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Re-irradiation with Radiosurgery for Recurrent Glioblastoma Multiforme

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Local tumor control remains a significant challenge in patients with glioblastoma multiforme (GBM). Despite aggressive radiation therapy approaches, most recurrences are within the high-dose field, limiting the ability to safely re-irradiate recurrence using conventional techniques. Fractionated stereotactic radiosurgery (fSRS) is a technique whose properties make it useful for re-irradiation. We retrospectively reviewed the charts of 14 patients with recurrent GBM treated with salvage radiosurgery. Seven patients were male and seven were female with a median age of 58 (range: 39-76). All patients had prior cranial radiation therapy to a median dose of 60 Gy (58-69). There were 18 lesions treated with a median tumor volume of 6.97 cm^3 (0.54-50.0 cm^3). fSRS was delivered in 1-3 fractions to a median dose of 24 Gy (18-30 Gy). Median follow-up for the cohort was 8 months (3-22 months). On follow-up MRI, 8 of 18 lesions had a radiographic response. The median time-to-progression following primary irradiation was 8 months (1-28 months) while the median time-to-progression (TTP) following fSRS was 5 months (1-16 months). Median local control following re-irradiation was 5 months and actuarial local control was 21% at 1-year. Overall survival following primary irradiation was 79% at 12 months and 46% at 2 years. Overall survival following re-irradiation was 79% at 6 months and 30% at 1 year. No significant treatment-related toxicity was seen in follow-up. These results indicate that re-irradiation for recurrent GBM using fSRS is well-tolerated and can offer a benefit in terms of progression-free survival (PFS).

Key words: Glioblastoma; Primary Brain Tumors; Recurrence; Radiotherapy; Re-irradiation; Radiosurgery.

Background

Despite advances in surgery, radiation, and systemic therapy, local recurrence remains a significant problem in patients with glioblastoma multiforme (GBM). Initial therapy generally consists of surgery followed by fractionated radiation therapy and chemotherapy (1). Following standard treatment, almost all patients will suffer from recurrence which leads to progressive neurological deficits and eventual death. The majority of these recurrences will develop in the site of previous surgical resection and high dose radiation therapy (2-4). Re-operation is an appropriate treatment option in a small subset of patients; however, an increased risk of neurological morbidity often limits the resection of these infiltrative tumors (5). Second-line systemic therapy, including enrollment in clinical trials, is another option for patients with recurrent GBM, but historically confers only a minimal long-term benefit (6-10).

Re-irradiation with 3D conformal radiation therapy (3D CRT), and more recently, IMRT is often difficult and limited by the previous radiation dose delivered after initial surgery. Localized re-irradiation with brachytherapy has been shown to be efficacious, but is associated with significant morbidity and is limited to a

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small subset of patients that present with focal recurrence only (11). Radiosurgery allows for the delivery of a relatively high dose of radiation to a defined target volume with a rapid fall-off of dose—thereby sparing adjacent healthy and/or previously radiated brain tissue (12). The experience of radiosurgery for recurrent GBM is somewhat limited, but published results have shown it to be safe and effective in prolongation of survival (13-14). At our institution, carefully selected patients are offered SRS or fractionated stereotactic radiosurgery (fSRS) for recurrent GBM. This study reports the results observed in that group of patients.

Materials and Methods

A retrospective review of all GBM patients treated with stereotactic radiosurgery (SRS) or fractionated stereotactic radiosurgery (fSRS) between March 2003 and March 2010 was completed at the University of Pittsburgh Cancer Institute. A total of 14 patients with18 lesions were identified. Detailed patient characteristics can be found in Table I. Seven patients were male and seven were female; the median age was 58 (range: 39-76). All patients had histologically confirmed GBM and had been treated with prior surgical resection, chemotherapy, and radiation to a median dose of 60 Gy using 1.8 Gy fractions (range: 60-69 Gy). Eleven of the 14 patients had gross total resection and three patients had partial resections at initial presentation. Based on the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA) for Glioblastoma Multiforme, 1 patient was RPA class III, 6 patients were RPA class IV and 6 patients were RPA class V (one patient's RPA classification could not be determined). At our institution, the majority of patients with recurrent GBM are placed on clinical trials involving systemic therapy. Patients suitable for re-irradiation with SRS or fSRS were selected by a multi-disciplinary committee consisting of a neurosurgeon, neuro-oncologist, and radiation oncologist. Median time-to-progression from completion of initial radiation was 8 months (range: 1-28 months), with progression defined as either radiographic tumor progression or death. Twelve of the 14 patients were on some form of systemic therapy around the time of re-irradiation, the majority of which was at least 2nd line chemotherapy. Four patients were on temozolomide, 3 patients were on CPT-11 and bevacizumab, 1 patient was on bevacizumab alone, 2 patients were on CPT-11 alone, 1 patient was on carboplatin and erlotinib, 1 patient was on carboplatin and bevacizumab and 1 patient was treated on protocol with NovoTTF-100A.

Table I
Patient characteristics.

