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Original Research

Improved survival of patients with stage III small-cell lung cancer with primary resection: A SEER-based analysis

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ABSTRACT

Introduction: : Small cell lung cancer (SCLC) is mostly diagnosed in stage III-IV patients and associated with poor prognosis. To date, surgery is no gold-standard treatment for any SCLC stage and evidence is lacking whether it is beneficial. Here we investigate the impact of surgery, with special attention to stage III SCLC patients, sub-stages and treatment combinations.

Methods: : The overall survival (OS) and cancer-specific survival (CSS) of 33,198 SCLC patients (SEER database) were analyzed retrospectively, using various statistical analyses, including propensity score matching (PSM), recursive partitioning, and sequential landmark analyses.

Results: : Independent of stage, the OS of patients with surgery-including treatments was almost always better than without surgery. This holds true for stage I-II patients, even after PMS analysis ($p < 0.017$). The same was found for stage IV patients that underwent surgery plus chemotherapy vs. chemotherapy alone ($p = 0.013$ after PSM). Stage III patients showed a robust improvement in OS and CSS after surgery (OS: 18 vs.13 months) or surgery plus chemotherapy (OS: 20 vs.15 months) as confirmed by well-balanced PSM and sequential landmark analyses of long-term survivors. More detailed analyses using two independent approaches showed prolonged OS in T3–4/N0–1 and T1–2/N2 stage III patients after surgery or surgery plus chemotherapy. Importantly, primary site surgery had a major survival advantage over surgery at regional sites ($p < 0.003$).

Conclusion: : Our study demonstrates that selected patients of all stages, including stage III T3–4/N0–1 and T1–2/N2, can benefit greatly from surgery-including treatments. Thus, surgery should be included into hospital treatment recommendations for specifically selected SCLC patients.

Condensed abstract

Primary resection in patients with stage III SCLC needs re-evaluation. Selected patients with stage III SCLC benefit significantly from surgery. Patients with T3–4/N0–1 and T1–2/N2 stage III SCLC should be considered for surgery.

Introduction

Small cell lung cancer (SCLC) accounts for approximately 15 % of all lung cancers, spreads early and rapidly, and has a poor prognosis. The median survival is 15–20 months, with only 5 % 2 year survival [1,2]. Chemotherapy and radiotherapy are the global standards of care for

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localized SCLC [1,3], and no clear evidence exists whether surgery improves the patients' outcome. Two randomized trials comparing surgery versus non-surgery, reported 30 decades ago that surgery is neither recommended nor opposed as part of a combination of treatments [4,5]. Notably, these studies are outdated and suffer from a substantial degree of bias with a relatively low quality of evidence [6].

In recent years, treatment guidelines in numerous areas of oncology have critically improved diagnosis, surgical tools, and treatment strategies [7]. A growing body of evidence supports surgical interventions in multimodal therapeutic approaches for early-stage SCLC patients [8,9]. However, according to the SEER patient cohort, approximately 25 % of SCLC patients have stage III when first diagnosed (Fig. 1). Although these patients usually respond well to chemotherapy initially, their overall prognosis remains poor, with only about 10 months of overall survival (OS) [6]. Currently, surgery is only suggested in exceptional cases for stage III patients [7], due to the uncertainty of the burden versus the benefit of a locally aggressive surgery. This results in scarcity of retrospective and prospective studies in large patient cohorts [10,11,12,13,14]. Combs et al. analyzed data from the National Cancer Database (NCDB, 1998–2011) from stage III SCLC patients undergoing surgery, reported that surgery does not appear to affect the prognosis of certain types of stage III patients [10]. This leads to hesitancy in considering surgical options in guideline administrations [1,15], and additional evidence is lacking to better guide treatment options [7,16]. To overcome this, the Surveillance, Epidemiology and End Results (SEER) program was used in this study to evaluate OS and/or cancer-specific survival (CSS) in stage I-IV SCLC patients treated using a variety of therapeutic approaches, including thoracic surgery.

Materials and methods

Patient selection and study design

The clinical database 'SEER program' collects cancer incidence, prevalence, and survival data from the U.S. Cancer Registry, covering approximately 28 % of the U.S. population from 18 states and representing all regions of the country [17]. Patient data for our study were retrieved from the SEER database according to the American Joint Commission on Cancer (AJCC) 7th edition for staging of tumor lymph node metastases (TNM). Eligible recruitment criteria: men and women aged >18 years, diagnosed with stage I-IV SCLC between 1975 and 2016, and pathological diagnosis of primary malignancies in lung and bronchus. All patients were pathologically confirmed before surgery. 33,198 patients with or without surgery were identified with stage I-IV SCLC, with complete clinical information on race, grading, staging, histology, health insurance, marital status, tumor size/lymph node (T/N) staging, chemotherapy, radiotherapy, and regional/distant surgical resection. To investigate the effects of surgery, all selected patients were divided into comparison modalities for simultaneous presentation, mainly comparing patients treated with chemotherapy or chemoradiation with or without surgery, or chemoradiation versus chemotherapy combined with surgery. Notably, although incorporation of different treatment paradigms is important, we unfortunately lack temporal data for each intervention paradigm, encompassing the timing and interval of each treatment. Therefore, the therapeutic paradigms mentioned here, may be single episodes of disease states.

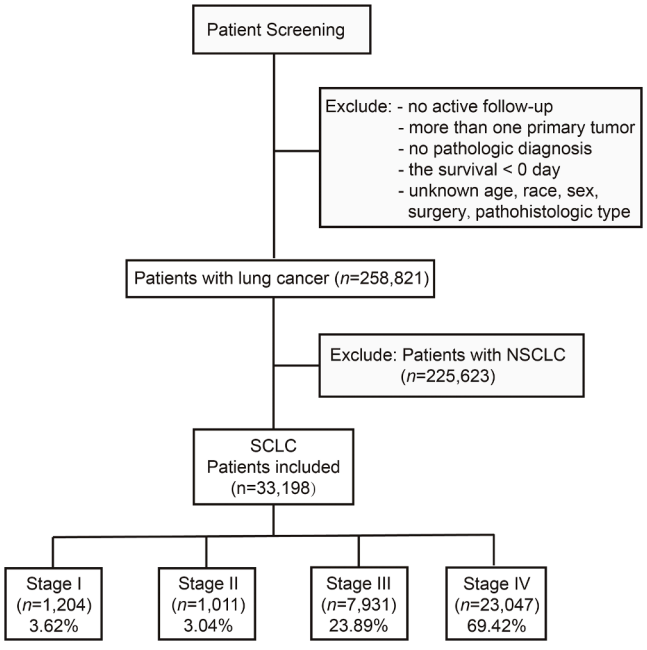

Fig. 1. Eligibility criteria for the inclusion of patient data with stage I-IV small cell lung cancer (SCLC) from the SEER database.

Additionally, we conducted a retrospective analysis of 634 patients diagnosed with pathologically confirmed small cell lung cancer (SCLC) at the Central Hospital of Dalian University of Technology between January 2014 and December 2023. Among these patients, 69 underwent surgical intervention. This study was approved by the Ethics Committee of the Central Hospital of Dalian University of Technology (Approval No YN2024–074–01), and the requirement for written consent was waived.

Data from the German cohort of patients were sourced from a study by Kauffmann-Guerrero et al., which analyzed a large dataset from the Munich Cancer Registry. Among these, 5043 were small cell lung cancer (SCLC) patients, of whom 161 underwent surgical treatment. [18]

Data analyses

The Kaplan-Meier method is a widely used nonparametric technique for estimating the survival function from time-to-event data. In our study, Kaplan-Meier analysis was employed to estimate and compare the survival curves between SCLC patients. This method allows for the estimation of survival probabilities over time and enables the comparison of survival outcomes between different treatment groups. OS and CSS were evaluated using the Kaplan-Meier method, and univariate comparisons were conducted utilizing the log-rank test and unadjusted Cox regression. A multivariate Cox proportional hazards model revised for other variables was employed to evaluate the hazard ratio (HR), 95 % confidence interval (CI), and *p*-value. The reverse Kaplan-Meier method was used to estimate the median follow-up [19].

The Propensity Score Matching (PSM) is a statistical technique used to reduce selection bias and balance covariates between treatment groups in observational studies. In our study, we employed PSM to address the inherent limitations of observational data by mimicking the random assignment of treatments in a randomized controlled trial (RCT). PSM approach allows us to assess the effects of different treatment strategies more accurately and provide more reliable evidence to support clinical practice. PSM was applied to adjust for individual differences in patients in the above comparison model of our study. Patients were selected using one-to-three nearest neighbor matching, and the caliper width was 0.05 times based on patient baseline characteristics. These characteristics included all known significant covariates (age, sex, race, marital and insurance status, T, N, and M stage, grade, regional or distant surgery, radiation, and chemotherapy administration). By this means, the bias due to confounding variables could be eliminated (estimation >99 %), as indicated in the corresponding tables.

