Local control of brain metastases by stereotactic radiosurgery in relation to dose to the tumor margin

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Object. The maximal tolerated dose (MTD) for stereotactic radiosurgery (SRS) for brain tumors was established by the Radiation Therapy Oncology Group (RTOG) in protocol 90-05, which defined three dose groups based on the maximal tumor diameter. The goal in this retrospective study was to determine whether differences in doses to the margins of brain metastases affect the ability of SRS to achieve local control.

Methods. Between 1997 and 2003, 202 patients harboring 375 tumors that met study entry criteria underwent SRS for treatment of one or multiple brain metastases. The median overall follow-up duration was 10.7 months (range 3–83 months). A dose of 24 Gy to the tumor margin had a significantly lower risk of local failure than 15 or 18 Gy (p = 0.0005; hazard ratio 0.277, confidence interval [CI] 0.134–0.573), whereas the 15- and 18-Gy groups were not significantly different from each other (p = 0.82) in this regard. The 1-year local control rate was 85% (95% CI 78–92%) in tumors treated with 24 Gy, compared with 49% (CI 30–68%) in tumors treated with 18 Gy and 45% (CI 23–67%) in tumors treated with 15 Gy. Overall patient survival was independent of dose to the tumor margin.

Conclusions. Use of the RTOG 90-05 dosing scheme for brain metastases is associated with a variable local control rate. Tumors larger than 2 cm are less effectively controlled than smaller lesions, which can be safely treated with 24 Gy. Prospective evaluations of the relationship between dose to the tumor margin and local control should be performed to confirm these observations.

KEY WORDS • brain metastasis • radiosurgery • local control

STEREOTACTIC radiosurgery has become an important and widely used tool for the treatment of brain metastases. Multiple retrospective studies and one National Cancer Institute–sponsored cooperative group prospective study have demonstrated either survival benefit, local control benefit, or both when SRS was added to WBRT in appropriately selected patients. It has remained unclear, however, whether SRS is equivalent, superior, or inferior to resection, and there has been some debate about the utility of SRS for surgically treatable lesions. This debate may be influenced, in part, by the nonuniform dosing strategies that have been the practice for SRS.

We would expect that the efficacy of SRS would be linked to the prescribed dose, which is commonly set at an isodose line that completely covers the tumor to be treated. To date, however, there has been only one published report in which the efficacy of SRS has been examined as a function of the prescribed dose, and this study included only patients whose tumors were 2 cm or less in maximal diameter. The MTD for SRS in patients with brain tumors who have been previously treated with fractionated radiotherapy was established by the RTOG in protocol 90-05. In the RTOG study, it was assumed that the MTD would depend on the maximal tumor diameter, and three groups of tumors were defined: Group 1, maximal diameter 20 mm or less; Group 2, 21 to 30 mm; and Group 3, 31 to 40 mm. The MTD for each group was as follows: Group 1, 24 Gy (highest dose tested, MTD not reached); Group 2, 18 Gy; and Group 3, 15 Gy. It would naturally follow that any evaluation of SRS treatment efficacy should be performed with the use of the MTDs that have been established for each of these groups. Nevertheless, with rare exceptions, this has not been the case.

Since 1997, our group has routinely attempted to follow the RTOG dosing guidelines for treatment of brain metastases. We now report our finding, established in a series of 202 patients, that local control following SRS is dependent on the dose to the tumor margin.

Clinical Material and Methods

Between January 1997 and June 2003, 436 patients harboring 626 tumors underwent SRS at the Cleveland Clinic.
for treatment of one or multiple brain metastases. Of these, 202 were identified who met the study entry criteria. These criteria included use of the RTOG 90-05 radiosurgical dosing scheme (81 of the 436 patients did not meet this criterion) and a required minimum of 3 months of clinical follow up with at least one imaging study available for our review (131 of the remaining 355 patients did not meet this criterion).

Reasons for deviation from the dosing scheme included proximity of the tumor to optic apparatus, proximity to other critical functional structures, or location in the brainstem. Twenty-two patients had brain metastases from small-cell carcinoma and were not included in this analysis. Hence, 375 tumors were treated in this subset of 202 patients. Patients could have either newly diagnosed brain metastases treated with SRS prior to or in lieu of WBRT, or residual or recurrent tumors treated after initial WBRT. Twenty-seven patients underwent a second or third radiosurgical procedure for newly discovered brain metastases; in no case was a brain metastasis that had been previously treated with SRS treated again with this therapy. Data for this study were extracted from a patient registry approved by the Cleveland Clinic Institutional Review Board.

