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Original Article

Efficacy evaluation of surgery combined with chemotherapy for stage IIIA small cell lung cancer patients: a retrospective analysis

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Background: The efficacy of surgery in combination of chemotherapy for stage IIIA small cell lung cancer (IIIA-SCLC) is controversial. The aim of the present study was to analyze the efficacy of surgery combined with chemotherapy, especially in the setting of neoadjuvant chemotherapy (NAC) followed by surgery for IIIA-SCLC.

Methods: Between 2004 and 2015, we reviewed 2,199 chemotherapy-treated stage IIIA (N1/2) SCLC cases in the Surveillance, Epidemiology, and End Results (SEER) database, and 32 NAC + intentional radical resection-treated, centrally-located IIIA-SCLC cases at Shanghai Pulmonary Hospital (SPH). Outcomes were compared between surgically and non-surgically treated patients from the SEER database after propensity score matching (PSM), and comparing lobectomy/bi-lobectomy and pneumonectomy patients from SPH. Prognostic factors were evaluated by Kaplan-Meier method and the Cox proportional hazards regression model.

Results: There was significantly higher overall survival (OS) in surgically treated IIIA-SCLC patients (OS, 44.8 *vs.* 21.2 months, P=0.048), and similar efficacy was observed between sub-lobectomy and lobectomy/bi-lobectomy patients (OS: 55.6 *vs.* 30.3 months, P=0.167) in SEER database. At SPH, significantly higher OS was associated with T1 stage (before NAC: T1 *vs.* T2–4, 48.7 *vs.* 32.2 months, P=0.025; after NAC: T1 *vs.* T2–4, 42.7 *vs.* 21.3 months, P=0.048). Female sex [hazard ratio (HR): 0.078, P=0.009], T1 stage (HR: 13.048, P=0.026), and pneumonectomy (HR: 0.095, P=0.009) were independent prognostic factors for IIIA-SCLC patients who received NAC + intentional radical resection.

Conclusions: For stage IIIA SCLC patients, complete resection combined with chemotherapy might improve the prognosis than patients without surgery. Post-NAC lobectomy was not found to be superior to sub-lobectomy, while pneumonectomy was considered suitable for central-type IIIA-SCLC patients after NAC treatment.

Keywords: Small cell lung cancer (SCLC); limited disease; neoadjuvant chemotherapy (NAC); surgery

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Introduction

Small cell lung cancer (SCLC) is one of the most aggressive type of lung cancer accounting for approximately 15% of thoracic malignancies (1-3). Although early diagnosis and the therapeutic regimens for SCLC have improved in the past 4 decades, improvement in overall survival (OS) remains rather poor (4-7). Previously published studies have demonstrated that patients with untreated limited and extensive SCLC (LD-SCLC and ED-SCLC) have an OS of about 6 and 2 months, respectively, and more than 80% of the patients undergoing standard therapies died within 2 years after diagnosis (8,9). For early-stage SCLC, particularly with no regional lymph node involvement, surgery combined with chemotherapy was the standard therapeutic regimen, and was found to significantly prolong OS (10-12). At the time of diagnosis, more than one third of patients who developed hilar and/or mediastinal lymph node (N1 and N2) involvement, which was defined as locally advanced SCLC (LA-SCLC) (13-15). Because of high recurrence and low OS rates for surgical treated LA-SCLC, surgery has been excluded from potential multimodality regimens since the 1990s (16-18). Current multimodality regimens based on surgery, chemotherapy, targeted therapy, immune checkpoint inhibitors (ICIs), and anti-angiogenic inhibitors (AAIs) have offered positive outcomes in the treatment of stage IIIA SCLC (IIIA-SCLC) disease, according to the TNM staging system for lung cancer (19-24). However, the therapeutic regimen for IIIA-SCLC is still controversial. A number of randomized clinical trials (RCT) on resectable stage I–IIIA SCLC have been carried out to analyze the efficacy of surgery combined with induction therapies (18,25).

In the present article, we reviewed chemotherapy-treated IIIA-SCLC patients in the Surveillance, Epidemiology, and End Results (SEER) database, and neoadjuvant chemotherapy (NAC) + intentional radical resection-treated, central-type IIIA-SCLC at Tongji University affiliated with Shanghai Pulmonary Hospital (SPH).

The aim of the present study was to analyze the efficacy of intentional radical resection in combination with chemotherapy for IIIA-SCLC patients, and to explore the potentially optimal surgical procedures and adjuvant therapeutic regimens. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-545/rc).

