Surgery in patients with small cell lung cancer: A period propensity score matching analysis of the Seer database, 2010-2015

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Abstract. Surgery as a therapeutic modality for non-small cell lung cancer is widely accepted in clinical practice. However, the role of surgery for small cell lung cancer (SCLC) remains controversial. Therefore, in the present study a period propensity score matching analysis using the Surveillance, Epidemiology and End Results (SEER) Registry database was performed to investigate the role of surgery on survival in patients with SCLC. Patients with SCLC between January 2010 and December 2015 were identified from the SEER database, and individual data for each case regarding general clinical characteristics, surgery of primary site (SPS), cause-specific death classification and survival time were retrieved. Differences of cause-specific survival (CSS) between subgroups were estimated by the log-rank test. Cox regression analysis was used to evaluate the effects of multiple variables on CSS, and differences between the incidences of cause-specific death were examined using a χ^2 test. A total of 1,707 records met the inclusion criteria and were retrieved for analysis. There were significant differences of CSS in the clinicopathological features of N (P=0.01), Stage (P<0.01) and Surgery (P<0.01) when comparing non-surgery with surgery, and in N (P<0.001), Stage (P=0.006) and Surgery (P=0.049) when comparing sublobectomy with lobectomy or bilobectomy (lobe/s). Patients who did not receive surgery (P<0.001) or who received sublobectomy (P=0.03) had an increased risk of mortality when compared with patients who received surgery and lobe/s. The findings of the present study indicate that surgery should be taken into consideration when an initial treatment strategy is made in patients for patients with SCLC at clinical stage I-IIA (T1-2,N0,M0), regardless of whether they are >50 years of age, their sex, histology and grade. The results suggest that certain patients with SCLC with stage IIB (N1) can also benefit from lobe/s, although further investigation is required. In addition, lobe/s is preferable to sublobectomy when surgery is performed. However, the present study was unable to comprehensively analyze the efficacy of pneumonectomy for SCLC.

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Introduction

Small cell lung cancer (SCLC) represents 13-15% of all lung cancer diagnoses in the United States between 2006 and 2017 (1,2). Similar to non-small cell lung cancer, the primary risk factor for SCLC remains smoking tobacco (3). Early diagnosis of SCLC is challenging due to the lack of specific symptoms and its extremely aggressive nature which is characterized by rapid tumor growth, quick doubling time and early metastasis. A statistically significant improvement in 2- and 5-year survival in limited- and extensive-stage SCLC cohorts from the Surveillance, Epidemiology, and End Results (SEER) Registry database, analyzed by Joinpoint regression, has been reported (1). However, the prognosis of patients with SCLC is poor with a 5-year survival rate of <5% and an average overall survival time of only 2-4 months for patients who do not receive effective treatment (4). At present, platinum and etoposide remain the preferred first-line chemotherapy regimen for the treatment of extensive-stage SCLC, and surgery is recommended for patients with limited-stage SCLC (5). Although SCLC is sensitive to chemotherapy and radiotherapy, the majority of patients relapse or progress after first-line therapy. Surgery in the form of lobectomy is a potential option for TNM stage I (T1-2N0M0) without mediastinal or supraclavicular involvement (6). However, the role of surgery in SCLC treatment remains controversial. Therefore, the present study performed a period propensity score matching analysis using the SEER database to examine the effects of surgery on survival in patients with SCLC.

Materials and methods

Patients and methods. This was a retrospective, population-based study using cases registered in the SEER database made publicly available through online access. Data were retrieved using the Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.3.5. Informed consent from the study population was waived, as the authors had no access to the identities of the patients, and no identifiable patient information was included.

Data collection. The following database was used for selection of cases: SEER Program (www.seer.cancer.gov) SEER*Stat Database: Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (2000-2015) <Katrina/Rita Population Adjustment> - Linked To County Attributes-Total U.S., 1969-2016 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission. Only patients with SCLC [based on International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) (7) codes: 8041/3-8045/3] between January 2010 and December 2015 were included in the present study. The exclusion criteria were: i) An ambiguous or unknown classification of observed clinical characteristics, ii) cause of death to site (COD) recode not as 'Alive' or 'Lung and Bronchus', iii) distant metastasis at the brain, liver and lung, iv) M1, v) T0 and finally vi) a survival time of <1 month (Fig. 1). Individual data for each case were retrieved from the database including sex, age at diagnosis, race, histology, grade, surgery to primary site (SPS), Tumor-Node-Metastasis (TNM) stage (8), COD and survival time.

Subgroup definitions. In the SEER database, grades were recorded as follows: i) Grade I, well differentiated; ii) grade II, moderately differentiated; iii) grade III, poorly differentiated and iv) undifferentiated and anaplastic. SPS was divided into: i) Non-surgery, no surgery of primary site; ii) Sublobectomy, Partial/Wedge/Segmental Resection, Lingulectomy, Partial Lobectomy, Sleeve Resection iii) lobe/s, lobectomy or bilobectomy; iv) Pneumonectomy. The T, N, M and Stage were recorded in the database accordingly to the AJCC cancer staging manual, 7th ed. (8).

Statistical analyses. Statistical analysis were performed using Stata 15.0 (Stata Corp. LLC). The propensity score matching was performed using the 'psmatch2' module in the software. Student's t-test was used to analyze the differences of means between two samples. Differences of cause-specific survival (CSS) between subgroups and the role of surgery in each subgroup was estimated using the Kaplan-Meier product method and compared by a log-rank test. Cox regression analysis was used to evaluate the effects of multiple variables on survival. The difference of incidence of COD was examined using χ^2 test. Quantitative data were converted into categorical data, with the exception of survival time. All statistical tests were two-sided and P<0.05 was considered to indicate a statistically significant difference.

Results

Patients selection and demography of included patients. Based on the patient selection criteria described previously (Fig. 1), 221,646 records of lung cancer between January 2010 and December 2015 were identified from the SEER database. Among them, 28,335 (12.78%) were SCLC, and 1,707 met the inclusion criteria of the present study and were subsequently extracted for analysis. After propensity score matching, 294 pairs were selected for comparison between non-surgery and surgery, 84 pairs were selected for comparison between sublobectomy and lobe/s and 10 pairs were selected for comparison between lobe/s and pneumonectomy. The results of the propensity score matching are presented in Tables I and II, and Fig. 2. Following matching, the clinicopathological features of grade, histology, stage, T and N were balanced in the non-surgery vs. surgery group, as well as T in the sub-lobectomy vs. lobe/s group and T and stage in the lobe/s vs. pneumonectomy group (P>0.05 in the matched groups; P<0.05 in the unmatched groups) (Table I). The mean and median biases in the matched groups were lower compared with those in the unmatched groups, and the overall differences in the clinicopathological features between the three different surgical groups were statistically insignificant (P=0.13, 0.96 and 0.28, respectively) (Table II; Fig. 2). Fig. 3 shows the distribution of survival time and age for each surgical group.

Role of surgery in SCLC. The potential prognostic factors were analyzed by univariate analysis using the Kaplan-Meier method and were compared with the log-rank test (Table III), which revealed that there were significant differences in CSS in N (P=0.01), Stage (P<0.001), and Surgery (P<0.001) when comparing non-surgery with surgery, and in N (P<0.001), Stage (P=0.006), and Surgery (P=0.049) when comparing sublobectomy with lobe/s (Fig. 4). However, the difference was not significant when comparing lobe/s with pneumonectomy. Cox regression analysis, (Table IV), which included all characteristics for clinical purposes revealed that the differences were significant for age [P<0.001; hazard ratio (HR)=1.21, 95% confidence interval (CI) 1.07-1.36] and surgery (P<0.001, HR 0.59, 95% CI, 0.47-0.76) when comparing non-surgery with surgery. However, no significant differences were detected when comparing sublobectomy with lobe/s, and lobe/s with pneumonectomy. The results of the survival functions of the clinicopathological features stratified by surgery are presented in Table V and Fig. 5. No statistical analysis was performed for certain subclinical features since the testing was not possible when no failures were observed and/or no observation was present in the database. There were significant differences among subgroups of 50-60 years, 70-80 years in age; male, female in sex; Caucasian in race; small cell cancer, not otherwise specified (NOS) in histology; grade III in grade; T1a in T; N0 in N; IA, IB in stage when comparing non-surgery with surgery. Significant differences were detected between 80-90 years in age and N0, N1 in N; IIA in stage when comparing sublobectomy with lobe/s (Table V). Although statistically insignificant, more patients in the following clinicopathological subgroups had survival benefits from surgery compared with non-surgery (Fig. 6): 60-70 and 80-90 years in age; Hispanic and African descent in Race; oat cell carcinoma, small cell carcinoma with intermediate cell, and

