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Surgery for small cell lung cancer

A Surveillance, Epidemiology, and End Results (SEER) Survey from 2010 to 2015

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Abstract

The role of surgery in small cell lung cancer (SCLC) is controversial. This study explored whether surgery offered a survival benefits for patients with SCLC.

Patients diagnosed with SCLC between 2010 and 2015 were selected from the Surveillance, Epidemiology, and End Results (SEER) database. The tumor, node, and metastasis (TNM) stage of SCLC in these patients was reclassified according to the 8th edition of the TNM classification for lung cancer. Overall survival (OS) was separately compared according to TNM stage between patients who underwent surgery and those who did not using Kaplan–Meier method. A Cox regression model was used to identify relevant variables affecting survival. Additional Kaplan–Meier curves were created to compare different types of surgery. Cox regression models and Forest plots were used to identify the predictors of survival in the surgery cohort.

A total of 26,659 patients with SCLC were included, among which 627 (2.4%) patients underwent surgery. Surgery was associated with longer survival in patients with stage IA (45.0 vs 20.0 months, $P<.001$), stage IB (47.0 vs 19.0 months, $P=.001$), stage IIA (16.0m vs NR, $P=.007$), stage III (18.0 vs 12.0 months, $P<.001$), and stage IV (9.0 vs 5.0 months, $P<.001$) disease, although the difference was not statistically significant for patients with stage IIB disease. Multivariate analysis identified surgery as an independent predictor of improved survival for all cohorts divided by stages except for stage IIB. Lobectomy was the most commonly performed procedure. Multivariate analysis in patients who underwent surgery identified lobectomy (hazard ratio [HR], 0.544; 95% confidence interval [CI], 0.341–0.869; $P=.011$) and chemotherapy (HR, 0.634; 95% CI, 0.487–0.827; $P<.001$) as independent predictors of improved survival in the surgery cohort.

In a national analysis, surgery was performed in some patients for both early and advanced-stage SCLC. Surgery for SCLC was associated with improved survival except for patients with stage IIB disease. These results support an increased role of surgery in multimodal therapy for SCLC.

Abbreviations: OS = overall survival, SCLC = small cell lung cancer, SEER = Surveillance, Epidemiology, and End Results, TNM = tumor, node, and metastasis.

Keywords: cancer survival, lung cancer, small cell lung cancer, surgery

1. Introduction

Lung cancer is a malignant tumor with the highest morbidity and mortality worldwide.[1] Among cases of lung cancer, 10–15% are small cell lung cancer (SCLC).[2] SCLC is highly malignant and often metastases when diagnosed. Following a randomized controlled study in 1973 that found no survival benefit from surgery versus radiotherapy,[3] surgery was excluded from the standard treatment for SCLC for a long time. However, only 34 of the 71 patients in the surgical group in that study actually underwent surgery and the lack of a good systemic chemotherapy program at that time made it difficult to guide current clinical practice.

Some retrospective studies have shown that surgery could improve survival in stage I patients compared to that for radiotherapy or concurrent chemoradiotherapy.[4–7] Current American Society of Clinical Oncology,[8] National Comprehensive Cancer Network,[9] and European Society for Medical Oncology[10] guidelines indicate that surgical resection should be considered only in patients with stage I SCLC. Most patients with SCLC have extensive or metastatic disease, making most cases unsuitable for radical surgery. Over the past 30 years, the treatment of SCLC has stagnated, with the comprehensive application of combined surgery, radiotherapy, and chemotherapy, the main treatment for most SCLC patients.[11]

However, surgery has been used in both early and advanced SCLC patients in the real world, either as part of a comprehensive treatment or as a means of pathologic confirmation. Thus, the role of surgery in SCLC is controversial.[12–14] The present study analyzed Surveillance, Epidemiology, and End Results (SEER) data from 2010 to 2015 to explore whether surgery offers a survival benefit for patients with SCLC.

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2. Methods

2.1. Ethics statement

We got internet access to SEER database with the reference number 12025-Nov2017. This study used a national dataset of deidentified patient information, which did not meet the General Hospital of Northern Theater Command's criteria for institutional review board (IRB) approval. Therefore, this study waived the need for IRB approval. The data of this observational are anonymous, and the requirement for informed consent was therefore waived.

2.2. Patients

The SEER Program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the United States that covers approximately 34.6% of the US population. After accessing the SEER*stat software version 8.3.5, the SEER-18 registry (with custom treatment fields) was explored to extract eligible cases. The inclusion criteria included: patients over 18 years of age, one primary SCLC only, diagnosed between 2010 and 2015, and site recode ICD-O-3/WHO 2008 of "lung and bronchus" and histologic type codes 8002 and 8041–8045. The tumor, node, and metastasis (TNM) stage for each patient was reclassified according to the 8th edition of the TNM classification. However, stages III and IV could not be divided into subgroups due to insufficient information. The exclusion criteria included: unknown survival time, unidentified surgery status, cases without a positive pathological diagnosis, multiple primary cancer, and TNM stage unable to be reclassified according to the 8th edition of the TNM classification. The following information was extracted: patient age at diagnosis, patient race, patient sex, TNM stages, tumor size and extension, primary site, histologic type, surgery procedure, radiotherapy or chemotherapy, survival (in months), and vital status.

2.3. Statistical analyses

Data were reported as means ± standard deviation for continuous variables and as n (%) for categorical variables. Continuous variables were compared using Student *t* tests. Categorical variables were performed using Chi-square tests. The primary exposure variable was surgery. M multivariable logistic regression model was used to identify the significant factors associated with surgery. Survival curves were constructed using the Kaplan–Meier method and compared using log-rank tests. A multivariable Cox regression model was used to identify relevant variables affecting survival. Additional Kaplan–Meier curves were created to compare the different types of surgery. Cox regression models and Forest plots were used to identify the predictors of survival in patients who underwent surgery. Two-sided P-value < .05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY) and the Forest plots were drawn using GraphPad Prism 5.01 (GraphPad Software, San Diego, CA).

