Postchemotherapy Resection of Residual Tumor in Limited Stage Small Cell Lung Cancer

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To determine the feasibility of post-chemotherapy resection of residual tumor in small cell lung cancer, 24 selected patients with limited-stage disease were evaluated for exploratory thoracotomy. All 24 patients achieved partial or complete clinical response to chemotherapy and were considered adequate medical candidates for surgical resection. Fifteen patients underwent a lobectomy or pneumonectomy, 13 of whom had residual tumor in the resected specimen. Of the nine remaining patients, seven had no tumor found on biopsy at thoracotomy and two had unresectable mediastinal node involvement. No chemotherapy was administered postoperatively in any patient until disease progression or relapse was documented. Median survival for the entire group was 19 months and did not differ according to the surgical procedure performed. Nineteen patients had relapse. Patients undergoing biopsy only recurred locally in six of seven cases a median of five months post-thoracotomy (range one to six months). Two “biopsy only” patients were tumor free at 34+ and 56+ months. Local recurrence was observed in six of 12 resected patients, while six patients experienced only extrathoracic metastases. Median time to recurrence for resected patients was also five months. Four resected patients experienced late recurrence 16 to 36 months postoperatively and were alive with tumor at 29+ to 42+ months. Two resected patients were tumor-free at 13+ and 37+ months. Post-chemotherapy surgical resection was feasible in limited-stage patients and improved local control of disease.

Of the 145,000 cases of lung cancer diagnosed in the United States each year, 25 percent are the small cell variety.1 Patients with small cell lung cancer (SCLC) clinically limited to the chest experience a high overall and complete response to combination chemotherapy.1 Unfortunately, only 10 to 15 percent of patients enjoy prolonged disease-free survival, as the vast majority eventually relapse even if a complete response has been obtained.1 Occasionally, recurrence occurs initially at the site of the primary intrathoracic lesion, presumably because chemotherapy controls distant micrometastases yet fails to sterilize the larger tumor deposit within the chest.1,4 In these circumstances, local recurrence may directly contribute to a patient's death. Thoracic irradiation can reduce the frequency of local recurrence, although up to 45 percent of patients will still have a recurrence in and around the irradiated field.5-7

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†American Cancer Society Junior Faculty Clinical Fellow.
‡American Cancer Society Clinical Professor of Oncology. Supported in part by PHS grant No. 1 R35 CA 38844-01, awarded by the National Cancer Institute, DHHS. Presented in part at the 22nd Annual Meeting, American Society of Clinical Oncology, Los Angeles, May 4-6, 1986. Manuscript received October 16; revision accepted January 8.
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Recently, surgery has been re-evaluated as a possible method of improving local control.8-10 Surgical resection prior to the administration of chemotherapy has the potential advantage of placing a patient into an immediate clinical remission (ie, eliminating bulk disease) without compromising bone marrow reserve. Theoretically at least, chemotherapy can then be used in a more effective setting, ie, when tumor burden is low.11 This approach appears to have been beneficial in a small number of patients in nonrandomized trials.8,9 However, prospective studies have shown that very few SCLC patients will actually be candidates for thoracotomy prior to chemotherapy or even after a brief course of treatment.10 An alternative approach, which has not yet been evaluated, would be to complete a full course of chemotherapy and attempt to resect any residual disease within the chest after establishing the absence of distant metastases. This approach has proven beneficial in advanced testicular cancer, another chemoresponsive neoplasm.12 Based on the germ cell cancer model, we undertook a pilot study designed to evaluate the feasibility and efficacy of surgery in limited-stage SCLC patients following completion of all planned chemotherapy.

METHODS AND PATIENTS

Study Design

Only patients with histologically confirmed, limited-stage small cell lung cancer were eligible for post-chemotherapy surgical resec-
Table 1—Clinical TNM Classification Pre-chemotherapy

<table>
<thead>
<tr>
<th>Stage</th>
<th>T2N0M0</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 2</td>
<td>T2N1M0</td>
<td>7</td>
</tr>
<tr>
<td>Stage 3</td>
<td>T2N2M0</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>T2N0-1M0</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>T2N2M1</td>
<td>*</td>
</tr>
</tbody>
</table>

*Supravclavicular node involvement.

tion. Initial staging evaluation consisted of physical examination, blood count and liver chemistry evaluations, PA and lateral chest x-ray examinations, radionuclide bone and liver scans (and/or abdominal computed tomographic [CT] scan), head CT scan and bone aspiration and biopsy. Individuals with tumor confined to one hemithorax with or without ipsilateral hilar, mediastinal, and/or supravacular lymph node involvement were considered to have limited-stage disease. Patients with bilateral mediastinal node involvement were not eligible for this study. Patients then received combination chemotherapy (vide infra).

