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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Effects of surgery on survival of elderly patients with stage I small-cell lung cancer: analysis of the SEER database

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Abstract

Introduction Surgery improves survival of small-cell lung cancer (SCLC) patients in early stage. However, the role of surgery in the elderly stage I SCLC patients is not well established. We designed this retrospective study to explore the efficacy of surgery on survival of this subset population.

Patients and methods Elderly patients aged ≥ 75 years with stage I SCLC diagnosed histologically from 1998 to 2013 were identified from the Surveillance, Epidemiology, and End Results (SEER) database. Included patients were divided into surgery group (received surgery, accompanied by chemotherapy, radiotherapy, or both or neither), non-surgical group (only received radiotherapy, chemotherapy, or combination), and untreated group. Overall survival (OS) and lung cancer-specific survival (LCSS) were compared among the three groups by the Kaplan–Meier analysis. Cox proportional hazards regression was used to identify factors associated with survival.

Results A total of 983 patients were included. Among all of the patients, 24.0% patients received surgery, 46.6% patients received non-surgical treatment, and 29.4% patients received no treatment. The 5-year OS rates of surgery, non-surgical and untreated groups were 31%, 12% and 6%, respectively ($P < 0.0001$). In multivariable analysis, surgery was an important factor that improved OS when compared with non-surgical treatment (HR 0.554; 95% CI 0.458–0.670 [$P < 0.0001$]). In subgroup analysis, surgery remained an independent factor for OS among patients aged 75–79 years (HR 0.506; 95% CI 0.391–0.655 [$P < 0.0001$]) and 80–84 years (HR 0.544; 95% CI 0.388–0.763 [$P < 0.0001$]), while did not reach statistical significance when compared to non-surgical treatment for patients age ≥ 85 years (HR 0.914; 95% CI 0.507–1.650; [$P = 0.766$]).

Conclusion Surgical resection significantly improved OS in stage I SCLC patients aged 75–84 years in our study, but further exploration in larger prospective clinical trials is needed.

Keywords Surgery · Small-cell lung cancer · Elderly · SEER

Introduction

Lung cancer is the leading cause of cancer-related death in the United States. Small-cell lung cancer (SCLC) accounts for approximately 15% of lung cancer and is characterized by rapid growth and early metastasis (Govindan et al. 2006; Siegel et al. 2018). The average age of patients diagnosed with SCLC increased, and one recently study revealed that the proportion of SCLC patients older than 70 years old had increased from 23% in 1975 to 44% in 2010, and almost half of patients with limited-stage SCLC were over 70 years old (Abdel-Rahman 2018; Lally et al. 2009).

Chemotherapy and radiotherapy are considered as the standard treatments for patients with SCLC. Recently, several retrospective studies noted that over survival (OS) was improved in patients with limited SCLC who undergo surgery, and the average 5-year survival rate was approximately 50% (Lim et al. 2008; Schreiber et al. 2010; Takei et al. 2014; Yu et al. 2010). Meanwhile, the NCCN Guidelines also stated that surgery should be first considered for stage I (T1–2, N0) SCLC patients (Kalemkerian et al. 2018). However, in clinical practice, surgery is mostly performed in relatively young patients, considering that older patients may

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be accompanied with decreased performance status, more medical comorbidities (Asmis et al. 2008) and increased postoperative complications (Okami et al. 2009; Rostad et al. 2006). Meanwhile conversely, several retrospective analyses suggested that age was not a contraindication to surgery, and appropriately selected patients aged 80 years old or over with stage I non-small-cell lung cancer (NSCLC) still benefited from surgical resection (Dalwadi et al. 2018; Ganti et al. 2016; Okami et al. 2009). Up to now, there is no study aimed to explore the role of surgery in elder patients with stage I SCLC.

In this retrospective study, we acquired data from SEER database and compared the efficacy of different treatment modalities, including surgery, non-surgical and no treatment on survival of Stage I SCLC patients aged ≥ 75 years old.

