Motor function after stereotactic radiosurgery for brain metastases in the region of the motor cortex

Clinical article

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Object. The authors sought to better define the clinical response of patients who underwent stereotactic radiosurgery (SRS) for brain metastases located in the region of the motor cortex.

Methods. A retrospective analysis was performed in 2026 patients with brain metastasis who underwent SRS with the Gamma Knife between 2002 and 2012, and multiple factors that affect motor function before and after SRS were evaluated. Ninety-four patients with tumors ≥ 1.5 cm in diameter located in or adjacent to the motor strip were identified, including 2 patients with bilateral motor strip metastases.

Results. Motor function improved after SRS in 30 (31%) of 96 cases, remained stable in 48 (50%), and worsened over time in 18 (19%) instances. Forty-seven patients had no motor weakness prior to radiosurgery; 10 (22%) developed new Grade 3/5–4/5 weakness. Thirty (68%) of 44 patients with ≥ 3/5 pre-SRS weakness improved, 6 (14%) remained stable, and 8 (18%) worsened. Three of 5 patients with < 3/5 pre-SRS motor function improved. Motor deficits prior to SRS did not correlate with a worse outcome; however, worse outcomes were associated with larger tumor volumes. The median tumor volume in patients whose function improved or remained stable was 5.3 cm³, but it was 9.2 cm³ in patients who worsened (p < 0.05). Tumor volumes > 9 cm³ were associated with a higher risk of worsening motor function. Adverse radiation effects occurred in 5 patients.

Conclusions. Most intact patients with brain metastases in or adjacent to motor cortex maintained neurological function after SRS, and most patients with symptomatic motor weakness remained stable or improved. Larger tumor volumes were associated with less satisfactory outcomes.

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Key Words • eloquent area • Gamma Knife • tumor • metastasis • oncology • stereotactic radiosurgery

The role of SRS in the management of metastatic brain tumors continues to expand. The efficacy of SRS for brain metastases is well documented, with tumor control varying from 70% to 90%. 2,10,12,15,17,19,21,24,29 Additionally, the need for hospitalization for craniotomy or frequent visits for fractionated external-beam radiation therapy are avoided, as are neurocognitive sequelae associated with whole-brain radiation therapy. 1,4,12 Patients with brain metastases tolerate the procedure well, with generally < 10% developing any signs of adverse radiation effects, such as progressive peritumoral edema.

Conformal and highly selective dose delivery during SRS is especially important when the tumor is located in or adjacent to critical brain anatomy such as the motor strip. 8,31 Because of concerns of SRS might worsen patients’ deficits for tumors in such locations, surgical removal of the tumor has been advocated to reduce local mass effect. 3,23

The goal of the current study was to define the clinical response of patients with motor strip brain metastases that were managed initially by SRS. We analyzed the response of patients with or without preexisting motor deficits and the risk of developing a new deficit after SRS.

Methods

We performed a retrospective analysis of 2026 patients with brain metastasis who underwent SRS with
after attachment of the stereotactic frame. A tumor directly in motor cortex or located directly adjacent to the precentral gyrus. Typical tumors are shown in Fig. 1. The motor strip was identified on imaging by using standard anatomical cues, including presence of an omega sign in the central sulcus, termination of the superior frontal sulcus into the prefrontal sulcus, and the paracentral lobule located directly anterior to the pars marginalis. No patient had undergone prior resection. All patients had pre- and postoperative neurological motor evaluations at selected intervals after the procedure.

Ninety-four patients with 96 motor strip tumors (2 had bilateral tumors) were included in this evaluation. Forty-five patients were male, and the mean age was 62.6 years. The motor strip tumor was solitary in 25 patients. The most common primary metastatic cancers were lung (48 patients), breast (17 patients), melanoma (12 patients), and colon (8 patients). Pretreatment SRS motor examination, tumor volumes, and marginal radiation doses were documented. The median dose to the tumor margin was 18 Gy (range 12–20 Gy). Total mean follow-up for patients following SRS was 7.3 months (range 0.5–124 months). Follow-up examinations at 2-week, 1-month, 3-month, and 6-month intervals were available in 13%, 44%, 60%, and 43% of patients, respectively.

Motor function was graded as normal (5/5), mild weakness (4/5), moderate weakness (3/5), or severe weakness (0, 1, or 2/5) in all patients according to the Medical Research Council scale (Table 1). Postprocedure motor function was analyzed at 3-month intervals after SRS. Adverse radiation effects were defined as new motor weakness in the absence of tumor hemorrhage or enlargement. Univariate and multivariate analyses were performed to determine which patient and tumor factors corresponded to worsening functional outcome. Factors evaluated included tumor volume, margin dose, patient age, multiple versus solitary metastases, histological origin, and whether the tumor was directly in motor cortex versus adjacent to it. The rates of functional change were evaluated by Kaplan-Meier analysis. We evaluated motor outcomes in patients both with and without deficits prior to SRS. We compared tumor volumes to the motor status of patients by using a Wilcoxon signed-rank test. Motor outcomes were compared in patients with tumor volume ≥ 9 cm³ versus those with a volume < 9 cm³. Also, motor outcomes in patients with pre-SRS peritumoral edema extending > 1.5 cm beyond the tumor margin on MRI were compared to outcomes in patients without such edema. These statistical comparisons were performed by chi-square analyses.

