Surgical treatment of brain metastases from lung cancer

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Thirty-five patients underwent surgical resection of brain metastases from non-oat-cell lung cancer between 1978 and 1981. Twenty-nine patients received postoperative radiation therapy to the brain. Twenty-three patients were male and 12 were female. Intracranial metastases occurred as the initial symptom of malignancy in 14 patients, and at varying periods following treatment of the primary tumor in 21 patients. The primary tumor and involved nodes were treated by definitive surgery in 18 patients, palliative resection and interstitial radiation in 10 patients, and by radiation therapy or chemotherapy alone in seven patients. The overall median survival time was 14 months. Favorable prognostic variables included: 1) absence of local or systemic disease at time of craniotomy (median 23 months survival time); 2) aggressive treatment of the primary tumor (median 18 months survival time); and 3) metachronous onset of brain metastases (median 15 months survival time). These survival data represent a considerable improvement over the historical 6 months median period of survival in such patients.

Key Words • brain metastasis • lung carcinoma • surgical treatment • metastatic tumor

Lung cancer is the leading cause of cancer deaths in men today. Recent data suggest a disproportionate rising incidence in women, and if this trend continues, it may outstrip breast cancer as the leading neoplasm. Approximately 135,000 cases are diagnosed annually in the United States alone, with 5-year survival rates of approximately 10%. This poor survival rate is attributed to two factors: failure to diagnose the disease early enough for it to be potentially curable by surgery, and the failure of current systemic therapy to control disseminated disease.

Brain metastases represent the most important form of systemic relapse in lung cancer; estimates for the frequency of this complication vary from 18% to 57%. The proclivity for brain metastases varies with histological type. Excluding oat-cell carcinoma, there is a much higher incidence in adenocarcinoma and large-cell undifferentiated carcinoma as compared to squamous carcinoma. At this institution, approximately 20% of lung cancer patients develop brain metastases, many within the 1st year after diagnosis of the primary tumor.

In patients with a single brain metastasis, surgical resection followed by irradiation is an important therapeutic option. Historically, the median survival time of such patients, including those with lung cancer, has been 6 months or less. In a previous report, we noted that the major determinant of survival in these patients was the extent of systemic metastasis. Furthermore, patients with lung cancer are particularly likely to have persistence of active disease in the chest at the time brain metastases become manifest. Recent improvements in treatment of the primary tumor have, however, been brought about by aggressive surgery alone, or in combination with brachytherapy. It is now possible to achieve "local control" in up to 70% of operable patients, compared to about 50% in the past (B Hilaris, unpublished data). These results should be reflected in the longer survival of those patients who suffer relapse in a form for which effective treatment exists, such as solitary brain metastasis. In addition, during the same time period, refinements in computerized tomography (CT) have allowed more accurate and perhaps earlier detection of patients with single brain metastases.

For these reasons, we have analyzed the results of surgical treatment of brain metastases from lung cancer within the past 4 years at the Memorial Sloan-Kettering Cancer Center.
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**Clinical Material**

From January, 1978, through September, 1981, 35 patients with brain metastases from non-oat-cell carcinoma of the lung underwent craniotomy by two of us (N.S. and J.H.G.) at this institution. Thirty-four of these patients had a single metastasis demonstrated by CT; one patient had two brain metastases. Twenty-three patients were male, and 12 were female. Their ages ranged from 34 to 67 years (median 51 years).

