Impact of treatment modality on long-term survival of stage IA small-cell lung cancer patients: a cohort study of the U.S. SEER database

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Background: The optimal treatment modality for patients with stage IA (T1N0M0) small-cell lung cancer (SCLC) is still unclear.

Methods: Patients who received surgical resection or chemo-radiotherapy (CRT) between January 2004 and December 2014 were identified from The Surveillance, Epidemiology and End Results (SEER) database. Surgical resection included lobectomy, wedge resection, segmentectomy with lymphadenectomy [examined lymph node (ELN) ≥1]. Propensity score match analysis was utilized to balance the baseline characteristics.

Results: A total of 686 stage IA SCLC cases were included: 337 patients underwent surgery and 349 patients were treated by CRT alone. Surgery achieved a better outcome than CRT alone, with an adjusted hazard ratio (HR) of 0.495. Patients who underwent lobectomy demonstrated a longer overall survival (OS), compared to those who received sublobectomy (crude cohort, median OS, 69 *vs.* 38 months; match cohort, median OS, 67 *vs.* 38 months). Patients with ELN >7 presented with longer OS than those with ELN ≤7 (crude cohort, median OS, 91 *vs.* 49 months; matched cohort, median OS, 91 *vs.* 54 months). The additional efficacy of chemotherapy or radiotherapy in patients receiving lobectomy was observed. The best prognosis was achieved in the lobectomy plus CRT cohort, with a 5-year survival rate of 73.5%.

Conclusions: The prolonged survival associated with lobectomy and chemotherapy or radiotherapy presents a viable treatment option in the management of patients with stage IA SCLC.

Keywords: Small-cell lung cancer (SCLC); SEER; treatment; early-stage lung cancer

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Introduction

Lung cancer is the leading cause of cancer incidence and mortality, with 2.1 million new lung cancer patients being diagnosed in 2018 around the world (1). Small-cell lung cancer (SCLC) constitutes 13% of all lung cancers and is characterized by a rapid doubling time, higher rate of relapse, and shorter survival (2). Up to 70% of SCLC patients have metastases at the time of diagnoses (3). Treatment advances for SCLC have been limited over the past few decades, with many patients facing a high likelihood of poor prognoses. Currently, chemotherapy and radiotherapy remain the mainstay management for most SCLC patients (4). In recent years, several studies have established a correlation between surgical intervention for early stage SCLC and improved outcomes (5-9). However, the details identifying the most effective resection type and required number of lymph nodes for assessment to achieve improved outcomes have not been determined. In addition, lobectomy has long been regarded indispensable in the management of operable lung cancer, whereas sub-lobectomy is traditionally introduced when the pulmonary function cannot tolerate lobectomy (10,11). Recent studies indicate that, the prognosis is fairly well in nature for non-small cell lung cancer (NSCLC) with T1N0M0 stage, and sublobar resection would achieve comparable prognosis to lobectomy in this cohort (12,13). We speculate that, same association might also exist in SCLC with T1N0M0 stage. Furthermore, the benefit of additional chemotherapy or radiotherapy for patients with resected SCLC remains unclear. To identify an appropriate treatment program for stage IA SCLC patients, the prognosis of this patient population who underwent surgery or chemo-radiotherapy (CRT) was examined. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-5525).

Methods

Patient population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) (14). Patients diagnosed with SCLC between January 2004 and December 2014 were identified from the SEER database. The SEER Program of the National Cancer Institute is responsible for the collection and reporting of cancer incidence and survival data from several population-based central cancer registries, covering approximately 30% of the U.S. population. The SEER-18 registries database was queried for all patients using SEER*Stat version 8.3.2.

