Cancer Management and Research

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ORIGINAL RESEARCH

Role of surgery in patients with early stage small-cell lung cancer

This article was published in the following Dove Press journal:
Cancer Management and Research

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Purpose: Currently, systemic chemotherapy combined with thoracic radiation is the standard treatment for patients with small-cell lung cancer (SCLC). However, the treatment of early stage SCLC remains controversial. This study evaluated the survival outcomes of surgical treatments and the effect of adjuvant chemotherapy and radiotherapy on lung cancer-specific survival (LCSS) in patients with early stage SCLC.

Methods: Using the Surveillance, Epidemiology, and End Results registry, we identified 2,453 patients with early stage SCLC (1,295 women and 1,158 men) who had complete clinical information between 2004 and 2015. The Kaplan-Meier analysis was used to determine the propensity score based on the characteristics of patients with early stage SCLC. LCSS was compared between patients treated with surgery and non-surgery after adjusting, stratifying, or matching patients with early stage SCLC. In addition, we compared the effects of chemotherapy and radiotherapy on LCSS in patients with early stage SCLC.

Results: Overall, 687 (28.0%) and 1,766 (72.0%) patients with early stage SCLC did and did not undergo surgery, respectively. Kaplan-Meier analysis demonstrated a statistically significant difference in survival curves between the surgery and non-surgery groups (log-rank $p<0.001$). Compared with the non-surgery group, the LCSS of the surgery group was better (hazard ratio [HR]:0.494, 95% confidence interval [CI]:0.415–0.587, $p<0.001$) in patients with early stage SCLC when using a Cox model for multivariate analysis. There was no statistically significant difference ($p=0.847$) in LCSS between patients with early stage SCLC with and without chemotherapy in the multivariate analysis. Radiotherapy had favorable effects on LCSS (HR: 0.579, 95% CI: 0.500–0.671, $p<0.001$) in patients with early stage SCLC using multivariate analysis.

Conclusions: Our study results suggest that LCSS conferred by surgery was higher than that conferred by non-surgery and that radiotherapy is associated with better survival in patients with early stage SCLC. This study findings should be confirmed in prospective studies.

Keywords: early stage small-cell lung cancer, surgery, lung cancer-specific survival, SEER, chemotherapy, radiotherapy

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Introduction

Lung cancer is a serious threat to human health and its incidence has risen rapidly in recent years. According to statistical data, lung cancer was the second most common cancer (approximately 13%) and the leading cause of tumor-related death (approximately 26%) in the United States in 2016.[1] Small-cell lung cancer (SCLC) is a pathological type, accounting for about 15% of all lung cancer.[2] Due to its aggressive nature and early metastasis, approximately two-thirds of SCLC patients are diagnosed with advanced disease and have a poor prognosis.[3] However, some

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http://doi.org/10.2147/CMAR.S202283

patients are diagnosed at a stage in which their disease may be curable.[4] Patients with early stage SCLC who underwent surgery had a reported five-year survival rate of 40% to 60%.[5–9]

Historically, SCLC was treated by surgery. However, the Medical Research Council performed a trial[10] in the 1960s that demonstrated the poor survival of patients who underwent surgery. This outcome resulted in the abandonment of surgery and the use of chemotherapy as a standard method for SCLC treatment. Subsequently, two meta-analyses[11,12] reported that systemic chemotherapy in combination with thoracic radiation improved survival, a treatment that has become the standard for patients with SCLC.

However, the treatment of SCLC remains controversial. Some institutions have reported good results in patients with early stage SCLC who received surgery.[5,13] Other studies have reported favorable results in patients with stage III SCLC who be interfered with surgery.[7,14] Therefore, this study aimed to investigate the effects of surgical resection on lung cancer-specific survival (LCSS) in patients with early stage SCLC. We also analyzed the effect of adjuvant chemotherapy and radiotherapy on the LCSS in these patients.

Methods

Data source

The data used in this study were from the Surveillance, Epidemiology, and End Results (SEER) database. The SEER database is sponsored by the National Cancer Institute of the US and provides registry information on cancer including pathological type, patient survival, surgery, and adjuvant therapy since 1973.

Study population

We limited the cohort to patients with early stage SCLC diagnosed from 2004 to 2015. All early stage SCLC patients were staged using American Joint Committee on Cancer with stage I or IIa (stage T1-2N0M0) disease. Patients who underwent surgery were staged pathologically and those without surgery had clinic staging. Complete patient information was available in the SEER database.

Covariates

The baseline characteristics based on 17 covariates included age, sex, race, tumor size, TNM stage, tumor location, differentiated grade, laterality, surgery, radiotherapy, chemotherapy, insurance status, year of diagnosis, marital status, geographic region, high school education, and median household income. To better analyze the effects of adjuvant therapy on LCSS, we created a new covariate called adjuvant therapy, defined as patients who received one or both treatments (chemotherapy, radiotherapy or chemoradiotherapy).

Statistical analyses

All data were analyzed using IBM SPSS, version 20.0 (IBM Corp, Armonk, NY, USA). Kaplan-Meier analysis was used to compare survival between the surgery and non-surgery groups. Propensity score methods were used to control for potential differences in baseline characteristics of the included patients. Cox regression was performed to assess the balance of the baseline covariates of the two groups after adjusting for the estimated propensity scores.

