior to sublobectomy and LDE and equivalent to lobectomy, which suggests that pneumonectomy may serve as a substitute for lobectomy in the treatment of LSCIS. Further studies need to be conducted to evaluate the differences between pneumonectomy and lobectomy in the treatment of LSCIS.

This study had some limitations. First, the SEER database is retrospective and thus some selection biases may have been introduced. Some advanced statistical methods were applied to balance the covariates among the arms; however, there were still some potential biases among the groups that were not adjusted. Second, information regarding comorbidities was not available from the SEER database. The patients who had undergone radiotherapy or surgery tended to have less comorbidities than those who were untreated at the baseline, so our results may be conservative. Moreover, data on targeted therapies and immunotherapies were lacking due to the constraints of the SEER database.

Conclusions

We found that the prognoses of LSCIS patients, in terms

of OS, PFS and LCSS, were similar to those of stage IA LSQCC patients but significantly inferior to those of LAIS patients. Surgery was an independent favorable prognostic factor for patients with LSCIS. Lobectomy should be the preferred surgical procedure, and will greatly improve the current outcomes of LSCIS patients.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-243/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-243/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-243/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-243/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Shanghai Pulmonary Hospital Institutional Review Board (No. KY2020-1), and the requirement of individual consent for this retrospective analysis was waived.

References

1. Brambilla E, Travis WD, Colby TV, et al. The new World Health Organization classification of lung tumours. Eur Respir J 2001;18:1059-68.
2. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015;10:1243-60.
3. Nicholson AG, Tsao MS, Beasley MB, et al. The 2021 WHO Classification of Lung Tumors: Impact of Advances Since 2015. J Thorac Oncol 2022;17:362-87.
4. Nicholson AG, Perry LJ, Cury PM, et al. Reproducibility of the WHO/IASLC grading system for pre-invasive squamous lesions of the bronchus: a study of inter-observer and intra-observer variation. Histopathology 2001;38:202-8.
5. Wood DE, Kazerooni EA, Baum SL, et al. Lung Cancer Screening, Version 3.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2018;16:412-41.
6. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
7. Thakrar RM, Pennycuick A, Borg E, et al. Preinvasive disease of the airway. Cancer Treat Rev 2017;58:77-90.
8. van Boerdonk RA, Smesseim I, Heideman DA, et al. Close Surveillance with Long-Term Follow-up of Subjects with Preinvasive Endobronchial Lesions. Am J Respir Crit Care Med 2015;192:1483-9.
9. Venmans BJ, van Boxem TJ, Smit EF, et al. Outcome of bronchial carcinoma in situ. Chest 2000;117:1572-6.
10. Banerjee AK. Preinvasive lesions of the bronchus. J Thorac Oncol 2009;4:545-51.
11. Kassambara A, Kosinski M, Biecek P. survminer: Drawing Survival Curves using "ggplot2" In. R package version