3. Results

3.1. Patient characteristics

A total of 26,659 patients with SCLC were included in the present cohort, 627 (2.4%) of whom underwent surgery. The baseline characteristics of the patients and the univariate associations with surgery are listed in Table 1. The numbers (percentage of the entire cohort) of patients with stage IA, IB, IIA, IIB, III, and IV SCLC were 547 (2.1%), 265 (1.0%), 113 (0.4%), 599 (2.2%), 6298 (23.6%), and 18,837 (70.7%), respectively. The numbers (percentage of stage-matched cohort) of patients who underwent surgery of the primary site with stage IA, IB, IIA, IIB, III, and IV SCLC were 163 (29.8%), 80 (30.2%), 11 (9.7%), 83 (13.9%), 145 (2.3%), and 145 (0.8%), respectively.

In multivariate analysis (Table 2), the likelihood of undergoing surgery for SCLC was significantly lower in patients older than 65 years of age than that in patients younger than 65 years (odds ratio [OR], 0.683; 95% confidence interval [CI], 0.571–0.817; $P < .001$). Patients who were black (OR, 0.717; 95% CI, 0.519–0.990; $P = .044$) or of another race (OR, 0.536; CI, 0.311–0.922; $P = .024$) were less likely to undergo surgery compared to white patients. Patients with combined histologic types were more likely to undergo surgery than patients with pure histologic types (OR, 8.964; 95% CI, 6.662–12.013; $P < .001$). Patients with upper lobe (OR, 1.602; 95% CI, 1.103–2.327; $P = .018$), lower lobe (OR, 1.781; 95% CI, 1.201–2.640; $P = .004$), and overlapping (OR, 2.609; 95% CI, 1.214–5.608; $P = .014$) lesions were more likely to undergo surgery compared to patients with main bronchus tumors. Patients with stage IIA (OR, 0.279; 95% CI, 0.143–0.546; $P < .001$), IIB (OR, 0.412; 95% CI, 0.302–0.562; $P < .001$), III (OR, 0.065; 95% CI, 0.050–0.084; $P < .001$), and IV (OR, 0.023; 95% CI, 0.018–0.030; $P < .001$) disease were less likely to undergo surgery compared to patients with stage IA disease.

There were no statistically significant differences in the likelihood of undergoing surgery between female and male patients (OR, 1.108; 95% CI, 0.929–1.321; $P = .254$), between right middle lobe and main bronchus lesions (OR, 1.454; 95% CI, 0.851–2.485; $P = .171$), and between stage IA and IB disease (OR, 1.000; 95% CI, 0.710–1.408; $P = .998$).

3.2. Survival and multivariable Cox regression analyses

The results of Kaplan–Meier survival analyses are shown in Figure 1 and Table 3. The median overall survival (OS) and 3-year OS rates for patients who underwent surgery and nonsurgery were 20.0 months and 36.2% and 7.0 months and 7.2%, respectively ($P < .001$). After adjusting for age, sex, race, TNM stage, histologic type, primary site, radiation, and chemotherapy, multivariate analysis of entire cohort identified surgery as an independent predictor of improved survival (HR, 0.573; 95% CI 0.512–0.643; $P < .001$), and that age, sex, race, TNM stage, primary site, histologic type, radiation, and chemotherapy were associated with survival (Table 4).

Surgery was associated with longer survival for all cohorts divided by stages, though the difference was not significant for patients with stage IIB disease. Surgery was associated with the greatest increase in median OS in patients with stage IA (45.0 months, 95% CI, 28.5–61.5 months vs 20.0 months, 95% CI, 17.6–22.3 months, $P < .001$) and IB (47.0 months, 95% CI, 8.1–85.9 months vs 19.0 months, 95% CI, 14.1–23.9 months, $P = .001$) disease. Furthermore, a significantly longer median OS in the surgery group was observed for stage IIA (16.0 months, 95% CI, 11.4–20.6 months vs NR, $P = .007$), stage III (18.0 months, 95% CI, 15.2–20.8 months vs 12.0 months, 95% CI, 11.6–12.4 months, $P < .001$), and stage IV (9.0 months, 95% CI, 7.5–10.5 months vs 5.0 months, 95% CI, 4.8–5.2 months, $P < .001$) disease. The 3-year survival rates for surgery and nonsurgery by stage were as follows: 59.7% vs 27.1% for stage

Table 1

Patients demographics (n = 26,659).

