Received: 9 June 2022 | Accepted: 22 July 2022

DOI: 10.1111/1759-7714.14604

ORIGINAL ARTICLE

WILEY

Different clinical characteristics and survival between surgically resected pure and combined small cell lung cancer

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Funding information
Shanghai Shen Kang Hospital Development Center Clinical Research Plan of SHDC, Grant/Award Number: SHDC2020CR4017; National Multi-disciplinary Treatment Project for Major Diseases, Grant/Award Number: 2020NMDTP; Nurture Project of Basic Research of Shanghai Chest Hospital, Grant/Award Number: 2020YNJCM06; Shanghai Science and Technology Committee Program, Grant/Award Number: 19QA1408000

Abstract

Background: Small cell lung cancer (SCLC) is the most malignant and common form of neuroendocrine lung cancer with pure (P-SCLC) and combined subtypes (C-SCLC). However, little is known about the differences between these two groups and in this study we aimed to provide a more comprehensive insight into SCLC.

Methods: Data from 580 postoperative patients with pathologically confirmed SCLC in Shanghai Chest Hospital from January 2010 to December 2020 were collected retrospectively. The clinical characteristics and prognosis were analyzed.

Results: A total of 357 P-SCLC patients and 223 C-SCLC patients were included. The results indicated that P-SCLC appeared to have a higher proportion of being located in the middle lobe than C-SCLC. The incidences of P-SCLC in patients with visceral pleural invasion (VPI) and in stage II were higher than C-SCLC, while C-SCLC was more likely to be accompanied by higher incidences of epidermal growth factor receptor (EGFR) mutation, anaplastic lymphoma kinase (ALK) rearrangement, and higher levels of CEA, SCCA and CYFRA21-1 than P-SCLC. The most common were SCLC combined with large cell neuroendocrine components among 223 C-SCLCs. Survival analysis confirmed a more favorable disease-free survival (DFS) ($p = 0.016$) and overall survival (OS) ($p = 0.024$) in patients with P-SCLCs compared with C-SCLCs. Histological type, tumor location, pN stage, adjuvant chemotherapy, serum NSE and CA125 levels were independent risk factors for survival rate in SCLC. In addition, adjuvant chemotherapy was beneficial in improving stage I P-SCLC and C-SCLC DFS and OS rates, and similar results were not seen in adjuvant radiation therapy.

Conclusions: Patients with C-SCLC have a poorer prognosis than P-SCLC patients. We determined that large cell neuroendocrine carcinoma was the most common additional component of C-SCLC, and patients with this component appeared to have a longer DFS and OS than other combined components.

KEYWORDS
combined small cell lung cancer, prognosis, pure small cell lung cancer, treatment

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INTRODUCTION

Small cell lung cancer (SCLC) is considered to be the most common histological type of pulmonary neuroendocrine tumors which currently represents about 15% to 20% of all patients with invasive lung cancer worldwide.[1,2] It also tends to be accompanied by an extremely high rate of rapid growth and early metastasis.

The great majority of SCLCs are pure SCLC (P-SCLC); however, in addition, some are defined as combined SCLC (C-SCLC) which are considered to be combined with additional components consisting of any histological components of non-small cell lung cancer (NSCLC) based on the World Health Organization (WHO) in 2015,[3] including adenocarcinoma (ADC), squamous cell carcinoma (SCC), large cell neuroendocrine carcinoma (LCNEC), and any other rare histological components. As reported in previous studies, the incidence of C-SCLC accounts for 2%–28% of all SCLC patients.[4–6]

Because of the complexity of diagnosis and the lack of C-SCLC clinical standardization, most previous studies take pure and combined SCLC as a whole.[4–6] As a result, there are limited studies about the differences between pure and combined SCLC. Most SCLC patients are found to be at an advanced stage of disease, and only 30% with early stage might benefit from surgery.[7,8] However, those operable patients were reported to have a high rate of recurrence and a poor prognosis, and whether stage I patients need adjuvant therapy after surgery still remains in debate.[9–11] Thus, we conducted this study to retrospectively investigate the clinical and pathological characteristics between P-SCLC and C-SCLC and to provide insights into their treatment.

METHODS

Patients

A total of 1137 patients who underwent resection for SCLC in Shanghai Chest Hospital from January 2010 to December 2020 were retrospectively analyzed. All surgically resected specimens were evaluated by two experienced pathologists to confirm the final diagnosis of C-SCLC or P-SCLC according to the most recent World Health Organization criteria for SCLC. The pathological criteria of C-SCLC included: (1) SCLC combined with any histological components of NSCLC, and (2) in SCLC combined with a large cell neuroendocrine carcinoma there should be at least a 10% lung cancer component. Our exclusion criteria included: (1) history of other tumor, (2) palliative surgery, (3) recieved other therapy as first-line treatment, (4) incomplete postoperative treatment information, (5) incomplete survival information, (6) overall survival (OS) <3 months, (7) no definitive diagnosis, (8) no lymph adenectomy, and (9) ECOG-PS ≥2.

The demographic and clinicopathological data of these patients were collected, including gender, age, smoking history, resection type, primary site, tumor laterality, tumor location, pathological T, N, tumor node metastasis (TNM) stage and adjuvant treatments. The tumor stage was assessed according to the eighth edition of the TNM staging classification system drafted by the International Association for the Study of Lung Cancer.[12] This retrospective study was approved by the Research Ethics Committee of Shanghai Chest Hospital, and informed consent was obtained from each patient.

Follow-up data

The last follow-up was in February 2022, and all patient follow-up data was acquired directly by regular outpatient reviews or family contact. In general, monthly outpatient follow-ups were carried out for the first 6 months after surgery, the timing and interval of follow-up were then determined based on the tumor status and the treatment recommended by the doctors. The endpoints of this study were disease-free survival (DFS) and OS. DFS was defined as the time between surgery and observation of tumor recurrence, or the last follow-up, OS was calculated from pathological diagnosis to death or final visit.

