Research Paper

Efficacy of surgery and prophylactic cranial irradiation in stage II and III small cell lung cancer

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Abstract

Background: The role of surgery for stage II and III small cell lung cancer (SCLC) remains controversial. The use of prophylactic cranial irradiation (PCI) for resected SCLC was limited. This study aimed to assess the efficacy of surgery in patients with stage II and III SCLC, and evaluate the value of PCI on resected disease.

Methods: A total of 269 consecutive patients with stage II-IIIA SCLC were retrospectively reviewed from January 2010 to December 2015. Of these, 116 patients received surgical resection, and 153 underwent non-surgical treatment. Resected patients were matched 1:1 with non-surgical patients (n=70 in each group).

Results: The median follow-up was 30 months. The 1-, 3- and 5-year overall survival (OS) for matched patients were 80.0%, 44.3% and 31.7% in surgical group, and 80.0%, 24.3% and 20.0% in non-surgical group (P=0.009), respectively. Multivariate analysis in matched patients showed that surgery (HR=0.603, 95%CI: 0.404-0.900) and PCI (HR=0.637, 95%CI: 0.427-0.950) were independent prognostic factors for OS. In subgroup analysis, OS benefit related to surgery was marginal for stage II (P=0.09) and IIIA patients (P=0.061), but was significant for selected stage IIIA patients who received adjuvant chemo-radiation and PCI (P=0.01). PCI was associated with improved OS for non-surgical patients (P=0.036), and stage IIIA of surgical patients (P=0.047).

Conclusions: These findings suggest a potential OS benefit of surgery in stages II and IIIA patients, particularly in selected stage IIIA patients who received adjuvant chemo-radiation and PCI. The use of PCI for surgical patients with stage IIIA was associated with improved OS.

Key words: Small cell lung cancer; Surgical resection; Chemotherapy; Radiotherapy; Prophylactic cranial irradiation

Introduction

Small cell lung cancer (SCLC) represents approximately 13-15% of all lung cancers [1, 2], and is characterized by rapid growth, early metastases, and poor prognosis [3]. The standard treatment in most of the patients with limited disease SCLC is the combination of chemotherapy and thoracic radiotherapy (RT) [4, 5]. However, local recurrences are reported to be as high as 50%, and the overall prognosis is poor [6-8]. Two randomized clinical trials

(RCT) performed two decades ago have proven that there is no survival advantage of surgery compared with non-surgical treatment [9, 10]. However, recent data from some retrospective studies including several population database studies have demonstrated a potential benefit from surgery in patients with limited disease [11-19].

The positive role of prophylactic cranial irradiation (PCI) on long-term survival has been

established for nonsurgical patients with limited disease and has been recommended by NCCN for patients who respond to treatment [20]. However, few studies have assessed the use of PCI for resected SCLC. Several retrospective studies have investigated the risk of brain metastasis according to the stage, but showed inconsistent results [21-25]. The value of PCI in this population needs further investigation.

Hence, this study aimed to assess the efficacy of surgery in stage II to III SCLC and evaluate the role of PCI in patients with resected SCLC.

Patients and methods

Patients

Between January 2010 and December 2015, 335 consecutive patients with limited stage SCLC were initially treated at our hospital. Most of the patients underwent standardized evaluation including thoracic and abdominal CT scanning or abdominal ultrasonography, brain magnetic resonance imaging (MRI) and bone radionuclide imaging, confirming the disease stage as stage II to III. TNM staging was determined according to the newly revised classification for lung cancer (American Joint Committee on Cancer seventh edition) [26]. Patients were excluded if they had stage IIIB disease (n=46), without pathological identification (n=5), who underwent incomplete resections (n = 4), who lost to follow-up or with missing or erroneous data (n = 11). After excluding, a total of 269 patients were included in this study. Of these, 153 underwent non-surgical treatment, and 116 received surgical resection. This retrospective study was approved by the Regional Ethics Committee of our institution, in compliance with the Helsinki Declaration (1996).

