Surgery of Small Cell Lung Cancer

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The role of surgical resection in the management of patients with small cell lung cancer remains to be defined. Some data suggest the potential benefit of resection in the few patients with very limited disease (peripheral T_N and T_N lesions), and there are chemotherapy regimens with 80-85% response rates in patients with more extensive but still localized disease. Interest has been reawakened in the role of adjuvant surgical resection in selected patients by 2 approaches: (1) in patients with peripheral T or T lesions with negative mediastinal exploration, initial surgical resection followed by an adequate chemotherapeutic regimen and prophylactic cranial irradiation has resulted in an 80% disease-free survival at 30 months; (2) initial chemotherapy in patients with only localized disease is followed by resection in the responders. Approximately 30% of the responders have undergone exploratory thoracotomy after completion of the chemotherapy. Local irradiation, as well as prophylactic cranial irradiation, generally has been used postoperatively. Early pilot studies suggest benefit of this approach in patients found to have T_N, N_disease but not in those with N_disease. Prospective, randomized, clinical trials by the Lung Cancer Study Group in North America and its counterparts in Europe are now being carried out in hopes of supplying definitive data relative to this multimodality therapy in small cell lung cancer. Unfortunately, no data are available to date.

During the past 50 years, surgical resection has been established as the major curative procedure in the treatment of non-small cell lung cancer. In this group, a potentially curative surgical resection may be done in 20-25% of patients. However, in patients with small cell lung cancer, the role of surgical resection has yet to be defined.

From the 1940s through the early 1970s, surgical resection was carried out as the curative modality in patients with small cell lung cancer who were judged to have resectable lesions by the criteria then in vogue for all lung cancers. Although the exact numbers are not known, most clinics reported that about 10% of patients with small cell cancer underwent exploration for possible resection. Of this number, far fewer than half who had exploratory thoracotomy had a complete resection of the disease process.

The results recorded in the major surgical series of resection of small cell lung cancer reported in the 1950s and 1960s varied from as low as 2.5% to as high as 21.4% 5-year survival (Table 1).1,3 The variance may be explained partially by patient selection and the possible inclusion of some patients who did not actually have small cell cancer. The microscopic criteria were less well defined than those used now, and undoubtedly some patients with bronchial carcinoids also were included.

Nonetheless, it was apparent from these early reports that surgical intervention, even in a relatively selected population of patients with small cell lung cancer, had little to offer. The long-term survivors were few, and unfortunately this number was often exceeded by the operative mortality at the time. The opinion of many as to the futility of resection was greatly reinforced by the results of the prospective trial of radiation therapy vs surgical resection conducted by the British Medical Research Council, reported in 1969 and 1973, in which there were no long-term survivors after surgical resection.4,7

A subsequent series of surgical resection in small cell lung cancer patients reported by Mountain et al7 in the United States also revealed no long-term survivors. Equally distressing, Matthews and colleagues8 reported in 1973 the presence of persistent disease in 70% (92% distant metastases and 5% residual local disease only) of 19 patients with small cell lung cancer who died within 30 days of what was thought to have been a curative surgical resection. As a result of these experiences, it was generally conceded in the middle and late 1970s that surgical resection had little or no role in the management of small cell lung cancer.

However, isolated reports of favorable results following surgical resection with or without irradiation or chemotherapy or both in selected patients (Table 2) reawakened interest in the role of surgical resection in the management of this disease.9,10 More important, the development of effective chemotherapeutic regimens has stimulated the concept of possible benefit of adjuvant surgical resection in patients with limited disease. In this subset of patients who have responded initially to the chemotherapy, approximately 50% will have the first site of failure within the chest. Also, when resection has been done in such patients, residual tumor of a cell type different from the original small cell tumor has been noted in over 25% of the resected specimens.11,12 The emergence of other cell types resistant to chemotherapy may be one explanation for failure of the treatment regimen.

