

Stereotactic Radiosurgery With or Without Whole Brain Radiotherapy for Patients With a Single Radioresistant Brain Metastasis

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Purpose: To examine the outcomes of patients with a single brain metastasis from radioresistant histologies (renal cell carcinoma and melanoma) treated with stereotactic radiosurgery (SRS) with or without whole brain radiotherapy (WBRT).

Methods and Materials: We reviewed the medical records of 27 patients treated at our institution between 2000 and 2007 with a single radioresistant brain metastasis. Patients were treated with Gamma Knife based SRS. Tumor histologies included renal cell carcinoma and melanoma.

Results: Patients were treated to a median marginal dose was 20 Gy (range, 15–22 Gy). At follow-up intervals ranging from 1.8 to 23.2 months, the radiographic responses were as follows: progression in 7 patients; stable in 5 patients; and shrinkage in 15 patients. Fifteen patients (56%) developed distant brain failure. Seven of the 27 patients were alive at last follow-up. The 3-, 6-, 9-, 12-, and 18-months after SRS local control rates were 82.8%, 77.9%, 69.3%, 69.3%, and 55.4%, respectively. None of the 5 patients who received WBRT developed distant brain failure although the follow-up intervals were short (range, 3.5–13.7 months; median, 5.1 months). WBRT did not appear to affect local control, progression free survival, and overall survival ($P = 0.32, 0.87, 0.69$). One patient developed worsening of symptoms attributable to SRS.

Conclusions: Gamma Knife SRS is a safe and feasible strategy for treatment of patients with a single radioresistant brain metastasis. Radiosurgery alone is a reasonable treatment option, but may carry a greater likelihood of distant brain recurrence.

Key Words: radioresistant, radiosurgery, single, metastasis, melanoma, renal cell carcinoma

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Metastatic brain tumors are by far the most common intracranial malignancy with autopsy studies estimating and incidence of up to 170,000 cases per year in the United States.¹ The incidence may increase in the future as a result of improvements in detection with modern imaging. The incidence of metastatic spread to the brain varies widely with different histologies. Melanoma and renal cell carcinoma are consistently reported as histologies more likely to spread to the brain.² The incidence of melanoma in the United States

has more than doubled in the last 25 years,³ and the incidence of renal cell carcinoma has risen at a similar rate.⁴ These factors, along with increasing detection rates related to modern imaging improvements, are likely to lead to an increase in the frequency of brain metastasis from melanoma and renal cell primary tumors in the future.

Treatment with whole brain radiotherapy (WBRT) results in symptomatic improvement and improved survival times.^{5,6} Long-term results however, are poor, with estimated 1 year intracranial local control rates of 0% to 14%.^{7,8} Melanoma and renal cell carcinoma have gained a reputation as “radioresistant” histologies because of their poor response to standard radiotherapy. A CT analysis of response rates of 336 measurable metastatic lesions after WBRT (3000 cGy in 10 fractions) showed complete response rates of 0% for melanoma and 0% for renal cell carcinoma, compared with 37% for small cell carcinoma, 35% for breast cancer, 25% for squamous cell carcinoma, and 13% for nonbreast adenocarcinoma.⁹

Stereotactic radiosurgery (SRS) is a procedure designed to deliver a highly conformal, high dose of radiation to a small volume in a single treatment. Multiple converging static fields or stereotactic arcs centered on a single isocenter are used to accomplish this. As SRS became more available in the United States, this technology has been used for some patients in the setting of a single brain metastasis to improve on the local control rates achieved with fractionated radiotherapy and to avoid the morbidity of surgical resection. Surgery remains the preferred choice in the setting of significant mass effect, severe neurologic deficit, or ventricular obstruction, and is usually preferred for larger (>4 cm) tumors.¹⁰ In the appropriately selected patients, however, SRS may be preferred and retrospective series have shown equivalent survival and improved local control with SRS compared with surgery.^{11,12} Multiple prior reports have described the effectiveness of SRS in addressing brain metastases from melanoma and renal cell carcinoma primaries.^{13–25} We report our experience with Gamma Knife SRS in the management of patients with a single radioresistant brain metastasis.

