Surgical treatment of brain metastases from melanoma: a retrospective study of 91 patients

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Object. Reports on the surgical treatment of brain metastases from melanoma in a large group of patients are sparse. The goal of this paper is to review the surgical experience in a series of 91 patients with brain metastases from primary melanoma treated at a single institution.

Methods. Seven hundred eighty patients underwent resection of brain metastases at Memorial Sloan-Kettering Cancer Center between 1974 and 1994. The records of 91 (11.7%) of these patients who had melanoma were retrospectively reviewed. The median time from diagnosis of the primary melanoma to diagnosis of the brain lesion was 14.1 months. The overall median length of survival following craniotomy was 6.7 months. Fifteen patients with resected multiple metastases had shorter median survival times than 76 patients with a single lesion (5.4 months compared with 7.8 months, p = 0.12). In eight patients with cerebellar metastases the median length of survival was significantly shorter than that found in patients with supratentorial lesions (2 compared with 7 months, p = 0.03). There was no difference in length of survival between 49 patients who underwent postoperative whole-brain radiation therapy (WBRT) and 29 patients who did not (9.5 compared with 8.3 months, p = 0.67). The incidence of brain metastasis recurrences in WBRT-treated and untreated patients was similar (56% and 45.7%, respectively). Only the presence of infratentorial metastases (p = 0.0013) and untreated recurrence of brain metastases (p = 0.0003) had an impact on outcome according to a Cox regression analysis. Five patients (5.5%) died within 31 days of surgery. Overall survival rates at 1, 2, 3, and 5 years were 36.3, 18.7, 13.2, and 6.6%, respectively.

Conclusions. Although melanoma metastatic to the brain carries a foreboding prognosis, patients who do not display preoperative neurological deficits, harbor a single lesion situated supratentorially, and have no lung or visceral metastases may derive significant palliative benefit from surgical resection of brain metastases.

Key Words • melanoma • brain metastasis • surgery

Cutaneous melanoma is one of the most common tumors to metastasize to the brain, ranking fourth after carcinomas of the lung, breast, and unknown primary tumors. Autopsy data demonstrate that 49 to 73% of patients who die of disseminated metastatic melanoma have brain involvement. In contrast, clinical data from large databases demonstrate that brain metastases are only diagnosed in approximately 10% of patients with primary melanoma during their lifetimes. Among 4200 patients with primary melanoma treated between 1981 and 1987 at MDACC, brain metastases were diagnosed in 425 cases (10%). Only a small minority of these patients (64 patients [15%]) were deemed suitable candidates for surgical resection. Sampson and associates reported on a series of 702 patients (10%) in whom metastases to the CNS were diagnosed among 6953 patients enrolled in the Melanoma Data Base at Duke University Medical Center. Among 9506 patients registered in the Sydney Melanoma Unit, brain metastases occurred in 567 cases (6%).

The aim of this paper is to review a surgical experience in a series of 91 patients with metastases to the brain from primary melanoma. The patients were treated in a single institution over a period of 20 years (1974–1994) during the era of CT scanning and MR imaging.

Clinical Material and Methods

From January 1974 to December 1994, 780 patients underwent resection of metastatic brain tumors at MSKCC. 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 surgical oncologists.

A review of clinical and pathological diagnoses showed that 91 patients had parenchymal brain metastases from primary melanoma tumors. Detailed follow-up review was conducted by letter and telephone contact with patients, family members, friends, or personal physicians. In the 84 patients (92%) who died during the follow-up period, the median length of survival was 7 months. The seven

Abbreviations used in this paper: CI = confidence interval; CNS = central nervous system; CT = computerized tomography; KPS = Karnofsky Performance Scale; MDACC = the M. D. Anderson Cancer Center; MR = magnetic resonance; MSKCC = Memorial Sloan-Kettering Cancer Center; WBRT = whole-brain radiation therapy.
TABLE 1

