Original Article

The extent of mediastinal lymph node dissection correlates with survival of small cell lung cancer patients after resection: a propensity score-matched cohort study analysis

Jinlin Cao[1], Jinming Xu[1], Haojie Yu[2], Pengxu Qian[3,4], Wang Lv[1], Tianyu He[1], Ping Yuan[5], Filippo Longo[6], Luca Bertolaccini[7], Kazuhiro Yasufuku[8], A. Justin Rucker[9], Jian Hu[1]

[1]Department of Thoracic Surgery, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China; [2]State Key Laboratory of Chemical Engineering, College of Chemical and Biological Engineering, Zhejiang University, Hangzhou, China; [3]Bone Marrow Transplantation Center, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China; [4]Liangzhu Laboratory, Zhejiang University Medical Center, Hangzhou, China; [5]Department of Thoracic Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [6]Department of Thoracic Surgery, Departmental Faculty of Medicine and Surgery, Università Campus Bio-Medico di Roma, Rome, Italy; [7]Department of Thoracic Surgery, IEO European Institute of Oncology IRCCS, Milan, Italy; [8]Division of Thoracic Surgery, Toronto General Hospital, University Health Network, Toronto, ON, Canada; [9]Division of Cardiovascular and Thoracic Surgery, Department of Surgery, Duke University Medical Center, Durham, NC, USA

Contributions: (I) Conception and design: J Cao, J Hu; (II) Administrative support: J Hu; (III) Provision of study materials or patients: J Cao, J Xu, T He; (IV) Collection and assembly of data: J Cao, J Xu, W Lv, T He; (V) Data analysis and interpretation: J Cao, J Xu, H Yu, P Qian, W Lv, T He, P Yuan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jian Hu, MD, PhD. Department of Thoracic Surgery, The First Affiliated Hospital, School of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou 310003, China. Email: dr_hujian@zju.edu.cn.

Background: Evidence on the importance of lymph node (LN) dissection during resection for small cell lung cancer (SCLC) is scarce. This study sought to investigate the clinical impact of the extent of lymphadenectomy on the survival of patients with SCLC.

Methods: Patients who underwent resection for primary SCLC between 2000 and 2016 were identified from the Surveillance, Epidemiology, and End Results (SEER) cancer registry. The patients were stratified based on the number of LNs dissected (0, 1–3, 4–11, and ≥12) via an X-Tile software analysis, and lung cancer-specific survival (LCSS) and overall survival (OS) were compared between these stratified groups using Kaplan-Meier curves. A propensity score-matched analysis and a Cox regression model were used to adjust for potential confounders.

Results: A total of 1,883 patients with SCLC met our criteria and were enrolled in the study. The LCSS and OS analyses revealed that patients who underwent LN dissection during surgery had longer survival times significantly than patients who did not. Similarly, patients who underwent more extensive LN dissection (≥4 LNs) had longer survival times than those who underwent less extensive LN dissection (1–3 LNs). However, no significant increase in survival time was found for patients who underwent the dissection of ≥12 LNs compared to those who underwent the dissection of 4–11 LNs. These results were confirmed in our propensity-matched and Cox regression analyses.

Conclusions: Our study revealed that patient survival after surgical resection for SCLC is associated with the number of dissected LNs, and the number of LNs for dissection ranges from 4 to 11 achieve the best survival outcome.

Keywords: Small cell lung cancer (SCLC); surgical resection; lymphadenectomy; prognosis; survival

Submitted May 06, 2022. Accepted for publication Jul 18, 2022.
doi: 10.21037/tlcr-22-489
View this article at: https://dx.doi.org/10.21037/tlcr-22-489

© Translational Lung Cancer Research. All rights reserved.

Introduction

Lung cancers, including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), are the leading cause of cancer-related mortality and morbidity worldwide (1). SCLC accounts for approximately 10–15% of all lung cancer cases and has a high propensity for early metastatic dissemination to distant sites and a poor prognosis (2,3). Historically, the standard treatment for most patients with SCLC is a combination of chemotherapy and radiotherapy. Surgical resection is not recommended for SCLC patients because, according to the findings of 2 influential trials performed in the 1960s and 1980s, it confers inferior survival compared to chemotherapy plus radiotherapy (4,5). Recent advances in radiological and imaging techniques, such as high-resolution chest computed tomography and positron emission tomography, have led to an evident increase in the detection of early-stage lung cancer (6). Further, due to advances in surgical techniques, the inclusion of surgical interventions in the multimodality treatment of SCLC has garnered increasing interest.

The current guidelines of the National Comprehensive Cancer Network (NCCN), American College of Chest Physicians, and the Japan Lung Cancer Society recommend surgical resection for patients with clinical stage I SCLC, while the guidelines of the European Society of Medical Oncology recommend surgical resection for a subset of patients with up to clinical stage II SCLC (7-9). Further, some researchers have found an association between surgical resection and improved survival, even in selected patients with more advanced clinical stages of up to IIIB (10). These researchers recommend a subsequent lobectomy as the optimal approach for medically fit patients (11).

Currently, evidence on the importance of lymph node (LN) dissection during surgical resection for SCLC is limited. Pathologic nodal upstaging is common after surgical resection of stage I SCLC and is associated with significantly poor survival outcomes (12). Several institutional studies have examined whether the number of dissected LNs affects the survival of patients with NSCLC (13-19). Notably, these studies found an association between patient survival and the number of dissected LNs, which in turn was correlated with more accurate nodal staging and long-term survival.

In this study, we used the sizeable population-based Surveillance, Epidemiology, and End Results (SEER) database to examine the clinical impact of the extent of lymphadenectomy on the postoperative survival of patients with SCLC. Our findings provide a rationale and support for LN dissection during surgical resection for SCLC. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-489/rc)

Methods

Patient population

Using SEER*Stat version 8.3.6.1, patients with SCLC were selected from the latest version of the SEER research database (18 registries, with additional treatment fields, 1975–2016) based on November 2018 submissions (20). The eligible patients comprised those with microscopically diagnosed primary SCLC who had undergone surgical resection between January 2000 and December 2016. Only those who were actively followed-up after surgery were included in the analysis of the eligible patients. The histologic type codes 8041–8045 and tumor site codes 341–343 according to the International Classification of Diseases for Oncology (3rd edition) were included in the study. Patients with an unknown number of dissected LNs or distant metastasis were excluded from the study. The selection codes for the SEER database queries and the study flow chart are shown in Appendix 1 and Figure S1. All the SCLC tumors were finally staged according to the 8th edition of the tumor-node-metastasis TNM classification system (21). We defined overall survival (OS) as the interval from surgery until death by any cause and lung cancer-specific survival (LCSS) as the interval from surgery until death due to lung cancer. The last follow-up date was December 31, 2016. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

The data were analyzed using SPSS 24.0 (IBM, Armonk, NY, USA). A 2-sided P value <0.05 was considered statistically significant for all the statistical analyses. The patients were stratified into subgroups based on the number of dissected LNs using X-Tile software (http://www.tissuearray.org/rimmlab) and the minimal P value approach (see Figure S2) (22). The categorical variables among the baseline characteristics were analyzed using Pearson's chi-square test. The Kaplan-Meier method was used to estimate the OS and LCSS for the various LN dissection subgroups, and the log-rank test was used to compare the statistical

© Translational Lung Cancer Research. All rights reserved.

differences between these subgroups. Survival curves were drawn using Prism 7.0 (GraphPad Software, La Jolla, CA, USA). To verify the results, we conducted a propensity score-matched comparative analysis to adjust for potential bias in the baseline characteristics of patients in the various LN dissection subgroups (1:1 matched for each paired group). For this purpose, an optimized performance-matching algorithm with a caliper setting of 0.1 was used (23). The standardized differences assessed the balance of covariates between the groups. Survival functions were compared using a univariate Cox proportional hazards regression analysis. Significant prognostic factors identified in the univariate analysis were included in the multivariate analysis.