MATERIALS AND METHODS

Exempt review was granted by our cancer hospital institutional review board for the collection of data for patients with radioresistant brain metastases treated with Gamma Knife SRS in our department. In the period from 2000 to 2007 a total of 97 patients with radioresistant brain metastases were treated with SRS. Patient clinical data, tumor volumetric data, and treatment details were retrospectively entered into a database. Vital status was obtained through the United States Social Security Database. Of the 97 patients, 27 (15 male and 12 female) had a single metastasis. Their age ranged from 39 to 81 years. Karnofsky performance status ranged from 50 to 100. Nine had renal cell carcinoma primary tumors, whereas 18 had melanoma. Twenty-four of the 27 tumors were located supratentorially. Distribution of RTOG recursive partitioning analysis classes was as follows: I, 1 patient; II, 25 patients;

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and III, 1 patient. The recursive partitioning analysis class III patient had her Karnofsky performance status improved to 70 after WBRT and was therefore offered a boost with SRS. Of the 27 patients, 4 had stable extracranial disease. Table 1 summarizes the characteristics of the 27 treated patients. Patients who developed a single brain metastasis as a recurrence after WBRT were excluded from the analysis.

SRS was carried out on the Leksell ⁶⁰Co Gamma Knife for all patients (Elekta AB, Stockholm, Sweden). Before June 2006, a B-model was used; starting June 06, a 4C-model was used. The morning of the procedure, a stereotactic, MRI compatible head frame was fixed to the patient with local anesthesia. A multiplanar, gadolinium enhanced MRI was performed for target delineation. A spoiled gradient recalled acquisition sequence was typically used for treatment planning. Every stereotactic double contrast MRI study was reviewed by a neurosurgeon, a radiation oncologist, and a neuroradiologist to confirm the number of metastasis prior to treatment planning. The target was delineated in 3 dimensions in the treatment planning software. The tumor volume ranged from 0.054 mL to 17.3 mL. The prescribed SRS dose was based on a clinical decision according to the tumor size, shape, and location. The dose ranged from 15 to 22 Gy (median 20 Gy). The prescribed dose was delivered to the 50% isodose line in most cases. All treatments were delivered in a single session. Five patients received WBRT in addition to SRS. Following the procedure, a CT or MRI was requested every 3 to 4 months for follow up. When MRI was used for follow-up, a spoiled gradient recalled acquisition sequence was typically included. Any significant increase in size of the tumors noted in the radiologic report was recorded as a local recurrence. Survival time in months was calculated from the date of the patient's first radiosurgery. Time to local tumor recurrence and distant brain recurrence was recorded in months.

TABLE 1. Patient Characteristics (n = 27)

	Value
Mean age (range)	56 (39–81)
Gender (%)	
Male	15 (56)
Female	12 (44)
Primary cancer, no. (%)	
Melanoma	18 (67)
Renal cell carcinoma	9 (33)
Median KPS (range)	70 (50–100)
RPA class, no. (%)	
I	1 (4)
II	25 (92)
III	1 (4)
Tumor location (%)	
Supratentorial	24 (89)
Infratentorial	9 (11)
Extracranial disease status (%)	
Stable	4 (15)
Progressing	23 (85)
Mean target volume, mL (range)	4.4 (0.054–17.3)
Mean prescription dose, Gy (range)	19 (15–22)
Initial treatment, no. (%)	
SRS alone	22 (81)
SRS + whole brain radiotherapy	5 (19)

Endpoints and Statistical Analysis

The endpoints included overall survival (OS), progression-free survival (PFS), local control (LC), and free-from-distant-brain-failure (FFDBF). OS was defined as survival with or without progression of intracranial disease; PFS was defined as survival without evidence of intracranial failure; LC was defined as absence of evidence of local progression; FFDBF was defined as absence of evidence of distant brain failure.