Sequential landmark analysis is used to evaluate the impact of time-varying treatment effects on survival outcomes in longitudinal studies. In our study, sequential landmark analysis was employed to assess survival outcomes at various time points following treatment initiation, allowing for the examination of how the effect of treatment may change over time. This method provides insights into the dynamic nature of treatment response and valuable insights into the optimal timing and

efficacy of different treatments in improving patient outcomes. Due to the different times of enrollment associated with surgical resection, we performed sequential landmark analysis of patients who survived >1 or >2-years after diagnosis to assess survival eliminating time-to-treatment bias.

Stratified analyses were conducted by subgroups, including age, sex, and T/N stage, to explore the prognostic factors responsible for the OS in each therapy sub-classification among patients with or without surgical treatment. Recursive partitioning analysis (RPA) was used to further elucidate disease burden, calculate significant differences in OS and classify all stage III SCLC patients into distinct risk subgroups based on these disease-specific parameters. Multivariate Cox regression was used to analyze the outcomes of surgical treatments for each partitioned subclass.

The number of patient benefits was estimated using the 3-year survival rate of patients improved by surgery in the cohort of the SEER database. Sensitivity analyses were performed to assess the robustness of the estimates. Briefly, we stratified patients based on age, sex, and stage to obtain a range of variability in survival.

Table 1
Patient with stage III SCLC information based on baseline characteristics before and after 1:3 propensity score matching (PSM) in surgery and no-surgery groups.

Characteristic	Before PSM				After PSM			
	Total No (%)	No surgery No (%)	surgery No (%)	P-value	Total No (%)	No surgery No (%)	surgery No (%)	P-value
All patients	7931	7742	189		689	512	177	
Age(years)				0.405				0.235
Median [Q1,Q3]	67.0 [60.0,74.0]	67.0 [60.0,74.0]	67.0 [60.0,73.0]		66.0 [59.0,73.0]	66.0 [59.0,72.0]	66.0 [59.0,74.0]	
Age				0.504				0.316
<65	3100 (39.1 %)	3026 (39.1 %)	74 (39.2 %)		294 (42.7 %)	227 (44.3 %)	67 (37.9 %)	
65–75	3111 (39.2 %)	3031 (39.2 %)	80 (42.3 %)		276 (40.1 %)	200 (39.1 %)	76 (42.9 %)	
>75	1720 (21.7 %)	1685 (21.8 %)	35 (18.5 %)		119 (17.3 %)	85 (16.6 %)	34 (19.2 %)	
Sex				0.698				1
Female	4401 (55.5 %)	4293 (55.5 %)	108 (57.1 %)		397 (57.6 %)	295 (57.6 %)	102 (57.6 %)	
Male	3530 (44.5 %)	3449 (44.5 %)	81 (42.9 %)		292 (42.4 %)	217 (42.4 %)	75 (42.4 %)	
Race				0.276				0.995
White	6880 (86.7 %)	6710 (86.7 %)	170 (89.9 %)		624 (90.6 %)	464 (90.6 %)	160 (90.4 %)	
Black	712 (9.0 %)	697 (9.0 %)	15 (7.9 %)		50 (7.3 %)	37 (7.2 %)	13 (7.3 %)	
Other	339 (4.3 %)	335 (4.3 %)	4 (2.1 %)		15 (2.2 %)	11 (2.1 %)	4 (2.3 %)	
Marital				0.0071				0.797
Married	3745 (47.2 %)	3637 (47.0 %)	108 (57.1 %)		393 (57.0 %)	294 (57.4 %)	99 (55.9 %)	
Other	4186 (52.8 %)	4105 (53.0 %)	81 (42.9 %)		296 (43.0 %)	218 (42.6 %)	78 (44.1 %)	
Insurance				0.548				0.827
Any Medicaid	1324 (16.7 %)	1295 (16.7 %)	29 (15.3 %)		97 (14.1 %)	71 (13.9 %)	26 (14.7 %)	
unknown	108 (1.4 %)	106 (1.4 %)	2 (1.1 %)		8 (1.2 %)	6 (1.2 %)	2 (1.1 %)	
Insured	4814 (60.7 %)	4689 (60.6 %)	125 (66.1 %)		473 (68.7 %)	357 (69.7 %)	116 (65.5 %)	
Insured/No specifics	1454 (18.3 %)	1427 (18.4 %)	27 (14.3 %)		93 (13.5 %)	66 (12.9 %)	27 (15.3 %)	
Uninsured	231 (2.9 %)	225 (2.9 %)	6 (3.2 %)		18 (2.6 %)	12 (2.3 %)	6 (3.4 %)	
T stage				<0.001				0.988
T0	99 (1.2 %)	98 (1.3 %)	1 (0.5 %)		6 (0.9 %)	5 (1.0 %)	1 (0.6 %)	
T1	1052 (13.3 %)	1003 (13.0 %)	49 (25.9 %)		160 (23.2 %)	117 (22.9 %)	43 (24.3 %)	
T2	1792 (22.6 %)	1740 (22.5 %)	52 (27.5 %)		193 (28.0 %)	144 (28.1 %)	49 (27.7 %)	
T3	1497 (18.9 %)	1452 (18.8 %)	45 (23.8 %)		161 (23.4 %)	119 (23.2 %)	42 (23.7 %)	
T4	2659 (33.5 %)	2628 (33.9 %)	31 (16.4 %)		121 (17.6 %)	90 (17.6 %)	31 (17.5 %)	
TX	832 (10.5 %)	821 (10.6 %)	11 (5.8 %)		48 (7.0 %)	37 (7.2 %)	11 (6.2 %)	
N stage				<0.001				0.929
N0	390 (4.9 %)	375 (4.8 %)	15 (7.9 %)		56 (8.1 %)	41 (8.0 %)	15 (8.5 %)	
N1	380 (4.8 %)	357 (4.6 %)	23 (12.2 %)		83 (12.0 %)	63 (12.3 %)	20 (11.3 %)	
N2	5510 (69.5 %)	5372 (69.4 %)	138 (73.0 %)		493 (71.6 %)	364 (71.1 %)	129 (72.9 %)	
N3	1594 (20.1 %)	1581 (20.4 %)	13 (6.9 %)		57 (8.3 %)	44 (8.6 %)	13 (7.3 %)	
NX	57 (0.7 %)	57 (0.7 %)	0 (0 %)					
Grade				<0.001				0.357
Grade I	7 (0.1 %)	6 (0.1 %)	1 (0.5 %)					
Grade II	14 (0.2 %)	10 (0.1 %)	4 (2.1 %)		4 (0.6 %)	3 (0.6 %)	1 (0.6 %)	
Grade III	707 (8.9 %)	655 (8.5 %)	52 (27.5 %)		173 (25.1 %)	129 (25.2 %)	44 (24.9 %)	
Grade IV	1177 (14.8 %)	1124 (14.5 %)	53 (28.0 %)		173 (25.1 %)	120 (23.4 %)	53 (29.9 %)	
Unknown	6026 (76.0 %)	5947 (76.8 %)	79 (41.8 %)		339 (49.2 %)	260 (50.8 %)	79 (44.6 %)	
Radiation				0.902				0.577
No	2757 (34.8 %)	2690 (34.7 %)	67 (35.4 %)		220 (31.9 %)	160 (31.3 %)	60 (33.9 %)	
Yes	5174 (65.2 %)	5052 (65.3 %)	122 (64.6 %)		469 (68.1 %)	352 (68.8 %)	117 (66.1 %)	
surgery to regional				0.867				1
No	7859 (99.1 %)	7671 (99.1 %)	188 (99.5 %)		684 (99.3 %)	508 (99.2 %)	176 (99.4 %)	
Yes	72 (0.9 %)	71 (0.9 %)	1 (0.5 %)		5 (0.7 %)	4 (0.8 %)	1 (0.6 %)	
chemotherapy				0.328				0.628
No	1631 (20.6 %)	1598 (20.6 %)	33 (17.5 %)		107 (15.5 %)	77 (15.0 %)	30 (16.9 %)	
Yes	6300 (79.4 %)	6144 (79.4 %)	156 (82.5 %)		582 (84.5 %)	435 (85.0 %)	147 (83.1 %)	

No, number of cases; Tx, not determined T; Nx, not determined N;.
PSM, a PSM was done in each subgroup using covariates including: age, sex, race, marital status, grade, T stage, N stage, chemotherapy, radiation, surgery to surgery to regional site/distant lymph node site, and etc.
Categorical variables were compared by using the Pearson χ^2 test, and continuous variables were compared by using the Mann-Whitney U test.
HR, hazard ratio; CI, confidence interval.