Results

Study cohort characteristics

We identified 2,453 patients with early stage SCLC, of whom 687 (28.0%) underwent surgery as a primary treatment and 1,766 (72.0%) did not between 2004 and 2015. Table 1 shows the baseline characteristics of all patients identified through the SEER database. The results of Kaplan-Meier analyses demonstrated statistically significant differences in LCSS between the two groups with regard to age ($p<0.001$), sex ($p=0.007$), tumor size ($p<0.001$), TNM stage ($p<0.001$), radiotherapy ($p=0.001$), chemotherapy ($p=0.026$), insurance status ($p<0.001$), adjuvant therapy ($p=0.007$), and year of diagnosis ($p<0.001$). However, no significant differences in LCSS were observed with respect to race ($p=0.396$), tumor location ($p=0.698$), differentiated grade ($p=0.063$), laterality ($p=0.611$), marital status ($p=0.426$), geographic region ($p=0.069$), high school education ($p=0.138$), and median household income ($p=0.470$) (Table 1).

A Cox model for multivariate analysis including the above significant covariates (TNM stage was excluded due to covariates tumor size and TNM stage linearly related) showed statistically significant differences for age ($p<0.001$), sex ($p=0.008$), tumor size ($p=0.002$), surgery ($p<0.001$), radiotherapy ($p<0.001$), and year of diagnosis ($p<0.001$). Covariates such as chemotherapy ($p=0.942$), insurance status ($p=0.495$), and adjuvant therapy ($p=0.839$) did not differ significantly (Table 2). Subsequent analysis using a new Cox model including five covariates (age, sex, tumor size, surgery, and radiotherapy) revealed statistically

Table 1 Baseline characteristics of patients treated with surgery or non-surgery in the Surveillance, Epidemiology and End Results (SEER) Program, 2004–2015

Characteristics	Early stage SCLC		Surgery		Non-surgery		*p*
	Number	%	Number	%	Number	%	
Age, year							<0.001
<45	14	0.6	4	0.6	10	0.6	
≥45, <55	150	6.1	35	5.1	115	6.5	
≥55, <65	490	20	177	25.8	313	17.7	
≥65, <75	940	38.3	300	43.6	640	36.2	
≥75	859	35	171	24.9	688	39	
Sex							0.007
Female	1295	52.8	375	54.6	920	52.1	
Male	1158	47.2	312	45.4	846	47.9	
Race							0.396
White	2172	88.5	627	91.3	1545	87.5	
Black	203	8.3	39	5.7	164	9.3	
Others	75	3.1	20	2.9	55	3.1	
Unknown	3	0.1	1	0.1	2	0.1	
Tumor size, cm							<0.001
≤1	162	6.6	97	14.1	65	3.7	
>1, ≤2	759	30.9	302	44	457	25.9	
>2, ≤3	739	30.2	176	25.6	563	31.9	
>3, ≤4	473	19.3	75	10.9	398	22.5	
>4, ≤5	317	12.9	36	5.3	281	15.9	
Unknown	3	0.1	1	0.1	2	0.1	
TNM stage							<0.001
Stage Ia1	162	6.6	97	14.1	65	3.7	
Stage Ia2	759	30.9	302	44	457	25.9	
Stage Ia3	739	30.2	176	25.6	563	31.9	
Stage Ib	473	19.3	75	10.9	398	22.5	
Stage IIa	317	12.9	36	5.3	281	15.9	
Unknown	3	0.1	1	0.1	2	0.1	
Tumor location							0.698
Upper lobe	1377	56.2	421	61.3	956	54.1	
Middle lobe	177	7.2	57	8.3	120	6.9	
Lower lobe	719	29.3	192	27.9	527	29.8	
NOS	64	2.6	7	1	57	3.2	
Overlapping lesion	8	0.3	2	0.3	6	0.3	
Main bronchus	108	4.4	8	1.2	100	5.7	
Differentiated grade							0.063
Grade I	12	0.5	7	1	5	0.4	
Grade II	27	1.1	16	2.3	11	0.6	
Grade III	413	16.8	206	30	207	11.7	
Grade IV	604	24.6	222	32.3	382	21.6	
Unknow	1397	57	236	34.4	1161	65.7	

(*Continued*)

Table 1 (Continued).

Characteristics	Early stage SCLC		Surgery		Non-surgery		*p*
	Number	%	Number	%	Number	%	
Laterality							0.611
Right-origin of primary	1389	56.6	406	59.1	983	55.7	
Left-origin of primary	1059	43.2	280	40.8	779	44.1	
Paired site, but no information concerning laterality	2	0.1	1	0.1	2	0.1	
Not a paired site	3	0.1	0	0	2	0.1	
Radiotherapy							0.001
No	1207	49.2	535	77.9	672	38.1	
Yes	1246	50.8	152	22.1	1094	61.9	
Chemotherapy							0.026
No	826	33.7	284	41.3	542	30.7	
Yes	1627	66.3	403	58.7	1224	69.3	
Adjuvant therapy							0.007
None	629	25.6	273	39.7	356	20.2	
Chemoradiotherapy	1049	42.8	141	13.4	908	86.6	
Chemotherapy only	578	23.6	262	45.3	316	54.7	
Radiotherapy only	197	8	11	5.6	186	94.4	
Insurance status							<0.001
Medicaid	242	9.9	56	8.2	186	10.5	
Uninsured	31	1.3	9	1.3	22	1.3	
Unknown	627	25.5	176	25.6	451	25.5	
Insured	1553	63.3	446	64.9	1107	62.7	0.426
Marital status							
Married	1195	48.7	364	53	831	47.1	
Single	272	11.1	72	10.5	200	11.3	
Divorced	354	14.4	98	14.3	256	14.5	
Widowed	541	22.1	127	18.5	414	23.4	
Unknown	90	3.7	25	3.6	65	3.7	
Unmarried or Domestic Partner	1	0	1	0.1	0	0	<0.001
Year of diagnosis							
2004–2007	807	32.9	230	33.5	577	32.7	
2008–2011	787	32.1	226	32.9	561	31.7	
2012–2015	859	35	231	33.6	628	35.6	0.069
Geographic region							
East	1284	52.3	395	57.5	889	50.3	
Northwest	777	31.7	197	28.7	580	32.9	
North	321	13.1	77	11.2	244	13.8	
Southwest	71	2.9	18	2.6	53	3	0.138
High school education							
≥21	449	18.3	129	18.8	320	18.1	
13–20	739	30.1	186	27.1	553	31.3	

(*Continued*)

Table 1 (Continued).