Results

Ultimately, 1,883 patients who met the eligibility criteria were included in this study, including 430 (22.8%) patients with no LNs dissected, 386 (20.5%) patients with 1–3 LNs dissected, 668 (35.5%) patients with 4–11 LNs dissected, and 399 (21.2%) patients with ≥12 LNs dissected. The median number of dissected LNs in this data set was 5 (range, 0–87). The median follow-up duration was 22 months (range, 0–204 months), and the 5-year OS rate of the entire cohort was 34%. The 30-day mortality rate was 2.5% (48 of 1,883), including 19 deaths (4.4%) in the no LN dissection group and 29 deaths (2.0 %) in the LN dissection group (P=0.011). The patients' characteristics are summarized in *Table 1*. The patients who underwent LN dissection were more likely to have higher indeterminate stage tumors and high-grade tumours than patients who underwent no LN dissection. Patients who underwent more extensive LN dissection were more likely to have undergone a lobectomy and to have been treated more recently than patients who underwent no or less extensive LN dissection.

A Kaplan-Meier analysis and log-rank test identified several LN dissection subgroups with significantly different survival outcomes among the entire cohort (see *Figure 1*). After propensity score matching, 392 pairs were formed between the no LN dissection and LN dissection groups, 342 were formed between the 1–3 and ≥ 4 LN dissection subgroups, and 396 were formed between the 4–11 and ≥12 LN dissection subgroups; thus, most of the available variables were well balanced (see Tables S1-S3). Patients who underwent surgical resection with LN dissection had longer survival times than those who underwent surgical dissection with no LN dissection (see *Figure 2A,2B*). Compared to less extensive LN dissection (1–3 LNs), more extensive LN dissection (≥4 LNs) further improved the survival outcomes of patients (see *Figure 2C,2D*). However, the dissection of ≥12 LNs did not result in a statistically significant increase in survival compared to the dissection of 4–11 LNs (see *Figure 2E,2F*).

Significant differences were observed between the LN groups concerning several potentially important prognostic factors, including age, sex, race, tumor size, T stage, N stage, TNM stage, grade, surgical procedure, and chemotherapy (see *Tables 2-4*). After adjusting for these variables, our multivariable Cox regression analysis also revealed that LN dissection was independently associated with superior LCCS and OS compared to no LN dissection (see *Table 2*). Further, a higher number of dissected LNs (≥4 LNs) was found to be independently associated with a longer LCCS and OS compared to a lower number of dissected LNs (1–3 LNs) (see *Table 3*). However, patients with ≥12 LNs dissected showed no incremental improvement in LCCS and OS relative to those with 4–11 LNs dissected (see *Table 4*). These results were confirmed in our propensity-matched analysis; however, the log-rank test results showed that LN dissection conferred an equivalent LCSS rate to that of no LN dissection (see Figure S3 and Tables S4-S6).

Discussion

Over the past 20 years, studies have increasingly demonstrated that the surgical resection of SCLC is associated with improved patient survival (10,24-29). The current NCCN guidelines recommend a lobectomy with LN dissection for patients undergoing definitive surgical resection (7). However, the recommended number of LNs to be dissected during surgical resection remains unclear. To our knowledge, this is the first study to explore the clinical impact of the extent of LN dissection in patients who underwent resection for SCLC. Our study of 1883 patients who underwent resection for SCLC revealed that an increase in the number of dissected LNs was directly associated with an increase in survival, which peaked when approximately 4–11 LNs were dissected. Both the multivariate Cox regression model and the propensity score-matched analysis demonstrated that compared to patients with no LN dissection and less extensive LN dissection (1–3 LNs), patients with LN dissection and more extensive LN dissection (4 LNs) exhibited improved LCCS and OS outcomes, respectively. However, compared to patients with 4–11 LNs dissected, those with ≥12 LNs dissected showed no statistically significant increase in survival.

© Translational Lung Cancer Research. All rights reserved.

Table 1 The characteristics of the patients included in the study

Variables	Number of LNs examined				P value
	0	1–3	4–11	≥12	
Number of patients	430	386	668	399	
Age (years), n (%)					0.066
<65	133 (30.9)	130 (33.7)	227 (34.0)	137 (34.3)	
65–75	184 (42.8)	171 (44.3)	318 (47.6)	188 (47.1)	
>75	113 (26.3)	85 (22.0)	123 (18.4)	74 (18.5)	
Sex, n (%)					0.332
Female	221 (51.4)	200 (51.8)	376 (56.3)	210 (52.6)	
Male	209 (48.6)	186 (48.2)	292 (43.7)	189 (47.4)	
Race, n (%)					0.441
White	380 (88.4)	351 (90.9)	605 (90.6)	365 (91.5)	
Black/other	50 (11.6)	35 (9.1)	63 (9.4)	34 (8.5)	
Location, n (%)					0.075
Metropolitan	348 (80.9)	318* (82.6)	535 (80.1)	344 (86.2)	
Non-metropolitan	82 (19.1)	67* (17.4)	133 (19.9)	55 (13.8)	
Year of diagnosis, n (%)					<0.001
2000–2004	121 (28.1)	126 (32.6)	155 (23.2)	80 (20.1)	
2005–2008	96 (22.3)	95 (24.6)	177 (26.5)	77 (19.3)	
2009–2012	131 (30.5)	96 (24.9)	171 (25.6)	97 (24.3)	
2013–2016	82 (19.1)	69 (17.9)	165 (24.7)	145 (36.3)	
Tumor site, n (%)					0.657
Upper	270 (62.8)	240 (62.2)	409 (61.2)	250 (62.7)	
Middle	26 (6.0)	30 (7.8)	49 (7.3)	19 (4.8)	
Lower	134 (31.2)	116 (30.1)	210 (31.4)	130 (32.6)	
Tumor size (mm), n (%)					<0.001
0–10	52 (12.1)	54 (14.0)	58 (8.7)	29 (7.3)	
11–20	161 (37.4)	155 (40.2)	231 (34.6)	133 (33.3)	
21–30	79 (18.4)	84 (21.8)	202 (30.2)	97 (24.3)	
31–40	29 (6.7)	43 (11.1)	87 (13.0)	59 (14.8)	
41–50	16 (3.7)	16 (4.1)	37 (5.5)	42 (10.5)	
>50	35 (8.1)	15 (3.9)	44 (6.6)	31 (7.8)	
Not determined	58 (13.5)	19 (4.9)	9 (1.3)	8 (2.0)	
T stage, n (%)					<0.001
T1	182 (42.3)	196 (50.8)	353 (52.8)	191 (47.9)	
T2	118 (27.4)	117 (30.3)	223 (33.4)	159 (39.8)	
T3	38 (8.8)	24 (6.2)	44 (6.6)	26 (6.5)	
T4	56 (13.0)	33 (8.5)	34 (5.1)	18 (4.5)	
Not determined	36 (8.4)	16 (4.1)	14 (2.1)	5 (1.3)	

Table 1 (*continued*)

© Translational Lung Cancer Research. All rights reserved.