Variable	Stage IA (n = 547, 2.1%)			Stage IB (n = 265, 1.0%)			Stage IIA (n = 113, 0.4%)			Stage IIB (n = 599, 2.2%)			Stage III (n = 6298, 23.6%)			Stage IV (n = 18,837, 70.7%)			Total (n = 26,659)		
	Surgery	No surgery	P	Surgery	No surgery	P	Surgery	No surgery	P	Surgery	No surgery	P	Surgery	No surgery	P	Surgery	No surgery	P	Surgery	No surgery	P
n, %	163 (29.8)	384 (70.2)		80 (30.2)	185 (69.8)		11 (9.7)	102 (90.3)		83 (13.9)	516 (86.1)		145 (2.3)	6153 (97.7)		145 (0.8)	18,692 (99.2)		627 (2.4)	26,032 (97.6)	
Age	67.9 ± 8.6	71.2 ± 9.2	<.001	65.7 ± 8.7	68.3 ± 9.3	.034	61.9 ± 9.9	69.3 ± 10.7	.031	66.6 ± 8.5	68.3 ± 9.4	.068	65.5 ± 9.7	66.2 ± 10.0	.38	64.5 ± 9.9	67.1 ± 10.0	.002	65.9 ± 9.2	67.0 ± 10.0	.011
Gender																					
Male	77 (47.2)	166 (43.2)	.399	34 (42.5)	88 (47.6)	.503	4 (36.4)	46 (45.1)	.725	32 (38.6)	214 (41.5)	.633	65 (44.8)	2799 (45.5)	.933	68 (46.9)	9773 (52.3)	.211	280 (44.7)	13,086 (50.3)	.006
Female	86 (52.8)	218 (56.8)		46 (57.5)	97 (52.4)		7 (63.6)	56 (54.9)		51 (61.4)	302 (58.5)		80 (55.2)	3354 (54.5)		77 (53.1)	8919 (47.7)		347 (55.3)	12,946 (49.7)	
Race																					
White	152 (93.3)	331 (86.2)	.128	70 (87.5)	150 (81.1)	.155	10 (90.9)	89 (87.3)	.547	74 (89.2)	439 (85.1)	.451	131 (90.3)	5263 (85.5)	.224	123 (84.8)	16,232 (86.8)	.814	560 (89.3)	22,504 (86.4)	.120
Black	8 (4.9)	36 (9.4)		8 (10.0)	26 (14.1)		0 (0)	8 (7.8)		5 (6.0)	54 (10.5)		12 (8.3)	583 (9.5)		17 (11.7)	1681 (9.0)		50 (8.0)	2388 (9.2)	
Other*	3 (1.8)	16 (4.2)		1 (1.3)	9 (4.9)		1 (9.1)	5 (4.9)		4 (4.8)	23 (4.5)		2 (1.4)	300 (4.9)		5 (3.4)	755 (4.1)		16 (2.6)	1108 (4.3)	
Unknown	0 (0)	1 (0.3)		1 (1.3)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	7 (0.1)		0 (0)	24 (0.1)		1 (0.2)	32 (0.1)	
Histologic type																					
SCLC	127 (77.9)	368 (95.8)	<.001	58 (72.5)	179 (96.8)	<.001	10 (90.9)	100 (98.0)	.267	67 (80.7)	510 (98.8)	<.001	128 (88.3)	6058 (98.5)	<.001	131 (90.3)	18,478 (98.9)	<.001	521 (83.1)	25,694 (98.7)	<.001
Combined SCLC	36 (22.1)	16 (4.2)		22 (27.5)	6 (3.2)		1 (9.1)	2 (2.0)		16 (19.3)	6 (1.2)		17 (11.7)	95 (1.5)		14 (9.7)	214 (1.1)		106 (16.9)	339 (1.3)	
Primary site																					
Main bronchus	1 (0.6)	9 (2.3)	.15	1 (1.3)	16 (8.6)	.158	0 (0)	13 (12.7)	.362	1 (1.2)	43 (8.3)	.033	12 (8.3)	718 (11.7)	<.001	18 (12.4)	2087 (11.2)	.23	33 (5.3)	2886 (11.1)	<.001
Upper lobe	114 (69.9)	227 (59.1)		48 (60.0)	1111 (60.0)		5 (45.5)	54 (52.9)		47 (56.1)	268 (51.9)		79 (54.5)	3131 (50.9)		70 (48.3)	8129 (43.5)		363 (57.9)	11,920 (45.8)	
Middle lobe†	8 (4.9)	34 (8.9)		6 (7.5)	7 (3.8)		0 (0)	4 (3.9)		3 (3.7)	27 (5.2)		6 (4.1)	270 (4.4)		6 (4.1)	620 (3.3)		29 (4.6)	962 (3.7)	
Lower lobe	38 (23.3)	104 (27.1)		23 (28.8)	47 (25.4)		6 (54.5)	29 (28.4)		30 (36.6)	152 (29.5)		41 (28.3)	1101 (17.9)		31 (21.4)	3600 (19.3)		169 (27.0)	5033 (19.3)	
Overlapping lesion	0 (0)	1 (0.3)		0 (0)	0 (0)		0 (0)	0 (0)		2 (2.4)	4 (0.8)		5 (3.4)	67 (1.1)		2 (1.4)	294 (1.6)		9 (1.4)	366 (1.4)	
NOS	2 (1.2)	9 (2.3)		2 (2.5)	4 (2.2)		0 (0)	2 (2.0)		0	22 (4.3)		2 (1.4)	866 (14.1)		18 (12.4)	3962 (21.2)		24 (3.8)	4865 (18.7)	
Radiation																					
Yes	73 (44.8)	180 (46.9)	.708	35 (43.8)	82 (44.3)	1.000	0 (0.0)	50 (49.0)	.001	39 (47.0)	257 (49.8)	.639	75 (51.7)	3032 (49.3)	.614	75 (51.7)	8221 (44.0)	.064	297 (47.4)	11,822 (45.4)	.351
No	90 (55.2)	204 (53.1)		45 (56.2)	103 (55.7)		11 (100)	52 (51.0)		44 (53.0)	259 (50.2)		70 (48.3)	3121 (50.7)		70 (48.3)	10,471 (56.0)		330 (52.6)	14,210 (54.6)	
Chemotherapy																0.039					
Yes	106 (65.0)	239 (62.2)	.562	48 (60.0)	129 (69.7)	.155	4 (36.4)	75 (73.5)	.017	66 (79.5)	415 (80.4)	.882	123 (84.8)	4886 (79.4)	.119	115 (79.3)	12,473 (66.5)	.001	462 (73.7)	18,181 (69.8)	
No	57 (35.0)	145 (37.8)		32 (40.0)	56 (30.3)		7 (63.6)	27 (26.5)		17 (20.5)	101 (19.6)		22 (15.2)	1267 (20.6)		30 (20.7)	6255 (33.5)		165 (26.3)	7851 (30.2)	

NOS = not otherwise specified, SCLC = small cell lung cancer.

* American Indian/AK Native, Asian/Pacific Islander.

† Right lung only.

Table 2

Multivariate analysis of factors associated with surgery.

Variable	OR (95% CI) for undergoing surgery	*P*
n		
Age		
<65	1	
≥65	0.683 (0.571–0.817)	<.001
Gender		
Male	1	
Female	1.108 (0.929–1.321)	.254
Race		
White	1	
Black	0.717 (0.519–0.990)	.044
Other*	0.536 (0.311–0.922)	.024
Unknown	1.366 (0.152–12.299)	.781
Histologic type		
SCLC	1	
combined SCLC	8.964 (6.662–12.013)	<.001
Primary Site		
Main bronchus	1	
Upper lobe	1.602 (1.103–2.327)	.018
Middle lobe†	1.454 (0.851–2.485)	.171
Lower lobe	1.781 (1.201–2.640)	.004
Overlapping lesion of lung	2.609 (1.214–5.608)	.014
NOS	0.587 (0.342–1.006)	.053
AJCC Stage Group, 8th ed		
IA	1	
IB	1.000 (0.710–1.408)	.998
IIA	0.279 (0.143–0.546)	<.001
IIB	0.412 (0.302–0.562)	<.001
III	0.065 (0.050–0.084)	<.001
IV	0.023 (0.018–0.030)	<.001

CI = confidence interval, NOS = not otherwise specified, OR = odds ratio, SCLC = small cell lung cancer.
* American Indian/AK Native, Asian/Pacific Islander.
† Right lung only.