Statistical analyses

Statistical analyses were performed using Stata/MP software version 14.1 (StataCorp LP, Texas, USA) and R software version 4.1.2 (R Core Team, Vienna, Austria). *p*-values for comparison of survival curves in multiple groups were corrected using the Benjamini-Hochberg procedure [20]. Mann-Whitney test and Kruskal-Wallis test were used to evaluate continuous variables, and the chi-square test was conducted to compare the baseline feature of categorical variables. Two-sided *p*-values <0.05 were considered statistically significant.

Results

Patient characteristics

In this study, patient data from the SEER cohort were analyzed to determine the effect of surgical intervention on patient survival. The selection process for including patients is shown in Fig. 1. Between 1975 and 2016, 33,198 stage I-IV SCLC patients in the SEER cohort met the eligibility criteria, with a median follow-up time of 3.8 years (43 months). At the time of diagnosis, a minority of patients were stage I

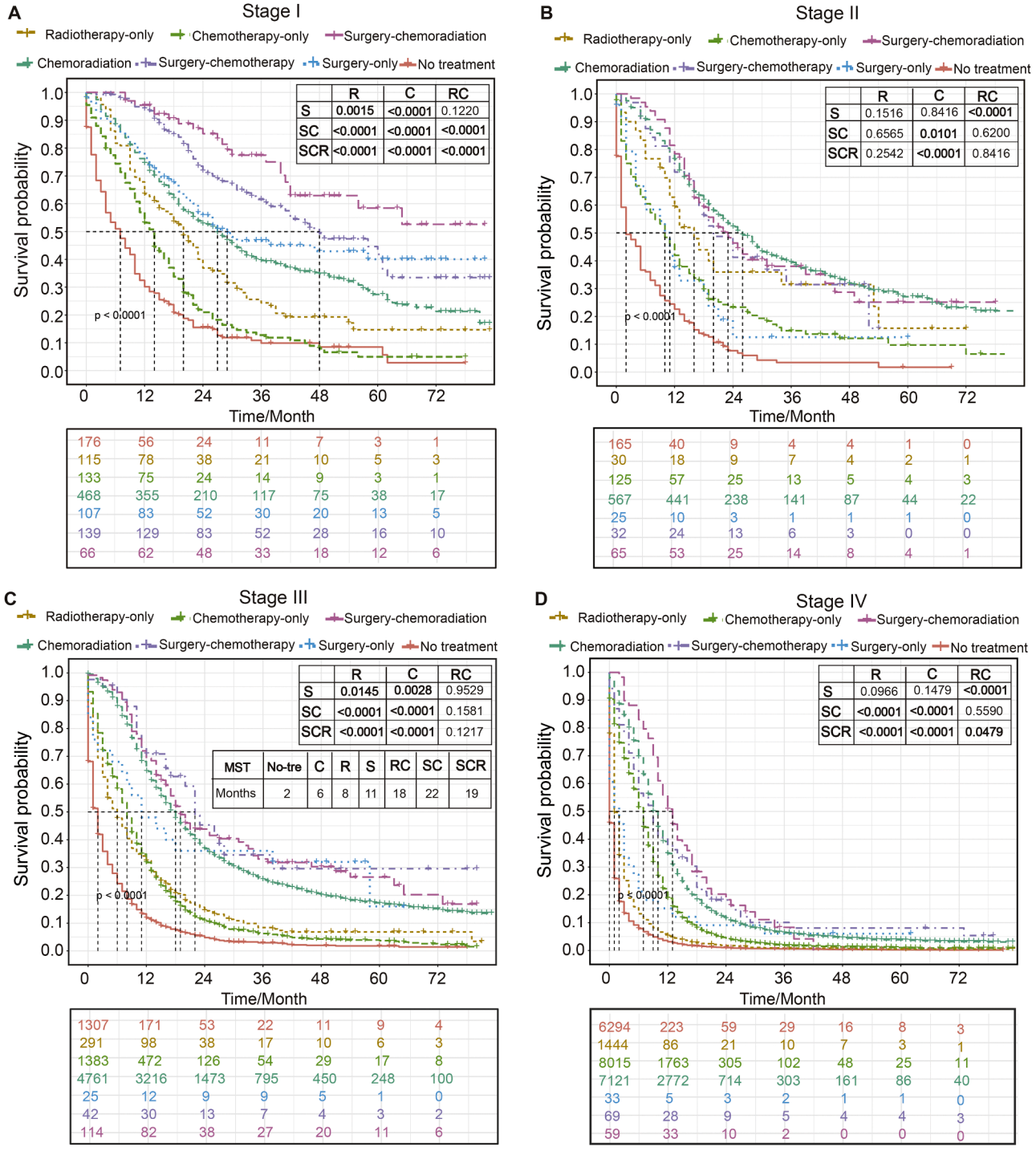

Fig. 2. Comparison of median survival times (MSTs) of patients with stage I-IV SCLC with various therapy modalities. (A) stage I. (B) stage II. (C) stage III. (D) stage IV. MST, median survival time; No-tre, No-treatment; C, chemotherapy; R, radiation; S, surgery; RC, chemoradiation; SC, surgery plus chemotherapy; SCR, surgery plus chemoradiation;; p, p-value.

(3.62 %) and stage II (3.04 %); 23.89 % were stage III, and the majority stage IV (69.42 %). Patient characteristics are depicted in Table 1 and Supplementary Tables 1, 2, 3, and 4. The patient's surgical approach is shown in Supplementary Table 5. Overall, the surgical approach for patients with stages I-III was mainly Wedge resection and Lobectomy with mediastinal lymph node dissection, which accounted for about 72 % . Pneumonectomy was mostly utilized in stage III patients accounting for about 5.9 %. The main surgical approach for stage IV patients was Wedge resection (27 %), followed by Local tumor destruction in about 14 % of patients. Overall, there was little difference in the surgical approach for SCLC patients with I-III; however, there was a significant decrease in the approach to Lobectomy WITH mediastinal lymph node dissection for SCLC patients with IV. (Supplementary Table 5).

Survival outcomes of various treatment modalities in stages I-IV

First, the overall survival of SCLC patients receiving different treatment modalities was compared within each stage using Kaplan-Meier analysis. Fig. 2 depicts the survival data of the patients stratified by clinical stage and treatment patterns. Overall, surgery-chemoradiation was among the treatments with highest survival, while chemotherapy-only, radiotherapy-only, and no treatment had the worst survival. Strikingly, in all stages, the OS for patients treated with a combination of surgery is almost always better than those treated without surgery (except stage III SCLC patients which had no benefit in OS with surgery plus chemoradiation compared to chemoradiation). The median OS (MST; months) of stage I SCLC patients differed significantly between the different treatment regimens. Only surgery-only versus chemoradiation presented a similarly good median OS, ranging mid-field among the other treatment modalities (Fig. 2A, Supplementary Table 1). Overall, patients who underwent surgery clearly showed elevated survival in stage I. In stage II SCLC patients, the MST is overall lower than for stage I patients, and survival of patients who received surgery additionally to chemotherapy was improved compared to chemotherapy-only. However, there was no significant difference in median OS between surgery and either chemotherapy or radiotherapy alone groups (Fig. 2B, Supplementary Table 2). Importantly, stage III SCLC patients treated with surgery only had superior survival compared with those treated with radiotherapy only, and survival differed significantly between surgery plus chemotherapy and chemotherapy alone. Nevertheless, the OS of patients who underwent surgery plus chemotherapy was not significantly different from that of patients who underwent chemoradiation (Fig. 2C, Supplementary Table 3). CSS demonstrated similar results to the analysis of OS in stage III patients (Supplementary Figure 1). In stage IV SCLC patients (OS analysis in Fig. 2D, Supplementary Table 4) a significant improvement in survival time between surgery plus chemotherapy and chemotherapy alone was observed. Meanwhile, the OS of all the treatment groups was significantly reduced.