Methods

Subjects

From January 2004 to December 2015, we reviewed patients diagnosed with IIIA-SCLC in the SEER database. The TNM stage of all patients was reclassified according to the American Joint Committee on Cancer TNM staging system (8th edition). The patient-selection process is outlined in *Figure 1*. The exclusion criteria were: (I) diagnosis prior to January 2004 or after December 2015; (II) age >80 years; (III) no cytologic/pathologic confirmation in the diagnostic information; (IV) no regional lymph node involvement; (V) missing clinical and/or follow-up information; (VI) patients not treated with chemotherapy; and (VII) patients with previous history of cancer.

Measures and procedures

Patient characteristics, including age at diagnosis, sex, differentiated grade, tumor laterality, tumor stage (T stage), lymph node stage (N stage), therapeutic regimens, and outcomes were collected. Patients were divided into the surgical group and non-surgical group. To eliminate the possibility of selection bias between the 2 groups, 1:1 propensity score matching (PSM) was performed by using the caliper match algorithm with a width of 0.1 of the standard deviation of the logit for the propensity score to evaluate the efficacy of surgical treatment for IIIA-SCLC patients with regional lymph node involvement (N1 or N2 according to TNM 8th edition). Surgically treated patients were separated into the lobectomy or bi-lobectomy group (LG), sub-lobectomy group (S-LG), and pneumonectomy group (PG) to compare the outcomes.

Between January 2004 and December 2015, 32 consecutive NAC plus radical resection-treated, central-type stage IIIA (N2) SCLC patients were reviewed at SPH. All patients in N2 stage were pathological confirmed. Postoperative follow-up was achieved by telephone contact or outpatient visit. The deadline for updating survival information in this study was June 30, 2017. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Shanghai Pulmonary Hospital ethics committee (No. K18-066), and informed consent was taken from all the patients.

Statistics

Statistical analyses were performed by SPSS software

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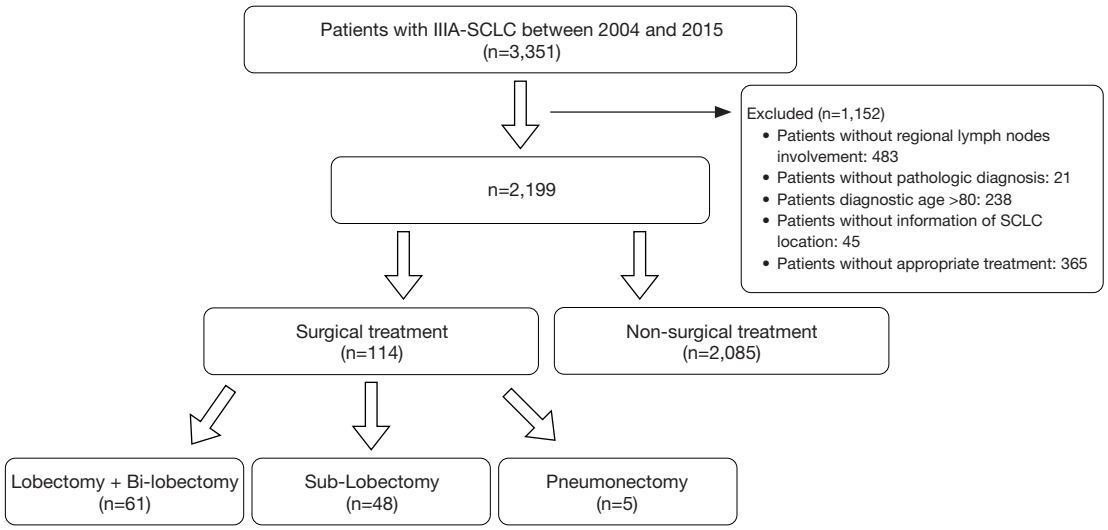

Figure 1 Flowchart of the Surveillance, Epidemiology, and End Results database research selection process. IIIA-SCLC, stage IIIA small cell lung cancer.

(version 26.0; IBM, Armonk, NY, USA). PSM was performed by R version 3.6.2 software (http://www.r-project.org/). Variables of patients' characteristics were compared by Student's *t*-test, χ^2-test, and Fisher's exact test. Kaplan-Meier method and log-rank test were used to compare outcomes. OS was calculated from the time of diagnosis to death. Recurrence-free survival was calculated from the time of surgery to disease relapse (SCLC relapse was confirmed by cytology and/or pathology). Independent predictive factors were calculated using the Cox proportional hazards regression model. Two-tailed P<0.05 was considered statistically significant.

