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The authors reviewed the records of 231 patients who underwent resection of brain metastases from nonsmall-cell lung cancer between 1976 and 1991. Data regarding the primary disease and the characteristics of brain metastasis were retrospectively collected. Median survival in the group from the time of first craniotomy was 11 months; postoperative mortality was 3%. Survival rates of 1, 2, 3, and 5 years were 46.3%, 24.2%, 14.7%, and 12.5%, respectively. One hundred twelve women survived significantly longer than 119 men (13.8 vs. 9.5 months, p < 0.02). Patients with single metastatic lesions (200 patients) survived longer than those (31 patients) with multiple metastases (11.1 vs. 8.5 months, p < 0.02). Patients with supratentorial tumors survived longer than patients with cerebellar lesions. A high Karnofsky performance scale score before surgery also indicated increased survival. In multivariate analyses, incomplete resection or no resection of primary lung tumor, male gender, infratentorial location, presence of systemic metastases, and age older than 60 years were significantly correlated with shorter survival. Approximately one-third of the patients died of neurological causes, one-third of systemic disease, and one-third of a combination of both. The results of this series confirm that the overall prognosis for patients with even a single resectable brain metastasis is poor, but that aggressive therapy can prolong life with quality of life preserved and can occasionally permit long-term survival.

KEY WORDS • brain metastasis • nonsmall-cell lung cancer • tumor • surgery

PRIMARY lung cancer is the leading cause of death from cancer in both women and men in the United States. It is estimated that there were 170,000 new cases of lung cancer in this country in 1994, resulting in 153,000 deaths. The incidence of brain metastases from lung cancer is reported to be approximately 34% in an autopsy series. Clinical studies show that between 20% and 24% of patients with nonsmall-cell lung cancer (NSCLC) are diagnosed as having brain metastases at some time during the course of their disease. As approximately 80% of patients with lung cancer have NSCLC, these percentages translate into 30,000 patients who will develop brain metastases from NSCLC each year. Only approximately 25% of these patients, however, will be eligible for surgical resection of their metastatic brain lesions.

In this article we report the results of a study of 231 patients who were treated by the Neurosurgery Service at Memorial Sloan-Kettering Cancer Center (MSKCC) over a period of 16 years (1976–1991) after the introduction of axial computerized tomography (CT) as a diagnostic tool. These patients, all of whom underwent resection of brain metastases from NSCLC, constitute the largest series of such patients ever reported. Some of them have also been included in earlier reports issued from this institution.

Clinical Material and Methods

Patient Population and Retrospective Study

A prospective log book of all of the neurosurgical procedures performed by three neurosurgeons at MSKCC was created in January 1972. Since 1976 623 patients have undergone resection of metastatic brain tumors, 241 of whom had brain metastases from lung cancer of differential histological types. The clinical data on these patients were collected retrospectively from their medical records, including operative and pathological reports, radiation therapy reports, and information from the office files of their neurosurgeons and thoracic surgeons.

Review of these patients’ clinical and pathological diagnoses showed that 231 patients had primary NSCLC during the period from January 1976 through December...
1991; these individuals constitute the focus of our study. Detailed follow-up study of these individuals was conducted by letter and telephone contact with patients, family members, friends, or personal physicians. The minimum follow-up period was 24 months; the last contact with a surviving patient took place on December 31, 1993. No patient was excluded from the statistical calculations.

For the purpose of this study, a brain metastasis diagnosed within 60 days of diagnosis of the primary NSCLC was considered synchronous. If the metastatic lesion was discovered after more than 60 days, it was considered metachronous.

Patients were considered eligible for complete resection of their brain lesions if they had single or multiple (two–three) tumors in surgically accessible areas, limited systemic disease, and a life expectancy judged to be at least 6 months. Preoperative workup included a detailed history and physical examination, chest radiography, and bronchoscopy. Brain, chest, and upper abdomen, including the adrenal glands and liver, were visualized using CT. The extent of resection of the brain lesion was documented in all patients by comparing the preoperative brain scan with a second one obtained no more than 3 to 7 days after surgery. Beginning in February 1986, magnetic resonance (MR) imaging was used instead of CT for diagnostic purposes as well as postoperative evaluation; a total of 83 patients (36%) were evaluated with MR imaging. In most patients, preoperative tumor localization was also performed.17,28

**Statistical Analysis**

Survival time in months was defined as beginning on the date of the patient’s first craniotomy. Survival curves and median survival time were calculated using the non-parametric Kaplan–Meier method.22 Comparisons of survival times and assessment of the strength of association between median survival and each of the variables were made using log-rank analysis.50 Multivariate regression analysis of survival times was calculated using a proportional hazards model.9 Frequency data analysis was performed with Fisher’s exact test. Statistical significance was defined as p < 0.05. Statistical calculations were made using a commercially available statistical software package (SAS Version 6.03; SAS Institute, Inc., Cary, NC).59