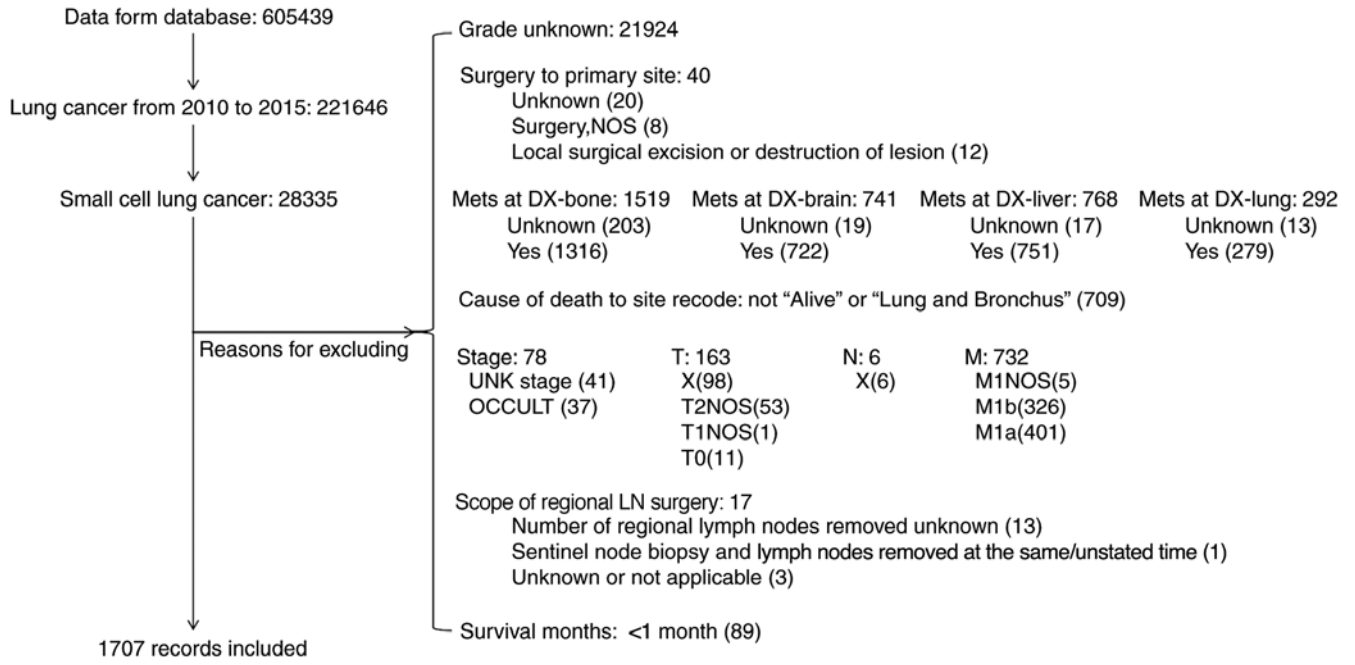

Figure 1. Diagram of data collection.

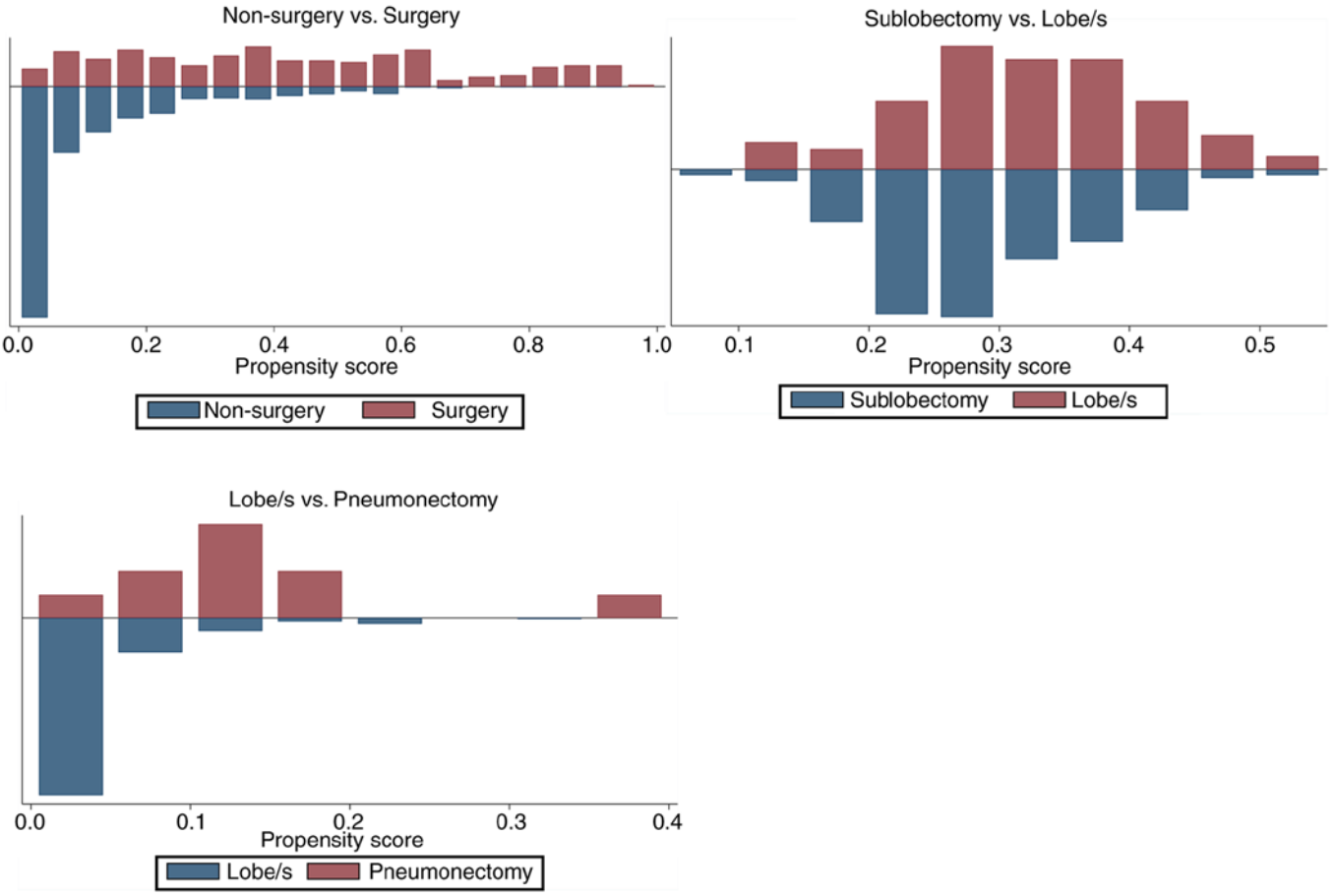

Figure 2. Histograms of propensity scores. Lobe/s, Lobectomy or bilobectomy.

combined small cell carcinoma in histology; Grade I, II, IV; T1b and T2a. Similar survival benefits in patients who received lobe/s compared with sublobectomy were observed in the following clinicopathological subgroups (Fig. 7): 60-70 years, 70-80 years in age; male and female in sex; African descent and Caucasian in race; small cell carcinoma with NOS and

Table I. Propensity score matching test between the surgery groups.

			Mean				t-test		
Surgery	Features	Un/Matched	Treated	Control	%bias	%reduct |bias|	t	P-value	V(T)/V(C)
Non-surgery vs. surgery	Sex	U	0.43197	0.43100	0.2		0.03	0.976	.
		M	0.43197	0.39116	8.2	-4,086.7	1.00	0.315	.
	Age	U	4.19730	4.19670	0.1		0.01	0.994	0.79[a]
		M	4.19730	4.37070	-17.3	-32,360.8	-2.15	0.032	0.87
	Grade (8)	U	3.35710	3.56480	-33.3		-5.66	<0.001	1.63[a]
		M	3.35710	3.30270	8.7	73.8	0.92	0.356	0.90
	Histology	U	2.07480	1.16140	67.6		14.41	<0.001	5.82[a]
		M	2.07480	1.91160	12.1	82.1	1.16	0.248	1.14
	Stage (8)	U	2.75170	4.77570	-131.9		-21.61	<0.001	1.33[a]
		M	2.75170	2.57480	11.5	91.3	1.29	0.197	0.96
	T (8)	U	2.54080	4.29650	-113.3		-17.05	<0.001	0.80
		M	2.54080	2.43200	7.0	93.8	0.90	0.366	1.00
	N (8)	U	0.60884	1.61220	-110.9		-16.30	<0.001	0.68[a]
		M	0.60884	0.54082	7.5	93.2	1.01	0.313	0.98
	Race	U	4.75170	4.68440	8.1		1.23	0.217	0.84
		M	4.75170	4.73810	1.6	79.8	0.21	0.836	0.98
Sub-lobectomy vs. lobe/s	Sex	U	0.40476	0.45000	-9.1		-0.70	0.485	.
		M	0.40476	0.38095	4.8	47.4	0.31	0.754	.
	Age	U	4.29760	4.17000	13.3		1.06	0.290	1.36
		M	4.29760	4.20240	10.0	25.4	0.63	0.529	1.22
	Grade (8)	U	3.40480	3.35000	7.9		0.61	0.541	1.03
		M	3.40480	3.36900	5.2	34.8	0.33	0.742	0.97
	Histology	U	1.85710	2.12500	-15.6		-1.18	0.240	0.85
		M	1.85710	1.61900	13.8	11.1	0.99	0.323	1.29
	Stage (8)	U	2.64290	2.74500	-6.0		-0.48	0.631	1.37
		M	2.64290	2.55950	4.9	18.4	0.32	0.751	1.34
	T (8)	U	2.22620	2.60500	-25.8		-2.04	0.042	1.29
		M	2.22620	2.20240	1.6	93.7	0.11	0.916	1.29
	N (8)	U	0.59524	0.60500	-1.2		-0.09	0.927	1.43
		M	0.59524	0.58333	1.4	-22.0	0.09	0.929	1.34
	Race	U	4.83330	4.73500	13.3		0.98	0.326	0.65
		M	4.83330	4.88100	-6.5	51.6	-0.50	0.616	1.33
Lobe/s vs. pneumonectomy	Sex	U	0.30000	0.45000	-30.6		-0.90	0.350	.
		M	0.30000	0.60000	-61.1	-100.0	-1.34	0.196	.
	Age	U	3.90000	4.17000	-23.4		-0.90	0.360	2.42
		M	3.90000	4.20000	-26.0	-11.1	-0.60	0.556	3.02
	Grade (8)	U	3.10000	3.35000	-31.8		-1.10	0.270	1.63
		M	3.10000	3.20000	-12.7	60.0	-0.25	0.806	0.91
	Histology	U	2.90000	2.12500	40.6		1.30	0.190	1.28
		M	2.90000	3.40000	-26.2	35.5	-0.55	0.591	0.96
	Stage (8)	U	3.80000	2.74500	66.5		2.10	0.040	1.09
		M	3.80000	3.80000	0.0	100.0	0.00	1.000	1.2
	T (8)	U	3.90000	2.60500	87.1		2.90	<0.001	1.35
		M	3.90000	4.00000	-6.7	92.3	-0.14	0.891	0.95
	N (8)	U	0.80000	0.60500	25.0		0.80	0.440	1.05
		M	0.80000	0.80000	0.0	100.0	0.00	1.000	1.56
	Race	U	4.40000	4.73500	-31.5		-1.20	0.220	2.43
		M	4.40000	4.10000	28.2	10.4	0.53	0.605	0.97

[a]If variance ratio outside (0.79; 1.26) for U and (0.79; 1.26) for M. Lobe/s, Lobectomy or bilobectomy; %bias, standardized percentage bias; %reduct |bias|, achieved percentage reduction in bias.

