Prognostic factors of patients with small cell lung cancer after surgical treatment

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Background: The current National Comprehensive Cancer Network guidelines recommend surgical treatment for patients with stages I–IIA small cell lung cancer (SCLC), but it still cannot deny the effect of surgical treatment on other limited-stage SCLC. Although more advanced diagnostic methods are now used for the diagnosis and classification of SCLC, the selection of surgical candidates is still arbitrary.

Methods: Data were collected from patients with SCLC who underwent surgery at the First Affiliated Hospital of Zhengzhou University from January 2011 to January 2021. Kaplan-Meier method was used to calculate cumulative survival curves, and log-rank test was used to evaluate differences among different subgroups. The Cox proportional hazard regression model was used to assess the predictive power of the variables for prognosis and survival.

Results: Smoking index, surgical resection method, TNM stage of postoperative pathology, and postoperative chemotherapy were significantly correlated with postoperative survival (P<0.05), which were independent predictors for postoperative survival. Patients with a smoking index >800 had a higher risk of death after surgery [hazard ratio (HR): 7.050, 95% confidence interval (CI): 3.079–16.143, P<0.001]. Compared with patients who underwent pulmonary lobectomy, those who underwent other pneumoresections (e.g., wedge resection, segmental resection, sleeve resection) had an increased risk of death (HR: 2.822, 95% CI: 1.030–7.734, P=0.044). Compared with stage I patients, stage II and stage III patients had an increased risk of death, with HRs of 6.039 and 3.145, respectively. Compared with those who received ≤4 courses of postoperative chemotherapy, those who received >4 courses of postoperative chemotherapy had reduced postoperative mortality risk (HR: 0.211, 95% CI: 0.097–0.459, P<0.001).

Conclusions: A high smoking index suggests worse prognosis; therefore, patients who smoke should be advised to quit smoking. Compared with stage II and stage III patients, surgical treatment is recommended for stage I SCLC patients. TNM staging, especially N staging, should be evaluated prior to surgery. Pulmonary lobectomy with mediastinal lymph node dissection should be the preferred surgical treatment for patients with SCLC. Patients should receive at least 5 courses of adjuvant chemotherapy after surgery.

Keywords: Small cell lung cancer (SCLC); surgical treatment; prognosis.

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Introduction

Lung cancer is the second most common cancer in the world and the leading cause of cancer death according to global cancer burden data by the International Agency for Research on Cancer of the World Health Organization in 2020 (1). Moreover, lung cancer has the highest morbidity and mortality among all cancers in China (1).

According to histopathological subtypes, lung cancer is often divided into the following two subtypes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). SCLC is a neuroendocrine malignancy originating from bronchial mucosa or glands, comprising roughly 15–20% of thoracic malignancies (2). It is characterized by rapid doubling time, high growth fraction, and the high incidence of distant metastasis. Therefore, the mortality rate of SCLC patients is very high. Most patients eventually develop cancer recurrence and/or metastasis, and the 5-year survival rate is less than 7% (3,4).

From a historical perspective, surgery used to be the primary treatment for SCLC. However, in recent decades, increasingly more studies have found that patients with SCLC receiving chemotherapy and/or radiotherapy have a better prognosis than those who undergo surgery; therefore, surgery is no longer the first choice for the treatment of SCLC (3,5). Systemic therapy, including chemotherapy, radiotherapy, and immunotherapy, has been widely accepted for the treatment of SCLC. Although the current National Comprehensive Cancer Network (NCCN) guidelines only recommend surgery for patients with clinical stages I–IIA SCLC (6), many studies have also found that patients with clinical stages II–III SCLC can also benefit from surgery (7-13). In addition, although more advanced diagnostic methods are now used for the diagnosis and classification of SCLC, the selection of surgical candidates for SCLC is still arbitrary.

