Efficacy of Stereotactic Radiosurgery as a Salvage Treatment for Recurrent Malignant Gliomas

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BACKGROUND. The objective of this prospective cohort study was to determine the efficacy of stereotactic radiosurgery (SRS) as a salvage treatment in patients with recurrent malignant gliomas.

METHODS. Between January 2000 and December 2006, 114 consecutive patients were treated with SRS as a salvage treatment for recurrent malignant gliomas at a single institution. Clinical outcome and its prognostic factors were analyzed and compared with the historical control group who were treated at the same institution between 1995 and 1999.

RESULTS. The median overall survival from the time of diagnosis was 37.5 months (95% confidence interval [95% CI], 11.7–63.2 months) for patients with grade 3 gliomas (according to World Health Organization criteria) and was 23 months (95% CI, 16.2–29.3 months) for patients with glioblastomas. The median progression-free survival after SRS was 8.6 months (95% CI, 1.1–16.2 months) for patients with grade 3 gliomas and 4.6 months for patients with glioblastomas (95% CI, 4.0–5.2 months). With regard to treatment-related complications, radiation-induced necrosis was observed in 22 of 114 patients (24.4%). Compared with this historic control group, SRS significantly prolonged survival as a salvage treatment in patients with recurrent glioblastomas (23 months vs 12 months; $P < .0001$), but it was not found to provide a significant surgical benefit in patients with recurrent grade 3 gliomas (37.5 months vs 26 months; $P = .789$). On univariate analysis of prognostic factors, tumor volume (<10 mL) and low histologic grade were found to significantly influence better survival ($P = .009$ and $P = .041$, respectively).

CONCLUSIONS. SRS is a safe and effective modality in selected patients with recurrent small-sized glioblastomas. However, the efficacy of SRS for recurrent grade 3 gliomas needs to be further evaluated in well-designed clinical studies. ***Cancer* 2008;112:2046–51.** © *2008 American Cancer Society.*

KEYWORDS: malignant glioma, recurrence, radiosurgery, survival.

Although temozolomide plus radiotherapy has recently been shown to improve the outcome for newly diagnosed glioblastoma (GBM) patients,[1] the treatment of recurrent malignant gliomas still remains a challenging task. The vast majority of gliomas usually spread by local invasion, which implies that it recurs within or adjacent to the original tumor bed.[2–4]

The efficacy of reirradiation in recurrent gliomas remains controversial because of the possibility of radiation-induced necrosis. In an attempt to spare adjacent normal cerebral tissue and at-risk organs, stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT) can be performed. To our knowledge, to date, the efficacy of SRS for malignant gliomas has been reported through several case series or retrospective cohort studies.[4–8] Considering

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the finding that the majority of gliomas have highly infiltrative patterns and ill-defined tumor margins, this characteristic of gliomas is difficult to overcome. SRS has some limitations in the treatment of gliomas because its therapeutic window between effective tumor control and radiation necrosis is very narrow. Nevertheless, there have been many studies suggesting that SRS is effective mainly for GBMs, more so than other gliomas.[4,5,9] Therefore, we prospectively investigated our clinical data to evaluate the efficacy of SRS as a salvage treatment and potential prolongation of survival time in 114 consecutive patients with recurrent grade 3 gliomas and GBMs.

MATERIALS AND METHODS

Eligibility

Between January 2000 and December 2006, 114 consecutive patients were treated with SRS using linear accelerator (5 cases) or gamma knife (109 cases) as salvage treatment for recurrent malignant gliomas. Inclusion criteria were: 1) pathologically confirmed diagnosis of malignant gliomas as World Health Organization (WHO) grade 3 gliomas or GBMs at the time of initial surgical resection or stereotactic needle biopsy; 2) patients who underwent subsequent fractionated brain irradiation; 3) patients who demonstrated the development of new or increasing contrast-enhanced lesions at the margin of primary origin in the follow-up imaging after fractionated radiotherapy, indicating tumor recurrence or progression; and 4) the size of the lesion was <3 cm in maximum dimension.