IA, 52.4% vs 33.0% for stage IB, 75.0% vs 20.5% for stage IIA, 29.3% vs 16.9% for stage III, and 6.8% vs 2.7% for stage IV (Fig. 2, Table 3).

After adjusting for age, sex, race, histologic type, primary site, radiation, and chemotherapy, multivariate analysis identified surgery as an independent predictor of improved survival for stage IA (hazard ratio [HR], 0.410; 95% CI, 0.298–0.564; $P < .001$), IB (HR, 0.548; 95% CI, 0.340–0.884; $P = .014$), IIA (HR, 0.069; 95% CI, 0.015–0.325; $P = .001$), III (HR, 0.574; 95% CI, 0.468–0.704; $P < .001$), and IV (HR, 0.684; 95% CI, 0.570–0.820; $P < .001$) disease (Table 5).

3.3. Effect of surgery type on survival

Of the total 627 surgical procedures, 39 (6.2%) were local tumor destruction, 233 (37.2%) were sublobar resection, 315 (50.2%) were lobectomy, 20 (3.2%) were pneumonectomy, and 20 (3.2%) were unknown. Lobectomy was the most commonly performed procedure for stage IA, IB, IIA, and IIB SLSC in 101 (62.0%), 56 (70.0%), 8 (72.7%), and 67 (80.7%) cases, respectively. Sublobar resection and lobectomy were performed for stage III disease in 59 (40.7%) and 62 (42.8%) cases, respectively. Sublobar resection was the most commonly performed procedure for stage IV disease in 80 (55.2%) cases (Table 6).

Kaplan–Meier survival analyses showed median OS of 11.0 months (95% CI, 8.3–13.7 months), 15.0 months (95% CI, 12.5–17.5 months), 35.0 months (95% CI, 28.4–47.6 months), 17.0 months (95% CI, 9.7–24.3 months), and 13.0 months (95% CI, 10.3–15.7 months) for local tumor destruction, sublobar resection, lobectomy, pneumonectomy, and unknown types, respectively ($P < .001$) (Fig. 3, Table 6).

Multivariate analysis also showed that age ≥65 years (HR, 1.536; 95% CI, 1.125–1.924; $P < .001$), stage IIB (HR, 2.584; 95% CI, 1.669–4.001; $P < .001$), stage III (HR, 2.591; 95% CI, 1.822–3.684; $P < .001$), and stage IV (HR, 5.340; 95% CI, 3.670–7.770, $P < .001$) were independent predictors of poor outcomes. In addition, the outcomes of patients treated with surgery were not affected by race, sex, primary site, histologic type, or radiation (Fig. 4).

4. Discussion

At present, the standard treatment for limited-stage SCLC is concurrent radiochemotherapy and the first-line standard treatment for extensive-stage SCLC is platinum-based systematic chemotherapy. For most patients with SCLC, surgery is not a major treatment. However, in recent years, researchers have evaluated the value of surgery for treatment of SCLC.[4]

In this retrospective study, most patients had advanced-stage disease and 619 (2.4%) patients underwent surgery. The later the stage, the lower the proportion of patients was receiving surgical treatment. The proportion of patients younger than 65 years who received surgery was slightly higher than that in those older than

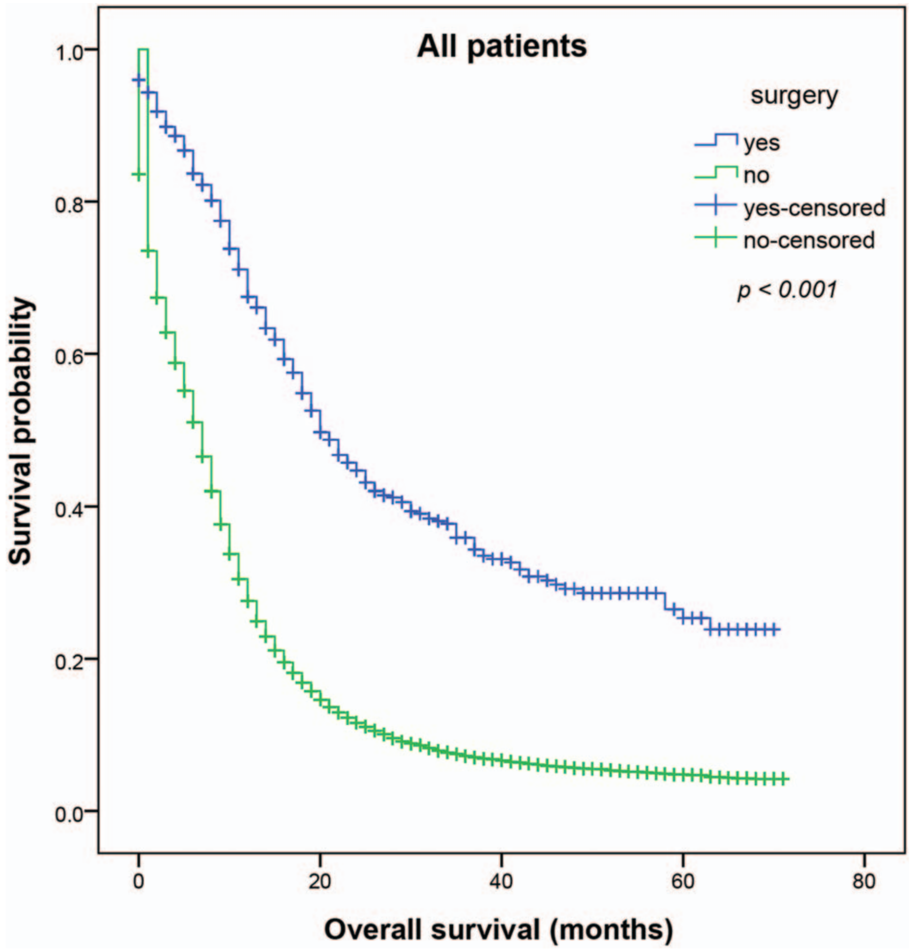

Figure 1. Overall survival of the entire cohort.