To reduce the effect of confounding covariates derived from clinical characteristics (e.g. age, sex, T/N/M stage), PSM analysis was performed, and treatment modalities with or without surgery were compared for stage III patients. The clinical features were satisfactorily modified for all covariates (Table 1, Supplementary Table 6, 7, and 8). Importantly, the improvement in OS and CSS in stage III patients with surgery compared to no-surgery was robust between pre-match and post-match analyses (Table 2) [OS: pre-match (Fig. 3A); post-match ([HR], 0.71; 95 % CI, 0.58–0.87, $p < 0.001$; Fig. 3B)]; [CSS: pre-match (Supplementary Figure 2A); post-match ([HR], 0.66; 95 % CI, 0.52–0.85, $p < 0.001$; Supplementary Figure 2B)]. Of note, this indicates that surgical intervention was an independent factor associated with improved OS and CSS compared with no-surgery. Similarly, longer OS

Table 2
Univariate and multivariate Cox regression analyses of different variables considered for OS and CSS for patients with III stage SCLC.

Characteristics	Univariate				Multivariate			
	OS		CSS		OS		CSS	
	HR(95 %CI)	P	HR(95 %CI)	P	HR(95 %CI)	P	HR(95 %CI)	P
Age (<65 as ref.)								
65–75	1.31 (1.238–1.386)	<0.0001	1.13 (1.055–1.203)	<0.001	1.29 (1.21–1.36)	<0.0001	1.11 (1.04–1.19)	0.002
>75	2.09 (1.963–2.233)	<0.0001	1.57 (1.45–1.698)	<0.0001	1.65 (1.54–1.77)	<0.0001	1.24 (1.14–1.35)	<0.0001
Sex(Female as ref.)	1.21 (1.154–1.273)	<0.0001	1.22 (1.148–1.29)	<0.0001	1.25 (1.19–1.31)	<0.0001	1.25 (1.17–1.32)	<0.0001
Race(White as ref.)								
Black	0.91 (0.836–0.995)	0.038	0.95 (0.863–1.057)	0.3729	0.89 (0.82–0.98)	0.0128	0.91 (0.82–1.01)	0.0626
Other	1.03 (0.909–1.159)	0.6756	1.1 (0.957–1.267)	0.177	0.89 (0.79–1.01)	0.0676	0.95 (0.83–1.1)	0.5211
Marital(Married as ref.)	1.14 (1.086–1.198)	<0.0001	1.12 (1.056–1.187)	<0.001	1.1 (1.05–1.16)	<0.001	1.09 (1.02–1.15)	0.0085
Insurance(Any Medicaid as ref.)								
Insured/No specifics	1 (0.919–1.083)	0.9537	0.93 (0.842–1.021)	0.1254	0.85 (0.78–0.93)	<0.001	0.85 (0.77–0.94)	0.0013
unknown	1.04 (0.84–1.297)	0.7001	0.94 (0.719–1.22)	0.6278	0.89 (0.71–1.11)	0.2985	0.86 (0.66–1.13)	0.2808
Uninsured	0.83 (0.709–0.974)	0.0225	0.89 (0.746–1.068)	0.2133	0.97 (0.83–1.14)	0.7255	0.99 (0.83–1.19)	0.9547
Insured	0.91 (0.846–0.968)	0.0038	0.85 (0.789–0.924)	<0.001	0.87 (0.81–0.93)	<0.001	0.88 (0.81–0.96)	0.0027
T stage(T1 as ref.)								
T2	1.33 (1.221–1.445)	<0.0001	1.49 (1.339–1.647)	<0.0001	1.36 (1.25–1.48)	<0.0001	1.5 (1.35–1.67)	<0.0001
T3	1.26 (1.153–1.375)	<0.0001	1.35 (1.209–1.502)	<0.0001	1.31 (1.2–1.43)	<0.0001	1.41 (1.26–1.57)	<0.0001
T4	1.34 (1.236–1.449)	<0.0001	1.58 (1.432–1.739)	<0.0001	1.48 (1.36–1.6)	<0.0001	1.71 (1.54–1.89)	<0.0001
TX	1.43 (1.296–1.584)	<0.0001	1.48 (1.311–1.679)	<0.0001	1.17 (1.06–1.3)	0.0021	1.21 (1.06–1.37)	0.0033
N stage(N0 as ref.)								
N1	0.92 (0.783–1.08)	0.3072	0.81 (0.666–0.977)	0.0281	1.1 (0.93–1.3)	0.2479	1.01 (0.83–1.23)	0.9535
N2	1.06 (0.943–1.191)	0.3285	0.98 (0.86–1.127)	0.8214	1.38 (1.22–1.56)	<0.0001	1.34 (1.16–1.54)	<0.001
N3	1.2 (1.056–1.356)	0.0048	1.17 (1.013–1.352)	0.0329	1.66 (1.46–1.9)	<0.0001	1.66 (1.42–1.93)	<0.0001
NX	1.47 (1.083–1.991)	0.0135	1.5 (1.06–2.125)	0.0221	1.12 (0.82–1.52)	0.4666	1.11 (0.78–1.57)	0.5565
Grade(Grade I and II as ref.)								
Grade III, IV, Unknown	1.82 (1.033–3.207)	0.0382	1.94 (0.967–3.873)	0.062	1.89 (1.07–3.35)	0.0285	1.93 (0.96–3.88)	0.0659
surgery to regional site(No as ref.)	0.93 (0.715–1.204)	0.5732	0.87 (0.635–1.203)	0.409	1.06 (0.81–1.37)	0.682	0.98 (0.71–1.34)	0.8835
Radiation(No as ref.)	0.34 (0.328–0.363)	<0.0001	0.36 (0.343–0.388)	<0.0001	0.46 (0.43–0.49)	<0.0001	0.46 (0.43–0.49)	<0.0001
Chemotherapy(No as ref.)	0.3 (0.283–0.318)	<0.0001	0.32 (0.295–0.339)	<0.0001	0.47 (0.44–0.5)	<0.0001	0.47 (0.43–0.51)	<0.0001
Surgery(No-surgery as ref.)	0.62 (0.516–0.734)	<0.0001	0.55 (0.44–0.685)	<0.0001	0.56 (0.47–0.67)	<0.0001	0.51 (0.41–0.64)	<0.0001

Tx, not determined T; Nx, not determined N; M1NOS, not determined M (M1a or M1b).
OS, overall survival; CSS, cancer-specific survival.
HR, hazard ratio; CI, confidence interval.