Treatment

Of the 116 patients who underwent complete tumor resection followed by adjuvant chemotherapy or chemoradiotherapy, 98 (84.5%) received lobectomy, 11 (9.5%) received wedge resection and 7 (6.0%) received pneumonectomy. Among them, 61 (52.6%) received PCI. Of the 153 patients who underwent non-surgical treatment, all patients received chemotherapy combined with thoracic RT, and 99 (64.7%) received PCI. The most frequently administered chemotherapy regimen was cisplatin and etoposide (PE) either in surgical group or non-surgical group, for every 3 weeks cycle, and used for a total of 4-6 cycles. Three-dimensional conformal RT (3D-CRT)/intensity modulated RT (IMRT) was used for patients receiving thoracic RT. The prescribed dose for thoracic RT was 50–60 Gy in 2.0-Gy daily fractions for patients in non-surgical group and 46–56 Gy in 2.0-Gy daily fractions for patients in surgical group. The prescribed dose for PCI was 30-40Gy in 2.0-3.0Gy daily fractions.

Follow-up

The last follow-up date was February 28, 2018. Most of the patients were followed up every 3-6 months for the first year, every 6 months for the next 2 years, and then annually until death. Survival information was collected via telephone if the patient could not visit the clinic on schedule.

Statistical analysis

Statistical analysis was performed using SPSS software version 24.0 (SPSS, Inc., Chicago, IL, USA). Overall survival (OS) was defined as the time from the initiation of treatment until death from any cause. Analysis of OS was carried out using the Kaplan–Meier method, and the difference between survival curves was tested by log-rank test. Variables with $P < 0.1$ were included for multivariate analysis using the Cox regression model. To reduce the effects of selection bias and confounding factors, propensity score matching (PSM) was performed to compare the groups. Patients were matched according to the propensity scores based on age, sex, TNM stage, and ECOG score with 1:1 ratio using the nearest neighbor matching method [27]. For all analyses, $P < 0.05$ was considered statistically significant.

Results

Characteristics of the study population before and after matching are shown in Table 1. Characteristics of the study population before and after matching between surgical and NST groups are shown in Table 2. ECOG score, N stage, and TNM stage in the overall study cohort were significantly different between surgical and NST groups (Table 2). The PSM cohort (including 70 patients in surgical group and 70 patients in non-surgical group) showed an expected balance of covariates in the two groups (Table 2). The detailed treatment regimens for the two groups before and after matching are shown in Table 3. For surgical group, matched patients receiving adjust chemo-radiation was relatively more than non-matched patients (71.4% vs. 50%). For NST group, the treatment was similar between matched and non-matched patients.

The response rates [complete response (CR) + partial response (PR)] were 74.5% (114/153) in non-surgical group. Median follow-up for all patients was 30 months (range, 3–87 months), with 32 months (range, 3–79 months) for surgical group patients, and 28 months (range, 5–87 months) for the non-surgical group patients.

Table 1. Characteristics of the study population before and after matching

Characteristic	Before Matching(n=269)	After Matching(n=140)
	No (%)	No (%)
Sex		
Male	173(64.3)	81(57.9)
Female	96(35.7)	59(42.1)
Age		
≥60	92(34.2)	47(33.6)
<60	177(65.8)	93(66.4)
Smoking history		
Yes	176(65.4)	88(62.9)
No	93(34.6)	52(37.1)
ECOG score		
0-2	259(96.3)	140(100)
3	10(3.7)	0(0)
Tumor location		
Central	122(45.4)	61(43.6)
Peripheral	147(54.6)	79(56.4)
T stage		
T1	51(19.0)	24(17.1)
T2	116(43.1)	67(47.9)
T3	97(36.1)	49(35.0)
T4	5(1.8)	0(0)
N stage		
N0	43(16.0)	19(13.6)
N1	86(32.0)	39(27.9)
N2	140(52.0)	82(58.6)
TNM Stage		
II	84(31.2)	38(27.1)
IIIA	185(68.8)	102(72.9)
Treatment		
Surgical	116(43.1)	70(50)
NST	153(56.9)	70(50)

Abbreviations: NST: non-surgical treatment.

