

Surgical Treatment in Small Cell Lung Cancer: Delayed Evaluation?

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ABSTRACT

Lung cancers are the most common solid organ cancers and are responsible for a major part of cancer deaths. They account for 1/3 or 1/4 of all deaths from cancer. Small cell lung cancers (SCLC) are known for having very poor outcomes in survival analyses, despite multiple treatment applications. Even though the traditional literature claims that treatment of this disease is essentially medical, surgical experiences do not confirm such claim. In this study, we examined whether small cell lung cancer is a non-surgical disease as it is believed to be. The medical literature in the thoracic and cardiovascular surgery and oncology network was reviewed, and studies, cases, and meta-analysis articles that provided small cell lung cancer treatment outcomes were examined. A discussion was made by also analyzing the survival data in the light of the available guidelines. It is seen that treatment of small cell lung cancer is not mainly medical and that the surgical option can be administered similarly to non-small cell lung cancer (NSCLC). Unfortunately, even the targeted treatment options do not provide recovery at a satisfactory level in the current state of cancer treatment. Surgery option keeps its validity as the most important weapon against all stages and cell types in lung cancer.

Keywords: Lung carcinoma, small cell, surgery

INTRODUCTION

Lung cancer is not only the most common organ cancer in men, but also the cancer type that leads to the most deaths (1/3 to 1/4 of all deaths from cancer). According to various study results, its incidence varies between 80-300/100,000. The American Cancer Society reported that 222,500 new lung cancer cases were seen in 2010 in the United States (1). Patients diagnosed with small cell lung cancer (SCLC) account for 10-15% of these new cases. Since 1926, the year when it was named and diagnosed, SCLC has been a type of cancer that is difficult to treat due to its aggressive nature and very high level of relapse (50-80%) (2, 3). However, the place of surgery among treatment options is unfortunately still contradictory. According to the National Comprehensive Cancer Network (NCCN) 2017-2 Guidelines, there are four main hypotheses. These are as follows: Treatment of small cell lung cancer is chemotherapy; tumors that exceed T1-2 do not benefit from surgery; surgical treatment must be lobectomy, then additional therapy must be given; and if nodal metastasis is observed, additional therapy must be performed with chemotherapy (4). Validity of such hypotheses are the subject matter of a study alone. Therefore, in this article, we will discuss the place of the surgical treatment option in small cell lung cancer whose treatment is very difficult and restricted.

Both electronic and printed literature were used while planning this review. In internet searches performed using the key words of "small cell lung cancer", a large amount of studies was found on various pages. For instance, in the scan performed on CTSNet,

we found between 1,700-32,000 articles depending on the different journals included in the review. Therefore, as the material of this article, we mainly tried to use the studies that include surgical series and can historically draw a direction for us. Most of these studies were research studies, while some were collected works, and a smaller part consisted of meta-analyses.

History

Small cell lung cancer (SCLC) entered the medical literature in the 1920s (5). The first written statement was made by Bernard in 1926 after attempts to understand it and the emergence of its definitions. This was followed by staging studies made between 1960 and 1980, and a period of recession started in the 1990s, which we attribute to the lack of options in treatment. In the past 25 years, the inclusion of some new medication within treatment, and the increase in the studies on these medications has supported non-preference of surgery as the primary option. However, the hypothesis that treatment of SCLC is mainly medical relies on the decision made by British Medical Council in the 1970s based on three studies (6). All these studies were published on *Lancet*, and when examined in detail, the methodology of these articles was problematic (7-9). Among these, in the article published by Miller et al. (8), full resection could be performed in only 48% of the patients that were included in the surgical treatment group, while survival analysis was performed on all 71 patients. Besides this, even though the number of patients that underwent exploration alone in the surgical patient group was 24, these patients were also included in the survival anal-

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ysis. Still, 24-month survival, 48-month survival and 60-month survival rates were found to be 4% and 10%, 3% and 7%, and 1% and 4%, respectively, in 71 surgical patients and 73 radiotherapy cases: As we can see, the radiotherapy group had no superiority compared to the surgery group.

In studies where the contribution of surgical treatment to survival was evaluated, we see that the 5-year survival data is not as bad as claimed. Even though they include a low number of patients, we see that in Stage 1-3A patients, the 5-year survival rate was between 15% and 60% (10-15).

Treatment Options

The most important reason behind the fact that small cell lung cancer is philosophically examined independently from other lung cancers is that there is no consistency between the tumor size and the spread rate of metastasis. In other words, even very small sized tumors can lead to lymphatic gland and distant organ metastasis. This is probably the reason why the majority of patients already have metastasis when they are diagnosed (16). However, today, the reversibility of this situation is increased due to the high accessibility to healthcare services, physicians’ sensitivity towards cancer, and the possibility of performing advanced level radiologic examinations at a lower cost and more easily. In Quoix et al. (17) study published in 1990, they found a pulmonary nodule in 25 of 408 SCLC patients during a 5-year period. Additionally, a total of 2301 patients with T1 and T2 N0 small cell lung cancer in the national cancer database between the years of 2003-2011 were reviewed in Yang et al. (18) latest article published in 2017. Surgical treatment and chemotherapy were used together in 681 of these patients who had a solitary pulmonary nodule.

