

The Role of Surgical Resection and the Effects of Neo-Adjuvant Therapy in the Management of Small Cell Lung Cancer

SHOJI NAMIKAWA, TAIRIKI DEN, MAKOTO KIMURA, and MINORU KUSAGAWA

The Department of Thoracic Surgery, Mie University School of Medicine, 2-174 Edobashi, Tsu, Mie, 514 Japan

Abstract: A study was conducted on 58 patients who underwent surgery for small cell lung cancer (SCLC) as resection or exploratory thoracotomy, and 43 patients encountered during the same period who received no surgical treatment. The following conclusions were drawn from our analysis: At stage I, an operation is desirable, regardless of the subtype of SCLC, but chemotherapy should be given first; at stages II and III, by the addition of surgery after neo-adjuvant chemotherapy, “state-of-the-art” results for limited SCLC can be surpassed; in patients with stage II disease on whom curative resection has been performed, particular attention must be paid to the possibility of metastasis to the brain; and finally, exploratory thoracotomy did not bring about the early death of patients or reduce the quality of life, but only delayed chemotherapy for about one week, while enabling the staging and histological subtype of SCLC to be clarified.

Key Words: small cell lung cancer, surgery, neo-adjuvant therapy

Introduction

Because small cell lung cancer (SCLC) already displays the characteristics of a systemic disease at the time of its onset, chemotherapy has become its main method of treatment. In fact, many consider that the number of patients who should be subjected to surgical treatment is very small. This approach has become more popular since reports from the Medical Research Council of Great Britain, published in 1966¹ and 1973,² compared the results of surgical resection and radiological therapy for SCLC, and revealed the latter modality to be superior. However, now that multidisciplinary treatment has been actively adopted, although the effects

of chemotherapy for a shorter period are considered superior, its effects over an extended period have not been established. Furthermore, recurrence is often found in the primary lesions and consequently, the effect of surgical treatment needs to be reviewed again as a possible means of achieving complete remission.³

Until the 1970s, we generally resected SCLC lesions, as we did for non-SCLC lesions, with very poor results; however, during the 1980s, we changed our plan of management by starting with chemotherapy, followed by surgery. We conducted a retrospective analysis of the patients with SCLC operated on at the Mie University Hospital between 1960 and 1986 to determine the role of surgery and evaluate the overall response to chemotherapy.

Patients and Methods

During the period between 1960 and 1986, a total of 58 patients underwent surgery for SCLC in our department: resection in 43 patients (group A) and exploratory laparotomy in 15 (group B). In addition, there were 43 patients with SCLC encountered during the same period who received no surgical treatment (group C).

When the differences in background factors of groups A, B, and C were examined, it was found that the proportion of men was higher in groups A and B, while that of women was higher in group C. When the mean period between the time of onset and the initiation of treatment was examined, it was found to be 2.4 months in group A, 2.9 months in group B, and 3.1 months in group C, with no significant differences. When all 101 patients were grouped according to subtype, there were 43 patients with oat cell type (OT) SCLC, 49 with intermediated type (IM) SCLC, and 9 with an unknown subtype. There was no difference of histological subtypes between the three groups. Data were collated and statistically analyzed using the paired *t*-test and the