Table 2. Characteristics of the study population before and after matching between surgical and NST groups.

Characteristic	Before Matching(n=269)			After Matching (n=140)		
	Surgical (n=116) No(%)	NST (n=153) No(%)	P value	Surgical (n=70) No(%)	NST (n=70) No(%)	P value
Sex						
Male	77(66.4)	96(62.7)	0.538	38(54.3)	43(61.4)	0.392
Female	39(33.6)	57(37.3)		32(45.7)	27(38.6)	
Age						
≥60	36(31.0)	56(36.6)	0.340	25(35.7)	22(31.4)	0.591
<60	80(69.0)	97(63.4)		45(64.3)	48(68.6)	
Smoking history						
Yes	75(64.7)	101(66.0)	0.817	43(61.4)	45(64.3)	0.726
No	41(35.3)	52(34.0)		27(38.6)	25(35.7)	
ECOG score						
0-2	116(100.0)	143(93.5)	0.013	70(100.0)	70(100.0)	--
3	0(0.0)	10(6.5)		0(0.0)	0(0.0)	
Tumor location						
Central	48(41.4)	74(48.4)	0.254	32(45.7)	29(41.4)	0.609
Peripheral	68(58.6)	79(51.6)		38(54.3)	41(58.6)	
T stage						
T1	22(19.0)	29(19.0)	0.227	9(12.9)	15(21.4)	0.148
T2	54(46.6)	62(40.5)		39(55.7)	28(40.0)	
T3	40(34.4)	57(37.3)		22(31.4)	27(38.6)	
T4	0(0)	5(3.2)		0(0)	0(0)	
N stage						
N0	28(24.1)	15(9.8)	<0.001	9(12.9)	10(14.3)	0.352
N1	43(37.1)	43(28.1)		16(22.9)	23(32.9)	
N2	45(38.8)	95(62.1)		45(64.3)	37(52.9)	
TNM stage						
II	65(56.0)	19(12.4)	<0.001	19(27.1)	19(27.1)	1.00
IIIA	51(44.0)	134(87.6)		51(72.9)	51(72.9)	

Abbreviations: NST: non-surgical treatment.

Table 3. The initial treatment before and after matching

Treatment	Before Matching, N(%)	After Matching, N(%)
Surgical group (n=116)		
Surgical schedule		
Surgery only	11(9.5)	5(7.1)
Surgery + CT	47(40.5)	15(21.4)
Surgery + CRT	58(50.0)	50(71.4)
Surgical procedure		
lobectomy	98 (84.5)	60(85.7)
wedge resection	11 (9.5)	6(8.6)
pneumonectomy	7 (6.0)	4(5.7)
PCI		
Yes	61(52.6)	44(62.9)
No	55(47.4)	26(37.1)
NST group (n=153)		
NST schedule		
CT only	0(0)	0(0)
RT only	0(0)	0(0)
CRT	153(100)	70(100)
PCI		
Yes	99(64.7)	44(62.9)
No	54(35.3)	26(37.1)

Abbreviations: NST: non-surgical treatment; CT: chemotherapy; RT: radiotherapy; CRT: chemoradiotherapy; PCI: prophylactic cranial irradiation.

Survival

The median survival for all patients was 30 months, with 38 months for the surgical group, and 28 months for the non-surgical group patients. The 1-, 3- and 5-year OS rates were 82.8%, 50.7% and 38.8% for surgical group, and 83.0%, 37.7% and 24.9% for non-surgical group (P=0.029), respectively, which showed statistical significance. These findings were confirmed in the matched patients. The median survival for all patients was 23 months, with 32 months for the surgical group, and 20 months for the non-surgical group. The 1-, 3- and 5-year OS were 80.0%, 44.3.0% and 31.7% for surgical group, and 80.0%, 24.3% and 20.0% for non-surgical group (P=0.009; Fig. 1A), respectively, which showed statistical significance.