Table II. The efficacy of the propensity score matching.

Group	Sample (n)	Ps R2	LR χ^2	P>χ^2	MeanBias	MedBias	B	R	%Var
Non-surgery vs. surgery	Unmatched (1,413)	0.309	484.81	<0.01	58.20	50.50	157.8[a]	1.15	71.00
	Matched (294)	0.015	12.59	0.13	9.30	8.50	29.4[a]	1.22	0.00
Sublobectomy vs. lobe/s	Unmatched (200)	0.030	10.19	0.25	11.50	11.20	41.5[a]	1.09	0.00
	Matched (84)	0.011	2.53	0.96	6.00	5.10	24.50	1.40	0.00
Lobe/s vs. pneumonectomy	Unmatched (200)	0.161	12.98	0.11	42.10	31.70	111.8[a]	1.78	0.00
	Matched (10)	0.353	9.78	0.28	20.10	19.40	109.9[a]	7.50*	0.00

[a]B>25%, R outside (0.5; 2); B, absolute standardized difference of the means of the linear index of the propensity score in the unmatched and matched groups; R, ratio of unmatched to matched variances of the propensity score index; %Var, the percentage of continuous variables that have variance ratios that exceed the 2.5th and 97.5th percentiles of the F-distribution; Lobe/s, lobectomy or bilobectomy.

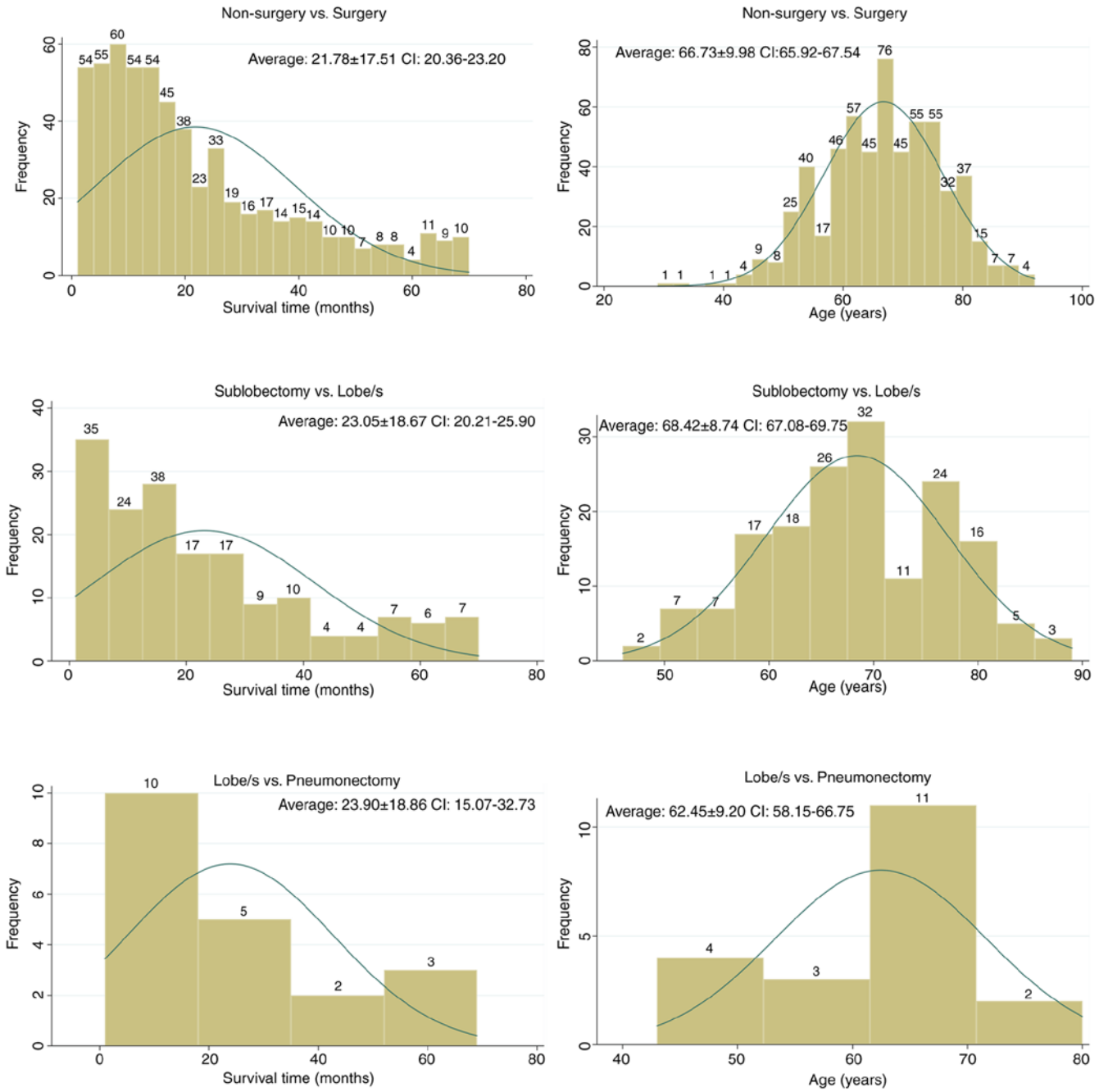

Figure 3. Distribution of survival time and age. Emerald curve, Normal-density plot. Lobe/s, Lobectomy or bilobectomy.

Table III. Demographics of the included patients and results of univariate analysis.

A, Non-surgery vs. surgery group

Features	NP	NE	NEE	P-value
Age, years				0.341
<40	3	2	2.02	
≥40, <50	22	10	12.62	
≥50, <60	114	51	60.07	
≥60, <70	214	91	98.62	
≥70, <80	178	92	79.70	
≥80, <90	53	28	21.19	
≥90, <100	4	2	1.78	
Sex				0.714
Male	252	118	120.99	
Female	336	158	155.01	
Race				0.279
Hispanic	15	5	7.69	
AI/AN	2	0	0.09	
API	12	7	5.15	
African descent	52	17	27.18	
Caucasian	506	247	235.81	
Unknown	1	0	0.09	
Histology				0.678
SCC, NOS	462	222	213.83	
OCC	11	5	5.69	
SCC, IC	4	2	2.89	
CSCC	111	47	53.59	
Grade (8)				0.149
I	10	2	3.93	
II	23	7	14.32	
III	281	127	125.92	
IV	274	140	131.83	
T (8)				0.135
T1a	189	86	92.83	
T1b	128	60	63.02	
T2a	173	77	79.92	
T2b	29	19	10.54	
T3	53	25	21.82	
T4	16	9	7.86	
N (8)				0.007
0	360	150	176.48	
1	105	54	45.92	
2	116	69	51.28	
3	7	3	2.33	
Stage (8)				0.003
IA	190	77	99.00	
IB	112	44	53.56	
IIA	108	56	45.88	
IIB	31	13	13.80	
IIIA	135	80	57.93	
IIIB	12	6	5.84	
Surgery				<0.001
No	294	161	125.40	
Yes	294	115	150.60	

Table III. Continued.

B, Sublobectomy vs. lobe/s group

Features	NP	NE	NEE	P-value
Age, years				0.384
<40	N/A	N/A	N/A	
≥40, <50	2	2	0.79	
≥50, <60	28	9	13.77	
≥60, <70	61	22	21.40	
≥70, <80	57	25	23.78	
≥80, <90	20	8	6.26	
≥90, <100	N/A	N/A	N/A	
Sex				0.586
Male	56	25	22.92	
Female	112	41	43.08	
Race				0.979
Hispanic	2	1	0.70	
AI/AN	N/A	N/A	N/A	
API	N/A	N/A	N/A	
African descent	8	4	4.17	
Caucasian	157	61	61.07	
Unknown	1	0	0.06	
Histology				0.743
SCC, NOS	144	57	55.32	
OCC	1	0	0.36	
SCC, IC	N/A	N/A	N/A	
CSCC	23	9	10.31	
Grade (8)				0.355
I	4	0	1.38	
II	5	1	2.54	
III	72	27	29.03	
IV	87	38	33.05	
T (8)				0.258
T1a	85	29	37.15	
T1b	27	11	11.03	
T2a	36	15	11.00	
T2b	2	2	0.85	
T3	12	6	3.82	
T4	6	3	2.15	
N (8)				<0.001
0	108	33	46.06	
1	23	12	6.44	
2	35	19	13.11	
3	2	2	0.39	
Stage (8)				0.006
IA	70	21	32.86	
IB	25	6	8.97	
IIA	22	12	6.30	
IIB	8	3	2.76	
IIIA	39	21	13.51	
IIIB	4	3	1.60	
Surgery				0.049
No	84	26	33.90	
Yes	84	40	32.10	

Table III. Continued.