Statistical analysis

We compared the clinicopathological differences between P-SCLC, C-SC/LC and C-SC/non-LC patients. For categorical variables, the percentage was calculated, and $\chi 2$ and Fisher's exact test were applied to determine significance of difference. Continuous variables were compared by student *t*-test or Mann-Whitney U test. The Kaplan–Meier method was used to estimate survival rates, with the log-rank test performed to analyze between-group survival differences. Cox proportional hazards models with step-down selection were used to identify significant independent risk factors for DFS and OS. All tests were two sided, $p < 0.05$ was considered statistically signifificant. Statistical analyses were performed using SPSS (version 26.0, IBM Corporation).

RESULTS

Patient clinical characteristics

From 2010 to 2020, a total of 580 eligible SCLC patients who met our criteria were included in this study (Supplementary Figure 1). The comparison of clinical characteristics between patients with and without complete follow-up information showed no significant difference (Supplementary Table 1).

A total of 357 patients (61.6%) were diagnosed with P-SCLC and 223 (38.4%) with C-SCLC. The clinical characteristics of patients are presented in Table 1. About 70.3% patients were ever, or current smokers. A total of 507 patients (87.4%) were male and 73 (12.6%) were female. Among 223 cases of

TABLE 1 Clinical characteristics of patients with pure and combined SCLC

Characteristics	Total cohort ($n = 580$) (%)	P-SCLC ($n = 357$) (%)	C-SCLC (n = 223)		*p*-value (P vs. C)	*p*-value (P-SC/LC vs. P-SC/non-LC)
			C-SC/LC ($n = 150$) (%)	SC/non-LC ($n = 73$) (%)		
Gender					0.243	0.246
Male	507 (87.4)	307 (86.0)	137 (91.3)	63 (86.3)		
Female	73 (12.6)	50 (14.0)	13 (8.7)	10 (13.7)		
Age (year)					0.063	0.761
<65	352 (60.7)	230 (64.4)	81 (54)	41 (56.2)		
≥65	228 (39.3)	127 (35.6)	69 (46)	32 (43.8)		
Smoking History					0.259	0.512
Yes	408 (70.3)	243 (68.1)	113 (75.3)	52 (71.2)		
No	172 (29.7)	114 (31.9)	37 (24.7)	21 (28.8)		
Resection type					**<0.001**	0.383
Pneumonectomy	33 (5.7)	25 (7)	6(4)	2 (2.7)		
Lobectomy	498 (85.9)	288 (80.7)	142(94.7)	68 (93.2)		
Sublobectomy	49 (8.4)	44 (12.3)	2(1.3)	3 (4.1)		
Primary site					**<0.001**	0.500
Upper lobe	245 (42.2)	120 (33.6)	81 (54)	44 (60.3)		
Middle lobe	78 (13.4)	71 (19.9)	4 (2.7)	3 (4.1)		
Lower lobe	257 (44.3)	166 (46.5)	65 (43.3)	26 (35.6)		
Laterality					0.404	0.181
Left	286 (49.3)	177 (49.6)	78 (52)	31 (42.5)		
Right	294 (50.7)	180 (50.4)	72 (48)	42 (57.5)		
Tumor location					0.078	0.349
Central	247 (42.6)	164 (45.9)	59 (39.3)	24 (32.9)		
Peripheral	333 (57.4)	193 (54.1)	91 (60.7)	49 (67.1)		
pT stage					0.503	0.493
T1-2	448 (77.2)	271 (75.9)	121 (80.7)	56 (76.7)		
T3-4	132 (22.8)	86 (24.1)	29 (19.3)	17 (23.3)		
pN stage					0.393	0.725
N0	224 (38.6)	133 (37.3)	60 (40.0)	31 (42.5)		
N1-2	356 (61.4)	224 (62.7)	90 (60.0)	42 (57.5)		
pTNM stage					**0.014**	**0.019**
I	161 (27.8)	99 (27.7)	40 (26.7)	22 (30.1)		
II	157 (27.1)	87 (24.4)	56 (37.3)	14 (19.2)		
III	262 (45.2)	171 (47.9)	54 (36)	37 (50.7)		
VPI					**<0.001**	**0.037**
With	394 (67.9)	300 (84.0)	56 (37.3)	38 (52.1)		
Without	186 (32.1)	57 (16.0)	94 (62.7)	35 (47.9)		
Adjuvant chemotherapy					0.708	0.572
Yes	465 (80.2)	289 (81)	120 (80)	56 (76.7)		
No	115 (19.8)	68 (19)	30 (20)	17 (23.3)		
PORT					0.151	0.342
Yes	183 (31.6%)	122 (34.2)	44 (29.3)	17 (23.3)		
No	397 (68.4%)	235 (65.8)	106 (70.7)	56 (76.7)		

Abbreviations: C-SCLC, combined small cell lung cancer; C-SC/LC, small cell lung cancer combined with large cell neuroendocrine carcinoma; C-SC/non-LC, small cell lung cancer combined with other NSCLC components; P-SCLC, pure small cell lung cancer; pTNM stage, pathological tumor node metastasis staging; PORT, postoperative adjuvant radiotherapy; SCLC, small cell lung cancer; VPI, visceral pleural invasion