The inclusion criteria included the following: (I) histologically confirmed SCLC; (II) receiving CRT or surgery (lobectomy, wedge resection, or segmentectomy) as the initial treatment; (III) IA stage (T1N0M0 status) according to the 8th edition tumor-node-metastasis (TNM) staging system. For patients who underwent surgery, lymphadenectomy with at least one examined lymph node (ELN) was required. Variables on demographics, stage of disease, tumor diameter, invasion scope, nodal status, distant metastasis, and survival were collected. Patients without documented variables, or diagnosed with SCLC from an autopsy or death certificate were excluded. Patient staging was performed in accordance with the American Joint Committee on Cancer (AJCC) 8thedition TNM staging system (15).

Statistics

The survival rate was calculated using the Kaplan-Meier method. Categorical variables were tabulated by frequency and percentage. Correlations among clinicopathological characteristics were assessed with Chi-squared testing. To identity the prognostic impact of resection type (lobectomy *vs.* sublobectomy) and ELN (≤7 *vs.* >7), propensity score matching (PSM) was conducted as described by Rosenbaum and Rubin (16,17). The propensity score for an individual was calculated on concomitant variables with potential prognostic significance (18). The concomitant variables in the PSM analysis for resection type (lobectomy *vs.* sublobectomy) and ELN (≤7 *vs.*>7) included age, gender, radiotherapy, and chemotherapy. Resection type was included as a concomitant variable in the PSM analysis for ELN. Additionally, ELN was an additional concomitant variable in the PSM analysis for resection type. Kernel density estimates indicated the distribution of propensity scores in each group (19), while univariate and multivariate

Table 1 Characteristics of stage IA SCLC patients

Variables	Case	5-year OS (%)	P[a]	Multivariate analysis		
				HR	95% CI	P[b]
Age (years)						
≤65	221 (32.2)	49.5	<0.001	Reference		<0.001
>65	465 (67.8)	31.1		1.656	1.312–2.089	
Gender						
Male	312 (45.5)	34.7	0.060	Reference		0.209
Female	374 (54.5)	39.1		0.878	0.716–1.076	
Location						
Upper	430 (62.7)	36.9	0.984			
Middle	54 (7.9)	38.8				
Lower	202 (29.4)	38.5				
Lateral						
Left	282 (41.1)	39.6	0.851			
Right	404 (58.9)	35.5				
T status						
T1a	68 (9.9)	47.3	0.039	Reference		0.213
T1b	327 (47.7)	34.4		1.385	0.925–2.074	
T1c	291 (42.4)	39.3		1.229	0.813–1.856	
Therapy						
CRT alone	349 (50.9)	24.7	<0.001	Reference		<0.001
Surgery	337 (49.1)	50.0		0.495	0.401–0.611	

[a], univariate Cox analysis; [b], multivariate Cox analysis. SCLC, small-cell lung cancer; OS, overall survival; HR, hazard ratio; CI, confidence interval; CRT, chemoradiotherapy.

analysis were performed to identify the independent prognostic factors. Multivariate analysis was used for factors that demonstrated statistical significance (P<0.1) in univariate analysis. Statistical significance was assumed at a two-sided probability value <0.05. All statistical analyses were performed with the SPSS 22.0 (IBM Corp., NY, USA) and R (version 3.3.2) software packages.

Results

Patient characteristics

A total of 686 stage IASCLC patients with were included in this study. Surgery was performed in 337 patients (49.1%) with the remaining 349 patients (50.9%) treated by CRT alone. The median age was 68 years (range, 43 to 89 years). For status, 68, 327, and 291 patients were classified with T1a, T1b, and T1c status, respectively. The median tumor size was 17 mm. Patient characteristics are listed in *Table 1*.

Lobectomy, wedge resection, and segmentectomy were performed in 247 (73.3%), 71 (21.1%), and 19 (5.6%) of patients who underwent surgery, respectively. The median ELN was 7 (ranging between 1 and 87). In patients with resected SCLC, additional radiotherapy and chemotherapy were performed in 74 patients (22.0%) and 189 patients (56.1%), respectively. Oligo-modality (surgery alone), bi-modality (surgery plus chemo/radiotherapy), and tri-modality (surgery plus CRT) therapies were applied in 146, 119, and 72 patients, respectively. The treatment details of patients with resected SCLC are listed in *Table S1*.