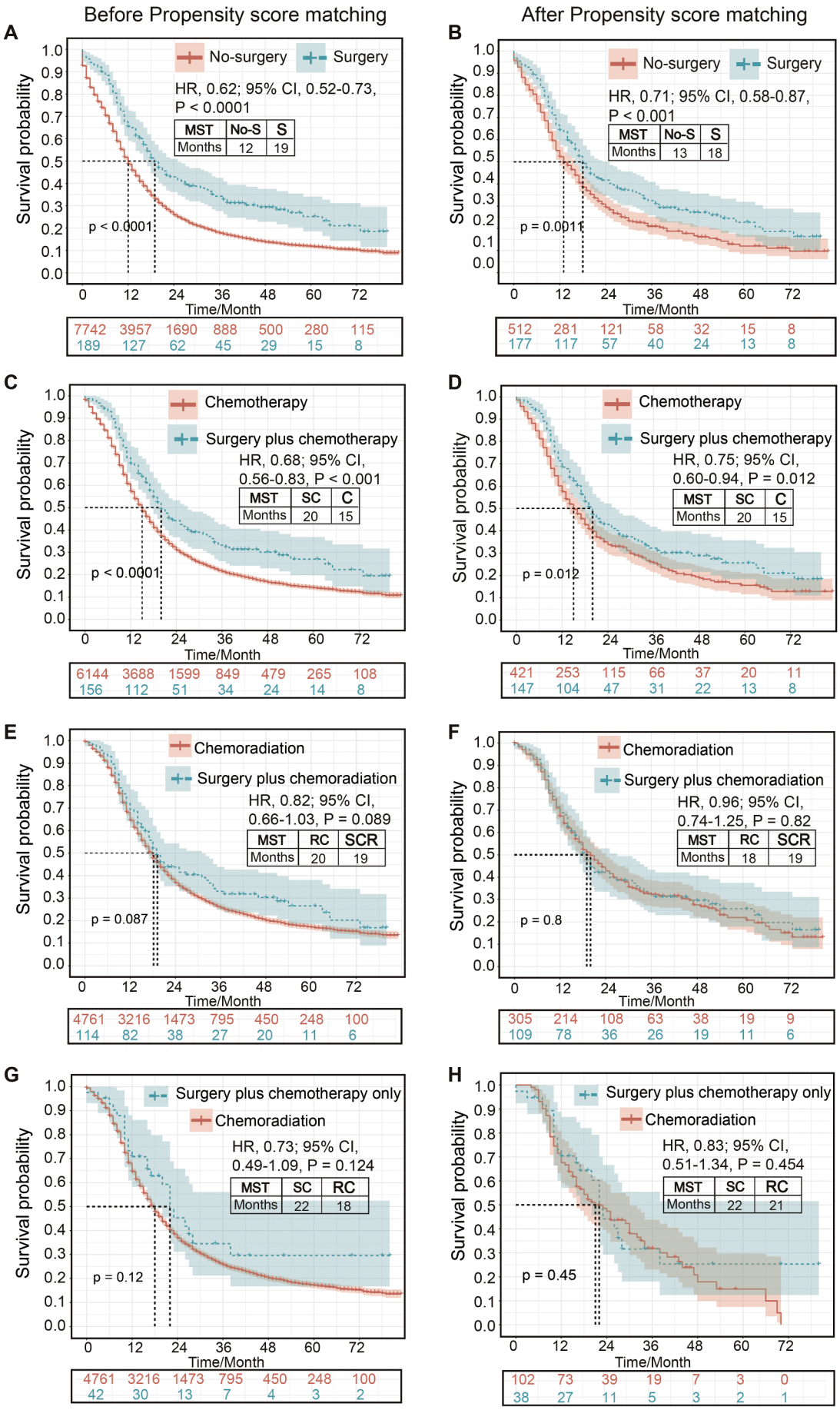

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Fig. 3. Comparison of the overall survival (OS) among stage III SCLC patients treated with surgery-combined patterns versus corresponding surgery-absent therapies, before and after propensity score matching (PSM). (A) and (B) PSM before and after, surgery versus no-surgery (OS). (C) and (D) PSM before and after, surgery plus chemotherapy versus chemotherapy (OS). (E) and (F) PSM before and after, surgery plus chemoradiation versus chemoradiation (OS). (G) and (H) PSM before and after, surgery plus chemotherapy versus chemoradiation (OS). HR, hazard ratio; CI, confidence interval; MST, median survival time; C, chemotherapy; R, radiation; S, surgery; RC, chemoradiation; SC, surgery plus chemotherapy; SCR, surgery plus chemoradiation; p, p-value.

and CSS benefits were obtained from surgery plus chemotherapy compared to chemotherapy alone using PSM analysis (Supplementary Table 9) [OS: pre-match (Fig. 3C); post-match ([HR], 0.75; 95 % CI, 0.60–0.94, $p < 0.05$; Fig. 3D)]; [CSS: pre-match (Supplementary Figure 2C); post-match ([HR], 0.73; 95 % CI, 0.55–0.96, $p < 0.05$; Supplementary Figure 2D)]. However, no differences in OS and CSS in stage III patients were observed between surgery plus chemoradiation and chemoradiation after PSM analysis (Fig. 3E, F; Supplementary Figure 2E, F) and between surgery plus chemotherapy (without radiation) and chemoradiation (Fig. 3G, H; Supplementary Figure 2 G, H).

Importantly, survival for all surgery-related treatment modalities in stage I and II patients was significantly better than that in controls without surgery ($p < 0.017$ after PSM) (Supplementary Figure 3). Additionally, a significant difference between surgery plus chemotherapy and chemotherapy alone ($p = 0.013$ after PSM) was observed in stage IV patients (Supplementary Figure 4). Since Kaplan-Meier and PSM analyses showed a robust and unexplored improvement in OS and CSS in stage III patients, we concentrated further on these.

Landmark analysis in stage III patients

To exclude external time bias, we performed sequential landmark analysis, set at one year (≥1-year survivors) and two years (≥2-year survivors) after diagnosis in stage III SCLC patients (Fig. 4). In line with our data above, the beneficial effect of surgical intervention remained in long-term survivors of ≥1- or ≥2-years (Fig. 4A-F and Supplementary Table 10 (for OS); Supplementary Figure 5A-F and Supplementary Table 11 (for CSS)). Patients in the surgery group had significantly higher OS than those in the non-surgery group ($p \leq 0.03$; Fig. 4A,B; Supplementary Table 10). Furthermore, surgery plus chemotherapy rather than chemotherapy alone was significantly associated with better OS (≥1-years, $p \leq 0.013$; Fig. 4C,D; Supplementary Table 10). In addition, patients in the surgery only group had significantly higher OS than those in the radiotherapy only group (for ≥1-years, $p \leq 0.014$; Fig. 4E,F; Supplementary Table 10). In addition, CSS of patients who underwent surgery (compared to no-surgery) or surgery plus chemotherapy (compared to chemotherapy alone) was improved ($p \leq 0.022$; Supplementary Figure 5A-D; Supplementary Table 11), while surgery only was significantly improved compared to radiotherapy-only (for ≥1-years, $p \leq 0.025$; Supplementary Figure 5E-F; Supplementary Table 11).

Effects of primary resection and surgery at regional sites on OS and CSS

In addition to the primary site, survival prognosis was assessed in stage III SCLC patients who underwent surgery at regional sites (Supplementary Figure 6 and 7, Supplementary Table 12) There was a striking and significant difference in survival (OS) between primary site surgery and no-surgery (19 vs. 12 months, $p < 0.0001$) and between primary site surgery and only surgery at regional sites (19 vs. 13 months, $p < 0.05$). Thus, stage III patients benefit from primary site surgery with increased OS and CSS rather than from surgery at regional sites (Supplementary Figure6 and 7).

Subgroup analysis to identify suitable surgical stage III candidates

To identify the most suitable surgical candidates from stage III patients, a 3-step analysis was performed. First, a subgroup analysis based on patient demographics and tumor factors was employed (Fig. 5). Forest plots showed that the degree of association between surgery and non-surgery and improved OS or CSS was more significant in the subgroups of patients: age, gender, T1–4, and N1–2 (Fig. 5). However, the OS benefit was independent of surgical treatment in N3 patients. Likewise, surgery plus chemotherapy was also demonstrated to be associated with improved survival in all patient subgroups except for age <65, T2–3, or N2–3 (Supplementary Figure 8).

To more precisely select appropriate stage III SCLC patients as candidates for surgery, we further analyzed the impact of surgery on survival in patients with a combination of characteristics, using data from the subgroup studies described above. In the surgery versus non-surgery group, results indicated that patients with the following characteristics had significantly better OS with surgery: T3–4/N0–1 (before/after PSM, Fig. 6A/B, Supplementary Table 13) and T1–2/N2 (before/after PSM, Fig. 6C/D, Supplementary Table 14) (for all: $p < 0.05$). However, in T3–4/N2 patients, surgery did not improve OS (before/after PSM, Fig. 6E/F). The results for surgery plus chemotherapy versus chemotherapy were nearly identical to those of the groups shown above (Supplementary Figure 9, Supplementary Table 15–16). To take into account the evolution of medical decision making and surgical conduct, we reanalyzed by selecting only patients with T3–4/N0–1 or T1–2/N2, which had been treated from 2006 to 2016. Despite reducing the power of our analysis, we observed similar results (Supplementary Figure 10). Collectively, these data demonstrate the optimal selection of patients for surgery: substages T3–4/N0–1 or T1–2/N2 (Supplementary Figure 11).

To independently confirm these selection criteria and enhance the ability to screen qualified surgical candidates, we applied recursive partitioning analysis (RPA) to classify SCLC patients into low-, intermediate-, high-, or very high-risk groups using a decision tree approach. The 3-year OS prognosis in different surgical versus non-surgical risk groups were 37.3% vs. 23.7 %, 48.1% vs. 19.51 %, 28.40% vs. 17.43 %, and 13.44% vs. 0.00 %, respectively (Supplementary Figure 12). Thus, this multivariate regression analysis confirmed that surgery improves OS in stage III SCLC patients. Of note, RPA identified four prognostic subgroups of stage III SCLC patients based on OS: subgroup 1 included low-risk patients with T0–1; subgroup 2 included intermediate-risk patients with T2–4,Tx/N0–1; subgroup 3 included high-risk patients with T2–4,Tx/N2; and subgroup 4 includes very high risk patients with T2–4, Tx/N3,Nx. (Supplementary Figure 12). In summary, this demonstrates that surgery is associated with OS benefits relative to no-surgery in low, intermediate, and high-risk stage III SCLC patients, but does not recommend surgery for N3 (very high risk) patients. This is in line with the data above which recommend surgery for stage T3–4/N0–1 or T1–2/N2 patients.