Table 1 (*continued*)

Variables	Number of LNs examined				P value
	0	1–3	4–11	≥12	
N stage, n (%)					<0.001
N0	302 (70.2)	219 (56.7)	419 (62.7)	218 (54.6)	
N1	17 (4.0)	66 (17.1)	139 (20.8)	93 (23.3)	
N2	84 (19.5)	100 (25.9)	107 (16.0)	84 (21.1)	
Not determined	27 (6.3)	1 (0.3)	3 (0.4)	4 (1.0)	
TNM stage, n (%)					<0.001
IA	150 (34.9)	127 (32.9)	244 (36.5)	120 (30.1)	
IB	74 (17.2)	58 (15.0)	123 (18.4)	73 (18.3)	
IIA	16 (3.7)	30 (7.8)	83 (12.4)	50 (12.5)	
IIB	30 (7.0)	39 (10.1)	60 (9.0)	45 (11.3)	
IIIA	66 (15.3)	94 (24.4)	119 (17.8)	88 (22.1)	
IIIB	42 (9.8)	25 (6.5)	23 (3.4)	15 (3.8)	
Not determined	52 (12.1)	13 (3.4)	16 (2.4)	8 (2.0)	
Grade, n (%)					<0.001
Grade I	2 (0.5)	2 (0.5)	11 (1.6)	2 (0.5)	
Grade II	13 (3.0)	9 (2.3)	22 (3.3)	16 (4.0)	
Grade III	97 (22.6)	118 (30.6)	221 (33.1)	127 (31.8)	
Grade IV	128 (29.8)	133 (34.5)	228 (34.1)	118 (29.6)	
Not determined	190 (44.2)	124 (32.1)	186 (27.8)	136 (34.1)	
Surgical procedure, n (%)					<0.001
Sublobar resection	274 (63.7)	190 (49.2)	91 (13.6)	34 (8.5)	
Lobectomy	62 (14.4)	147 (38.1)	529 (79.2)	330 (82.7)	
Other	94 (21.9)	49 (12.7)	48 (7.2)	35 (8.8)	
Radiation, n (%)					0.172
Yes	163 (37.9)	143 (37.0)	216 (32.3)	132 (33.1)	
No	267 (62.1)	243 (63.0)	452 (67.7)	267 (66.9)	
Chemotherapy, n (%)					0.164
Yes	266 (61.9)	242 (62.7)	441 (66.0)	273 (68.4)	
No/unknown	164 (38.1)	144(37.3)	227 (34.0)	126 (31.6)	

*, one patient's location is undetermained (missing data). LN, lymph node.

Several studies of NSCLC have found that the dissection of a greater number of LNs during surgical resection is associated with better survival outcomes. Using the SEER database, Ludwig *et al.* concluded that 11–16 LNs should be dissected to achieve the best survival outcome (14). Similarly, Ou and Zell observed the best survival outcome in patients for whom >15 LNs had been dissected during resection (15). Varlotto *et al.* found that the optimal number of dissected LNs was 11–16 when only the N1 LNs were removed and 7–10 when only the N2 LNs were removed (16). Osarogiagbon *et al.* found that the dissection of approximately 18–20 LNs was optimally associated with reduced mortality risk (17). In more recent studies of the United States SEER database and a Chinese multi-institutional registry,

© Translational Lung Cancer Research. All rights reserved.

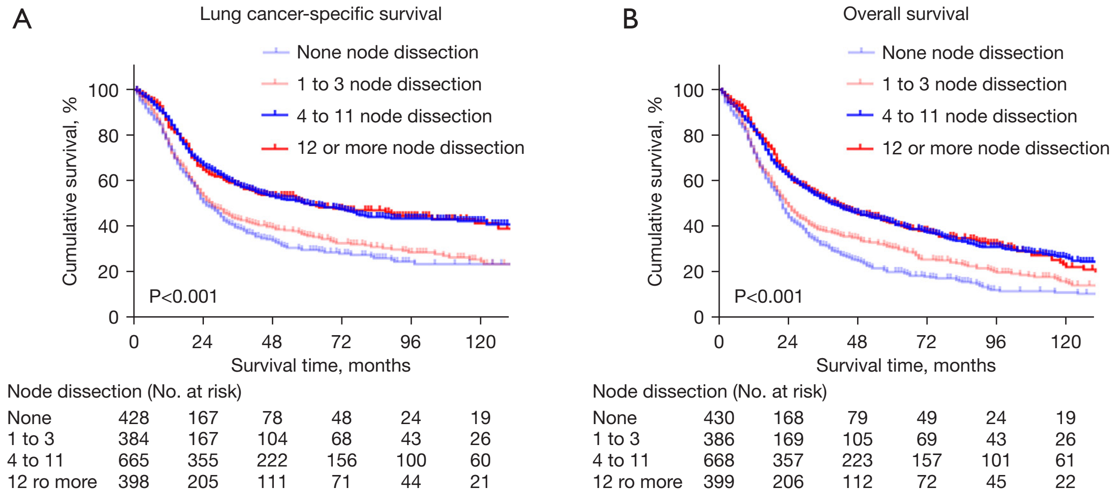

Figure 1 Kaplan-Meier curves of the survival estimates for our entire cohort of patients. (A) LCSS data of patients who underwent surgical resection for SCLC. (B) OS data of patients who underwent surgical resection for SCLC. LCSS, lung cancer-specific survival; SCLC, small cell lung cancer; OS, overall survival.

