Stereotactic radiosurgery for cerebral metastatic melanoma

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To determine local tumor control rates and survival of patients with melanoma metastases to the brain, the authors reviewed the results of 23 consecutive patients with a total of 32 tumors (19 patients had a solitary tumor and four had multiple tumors) who underwent adjuvant stereotactic radiosurgery. Tumor locations included the cerebral hemisphere (24 cases), brain stem (four cases), basal ganglia (two cases), and cerebellum (two cases). Fifteen patients had associated cranial symptomatology and eight had incidental metastases. All patients had tumors of 3 cm or less in diameter (mean tumor volume 2.5 cu cm), and all received fractionated whole-brain radiation therapy (30 Gy) in addition to radiosurgery (mean tumor margin dose 16 Gy). Nineteen patients were managed with both modalities at the time of diagnosis; four underwent radiosurgery 3 to 12 months after fractionated whole-brain radiotherapy. The mean patient follow-up period was 12 months (range 3 to 38 months).

After radiosurgery, eight patients improved, 13 remained stable, and two deteriorated. One patient subsequently required craniotomy because of intratumoral hemorrhage; this patient and three others are living 13 to 38 months after radiosurgery. Nineteen patients died, 18 from progression of their systemic disease and one from another hemorrhage into a new brain metastasis. The local tumor control rate was 97%. Only two patients subsequently developed new intracranial metastases. The median survival period after diagnosis was 9 months (range 3 to 38 months). The authors believe that stereotactic radiosurgery coupled with fractionated whole-brain irradiation is an effective management strategy for cerebral metastases from a melanoma. Multi-institutional trials are warranted to confirm that stereotactic radiosurgery results equal or surpass the outcome achieved with craniotomy and tumor resection.

Key Words: stereotactic radiosurgery • metastatic melanoma • brain neoplasm • metastasis

Malignant melanoma is the third most common cause of central nervous system (CNS) metastasis, preceded in incidence only by carcinoma of the breast and lung. Between 6% and 46% of patients with melanoma develop CNS metastases, often the precipitating terminal event. Approximately one-third of all patients with melanoma die because of CNS involvement, regardless of the treatment strategies employed. Thus, therapeutic objectives in the management of intracerebral metastases are limited to palliation of symptoms and prolongation of life. Chemotherapeutic agents, various protocols for fractionated radiation therapy, and immunotherapy have been used alone or sometimes after surgical resection. Despite these efforts, the prognosis for a patient with single or multiple melanoma metastasis to the brain remains poor (median survival 2 to 3 months).

Stereotactic radiosurgery is an attractive therapeutic strategy less invasive than other modalities that provides high-dose, single-session irradiation to a localized tumor volume. Recent reports indicate that radiosurgery is being used in an increasing number of patients with metastatic cancer, not only for smaller tumors but even as primary management for some tumors as large as 4 cm in average diameter. In order to assess the specific outcome of adjuvant radiosurgery for patients with cerebral metastatic melanoma, this report analyzes our initial 4-year experience.

Clinical Material and Methods

Patient Population
We performed a retrospective analysis of 23 patients with metastatic melanoma who underwent stereotactic radiosurgery between May, 1988, and May, 1992. All
patients underwent preoperative neuroimaging: contrast-enhanced computerized tomography (CT) in 22 patients and/or magnetic resonance (MR) imaging in 18 patients. Follow-up evaluation varied from 3 to 38 months (mean 12 months).

Patients ranged in age from 24 to 77 years (mean 46 years), and 19 of the 23 patients were men. The mean Karnofsky performance rating before radiosurgery was 85% (range 50% to 90%). The sites of brain metastases are presented in Table 1. Twenty-one patients suffered from active systemic melanoma. Histological tumor confirmation was not obtained routinely because all patients had contrast-enhancing mass lesions in conjunction with systemic melanoma or newly diagnosed skin melanoma. By protocol, stereotactic biopsies are performed when imaging features are atypical or the diagnosis of primary malignancy is remote (no case in this series).

