A Pilot Phase 2 Study of Surgical Treatment After Induction Chemotherapy for Resectable Stage I to IIAA Small Cell Lung Cancer*

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**Background:** To evaluate the feasibility and efficacy of surgical resection of the primary tumor and regional lymph nodes in patients with resectable stage I to IIAA small cell lung cancer (SCLC) who had responded to induction chemotherapy.

**Methods and results:** Twenty-two patients (age, 39 to 70 years; median, 60.5 years) with resectable stage I to IIAA SCLC were identified as candidates for induction chemotherapy. All patients received two to four cycles of preoperative chemotherapy IV every 3 weeks (CAV II: cisplatin, 80 mg/m², day 1; doxorubicin hydrochloride (Adriamycin), 30 mg/m², day 1; etoposide (VePesid), 60 mg/m² day 1 to 5). The overall response rate to induction chemotherapy was 95.5% (complete response, 5 of 22; and partial response, 16 of 22). After induction chemotherapy, 21 patients (95.5%) underwent a surgical resection (one pneumonectomy, 19 lobectomies, one segmentectomy). The postoperative pathologic study revealed only SCLC in 15 patients, only adenocarcinoma in one patient. The median survival time was 61.9 months for both the 21 surgical patients and all 22 patients, while their actuarial 3-year survival rates were 66.7% and 63.6%, respectively, for a follow-up period from 41.1 to 107.6 months (median, 59.8 months). Patients with clinical stages I and II disease had significantly longer survival times than did those with stage IIIA disease (3-year survival rates, 73.3% and 42.9%, respectively; p=0.018). The major adverse reaction was an operation-related death for one patient with N2 disease, but no other serious side effects were observed.

**Conclusion:** This induction chemotherapy followed by surgery is feasible and may be beneficial for the treatment of resectable stage I to IIAA SCLC.

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**Key words:** induction chemotherapy; lung cancer; prospective study; small cell lung cancer; surgery

**Abbreviations:** CAV II = cisplatin, doxorubicin hydrochloride (Adriamycin), and etoposide (VePesid); CR = complete remission or response; CV = cisplatin and etoposide; LD = limited stage; MST = median survival time; PS = performance status; SCLC = small cell lung cancer

Small cell lung cancer (SCLC) is usually a systemic disease at the time of initial diagnosis. It has a rapid growth rate and is metastatic outside the thorax in most patients at initial presentation.1,2 However, SCLC is sensitive to chemotherapeutic agents and radiation,3 so combination chemotherapy is useful in the treatment of SCLC.4 Responses occur in 80 to 90% of patients with limited-stage (LD) SCLC (LD-SCLC) treated with combination chemotherapy, with a median survival time (MST) of 12 to 16 months and 2-year survival rates of 20 to 30%.4,6 Although 40 to 80% of patients with LD-SCLC achieve a complete remission (CR), only 15% are continuously disease free for 2 years.7 Most initial relapses are intrathoracic.8 Thoracic radiation therapy does not appear to prevent local recurrence.7,9
Recent reports indicate that pulmonary resection in SCLC may offer extended survival and lessen the incidence of local recurrence. Resection may provide protection from local recurrence. According to Davis et al. in their study of 1,538 SCLC patients, the only factor that correlated with greater than 2-year survival was whether surgery was performed as part of the initial therapy. Surgical resection in combination with chemotherapy for stage I and probably stage II disease is now commonly accepted in the management of SCLC. More recently, Meyer et al. and Shepherd et al. have reported the possibility that surgical resection after chemotherapy for SCLC improved local control and also prolonged survival. In the present study for resectable stage I to IIIA SCLC, we evaluated the feasibility and efficacy of induction chemotherapy followed by surgical excision of the primary tumor and any regional lymph node metastases for providing better local control of the tumor and a longer survival time than “state-of-the-art” therapy.

Materials and Methods

Patients

Between March 26, 1987 and March 30, 1993, 22 patients with histologic or cytologic proof of SCLC, who were believed to be surgical candidates on the basis of resectable stage I to IIIA disease (N0, N1, or early N2 disease), were eligible for this study. Cytologic diagnoses were confirmed during a central review by the Niigata Cancer Center Hospital Pathology Committee. All preoperative and postoperative pathology samples were reviewed by two or more pathologists. The patients had no prior treatment with chemotherapy or radiation and had an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1. All patients were younger than 70 years old. Pretreatment studies included history, physical examination, CBC counts, standard blood chemistry studies, a chest radiograph, CT scans of the brain, thorax, and abdomen, a bone scan, bone marrow aspiration, and bronchoscopy. Mediastinoscopy was not used to determine the pathology N2 staging. Contraindications to protocol treatment included a WBC count <4,000/µL, a platelet count <100,000/µL, a creatinine concentration >1.3 mg/dL, an uncontrolled infection, poor cardiopulmonary function, or other serious illnesses. Patients with a history of cancer, unless they had at least a 3-year disease-free interval without treatment, were excluded. All patients provided informed consent.

