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Role of Surgical Resection for Patients with Limited Disease-Small Cell Lung Cancer

Running Head: Surgical resection for LD-SCLC

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Highlights

- We examined the outcomes of 277 patients with LD-SCLC.
- Surgery is effective for the patients with stage I and some cases of stage II or III.
- The outcomes of treatment for LD-SCLC have been improved beginning in the 2000s.

Abstract

Objectives

Although Chemotherapy and radiotherapy are recommended for patients with limited disease small cell lung cancer (LD-SCLC), several series have reported favorable survival outcomes even in patients with stage II and III disease who underwent surgical resection. The purpose of this study is to compare the outcomes of the use of surgical resection to the other conventional non-surgical treatments in patients with LD-SCLC with respect to each clinical stage.

Materials and Methods

We retrospectively reviewed 277 patients who received treatment for LD-SCLC and compared the outcomes of the use of surgical resection to the other conventional non-surgical
treatments.

**Results**

The clinical stage was stage I in 50 cases (18%), stage II in 53 cases (19%) and stage III in 174 cases (63%). Eighty-eight patients received surgical resection and 189 patients were treated with non-surgical treatment. Surgery was performed in 44 patients (88%) with stage I, 27 patients (52%) with stage II and 17 patients (10%) with stage III disease. The five-year survival rates of the patients according to clinical stage were 58% in stage I, 29% in stage II and 18% in stage III. The five-year survival rates of the patients with and without surgical resection according to clinical stage were as follows; 62% and 25% in stage I (p<0.01), 33% and 24% in stage II (p=0.95), 18% and 18% in stage III (p=0.35), respectively. In 44 propensity score-matched pairs with stage II and III disease, including matching for variables such as age, gender and the PS, the five-year survival rates was better in patients with surgical resection than in those without surgery (p=0.04).

**Conclusion**

Surgical resection is effective for the patients with stage I LD-SCLC and some cases of stage II or III disease.

**Key words:** limited disease-small cell lung cancer, surgery, overall survival, chemotherapy,
Introduction

Lung cancer continues to be the most common type of cancer, with approximately 1.6 million new cases diagnosed each year in the world\(^1\). This number is predicted to increase worldwide\(^1\). Small cell lung cancer (SCLC) represents 10 to 15% of all lung cancers, and the incidence of SCLC has been slowly decreasing over the past few years in the United States and Japan\(^2,3\). SCLC is one of the most aggressive cancers; therefore, more than 60% of SCLC is already extended disease at diagnosis, and stage I disease is diagnosed in less than 5% of the patients with SCLC\(^4\). On the other hand, due to the advances in new and more powerful diagnostic tools, such as chest computed tomography (CT) and positron emission tomography (PET), an increase in the detection of SCLC as small nodules is expected.
Generally, due to SCLC responds chemotherapy and radiotherapy, surgical treatment is considered to be an option for early stage SCLC, while its clinical benefit is considered to be limited in patients with more advanced disease\textsuperscript{5, 6}. The most recent National Comprehensive Cancer Network guidelines recommend that patients with SCLC that is clinical stage I (T1-2, N0) after a standard staging evaluation may be considered for surgical resection\textsuperscript{5}. Furthermore, this guideline states that patients with disease exceeding T1-T2, N0 do not benefit from surgery\textsuperscript{5}. The recommended treatment in cases of limited stage excess T1-T2, N0 with a good PS is chemotherapy with concurrent radiotherapy\textsuperscript{5}. Similarly, according to the American College of Chest Physicians guidelines, in patients with clinical stage I SCLC after a thorough distant and invasive mediastinal stage evaluation, surgical resection is suggested over non-surgical treatment based on grade 2C evidence\textsuperscript{6}. On the other hand, several authors reported favorable results for surgical resection not only for stage I disease but also for more advanced disease\textsuperscript{7-12}.

In this study, we retrospectively compared the outcomes of the use of surgical resection compared to the other conventional non-surgical treatments in patients with LD-SCLC with respect to each clinical stage.
Materials and Methods

Patients and Methods

From 1974 through 2011, 605 consecutive patients were diagnosed with SCLC at the National Kyushu Cancer Center. Of those, 277 patients were treated for LD-SCLC. We retrospectively reviewed and analyzed the outcomes of these cases in terms of the role of surgical resection. Demographic, clinical and treatment data were abstracted from an institutional database that included all patients who had received treatment. The definition of LD-SCLC in this study was based on the International Association for the Study of Lung Cancer (IASLC) definition except for malignant pleural effusion or pleuritis carcinomatosa. The institutional review board gave its approval for this study.
Diagnostic Examinations

The diagnosis and staging procedure for the majority of patients was standardized to include bronchoscopy, laboratory parameters, CT of the chest and upper abdomen, brain CT or magnetic resonance imaging and a radionuclide bone scan and/or positron emission tomography with fluorine-18 fluorodeoxyglucose. Mediastinoscopy and endobronchial ultrasound mediastinal lymph nodes biopsies were performed as needed. Fifty-four patients (61%) in the surgical resection group received a pathological diagnosis prior to surgery. The TNM stage was determined according to the newly revised classification for lung cancer (American Joint Committee on Cancer seventh edition)\textsuperscript{14}.

