

Salvage reirradiation for recurrent glioblastoma with radiosurgery: radiographic response and improved survival

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Received: 1 August 2008 / Accepted: 17 November 2008 / Published online: 9 December 2008
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Abstract *Purpose* To determine the radiographic and clinical efficacy of stereotactic single dose radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) as salvage therapy for glioblastoma (GBM) at recurrence. *Methods* Thirty-six patients with pathologically proven recurrent GBM were treated with salvage reirradiation by either SRS or FSRT between March of 2001 and August of 2006. Thirty-one patients had an initial diagnosis of GBM. Five patients had a malignant transformation. All patients had received radiotherapy with a dose of 50–60 Gy, a median 13.6 months prior to reirradiation (range: 0.8–119 months). At the time of recurrence, 26 patients were treated with SRS with a median dose of 18 Gy (range: 12–20 Gy). FSRT was performed in ten patients with a dose of 36 Gy in six fractions, twice weekly. Follow-up included MRI and clinical examination every 2 months. *Results* Median survival time after SRS was 8.5 months, compared to 7.4 months after FSRT ($P = 0.81$). Of 26 patients treated with SRS, radiographic tumor response or stable disease was observed in eight (35%) patients and tumor progression was seen in 18 (65%) patients. Of 10 patients treated by FSRT, radiographic tumor response or stable disease was observed in four (40%) patients and tumor progression was observed in four (40%) patients (two lost to follow-up). Patients who responded to treatment had statistically improved survival compared to non-responders, with median survival of 15.8 vs. 7.3 months ($P < 0.05$). *Conclusion* Salvage reirradiation with SRS or FSRT for recurrent GBM results in radiographic response in a proportion of patients. Survival was significantly improved among patients who

either responded or had stable disease after salvage reirradiation, compared to non-responders. Further study is warranted to investigate the method and time of reirradiation for recurrent GBM.

Keywords Glioblastoma · Recurrence · Radiotherapy · Reirradiation · Radiosurgery

Introduction

Standard treatment of glioblastoma (GBM) consists of surgical resection followed by adjuvant treatment using radiotherapy and chemotherapy. With the recent advancement in treatment, tumor control and survival have improved significantly with the use of temozolomide and radiation therapy [1]. Despite improvement in combined modality treatment, nearly all patients develop tumor recurrence at the site of primary tumor where maximum surgical resection and high dose radiation therapy was delivered [2–4]. This poses a challenge for further treatment of recurrent disease. While surgical resection can reduce the tumor burden, only a subset of patients with recurrent GBM may be surgically resectable. In addition, the infiltrative nature of disease, which requires a more aggressive resection, increases the probability of surgery-related side effects [5].

Various second line chemotherapy regimens and targeted agents have also been utilized with limited success. Recent use of bevacizumab and irinotecan have demonstrated efficacy in delaying tumor recurrence, and thus have been widely used as the second line therapy for recurrent GBM [6, 7]. However, tumor progression and failure inevitably occurs in the primary disease site or vicinity. Conventional fractionated radiation therapy using 3-dimensional or intensity-modulated radiation technology, either alone or combined

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with chemotherapy is limited due to the relatively low dose of radiation and associated long term neurotoxicity [8]. Radiosurgical techniques, however, utilize image guidance and improved immobilization thus allowing smaller target volumes, reducing the dose to normal brain tissue [9]. Reirradiation can be useful for well-localized recurrent tumors enabling delivery of a high dose of radiation with potential to achieve local tumor control.

The experience of reirradiation with radiosurgery for recurrent GBM is limited. At our institution, we have performed Single Fraction reirradiation (SRS) and Fractionated Stereotactic Radiation Therapy (FSRT) in selected patients with relatively well defined recurrent tumors as visualized on imaging studies. In this study we report the results of radiographic response and overall survival in patients with recurrent GBM treated using SRS or FSRT.