The mean time between the primary skin excision and diagnosis of brain involvement was 42.5 months (range 1 to 216 months). All patients with newly diagnosed metastatic disease received fractionated whole-brain radiation therapy (30 Gy in 12 fractions). Nineteen patients underwent radiosurgery immediately following radiotherapy and four had radiosurgery 3 to 12 months later. Patients who received whole-brain radiotherapy more than 3 months before radiosurgery also received an additional dose of 10 Gy (in four fractions either to whole-brain fields or to local tumor radiation fields) immediately before or after radiosurgery. Of the 21 patients with systemic disease, 11 received chemotherapy (seven before and four after radiosurgery) and seven underwent immunotherapy (four before and three after radiosurgery). Intratumoral hemorrhage was identified in eight patients prior to radiosurgery. Seizures were the predominant symptom in six of these patients.

Clinical and neuroimaging follow-up evaluation was obtained for all patients from 3 to 40 months after radiosurgery. Computerized tomography or MR imaging was performed every 3 months for 1 year after radiosurgery, and then at 6-month intervals thereafter as indicated. Follow-up monitoring was designed to detect delayed local or distant tumor recurrence even when tumor shrinkage or growth arrest was detected initially after radiosurgery.

**Radiosurgical Technique**

In all 23 patients a stereotactic coordinate frame was applied under local anesthesia supplemented with mild sedation. High-resolution stereotactic CT with multiplane reformatted images or stereotactic gadolinium-enhanced MR imaging was performed during radiosurgery for target coordinate determination and dose-planning. A 201-source 60Co gamma unit was used for radiosurgery.†

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* Leksell Model G stereotactic coordinate frame manufactured by Elekta Instruments, Atlanta, Georgia.
† Gamma unit manufactured by Elekta Instruments, Atlanta, Georgia.

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The irradiation field was determined and shaped to the tumor margin in all 32 tumors, using one isocenter in 26 tumors and two isocenters in six. Nineteen patients had a solitary tumor and four had multiple metastases ranging from two to four tumors. The average tumor diameter was 15.7 mm (range 8 to 25 mm). The mean spherical volume was 2.5 cu cm (range 0.26 to 7.5 cu cm).

Perioperative corticosteroid agents were used in 15 patients with symptomatic peritumoral edema identified on CT scans or MR images. An intravenous

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**TABLE 1**

<table>
<thead>
<tr>
<th>Site of Tumor</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Percent</td>
</tr>
<tr>
<td>solitary tumor</td>
<td>15</td>
</tr>
<tr>
<td>lobar</td>
<td>1</td>
</tr>
<tr>
<td>basal ganglia</td>
<td>1</td>
</tr>
<tr>
<td>pons/midbrain</td>
<td>3</td>
</tr>
<tr>
<td>multiple tumors</td>
<td></td>
</tr>
<tr>
<td>lobar</td>
<td>1</td>
</tr>
<tr>
<td>lobar, brain stem</td>
<td>1</td>
</tr>
<tr>
<td>lobar, cerebellum</td>
<td>1</td>
</tr>
<tr>
<td>lobar, cerebellum, basal ganglia</td>
<td>1</td>
</tr>
</tbody>
</table>

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**FIG. 1**. Contrast-enhanced axial magnetic resonance images in a 39-year-old man with active systemic disease. A: Image showing a melanoma metastasis within the substance of the pons. B: The tumor was barely visible 3 months after radiosurgery (16 Gy to the 50% isodose margin) and whole-brain radiotherapy. At 10 months after radiosurgery, the pons lesion remained unchanged, but the patient developed multiple tumors in both cerebral hemispheres.
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TABLE 2
Imaging-defined response of 32 metastatic melanomas after radiosurgery

<table>
<thead>
<tr>
<th>Response</th>
<th>Tumors</th>
<th>No.</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>irradiated tumor volume</td>
<td>32</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>decreased</td>
<td>13</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>unchanged</td>
<td>19</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>increased</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>peritumoral edema</td>
<td>15</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>decreased</td>
<td>9</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>unchanged</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>intratumoral contrast enhancement</td>
<td>32</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>decreased</td>
<td>23</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>unchanged</td>
<td>9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>delayed tumor hemorrhage</td>
<td>1</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>delayed remote hemorrhage</td>
<td>1</td>
<td>3.1</td>
<td></td>
</tr>
</tbody>
</table>

Clinical outcome after stereotactic radiosurgery for metastatic melanoma in 23 patients

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>No. (%) of Cases Before Radiosurgery At Latest Contact*</th>
</tr>
</thead>
<tbody>
<tr>
<td>no neurological symptoms</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>neurological symptoms</td>
<td>15 (65.2)</td>
</tr>
<tr>
<td>seizures only</td>
<td>4</td>
</tr>
<tr>
<td>seizures &amp; deficit</td>
<td>3</td>
</tr>
<tr>
<td>neurological deficit alone</td>
<td>8</td>
</tr>
</tbody>
</table>

* Current follow-up evaluation or neurological status at time of death.
† After radiosurgery and institution of anticonvulsant therapy.