The following data were obtained from the medical records: patients’ age and sex, the histological type of the primary tumor, status of metastatic disease, status of primary tumor, KPS status, maximal lesion diameter and volume, number of metastases, use and timing of WBRT, and SRS treatment prescriptions. Two hundred two patients with 375 treated brain metastases were included in this study. The median overall follow-up duration (broken down by tumor) was 10.7 months (range 3–83 months). The patients’ clinical tumor, KPS status, status of primary disease, or timing of WBRT. Patients in the group receiving the 24-Gy dose were slightly younger than those in the 15- or 18-Gy treatment groups. A significantly greater number of patients in the 24-Gy group had extracranial metastasis or multiple brain metastases. These patients also had more tumors located in the supratentorial compartment. A larger number of tumors in the 24-Gy treatment group were melanomas; more metastases in the 18-Gy group were from a lung cancer primary.

**Kaplan–Meier Analysis of Time to Local Failure**

Figure 1 shows the Kaplan–Meier curves of time to local treatment failure, stratified by SRS dose. Comparisons among the three groups show that a dose of 24 Gy to the tumor margin had a significantly lower hazard (longer time to local failure) for patients treated with 24-Gy compared to patients treated with 15- or 18-Gy dose.

Statistical Analysis

Patient and tumor characteristics were compared across three SRS dose groups by using the ANOVA F-test, Kruskal–Wallis test, chi-square test, and the Fisher exact test, wherever appropriate. For univariate analysis, the Kaplan–Meier method was used to summarize the time to local treatment failure/death for the three groups being compared. The log-rank test was used to test for difference in survival. Multivariate analysis with the Cox model was performed to account for the effect of covariates. Robust standard errors were used to adjust for possible correlations between multiple tumors in the same patient in the analysis of local failure. All tests were two-sided. The Type I error of tests was 0.05. The analysis was performed using SAS version 9.0 software (SAS Institute, Cary, NC) and S-PLUS version 6.2 (Insightful Corp., Seattle, WA).

**Results**

**Patient and Tumor Characteristics**

The majority of patients were younger than 65 years of age and had a KPS score greater than 70. In more than half, the primary disease was controlled but the patients had active systemic metastases. Most had more than one brain metastasis, and 18% had more than three. The majority of metastases were from non–small cell lung cancer.

Forty-eight patients (24%) were treated with SRS alone, 117 (58%) were treated with WBRT prior to SRS, and 37 (18%) were treated with WBRT following SRS.

**Treatment Variables**

The treatment variables, sorted by prescribed dose to the tumor margin, are shown in Table 2. There were no statistically significant relationships between treatment group and sex, KPS score, status of primary disease, or timing of WBRT. Patients in the group receiving the 24-Gy dose were slightly younger than those in the 15- or 18-Gy treatment groups. A significantly greater number of patients in the 24-Gy group had extracranial metastasis or multiple brain metastases. These patients also had more tumors located in the supratentorial compartment. A larger number of tumors in the 24-Gy treatment group were melanomas; more metastases in the 18-Gy group were from a lung cancer primary.

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to local failure) than the 15- and 18-Gy groups (p = 0.0005; HR 0.277, CI 0.134–0.573), whereas the 15- and 18-Gy groups were not significantly different from each other (p = 0.82; HR for 18 Gy compared with 15 Gy, 0.925; CI 0.476–1.8). Other covariates, such as age, KPS score, site of primary cancer, lesion location (supratentorial compared with infratentorial), the total number of brain metastases, whether the primary disease was under control, the presence of extracranial disease, and the timing of WBRT, were entered into a Cox model together with SRS dose, and stepwise and backward model selection procedures were applied, but none of these covariates were significantly associated with time to local failure. Table 3 shows the estimated proportions of patients with time to local failure exceeding 3, 6, 9, and 12 months.

The median duration of local control for lesions treated with 24 Gy was not reached; for 18 Gy it was 11.57 months (95% CI 8.6–19.37) and for 15 Gy it was 11.83 months (95% CI 6.03–41.9) (p < 0.0001 by log-rank test for 24 Gy compared with 18 or 15 Gy). The 1-year local control rate was 85% (95% CI 78–92%) in tumors treated with 24 Gy, compared with 49% (30–68%) in tumors treated with 18 Gy, and 45% (23–67%) in tumors treated with 15 Gy.