Materials and methods

Patients

The Henry Ford stereotactic radiosurgery database was reviewed for patients treated for recurrent GBM identified on neuroimaging between March 2001 and August 2006. A total of 51 patients were treated with either SRS or FSRT. We excluded 15 patients due to incomplete medical information, loss to follow up, or receipt of palliative fractionated conventional radiotherapy. We analyzed data from the remaining 36 patients who were treated with SRS or FSRT to the contrast enhancing tumor seen on the MRI. Of these 36 patients, 26 (72%) were treated with SRS and 10 (28%) were treated with FSRT. The medical record was reviewed to obtain patient Karnofsky Performance Score (KPS), age at diagnosis, and location of tumor at recurrence. Pathology slides of patients whose initial tumor resection occurred at an outside institution were reviewed and confirmed by the neuropathologist at our institution.

All patients were initially treated with a combination of surgery, chemotherapy and radiation therapy. Patients who underwent definitive treatment within the Henry Ford Health System were followed with clinical examination and neuroimaging studies every 2 months. Patient findings were reviewed at the multidisciplinary brain tumor board. Treatment of recurrence included judicious use of surgery, chemotherapy and radiation. In particular, patients were considered for various phase I trials through New Approaches to Brain Tumor Therapy (NABTT) [10]. Whenever possible, surgical resection was attempted to reduce tumor burden at recurrence. All patients received chemotherapy either prior to or after salvage radiation therapy. However, no chemotherapy was given concurrent with salvage SRS or FSRT.

Frame-less image-guided SRS/FSRT

Immobilization was achieved using thermoplastic mask. Simulation CT (Phillips, Cleveland, OH) with intravenous contrast was obtained with 2–3 mm slice thickness. Stereotactic localization box and ExacTrac image guidance system (BrainLab Inc, Heimstetten, Germany) were used to associate the treatment isocenter with the stereotactic coordinator system determined by the fiducial lines. The isocenter position was defined for each patient. The simulation CT images were transferred to a dedicated treatment planning computer system (Brain Scan 5.3). Both T1 (with gadolinium) and T2 FLAIR MRI images were fused with the simulation CT images using an automatic fusion algorithm. The reirradiation target volume for radiosurgery was defined as the gadolinium contrast-enhancing tumor shown on T1 weighted MRI. These tumors were treated with SRS to a median dose of 18 Gy (range: 12–20 Gy). The size of the target volume and the location of the lesion along with the proximity to critical structures were taken into account to determine SRS versus FSRT treatment. Critical normal tissues were contoured including the optic chiasm, optic nerves, fornix, and brainstem. When there was a rapid increase in FLAIR imaging signal, this was also taken into consideration and patients were treated with FSRT. The area of FLAIR signal change was not included in the radiosurgery target volume. Stereotactic treatment planning was achieved by using either five dynamic conformal arcs or six to nine intensity-modulated non-coplanar beams to minimize dose to critical organs [11].

Radiation dose was prescribed to the 90% isodose line. The prescribed dose for reirradiation was chosen with respect to prior radiation volume, total dose, and interval between treatments. The prescribed reirradiation dose was evaluated in relation to the final radiation isodose distribution. Once all the requirements were met, the patient was brought to the treatment room.

The patient was first positioned using the thermoplastic mask based stereotactic localization box. The ExacTrac image guidance system was used to finally adjust the patient position [12]. The ExacTrac system used a six degree of freedom image fusion algorithm to automatically register the simulation CT images through various digitally reconstructed radiographs to the set of stereoscopic images obtained on the treatment table. Before delivery of radiation treatment, orthogonal portal films were obtained for final position verification as part of the patient-specific quality assurance program of the irradiation treatment. Patients were maintained on steroids prior to treatment and slowly tapered thereafter.