Results

Characteristics of SEER patients

A total of 2,199 patients in the SEER database who had received chemotherapy were included (*Figure 1*). A total of 114 and 2,085 patients received surgical and non-surgical treatment, respectively. The proportion of patients who received radiotherapy in the surgical group was significantly higher than that in the non-surgical group (71.9% *vs.* 24.1%, P<0.001). No significant difference in age at diagnosis was observed between the 2 groups (64 *vs.* 64.4 years, P=0.907). There was no significant difference in the distribution of other variables between the 2 groups. PSM was performed between the surgical and non-surgical subgroups. The number of patients in these 2 subgroups after PSM was 108 in each (*Table 1*).

OS analysis of patients in the SEER database

The results of univariate survival analyses after PSM were listed in *Table 2*. Compared with the non-surgical subgroup, a significantly higher OS was observed in IIIA-SCLC patients who received surgery + chemotherapy (OS, surgery *vs.* non-surgery, 44.8 *vs.* 21.2 months, P=0.048) (*Figure 2A*). As shown in *Tables 3,4*, 61 and 48 patients received lobectomy/bi-lobectomy and sub-lobectomy, respectively. Compared with lobectomy, sub-lobectomy could provide similar OS in NAC treated IIIA stage SCLC (OS, sub-lobectomy *vs.* anatomical lobectomy, 55.6 *vs.* 30.3 months, P=0.167) (*Figure 2B*).

Characteristics of patients from SPH

A total of 32 centrally-located IIIA-SCLC patients (age range, 37–76 years) received NAC at SPH, and 29 patients received 2 NAC cycles (90.6%). Etoposide + carboplatin/cisplatin (EP/EC) were given to 26 patients (81.3%). Significantly better OS was observed in patients with NAC plus intentional radical resection compared with patients who received non-surgical treatment (29.7 *vs.* 16.2 months). According to paired-samples Student's *t*-test, the median tumor size decreased significantly after NAC treatment (maximum dimension of SCLC, pre-NAC *vs.* post-NAC, 43

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Table 1 Baseline characteristics of patients with chemotherapy-treated IIIA-SCLC before and after PSM in the SEER database

Variables	Subtypes	Unmatched			PSM		
		Surgery	No surgery	P value	Surgery	No surgery	P value
Age (years)		64.0	64.4	0.907	64.2	63.5	0.521
Sex, n (%)	Male	50 (43.9)	906 (43.5)	0.932	50 (46.3)	45 (41.7)	0.583
	Female	64 (56.1)	1,179 (56.5)		58 (53.7)	63 (58.3)	
Location, n (%)	Left	52 (45.6)	776 (37.2)	0.072	51 (47.2)	50 (46.3)	1.000
	Right	62 (54.4)	1,309 (63.8)		57 (52.8)	58 (53.7)	
T stage, n (%)	T1	47 (41.2)	778 (37.3)	0.227	47 (43.5)	55 (50.9)	0.503
	T2	55 (48.2)	1,155 (55.4)		55 (50.9)	49 (45.4)	
	T3–4	12 (10.5)	152 (7.3)		6 (5.6)	4 (3.7)	
N stage, n (%)	N1	12 (10.5)	152 (7.3)	0.200	6 (5.6)	4 (3.7)	0.436
	N2	102 (89.5)	1,933 (92.7)		102 (94.4)	104 (96.3)	
Radiotherapy, n (%)	With	82 (71.9)	502 (24.1)	<0.001	76 (70.4)	76 (70.4)	1.000
	Without	32 (28.1)	1,583 (75.9)		32 (29.6)	32 (29.6)	
Total		114	2,085		108	108	

IIIA-SCLC, stage IIIA small cell lung cancer; PSM, propensity score matching; SEER, Surveillance, Epidemiology, and End Results database.

Table 2 Univariate analysis for OS of chemotherapy-treated IIIA-SCLC after PSM in the SEER database

Variables	Subtypes	OS			
		Rate (%)	Time (month)	95% CI	P value
Age (years)	≤65	31.0	37.8	28.7–47.0	0.856
	>65	36.0	36.8	27.0–46.6	
Sex	Male	33.7	36.2	26.8–45.6	0.692
	Female	33.1	37.6	28.8–46.4	
Location	Left side	41.6	38.0	28.7–47.3	0.373
	Right side	26.1	35.8	27.3–44.3	
T stage	T1	37.3	42.6	31.7–53.5	0.442
	T2	28.8	32.1	24.8–39.4	
	T3–4	40.0	15.6	11.9–19.4	
N stage	N1	40.0	15.6	11.9–19.4	0.419
	N2	33.0	38.7	31.6–45.7	
Surgery	With	34.3	44.8	34.5–55.2	0.048
	Without	32.4	21.2	21.5–34.9	
PORT	With	36.2	41.2	32.7–49.8	0.077
	Without	26.6	30.6	20.0–41.3	

OS, overall survival; IIIA-SCLC, stage IIIA small cell lung cancer; PSM, propensity score matching; SEER, Surveillance, Epidemiology, and End Results database; CI, confidence interval; PORT, postoperative radiotherapy.