65 years, possibly because the younger patients had a better physical status and fewer complications. White Americans were more likely to receive surgery than black people and others, comparable to the results of another recent SEER-based retrospective analysis.[15] African American patients' perception of physicians and higher rates of implicit racial bias may play important roles in treatment choices.[16] In terms of tumor location, patients with tumors located in the main bronchus had the lowest proportion of receiving surgery. Surgery at this site is difficult, heavily traumatic, and difficult to reach R0 resection,

Table 3

Stage-matched survival analysis (mo).

AJCC 8th stage	Surgery	1-year survival	3-year survival	5-year survival	Median OS	95% CI	*P*
IA	No	62.2	27.1	19.2	20.0	17.6–22.3	<.001
	Yes	85.6	59.7	43.9	45.0	28.5–61.5	
IB	No	64.0	33.0	23.5	19.0	14.1–23.9	.001
	Yes	82.3	52.4	41.7	47.0	8.1–85.9	
IIA	No	55.7	20.5	0.0	16.0	11.4–20.6	.007
	Yes	75.0	75.0	75.0	–	–	
IIB	No	62.7	29.3	16.0	18.0	15.9–20.1	.069
	Yes	76.6	35.7	26.8	20.0	16.4–23.6	
III	No	48.0	16.9	11.8	12.0	11.6–12.4	<.001
	Yes	63.5	29.3	17.9	18.0	15.2–20.8	
IV	No	18.8	2.7	1.7	5.0	4.8–5.2	<.001
	Yes	37.4	6.8	5.6	9.0	7.5–10.5	
All patients	No	27.6	7.2	5.0	7.0	6.9–7.1	<.001
	Yes	67.4	36.2	25.7	20.0	17.6–22.4	

CI = confidence interval, OS = overall survival.

Table 4

Multivariate analysis of overall survival for entire cohort.

Variable	Hazard ratio	95% CI	*P* value
Age			
<65			
≥65	1.238	1.204–1.273	<.001
Gender			
Male			
Female	0.881	0.858–0.905	<.001
Race			
White	1		
Black	0.888	0.847–0.930	<.001
Other*	0.934	0.875–0.998	.044
Unknown	0.482	0.311–0.747	.001
AJCC Stage Group, 8th ed			
IA	1		
IB	1.065	0.867–1.308	.547
IIA	1.662	1.288–2.145	<.001
IIB	1.488	1.271–1.743	<.001
III	2.253	1.992–2.548	<.001
IV	4.577	4.054–5.168	<.001
Primary site			
Main bronchus	1		
Upper lobe	0.942	0.901–0.986	.009
Middle lobe†	0.938	0.865–1.016	.117
Lower lobe	0.991	0.942–1.042	.715
Overlapping lesion of lung	0.995	0.886–1.118	.939
NOS	1.044	0.992–1.098	.097
Histologic type			
SCLC	1		
Combined SCLC	0.897	0.801–1.004	.058
Surgery			
No	1		
Yes	0.573	0.512–0.643	<.001
Radiation			
No	1		
Yes	0.901	0.878–0.926	<.001
Chemotherapy			
No	1		
Yes	0.292	0.284–0.301	<.001

CI = confidence interval, NOS = not otherwise specified, SCLC = small cell lung cancer.
* American Indian/AK Native, Asian/Pacific Islander.
† Right lung only.

which explains the lower rates of surgery for this location. In addition, the proportion of patients with combined histologic type undergoing surgery was significantly higher than that of patients with pure histologic types (OR: 9.146). Combined SCLC is somewhat difficult to diagnose by preoperative biopsy.[17] Therefore, the significant difference in the proportion of surgery may be due to selection bias.

The results of this study suggest a certain degree of survival benefits from surgical treatment of SCLC. Multivariate analysis showed that surgery was an independent prognostic factor for prolonged survival. Stage I patients had the greatest survival benefit, consistent with findings of previous studies.[5–7,18] There was no statistically significant difference in the proportion of stage I patients receiving radiotherapy and chemotherapy, indicating that surgical treatment did not affect the treatment decision to receive radiotherapy or chemotherapy.

In this study, the data indicated that surgery was an independent prognostic factor for survival in patients with stage IIA and III SCLC. There was no statistically significant difference in survival between the surgery and the nonsurgery groups in patients with stage IIB disease. Jin et al[5] analyzed data of early SCLC patients in the SEER database from 2004 to 2013 and also reported no survival benefits for surgery compared to radiotherapy in patients with stage IIB disease. Patients who underwent surgery did not have a higher 5-year OS than that in patients who received radiotherapy (T3N0: 16.2% vs 26.5%; T1-2N1: 20.3% vs 29.0%). However, Yang et al[19] reported improved 5-year survival for surgery with adjuvant chemotherapy with or without radiation compared to concurrent chemoradiation (31.4% vs 26.3%) in patients with stage cT1-3N1M0 (approximately equivalent to AJCC 8th edition stage IIB/IIIA) SCLC in the National Cancer Database (NCDB) from 2003 to 2011. Wakeam et al[18] showed longer survival with surgery for IIB/IIIA but node-negative (T3/T4N0) disease (median overall survival 33.0 vs 16.8 months, $P = .008$) in SCLC patients in the NCDB from 2004 to 2013. Therefore, whether patients with stage II/III can benefit from surgical treatment requires further study.

To our knowledge, this study is the first to investigate the effect of surgery on survival in patients with stage IV SCLC.