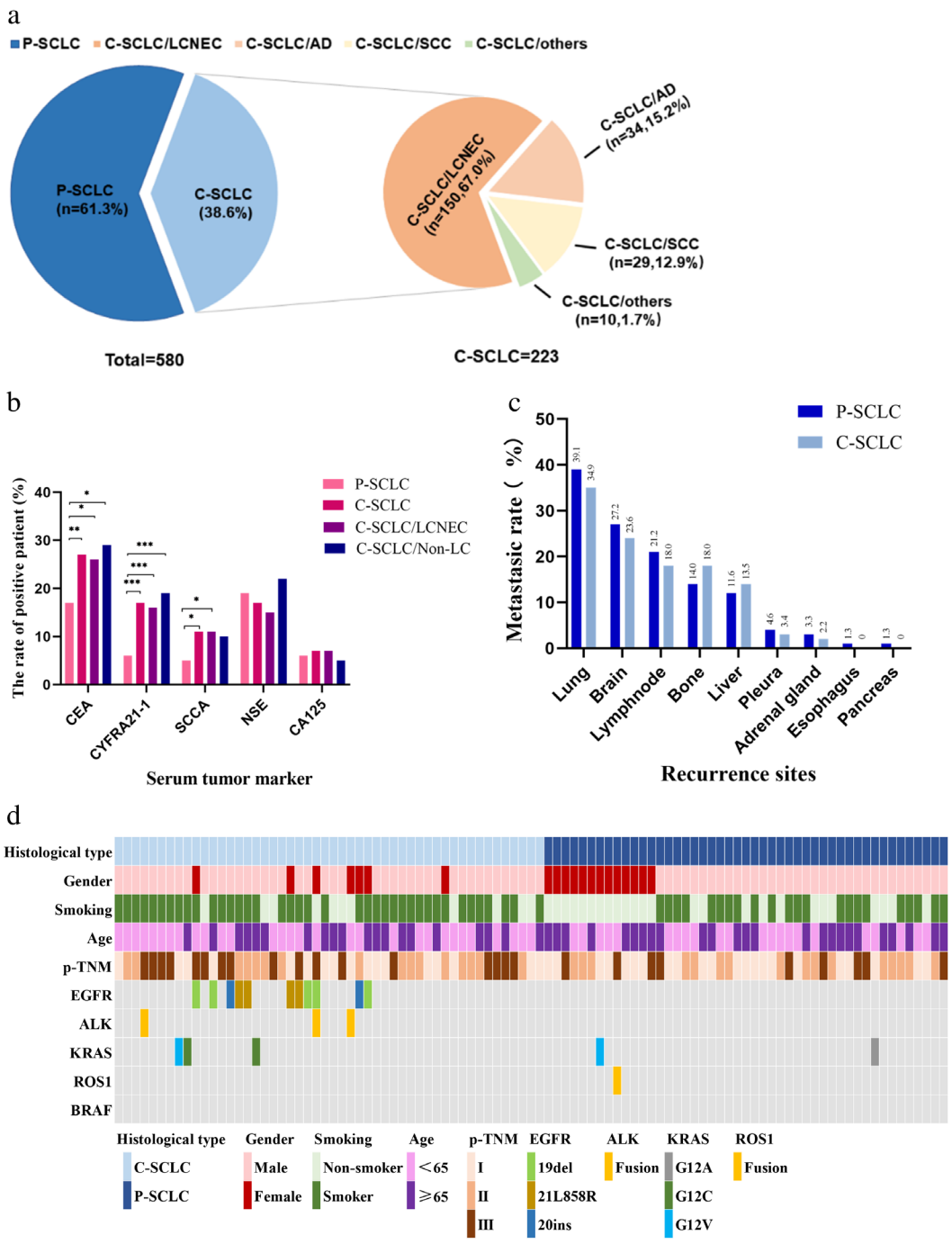

FIGURE 1 Constitutional diagram of small cell lung cancer (SCLC) (a), comparison of serum tumor markers (b), recurrence sites (c) and molecular alterations between P-SCLC and C-SCLC (d). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Abbreviations: C-SCLC/LCNEC, small cell lung cancer combined with large cell neuroendocrine carcinoma; C-SCLC/ADC, small cell lung cancer combined with adenocarcinoma; C-SCLC/SCC, small cell lung cancer combined with squamous cell carcinoma; C-SCLC/others, small cell lung cancer combined with other NSCLC components

C-SCLCs, the most common were SCLC combined with large cell neuroendocrine components (SCLC/LCNEC, 67.0%, $n = 150$), then SCLC combined with adenocarcinoma (SCLC/AD, 15.2%, $n = 34$), and finally SCLC combined with SCC (SCLC/SCC, 12.9%, $n = 29$).

In addition to the above cases, the remaining 10 cases were combined with other NSCLC components, such as carcinoid tumor, adenosquamous carcinoma, giant cell carcinoma, or spindle cell carcinoma (SCLC/others, 1.7%, $n = 10$; Figure 1a).

Comparison between different pathological groups

Of 223 C-SCLC patients included in this analysis, tumors in the C-SC/non-LC group showed a higher incidence of visceral pleural invasion (VPI) compared to the C-SC/LC group (52.1% vs. 37.3%, $p = 0.037$). Among these surgically treatable C-SCLCs, the most common were stage III (40.8%), followed by stage II (31.4%) and stage I (27.8%)