Although there have been many clinical studies on the prognosis of small cell lung cancer, the sample size of some studies is not large enough. Some studies use data from the SEER database, but lack the necessary clinical details. Therefore, more retrospective clinical studies are needed to explore factors related to the prognosis of SCLC surgery. In the present study, we collected institutional data from the First Affiliated Hospital of Zhengzhou University to gain insight into the use of surgery-centered systemic treatment in resected stages I–III SCLC. We analyzed data to explore factors that may predict the outcome of surgical treatment, and determined indicators that can be used to screen patients who are most likely to benefit from surgery.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-2912).

Methods

Data were collected from patients with SCLC who underwent surgery at the First Affiliated Hospital of Zhengzhou University from January 2011 to January 2021. All patients enrolled in the group received complete radical lung resection, and postoperative pathology confirmed the diagnosis of SCLC. Patients who underwent palliative tumor resection surgery, those who had other malignant tumors, and those with missing data regarding postoperative pathological TNM staging were excluded from the present study.

The primary outcome measure was overall survival (OS). Telephone follow up of all enrolled patients was completed on February 6, 2021. Patients who declined to speak with us and who were lost to follow up were also included. In the data, if the missing value of a factor exceeded 20%, we did not include it in the statistical analysis.

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University (No.: 2020-KY-276) and the ethics committee approved the exemption from signing the informed consent.

Data were analyzed using SPSS version 21.0 (IBM, Armonk, NY, USA). $P<0.05$ indicated statistical significance. Kaplan-Meier method was used to calculate cumulative survival curves, and log-rank test was used to evaluate differences among different subgroups. The Cox proportional hazard regression model was used to assess the predictive power of the variables for prognosis and survival.

Statistical analysis

Continuous variables are grouped by median and categorical variables are grouped by category. First perform univariate Kaplan-Meier analysis for all variables. Then, variables with $P<0.2$ in the univariable analyses were included in the Cox multivariable analyses.

Results

We enrolled 142 patients with SCLC and analyzed the data.

A total of 135 patients (95%) have observed the end-point event, of which 12 patients have died, but the specific time of death has not been followed up. Therefore, only 123 (86.6%) patients achieved accurate OS.

General information

Of the 142 patients, 101 (71.1%) were male and 41 (28.9%) were female. The median age was 60 years (range, 36–79 years); 61 years (range, 36–79 years) for men and 58 years (range, 40–74 years) for women. A total of 78 patients (54.9%) were current or former smokers, with a median smoking index of 800 (range, 10–2,400) (*Table 1*).

Treatment

A total of 27 patients (19%) received neoadjuvant therapy. Lobectomy was performed in 131 patients (92.3%), and other pneumoresections were performed in 11 patients (7.7%). Of these patients, 8 underwent wedge resection, 2 underwent sleeve resection, and 1 underwent segmental resection. All operations were performed with regional lymph node dissection. After surgical treatment, there were 92 patients (64.8%) received ≤4 courses of postoperative chemotherapy, and 50 patients received >4 courses of postoperative chemotherapy. Only 18 patients (12.7%) received postoperative radiotherapy (*Table 1*).

Postoperative pathology and TNM staging

The final pathology examination revealed that 116 (81.7%) of the specimens were confirmed to be pure SCLC (P-SCLC), 26 (18.3%) had mixed histology (C-SCLC), 16 were SCLC + large cell lung cancer (LCLC), 9 were SCLC + unspecified NSCLC type, and 1 was SCLC + LCLC + unspecified NSCLC type. Patients were diagnosed with stages I, II, and III disease in 54 (38%), 28 (19.7%), and 60 (42.3%) patients, respectively (*Table 1*).