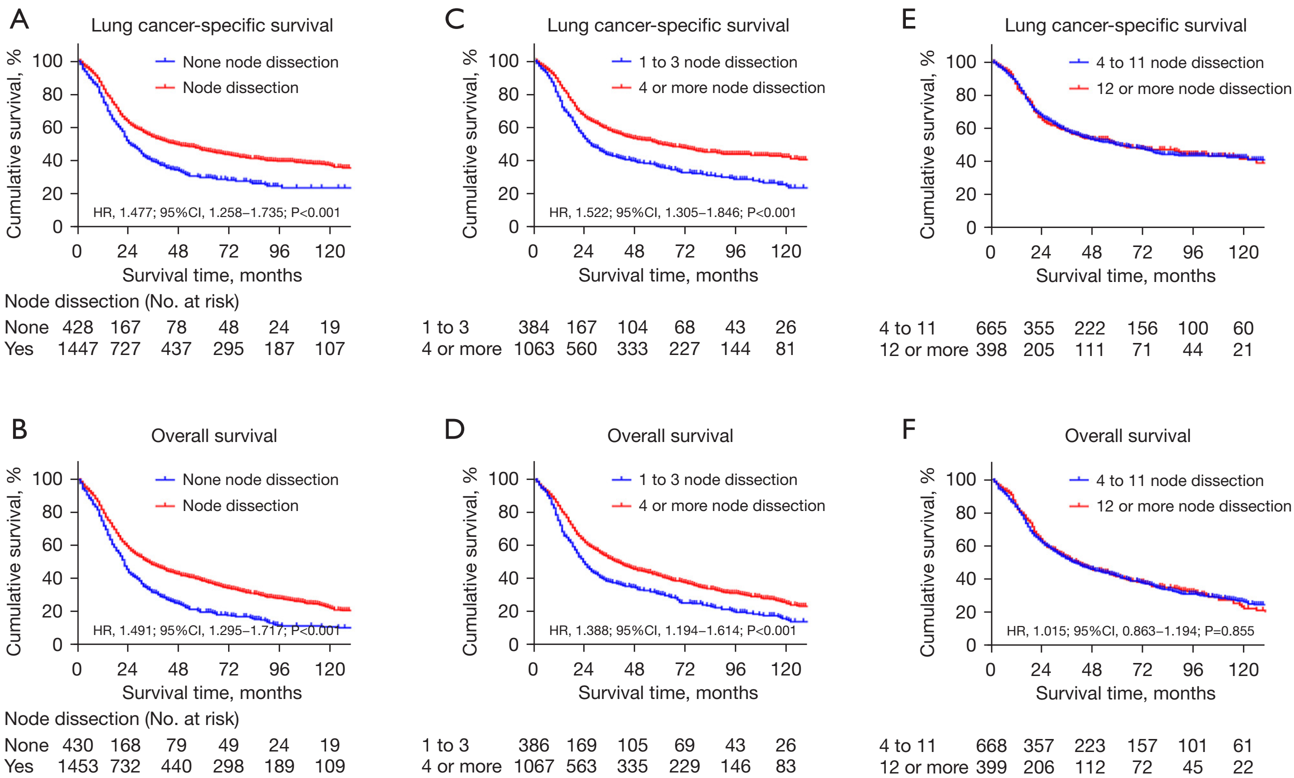

Figure 2 Kaplan-Meier curves of the survival estimates for the stratified groups of patients. (A,B) LCSS and OS for patients with or without LNs dissected. (C,D) LCSS and OS for patients with 1–3 LNs dissected or ≥4 LNs dissected. (E,F) LCSS and OS for patients with 4–11 LNs dissected or ≥12 LNs dissected. LCSS, lung cancer-specific survival; OS, overall survival; LN, lymph node.

© Translational Lung Cancer Research. All rights reserved.

Table 2 Univariable and multivariable Cox regression analyses for patients who underwent surgery for SCLC with or without LN dissection in the entire cohort

Variables	LCSS				OS			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)		<0.001		<0.001		<0.001		<0.001
<65	Reference		Reference		Reference		Reference	
65–75	1.273 (1.100–1.474)	0.001	1.350 (1.164–1.567)	<0.001	1.419 (1.249–1.613)	<0.001	1.451 (1.274–1.654)	<0.001
>75	1.786 (1.502–2.123)	<0.001	1.850 (1.548–2.211)	<0.001	1.945 (1.670–2.267)	<0.001	1.913 (1.633–2.241)	<0.001
Sex		<0.001		0.001		<0.001		<0.001
Female	Reference		Reference		Reference		Reference	
Male	1.298 (1.144–1.471)		1.250 (1.100–1.420)		1.309 (1.174–1.461)		1.281 (1.145–1.432)	
Race		0.107				0.037		0.028
White	Reference				Reference		Reference	
Black/other	0.835 (0.670–1.040)				0.818 (0.677–0.988)		0.804 (0.662–0.977)	
Location		0.604				0.267		
Metropolitan	Reference				Reference			
Non-metropolitan	0.958 (0.815–1.127)				0.922 (0.799–1.064)			
Year of diagnosis		0.023		0.131		0.037		0.213
2000–2004	Reference		Reference		Reference		Reference	
2005–2008	0.920 (0.780–1.084)	0.319	1.029 (0.865–1.224)	0.745	0.918 (0.796–1.059)	0.240	0.988 (0.850–1.148)	0.870
2009–2012	0.891 (0.755–1.051)	0.170	0.970 (0.815–1.155)	0.733	0.934 (0.807–1.080)	0.355	0.972 (0.834–1.133)	0.717
2013–2016	0.717 (0.580–0.886)	0.002	0.792 (0.632–0.993)	0.043	0.755 (0.624–0.913)	0.004	0.815 (0.667–0.996)	0.046
Tumor site		0.127				0.273		
Upper	Reference				Reference			
Middle	0.914 (0.701–1.192)	0.508			0.940 (0.748–1.182)	0.599		
Lower	1.130 (0.987–1.294)	0.077			1.089 (0.967–1.226)	0.160		
Tumor size (mm)		<0.001		0.022		<0.001		0.154
0–10	Reference		Reference		Reference		Reference	
11–20	1.224 (0.966–1.552)	0.095	1.313 (1.033–1.669)	0.026	1.155 (0.949–1.406)	0.151	1.204 (0.986–1.469)	0.068
21–30	1.337 (1.045–1.710)	0.021	1.445 (1.124–1.859)	0.004	1.187 (0.966–1.458)	0.103	1.274 (1.033–1.573)	0.024
31–40	1.586 (1.204–2.090)	0.001	1.653 (1.209–2.259)	0.002	1.309 (1.034–1.657)	0.025	1.367 (1.044–1.791)	0.023
41–50	1.583 (1.148–2.183)	0.005	1.406 (0.985–2.007)	0.060	1.195 (0.898–1.592)	0.222	1.104 (0.804–1.515)	0.541
>50	1.881 (1.384–2.556)	<0.001	1.605 (1.138–2.263)	0.007	1.508 (1.156–1.968)	0.002	1.329 (0.985–1.793)	0.063
Not determined	2.731 (2.002–3.725)	<0.001	1.772 (1.224–2.564)	0.002	2.126 (1.613–2.802)	<0.001	1.431 (1.030–1.988)	0.033
T stage		<0.001		0.368		<0.001		0.355
T1	Reference		Reference		Reference		Reference	
T2	1.433 (1.240–1.655)	<0.001	1.094 (0.859–1.393)	0.468	1.259 (1.112–1.426)	<0.001	1.120 (0.901–1.392)	0.309
T3	1.963 (1.542–2.501)	<0.001	1.424 (1.005–2.017)	0.047	1.706 (1.371–2.123)	<0.001	1.402 (1.022–1.925)	0.036
T4	2.124 (1.710–2.638)	<0.001	1.365 (0.849–2.196)	0.199	1.686 (1.385–2.053)	<0.001	1.224 (0.794–1.887)	0.359
Not determined	1.833 (1.370–2.454)	<0.001	1.063 (0.597–1.893)	0.835	1.592 (1.231–2.058)	<0.001	1.134 (0.669–1.923)	0.640

Table 2 (*continued*)

© Translational Lung Cancer Research. All rights reserved.