Table 1—Long-term Survival After Resection of Small Cell Lung Cancer, 1955-69

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Date of Report</th>
<th>% 5-Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirkin et al1</td>
<td>1955</td>
<td>5.0</td>
</tr>
<tr>
<td>Siddons4</td>
<td>1962</td>
<td>21.4</td>
</tr>
<tr>
<td>Taylor et al3</td>
<td>1963</td>
<td>12.4</td>
</tr>
<tr>
<td>Goldman4</td>
<td>1965</td>
<td>2.5</td>
</tr>
<tr>
<td>Lennox et al2</td>
<td>1969</td>
<td>10.8</td>
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Resection, when feasible, may forestall these events. However, before discussing the possibility of adjuvant surgical resection after response to chemotherapy, the data from various studies, the review of which suggests that resection may result in improved long-term survival in a small subset of selected patients, should be presented.

Review of the data reported from the Armed Forces Asymptomatic Solitary Pulmonary Nodule Study, although the number of patients with small cell lung cancer was small, suggested that the prognosis of patients with a peripheral nodule without lymph node metastases had essentially the same prognosis regardless of the cell type (approximately 36% five-year survival). Likewise, the review of data collected by the Veterans Administration Surgical Oncology Group (VASOG) furthered the concept that resection was beneficial in selected patients.

In the VASOG report, 148 patients with small cell lung cancer had been entered into the 4 major prospective lung trials conducted by the group. Each was thought to have undergone a potentially curative resection for carcinoma of the lung in these trials. Each of the resected patients except those who died in the postoperative period were classified postsurgically by the TNM system. Exclusive of the postoperative deaths (16 deaths), 132 patients with small cell lung cancer in this series were evaluable for long-term survival. The 5-year survival computed by the life table method was 23.0%. The actuarial survival of patients with tumors of each TNM category at 5 years were: T,N,M0, 59.5%; T,N,M1, 31.3%; T,N,M2, 27.9%; T,N,M3, 9.0% and T1 or N0, 3.6%. Each stage had a survival pattern that was more favorable than the next advanced stage, but only the difference between T,N,M0 and the other categories was significant (p<0.001).

Twenty-three patients in the series had survived 5 years or longer. The number of 5-year survivors in each TNM category was: T,N,M0, 11 patients; T,N,M1, 4; T,N,M2, 4; T,N,M3, 3; and T1 or N0, 1 patient. The tumor in 6 of the 11 5-year survivors in the T,N,M0 category was located in the periphery of the lung, whereas 5 were located centrally. In the 5-year survivors, all tumors categorized as T,N,M0 lesions were located peripherally. Two-thirds of the long-term survivors had no lymph node metastases, and one-third had such involvement. In 7 long-term survivors with metastases to the nodes, the involved nodes were lobar or hilar or both, and in only 1 patient was it mediastinal.

In the entire group of 148 patients who had undergone a curative resection for the removal of a small cell lung cancer, 80 patients had been randomized to receive postoperative adjuvant chemotherapy. The other 68 patients, randomized not to receive such therapy, served as the control (or surgery-only) population. No beneficial effect of postoperative adjuvant chemotherapy was noted in either regimen of 1 or 2 courses of a single drug (nitrogen mustard, HN2, or cyclophosphamide, cyclophox). A possible benefit, although not significant, was noted in the first prolonged intermittent chemotherapy trial (cytoxan or cyclophox and methotrexate). In the second prolonged intermittent trial (1-[2 chloroethyl]-3-cyclohexyl-1-nitrosourea, CCNU, and hydroxyurea), a similar benefit was suggested by review of the data, but due to the number of patients, all treated-control differences were too small to rule out chance as a possible cause. However, none of the aforementioned chemotherapeutic regimens would be considered now to have been appropriate for the treatment of patients with small cell lung carcinoma.

With these data as a background, the development of effective chemotherapeutic regimens, one of which is the combination of cyclophoxamide, doxorubicin (Adriamycin), and vincristine (CAV) with or without etoposide (VP-16) (CAVE), has stimulated the reevaluation of surgical resection in patients with limited disease. Numerous pilot studies, both randomized and nonrandomized, recently have been carried out in Europe and America in an attempt to assess a possible role of surgical resection along with adequate chemotherapy either in the preoperative or postoperative period. In many of the studies, postoperative local irradiation as well as prophylactic cranial irradiation has also been utilized.