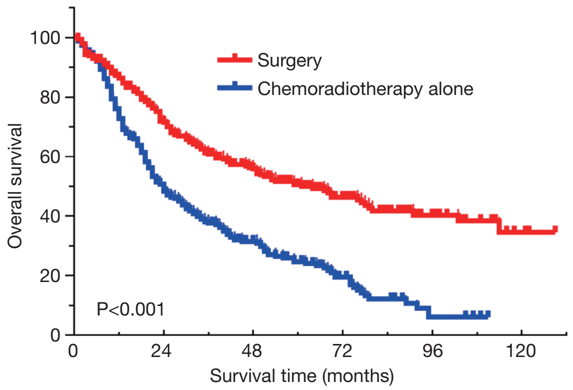

Figure 1 Surgery lead to better outcome compared to CRT alone in stage IA SCLC. CRT, chemoradiotherapy; SCLC, small-cell lung cancer.

Surgery improved outcomes compared to CRT alone

The median OS for the entire cohort was 35 months. The 5-year survival rate for patients who underwent surgery and CRT alone was 50.0% and 24.7%, respectively (P<0.001) (*Figure 1*). The superiority of surgery was further confirmed in multivariate analysis, with the adjusted hazard ratio (HR) of 0.495 [95% confidence interval (CI), 0.401–0.611] (*Table 1*). Age was identified as the other independent prognostic factor.

For patients with resected SCLC, the 5-year survival rate for tri-modality, bi-modality, and oligo-modality therapy was 66.9%, 46.0%, and 43.8%, respectively (*Figure S1*). Tri-modality led to a better outcome than surgery alone (adjusted HR, 0.543; 95% CI, 0.331–0.889) and bi-modality (adjusted HR, 0.641; 95% CI, 0.389–1.057).

For patients with resected SCLC, lobectomy demonstrated an improved outcome compared to sublobectomy (median OS, 69 *vs.* 38 months, P=0.051; *Figure 2A*). However, after PSM analysis, the superiority of lobectomy on survival was not significant in the matched cohort (n=188) (median OS, 67 *vs.* 38 months, P=0.223; *Figure 2B*). Distribution of propensity-scores indicated balanced basic characteristics after PSM analysis (*Figure 2C,D*).

Resected SCLC patients with ELN >7 was associated with a better outcome (median OS, 91 *vs.* 49 months, P=0.038; *Figure 2E*). However, following PSM analysis, the superiority of ELN >7 on survival was not significant in the matched cohort (n=304) (median OS, 91 *vs.* 54 months, P=0.105; *Figure 2F*). The distribution of the propensity-score indicated balanced basic characteristics after PSM analysis (*Figure 2G,H*).

To evaluate the interaction between surgery and additional treatment modalities in resected SCLC, univariate analysis was performed in oligo-modality, bi-modality, and tri-modality cohorts. Compared with sublobectomy, the HR for lobectomy was 1.058, 0.569, and 0.385 in the oligo-modality, bi-modality, and tri-modality cohorts, respectively; compared with ELN ≤7, the HR for ELN >7 was 0.704, 0.660, and 0.722 in the oligo-modality, bi-modality, and tri-modality cohorts, respectively. There seems to be asynergistic interaction between surgery and additional chemo/radiotherapy (*Table 2*).