**Results**

Overall, motor function improved after SRS in 30 (31%), remained stable in 48 (50%), and worsened over time in 18 (19%) instances after radiosurgery. Forty-seven patients had normal motor function prior to radiosurgery, and 10 (22%) of these patients developed new mild or moderate weakness. No patient with normal motor function before SRS developed severe weakness (function < 2/5) after SRS. Forty-four patients had mild or moderate pre-SRS weakness; 27 (61%) improved, 9 (20%) remained stable, and 8 (18%) had further worsening of motor function. Two patients with mild pre-SRS weakness progressed to severe weakness. Three of 5 patients with severe pre-SRS weakness had improvement in motor function. Presentation with a motor deficit prior to SRS did not significantly correlate with a worsening motor function after SRS. Motor function deteriorated in 4 patients (24%) with breast cancer, in 7 patients (15%) with lung cancer, and in 4 patients (33%) who had metastatic melanoma.

Motor deterioration after the procedure was significantly associated with larger tumor volumes. The mean and median tumor volumes in patients whose motor function improved or remained stable were 6.9 and 5.3 cm³, respectively, but these volumes were 9.6 and 9.2 cm³ in patients who had deterioration in motor function (p < 0.05). Twenty-five patients presented with a total of 27 tumors ≥ 9 cm³ in volume, and 10 patients (37%) had wors-

**Fig. 1.** Typical metastatic tumors selected for SRS with the Gamma Knife are defined using a contrast-enhanced MRI with axial 2-mm slices after attachment of the stereotactic frame. A tumor directly in motor cortex is shown (left) as well as a tumor adjacent to motor cortex (right). Note that > 1.5 cm of peritumoral edema is present in the lesion in the right panel but not the one in the left panel.

**TABLE 1: Categorization of motor function in patients with brain metastases**

<table>
<thead>
<tr>
<th>Motor Examination Finding* Category</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/5, 4+/5</td>
<td>mild</td>
</tr>
<tr>
<td>3/5</td>
<td>moderate</td>
</tr>
<tr>
<td>0/5, 1/5, 2/5</td>
<td>severe</td>
</tr>
</tbody>
</table>

* Graded on the Medical Research Council scale.
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enanced motor function after SRS. In comparison, in 8 (12%) of 69 tumors < 9 cm³ treated in 68 patients, the patients developed increased weakness after radiosurgery. Tumor volumes ≥ 9 cm³ were significantly associated with a higher risk of worsened motor function (p < 0.05).

Pre-SRS peritumoral edema (defined in this report as T2 signal hyperintensity) extending > 1.5 cm beyond the mass was detected in 61 patients; 11 (18%) developed increased motor deficits after SRS. The rate of developing new or increasing motor dysfunction was not increased in patients with surrounding edema (7 [20%] of 35 such patients). Similarly, the presence of tumor directly within versus being just adjacent to motor cortex did not correlate with worsened outcome following SRS (p = 0.586). The median margin radiation dose (16 Gy) was significantly lower in patients who had delayed deterioration in motor function compared with the median margin dose delivered to patients who either remained stable or improved (18 Gy, p < 0.05). Table 2 compares motor strength after radiosurgery to preradiosurgery strength. This effect is further shown in Fig. 2.

The rates of improvement and worsening following SRS are demonstrated in Fig. 3. We performed univariate and multivariate analyses of factors potentially related to motor deterioration, including tumor volume, margin dose, patient age, number of metastatic tumors, and tumor type. Univariate analysis found that tumor volume ≥ 9 cm³ (p = 0.001), margin dose < 18 Gy (p = 0.004), and melanoma pathology (p = 0.018) were significant. Multivariate analysis found that only tumor volume ≥ 9 cm³ was significantly associated with a worse motor outcome (p = 0.013). Motor improvement after SRS was not significantly correlated with any of these factors.

Adverse radiation effects (defined as worsening neurological function associated with reactive changes on surveillance MRI in the absence of tumor growth) were seen in 5 patients. Their mean tumor volume was 8.9 cm³ (range 2–15.5 cm³). Surgical intervention was performed in 2 patients with melanoma metastases: one patient developed an intratumoral hemorrhage and the other developed a tumor-associated cyst.

Discussion

The Role of Radiosurgery

Radiosurgery has become a mainline management for metastatic tumors in the brain. The efficacy and safety profile of SRS for metastases is well described, and applications continue to grow.6,13,14,20,22,25,26,30 In the past 10 years, studies have shown the potential for SRS in the treatment of multiple metastases, larger metastases, and the tumor bed after resection. Radiosurgery is an important tool in optimizing regional control in various settings of brain metastases, and greatly increases the disease management options for such patients.