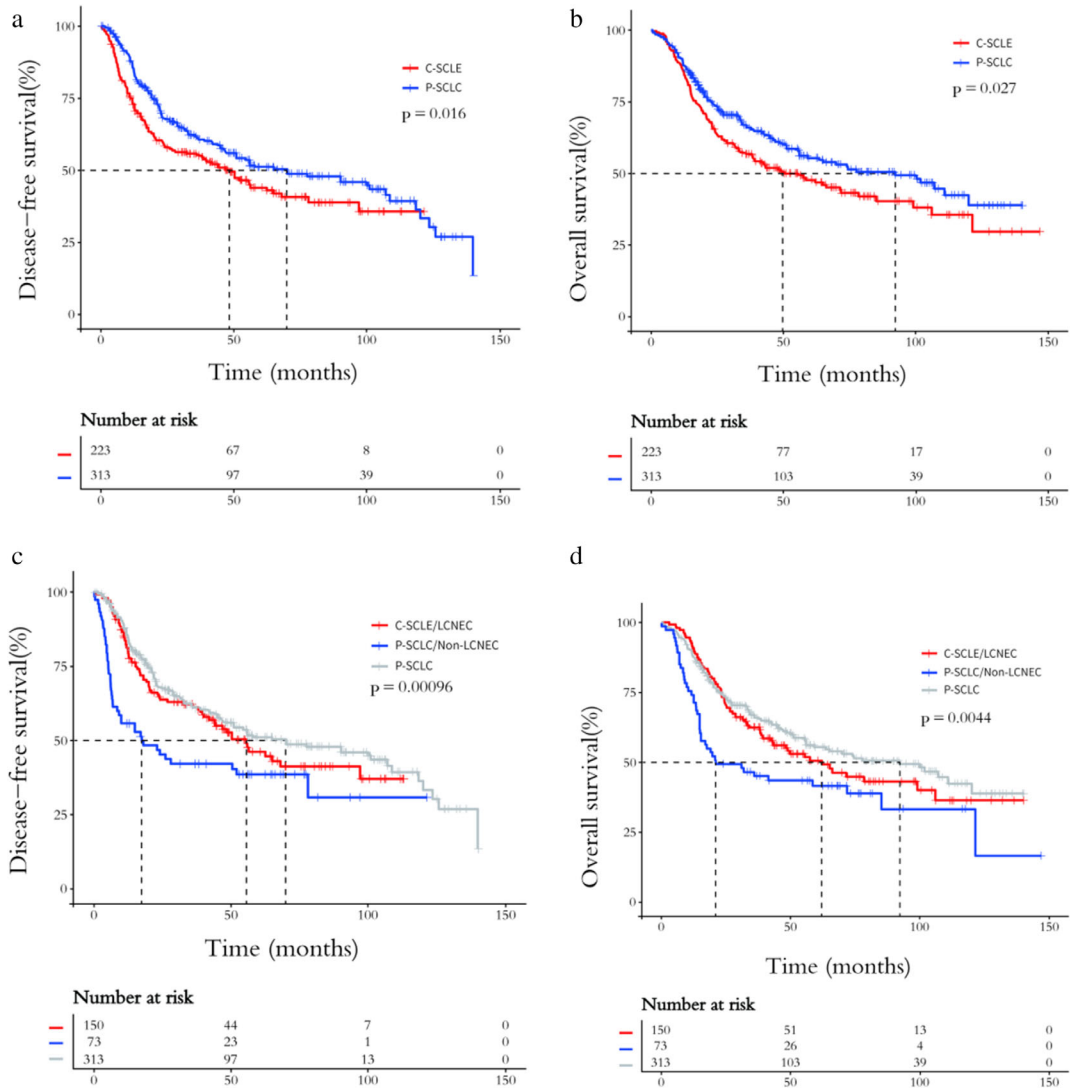

FIGURE 2 Disease-free survival (DFS) and overall survival (OS) in patients with small cell lung cancer (SCLC). (a and b) Graphs show DFS (A) and OS (b) in patients with P-SCLC versus patients with C-SCLC. (c and d) Graphs show DFS (c) and OS (d) in patients with P-SCLC, patients with SCLC combined with large cell neuroendocrine carcinoma (LCNEC), and patients with SCLC combined with other histological types of cancer.

according to the AJCC eighth TNM staging which showed inconsistencies in the three-stage distribution with a statistically significant difference ($p = 0.019$) (Table 1).

With regard to the differences between P-SCLC and C-SCLC patients, there was no significant difference in terms of patient sex ($p = 0.063$), patient age ($p = 0.063$), smoking history ($p = 0.259$), pathological T status ($p = 0.503$), pathological N status ($p = 0.393$), tumor laterality ($p = 0.404$), tumor location ($p = 0.078$), and adjuvant chemotherapy ($p = 0.708$) or radiotherapy ($p = 0.151$) among both groups (Table 1).

However, P-SCLC appeared to have a higher incidence of being located in the middle lobe than C-SCLC (19.9 vs. 6.8%, $p < 0.001$). Compared with the C-SCLC group, P-SCLC tended to have a higher risk of tumor VPI (83.7 vs. 41.2%, $p < 0.001$). There were obvious differences in the distribution of pathological TNM staging between P-SCLC and C-SCLC, the number of patients in stage I was similar (27.7 and 27.8%, respectively), but the proportion of patients in stage II of P-SCLC was significantly higher than that of C-SCLC, while in stage III, the opposite was the same, and the difference was statistically significant (24.4 vs. 31.4%, 47.9 vs. 40.8%, $p = 0.014$). With regard to the extent of surgical resection, significant statistical difference was shown in the proportion of surgical resection range of whole lung, lung lobe and sublobe between both groups (7 vs. 3.6%, 80.7 vs. 94.2%, 12.3 vs. 2.8%, $p < 0.001$) (Table 1).

Preoperative serum tumor markers were evaluated in 484 patients in our study. There was a statistically significant difference in the positive rate of CEA (17.7 vs. 27.5%), CYFRA21-2 (6.4 vs. 17.5%), and SCCA (5.7 vs. 11.1%) between P-SCLC and C-SCLC ($p = 0.01$, < 0.0001, 0.032, respectively). However, no significant differences were seen between the different types of C-SCLC (Figure 2b).

A gene test was carried out on 98 surgical samples, of which 19 samples carried genetic alterations (Figure 2c). Eleven patients (11.2%) developed epidermal growth factor