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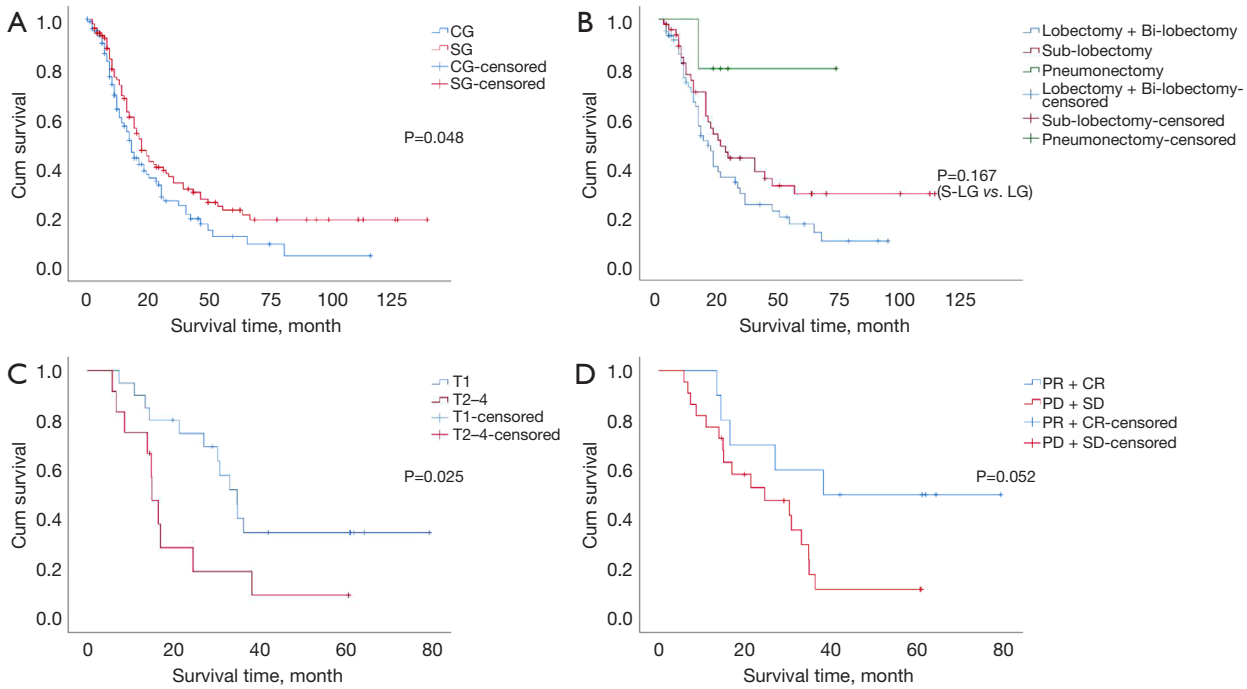

Figure 2 OS of chemotherapy-treated IIIA-SCLC with or without surgery (SG *vs.* CG) (A) and different surgery types (B) according to the Surveillance, Epidemiology, and End Results database patient analysis. OS of radical resection-treated IIIA-SCLC concerning different T-stage pre-NAC (C) and different responses to NAC (D) according to the SPH patient analysis. OS, overall survival; IIIA-SCLC, stage IIIA small cell lung cancer; SG, surgery group; CG, non-surgery group; S-LG, sub-lobectomy group; LG, lobectomy/bi-lobectomy group; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NAC, neoadjuvant chemotherapy; SPH, Shanghai Pulmonary Hospital.