C, Lobe/s vs. pneumonectomy group

Feature	NP	NE	NEE	P-value
Age, years				0.210
<40	-	-	-	
≥40, <50	2	1	1.27	
≥50, <60	4	1	0.85	
≥60, <70	10	8	4.75	
≥70, <80	3	0	2.44	
≥80, <90	1	0	0.68	
≥90, <100	N/A	N/A	N/A	
Sex				0.544
Male	6	3	3.91	
Female	14	7	6.09	
Race				0.632
Hispanic	1	0	0.68	
AI/AN	1	0	<0.001	
API	1	1	0.31	
African descent	4	2	1.68	
Caucasian	13	7	7.33	
Unknown	N/A	N/A	N/A	
Histology				0.235
SCC, NOS	7	2	3.62	
OCC	N/A	N/A	N/A	
SCC, IC	1	0	0.88	
CSCC	12	8	5.50	
Grade (8)				0.438
I	1	1	0.31	
II	4	2	2.83	
III	8	3	3.97	
IV	7	4	2.90	
T (8)				0.113
T1a	1	0	0.88	
T1b	N/A	N/A	N/A	
T2a	5	2	3.14	
T2b	2	1	0.17	
T3	8	4	4.28	
T4	4	3	1.52	
N (8)				0.710
0	6	2	3.09	
1	9	5	4.59	
2	5	3	2.32	
3	N/A	N/A	N/A	
Stage (8)				0.650
IA	1	0	0.88	
IB	2	1	1.27	
IIA	3	1	1.19	
IIB	1	0	0.88	
IIIA	12	7	5.30	
IIIB	1	1	0.48	

Table III. Continued.

Feature	NP	NE	NEE	P-value
Surgery				0.185
No	10	6	4.02	
Yes	10	4	5.98	

Lobe/s, lobectomy or bilobectomy; NP, Number of Patients; NE, Number of Events; NEE, Number of Expected Events; AI/AN, American Indian/Alaska Native; API, Asian or Pacific Islander; SCC, Small cell carcinoma; OCC, Oat cell carcinoma; IC, Intermediate cell; CSCC, Combined small cell carcinoma; N/A, No observation in the database.

combined small cell carcinoma in histology; Grade III and IV; T1a and T1b. Generally, patients who did not receive surgery (P<0.001) or received sublobectomy (P=0.03) were at an increased risk of mortality when compared with patients who received surgery or lobe/s respectively (Table VI). Fig. 8 shows the cumulative survival curves of each group.

Discussion

As SCLC responds to chemotherapy and radiotherapy, surgical treatment is considered to be an option for stage I-IIA (T1-2, N0, M0) SCLC (9,10). The most recent National Comprehensive Cancer Network (NCCN) guidelines recommend that patients with SCLC at clinical stage I-IIA (T1-2, N0, M0) after a standard staging evaluation may be eligible for surgical resection (9). After analyzing the SEER database, Schreiber *et al* (11) concluded that the use of surgery, and particularly lobectomy, in selected patients with limited-stage SCLC was associated with improved survival outcomes. However, there was inherent selection bias in their study (11). Therefore, the present study performed the period propensity score matching analysis using the SEER database to further examine the role of surgery on survival in patients with SCLC.

Following propensity score matching analysis, the present study identified that the clinicopathological features of N stage and surgery were important factors for postoperative CSS in patients with SCLC who received surgery, including sublobectomy, lobe/s and pneumonectomy. This finding was corroborated by the results of previous studies (5,11,12). The IASLC proposals (12) demonstrated that there was a significant difference in the survival of patients who underwent surgery between N0 patients and those with node-positive disease for both clinical and pathological staging, independent of T category. Takenaka *et al* (5) reported that the 5-year survival rates of the patients with SCLC with or without surgical resection, according to the clinical stage were as follows: 62 and 25% in stage I (P<0.01), 33 and 24% in stage II (P=0.95) and 18 and 18% in stage III (P=0.35). The study of Schreiber *et al* (11) also demonstrated that the overall survival for patients with SCLC with N0, N1 and N2 who received surgery were significantly improved, when compared with those who did not receive surgery (P<0.01). In addition, the significance of surgery was corroborated following Cox regression analysis (P<0.001) (Table IV). These results suggested that the role of surgery for patients with SCLC was significant.

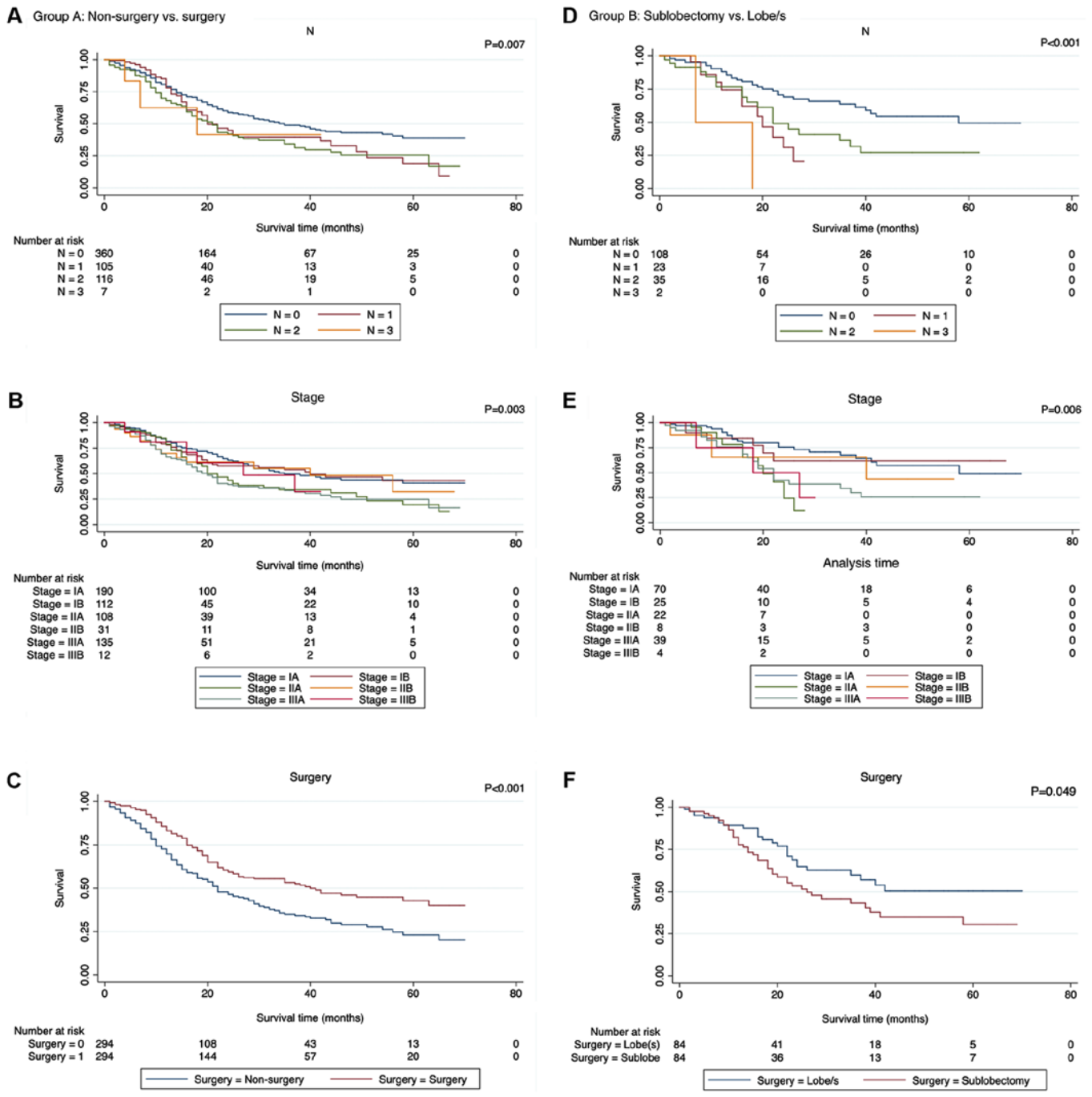

Figure 4. Potential prognostic factors analyzed by Kaplan-Meier. (A) N stage, (B) stage and (C) surgery comparing non-surgery with surgery and (D) N stage, (E) stage and (F) surgery comparing sublobectomy with lobe/s. Lobe/s, lobectomy or bilobectomy.

To further identify who would benefit from surgery, the survival functions of surgery stratified by the clinicopathological features were analyzed using log-rank tests (Table V). The results revealed that patients who did not receive surgery in any of the subgroups, including sex, histology and grade had an increased risk of COD compared with patients who received surgery. These results suggest that surgery should be performed irrespective of sex, histology, grade and clinicopathological features. Previous studies have reported that increasing age was an independent adverse prognostic factor in SCLC (13-15). However, the results of the present study demonstrated that patients between 50 and 90 years of age benefited from surgery, although analysis was not tested in the subgroups of age <40 years or between 90 and 100 years. Furthermore, age was an independent prognostic factor (P<0.001; Table IV), which suggested that surgery should also be performed even in elderly patients with SCLC. This result was similar with the treatment of thoracic irradiation for limited-stage SCLC, in which it was reported that in the dose range examined, age did not appear to have an effect on the delivery, tolerance or efficacy of TI in the combined modality management of SCLC (16). Concerning T, there was significant difference in the T1a subgroup (P<0.001) and better survival trends in the T1b and T2a subgroups. Furthermore, patients

Table IV. Multivariate analysis of different surgery types.