StatView software (SAS Institute, Inc, Cary, NC) was used for statistical analysis. Kaplan-Meier analysis was used to calculate OS, PFS, LC, and FFDBF rates. Crude rates were used to calculate the response and distant brain failure rates.

RESULTS

Survival

At follow up intervals ranging from 1.8 to 23.2 months, 7 patients were still living and 20 patients had died. The median survival was 8.1 months. The 3-, 6-, 9-, 12-, and 18-months after radiosurgery overall survival rates were 85.2%, 53.6%, 48.7%, 43.8%, and 26.3% (see Fig. 1). The corresponding progression free survival (PFS) rates were 63%, 42.5%, 38%, 28.5%, and 12.7% for all patients; the PFS rates were 75%, 50%, 50%, 50%, and 50% for patients who had WBRT, and 60.9%, 47%, 35.2%, 23.5%, and 11.7% for those who did not have WBRT. The median overall survival for renal cell carcinoma primaries was 13.5 months and for melanoma was 6 months ($P = 0.78$, log-rank test).

Local Control

The 3-, 6-, 9-, 12- and, 18-months after radiosurgery local control (LC) rates were 82.8%, 77.9%, 69.3%, 69.3%, and 55.4%, respectively (see Fig. 2). The median local control was not reached. The 3-, 6-, 9-, 12-month LC rates for patients with RCC and melanoma were 100%, 100%, 100%, and 100%, and 74.3%, 66.9%, 53.5%, and 53.5%, respectively ($P = 0.19$, logrank test). Eight (88.9%) of 9 patients with RCC and 12 (66.7%) of 18 patients with melanoma achieved local control. Among the 5 patients who received WBRT, 2 (40%) developed local failure compared with 5 (22.7%) of 22 patients who did not receive WBRT.

Free-From-Distant-Brain-Failure

Fifteen (55.6%) of the 27 patients developed distant brain failure; 5 (55.6%) of the 9 patients with RCC brain metastasis and 10 (55.6%) of 18 patients with melanoma developed distant brain failure. The 3-, 6-, 9-, 12-, and 18-months after radiosurgery FFDBF rates were 74.4%, 60.2%, 54.1%, 40.6%, and 22.6%. (see Fig. 3) The median FFDBF was 9.3 months. None of the 5 patients (1 with RCC and 4 with melanoma) treated with up front WBRT experi-

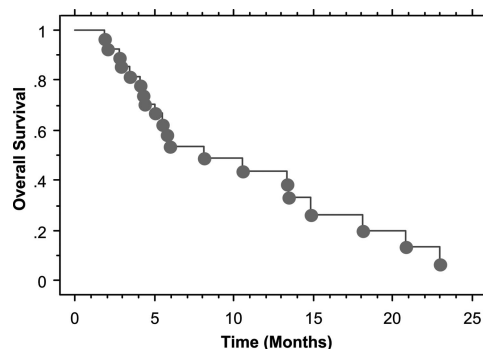


FIGURE 1. Kaplan-Meier plot showing overall survival from the time of radiosurgery for all patients.

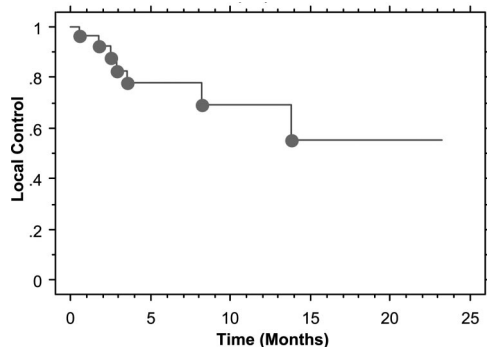


FIGURE 2. Kaplan-Meier plot showing local control at the radiosurgical site from the time of radiosurgery.