The histology of the primary tumor was adenocarcinoma in 29 patients, squamous cell carcinoma in five patients, and bronchiolar carcinoma in one patient. In 14 patients, the onset of brain metastases was synchronous (that is, these patients presented with brain metastases as the initial manifestation of cancer), and in 21 patients metachronous (that is, brain metastases occurred at varying periods following treatment of the primary tumor). The median duration of the interval between diagnosis of the primary tumor and diagnosis of the brain metastasis was 4 months (range 0 to 48 months) for the entire series. If only patients with metachronous onset of brain metastases are considered, the median duration of this interval was 10 months. The primary lung tumor was treated by surgery (lobectomy and pneumonectomy) alone in 18 patients; 10 patients underwent palliative resection with radioactive implants (iridium-192), and seven patients had no surgical treatment of the primary tumor. In those patients who underwent thoracotomy, the lung tumors were staged using the TNM system of the American Joint Committee for Cancer Staging and End Results Reporting. The extent of systemic disease was evaluated in all patients by chest x-ray films and radionuclide bone and liver scans. Twenty-one patients had disease limited to the brain. Fourteen patients had persistent active tumor in the chest, and, of these, six also had metastases to bone and one had liver metastases.

Thirty-two patients underwent elective craniotomy. In these patients, corticosteroid therapy was begun at least 3 days prior to surgery and all had localizing CT scans. These preoperative measures were not carried out in three patients who underwent emergency craniotomy. Five tumors presented on the surface of the brain of which four involved the overlying dura, and 30 tumors were subcortical. A standard surgical technique was used. In every patient, all tumor identifiable with × 4.5-power loupes was removed. Whenever feasible (in 18 cases), the tumor was removed as a single specimen.

Postoperatively, 29 patients received radiation therapy. Whole-brain irradiation was given in 26, and focal irradiation to the tumor bed in three. Treatment with corticosteroids was maintained during postoperative radiation therapy, then tapered and successfully stopped in all 29 patients. Five patients were operated on after radiation therapy had failed to stem the disease, and one patient died without receiving irradiation. Two of these patients were successfully weaned off steroids. Follow-up review with serial CT scans was carried out in 33 patients.

Survival data were calculated using the life-table method. Factors evaluated for prognostic significance included: 1) the extent of resection of the primary tumor; 2) the nodal status at thoracotomy; 3) the presence of recurrent disease in the chest or extra-cranial metastases at time of craniotomy; and 4) the time of onset of brain metastases. Comparisons between subgroups were performed with the Wilcoxon and Mantel-Cox tests. Preoperative and postoperative neurological status was evaluated by means of the Karnofsky scale. We further estimated time from operation to neurological progression, using the life-table method. For this index, all patients who developed neurological symptoms due to recurrent tumor, or for other reasons, were considered "deaths." Deaths occurring while the patient was experiencing stable neurological function were censored.

**Results**

One patient died of pulmonary embolus in the postoperative period, giving a mortality of 3%. Two patients developed postoperative clots, with subsequent uneventful courses after evacuation. Three patients had increased neurological deficits postoperatively. In two of these patients, one with a parietal lobe syndrome and another with aphasia and hemiparesis, the deficits improved to the point that they were both able to return to work. A third patient who developed dysphasia and hemiparesis recovered completely. All but three patients were weaned off steroids within 6 weeks posttreatment. These three patients were among the group in which radiation therapy had failed, and they had required chronic use of corticosteroids preoperatively.

The survival data are shown in Figs. 1 through 6. The overall median period of survival was 14 months.
FIG. 2. Period of survival by treatment of primary tumor. Curative resection was achieved in 18 patients (black circles), with a median survival time of 18 months; 10 patients had resection and radioactive implant (open circles), with a median survival time of 15 months; seven patients had no resection of the primary tumor (triangles), with a median survival time of 24 months. Thus, an untreated primary tumor was associated with significantly poor survival (p < 0.001).

(Fig. 1). The overall 1-year survival rate was 53%, and the 2-year survival rate was 25%. Factors associated with a longer survival time included aggressive surgical treatment of the primary tumor (median survival time 15 to 18 months, Fig. 2); detectable disease limited to the brain only (median survival time 23 months, Fig. 3), and metachronous onset of metastases (median survival time 15 months, Fig. 5). Unfavorable factors included untreated primary tumor (median survival time 24 months, Fig. 2), and the presence of recurrent lung tumor or systemic metastases at the time of craniotomy (median survival time 5 months, Fig. 3). We were unable to demonstrate any significant association between nodal status and length of survival (Fig. 4).