Kaplan–Meier Analysis of Survival Time, Based on Minimal Dose for Each Patient

In this analysis, if a patient had multiple lesions, the dose was set to correspond to the smallest one used for SRS. The analysis was similar to that for time to local control. No statistically significant difference was found among the three treatment groups (p = 0.9364; Fig. 2). Two covariates were found to be significantly associated with survival. They were 1) total number of lesions (p = 0.0005; HR for each incremental number, 1.165; CI 1.069–1.269) and 2) systemic disease (p = 0.0062; HR for presence compared with absence, 1.551; CI 1.133–2.123).

Kaplan–Meier Analysis of Survival Time, Based on MTD for Each Patient

In this analysis, if a patient had multiple lesions, the dose was set to correspond to the largest one used for SRS. The analysis was similar to that for time to local control. No statistically significant difference was found among the treatment groups (p = 0.5362; Fig. 3). Two covariates were found to be significantly associated with survival. They were 1) total number of lesions (p < 0.0001; HR for each incremental number, 1.165; CI 1.069–1.269) and 2) primary tumor controlled (p = 0.0235; HR for controlled compared with not controlled, 0.680; CI 0.488–0.95). Systemic disease was borderline significant at the 0.05 level (p = 0.0548; HR of presence compared with absence, 1.551; CI 1.133–2.123).

Discussion

Stereotactic radiosurgery is an important tool for the treat-
ment of patients with brain metastases. It is of particular utility for the treatment of patients with unresectable brain metastases, in whom the use of SRS after WBRT is associated with improved local control, and, in the case of single brain metastases, improved survival when compared with WBRT alone.\(^2\)

In patients who have brain metastases that can be surgically removed, however, few studies have been conducted to address the question of whether SRS or surgery is the better treatment modality.\(^4\) In one published study,\(^4\) 62 patients who underwent surgery for removal of brain metastases were retrospectively matched with 31 patients who underwent SRS. The authors reported an improvement in the median survival duration for patients treated with surgery or radiosurgery (16.4 compared with 7.5 months). They believed that this difference was due to a higher local recurrence rate in the patients treated with SRS. It is important to note that in this report the range of tumor volumes treated with SRS was 0.41 to 8.25 ml (median 1.96 ml) and that the range of prescribed doses to the tumor margin was 17 to 22 Gy (median 18.7 Gy). By extrapolation it would follow that the majority of tumors were less than 2 cm in maximal diameter. Hence, the fact that the highest prescribed dose was 22 Gy and that the median was less than 20 Gy strongly suggests that the SRS dosing scheme used in this study was well below the MTD reported in RTOG 90-05.\(^{15}\)

We report in this retrospective analysis of our single-center SRS experience that the efficacy of SRS, specifically as it relates to local control, is significantly dependent on the prescribed dose to the tumor margin. We found that tumors treated with a dose of 15 or 18 Gy to the tumor margin had an approximately threefold increase in risk of local failure compared with tumors treated with 24 Gy to the margin. Local control at 1 year was 85% for tumors treated with a
prescribed dose of 24 Gy, compared with 49 and 45% for tumors treated with 18 or 15 Gy, respectively. These findings are remarkable, especially in light of a slightly higher preponderance of melanomas, which tend to be radioresistant, in the 24-Gy dose group.

It is difficult to compare our results directly with most of the earlier series because, with rare exceptions, the control rates were not reported as a function of tumor diameter or prescribed dose. In one study of radiosurgery in which the maximal tumor diameter was limited to 2 cm or less, 1- and 3-month local control rates of 96% were reported for SRS plus WBRT and 77% for SRS alone. Our local control rates of 85%, which includes both patients who received SRS alone and those who underwent SRS plus WBRT for similar-sized lesions appears to show a similar control rate. We are not aware of other studies in which the local control rates in tumors larger than 2 cm were specifically examined. The results reported here support the suggestion that analyses of local control rates post-SRS that lump together tumors that are larger and smaller than 2 cm may yield unrealistically high (for large tumors) and low (for small tumors) estimates of the efficacy of this therapy.

In the RTOG 90-05 protocol, the acute (\(\leq 3\) months) and chronic (\(> 3\) months) risks of SRS were determined and stratified by lesion size. Notably, SRS was performed following the completion of fractionated radiotherapy regimens in these patients. For tumors larger than 30 mm, there were no cases of acute toxicity and a 14% incidence of chronic toxicity in the 15-Gy treatment group. This dose was selected as the MTD after a 50% risk of acute and chronic toxicity was identified for the 18-Gy treatment group. For tumors between 21 and 30 mm, there were no cases of acute toxicity and a 20% incidence of chronic toxicity in the 18-Gy treatment group. This dose was selected as the MTD after a 38% risk of acute and chronic toxicity was identified for the 18-Gy treatment group.