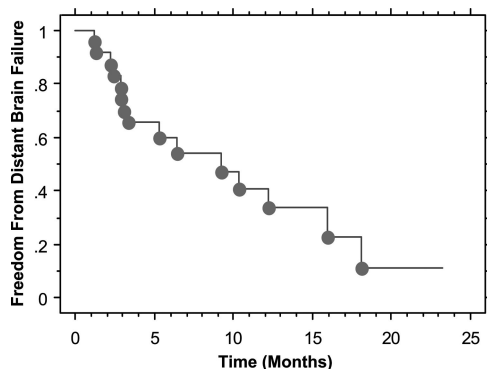


FIGURE 3. Kaplan-Meier plot showing freedom from distant brain failure from the time of radiosurgery.

TABLE 2. Radiographic Response of RCC and Melanoma Brain Metastases (n = 27)

	Progression	Stable	Shrinkage
RCC	1	2	6
Melanoma	6	3	9
All	7	5	15

enced a distant brain recurrence compared with 15 (68.2%) of 22 patients who did not receive WBRT. Follow up intervals for this subgroup were short (range, 3.5–13.7 months; median, 5.1 months). WBRT did not appear to affect LC, PFS, and OS ($P = 0.32, 0.87, 0.69$, logrank test).

Radiographic Response

Overall, the radiographic response was progression in 7 patients (25.9%), stable findings in 5 patients (18.5%), and shrinkage in 15 patients (55.6%). Table 2 summarizes the response according to histology.

Salvage Treatment

Eighteen patients developed intracranial failure (3 local only, 11 distant only, and 4 local and distant). Among those 18 patients who failed, 10 (56%) went on to receive salvage therapy. Three received systemic chemotherapy with temozolomide, 1 underwent intra-arterial chemotherapy, and 6 underwent repeat SRS.

Toxicities

Five patients developed worsening of neurologic symptoms within 6 months after SRS. Only 1 incident was attributable to post-SRS effects and the rest were deemed to be related to disease progression or effects of other cancer therapies. No late toxic effects were observed and this was most likely related to the short survival times of most patients.

DISCUSSION

Acceptable treatment options for patients with a single radio-resistant brain metastasis include surgery, WBRT, SRS, or a combination approach. There are advantages and disadvantages associated with each approach. Surgery results in excellent local control, but is the most invasive option. Adding WBRT after resection of a single brain metastasis has been shown to reduce the risk or recurrence at the surgical site and elsewhere in the brain. Patchell and colleagues from the University of Kentucky conducted a randomized trial addressing evaluating the value of WBRT in the postoperative setting.²⁶ After resection of a single brain metastasis patients were randomly assigned to observation or WBRT (50.4 Gy). Risk of tumor recurrence anywhere in the brain was 70% without and 18% with adjuvant WBRT. Adjuvant WBRT reduced recurrences in the surgical bed as well as recurrences at sites apart from the operative bed. Risk of neurologic death was reduced, but overall survival (a secondary end point for which the study was not actually powered) was not influenced by the addition of WBRT.

Certain tumor locations may make surgery especially high risk. Compared with surgery, SRS is a less invasive modality yielding local control rates comparing favorably with surgery for properly selected patients.^{11,12} The primary advantage of adding WBRT to SRS is that it addresses micrometastatic disease which may exist elsewhere in the brain. Additionally, the total dose to the primary target is increased, possibly increasing the local tumor control as well. Aoyama et al reported the results of a phase III trial comparing SRS alone to SRS + WBRT for 132 patients with 1 to 4 brain metastases.²⁷ Both local control ($P = 0.002$) and risk of distant brain recurrence ($P = 0.003$) were significantly improved in patients treated with SRS + WBRT. There was no significant difference in overall survival.