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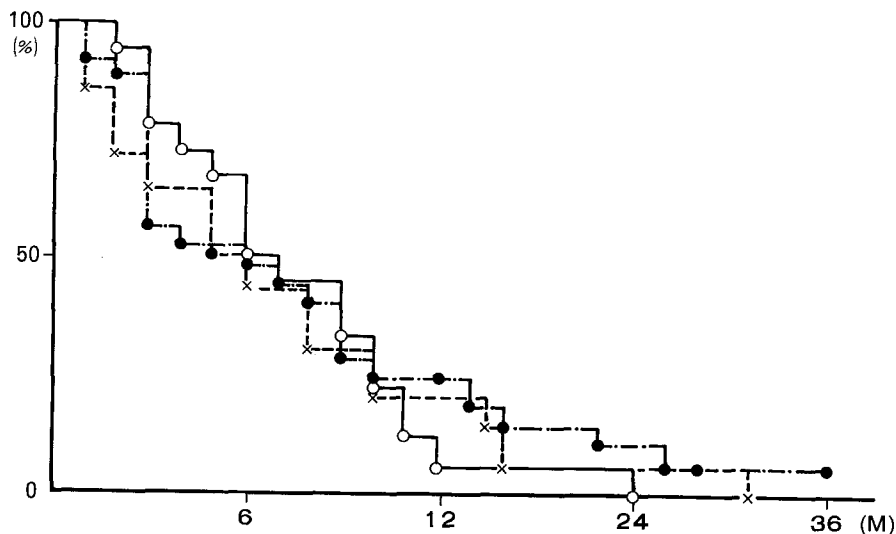


Fig. 1. Comparison of the survival of patients who underwent a non-curative operation (solid line, $n = 20$), those who underwent exploratory thoracotomy (dashed line, $n = 15$), and those who were given chemotherapy alone (chained line, $n = 43$)

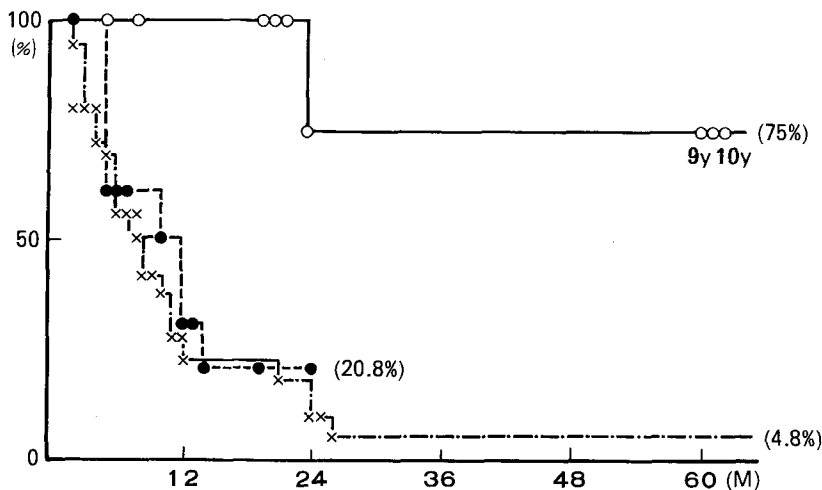


Fig. 2. Postoperative survival of patients with small cell lung cancer (SCLC) stratified by post-surgical staging (UICC 1987). The solid line represents stage I ($n = 9$), the dashed line represents stage II ($n = 10$), and the chained line represents stage IIIa ($n = 23$). $P < .05$ for stage I vs stage II or stage IIIa

generalized Wilcoxon test. Statistical significance was tested at the 95% confidence level.

Results

When the mean survival time (MST) of patients from the initiation of therapy was studied, it was found to be 8.1 months in group A, 5.1 months in group B, and 5.2 months in group C. Thus, in group A a mean 2-month prolongation of life was observed. When a comparison was made between the 20 patients who underwent non-curative surgery, the 15 who underwent thoracotomy only, and the 43 given chemotherapy alone, no difference was noted among these three groups. Accordingly, it seems that treatment for patients who are afraid of undergoing noncurative surgery should stop at explor-

atory thoracotomy, in consideration of the subsequent intensive chemotherapy and attempts to maintain the quality of life (Fig. 1).