0.4.9 ed; 2021. Available online: https://CRAN.R-project.org/package=survminer
12. Therneau T. A Package for Survival Analysis in R. In. R package version 3.3-1 ed; 2022. Available online: https://CRAN.R-project.org/package=survival
13. Team RC. R: A Language and Environment for Statistical Computing; 2022. Available online: https://www.r-project.org
14. Bota S, Auliac JB, Paris C, et al. Follow-up of bronchial precancerous lesions and carcinoma in situ using fluorescence endoscopy. Am J Respir Crit Care Med 2001;164:1688-93.
15. Kutlu CA, Urer N, Olgac G. Carcinoma in situ from the view of complete resection. Lung Cancer 2004;46:383-5.
16. Yotsukura M, Asamura H, Motoi N, et al. Long-Term Prognosis of Patients With Resected Adenocarcinoma In Situ and Minimally Invasive Adenocarcinoma of the Lung. J Thorac Oncol 2021;16:1312-20.
17. Moro-Sibilot D, Fievet F, Jeanmart M, et al. Clinical prognostic indicators of high-grade pre-invasive bronchial lesions. Eur Respir J 2004;24:24-9.
18. Fukui T, Taniguchi T, Kawaguchi K, et al. Comparisons of the clinicopathological features and survival outcomes between lung cancer patients with adenocarcinoma and squamous cell carcinoma. Gen Thorac Cardiovasc Surg 2015;63:507-13.
19. Wang BY, Huang JY, Chen HC, et al. The comparison between adenocarcinoma and squamous cell carcinoma in lung cancer patients. J Cancer Res Clin Oncol 2020;146:43-52.
20. Woolner LB, Fontana RS, Cortese DA, et al. Roentgenographically occult lung cancer: pathologic findings and frequency of multicentricity during a 10-year period. Mayo Clin Proc 1984;59:453-66.
21. Deygas N, Froudarakis M, Ozenne G, et al. Cryotherapy in early superficial bronchogenic carcinoma. Chest 2001;120:26-31.
22. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33.
23. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
24. Talcott WJ, Miccio JA, Park HS, et al. Rates of invasive disease and outcomes in NSCLC patients with biopsy suggestive of carcinoma in situ. Lung Cancer 2021;157:17-20.
25. Salaün M, Bota S, Thiberville L. Long-term follow-up of severe dysplasia and carcinoma in situ of the bronchus. J Thorac Oncol 2009;4:1187-8.
26. Ettinger DS, Wood DE, Aisner DL, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2.2021. J Natl Compr Canc Netw 2021;19:254-66.
27. Ettinger DS, Wood DE, Aggarwal C, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 1.2020. J Natl Compr Canc Netw 2019;17:1464-72.
28. Kelly K, Kittelson J, Franklin WA, et al. A randomized phase II chemoprevention trial of 13-CIS retinoic acid with or without alpha tocopherol or observation in subjects at high risk for lung cancer. Cancer Prev Res (Phila) 2009;2:440-9.
29. Recchia F, De Filippis S, Pompili PL, et al. Carboplatin, vindesine, 5-fluorouracil-leucovorin and 13-cis retinoic acid in the treatment of advanced non-small cell lung cancer. A phase II study. Clin Ter 1999;150:269-74.
30. Lam S, Mandrekar SJ, Gesthalter Y, et al. A Randomized Phase IIb Trial of myo-Inositol in Smokers with Bronchial Dysplasia. Cancer Prev Res (Phila) 2016;9:906-14.
31. Qiu Y, Shen-Tu Y. Advance in Diagnose and Treatment Strategies of Adenocarcinoma in Situ. Zhongguo Fei Ai Za Zhi 2017;20:641-4.
32. Senan S, Paul MA, Lagerwaard FJ. Treatment of early-stage lung cancer detected by screening: surgery or stereotactic ablative radiotherapy? Lancet Oncol 2013;14:e270-4.
33. Haasbeek CJA, Palma D, Visser O, et al. Early-stage lung cancer in elderly patients: a population-based study of changes in treatment patterns and survival in the Netherlands. Ann Oncol 2012;23:2743-7.
34. Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. Int J Radiat Oncol Biol Phys 2012;84:1060-70.
35. Baltayiannis N, Chandrinos M, Anagnostopoulos D, et al. Lung cancer surgery an up to date. J Thorac Dis 2013;5 Suppl 4:S425-39.
36. Sihoe ADL. Video-assisted thoracoscopic surgery as the gold standard for lung cancer surgery. Respirology 2020;25 Suppl 2:49-60.
37. Pasic A, Grünberg K, Mooi WJ, et al. The natural history of carcinoma in situ involving bronchial resection margins. Chest 2005;128:1736-41.
38. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
39. Moro-Sibilot D, Brambilla C. Photodynamic therapy where do we go from here Eur Respir J 2003;22:399-400.
40. Dai C, Shen J, Ren Y, et al. Choice of Surgical Procedure