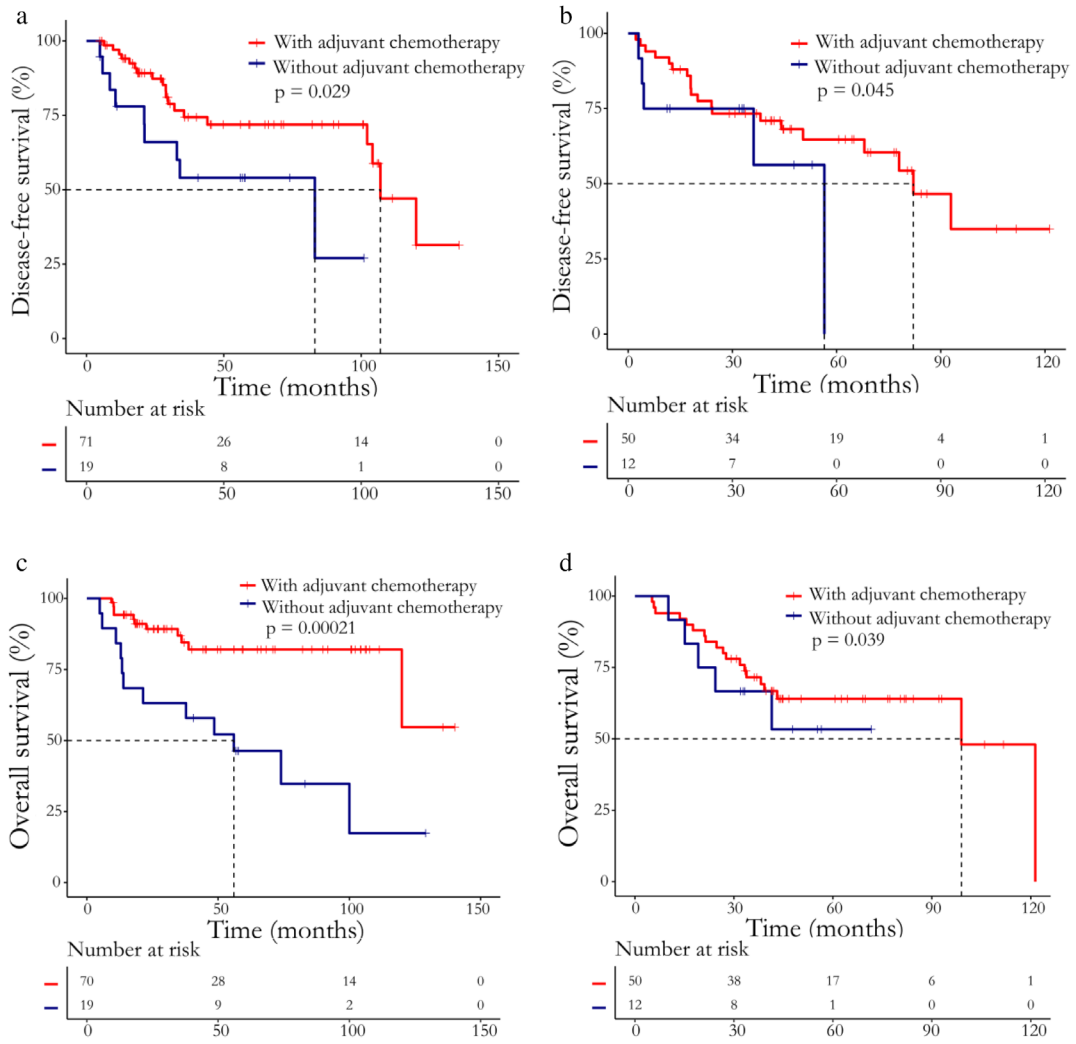

FIGURE 3 Disease-free survival (DFS) and overall survival (OS) in SCLC patients who underwent adjuvant chemotherapy. (a and b) Graphs show DFS in patients with P-SCLC (a) and patients with C-SCLC (b) with or without adjuvant chemotherapy. (c and d) Graphs show OS in patients with P-SCLC (c) and patients with C-SCLC (d) with or without adjuvant chemotherapy.

receptor (EGFR) mutations, all were detected in C-SCLC, including four EGFR exon 21 L858R mutations, two EGFR exon 20 insertions, and five EGFR exon 19 deletions. Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations were found in five patients, among them, three cases (KRAS G12C/G12V) were detected in C-SCLC and two cases (KRAS G12A/G12V) were detected in P-SCLC. Anaplastic lymphoma kinase (ALK) rearrangements were identified in three patients, all of which were C-SCLC. What is more, 1 ROS1 (ROS proto-oncogene 1) rearrangement was detected in P-SCLC. It should be noted that one patient carried EGFR exon 19 deletion and ALK rearrangement comutation.

Comparison of stage I patients with or without adjuvant therapy

A total of 161 (27.8%) SCLC patients were at stage I in our research, of which 41 (25.5%) patients received adjuvant radiotherapy and 125 (77.6%) patients received adjuvant chemotherapy. It appeared that among the stage I patients who received adjuvant radiotherapy, there was a significantly higher proportion of P-SCLC than C-SCLC (75.6 vs. 24.4%, $p = 0.039$), and no significant difference was seen in adjuvant chemotherapy between both groups (Supplementary Table 2).

Further survival analysis showed that adjuvant chemotherapy was beneficial in improving stage I P-SCLC and C-SCLC DFS (DFS $p = 0.029$, 0.045, respectively; Figure 3a, b) and OS rate (OS $p = 0.00021$, 0.039, respectively, Figure 3c, d), but similar results were not seen in adjuvant radiation therapy (DFS $p = 0.54$, 0.19, OS $p = 0.34$, 0.16, respectively, Supplementary Figure 2A, 2B, 2C, 2D). Factors that might affect DFS and OS in stage I SCLC patients with (blue line) or without adjuvant chemotherapy were enrolled (Figure 4). In the univariate analysis, we found that gender was the main DFS modulator for stage I SCLC patients without adjuvant chemotherapy ($p = 0.034$).