Statistics

The primary endpoint was median survival after salvage radiation therapy, which was measured from the completion day of SRS or FSRT to death. Patient medical records and the Social Security Death Index were used to assess vital status during the follow-up period. A secondary endpoint was imaging progression on MRI as defined by the neuroradiologist. In cases where tumor progression versus necrosis was equivocal, MR spectroscopy and perfusion CT were obtained to aid in differentiating the MRI findings. Univariate and multivariate analysis were used to examine relationships of variables such as age, KPS, tumor volume, extent of resection, and SRS or FSRT with survival. Survival functions were estimated using the Kaplan–Meier method. Log-rank tests were used to assess the statistical significance of differences in survival between groups. All patients had at least 6 months of follow-up. For survival analysis purposes, death was considered an event, and patients who were alive at the end of the follow-up period were censored. Statistical analyses were performed using SAS version 9.0 (SAS Institute, Inc., Cary, NC).

Results

Patient and treatment characteristics at initial diagnosis

There were a total of 36 patients with 22 males and 14 females. Thirty-one patients (86%) had biopsy-proven GBM at initial diagnosis. The remaining five patients (14%) had biopsy proven malignant transformation from the initial diagnoses of anaplastic astrocytoma ($n = 1$), anaplastic oligodendroglioma ($n = 2$), and low grade glioma ($n = 2$). The median age of patients initially diagnosed with GBM was 57 years (range: 25–70). Among those patients who had a malignant transformation, the median age at diagnosis was 39 years (range: 29–68). Initial treatment included surgical resection and radiotherapy. Gross total resection was performed in 12 patients (33%), subtotal resection in 22 (61%), and biopsy in 2 (6%). All patients received adjuvant radiotherapy (50–60 Gy). Chemotherapy was given to 33 patients. The most common regimens included: temozolomide; carmustine; oxaliplatin; irinotecan; and procarbazine, lomustine, and vincristine (PCV). The most common site of recurrence was in the temporal lobe and corpus callosum.

Patient and treatment characteristics at recurrence

The median interval between primary radiation therapy and recurrence was 13.6 months (range: 0.8–119). In the SRS group, the time from primary radiation to reirradiation was 12.5 months (range: 0.77–119), compared to 14.9 months

(range: 3.7–31.2) in the FSRT group. The patient characteristics at the time of recurrence are summarized in Table 1. For the treatment of recurrent tumor, gross total resection was performed in three patients (8%), subtotal resection in 14 (39%), and biopsy in 1 (3%) and no surgical procedure was performed in the remaining 18 patients (50%). The reirradiation target volume was the most important factor determining whether patients received SRS ($n = 26$) or FSRT ($n = 10$). The median target volumes were 10.4 ml (0.3–60.1) in the SRS group versus 51.1 ml (16.1–123) in the FSRT group ($P < 0.01$). There was no difference in survival based on tumor volume ($P = 0.47$).

While chemotherapy was not given concurrently during SRS or FSRT, all patients were subsequently treated with various agents such as irinotecan, erlotinib, bevacizumab, carmustine, lomustine, and temozolomide.

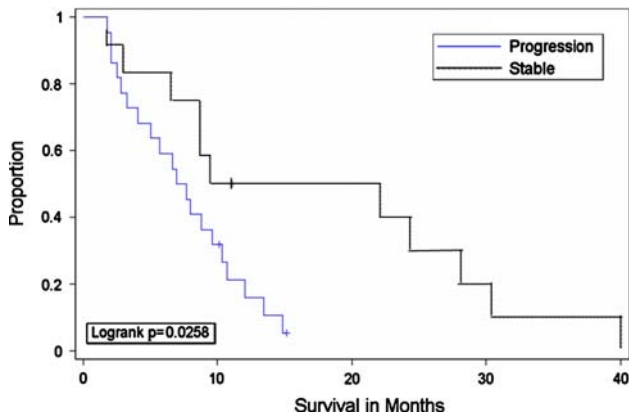
Radiographic tumor response, including stable appearance, was seen in 12 patients (33%), whereas 22 patients (61%) had imaging progression. The response was unknown in two patients (6%). Tumor control was seen in 31% of patients in the SRS group and 50% in the FSRT group (Table 2). There was no statistical difference between response in either FSRT or SRS group ($P = 0.29$). However, the tumor response was an important factor determining the