Clinical Response

No mortality or neurological deterioration was caused by radiosurgery. No patient died or developed a new or progressive neurological deficit from growth of a tumor managed with radiosurgery. Eight of 15 patients who had neurological deficits at the time of radiosurgery had subsequent marked improvement (Table 3). Transient complications of radiosurgery were limited to three patients who experienced perioperative nausea, emesis, and/or dizziness. All patients with seizures were controlled effectively with anticonvulsant medication.

Survival Time

Nineteen patients died 3 to 35 months after management. Four patients were still alive (three with solitary metastasis and one with multiple tumors) 13, 26, 38, and 13 months after radiosurgery. The median survival time was 9 months after diagnosis (95% confidence

40-mg dose of methylprednisolone was administered immediately after radiosurgery. Therapeutic anticonvulsant drug levels were achieved in all patients with subcortical lobar tumors. The mean radiosurgical tumor margin dose was 16 Gy; in most patients the 50% isodose line was used to match the tumor margin. Dose was selected based on a predicted dose-response relationship for brain necrosis of 3%.15

Results

Neuroimaging Response

The imaging-defined tumor response is detailed in Table 2 and illustrated in Fig. 1. Local control was achieved in 31 (97%) of the 32 tumors and 22 (96%) of the 23 patients. There were two cases of distant cerebral recurrence (Fig. 2).

![Fig. 2. Neuroimaging studies in a 53-year-old man managed with radiosurgery (16 Gy to the 50% isodose margin) in addition to whole-brain radiotherapy. a: Contrast-enhanced magnetic resonance image obtained at radiosurgery demonstrating a right medial parietal metastatic melanoma. b: Magnetic resonance image obtained 11 months after radiosurgery. The tumor volume is slightly reduced. c: Computerized tomography scan obtained 12 months after radiosurgery showing two new tumors in the left hemisphere (arrows).](image)
interval 6 to 19 months), and 7 months after radiosurgery (95% confidence interval 4 to 8 months). Figure 3 demonstrates a Kaplan-Meier survival curve for this series of 23 patients. The 1-year actuarial survival rates were 26% postradiosurgery and 39% postdiagnosis. The median survival time after diagnosis was 9 months for patients with solitary tumors and 7 months for patients with multiple metastases (p = 0.86, log-rank test). Eighteen patients died due to progression of their systemic disease, and one from intratumoral hemorrhage into an additional lesion not treated with radiosurgery. Mean survival time after diagnosis of the primary melanoma of the skin was 56 months (range 10 to 218 months).

Two patients had surgical resection of metastatic tumors after radiosurgery. One patient developed dysphasia and hemiparesis 1 month after radiosurgery due to an intratumoral frontal lobe hemorrhage and is neurologically normal 22 months after the hematoma was removed. A second patient with a brain-stem metastasis had a catastrophic intracranial hemorrhage 7 months after radiosurgery due to a new tumor deposit. Despite surgical evacuation, the patient died 11 days after craniotomy.

Discussion

Melanoma patients who develop brain metastases continue to challenge the skills of their physicians. Despite modern multidisciplinary therapies, patient survival data remain dismal. Minimization of treatment-related morbidity is an important goal in order to preserve quality of life after diagnosis. Palliative therapies designed to reduce neurological symptoms and prolong survival include corticosteroid agents, radiotherapy, surgery, and chemotherapy, either alone or in combination. Stereotactic radiosurgery promises to be an important addition to the therapeutic options available for melanoma patients. In one recent study as many as one-third of patients with metastatic melanoma developed intracranial tumors of a size suitable for radiosurgery. The median survival time of patients with untreated melanoma metastasis to the brain is approximately 1 month. Although corticosteroid agents can reduce regional brain edema, they extend survival for an average of only 1 month. The median survival time of patients treated with fractionated whole-brain radiotherapy alone varied between 2 and 4 months.

Previous studies have shown that CNS metastasis is the most common cause of death in melanoma patients; hemorrhage is a frequent cause of neurological deterioration. In the present study we found that 18 of 19 patients who died did so due to progression of their systemic disease; growth of a treated tumor was not observed. These results give strong evidence that stereotactic radiosurgery provides tumor control and that patient survival time may be related to the success or failure with which adjuvant therapies control the progression of extracranial systemic disease.