Characteristics	Early stage SCLC		Surgery		Non-surgery		*p*
	Number %		Number %		Number %		
7–12	1083	44.2	319	46.4	764	43.3	
<7	182	7.4	53	7.7	129	7.3	0.47
Median household income (dollar, in tens)							
<38000	221	9	69	10.1	152	8.6	
38000–47999	488	19.9	119	17.3	369	20.9	
48000–62999	942	38.4	250	36.4	692	39.2	
>63000	802	32.7	249	36.2	553	31.3	

Abbreviations: SCLC, small-cell lung cancer; NOS, not otherwise specified.

significant differences for age ($p<0.001$), sex ($p=0.014$), tumor size ($p=0.006$), surgery ($p<0.001$), and radiotherapy ($p<0.001$) (Table 3).

Comparison of disease-specific mortality and median survival time between the surgery and non-surgery groups

The overall lung cancer-specific mortality rate in patients with early stage SCLC was 35.8% (879/2453). The mortality rates were 35.2% (242/687) and 36.1% (637/1766) for the surgery and non-surgery groups, respectively. The overall median survival time for patients with early stage SCLC was 17 months. The median survival times in the surgery and non-surgery groups were 26 and 15 months, respectively (Table 4). Compared to that in the non-surgery group, the crude hazard ratio (HR) and 95% confidence interval (CI) was 0.590 (0.508–0.686, $p<0.001$) for the surgery group in patients with early stage SCLC. After adjusting for age, sex, tumor size, surgery, and radiotherapy, the HR (95% CI) for the surgery group was 0.494 (0.415–0.587, $p<0.001$) (Table 3). The median survival time and HR of the surgery group were significantly better than those in the non-surgery group.

Kaplan-Meier analysis of disease-specific survival between the surgery and non-surgery groups

Kaplan-Meier analysis revealed statistically significant differences in survival curves and log-rank tests between the two groups. Among all patients with early stage SCLC, the survival (log-rank $p<0.001$) of the surgery group was better than that of the non-surgery group (Figure 1A). Similarly, the survival (log-rank $p<0.001$) of the surgery group was better than that of the non-surgery group in patients aged ≥75 years (Figure 1B). The survival advantage (log-rank $p<0.001$) in the surgery group persisted in patients aged <75 years (Figure 1C). In addition, the survival (log-rank $p<0.001$) of the surgery group was better than that of the non-surgery group for patients with tumor size T1 (≤3 cm) (Figure 1D). The survival advantage (log-rank $p=0.002$) in the surgery group persisted in patients with tumor size T2 (3 cm< and ≤5 cm) (Figure 1E). Our data demonstrated the significant effect of surgery on disease-specific survival in patients with early stage SCLC.

Comparison of the effects of adjuvant therapy in patients with early stage SCLC

Kaplan–Meier analysis showed a statistically significant difference ($p=0.026$) in the LCSS in patients with early stage SCLC who received chemotherapy (Table 1). However, this difference disappeared in the Cox model ($p=0.847$) (Table 2). Similarly, there was a significant difference ($p=0.031$) in LCSS in patients with early stage SCLC who received adjuvant therapy (Table 1), which also disappeared in the Cox model ($p=0.839$) (Table 2).

Kaplan-Meier analysis also revealed a statistically significant difference ($p=0.001$) in LCSS in patients with early stage SCLC who received radiotherapy by (Table 1). In a Cox model including nine covariates, the HR (95% CI) was 0.572 (0.479–0.682, $p<0.001$) for patients who received radiotherapy compared to those without (Table 2). After adjusting for age, sex, tumor size, surgery, and radiotherapy, the HR (95% CI) was 0.579 (0.500–0.671, $p<0.001$) in patients who received radiotherapy (Table 3).

The effects of radiotherapy on LCSS are also shown in Table 6. The HR (95% CI) of patients with radiotherapy was 0.804 (0.704–0.918, $p=0.001$) compared to patients without radiotherapy. Similarly, compared to patients

Table 2 Multivariate analysis using a cox proportional hazards model in patients with early stage SCLC

Variable	Multivariable analysis[a]		
	HR	95% CI	*p*
Age, year			<0.001
<45	Reference		
≥45, <55	4.961	1.208–20.374	0.026
≥55, <65	5.008	1.238–20.257	0.024
≥65, <75	5.618	1.391–22.681	0.015
≥75	7.381	1.824–29.870	0.005
Sex			0.008
Female	Reference		
Male	1.201	1.050–1.374	
Tumor size, cm	Reference		0.002
≤1	1.18	0.868–1.604	
>1, ≤2	1.217	0.893–1.658	0.292
>2, ≤3	1.346	0.975–1.858	0.213
>3, ≤4	1.77	1.268–2.471	0.071
>4, ≤5	1.192	0.163–8.735	0.001
Unknown			0.863
Surgery	Reference		<0.001
No	0.499	0.420–0.594	
Yes			
Radiotherapy	Reference		<0.001
No	0.552	0.411–0.742	
Yes			
Chemotherapy	Reference		0.942
No	0.993	0.822–1.200	
Yes	Reference		
Adjuvant therapy	1.035	0.742–1.445	0.839
None			
Chemoradiotherapy	Reference		
Insurance status	1.288	0.724–2.290	0.495
Medicaid	0.869	0.621–1.215	
Uninsured	0.9	0.709–1.142	0.39
Unknown			0.411
Insured	Reference	0.975–1.617	0.386
Year of diagnosis	1.255	1.828–3.075	<0.001
2004–2007	2.371		
2008–2011			0.078
2012–2015			<0.001