Materials and methods

Data sources

This retrospective study was based on Incidence–SEER 18 Regs Custom Data (with additional treatment fields), Nov 2017 Sub (1973–2015 varying). The SEER database consists of 18 population-based cancer registries that covers approximately 28% of the United States population, and is freely available for cancer-based epidemiology investigation and survival analysis. Permission to access the custom data file in the SEER program was obtained and the reference number was 13775-Nov 2017. We retrieved variables of interest using the SEER*Stat software Version 8.3.5.

Study population

Patients aged ≥ 75 years who were histologically diagnosed with stage I SCLC from January 1998 to December 2013 were evaluated by the filter criteria. The third EditionInternational Classification of Disease for Oncology (ICD-O-3) was used to identify SCLC. The site code "lung and bronchus" and the histology/behavior codes 8041/3, 8042/3, 8043/3, 8044/3, 8045/3 were included. Stage I was defined clinically or pathologically in accordance with the American Joint Committee on Cancer (AJCC) Staging systems (3rd system code 10 for patients diagnosed from 1998 to 2003, derived 6th system codes IA and IB for patients diagnosed 2004–2013). In addition, patients diagnosed by autopsy/death certificate, without sufficient survival data (survival months unknown, survival months flag incomplete or not calculated) and surgery unknown were excluded. Patients from 1973 to 1998 without pathologic staging or surgery information were also not included.

The following data were extracted for each case: patient ID, year and age at the time of diagnosis, gender, race, location of tumor, neoplastic grade, AJCC staging information, treatments (surgery or chemotherapy or radiation), reasons of no cancer-directed surgery, cause-specific death classification, survival months and vital status.

Statistical analysis

In this study, SCLC patients were classified into surgery, non-surgical, and untreated groups. The clinicopathological characteristics between the three groups were evaluated using the Pearson χ^2 test. Kaplan–Meier analysis with the log-rank test was used to estimated OS and LCSS. Multivariate Cox models were performed to identify the predictors of survival. All statistical analyses were made using IBM SPSS 22. P values were two sided and $P < 0.05$ were considered significant.

Results

Patient characteristics

Total 983 patients met the filter criteria and were included in the study analysis. Characteristics of patients are shown in Table 1. Among all patients, 49.3% were females and 50.7% were males. The percentage of patients race of whites, blacks and other were 87.0%, 7.9%, and 5.1%, respectively ($P = 0.012$). The most common locations of the primary tumor site were upper lobe (51.7%), followed by lower lobe (33.5%), other (8.2%) and middle lobe (6.6%) ($P < 0.0001$).

In distribution fraction of treatment, 236 (24.0%) patients underwent surgery, 458 (46.6%) patients received non-surgical treatment, and 289 (29.4%) patients had no treatment. The percentage of surgical was 29.3%, 19.1%, and 16.4% in patient aged 75–79, 80–84, and ≥ 85 years old, respectively ($P < 0.0001$). The percentage of patients receiving no treatment was 22.8% in 75- to 79-year-old group, 31.7% in 80- to 84-year-old group, and 49.2% in 85-year-old group ($P < 0.0001$). No significant difference of the treatment patterns in all treatment periods was observed ($P = 0.553$).

The reasons for 747 patients in stage I without surgery were analyzed. 615 patients (82%) were not recommended for surgery, surgical contraindication was in 51 patients (7%), 67 patients (9%) for some unknown reasons and 13 patients (2%) refused surgery.