The next comparison was made between those patients who underwent resection, who were classified by the TNM staging (Fig. 2). In nine patients classified as stage I, the 5-year survival rate was 75%, which was by no means inferior to that for any other histological cell type of primary lung cancer. However, at stage 2, survival after surgery was only about 2 years, and the 2-year survival rate remained at only 20.8%, although the 5-year survival rate of patients at stage III was 4.8%, with no difference from the results achieved in patients treated with chemotherapy for limited disease. The results of patients at stage I were significantly superior to those of patients at stages II and III regardless of whether their treatment started with chemotherapy or

Table 1. Summary of data on five patients who died within 2 years after curative resection

Patient	Age	Sex	Disease period	Operation	TNM	Histologic subtype	Adjuvant therapy	Prognosis Cause of death
1	50	Male	1M	R.U.L	T2N1M0	oat	BAI+METT	5M Brain meta.
2	63	Male	1M	L.U.L	T2N1M0	int.	(-)	12M Brain meta.
3	55	Male	5M	R.L.L	T2N1M0	oat	(-)	12M Brain meta.
4	45	Male	4M	R.P	T2N0M0	int.	(pre) METT+Ra. (post) METT	24M Brain meta.
5	37	Male	1M	R.M.L	T1N2M0	int.	MMC, METT	21M Local recurrence

R.U.L, right upper lobectomy; L.U.L, left upper lobectomy; R.L.L, right lower lobectomy; R.P, right pneumonectomy; R.M.L, right middle lobectomy; int., intermediate; MMC, mitomycin C; METT, mitomycin C + cyclophosphamide + toyomycin + tespamin; Ra, radiotherapy; meta., metastasis; M, month

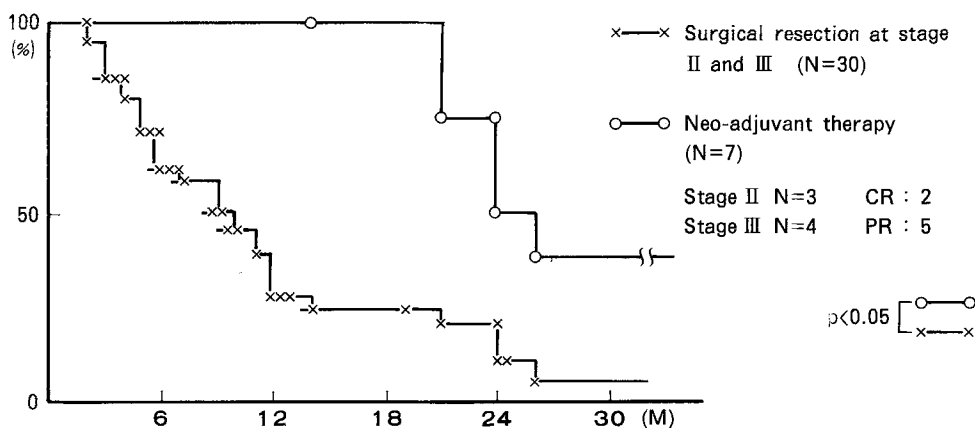


Fig. 3. Comparison of the survival of patients with stage II or III SCLC treated by surgical resection and mild chemotherapy, with those treated with neo-adjuvant therapy. CR, complete response to chemotherapy; PR, partial response to chemotherapy

their surgery was followed by chemotherapy. The N-factor could not be accurately assessed preoperatively and thus, surgical resection was performed for total removal of the cancerous tissue. For patients at stage II or III, unequivocal success of surgical treatment cannot be expected, and we have now therefore decided to treat such patients with neo-adjuvant therapy based mainly on chemotherapy. All of the patients who underwent curative resection died within 2 years (Table 1). Moreover, all four patients on whom an "absolute curative" operation was performed died of metastasis. Thus, even for patients who undergo "absolute curative" resection, postoperative chemotherapy must definitely be provided, together with cerebral computed tomography (CT) performed every 2 months to detect metastasis to the brain as the survival rate may be improved by giving whole-cranial irradiation. According to Rosen et al.,⁴ prophylactic cranial irradiation (PCI), resulted in decreased mortality. Because the effects of surgical treatment for SCLC at stages II and III has

been very unsatisfactory, we have decided to adopt neo-adjuvant therapy by initiating a course of intensive chemotherapy followed by surgery. So far, this trial has been performed on three patients at stage II and four at stage III. Complete response (CR) was achieved after chemotherapy in two patients, while a partial response (PR) was achieved in five (Fig. 3). When a comparison of the survival rates of these 7 patients and the 30 patients for whom resection was performed at stages II and III, was made with the Kaplan-Meier method, the MST was found to be 26 months in the former group and 11 months in the latter group, showing a significant difference ($P < 0.005$).