**TABLE 1**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Cases</th>
<th>Median Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>total no. of patients</td>
<td>231</td>
<td>11.0</td>
</tr>
<tr>
<td>age range at time of craniotomy</td>
<td>34–79 yrs</td>
<td>(median 56 yrs)</td>
</tr>
<tr>
<td>sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>119 (51.5%)</td>
<td>9.5</td>
</tr>
<tr>
<td>female</td>
<td>112 (48.5%)</td>
<td>13.8</td>
</tr>
<tr>
<td>onset of brain metastases*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>synchronous</td>
<td>86 (37.2%)</td>
<td>9.2</td>
</tr>
<tr>
<td>metachronous</td>
<td>145 (62.8%)</td>
<td>13.0</td>
</tr>
<tr>
<td>single metastasis</td>
<td>200 (86.6%)</td>
<td>11.1</td>
</tr>
<tr>
<td>multiple metastases</td>
<td>31 (13.4%)</td>
<td>8.5</td>
</tr>
<tr>
<td>multiple cerebellar</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>site of tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lt hemisphere</td>
<td>94 (40%)</td>
<td></td>
</tr>
<tr>
<td>rt hemisphere</td>
<td>110 (47%)</td>
<td></td>
</tr>
<tr>
<td>cerebellum (single)</td>
<td>27 (13%)</td>
<td></td>
</tr>
<tr>
<td>location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>supratentorial</td>
<td>204 (87%)</td>
<td>10.8</td>
</tr>
<tr>
<td>regional distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>frontal</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>frontotemporal</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>frontoparietal</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>parietal</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>parietooccipital</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>parietotemporal</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>occipital</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>temporal</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>other area</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

* Synchronous = brain metastasis diagnosed within 60 days of diagnosis of primary lung tumor; metachronous = brain metastasis diagnosed more than 60 days after diagnosis of primary lung tumor.
Brain metastases from lung cancer

### Characteristics of seven patients who died within 30 days of surgery or while still hospitalized following surgery

<table>
<thead>
<tr>
<th>Age at Death</th>
<th>Year of Death</th>
<th>Days After Surgery</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 37, F</td>
<td>1979</td>
<td>39</td>
<td>disseminated metastatic disease, inoperable primary lung tumor</td>
</tr>
<tr>
<td>2, 37, F</td>
<td>1982</td>
<td>32</td>
<td>respiratory failure, mediastinal disease, recurrent aspirations</td>
</tr>
<tr>
<td>3, 64, F</td>
<td>1984</td>
<td>19</td>
<td>cardiac failure, multiple metastases</td>
</tr>
<tr>
<td>4, 60, F</td>
<td>1988</td>
<td>42</td>
<td>meningeal carcinomatosis</td>
</tr>
<tr>
<td>5, 61, M</td>
<td>1988</td>
<td>15</td>
<td>multiple metastases</td>
</tr>
<tr>
<td>6, 68, M</td>
<td>1989</td>
<td>31</td>
<td>sepsis, mediastinal disease</td>
</tr>
<tr>
<td>7, 51, M</td>
<td>1990</td>
<td>30</td>
<td>unknown, died at home after having left hospital against medical advice</td>
</tr>
</tbody>
</table>

### Results

#### Overall Survival

A total of 295 craniotomies were performed in a cohort of 231 patients; 47 of the patients had two craniotomies and six underwent craniotomy three times or more (maximum five times). Patient characteristics are shown in Table 1. The overall median survival time for the entire cohort was 11 months from the time of first craniotomy (mean 21 months) (Fig. 1 upper). Median survival time calculated from the date of diagnosis of the first brain metastasis was 13 months. Median survival time calculated from the date of diagnosis of the primary lung tumor in the 185 patients who had lung surgery was 27 months. For the remaining 46 patients whose lung tumors were not resectable and thus did not undergo lung surgery, median survival time following diagnosis of the primary lung tumor was only 11 months.

Perioperative mortality (within 30 days of surgery) was 1.3% (three patients). However, Table 2 lists the characteristics of four additional patients (for a total of seven or 3%), who died after the 30-day period but while still hospitalized following craniotomy. This more accurately reflects postsurgical mortality. The 1-year survival rate was 46.3%; 2-year survival, 24.2%; and 3-year survival, 14.7%. The predicted 5-year survival rate is 12.5%; and the 10-year survival, 4.9%. Postoperative complications are listed in Table 3.

By the end of the study period, 198 (85.7%) of the 231 patients had died. In only 15 (7.5%) of these cases was there an autopsy. Causes of death are listed in Table 4; in 23 patients (11.6%) the cause was unknown. Approximately 55% of the patients died of neurological causes; 30% died of systemic disease. The median stay in hospital was 19 days (mean 23 days; range 5–86 days), during which many patients underwent a second surgery—thoracotomy—and/or received radiation therapy to the brain.

#### Presenting Signs and Symptoms

The average time from onset of neurological symptoms to diagnosis of a central nervous system lesion was 5.3 weeks (median 3 weeks; range 0–50 weeks). The most frequent presenting signs and symptoms were headache (91 patients), focal neurological deficit (48 patients), seizures (34 patients), speech disturbances (23 patients), visual dysfunction (48 patients), memory impairment (eight patients), ataxia (seven patients), personality changes (five patients), and vertigo (four patients). Two patients were asymptomatic, and their lesions were discovered by routine preoperative CT scan of the brain before lung surgery.