Survival outcomes

In general, patients who received surgery had a longer OS and LCSS, followed by patients receiving non-surgical treatment, and neither. The median OS (mOS) was 25 months (95% confidence interval [CI] 18.5–31.5 months) in the surgery group, 13 months (95% CI 11.7–14.3 months) in the

Table 1 Baseline characteristics of small-cell lung cancer patients

Characteristic	No. (%) $N=983$	No treatment $N=289$ (29.4)	Non-surgical $N=458$ (46.6)	Surgery $N=236$ (24.0)	P
Gender					0.201
Male	498 (50.7)	138 (27.7)	246 (49.4)	114 (22.9)	
Female	485 (49.3)	151 (31.1)	212 (43.7)	122 (25.2)	
Age (year)					< 0.0001
75–79	505 (51.4)	115 (22.8)	242 (47.9)	148 (29.3)	
80–84	350 (35.6)	111 (31.7)	172 (49.1)	67 (19.1)	
≥ 85	128 (13.0)	63 (49.2)	44 (34.4)	21 (16.4)	
Race					0.012
White	855 (87.0)	246 (28.8)	388 (45.4)	221 (25.8)	
Black	78 (7.9)	26 (33.3)	41 (52.6)	11 (14.1)	
Other[a]	50 (5.1)	17 (34.0)	29 (58.0)	4 (8.0)	
Primary site					< 0.0001
Upper lobe	508 (51.7)	127 (25.0)	239 (47.0)	142 (28.0)	
Middle lobe	65 (6.6)	18 (27.7)	29 (44.6)	18 (27.7)	
Lower lobe	329 (33.5)	98 (29.8)	157 (47.7)	74 (22.5)	
Other[b]	81 (8.2)	46 (56.8)	33 (40.7)	2 (2.5)	
Grade					< 0.0001
Grade I–Grade II	16 (1.6)	2 (12.5)	4 (25.0)	10 (62.5)	
Poorly differentiated; Grade III	173 (17.6)	40 (23.1)	55 (31.8)	78 (45.1)	
Undifferentiated; anaplastic; Grade IV	291 (29.6)	82 (28.2)	130 (44.7)	79 (27.1)	
Unknown	503 (51.2)	165 (32.8)	269 (53.5)	69 (13.7)	
Year of diagnosis					0.553
1998–2003	215 (21.9)	57 (26.5)	103 (47.9)	55 (25.6)	
2004–2008	368 (37.4)	104 (28.3)	179 (48.6)	85 (23.1)	
2009–2013	400 (40.7)	128 (32.0)	176 (44.0)	96 (24.0)	
Reasons of no surgery[c]					0.004
Not recommended	615 (82.0)	221 (35.9)	394 (64.1)	–	
Contraindicated due to other cond	51 (7.0)	26 (51.0)	25 (49.0)	–	
Unknown reason	67 (9.0)	33 (49.3)	34 (50.7)	–	
Patient refused	13 (2.0)	9 (69.2)	4 (30.8)	–	
Adjuvant therapy					
Yes	–	–	–	108 (45.8)	
No	–	–	–	128 (54.2)	

[a]Other includes American Indian, Alaska Native, Asian/Pacific Islander, and unspecified

[b]Other includes main bronchus, overlapping lesion of lung, and unspecified

[c]Reasons of no surgery: one patient who received non-surgical treatment, was registered as "surgery performed". This contradictory record was excluded from the analysis

non-surgical group and 6 months (95% CI 4.6–7.4 months) in untreated group. The 5-year OS rate was 31%, 12%, 6% for patients who received surgery, non-surgical and no treatment, respectively ($P < 0.0001$) (Fig. 1a). The 5-year LCSS rate in surgery, non-surgical and no treatment group was 59%, 33% and 25% respectively ($P < 0.0001$) (Fig. 1b). The multivariate Cox analysis of factors affecting outcomes among the study population is listed in Table 2. Factors associated with improved OS and LCSS included surgery, non-surgical treatment, and a diagnosis after 2009. Younger and female patients were found to be significantly associated with OS, whereas marginal significantly associated with LCSS. Primary tumor site in the middle lobe was also a risk factor for prognosis. Race and neoplastic grade did not significantly affect survival outcomes.