Because SRS does not physically remove a metastatic tumor, successful management requires that patients have symptomatic resolution of tumor-related edema as well as a low risk of treatment-related adverse radiation effects.7,8,16,27 In many patients radiosurgery represents the only reasonable option when tumors are located in critical brain regions such as the brainstem, diencephalon, and functional motor and speech areas.9,11,18 Because tumors found in motor cortex represent more accessible sites for surgical removal, we sought to define the outcomes of patients who underwent primary radiosurgery instead of resection.

The ability to retain or improve motor function has a major impact on subsequent quality of life in patients with brain metastases.11–5,23,26 Cai et al.4 found an increased risk of peritumoral edema after SRS for meningiomas with larger tumor volumes. Pan et al.23 recently reported that neurocognitive outcomes were improved when Gamma Knife SRS was used, in comparison with other radiation therapy options, even in patients with significant peritumoral edema.

Motor Function After Radiosurgery

The results of the current study indicate that SRS provides both tumor control and a relatively low risk of developing motor deficits in most patients with motor-

TABLE 2: Risk factors and association with outcomes in 96 cases of brain metastases

<table>
<thead>
<tr>
<th>Motor Outcome</th>
<th>Large Vol*</th>
<th>Edema†</th>
<th>Pre-SRS Deficit</th>
<th>≤18-Gy Margin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>improved</td>
<td>5 (17%)</td>
<td>21 (70%)</td>
<td>not applicable</td>
<td>21 (70%)</td>
<td>30</td>
</tr>
<tr>
<td>stable</td>
<td>12 (25%)</td>
<td>29 (60%)</td>
<td>11 (23%)</td>
<td>30 (62%)</td>
<td>48</td>
</tr>
<tr>
<td>worsened</td>
<td>10 (56%)</td>
<td>11 (61%)</td>
<td>8 (44%)</td>
<td>6 (33%)</td>
<td>18</td>
</tr>
</tbody>
</table>

* Tumor volume > 9 cm³.
† Edema extending > 1.5 cm from solid tumor margin on imaging.
region metastases. Worsening of motor function within 6 months of treatment occurred in < 20% of patients; most of whom had only mild deterioration in function. Only 2 (2%) of 91 patients without preexisting severe motor weakness developed new motor deficits after radiosurgery. Evaluation of the time course of worsened symptoms failed to reveal a clear relationship to the timing of the postprocedure evaluation. In this study SRS successfully eliminated the need for surgical removal of tumor in all but 4 patients.

Predictably, as tumor volumes (and therefore treatment volumes) increased in size, more patients sustained new or worsened motor deficits. We found that patients whose tumors exceeded 9 cm³ in volume had worsened motor outcomes. Neither the presence of a preexisting deficit, significant peritumoral edema, tumor directly in the motor cortex, primary pathology, nor higher marginal dose was associated with worse outcomes. In contrast, a higher risk of motor deterioration was associated with lower tumor marginal doses, which may be a reflection of dose reduction prescribed for larger-volume tumors. Melanoma pathology was also associated with heightened rate of motor deterioration. For patients eligible for craniotomy, it seems likely that surgical removal is the best option for tumors > 9 cm³ in volume.

**Limitations of This Study**

The primary limitation of the current study is its retrospective nature. As a result, serial motor examinations were not truly standardized or staggered at the same intervals. In addition, examinations were not always performed by the same physician at each available time.
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point. Although motor examination scores are relatively straightforward, there is always the possibility of differences in interpretation between examiners. Similarly, using MRI studies, it is relatively simple to identify lesions in proximity to the motor cortex. Dedicated functional imaging (for example, functional MRI or magnetoencephalography) in each patient might have provided a better predictive accuracy of the functional motor location. The selection of a peritumoral volume of 1.5 cm as a threshold for significant imaging-defined edema was arbitrary. Data detailing the exact timing of discontinuation of corticosteroids after SRS, and its effect on motor function, was not available in the majority of patients.

Conclusions

The use of SRS for motor region metastases was an effective and safe management option in the majority of patients, particularly for those with tumors < 9 cm³. Tumors that produced local mass effect, the presence of motor dysfunction prior to SRS, and imaging evidence of peritumoral edema did not preclude successful radiosurgical management. Additional investigations that focus on quality of life and other functional outcomes after SRS, in particular those implementing standardized neurocognitive methods to determine outcome, are warranted.

Disclosure

Drs. Lunsford and Kondziolka are consultants for Elekta AB; Dr. Lunsford is also a stockholder in the company.

Author contributions to the study and manuscript preparation include the following. Conception and design: Luther, Kondziolka, Flickinger, Lunsford. Acquisition of data: Luther, Kano, Mousavi. Analysis and interpretation of data: Luther, Kondziolka, Kano, Lunsford. Drafting the article: Luther. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Luther. Statistical analysis: Luther. Study supervision: Kondziolka, Lunsford.

References


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