Table 2 (*continued*)

Variables	LCSS				OS			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
N stage		<0.001		0.003		<0.001		0.003
N0	Reference		Reference		Reference		Reference	
N1	1.827 (1.550–2.154)	<0.001	1.536 (1.168–2.022)	0.002	1.565 (1.353–1.811)	<0.001	1.538 (1.202–1.969)	0.001
N2	2.232 (1.918–2.596)	<0.001	1.905 (1.319–2.751)	0.001	1.824 (1.593–2.089)	<0.001	1.686 (1.199–2.371)	0.003
Not determined	2.021 (1.339–3.049)	0.001	1.258 (0.699–2.265)	0.444	1.566 (1.083–2.262)	0.017	1.193 (0.702–2.025)	0.514
TNM stage		<0.001		0.003		<0.001		0.106
IA	Reference		Reference		Reference		Reference	
IB	1.379 (1.121–1.695)	0.002	1.202 (0.888–1.627)	0.235	1.173 (0.988–1.392)	0.069	1.059 (0.813–1.380)	0.673
IIA	2.340 (1.870–2.927)	<0.001	2.106 (1.507–2.943)	<0.001	1.743 (1.430–2.125)	<0.001	1.590 (1.181–2.141)	0.002
IIB	2.280 (1.804–2.882)	<0.001	1.584 (1.088–2.307)	0.016	1.827 (1.495–2.234)	<0.001	1.335 (0.957–1.863)	0.089
IIIA	2.557 (2.134–3.064)	<0.001	1.409 (0.908–2.185)	0.126	1.917 (1.642–2.239)	<0.001	1.240 (0.831–1.851)	0.291
IIIB	3.040 (2.345–3.941)	<0.001	1.353 (0.688–2.663)	0.381	2.189 (1.734–2.763)	<0.001	1.245 (0.672–2.307)	0.486
Not determined	2.247 (1.697–2.977)	<0.001	1.250 (0.668–2.339)	0.486	1.705 (1.335–2.176)	<0.001	1.034 (0.584–1.829)	0.909
Grade		0.006		0.008		<0.001		0.001
Grade I	Reference		Reference		Reference		Reference	
Grade II	2.166 (0.842–5.572)	0.109	1.615 (0.624–4.178)	0.323	2.337 (0.989–5.521)	0.053	1.730 (0.726–4.126)	0.216
Grade III	2.257 (0.932–5.467)	0.071	2.009 (0.826–4.889)	0.124	2.662 (1.188–5.965)	0.017	2.271 (1.005–5.130)	0.048
Grade IV	2.454 (1.014–5.937)	0.046	2.306 (0.949–5.602)	0.065	2.753 (1.230–6.165)	0.014	2.474 (1.095–5.586)	0.029
Not determined	2.868 (1.186–6.934)	0.019	2.510 (1.034–6.097)	0.042	3.322 (1.484–7.435)	0.003	2.827 (1.253–6.378)	0.012
Surgical procedure		<0.001		<0.001		<0.001		<0.001
Sublobar resection	Reference		Reference		Reference		Reference	
Lobectomy	0.640 (0.557–0.735)	<0.001	0.665 (0.565–0.782)	<0.001	0.637 (0.564–0.719)	<0.001	0.701 (0.607–0.808)	<0.001
Other	1.117 (0.919–1.358)	0.266	0.870 (0.702–1.079)	0.206	1.037 (0.872–1.235)	0.680	0.909 (0.750–1.103)	0.334
Radiation		0.361				0.662		
Yes	Reference				Reference			
No	0.941 (0.827–1.072)				1.026 (0.915–1.150)			
Chemotherapy		0.039		<0.001		0.001		<0.001
Yes	Reference		Reference		Reference		Reference	
No/unknown	1.148 (1.007–1.309)		1.420 (1.234–1.635)		1.217 (1.087–1.363)		1.438 (1.274–1.624)	<0.001
LN dissection		<0.001		0.001		<0.001		<0.001
Yes	Reference		Reference		Reference		Reference	
None	1.513 (1.313–1.744)		1.341 (1.131–1.588)		1.526 (1.348–1.727)		1.372 (1.182–1.593)	

SCLC, small cell lung cancer; LN, lymph node; LCSS, lung cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; TNM, tumor-node-metastasis.

© Translational Lung Cancer Research. All rights reserved.

Table 3 Univariable and multivariable Cox regression analyses for patients who underwent surgery for SCLC with the dissection of 1 to 3 LNs or ≥4 LNs in the entire cohort

Variables	LCSS				OS			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)		<0.001		<0.001		<0.001		<0.001
<65	Reference		Reference		Reference		Reference	
65–75	1.334 (1.126–1.580)	0.001	1.418 (1.192–1.685)	<0.001	1.456 (1.257–1.687)	<0.001	1.504 (1.293–1.748)	<0.001
>75	1.678 (1.364–2.065)	<0.001	1.742 (1.409–2.155)	<0.001	1.814 (1.511–2.177)	<0.001	1.789 (1.481–2.159)	<0.001
Sex		0.001		0.003		<0.001		0.001
Female	Reference		Reference		Reference		Reference	
Male	1.279 (1.105–1.482)		1.253 (1.078–1.456)		1.268 (1.116–1.441)		1.243 (1.090–1.418)	
Race		0.074		0.049		0.033		0.045
White	Reference		Reference		Reference		Reference	
Black/other	0.783 (0.598–1.024)		0.759 (0.576–0.998)		0.780 (0.621–0.981)		0.786 (0.620–0.995)	
Location		0.866				0.523		
Metropolitan	Reference				Reference			
Non-metropolitan	0.984 (0.814–1.189)				0.947 (0.800–1.120)			
Year of diagnosis		0.158				0.188		
2000–2004	Reference				Reference			
2005–2008	0.943 (0.779–1.141)	0.547			0.910 (0.772–1.074)	0.267		
2009–2012	0.844 (0.692–1.029)	0.094			0.885 (0.744–1.052)	0.166		
2013–2016	0.785 (0.616–0.999)	0.049			0.793 (0.637–0.987)	0.037		
Tumor site		0.116				0.504		
Upper	Reference				Reference			
Middle	0.939 (0.695–1.270)	0.684			0.914 (0.703–1.187)	0.500		
Lower	1.167 (0.997–1.366)	0.055			1.059 (0.922–1.217)	0.414		
Tumor size (mm)		0.001		0.078		0.043		0.248
0–10	Reference		Reference		Reference		Reference	
11–20	1.313 (0.989–1.744)	0.060	1.454 (1.091–1.938)	0.011	1.206 (0.955–1.524)	0.115	1.341 (1.098–1.767)	0.015
21–30	1.444 (1.080–1.931)	0.013	1.582 (1.174–2.131)	0.003	1.240 (0.974–1.579)	0.080	1.370 (1.132–1.859)	0.013
31–40	1.636 (1.188–2.252)	0.003	1.754 (1.216–2.529)	0.003	1.317 (1.004–1.728)	0.046	1.474 (1.075–2.021)	0.016
41–50	1.707 (1.177–2.475)	0.005	1.704 (1.120–2.592)	0.013	1.317 (0.951–1.823)	0.097	1.414 (0.978–2.045)	0.066
>50	1.708 (1.171–2.492)	0.005	1.549 (1.015–2.366)	0.043	1.421 (1.031–1.959)	0.032	1.448 (1.005–2.088)	0.047
Not determined	2.527 (1.613–3.959)	<0.001	1.649 (0.977–2.783)	0.061	1.966 (1.313–2.945)	0.001	1.327 (0.832–2.115)	0.235
T stage		<0.001		0.038		<0.001		0.156
T1	Reference		Reference		Reference		Reference	
T2	1.391 (1.181–1.639)	<0.001	1.130 (0.864–1.478)	0.371	1.203 (1.043–1.386)	0.011	1.069 (0.838–1.363)	0.592
T3	1.882 (1.408–2.514)	<0.001	1.761 (1.171–2.646)	0.007	1.583 (1.215–2.063)	0.001	1.515 (1.040–2.208)	0.030
T4	1.758 (1.331–2.322)	0.001	2.297 (1.248–4.227)	0.008	1.449 (1.128–1.862)	0.004	1.799 (1.027–3.151)	0.040
Not determined	1.687 (1.113–2.557)	0.014	1.599 (0.692–3.698)	0.272	1.508 (1.057–2.151)	0.023	1.547 (0.677–3.535)	0.301

Table 3 (*continued*)

© Translational Lung Cancer Research. All rights reserved.