After completing the prescribed course of chemotherapy, patients were evaluated for thoracotomy by repeating the initial staging studies plus a bronchoscopic examination. Response to chemotherapy was assessed according to standard criteria. Patients were required to be suitable medical candidates for thoracotomy, meaning no recent (ie, <3 months) history of myocardial infarction, FEV1 ≥1.5 L, and a performance status of ≥70 percent. In addition, there would be no gross evidence of mediastinal lymph node involvement by chest x-ray or chest CT scan results. Mediastinoscopy was performed and those with positive findings were considered ineligible for resection. All patients gave informed consent. After meeting these criteria, patients underwent thoracotomy; biopsy samples and frozen section examinations were made from any abnormal-appearing area. Lymph nodes were sampled from the hilar, subcarinal, and paratracheal areas. If no evidence of malignancy was found, no resection was performed as our intent was to resect only those with obvious or apparently residual tumor. In cases where biopsy revealed residual tumor or the frozen section results were equivocal, lobectomy or pneumonectomy was performed at the surgeon’s discretion. An effort was made to remove all residual tumor. Following thoracotomy, no additional treatment was administered regardless of pathologic findings until such time as disease relapse or progression was documented.

Patient Characteristics

A total of 24 limited stage patients met the above criteria and gave their informed consent for post-chemotherapy surgical resection. All but six patients were operated on by the same surgeon. The group included 15 men and nine women with a median age of 55.5 years (range 40 to 70 years) and a median performance status of 80 percent (range 70 to 90 percent). Prior to chemotherapy, utilizing initial staging data which did not routinely include chest CT scan or mediastinoscopy, the patients were clinically classified as stage 1 (three), stage 2 (seven), and stage 3 (14). TNM classifications are given in Table 1.

Twenty-one patients received chemotherapy according to the Southeastern Cancer Study Group (SECSG) protocol consisting of cyclophosphamide, doxorubicin, and vincristine (CAV) for six cycles with or without concomitant chest radiotherapy, followed by randomization to no further chemotherapy or two courses of cis-platin and etoposide, as previously described. Only four of the 21 patients treated according to the SECSG study also received thoracic irradiation. Two patients received six cycles of cyclophosphamide, doxorubicin, and etoposide while one patient received two cycles of cis-platin and etoposide followed by six cycles of CAV as part of separate institutional protocols. There were 11 complete and 13 partial responses to chemotherapy. Fourteen of the 24 patients also received prophylactic cranial irradiation (3,000 cGy in ten fractions).

Although it was not our intention to determine the exact frequency with which SCLC patients would be candidates for a post-chemotherapy surgical resection, it should be noted that 21 (8 percent) of our cases were chosen from 118 patients treated according to an SECSG protocol being conducted at Indiana and Vanderbilt Universities during the time encompassed by this study.

RESULTS

Surgical Results

One patient (a clinical PR), was preoperatively found to have grossly positive mediastinal lymph node involvement by mediastinoscopy and did not undergo further surgical exploration. Of the remaining patients who underwent exploratory thoracotomy, biopsy only was performed in eight (clinical response six CR, two PR). Seven of these patients had no gross or microscopic evidence of tumor and thus no further surgical procedure was performed. One patient had grossly evident involvement of mediastinal lymph nodes and was not felt to be a candidate for curative resection. Therefore, nine patients did not undergo resection but had a biopsy only (including the one patient who did not undergo thoracotomy); seven were tumor-free and two had positive unresectable mediastinal lymph nodes (Table 2).