Characteristics of 91 patients with brain metastases from melanoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>Survival Time (mos)</th>
<th>p Value (log-rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median patient age 47.3 yrs</td>
<td>47</td>
<td>8.6</td>
<td>4.7–11.6</td>
</tr>
<tr>
<td>&gt; median</td>
<td>8</td>
<td>2.6</td>
<td>1.4–5.2</td>
</tr>
<tr>
<td>&lt; median</td>
<td>30</td>
<td>7.6</td>
<td>4.7–18.4</td>
</tr>
<tr>
<td>sex</td>
<td>61</td>
<td>5.8</td>
<td>4.2–9.5</td>
</tr>
<tr>
<td>female</td>
<td>30</td>
<td>7.6</td>
<td>4.7–18.4</td>
</tr>
<tr>
<td>lung metastasis</td>
<td>33</td>
<td>8.8</td>
<td>5.2–19.2</td>
</tr>
<tr>
<td>absent</td>
<td>8</td>
<td>5.4</td>
<td>2.0–9.6</td>
</tr>
<tr>
<td>present</td>
<td>30</td>
<td>7.6</td>
<td>4.7–18.4</td>
</tr>
<tr>
<td>no. of metastases</td>
<td>76</td>
<td>7.8</td>
<td>5.0–12.0</td>
</tr>
<tr>
<td>single</td>
<td>15</td>
<td>5.4</td>
<td>4.2–9.6</td>
</tr>
<tr>
<td>multiple</td>
<td>33</td>
<td>8.8</td>
<td>5.2–19.2</td>
</tr>
<tr>
<td>location of metastasis</td>
<td>83</td>
<td>7.0</td>
<td>5.2–10.8</td>
</tr>
<tr>
<td>supratentorial</td>
<td>8</td>
<td>2.0</td>
<td>1.1–16.5</td>
</tr>
<tr>
<td>infratentorial</td>
<td>8</td>
<td>2.0</td>
<td>1.1–16.5</td>
</tr>
<tr>
<td>diameter of metastasis</td>
<td>41</td>
<td>8.3</td>
<td>5.7–12.9</td>
</tr>
<tr>
<td>≤ 3 cm</td>
<td>50</td>
<td>5.5</td>
<td>4.1–9.6</td>
</tr>
<tr>
<td>&gt; 3 cm</td>
<td>31</td>
<td>5.0</td>
<td>4.2–7.5</td>
</tr>
<tr>
<td>WBRT †+</td>
<td>49</td>
<td>9.5</td>
<td>5.6–13.2</td>
</tr>
<tr>
<td>yes</td>
<td>29</td>
<td>8.3</td>
<td>4.0–23.3</td>
</tr>
<tr>
<td>no</td>
<td>41</td>
<td>8.3</td>
<td>5.2–14.6</td>
</tr>
<tr>
<td>brain recurrence (local or distant)</td>
<td>11</td>
<td>20.1</td>
<td>9.6–35.6</td>
</tr>
<tr>
<td>absent</td>
<td>44</td>
<td>7.9</td>
<td>5.0–11.6</td>
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<tr>
<td>present</td>
<td>44</td>
<td>7.9</td>
<td>5.0–11.6</td>
</tr>
<tr>
<td>resection of recurrence</td>
<td>50</td>
<td>5.5</td>
<td>4.1–9.6</td>
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<tr>
<td>no resection of recurrence</td>
<td>31</td>
<td>5.0</td>
<td>4.2–7.5</td>
</tr>
<tr>
<td>carcinomatosis meningitisp§</td>
<td>71</td>
<td>9.0</td>
<td>5.8–13.2</td>
</tr>
<tr>
<td>absent</td>
<td>71</td>
<td>9.0</td>
<td>5.8–13.2</td>
</tr>
<tr>
<td>present</td>
<td>15</td>
<td>4.7</td>
<td>2.0–5.7</td>
</tr>
<tr>
<td>median survival time after diagnosis of primary tumor</td>
<td>30</td>
<td>6.8</td>
<td>4.2–9.5</td>
</tr>
<tr>
<td>brain metastasis diagnosis</td>
<td>91</td>
<td>65.3</td>
<td>53.7–76.5</td>
</tr>
<tr>
<td>resection of brain metastasis</td>
<td>84</td>
<td>8.2</td>
<td>5.7–11.6</td>
</tr>
</tbody>
</table>

* Statistically significant difference in length of survival (log-rank test).
† Patients who underwent WBRT that failed before surgery are not included.
‡ Seven patients who died postoperatively are not included.
§ Five patients in whom diagnosis was unknown are not included.

Results

The clinical characteristics of all patients are shown in Table 1. The primary sites of the cutaneous melanoma were on the trunk in 46 patients (50.5%), on the upper or lower limbs in 23 patients (25.3%), in the head and neck region in 12 patients (13.2%), and within the pelvis in one patient (1.1%). In nine patients the site of the primary lesion was unknown at the time of craniotomy; in four of these the site was identified later. The histological diagnosis of metastatic melanoma was made in all 91 patients who underwent craniotomy. Three patients harbored an amelanotic melanoma.

In five patients, the brain metastasis was the initial manifestation of cancer and the search for the primary location followed the craniotomy. In the remaining 86 patients, the median time from diagnosis of the primary tumor to diagnosis of the brain metastases was 14.4 months (mean 26.4 months, range 2.1–187 months; 95% CI 10.6–16.4 months). In five patients the brain metastasis was asymptomatic and was only detected during disease staging, which was required as part of an immunotherapy trial.

In only 30 patients were the brain metastases solitary (only one site of disease and no sign of systemic involvement). In 27 patients (29.7%) the brain was the first site of recurrent disease, in 33 patients it represented the second site, and in 20 it was the third site. The other most frequent sites for first recurrence in this group of patients were visualized using CT scanning. 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 5 days after craniotomy. Beginning in February 1986, MR imaging replaced CT scanning for diagnostic purposes as well as for postoperative evaluation; a total of 52 patients (57%) were evaluated using MR imaging. In many patients, a preoperative localization brain image was obtained to facilitate the surgical resection.  