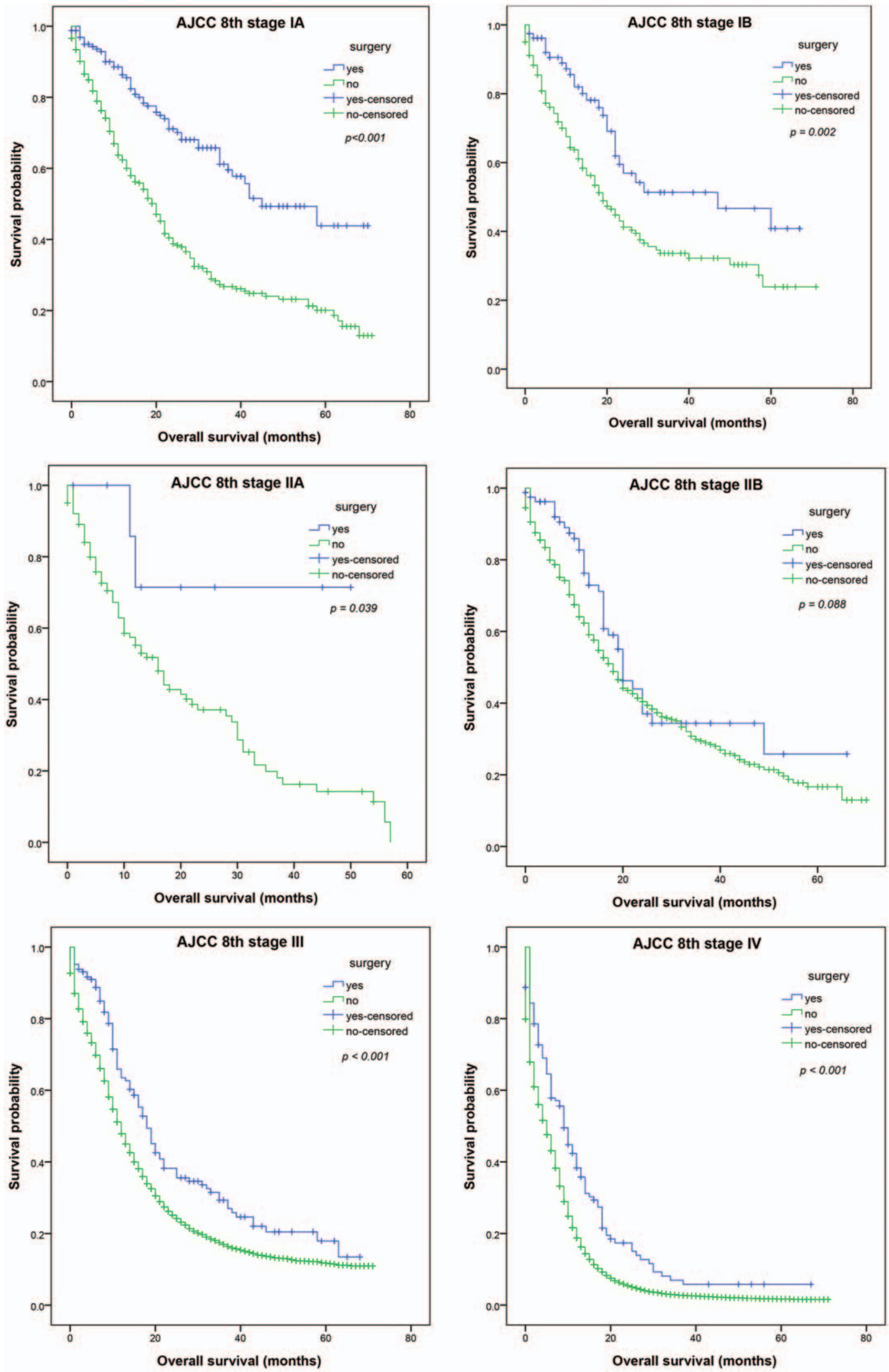

Figure 2. Overall survival based on tumor, node, and metastasis (TNM) stages.

Although the proportion of patients with stage IV disease who underwent surgery was very low, there was a significant difference in survival between the surgery and the nonsurgery groups and multivariate analysis showed surgery to be an independent prognostic factor for survival in patients with stage IV disease.

Table 5

Multivariate analysis for surgery versus no surgery in patients with each stage of SCLC.

AJCC 8th stage	Hazard ratio	95% CI	*P* value
IA	0.410	0.298–0.564	<.001
IB	0.548	0.340–0.884	.014
IIA	0.069	0.015–0.325	.001
IIB	0.670	0.461–0.973	.035
III	0.574	0.468–0.704	<.001
IV	0.684	0.570–0.820	<.001

CI=confidence interval, SCLC=small cell lung cancer.

Table 6

Types of surgery (n, %) and type-matched survival (mo).

	Stage IA	Stage IB	Stage IIA	Stage IIB	Stage III	Stage IV	Total	Median OS	95% CI
Local tumor destruction	2 (1.2)	0 (0.0)	0 (0.0)	2 (2.4)	13 (9.0)	22 (15.2)	39 (6.2)	11.0	8.3–13.7
Sublobar resection	57 (35.0)	23 (28.8)	2 (18.2)	12 (14.5)	59 (40.7)	80 (55.2)	233 (37.2)	15.0	12.5–17.5
Lobectomy	101 (62.0)	56 (70.0)	8 (72.7)	67 (80.7)	62 (42.8)	21 (14.5)	315 (50.2)	35.0	28.4–47.6
Pneumonectomy	2 (1.2)	1 (1.3)	1 (9.1)	2 (2.4)	7 (4.8)	7 (4.8)	20 (3.2)	17.0	9.7–24.3
NOS	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.8)	15 (10.3)	20 (3.2)	13.0	10.3–15.7
Total	163	80	11	83	145	145	627	20.0	17.6–22.4

CI=confidence interval, NOS=not otherwise specified, OS=overall survival.