Nine patients (clinical response three CR, six PR) had lobectomy, all of whom had residual tumor involving a bronchus. Six patients had negative lymph nodes, one had positive peribronchial node involvement and one patient had residual tumor extending into the mediastinum. However, the last patient was felt to have had all tumor resected. The remaining patient was

Table 2—Surgical Procedure and Pathologic Results

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. of patients</th>
<th>Clinical response</th>
<th>Pathology</th>
<th>Residual + tumor/– nodes</th>
<th>Residual + tumor/+ nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Negative for tumor.
†One patient had a positive surgical margin.

Postchemotherapy Resection of Residual Tumor (Johnson et al)
found to have negative nodes but a microscopically positive surgical margin (Table 2). Thus, of the nine patients undergoing lobectomy, eight were felt to have had a complete resection of all residual disease.

Six patients (clinical response two CR, four PR) underwent pneumonectomy, two of whom had no tumor found in the surgical specimen. One patient had microscopic tumor confined to the bronchus, two had peribronchial node involvement and one patient had microscopic tumor found in mediastinal nodes (Table 2). Nevertheless, all patients were felt to have had complete resection of residual tumor.

None of the patients with residual tumor at thoracotomy were found to have a mixed or pure non-small cell histology. All residual tumor was pure small cell carcinoma.

Of the 11 clinical complete remissions (all of whom had undergone preoperative bronchoscopy), only six were actually found to be tumor-free at thoracotomy. On the other hand, ten of 13 patients classified as partial remissions were found to have residual tumor at the time of surgical exploration.

**Survival**

Median survival for the entire group of patients was 19 months (range 7 to 56+ months). The "biopsy-only" patients survived a median of 18 months (range 7 to 56+) and two were disease free at 34+ and 56+ months (Table 3). All seven remaining patients died of recurrent SCLC. Resected patients survived a median of 20 months (range 7 to 42+ months). Of the nine patients undergoing lobectomy, one was disease-free at 13+ months and three were alive with recurrent tumor at 32+, 41+, and 42+ months. The five remaining lobectomy patients, including the patient with a positive surgical margin, have died of recurrent tumor. Median survival of the lobectomy patients was 15 months (range 9 to 42+ months) (Table 3). Four pneumonectomy patients have died, three of recurrent SCLC and one of an intercurrent illness (bronchopleural fistula, no clinical evidence of disease). One pneumonectomy patient was disease-free at 37+ months and one was alive with recurrent disease at 29+ months. Pneumonectomy patients survived a median of 21 months (range 7 to 37+) (Table 3). Survival according to pathologic findings at thoracotomy is shown in Table 4.

Of the four patients who received thoracic irradiation with induction chemotherapy, two had biopsy only and both were free of tumor (survival seven and 56+ months). One irradiated patient underwent lobectomy for residual tumor confined to the bronchus (survival 12 months) and one underwent pneumonectomy but had no tumor in the resected specimen (survival 37+ months).

**Sites of Recurrence**

Nineteen patients have progressed or relapsed since surgery, including seven of nine "biopsy-only" patients and 12 of 15 patients who underwent lobectomy or pneumonectomy (Table 5). Progression occurred within the chest at the site of the original lesion in 12 patients, eight of whom had no evidence of distant metastases. Not unexpectedly, patients who underwent biopsy-only were more prone to develop local recurrence than were those patients who had a resection (Table 5). Four patients experienced a simultaneous local and extrathoracic recurrence, three of whom had had either a lobectomy or pneumonectomy. Seven patients failed initially outside of the chest. With one exception, these patients had all undergone resection of residual tumor (Table 5).

Recurrence patterns according to pathologic findings at thoracotomy are shown in Table 6. Of the eight

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**Table 3—Survival Outcome According to Procedure Performed**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. of patients</th>
<th>Survival (range)</th>
<th>NED* &gt;2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>9</td>
<td>18 mos (7-56+)</td>
<td>2</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>9</td>
<td>15 mos (9-42+)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>6</td>
<td>21 mos (7-37+)</td>
<td>1</td>
</tr>
</tbody>
</table>

*No evidence of disease.