In subgroup analyses stratified by age, the mOS of surgery, non-surgical and untreated groups was 33 months (95% CI 20.4–45.6 months), 14 months (95% CI 11.8–16.2 months) and 7 months (95% CI 3.9–10.1 months) for patients aged 75–79 years, respectively. The 5-year OS

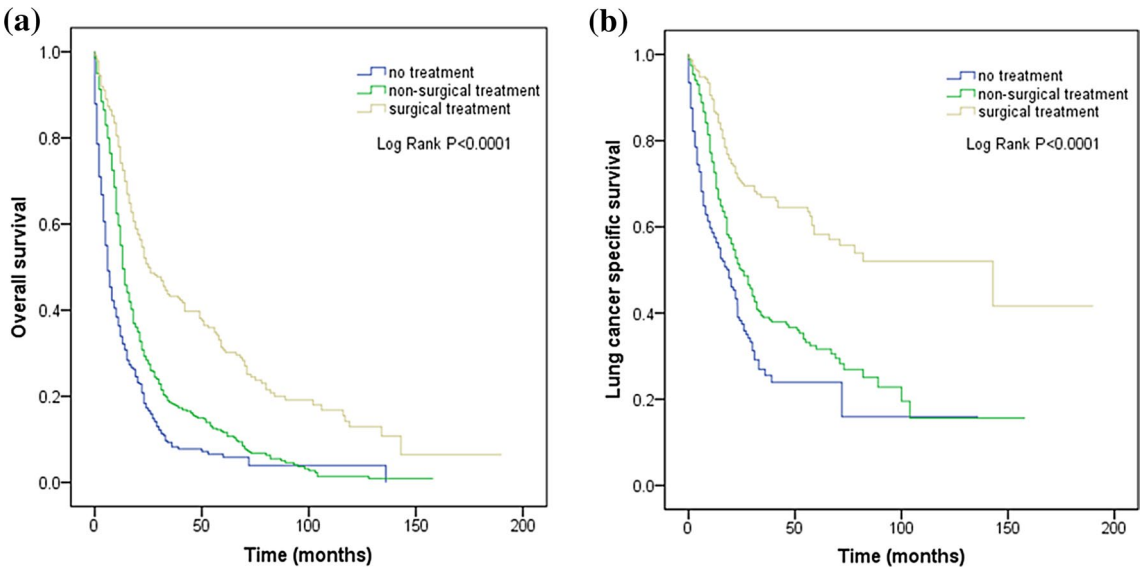

Fig. 1 Kaplan–Meier estimates of OS and LCSS in theoverall cohort based on treatment type

rate of surgery, non-surgical and untreated groups was 34%, 13% and 7%, respectively. ($P < 0.0001$) (Fig. 2a). The 5-year LCSS rate was 61% in patients who had surgery, 36% in patients who received non-surgical treatment and 21% in no treatment group ($P < 0.0001$) (Fig. 2b). In multivariable analysis, compared with non-surgical treatment, surgery was significantly associated with a longer OS (HR 0.506; 95% CI 0.391–0.655 [$P < 0.0001$]) and LCSS (HR 0.449; 95% CI 0.309–0.653 [$P < 0.0001$]) (Table 3).

Similar results were observed in patients aged 80–84 years. The mOS was 23 months (95% CI 16.1–29.9 months) in surgery group, 13 months (95% CI 11.4–14.6 months) in non-surgical group, and 6 months (95% CI 4.2–7.8 months) in untreated group. The 5-year OS rate was 30% for patients who underwent surgery, 10% in non-surgical treatment, and 6% in no treatment group ($P < 0.0001$) (Fig. 2c). The 5-year LCSS rate for patients who underwent surgery, non-surgical treatment and no treatment was 54%, 28% and 32%, respectively ($P < 0.0001$) (Fig. 2d). In multivariable analysis, compared with non-surgical treatment, surgery remained as an independent significant predictor of improved OS (HR 0.544; 95% CI 0.388–0.763 [$P < 0.0001$]) and LCSS (HR 0.452; 95% CI 0.279–0.733 [$P = 0.001$])(Table 3).