Preoperative clinical staging was reported according to the new international staging system for lung cancer. The World Health Organization response criteria were used to assess the response to therapy.

Treatment Program

The first group of patients received combination chemotherapy consisting of cisplatin (80 mg/m²) and doxorubicin hydrochloride (Adriamycin) (30 mg/m²), all given on day 1, and etoposide (VePesid) (60 mg/m²), given daily for 5 days (CAV II regimen). CAV II was repeated IV every 3 weeks, for two cycles. At the completion of chemotherapy, the previous staging procedures were repeated to confirm response and exclude progressive disease. Responding patients underwent surgical resection, which was determined by the site of the primary disease at the initial presentation. All the patients received a radical mediastinal lymph node dissection. About 4 weeks after surgery, the responding patients with good PS received CAV II for three additional cycles.

After March 1990, the postoperative chemotherapy regimen was changed to cisplatin (80 mg/m²) given on day 1, and etoposide (VePesid), 100 mg/m², given daily for 3 days (CV regimen). After November 1991, patients with N1 and N2 disease received preoperative CAV II chemotherapy for four cycles, and no postoperative chemotherapy. The patients with N0 disease received the same preoperative and postoperative (CAV II and CV, respectively) regimens as previously described.

Statistical Methods

All patients have been followed up for at least 41 months, and their survival times have been calculated from the date of first treatment with chemotherapy until the date of death or last follow-up visit. Actuarial survival curves were prepared using the Kaplan-Meier method, and comparisons of survival were done with the log-rank test. Differences with p values <0.05 were considered to be statistically significant. The survival curves were generated on the basis of their pretreatment clinical stage, whether or not the patients underwent a surgical resection.

Results

During this study period, approximately 150 patients with SCLC were treated at our institution. Twenty-two patients entered into this study. There were 21 men and one woman with a median age of 60.5 years (range, 39 to 70 years). Pretreatment clinical TNM staging revealed 11 patients with stage I tumors, four with stage II tumors, and seven with stage IIIA tumors. The preoperative histologic examination revealed four cases of oat cell type and 18 of intermediate cell type.

The overall response rate to chemotherapy was 95.5% (CR, five of 22 [22.7%] and partial response, 16 of 22 [72.7%]). One patient achieved a minor response (a decrease from 25 to 50% in the average sum of the diameters of the measurable lesions) while receiving chemotherapy. Following reassessment after induction chemotherapy, all patients were believed to be candidates for surgical resection. The mean duration from the start of chemotherapy until the operation was 6.9 days, while the mean duration for two or four cycles of chemotherapy was 61 and 99 days, respectively. Twenty-one of the patients underwent a thoracotomy. One patient was considered ineligible for the operation because of a cerebrovascular accident after chemotherapy. Of the 21 patients who underwent a thoracotomy, 19 required a lobectomy, one a pneumonectomy, and one a segmentectomy. There was one operative death because of an uncontrolled postoperative infection.
The postoperative pathologic examination showed no residual tumor in five patients, only SCLC in 15, and only adenocarcinoma in one. After the postoperative pathologic examination and TNM staging, five patients had T0N0 disease, 10 had stage I disease, four had stage II disease, and two had stage IIIA disease.

The overall survival for all 22 patients is shown in Figure 1. Their median survival was 61.9 months and the actuarial 3-year survival rate was 63.6%. Eleven patients are currently alive. Four patients have survived longer than the MST (61.9 months), another five have survived for more than 45 months, and the remaining two survivors have survived for more than 36 months. The median survival for the 21 patients undergoing a thoracotomy also was 61.9 months, and their actuarial 3-year survival rate was 66.7%. Within this group, patients with clinical stages I and II disease (N0 and N1, 14 patients) had significantly longer survival times than did patients with clinical stage IIIA disease (N2, seven patients) (actuarial 3-year survival rates of 73.3% and 42.9%, respectively; p=0.018) (Fig 2). A similar statistically significant difference in survival was not observed when the 21 surgical patients were analyzed according to their postoperative pathologic stage, because only two patients had pathologic stage IIIA disease.