Notes: [a]Multivariate analysis for age, sex, tumor size, surgery, radiotherapy, chemotherapy, insurance status, adjuvant therapy and year of diagnosis.
Abbreviations: SCLC, small-cell lung cancer; HR, hazard ratio; CI, confidence interval.

without radiotherapy, the HR (95% CI) was 0.804 (0.683–0.947, p=0.009) among patients aged <75 years. However, compared to patients without radiotherapy aged ≥75 years, there was no significant difference (p=0.102) in LCSS. Among patients with T1 (tumor size ≤3 cm), the HR (95% CI) of patients who received radiotherapy was 0.830 (0.703–0.980, p=0.028) compared to those without radiotherapy. Compared to patients without radiotherapy, the HR (95% CI) of patients with radiotherapy was 0.705 (0.565–0.880, p=0.002) in patients with T2 (3 cm< and ≤5 cm). In addition, the HR (95% CI) of patients with radiotherapy was 0.544 (0.463–0.639, p<0.001) compared to those without radiotherapy or surgery. However, there was no statistically significant difference (p=0.079) in LCSS regardless of radiotherapy among patients who underwent surgery (Table 5).

The effects of radiotherapy on the survival curves are shown in Figure 2. In patients with early stage SCLC, the survival curve (log-rank p<0.001) of patients with radiotherapy was better than that in those without radiotherapy (Figure 2A). However, there was no statistically significant difference in survival curve (log-rank p>0.05) between patients with and without radiotherapy among those aged ≥75 years (Figure 2B). However, the survival curve (log-rank p<0.05) of patients with radiotherapy was better than that of those without radiotherapy among those aged <75 years (Figure 2C). Among patients with T1 (tumor sizes ≤3 cm) (log-rank p<0.05) and T2 (3 cm< and ≤5 cm), the survival curves of patients with radiotherapy were better than those of patients without radiotherapy (log-rank p<0.05) (Figure 2D and E). In patients with surgery, there was no significant difference in survival curves (log-rank p>0.05) between patients with and without radiotherapy (Figure 2F). However, among those without surgery, the survival curve (log-rank p<0.001) of patients with radiotherapy was better than that of those without radiotherapy (Figure 2G).

Comparison of the effects of treatment combinations in patients with early stage SCLC

According to the patient's adjuvant therapy plans, we divided the patients with early stage SCLC into four cohorts: patients with chemoradiotherapy (cohort 1), patients without any adjuvant therapy (cohort 2), patients with chemotherapy only (cohort 3) and patients with chemoradiotherapy plus without any adjuvant therapy (cohort 4). Subsequently, we set up treatment combinations: non-surgery plus chemoradiotherapy group and surgery plus chemoradiotherapy group in cohort 1, non-surgery plus no adjuvant therapy group and surgery plus no adjuvant therapy group in cohort 2, non-

Table 3 Univariable and multivariable analyses on LCSS in patients with early stage SCLC

Variable	Univariable analysis			Multivariable analysis[a]		
	HR	95% CI	*p*	HR	95% CI	*p*
Age, year			<0.001			<0.001
<45	Reference			Reference		
≥45, <55	4.346	1.061–17.796	0.041	4.477	1.092–18.351	0.037
≥55, <65	4.158	1.031–16.771	0.045	4.615	1.143–18.638	0.032
≥65, <75	4.695	1.168–18.878	0.029	5.418	1.345–21.820	0.017
≥75	6.492	1.613–26.131	0.008	6.9	1.711–27.826	0.007
Sex			0.007			0.014
Female	Reference			Reference		
Male	1.199	1.050–1.370		1.184	1.035–1.354	
Tumor size, cm			<0.001			0.006
≤1	Reference			Reference		
>1, ≤2	1.299	0.959–1.759	0.091	1.183	0.870–1.607	0.284
>2, ≤3	1.363	1.006–1.847	0.045	1.175	0.863–1.600	0.307
>3, ≤4	1.597	1.167–2.187	0.003	1.319	0.956–1.820	0.092
>4, ≤5	1.963	1.422–2.710	0	1.685	1.208–2.349	0.002
Unknown	1.129	0.156–8.178	0.904	1.14	0.156–8.315	0.897
Surgery			<0.001			<0.001
No	Reference			Reference		
Yes	0.59	0.508–0.686		0.494	0.415–0.587	
Radiotherapy			0.001			<0.001
No	Reference			Reference		
Yes	0.804	0.704–0.918		0.579	0.500–0.671	

Notes: [a]Multivariate analysis for age, sex, tumor size, radiotherapy, surgery and chemotherapy.
Abbreviations: LCSS, lung cancer-specific survival; SCLC, small-cell lung cancer; HR, hazard ratio; CI, confidence interval.

