Effect of Surgery on Clinical Outcomes on Limited-Stage Small Cell Lung Cancer

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Abstract

Background: The role of surgery in limited stage Small Cell Lung Cancer (SCLC) remains a topic of debate. Survival outcomes for surgical resection of limited disease SCLC compared to nonsurgical treatment were examined.

Methods: The study population included patients with histologically confirmed SCLC at the Department of Thoracic Surgery Chinese PLA General Hospital From 2005 to 2017. All the included patients were identified by either examination of pretreatment biopsy or final postoperative pathology reports. Patients with clinical stage IV or unknown clinical stage were excluded. Overall Survival (OS) was assessed using Kaplan-Meier and multivariable Cox models.

Results: Two hundred and four clinical stages I-III SCLC patients, including 152 undergoing surgery, were included. Treatment consisted of surgery with adjuvant chemotherapy therapy in 49.0% (100/204), and surgery with adjuvant chemo-radiation therapy in 55% (52/204). Chemotherapy has been administered to all patients. The 5-year survival of the entire cohort was 32.7%. The overall survival rate at 1, 3, and 5 years stratified by pathologic stage were 96.9%, 81.8%, 70.3% (stage I), 95.9%, 60.3%, 32% (stage II), 80.9%, 13.6%, 0% (stage III), respectively. The median OS of patients with stage I was 106 months (95% CI 53.50–158.5 months). Surgery provided the greater survival benefit for patients with stage II (median OS, 76 months; 95% CI: 33.0–119.0 *vs.* 33 months; 95% CI: 27.2–38.8, P<0.0001) and stage III (median OS, 28.0 months; 95% CI: 25.4–30.6 *vs.* 18.0, 95% CI: 15.7–20.3, P=0.01). The independent predictors of morbidity include margin status (R1), male, clinical stage and smoking.

Conclusion: There was a significant survival benefit for patients with limited stage SCLC in the operation group.

Keywords: Limited stage small cell lung cancer; Surgery; Clinical outcomes

Introduction

Small Cell Lung Cancer (SCLC) represents approximately 13% of all lung cancer diagnoses [1]. Around 40% of the patients present with early stage disease, classified as Limited Stage (LS) by the VALSG system or as M0 by the TNM system [2], and 60% with Extensive Stage (ES) [3]. LS mainly include AJCC stages I–III patients. SCLC has long been one of the challenges faced by oncologist due to its very rapid growth rate, high metastatic potential and poor clinical outcomes. Despite its sensitivity to both chemotherapy and radiotherapy of all histologic types, the vast majority of SCLC remains incurable, and the overall 5-year survival is poor. The median overall survival for patients with SCLC receiving standard chemotherapy has remained in range of 9 to 11 months over the past decade [4-8]. The role of surgery in SCLC is controversial and opinions regarding the best treatment strategy remain varied. In the 1960s and 1970s, two large, randomized, prospective trials reported that surgery and radiotherapy were equally ineffective for limited stage SCLC [9,10]. One recent analysis reported that selected patients with early stage SCLC may benefit from surgical resection [11]. With the advent of new, powerful diagnostic tools, such as spiral computed tomography and positron emission tomography, along with traditional mediastinoscopy allow for very limited disease to be more readily identified and to be adequately staged preoperatively. Many cases had undergone resection without a diagnosis of SCLC histology prior to surgery, which allowed the role of surgery to be reevaluated. In order to help define the role of surgery in the modern therapy of SCLC, we examined our experience during the last 17 years and compared the survival difference

between patients treated surgically and non-surgically in patients with clinical stage I-III SCLC (cT1-3N0-3).

Patients and Methods

Patient selection and methods for clinical staging

The study population included patients with histologically confirmed small cell lung cancer at the Department of Thoracic Surgery Chinese PLA General Hospital From 2000 to 2017. Diagnostic investigations routinely included a history taking, physical examination, routine laboratory tests, a neck and thoracoabdominal CT scan, selective fiberoptic bronchoscopic examination and tran-skin puncture biopsy of lung lesion under CT guiding. Clinical and pathological stages are reported according to the 7th edition of AJCC's Tumor, Node, Metastases (TNM) staging criteria.