Table 1 Patient and treatment characteristics at recurrence

Characteristic	SRS ($n = 26$)	FSRT ($n = 10$)
Interval between primary radiation therapy and reirradiation (months)		
Median	12.5	14.9
Range	(0.8–119)	(3.7–31.2)
Age		
Median	53	44
Range	(25–70)	(28–60)
Karnofsky performance score		
Median	80	90
Range	(50–100)	(70–90)
Site of recurrence		
Frontal	4 (15%)	2 (20%)
Parietal	2 (8%)	2 (20%)
Temporal	10 (38%)	3 (30%)
Occipital	3 (12%)	0 (0%)
Corpus callosum	6 (23%)	3 (30%)
Cerebellum	1 (4%)	0 (0%)
Tumor volume (ml)		
Median	10.4	51.1
Range	0.3–60.1	16.1–123.3
Extent of resection		
Biopsy only	0 (0%)	1 (10%)
Subtotal resection	10 (38%)	4 (40%)
Total resection	1 (4%)	2 (20%)

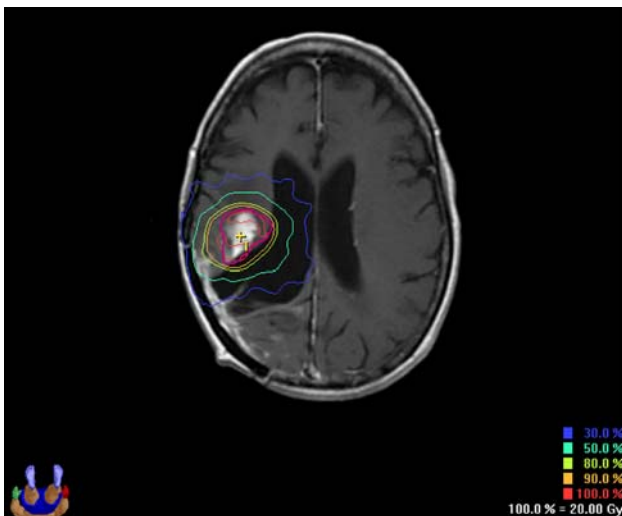
Table 2 Imaging response and survival after SRS/FSRT

Characteristic	SRS	FSRT	<i>P</i> value
Median survival (months)			
From diagnosis	24.4	24.1	0.47
From salvage	8.4	7.5	0.42
Imaging response			
Response or stable disease	8 (31%)	4 (50%)	0.29
Progression	18 (69%)	4 (50%)	0.20

**Fig. 1** Survival in patients with imaging response versus progression

survival after reirradiation. The median survival of responders was 15.8 months, compared to 7.3 months in non-responders ($P < 0.05$). This is illustrated in Fig. 1.

In general, patients tolerated treatment well with limited toxicity. Two patients in the SRS group at imaging

**Image 1** 57-year-old patient with recurrent glioblastoma of the right temporal lobe anterior to the surgical resection cavity. The targeted volume was 12.3 ml. The patient was treated with SRS to a dose of 18 Gy prescribed to the 90% isodose line**Image 2** 44-year-old patient with recurrent glioblastoma of the right temporal lobe. The targeted volume was 123.3 ml. The patient was treated with FSRT to a dose of 36 Gy in six fractions prescribed to the 90% isodose line due to the large tumor volume and close proximity of critical structures

progression were found to have necrosis at the time of resection. One patient underwent subtotal resection 3 months after salvage SRS and another had biopsy 2 months after treatment. The final pathology revealed mixed tumor and necrosis. In the second patient who underwent biopsy, only necrosis was visualized in the specimen. In the FSRT group, one patient's biopsy specimen revealed mixed residual tumor and necrosis 11 months after salvage treatment.

The median overall survival from the initial diagnosis in the SRS group was 24.4 months compared to the median survival of 24.1 months in the FSRT group ($P = 0.47$). The median survival after salvage SRS was 8.4 months, and that of FSRT was 7.4 months ($P = 0.42$).