Estimation of the number of patients in China and Germany who could potentially benefit from the procedure each year

We obtained data on 634 small cell lung cancer (SCLC) patients treated at the Central Hospital of Dalian University of Technology between 2014 and 2023. Among them, 69 patients (10.88 %) underwent surgical treatment. According to national statistics, approximately 828,100 individuals are diagnosed with lung cancer annually in China, with SCLC accounting for about 15 % of these cases, translating to roughly 124,215 patients [21,22]. We selected the 3-year survival rate as our assessment index and utilized the survival improvement rate observed in the SEER database cohort (30.89 %) to estimate the number of patients who could benefit from surgery. Sensitivity analysis indicated a range of survival benefits from 6.2 % to 34.2 %. Based on these, we estimate that annually, approximately 38,369 (7700- 42,480)

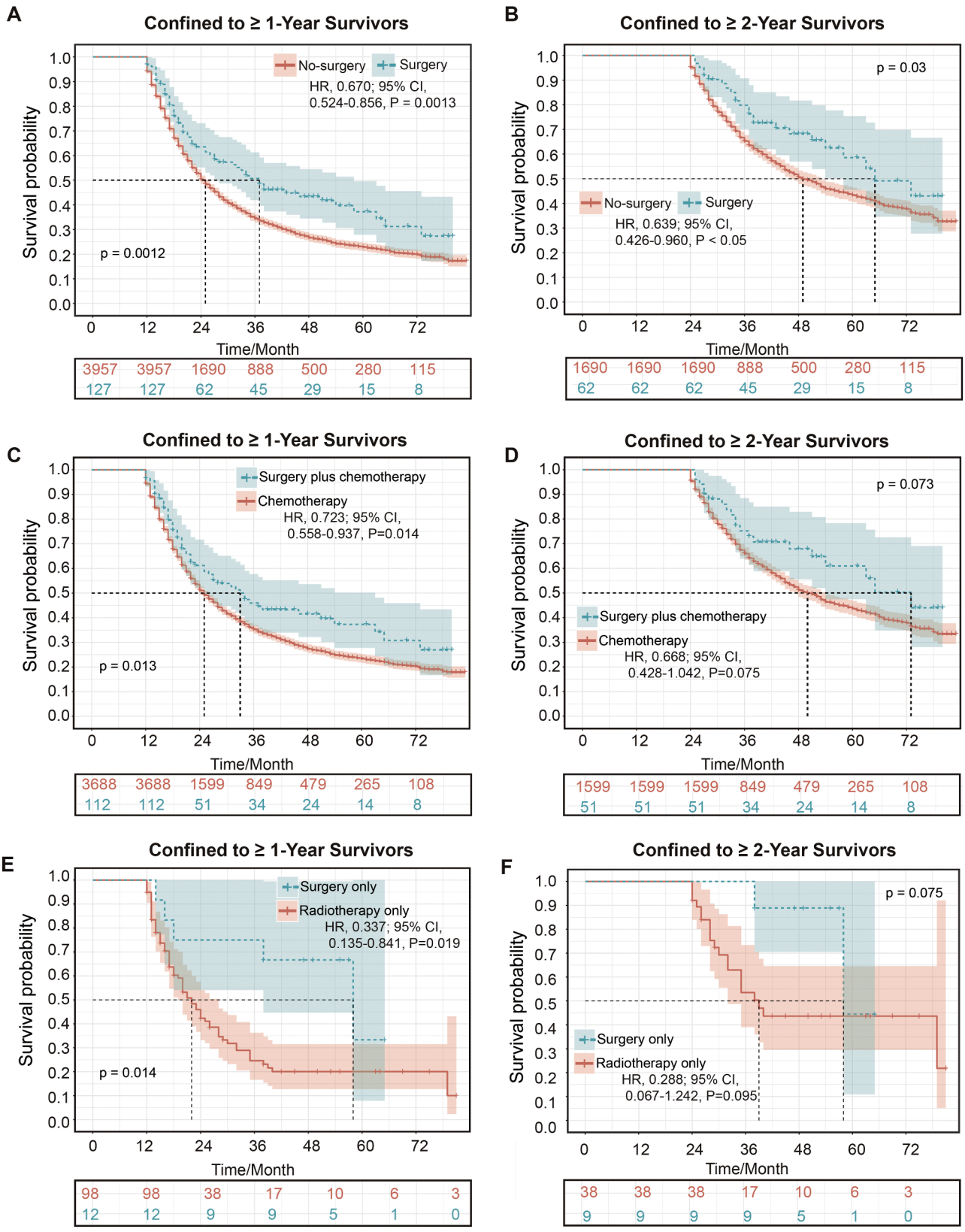

Fig. 4. Landmark analyses of OS for ≥1- or ≥2- year survivors with stage III SCLC undergoing surgery-combined versus no-surgery therapy paradigms. (A) and (B), surgery versus no-surgery. (C) and (D), surgery plus chemotherapy versus chemotherapy. (E) and (F), surgery only versus Radiotherapy-only.HR, hazard ratio; CI, confidence interval; p, p-value.

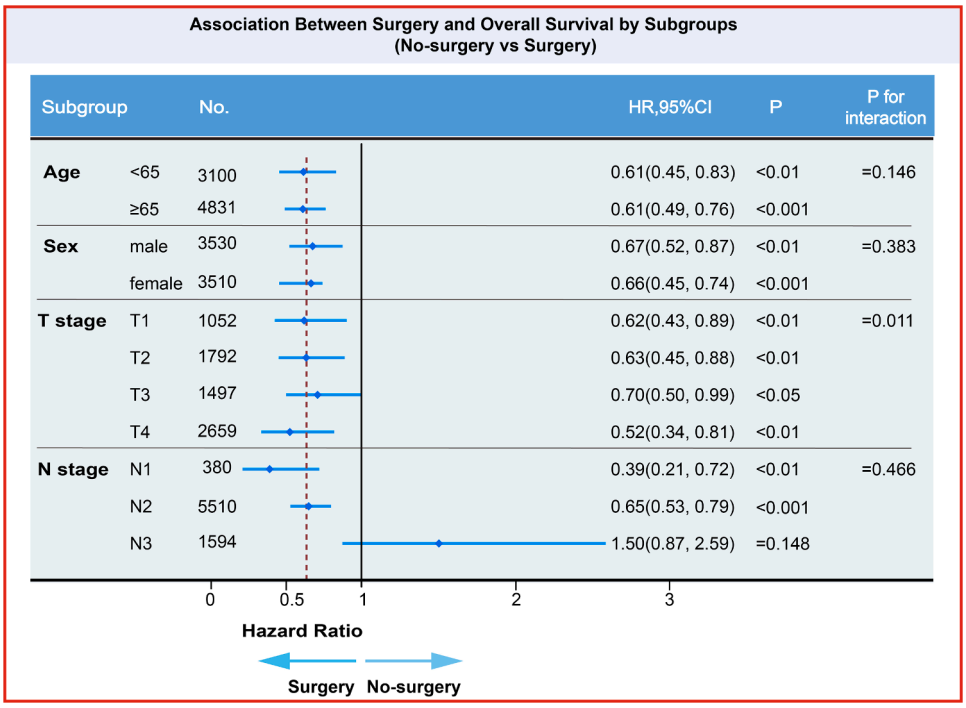

Fig. 5. Subgroup analysis among the stage III SCLC patients of the association between surgery and OS using forest plot (Surgery versus No-surgery). HR, unadjusted hazard ratio related to surgery (no-surgery for control [HR =1]); CI, low and upper of the 95 % confidence interval. T, tumor stage; N, nodal stage; p, p-value.

patients with SCLC in China could potentially benefit from surgical intervention (Supplementary Table 17). A study by Kauffmann-Guerrero et al. included a total of 5043 patients with small cell lung cancer (SCLC) treated between 2002 and 2015. Among these, 161 patients (3.19 %) underwent surgical intervention. According to the report, approximately 7000 individuals are diagnosed with SCLC annually in Germany [23]. Based on this data, we estimated that around 2612 patients (434 – 2393) could benefit from surgical treatment each year in Germany (Supplementary Table 18).

Discussion

To date, surgery is controversial in SCLC patients, independent of stage. Here, we provide evidence based on a large cohort of patients from the SEER database that surgery improves survival in stage I-III SCLC patients. Specifically, our data demonstrate that T3–4/N0–1 and T1–2/N2 stage III SCLC patients had a longer OS and CSS with primary resection or in combination with chemotherapy (Fig. 6 and Supplementary Figure 12).