Surgery with CRT was the optimal treatment for stage IA SCLC patients

To determine the most effective therapeutic option, SCLC patients who underwent surgery were divided into the following groups, according to their treatment: sublobectomy (n=38), lobectomy (n=108), sublobectomy plus chemo/radiotherapy (n=30), lobectomy plus chemo/radiotherapy (n=89), sublobectomy plus CRT (n=22), and lobectomy plus CRT (n=50) (*Table 3*). As shown in *Figure 3*, patients who received lobectomy plus CRT showed the best prognosis, with the estimated 5-year OS rate of 73.5%. The adjusted HR for lobectomy alone, lobectomy plus chemo/radiotherapy, and lobectomy plus CRT was 1.095, 0.851, and 0.438, respectively (P=0.012), suggesting an enhanced survival benefit from additional chemotherapy or radiotherapy for patients who undergo lobectomy. This phenomenon was not observed in patients who received sublobectomy. The adjusted HR for sublobectomy alone, sublobectomy plus chemo/radiotherapy, and sublobectomy plus chemo-radiotherapy was 1.000, 1.304, and 1.220, respectively (P=0.752).

Discussion

In this study, we investigated the prognosis of patients with stage IA SCLC and found lobectomy plus CRT to be the optimal treatment program which provides the best prognosis.

The efficacy of surgery in limited staged SCLC has been reported by several studies over the past few decades (5-8). In this study, patients who underwent surgery showed significantly longer survival than those treated with CRT alone, with the median OS of 59 and 24 months, respectively. In addition, Zeng *et al.* included stage IA SCLC patients and compared the long-term survival between