Table 3 (*continued*)

Variables	LCSS				OS			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
N stage		<0.001		<0.001		<0.001		<0.001
N0	Reference		Reference		Reference		Reference	
N1	2.218 (1.854–2.654)	<0.001	1.845 (1.307–2.604)	<0.001	1.866 (1.594–2.184)	<0.001	1.910 (1.405–2.596)	<0.001
N2	2.523 (2.108–3.020)	<0.001	3.059 (1.789–5.232)	<0.001	2.077 (1.771–2.436)	<0.001	2.740 (1.687–4.448)	<0.001
Not determined	2.019 (0.900–4.532)	0.088	2.308 (0.719–7.415)	0.160	1.498 (0.710–3.162)	0.289	2.017 (0.664–6.127)	0.216
TNM stage		<0.001		0.040		<0.001		0.357
IA	Reference		Reference		Reference		Reference	
IB	1.330 (1.040–1.702)	0.023	1.115 (0.790–1.573)	0.536	1.102 (0.899–1.352)	0.348	1.003 (0.743–1.354)	0.987
IIA	2.598 (2.029–3.326)	<0.001	1.592 (1.058–2.394)	0.026	1.863 (1.500–2.315)	<0.001	1.230 (0.860–1.759)	0.257
IIB	2.448 (1.876–3.195)	<0.001	1.294 (0.827–2.026)	0.260	1.940 (1.547–2.431)	<0.001	1.153 (0.777–1.712)	0.478
IIIA	2.793 (2.266–3.444)	<0.001	0.807 (0.441–1.478)	0.488	2.060 (1.725–2.461)	<0.001	0.772 (0.449–1.326)	0.348
IIIB	2.529 (1.794–3.563)	<0.001	0.504 (0.196–1.293)	0.154	1.884 (1.392–2.550)	<0.001	0.550 (0.235–1.289)	0.169
Not determined	1.983 (1.290–3.048)	0.002	0.759 (0.300–1.925)	0.562	1.601 (1.118–2.292)	0.010	0.732 (0.301–1.784)	0.493
Grade		0.211				0.052		0.077
Grade I	Reference				Reference		Reference	
Grade II	1.683 (0.640–4.428)	0.291			1.786 (0.741–4.302)	0.196	1.379 (0.567–3.356)	0.478
Grade III	1.924 (0.793–4.668)	0.148			2.235 (0.996–5.017)	0.051	1.857 (0.821–4.202)	0.137
Grade IV	1.967 (0.811–4.770)	0.135			2.242 (0.999–5.030)	0.050	1.917 (0.847–4.339)	0.119
Not determined	2.214 (0.913–5.371)	0.079			2.538 (1.131–5.696)	0.024	2.113 (0.934–4.781)	0.073
Surgical procedure		<0.001		0.056		<0.001		0.016
Sublobar resection	Reference		Reference		Reference		Reference	
Lobectomy	0.661 (0.556–0.785)	<0.001	0.783 (0.639–0.961)	0.019	0.674 (0.578–0.785)	<0.001	0.771 (0.645–0.992)	0.004
Other	0.938 (0.716–1.231)	0.646	0.786 (0.584–1.057)	0.111	0.951 (0.751–1.205)	0.677	0.866 (0.668–1.122)	0.275
Radiation		0.188				0.985		
Yes	Reference				Reference			
No	0.903 (0.775–1.051)				0.999 (0.873–1.143)			
Chemotherapy		0.347				0.059		<0.001
Yes	Reference				Reference		Reference	
No/unknown	1.077 (0.922–1.258)				1.137 (0.995–1.299)		1.377 (1.195–1.588)	<0.001
LN dissection		<0.001		<0.001		0.002		0.009
4 or more	Reference		Reference		Reference		Reference	
1 to 3	1.526 (1.305–1.784)		1.430 (1.195–1.711)		1.379 (1.201–1.584)		1.234 (1.054–1.445)	

SCLC, small cell lung cancer; LN, lymph node; LCSS, lung cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; TNM, tumor-node-metastasis.

© Translational Lung Cancer Research. All rights reserved.

Table 4 Univariable and multivariable Cox regression analyses for patients who underwent surgery for SCLC with the dissection of 4–11 LNs or ≥12 LNs in the entire cohort

Variables	LCSS				OS			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)		<0.001		<0.001		<0.001		<0.001
<65	Reference		Reference		Reference		Reference	
65–75	1.365 (1.112–1.677)	0.003	1.434 (1.162–1.770)	0.001	1.446 (1.214–1.723)	<0.001	1.513 (1.266–1.808)	<0.001
>75	1.670 (1.291–2.161)	<0.001	1.623 (1.241–2.122)	<0.001	1.771 (1.418–2.213)	<0.001	1.757 (1.400–2.206)	<0.001
Sex		0.026		0.082		0.013		0.059
Female	Reference		Reference		Reference		Reference	
Male	1.226 (1.024–1.466)		1.181 (0.979–1.425)		1.215 (1.042–1.416)		1.167 (0.994–1.369)	
Race		0.084		0.046		0.049		0.054
White	Reference		Reference		Reference		Reference	
Black/other	0.744 (0.532–1.040)		0.703 (0.498–0.993)		0.758 (0.575–0.999)		0.756 (0.568–1.005)	
Location		0.428				0.315		
Metropolitan	Reference				Reference			
Non-metropolitan	0.909 (0.717–1.151)				0.900 (0.733–1.105)			
Year of diagnosis		0.610				0.600		
2000–2004	Reference				Reference			
2005–2008	0.989 (0.779–1.257)	0.931			0.927 (0.756–1.135)	0.462		
2009–2012	0.880 (0.686–1.128)	0.312			0.897 (0.725–1.111)	0.320		
2013–2016	0.869 (0.653–1.158)	0.338			0.848 (0.656–1.095)	0.205		
Tumor site		0.034		0.387		0.226		
Upper	Reference		Reference		Reference			
Middle	0.954 (0.651–1.399)	0.810	0.983 (0.664–1.454)	0.931	0.928 (0.671–1.285)	0.654		
Lower	1.275 (1.054–1.543)	0.013	1.144 (0.939–1.394)	0.181	1.140 (0.967–1.345)	0.119		
Tumor size (mm)		0.028		0.516		0.360		
0–10	Reference		Reference		Reference			
11–20	1.378 (0.940–2.020)	0.101	1.409 (0.957–2.075)	0.083	1.186 (0.878–1.603)	0.266		
21–30	1.530 (1.041–2.249)	0.031	1.406 (0.951–2.079)	0.087	1.187 (0.874–1.613)	0.273		
31–40	1.738 (1.145–2.639)	0.009	1.534 (0.959–2.453)	0.074	1.307 (0.932–1.834)	0.120		
41–50	1.924 (1.214–3.049)	0.005	1.495 (0.898–2.490)	0.122	1.367 (0.925–2.021)	0.117		
>50	1.913 (1.201–3.046)	0.006	1.265 (0.759–2.109)	0.367	1.427 (0.973–2.093)	0.069		
Not determined	2.184 (1.100–4.335)	0.026	0.964 (0.416–2.231)	0.931	1.741 (0.981–3.092)	0.058		
T stage		<0.001		0.017		0.001		0.051
T1	Reference		Reference		Reference		Reference	
T2	1.405 (1.153–1.713)	0.001	1.116 (0.804–1.549)	0.511	1.241 (1.049–1.469)	0.012	1.143 (0.886–1.476)	0.304
T3	2.131 (1.517–2.993)	<0.001	2.198 (1.334–3.621)	0.002	1.754 (1.284–2.394)	<0.001	1.932 (1.245–2.998)	0.003
T4	1.624 (1.125–2.344)	0.010	2.480 (1.109–5.544)	0.027	1.408 (1.020–1.944)	0.037	1.872 (0.911–3.849)	0.088
Not determined	1.545 (0.863–2.769)	0.143	3.681 (0.682–19.87)	0.130	1.407 (0.872–2.269)	0.162	2.429 (0.525–11.25)	0.256

Table 4 (*continued*)

© Translational Lung Cancer Research. All rights reserved.