Only three patients (10%) had CT evidence of recurrence at the site of the original brain metastasis.

FIG. 3. Period of survival by extent of the disease. Of the 35 patients, 21 had negative bone scans and no local disease (black circles), with a median survival time of 23 months, and 14 had positive bone or liver scans or local disease (open circles), with a survival time of 5 months. Thus, the presence of local disease with positive bone/liver scans was associated with poor prognosis (p < 0.001).

FIG. 4. Period of survival by nodal status at thoracotomy. N₀ denotes no involvement of nodes; N₁ indicates positive findings at the hilar, interlobar, lobar, or parenchymal nodes; N₂ indicates positive findings at the superior mediastinal, aortic, or inferior mediastinal nodes. Six unclassified patients had no surgical staging because they did not undergo thoracotomy.

FIG. 5. Period of survival by time of onset of the metastases. Synchronous onset was associated with shorter median survival, but the difference was not statistically significant.
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Reoperation in one of these patients resulted in wound infection and meningitis. Four patients developed a second intracranial metastasis distant from the primary site; two underwent repeat surgery, and two received additional radiation therapy. One patient in this group became dysphasic following reoperation. Two other patients developed carcinomatous meningitis. Radiation-related complications were found in two patients: radiation necrosis with hemiparesis in one, and ataxia and hydrocephalus in the other. Three patients developed deafness due to nerve dysfunction (two complete, and one partial), presumably from the combination of radiation and chemotherapy. Eight patients showed CT evidence of hydrocephalus and white matter attenuation, most likely from radiation-induced leukoencephalopathy, but they were clinically asymptomatic.

Table 1 shows the functional status of the patients as assessed by the Karnofsky scale approximately 1 month after craniotomy as compared to that before operation. Calculated by actuarial methods, Fig. 7 shows that 75% of patients were improved or neurologically stable for 6 months or more, and that 65% retained improvement for 14 months.

Discussion

The survival data presented here represent a considerable improvement over previous surgical series reported from this and other institutions. Among the possible explanations for this improvement must be included 1) better patient selection; 2) improved treatment of the primary tumor and systemic metastases; and 3) improved treatment of the intracranial tumor.

At this institution, 13% of patients with brain metastases from lung cancer underwent craniotomy between 1978 and 1980 as compared to less than 10% in two other series. Tables 2 and 3 compare other important patient parameters between the present 1978–1981 series and the patients operated on between 1972 and 1977. The more recent group of patients were in better neurological condition, and fewer had systemic metastases, but a greater proportion had early onset of brain metastases (Table 2). Of unknown but indeterminable significance is the role of CT scanning in detecting truly single brain metastases at an earlier date in the present series, and the fact that bone and liver/spleen scans were not routinely used for determining extent of disease in the earlier group.

Although surgical treatment of the primary tumor appears comparable in the two groups, as noted previously, recent advances evaluated in a larger group of patients have resulted in better local control. In addition, five out of 15 patients who received chemotherapy displayed either partial or complete regression of systemic tumor. While both of these factors may have played a role in improved survival, their impact in this small series is impossible to gauge.

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td><strong>Comparison of pre- and postoperative functional status</strong></td>
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<tr>
<td>Preoperative Karnofsky Score</td>
</tr>
<tr>
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</tr>
<tr>
<td>80–100</td>
</tr>
<tr>
<td>60–79</td>
</tr>
<tr>
<td>50–59</td>
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<tr>
<td>10–29</td>
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* This patient died 2 weeks postoperatively.