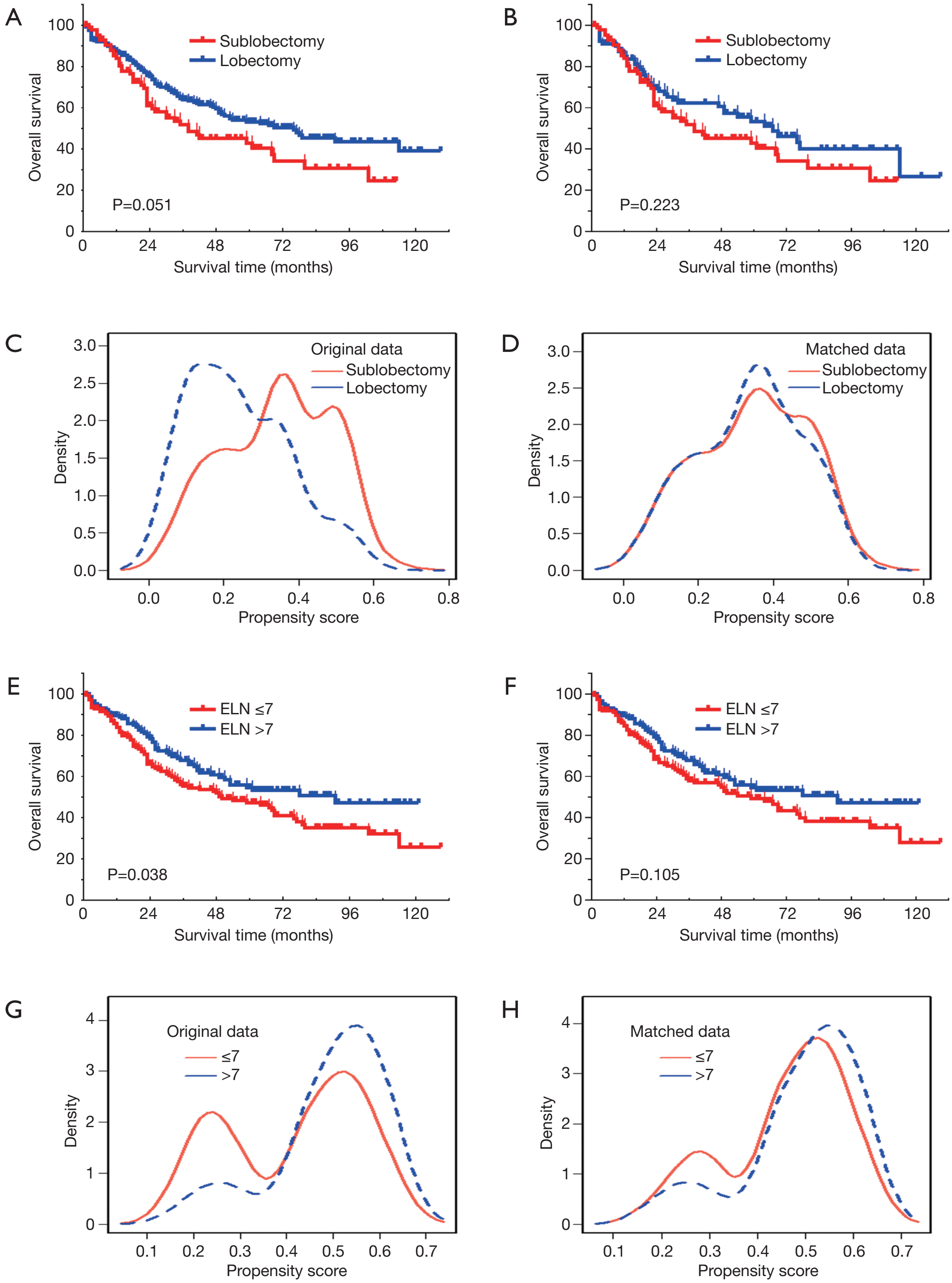

Figure 2 Comparison of OS between sublobectomy and lobectomy in the crude cohort (A) and matched cohort (B) of resected SCLC; distribution of propensity score of the crude cohort (C) and matched cohort (D) between sublobectomy and lobectomy in patients with resected SCLC; comparison of OS between ELNs ≤7 and ELN >7 in the crude cohort (E) and matched cohort (F) of resected SCLC; distribution of propensity score of the crude cohort (G) and matched cohort (H) between ELN ≤7 and ELN >7 in patients with resected SCLC.SCLC, small-cell lung cancer; ELN, examined lymph node.

Table 2 Interaction between surgical parameters and treatment modalities in stage T1N0M0 SCLC

Variables	Oligo-modality cohort (n=146)			Bi-modality cohort (n=119)			Tri-modality cohort (n=72)		
	HR	95% CI	P[a]	HR	95% CI	P[a]	HR	95% CI	P[a]
Resection type									
Sublobectomy	Reference			Reference			Reference		
Lobectomy	1.058	0.640–1.751	0.826	0.569	0.315–1.027	0.061	0.385	0.163–0.909	0.030
ELN									
≤7	Reference			Reference			Reference		
>7	0.704	0.436–1.136	0.151	0.660	0.383–1.136	0.134	0.722	0.365–2.010	0.857

[a], univariate Cox analysis. SCLC, small-cell lung cancer; ELN, examined lymph nodes; HR, hazard ratio; CI, confidence interval.

Table 3 Impact of treatment on overall survival in patients with resected SCLC with T1N0M0 status

Treatment group	Univariate analysis			P_{trend}[a]	Multivariate analysis			P_{trend}[b]
	HR	95% CI	P[a]		HR	95% CI	P[b]	
Sublobectomy	Reference			0.011	Reference			0.047
Lobectomy	1.060	0.641–1.752	0.822		1.095	0.662–1.811	0.725	
Sublob + chemo/radio	1.274	0.664–2.443	0.467		1.304	0.680–2.501	0.425	
Lob + chemo/radio	0.750	0.439–1.282	0.293		0.851	0.494–1.465	0.561	
Sublob + chemo + radio	1.049	0.480–2.293	0.904		1.220	0.554–2.687	0.621	
Lob + chemo + radio	0.377	0.189–0.754	0.006		0.438	0.217–0.882	0.021	

[a], univariate Cox analysis; [b], multivariate Cox analysis. SCLC, small cell lung cancer; HR, hazard ratio; CI, confidence interval; sublob + chemo/radio, sublobectomy + chemotherapy/radiotherapy; lob + chemo/radio, lobectomy + chemotherapy/radiotherapy; sublob + chemo + radio, sublobectomy + chemotherapy + radiotherapy; lob + chemo + radio, lobectomy + chemotherapy + radiotherapy.