Treatments

Surgical resection was performed for 88 patients, and included pneumonectomy ($n=10$), lobectomy ($n=74$) and limited resection ($n=4$), such as wedge resection or segmentectomy. Chemotherapy was administered to 255 patients as the first-line treatment or in the adjuvant setting. The chemotherapy regimen most frequently administrated as an initial treatment was cisplatin and etoposide (PE) in 130 cases, followed by carboplatin and etoposide (CE) in 33 cases; vincristine, endoxan, mitomycin C and toyomycin (VEMT) in 30 cases; cyclophosphamide, adriamycin and vincristine (CAV) in 24 cases and cisplatin and irinotecan (PI) in 10 cases. Other combinations were administrated to 10% (28 cases) of all patients.
Irradiation of the primary tumor and mediastinal lymph nodes was performed for 161 patients with or without chemotherapy and surgical resection. The radiation dose given as the initial treatment was 30 Gy to 75 Gy.

Statistical Analysis

Comparisons of continuous and dichotomous variables between groups were performed with the Student t test and $\chi^2$-test, respectively. The probability of survival was estimated using the Kaplan-Meier method. Differences in survival were evaluated by means of the log-rank test. An exploratory survival analysis such as a propensity matching analysis was added in the patients with stage II and III disease in order to balance the background of the patients. Patients with surgical resection in stage II and III disease were matched with those who received non-surgical therapy according to age, gender, ECOG PS and clinical stage. The analysis was conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA). All p-values < 0.05 were considered to be statistically significant.
Results

The age of the patients ranged from 38 to 89 years old (median, 66) and the patients included 225 males and 52 females (Table 1). The clinical stage was stage I in 50 cases (18%), stage II in 53 cases (19%) and stage III in 174 cases (63%). Thirty-six patients received treatment in the 1970s, 66 patients in the 1980s, 72 patients in the 1990s and 103 patients in the 2000s (Table 1). The distribution of treatments according to the clinical stage is shown in Table 2.

There were a total of 277 patients, 88 of whom underwent surgical resection and 189 of whom were treated with non-surgical treatments. Surgery was performed in 44 patients (88%) in stage I, 27 patients (52%) in stage II and 17 patients (10%) in stage III. Twenty-seven patients in the surgical resection group received induction chemotherapy and two patients received induction chemoradiotherapy. Chemoradiotherapy was performed as the non-surgical treatment in 4 patients (8%) in stage I, 17 patients (32%) in stage II and 125 patients (72%) in stage III (Table 2). The agreement between the clinical and pathological stages of the patients who underwent surgery was as follows: 86% in stage I, 33% in stage II and 53% in stage III.

The median follow-up time for all cases was 16 months, and the median survival time (MST) for all cases was 18 months. The five-year survival rates of the patients according to clinical stage were 58% for stage I, 29% for stage II and 18% for stage III (Figure 1A). The
MST of the patients according to clinical stage was 75 months in the stage I cases, 18 months for stage II and 15 months for stage III (Figure 1A). The five-year survival rates of the patients underwent surgery according to the pathological stage were 59% for those in stage I, 39% in stage II and 14% for those in stage III (Figure 1B). The results of the Kaplan Meier analyses of patients according to the clinical stage and with or without surgical treatment are shown in Figure 2. The five-year survival rates of the patients with or without surgical resection according to the clinical stage were as follows: 62% and 25% in stage I (p<0.01), 33% and 24% in stage II (p=0.95) and 18% and 18% in stage III (p=0.35), respectively (Figures 2A-C). A survival advantage related to surgery was observed in the patients with stage I disease, whereas in patients with stage II and stage III disease, no significant difference was observed in these groups (Figures 2A-C). Comparison of long-term survival between the two groups after propensity matching analysis is shown in Figure 2D. Forty-four pair patients were matched in each group. The five-year survival rates of the patients with or without surgical resection according to the analysis were as follows: 28% in surgical resection group and 11% in non-surgical group (p=0.04). The propensity matching analysis demonstrated that the surgical resection group had a significant better survival than the non-surgical group in the cases of stage II and III LD-SCLC (Figure 2-D).