Postoperative conditions

Postoperative complications occurred in 22 patients (15.5%). Sixty patients (42.3%) developed cancer recurrence and/or metastasis after surgery. During the follow-up period, 77 patients (54.2%) were found to have survived, and of the 58 patients (40.8%) who died, 4 (6.9%) died of postoperative complications, 44 (75.9%) died of cancer recurrence and metastasis, 2 (3.4%) died of other

Table 1 Patient characteristics

Variables	Overall (n=142), n (%) or median
Sex	
Female	41 (28.9%)
Male	101 (71.1%)
Age (years)	60 (36–79)
Female	58 (40–74)
Male	61 (36–79)
≤60	72 (50.7%)
>60	70 (49.3%)
Smoker	78 (54.9%)
Smoking index	
Total	270 (0–2,400)
Smoker	800 (10–2,400)
≤800	112 (78.9%)
>800	30 (21.1%)
Neoadjuvant therapy	27 (19.0%)
Surgical resection method	
Pulmonary lobectomy	131 (92.3%)
Other pneumoresection	11 (7.7%)
Wedge resection	8
Sleeve resection	2
Segmental resection	1
Surgical duration (min)	170 (72–465)
≤170	75 (52.8%)
>170	67 (47.2%)
Postoperative complications	22 (15.5%)
Severe pulmonary infection	6
Atelectasis	10
Respiratory failure	3
Bronchopleural fistula	2
Myocardial infarction	1
Histological subtype	
P-SCLC	116 (81.7%)
C-SCLC	26 (18.3%)
SCLC + LCLC	16

Table 1 (*continued*)

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Variables	Overall (n=142), n (%) or median
SCLC + NSCLC	9
SCLC + LCLC + NSCLC	1
Pathological TNM stage	
I	54 (38.0%)
II	28 (19.7%)
III	60 (42.3%)
Postoperative chemotherapy	
≤4 courses	92 (64.8%)
No chemotherapy	22
1 course	17
2 courses	8
3 courses	6
4 courses	39
>4 courses	50 (35.2%)
5 courses	8
6 courses	31
7 courses	1
8 courses	4
9 courses	1
10 courses	2
11 courses	1
12 courses	1
13 courses	1
Postoperative radiotherapy	18 (12.7%)
Recurrence and/or metastasis	
Yes	60 (42.3%)
No	73 (51.4%)
NA	9 (6.3%)
Outcome	
Survival	77 (54.2%)
Death	58 (40.8%)
Postoperative complications	4
Recurrence and/or metastasis	44
Other malignant tumors	2
Complications of radiotherapy and chemotherapy	5
Other non-tumor diseases	3
NA	7 (5.0%)
Overall survival (months)	57 (0–104)
Survival rate	
1 year	78.90%
3 years	58.70%
5 years	49.40%

Table 1 (*continued*)

LCLC, large cell lung cancer; NA, lost to follow up; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

malignant tumors, 5 (8.6%) died of postoperative radiation and chemotherapy complications, and 3 (5.2%) died of other non-tumor diseases. Seven patients (5%) were lost to follow up. The median survival time for the entire cohort was 57 months (range, 0–104 months). The 1-year survival rate was 78.9%, the 3-year survival rate was 58.7%, and the 5-year survival rate was 49.4% (*Table 1*).

Univariate Kaplan-Meier analysis results

Univariate analysis was performed on the factors that might affect patient survival, such as sex, smoking status and smoking index, tumor location (peripheral/central), neoadjuvant therapy, surgical resection method, postoperative pathological type (P-SCLC/C-SCLC), postoperative complications, postoperative TNM stage of pathology, postoperative chemotherapy treatment, and postoperative radiotherapy treatment. The results showed that smoking index, postoperative pathological TNM stage, and postoperative chemotherapy would affect the survival of patients with SCLC after surgical treatment (*Figures 1-3* and *Table 2*).