Analysis of factors related to OS

Univariate analysis of all and matched patients demonstrated that surgery (P=0.029 and P=0.009) and PCI (P=0.03 and P=0.037) were significantly associated with improved OS (Tables 4, 5). Lower TNM stage was significantly considered to be a positive prognostic factor for all patients (P=0.024; Table 4).

In multivariate Cox regression analysis, PCI was an independent prognostic factor for OS of all [hazards ratio (HR)=0.665, 95% confidence interval (CI): 0.492-0.899; (Table 4) and matched patients (HR=0.637, 95%CI: 0.427-0.950; Table 5). Additionally, surgery was an independent prognostic factor in matched patients (HR=0.603, 95%CI: 0.404-0.900; Table 5).
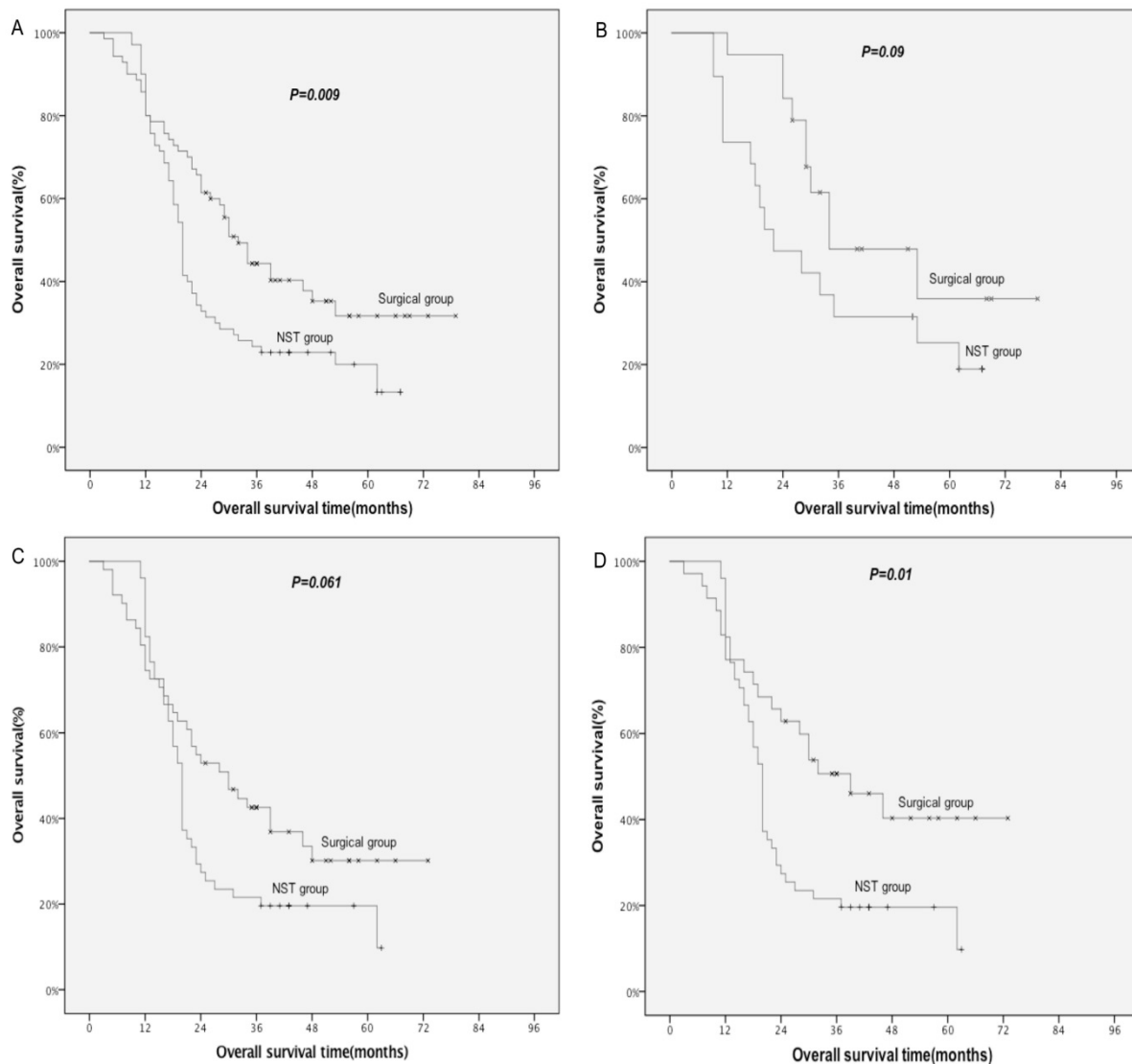
Figure 1. Comparison of OS between NST group and surgical group in matched patients. A: all; B: stage II; C: stage IIIA; D: selected stage IIIA. NST: non-surgical treatment; selected stage IIIA: surgical patients who received adjuvant chemo-radiation and prophylactic cranial irradiation.