Follow-up MR images were obtained every 3 months during the 1st year after surgery, every 6 months during the 2nd year, and once a year thereafter. Approximately 90% of surviving patients underwent CT or MR imaging at 3 months and approximately 70% at 6 months postoperatively.

Statistical Analysis

Survival time was measured in months from the date of the patient’s first craniotomy to the date of death or the date of the last follow-up evaluation for patients who were still alive. Survival curves and median survival time were calculated using the nonparametric Kaplan–Meier method.  

Comparisons of survival times and assessment of the strength of association between median survival times and each of the variables were performed using log-rank analysis.  

Multivariate regression analysis of survival times was calculated using a proportional hazards model. Variables’ effects on the length of survival were examined using a stepwise multivariate Cox analysis.  

Statistical significance was defined as a probability value less than 0.05.  

Statistical calculations were performed using a commercially available statistical software package (SAS Version 6.11; SAS Institute, Inc., Cary, NC).
lymph nodes (33 patients), lung (14 patients), skin (five patients), thighs (two patients), and other sites (10 patients).

Omitting the five asymptomatic patients, the following neurological symptoms were found in those remaining: severe headaches in 49, neurological deficit in 26, seizures in 23, confusion and memory problems in 12, and impaired vision in 10. On average, symptoms appeared approximately 3 weeks before diagnosis of brain metastases (median 2 weeks).

Computerized tomography and/or MR imaging revealed acute hemorrhage into the tumor in 36 patients (39.6%), 21 of whom underwent cerebral angiography. Twenty patients underwent evacuation of a large intracerebral hematoma that resulted from bleeding of the melanoma.

The overall median length of survival in 91 patients, calculated from diagnosis of their primary melanoma, was 65.3 months. Survival time calculated from diagnosis of brain metastases was 8.5 months and that calculated from craniotomy was 6.7 months (mean 22.2 months; 95% CI 5–9.6 months). The median delay between diagnosis of brain metastasis and the day of craniotomy was 14 days. Five patients (5.5%) died within 31 days after surgery due to fulminant progression of metastatic disease or meningeal carcinomatosis (Table 2). If these patients are excluded from further analysis, the overall median length of survival after craniotomy was 8.2 months. At the end of the study (June 1997) only seven patients (7.7%) remained alive at 34, 40, 43, 59, 83, 112, and 128 months after craniotomy, respectively.

Overall survival rates at 6 months and at 1, 2, 3, and 5 years postoperatively were 53, 36.3, 18.7, 13.2, and 6.6%, respectively.

As to the cause of death, 43 patients (47.2%) died of neurological causes, including 15 who died of meningeal carcinomatosis (Fig. 1) and one patient who died during a course of WBRT. Progression of extracranial systemic disease caused death in 35 patients (38.5%); in six patients the cause of death remained unknown. Table 2 contains the characteristics of 13 patients who died within 62 days of craniotomy.

The median hospital stay related to craniotomy was 14 days (range 5–51 days); however, during the last 3 years the stay was shortened to 7 days. In all but one case, the metastatic brain lesions were resected totally, as confirmed by postoperative CT or MR imaging studies. Complications after craniotomy are listed in Table 3. Central nervous system complications occurred in 17 patients (18.7%).

There was no difference in length of survival between the 30 female and 61 male patients (median 7.6 months compared with 5.8 months, respectively; p = 0.28). In 15 patients (16.5%) two or three metastases were resected. The median length of survival in this subgroup was not significantly different when compared with that of

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Death (yrs), Sex</th>
<th>KPS Score</th>
<th>Lesion Site (diameter [cm])</th>
<th>No. of Days After Craniotomy</th>
<th>Year of Death</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32, M</td>
<td>60</td>
<td>rt occipital (4)</td>
<td>14</td>
<td>1987</td>
<td>N (CA meningitis &amp; other metastases)</td>
</tr>
<tr>
<td>2</td>
<td>63, F</td>
<td>70</td>
<td>rt frontal (3)</td>
<td>14</td>
<td>1986</td>
<td>S (pulmonary embolism &amp; lung metastases)</td>
</tr>
<tr>
<td>3</td>
<td>54, M</td>
<td>70</td>
<td>cerebellar (2)</td>
<td>20</td>
<td>1991</td>
<td>S (GI hemorrhage from abdominal metastasis)</td>
</tr>
<tr>
<td>4</td>
<td>61, M</td>
<td>70</td>
<td>lt parietal (4)</td>
<td>31</td>
<td>1990</td>
<td>N (CA meningitis)</td>
</tr>
<tr>
<td>5</td>
<td>47, M</td>
<td>90</td>
<td>rt frontal (2)</td>
<td>31</td>
<td>1988</td>
<td>N (hemorrhage to brain [at home])</td>
</tr>
<tr>
<td>6</td>
<td>43, M</td>
<td>90</td>
<td>cerebellar (2)</td>
<td>33</td>
<td>1982</td>
<td>S (lung metastases)</td>
</tr>
<tr>
<td>7</td>
<td>46, F</td>
<td>60</td>
<td>lt frontal (5)</td>
<td>36</td>
<td>1991</td>
<td>N (hemorrhage to brain)</td>
</tr>
<tr>
<td>8</td>
<td>62, M</td>
<td>90</td>
<td>lt frontal (4)</td>
<td>40</td>
<td>1993</td>
<td>SN (new widespread metastases [brain, lung, liver])</td>
</tr>
<tr>
<td>9</td>
<td>57, M</td>
<td>70</td>
<td>cerebellar (2)</td>
<td>41</td>
<td>1987</td>
<td>S (pulmonary embolism &amp; new vertebral metastases)</td>
</tr>
<tr>
<td>10</td>
<td>28, M</td>
<td>50</td>
<td>lt temporal (5)</td>
<td>54</td>
<td>1979</td>
<td>N (CA meningitis)</td>
</tr>
<tr>
<td>11</td>
<td>54, M</td>
<td>50</td>
<td>rt frontotemporal (4)</td>
<td>57</td>
<td>1977</td>
<td>S (lung, liver, &amp; bone metastases)</td>
</tr>
<tr>
<td>12</td>
<td>37, M</td>
<td>40</td>
<td>cerebellar/frontotemporal (3)</td>
<td>61</td>
<td>1988</td>
<td>SN (lung metastases &amp; brain recurrence)</td>
</tr>
<tr>
<td>13</td>
<td>54, M</td>
<td>80</td>
<td>rt frontotemporal (4)</td>
<td>62</td>
<td>1979</td>
<td>SN (lung metastases &amp; CA meningitis)</td>
</tr>
</tbody>
</table>