Further, in the subgroup of patients aged ≥ 85 years, the mOS in surgery group was 18 months (95% CI 15.0–21.0 months), 14 months (95% CI 8.6–19.4 months) in non-surgical group, and 7 months (95% CI 4.4–9.6 months) in the untreated group. The 5-year OS rate in surgery, non-surgical, and no treatment group was 18%, 14%, and 4%, respectively ($P = 0.002$) (Fig. 2e). The 5-year LCSS for patients who received surgery was 55%, for those received non-surgical therapy was 40%, and 20% for patients received no treatment ($P = 0.013$) (Fig. 2f). In multivariable analysis, compared with non-surgical treatment, surgery was not an independent factor for OS (HR 0.914; 95% CI 0.507–1.650; [$P = 0.766$]), and LCSS (HR 0.656; 95% CI 0.266–1.615; [$P = 0.359$]) (Table 3).

Analysis of adjuvant therapy

236 patients receiving surgery were included in this analysis. Among those, 108 patients (45.8%) had adjuvant therapy after surgery and 128 (54.2%) received surgery alone. The mOS was 39 months (95% CI 25.2–52.8 months) in the postoperative adjuvant group and 19 months (95% CI 12.8–25.2 months) in the surgery-alone group. The 5-year OS rate was 37% in postoperative adjuvant therapy and 27% in surgery alone ($P = 0.033$) (Fig. 3a). The 5-year LCSS rate was 66% in patients who had postoperative adjuvant, 52% in those received surgery alone ($P = 0.035$) (Fig. 3b).

Discussion

Recently, several retrospective studies have reported favorable outcomes for surgery in early-stage SCLC patients. Weksler's study (Lim et al. 2008) indicated the overall 5-year survival rate was 52% in 59 patients with SCLC treated with complete R0 resection, which supported the need to reevaluate surgery as the primary treatment and use of cTNM criteria in the selection of patients who were potentially suitable for surgery. Analyses of SEER database also proved the important role of surgery in localized SCLC (Ahmed et al.

Table 2 Multivariate analysis of clinicopathological factors affecting outcomes in older SCLC patients

Clinical parameters	OS			LCSS		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years)						
75–79			0.017			0.319
80–84	1.205	1.039–1.396	0.014	1.168	0.951–1.433	0.138
≥ 85	1.255	1.017–1.550	0.035	1.116	0.826–1.506	0.475
Gender						
Male						
Female	0.820	0.716–0.939	0.004	0.923	0.764–1.115	0.404
Race						
White			0.125			0.735
Black	0.960	0.749–1.232	0.749	0.976	0.689–1.385	0.894
Other[a]	0.729	0.537–0.989	0.042	0.854	0.574–1.269	0.435
Primary site						
Upper lobe			0.041			0.033
Middle lobe	1.401	1.067–1.841	0.015	1.542	1.051–2.262	0.027
Lower lobe	0.963	0.827–1.120	0.622	1.026	0.830–1.268	0.812
Other[b]	1.163	0.906–1.495	0.236	1.408	1.021–1.941	0.037
Grade						
Grade I–II			0.380			0.484
Grade III	1.670	0.901—3.093	0.103	1.371	0.592–3.175	0.461
Grade IV	1.607	0.875–2.953	0.126	1.539	0.677–3.502	0.304
Unknown	1.691	0.920–3.108	0.091	1.337	0.587–3.046	0.490
Therapy						
No treatment			< 0.0001			< 0.0001
Non-surgical treatment	0.628	0.536–0.735	< 0.0001[a]	0.620	0.499–0.769	< 0.0001[a]
Surgery	0.348	0.282–0.429	< 0.0001[b]	0.291	0.216–0.393	< 0.0001[b]
	0.554	0.458–0.670	< 0.0001[c]	0.470	0.356–0.620	< 0.0001[c]
Year of diagnosis						
1998–2003			0.002			< 0.0001
2004–2008	0.903	0.758–1.074	0.249	0.808	0.641–1.017	0.070
2009–2013	0.730	0.608–0.878	< 0.001	0.551	0.428–0.709	< 0.0001