Subgroup analysis of matched patients (Table 6) demonstrated a marginal OS benefit from surgery for stage II (P=0.09; Fig. 1B) and IIIA (P=0.061; Fig. 1C). A significantly improved OS was observed for selected stage IIIA patients who received adjuvant chemoradiotherapy and PCI in surgical group when compared with stage IIIA patients in non-surgical group (P=0.01; Fig. 1D).

Improved OS related to PCI was found for non-surgical patients (P=0.036), but not for surgical patients (P=0.172; Table 7; Fig. 2A). Further subgroup analysis of surgical patients demonstrated a survival advantage with the use of PCI in stage IIIA patients (P=0.047; Table 7; Fig. 2B).

Discussion

The role of surgery for limited-stage SCLC remains controversial due to lack of conclusive evidence. A recent review by Barnes et al. examined three RCTs [9, 10, 28] that evaluated surgery versus nonoperative management for SCLC [29]. The study concluded that the current evidence does not support a role for surgical resection in the management of limited-stage SCLC. However, these RCTs were conducted more than two decades ago were of very low quality and had some limitations. For example, for the Fox' trial [9], chemotherapy was not included as part of the standard treatment protocol, and only 34/71 participants underwent surgical resection in the surgical arm. Since the time these trials were conducted, there have been many developments in SCLC therapy such as modern RT technique, and better diagnostic and surgical tools. Recently, data from a series of observational studies have supported a role for surgery in the management of limited-stage SCLC [11-19]. In the present study, the 1-, 3- and

5-year OS rates in surgical group were significantly higher than in non-surgical group. The survival benefits from surgery were maintained in the propensity matched patients.

Table 4. Univariate and multivariate analysis of factors related to OS (before matching, n=269)

Variable	No.	1-Yr (%)	3-Yr (%)	5-Yr (%)	Univariate P value	Multivariate HR (95%CI)	P value
Sex							
Male	173	79.8	40.1	28.3	0.169		
Female	96	88.5	49.1	34.7			
Age							
≥60	92	79.3	39.9	25.1	0.180		
<60	177	84.7	45.1	33.6			
Smoking history							
Yes	176	80.1	41.3	31.5	0.652		
No	93	88.2	47.0	29.5			
Tumor location							
Central	122	83.6	42.4	30.6	0.962		
Peripheral	147	82.3	44.2	30.9			
T Stage							
T1	51	90.2	41.8	35.5	0.161		
T2	116	83.6	48.8	34.8			
T3	97	80.4	37.9	23.7			
T4	5	40.0	40.0	40.0			
N Stage							
N0	43	79.1	46.2	34.4	0.470		
N1	86	88.4	43.8	35.6			
N2	140	80.7	41.9	26.4			
TNM Stage							
II	84	85.7	51.2	41.0	0.024	0.713(0.478-1.062)	0.096
IIIA	185	81.6	39.7	25.7			
Surgery							
Yes	116	82.8	50.7	38.8	0.029	0.808(0.563-1.158)	0.246
No	153	83.0	37.7	24.9			
PCI							
Yes	160	83.8	48.8	35.5	0.030	0.665(0.492-0.899)	0.008
No	109	81.7	35.2	23.0			

Abbreviations: PCI: prophylactic cranial irradiation.