* CA = carcinomatosis; GI = gastrointestinal; N = neurological cause of death; S = systemic cause of death; SN = mixed cause of death.

**FIG. 1.** Graph depicting actuarial survival times in 15 patients with resected brain metastases from melanoma in whom meningeal carcinomatosis (CA meningitis) was diagnosed during the course of their disease. Patients not diagnosed with CA meningitis survived longer, and the difference was statistically significant. N = number of patients.
76 patients with a single metastasis (5.4 months compared with 7.8 months; \( p = 0.12 \)); however, a trend toward shorter survival times in patients with multiple metastases was clearly visible.

As shown in Fig. 2, eight patients underwent resection of a cerebellar metastasis, and their median length of survival was significantly shorter than that of 83 patients with supratentorial lesions (2.1 months compared with 7 months; \( p = 0.03 \)).

The mean diameter of the resected lesion was 3.7 cm, and the impact of diameter on the length of survival is shown in Fig. 3. Greater lesion diameter was not clearly associated with shorter survival time (Table 4).

Lung metastases were diagnosed before craniotomy in 58 patients (63.7%), and the overall median length of survival in these patients was shorter than that of 33 patients without metastatic lung disease. The median survival duration after craniotomy was 9.5 months in patients receiving WBRT compared with 8.8 months in 29 patients who did not receive WBRT after surgery (\( p = 0.05 \)); this latter group included six patients in whom radiation therapy had failed before they underwent craniotomy. Incidences of brain recurrences in WBRT-treated and untreated patients were similar (56% compared with 45.7%).

Local or distant recurrences were diagnosed in 44 patients, and their median survival time was 7.9 months. The median interval from the initial craniotomy to diagnosis of recurrence in the brain was 3.7 months (range 1.3–50.7 months). In 11 of these patients the recurrent tumor was resected (Fig. 6), and this subgroup survived significantly longer than the 31 patients who did not undergo repeated resection (median survival time 20.1 months compared with 5 months, respectively; \( p = 0.0005 \)). In two other patients recurrences were treated by stereotactic radiosurgery, and survival times were 16 and 28.1 months, respectively.

Steroid and anticonvulsant medications were prescribed to patients immediately after diagnosis of metastatic brain lesions. The majority of the patients were weaned off steroids 2 to 3 weeks after craniotomy and WBRT.

Focusing on the year in which craniotomy was performed, we also analyzed survival times by dividing the cohort into three groups according to the year in which they underwent resection of their brain lesion. The first group (operations performed during 1974–1980) included 21 patients with a median survival time of 5.8 months (95% CI 3.4–12 months); in the second group (operations performed during 1981–1987) were 30 patients with a median survival time of 6 months (95% CI 3.8–19.2 months);
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and the third group (operations performed during 1988–1994) consisted of 40 patients with a median survival time of 8.7 months (95% CI 5.6–13 months). This difference in survival time was not statistically significant (p = 0.61).

Results of Cox Multivariate Analysis

In a stepwise Cox multivariate analysis, 13 variables were analyzed (patient sex, KPS score before and after craniotomy, presence of lung metastases, resection of lung metastases, patient age greater or less than 50 years, presence or absence of intratumoral hemorrhage, single or multiple metastases, supra- or infratentorial location, piecemeal or en bloc resection, diameter of resected brain lesion 3 cm or less compared with greater than 3 cm, use of radiotherapy after craniotomy, presence of recurrence in the brain, and resection of a recurrent lesion in the brain).