Table 3 Baseline characteristics of surgery + chemotherapy-treated IIIA-SCLC in the SEER database

Variables	Subtypes	S-LG	LG	PG	P value
Age (years), median (range)		64.6 (62.2–67.0)	63.6 (61.3–65.9)	62.6 (47.4–77.9)	0.807
Sex, n (%)	Male	18 (37.5)	30 (49.2)	2 (40.0)	0.438
	Female	30 (62.5)	31 (50.8)	3 (60.0)	
Location, n (%)	Left	24 (50.0)	24 (39.3)	4 (80.0)	0.175
	Right	24 (50.0)	37 (60.7)	1 (20.0)	
T stage, n (%)	T1	24 (50.0)	23 (37.7)	0 (0.0)	0.004
	T2	23 (47.9)	30 (49.2)	2 (40.0)	
	T3–4	1 (2.1)	8 (13.1)	3 (60.0)	
N stage, n (%)	N1	1 (2.1)	8 (13.1)	3 (60.0)	0.002
	N2	47 (97.9)	53 (86.9)	2 (40.0)	
PORT, n (%)	With	36 (75.0)	44 (72.1)	2 (40.0)	0.241
	Without	12 (25.0)	17 (27.9)	3 (60.0)	
Total		48	61	5	

IIIA-SCLC, stage IIIA small cell lung cancer; SEER, Surveillance, Epidemiology, and End Results database; S-LG, sub-lobectomy group; LG, lobectomy/bi-lobectomy group; PG, pneumonectomy group; PORT, postoperative radiotherapy.

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Table 4 Univariate analysis for OS and lung CSS of surgery + chemotherapy-treated IIIA-SCLC in the SEER database

Variables	Subtypes	OS				CSS			
		Rate (%)	Time (month)	95% CI	P value	Rate (%)	Time (month)	95% CI	P value
Age (years)	<65	39.0	51.8	36.7–66.9	0.358	39.0	51.8	36.7–66.9	0.670
	≥65	32.7	37.7	25.2–50.2		40.0	41.1	27.4–54.8	
Sex	Male	32.0	43.1	33.7–60.4	0.946	34.0	43.9	29.7–58.1	0.784
	Female	39.1	47.1	29.1–57.0		43.8	50.4	36.4–64.5	
Location	Left side	38.5	41.6	29.2–53.9	0.652	44.2	44.8	31.6–57.9	0.656
	Right side	33.9	45.9	32.1–59.7		35.5	46.9	32.7–60.7	
T stage	T1	40.4	55.6	38.4–72.7	0.297	42.6	56.7	39.4–74.1	0.393
	T2	29.1	32.9	23.4–42.4		34.5	34.9	24.7–45.1	
	T3–4	50.0	38.1	20.3–55.9		50.0	38.1	20.3–55.9	
N stage	N1	50.0	38.1	20.3–55.9	0.864	50.0	38.1	20.3–55.9	0.989
	N2	34.3	45.8	35.2–56.5		38.2	48.1	36.9–59.2	
Surgery	Lobectomy	29.5	30.3	22.7–37.9	0.052	31.1	30.8	23.1–38.6	0.031
	Sub-lobectomy	39.6	55.6	38.7–72.5		45.8	60.0	42.2–77.8	
	Pneumonectomy	80.0	60.8	41.2–80.4		80.0	60.8	41.2–80.4	
PORT	With	36.6	50.3	38.1–62.3	0.111	40.2	52.3	39.7–65.0	0.104
	Without	34.4	37.1	19.5–54.6		37.5	41.7	22.9–60.5	

OS, overall survival; CSS, cancer-specified survival; IIIA-SCLC, stage IIIA small cell lung cancer; SEER, Surveillance, Epidemiology, and End Results database; CI, confidence interval; PORT, postoperative radiotherapy.

vs. 19.4 mm, P<0.001). Compared with patients in the LG, the median tumor size after NAC was significantly larger in the PG (26.8 *vs.* 18.9 mm, P=0.014) (*Table 5*).

SPH patients outcomes

Table 6 manifested that compared with patients with advanced T stage, significantly higher OS was observed in patients with T1 stage (before NAC: 48.7 *vs.* 32.2 months, P=0.025; after NAC: 42.7 *vs.* 21.3 months, P=0.048) (*Figure 2C*, *Table 6*). Cox proportional hazards regression model revealed that the female [female: male, hazard ratio (HR): 0.078, 95% confidence interval (CI): 0.012–0.525, P=0.009], T1 stage at diagnosis (T2–4: T1, HR: 13.048, 95% CI: 1.358–125.385, P=0.026), and pneumonectomy (pneumonectomy: lobectomy, HR: 0.095, 95% CI: 0.016–0.555, P=0.009) were independent prognostic factors for OS (*Table 7*).