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**Table 4—Survival Outcome According to Pathology at Surgery**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>No. of patients</th>
<th>NED*</th>
<th>AWD†</th>
<th>DOD‡</th>
<th>Median survival (range)</th>
<th>NED &gt;2 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPT$</td>
<td>9</td>
<td>3</td>
<td>0</td>
<td>6</td>
<td>19 (7-56+)</td>
<td>3</td>
</tr>
<tr>
<td>+ tumor/− nodes</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>20 (12-42+)</td>
<td>0</td>
</tr>
<tr>
<td>+ tumor/+ nodes</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>16 (7-41+)</td>
<td>0</td>
</tr>
</tbody>
</table>

*No evidence of disease.
†Alive with disease.
‡Died of disease.
Recurrences confined to the chest, four occurred in patients with no tumor found at thoracotomy (all of whom underwent biopsy only). The four remaining local recurrences occurred in patients who had resection with either positive nodes or a positive surgical margin. Four patients had recurrences, both within the chest and with distant metastases, all of whom had residual tumor found at thoracotomy and three of whom had nodal involvement. One of these patients had biopsy only; the others had undergone resection. Of the seven recurrences occurring outside the chest, only one took place in a patient without tumor in the post-chemotherapy surgical specimen (ie, a non-resected patient). The six remaining patients had residual tumor resected with or without positive lymph nodes (three lobectomies and three pneumonectomies). Two of these six patients occurred solely within the central nervous system and included one patient with carcinomatous meningitis. The latter patient had received prophylactic cranial irradiation.

Median interval to recurrence from the time of thoracotomy was five months (range one to 36 months), with most relapses occurring within seven months. "Biopsy-only" patients had recurrence at a median of five months postoperatively (range one to seven months). Resected patients also had recurrences at a median of five months (range two to 36 months). However, four resected patients recurred late at 16 to 36 months postoperatively. Recurrence in these four patients was local in two and distant in two.

Surgical Complications

There was no perioperative death, although one patient died of progressive disease six weeks postoperatively. A second patient died one year after pneumonectomy probably as a result of a bronchopleural fistula. Although the patient was clinically free of tumor, an autopsy was not performed.

Nine relapsing patients have received salvage therapy with cis-platin and etoposide or cyclophosphamide, methotrexate and lomustine with or without thoracic irradiation without incurring unusual or unexpectedly severe toxicities.

Discussion

In analyzing failure patterns of SCLC following chemotherapy, it is evident that most patients die with disseminated disease. However, it is equally apparent that a small number of patients relapse initially within the chest at the site of the primary lesion, some of whom die without ever developing clinical evidence of distant metastases. For example, Byhardt and co-workers recently reported that, following treatment with chemotherapy plus thoracic irradiation, nine of 27 (33 percent) recurrences in limited-stage patients occurred solely at the site of the original tumor or regional lymph nodes. In all nine patients, local failure was a major cause of death and the sole cause of death in six cases. Among patients achieving complete remission, nearly 25 percent initially progressed at the site of the primary tumor, some of whom never developed extrathoracic metastases prior to death.

Since local recurrence may directly contribute to a patient’s demise even in the absence of overt distant metastases, control of the primary lesion clearly remains a significant problem. Although higher radiation doses could potentially improve the control of intrathoracic disease, the additional toxicity encountered precludes its use in conjunction with many current chemotherapy regimens. Thus, surgical resection has come under active investigation as an alternative. While local control has been improved in some studies, patients most likely to benefit from an early resection are those with peripheral or low stage lesions which represents a minority of SCLC patients. As a result, we decided to explore the use of post-chemotherapy surgical resection on the assumption that some limited-stage patients may have extrathoracic micrometastases eradicated with chemotherapy and are left with tumor only at the original intrathoracic site of disease. Resection of this presumably chemo-resistant residual tumor would then render the patient disease-free.

The patients chosen for this pilot study had completed six to eight cycles of a standard chemotherapy prior to being evaluated for exploratory thoracotomy. Only four patients had also received thoracic irradiation. Postoperatively, no patient received any additional chemotherapy or radiotherapy until disease relapse or progression was documented, regardless of the findings at thoracotomy. In this respect our treatment plan differed from that usually employed in testicular cancer patients, who commonly receive additional postoperative chemotherapy if residual tumor is found at surgery.