According to the National Comprehensive Cancer Network 2017-2 Guidelines, the publication used most in the surgical treatment section of the SCLC guidelines has been the study performed by Lad et al. (19) in 1994. This study seems to have gained importance due to its prospective randomized design. However, considering the fact that only 11 of the 235 articles found in the guidelines included surgical series, the realistic extent of the obtained analyses is open to questioning. Lad et al. (19) divided their series consisting of 328 patients with SCLC, who received systemic chemotherapy, into surgical and non-surgical groups through randomization. As a result, we can see that 146 of the patients who received chemotherapy were included in the study. The responses of patients to chemotherapy were also stated, among which 90 were identified to have responded fully. The number of patients with no response was 111. The meaning of how the patients responded to chemotherapy is shown in Table 1. Looking at the data presented in the article, the randomization method seems to be insufficient in selecting a treatment that is suitable for the patient and there are suspicions as to whether these are the right methods. This is because it is not known how many of the cases were suitable for surgery before randomization. Besides this, to the extent that is understood from the article, full response rate was 19% in the surgical group, while it was 40% in the non-surgical one. Number of patients that could receive full resection in the surgical group was 54. Therefore, no surgical treatment was performed on 16 cases. However, all these cases were included in the total survival analysis.

In a meta-analysis performed for radiotherapy, a total of 2573 cases were included in 13 randomized studies, and 2013 of these cases that were discovered to have limited disease were able to receive chemotherapy or chemotherapy and concurrent radiotherapy (20). Five-year survival was 4.8% in chemotherapy patients, and 7.2% in the cases that also received radiotherapy. It is seen that contribution of non-surgical treatment modalities to survival is limited. However, 5-year survival rates exceed 60% especially in small tumors in some series with surgery and additional practices (chemotherapy and/or radiotherapy) (21, 22).

In Badzio et al. (23) study performed in 2004, they compared adjuvant chemotherapy and surgery combination with definitive chemotherapy treatment in limited stage patients. The mean survival rate was found to be 22.3 months and 11.2 months, respectively, in operative and non-operative groups. Five-year survival was 27% for the surgical group, and 4% for the non-surgical group. Relapse occurred within an average of 20.9 months in 53% of the surgical patients, whereas this figure decreased to an average of 7 months in 86% of the non-surgical patients. However, such superiorities of surgery could not be observed in patients with N2 disease. Even though the small number of patients was a disadvantage, it is clear that the results of the treatment options were akin to those in the NSCLC group. A similar study was performed by Schreiber (24). The 5-year survival data of the surgical and non-surgical groups was 34.6% and 9.9%, respectively.

Takenaka et al. (25) compared the results of patients who underwent resection (consisting of patients who received and did not receive adjuvant chemotherapy and radiation treatment) and did not undergo resection. In this study, the 5-year survival of these groups was compared for each stage. A statistically significant difference was seen in 5-year survival only in Stage I patients (62% in the operative and 25% in non-operative group), while the difference was not statistically significant in Stage II patients, but an apparent five-year survival advantage seemed in favor of the operative group (33% vs. 24%). For Stage III disease, there was no survival advantage in the surgical resection group, and 5-year survival was found to be 18% in both groups.

Type of Surgical Treatment

The type of resection can play a key role in patient outcomes. In a study by Schreiber et al. (24) where they evaluated the operative and non-operative treatment of patients with limited stage CSLC,

Table 1. Classification of the response given to chemotherapy

Term	Definition
Full Response	Disappearance of all targeted lesions during or after treatment
Partial Response	A minimum of 30% reduction in the largest diameters of the targeted lesions
Stable Disease	Lack of change in the targeted lesions
Progressive Disease	A minimum of 20% increase or enlargement in the targeted lesions or new lesion(s)

Table 2. Summary of the retrospective surgery studies that evaluated 5-year survival by resection type in limited stage small cell lung cancer

Study team	Year	Number of patients	5 year survival rates by resection type	
			Sublobar (%)	Lobectomy (%)
Brock et al. (22)	2005	82	20	50
Schreiber et al. (24)	2010	863	—	52.6
Varlotto et al. (30)	2011	584	28.5	47.4
Weksler et al. (27)	2012	895	18.70	30.10
Takei et al. (29)	2014	243	30.6	58.3
Stish et al. (26)	2015	54	15	48
Combs et al. (28)	2015	2476	40	21