First, we showed that primary resection in stage III SCLC patients leads to survival benefits by screening various theoretically feasible treatment modalities. As shown in Fig. 2C, surgical treatment alone was superior to almost any other monotherapy regimen in terms of OS and CSS in stage III patients. Notably it was comparable to chemoradiation (the current gold standard treatment) when surgery was combined with chemotherapy. These findings are partially consistent with the results described by Combs et al. [10] which demonstrated that the OS of stage III SCLC patients is improved after surgery and chemotherapy. Despite the innate limitations of any retrospective study, we confirmed our data using PSM analysis under balanced confounding covariates. Our finding that surgical treatment in selected stage III SCLC patients is beneficial, is supported by the literature [10,14]' [24]. In a retrospective single-center study, Takenaka et al. showed that surgical treatment of stage III SCLC was associated with improved survival in an adjusted PSM analysis compared with previously published data [14]. In a meta-analysis, Liu et al. reported that surgery-based multimodal therapy was associated with a favorable survival advantage in selected stage III SCLC patients [24].

Since combined treatment modalities are important in controlling stage III SCLC, we focused on the beneficial OS and CSS in surgery plus chemotherapy versus chemotherapy and confirmed it by PSM analysis, indicating the reliability of the retrieved data. In a multicenter, prospective, phase II study including 62 patients, Tsuchiya et al. found that postoperative chemotherapy was feasible with reasonable OS [25]. In addition, a clinical trial study showed the MST was 39.5 months [26] in limited-stage SCLC after pembrolizumab with chemoradiation, while our results showed an MST of 38 months (data not shown) in patients receiving chemotherapy plus surgery. This further indicates the feasibility of surgery plus chemotherapy for localized SCLC. Interestingly, after PSM our data suggest that OS and CSS of stage III patients treated with standard therapy (chemoradiation) were not superior to those treated with surgery plus chemotherapy alone with the latter having a slightly longer MST (21 vs. 22 months). This provides an option for patients not receiving radiotherapy or without local radiotherapy facilities [15]. The OS and CSS of stage III patients were not statistically different between surgery plus chemoradiation and chemoradiation alone, in contrast to stage I or II patients. We speculate this being caused by a relatively small surgical resection range of stage I-II tumors leading to positive resection margins, which respond actively to local radiotherapy. In contrast, the extent of surgical resection in stage III may be more aggressive (lobectomy or pneumonectomy), leaving no residual tumor cells, leading to ineffective local radiotherapy. However, adding primary site surgery to systemic therapy including chemotherapy and radiotherapy, might increased OS and CSS for selected stage I-II SCLC patients. This suggests that new randomized trials should evaluate triple modality therapy in stage I/II disease [27].

In order to focus on differences in OS and CSS of ≥1- and ≥2-year survivors, sequential landmark analysis was employed to exclude time-to-treatment bias (Fig. 4). Notably, at these two time points, our data suggest that surgery (versus no-surgery) and, surgery plus chemotherapy (versus chemotherapy alone) led to improvements in OS and CSS in univariate and multivariate analyses of long-term survivors, which is a novel finding. Thus, the OS benefit of stage III SCLC patients at different time points after surgical intervention is consistent.

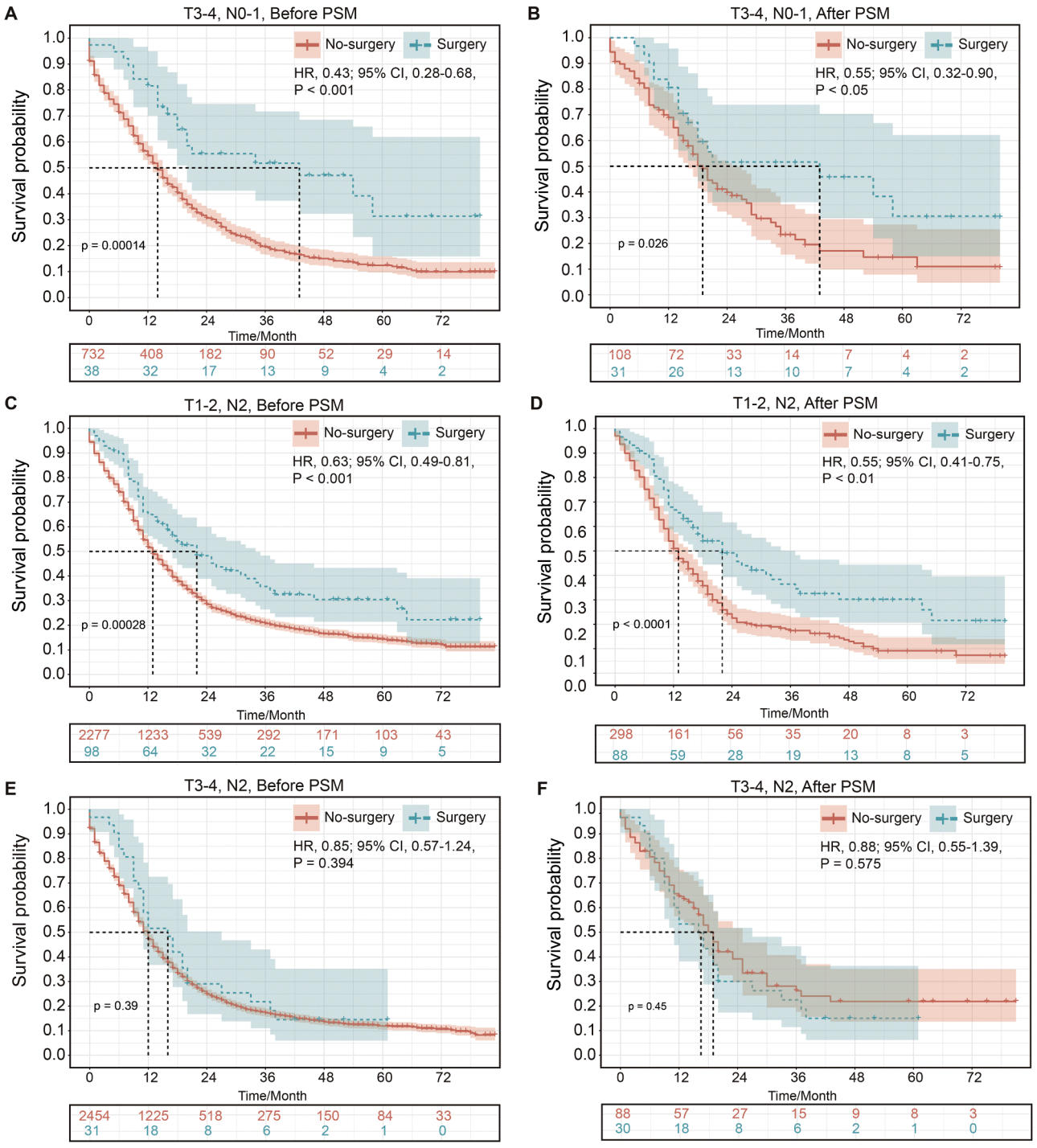

Fig. 6. Comparison of OS among stage III patients with varied combinations of tumorous biological characteristics and receiving surgery (versus no-surgery). (A), T3–4, N0–1, before PSM; (B), T3–4, N0–1, after PSM; (C), T1–2, N2, before PSM; (D), T1–2, N2, after PSM; (E), T3–4, N2, before PSM; (F), T3–4, N2, after PSM. HR, hazard ratio; CI, confidence interval; PMS, propensity score matching; p, p-value.

Additionally, in long-term survivors receiving surgery only, CSS and OS were superior to those of radiotherapy only patients, further demonstrating surgical intervention benefits in stage III SCLC patients.

Likewise, our results are the first to show that OS or CSS benefit from surgery at the primary site (Supplementary Figure 6). However, surgery at regional sites did not improve OS or CSS, independent of knowing the exact timing of the different surgeries, or the number of regional sites removed. Interestingly, OS and CSS of stage III patients who underwent regional site surgery were comparable to the non-surgery group, whereas OS and CSS after primary site surgery were significantly better compared to non-surgery. These data illustrate the importance of removing primary lung lesions.

In both treatment settings, subgroup analyses showed the survival benefit of primary site surgery strongly correlating with either patient or tumor-specific variables (Fig. 5). These data suggest that specific subgroups, but not all stage III SCLC patients benefit from primary surgical intervention. This highlights the importance of selecting patient groups, and these findings need to be supported by additional clinical evidence in the future. For instance, any T or N1–2 stage patients appear to benefit most from surgery. They have higher OS and CSS than N3 patients,

suggesting the importance of lymph node involvement and essentiality in patient selection. However, Zhang et al. reported that the survival of all stage III SCLC patients (including N3) could benefit from surgical intervention, owing to the absence of a stratified analysis of patients [28]. Several previous studies have reported that primary surgical treatment may benefit N2 patients, which partially supports our findings [29,30,31].Zhao et al. found that N2 patients had good OS after surgical resection of the primary lung site, with a 5-year survival rate of 35.7% [29]. In their report, Chai et al. described a median OS of 20 months in the surgical group and 15 months in the non-surgical group, demonstrating the beneficial outcome of surgery in N2 patients [30]. Bian et al. showed that surgery plus chemotherapy improved OS in all stage IIIA SCLC patients (including N2) compared with chemotherapy [31]. However, there are also individual reports stating that N2 is a contraindication for surgery [32].