[a]*P* for comparison of untreated group vs non-surgical group

[b]*P* for comparison of untreated group vs surgery group

[c]*P* for comparison of non-surgical group vs surgery group

2017; Che et al. 2018; Schreiber et al. 2010; Yu et al. 2010; Weksler et al. 2012). Meanwhile, the NCCN Guidelines have stated that surgery should be considered for patients with stage I (T1–2, N0) SCLC. However, the median age of patients in above-mentioned retrospective studies was 62–74 years old (Ahmed et al. 2017; Che et al. 2018; Lim et al. 2008; Schreiber et al. 2010; Yu et al. 2010). To the best of our knowledge, no prospective or retrospective studies are available to evaluate the survival outcomes of surgery for these specific older SCLC patients. Based on current situation, our study selected patients aged ≥ 75 years to elucidate the clinical value of surgery in the treatment of elderly patients with SCLC.

In clinical practice, surgery is rarely performed in elderly patients, considering that increasing age is associated with decreased functional status, increased comorbidity (Asmis et al. 2008; Pal and Hurria 2010), more postoperative complications (Okami et al. 2009) and relatively high mortality (Rostad et al. 2006). In our study, we also observed that the rate of surgery was decreased with age increasing (29.3%, 19.1% and 16.4% for the age subgroups 75–79 years, 80–84 years, and ≥ 85 years, respectively). Contradictorily, some studies showed that age was not independent prognostic factor affecting survival, performance status and treatments appeared as prognostic factors (Pal and Hurria 2010). Appropriately selected octogenarian patients with stage I NSCLC had a satisfactory long-term outcome when performed by surgical resection (Ganti et al. 2016; Matsuoka et al. 2005; Okami et al. 2009; Port et al. 2004).