Only the lack of resection of recurrent brain tumor (p = 0.0003) and infratentorial location of brain metastases (p = 0.0013) had an adverse impact on survival. The diameter of resected metastases greater than 3 cm nearly approached, but did not reach, statistical significance (p = 0.0514).

Discussion

The diagnosis of brain metastasis in patients with melanoma is associated in general with a poor prognosis. A nihilistic approach and withholding of treatment results in steady neurological deterioration and death within 3 to 4 weeks in the majority of cases. Treatment with steroid medications increases the length of survival in most patients to 6 to 8 weeks. Surgical resection of brain metastases has been in use for many years. The first surgical series was published in 1940, including one patient who survived for 4 years. In the last 15 years many reports have been published on the outcome of surgery as a treatment of brain metastases from melanoma. Median survival times varied from 6 to 12 months, with a 1-year-long survival time in 16 to 35% of patients (and with smaller series generally reporting longer survival duration).

Despite advances in neurosurgery, the impact of surgery on long-term survival of patients with metastatic melanoma remains dismal. Among our patients, 60% died within 1 year of craniotomy and only eight survived 5 years. The poor outcome is most likely a function of the biological aggressiveness of most melanomas and their tendency to progress systemically. In this sense, metastatic melanomas to the brain are not different from metastatic melanomas to other organs. Balch and colleagues reported in 1983 that the median length of survival in 200 melanoma patients with different distant metastases, was 6 months and that the 5-year survival rate in this group was 5%. Twenty percent of these patients had brain metastases, and the 1-year survival rate in this subgroup was 10%. Fourteen years later, in a report from the University of Tübingen, Germany, on 442 melanoma patients with distant metastases the authors described nearly identical findings: the median length of survival was 7 months and the 5-year survival rate was 6.7%.

The finding that the presence or absence of lung metastases was a statistically significant factor in univariate analysis strongly suggests that clinical progression of extracranial disease is the important factor responsible for

<table>
<thead>
<tr>
<th>Diameter of Metastasis (cm)</th>
<th>No. of Patients</th>
<th>Median Survival Time (mos)</th>
<th>95% CI (mos)</th>
<th>Average Survival Time (mos)</th>
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</thead>
<tbody>
<tr>
<td>1 &amp; 2</td>
<td>17</td>
<td>8.8</td>
<td>2.1–25.28</td>
<td>28.8</td>
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<td>3</td>
<td>24</td>
<td>7.7</td>
<td>5.8–12.9</td>
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</tr>
<tr>
<td>total 1, 2, &amp; 3</td>
<td>41</td>
<td>8.3</td>
<td>5.7–12.9</td>
<td>21.2</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>4.3</td>
<td>3.4–7.5</td>
<td>14.3</td>
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<tr>
<td>5 &amp; 6*</td>
<td>19</td>
<td>9.6</td>
<td>4.7–14.6</td>
<td>15.1</td>
</tr>
<tr>
<td>total 4, 5, &amp; 6</td>
<td>50</td>
<td>5.5</td>
<td>4.1–9.6</td>
<td>15.3</td>
</tr>
</tbody>
</table>

* Three patients in group.
the patient’s length of survival. Some clinicians strongly believe that the disease-free interval, which is another measure of biological aggressiveness of tumors, has an impact on survival in patients with recurrent melanoma.\(^{14}\)

Metastatic melanoma in the brain is often associated with intratumoral hemorrhage, and the clinical presentation may mimic an evolving stroke or even a subdural hematoma.\(^{47}\) In the pre–MR imaging era nearly 25% of our patients underwent angiography following CT scanning because the clinical picture was similar to that of a stroke. The CT scans revealed a subdural or intracerebral hematoma.\(^{47}\) In the pre–MR imaging era nearly 25% of our patients underwent angiography following CT scanning because the clinical picture was similar to that of a stroke.

Although patients with multiple brain metastases are rarely candidates for craniotomy, 15 of our patients with more than one metastasis underwent complete surgical resection in one or two operations. None of these patients survived 2 years; the longest survival was 14 months. The difference in survival times between patients in whom a single brain metastasis was resected and those in whom multiple brain metastases were resected was not statistically significant, which is similar to data reported by Bin-}

A review of the literature\(^{17,19,34,41,44}\) demonstrated that surgeons are less rigid in their indications for surgery in patients with brain metastases from melanoma. These patients are more readily accepted for resection of multiple brain metastases and/or multiple resections of recurrent lesions than patients with brain metastases from other primary tumors. In one report\(^{69}\) one patient underwent resection seven times. Compared with patients with other forms of brain metastasis, patients with melanoma tend to be younger (\(<\ 50\) years), often have excellent KPS scores, and have a longer disease-free interval. These factors likely represent the reasons why patients with melanoma are more likely to undergo craniotomy than patients with other types of brain metastases (Table 5).