Discussion

The salient finding of this study is that survival was significantly improved among patients who either responded or had stable disease after salvage reirradiation. Radiographic tumor response to SRS and FSRT by MRI was a useful predictor of clinical course. Our finding of inferior survival in treatment non-responders is similar to the results of RTOG 90-06 which reported poorer survival in those with imaging progression. They found no difference in survival amongst patients who had stable disease, partial response or complete response [13]. Other investigators have also demonstrated that imaging after treatment is predictive of clinical outcome [14]. Although MRI is the most reliable radiographic investigation at follow-up, evaluation is not always straightforward. Due to the development of changes from

radiation treatment, it often becomes difficult to distinguish true tumor progression from radiation effect. This has been defined as pseudoprogression by other investigators [15]. This effect is particularly evident when radiation is combined with temozolomide. The imaging change is presumably caused by radiation-induced injury leading to vasodilation, disruption of the blood brain barrier and edema [16]. We have used more sophisticated imaging modalities with MRS and/or CT perfusion to distinguish tumor (as increased blood flow and blush) and necrosis (no perfusion). This appears to be a useful imaging tool in addition to MRI. However, these techniques are plagued with difficulties in reproducibility and results which can be altered with the use of steroids [17, 18]. In our study, there were three cases of biopsy confirmed radiation necrosis seen after MRI and perfusion computed tomographic (PCT) imaging with decrease in cerebral blood volume. All these patients had pathologic evidence of necrosis, while two of the three also had viable tumor cells in the specimen. In general, while there were three cases of necrosis, radiation toxicity was not a common event in this study.

Radiosurgery has been utilized as part of the initial treatment for patients diagnosed with GBM. In a retrospective review by Nwokedi et al., median EBRT dose was 59.7 Gy (range: 28–70.2) and the median gamma knife SRS boost dose was 17.1 Gy (range: 10–28 Gy). There was a statistically significant median overall survival benefit of 13 months in the external beam radiation therapy only group versus 25 months in the external beam plus SRS group [19]. Buatti et al. report on six patients with GBM and five patients with anaplastic astrocytoma with a median tumor volume of 14 ml. Patients were treated with external beam radiation to a dose of 60 Gy, although most received treatment with a twice-daily schedule followed by Linac based SRS to a median dose of 12.5 Gy. Despite rigorous selection and aggressive stereotactic boost irradiation, median actuarial survival was only 17 months [20].

In a prospective trial of radiosurgery for patients with GBM, the RTOG 93-05 study randomized patients to SRS followed by external beam radiation therapy (EBRT) with Carmustine (BCNU) versus patients who received EBRT plus Carmustine alone. There was no survival benefit with the addition of the upfront SRS treatment. The interval between SRS and EBRT was less than 1 week [21]. Due to the lack of survival benefit and tumor progression at the treated site, reirradiation has been largely abandoned even in the salvage treatment setting.

In another study by Kondziolka et al. during an 8 year interval, the survival benefit of gamma-knife SRS performed in 64 patients with GBM and 43 patients with anaplastic astrocytoma was reviewed. Adjuvant radiosurgery was performed before disease progression or for recurrent tumor at the time of disease progression. Of the

entire series, the median survival of patients with GBM was 26 months. In comparison to historical controls there was an improved survival benefit after radiosurgery for patients with GBM. However, the mean tumor volume treated in this study was 6.5 ml (range: 0.88–31.2). In fact, the authors state that there may have been a benefit in terms of patient selection with treated patients having smaller tumor volumes [22]. The median tumor volume in our FSRT treated group was 51.1 ml with a similar median survival.

Chemotherapy has been widely used as second line therapy for recurrent tumor. Many different chemotherapeutic agents have been tested. More recently, bevacizumab and irinotecan have shown promising results in delaying tumor progression [6, 7]. However, patients who fail second line therapy with bevacizumab and irinotecan have limited options. Although radiation is an active treatment modality of gliomas, reirradiation with full dose is not always feasible. In the recurrent setting a prolonged time interval between initial treatment and reirradiation, may serve to enable repair of tissue. Delaying reirradiation to the third-line may serve to increase the interval between initial radiation therapy and salvage therapy providing a safer treatment alternative.