Table 5. Univariate and multivariate analysis of factors related to OS (after matching, n=140)

Variable	No.	1-Yr (%)	3-Yr (%)	5-Yr (%)	Univariate P value	Multivariate HR (95%CI)	P value
Sex							
Male	81	76.5	30.7	21.7	0.325		
Female	59	84.7	39.8	31.6			
Age							
≥60	47	74.5	30.9	17.2	0.414		
<60	93	82.8	36.0	30.8			
Smoking history							
Yes	88	78.4	34.1	27.0	0.894		
No	52	82.7	34.6	24.7			
Tumor location							
Central	61	78.7	37.5	28.7	0.612		
Peripheral	79	81.0	31.8	23.7			
T Stage							
T1	24	87.5	26.5	26.5	0.176		
T2	67	80.6	42.9	31.6			
T3	49	75.5	26.0	17.1			
N Stage							
N0	19	84.2	35.1	26.3	0.789		
N1	39	84.6	32.6	23.2			
N2	82	76.8	35.0	27.6			
TNM Stage							
II	38	84.2	39.9	31.1	0.081	0.648(0.409-1.026)	0.064
IIIA	102	78.4	32.1	24.4			
Surgery							
Yes	70	80.0	44.3	31.7	0.009	0.603(0.404-0.900)	0.013
No	70	80.0	24.3	20.0			
PCI							
Yes	88	84.1	40.2	32.6	0.037	0.637(0.427-0.950)	0.027
No	52	73.1	25.0	14.4			

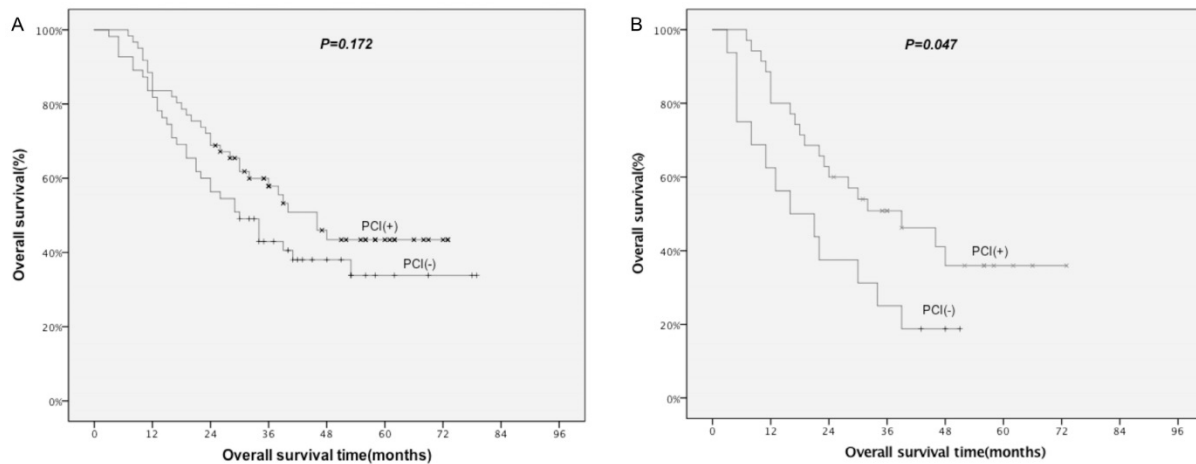Abbreviations: PCI: prophylactic cranial irradiation.

Figure 2. Comparison of OS by PCI for surgical patients. A: all patients; B: patients with stage IIIA. PCI: prophylactic cranial irradiation.

