

Surgical Treatment in Small-Cell Lung Cancer: Single-Center Experience and Survival

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Abstract

OBJECTIVE: To evaluate the clinical outcomes of patients with different stages of small-cell lung cancer (SCLC) who underwent surgical treatment.

MATERIAL AND METHODS: This retrospective study consisted of 13 patients with SCLC at a tertiary care health center. This study was conducted between 2011 and 2018 at Gaziantep University Faculty of Medicine, Thoracic Surgery Department. Patient follow-up data were collected from medical files. Patients were analyzed according to age, sex, site of resection, clinical stage, pathological stage, recurrence, operation type, chemotherapy, radiotherapy.

RESULTS: The study group consisted of 3 females and 10 males ($n = 13$). The mean age of the patients was 65 ± 9.3 (52-85) years. The most common location of the primary tumor was the right upper lobe (6 patients, 46.2%). The mean tumor size was 4.36 ± 2.38 cm (1-8.5). In our study, 3 patients had already metastases (2 brain and 1 had metastases in more than 2 anatomic sites). Patients with solitary metastases, who underwent lung resection and metastasis excision had similar survival according to patients without metastases.

CONCLUSION: Our results show that surgical treatment in SCLC could be contributed to the survival of patients. Therefore, patients must be given a chance for surgery, especially considering that the advances in diagnostic and surgical capabilities have increased the likelihood of early diagnosis and effective surgery.

KEYWORDS: Small-cell lung carcinoma, surgery, solitary metastasis

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INTRODUCTION

Small-cell lung cancer (SCLC), which is a form of lung cancer primarily known for its lack of consistency regarding size and metastasis spread, is an important cause of mortality and shows distinct characteristics compared to other lung cancers, both biologically and clinically. It comprises approximately 15% of all newly diagnosed lung cancers worldwide, which accounts for around 180 000 cases per year. It is particularly associated with tobacco use: 90% of those with SCLC are or were heavy smokers. In addition, SCLC is also frequent among those working in uranium mining and processing due to exposure to radon by-products and gamma radiation.¹

Clinically SCLC tends to present in current or ex-smokers over 70 years of age and progresses rapidly. Chest imaging usually shows bulky tumors which centrally located and tend to spread early.² However, today, early diagnosis is not a rare occurrence due to increased accessibility of healthcare services, physicians' sensitivity toward cancer, and the possibility of performing advanced level radiologic examinations at a lower cost. SCLC is highly responsive to chemotherapy; however, there is substantial historical experience documenting the futility of surgery and/or radiation therapy (RT) without systemic chemotherapy. Prior to the introduction of systemic chemotherapy, median survival for patients with limited stage (LS) disease (limited to the ipsilateral hemithorax and regional lymph nodes) and extensive stage disease were approximately 12 and 5 weeks, respectively. However, with the advance in surgical methods and experience, lung lobectomy and mediastinal lymph node dissection have become a recommended approaches in patients with early stage SCLC without mediastinal lymph node metastasis. In cases with M1 stage disease, surgical approach was not even considered until recently. However, promising results showing prolonged survival via resection of synchronous or metachronous isolated solitary metastases in selected cases of solitary organ metastasis have encouraged physicians to consider and assess surgical treatment and its outcomes.³⁻⁶

SCLC are known for having very poor outcomes in survival analyses, despite multiple treatment applications. Although the literature argues that the treatment of this disease is essentially medical, surgical experiences have opened a venue for detailed research on this topic.^{3,7}

The aim of this study was to evaluate the clinical outcomes of patients with SCLC who underwent different forms of surgery.

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MATERIAL AND METHODS

Study Group

In this study, we included 13 SCLC cases at various stages of the disease. All patients were treated and followed by the Department of Thoracic Surgery from 2011 to 2018.

Inclusion criteria were as follows: (1) having a pathologically confirmed diagnosis of SCLC and (2) the existence of a complete medical record, including demographics, site of the primary tumor, and pathologic reports. The exclusion criteria were as follows: (1) receiving chemotherapy or radiotherapy for another malignancy, (2) presence of unresectable tumor, albeit received neoadjuvant chemotherapy, and (3) psychological disabilities to complete the prescribed regimen. The medical files of all SCLC cases were very well maintained; thus, no patients were excluded from the study.

Patient follow-up data were collected from the medical file records of our hospital. Patients were analyzed according to age, sex, site of resection, clinical stage, pathological stage, recurrence, operation type, chemotherapy, radiotherapy. SCLC staging was performed according to the IASLC-TNM 8 (International Association for the Study of Lung Cancer) staging system.