The data is abstracted by trained clinical reviewers and is audited for accuracy. The database contains detailed information about the diagnosis, staging, and treatment for each patient. The medical charts were reviewed to obtain clinical data by using a standardized data collection sheet. Data on patients and hospital characteristics, laboratory and radiographic studies, cancer diagnosis, staging, treatments, and outcomes were collected.

Surgery

All operations were elective. If the lesion was completely resectable, the general medical condition of the patient was good, and respiratory mechanics and gas exchange were satisfactory, lobectomy was the preferred operation. Intraoperative mediastinal lymph node sampling was performed as systematic sampling of levels R2, R4, R7, R8, R9, R10 and R11 on the right side, and L5, L7, L9, L10 and L11 on the left side, if present. Nodes were labeled according to the American Thoracic Society lymph node mapping system. All patients who underwent segmental or greater resections also underwent mediastinal nodal sampling. Adjuvant treatment was recorded as radiotherapy, chemotherapy, or both as appropriate.

Inclusion and exclusion criteria

The inclusion criteria were histological diagnosis of limited-stage small cell lung cancer, with no other history of malignancy diagnosed 2000 to 2017. All the included patients were identified by either examination of pretreatment biopsy or final postoperative pathology reports. Patients with clinical stage IV or unknown clinical stage were excluded.

Follow-up and evaluation

Follow-up data were obtained by phone, outpatient and clinical databases. Compared survival between patients who underwent surgical resection and those who did not, stratified by stage were compared. Overall Survival (OS) for all patients was calculated from the start of initial treatment, that is, the first day of adjuvant treatment for the non-surgery group and the day of surgery for the surgery group, until death from any cause, or censored at the final follow-up visit.

The study was approved by the Ethics Committee of Chinese PLA General Hospital, Beijing, China.

Statistical analysis

Means and standard deviations were calculated, and differences were identified using Student's t-test. The chi-squared test was used to compare factors between categories. The Kaplan-Meier product limit method and the log-rank test were used for survival analysis.

The association of factors with time to event end points was estimated with the Cox proportional hazards model for multivariate analysis. All analyses were accomplished with the STATA statistical software package (Stata Corporation, College Station, Tex) and differences were considered significant for $P<0.05$.

Results

Patient selection and characteristics

During the study period (2000 to 2017), of the 512 cases of SCLC, 238 patients were excluded because of stage IV or missing surgical details. Thus, 204 patients were included, 152 patients were in the surgery group, and 52 patients were included in the non-surgery group. The patient characteristics are shown in Table 1. Of 204 patients 82.4% were male, 32 were stage I, 112 stage II, and 60 were stage III. There were no significant differences in most of the patients' back-grounds and clinicopathological factors except age, detected during a routine check-up and radiation therapy between the surgery and non-surgery groups. Median age at surgery was 61 years.

All operations were elective. Most patients underwent lobectomy (n=188, 92.2%). Six patients underwent pneumonectomy, and 3 patients underwent bilobectomy. Seven patients under-went only wedge resection. There were no intraoperative and 30-day (both in-hospital and out of hospital) operative mortalities.

Treatment consisted of surgery with adjuvant chemotherapy therapy in 44.6% (91/204), and surgery with adjuvant chemo-radiation therapy in 29.9% (61/204). Chemotherapy has been administered to all patients. Patients with stage III disease were more likely to receive adjuvant radiation than stage II (75.0% *vs.* 47.3% P=0.000) and stage I (75.0% *vs.* 25% P=0.000).

Effect of surgery on overall survival rate

The estimated median follow-up was 40 months. The 5-year survival of the entire cohort was 32.7%. The overall survival rate at 1, 3, and 5 years stratified by pathologic stage were 96.9%, 81.8%, 70.3% (stage I), 95.9%, 60.3%, 32% (stage II), 80.9%, 13.6%, 0% (stage III), respectively (Figure 1).