Discussion

SCLC remains a very aggressive and lethal malignant disease. The core treatment for SCLC is chemotherapy in combination with anti-PD-L1 antibodies, for which EP/EC plus Atezolizumab/Durvalumab, particularly for LA-SCLC and ED-SCLC, is most used and significantly improved prognosis (7,22,25-29). The efficacy of surgery combined with chemotherapy for LA-SCLC remains controversial (10). In the past 3 decades, surgically treated LA-SCLC has been relatively rare, particularly SCLC with regional lymph node involvement (4-6). Our analysis of patients in the SEER database indicated that, compared with non-surgical treated LA-SCLC, a significantly higher OS was associated with surgery plus chemotherapy (median OS: 44.8 *vs.* 21.2 months). The results of the SPH patient analysis largely verified our findings from our SEER database analysis that NAC plus surgery is potentially an effective treatment for IIIA-SCLC.

Previously published studies have demonstrated that the strongest prognostic factor for SCLC is regional lymph node involvement (30). Significantly higher OS has been observed in patients with neoadjuvant therapy plus radical resection (19,20,31). Based on these findings, surgical

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Table 5 Baseline characteristics of neoadjuvant chemotherapy + radical surgery-treated IIIA-SCLC in SPH patients

Variables	Subtypes	LG (%)	PG (%)	P value
Age (years)		58.0	53.0	0.424
Tumor size (mm)	Pre-NAC	36.2	49.9	0.281
	Post-NAC	18.9	26.8	0.014
Sex	Male	11 (73.3)	15 (88.2)	0.383
	Female	4 (26.7)	2 (11.8)	
Smoking status	Yes	6 (40.0)	7 (41.2)	0.946
	No	9 (60.0)	10 (58.8)	
Location	Left	4 (26.7)	10 (58.8)	0.067
	Right	11(73.3)	7 (41.2)	
T stage (pre-NAC)	T1	6 (40.0)	0 (0.0)	0.006
	T2–4	9 (60.0)	17 (100.0)	
T stage (post-NAC)	T1	9 (60.0)	11 (64.7)	0.784
	T2–4	6 (40.0)	6 (35.3)	
N stage (post-NAC)	N0–1	6 (40.0)	3 (17.6)	0.157
	N2	9 (60.0)	14 (82.4)	
Pathology	Pure SCLC	11 (73.3)	11 (64.7)	0.599
	Combined SCLC	4 (26.7)	6 (35.3)	
ADC	With	12 (80.0)	16 (94.1)	0.228
	Without	3 (20.0)	1 (5.9)	
ADR	With	4 (26.7)	8 (47.1)	0.234
	Without	11(73.3)	9 (52.9)	
Recurrence	With	9 (60.0)	9 (52.9)	0.688
	Without	6 (40.0)	8 (47.1)	
Total		15	17	

IIIA-SCLC, stage IIIA small cell lung cancer; SPH, Shanghai Pulmonary Hospital database; LG, lobectomy/bi-lobectomy group; PG, pneumonectomy group; NAC, neoadjuvant chemotherapy; ADC, adjuvant chemotherapy; ADR, adjuvant radiotherapy.

treatment might not be considered as a contraindication for IIIA-SCLC, and neoadjuvant and adjuvant chemotherapy or immunotherapy should be planned to enhance therapeutic effects.

The criteria for IIIA-SCLC surgery needs to be improved. First, NAC-treated patients whose tumor size reduces to less than 3 cm and receives radical resection could have significantly better OS. Therefore, a significantly better OS could be offered through radical-resection surgery to patients who have a consistent response to NAC. Moreover, IIIA-SCLC OS could be prolonged by chemotherapy plus surgery, regardless of the status of regional lymph node involvement. These results also support the findings of a previously published study that reported that a significant difference in OS was not observed between N1 and N2 lymph node-positive patients (19). Then, compared with patients who achieved complete or partial response after NAC, SCLC patients with stable disease followed by surgery could have worse OS, although no statistical difference is observed (*Figure 2D*). Therefore, no matter how neoadjuvant therapeutic responses are, NAC plus surgery, including pneumonectomy, is potentially beneficial for IIIA-SCLC patients.