### Age of Patients

The median age at the time of craniotomy was 56 years (range 34–79 years). Age did not have a significant impact on survival when calculated by the log-rank test. Patients aged 60 years or less lived a median of 6 weeks longer than patients aged more than 60 years (11.1 vs. 9.5 months) (p = 0.37, log-rank test). However, multivariate Cox analysis (with assigned numerical values) did show a statistical difference in survival (p = 0.03) between these two age groups. Moreover, in the present study there was no statistical difference (as determined by both log-rank and multivariate analysis) in survival between patients aged more than 65 years (36 patients) and those 65 years or younger (195 patients) (12 vs. 10.5 months; p = 0.93 log-rank test; p = 0.28 multivariate analysis).

#### Gender of Patients

As Fig. 1 lower shows, the median survival time of male patients (119 patients) was significantly shorter (p < 0.01) than that of female patients (112 patients) (9.5 vs. 13.8 months). The median age of women at the time of craniotomy was 59 years (range 37–76 years) and of men 57 years (range 34–79 years). Five women were older

### Postoperative complications involving the central nervous system after resection of brain metastases in 231 patients

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>subdural hematoma</td>
<td>6</td>
</tr>
<tr>
<td>subdural hygroma</td>
<td>6</td>
</tr>
<tr>
<td>acute hydrocephalus</td>
<td>6</td>
</tr>
<tr>
<td>infection</td>
<td>2</td>
</tr>
<tr>
<td>mild neurological deficit</td>
<td>9</td>
</tr>
<tr>
<td>cerebrospinal fluid leak</td>
<td>1</td>
</tr>
<tr>
<td>tension pneumocephalus</td>
<td>1</td>
</tr>
<tr>
<td>endocrine abnormalities</td>
<td>2</td>
</tr>
<tr>
<td>acute psychosis</td>
<td>6</td>
</tr>
<tr>
<td>total</td>
<td>39 (17%)</td>
</tr>
</tbody>
</table>

### Cause of death in 198 patients who underwent resection of brain metastases from nonsmall-cell lung cancer

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No. of Cases</th>
<th>Percent</th>
<th>Median Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>postoperative death</td>
<td>7</td>
<td>3.5</td>
<td>1.0</td>
</tr>
<tr>
<td>neurological</td>
<td>77</td>
<td>39.0</td>
<td>9.0</td>
</tr>
<tr>
<td>neurological &amp; systemic</td>
<td>31</td>
<td>15.7</td>
<td>8.0</td>
</tr>
<tr>
<td>systemic</td>
<td>60</td>
<td>30.3</td>
<td>9.5</td>
</tr>
<tr>
<td>unknown</td>
<td>23</td>
<td>11.6</td>
<td>9.5</td>
</tr>
</tbody>
</table>

J. Neurosurg. / Volume 83 / October, 1995
than 70 years and 20% of our female patients are still alive, whereas 11 men were older than 70 years and only 9.2% of our male patients are still alive. When the median survival of our patients was calculated from the time when the primary lung disease was diagnosed, women again survived longer than men: 26 versus 22 months in men. This difference is statistically significant (p = 0.03).

Performance Status

Of the patients described here, 143 who had normal performance status or minimal neurological deficit (Karnofsky performance scale<sup>23</sup> (KPS) score 80–100) prior to craniotomy survived a median time of 12.5 months, whereas 75 patients with moderate neurological deficit (KPS score 60–70) survived a median time of 8 months and 13 patients with severe neurological deficit (KPS score 20–50) survived a median time of 5 months. These differences were statistically significant (p < 0.015, log-rank test). The same calculations including only 196 patients with a single metastasis (four patients who died within the perioperative period were excluded) resulted in a median survival of 10.8 months. The number of patients with a KPS score less than 50 was small because, generally speaking, patients with a low KPS score are not considered good candidates for craniotomy. Presurgical treatment with steroids for 4 to 7 days improved patients’ performance score, and it was the latter performance score that was used in the analysis.

Onset of Cerebral Metastases

In 86 patients (37.2%), brain lesions were diagnosed synchronously (median 25 days after diagnosis of lung cancer; median survival 9.2 months); in 145 patients (62.8%) they were diagnosed metachronously (median survival 187 days; median survival 13 months). The difference in survival is statistically significant (p = 0.03) (Fig. 2, upper left).

The length of the time interval between diagnosis of the primary tumor and diagnosis of one or more brain metastases had no impact on survival in the patients with metachronous lesions. When we defined an interval time as “short,” that is, more than 95 but less than 270 days, we found that only 41 patients had a median survival of 10.8 months. With an interval defined as “long,” that is, more than 270 days, we found 99 patients whose median survival was 14.6 months, but this difference was not statistically significant (p = 0.83). If the interval was “short,” more than 100 but less than 364 days, 62 patients had a median survival of 12.8 months, versus “long,” that is, more than 365 days, in which the patients’ median survival was 14 months. The difference was not statistically significant and the percentage of patients alive when the study ended was nearly the same: 19% and 15%, respec-