Discussion

The incidence of SCLC among all the histological cell types of primary lung cancer is between 10% and 20%; however, in recent years the incidence has been in-

creasing, and a drastic change in the concepts of treatment of SCLC has been taking place. Until the 1960s, surgical resection was the main method of treatment for lung cancer, but the results were extremely poor. In the late 1960s and early 1970s, the reports from the Medical Research Council of Great Britain were presented, which marked a great change in the history of treatment for SCLC. Since these reports dealt mainly with a comparison between surgery and radiation therapy, the latter modality began to be used more frequently, while physicians became more cautious about performing surgery. However, since radiation therapy is local therapy like surgery, it naturally has its limits, and the oncologist began to look for effective chemotherapy which would provide a systemic method for attacking the cancer.

In 1968, the Veterans' Administration Lung Cancer Study Group (VALSG) reported⁵ that the administration of cyclophosphamide to patients with extensive SCLC resulted in a 2.5-fold prolongation of the MST, and thereafter an explosion in the use of chemotherapy began. In recent years, reviews of surgical treatment for SCLC at stages I and II, together with a report by Salazar⁶ which revealed a higher frequency of local recurrence after treatment by chemotherapy alone, have brought about renewed recognition of the benefits of local treatment, such as surgery or radiation. Therefore, it may be very significant to emphasize the role of surgery in this study. Through our analysis of the patients who underwent surgical resection in our department, we reached the consensus that surgical treatment is the best possible therapy for SCLC at stage I, regardless of its subtype. Ohta et al.³ examined 195 cases collected from seven institutes in Japan, and came to the conclusion that SCLC at stages I and II, regardless of the subtype, should be resected. They also revealed good results in a group of patients to whom chemotherapy was given in combination with surgery. In our study, the 5-year survival rate of those patients with stage I disease was 75%, a figure which supports their findings. Although there have been divergent opinions as to whether chemotherapy should precede⁷ or follow surgery, we are of the opinion that it should precede surgery in view of the fact that the rate of accuracy of imaging, even for N1 disease, is about 65%. In our study, the 2-year survival rate of patients with stage II disease was only 20.8%. This poor survival rate arose because surgical resection was only performed on a few patients at this stage, three of whom later developed metastasis to the brain, and died within 2 years. Although PCI is considered to be the most suitable treatment, there are adverse effects. Craig et al.⁸ reported that, following whole cranial irradiation, evidence of parenchymal damage was found by CT imaging, while Ferguson et al. reported that they were

hesitant to even give PCI, since without it, metastasis to the brain would not occur in 75% of patients. We believe that strict follow-up with CT of the brain to allow for the early discovery of such lesions may be necessary.

The prognosis of those patients in whom exploratory thoracotomy was performed was miserable, although it is reassuring that none of them died within 1 month of the operation, since thoracotomy carries the advantages of enabling the staging and subtype of the disease to be clarified, so that it is not totally without clinical value. Meyer et al.⁹ have been expanding the indications for surgery to patients with stage III disease, provided that intensive chemotherapy is given preoperatively, and that an effect of chemotherapy is evident. According to their findings, the prognosis of patients with N2 disease is so poor that surgery would not be indicated; a view which is also shared by Ohta et al.³ However, Wada et al.¹⁰ have been using aggressive surgical treatment even for patients with N2 disease, and further results are awaited.

In conclusion, our results with neo-adjuvant therapy using "state-of-the-art" chemotherapy are superior, in terms of the MST of patients with early SCLC and overall survival rates, to those recently compiled by Aisner et al.¹¹

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