lobectomy and sublobar resection (20). In that study, patients who underwent chemoradiotherapy (CRT) has not yet been recruited. As is well known, CRT is the mainstay treatment for limited stage SCLC. Therefore, although better prognosis was found in patients who received lobectomy, it is still uncertain that it is the optimal treatment for SCLC with IA stage. Our result is consistent with the National Comprehensive Cancer Network (NCCN) guideline, which recommends surgical intervention for patients with stage I (T1-2N0M0) SCLC (21). The highlight of our study is that, patients with IA stage SCLC who underwent CRT and surgery and multimodality treatment were all included in this study. It is plausible that the study design might help to identify the optimal treatment in this cohort.

Lobectomy has long been considered as the standard surgical option for lung cancer. Goldstein *et al.* observed residual tumors in 45% of lobectomy specimens from 31 stage IA lung cancer patients, diagnosed by wedge resection (22). Lobectomy has been repeatedly established as superior to sublobectomy in providing better outcomes in most operable non-small cell lung cancer (NSCLC) patients (11,23,24). Recently, sublobectomy was indicated to deliver prognoses comparable to lobectomy in stage IA NSCLC (12,25). In this study, the PSM analysis showed no significance between lobectomy and sublobectomy on long-term survival (P=0.223). However, lobectomy is still recommended for two reasons. Firstly, the absolute risk was reduced in the lobectomy group (crude cohort: HR =0.710, 95% CI, 0.502–1.006; matched cohort: HR =0.771, 95% CI, 0.506–1.177). The survival duration was numerically longer for the lobectomy group (crude cohort, 69 *vs.* 38 months; matched cohort, 67 *vs.* 38 months), and the superiority of lobectomy was easily observed according to the survival curve. We speculate that the insignificant survival benefit among patients that received lobectomy

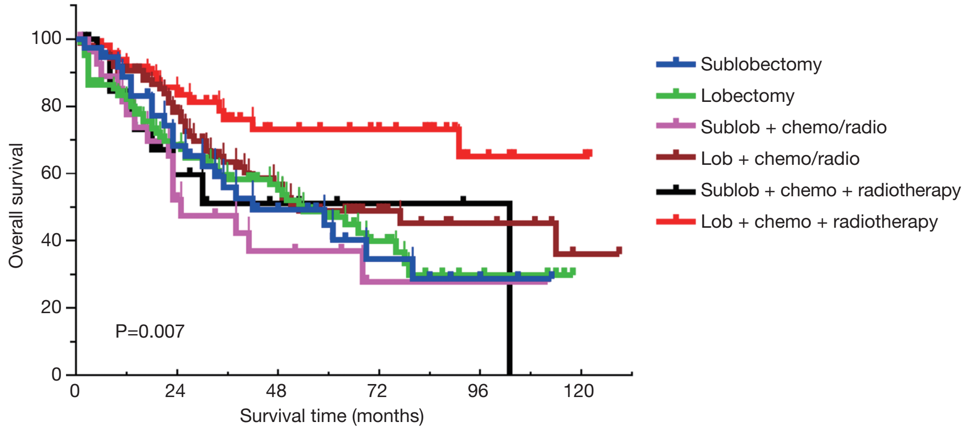

Figure 3 Comparison among different treatment modalities in patients with resected SCLC. SCLC, small-cell lung cancer; Sublob, sublobectomy; lob, lobectomy; chemo/radio, chemo/radiotherapy; chemo + radiotherapy, CRT.

is probably attributable to the limited sample size of the matched cohort (n=188). Secondly, the synergistic effect of additional chemo/radiotherapy was only observed in patients who underwent lobectomy.