Generally, in patients with clinical stage I and II disease (often confirmed by negative mediastinal exploration) initial surgical resection was done followed by chemotherapy and at times by radiation therapy. Meyer and colleagues have been active in this approach in this country. They reported that the prognosis of selected patients with stage I and II disease (primary tumor surrounded by aerated lung and negative mediastinal exploration, Table 3) was improved by initial surgical resection followed by adequate chemotherapy and prophylactic cranial irradiation. A 30-month survival rate of 83% was noted for patients with the postsurgical classifications of T,N,M0, T,N,M1, T,N,M2, and was 75% in patients classified as T,N,M3. The data of Ginsberg et al, as well as that of Valdivieso et al, although not as complete as the former authors', lend support to the efficacy of this approach in stage I and stage II patients.

Review of the data of Karrer et al, Vogt-Moykopf, and Merkle et al has shown that initial surgery followed by chemotherapy is superior to resection alone. A 33% long-term survival in the combined treatment group compared

Table 2—Long-term Survival After Resection of Small Cell Lung Cancer, 1970-82

<table>
<thead>
<tr>
<th>Author</th>
<th>Date of Report</th>
<th>% 5-Yr Survival</th>
</tr>
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<tbody>
<tr>
<td>Bates et al</td>
<td>1974</td>
<td>27.0</td>
</tr>
<tr>
<td>Higgins et al</td>
<td>1975</td>
<td>36.0</td>
</tr>
<tr>
<td>Shore and Paneth</td>
<td>1980</td>
<td>25.0</td>
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<td>Shields et al</td>
<td>1982</td>
<td>23.0</td>
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Table 3—Results of Initial Surgery Followed by Chemotherapy in Patients with Small Cell Lung Cancer*

<table>
<thead>
<tr>
<th>Extent of Disease</th>
<th>No. of Patients</th>
<th>Alive</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>T,N</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>T,N</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T,N</td>
<td>4</td>
<td>3</td>
<td>1†</td>
</tr>
<tr>
<td>T,N</td>
<td>4</td>
<td>2</td>
<td>2‡</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

†Postoperative death.
‡Second primary in one patient.
with only an 8% survival in the surgical resection only group was observed in the major cooperative trial reported by Karrer et al.\textsuperscript{58} The lower overall survival rate in the chemotherapy group compared with that observed by the Meyer group probably is the result of inclusion in the European studies of several patients with stage II disease.

In patients with more advanced but still local disease (stage III M\(_0\)), most investigators have used initial chemotherapy (two or three cycles) followed by thoracotomy and resection, when feasible, in the complete or partial responders who were judged to be able to tolerate such a procedure.\textsuperscript{14,34-37,39} Chemotherapy, as well as irradiation in most, was continued in the post-operative period.

In some centers, all preoperatively diagnosed localized cases of small cell lung cancer (stage I, II, as well as localized stage III) are now managed in this manner. At present, the Lung Cancer Study Group (LCSG) is conducting a prospective, randomized trial in such patients,\textsuperscript{59} in which all patients determined to have localized disease only are treated with five cycles of chemotherapy (CAV). The complete and partial responders are then randomized into 2 groups: 1 to undergo exploration for resection followed by local and prophylactic cranial irradiation, and a control group to receive similar irradiation after the initial 5 cycles without the interposition of a surgical procedure. To date, 65 patients have been entered into the trial, but not data are yet available for review (personal communication, E. C. Holmes, 1985).

However, the results of similar nonrandomized pilot studies have not been encouraging in the majority of patients with localized stage III disease, particularly those with N\(_2\) disease. In the studies from Vanderbilt University,\textsuperscript{60} M. D. Anderson Hospital,\textsuperscript{61} and the ECOG group,\textsuperscript{62} fewer than a third of the evaluable patients (28%) were found to be candidates for surgical resection after intensive chemotherapy.