Preoperative and Postoperative Evaluation of Patients

Patients are initially evaluated clinically and radiologically with a preliminary diagnosis of lung cancer. All patients undergo rigid or flexible bronchoscopy for diagnosis. Invasive procedures such as true cut biopsy, bronchoscopy, or VATS are performed for the diagnosis. Patients who cannot be diagnosed with these methods are diagnosed pathologically with lung cancer by frozen section during the operation and then underwent anatomic resection. All patients were screened with PET CT for preoperative evaluation of mediastinal lymph node and distant metastasis. Endobronchial ultrasound (EBUS) or mediastinoscopy were performed preoperatively for the patients with suspected involvement of mediastinal lymph nodes and then patients without lymph node metastasis are taken to the operation. All patients, including those with advanced lung cancer, were first evaluated by a council, which includes physicians from chest diseases and oncology departments. The decision of the surgeries or the prescribing of chemotherapy/radiotherapy made by the council. The

patients are reevaluated with postoperative pathological staging results. Treatment modalities were revised according to postoperative evaluation.

Ethical approval was obtained from Gaziantep University Clinical Research Ethical Committee (no. 2019/276), and all steps of the current study were conducted according to the principles put forth by the Helsinki Declaration and Good Clinical Practice guidelines.

The Statistical Package for Social Sciences version 20.0 software (IBM Corp.; Armonk, NY, USA). Continuous variables are presented as mean \pm standard deviation and minimum–maximum values.

RESULTS

The study group consisted of 3 females and 10 males ($n = 13$). Mean age of the patients was 65 ± 9.3 (52-85) years. The most common localization of the primary tumor was the right upper lobe (6 patients, 46.2%). Mean tumor size was 4.36 ± 2.38 cm. Three patients had metastasis. Metastasis locations were the brain ($n = 2$), and the remaining patient had developed metastasis to more than 2 anatomic sites.

The mean survival time was 26.61 ± 26.92 months. 1-year survival rate was 76.9%. 2-year survival rate was 30.7%. Five-year survival rate was 15.4%.

The patient with the highest survival was case 1 (84 months), who had a 4 cm-diameter mass in the left lower lobe which was staged as stage 2B. The patient underwent left lower lobectomy + MLND (Mediastinal Lymph Node Dissection). The patient with the lowest survival was case 5 (1 month). The patient had an 8 cm-diameter tumor in the right upper lobe which was staged as stage 3A cancer after postoperative detection of pleural metastasis. The patient underwent right pneumonectomy + MLND.

In this study, all patients underwent standard anatomic resections except for 2 patients who underwent sublobar resection because the lesion was small and peripheral (cases 2 and 7).

Postoperative chemotherapy decisions were taken if the patient's tumor is determined to be totally resectable (lesions that can be totally removed surgically and do not have distant organ metastasis or lymph node involvement), we perform the surgery, and then chemotherapy is given postoperatively (with the decision of the council). One patient was referred to neoadjuvant treatment and received CT because the tumor was initially found to be large and unresectable. Resection was performed after chemotherapy. Postoperative pathology was negative as the tumor had significantly benefited from chemotherapy (case 12). Some of the patients who did not receive chemotherapy after the operation were patients with general condition disorder and some of them accepted at first and then rejected the procedure.

Lobectomy + MLND surgery was performed in cases 1, 4, 6, 9, 10, and 11. The survivals of these patients were: 7 years, 23 months, 16 months, 82 months, 38 months, and 29 months, respectively.

Main Points

- Surgical treatment in SCLC could be contributed to the survival of patients.
- In patients with solid organ metastasis, metastasectomy in addition to primary tumor excision positively influence survival.
- Patients must be given a chance for surgery, especially considering that the advances in diagnostic and surgical capabilities have increased the likelihood of early diagnosis and effective surgery.
- The development of diagnostic and surgical treatment technology also provides better chances to perform effective surgery.

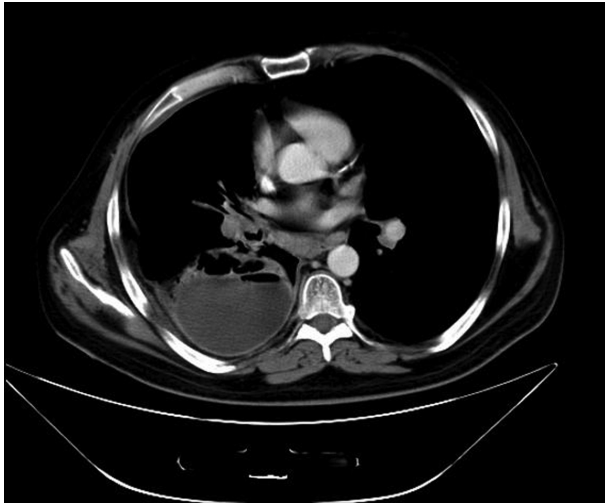


Figure 1. CT image of thoracic cavity lesion of the lower lobe of the right lung (case 11).