In the present study, all the patients with stage I accept surgery. The median OS of patients with stage I was 106 months (95% CI 53.50–158.5 months). Surgery provided the greater survival benefit
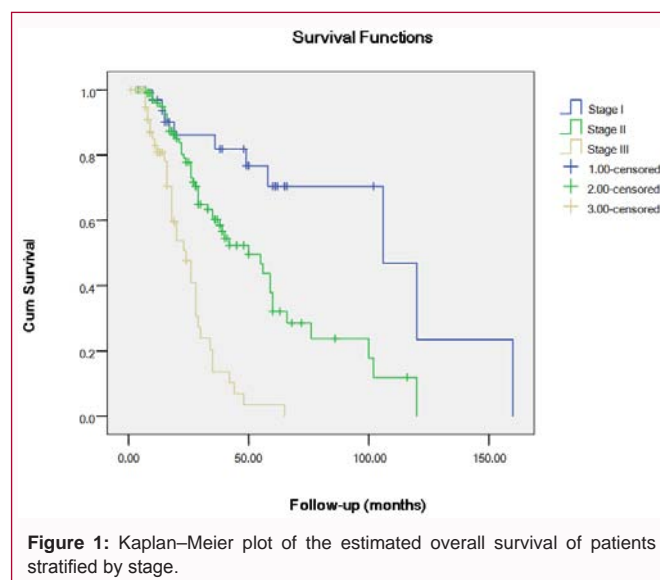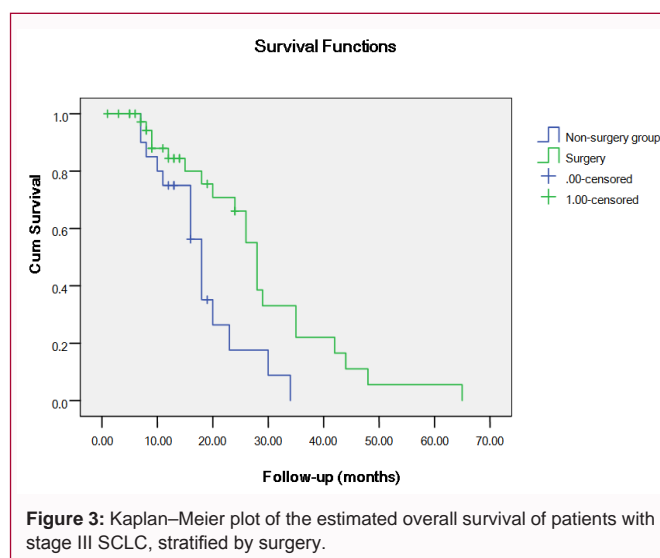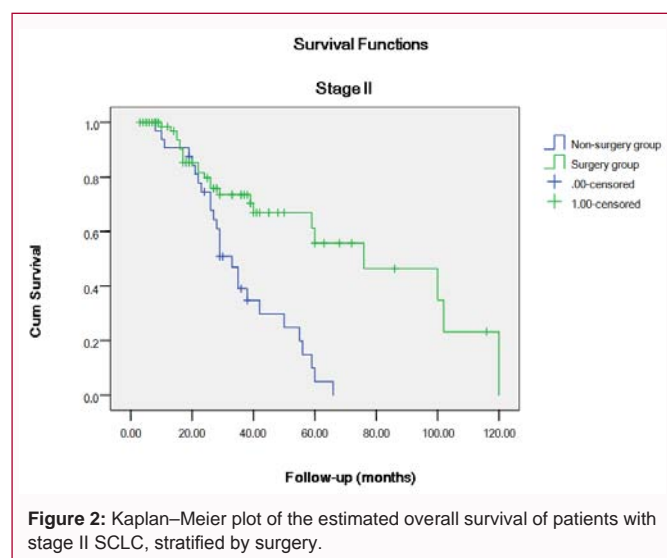

Figure 1: Kaplan–Meier plot of the estimated overall survival of patients stratified by stage.

Table 1: Basic demographic and clinical characteristics of the included patients.