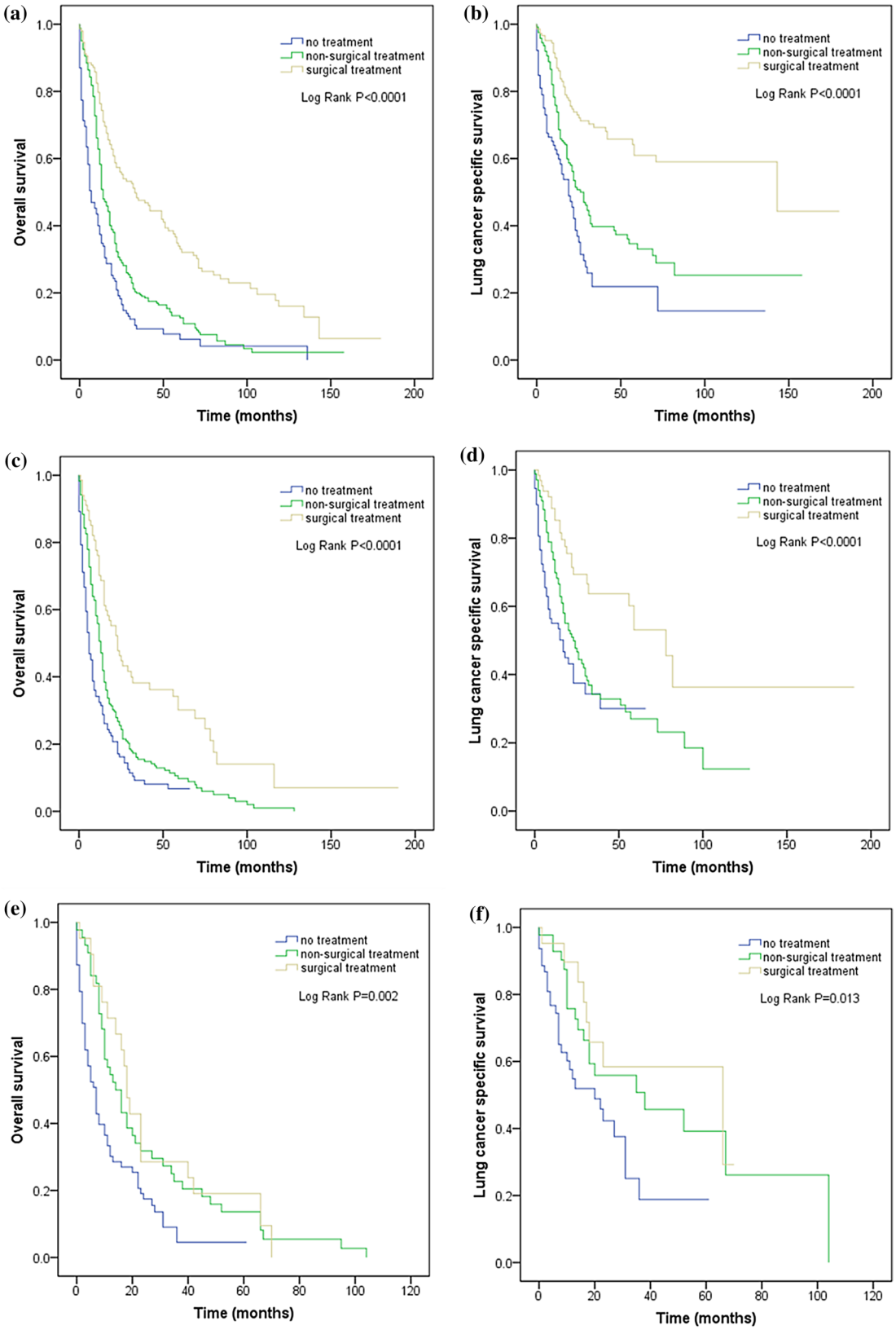

Fig. 2 Kaplan–Meier estimates of OS and LCSS for all 3 age groups based on treatment type. **a**, **b** patients aged 75–79 years, **c**, **d** patients aged 80–84 years, and **e**, **f** patients aged ≥ 85 years

Table 3 Adjusted hazards ratios for the effect of surgery, non-surgical treatment versus no treatment on OS and LCSS in each age subgroup

Subgroup	OS			LCSS		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age ≥ 75 years						
No treatment			< 0.0001			< 0.0001
Non-surgical treatment	0.609	0.480–0.772	< 0.0001[a]	0.596	0.434–0.818	< 0.0001[a]
Surgery	0.308	0.229–0.414	< 0.0001[b]	0.268	0.177–0.405	< 0.0001[b]
	0.506	0.391–0.655	< 0.0001[c]	0.449	0.309–0.653	< 0.0001[c]
Age ≥ 80 years						
No treatment			< 0.0001			< 0.0001
Non-surgical treatment	0.661	0.510–0.858	0.002[a]	0.715	0.500–1.023	0.067[a]
Surgery	0.360	0.250–0.518	< 0.0001[b]	0.323	0.193–0.543	< 0.0001[b]
	0.544	0.388–0.763	< 0.0001[c]	0.452	0.279–0.733	0.001[c]
Age ≥ 85 years						
No treatment			0.001			0.003
Non-surgical treatment	0.455	0.286–0.723	0.001[a]	0.399	0.202–0.791	0.008[a]
Surgery	0.416	0.230–0.750	0.004[b]	0.262	0.108–0.637	0.003[b]
	0.914	0.507–1.650	0.766[c]	0.656	0.266–1.615	0.359[c]