**Fig. 2.** Graphs showing actuarial survival from the time of craniotomy for brain metastasis from non-small-cell lung cancer. Dotted curves with appropriate small symbols show lower and upper endpoint of the a-level 95% survival confidence interval for each survival curve. **Upper Left:** Actuarial survival in patients with metachronous versus synchronous diagnoses of lung cancer and brain metastases. Difference in survival is significant in log-rank test but not in Cox multivariate analysis. **Upper Right:** Actuarial survival in patients who underwent resection for supratentorial versus infratentorial brain metastases. There is a significant difference in survival time, both in the log-rank test and Cox multivariate analysis favoring the group with supratentorial lesions. **Lower:** Actuarial survival in patients with single versus multiple brain metastases. Difference in survival is only significant in the log-rank test.
Brain metastases from lung cancer

...patients with multiple metastases succumbed during the 2nd year to recurrent intracranial disease. Although 38% survived the 1st year following resection, only one patient survived more than 5 years, dying at Month 64. As of this writing, only one patient is still alive 31 months after surgery, which reflects the failure of patients with multiple metastases to achieve long-term survival.

Eighteen patients (58%) with multiple tumors received postoperative whole-brain radiation therapy (WBRT) whereas 11 patients (35%) had been unsuccessfully treated with WBRT before surgery and were unable to receive additional doses of radiation to the brain postsurgically. Two patients chose not to receive WBRT after craniotomy.

Extent of Brain Tumor Resection

Gross total resection of the brain metastasis as determined by both the surgeon's report and postoperative CT scan was achieved in 94.4% of our patients. There was no discrepancy between operative protocol and post-surgery CT. Among the 218 patients who underwent total resection, median survival was 11.3 months and 33 of these individuals are still alive as of this writing. Among the 13 patients (5.6%) who underwent partial resection, as reported by the surgeon and confirmed by CT scan immediately after surgery, median survival was only 7.5 months and none of these individuals survived 2 years (p < 0.01, log-rank test).

Characteristics of Tumors

Operative and pathology reports provided the following information on the physical characteristics of the tumors: cystic, 33 patients (14.3%), median survival 14.5 months; friable, 21 patients (9.1%), median survival 9.5 months; firm, 30 patients (13%), median survival 14.3 months; necrotic, 40 patients (17%), median survival 7.8 months; and soft, 31 patients (13.4%), median survival 10 months. For 76 patients (33%), this information was not available; the median survival time for this subgroup was 9.4 months. There was no statistical difference (p < 0.46, log-rank test) in survival time associated with these characteristics.

Whether the tumor was removed in one piece or piece-meal (as reported by the surgeon) did influence median survival time—12 and 8.5 months, respectively—but this difference did not approach statistical significance (p = 0.24, log-rank test).

Diameter of Cerebral Metastatic Lesion

The diameter of the resected metastatic lesion (≥ 3 cm vs. ≤ 2 cm) had no significant effect on survival according to multivariate analysis (p = 0.083), although the effect approached statistical significance with the log-rank test) (p = 0.07). When we restricted our analysis to the 200 patients with a single metastatic tumor and divided the tumors into three groups according to size—Group I, 1 and 2 cm; Group II, 3 and 4 cm; and Group III, 5, 6, and 7 cm—the difference in survival times was still not statistically significant: 12.3, 10, and 4.5 months, respectively (p = 0.2, log-rank test). Again, when we considered only those patients who had undergone complete resection of

Histological Findings

Findings of adenocarcinoma accounted for 159 (68.8%) of our patients (median survival time 11.3 months), squamous cell cancer for 44 (19%) (median survival time 11.7 months), and large-cell carcinoma for 28 (12.1%) patients (median survival 9.6 months). The particular subtype of our patients’ lung cancer had no statistically significant impact on their survival (p = 0.34), although there was a trend toward longer survival in patients with adenocarcinoma. None of the 28 patients with large-cell carcinoma survived more than 4 years following craniotomy. In contrast, there were 19 5-year survivors in the adenocarcinoma group and two long-term survivors with squamous cell cancer.

Location of Lesion

Table 1 shows the location of the metastatic brain lesions in our patients. The lesions were supratentorial in 204 patients, whose median survival time was 10.8 months. A single infratentorial tumor was diagnosed in 27 patients. For this group median survival time was 10.4 months, but it did not extend beyond 36 months following brain metastatectomy in any of these individuals (Fig. 2 upper right). Five of the patients with supratentorial lesions also had cerebellar lesions, for a total of 32 patients (14%) with cerebellar metastases. When the survival curve of these 32 patients was compared to that of the 199 patients who had metastases only in the supratentorial compartments, a statistically significant difference emerged (p < 0.04, log-rank test). The latter group had a mean survival time of 24.5 months, twice as long as the mean survival of 12 months following resection of cerebellar metastases. Only one patient (3%) who underwent infratentorial surgery was alive at the end of the study, compared to 32 patients (16%) in the supratentorial group. Calculating survival times among those patients with only a single brain metastasis (200 patients), we found that 174 patients who had undergone resection of a supratentorial lesion survived a median of 11.1 months, compared to 27 patients with a cerebellar tumor, whose median survival time was 10.4 months. This difference approached but did not reach statistical significance (p = 0.09, log-rank test).