These findings indicate that the prescribed doses for metastatic tumors larger than 2 cm cannot be increased safely and that resection remains an important tool for the management of these lesions. It must be noted, however, that the

TABLE 3
Estimated percentage of patients in whom time to local failure exceeded 3, 6, 9, and 12 months*

<table>
<thead>
<tr>
<th>Factor</th>
<th>15 Gy</th>
<th>18 Gy</th>
<th>24 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>total no. of lesions</td>
<td>41</td>
<td>85</td>
<td>249</td>
</tr>
<tr>
<td>follow-up interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mos</td>
<td>100%</td>
<td>99% (96–100%)</td>
<td>100%</td>
</tr>
<tr>
<td>no. of lesions at risk</td>
<td>31</td>
<td>56</td>
<td>166</td>
</tr>
<tr>
<td>6 mos</td>
<td>71% (54–88%)</td>
<td>87% (77–96%)</td>
<td>92% (87–97%)</td>
</tr>
<tr>
<td>no. of lesions at risk</td>
<td>37</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>9 mos</td>
<td>63% (44–81%)</td>
<td>64% (49–80%)</td>
<td>85% (78–92%)</td>
</tr>
<tr>
<td>no. of lesions at risk</td>
<td>13</td>
<td>18</td>
<td>60</td>
</tr>
<tr>
<td>12 mos</td>
<td>45% (23–67%)</td>
<td>49% (30–68%)</td>
<td>85% (78–92%)</td>
</tr>
<tr>
<td>no. of lesions at risk</td>
<td>6</td>
<td>8</td>
<td>37</td>
</tr>
</tbody>
</table>

* Metastases are categorized according to prescribed SRS dose. The probability value for all follow-up intervals was less than 0.0001 and was calculated using the log-rank test.

† These values represent the number of lesions that were controlled and were still being followed with MR imaging or computerized tomography studies at each interval (lesions at risk of further spread).

RTOG 90-05 protocol included tumors of various histological types (both primary and metastatic brain tumors) that had been previously treated with a variety of fractionated radiotherapy regimens and that the true MTD for radiation-naive metastases may be higher.

The MTD for tumors that had a maximal diameter of 2 cm was not actually reached in the RTOG 90-05 protocol. The investigators chose to end the study after reaching a prescribed dose of 24 Gy, despite finding no cases of acute and only a 10% incidence of chronic toxicity, which was below their definition of dose-limiting toxicity. Notably, Shehata, et al., observed even lower rates of Grade 3 or 4 neurotoxicity for tumors treated with doses of less than 20 Gy in combination with WBRT.

We did not observe an effect of the timing of fractionated radiotherapy on the local control rate observed after treatment with SRS. This finding is consistent with other published reports. A more definitive evaluation of the role of WBRT in patients treated with SRS was initiated in a prospective randomized study (American College of Surgeons Oncology Group Z0300).

The results and conclusions of this study are limited by the fact that it is a retrospective analysis of the experience at a single institution. Further prospective evaluation of the...
The relationship between radiation dose to the tumor margin as the most significant barrier to a prospective evaluation of tumor control. On the other hand, we believe that this technical limitation serves to disprove this important distinction, and we believe that this technical limitation serves as the most significant barrier to a prospective evaluation of the relationship between radiation dose to the tumor margin and local control.

Conclusions

The findings in this study have relevance to the management of metastatic brain tumors in the clinic. When considering the treatment options for a patient with newly diagnosed brain metastases, clinicians are faced with the question of whether surgery or radiosurgery would be the best management strategy. Although radiosurgical treatment has the advantages of less morbidity and patient discomfort as well as no need for hospitalization, based on the results of this study we would suggest that its efficacy may not be durable for lesions larger than 2 cm due to a restriction in the tumor-margin dose that can be used safely. Although many other factors, including tumor location, extent and status of systemic disease, and medical comorbidities must be taken into account when selecting the most appropriate management strategy for these patients, based on our results we would suggest that although radiosurgery may be a preferable option for metastases less than 2 cm in maximal diameter, it may not be the best strategy for many tumors larger than 2 cm.

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References


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