Table 4 Association with cancer-specific mortality and median survival time among patient groups (SEER database, 2004–2015)

Group	Mortality, % (n/N)	Median survival time (months)
Overall	35.8% (879/2453)	17
Non-surgery	35.2% (242/687)	15
Surgery	36.1% (637/1766)	26

Abbreviations: SEER, Surveillance, Epidemiology and End Results.

surgery plus chemotherapy only group and surgery plus chemotherapy only group in cohort 3 as well as non-surgery plus chemoradiotherapy group and surgery plus no adjuvant therapy group in cohort 4. In all cohorts, there were significant differences in survival curves and log-rank tests between the two groups in the same cohort (Figure 3). The survival curve (log-rank $p<0.001$) of the surgery plus chemoradiotherapy group was better than that of the non-surgery plus chemoradiotherapy group in cohort 1 (Figure 3A). Similarly, the survival curve (log-rank $p<0.001$) of the surgery plus no adjuvant therapy group was better than that of the non-surgery plus no adjuvant therapy group in cohort 2 (Figure 3B), and the survival curve (log-rank $p<0.001$) of the surgery plus chemotherapy only group was better than that of the non-surgery plus chemotherapy only group in cohort 3 (Figure 3C). In addition, the survival curve (log-rank $p=0.005$) of the surgery plus no adjuvant therapy group was also better than that of the non-surgery plus chemoradiotherapy group in cohort 4 (Figure 3D).

Analogous results were showed in Table 7 by univariable analysis. Compared to the non-surgery plus chemoradiotherapy group, the HR (95% CI) of the surgery plus chemoradiotherapy group was 0.581 (0.429–0.787, $p<0.001$) in cohort 1. The HR (95% CI) of the surgery plus no adjuvant therapy group was 0.401 (0.300–0.536, $p<0.001$) compared to the non-surgery plus no adjuvant therapy group in cohort 2. The HR (95% CI) of the surgery plus chemotherapy only group was 0.462 (0.353–0.605, $p<0.001$) compared to the non-surgery plus chemotherapy only group in cohort 3. The HR (95% CI) of the surgery plus no adjuvant therapy group was 0.709 (0.557–0.903,

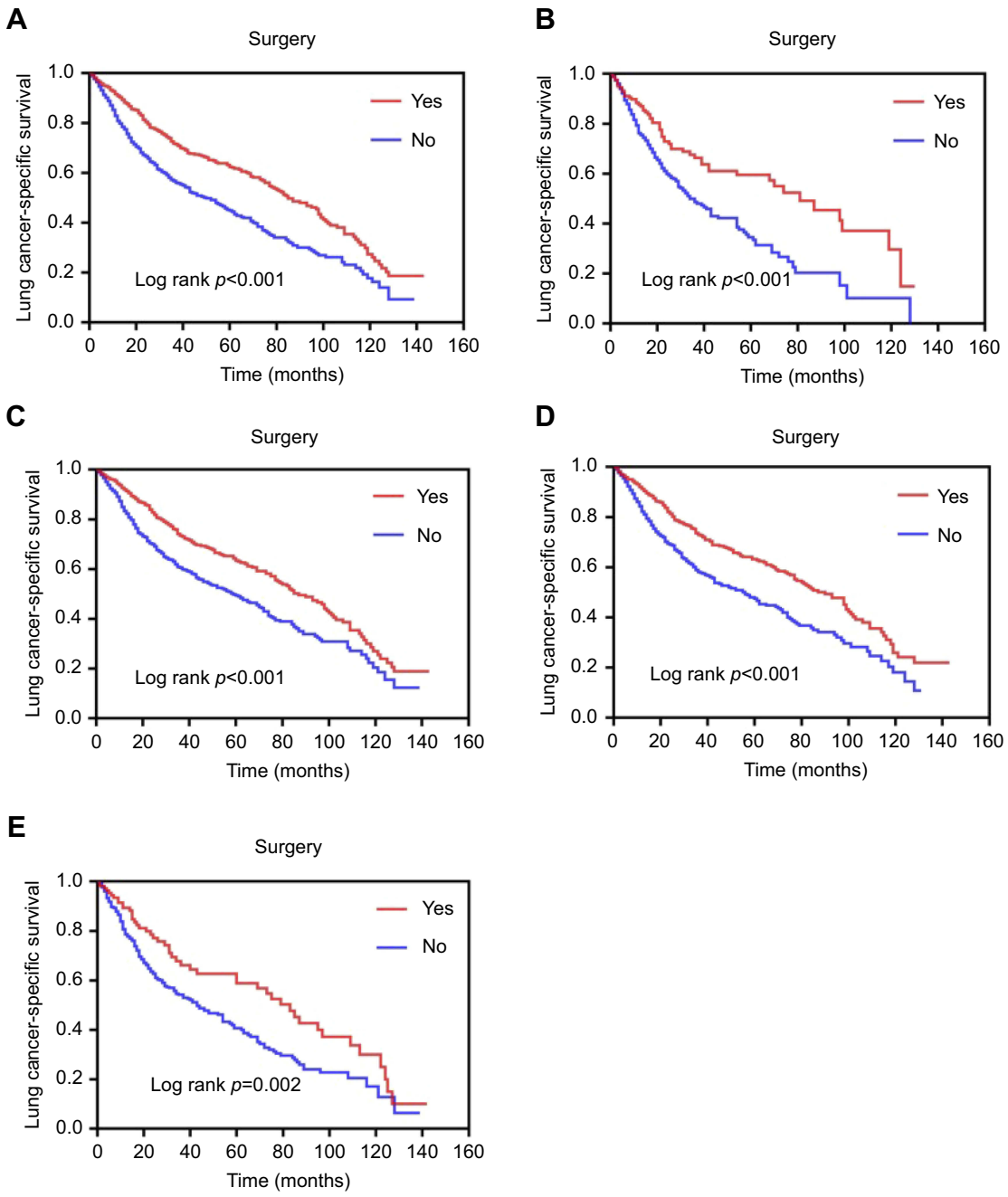

Figure 1 Survival curves based on Kaplan–Meier analysis comparing treatment with surgery versus non-surgery. (**A**) LCSS (p<0.001) in patients with early stage SCLC; (**B**) LCSS (p<0.001) in patients with age ≥75 years; (**C**) LCSS (p<0.001) in patients with age <75 years; (**D**) LCSS (p<0.001) in patients with tumor size T1 (sizes ≤3 cm); (**E**) LCSS (p=0.002) in patients with tumor size T2 (3 cm< sizes ≤5 cm).