Characteristics	Total S N=152	NS N=52	p	Stage I S N=32	NS N=0	Stage II S N=80	NS N=32	p	Stage III S N=40	NS N=20	p
Age, median	60.84 ± 9.67	55.8 ± 8.0	0.001	63.0 ± 10.7	0	60.5 ± 10.1	56.0 ± 7.0	0.025	59.9 ± 7.8	55.4 ± 8.7	0.047
Male, n (%)	128 (84.2)	40 (76.9)	0.291	24 (75)	0	68 (85)	20 (62.5)	0.020	36 (90)	20 (100)	0.291
Smoking n (%)	124 (81.6)	36 (69.2)	0.078	24 (75)	0	64 (80)	20 (62.5)	0.089	36 (90)	16 (80)	0.422
Drinking n (%)	54 (35.5)	19 (36.5)	0.892	11 (34.4)	0	27(33.8)	12 (37.5)	1	16(40)	7 (35)	0.672
Hyperlipemia n (%)	27 (17.8)	7 (13.5)	0.526	7 (21.9)	0	12(15)	4 (12.5)	1	8 (20)	3 (15)	0.736
Bloody sputum n (%)	35 (23.0)	11 (21.2)	0.850	0	0	11 (13.8)	3 (9.4)	0.754	24 (60)	8 (40)	0.176
Detected during a routine check-up n (%)	93 (61.2)	21 (40.4)	0.01	32 (100)	0	45 (56.3)	12 (37.5)	0.095	16 (40)	9 (45)	0.785
BMI, median(kg/m²)	24.56 ± 2.20	23.78 ± 1.48	0.017	24.05 ± 1.58	0	24.89 ± 2.76	23.78 ± 1.73	0.030	24.33 ± 0.91	23.78 ± 1.84	0.122
Radiation Therapy n (%)	61 (40.1)	45 (86.5)	0.000	8 (25)	0	24 (30)	29 (90.6)	0.000	29 (72.5)	16 (80)	0.753
PCIn (%)	16 (10.5)	8 (15.4)	0.331	3 (9.4)	0	8 (10)	8 (25)	0.069	5 (12.5)	0 (0)	0.159

PCI: Preventive radiotherapy of whole brain

Figure 2: Kaplan–Meier plot of the estimated overall survival of patients with stage II SCLC, stratified by surgery.

Figure 3: Kaplan–Meier plot of the estimated overall survival of patients with stage III SCLC, stratified by surgery.

for patients with stage II (median OS, 76 months; 95% CI: 33.0–119.0 *vs.* 33 months; 95% CI: 27.2–38.8, P<0.0001) and stage III (median OS, 28.0 months; 95% CI: 25.4–30.6 *vs.* 18.0, 95% CI: 15.7–20.3, P=0.01). These results are presented in Figure 2, 3.

Prognostic factors for clinical stage I- III SCLC: Multivariate analysis

The multivariable logistic regression model was created to identify independent predictors of morbidity. The results of this analysis are listed in Table 2. Operation offers a statistically significant long-term survival advantage when compared with non-surgery (OR for morbidity alone 0.328, 95% CI: 0.174-0.618, p=0.001) in the morbidity analysis. The independent predictors of morbidity include margin status (R1) (OR for morbidity alone 4.030, 95% CI: 2.086-7.785, p=0.000), male (OR for morbidity alone 2.535, 95% CI: 1.307-4.914, p=0.006), clinical stage (OR for morbidity alone 4.759, 95% CI: 2.725-8.311, p=0.000) and smoking (OR for morbidity alone 2.590, 95% CI: 1.082-6.202, p=0.033).

Discussion

This study indicates that surgery was associated with improved survival in all the groups stratified by stage. Patients with stage I SCLCs accepted surgical resection and postoperative platinum chemotherapy. Only 5% (32/512) of the patients with SCLC present with stage I disease. The prognosis was relatively well. The median overall survival of the operation group for patients with stage II was two times higher than that of the non operation group. There was also a significant survival benefit for patients with stage III in the operation group.