To determine whether surgery improves OS in N2 patients, we subdivided stage III SCLC patients into T3–4/N0–1, T1–2/N2, and T3–4/N2. After PSM analysis, we found that not all N2 patients had improved OS after surgery or surgery plus chemotherapy compared to non-surgery or chemotherapy. Those with T1–4 combined with N0–1 or T1–2 combined with N2 achieved improved OS, whereas those with T3–4 combined with N2 did not. The reason for this may be that the above studies did not subgroup the patients with N2, improving the combined T3–4 N2 OS and CSS indirectly, making the OS of all N2 patients appear to benefit from surgery. These findings reaffirm the need to select eligible patients, which have not been previously considered. However, since the studies described above are retrospective, the validity of the survival benefit due to patient selection needs to be validated by additional evidence.

Finally, we performed RPA analysis, which is an extension of the more detailed subgroup study (forest plot). In case of surgery (versus non-surgery), all stage III SCLC patients who underwent surgery were classified into four risk strata, ranked from lowest to highest based on patient OS outcomes. Notably, a survival benefit was obtained for all risk categories except for the highest risk category encompassing N3 patients, with the following rule: the greater the risk, the less the benefit. In other words, patients selected for lower or earlier risks were likely to receive more surgical rewards. To the best of our knowledge, to date there is no available analysis of RPA associated with surgery in stage III SCLC patients.

In a study conducted at the Central Hospital of Dalian University of Technology, we included 634 patients diagnosed with small cell lung cancer (SCLC) between 2014 and 2023. Our findings revealed that 10.88 % of these patients underwent surgical treatment. This proportion is significantly higher than the 3.19 % surgical intervention rate observed in a study by Kauffmann-Guerrero et al., which analyzed 5043 SCLC patients in Germany from 2002 to 2015. This discrepancy may be attributed to differences in clinical practice patterns, healthcare accessibility, and patient demographics between the two countries. Our analysis suggests that approximately 38,369 patients (7700 – 42,480) in China could potentially benefit from surgical treatment annually. This estimate underscores the substantial impact of surgical intervention on improving survival outcomes for Chinese SCLC patients. Similarly, in Germany, around 2162 patients (434 - 2393) could benefit from surgery each year. The lower number in Germany compared to China may be due to fewer SCLC patients and a lower surgical intervention rate. Sensitivity analysis indicated a range of survival benefits from 6.2 % to 34.2 %, highlighting the variability in treatment outcomes and underscoring the necessity for personalized patient care. Factors such as the stage at diagnosis influence the potential benefits of surgery.

These findings emphasize the importance of individualized treatment strategies to maximize survival benefits for SCLC patients. To conclude, our study indicates that a significant number of patients in both China and Germany could benefit from the procedure on an annual basis.

Overall, our data suggest that only screened stage III SCLC patients benefit from OS and/or CSS after surgery [10,12,33,34]. However, others have described a different clinical scenario where pulmonary surgery may not be appropriate for stage III [12]. The ESMO guidelines only recommend T1–2 N0 M0 SCLC patients for surgery [35]. Tadeusz Lewiński et al. showed that long-term survivors after surgery were mainly N0 and N1 patients, but not N2 patients [36]. Badzio et al. reported a survival advantage for patients with N1 disease who underwent surgery but not for those with N2 disease [37]. Our refined subgroup analysis (Fig. 6) comparing surgery versus non-surgery and, surgery plus chemotherapy versus chemotherapy, showed no benefit in stage III patients with T3–4/N2 or N3. Therefore, we attempt to convey the idea that surgical intervention should not be performed on every patient at this stage; instead, candidates need to be carefully selected before surgery is performed.

Although we demonstrated a positive impact of surgery in stage III SCLC, the retrospective nature of our study underlies its inherent limitations [14,37,38]. First, there is currently no information on the timing and sequence of each treatment modality, including treatment intervals, specific chemotherapy agents, duration of systemic therapy, immunotherapy, and relapse in stage III SCLC. Second, some pathological variables (e.g., marginal status) and surgical details such as lymph node detection are lacking. Third, the bias in the surgical selection of stage III patients may favor those whose general condition is more acceptable before surgery. Individual reports suggest that good functional status may influence OS in patients, information that is lacking in the SEER database [8]. All above-mentioned unbalanced and unquantified covariates may have contributed to the positive results to some extent. To remedy this, the 7th edition of the AJCC staging system from SEER was employed in our analysis to assess TNM-related staging. We also chose several different analytical methods, including PSM, in which all significant confounders were matched and compared to explore more reliable OS-specific factors. Importantly, all results showed a positive correlation between surgery and patient OS and CSS by the analytical methods described above. Yet, in this study we could only include disease-related factors available in the SEER database and no further important information concerning patients clinical background and comorbidities. For example, due to smoking exposure, SCLC patients might have comorbidities that would preclude surgery, such as COPD or cardiac disease, which could not be accounted for in the PSM. This highlights the significance of a selected patient cohort, that could support our findings by additional clinical evidence in the future. However, in our study the results obtained for OS and CSS were very similar, implying that the above comorbidities may not interfere significantly with the outcomes. There may be differences in radiotherapy techniques and chemotherapy regimens between the past and the present, affecting treatment outcomes. However, while these advances represent substantial progress in SCLC treatment, the core principles guiding the management of SCLC remain consistent. The primary goals of achieving maximum tumor control, prolonging survival, and minimizing toxicity continue to underpin treatment decisions. Although our study may reflect historical practice, our findings still provide valuable insights for evaluating the effectiveness of surgery and combined in treating SCLC.

Animal experimentation is essential to scientific research, especially in mechanistic studies and the initial evaluation of new therapies. However, our study did not reveal any new treatments. According to our literature search, we found that the current animal models of SCLC are mainly used to study the mechanism of SCLC and to develop drugs [39,40]. We found no literature on managing surgery, chemotherapy, or radiotherapy in SCLC mouse models. Importantly, animal models face challenges in simulating the clinical scenario of SCLC, particularly disease staging and complex treatment combinations (e.g., surgery combined with chemotherapy). In addition, the effectiveness of surgical treatment largely depends on factors such as surgical technique, patient's specific pathological characteristics, comprehensive treatment strategy, postoperative management, and patient recovery process, which are difficult to reproduce in animal models accurately. Therefore, while we acknowledge the importance of animal studies in some areas,

in the context of our study, a retrospective analysis based on extensive population data more accurately reflects the impact of surgical treatment on the survival of SCLC patients. Our findings provide evidence-based support for treatment strategies, including surgery, especially for patients with specific stages of SCLC.

Despite the lack of additional prospective randomized clinical trials, our large retrospective study based on the SEER database suggests that OS in stage I-III SCLC patients can be improved by surgery, provided these surgical candidates are suitably selected. According to our extensive analysis, patients with stage III T3–4/N0–1 or T1–2/N2 will most likely benefit from primary site surgery or in combination with chemotherapy.

The findings of our study have implications for current treatment guidelines for SCLC. While surgery has traditionally been less commonly utilized in the management of SCLC due to its aggressive nature and propensity for metastasis, our results suggest that surgical intervention may confer survival benefits, particularly in selected patient populations and disease stages. These findings challenge the conventional approach to SCLC treatment and may warrant revisions or updates to existing treatment guidelines to incorporate surgery as a viable option in certain cases.

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CRediT authorship contribution statement

Jianlong Jia: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lilith Trassl:** Writing – review & editing, Validation, Formal analysis. **Fanli Kong:** Conceptualization, Data curation, Investigation, Resources, Validation. **Benteng Deng:** Formal analysis. **Ruonan Liu:** Validation, Methodology. **Zhengwu Sun:** Data curation, Resources. **Xiaoyan Lan:** Data curation, Resources. **Ali Ö. Yildirim:** Supervision, Project administration, Conceptualization. **Georgios T. Stathopoulos:** Supervision, Project administration, Conceptualization. **Isis E. Fernandez:** Supervision, Project administration, Conceptualization. **Andrea C. Schamberger:** Writing – review & editing, Supervision, Project administration, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2024.102070.

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