The median survival time of SCLC patients with a smoking index ≤800 was 63 months, while for those with a smoking index >800, it was for 20 months. The difference was statistically significant (P=0.002). The cumulative survival rate was >50% for patients with postoperative pathological TNM stage I; the median survival time was 20 months for patients with stage II and 46 months for patients with stage III. The difference between the

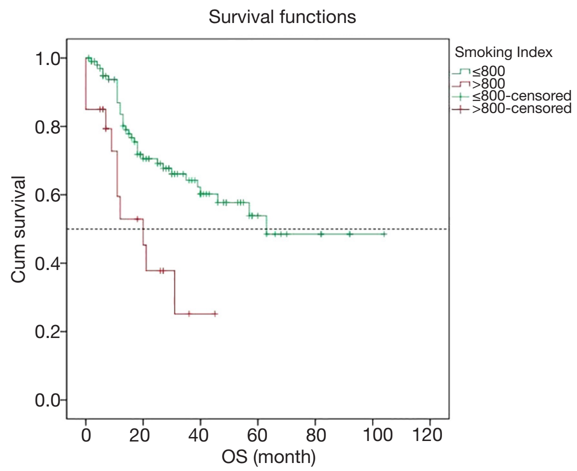

Figure 1 Kaplan-Meier survival curve of smoking index >800 group and ≤800 group in SCLC patients treated by surgery. SCLC, small cell lung cancer.

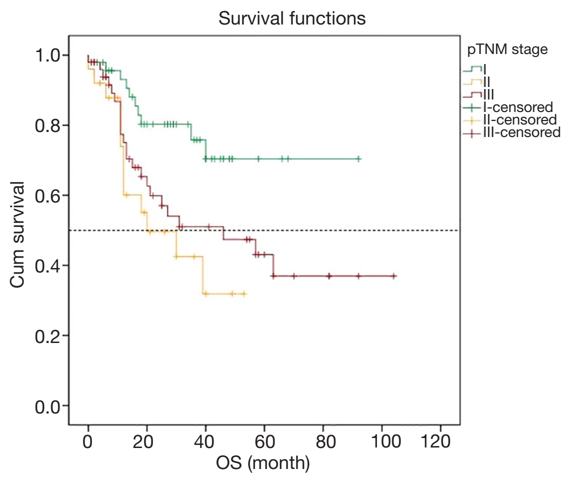

Figure 2 Kaplan-Meier survival curve of SCLC patients with stage I, II, and III after surgery. SCLC, small cell lung cancer.

stage I patient group and the stages II andIII groups was statistically significant (stage I *vs.* stage II P=0.003, stage I *vs.* stage III P=0.019). However, there was no statistical difference in survival between stage II patients and stage III patients (P=0.332). The median survival was 35 months for patients who received ≤4 courses of postoperative chemotherapy after surgery, and the median OS was not reached for patients who received >4 courses of postoperative chemotherapy. The difference was statistically significant (P=0.003).

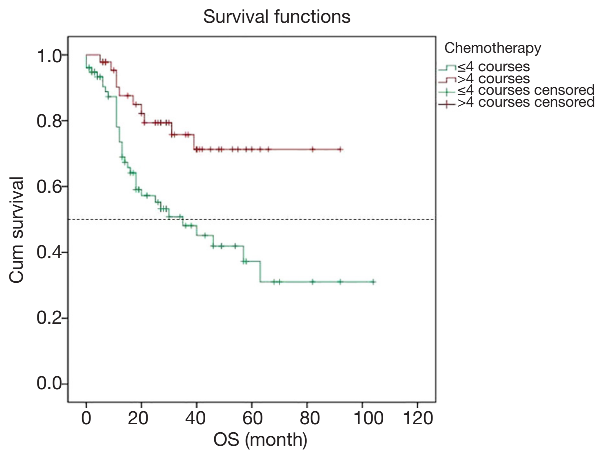

Figure 3 Kaplan-Meier survival curve of postoperative chemotherapy >4 courses group and ≤4 courses group in SCLC patients treated by surgery. SCLC, small cell lung cancer.