The five-year survival rates of the patients according to the treatment period were as
follows: 20% in the 1970/80s, 21% in the 1990s and 40% in the 2000s (p<0.01) (Figure 3).
Discussion

Two randomized prospective trials of surgery versus radiotherapy organized by the British Medical Research Council reported that surgery and radiotherapy were equally effective for limited stage SCLC. According to these reports, fewer than 2% of patients survived more than two years after the resection. Later, in 1994, Lad et al. reported the results of a randomized trial evaluating the role of surgery in limited-stage SCLC conducted by the Lung Cancer Study Group. This study included 144 SCLC patients, all administrated chemotherapy followed by chest irradiation. The patients were then randomized to a surgery group or a non-surgery group. According to the report, no significant impact of surgery on survival was found, with the two-year survival rate being 20% for all cases. Based on those studies, surgical treatment for SCLC is considered to be an option for early stage disease, but its clinical benefit is considered to be limited, especially for more advanced disease. However, several decades have passed since these reports were published. During that time, several authors have reported the efficacy of surgical resection for LD-SCLC, especially when it is used as part of multidisciplinary therapy.

Recently, the role of surgery in SCLC has been analyzed using a large population data base. The Surveillance, Epidemiology, and End Results (SEER) data base identified 14,179 patients with SCLC, including 863 patients who underwent surgery. According to
those results, the patients who underwent surgery had better survival rates than those who did not for both localized disease and regional disease, even in cases of N1 or N2 disease\textsuperscript{12}.

Another study using the SEER database reported that the five-year survival rate of the patients with stage I disease who underwent lobectomy was 50.3\% and that of the patients who received external beam radiation alone was 14.9\%, respectively\textsuperscript{18}. The IASLC reported on 12,630 patients with SCLC, 349 of whom underwent surgical therapy\textsuperscript{19}. According to the report, the five-year survival rates of the patients with pathological stage IA, IB, IIA, IIB, IIIA and IIIB disease were 56\%, 57\%, 38\%, 40\%, 12\% and 0\%, respectively\textsuperscript{19}. The stages of the reports were classified using the seventh edition of the TNM grouping\textsuperscript{19}.

In the present study, we evaluated the outcomes of LD-SCLC patients reclassified using the TNM seventh edition. According to our results, the seventh edition of the TNM classification correctly reflected the prognosis of LD-SCLC. We also evaluated the outcomes of the patients with or without surgical resection according to the clinical stage. In this study, the use of surgery led to a satisfactory result in the patients with stage I disease, with a five-year survival rate of 62\% for the surgical resection group and 25\% for the non-surgical group. On the other hand, no significant benefit of surgical resection was observed in the patients with clinical stage II and III disease. Although the therapeutic strategy was not assigned randomly, more than 80\% of the patients who underwent surgical resection also received chemotherapy or
chemoradiotherapy. In addition, only three patients were treated with surgical resection alone in the clinical stage II and III group as the initial treatment. Although there was no difference in the overall survival between the patients treated with or without surgical resection in the overall cases, the propensity matching analysis demonstrated the efficacy of surgical resection in the patients with stage II and III LD-SCLC. In addition, the five-year survival rates according to the pathological stage were 59% in patients with stage I, 39% in those with stage II and 14% in those with stage III disease. Based on these results, some patients with stage II and III disease obtain a relatively good prognosis following surgical resection. One of the reasons for the differences in the outcome between clinical and pathological stages was the existence of upstaged cases. In this series, 18 of the surgical cases were underestimated in terms of the clinical stage. The IASLC report analyzed the concordance between the clinical and pathological stages\(^1\). According to that report, 20% of the patients diagnosed with clinical stage I/II disease were upstaged, with pathological evidence of mediastinal lymph node metastases, and the five-year survival rate based on the pathological stage was better than that based on the same clinical stage\(^1\). In our series, some of the patients were not staged according to today's standards tools, such as PET or mediastinoscopy; therefore, the diagnosis of the clinical stage was less accurate than is now possible. The staging concordance using PET or PET/CT was reported to be 83% to 100% in the prospective setting\(^1\). In fact, the
agreement between the clinical and pathological stages of all of the patients who underwent surgery was 87.5% in the 2000s in this study. Two decades have passed since the last prospective randomized trial evaluating the role of surgery was reported, and there have been new diagnostic tools and therapeutic techniques have developed during that time. In fact, our data suggested that the outcomes of treatment have been improved beginning in the 2000s. Similarly, Hanagiri et al. reported that the outcomes of the patients who received treatment for SCLC after the 1994, including surgery, improved compared to that before. At any rate, it is currently uncertain whether all of the LD-SCLC cases except for those stage I disease are not indicated for surgical resection; therefore, further prospective studies might be considered to extend the indications for surgery for LD-SCLC based on the present diagnostic modalities and improved surgical techniques.