Study Population

Of 114 patients with a diagnosis of malignant gliomas, 69 (60.5%) were men and 45 (39.5%) were women. The median age at presentation was 49 years (range, 5–75 years). Pre-SRS Karnofsky performance status (KPS) values ranged from 50 to 100 (median of 80). At the time of the initial diagnosis, 65 patients were diagnosed as having GBM (57.0%) and 49 patients (43%) as having WHO grade 3 gliomas, including gliomatosis cerebri (GC; 10 patients [20.4%]), anaplastic astrocytomas (AA; 5 patients [10.2%]), anaplastic oligoastrocytoma (AOA; 19 patients [38.8%]), and anaplastic oligodendrogliomas (AO; 15 patients [30.6%]) (Table 1). A complete resection was performed in 62 patients (57.4%), a subtotal resection was performed in 34 patients (29.8%), and a biopsy was conducted in 18 patients (14.3%). All patients included in this study received a standard course of radiotherapy after surgical resection or biopsy with a median dose of 60 grays (Gy) (range, 54–70 Gy) in conventional fractionations of 2 Gy per day. After radiotherapy, 32 patients had subsequently received at least 1 chemotherapeutic regimen including temozolomide; carmustine; procarbazine, cyclophosphamide, and vincristine (PCV); or nimustine (ACNU). The median time from the initial diagnosis to disease recurrence was 4.3 months (range, 1.5–27.0 months) for GBM patients and 11.0 months (range, 2.0–68.0 months) for patients with grade 3 gliomas.

TABLE 1
Clinical Features of 114 Patients With Recurrent Malignant Gliomas Who Were Treated With Stereotactic Radiosurgery

	Historic control group	SRS group
No. of patients	360	114
Men	217 (60.3%)	69 (60.5%)
Women	143 (39.7%)	45 (39.5%)
Median age (range), y	53 (4–89)	49 (5–75)
Grade 3 gliomas	96	49
Anaplastic astrocyctoma	(42)	(5)
Anaplastic oligodendroglioma	(11)	(19)
Anaplastic	(8)	(15)
Astrooligodendroglioma	(35)	(10)
Gliomatosis cerebri		
Grade 4 gliomas		
glioblastomas	264	65
Extent of resection		
Macroscopic total resection	184 (51.1%)	62 (57.4%)
Partial resection	103 (28.6%)	34 (29.8%)
Biopsy only	73 (20.3%)	18 (14.3%)
Preoperative median KPS (range)	100 (40–100)	100 (50–100)

SRS indicates stereotactic radiosurgery; KPS, Karnofsky performance status.
$P > .05$ by the Pearson chi-square test and Fisher exact test.

Stereotactic Radiosurgery

All patients were initially placed in a stereotactic head frame, followed by contrast-enhanced magnetic resonance imaging (MRI) for treatment planning. A staff physician and a physicist were involved in treatment planning and target volume determinations for all patients. Before the gamma knife was introduced to our institute in 2001, SRS was performed with a linear accelerator (Varian Medial Systems, Palo Alto, Calif) in 5 patients and, thereafter, it was used with gamma knife radiosurgery (Elekta, Sweden) in 109 patients. The median tumor volume was 10.6 mL (range, 0.09–79.6 mL) and the median number of isocenters used in the treatment plans was 13 (range, 1–30 isocenters). The median marginal dose of 16 Gy (range, 12–50 Gy) was given to the 50% isodose line (range, 24.3%–96.2%) with a gamma knife or 80% with a linear accelerator (Table 2).

TABLE 2
Radiation Dose of Stereotactic Radiosurgery Using Gamma Knife

Radiosurgery dose	Median (Range)
Treatment volume	10.6 mL (0.09–79.6 mL)
Peripheral dose	16 Gy (12–50 Gy)
Isodose line	50% (24.3–96.2%)

Gy indicates grays.

Disease Progression After SRS

The tumor progression was usually confirmed with a subsequent MRI without histologic confirmation. It represented the semiquantitative analysis of the tumor extent on the T1-weighted MRI images with contrast enhancement by measurement with commercially available image software (Scion, Frederick, MD). To avoid confusion of the interpretation, we defined tumor progression as an increase of ≥25% signal change of the treated lesion on at least 2 subsequent follow-up MRI scans, or the radiographic appearance of a new enhancing lesion of the SRS field, or a tumor condition accompanying neurologic deterioration of a KPS of ≥20. Magnetic resonance spectroscopy (MRS) or positron emission tomography (PET) examinations were performed as needed to differentiate tumor progression from radiation necrosis. After SRS, 21 patients (13 with GBM and 8 with grade 3 gliomas) received an additional chemotherapeutic regimen including temozolomide or PCV.