In this study, tri-modality (surgery plus CRT)treatment demonstrated significantly better outcomes for patients with resected stage IA SCLC compared with bi-modality (surgery plus chemo/radiotherapy) and oligo-modality (surgery alone) (5-year OS, 66.9% *vs.* 46.0% *vs.* 43.8%; P=0.011). Similar results were also reported by Ahmed *et al.*, who observed the highest survival rate in stage IA SCLC patients who received surgery plus radiation (60%), followed by surgery alone (50%), radiation alone (27%), and no surgery or radiation (16%) (6). We attribute this to the unique biological characteristics of SCLC. Compared with NSCLC, SCLC is characterized by rapid doubling, high growth fraction, and the early development of widespread metastases (21,26). Most patients with SCLC present with hematogenous metastases, approximately one-third present with limited disease confined to the chest, and fewer than 5% of patients have true stage I SCLC (27,28). In this study, the 5-year OS for resected SCLC with stage I disease was significantly lower (48.9%) than that of stage I NSCLC, but similar to that of stage IIIA NSCLC (15). These results suggest that SCLC is an aggressive disease even in the early stage, warranting multi-modality therapy. Further analysis after classification by resection type revealed that the efficacy of additional chemotherapy or radiotherapy on long-term survival was significant in the lobectomy cohort (P=0.012) but not in the sublobectomy cohort (P=0.752). As indicated by previous studies, postoperative chemo-radiotherapy might be beneficial to patients with resected lung cancer (29,30). We speculate that the efficacy of surgery is limited for patients who undergo sublobectomy, and further restricts the efficacy of additional chemo/radiotherapy. Similarly, Veluswamy *et al.* found adjuvant radiotherapy and chemotherapy was associated with increased toxicity and decreased survival in 1,929 NSCLC patients who underwent limited resection (31).

Extended lymphadenectomy with more lymph nodes examined has long been regarded as essential to accurate staging and long-term survival for operable lung cancer patients. This is also applicable to those with declared node-negative disease (32,33). In this study, the survival difference between ELN ≤7 and ELN >7 was not significant based on PSM analysis (P=0.105). However, the absolute risk was reduced in patients with ELN >7 (crude cohort: HR =0.709, 95% CI, 0.511–0.984; matched cohort: HR =0.755, 95% CI, 0.535–1.065), the survival duration of ELN >7 was longer than that of ELN ≤7 (crude cohort, 91 *vs.* 38 months; matched cohort, 91 *vs.* 54 months), and the superiority of more ELN scan be observed in survival curves. Therefore, extended lymphadenectomy with increased ELNs is still recommended for stage IA SCLC. In addition, the reduced hazard ratio of the ELN >7 group was similar to that in patients with oligo-modality therapy, suggesting that the impact of lymphadenectomy on long-term survival may be independent of perioperative CRT.

To date, improving the prognosis for SCLC patients has been the subject of numerous investigations. Some recent reports established the link between surgery and improved prognosis for early-stage SCLC. For example, Xu *et al.*

found that stage IA SCLC patients who underwent surgery displayed a significantly longer median OS of 45 months, compared to those who did not receive surgery (20.0 months, P<0.001) (34). In addition, Yang *et al.* observed a higher 5-year OS rates in SCLC patients with cT1-2N0M0 who received surgery than in those who underwent chemoradiation (47.6% *vs.* 29.8%, P<0.01) (35). To address uncertainties surrounding the appropriate operation plan, Gu *et al.* suggested that the prognosis of sublobectomy is comparable to that of lobectomy for IA stage SCLC (36). Our findings in this study further confirm the current understanding of early surgical intervention and its association with improved survival. In addition, this study demonstrates the benefits of additional chemo/radiation (median OS, 91 *vs.* 50 months; estimated 5-year OS, 54.0% *vs.* 45.1%, P<0.001) in resected, stage IA SCLC patients. The most promising prognosis was observed in patients who received lobectomy plus CRT (median OS, unreached; estimated 5-year OS, 73.0%). Therefore, we believe that our investigation holds special significance and provides supplementary information to the existing evidence on stage IA SCLC.