Table 4 (*continued*)

Variables	LCSS				OS			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
N stage		<0.001		0.001		<0.001		<0.001
N0	Reference		Reference		Reference		Reference	
N1	2.416 (1.951–2.992)	<0.001	1.961 (1.274–3.017)	0.002	1.987 (1.653–2.390)	<0.001	1.976 (1.375–2.839)	<0.001
N2	2.817 (2.247–3.531)	<0.001	3.706 (1.864–7.366)	<0.001	2.280 (1.870–2.781)	<0.001	3.084 (1.703–5.584)	<0.001
Not determined	3.334 (1.480–7.509)	0.004	7.304 (1.362–39.17)	0.020	2.589 (1.224–5.478)	0.013	4.581 (1.010–20.77)	0.048
TNM stage		<0.001		0.094		<0.001		0.480
IA	Reference		Reference		Reference		Reference	
IB	1.345 (0.993–1.821)	0.056	1.153 (0.760–1.749)	0.504	1.141 (0.895–1.455)	0.288	1.058 (0.743–1.507)	0.753
IIA	2.962 (2.213–3.964)	<0.001	1.604 (0.968–2.657)	0.066	2.126 (1.656–2.729)	<0.001	1.211 (0.792–1.849)	0.377
IIB	2.483 (1.794–3.438)	<0.001	1.202 (0.690–2.095)	0.516	1.876 (1.430–2.460)	<0.001	0.973 (0.604–1.567)	0.910
IIIA	3.217 (2.482–4.169)	<0.001	0.824 (0.381–1.782)	0.622	2.328 (1.874–2.892)	<0.001	0.722 (0.371–1.406)	0.338
IIIB	2.320 (1.451–3.709)	<0.001	0.452 (0.131–1.556)	0.208	1.853 (1.244–2.760)	0.002	0.520 (0.177–1.526)	0.234
Not determined	2.446 (1.444–4.146)	0.005	0.412 (0.070–2.420)	0.326	1.884(1.218–2.915)	0.004	0.493 (0.096–2.544)	0.398
Grade		0.816				0.190		
Grade I	Reference				Reference			
Grade II	1.443 (0.539–3.866)	0.465			1.504 (0.612–3.696)	0.373		
Grade III	1.585 (0.650–3.862)	0.311			1.953 (0.867–4.399)	0.106		
Grade IV	1.563 (0.641–3.809)	0.326			1.859 (0.825–4.187)	0.135		
Not determined	1.660 (0.680–4.049)	0.266			2.120 (0.941–4.776)	0.070		
Surgical procedure		0.234				0.038		0.173
Sublobar resection	Reference				Reference		Reference	
Lobectomy	0.861 (0.652–1.138)	0.294			0.805 (0.636–1.019)	0.071	0.795 (0.623–1.014)	0.065
Other	1.091 (0.732–1.626)	0.668			1.063 (0.758–1.490)	0.725	0.856 (0.600–1.221)	0.391
Radiation		0.037		0.417		0.280		
Yes	Reference		Reference		Reference			
No	0.820 (0.681–0.988)		1.087 (0.889–1.328)		1.094 (0.929–1.287)			
Chemotherapy		0.769				0.307		
Yes	Reference				Reference			
No/unknown	1.029 (0.849–1.247)				1.088 (0.925–1.279)			
LN dissection		0.903		0.355		0.795		0.216
12 or more	Reference		Reference		Reference		Reference	
4 to 11	0.988 (0.820–1.191)		1.095 (0.903–1.328)		1.022 (0.870–1.200)		1.109 (0.941–1.307)	

SCLC, small cell lung cancer; LN, lymph node; LCSS, lung cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; TNM, tumor-node-metastasis.

© Translational Lung Cancer Research. All rights reserved.

Liang *et al.* found that 16 is the minimum number of dissected LNs required for a quality evaluation of the LNs and a postoperative declaration of node-negative disease (18). Our group previously found significantly improved survival rates in patients who underwent sublobar resection for stage IA NSCLC tumors ≤2 cm in size and the dissection of at least 4 LNs (19). These findings suggest that an adequate number of dissected LNs should be interpreted in association with more accurate nodal staging to reduce stage migration and provide appropriate systemic therapy.

Due to the inherently poor prognosis of SCLC, patients who undergo surgical resection for SCLC should generally be treated with postoperative systemic therapy (30). Nodal staging is critical in guiding clinicians in the formulation of appropriate therapeutic strategies. In a National Cancer Data Base analysis, surgery with adjuvant chemotherapy for node-negative SCLC was associated with more prolonged survival than concurrent chemoradiation (29). Adjuvant mediastinal radiotherapy is associated with more prolonged survival in node-positive patients, especially those with pN2 disease (31). The NCCN recommends that patients without LN metastases should be treated with systemic therapy alone (7). For N1 LN metastasis, postoperative mediastinal radiation should be administered; for N2 or N3 LN metastasis, postoperative concurrent or sequential systemic therapy and mediastinal radiation therapy should be considered (7). Thus, a more significant number of dissected LNs is associated with a lower risk of missing a positive LN, which increases the accuracy of nodal staging and improves the survival rate.

Given the aggressive clinical behavior of SCLC and its high propensity for metastatic dissemination to nodes and distant sites, more comprehensive nodal dissection may not significantly increase the survival outcomes after resection. Our study found that the survival benefit peaked when approximately 4–11 LNs were dissected. Comprehensive LN dissection may prolong the operative time and lead to severe postoperative complications, such as pneumonia, pulmonary edema, bronchopleural fistula, nerve injury, and venous thromboembolism, and has increased risks of impaired lymphatic drainage, hemothorax, and chylothorax (32-34). LN dissection did not increase the postoperative 30-day mortality rate in our study; however, Varlotto *et al.* showed that patients who underwent aggressive N2-only mediastinal dissection had an increased risk of postoperative mortality, but this was not observed in patients who underwent extensive N1-only dissection (16).

This study had several limitations. First, the SEER database does not provide information about several factors associated with survival, including the patient's performance status, smoking history, comorbidities, pulmonary function, surgeon's experience, institutional volume, clinical-stage, surgical approach (video-assisted or open procedures), resection margin, immunotherapy and induction therapy details (35). Second, many cases have been excluded after the propensity score matching process that could jeopardize the validity of the results since the population in the analysis do not represent their parent group of cases (36). While most of the available variables were well balanced in the propensity score-matched analysis, several subgroup variables were adjusted in the regression model, including the year of diagnosis, N stage, and surgical procedure. Third, the SEER database records the total number of dissected LNs and does not discriminate between LN sampling and systematic LN dissection. Thus, it is possible that some of the LNs in our data set were fragments, and the correct number of LNs may have been overestimated. This ambiguity regarding the dissected LNs may limit the determination of the optimal number of dissected LNs (16). Thus, we included the appropriate LN ranges in the study.