Multiple Lesions

Preoperative CT scans and/or MR images revealed that 31 (13.4%) of the 231 patients had multiple metastases. In the subgroup of patients with multiple lesions (90% of whom had all brain metastases resected), median survival time was 8.5 months compared to 11.1 months in 200 patients with a single lesion (p = 0.02, log-rank test) (Fig. 2 lower). However, in multivariate analysis, this difference was not statistically significant. The majority of
their primary tumor, the size of the lesion did not have a significant effect on survival.

Extent of Primary Lung Tumor Resection

At the time of craniotomy, four patients had active systemic metastases other than lung disease; another 74 patients developed recurrent systemic disease at various times after resection of their brain lesions. One hundred eighty-five patients (80%) underwent thoracotomy. The other 46 patients had unresectable or poorly controlled primary tumors and were treated by chemotherapy and/or radiation therapy. Recurrence of lung tumor occurred in 96 patients (41.6%) within a median of 299 days from the original diagnosis of their cancer.

A significant correlation emerged between the extent of resection of the lung tumor and survival time, whether calculated from the date when the diagnosis of lung cancer was made or from the date of craniotomy. Analyzing the total cohort of 231 patients, we found that 144 patients who underwent complete resection of their primary lung tumor survived a median of 14.4 months, whereas 87 patients whose lung tumor was not resected or was partially resected survived a median of 6.6 months (p = 0.0001) (see Fig. 3 upper). Thirty-one (21.5%) of the patients who had undergone complete resection were alive at the end of the study, compared to two patients (2.2%) whose tumor was not removed. This finding is consistent with our observation that the 185 patients who underwent lung surgery survived longer from the date of diagnosis of their lung tumor (median survival 27 months) than the 46 patients who had no surgery (median survival 11 months). The difference is statistically significant (p = 0.0001).

In 126 patients with a single brain metastasis diagnosed synchronously (38 patients) or metachronously (88 patients), in which both groups underwent complete resection of the primary lung malignancy, median survival time was 12.4 and 19.2 months, respectively. However, this difference was not statistically significant (p = 0.25). At the end of the study, 26% of patients from the metachronous group were still alive, compared to 18.4% of patients from the synchronous group. The overall median survival of these 126 patients was 17 months.

When the difference in survival between patients with a synchronous versus metachronous presentation was calculated for the entire set of 200 patients with a single brain metastasis, the result was statistically significant (9.5 vs. 13.1 months, p = 0.03).

Recurrence of Brain Metastases

Recurrent brain metastases were diagnosed in 113 patients (49%); in 55 of these individuals, the tumor recurred at the operative site. Another 13 patients had both a recurrence at the operative site and additional new lesions. Seven patients relapsed with multiple lesions. Thirty-eight patients (33.6%) had a new single metastasis distant from the original site. The median survival time of the 118 patients who did not have relapse (of total of 231 patients) was 10 months. In the recurrence group, median survival was 11.3 months (p < 0.25, log-rank test).

Relapse of Systemic Metastases

The presence of extracranial metastases in 78 patients (74 of whom were diagnosed after craniotomy) significantly decreased the median survival in this group. These patients lived a median of 8.5 months, whereas patients with no evidence of systemic disease survived 12.7 months (p < 0.005, log-rank test).

Radiation Therapy

One hundred ninety-four patients (84%) received WBRT either before or after craniotomy and their median survival time was 14 months. The mean dose was 3000 cGy (mean 2712 cGy). The thirty-seven patients (16%)
Brain metastases from lung cancer

who did not receive WBRT at any time survived 10 months (p < 0.5). Forty-nine of those patients (25.3%) who received WBRT failed it before surgery (including 11 patients who received WBRT both before and after surgery); median survival time for this subgroup was 7.5 months from the time of craniotomy. One hundred eighty-two patients (78.8% of the whole cohort of 231 patients) who had no WBRT before surgery survived 11.8 months, a difference with statistical significance (p = 0.03, log-rank test) (Fig. 3 lower). The majority of patients (153 patients, 66.2%) were treated with postoperative WBRT and survived 12 months. In 78 patients (33.8% of the whole cohort) who did not receive postoperative WBRT, the median survival time was 8.5 months, a difference that approaches but does not reach statistical significance (p = 0.07, log-rank test). This group included patients who failed radiation preoperatively.

Excluding patients in whom presurgical WBRT failed (49 patients), 41 patients who were not treated with postsurgical WBRT survived 9.4 months, whereas 141 patients who did receive WBRT survived 12.5 months. The difference between survival times was not statistically significant (p = 0.4). The same percentage of patients (approximately 15%) who did and did not receive radiation were alive at the end of the study.

Impact of Year of Resection

We analyzed survival focusing on the year of craniotomy by dividing the cohort into three groups according to the year of resection of brain metastases. The first group (1976–1981) contained 49 patients who had a median survival of 12.7 months. The second group (1982–1986) had 78 patients who survived a median of 10.2 months, and the third group (1987–1991) had 104 patients who survived a median of 11.2 months. This difference in survival was not statistically significant (p < 0.5). In the most recent group 20% of patients were still alive at the end of study compared to 6% and 7% of patients still alive in the first and second groups, respectively.