Historic Control

From January 1995 through December 1999, a total of 360 patients with malignant gliomas (96 with grade 3 gliomas and 264 with GBM) were treated at the same institution. On the basis of the retrospective review of overall survival (OS) in this historic group, we compared and analyzed OS in a prospective cohort group.

Statistical Analysis

The primary endpoint of the analysis was OS and progression-free survival (PFS). OS was calculated from the time of histologic diagnosis of the tumor and PFS from reirradiation was calculated from the time of SRS to tumor progression. MRI scans were performed at a regular interval of 3 months or when clinical worsening developed. The OS and PFS were calculated according to the Kaplan-Meier method. A multivariate Cox proportional hazards model was also developed using stepwise regression with the predictive variables. A P value $<.05$ were considered to be statistically significant for all tests using SPSS software (version 12.0; SPSS Inc, Chicago, Ill). OS collected from this prospective cohort study was compared with the historic control data using the log-rank test to determine the efficacy of SRS for malignant gliomas according to WHO grade.

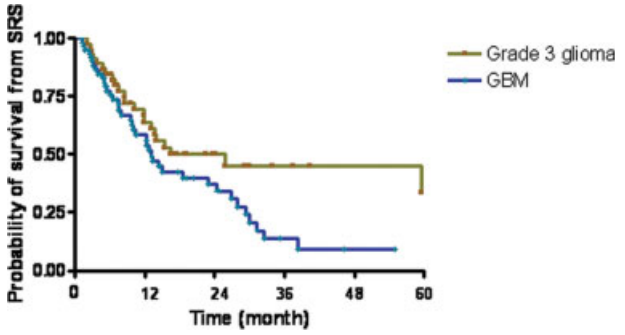

FIGURE 1. Probability of survival after stereotactic radiosurgery (SRS) for reirradiation in 114 patients ($P = .041$). GBM indicates glioblastoma.

RESULTS

SRS was performed completely in all of the intent-to-treat group. At the time of this analysis, 19 of 49 patients with grade 3 glioma (38.8%) and 25 of 65 patients with GBM (38.5%) were alive. The median follow-up period after SRS was 11.2 months (range, 1.5–99.5 months). On the Kaplan-Meier survival analysis, the median OS for WHO grade 3 gliomas was 37.5 months (95% confidence interval [95% CI], 11.7–63.2 months) and that for patients with GBMs was 23.0 months (95% CI, 16.2–29.3 months). The median survival from the time of SRS was 13 months (95% CI, 10.6–16.0 months) for GBMs and 26 months (95% CI, 1.0–62.0 months) for grade 3 gliomas ($P = .041$). At the 1-year follow-up after SRS, the survival rate was 58.4% for GBM patients and 64.1% for patients with grade 3 gliomas (Fig. 1). The median PFS after SRS was 4.6 months (95% CI, 4.0–5.2 months) for patients with GBM and 8.6 months (95% CI, 1.1–16.2 months) for patients with grade 3 gliomas ($P = .004$). The 1-year PFS rate was 20.5% for GBM patients and 49.4% for patients with grade 3 gliomas (Fig. 2).

Treatment-related Complications

Common adverse effects of SRS included nausea, vomiting, and headache, which were usually controlled with steroid medications. On the follow-up MRI scans, radiation necrosis induced by SRS was observed in 22 of 114 patients (24.4%); however, the majority of the patients were not histologically confirmed. Only 4 patients with suspicious radiation-induced necrosis underwent surgical resection for

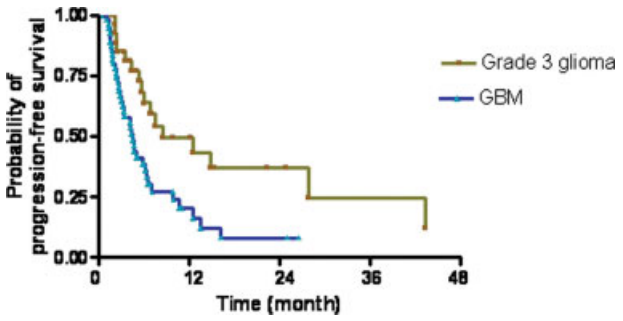

FIGURE 2. Probability of progression-free survival after stereotactic radiosurgery in 114 patients ($P = .004$). GBM indicates glioblastoma.