for Patients With Non-Small-Cell Lung Cancer ≤ 1 cm or > 1 to 2 cm Among Lobectomy, Segmentectomy, and Wedge Resection: A Population-Based Study. J Clin Oncol 2016;34:3175-82.
41. Dolan DP, White A, Mazzola E, et al. Outcomes of superior segmentectomy versus lower lobectomy for superior segment Stage I non-small-cell lung cancer are equivalent: An analysis of 196 patients at a single, high volume institution. J Surg Oncol 2021;123:570-8.
42. Kamel MK, Lee B, Harrison SW, et al. Sublobar resection is comparable to lobectomy for screen-detected lung cancer. J Thorac Cardiovasc Surg 2022;163:1907-15.
43. Sakurai H, Asamura H, Watanabe S, et al. Clinicopathologic features of peripheral squamous cell carcinoma of the lung. Ann Thorac Surg 2004;78:222-7.
44. Jeremy George P, Banerjee AK, Read CA, et al. Surveillance for the detection of early lung cancer in patients with bronchial dysplasia. Thorax 2007;62:43-50.
45. Jeanmart M, Lantuejoul S, Fievet F, et al. Value of immunohistochemical markers in preinvasive bronchial lesions in risk assessment of lung cancer. Clin Cancer Res 2003;9:2195-203.
46. Yang H, Sun Y, Yao F, et al. Surgical Therapy for Bilateral Multiple Primary Lung Cancer. Ann Thorac Surg 2016;101:1145-52.
47. Huo JW, Luo TY, He XQ, et al. Radiological classification, gene-mutation status, and surgical prognosis of synchronous multiple primary lung cancer. Eur Radiol 2022;32:4264-74.
48. Falcoz PE, Conti M, Brouchet L, et al. The Thoracic Surgery Scoring System (Thoracoscore) risk model for in-hospital death in 15,183 patients requiring thoracic surgery. J Thorac Cardiovasc Surg 2007;133:325-32.
49. Fernandez FG, Kosinski AS, Burfeind W, et al. The Society of Thoracic Surgeons Lung Cancer Resection Risk Model: Higher Quality Data and Superior Outcomes. Ann Thorac Surg 2016;102:370-7.
50. Kopec SE, Irwin RS, Umali-Torres CB, et al. The postpneumonectomy state. Chest 1998;114:1158-84.
51. Brunelli A, Salati M, Rocco G, et al. European risk models for morbidity (EuroLung1) and mortality (EuroLung2) to predict outcome following anatomic lung resections: an analysis from the European Society of Thoracic Surgeons database. Eur J Cardiothorac Surg 2017;51:490-7.
52. Chen J, Soultanis KM, Sun F, et al. Outcomes of sleeve lobectomy versus pneumonectomy: A propensity score-matched study. J Thorac Cardiovasc Surg 2021;162:1619-1628.e4.