In the largest pilot study, 40 patients with initially limited small cell lung cancer were managed by the initial chemotherapy (CAVE); 39 patients were evaluated for surgical resection.\textsuperscript{63} Thirteen patients (33%) had complete responses (CR), 21 (54%) partial responses (PR), and 5 (13%) had stable disease. Of the 39 patients in the entire group, 6 refused operation, 5 had medical contraindications to operation, and 11 were considered to have unresectable disease based on the standard criteria for resection. Of the remaining 11, only 8 patients (20% of the initial group) had resections. The most recent follow-up information available (personal communication, F. A. Greco, 1985) is that in the 8 resections, 5 relapses have been noted, and only 3 (7% of the total group) patients remain free of disease at a minimum follow-up of about 30 months. Of the 3 patients with clinical N\(_2\) disease in the group of 11, only 1 had the disease resected, and this patient died of recurrent disease within 6 months of the resection.

Meyer et al\textsuperscript{66} reported the results in 20 patients with clinically localized stage III disease. Sixteen patients were staged initially as having N\(_2\) disease with any T and 4 patients with T\(_2\) disease with N\(_2\) involvement. All patients were treated preoperatively without 2 cycles of chemotherapy. In the 4 patients with T\(_2\) without N\(_2\) disease, resection was accomplished in 3 patients but was microscopically incomplete in 1. One of the 2 patients with complete resection died free of disease at 34 months, and the other patient remains alive and well 50 months after the initiation of treatment. In contrast, however, in the 16 patients with initial N\(_2\) disease, only 10 patients underwent resection, and in all 10 recurrent disease occurred within 5-30 months. One patient with N\(_2\) disease who was not explored for resection remains alive in complete response at 30 months.\textsuperscript{68} Interestingly, most recurrent disease in the surgically treated group was noted at a distant site (the CNS being the most common site), not in the ipsilateral hemithorax. The observation has also been noted by others.\textsuperscript{34,47,38}

Pathologic, postsurgical staging, of course, is essential in the resected patients. In reporting the results, the initial clinical TNM classification as well as the final pathologic TNM classification should be recorded. The use of stage groupings alone is inadequate.

In regard to the pathologic specimens that have been resected after chemotherapy, the observation of the failure to identify viable tumor in some specimens (20-33%), as well as the identification of a tumor of a cell type other than the initial small cell carcinoma, has been noted by numerous investigators.\textsuperscript{14-18} The incidence of this latter observation has varied between 20% and 40%, and the more common cell types have been large cell and adenocarcinoma. The significance of this change in histologic pattern has yet to be discerned.

From the review of the data now available, it appears reasonable to suggest several tentative conclusions. One is that surgical resection does have a role in a highly selective subset of patients with small cell lung cancer. Patients with peripheral T\(_1\) or T\(_2\) disease without N\(_2\) involvement may be satisfactorily managed by initial surgical resection followed by an adequate chemotherapeutic regimen and prophylactic cranial irradiation. The most appropriate chemotherapeutic regimen is unknown, but the prospective trial being conducted in Europe by Karrer and colleagues (personal communication) may help to answer this question. The second conclusion is that patients with central T\(_2\), or T\(_3\) or localized stage III disease without N\(_2\) involvement should receive initial chemotherapy followed by exploratory thoracotomy and surgical resection, when possible, in the complete or partial responders. A third conclusion is that it appears from the aforementioned data that N\(_2\) disease is a poor prognostic finding. It seems reasonable that at the time patients are being evaluated for possible resection after initial chemotherapy, CT scans and mediastinal exploration should be essential parts of the preoperative restaging procedure. Any persistent, identifiable N\(_2\) disease probably should be considered a contraindication to resection. However, the proper management and the role of adjuvant surgical resection in this subset of patients are yet to be determined. The early results reported in this subset have been poor, but the final answer must await the results of the prospective, randomized trials being carried out now by the LCSG and its European counterparts.

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