In a previous publication from MSKCC the survival of 35 patients who underwent resection of a single brain metastasis from melanoma was analyzed.\(^{27}\) This study reported that female patients had a significantly shorter survival time than male patients. In the current study of 91 patients, sex did not affect the length of survival. After excluding from calculation patients with multiple brain metastases, we observed that 25 women had median survival of 10.8 months (95% CI 4.7–20.1 months), which was nearly twice as long as 51 men with a median survival of 5.8 months (95% CI 4.1–11.6 months), although this was not significant (\(p = 0.19\)). Fell, et al.,\(^{18}\) previously reported that the median length of survival in both sexes is similar.

Five patients in our series presented with “cerebral melanoma” with no known primary site. Sampson, et al.,\(^{56}\) reviewed a series of 76 patients with “primary” cerebral melanoma, who were treated over a 20-year period. These researchers reported that the median length of survival was 4 months in the whole group and 7.3 months in those who underwent surgery; however, the number of patients who underwent surgery was not stated. The authors observed that, even after an exhaustive search, the primary site often remains elusive. In almost all patients with primary cerebral melanoma multiple systemic metastases develop throughout the course of their disease. The outcome of our five patients with metastatic melanoma to the

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### Table 5

Comparison of median survival times after resection of brain metastases from different primary tumors treated at the same institution*

<table>
<thead>
<tr>
<th>Origin of Brain Metastases</th>
<th>No. of Patients</th>
<th>Median Age (yrs)</th>
<th>Median Survival Time (mos)</th>
<th>Percentage Survival 1 Year</th>
<th>Percentage Survival 2 Years</th>
<th>No. of Patients Alive†</th>
<th>No. of Deaths W/in 31 Days (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>breast carcinoma</td>
<td>70</td>
<td>50</td>
<td>13.9</td>
<td>55.3</td>
<td>25.7</td>
<td>5</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td>renal adenocarcinoma</td>
<td>50</td>
<td>60</td>
<td>12.6‡</td>
<td>51.0</td>
<td>24.0</td>
<td>4</td>
<td>5 (10)</td>
</tr>
<tr>
<td>lung carcinoma (NSLC)</td>
<td>231</td>
<td>56</td>
<td>11.0</td>
<td>46.3</td>
<td>24.2</td>
<td>33</td>
<td>7 (3)</td>
</tr>
<tr>
<td>colorectal carcinoma</td>
<td>73</td>
<td>61</td>
<td>8.3</td>
<td>31.5</td>
<td>6.8</td>
<td>3</td>
<td>3 (4)</td>
</tr>
<tr>
<td>melanoma</td>
<td>91</td>
<td>47</td>
<td>8.2‡</td>
<td>36.3</td>
<td>18.7</td>
<td>7</td>
<td>5 (5.5)</td>
</tr>
<tr>
<td>sarcoma</td>
<td>25</td>
<td>25</td>
<td>7.0‡</td>
<td>40.0</td>
<td>16.0</td>
<td>4</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

* Survival times are calculated from the time of craniotomy. The table is adapted from Wroński and Arbit, 1999; it includes data from the present paper and from references 62–66. Abbreviation: NSLC = non–small cell lung cancer.
† Number of patients alive at end of study.
‡ Patients who died postoperatively are not included.
Brain metastases from melanoma

Brain metastases from melanoma are a common complication for patients with advanced disease. The incidence of brain metastases in patients with melanoma is estimated to be between 20% and 50%, with the highest risk occurring in patients with stage IV disease. 

**Survival times in different subgroups of patients according to metastasis recurrence and whether patients underwent WBRT**

<table>
<thead>
<tr>
<th>Group</th>
<th>WBRT</th>
<th>No. of Patients</th>
<th>F/M Ratio</th>
<th>Median Age in Years (range)</th>
<th>Length of Survival (mos)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median (95% CI)</td>
<td>Mean</td>
</tr>
<tr>
<td>Group A</td>
<td>no</td>
<td>18</td>
<td>6:12</td>
<td>(27–73)</td>
<td>9.6 (4.1–49.1)</td>
<td>24.5</td>
</tr>
<tr>
<td>Group B</td>
<td>yes</td>
<td>19</td>
<td>8:11</td>
<td>(26–86)</td>
<td>13 (5.2–18.4)</td>
<td>28.5</td>
</tr>
<tr>
<td>Group C</td>
<td>no</td>
<td>14</td>
<td>5:9</td>
<td>(28–65)</td>
<td>5.8 (4.0–14.5)</td>
<td>17.5</td>
</tr>
<tr>
<td>Group D</td>
<td>yes</td>
<td>27</td>
<td>9:19</td>
<td>(23–76)</td>
<td>9.6 (6.5–16.5)</td>
<td>13.1</td>
</tr>
</tbody>
</table>

*There are no differences in median length of survival between the four groups. Fifteen patients who died within the first 65 days after craniotomy have been deleted from the calculations.

† Group A compared with Group B.
‡ Group B compared with Group D.
§ Group C compared with Group A.
\ Group C compared with Group D.

**Brain metastases from melanoma**

Brain from an unknown primary site was similarly poor, with a median survival time of 4.7 months and only one patient surviving 17 months. These results suggest that these patients have a particularly aggressive tumor.