A, Non-surgery vs. surgery group

	Multivariate analysis		
Characteristic	Hazard ratio	95% Confidence interval	P-value
Age	1.21	1.07-1.36	<0.01
Sex	0.97	0.76-1.23	0.78
Race	1.11	0.92-1.35	0.27
Histology	0.98	0.90-1.06	0.60
Grade	1.11	0.91-1.36	0.29
T	1.13	0.98-1.30	0.09
N	1.27	0.85-1.88	0.24
Stage	1.01	0.81-1.27	0.92
Surgery	0.59	0.47-0.76	<0.01

B, Sublobectomy vs. lobe/s group

	Multivariate analysis		
Characteristic	Hazard ratio	95% Confidence interval	P-value
Age	1.23	0.94-1.61	0.92
Sex	1.03	0.61-1.71	0.92
Race	0.84	0.51-1.40	0.51
Histology	0.99	0.81-1.20	0.91
Grade	1.64	1.03-2.60	0.29
T	1.27	1.00-1.63	0.05
N	2.04	0.90-4.64	0.09
Stage	0.83	0.52-1.32	0.92
Surgery	1.67	0.96-2.90	0.07

C, Lobe/s vs. Pneumonectomy group

	Multivariate analysis		
Characteristic	Hazard ratio	95% Confidence interval	P-value
Age	0.28	0.05-1.47	0.13
Sex	0.22	0.03-1.58	0.13
Race	0.20	0.03-1.59	0.51
Histology	2.47	0.93-6.52	0.07
Grade	0.77	0.18-3.37	0.73
T	2.80	0.20-39.85	0.45
N	0.86	0.13-5.87	0.88
Stage	2.06	0.12-34.16	0.61
Surgery	2.39	0.18-32.14	0.51

Lobe/s, lobectomy or bilobectomy.

with SCLC with N0 (P<0.001) and stage Ia (P<0.001) and Ib (P<0.001) would have an increased benefit from surgery. These results, which were in accordance with those reported by the IASLC (12), clarified why the most recent NCCN guidelines

Table V. Survival functions of clinicopathological features stratified by surgery.

A. Non-surgery vs. surgery group

	Non-surgery		Surgery		
Feature	NE	NEE	NE	NEE	P-value
Age, years					<0.01
<40	2	2.0	NT	NT	NS
≥40, <50	6	6.2	4	3.8	0.91
≥50, <60	33	20.8	18	30.2	<0.01
≥60, <70	46	39.6	45	51.4	0.17
≥70, <80	53	39.8	39	52.2	<0.01
≥80, <90	19	15.5	9	12.5	0.17
≥90, <100	2	2.0	NT	NT	NS
Sex					<0.01
Male	65	54.0	53	64.0	0.04
Female	96	71.3	62	86.7	<0.01
Race					<0.01
Hispanic	2	1.9	3	3.1	0.89
AI/AN	NT	NT	NT	NT	NS
API	3	3.1	4	3.9	0.91
African descent	9	8.1	8	8.9	0.66
Caucasian	147	111.3	100	135.7	<0.01
Histology					<0.01
SCC, NOS	139	113.5	83	108.5	<0.01
OCC	5	4.2	0	0.8	0.29
SCC, IC	2	0.8	0	1.2	0.09
CSCC	15	9.7	32	37.3	0.05
Grade (8)					<0.01
I	1	0.5	1	1.5	0.37
II	3	2.0	4	5.0	0.42
III	77	55.6	50	71.4	<0.01
IV	80	69.5	60	70.5	0.07
T (8)					<0.01
T1a	56	34.5	30	51.5	<0.01
T1b	42	36.8	18	23.2	0.16
T2a	38	29.7	39	47.4	0.05
T2b	15	15.1	4	3.9	0.96
T3	7	9.1	18	15.9	0.36
T4	3	2.5	6	6.5	0.68
N (8)					<0.01
0	100	68.6	50	81.4	<0.01
1	22	24.3	32	29.7	0.49
2	38	32.2	31	36.8	0.15
3	1	1.8	2	1.2	0.31
Stage (8)					<0.01
IA	50	31.1	27	45.9	<0.01
IB	31	20.8	13	23.2	<0.01
IIA	32	32.0	24	24.0	1.00
IIB	7	7.2	6	5.9	0.93
IIIA	39	33.5	41	46.5	0.20
IIIB	2	2.7	4	3.3	0.58

Table V. Continued.

B, Sublobectomy vs. lobe/s group

Feature	Sub-lobectomy NE	Sub-lobectomy NEE	lobe/s NE	lobe/s NEE	P-value
Age, years					0.05
<40	N/A	N/A	N/A	N/A	NS
≥40, <50	2	2.0	NT	NT	NS
≥50, <60	5	5.5	4	3.5	0.75
≥60, <70	12	9.6	10	12.4	0.30
≥70, <80	14	11.3	11	13.7	0.28
≥80, <90	7	4.0	1	4.1	0.03
≥90, <100	N/A	N/A	N/A	N/A	NS
Sex					0.06
Male	17	14.9	8	10.1	0.38
Female	23	17.7	18	23.3	0.09
Race					0.05
Hispanic	1	1.0	NT	NT	NS
AI/AN	N/A	N/A	N/A	N/A	N/A
API	N/A	N/A	N/A	N/A	NS
African descent	3	2.8	1	1.2	0.81
Caucasian	36	28.4	25	32.6	0.05
Histology					0.04
SCC, NOS	32	25.1	25	31.9	0.06
OCC	NT	NT	NT	NT	NS
SCC, IC	N/A	N/A	N/A	N/A	NS
CSCC	8	6.8	1	2.2	0.36
Grade (8)					0.06
I	NT	NT	NT	NT	NS
II	1	1.0	0	0.0	1.00
III	18	14.5	9	12.5	0.17
IV	21	17.0	17	21.0	0.19
T (8)					0.07
T1a	14	10.7	7	10.4	0.52
T1b	5	3.5	1	2.5	0.48
T2a	5	1.0	7	11.0	0.22
T2b	1	0.6	2	2.4	0.32
T3	12	12.6	9	8.4	0.24
T4	3	3.0	NT	NT	NS
N (8)					0.02
0	22	16.2	11	16.8	0.04
1	5	1.2	7	10.8	<0.001
2	11	12.2	8	6.8	0.56
3	2	2.0	NT	NT	NS
Stage (8)					0.02
IA	14	10.7	7	10.4	0.14
IB	5	3.5	1	2.5	0.20
IIA	5	1.0	7	11.0	<0.01
IIB	1	0.6	2	2.4	0.56
IIIA	12	12.6	9	8.4	0.77
IIIB	3	3.0	NT	NT	NS

Table V. Continued.

C, Lobe/s vs. Pneumonectomy group

Feature	lobe/s NE	lobe/s NEE	Pneumonectomy NE	Pneumonectomy NEE	P-value
Age, years					0.42
<40	N/A	N/A	N/A	N/A	NS
≥40, <50	NT	NT	1	1.0	NS
≥50, <60	0	0.0	1	1.0	1.00
≥60, <70	6	6.7	2	1.3	0.42
≥70, <80	NT	NT	NT	NT	NS
≥80, <90	NT	NT	NT	NT	NS
≥90, <100	N/A	N/A	N/A	N/A	NS
Sex					0.18
Male	2	1.2	1	1.9	0.3
Female	4	2.8	3	4.2	0.35
Race					0.24
Hispanic	NT	NT	NT	NT	NS
AI/AN	NT	NT	NT	NT	NS
API	1	1.0	N/A	N/A	NS
African descent	1	0.5	1	1.5	0.32
Caucasian	4	2.9	3	4.1	0.39
Histology					0.70
SCC, NOS	1	0.2	1	1.8	0.03
OCC	N/A	N/A	N/A	N/A	NS
SCC, IC	NT	NT	NT	NT	NS
CSCC	5	5.3	3	2.7	0.80
Grade (8)					0.20
I	1	1.0	NT	NT	NS
II	1	0.8	1	1.3	0.71
III	2	1.7	1	1.3	0.70
IV	2	0.9	2	3.1	0.14
T (8)					0.31
T1a	NT	NT	NT	NT	NS
T1b	N/A	N/A	N/A	N/A	NS
T2a	1	0.2	1	1.8	0.05
T2b	0	0.0	1	1.0	1.00
T3	3	2.9	1	1.1	0.91
T4	2	1.7	1	1.3	0.69
N (8)					0.24
0	0	0.5	2	1.6	0.45
1	4	2.1	1	2.9	0.06
2	2	1.8	1	1.2	0.78
3	N/A	N/A	N/A	N/A	NS
Stage (8)					0.48
IA	NT	NT	NT	NT	NS
IB	1	1.0	N/A	N/A	NS
IIA	1	0.5	0	0.5	0.32
IIB	NT	NT	NT	NT	NS
IIIA	4	3.6	3	3.4	0.74
IIIB	1	1.0	NT	NT	NS

Lobe/s, lobectomy or bilobectomy; NP, Number of Patients; NE, Number of Events; NEE, Number of Expected Events; AI/AN, American Indian/Alaska Native; API, Asian or Pacific Islander; SCC, Small cell carcinoma; OCC, Oat cell carcinoma; IC, Intermediate cell; CSCC, Combined small cell carcinoma; NT, No test possible because of no failures observed; N/A , No observation in the database.