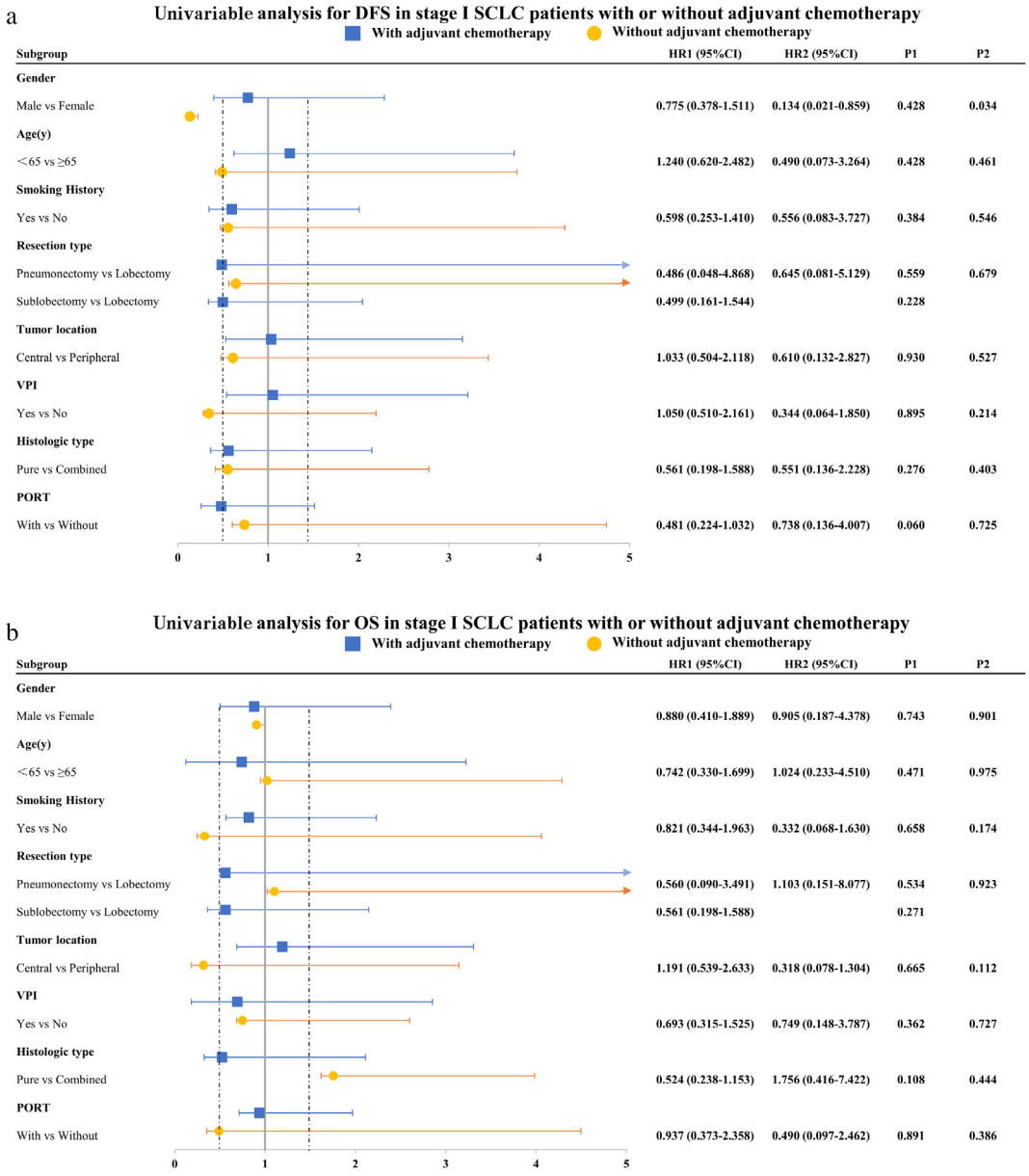

FIGURE 4 Univariable analysis for disease-free survival (DFS) (a) and overall survival (OS) (b) in 161 cases of stage I small cell lung cancer (SCLC) patients with (blue line) or without adjuvant chemotherapy (yellow line). CI, confidence interval; HR, hazard ratio. HR1 and P1 represent the parameters for stage I SCLC patients with adjuvant chemotherapy, HR2 and P2 represent the parameters for stage I SCLC patients without adjuvant chemotherapy

Survival analysis

Among a total of 580 patients, tumor recurrence occurred in 240 patients by the end of follow-up, and the most common form of recurrence was local recurrence (43.8%, $n = 105$), followed by distant metastatic recurrence (40.8%, $n = 98$) and patients with both local and distant metastatic recurrence (15.4%, $n = 37$). In patients with local recurrence, the lung was the most common site (90/105, 85.7%), and brain was the most common site (62/98, 63.3%) of distant metastatic recurrence (Figure 2b).

The survival outcomes analysis between P-SCLC and C-SCLC showed that patients with P-SCLC had a significantly longer DFS and OS than C-SCLC (DFS HR = 0.738, 95% CI: 0.575–0.947 $p = 0.016$, OS HR = 0.755, 95% CI: 0.587–0.970 $p = 0.027$, Figure 2a, b). What is more, the combined components in C-SCLC also had an obvious impact on survival time, and a log-rank test indicated that patients with C-SCLC/LCNECs had a superior survival time than C-SCLC/non-LCNECs (DFS HR = 0.665, 95% CI: 0.455–0.928 $p = 0.00096$, OS HR = 0.716, 95% CI: 0.509–0.977 $p = 0.0044$; Figure 2c, d).

Factors that might affect DFS and OS in P-SCLC and C-SCLC patients were enrolled (Table 2, 3). In the univariate analysis, histological type, tumor location, pN stage, adjuvant chemotherapy, serum NSE and CA125 levels were

TABLE 2 Univariable and multivariable analysis for disease-free survival (DFS) in patients with resected SCLC

	Univariable analysis			Multivariable analysis		
Characteristics	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Gender			0.989			
Male	Reference					
Female	1.003	0.698–1.44				
Age (year)			0.751			
<65	Reference					
≥65	1.009	0.747–1.234				
Smoking History			0.250			
Yes	Reference					
No	1.173	0.894–1.539				
Resection type			0.978			
Pneumonectomy	Reference					
Lobectomy	0.937	0.478–1.836	0.850			
Sublobectomy	0.992	0.640–1.54	0.973			
Tumor location			**0.039**			**0.009**
Central	Reference			Reference		
Peripheral	1.297	1.014–1.66		1.424	1.090–1.860	
VPI			0.236			
With	Reference					
Without	1.173	0.901–1.526				
pT stage			0.282			
T1-2	Reference					
T3-4	0.853	0.638–1.14				
pN stage			**<0.001**			**<0.001**
N0	Reference			Reference		
N1-2	0.543	0.416–0.708		0.557	0.421–0.737	
Adjuvant chemotherapy			**<0.001**			**<0.001**
Yes	Reference			Reference		
No	1.899	1.413–2.552		2.208	1.600–3.047	
PORT			0.291			
Yes	Reference					
No	0.868	0.667–1.129				
Histological type			**0.001**			**<0.001**
P-SCLC	Reference			Reference		
C-SC/LC	1.453	1.019–2.070	0.311	1.305	0.969–1.757	0.080
C-SC/non-LC	1.903	1.352–2.679	**<0.001**	2.404	1.668–3.466	**<0.001**
CEA, ng/ml	1.007	0.999–1.015	0.075			
CYFRA21-1, ng/ml	1.031	0.998–1.065	0.070			
SCCA, ng/ml	1.018	0.950–1.090	0.615			
NSE, ng/ml	1.018	1.010–1.027	**<0.001**	1.014	1.005–1.023	**0.002**
CA125, kU/l	1.008	1.004–1.012	**<0.001**	1.005	1.001–1.01	**0.019**