TABLE 3
Univariate and Multivariate Analyses of Prognostic Factors for Overall Survival

Variable	*P* for univariate analyses	*P* for multivariate analyses
Age	.086	—
Planning tumor volume	.016	.091
Preradiosurgery KPS	.592	—
Extent of initial surgical resection	.690	—
Time from primary diagnosis to disease recurrence	.145	—
Histologic grade	.041	.417
Combined chemotherapy	.121	—

KPS indicates Karnofsky performance status.

the mass effect. Instead, repeated MR follow-up images, MRS, or PET scans were used to differentiate tumor recurrence and radiation-induced necrosis. Their histologic findings were proven to be necrosis intermingled with tumor infiltration. No other National Cancer Institute (NCI) Common Toxicity Criteria grade 3 or 4 toxicities were obtained.

Univariate and Multivariate Analysis for Better Prognosis

In this cohort group, several prognostic factors including age (<65 years vs ≥65 years), size of the planning tumor volume (<10 mL vs ≥10 mL), KPS (<70 vs ≥70), extent of surgical resection, time from initial diagnosis to disease recurrence, histologic grade (grade 3 glioma vs GBM), and combination with chemotherapy (yes or no) were analyzed. On the univariate analysis of these independent variables, tumor volume (<10 mL) remained the strongest influence on survival ($P = .016$). Lower histologic grade also was found to influence better survival significantly ($P = .041$). However, no prognostic factors could be identified on the multivariate analysis (Table 3).

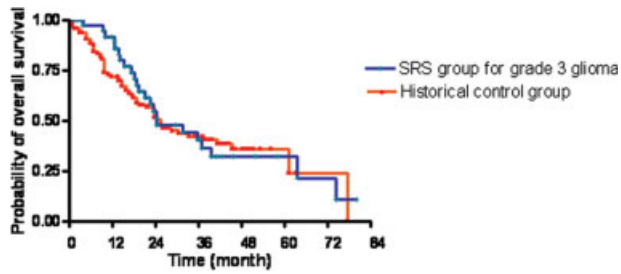

FIGURE 3. Comparison of probability of overall survival from the time of primary diagnosis in 145 patients with grade 3 gliomas ($P = .789$). SRS indicates stereotactic radiosurgery.

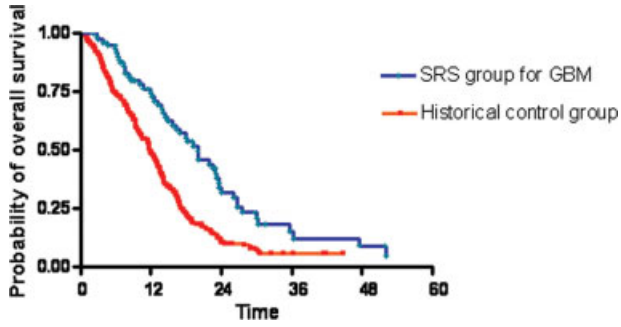

FIGURE 4. Comparison of probability of overall survival from the time of primary diagnosis in 329 patients with glioblastoma (GBM) ($P < .0001$). SRS indicates stereotactic radiosurgery.

Comparison With Historic Control Group

On the retrospective analysis performed between January 1995 and December 1999, the historic control group at our institute (a total of 264 patients with GBM and 96 patients with grade 3 glioma) demonstrated a median OS of 12 months (95% CI, 10.4–13.6 months) for GBMs and 26 months (95% CI, 19.8–32.2 months) for grade 3 gliomas (unpublished data). Compared with this historic control group, SRS significantly prolonged survival as a salvage treatment in patients with recurrent GBM (23 months vs 12 months; $P < .0001$) (Fig. 3), but it did not provide any significant surgical benefit in patients with recurrent grade 3 gliomas (37.5 months vs 26 months; $P = .789$) (Fig. 4).