In conclusion, our population-based analysis of SEER data revealed that patient survival after surgical resection for SCLC is associated with the number of dissected LNs. Our results suggest that the optimal number of dissected LNs ranges from 4 to 11. The bias might not have been wholly eliminated despite using multivariate and propensity score-matched analyses to adjust for inherent bias. More evidence is needed to verify our results. Our data may have implications for guidelines on LN dissection during surgical resection for SCLC.

Conclusions

Our study revealed that patient survival after surgical resection for SCLC is associated with the number of dissected LNs, and the number of LNs for dissection ranges from 4 to 11 achieve the best survival outcome.

Acknowledgments

The authors acknowledge the efforts of the Surveillance, Epidemiology, and End Results (SEER) program tumor registries in the creation of the SEER database. The authors appreciate the academic support from the AME Thoracic Surgery Collaborative Group. The authors also appreciate the great support from Dr. Gonzalo Varela (Salamanca

© Translational Lung Cancer Research. All rights reserved.

University Hospital, Spain) in improving the quality of this paper.

Funding: This work was supported by The Key Project of Zhejiang Province Science and Technology Plan, China (No. 2014C03032), and The National Key Research and Development Program of China (No. 2017YFC0113500).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-489/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-489/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

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;68:394-424.
2. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 2006;24:4539-44.
3. van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. Lancet 2011;378:1741-55.
4. Lad T, Piantadosi S, Thomas P, et al. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. Chest 1994;106:320S-3S.
5. 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.
6. Aberle DR, DeMello S, Berg CD, et al. Results of the two incidence screenings in the National Lung Screening Trial. N Engl J Med 2013;369:920-31.
7. National Comprehensive Cancer Network. Clinical practice guidelines in oncology: small cell lung cancer V 1.2020; 20206. Available online: http://www.nccn.org/professionals/physician_gls/PDF/sclc.pdf. Accessed September 10, 2020.
8. Rudin CM, Ismaila N, Hann CL, et al. Treatment of Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American College of Chest Physicians Guideline. J Clin Oncol 2015;33:4106-11.
9. Früh 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.
10. Takenaka T, Takenoyama M, Inamasu E, et al. Role of surgical resection for patients with limited disease-small cell lung cancer. Lung Cancer 2015;88:52-6.
11. Turner SR, Butts CA, Debenham BJ, et al. Is lobectomy superior to sublobar resection for early-stage small-cell lung cancer discovered intraoperatively? Interact Cardiovasc Thorac Surg 2019;28:41-4.
12. Thomas DC, Arnold BN, Rosen JE, et al. Defining outcomes of patients with clinical stage I small cell lung cancer upstaged at surgery. Lung Cancer 2017;103:75-81.
13. Gajra A, Newman N, Gamble GP, et al. Effect of number of lymph nodes sampled on outcome in patients with stage I non-small-cell lung cancer. J Clin Oncol 2003;21:1029-34.
14. Ludwig MS, Goodman M, Miller DL, et al. Postoperative survival and the number of lymph nodes sampled during resection of node-negative non-small cell lung cancer. Chest 2005;128:1545-50.
15. Ou SH, Zell JA. Prognostic significance of the number of lymph nodes removed at lobectomy in stage IA non-small cell lung cancer. J Thorac Oncol 2008;3:880-6.
16. Varlotto JM, Recht A, Nikolov M, et al. Extent of lymphadenectomy and outcome for patients with stage I

© Translational Lung Cancer Research. All rights reserved.

nonsmall cell lung cancer. Cancer 2009;115:851-8.
17. Osarogiagbon RU, Ogbata O, Yu X. Number of lymph nodes associated with maximal reduction of long-term mortality risk in pathologic node-negative non-small cell lung cancer. Ann Thorac Surg 2014;97:385-93.
18. Liang W, He J, Shen Y, et al. Impact of examined lymph node count on precise staging and long-term survival of resected non–small cell lung cancer: a population study of the US SEER database and a Chinese multiinstitutional registry. J Clin Oncol. 2017; 35:1162-1170.
19. Cao J, Xu J, He Z, et al. Prognostic impact of lymphadenectomy on outcomes of sublobar resection for stage IA non-small cell lung cancer ≤2 cm. J Thorac Cardiovasc Surg 2018;156:796-805.e4.
20. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) program. Public-use data (2000-2017). Available online: http://www.seer.cancer.gov. Accessed July 06, 2020.
21. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2015;10:990-1003.
22. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res 2004;10:7252-9.
23. Winger DG, Nason KS. Propensity-score analysis in thoracic surgery: When, why, and an introduction to how. J Thorac Cardiovasc Surg 2016;151:1484-7.
24. Weksler B, Nason KS, Shende M, et al. Surgical resection should be considered for stage I and II small cell carcinoma of the lung. Ann Thorac Surg 2012;94:889-93.
25. Lüchtenborg M, Riaz SP, Lim E, et al. Survival of patients with small cell lung cancer undergoing lung resection in England, 1998-2009. Thorax 2014;69:269-73.
26. Yokouchi H, Ishida T, Yamazaki S, et al. Prognostic impact of clinical variables on surgically resected small-cell lung cancer: Results of a retrospective multicenter analysis (FIGHT002A and HOT1301A). Lung Cancer 2015;90:548-53.
27. 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.
28. Wakeam E, Byrne JP, Darling GE, et al. Surgical treatment for early small cell lung cancer: variability in practice and impact on survival. Ann Thorac Surg 2017;104:1872-80.
29. 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.
30. Buddharaju LNR, Ganti AK. Immunotherapy in lung cancer: the chemotherapy conundrum. Chin Clin Oncol 2020;9:59.
31. Wakeam E, Giuliani M, Leighl NB, et al. Indications for adjuvant mediastinal radiotherapy in surgically resected small cell lung cancer. Ann Thorac Surg 2017;103:1647-53.
32. Czerny M, Fleck T, Salat A, et al. Sealing of the mediastinum with a local hemostyptic agent reduces chest tube duration after complete mediastinal lymph node dissection for stage I and II non-small cell lung carcinoma. Ann Thorac Surg 2004;77:1028-32.
33. Doddoli C, Aragon A, Barlesi F, et al. Does the extent of lymph node dissection influence outcome in patients with stage I non-small-cell lung cancer? Eur J Cardiothorac Surg 2005;27:680-5.
34. Kakkar AK. Prevention of venous thromboembolism in the cancer surgical patient. J Clin Oncol 2009;27:4881-4.
35. Park HS, Lloyd S, Decker RH, et al. Limitations and biases of the Surveillance, Epidemiology, and End Results database. Curr Probl Cancer 2012;36:216-24.
36. Streiner DL, Norman GR. The pros and cons of propensity scores. Chest 2012;142:1380-2.

(English Language Editor: L. Huleatt)

Cite this article as: Cao J, Xu J, Yu H, Qian P, Lv W, He T, Yuan P, Longo F, Bertolaccini L, Yasufuku K, Rucker AJ, Hu J. The extent of mediastinal lymph node dissection correlates with survival of small cell lung cancer patients after resection: a propensity score-matched cohort study analysis. Transl Lung Cancer Res 2022;11(7):1453-1467. doi: 10.21037/tlcr-22-489

© Translational Lung Cancer Research. All rights reserved.