A benefit of treatment with stereotactic reirradiation (SRS) is the increased conformality of treatment which can spare previously irradiated tissue thus limiting toxicity. This enables the escalation of dose to potentially achieve local tumor control. In our study, selection of the reirradiation dose was based on radiobiologic principles coupled with clinical outcomes and experience. Biologically equivalent doses (BED_{10}) for tumors in our study are 42 and 50 Gy for 16 and 18 Gy SRS, respectively. The BED_{10} is 58 Gy for the FSRT dose/fractionation of 36 Gy in six fractions. Although one of the limitations of using the BED formulation is the lack of experimental validity for large doses per fraction and short overall treatment time, it currently serves as a useful model for biological comparison of different fractionations. Retreatment with various regimens including 20–50 Gy in 5 Gy fractions [23] or 20–30 Gy in 4–10 Gy fractions [24] has demonstrated a total dose greater than 40 Gy as a possible predictor of radiation damage.

Performance status, relevant debulking, and local recurrence without multifocality determine whether a patient may benefit from surgical resection. Approximately, one quarter of patients with GBM develop a type of recurrence which enables repeated resection [25]. Therefore, in most instances where surgical resection is not possible, reirradiation and chemotherapy may provide a benefit. The majority of patients in our study received chemotherapy during the course of their recurrent disease. In a study by Lederman et al., patients were treated with a

median dose of 24 Gy (range: 18–36 Gy) in four weekly fractions with concurrent paclitaxel [26]. Volume was described as an important factor in predicting survival. The study reported that patients with tumor volumes greater than 30 cubic centimeters experienced a survival of 5.7 vs. 9.4 months for volumes less than 30 cc. In our study, volume was not a factor which predicted survival, but patients with larger volumes underwent FSRT.

More recently, targeted agents combined with hypofractionated radiation therapy are being studied in the treatment of recurrent tumors. A phase I dose escalation trial of FSRT with gefitinib in 15 patients with recurrent gliomas demonstrated that a dose of 36 Gy in three fractions is well tolerated with a daily dose of 250 mg of gefitinib [27]. Thus, combined modality efforts to improve tumor response may be promising. Our patients were not treated concurrently with reirradiation and chemotherapy. Since reirradiation targets only the area of abnormal enhancing tumor or of rapidly progressing radiographic changes, we believe it can maximize the therapeutic ratio with sequential chemotherapy to prevent tumor progression. With this rationale, we are planning a clinical trial to establish a treatment scheme of reirradiation with sequential chemotherapy as a third-line therapy for recurrent/progressive GBM. In addition, clinical improvement and prolonged time to functional decline were seen in this retrospective study population; however these were not systematically captured.

As with all retrospective studies, one limitation of this study is selection bias. A select group of patients with recurrent glioblastoma are candidates for salvage radiosurgery. While the addition of FSRT was introduced as a means to treat patients who may not have been candidates for radiosurgery due to prohibitively large target volumes and suboptimal tumor locations, there are many patients who face recurrent glioblastoma without the possible benefit of reirradiation.

In general, patients who have a higher performance status tend to receive more aggressive forms of treatment. In our study the use of chemotherapy and surgery before and after salvage radiation therapy were not controlled for. Albeit, there was no statistical difference in the SRS versus FSRT groups related to therapies following reirradiation. Patients who were followed more closely tended to have a higher performance status as they were able to return for their follow-up appointments and obtain the necessary imaging and clinical evaluation. We intend to formalize a prospective trial where performance measures and quality of life outcomes can be captured. While, selection bias will continue to be an issue for studies of patients with glioblastoma, a prospective trial with strict eligibility criteria and formal indications for systemic therapy and surgical resection may serve to improve upon the quality of research in this area.

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