Table 6. Comparison of survival between surgical and NST group by stage (after matching)

	N	1-Yr (%)	3-Yr (%)	5-Yr (%)	P value
Stage II	38				
Surgical	19	94.7	47.8	35.9	0.09
NST	19	73.7	31.6	25.3	
Stage IIIA	102				
Surgical	51	74.5	42.6	30.2	0.061*
Surgical-selected[a]	35	77.1	50.7	40.3	0.010*
NST	51	82.4	21.6	19.6	

Abbreviations: NST: non-surgical treatment; a: stage IIIA patients who received adjuvant chemoradiotherapy and prophylactic cranial irradiation in surgical group; *: compared with NST.

Table 7. Comparison of survival by PCI

	N	1-Yr (%)	3-Yr (%)	5-Yr (%)	P value
NST	153				
PCI(+)	99	83.8	43.4	30.7	0.036
PCI(-)	54	81.5	27.0	13.2	
Surgical	116				
PCI(+)	61	83.6	57.9	43.4	0.172
PCI(-)	55	81.8	43.0	33.8	
Surgical-stage IIIA	51				
PCI(+)	35	80.0	50.8	35.9	0.047
PCI(-)	16	62.5	25.0	18.8	

Abbreviations: NST: non-surgical treatment; PCI: prophylactic cranial irradiation.

As SCLC responds well to chemotherapy and radiotherapy, surgery is considered to be a standard treatment option mainly for early stage SCLC. Current NCCN guidelines have recommended surgical resection for clinical stage I (T1-2, N0) disease [20]. However, no consensus was drawn for the role of surgery in stage II and stage III diseases. Gaspar, et al. [30] analyzed the National Cancer Database (NCDB) and found that surgery was significantly associated with improved survival in patients with stage II and stage III SCLC. Conversely, another NCDB based Propensity-Matched Analysis for limited-stage SCLC [11] showed that surgery was related to longer survival time for stage I patients, but survival differences were attenuated for stage II and IIIA. However, in their study, only 35.5% received lobectomy, and less than 50% of stage IIIA surgical patients were adjusted for chemo-radiation. A retrospective analysis of the Surveillance, Epidemiology, and End Results (SEER) between 1988 and 2002 identified 863 patients with SCLC who underwent surgery [13]. Results revealed that lobectomy was associated with the best outcomes, and there was a significant survival benefit from the addition of PORT in patients with N2 disease. In our study, most of the matched surgical patients with stage IIIA were adjusted for chemo-radiation, and all surgical patients underwent complete tumor resection, and 85.7% of them received lobectomy. All these findings might help to improve OS for surgical patients. We found a marginal OS benefit from surgery for stages II and IIIA patients. In further subgroup analysis of stage IIIA, a significantly improved OS from surgery was observed in patients who received adjuvant chemo-radiation and PCI (P=0.01). These results suggested a potential OS benefit of surgery in stages II and IIIA, particularly in selected stage IIIA patients.

The positive role of PCI has been recognized for patients with limited SCLC who respond to treatment. However, few studies have investigated the value of PCI for resected disease. Several scholars have retrospectively assessed the risk of brain relapse after surgery for limited SCLC, suggesting that PCI might have a role in surgically resected stages (p-stage) II and III patients because of their relatively high frequency of brain metastasis, but not for stage (p-stage) I disease due to lower incidence of brain metastases [22-25,31-32]. In the present study, PCI was considered to be an independent prognostic factor for OS. Improved OS related to PCI was found for non-surgical patients, but not for surgical patients. However, further subgroup analysis showed a survival advantage with the use of PCI in patients with stage IIIA (P=0.047).

Our study has several limitations. Firstly, this is a retrospective analysis. However, we performed PSM, which eliminated potential bias by creating two comparable groups. Secondly, modern tools such as positron emission tomography-computed tomography (PET-CT) or mediastinoscopy were not routinely used. Therefore, the diagnosis of clinical stage was less accurate.

Conclusions

In summary, these results suggest a potential OS benefit of surgery in stages II and IIIA patients, particularly in selected stage IIIA patients who received adjuvant chemoradiotherapy and PCI. The use of PCI for surgical patients with stage IIIA was associated with improved OS. Further prospective RCTs are needed to confirm these findings.

Competing Interests

The authors have declared that no competing interest exists.

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