There are a few studies has examined the role of surgery in SCLC [9-19]. The vast majority of the data supports the benefit of surgery for the patients with SCLC present with early stage. Two prospective randomized trials failed to demonstrate a survival benefit from surgery for patients with SCLC. Surgery should not be offered to patients with any degree of lymph node involvement (N1/N2/N3). However, more recent results have raised important questions regarding the role of surgery in limited stage SCLC. In our present study, among patients with SCLC present with stage II and stage III showed a significantly increased OS: Stage II (76 *vs.* 33 months) and stage III (28 *vs.* 18 months). Thus, our observations indicated that if complete surgical removal of the lesion is possible, patients with limited stage SCLC may benefit from surgery. For therapeutic purposes, lobectomy plus mediastinal lymph node dissection should be considered.

In patients with stages II, a subgroup analysis found that trimodality therapy was associated with significant survival benefit when compared to chemoradiation alone group. To examine the utility of radiation therapy after surgical resection in patients with stages II and III, a subgroup analysis founded that trimodality

Table 2: Predictors of late death.

Risk factors	B	SE	Waldx^2	p	Hazard Ratio
Male sex	0.930	0.338	7.581	0.006	2.535 (1.307, 4.914)
Age	-0.014	0.018	0.608	0.435	0.986 (0.953, 1.021)
Clinical stage	1.560	0.284	30.080	0.000	4.759 (2.725, 8.311)
BMI	0.024	0.095	0.066	0.798	1.025 (0.850, 1.235)
Smoking	0.952	0.445	4.565	0.033	2.590 (1.082, 6.202)
Hyperlipemia	0.366	0.348	1.101	0.294	1.441 (0.728, 2.853)
Detected during a routine check-up	0.037	0.260	0.020	0.888	1.037 (0.623, 1.727)
Bloody sputum	0.192	0.341	0.317	0.573	1.212 (0.621, 2.363)
Operation	-1.114	0.322	11.934	0.001	0.328 (0.174, 0.618)
Margin status	1.511	0.320	27.632	0.000	4.030 (2.086, 7.785)
Adjuvant Radiotherapy	0.368	0.298	1.526	0.217	1.445 (0.806, 2.590)

therapy demonstrate a survival benefit when compared to surgery plus chemotherapy group presented with stage III, however it was not statistically significant for stage II. The vast majority of LS-SCLCs have mediastinal lymph node involvement at the time of diagnosis. The optimal treatment for these cancers is concurrent chemotherapy and radiation. The role of postoperative radiation therapy is less well defined [20]. A retrospective analysis to evaluate survival in stage I and II SCLC treated with surgery alone, radiation alone, or surgery and radiation [14]. In this study, patients treated with surgery alone had longer median survival as compared to patients treated with radiation alone (50 months for lobar resection, 30 months for sublobar, and 20 months for radiation). Moreover, the addition of radiation therapy to surgery had no significant effect on survival.

Although RCTs are considered the top level of evidence by most hierarchies, this study design may not be feasible to evaluate the role of surgery in SCLC for two major reasons. First, the rarity of the disease: Node-negative, localized tumors make up a small minority of all SCLC, a histology which itself makes up a small minority of all lung cancers. Accruing the number of patients needed to ensure adequate power would require multiple sites and a long recruitment period. Second, patient willingness to be randomized to one of two very disparate treatments (e.g., surgery and chemoradiation) is often less than between similar treatments (e.g., different chemotherapy regimens).

The multivariate analysis identified patient factors such as stage, surgery, tobacco exposure, and sex as significantly predictors influencing survival outcome in this study. Tobacco exposure is more closely associated with SCLC than with any other cancer histologic type [21].

This study was not randomized, and the surgical patients were highly selected. Because this study was a hospital-based, retrospective review spanning 17 years and involving many practitioners and multiple drug combinations and dosages, we did not attempt to analyze individual doses of chemotherapy and radiotherapy.

In summary, our data concluded that surgical resection is associated with improved OS in limited-stage SCLC.

Acknowledgement

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