Multivariate Analysis

Cox multivariate analysis was used to test the association of survival in all 231 patients with 15 variables commonly considered to be prognostic factors (Table 5). All assigned dichotomous values were replaced by numerical data. Although nine of these variables were significantly correlated with survival when considered individually in univariate analysis (log-rank test), only five were found to be significant when the full model was used. These five were: extent of primary lung tumor resection (p = 0.0002), gender (p = 0.0088), location of lesion (p = 0.0497), systemic metastases (p = 0.0083), and age above or below 60 years (p = 0.0398). Two additional factors, presurgical WBRT and diameter of the brain tumor, approached but did not reach statistical significance (p = 0.05).

Discussion

Review of the Literature

The results from this study confirm that the prognosis for patients with even a single brain metastasis from NSCLC is grim. However, we have also confirmed that 5-year survival is possible in up to 12.5% of patients, which is in fact better than the 5-year survival rate in patients with glioblastoma multiforme.7 In the present study, the overall median survival time of 231 patients was 11 months, slightly less than the 12 months’ median survival calculated from the date of craniotomy of 185 patients with NSCLC treated in our institution between 1974 and 1989.8 For that group of 185 patients, median survival calculated from the date of diagnosis of brain metastases was 14 months.5 Previous studies of 50 patients who underwent surgery at MSKCC between 1978 and 198036 and of 41 patients66 found that their overall median survival time was 18 months and 14 months, respectively.

Other investigators have reported similar median survival times. Meneses and colleagues36 at the University Hospital of Rouen, France, treated 76 patients with brain metastases from lung cancer between 1975 and 1986, but only 46 (60%) underwent brain metastatectomy. The median survival time for these patients was 8 months. Macchiarini, et al.,31 reported a highly select group of 37 patients in whom they diagnosed and resected a primary lung tumor and a single brain metastasis between 1975 and 1988. The overall median survival for these patients was 19 months.33 Demange and coworkers12 accepted only 22 patients (41%) for resection of a single brain metastasis from among 54 patients treated for NSCLC between 1980 and 1985; their median survival time was 8.5 months. Trillet and coworkers70 reported a 10-month median survival time in 20 patients whose single brain

**TABLE 5**

<table>
<thead>
<tr>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
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<tbody>
<tr>
<td>Factor</td>
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* Values assigned were changed to numerical values. Abbreviations: ADCA = adenocarcinoma; EPID = squamous cell cancer; LARG = large cell carcinoma; NT = no thoracotomy; CR = complete resection; NR = thoracotomy but tumor not resectable; PR = partial resection; KPS = Karnofsky performance scale; WBRT = whole-brain radiation therapy.
† Not statistically significant.
metastases were resected surgically. Other recent reports on the outcome of resection of single brain metastases in patients with different primary tumors have included data on survival after resection of metastatic brain lesions in patients with NSCLC. Median survival time varied from 6.5 months\(^5\) (71 patients) to 16 months\(^4\) (41 patients).

As can be seen from this short review of recently published papers on resection of brain metastases, the number of highly select cases is small and this median survival tends to be higher than that which we report.

The overall 1-year survival rate of 46.3\% reported here was slightly lower than rates we have reported in the past (1-year 53\%, 2-year 25\%/\(^6\) and 1-year 55\%, 2-year 27\%/\(^5\)). In the latter study, we calculated the median survival of 185 patients from the date of diagnosis of their brain metastases because 32 of the patients had a failed pre-operative course of WBRT.\(^3\) In the same group of 185 patients, when survival was calculated from the date of craniotomy,\(^8\) 1- and 2-year survival rates were 44\% and 23.3\%, respectively. Rossi, et al.,\(^5\) described a group of 62 patients who underwent craniotomy for brain metastasis from NSCLC whose 1-year survival rate was 48\%. Matsutani, et al.,\(^3\) described 42 comparable patients treated between 1976 and 1986 whose 1-year survival rate was 57.2\% and whose median survival was 14.5 months. Analyzing the data from the Brain Tumor Registry in Japan, Sano\(^8\) found that among 338 patients with NSCLC who underwent complete resection of metastatic brain lesions by different neurosurgical teams in Japanese medical centers, the 1- and 2-year survival rates were 36.7\% and 13.8\%, respectively. Before the advent of CT scanning, 115 patients underwent similar brain surgery at the National Cancer Center in Tokyo; only 22.5\% were alive a year later.\(^6\) Another recent report from Japan on 89 patients treated between 1978 and 1990 quoted 1-year survival rates as 24\% and overall mean predictive survival time as 11.6 months.\(^4\) Dutch researchers recently reported that 17 patients who underwent resection followed by WBRT had a median survival of 8.5 months and a 12-month survival rate of 35\%.\(^7\)

**Age of Patients**

The fact that older age (> 65 years) was not linked with longer median survival in the patients described here contradicts some of our earlier findings but is consistent with other reports from our center.\(^3\) In a smaller group of our patients (185 patients),\(^8\) those younger than 60 years lived longer (13 vs. 9 months), a difference that was found to be statistically significant (p = 0.02, log-rank test). The same observation was made in the present study, but the significance appeared only on multivariate Cox regression analysis (p < 0.04). Similar results were reported for a group of 352 patients with primary lung cancer, in which patients under 60 years survived 11.6 months whereas patients aged 60 years or over had a median survival of 8.6 months (p < 0.001).\(^3\) Vecht and coauthors\(^7\) reported that in a group of 63 patients with a single metastatic brain lesion of whom 50\% underwent craniotomy, age greater than 60 years is a poor prognostic factor regardless of tumor type (52\% of these patients had carcinoma of the lung). This view is also supported by the opinion of Salcman,\(^5\) who estimated that only 10\% of patients older than 65 years survived longer than 12 months after surgery.