As shown in Table 1, 11 of the 21 surgical patients were disease free from 41.1 to 107.6 months. One patient died at 48.0 months because he developed brain metastases after 16 months. Five died after suffering relapses at 10.3, 12.6, 17.1, 19.1, 36.1 months after the start of chemotherapy. One patient died of another malignancy (esophageal cancer) at 61.9 months. Three patients died of recurrences, but whether it was from local or distant recurrences could not be determined because they died at other hospitals. One patient with N2 disease died because of an operation-related infection. Five of the six patients with recurrent disease had lymph node metastases.

**DISCUSSION**

SCLC is a rapidly progressive and has a high metastatic potential.**1,2** Until the 1960s, surgical resection was the main form of therapy for SCLC, but the results were extremely poor. In 1973, the British Medical Research Council Study**21** presented data that resulted in a significant change in the treatment of SCLC. This report suggested that surgical resection for SCLC should be replaced by radiation therapy. Since then, surgical resection generally has not been employed as part of standard therapy for SCLC. In 1968, the Veterans Administration Lung Cancer Study Group**22** reported that chemotherapy (the administration of cyclophosphamide) for SCLC resulted in a prolongation of the MST. After single-agent chemotherapy, three- and four-drug combinations for the initial therapy of SCLC began.**4,6** Nevertheless, long-term survival (>3 years) can be achieved only in 15 to 20% of patients with limited SCLC.**5-7,16** More than half of the recurrences occur at or near the primary tumor site in treated SCLC patients, so attempts at local control are likely to be helpful in prolonging survival. Surgical resection may offer the best approach for local control. In other words, this high failure rate of chemotherapy and radiotherapy has led again to the use of surgery as part of a combined modality approach.**13-15**

This first prospective study in Japan was undertaken to assess its feasibility. We also tried to gather...
Table 1—Clinical Features of All 22 Patients Treated With Induction Chemotherapy*