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Supplementary

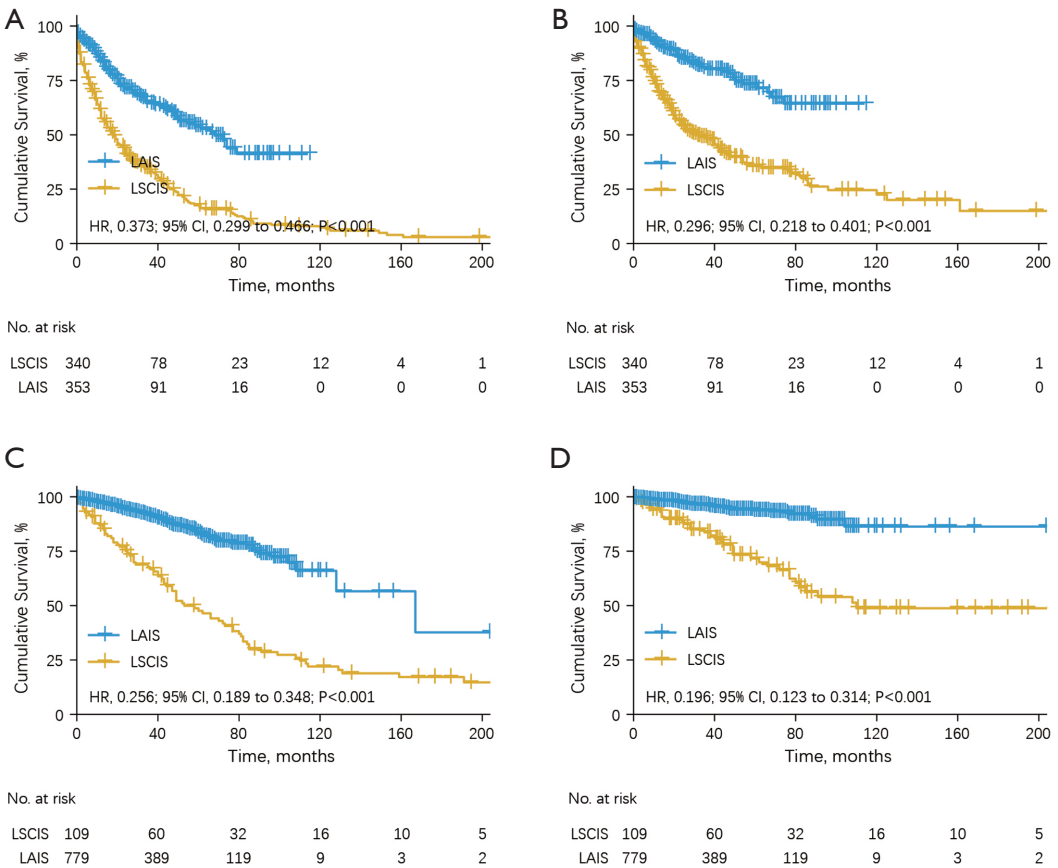

Figure S1 Kaplan-Meier curves of the patients with LSCIS and LAIS in the SEER cohort. (A,B) OS and LCSS of the patients with LSCIS and LAIS in the non-surgery group; (C,D) OS and LCSS of the patients with LSCIS, and LAIS in the surgery group. LSCIS, lung squamous cell carcinoma in situ; LAIS, lung adenocarcinoma in situ; OS, overall survival; LCSS, lung cancer-specific survival; HR, hazard ratio; CI, confidence interval; SEER, Surveillance Epidemiology and End Results.

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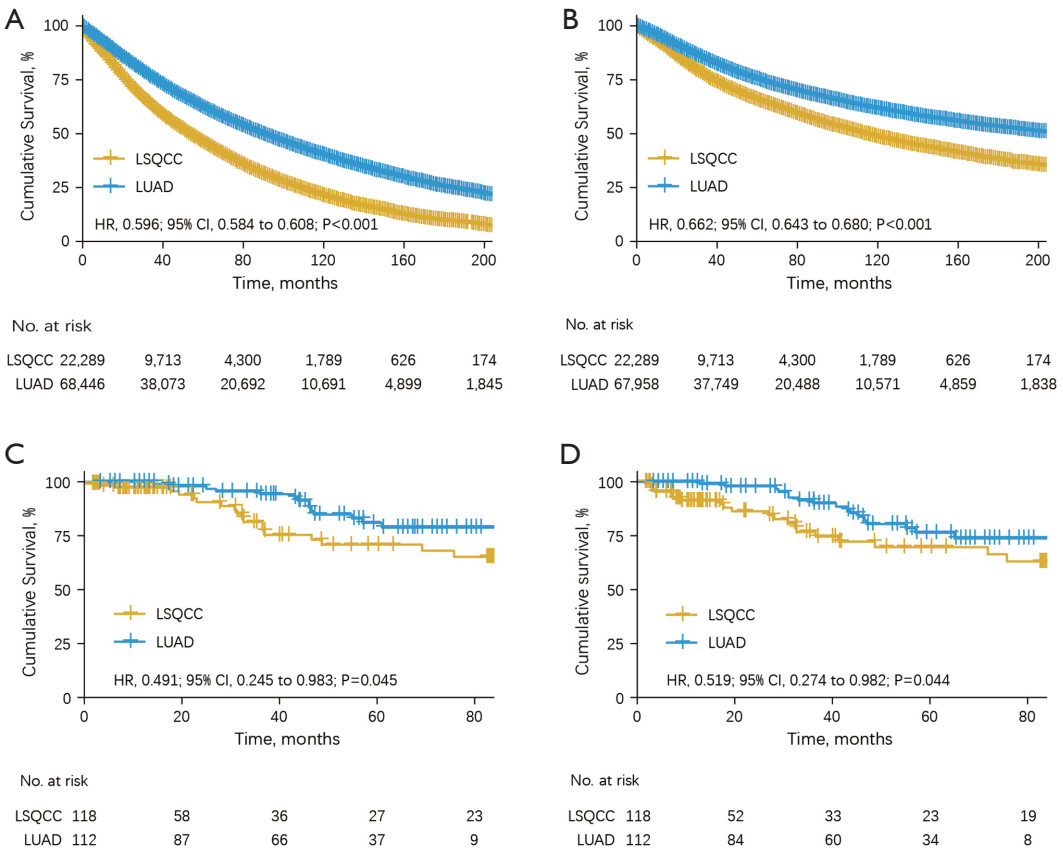

Figure S2 Kaplan-Meier curves of the patients with stage IA LUAD and stage IA LSQCC. (A,B) OS and LCSS of the patients with stage IA LUAD and stage IA LSQCC in the SEER cohort; (C,D) OS and PFS of the patients with stage IA LUAD and stage IA LSQCC in the Shanghai Pulmonary Hospital cohort. LUAD, lung adenocarcinoma; LSQCC, lung squamous cell cancer; OS, overall survival; LCSS, lung cancer-specific survival; SEER, Surveillance Epidemiology and End Results; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