In our opinion, in patients with lung cancer and brain metastases, age greater than 60 years is not always an unfavorable factor, as has been claimed by a recent report.\(^4\) The authors of that report, who analyzed patients with brain metastases from different primary tumors, suggested that patients over 60 years of age should not be accepted for craniotomy.\(^5\) This is questionable with regard to patients with lung cancer; in this instance younger patients (< 50 years old) have worse survival rates because of biology and aggressiveness of tumor.\(^2\)

It is interesting that in the present study there was no statistical difference in survival between patients older than 65 years and those 65 years or younger. Certainly, the fact that our 36 patients over 65 years of age had a median survival time of 12 months is a persuasive argument for craniotomy as a therapeutic option for patients in this age group. The same observation was also recently reported by Nakagawa, et al.\(^4\)

**Gender of Patients**

The impact of gender on survival has not been an issue until recently because reported case material until the late 1980s was dominated by men.\(^5\) In our series, the number of men and women was similar (ratio 1:1) and women survived longer by 4.3 months. Similarly, in most published series of patients who have undergone surgical treatment of primary lung cancer, women have had a better prognosis than men.\(^3\) In studies on resection of brain metastases in patients with other primary tumors\(^5\), women again tended to live longer than men.

**Histopathological Findings**

With respect to histopathology, in this study patients with adenocarcinoma tended to survive somewhat longer than those with squamous or large-cell carcinoma, but the difference was not statistically significant. Others have reported similar findings.\(^3\) In general, the median interval between the diagnosis of lung cancer and the discovery of brain metastases is 6 months, but 10\% of our patients with adenocarcinoma did not receive a diagnosis of brain metastasis until more than 2 years after diagnosis of their primary tumor. For five patients, the interval was even longer—more than 5 years—a time period that was also reported by Komaki and colleagues.\(^2\) Adenocarcinoma metastasizes to the brain three times more often than other types of NSCLC.\(^7\) Nearly 69\% of our patients had this subtype of lung cancer, which is similar to the percentage reported by Tarver, et al.\(^8\)

**Cerebellar Location of Metastatic Lesion**

Many neurosurgeons believe that metastases that occur in the posterior fossa have a poor prognosis.\(^4\) In 1978, Sharr and Garfield\(^6\) reported that their 39 patients with cerebellar metastases from the lung had a median survival time of 3.1 months compared to 6.3 months for patients whose metastases occurred in the supratentorial compartment. Poor survival in patients with cerebellar metastases was also reported by Kuo, et al.,\(^9\) who reported a 1-year survival rate of 25\% in a group of 11 patients with differ-
Brain metastases from lung cancer

dent primary tumors; none of these patients survived a 3rd year. In a multivariate analysis of 229 patients with different primary tumors who underwent resection of a single brain metastasis, infratentorial location was associated with statistically shorter survival (p < 0.001) for 63 patients (28%) who had a cerebellar lesion. Vecht and colleagues noted that, of a total of eight patients with a single metastatic lesion in the cerebellum, three persons died within 30 days of surgery. We reported in 1985 that 19 patients with posterior fossa metastases from a variety of primary tumors, only three of which were lung cancer, survived for 7 months, whereas 106 patients with supratentorial metastases, of whom 47 had lung cancer, survived 13 months. The difference was statistically significant with the log-rank test (p < 0.05) but failed to reach significance with the Breslow test.

A review of the literature on cerebellar metastases yields little information, most of which is concerned with the clinical and neuroradiological aspects of the problem. Kitaoka, et al. analyzed the surgical aspects of cerebellar tumors in 12 patients, including seven with lung cancer, and found that carcinomatous meningitis frequently develops shortly after surgery; this occurred in 30% of patients whose lesions were metastatic from lung cancer. Nevertheless, these authors suggest, and we concur, that in the presence of a cerebellar metastasis from lung cancer, resection of the lesion is the best way to relieve severe neurological symptoms and prevent obstruction of cerebrospinal fluid pathways. We recommend this approach even though resectability of the primary lesion is not guaranteed and its diagnosis may be uncertain.

Multiple Metastases

As many as 54% of patients with brain metastases have multiple lesions. Sano reported that 30% of patients hospitalized with brain metastases in Japan had multiple lesions. The role of surgery in such cases remains controversial. Most neurosurgeons oppose it even when the lesions are surgically accessible. However, some neurosurgeons began to operate on such patients in the early 1970s, and in 1982 Takakura and colleagues presented a series of 31 patients whose multiple brain metastases were resected. The median survival in this group was 4.4 months, compared to 9 months in 94 patients with a single metastasis. Nomura and coworkers reported that they operated on 15 patients with multiple metastases; those individuals represented 40% of the whole series. At MSKCC, patients with multiple metastases have undergone surgical resection since 1973; since that time, neurosurgeons at other centers have accepted this approach. Recently Bindal and coworkers at the M. D. Anderson Cancer Center in Houston reported a 14-month median survival time in 26 patients who had their multiple metastases resected; this interval was comparable to the median survival of patients with a single brain lesion.