Abbreviations: CI, confidence interval; CLC, small cell lung cancer; C-SCLC: combined small cell lung cancer; C-SC/LC, small cell lung cancer combined with large cell neuroendocrine carcinoma; C-SC/non-LC, small cell lung cancer combined with other NSCLC components; HR, hazard ratio; PORT: postoperative adjuvant radiotherapy; P-SCLC: pure small cell lung cancer

the main DFS modulators for SCLC patients with statistical significance ($p = 0.039$, <0.001, 0.001, <0.001, <0.001, <0.001, respectively; Table 2). Further, we included the above statistically distant different variables into multivariate analysis and results showed that all of these variables were also independent factors for DFS ($p = 0.009$, <0.001,

TABLE 3 Univariable and multivariable Cox regression analysis for overall survival (OS) in patients with resected SCLC

	Univariable analysis			Multivariable analysis		
Characteristics	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Gender			0.903			
Male	Reference					
Female	0.977	0.674–1.417				
Age (year)			0.133			
<65	Reference					
≥65	0.824	0.639–1.061				
Smoking History			0.900			
Yes	Reference					
No	1.018	0.765–1.356				
Resection type			0.790			
Pneumonectomy	Reference					
Lobectomy	0.873	0.426–1.789				
Sublobectomy	1.060	0.670–1.678				
Tumor location			0.114			
Central	Reference					
Peripheral	1.226	0.953–1.577				
VPI			0.085			
With	Reference					
Without	1.267	0.968–1.660				
pT stage			0.093			
T1-2	Reference					
T3-4	0.781	0.586–1.042				
pN stage			**<0.001**			**<0.001**
N0	Reference			Reference		
N1-2	0.541	0.413–0.711		0.510	0.382–0.682	
Adjuvant chemotherapy			**<0.001**			**<0.001**
Yes	Reference			Reference		
No	2.742	2.082–3.612		3.185	2.363–4.294	
PORT			0.113			
Yes	Reference					
No	1.26	0.947–1.677				
Histological type			**0.005**			**<0.001**
P-SCLC	Reference			Reference		
C-SCLC (LCNEC)	1.158	0.870–1.542	0.314	1.333	0.989–1.798	0.059
C-SCLC (non-LCNEC)	1.770	1.258–2.490	**0.001**	2.105	1.463–3.029	**<0.001**
CEA, ng/ml	1.012	1.006–1.018	**<0.001**	1.012	1.005–1.018	**<0.001**
CYFRA21-1, ng/ml	1.025	0.987–1.064	0.201			
SCCA, ng/ml	1.030	0.967–1.098	0.356			
NSE, ng/ml	1.020	1.011–1.029	**<0.001**	1.013	1.004–1.022	**0.006**
CA125, kU/l	1.010	1.006–1.014	**<0.001**	1.008	1.004–1.013	**<0.001**

Abbreviations: CI, confidence interval; HR, hazard ratio; C-SCLC: combined small cell lung cancer; C-SC/LC, small cell lung cancer combined with large cell neuroendocrine carcinoma; C-SC/non-LC, small cell lung cancer combined with other NSCLC components; PORT, postoperative adjuvant radiotherapy; P-SCLC, pure small cell lung cancer; SCLC, small cell lung cancer

<0.001, <0.001, 0.002, 0.019, respectively; Table 3). With regard to OS, univariate analysis found that histological type, pN stage, adjuvant chemotherapy, serum CEA, NSE and CA125 levels were considered as independent predictive factors (p = 0.005, <0.001, <0.001, <0.001, <0.001, <0.001, respectively; Table 3), and further multivariate analysis

indicated that all of these variables were also independent risk factors for OS ($p < 0.001$, <0.001, <0.001, <0.001, = 0.006, <0.001, respectively; Table 3).

DISCUSSION

Because of the complexity of diagnosis and the rarity of the cases, our understanding of the difference between operable P-SCLC and C-SCLC is mainly derived from small cohort size retrospective studies and case reports.[13–15] Currently, tumor pathological tissue biopsy is the gold standard for diagnosing SCLC patients. Bronchial biopsy or needle aspiration might cause limited size of biopsy specimens and presence of crush artifact which easily lead to misdiagnosis, while after thorough pathological evaluation of surgically removed specimens, the diagnostic rate of P-SCLC and C-SCLC was relatively higher.[16] Therefore, greater cohort size studies are needed to enhance the overall understanding.