There are some limitations associated with this study. One of the limitations is the retrospective and non-randomized setting of this study. To compare the efficacy of surgical resection, it is important to evaluate the findings in a prospective and randomized setting. On the other hand, since few cases of limited disease are diagnosed each year, a prospective study would be difficult to carry out; therefore, it is important to accumulate retrospective data. Second, the sample size of this study was relatively small and the treatments were lacking in uniformity. However, to our knowledge, there have been few reports that have evaluated the
outcomes of LD-SCLC cases restaged based on the TNM seventh edition as part of a single-institution study. Despite these several limitations, the present study reflects the actual clinical outcomes of LD-SCLC patients.

In conclusion, surgical resection provided a survival benefit for the patients with clinical stage I SCLC and some cases of stage II or III disease in this study. The outcomes of treatment for SCLC have been improved beginning in the 2000s. A further prospective study is warranted to clarify the possibility of extending the indications for surgical resection to curatively treat LD-SCLC in the present situation.
References


Figure Legends

Figure 1. The Kaplan-Meier curves of the overall survival according to (A) the clinical TNM stage and (B) the pathological TNM stage (seventh edition of the TNM).

Figure 2. The Kaplan-Meier curves of the overall survival of patients with or without surgical resection. (A) Stage I, (B) stage II, (C) stage III and (D) matched cohorts in stage II and III.

Figure 3. The Kaplan-Meier curves of the overall survival according to the treatment period.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=277)</th>
<th>Surgery (n=88)</th>
<th>Non-surgery (n=189)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range)</td>
<td>66 (38 to 89)</td>
<td>66 (43-83)</td>
<td>66 (38-89)</td>
<td>0.72</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>225 (81%)</td>
<td>72 (81%)</td>
<td>153 (81%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Female</td>
<td>52 (19%)</td>
<td>16 (19%)</td>
<td>36 (19%)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>162 (58%)</td>
<td>68 (77%)</td>
<td>94 (50%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>1</td>
<td>94 (34%)</td>
<td>18 (21%)</td>
<td>76 (40%)</td>
<td></td>
</tr>
<tr>
<td>2, 3</td>
<td>21 (8%)</td>
<td>2 (2%)</td>
<td>19 (10%)</td>
<td></td>
</tr>
<tr>
<td>cTNM stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>50 (18%)</td>
<td>44 (50%)</td>
<td>6 (3%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stage II</td>
<td>53 (19%)</td>
<td>27 (31%)</td>
<td>26 (14%)</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>174 (63%)</td>
<td>17 (19%)</td>
<td>157 (83%)</td>
<td></td>
</tr>
<tr>
<td>treatment period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1970s</td>
<td>36 (13%)</td>
<td>12 (14%)</td>
<td>24 (13%)</td>
<td>0.07</td>
</tr>
<tr>
<td>1980s</td>
<td>66 (24%)</td>
<td>26 (29%)</td>
<td>40 (21%)</td>
<td></td>
</tr>
<tr>
<td>1990s</td>
<td>72 (26%)</td>
<td>27 (31%)</td>
<td>45 (24%)</td>
<td></td>
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<tr>
<td>2000s</td>
<td>103 (37%)</td>
<td>23 (26%)</td>
<td>80 (42%)</td>
<td></td>
</tr>
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</table>
Table 2. The Initial Treatment for LD-SCLC

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>c-stage I (n=50)</th>
<th>c-stage II (n=53)</th>
<th>c-stage III (n=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical treatment (n=88)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery only</td>
<td>13 (26%)</td>
<td>2 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Surgery+chemotherapy</td>
<td>30 (60%)</td>
<td>21 (40%)</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>Surgery+chemoradiotherapy</td>
<td>1 (2%)</td>
<td>4 (8%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Non-surgical treatment (n=189)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>1 (2%)</td>
<td>6 (11%)</td>
<td>30 (17%)</td>
</tr>
<tr>
<td>Radiotherapy only</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Chemoradiotherapy</td>
<td>4 (8%)</td>
<td>17 (32%)</td>
<td>125 (72%)</td>
</tr>
</tbody>
</table>
Figure 1A

The figure compares the survival rates of three different stages of a disease: c-stage I (n=50), c-stage II (n=53), and c-stage III (n=174). The survival rates are plotted over a period of 5 years.

- c-stage I: 50, 39, 30, 25, 24, 24
- c-stage II: 53, 35, 20, 17, 13, 13
- c-stage III: 174, 112, 50, 33, 26, 22

The p-value for the comparison is less than 0.01, indicating a statistically significant difference in survival rates between the stages.
Figure 1B

- p-stage I (n=51)
- p-stage II (n=15)
- p-stage III (n=22)

Survival rates over 5 years:
- p-stage I: 51, 41, 32, 27, 26, 25
- p-stage II: 15, 13, 8, 7, 5, 5
- p-stage III: 22, 13, 5, 2, 2, 2

p<0.01
Figure 2B

c-stage II

resection (n=27)
non-resection (n=26)

p=0.95

(years)
Figure 2D

c-stage II and III

- resection (n=44)
- non-resection (n=44)

p=0.04