All *P* adjusted for gender, race, primary site, grade, year of diagnosis

[a]*P* for comparison of untreated group vs non-surgical group

[b]*P* for comparison of untreated group vs surgery group

[c]*P* for comparison of non-surgical group vs surgery group

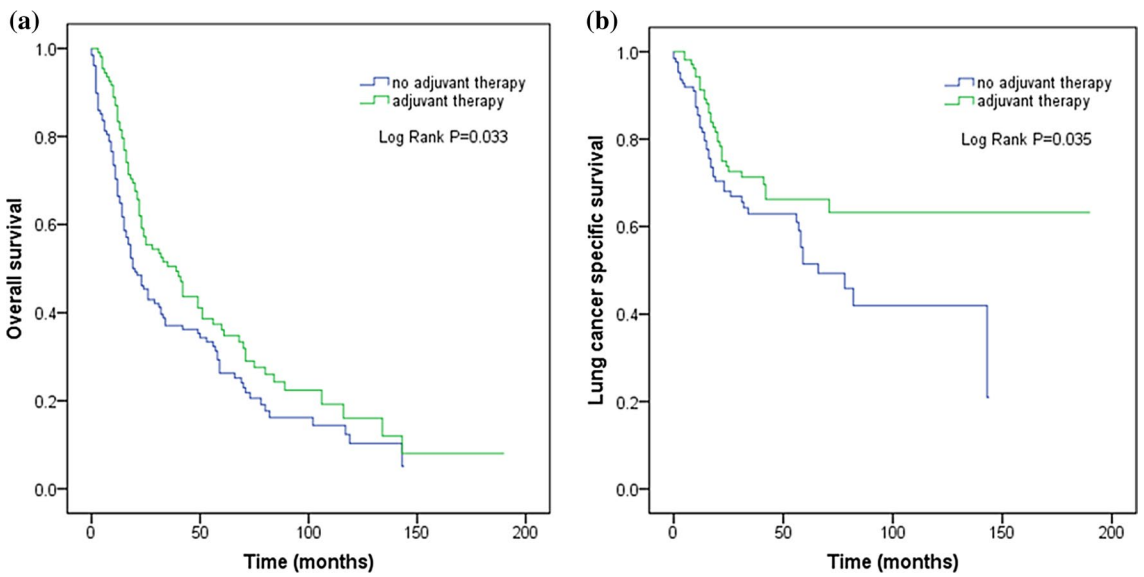

Fig. 3 OS and LCSS of patients stratified by no adjuvant therapy versus adjuvant therapy

The median OS of the surgery group was significantly longer than non-surgical group in our study. By subgroup analysis, we found that the clinical benefit of surgery was observed in patients aged 75–79 years old and even in populations aged 80–84 years old who traditionally assumed less likely to benefit from lung resection. In the 85 years and older group, patients who received surgical or non-surgical treatment had a better OS and LCSS than those who received no treatment, while no significant difference between surgical and non-surgical treatment was observed. Based on our study, surgery might be an accepted element of multimodality treatment in elder patients aged 75–84 years. Furthermore, we analyzed the role of postoperative adjuvant therapy in elderly patients. There was a survival benefit for postoperative adjuvant therapy compared with operation alone.

The present study had some limitations. First, as a retrospective analysis, inherent selection bias was inevitable; it is possible that patients in the surgery group were healthier than those in non-surgical group and untreated group. Second, SEER database did not include specific details regarding chemotherapy/radiotherapy regimens, performance status, comorbid conditions and so on.

In summary, stage I SCLC patients aged 75–84 years appeared to benefit from surgical resection, with a 5-year OS rate of 30.4% and 5-year LCSS rate of 57.7%, and the performance of surgical resection might be one promising treatment for elder patients with stage I SCLC in future.

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Compliance with ethical standards

Conflict of interest Authors declare that they have no conflicts of interest related to this paper.

Ethical approval No personal identifying information was used in the study. Hence, we did not require Institutional Review Board approval or patient informed consent.

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