Surgery or Radiosurgery?

Surgical removal of solitary and occasionally multiple melanomas may be associated with enhanced survival periods. Patients who undergo surgical extirpation of the metastasis not only appear to survive longer, but are also in better neurological condition than patients who do not undergo surgery. However, the risks of craniotomy and surgical removal may be unacceptable if the metastasis is in a deep location or if the patient's clinical condition is poor (Karnofsky score ≤ 70%). Despite improved surgical techniques and instrumentation, the potential of operative morbidity and mortality continue to influence surgical decision-making.

Brega et al., reported 13 patients who underwent 19 craniotomies; complete tumor removal was believed to be accomplished in 18 operations. In that series the percentage of patients with multiple tumors was greater than in ours, and there was no restriction as to tumor size. Five (38%) of the 13 patients underwent a second operation. Perioperative morbidity included deep venous thrombosis, steroid psychosis, infection, and seizure (once each in four patients). The 30-day mortality rate was zero; five of seven patients who subsequently died did so as a result of recurrent brain metastases. A median survival period of 10 months was achieved. Wornom et al., reported 22% morbidity and 11% mortality rates after resection in their series of 17 patients. Fell et al., detailed an operative mortality rate of 5.4%. Major complications from surgery occurred in 17% of 31 patients in the series reported by Guazzo et al., Hafström et al., noted that seven of 25 patients who underwent surgery died within 1 month after craniotomy; three of these died from postoperative complications and four from tumor progression. In contrast to these experiences, we noted no morbidity or treatment-related mortality after radiosurgery. We obtained postradiosurgery neurological improvement in eight (53%) of 15 symptomatic patients and stabilization of neurological symptoms in an additional five patients (33%); the eight asymptomatic patients remained so. A confounding variable in studies that attempt to compare surgical and nonsurgical management of melanoma metastases is preselection of patients in better neurological condition for surgical removal. In the present series 91% of the patients...
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had active systemic disease at the time of radiosurgery, and four patients had brain-stem tumors that we deemed unresectable with acceptable morbidity.

We found a median survival time of 9 months, longer than in the majority of surgical reports. Such survival is related not only to radiosurgery, but also to the potential benefit provided by systemic chemotherapy (11 cases), immunotherapy (seven cases), and adjuvant radiotherapy. The individual contributions of these therapies are unknown. Sampson and colleagues, in a recent oral presentation, reviewed 6953 melanoma patients of whom 702 had CNS disease; median survival time in that group was 3 months.

Role of Fractionated Whole-Brain Radiotherapy With Radiosurgery

We use fractionated whole-brain irradiation to treat residual disease that is ill-defined even by contrast-enhanced MR imaging but may exist around the tumor or in other regions of the brain. Radiotherapy is effective in reducing subsequent tumor recurrence in this clinical context.

Thus, our current approach to the management of cerebral melanoma is multidisciplinary. In solitary tumors, stereotactic radiosurgery in conjunction with whole-brain radiation therapy proves beneficial in controlling the growth of tumors less than 3 cm in diameter. Metastases with an average diameter greater than 3 cm are not usually suitable for radiosurgery because of associated clinical factors, an increased risk of complications associated with larger volumes, and a reduction in efficacy due to reduction in dose; in these patients conventional resection followed by whole-brain radiation therapy is advocated when feasible. Occasionally, modified linear accelerator radiosurgery has been used to irradiate larger-volume tumors at lower doses. In multiple metastases, we have observed preliminarily in four patients that local tumor control can be achieved; the symptomatic response is similar to that of solitary metastases. A randomized prospective trial is underway that evaluates the use of radiosurgery for multiple metastases (two to four tumors), including melanoma. Patients are randomly assigned to groups receiving fractionated whole-brain radiotherapy plus radiosurgery to each tumor, or whole-brain radiotherapy alone. A separate randomized trial has begun that compares fractionated whole-brain radiotherapy (30 Gy) plus radiosurgery to radiosurgery alone. Patients with newly diagnosed solitary tumors in the setting of active systemic disease (a biopsy is performed only if the history of melanoma is remote or imaging features are atypical) are randomly assigned according to the latter trial. Patients with recurrent tumors are randomly assigned to receive a whole-brain boost plus radiosurgery, or radiosurgery alone.

References

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