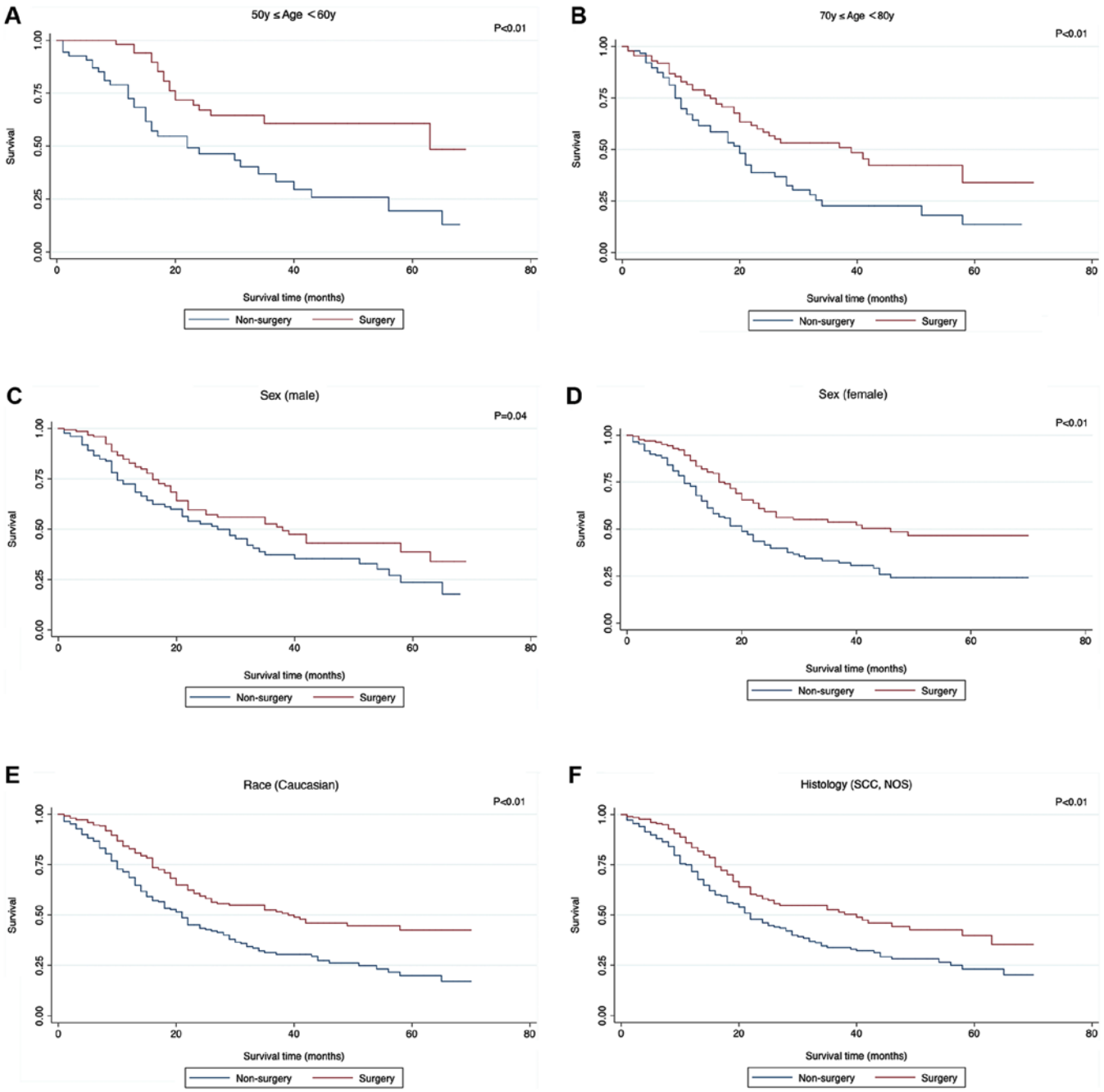

Figure 5. Significant survival functions of surgery stratified by clinicopathological features when comparing Non-surgery with surgery. (A) Age, ≥60 and <70 years; (B) age, ≥70 and <80 years; (C) sex, male; (D), sex, female; (E) race, Caucasian; (F) histology, SCC, NOS; SCC, small cell cancer; NOS, not otherwise specified.

recommend that patients with SCLC with clinical stage I-IIA (T1-2, N0, M0) after a standard staging evaluation may be considered for surgical resection (9).

As with the comparison of non-surgery with surgery, following propensity score matching analysis, the present study identified that the clinicopathological features of N, stage and surgery were important factors in postoperative CSS in patients with SCLC who received sublobectomy compared with those who received lobe/s. However, no independent prognostic factor was identified in the Cox regression model.

When the survival functions of surgery stratified by clinicopathological features were analyzed using log-rank tests (Table V), more patients who received sublobectomy in all subgroups of sex, histology were at risk of COD compared with those who received lobe/s. On the other hand, the results also demonstrated that there were more patients between 60 and 90 years of age, who benefited from lobe/s, although this analysis was not performed in the subgroups ages <50 years, as no failure events were observed, and in the subgroups ages <40 years and between 90 and 100 years, due to the absence of observations. Another study comparing treatment strategies for stage I SCLC using the National Cancer Database (17) demonstrated that lobectomy was associated with an improved survival compared with limited resection (HR 0.64; 95% CI, 0.53-0.78; P<0.001). Schreiber *et al* (11) revealed that the median survival time for lobectomy and sublobectomy was 40 and 23 months, respectively

Table VI. The incidence of cause of death to site.

Surgery	Alive	Death	Total	P
Non-surgery	133	161	294	<0.01[a]
Surgery	179	115	294	
Sublobectomy	44	40	84	0.03[a]
Lobectomy or bilobectomy	58	26	84	
Lobectomy or bilobectomy	4	6	10	0.37
Pneumonectomy	6	4	10	

[a]P<0.05.

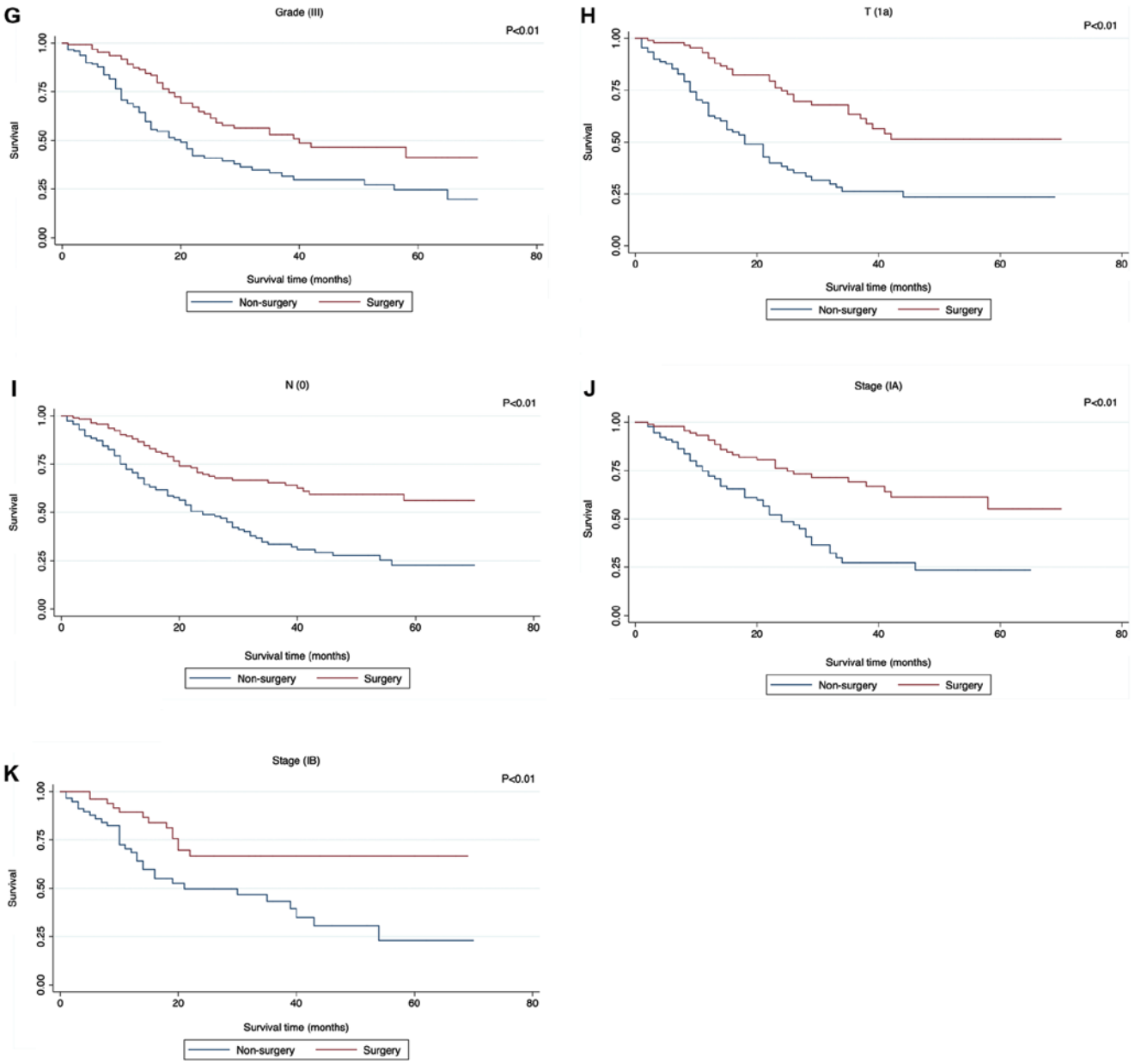

Figure 5. Continued. (G) grade III; (H) T1a; (I) N0; (J) Stage IA; (K) Stage IB. SCC, small cell cancer; NOS, not otherwise specified.

(P<001). These results confirmed that, similar with the NCCN recommendation (9), bi-/lobecotomy was the preferred operation for SCLC compared with sublobectomy, even in elder patients irrespective of sex and histology. When analyzing T, although