Parameter	Number	Percentage
Number of Patients	14	
Male	7	50%
Female	7	50%
Age at recurrence		
Median (range)	58 years (39-76)	
Number of recurrent lesions	18	
Recurrence pattern		
Solitary	12	86%
Multifocal	2	14%
In field	13	72%
Time from treatment to recurrence		
Median (range)	8 months (1-28)	
Prior RT Dose		
Median (range)	60 Gy (58-69)	
Prior Surgery		
Complete initial resection	11	79%
Partial initial resection	3	21%
Salvage for recurrence	3	21%
Patients on salvage chemotherapy	12	86%
RPA Classification		
Class III	1	7%
Class IV	6	43%
Class V	6	43%
NR	1	7%

SRS and fSRS were delivered with the Cyberknife (Accuray, Sunnyvale, CA) using 6 MV photons. Fractionated treatment was delivered every other day. Head CT (contrast and non-contrast) and gadolinium-enhanced MRI of the brain with 1.5mm thickness slices were acquired and transferred to the treatment planning system (Multiplan™, Accuray, Sunnyvale, CA). The images were then fused for treatment planning. The target volume was defined as the gadolinium contrast-enhancing tumor shown on the spoiled gradient (SPGR) MRI series. The isodose line best encompassing the tumor was used for treatment (Figure 1). The size and location of the tumor were primarily used to determine whether to use SRS or fSRS, while age, performance status and prior treatment history were additional factors. Critical structures that were contoured included the optic nerves, optic chiasm, and brainstem. Patients were immobilized using a lightweight thermoplastic mask, aligned to the pre-operative CT scan, and tracked with intra-operative imaging.

Following re-irradiation, patients were seen for follow up at 1-2 month intervals. At each follow-up, a thorough history and neurological exam were performed and a gadolinium-enhanced MRI of the brain was obtained. Primary endpoints for analysis were overall and progression-free survival (PFS). Overall survival was calculated from the time of completing initial fractionated radiation therapy and from subsequent SRS re-irradiation. Progression-free survival was calculated from the time of re-irradiation until documented tumor progression or death. Secondary endpoints included any documented treatment-related toxicity and radiological response seen on follow up MRI. Survival functions were estimated using the Kaplan–Meier method. All statistical analysis was carried out using SPSS, version 15.0 (SPSS, Chicago, IL).

Table II
Tumor and treatment characteristics.

Characteristic	Number	Percentage
Median follow up (range)		
From initial diagnosis	13 months (5-30)	
From re-irradiation	8 months (3-22)	
Tumor Volume (GTV)		
Median (range)	6.97 cc (0.54-50)	
Treated with single fx	1.65 cc (0.54-7)	
Treated with multi fx	9.20 cc (0.98-50)	
SRS Dose		
Median (range)	24 Gy (18-30)	
Single fraction	21 Gy (19-24)	
Two fractions	22 Gy (20-24)	
Three fractions	27 Gy (18-30)	
Number of lesions receiving SRS fraction and total dose		
Single fraction	6	33%
Two fractions	2	11%
Three fractions	10	56%

Results

Detailed tumor and treatment characteristics can be found in Table II. Median follow-up from time of initial treatment was 13 months (range: 5-30 months). The median follow-up after re-irradiation with SRS or fSRS was 8 months (range: 3-22 months). Six of the 18 lesions were treated with single fraction SRS and 12 of the lesions were treated with fSRS using 2-3 fractions. Twelve patients had single volumes treated, while 2 patients had multiple areas treated. Three patients had re-irradiation in combination with reoperation (one in the pre-operative setting and two patients post-operatively). Treatment was well-tolerated by all patients. There were no documented acute or late toxicities related to re-irradiation.

The median tumor volume for all lesions was 6.97 cm^3 (range: 0.54-50.0 cm^3). For lesions treated with a single fraction, the median volume was 1.65 cm^3 (0.54-7.7 cm^3) and for lesions treated with 2-3 fractions the median volume was 9.2 cm^3 (range: 1.7-50 cm^3). Lesions that were treated using SRS had a median dose of 21 Gy prescribed to the 80% isodose line (range: 19-24 Gy). For lesions treated with fSRS (2-3 fractions), the median dose was 27 Gy prescribed to the 80% isodose line (18-30 Gy). The median coverage of the planning target volume (PTV) by the prescribed dose was 97% (range: 77-100%).

Thirteen of the 14 patients had documented progression at time of analysis. Eleven of the recurrences were in the field of radiosurgery. Nine of the 14 patients had died from progression of disease and the remaining 5 were alive at the time of analysis. Median overall survival from time of initial treatment was 21 months, while median overall survival from re-irradiation was 10 months. The overall survival rate at 1 year was 79% and 46% at 2 years (Figure 2). After re-irradiation, there was an overall survival rate of 79% at 6 months and 30% at 1 year (Figure 3). Median time-to-progression (TTP)