<table>
<thead>
<tr>
<th>Case No./Age, yr</th>
<th>Sex</th>
<th>cStage (TNM)</th>
<th>Histology</th>
<th>Pre-Cx (Courses)</th>
<th>Response</th>
<th>Duration From Cx to Ope, d</th>
<th>Operation</th>
<th>pStage (TNM)</th>
<th>Post-Cx (Courses)</th>
<th>Relapse Sites</th>
<th>Survival, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/56/M</td>
<td>0</td>
<td>T2N0</td>
<td>Intermediate</td>
<td>2</td>
<td>PR</td>
<td>63</td>
<td>RLL</td>
<td>T2N2</td>
<td>2</td>
<td>—</td>
<td>Died, 29.5</td>
</tr>
<tr>
<td>2/60/M</td>
<td>0</td>
<td>T3N2</td>
<td>Intermediate</td>
<td>2</td>
<td>PR</td>
<td>63</td>
<td>RLL</td>
<td>T0N0</td>
<td>—</td>
<td>Ope-related death</td>
<td>Died, 2.5</td>
</tr>
<tr>
<td>3/58/M</td>
<td>0</td>
<td>T1N0</td>
<td>Oat</td>
<td>2</td>
<td>CR</td>
<td>76</td>
<td>RML</td>
<td>T0N0</td>
<td>3</td>
<td>—</td>
<td>Alive, 107.6</td>
</tr>
<tr>
<td>4/54/M</td>
<td>0</td>
<td>T2N2</td>
<td>Intermediate</td>
<td>2</td>
<td>CR</td>
<td>70</td>
<td>RUML</td>
<td>T0N0</td>
<td>1</td>
<td>Brain</td>
<td>Died, 17.1</td>
</tr>
<tr>
<td>5/65/M</td>
<td>0</td>
<td>T2N0</td>
<td>Intermediate</td>
<td>2</td>
<td>MR</td>
<td>66</td>
<td>LLL</td>
<td>T1N0</td>
<td>ND</td>
<td>Second cancer</td>
<td>Died, 61.9</td>
</tr>
<tr>
<td>6/55/M</td>
<td>0</td>
<td>T1N2</td>
<td>Oat</td>
<td>2</td>
<td>PR</td>
<td>57</td>
<td>RMLLL</td>
<td>T1N2</td>
<td>1</td>
<td>Lung</td>
<td>Died, 36.1</td>
</tr>
<tr>
<td>7/68/M</td>
<td>0</td>
<td>T2N0</td>
<td>Oat</td>
<td>2</td>
<td>PR</td>
<td>64</td>
<td>LUL</td>
<td>T1N0</td>
<td>3</td>
<td>—</td>
<td>Alive, 82.8</td>
</tr>
<tr>
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<td>Intermediate</td>
<td>2</td>
<td>PR</td>
<td>57</td>
<td>LLL</td>
<td>T1N0</td>
<td>3</td>
<td>—</td>
<td>Alive, 82.1</td>
</tr>
<tr>
<td>9/65/M</td>
<td>0</td>
<td>T2N2</td>
<td>Intermediate</td>
<td>2</td>
<td>PR</td>
<td>58</td>
<td>RMLL</td>
<td>T1N1</td>
<td>3</td>
<td>Brain</td>
<td>Died, 19.1</td>
</tr>
<tr>
<td>10/59/M</td>
<td>0</td>
<td>T2N0</td>
<td>Intermediate</td>
<td>2</td>
<td>PR</td>
<td>56</td>
<td>RUL</td>
<td>T1N0</td>
<td>3</td>
<td>—</td>
<td>Died, 79.2</td>
</tr>
<tr>
<td>11/69/M</td>
<td>0</td>
<td>T2N2</td>
<td>Intermediate</td>
<td>2</td>
<td>PR</td>
<td>56</td>
<td>RUL</td>
<td>T1N0</td>
<td>1 (CV)</td>
<td>Brain</td>
<td>Died, 10.3</td>
</tr>
<tr>
<td>12/55/M</td>
<td>0</td>
<td>T1N2</td>
<td>Oat</td>
<td>2</td>
<td>PR</td>
<td>48</td>
<td>RUL</td>
<td>T0N0</td>
<td>ND</td>
<td>—</td>
<td>Died, 13.9</td>
</tr>
<tr>
<td>13/60/M</td>
<td>0</td>
<td>T1N0</td>
<td>Intermediate</td>
<td>2</td>
<td>CR</td>
<td>49</td>
<td>LUL</td>
<td>T1N0</td>
<td>2 (CV)</td>
<td>—</td>
<td>Alive, 60.6</td>
</tr>
<tr>
<td>14/62/M</td>
<td>0</td>
<td>T1N0</td>
<td>Intermediate</td>
<td>2</td>
<td>PR</td>
<td>49</td>
<td>LLL</td>
<td>T1N1</td>
<td>3 (CV)</td>
<td>—</td>
<td>Alive, 59.8</td>
</tr>
<tr>
<td>15/66/M</td>
<td>0</td>
<td>T2N2</td>
<td>Intermediate</td>
<td>4</td>
<td>PR</td>
<td>95</td>
<td>LLL</td>
<td>T2N0</td>
<td>ND</td>
<td>—</td>
<td>Alive, 57.6</td>
</tr>
<tr>
<td>16/66/M</td>
<td>0</td>
<td>T1N1</td>
<td>Intermediate</td>
<td>4</td>
<td>PR</td>
<td>92</td>
<td>RUL</td>
<td>T1N0</td>
<td>ND</td>
<td>—</td>
<td>Alive, 54.0</td>
</tr>
<tr>
<td>17/39/M</td>
<td>0</td>
<td>T2N1</td>
<td>Intermediate</td>
<td>4</td>
<td>CR</td>
<td>105</td>
<td>LLL</td>
<td>T1N1</td>
<td>ND</td>
<td>—</td>
<td>Alive, 53.5</td>
</tr>
<tr>
<td>18/67/M</td>
<td>0</td>
<td>T2N2</td>
<td>Intermediate</td>
<td>4</td>
<td>PR</td>
<td>104</td>
<td>L-PN</td>
<td>T0N0</td>
<td>ND</td>
<td>Brain</td>
<td>Died, 48.0</td>
</tr>
<tr>
<td>19/70/M</td>
<td>1</td>
<td>T1N0</td>
<td>Intermediate</td>
<td>2</td>
<td>PR</td>
<td>76</td>
<td>S5-S</td>
<td>T1N0</td>
<td>ND</td>
<td>—</td>
<td>Alive, 44.9</td>
</tr>
<tr>
<td>20/58/F</td>
<td>0</td>
<td>T2N1</td>
<td>Intermediate</td>
<td>3</td>
<td>CR</td>
<td>95</td>
<td>LUL</td>
<td>T1N1</td>
<td>ND</td>
<td>Liver</td>
<td>Died, 12.6</td>
</tr>
<tr>
<td>21/68/M</td>
<td>0</td>
<td>T1N1</td>
<td>Intermediate</td>
<td>4</td>
<td>PR</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Died, 15.6</td>
</tr>
<tr>
<td>22/53/M</td>
<td>0</td>
<td>T1N1</td>
<td>Intermediate</td>
<td>2</td>
<td>PR</td>
<td>68</td>
<td>LUL</td>
<td>T1N0</td>
<td>ND</td>
<td>—</td>
<td>Alive, 41.1</td>
</tr>
</tbody>
</table>