Most patients with brain metastases from melanoma receive palliative WBRT, and their reported median survival time is 3 to 4 months. The high CNS recurrence rate after surgical extirpation alone (50%) and the potential for micrometastases at the time of diagnosis have been the main rationale to use adjuvant WBRT following craniotomy. Analysis of a series of 35 patients with single brain metastasis, who underwent resection at MSKCC between 1972 and 1987, showed that postoperative radiation therapy had no impact on the median duration of survival, but it decreased the incidence of CNS relapses (37% compared with 69%, respectively). The present data, shown in Table 6, did not corroborate this observation. Because we had no specific information on why some patients received WBRT and some not, a selection bias may account for this finding.

Recently, researchers from the Duke University Medical Center found that there was no statistical difference in median length of survival among 52 patients who underwent only surgery and 87 patients who received WBRT after surgery (6.4 months compared with 8.8 months, respectively; p = 0.99). However, those “receiving postoperative radiation therapy were more likely to remain without neurological deficits or experience an improvement (81.7%) after completion of therapy than those who did not.”

Skibber and associates analyzed the outcome of treatment in 34 melanoma patients with solitary brain metas-

tases treated by resection, 12 without and 22 with WBRT, following surgery. The median survival time in the first subgroup was 6 months (range 1.2–52.8 months) and that in the second group was 18 months (range 3.6–129.6 months). The selection criteria for postoperative WBRT were not stated. The time interval between treatment and first relapse (4.8 months compared with 6 months) and the percentage of patients without relapse (17% compared with 18%) was similar in those who did not and those who received WBRT, respectively. The brain as the only site of relapse was observed in three patients (30%) in the first group of 10 patients and in four patients (22%) in the second group of 18 patients. The overall rates of recurrence at any site were similar in both groups (82% compared with 83.5%). Six patients continue to have no evidence of disease more than 5 years after craniotomy. Based on these results the authors suggest that adjunctive cranial ir-
radiation of tumor is beneficial after craniotomy of solitary brain metastasis.

Half of our patients (44 of 86) experienced an intracranial recurrence, with 40% of lesions recurring locally at the site of previous resection. Eleven (25%) of these patients met the criteria for a second resection, that is, good KPS score, controlled extracranial metastases, and a strong desire to fight the disease. Their median survival time reached 20.1 months after the initial craniotomy. For a comparison, a group of 32 patients with recurrent brain metastases from non–small cell lung cancer who underwent repeated resection at MSKCC had an overall survival length of 15 months.

In a similar series of 48 cases reported from MDACC, including 14 patients (29.2%) with recurrent melanoma, 11 (22.9%) with lung carcinoma, and 10 (20.8%) with breast carcinoma, the median survival time after repeated resection was 11.5 months. The median time interval between craniotomies was 6.7 months. This last information allows us to assess that, in 14 patients from the melanoma subgroup, the probable median survival duration varied from 15 to 18 months, a figure similar to our own.

**Stereotactic Radiosurgery**

A treatment alternative for patients with single or double brain metastases is stereotactic radiosurgery, and the indications for its use are being defined. It is estimated that one third of patients with metastatic melanoma to the brain are suitable candidates for radiosurgery. The preliminary results of treatment in 23 patients who underwent gamma knife radiosurgery (1600-cGy median dose) demonstrated a 97% local control rate and a median survival duration of 7 months. A report from the University of San Francisco by Seung and colleagues presented data in 40 patients with brain metastases from melanoma treated by gamma knife radiosurgery. The median length of survival in all patients was 8 months (35 weeks). Nine patients had undergone surgical resection followed by recur-
rence before undergoing radiosurgery, and another 12 had been treated with WBRT before radiosurgery, which suggests that 50% of their patients had recurrent lesions. The median follow-up duration was 6.2 months, with 12 patients (30%) still alive at the end of the study.

In an updated version of their aforementioned paper, Seung and colleagues\(^6\) added 15 more patients with brain metastases from melanoma. The new cohort of 55 patients also survived a median of 8 months. Twenty-nine patients (52.7%) had recurrent lesions that were treated initially by WBRT (16 patients) or surgical resection (13 patients). The median diameter of the radiosurgically treated lesion was 1.3 cm and the median total target volume per patient was 6.1 cm\(^3\). Fourteen patients with a total target volume greater than 12 cm\(^3\) survived a median of 3.5 months. At the end of the study, nine patients (16.4%) were alive. The authors found that total volume is the only statistically significant factor affecting length of survival according to multivariate analysis.