Cox multivariate analysis

Multivariate analysis show that smoking index, surgical resection method, TNM stage of postoperative pathology, and postoperative chemotherapy were significantly correlated with postoperative survival (P<0.05), which were independent predictors of postoperative survival. Patients with a smoking index >800 had a higher risk of death after surgery [hazard ratio (HR): 7.050, 95% confidence interval (CI): 3.079–16.143, P<0.001]. Compared with patients who underwent pulmonary lobectomy, those who underwent other pneumoresections (e.g., wedge resection, segmental resection, sleeve resection) had an increased risk of death (HR: 2.822, 95% CI: 1.030–7.734, P=0.044). Compared with stage I patients, stage II and stage III patients had an increased risk of death, with HRs of 6.039 (2.460, 14.823) and 3.145 (1.453, 6.811), respectively. Compared with those who received ≤4 courses of postoperative chemotherapy, patients who received >4 courses of postoperative chemotherapy had reduced postoperative mortality risk (HR: 0.211, 95% CI: 0.097–0.459, P<0.001) (*Table 3*).

Stratified analysis of prognostic factors

We conducted a stratified analysis of postoperative TNM staging. We found that, in stage I and stage III patients, surgical methods and postoperative chemotherapy did not affect prognosis, while >4 courses of postoperative chemotherapy treatment could significantly improve the

Table 2 Kaplan-Meier univariable analysis

Variables	Median overall survival (months)	P value
Sex		
Female	NA*	0.067
Male	35	
Age (years)		
≤60	63	0.479
>60	57	
Smoking status		
Never	63	0.367
Even or current	46	
Smoking index		
≤800	63	0.002
>800	20	
Tumor location		
Peripheral	63	0.231
Central	20	
Neoadjuvant therapy		
No	63	0.36
Yes	31	
Surgical resection method		
Pulmonary lobectomy	63	0.124
Other pneumoresection	27	
Histological subtype		
P-SCLC	46	0.375
C-SCLC	NA*	
Pathological TNM stage		0.01
Stage I *vs.* stage II	NA	0.003
Stage I *vs.* stage III	20	0.019
Stage II *vs.* stage III	46	0.332
Postoperative chemotherapy		
≤4 courses	35	0.003
>4 courses	NA*	
Postoperative radiotherapy		
No	57	0.886
Yes	NA*	

NA*, cumulative survival rate was greater than 50% across the entire survival curve. C-SCLC, mixed histology small cell lung cancer; P-SCLC, pure small cell lung cancer.

prognosis of stage II patients, with cumulative survival >50%. In addition, stages II and III patients with a smoking index >800 had a worse prognosis than those with a smoking index ≤800 (*Table 4*).

We conducted a stratified analysis of surgical resection methods. In patients undergoing pulmonary lobectomy, those who received >4 courses of postoperative chemotherapy had a significantly improved prognosis (P=0.006), with a cumulative survival rate of more than 50%. The median survival time of the patients who received ≤4 courses of postoperative chemotherapy was 40 months (*Table 4*).

Discussion

For limited-stage SCLC, patients with a good performance status should receive concurrent chemoradiotherapy (14). Chemotherapy should consist of 4 cycles of a platinum agent and etoposide, followed by thoracic radiotherapy, preferably beginning with cycle 1 or 2 of chemotherapy (14).

Although surgical treatment is controversial, studies have shown that surgical treatment may play a role in several settings (15). Patients with clinical stages T1–2 N0 SCLC may benefit from surgery combined with chemotherapy. For patients with a combined histology tumor, surgical resection may be required. Surgery-based comprehensive treatment is a feasible and promising strategy for some patients with SCLC (15). Therefore, in the present study, we analyzed the data of patients with SCLC undergoing surgery to determine the relevant factors that may indicate the prognosis of surgery for the clinical treatment of SCLC and selection of candidates for surgery. We found that smoking index, surgical resection method, TNM stage of postoperative pathology, and postoperative chemotherapy were independent predictors for postoperative survival.