Based on the surgical procedure performed at the time of the exploratory thoracotomy, our patients were divided into two groups: group 1—patients in whom surgical resection of all residual tumor was attempted (ie, lobectomy or pneumonectomy); and group 2—patients undergoing a procedure not considered to be an adequate cancer operation, ie, biopsy only. Although all group 1 patients were thought to have residual tumor at operation, two had no tumor found in the resected specimen. Group 1 patients might have

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Local only</th>
<th>Local + distant</th>
<th>Distant only</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFT*</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>+ tumor/− nodes</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>+ tumor/+ nodes</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

*Negative for tumor.
been expected to do poorly since no immediate post-operative chemotherapy was given and most had residual tumor despite completion of multiple courses of chemotherapy. However, median survival in this group was 20 months, which compares favorably with the median survival of the biopsy-negative group 2 patients. Two group 1 patients were alive without evidence of tumor at 13+ and 37+ months post-thoracotomy, while a third patient died clinically free of disease at 19 months. Two of these three patients had had no tumor in their resected specimens. Twelve group 1 patients have relapsed and eight have died. The four surviving patients are presently receiving salvage chemotherapy. Interestingly, these four patients relapsed between 16 and 36 months post-operatively, whereas the eight patients who have died relapsed within six months of thoracotomy (range two to six months). Presumably these four patients would have experienced earlier had resection not been performed, although this is obviously speculative. Half (six of 12) of the relapses in group 1 occurred solely outside of the chest. The six remaining group 1 patients experienced local recurrence with (three) and without (three) distant metastases. Altogether, five group 1 patients have survived beyond two years, although four are currently receiving salvage chemotherapy for late recurrences.

There was only one significant postoperative complication in group 1, a bronchopleural fistula which contributed to the death of the patient. Otherwise, no untoward complications were observed regardless of the surgical procedure performed. Postoperative recovery did not appear to be delayed regardless of preoperative treatment (ie, chemotherapy alone vs chemotherapy plus chest irradiation).

Group 2 patients did not undergo surgical resection, either because no tumor was found at thoracotomy or because the residual tumor was deemed unresectable. Not surprisingly, this group also fared reasonably well since the majority clearly had a minimal tumor burden following completion of chemotherapy. However, these patients might have done even better had a resection of the pre-chemotherapy region of tumor involvement been carried out. Indeed, of the seven group 2 patients who have relapsed (all of which occurred within six months of thoracotomy), six experienced a local recurrence. Four local recurrences occurred in patients who had negative biopsies at thoracotomy. It is possible these patients would have benefitted from surgical resection despite the absence of apparent tumor, and additional studies are required to address this possibility.

These data suggest that post-chemotherapy surgical resection of residual disease is possible in SCLC patients with limited-disease and is not associated with any unexpected or unusual surgical complications. The data also indicate that post-chemotherapy resection of residual disease may lower the incidence of local recurrences. Unfortunately, resected patients continue to relapse but with a higher frequency of extra-thoracic metastases (Table 5). Had adjuvant chemotherapy been used postoperatively, particularly a non-cross-resistant regimen, it is possible that the group 1 patients who experienced relapse outside the chest would have fared even better, since it appears their post-resection tumor burden was quite low. However, our study was not designed to address this possibility.

Although none of our patients was found to have mixed histology or pure non-small cell tumor at thoracotomy, others have reported an incidence of up to 25 percent following chemotherapy. Postchemotherapy surgical resection may be particularly beneficial in these patients since chemotherapy could not be expected to eradicate the non-small cell component.

In summary, postchemotherapy surgical resection of residual tumor is possible in SCLC patients with limited-stage disease and may improve local control of tumor. Patients most likely to benefit from this approach appear to be those with residual disease confined to a bronchus following chemotherapy (ie, any lymph node involvement may prove to be a contraindication). However, even patients without obvious residual tumor may benefit from resection as the majority still experience local recurrence. A prospective clinical trial will be necessary to address this issue and to compare the efficacy of thoracic irradiation vs surgical resection. Although we believe these data support the continued investigation of post-chemotherapy resection, inadequate systemic therapy clearly remains the major therapeutic obstacle in the management of this disease.

ACKNOWLEDGMENT: The authors thank Ms. Nancy Settles for her assistance in typing the manuscript.

REFERENCES
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