It should be stressed that some authors reported that only small (≤1 cm) melanoma metastases could disappear after single-fraction radiosurgery.\(^21\)

Mori and colleagues\(^39\) from the University of Pittsburgh reviewed 60 patients with melanoma whose 118 metastatic lesions were treated by gamma knife radiosurgery over a 9-year period. The authors used mean rather than median figures in reporting their results, which sometimes make it impossible to compare with other comparable series. Twelve of their patients experienced recurrent brain metastases after WBRT and 13 others underwent surgical resection before radiosurgery. In 58% of patients the tumor diameter was 2 cm or smaller and the treated target volume was less than 4 cm\(^3\). The median length of survival was 10 months from diagnosis of brain metastases and 7 months from radiosurgery. The 1-year actuarial survival rate was 21%, and the 2-year survival rate was 11%, with 10 (16.7%) of 60 patients still alive. The median length of survival in a subgroup with multiple brain metastases (24 patients) was 4 months. The multivariate analysis demonstrated that only the absence of active systemic disease and the presence of single metastasis had an impact on increased duration of survival.

Grob and associates\(^23\) from l’Hôpital de la Timone, Marseilles, France, evaluated the effectiveness of gamma knife radiosurgery in 35 patients with 70 cerebral melanoma lesions (maximum diameter 3.2 cm, mean 1.8 cm). Although neither pre- nor poststradiography WBRT was used, the median length of survival from the day of radiosurgery was 8 months.

In the most recent paper in which the result of gamma knife radiosurgery was given, Lavine and colleagues\(^43\) from the University of Southern California at Los Angeles treated 45 patients with intracranial metastatic melanoma (≤3.5 cm). Six patients were treated surgically before undergoing radiosurgery and only 40% had a single lesion. The median treatment volume for 93 treated lesions was 3 cm\(^3\). The median diameter of the treated lesion was not stated. Follow-up imaging was obtained in only 32 patients. The median length of survival postradiosurgery was 8 months. Forty-two percent of patients remained alive, with a median follow-up time of 12 months.

Another frequently cited study of 248 patients with brain metastases from various primary tumors (among them 40 patients with melanoma) who were treated with the gamma knife, reported a median length of survival of 9.2 months for the whole cohort, noting that the tumor’s histological characteristics did not influence the length of survival.\(^1\) The entire cohort contained 76% patients with recurrent brain metastases, 27% of whom were still alive at the end of the study, which probably artificially inflated the reported median length of survival. These results are nearly identical to the 9.4-month survival time reported from a large neurosurgical series of 583 patients with a single brain metastasis.\(^2\) However, only 9.4% of patients were alive when the study ended 24 months after the date of the last patient’s treatment.

Although radiosurgery seems to be a safe and efficient method to treat even surgically inaccessible metastatic lesions, patients with infratentorial tumors and lesions with a diameter\(^1\) larger than 3 cm or, according to some researchers,\(^21\) even larger than 1 to 2 cm, are less likely to attain control of their disease.

In a retrospective study\(^7\) from MDACC, 62 patients with brain metastases from different primary tumors who were treated with surgery had a median length of survival of 16 months, compared with 7.5 months in 31 similar patients treated with radiosurgery (p = 0.0001). The authors found that the tumor control rate was higher when using conventional surgery and suggested that radiosurgery should be indicated only in cases in which the lesions are surgically inaccessible. Several prospective randomized trials in which the two treatment modalities are being compared are underway to examine this issue further.

To summarize the results of radiosurgery for brain metastases, we would like to draw attention to the fact that, in the majority of published papers, the long, impressive median length of survival was partly generated by treatment of patients with recurrent brain metastases (who as a specific subgroup frequently survive longer). Also, the authors of those series rarely reported their current 1-year survival rates but had an unusually high (and normally not seen in surgical series) rate of surviving patients (27–50%). Such a high percentage of living patients (easily obtained by including approximately 10–15 recently treated patients and closing the study 3–4 months after the most recent date of treatment) is also a cause of an inflated median survival time. It also has to be remembered that a median diameter of radiosurgically treated lesions is approximately 2 cm.

In comparison, our surgical series included mostly de novo treated patients in whom the median diameter of treated lesions was approximately 3 to 4 cm and in whom the calculation of median survival time was made a minimum of 1 year after the treatment of the last patient. Hence, we agree with the statement of Sawaya\(^2\) that “surgically treated patients survive longer and have better local tumor control.”

**Conclusions**

Our data show that patients with brain metastases from melanoma who undergo resection have good palliation, but a relatively short overall survival time after craniotomy. In our series, postoperative radiation therapy was not correlated with a survival benefit or local (intracranial)
Brain metastases from melanoma

control, and half of the patients died of neurological recurrence. Prognostic factors favoring improved length of survival include a single supratentorial lesion, repeated resection of recurrent tumor, absence of preoperative neurological deficits, and no systemic metastases. Patients meeting these criteria may derive palliative benefit from surgical resection of their brain metastases.

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References

37. Moersch FP, Love JG, Kernohan JW: Melanoma of the central nervous system. Report of thirty-four cases, in nineteen of which the diagnosis was verified by operation or necropsy. JAMA 115:2148–2155, 1940
41. Moser RP, Johnson ML: Surgical management of brain me-
tastases: how aggressive should we be? *Oncology* 3:123–128, 1989


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The data used in this paper were accrued during the authors’ appointments at MSKCC, but the opinions expressed herein are their own and do not necessarily reflect current treatment policy at MSKCC.

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