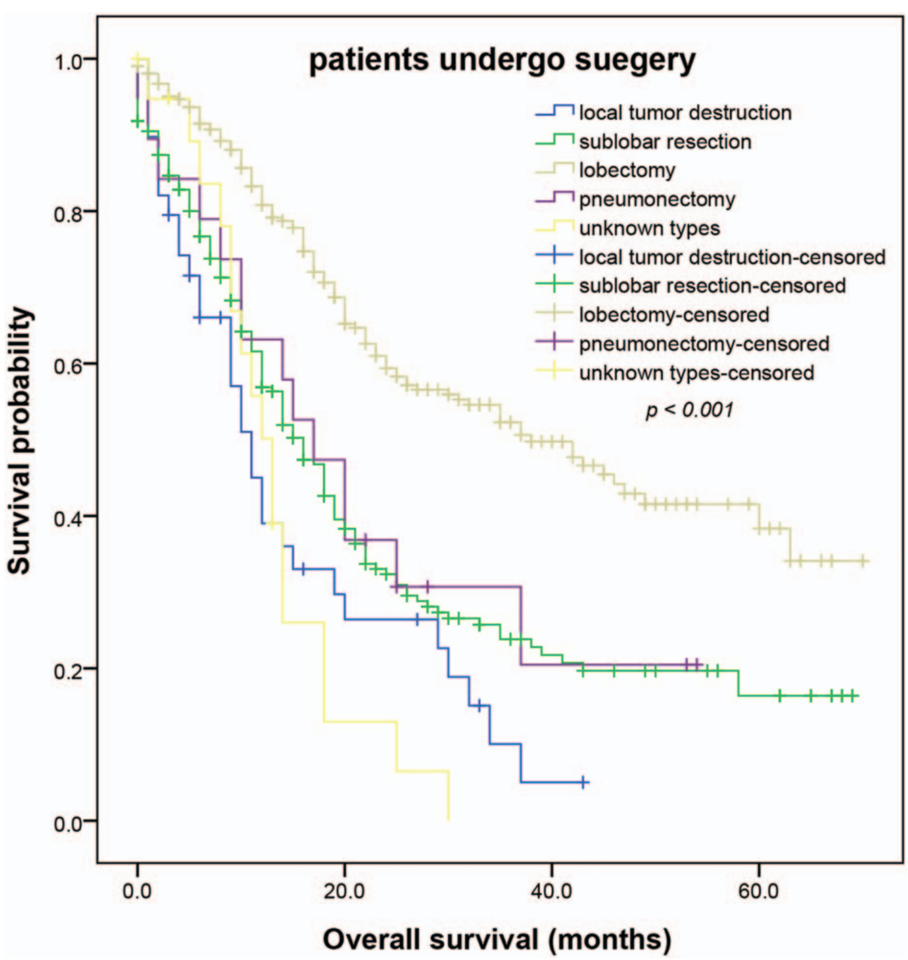

Figure 3. Overall survival of the surgery group according to surgery types.

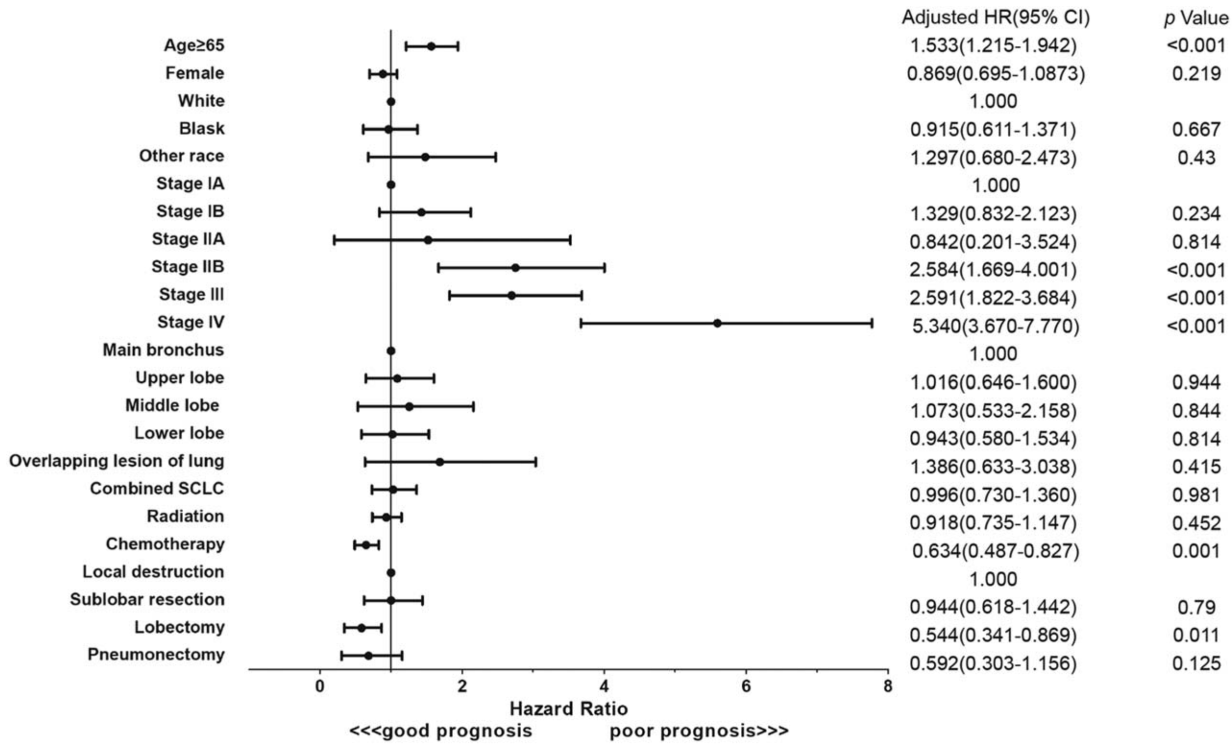

Figure 4. Forest plot of the predictors of prognosis in patients who underwent surgery.