Abbreviations: LCSS, lung cancer-specific survival; SCLC, small-cell lung cancer.

p=0.005) compared to the non-surgery plus chemoradiotherapy group in cohort 4.

Discussion

Currently, chemoradiotherapy is the standard treatment for early stage SCLC, providing a median overall survival of 16–20 months.[15,16] However, the optimal treatment of early stage SCLC remains controversial. An increasing number of studies suggest that surgical treatment can improve survival outcomes in patients with SCLC, especially in early stage disease.[2,7,13,14,17–21] Retrospective studies have reported favorable outcomes for surgery in

Table 5 Comparison of the effects of surgery (yes vs no) on LCSS in patients groups by univariate analysis

Group	Number	Univariable analysis		
		HR	95%CI	*p*
All patients	2453	0.590	0.508–0.686	<0.001
Age≥75	859	0.529	0.393–0.712	<0.001
Age<75	1594	0.639	0.536–0.763	<0.001
Size≤3	1660	0.612	0.512–0.730	<0.001
3<size≤5	790	0.610	0.445–0.836	0.002

Abbreviations: LCSS, lung cancer-specific survival; HR, hazard ratio; CI, confidence interval.

Table 6 Comparison of the effects of radiotherapy (yes vs no) on LCSS in patients groups by univariate analysis

Group	Number	Univariable analysis		
		HR	95%CI	*p*
All patients	2453	0.804	0.704–0.918	0.001
Age≥75	859	0.827	0.659–1.038	0.102
Age<75	1594	0.804	0.683–0.947	0.009
Size≤3	1660	0.830	0.703–0.980	0.028
3<size≤5	790	0.705	0.565–0.880	0.002
Surgery	687	0.761	0.560–1.032	0.079
Non-surgery	1766	0.544	0.463–0.639	<0.001

Abbreviations: LCSS, lung cancer-specific survival; HR, hazard ratio; CI, confidence interval.

patients with stage I SCLC.[22,23] A growing number of patients with early stage SCLC receive surgical treatment, resulting in a favorable overall median survival of 29–91 months.[24–27] The present study evaluated the survival outcomes of surgery versus non-surgery in patients with early stage SCLC, finding that surgery resulted in a better LCSS than that of non-surgery. To further analyze the effect of surgery on LCSS in elderly patients with early stage SCLC, we divided the age covariates into ≥75 and <75 years. The LCSS of patients receiving surgical treatment was better than that of non-surgery in patients aged ≥75 years. Better survival was also observed in surgical patients aged <75 years than that in those without surgery. We also analyzed the effect of surgery on LCSS in patients with early stage SCLC with varying tumor sizes. We divided the patients into T1 (≤3 cm) and T2 (3 cm< and ≤5 cm) based on tumor size. Our results showed a superior LCSS in patients with surgery compared to non-surgery for both T1 and T2. Our results show that surgical treatment is superior to non-surgical in patients with early stage SCLC. This result is consistent with those of the above studies.

At present, chemotherapy is the main treatment for early stage SCLC. We analyzed the effect of chemotherapy on LCSS in patients with early stage SCLC. Univariate analysis revealed statistically significant differences in LCSS between chemotherapy and non-chemotherapy patients with early stage SCLC. However, a Cox model for multivariate analysis indicated no statistically significant difference in LCSS between these groups. In addition, we defined one or two rounds of chemotherapy and radiotherapy as adjuvant therapy. We found a significant difference in univariate analysis, which disappeared in multivariate analysis. According to these outcomes, chemotherapy did not provide significant survival benefits for patients with early stage SCLC. This result may provide a reference for clinicians to select appropriate treatment methods for these patients.

Because SCLC is radiosensitive, radiotherapy can provide local control for patients with SCLC.[4] We analyzed the effect of radiotherapy on LCSS in patients with early stage SCLC. In univariate analysis, the LCSS of patients with radiotherapy was better than that in non-radiotherapy patients. A Cox model for multivariate analysis (included covariates: age, sex, tumor size, surgery, and radiotherapy) also revealed a better LCSS in patients with radiotherapy than that in non-radiotherapy patients. These results suggest that radiotherapy has a significant effect on LCSS in patients with early stage SCLC. The patients were further divided into groups according to age (≥75 or <75 years), tumor size (T1 or T2), and surgery (yes or no) to analyze the effects of radiotherapy on LCSS in univariate analysis. Compared to that in non-radiotherapy patients, the LCSS of patients with radiotherapy was significantly better among those aged <75 years. Similarly, the LCSS of patients with radiotherapy was significantly better than that in those without radiotherapy and without surgery. However, among patients aged ≥75 years or with surgery, there was no advantage for radiotherapy compared to non-radiotherapy. In addition, radiotherapy can provide a benefit in LCSS for radiotherapy patients, whether T1 or T2.

Patients with early stage SCLC might receive multiple treatments including surgery, radiotherapy and chemotherapy.

