REVIEW·

The Role of Surgical Resection in Treating Small Cell Lung Cancer

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[ABSTRACT] Compares with non-small cell lung cancer, small cell lung cancer (SCLC) generally has a more rapid doubling time, a higher growth fraction, and earlier development of widespread metastases. Surgical operation has little impact on long-term survival of SCLC patients. Chemotherapy with combined radiotherapy has been recommended as the main treatment of SCLC. Patients with SCLC in excess of stage T2N0 do not benefit from surgical operation. But some data suggest the potential benefit of surgcial resection in the few patients with very limited disease, especially peripheral T1-2N0 lesions. Surgical resection can also prevent the recurrence of local disease. The role of surgical resection in the management of SCLC remains to be defined.

KEYWORDS: Lung neoplasm/surgical operation; Small cell lung cancer; Efficacy

Compared with non-small cell lung cancer (NSCLC), it is believed for a long term that, the effect of surgical operation against small cell lung cancer (SCLC) is poorer. Many studies abroad suggest that operation combined with chemotherapy could achieve a better effect for SCLC, and the recurrence can also be controlled. Potential benefits of surgical resection have been revealed in some patients with very limited cancerous lesions at early stages, especially peripheral T1-2N0 lesions. But for SCLC patients with the stage of above T2N0, surgical operation would do no good for the long term survival. We reviewed the therapeutic history and current status of SCLC treated by operation.

1. History of surgical operation in therapy of SCLC

In the 1960s, researchers found that the effect of operation alone was poor for SCLC [1], and nearly no patient had a long term survival. In the 1970s, UK Medical Research Council compared the therapeutic effects of operation alone and radiotherapy in treating SCLC [2, 3]. They found that, none of the 71 cases treated by surgical operation achieved long term survival; four cases out of 73 cases treated by radiotherapy achieved long term survival. The median survival time was 199 days for patients treated by the surgical method and 310 days for patients treated by radiotherapy. Therefore, it was believed that the therapeutic effect of radiotherapy is superior to surgical operation.

It is found that the doubling time of SCLC, squamous cell carcinoma and adenocarcinoma were 23 days, 88 days and 161 days, respectively[4-6]. The rapid growth of SCLC benefits early metastases of cancer cells. It is believed that, SCLC is a general disease [2, 7], which radiotherapy or surgical operation only has

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limited efficiency.

In the 1980s, when combined chemotherapy was applied in clinic, more than 80% of SCLC patients were alleviated at varied extents [8], and chemotherapy gradually became the major measure for SCLC. However, the effect of chemotherapy alone was not satisfactory, and the major reason was the recurrence of primary lesions. It was found by autopsy that, residual cancer was found in the primary focus in 64% patients who were clinically cured [9]. It has been indicated in a recent study [10] that non-small cell lung cancer cells are usually not sensitive to chemotherapy, which would cause local recurrence and ultimate failure of chemotherapy. Many scholars suggest that chemotherapy plus radiotherapy should be used to control local recurrence, Lichter *et al.* [11], however, found that, when chemotherapy plus radiotherapy was applied, primary local recurrence was still found in 28% -47% patients. Thus, controlling local recurrence has become a very important issue. In the middle and late 1980s, many researchers [12-21] reported good therapeutic effects of surgical operation plus chemotherapy against SCLC, and that local recurrence was controlled.

2. Synergistic effect of surgical operation for SCLC in combined therapy

There are many reports on the application of surgical operation in combined therapy for SCLC. In the middle and late 1980s, many scholars reported good effects of surgical operation when it was applied in combined therapy. Karrer *et al.* [12] reported 112 cases treated by chemotherapy after surgical operation, and the 3-year survival rates of patients of stage Ⅰ, Ⅱ, and ⅢA were 62%, 50% and 41%, respectively. The therapeutic effects for stage Ⅰ patients were particularly good, and the 5-year survival rate was as high as 60%. Salzer *et al.* [13] reported 11 cases of stage ⅢA (N2) treated by chemotherapy after surgical operation, and the 5-year survival rate was 24%. They also emphasized the effect of preoperative chemotherapy. In the 1990s, Fujimori *et al.* [14] reported 21 cases who were firstly administrated with cis-platinum, adriamycin and etoposide, and then performed surgical operation. The 3-year survival rate was 73.3% for stage Ⅰ and stage Ⅱ patients, significantly higher than 42.9% of stage ⅢA patients. Ichinose *et al.* [15] divided stage Ⅰ-ⅢA patients into operation plus chemotherapy group and radiotherapy alone or chemotherapy alone group. The results indicated that, the 5-year survival rate was 67.7% for stage Ⅰ patients in the operation group, and the local recurrence was completely controlled; there was no significant difference in the survival rate and the local recurrent rate in stage Ⅱ-ⅢA patients in the two groups. Therefore, it was believed that surgical operation is suitable for stage Ⅰ patients. In recent years, Japanese Lung Caner Group reported 62 cases who were firstly performed operation and then administrated with cis-platinum and etoposide. The 3-year survival rate was 68% for stage Ⅰ patients, 56% for stage Ⅱ patients, and 13% for stage ⅢA patients. Brock *et al.* [17] reported 82 cases, and the 5-year survival rate was 42%. The 5-year survival rates of 56 cases performed chemotherapy with or without platinums were 86% and 42%, and the effect of operation combined therapy was emphasized. Chandra *et al.* [18] reported 67 cases who were firstly performed operation, and then chemotherapy or/and radiotherapy; the 5-year survival rate was 27%, and it was 38% for stage Ⅰ and Ⅱ patients. Zhang *et al.* [19] reported 104 cases treated by operation as the major therapeutic measure, and the 5-year survival rate was 27.5%. The 5-year survival rate was 16.7% for patients in operation group, 32.4% for patients in operation plus postoperative chemotherapy group; 40.0% for stage Ⅰ patients, 16.6% for stage Ⅱ patients and 33.3% for stage ⅢA patients in operation plus postoperative chemotherapy group. Wang *et al.* [20] reported 272 cases with limited SCLC, and the 5- year survival rates were 4.3%, 31.9% and 49.5% for patients in chemotherapy group, postoperative chemotherapy group, and chemotherapy plus operation plus chemoradiotherapy group. Zhao *et al.* [21] reported 145 SCLC cases treated by synergistic measures (including operation), and the 5-year survival rate was 33.3% for stage Ⅰ patients, 22.7% for stage Ⅱ patients and 5% for stage ⅢA patients. The 5-year survival rate was 37.5% for stage Ⅰ patients, 33.3% for stage Ⅱ patients and 4.2% for stage ⅢA patients in chemoradiotherapy + operation + chemoradiotherapy group.