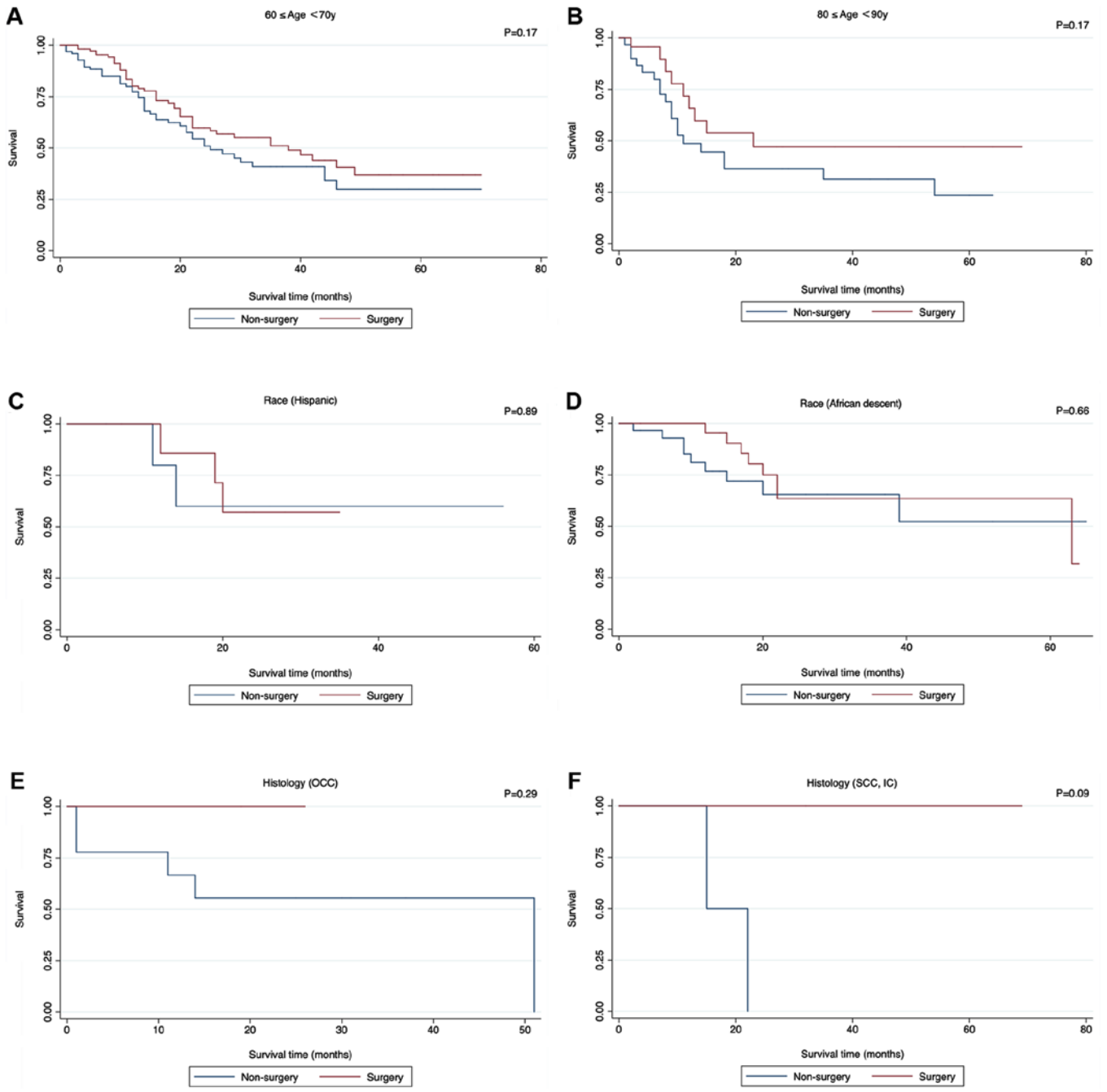

Figure 6. Insignificant survival functions of surgery stratified by clinicopathological features when comparing Non-surgery with surgery. (A) Age, ≥60 and <70 years; (B) age, ≥80 and <90 years; (C) race, Hispanic; (D); race, African descent; (E); histology, OCC; (F) histology, SCC, IC. OCC, Oat cell carcinoma; SCC, IC, Small cell carcinoma, Intermediate cell; CSCC, Combined small cell carcinoma.

there was no significant difference, it was the patients with SCLC with T1a to T2b, who had received lobe/s, who exhibited better survival trends. Simultaneously, the present study also demonstrated that more patients with N0-1, stage Ia-IIb who received sublobectomy, rather than lobe/s, were at risk of COD. Despite the recommendation in the most recent NCCN guidelines that patients with SCLC with clinical stage I-IIA (T1-2, N0, M0) after a standard staging evaluation may be considered for surgical resection (9) and multiple medical societies concluding that the survival advantage of surgical resection is only observed in patients with stage I disease (5,10,18,19), the results of the present study suggest that patients with SCLC with up to stage IIB (N1) may benefit from lobe/s. Combs *et al* (20) also stated that patients with stages I, II and III SCLC that underwent surgical resection as part of the initial treatment with chemotherapy may exhibit an improved overall survival rate.

Due to the inclusion criterion, only 10 patients who received pneumonectomy were included in the present study, and therefore results were too limited to be extensively discussed. Despite the large sample size, a limitation of the SEER database, and consequently of the present study, was the lack of information regarding performance and smoking status, which may have an important impact on postoperative survival, and the use of perioperative effective treatments,

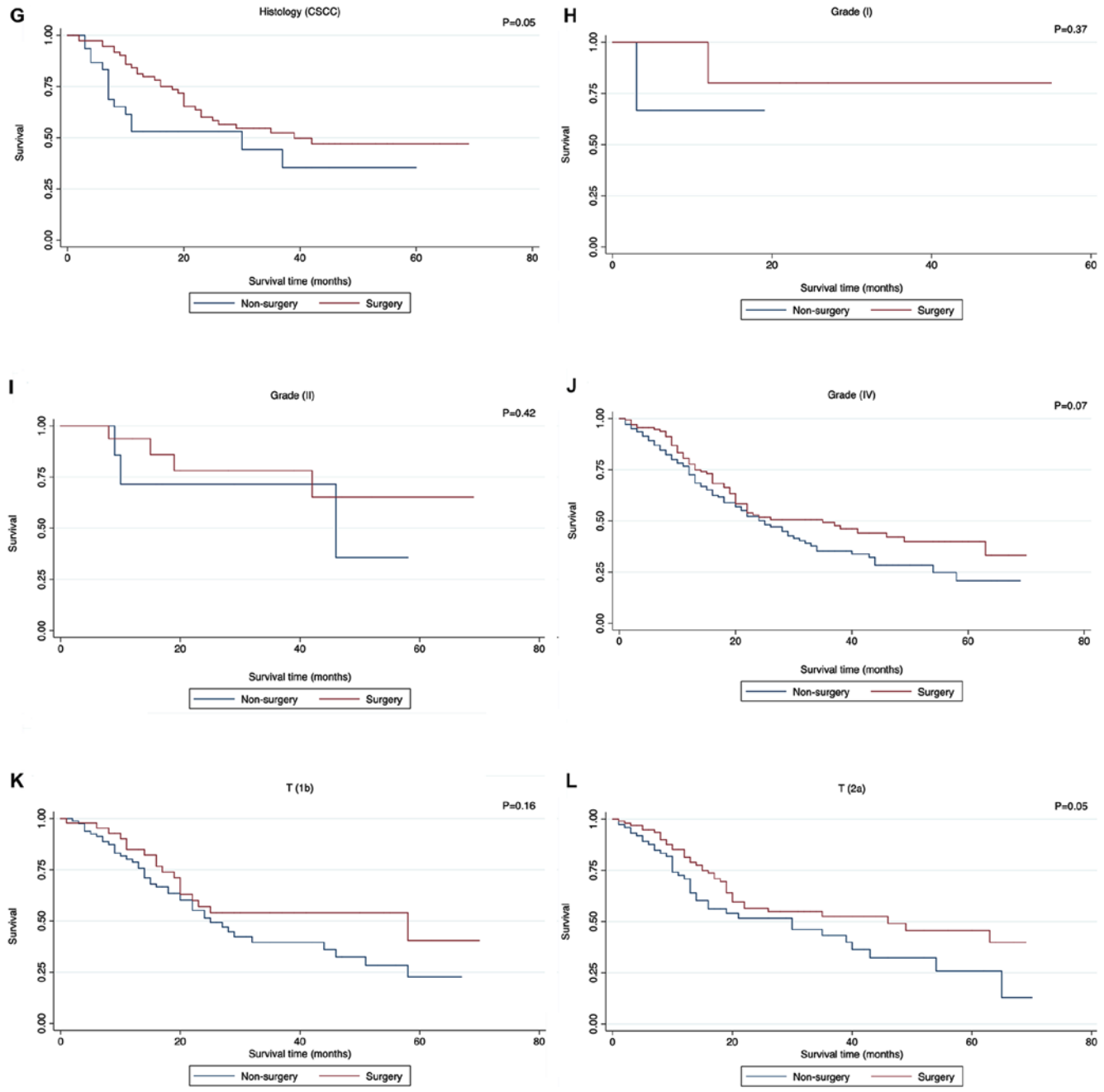

Figure 6. Continued. (G) Histology (CSCC); (H) Grade I; (I) Grade II; (J) Grade IV; (K) T1b; (L) T2a. CSCC, Combined small cell carcinoma.

including systemic therapy, mediastinal radiation therapy and prophylactic cranial irradiation. In addition, the different surgical types of lobectomy and bilobectomy were recorded as a single category 'lobectomy or bilobectomy', and the present study was unable to analyze the difference between them.

In conclusion, surgery should be taken into consideration when initial treatment strategy is made in patients with SCLC with a clinical stage I-IIA (T1-2, N0, M0), and should not be overlooked in patients >50 years, irrespective of sex, histology and the grade of the clinicopathological features. There is also evidence to suggest that certain patients with SCLC with stage IIB (N1) may also benefit from lobectomy or bilobectomy, although further investigation is required. In addition, lobe/s is preferred compared with sublobectomy when surgery is performed. However, the present study was unable to conclusively state the role of pneumonectomy for SCLC.