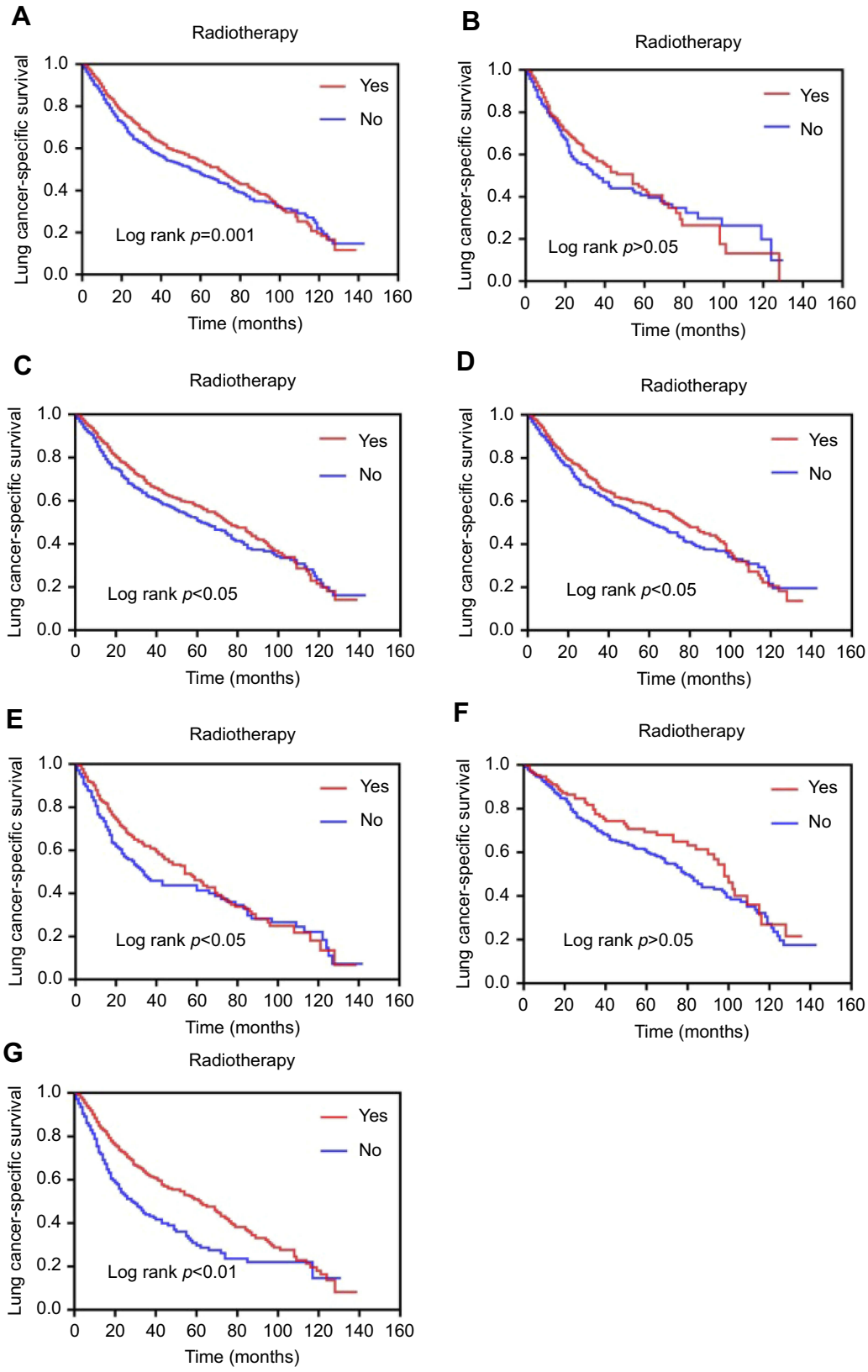

Figure 2 Comparison of the effects of radiotherapy on LCSS based on Kaplan–Meier analysis. (**A**) LCSS (p=0.001) in patients with early stage SCLC; (**B**) LCSS (p>0.05) in patients with age ≥75 years; (**C**) LCSS (p<0.05) in patients with age <75 years; (**D**) LCSS (p<0.05) in patients with T1 (tumor sizes ≤3 cm); (**E**) LCSS (p<0.05) in patients with T2 (3 cm< sizes ≤5 cm); (**F**) LCSS (p>0.05) in patients with surgery; (**G**) cancer-specific survival (p<0.001) in patients with non-surgery.
Abbreviations: LCSS, lung cancer-specific survival; SCLC, small-cell lung cancer.