With the expansion of surgical indications for LA-

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Table 6 Univariate analysis for OS and RFS of neoadjuvant chemotherapy + radical surgery-treated IIIA-SCLC in SPH patients

Variables	Subtypes	RFS				OS			
		Rate (%)	Time (month)	95% CI	P value	Rate (%)	Time (month)	95% CI	P value
Age	<55 years	40.0	29.7	16.1–43.4	0.632	26.7	30.4	19.6–41.2	0.640
	≥55 years	47.1	38.8	21.5–56.0		35.3	38.4	24.5–51.9	
Sex	Male	46.2	37.6	23.5–51.7	0.890	30.8	35.3	24.7–45.9	0.693
	Female	33.3	28.8	11.0–46.6		33.3	33.5	16.5–50.5	
Smoking status	Yes	46.2	29.8	13.8–45.8	0.672	30.8	26.7	15.1–38.3	0.353
	No	42.1	37.2	22.0–52.3		31.6	39.8	27.6–52.0	
Location	Left side	28.6	23.2	10.3–36.0	0.109	28.6	29.2	17.3–41.0	0.367
	Right side	55.6	44.6	27.6–61.7		33.3	39.3	26.9–51.7	
T stage (pre-NAC)	T1	50.0	36.2	15.3–57.1	0.545	66.7	48.7	35.8–61.6	0.025
	T2–4	42.3	34.4	20.6–48.1		23.1	32.2	22.1–43.4	
T stage (post-NAC)	T1	45.5	39.7	25.1–54.2	0.325	40.9	42.7	30.6–54.8	0.048
	T2–4	40.0	20.5	10.5–30.5		10.0	21.3	11.6–31.1	
N stage (post-NAC)	N0–1	44.4	33.9	16.3–51.5	0.625	44.4	40.7	26.2–55.2	0.166
	N2	43.5	33.3	18.7–48.1		26.1	31.1	20.8–41.5	
Response to NAC	Downstaging	50.0	44.4	22.9–65.9	0.340	50.0	50.6	32.3–68.9	0.052
	No downstaging	40.9	25.8	15.1–36.5		22.7	26.3	19.1–33.4	
Pathology	Pure SCLC	45.5	40.3	26.0–54.6	0.164	40.9	41.4	28.7–54.1	0.230
	Combined SCLC	40.0	27.3	9.3–45.4		10.0	25.4	15.1–35.7	
NAC plan	EC/EP	46.2	39.8	26.1–53.5	0.161	34.6	39.4	28.8–50.0	0.062
	Other	33.3	18.7	4.0–33.3		16.7	19.7	4.5–34.9	
Surgery	Lobectomy/bi-lobectomy	40.0	27.7	14.3–41.2	0.643	33.3	31.9	21.1–42.6	0.983
	Pneumonectomy	47.1	38.5	21.5–55.4		29.4	36.7	33.7–49.8	
ADC	With	42.9	34.4	20.8–48.0	0.382	28.6	33.4	23.3–43.6	0.191
	Without	50.0	32.8	20.7–44.8		50.0	46.1	31.6–60.7	
ADR	With	33.3	32.5	14.5–50.4	0.723	33.3	38.4	24.6–52.2	0.566
	Without	50.0	34.5	21.9–47.1		30.0	30.3	20.2–40.3	

OS, overall survival; RFS, recurrence-free survival; IIIA-SCLC, stage IIIA small cell lung cancer; SPH, Shanghai Pulmonary Hospital database; CI, confidence interval; NAC, neoadjuvant chemotherapy; ADC, adjuvant chemotherapy; ADR, adjuvant radiotherapy; EC/EP, etoposide + carboplatin/cisplatin.

SCLC, the investigation of what surgery was performed is also carried out. In clinical work, individualized surgical strategy for different patients is in line with the basic surgical principles. Firstly, it is understandable that N1 involvement and advanced clinical T stage LA-SCLC patients were treated by lobectomy or bi-lobectomy. They could remove disease completely and could significantly improve patients' outcomes. Second, for IIIA-SCLC with N2 involvement and a relatively smaller tumor size, radical resection is difficult, while sub-lobectomy could meet the needs of complete resection for primary lesions and preserve the postoperative pulmonary function of patients (32). According to the results of the SEER database analysis, a better outcome of IIIA-SCLC was not observed

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Table 7 Multivariate analysis for OS and RFS of neoadjuvant chemotherapy + radical surgery-treated IIIA-SCLC in SPH patients