We reported previously that there was no statistically significant difference in median survival calculated from the date of diagnosis between patients with multiple metastases (20 patients) and with single metastases (165 patients). Other observations of the same patients (185 patients) found that both groups survived a median of 11 months, or 6 months longer than 18 patients with multiple metastases reported by Hazuka, et al., whose median survival was only 5 months. This short survival time may reflect the presence of cerebellar metastases in nine of their patients (50%).

Diameter of Brain Metastasis

Our findings corroborate those of Smallley, et al., who using multivariate analysis found that the diameter (small (< 2 cm) vs. large (> 4 cm)) of the resected metastatic brain lesion had no impact on survival.

Whole-Brain Radiation Therapy

The role of postsurgical WBRT remains controversial. Although many authors have achieved encouraging results using this approach, there is still no consensus as to “whether whole-brain irradiation is necessary in those patients in whom total surgical removal of the tumor is believed to have been achieved, and who show no evidence of tumor on postoperative scans.” Patchell and colleagues after conducting a randomized trial on a series of 48 patients, concluded that patients with a single metastasis who received treatment with surgical resection plus subsequent WBRT live longer, have fewer recurrences of cancer in the brain, and have a better quality of life than similar patients treated with radiotherapy alone.

In our experience, patients who received WBRT before surgery have a shorter median survival after craniotomy than patients who did not. Both groups had approximately the same male/female ratio and median age. This result contradicts an earlier report from our group, in which we noted no difference in survival time between patients who received postoperative radiation and those who had failed preoperative radiation.

Based on CT findings, it was reported in 1990 that WBRT is not effective when the tumor diameter is greater than 1.5 cm. Stereotactic radiosurgery is expected to become an important treatment approach in such cases; this technique is currently undergoing extensive clinical trials. The latest reports show a median survival of 10 months in 68 patients with resected single metastases and a median survival of 14 months in 18 patients who underwent craniotomy followed by radiosurgery. In a less encouraging study, the 40 patients survived a median of only 6.5 months and only 25% survived 1 year. It should be emphasized that, in the latter study, complete response was achieved in only 61% of brain lesions (not patients) with a volume of less than 2 cm³. Investigators conducting a recent multiinstitutional trial of stereotactic radiotherapy in 116 patients with solitary brain metastasis from different primary tumors reported an 11-month actuarial median survival time. Tumor diameter ranged from 3 to 66 mm, with a mean of 18.7 mm. Thirty-five percent of these patients had NSCLC, but their survival time as a subgroup was not reported.

Primary Lung Tumor

The extent of resection of the primary lung tumor is the second most important factor in predicting the survival of patients with resected brain metastases. It has been report-
ed that complete resection of the primary lung tumor including lymph nodes, not the stage of the locoregional primary lesion, is the main determinant in the survival time of such patients.\(^3\) We compared the survival time of 32 patients with synchronously diagnosed brain metastases who underwent complete resection of the primary lung tumor with that of 33 patients with synchronously diagnosed brain lesions who did not undergo lung surgery. Median survival time was 21 and 10 months, respectively (\(p = 0.0006\)).\(^3\)

We do not agree with other investigators who believe “that patients with systemic disease present at the time of diagnosis of cerebral metastatic disease should rarely, if ever, be managed by craniotomy.”\(^61\) Fourteen of our patients with unresectable disease at the time their brain metastases were diagnosed survived for 12 to 24 months after craniotomy, with minimal neurological dysfunction. Such a long survival period is rarely seen in patients treated only with WBRT.\(^13\)

**Performance Status**

Both our group\(^{18,32,65,66}\) and others\(^{88,87}\) have found that performance status and neurological status are two of the most important pretreatment variables to affect median survival, both in patients treated with WBRT alone\(^13\) and in patients undergoing craniotomy. Present findings confirm these earlier reports.

**Conclusions**

Most single cerebral metastases are amenable to total resection, which was performed on 94% of the patients in this series with low mortality and morbidity. Despite total extirpation of the metastasis, local failure occurs in 30% of patients. Univariate and multivariate analyses of prognostic variables show that the absence of systemic disease and the resectability of the primary lung cancer have the strongest association with a longer median survival. Other variables associated with a longer median survival included female gender, age less than 60 years, high KPS score, supra-tentorial location, and completeness of resection of the metastasis. Variables found not to affect the length of survival included age older than 65 years, histological subtype, WBRT, tumor size, and morphological characteristics. The median survival in our group was 11 months with a 1-year survival rate of 46.3%; 2-year 24.2%; and predicted 5-year survival rate of 12.5% of patients. Approximately one-third of patients succumbed to neurological causes, one-third to systemic disease, and one-third to a combination of cerebral and systemic disease. The results of this series confirm that the overall prognosis for patients with even a single resectable brain metastasis is poor, but that aggressive therapy can prolong life with quality of life preserved and can occasionally permit long-term survival.

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Brain metastases from lung cancer


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