Over the last 10 years, use of SRS for patients with a limited number of brain metastasis has increased in the United States. Because of the known radioresistance of melanoma and renal cell carcinoma histologies, the value of adding WBRT to SRS for patients with a limited number of radioresistant brain metastases has been particularly called into question. Eastern Cooperative Oncology Group published results of a phase II prospective study evaluating the feasibility of up front SRS alone in patients with 1 to 3 radioresistant brain metastases.²⁴ Thirty-six patients were accrued on the trial. The reported intracranial failure rates at 3 and 6 months were 25.8% and 48.3%, respectively. These rates were higher than what was suggested from retrospective series and the authors suggest the possible explanation of selection bias in the retrospective literature.

The primary argument made against the use of WBRT is that more focal therapies (surgery, SRS) allow patients to avoid the risk of late neurocognitive toxicity associated with this treatment. Cranial irradiation can induce a syndrome known as toxic leukoencephalopathy, a structural alteration of cerebral white matter. Mild cases of this syndrome thought to be associated with cranial radiation can result in symptoms such as memory loss, chronic confusion, inattention, or emotional dysfunction.²⁸ Risk of developing this syndrome raises concerns in all patients. It is important however, to consider competing causes of neurocognitive decline. Analysis of

neurocognitive outcomes for the patients treated on the first prospective trial comparing SRS with SRS + WBRT was accomplished using the Mini-Mental State Examination.²⁹ The primary factor affecting neurocognitive decline appeared to be control of tumors within the brain. Because 90% of patients had died by 3 years on both arms, the late effects of WBRT were somewhat difficult to analyze. In a study from M.D. Anderson Cancer Center, Chang et al did a pilot study of neurocognitive function in patients with 1 to 3 new brain metastases initially treated with SRS alone. At baseline, 67% of the patients had impairment on one or more tests of neurocognitive function including executive function, motor dexterity, and learning/memory. Brain metastasis volume measured at the time of initial SRS was associated with worse performance on a measure of attention.³⁰ At 1 month after SRS, deterioration in the learning/memory and motor dexterity domains were most common. The majority of 5 long-term survivors (alive >200 days after SRS) had stable or improved neurocognitive performance across executive function, learning/memory, and motor dexterity.³⁰ These findings suggest that control of intracranial metastasis has a significant impact on neurocognitive function. Recently, the results of a phase III randomized trial conducted at M.D. Anderson Cancer Center comparing SRS and SRS combined with WBRT in patients with 1 to 3 brain metastases were presented as a late breaking abstract at the plenary session of the American Society of Therapeutic Radiology and Oncology annual meeting. The primary end point was the cognitive decline in learning and memory that was evaluated using Hopkins Verbal Learning Test. For patients randomized to receiving WBRT, a dose of 30 Gy in 12 fractions was given. Despite inferior local control and distant brain control in patients who received SRS alone, there is a lower probability of neurocognitive decline (23% vs. 49% in patients who also had WBRT). Prospective data from this study suggest that the post-treatment decline in learning and memory are more likely related to WBRT than intracranial tumor progression.

To our knowledge, this is the first published report looking at SRS only in patients with a single radioresistant metastasis. Our study of patients with a single radioresistant brain metastasis is subject to the weaknesses of small numbers and retrospective bias. Nevertheless, the results appear consistent with prior reports of the use of radiosurgery in patients with metastatic melanoma and renal cell carcinoma.^{14,15,17–25,31–39} Survival and local control were consistent with historical controls. Free-from-distant-brain-failure may be improved for patients who receive WBRT in addition to SRS.

Patients with a single radioresistant brain metastasis may be suitable candidates for SRS monotherapy, understanding that their risk for local and distant brain failure may be higher, and that vigilant surveillance is needed. Combined SRS + WBRT can also be reasonably employed in this setting, understanding that the few patients with long-term survival (years rather than months) will have an increased risk for experiencing neurocognitive decline associated with radiation induced toxic leukoencephalopathy. Predicting which patients are more likely to survive long term becomes an important challenge.

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