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TABLE 2
Comparison of patients operated on 1972–1977 (Group A), with those operated on 1978–1981 (Group B)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A</th>
<th>Group B</th>
</tr>
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<tbody>
<tr>
<td>No. Percent</td>
<td>No. Percent</td>
<td></td>
</tr>
<tr>
<td>clinical presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>synchronous onset</td>
<td>5 28</td>
<td>14 40</td>
</tr>
<tr>
<td>metastasis &lt; 1 yr after pri-</td>
<td>12 67</td>
<td>28 80</td>
</tr>
<tr>
<td>primary neurological grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 (minimal or no deficit)</td>
<td>3 17</td>
<td>22 63</td>
</tr>
<tr>
<td>Grade 2 (moderate deficit)</td>
<td>12 67</td>
<td>10 29</td>
</tr>
<tr>
<td>Grade 3 (severe neurological deficit)</td>
<td>3 16</td>
<td>3 9</td>
</tr>
<tr>
<td>extent of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intracranial lesion only</td>
<td>8 47</td>
<td>21 60</td>
</tr>
<tr>
<td>local or systemic disease present</td>
<td>9 50</td>
<td>14 40</td>
</tr>
<tr>
<td>unknown surgical treatment of primary tumor</td>
<td>1 3</td>
<td>0</td>
</tr>
<tr>
<td>none</td>
<td>4 22</td>
<td>7 20</td>
</tr>
<tr>
<td>implant</td>
<td>3 17</td>
<td>10 29</td>
</tr>
<tr>
<td>resected</td>
<td>11 61</td>
<td>18 51</td>
</tr>
<tr>
<td>total cases</td>
<td>18</td>
<td>35</td>
</tr>
</tbody>
</table>

It is quite evident that the major difference between the two series is the increased survival time of patients with disease limited to the brain (Table 3), and that a substantial proportion of the improvement occurred after treatment of the brain metastases. In this regard, precise localization of the intracranial tumor by CT scanning has recently allowed removal of very small subcortical tumors as well as complete gross resection of larger neoplasms, with minimal morbidity. Despite the fact that several different irradiation protocols were used following surgery in the two groups, recent data showed no substantial difference in the effectiveness of varying dose-fractionations used for whole-brain radiation therapy.12

Aside from period of survival, another important consideration is the quality of neurological palliation provided by surgery. Table 1 shows that 75% of our patients improved or maintained their neurological status following surgery. More recently, the Radiation Therapy Oncology Group introduced two further indices to evaluate neurological palliation.12 These included “time to neurological progression,” and the proportion of patients who were neurologically symptom-free until death. In comparison with results reported in that pooled study, the surgically treated patients in our series showed a greater period of relief from neurological symptoms, and a larger proportion of these patients maintained this improvement until death (Fig. 7). Additionally, all but three patients were weaned off steroids posttreatment, thus avoiding the complications of long-term steroid therapy.4

An important clinical problem on which the present data bear is the management of a patient presenting with a solitary cerebral neoplasm, and who is discovered to have a possible primary lesion in the lung on chest x-ray film. Although our data suggest that synchronous onset of metastases carries a poorer prognosis, our series includes five patients in whom the primary lesion was considered inadequately treated at another institution. In a subset of eight patients (Fig. 6) who underwent craniotomy followed by thoracotomy at this institution, the median survival time exceeded 1 year. Only the three patients who were found to have unresectable mediastinal nodes at thoracotomy died within the 1st year. We believe, therefore, that an aggressive therapeutic approach is indicated in patients who present with synchronous onset of metastases, if the lung lesion is deemed resectable. Tissue diagnosis by needle biopsy of the lung prior to surgery is important to exclude oat-cell carcinoma.

Although the prognostic variables identified in this and other series10,21 are helpful in selecting patients who might best benefit from resection of an intracranial metastasis, other considerations must be given weight.10 Patients who deteriorate acutely from intracranial hemorrhage, or who are otherwise symptomatic from a large mass lesion can often receive neurological palliation by resection of the intracranial mass, even though the ultimate prospects for long-term survival appear poor. In addition, as more effective systemic treatment for lung cancer becomes available, the pool of patients who are candidates for surgical removal of solitary brain metastases should increase.

Acknowledgment

We would like to thank Basil Hilaris, M.D., Chief, Brachytherapy Service, Memorial Sloan-Kettering Cancer Center, for providing helpful criticism and clinical data relevant to this paper.
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References


Manuscript received September 24, 1982.
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