* cStage=clinical stage; pStage=pathologic stage; Cx=chemotherapy; Ope=operation; PR=partial response; MR=minor response; RLL=right lower lobectomy; RML=right middle lobectomy; RUML=right upper middle lobectomy; LLL=left lower lobectomy; RMLLL=right middle and lower lobectomy; LUL=left upper lobectomy; RUL=right upper lobectomy; L-PN=left pneumonectomy; S5=S segmentectomy; ND=not done.

information as to whether a randomized study could be helpful in evaluating the role of surgery after induction chemotherapy for resectable stage I to IIIA SCLC. Although similar studies have been reported in Japan,23,24 both were retrospective.  

Our prospective pilot phase 2 study of surgical resection after induction chemotherapy (CAY II) for 21 patients with stage I to IIIA SCLC yielded an MST of 61.9 months and a 3-year survival rate of 66.7%. The probability of long-term survival was very high for patients with stage I and II disease. Long-term survival may still be achieved in a few patients with resectable stage IIIA disease. In our patients with resectable stage IIIA disease without bulky N2, the addition of surgery after induction chemotherapy achieved results for SCLC superior to that of “state-of-the-art” therapy.16 Lad et al25 and Gatzemeier et al26 have reported negative findings for the efficacy of surgery for LD-SCLC. Lad et al25 have undertaken a prospective randomized trial to evaluate whether surgery is efficacious for LD-SCLC patients whose tumors responded to chemotherapy. They have suggested that the survival curves for the two arms are not different. Although this study recruited 70 surgical patients, namely, 13 patients with stage I tumors, 12 with stage II tumors, and 45 with stage IIIA tumors, the MST was 15.4 months. However, Gatzemeier and coworkers26 have reported the results of a comparative trial with 38 patients who received chemoradiotherapy followed by surgery and 62 patients who received chemoradiotherapy only. Their overall results in LD-SCLC are similar with chemoradiotherapy or chemoradiotherapy plus surgery (60% vs 49% in 3-year survival for those with stage I and II disease). The subjects in those two studies were different from those in our study because our study contained more patients with early-stage disease (stage I and II) and more peripheral nodular lesions. In other words, there were 15 of 22 patients with stage I and II disease (68.2%) in our study, and patients with clinical stage I and II disease had a 73.3% 3-year survival while it was 42.9% for those with clinical IIIA disease. Shields et al13 reviewed 148 patients of whom 132 survived at least 30 postoperative days. The 5-year survival rate depended on the TNM stage and varied from 59.5 (T1N0M0) to about 30% (T1N1M0 or T2N0M0). The introduction of adjuvant surgery is based on the premise that induction chemotherapy would allow surgical resection and enhance long-term survival. We believe that surgery after induction chemotherapy may yield a good outcome for those with early-stage SCLC (stage I and II) in LD-SCLC.  

Improvement of local control, one important aim of this study, was accomplished by the surgical
treatment because only one patient (case 6) had a primary site relapse and five patients (cases 4, 9, 11, 18, and 20) had distant metastases. Although most recurrences involved patients with N2 disease (cases 4, 6, 9, and 18) and distant metastases (cases 4, 9, and 18), we postulated that the preoperative chemotherapy was not sufficient. Therefore, we increased the preoperative chemotherapy. Beginning in November 1991, we changed the protocol to four cycles of preoperative chemotherapy for N1 or N2 cases. As a result, four patients (cases 15, 16, 17, and 18; these were N1 or N2 cases) received four preoperative cycles of chemotherapy (case 21 did not undergo surgery), and three are disease-free survivors.

The mean (±SD) interval from the start of chemotherapy for two or four cycles to the operation was 61±5.8 and 99±6.5 days, respectively. The only major adverse reaction was an operation-related death of one patient with N2 disease, but other serious side effects were not seen. So, this regimen of induction chemotherapy (CAV II) is feasible.

In conclusion, surgical treatment after induction chemotherapy for those with up to resectable stage IIIA SCLC is feasible, and we have achieved good local control and long-term survival in those with clinical stage I and II disease. However, a remaining problem is distant relapses, suggesting that the chemotherapeutic dose intensity was not sufficient. New drugs or new combinations are needed to battle this disease. We hope to undertake a cooperative randomized trial in stage I and II SCLC patients who undergo surgery after induction chemotherapy vs chemoradiotherapy alone.

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