The sample size included in our study was the largest in the same type of research. C-SCLC enrolled accounted for 38% of total SCLC, which was similar to a previous reported incidence rate of 2%–30%.[17,18]

As for combined components, we identified that large cell neuroendocrine carcinoma was the most common (67.0%, $n = 105$) additional component of C-SCLC, followed by adenocarcinoma (15.2%, $n = 34$) and squamous cell carcinoma (12.9%, $n = 29$); similar results were also observed in other studies.[13,19] After comparing the clinical characteristics difference between operable 150 C-SCLC/LCNECs and 73 C-SCLC/non-LCNECs, we found that C-SCLC/non-LCNECs had a higher incidence of III stage than C-SCLC/LCNECs, While the proportion of VPI of C-SCLC/LCNECs was higher than that of C-SCLC/non-LCNECs, similar results were found in other published analysis.[19]

With regard to the differences between P-SCLC and C-SCLC, previous retrospective studies have indicated that C-SCLC is mainly located in the upper lobe;[20,21] in our cohort, P-SCLC appeared to have a higher incidence of being located in the middle lobe than C-SCLC. In addition, P-SCLC had shown a higher incidence of VPI. We also analyzed the level of preoperative serum tumor markers which revealed a statistically significant difference in the positive rate of CEA (17.7 vs. 27.5%), CYFRA21-2 (6.4 vs. 17.5%), and SCCA (5.7 vs. 11.1%) between P-SCLC and C-SCLC. In clinical practice, lung squamous cell carcinoma is usually accompanied with elevated levels of SCCA and CYFRA21-1, while lung adenocarcinoma appears to have higher CEA and CYFRA21-1 levels,[22,23] suggesting that preoperative serum tumor markers level might help to distinguish C-SCLC from P-SCLC. However, no significant difference in preoperative serum tumor markers was found between C-SCLC/LCNECs and C-SCLC/non-LCNECs. The number of C-SCLCs enrolled in our cohort was relatively small, and may have caused additional types to be homologized by small cell lung cancer.

Histopathology plays a critical role in predicting prognosis in SCLC patients. In our study, the survival outcomes analyzed between P-SCLC and C-SCLC showed that P-SCLC had a significantly superior survival rate than C-SCLC, both in DFS and OS. However, from two related studies with small cohorts, Guo et al. compared 251 P-SCLC cases with 46 C-SCLC cases after surgery and identified no significant difference in survival outcomes between C-SCLCs and P-SCLCs (RFS $p = 0.994$, OS P = 0.683).[14] In addition, Woo et al. included 16 P-SCLC patients and 25 C-SCLC patients in analysis and found that there were no significant differences in their clinical features and prognosis.[11] Although our findings were inconsistent with previous small sample retrospective studies, the number of cases we enrolled in analysis is the largest, which may provide a clinical reference, and greater cohort size studies are needed to fill this gap. Furthermore, we performed a survival analysis between C-SCLC/LCNECs and C-SCLC/non-LCNECs which showed that C-SCLC/LCNECs had a significantly superior survival rate than C-SCLC/non-LCNECs, and similar results were found in another retrospective analysis.[19] Although the reason for this had not yet been reported, from our study it could be clearly seen that adjuvant chemotherapy is an independent risk factor for SCLC patients, the majority of them being administered an SCLC regimen such as EP/EC (etoposide plus platinum), IP/IC (irinotecan plus platinum), etc.[24,25] SCLC and large cell neuroendocrine carcinoma are both neuroendocrine cancers, which may result in C-SCLC/LCNEC patients responding better to conventional postoperative chemotherapy regimens and possibly account for a superior survival rate in patients than C-SCLC/non-LCNECs.

As for treatment modalities, the vital question of whether adjuvant therapy is required after surgery in stage I patients still remains to be determined. In our study, among the stage I patients who recieved adjuvant radiotherapy, P-SCLC had a significantly higher proportion than C-SCLC, and no significant difference was seen in adjuvant chemotherapy between two groups. Further analysis determined that in patients with stage I SCLC, both P-SCLC and C-SCLC could benefit from adjuvant chemotherapy, but similar results were not seen in adjuvant radiation therapy. According to previous prospective clinical trials,[26–28] adjuvant chemotherapy without radiotherapy is recommended postoperatively in stage I P-SCLC patients. However, the relevant results in C-SCLC have not yet been reported. Stage I C-SCLC patients were treated with the postoperative adjuvant treatment model which refer to stage I P-SCLCs treatment regimen, while no specific clinical trial data could support it. Our research might provide a strong reference value for clinical practice.

Targeted therapy has been widely used in patients with NSCLC in recent decades. As for P-SCLC, Thomas et al.[6] discovered three *EGFR* mutations in 329 patients. In our study, we found 19 samples carried genetic alterations among 98 surgical samples which were gene tested. After recurrence, all C-SCLC patients carried *EGFR* mutations

and one C-SCLC patient carried ALK rearrangements receiving TKIs benefited from the treatment, indicating the effectiveness of targeted therapy for C-SCLC. Unfortunately, we did not investigate the relationship between genetic mutations and chemotherapy efficacy because of the small size of samples.

Several possible limitations can be seen in our research. First, it was a retrospective and single-center study which inevitably caused selection bias. Second, our cohort size was relatively larger than previous retrospective studies, but because of the rarity of C-SCLC in clinics, the limited sample size when the C-SCLC group was divided into C-SCLC/LCNECs and C-SCLC/non-LCNECs may have reduced the statistical power. Third, a comprehensive genetic test was not performed in the majority of patients, thus we could not analyze the above differences from molecular levels. Therefore, multicenter prospective researches and large-sample studies are expected to provide more comprehensive insights into SCLC in the future.

In conclusion, our research indicated that patients with C-SCLC carry a poorer prognosis than those P-SCLC patients. LCNEC was the most common additional component of C-SCLC, and patients with this component appeared to have a longer DFS and OS than patients with other combined components. In addition, adjuvant chemotherapy was beneficial in improving stage I P-SCLC and C-SCLCs DFS and OS rates in patients, and similar results were not seen in patients undergoing radiation therapy.

ACKNOWLEDGMENTS

The authors would like to thank the study participants for their contribution to the research.

FUNDING INFORMATION

This research was supported by grants from Shanghai Shen Kang Hospital Development Center Clinical Research Plan of SHDC (SHDC2020CR4017), Shanghai Science and Technology Committee Program (19QA1408000), the Nurture Project of Basic Research of Shanghai Chest Hospital (2020YNJCM06) and National Multi-disciplinary Treatment Project for Major Diseases (2020NMDTP).

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Li Y, Wang Y, Zhou W, Chen Y, Lou Y, Qian F, et al. Different clinical characteristics and survival between surgically resected pure and combined small cell lung cancer. Thorac Cancer. 2022;13(19):2711–22. https://doi.org/10.1111/1759-7714.14604