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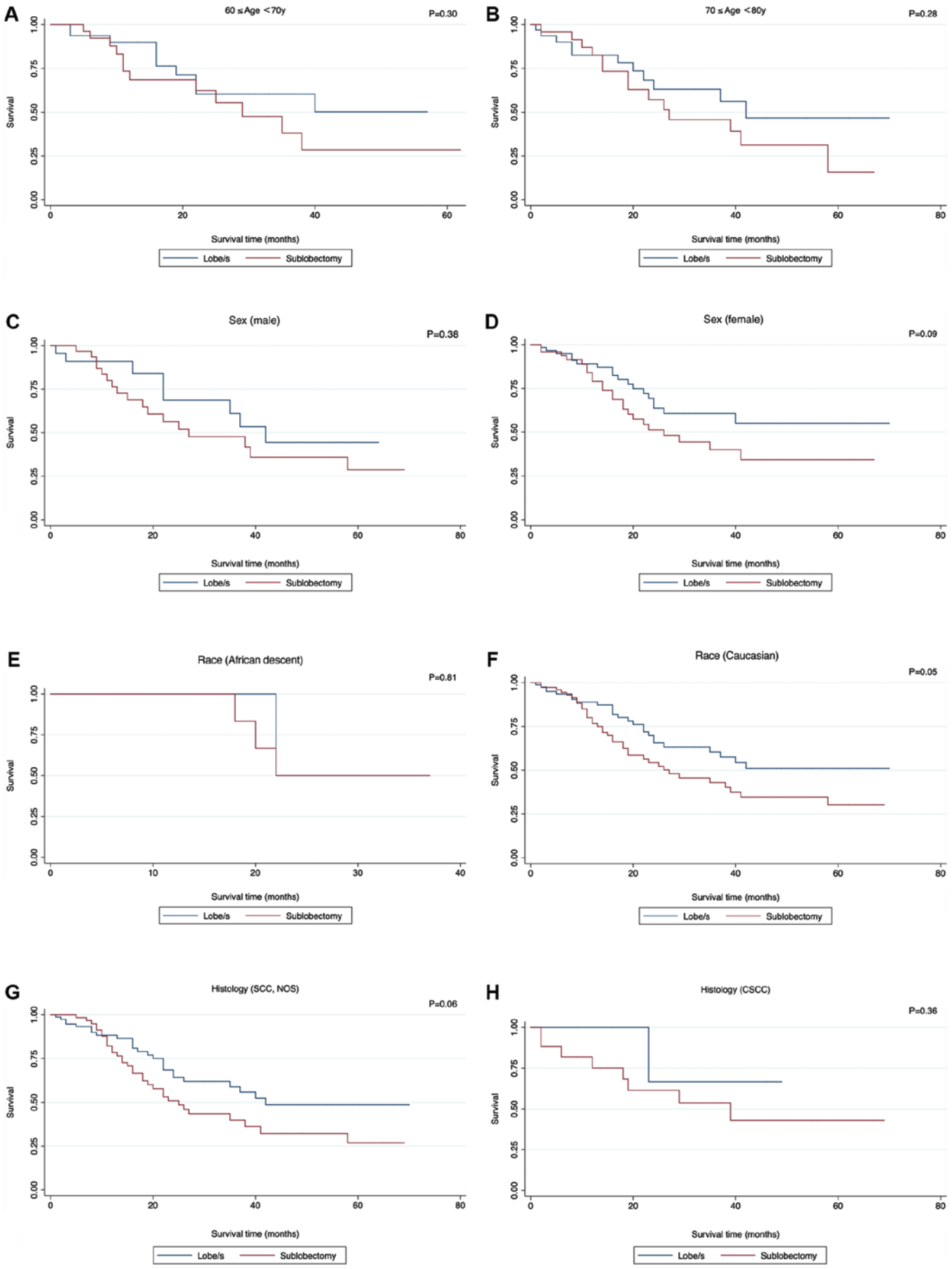

Figure 7. Insignificant survival functions of surgery stratified by clinicopathological features when comparing Sublobectomy with Lobe/s. (A) Age, ≥60 and <70 years; (B) age, ≥70 and <80 years; (C) sex, male; (D), sex, female; (E) race, African descent; (F) race, Caucasian; (G) histology, SCC, NOS; (H) histology, CSCC; SCC, small cell cancer; NOS, not otherwise specified; CSCC, combined small cell carcinoma.

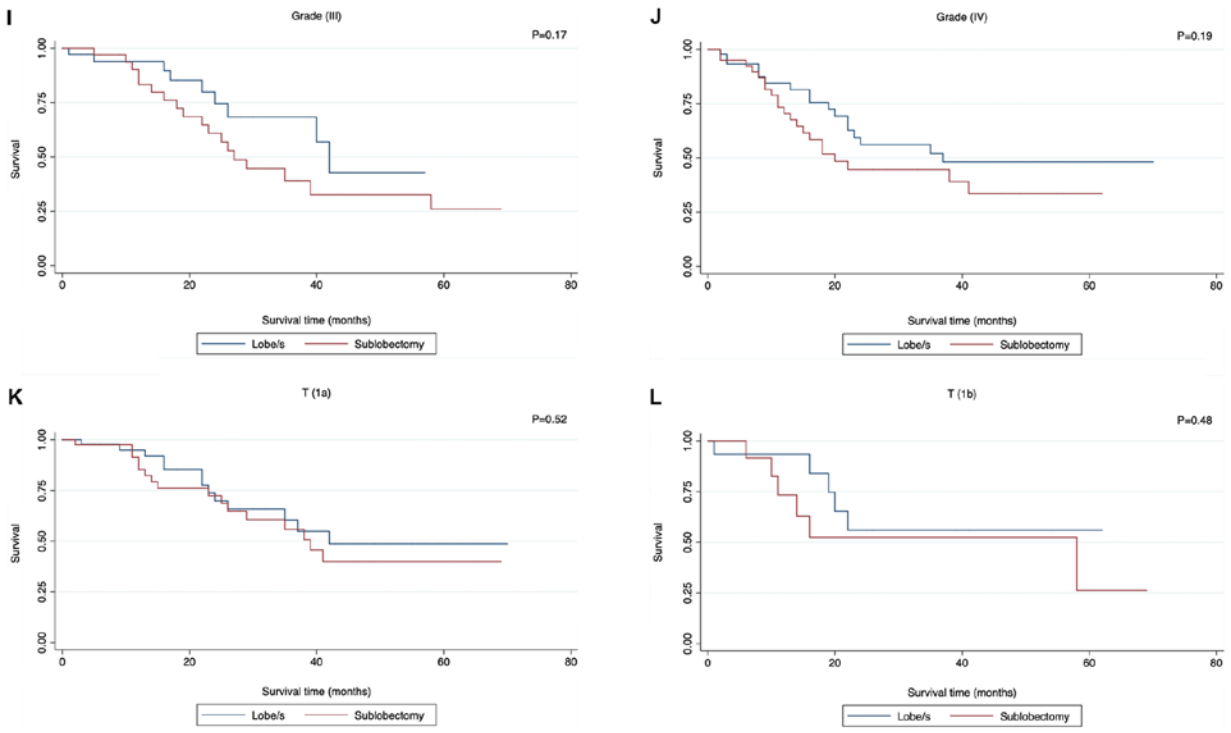

Figure 7. Continued. (I) grade III; (J) grade IV; (K) T1a; (L) T1b. SCC, small cell cancer; NOS, not otherwise specified; CSCC, combined small cell carcinoma.

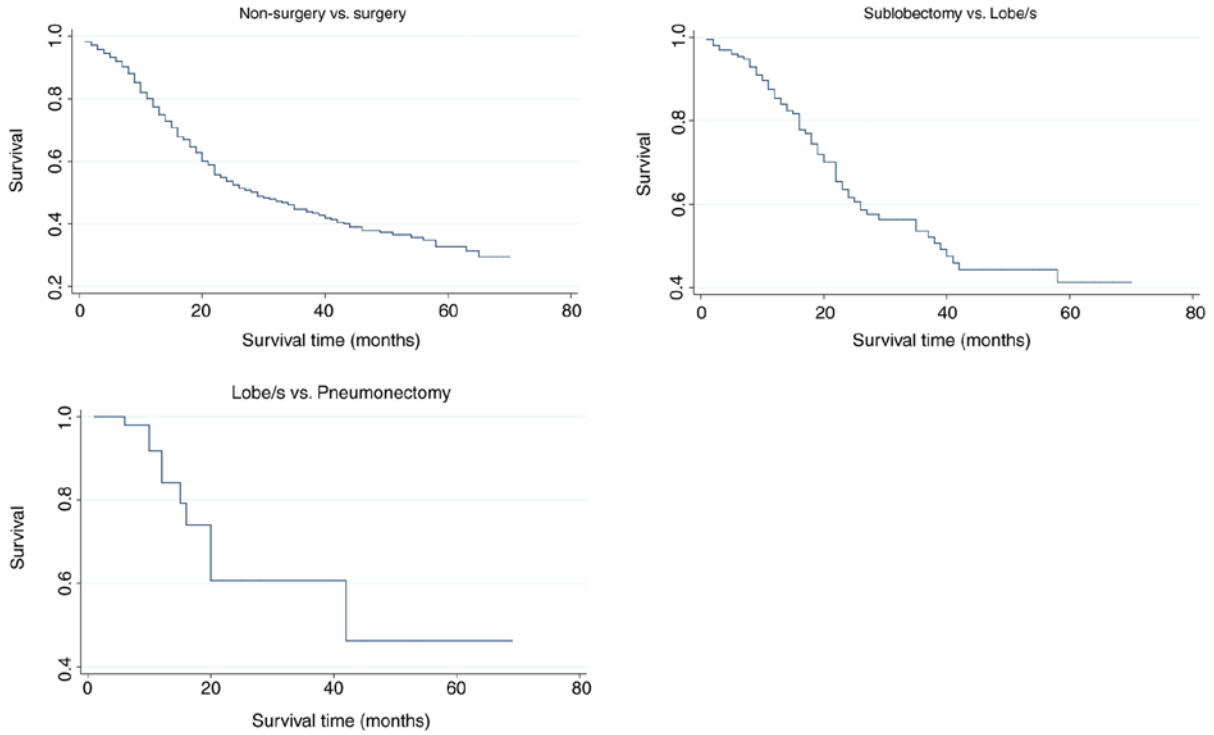

Figure 8. The cumulative survival curves at the mean value of the covariates. Lobe/s, Lobectomy or bilobectomy.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available in the Surveillance, Epidemiology, and End Results (SEER; www.seer.cancer.gov) Program SEER*Stat Database.

Authors' contributions

XD, DT, JX, WL, SY, HZ and JZ participated in the design of the study and performed statistical analysis. LL, ZT and XC contributed to the acquisition and interpretation of data and critically revised the article for intellectual content. All

authors were involved in the writing of the manuscript and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that there is no competing interests.

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