One patient (case 11) was stage 4B cancer. The patient had a cavitary lesion in the right lower lobe, and a right lower lobectomy was performed for palliative purposes. The patient received chemotherapy after surgery, and survival was 29 months (case 11) (Figure 1 and 2).

Two patients had brain metastasis. In these patients, the initial approach was to excise the brain tumor, followed by surgery for the lung. The patient's survival was 9 months (case 3) and 11 months (case 12).

The clinical and pathological characteristics of the patients are given in Table 1.

DISCUSSION

Lung cancer is the most common organ cancer in men, leading to the highest number of mortalities. The main reason for evaluating SCLC differently from other lung cancers is that there is no consistency between tumor size and the rate of metastasis spread. Most patients have metastasis when diagnosed. However, in recent years, early diagnosis has become more common, possibly due to high accessibility to health services, physicians' sensitivity to cancer, and the increased frequency and quality of radiological examinations.

SCLC is highly responsive to chemotherapy; however, the use of surgical treatment remains a controversial topic. Even though current data with surgical success is limited, several international guidelines such as those published by the American, European, and Japanese medical associations recommended surgery for patients with early stage N0 SCLC. In recent years, Yang et al.⁸ conducted a large study involving 2301 patients with T1 and T2 N0 SCLC. Among these patients, 681 had received surgical treatment in addition to chemotherapy, and this approach was found to be associated with a higher overall survival (OS) compared to concurrent chemoradiation (5-year OS 47.6% vs. 29.8%, $P < .01$).⁸ Takenaka et al.,⁹ in their study comparing the 5-year survival of patients with various disease stages, found that those with stage I disease who underwent resection with or without chemotherapy and/or radiotherapy had significantly higher 5-year survival

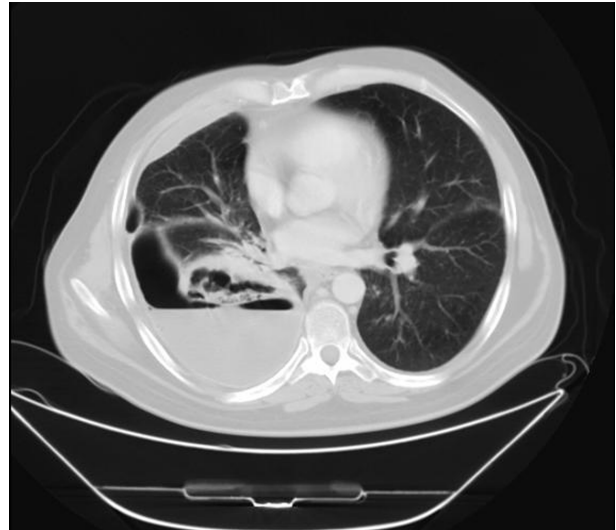


Figure 2. Different sections and images of the same patient (case 11).

rates than those who did not undergo any form of resection (62% in the operative and 25% in non-operative group). In Stage II patients, 5-year survival rates were also higher in the operative group (33% vs. 24%). In patients with Stage III disease, 5-year survival rates were the same (18%).⁹ Similar survival outcomes have also been reported in other studies, with 5-year survival rates significantly higher in those undergoing surgery than non-surgical treatments.¹⁰⁻¹² Despite these remarkable findings, there is an ongoing debate about the efficacy of surgery; some have suggested that these survival advantages are actually associated with systemic treatments and patient selection methods.¹³

Studies show that the type of resection may play an important role in survival rates and the relapse of disease. Schreiber et al.¹⁴ evaluated surgical versus non-surgical treatment in patients with LS SCLC and found that the median survival times were 40, 20, and 23 for lobectomy, pneumonectomy, and sublobar resection, respectively.¹⁴ In a study assessing outcome regarding relapse development, Stish et al.¹⁵ reported that the incidence of intrathoracic relapse was higher in patients who underwent sublobar resection.¹⁵ Findings of these studies have been supported by many other studies, indicating that lobectomy provides better chance for higher survival and lower risk for local relapse compared to sublobar resection.¹⁶⁻¹⁹ In our study, we performed lobectomy + MLND in cases 1, 4, 6, 9, 10, and 11. The survival of these patients was, respectively: 7 years, 23 months, 16 months, 82 months, 38 months, and 29 months.

We decide firstly that the distant metastasis could be removed completely or not by discussing with the relevant departments for the patients with advanced stages. In our study, we only had patients with brain metastases. They were operated by neurosurgeons and radiotherapy was applied if necessary. If there was no distant organ and mediastinal lymph node involvement in the re-evaluation, the patient was taken into operation. Postoperative chemotherapy was applied. Only 1 patient with diffuse metastasis underwent palliative resection.