Several studies have shown that sex, age, and smoking status are related to prognosis (16-18). However, in the present study, there was no significant correlation between patients' sex and age and prognosis. In the univariate analysis, there was no statistical difference in the postoperative survival rate between smokers and non-smokers; however, the smoking index in the multivariate Cox regression analysis was significantly related to patients' prognosis. A retrospective study analyzed data from 7,059 participants who were diagnosed with initial primary lung cancer (IPLC) in a multiethnic cohort from 1993 to 2017. The results showed that smoking pack-years and smoking intensity were significantly associated

Table 3 Cox multivariable analysis

Variables	Hazard ratio (95% confidence interval)	P value
Sex	1.018 (0.490–2.116)	0.962
Smoking index	7.050 (3.079–16.143)	<0.001
Surgical resection method	2.822 (1.030–7.734)	0.044
Pathological TNM stage		<0.001
Stage I *vs.* stage II	6.039 (2.460–14.823)	<0.001
Stage I *vs.* stage III	3.145 (1.453–6.811)	0.004
Postoperative chemotherapy	0.211 (0.097–0.459)	<0.001

with increased second primary lung cancer (SPLC) risk, and smoking cessation after IPLC diagnosis may reduce the risk of SPLC (19). Another study retrospectively examined clinicopathological factors in 453 patients with pathologically proven stage I NSCLC, and found that ≥10 years of smoking cessation would improve RFS following resection (20). In a prospective study by Mason *et al.* that included 7,965 patients who had undergone surgery for lung cancer, the mortality rate of smokers or past smokers was 5 times that of non-smokers (1.5% *vs.* 0.3%) (21). Long-term exposure to tobacco smoke can lead to increased serum carboxyhemoglobin levels, chronic bronchitis, ciliated epithelial dysfunction, increased secretion of respiratory mucosa, and dysfunction of macrophages in the lungs, thereby reducing the efficiency of local defense mechanisms. These are the main reasons why smoking affects postoperative complications (22-24).

Some studies have shown that neoadjuvant chemotherapy combined with surgery can improve the prognosis of SCLC patients, as neoadjuvant chemotherapy may reduce the T or N stage of the tumor, thereby reducing the risk of death (25-27). Among patients with nodal metastases, only those with negative nodes following induction chemo/chemoradiotherapy should be candidates for surgery (15). Conversely, other studies have shown that neoadjuvant chemotherapy combined with surgery does not benefit patients, because increased complications caused by preoperative chemotherapy may result in poor physical condition and an inability undergo surgery (28). In the present study, there was no significant correlation between preoperative neoadjuvant therapy and postoperative survival. Among the 27 patients who received neoadjuvant therapy, lymph node metastasis before and after neoadjuvant therapy was not determined; therefore, it is impossible to evaluate the effect of neoadjuvant therapy and further discussion.

A number of recent studies have found that patients with C-SCLC have a better prognosis and benefit more from surgical treatment than patients with P-SCLC (15,29). Woo *et al.*'s study showed that the most common histological subgroup in patients with C-SCLC was SCLC + LCLC (30). Among the 26 patients with C-SCLC in our study, the most common histological subgroup was SCLC + LCLC, with a total of 16 cases (61.5%), which was consistent with the results of Woo *et al.* A retrospective study by Qin *et al.* found that OS between C-SCLC and pure SCLC patients was similar; however, patients with C-SCLC had a better prognosis compared with those with the pure small-cell type, benefiting from surgery. They found that, because C-SCLC contains NSCLC components, the sensitivity of C-SCLC to chemotherapy is relatively low, and surgery plays a more important role in the comprehensive treatment of C-SCLC (29). However, there was no statistical difference in the correlation between pathological subgroup types of SCLC and survival prognosis of patients in our study.