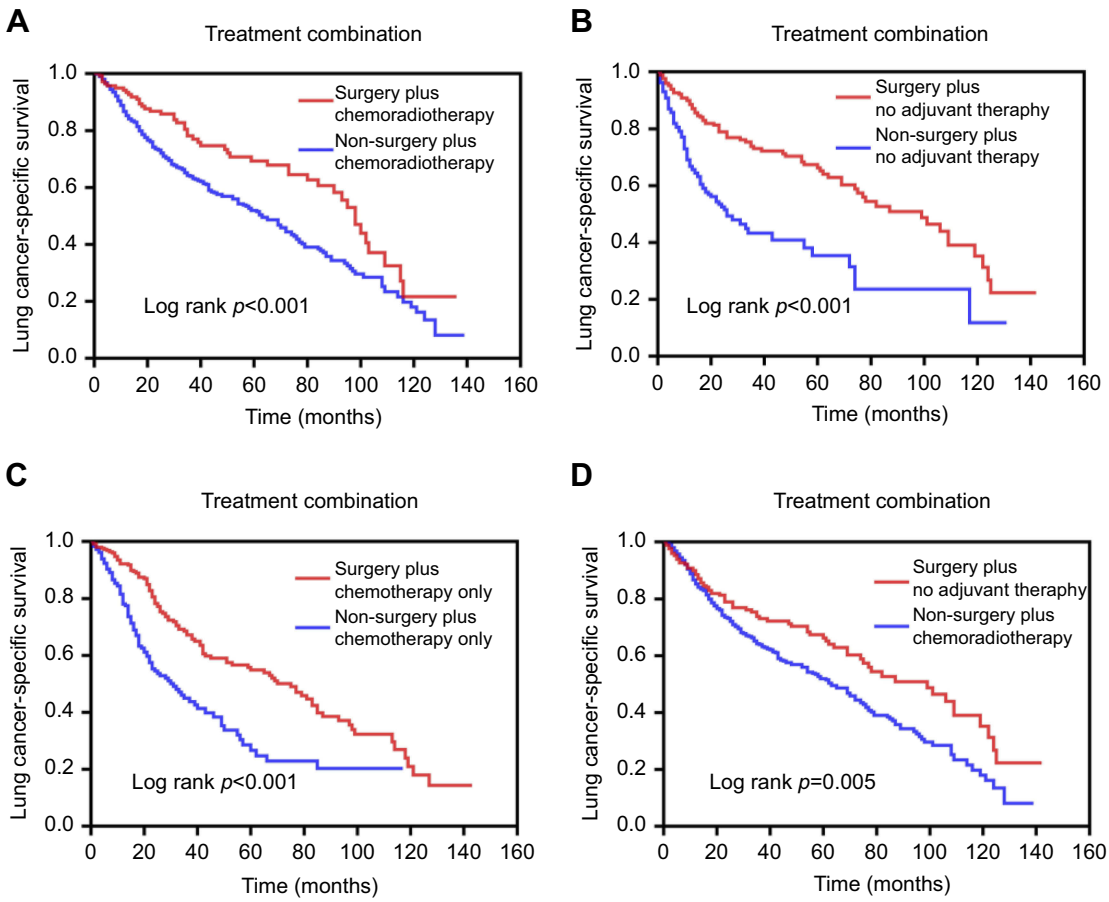

Figure 3 Comparison of the effects of treatment combinations in patients with early stage SCLC. (**A**) LCSS (p<0.001) in patients with chemoradiotherapy; (**B**) LCSS (p<0.001) in patients without any adjuvant therapy; (**C**) LCSS (p<0.001) in patients with chemotherapy only; (**D**) LCSS (p=0.005) in patients with chemoradiotherapy plus without any adjuvant therapy.

Abbreviations: SCLC, small-cell lung cancer; LCSS, lung cancer-specific survival.

Therefore, it was necessary to further discuss the significance of surgery in different treatment combinations. Due to the small number of patients undergoing surgery plus radiotherapy, we did not discuss it further. Our results showed that the combination comprising surgery was superior to the combination without surgery on LCSS in the same cohort. Moreover, surgical treatment was superior to chemoradiotherapy in patients with early stage SCLC (Figure 3D, Table 7). This study further indicates that surgical treatment is a better option for patients with early stage SCLC.

Due to its retrospective design, our study has some limitations. One is the lack of information showing the status of performance or other indicators of the patient's physical condition. Another limitation is the lack of specific treatment information for the patient, such as chemotherapy regimen, radiation dose and method, and the surgical procedure. However, with the inclusion of 18 covariates and nearly 2,500 patients in our cohort, the present study represents a well-balanced analysis between surgery and non-surgical methods. Thus, in the absence of data from prospective trials, our findings provide useful information for the management of patients with early stage SCLC.

In summary, the prognosis of patients with early stage SCLC was related to a variety of factors. According to the results of our study, surgery was superior to non-surgery in patients with early stage SCLC; therefore, we recommend surgical resection as the more favorable choice. In addition, because radiotherapy may be beneficial for patients with early stage SCLC, it should be recommended, especially in patients not undergoing surgery and aged <75 years. Understanding this information is critical to the prognosis of patients with early stage SCLC and our findings help in determining the best treatment strategies for these patients.

Table 7 Comparison of the effects of treatment combinations on LCSS in patients with early stage SCLC by univariate analysis

Treatment Combination	Number	Univariable Analysis		
		HR	95%CI	*p*
Cohort 1				
Non-surgery plus Chemoradiotherapy	908	Reference		
Surgery plus Chemoradiotherapy	141	0.581	0.429–0.787	<0.001
Cohort 2				
Non-surgery plus No adjuvant therapy	356	Reference		
Surgery plus No adjuvant therapy	273	0.401	0.300–0.536	<0.001
Cohort 3				
Non-surgery plus Chemotherapy only	316	Reference		
Surgery plus Chemotherapy only	262	0.462	0.353–0.605	<0.001
Cohort 4				
Non-surgery plus Chemoradiotherapy	908	Reference		
Surgery plus No adjuvant therap	273	0.709	0.557–0.903	0.005

Abbreviations: LCSS, lung cancer-specific survival; SCLC, small-cell lung cancer; HR, hazard ratio; CI, confidence interval.

Abbreviation list

SCLC, small-cell lung cancer; SEER, Surveillance, Epidemiology and End Results; LCSS, lung cancer-specific survival; HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent is waived.

Acknowledgments

We would like to thank all the staff of the National Cancer Institute for their efforts in the SEER program. This work was supported by the National Natural Science Foundation of China ([NSFC] nos. 81472180, 81802262), Shanghai Tenth Hospital's improvement plan for NSFC (nos. 04.03.17.032, 04.01.18. 048),the Fundamental Research Funds for the Central Universities (nos. 22120180584) and Shanghai Chongming district "sustainable development science and technology " (nos. CKY2019-9).

Disclosure

The authors declare there are no potential conflicts of interest related to this study.

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