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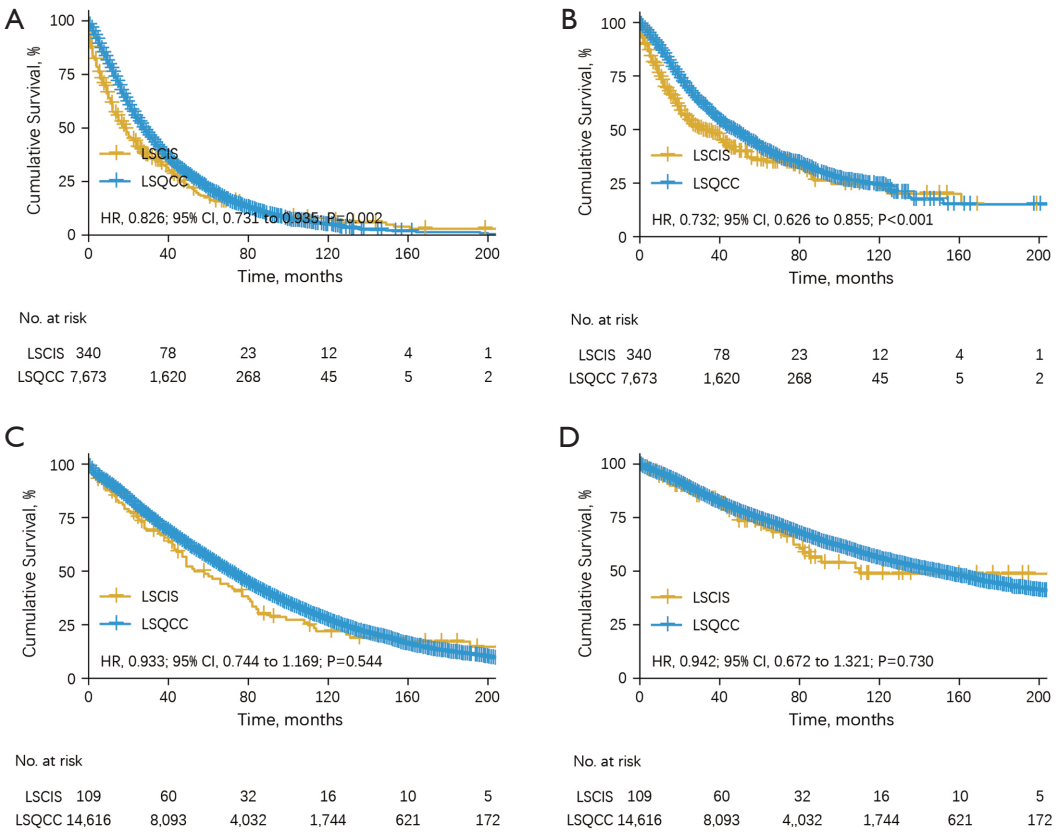

Figure S3 Kaplan-Meier curves of the patients with LSCIS and stage IA LSQCC in the SEER cohort. (A,B) OS and LCSS of the patients with LSCIS and stage IA LSQCC in the non-surgery group; (C,D) OS and LCSS of the patients with LSCIS, and stage IA LSQCC in the surgery group. LSCIS, lung squamous cell carcinoma in situ; LSQCC, lung squamous cell cancer; OS, overall survival; LCSS, lung cancer-specific survival; HR, hazard ratio; CI, confidence interval; SEER, Surveillance Epidemiology and End Results.