Considering the retrospective study design, the effect of selection bias on the results cannot be ruled out; however, to a certain extent, the selection of appropriate patients to include surgery in their comprehensive treatment may have had survival benefits. The SEER database had no specific information about the purpose, timing, and results of surgery; moreover, patients with extensive or metastatic disease are often complicated. Therefore, multidisciplinary comprehensive evaluations are needed to determine which patients should be recommended surgical treatment in clinical practice. At present, with the continuous progress of surgical technology to reduce surgical trauma and reduce postoperative recovery times, surgery may play a role in patients with advanced-stage disease without affecting their physical status or systemic treatment.[20]

In this study, lobectomy was the most common type of surgery, followed by sublobectomy. Most patients with stage I disease were treated with lobectomy. Survival analysis showed that patients undergoing lobectomy had a longer survival time, consistent with previous studies.[18] The prognosis of the surgical group was better for patients aged is less than 65 years; therefore, age should be an important factor in deciding whether to perform surgery in clinical practice. Chemotherapy was an independent prognostic factor for survival in the surgical group, while radiotherapy was not. This finding suggested that systemic chemotherapy should be recommended even for patients undergoing surgery.

Because it is difficult to perform randomized controlled trials in SCLC, the results of retrospective studies can provide important references for clinical practice. To our knowledge, this is the first comprehensive and systematic study to investigate the status and significance of surgery in patients with various stages of SCLC. The results indicate that surgery has some positive significance in patients with various stages of SCLC. In particular, we found for the first time that patients with stage IV disease who underwent surgery had longer survival times than those in patients in the nonsurgery group. These results indicate the need for more in-depth studies on the application of surgery in various stages of SCLC.

This study had some limitations. First, this was a retrospective study; thus, selection bias was inevitable. Second, the proportion of patients in the surgery group was lower than that in the nonsurgery group, especially for stage IV patients. This objective reality may lead to a decrease in statistical efficiency. Third, we only knew which patients received surgical treatment but not the conditions, timing, and reasons that these patients received surgical treatment and other detailed information that is important for making treatment decisions in clinical practice. Thus, the results of this study can only be used as a reference for clinical decision-making.

5. Conclusions

In summary, surgery has been used in the minority of patients with SCLC in the real world and has shown the benefits of survival. These results support an increased role of surgery in multimodal therapy for SCLC.

Author contributions

Conceptualization: Long Xu.
Data curation: Long Xu.
Formal analysis: Long Xu, Guanzhong Zhang.
Investigation: Guanzhong Zhang, Zhendong Zheng.
Project administration: Guanzhong Zhang, Shuxi Song, Zhendong Zheng.

Resources: Shuxi Song.
Writing – original draft: Long Xu, Shuxi Song.
Writing – review & editing: Zhendong Zheng.

References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;0:1–31.
[2] Society AC. Key Statistics for Small Cell Lung Cancer. [Internet]. 2018; https://www.cancer.org/cancer/small-cell-lung-cancer/about/key-statistics.html. (Accessed Oct 30, 2018).
[3] Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. Lancet 1973;2:63–5.
[4] Low M, Ben-Or S. Thoracic surgery in early-stage small cell lung cancer. Thorac Surg Clin 2018;28:9–14.
[5] Jin K, Zhang K, Zhou F, et al. Selection of candidates for surgery as local therapy among early-stage small cell lung cancer patients: a population-based analysis. Cancer Commun (Lond) 2018;38:5.
[6] Yang CJ, Chan DY, Shah SA, et al. Long-term survival after surgery compared with concurrent chemoradiation for node-negative small cell lung cancer. Ann Surg 2018;268:1105–12.
[7] Wakeam E, Varghese TKJr, Leighl NB, et al. Trends, practice patterns and underuse of surgery in the treatment of early stage small cell lung cancer. Lung Cancer 2017;109:117–23.
[8] Rudin CM, Giaccone G, Ismaila N. Treatment of small-cell lung cancer: American Society of Clinical Oncology Endorsement of the American College of Chest Physicians Guideline. J Oncol Pract 2016;12:83–6.
[9] Network NCC. NCCN Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer (2019V1).[Internet]. 2018; https://www.nccn.org/professionals/physician_gls/default.aspx#sclc. (Accessed Oct 10, 2018).
[10] Fruh M, De Ruysscher D, Popat S, et al. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(Suppl 6):vi99–105.
[11] Koinis F, Kotsakis A, Georgoulias V. Small cell lung cancer (SCLC): no treatment advances in recent years. Transl Lung Cancer Res 2016;5:39–50.
[12] Verma V, Simone CB2nd. Surgery versus conventional radiation therapy for T1-2 N0 M0 small-cell lung cancer: a fair comparison? Clin Lung Cancer 2018;19:e69–70.
[13] Hoda MA, Klikovits T, Klepetko W. Controversies in oncology: surgery for small cell lung cancer? It's time to rethink the case. ESMO Open 2018;3:e000366.
[14] Wakeam E. Surgery for small cell lung cancer in the modern era: opportunities and challenges. J Thorac Dis 2017;9:E1145–7.
[15] Ahmed Z, Kujtan L, Kennedy KF, et al. Disparities in the management of patients with stage I small cell lung carcinoma (SCLC): A Surveillance, Epidemiology and End Results (SEER) analysis. Clin Lung Cancer 2017;18:e315–25.
[16] Penner LA, Dovidio JF, Gonzalez R, et al. The effects of oncologist implicit racial bias in racially discordant oncology interactions. J Clin Oncol 2016;34:2874–80.
[17] Babakoohi S, Fu P, Yang M, et al. Combined SCLC clinical and pathologic characteristics. Clin Lung Cancer 2013;14:113–9.
[18] Wakeam E, Acuna SA, Leighl NB, et al. Surgery versus chemotherapy and radiotherapy for early and locally advanced small cell lung cancer: a propensity-matched analysis of survival. Lung Cancer 2017;109:78–88.
[19] Yang CJ, Chan DY, Speicher PJ, et al. Surgery versus optimal medical management for N1 small cell lung cancer. Ann Thorac Surg 2017;103:1767–72.
[20] Migliore M, Halezeroglu S, Lerut A. Surgery for "advanced" lung and esophageal cancer: new horizons or false dawn? Future Oncol 2018;14 (6s):1–4.