According to our results, we recommend regular positron emission tomography/computed tomography (PET/CT) scanning during preoperative examination prior to lobectomy plus CRT for stage IA SCLC patients. In addition, more studies are needed to uncover other surgery-related prognostic factors beyond traditional staging, such as the required scope of lymphadenectomy and the minimal number of ELNs. The impact of emerging prognostic factors in NSCLC, such as "GGN (ground glass nodule) ratio" and "standardized uptake value in PET", also need to be clarified in the SCLC population (37,38). Incorporating these factors will be vital in developing future guidelines for application into clinical practice and understanding the greater policy implications.

The underlying mechanism of our results is still unclear. However, we speculate that this might be partly attributable to the aggressive biological behavior of SCLC. For stage IA SCLC, although the disease is limited and surgery is able to achieve better outcome than CRT. However, the biological characteristics including aggressive invasion and early metastasis made greater margin distance an essential condition for operable SCLC. Besides, because SCLC is sensitive to chemo/radiotherapy, therefore operative chemo/radiotherapy is associated with improved outcome in this cohort.

This retrospective study utilized the SEER database for patient selection. Heterogeneities, including those associated with the basic characteristics of patients involving race, education, and income or the determination of treatment, were unavoidable. In addition, the sample size of each treatment modality was limited, possibly leading to bias in the analysis. Further validation from multicenter, prospective studies are warranted to overcome the limitations associated with the population size, heterogeneity, and potential study bias.

Conclusions

In conclusion, lobectomy plus CRT treatment is associated with longer survival and should be considered as part of the clinical management of stage IA SCLC patients.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-5525). 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).

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Supplementary

Table S1 Treatment characteristics in patients with resected SCLC

Variables	Case (%)
Total	337
Surgical resection	
Lobectomy	247 (73.3)
Sublobectomy	90 (26.7)
Examined lymph nodes	
≤7	185 (54.9)
>7	152 (45.1)
Chemotherapy	
Yes	189 (56.1)
No/unknown	148 (43.9)
Radiotherapy	
Yes	74 (22.0)
No/unknown	263 (78.0)
Treatment modality	
Oligo-modality	146 (43.3)
Bi-modality	119 (35.3)
Tri-modality	72 (21.4)

SCLC, small cell lung cancer.

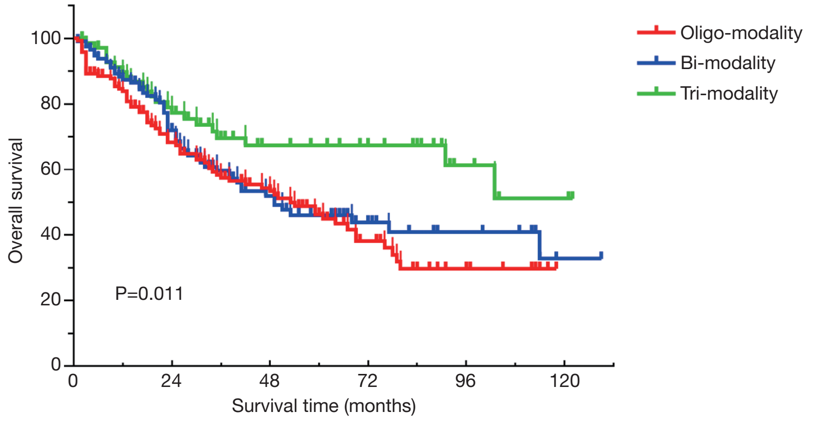

Figure S1 Comparison among oligo-modality (surgery alone), bi-modality (surgery plus chemo/radiotherapy), and tri-modality (surgery plus chemoradiotherapy) in patients with resected SCLC. SCLC, small cell lung cancer.