Table 1. Clinicopathologic Characteristics of 13 Patients with Small-Cell Lung Cancer

No.	Sex	Age	Localization (Lobe)	Grade	Operation	RT	CT	Complication	Survival (Months)	Relapse	Metastasis
1	M	56	Left lower	2B	Lobectomy	-	+	CTX	84	No	No
2	M	72	Left upper-lower	3A	Sublobar resection	-	-	-	23	Yes	No
3	M	73	Right lower	4A	Pneumonectomy	+	+	-	9	No	Yes (brain)
4	M	72	Right upper	2A	Lobectomy	+	+	-	23	No	No
5	F	67	Right upper	3A	Pneumonectomy	-	-	-	1	No	No
6	F	68	Right lower	3A	Lobectomy	-	-	-	16	No	No
7	M	68	Right upper	1B	Sublobar resection	+	+	-	12	No	No
8	M	85	Left upper	3B	Pneumonectomy	-	-	-	12	No	No
9	M	59	Right upper	3A	Lobectomy	-	+	-	82	No	No
10	F	66	Left upper	2B	Lobectomy	-	+	-	38	No	No
11	M	52	Right upper	4B	Lobectomy	-	+	BPF	29	Yes	Yes (more than one)
12	M	54	Left lower	4A	Pneumonectomy	-	+	BPF	11	Yes	Yes (brain)
13	M	57	Right upper	3B	Pneumonectomy	+	+	-	6	No	No

RT/CT, radiotherapy/chemotherapy; M, male; F, female; CTX, chilothorax; BPF, bronchopleural fistula.

We believe the results of case 11, who had stage 4B SCLC, cavitory lesion in the right lower lobe and underwent right lower lobectomy for palliative purposes followed by chemotherapy, were indicative of the efficacy of surgery in increasing survival time this patient's survival was 29 months.

Furthermore, cases 3 and 12 had stage 4A SCLC with brain metastasis. Pneumonectomy + MLND were performed on the patient after excision of the brain metastasis. The patient's survival was 9 and 11 months. Considering these findings, we believe that if lung and metastatic tumors can be completely resected in lung cancer patients with single solid organ metastasis, survival will be positively affected.

In the literature, there exist several studies that report metastasectomy results with solitary brain metastasis. In a study comprised of 65 patients who were operated on for NSCLC and brain metastasis, survival after metastasectomy was found to be longer.²⁰ In another study, which included 24 patients who developed solitary brain metastasis after surgical treatments were applied to the lung, it was reported that the duration between lung surgery and brain surgery was significantly effective on the duration of survival.²¹ Furthermore, complete resection of the adrenal gland and lung tumor in lung cancer patients with solitary adrenal metastasis was found to be the most important parameter affecting the duration of survival in a study by Kim et al.²² Although the approach to the treatment of other metastasis is limited, due to the low number of studies performed in these patients,²³⁻²⁵ it is apparent that surgical treatments for solitary metastasis are worth exploring. With the addition of future studies on this topic and subsequent increase in surgical experience, it may be possible to conclude in these cases and suggest a common approach to metastasis in SCLC.

This study was a single-centered case series focused on conveying our approach and results in patients with SCLC. Therefore, due to the low number of patients, survival analyses could not be performed. However, this study adds further data to the literature regarding the use of surgical approach in patients with SCLC and demonstrates that patients with solitary metastases can possibly benefit from surgery in addition to usual treatments. Nevertheless, due to the limited number of patients, it is apparent that our results should be evaluated with care. Studies with a higher number of patients, especially those with metastasis, should be performed on this topic.

CONCLUSION

Regardless of the stage of the disease, we think our results show that surgical treatment in SCLC can contribute to the survival of patients. Furthermore, our results suggest that, in patients with solid organ metastasis, metastasectomy in addition to primary tumor excision positively influences survival. Therefore, patients must be given a chance to undergo surgical treatment to possibly benefiting from this approach. The development of diagnostic and surgical treatment technology also provides better chances to perform effective surgery.

Ethics Committee Approval: This study was approved by Ethics committee of Gaziantep University Clinical Research Ethical Committee, (Approval No: 2019/276).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer Review: Externally peer-reviewed.

Author Contributions: Supervision – A.U.; Design – İ.E.T.; Resources – M.Ş.; Materials – İ.E.T.; Data Collection and/or Processing – İ.E.T.; Analysis and/or Interpretation – M.Ş.; Literature Search – A.U.; Writing Manuscript – A.U.; Critical Review – A.İ.

Conflict of Interest: The authors have no conflict of interest to declare.

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