Pulmonary lobectomy has been shown in many studies to be associated with better outcomes compared to other pneumoresections (6,12,31). A retrospective study of Surveillance, Epidemiology, and End Results (SEER) data found a median OS of 15 months (95% CI: 12.5–17.5 months) and 35 months (95% CI: 28.4–47.6 months) for sublobar resection and lobectomy, respectively (P<0.001) (12). In our study, univariate analysis showed that there was no statistically significant difference for survival between patients who underwent pulmonary lobectomy and other pneumoresection. However, in the multivariate Cox regression analysis, we found that surgical method is an independent prognostic factor of postoperative survival, and the prognosis of pulmonary lobectomy was better than other pneumoresections. Zhao *et al.*'s study

Table 4 Multivariate analysis

Variables	n	Median overall survival (months)	P value	Survival rate (%)		
				1 year	3 years	5 years
Pathological TNM stage						
Stage I						
Pulmonary lobectomy	43	NA*	0.258	94.9	80.7	74.5
Other pneumoresection	5	35		75.0	50.0	0
Chemotherapy ≤4 courses	32	NA*	0.056	89.3	66.4	56.9
Chemotherapy >4 courses	16	NA*		100	92.3	92.3
Smoking index ≤800	40	NA*	0.440	97.2	71.1	71.1
Smoking index >800	8	NA*		70.0	70.0	70.0
Stage II						
Pulmonary lobectomy	25	20		60.1	42.5	0
Other pneumoresection	0					
Chemotherapy ≤4 courses	14	12	0.006	62.3	0%	0
Chemotherapy >4 courses	11	NA*		77.8	77.8	0
Smoking index ≤800	22	30	0.007	69.3	49.0	0
Smoking Index >800	3	11		0	0	0
Stage III						
Pulmonary lobectomy	46	57	0.062	78.2	55.5	46.8
Other pneumoresection	4	11		33.3	0	0
Chemotherapy ≤4 courses	31	25	0.120	70.8	44.9	34.2
Chemotherapy >4 courses	19	NA*		82.1	60.8	60.8
Smoking index ≤800	41	63	0.013	80.8	43.1	43.1
Smoking index >800	9	20		61.0	0	0
Surgical resection method						
Pulmonary lobectomy						
Chemotherapy ≤4 courses	68	40	0.006	75.5	51.9	39.8
Chemotherapy >4 courses	46	NA*		87.6	75.8	71.3
Smoking index ≤800	94	NA*	0.001	85.7	68.3	57.5
Smoking index >800	20	20		52.9	25.2	0
Other pneumoresection						
Chemotherapy ≤4 courses	9	27		57.1	28.6	0
Chemotherapy >4 courses	0					
Smoking index ≤800	9	27		57.1	28.6	0
Smoking index >800	0					

NA*, cumulative survival rate was greater than 50% across the entire survival curve.

showed that the 5-year survival rates of SCLC patients with stages I, II, and III after pulmonary lobectomy were 63.8%, 65.5%, and 34.9%, respectively (32). In our study, the 5-year survival rates of SCLC patients with stages I, II, and III who underwent pulmonary lobotomy were 74.5%, 0%, and 46.8%, respectively, and the results for stages I and III were better than those of Zhao *et al.*'s study. Preoperative clinical data of stage II patients are incomplete, so it is impossible to further explore the reasons for the abnormal 5-year survival rate. In the stratified analysis of TNM staging of postoperative pathology, there was no statistically significant difference in prognosis between pulmonary lobectomy and other pneumoresections in stages I and III patients, and pulmonary lobectomy was performed in all stage II patients. However, studies have shown that pulmonary lobectomy has a greater advantage for patients with early SCLC (12,31). Turner *et al.* analyzed approximately 360 papers, of which 7 reported that lobectomy is associated with improved survival among patients with early-stage SCLC compared with sublobar resection, and 1 paper demonstrated both improved survival and freedom from local recurrence (31). Moreover, Jones *et al.* noted that SCLC, determined by the intraoperative frozen section of a resected nodule, should mandate conversion to lobectomy (33). In addition, lymph node dissection is necessary for the surgical treatment of any staged SCLC (6,34).