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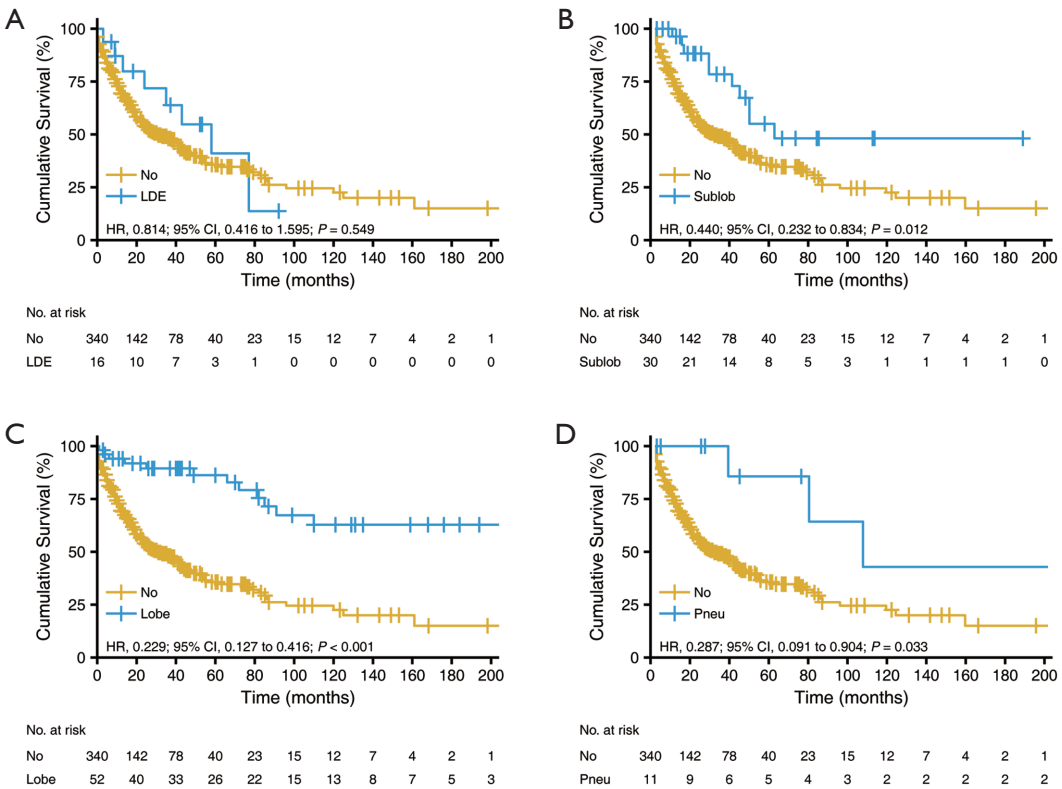

Figure S4 Kaplan-Meier curves of the patients with LSCIS in the SEER cohort according to the surgical procedures. (A-D). LCSS of the patients with LSCIS in the non-surgery, LDE, sublobectomy, lobectomy, and pneumonectomy groups. LSCIS, lung squamous cell cancer in situ; LCSS, lung cancer-specific survival; No, non-surgery; LDE, local destructed or excised; Sublob, sublobectomy; Lobe, lobectomy; Pneu, pneumonectomy; HR, hazard ratio; CI, confidence interval.

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Table S1 Demographics and clinicopathologic characteristics of the patients with LSCIS in the SEER cohort

Characteristics	Non-surgery, N (%)	Surgery, N (%)	P
Total	340 (100.0)	109 (100.0)	
Age (years)			0.013
≤60	70 (20.6)	27 (24.8)	
>60 to 70	107 (31.5)	47 (43.1)	
>70	163 (47.9)	35 (32.1)	
Gender			0.472
Male	237 (69.7)	80 (70.6)	
Female	103 (30.3)	29 (26.6)	
Race			0.101
White	274 (80.6)	97 (89.0)	
Black	48 (14.1)	7 (6.4)	
Asian/other	18 (5.3)	5 (4.6)	
Primary site			0.335
Main bronchus	36 (10.6)	10 (9.2)	
Upper lobe	174 (51.2)	63 (57.8)	
Middle lobe	15 (4.4)	8 (7.3)	
Lower lobe	95 (27.9)	25 (22.9)	
Unspecific	20 (5.9)	3 (2.8)	
Chemotherapy			<0.001
No	266 (78.2)	106 (97.2)	
Yes	74 (21.8)	3 (2.8)	
Radiotherapy			<0.001
No	241 (70.9)	102 (93.6)	
Yes	99 (29.1)	7 (6.4)	
Reason of non-surgery			
Not recommended	295 (86.8)		
Recommended but not performed	45 (13.2)		

LSCIS, lung squamous cell cancer in situ.

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Table S2 Outcomes of the patients with LSCIS after surgery in the Shanghai Pulmonary Hospital cohort

Characteristics	LSCIS	Progression/Recurrence			Death		
	Number	Number	OR (95% CI)	P	Number	OR (95% CI)	P
LDE							
No	23	-					
Yes	11	11					
Surgery			0.969 (0.910–1.031)	0.941		7.000 (0.362–135.517)	0.276
Lobectomy	32	1			4		
Pneumonectomy	2	0			1		

LSCIS, lung squamous cell cancer in situ; OR, odds ratio; CI, confidence interval; LDE, local destructed or excised.

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