In summary, the effect of surgical operation has been confirmed in the treatment for SCLC. The operative effects for stage Ⅰ and Ⅱ patients are good when operation is combined with chemotherapy. Currently, it is still controversial to determine the type of SCLC suitable for surgical operation.

3. Operative indications of SCLC

Some researchers [14-18] generally believe that stage Ⅰ and Ⅱ SCLC patients are suitable for surgical therapy, and radiochemotherapy should be applied before or after operation. Others [19-21] believe that operative indications should be expanded, and surgical operation is suitable for stage Ⅰ, Ⅱ and ⅢA patients when radiotherapy and chemotherapy are combined. Most of these reports are retrospective studies, and the most convincing one was reported by Lad *et al.* [22] in 1994. They prospectively studied the effect of operation on SCLC using a random control study, and reported 146 cases with response after 5 cycles of cyclophosphamide, adriamycin and vinblastine. The patients were randomly divided into operation group (70 cases) and non-operation group (76 cases). All the patients received chest radiotherapy and preventive irradiation on head, and the survival curves of patients in the two groups were similar. The study indicated that only stage Ⅰ patients were suitable for operation, who usually obtained pathological results by fine needle aspiration. However this method could not identify carcinoid from SCLC, and it also could not differentiate other lung cancers from small carcinoma cells. We suppose that patients with SCLC above stage T2N0 are unsuitable for operation, which was also considered as the principle in the Guide (2006) edited by National Comprehensive Cancer Network (NCCN).

4. Current viewpoints

In NCCN guide (2006), it is pointed out that, operation is only suitable when clinical stage is confirmed as T2N0. The standard staging evaluation includes the following examinations: chest, epigastric and cerebral CT, bone scanning, or even PET imaging. Before operation, all the patients should be performed with mediastinoscope or other surgical measures to exclude potential metastasis of mediastinal lymph nodes. Patients underwent radical treatment (pulmonary lobectomy, dissection of mediastinal lymph nodes and so on) should receive postoperative chemotherapy. Patients without lymphatic metastasis should only receive chemotherapy, but patients with lymphatic metastasis are recommended to receive simultaneous chemotherapy and postoperative radiotherapy. Because preventive cerebral irradiation can improve the total survival rate, when the patients who receive radical treatment complete auxiliary chemotherapy, preventive cranial irradiation should be considered. For many suprapulmonic nodes, SCLC can only be confirmed by thoracotomy. Under this condition, when frozen pathological examination shows SCLC during operation, lobectomy plus lymphatic dissection should be performed even if there is lymphatic metastasis (stage Ⅱ patients). If the carcinoma tissues can be removed only by pneumonoresection, pneumonoresection should not be performed, because the death rate of pneumonoresection is higher than that of lobectomy. The postoperative chemotherapy and radiotherapy should be performed as early as possible.

5. Controversial problems and problems to be studied

For those patients with no preoperative pathological diagnosis but only with postoperative pathological one, chemotherapy and/or radiotherapy should be performed after operation. However, for those patients with preoperative diagnosis, it is still controversial whether operation is beneficial for the patients. And the following problems should be further studied:

(1) Whether operation should be performed or not on stage Ⅱ-ⅢA patients.

(2) Which clinical stage is suitable for operation when new auxiliary chemotherapy is effective on patients of stage Ⅱ-ⅢA or even stage ⅢB, especially for those patients whose pulmonary mass completely disappeared after radiochemotherapy and relapsed shortly in the primary focus; and whether lobectomy should be performed or not on this kind of patients before recurrence.

(3) Though new auxiliary chemotherapy can decrease the carcinoma volume and lower the clinical stage, preoperative chemotherapy would increase the difficulty of surgical operation. There are few studies on how many cycles of chemotherapy should be performed. Whether preoperative chemotherapy of varied cycles should be performed with different chemotherapy drugs needs further investigation.

(4) In 1994, Lad *et al.* [22] reported a prospective study in which patients were treated with non-platinum chemotherapy combined with operation; and proposed that patients with SCLC above stage T2N0 were unsuitable for operation. However, there are

no prospective random control studies on patients who were treated by operation after using the first line drugs.

(5) Chemotherapy is the major therapeutic measure for SCLC. The major objective of operation is to dissect the primary focus, prevent recurrence, and alleviate tumor load, and then determine whether Wedge dissection is more favorable for patients, rather than lobectomy plus dissection of mediastinal lymph nodes performed for SCLC.

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