The current NCCN guidelines recommend postoperative chemotherapy for surgically treated patients with stages I–IIA SCLC (6). Many studies have indicated similar findings, supporting the recommendations of the guidelines (2,35-37). A retrospective study, comparing the efficacy of surgery followed by chemotherapy and non-surgical treatment in patients with early-stage SCLC, found that the effectiveness rate, disease progression, and 1-, 3-, and 5-year survival rate scores of the surgery followed by chemotherapy group were higher than those of patients without surgical treatment (38). Yang *et al.* analyzed National Cancer Data of stage I SCLC patients and found that, compared with surgery alone, surgery followed by chemotherapy is associated with improved survival (37). In our study, we found that patients who received >4 courses of postoperative chemotherapy after surgery had a better prognosis than those who received ≤4 courses of postoperative chemotherapy, especially for those with stage II SCLC. In our study, postoperative radiotherapy (including thoracic radiotherapy and craniocerebral prophylactic radiotherapy) was not an influencing factor for postoperative survival. However, some studies have shown that stages II and IV patients have better outcomes with postoperative prophylactic radiotherapy to the brain (2). A retrospective study compared 115 patients with postoperative prophylactic cranial irradiation (PCI) therapy and 234 patients with surgery alone, and the results showed that, for stages II and III patients, the OS of the PCI-treated cohort was longer than that of the non-PCI-treated cohort (39). Another study evaluated the role of PCI on patients with surgically resected SCLC and found that PCI could improve the OS of patients with surgically resected SCLC, but not for pathological stage I patients (40).

Our study found that patients with stage I had better postoperative outcomes compared with patients with stages II–III. Weksler *et al.* found that patients with stage I had a median OS of 38 months with surgery and 16 months without surgery (P<0.001) (41). Wakeam *et al.* found that surgical treatment improved OS (median OS 38.6 *vs.* 22.9 months, P<0.001) for patients with stage I SCLC (36). The cumulative survival rate of stage I patients in our study was greater than 50%, with an OS range of 0–104 months, which was better than that of the stage I patients in the above studies. These results suggest that accurate clinical TNM staging, especially N staging, is important before surgical treatment is selected. In recent years, increasing attention has been paid to physical examination, and computed tomography (CT) has become the main early screening modality of pulmonary nodules. Patients with SCLC can be diagnosed by needle biopsy, and those who are suspected of having lymph node metastasis can be screened using positron emission tomography-CT and lymph node biopsy (42). Due to the randomness of doctors' choice of surgical patients and patients' subjective choice of treatment methods, many patients with stages II–III SCLC still receive surgical treatment. Patients with stage II SCLC require surgical treatment after an adequate preoperative evaluation, including mediastinoscopy (33). For patients with stage III SCLC, Zhang *et al.* found that surgical treatment is associated with a better prognosis (7). In our study, the median survival time for stage III patients was 46 months, and a 5-year survival rate of 46.8%, which was better than that of stage II patients (20 months, 0%), although the difference was not statistically significant. Combined with previous discussions of neoadjuvant therapy, chemotherapy and radiotherapy, more clinical studies are needed to verify the role of surgery-based treatment for SCLC.

There are several limitations to our study. Clinicians' random selection of surgical patients and patients' subjective wishes for treatment methods led to certain bias among enrolled patients. Multiple confounding factors, such as the treatment time span of patients, was large, the specific methods of postoperative chemotherapy and radiotherapy were unknown, preoperative clinical data were incomplete (i.e., physical condition, nutritional status, tumor markers, immunohistochemical, imaging performance), the protocols and efficacy of neoadjuvant therapy were unknown, and some patients were lost to follow up, which affected the effectiveness of the study.

Conclusions

A high smoking index suggests worse prognosis; therefore, patients who smoke should be advised to quit smoking. Compared with stages II and stage III patients, surgical treatment is recommended for stage I SCLC patients. TNM staging, especially N staging, should be evaluated before surgery. Pulmonary lobectomy with mediastinal lymph node dissection should be the preferred surgical treatment for patients with SCLC. Patients should receive at least 5 courses of adjuvant chemotherapy after surgery, especially those with stage II SCLC. Further study on the relationship between preoperative clinical indicators and postoperative prognosis in patients with SCLC is warranted, so as to guide clinicians to select patients who would most benefit from surgical treatment.

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Footnote

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