Variables (reference)	Subtypes	RFS			OS		
		Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age, years (<55)	≥55	0.435	0.125–1.517	0.192	0.772	0.225–2.655	0.682
Sex (male)	Female	0.483	0.066–3.529	0.474	0.078	0.012–0.525	0.009
Smoking status (no)	Yes	0.585	0.258–11.025	0.585	0.772	0.151–3.950	0.756
Location (left side)	Right side	0.179	0.046–0.704	0.014	0.543	0.151–1.945	0.348
Pre-NAC T stage (T1)	T2–4	2.773	0.231–33.260	0.421	13.048	1.358–125.385	0.026
Post-NAC T stage (T1)	T2–4	0.924	0.088–9.651	0.947	3.473	0.697–17.299	0.129
Post-NAC N stage (N0–1)	N2	1.223	0.434–3.450	0.703	2.774	0.778–9.895	0.116
Response to NAC (DS)	Non-DS	1.197	0.313–4.575	0.793	2.887	0.731–11.410	0.131
Pathology (pure SCLC)	Combined SCLC	8.424	1.177–60.295	0.034	0.905	0.265–3.088	0.873
NAC plan (EC/EP)	Other	3.185	0.578–17.552	0.183	4.446	0.801–24.686	0.088
Surgery (lobectomy/bi-lobectomy)	Pneumonectomy	0.195	0.028–1.349	0.098	0.095	0.016–0.555	0.009
ADC (without)	With	1.187	0.087–16.1805	0.898	2.831	0.322–24.9093	0.348
ADR (without)	With	4.268	0.631–28.847	0.137	1.215	0.220–6.701	0.823

OS, overall survival; RFS, recurrence-free survival; IIIA-SCLC, stage IIIA small cell lung cancer; SPH, Shanghai Pulmonary Hospital database; NAC, neoadjuvant chemotherapy; DS, downstaging; ADC, adjuvant chemotherapy; ADR, adjuvant radiotherapy; CI, confidence interval.

by extended resection, especially for patients with N2 involvement. Sub-lobectomy combined with appropriate adjuvant therapies is a safe and effective treatment, and offers beneficial outcomes. On the other hand, sub-lobar resection is as effective as lobectomy, surgery itself might have a limited role as prognostic factor. The results for the SPH analysis for central-type disease confirm that radical resection on primary tumors is an important procedure. Therefore, for central-type IIIA-SCLC patients who received NAC, pneumonectomy is associated with the best prognosis.

Analysis of the selection and use of postoperative adjuvant therapy, particularly for NAC-treated LA-SCLC patients, is the most crucial step in research to be performed next. Previously published studies have reported that standard treatments for postoperative SCLC are platinum-based chemotherapy with thoracic radiation; however, the effect of postoperative treatment remains clear (33,34). Based on the findings from the SPH patient analysis, the effect of existing postoperative adjuvant therapy is relatively limited. Adjuvant chemotherapy was not found to improve the OS of patients who received NAC plus radical resection. With the development of ICIs and AAIs for the treatment of ED-SCLC, the next step is to discuss their role in neoadjuvant and adjuvant therapy, which should be confirmed by RCTs (26,35). There is a high rate of SCLC treatment failure due to brain metastasis (13,14). Therefore, according to the current National Comprehensive Cancer Network guidelines, chemoradiotherapy in combination with adjuvant prophylactic cranial irradiation (PCI) is recommended as the standard treatment for IIIA-SCLC (7,36). The effect of adjuvant radiotherapy and PCI for NAC plus radical resection IIIA-SCLC patients warrants further research (37).

Limitations

This retrospective study based on SEER and SPH database had some limitations inevitably. First, the information of dosage and cycle of chemotherapy could not be enrolled in SEER. Second, SEER would not contain the information on whether surgery or chemotherapy was administered first. Third, we would not know the reason clearly why the proportion of patients underwent sub-lobal resection was high in SEER. Fourth, the sample size of SPH is small relatively, which limits the possibility of utilizing

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more advanced statistical methods and discussing more prognostic factors for LA-SCLC, especially PCI and radiotherapy. In next work, prospective clinical trials concerning NAC or chemotherapy in combination with immunotherapy followed by radical surgery for LA-SCLC has been conducted in our center. We attempted to explain the confusions caused by these limitations by the next work.

Conclusions

Compared with non-surgical regimens, NAC followed by complete resection might improve the prognosis for IIIA-SCLC patients. After NAC treatment, IIIA-SCLC, particularly primary tumors with consistent response to NAC, surgical treatment should be performed surgical treatment as long as the patients can tolerate it. The efficacy of radical sub-lobectomy seems to be inferior compared with lobectomy alone for NAC-treated IIIA-SCLC. For central-type disease, NAC followed by intentional radical primary tumor resection is a suitable therapeutic approach. Further studies on postoperative adjuvant treatments are warranted, and relevant conclusions should be verified by RCTs.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Shanghai Pulmonary Hospital ethics committee (No. K18-066), and informed consent was taken from all the patients.

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