Table 3. Role of surgery in small cell lung cancer

Study	Protocol/Patient (Surgical/total patients)	Local Relapse	Survival
Fujimori et al. (21)	CT + Surgery (21/22)	5%	Median survival 61.9 months Stage 1–2: 73% (3 years) 3A: 42.9% (p=0.018)
Eberhardt et al. (36)	CT + Surgery (30/46)	0%	Overall Survival (46 patients): 5 year survival: 39% 10 year survival: 35% Stage 2B–3A (22 patients) 5 year survival: 44% 10 year survival: 41%
Rostad et al. (37)	Surgery + CT (38)		5 year survival for Stage 1: 44.9%
Brock et al. (22)	Surgery + CT (82)		5 year survival for Stage 1: 58% Stage 2, 3 and 4 survival, respectively: 18%; 23%; 0%
Tsuchiya et al. (38)	Surgery + CT (62)	10%	Stage 1–3A 5 year survival, respectively: 73%; 38%; 39%
Bischof (39)	Surgery + CT +/- RT+PCR (39)		Median 47 months 1.3 and 5 year survival, respectively: 97%; 58%; 49%
Lim et al. (40)	Surgery or Surgery + CT		5 year survival: 52%

PCR: Prophylactic cranial radiotherapy, CT: Chemotherapy, RT: Radiotherapy

it was found that the resection type affected the survival rates in the surgical group. The median survival rate was 40 months, 20 months and 23 months for lobectomy, pneumonectomy, and sublobar resection, respectively. However, they emphasized that the median survival rate was 65 months in the patients that had lobectomy for localized disease. Lobectomy achieves a 25-month median survival rate in the regional disease. Five-year survival was observed in 52.6% of those that underwent lobectomy in both groups.

Stish et al. (26) evaluated the type of resection in terms of intrathoracic relapse, and they found that the incidence of intrathoracic relapse was higher in patients that underwent sublobar resection. Therefore, they stated that resection type can affect

not only the 5-year survival, but also the relapse risk. Findings of Schreiber and Stish have been supported by many studies as lobectomy has a better survival and carried lower local relapse risk compared to sublobar resection (22, 27–30) (Table 2). Additionally, NCCN has been recommending lobectomy treatment for Stage I SCLC since 2017 (19).

Stage I Small Cell Lung Cancer

Many studies conducted on Stage I SCLC patients have shown that survival was better in patients who received chemotherapy together with surgical resection, compared to those who underwent surgery alone (22, 28, 31). Combs et al. (28) examined 2476 patients who underwent surgery for SCLC, and divided the patients into two groups; surgery, and chemotherapy with surgery,

depending on their treatment type. They found that mortality was lower in patients who were operated on after chemotherapy. In Stage 1 SCLC patients, 5-year survival was found to be higher in the group that received chemotherapy with surgery, compared to those who underwent operation only (51% vs. 38%). The effects of surgery and chemotherapy treatment on the life expectancy of patients found in various studies have been summarized in Table 3.

However, the debate as to whether adjuvant treatment is superior to neoadjuvant chemotherapy is still ongoing (31). Furthermore, no study has shown that the use of post-operative radiation provides an important advantage for Stage I disease (24, 30). The current recommendation of the American Society of Clinic Oncology (ASCO), American College of Clinical Pharmacy (ACCP) and NCCN is the performance of platin based adjuvant chemotherapy on all Stage I SCLC patients who have undergone curative surgery resection (4, 32, 33). The current ASCO, NCCN and ACCP guidelines indicate that surgical resection might be considered in Stage I SCLC patients. Besides this, some new studies give rise to the thought that surgery might also have a role in patients with N1 and N2 involvement. Yang et al. (34) compared patients who had N1 disease and received adjuvant chemotherapy with surgical resection with patients who received concurrent chemoradiotherapy only (34). The use of chemotherapy in addition to the operation was determined to be associated with improvement in the overall survival level and 5-year survival (31.4% vs. 26.3%); however, such difference was not statistically significant.

Granetzny et al. (35). evaluated the N0 patients who underwent surgical resection and N2 patients who underwent surgical resection after neo-adjuvant chemotherapy treatment, they showed that patients with N2 involvement whose tumor load in the lymph nodes totally regressed histologically (patients downstaging pN0) had a median survival that was comparable to the N0 patient group (N0: 31.3 months vs. N2: 31.7 months). However, it was found that patients with permanent N2 disease had a worse survival rate (12.4 months).

CONCLUSION

Speculations on the treatment of small cell lung cancer must be illuminated. This is because patients must be given the chance to undergo a surgery and benefit from such opportunity. Today, pre-surgery diagnosis and surgical treatment technology has developed, and it would be suitable to plan the treatment for SCLC just as it is planned for NSCLC. Regardless of whether they were retrospective or prospective, the studies performed show that 5-year survival chance can be achieved with a multimodal treatment approach which includes surgery.

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