DISCUSSION

Irradiation was attempted as a first-line or second-line treatment modality for brain tumors. Although there have been recent advances in novel chemotherapeutic regimens such as combined chemoradiotherapy using temozolomide or several small-molecule kinase inhibitors,[7,10–12] reirradiation with FSRT or SRS is still an attractive modality because these mod-

alities can deliver a high dose of radiation while sparing adjacent normal cerebral tissues.

However, it remains unclear whether radiosurgery provides any survival benefit for patients with malignant gliomas, including grade 3 gliomas and GBMs. Compared with the historic control group in this study, SRS did not significantly provide a survival benefit in patients with recurrent grade 3 gliomas (37.5 months vs 26 months; $P = .789$), whereas it prolonged survival when used as a salvage treatment in patients with recurrent GBM (23 months vs 12 months; $P < .0001$). Although we acknowledge that a comparison study with a historic control group is statistically less powerful, this result still has merit for several reasons. First, lower-grade gliomas have a possibility of being less responsive to radiosurgery than higher-grade gliomas because grade 3 gliomas have slower progressive patterns. In addition, recurrence of grade 3 gliomas does not necessarily indicate malignant transformation into GBMs. Finally, the subtypes of grade 3 gliomas may have a very different response to SRS because this study used a heterogeneous group including AA, AO, AOA, and GC. Accordingly, to accurately determine the efficacy of SRS in grade 3 gliomas, survival should be analyzed according to each subdivision of grade 3 gliomas.

With regard to GBM, the results of the Radiation Therapy Oncology Group (RTOG) 93-05 study,[6] which did not demonstrate a survival advantage, may not appear to be consistent with our results. However, that phase 3 trial examined the role of an upfront radiosurgery boost to conventional radiation and carmustine for newly diagnosed GBMs, and not for salvage radiosurgery, as was the case in the current study. Therefore, the results of the current study indicate that salvage radiosurgery may play a role in this patient population. In this study, however, the historic control group is problematic because radiation necrosis and pure tumor progression could not be distinguished radiographically. This might lead to interpretation errors in the comparison of PFS. This study also included some methodologic limitations. Because all of the patients in this cohort group had received a full course of external beam radiotherapy, it was possible that some of these patients had radiation necrosis in these regions, and not true tumor progression. However, a routine course of external beam radiotherapy below 6000 centigrays reportedly has a low incidence of radiation necrosis. Conversely, because this cohort group included tumors measuring $\leq$3 cm in maximal dimension, more biologically aggressive and infiltrative tumors might not be included in this study. This possibility can account for the lengthy survival of 8.5 months after progression from SRS. In contrast, the historic control group did not have any limitations with regard to the size of the lesion at the time of treatment. Therefore, control patients were more likely to have larger and more biologically aggressive/infiltrative tumors, with shorter survival times. Although this study cannot avoid the limitations of selection bias and not having an ideal control group, the result suggests evidence of a defined role of SRS in selected patients with recurrent GBMs.[5,13–20]

It was interesting to note that the rate of macroscopic total resection was approximately 57.4% in the current series. This value was very high compared with previous studies (only 7%–21.8% of total patients or not described).[3–6,9,21] In the current series, recurrent tumors might be smaller-sized lesions than those in other studies because approximately 50% of tumors were macroscopically/completely removed. This might result in a more improved survival outcome. Generally, radiosurgery has a limited role for large-sized tumors. Our univariate analysis demonstrated that recurrent tumors with smaller volume (<10 mL) had better survival after SRS.

In conclusion, SRS is a relatively safe treatment modality for patients with recurrent small-sized GBMs and can be efficiently used with acceptable morbidity in a highly selected patient population. The efficacy for recurrent grade 3 gliomas should be evaluated further in well-designed clinical studies.

REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987–996.
2. Sneed PK, Gutin PH, Larson DA, et al. Patterns of recurrence of glioblastoma multiforme after external irradiation followed by implant boost. *Int J Radiat Oncol Biol Phys*. 1994;29:719–727.
3. Combs SE, Gutwein S, Thilmann C, Huber P, Debus J, Schulz-Ertner D. Stereotactically guided fractionated reirradiation in recurrent glioblastoma multiforme. *J Neurooncol*. 2005;74:167–171.
4. Combs SE, Widmer V, Thilmann C, Hof H, Debus J, Schulz-Ertner D. Stereotactic radiosurgery (SRS): treatment option for recurrent glioblastoma multiforme (GBM). *Cancer*. 2005;104:2168–2173.
5. Hsieh PC, Chandler JP, Bhangoo S, et al. Adjuvant gamma knife stereotactic radiosurgery at the time of tumor progression potentially improves survival for patients with glioblastoma multiforme. *Neurosurgery*. 2005;57:684–692; discussion, 684–692.
6. Souhami L, Seiferheld W, Brachman D, et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. *Int J Radiat Oncol Biol Phys*. 2004;60:853–860.

7. Butowski NA, Sneed PK, Chang SM. Diagnosis and treatment of recurrent high-grade astrocytoma. *J Clin Oncol*. 2006;24:1273–1280.
8. Robins HI, Chang S, Butowski N, Mehta M. Therapeutic advances for glioblastoma multiforme: current status and future prospects. *Curr Oncol Rep*. 2007;9:66–70.
9. Nwokedi EC, DiBiase SJ, Jabbour S, Herman J, Amin P, Chin LS. Gamma knife stereotactic radiosurgery for patients with glioblastoma multiforme. *Neurosurgery*. 2002;50:41–46; discussion, 46–47.
10. Badruddoja MA, Penne K, Desjardins A, et al. Phase II study of cloretazine for the treatment of adults with recurrent glioblastoma multiforme. *Neuro Oncol*. 2007;9:70–74.
11. Reardon DA, Rich JN, Friedman HS, Bigner DD. Recent advances in the treatment of malignant astrocytoma. *J Clin Oncol*. 2006;24:1253–1265.
12. Reardon DA, Wen PY. Therapeutic advances in the treatment of glioblastoma: rationale and potential role of targeted agents. *Oncologist*. 2006;11:152–164.
13. Stieber VW, Ellis TL. The role of radiosurgery in the management of malignant brain tumors. *Curr Treat Options Oncol*. 2005;6:501–508.
14. Szeifert GT, Prasad D, Kamyrio T, Steiner M, Steiner LE. The role of the gamma knife in the management of cerebral astrocytomas. *Prog Neurol Surg*. 2007;20:150–163.
15. Yoshikawa K, Saito K, Kajiwara K, Nomura S, Ishihara H, Suzuki M. CyberKnife stereotactic radiotherapy for patients with malignant glioma. *Minim Invasive Neurosurg*. 2006;49:110–115.
16. Ulm AJ 3rd, Friedman WA, Bradshaw P, Foote KD, Bova FJ. Radiosurgery in the treatment of malignant gliomas: the University of Florida experience. *Neurosurgery*. 2005;57:512–517; discussion, 512–517.
17. McDermott MW, Berger MS, Kunwar S, Parsa AT, Sneed PK, Larson DA. Stereotactic radiosurgery and interstitial brachytherapy for glial neoplasms. *J Neurooncol*. 2004;69:83–100.
18. Szeifert GT, Massager N, Brotchi J, Levivier M. Morphological redifferentiation in a malignant astrocytic tumor after gamma knife radiosurgery. *J Neurosurg*. 2002;97:627–630.
19. Kondziolka D, Flickinger JC, Bissonette DJ, Bozik M, Lunsford LD. Survival benefit of stereotactic radiosurgery for patients with malignant glial neoplasms. *Neurosurgery* 1997;41:776–783; discussion, 783–775.
20. Friedman WA, Foote KD. Linear accelerator radiosurgery in the management of brain tumours. *Ann Med*. 2000;32:64–80.
21. Combs SE, Thilmann C, Edler L, Debus J, Schulz-Ertner D. Efficacy of fractionated stereotactic reirradiation in recurrent gliomas: long-term results in 172 patients treated in a single institution. *J Clin Oncol*. 2005;23:8863–8869.