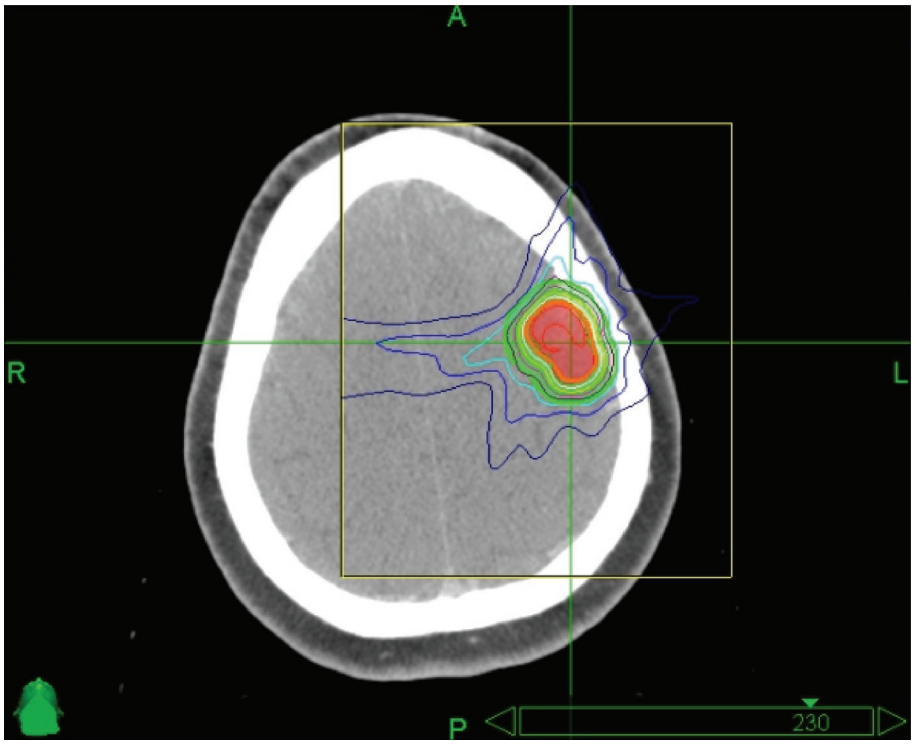

Figure 1: 39-year-old women with recurrent glioblastoma of the left frontal lobe. The targeted volume was 2.6 ml. The patient was treated with SRS to a dose of 19 Gy prescribed to the 80% isodose line.

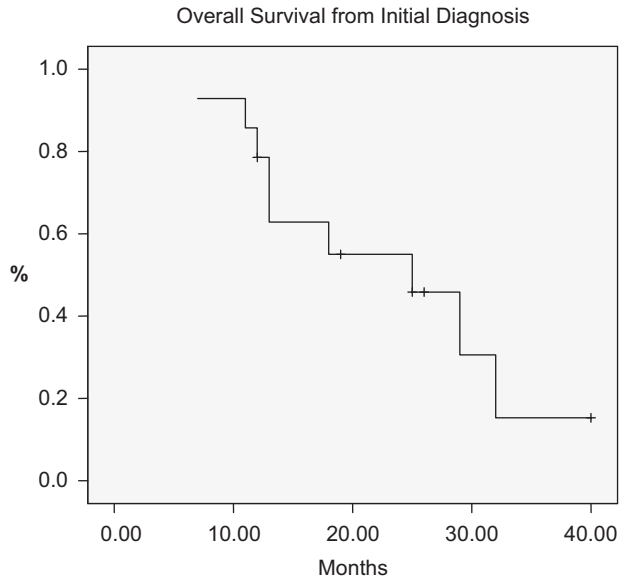

Figure 2: Overall survival since primary treatment (median overall survival of, overall survival of 79% and 46% at 1 and 2 years, respectively).

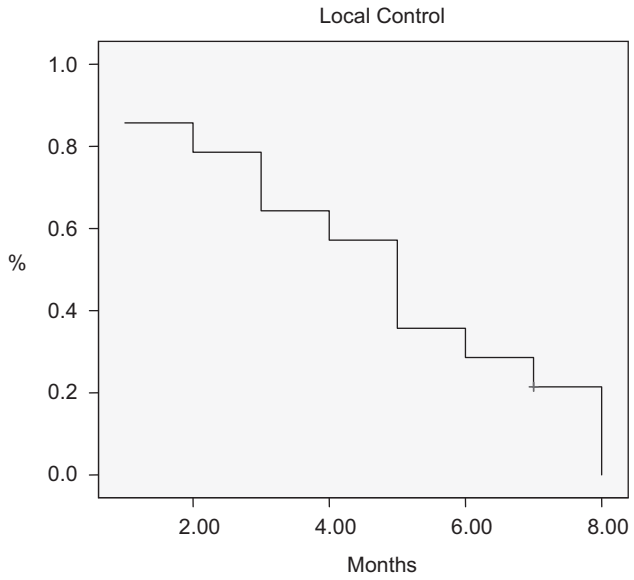

Figure 4: Local control from time of re-irradiation with SRS or fSRS (median local control of 5 months, 21% local control at 1 year).

following re-irradiation was 5 months (range: 1-16 months), with 1 patient showing no sign of progression at the time of analysis. Median local control was 5 months, with a 21% local control rate at one year (Figure 4).

Follow-up MRI was available for review in all patients. In 7 patients (50%), there was a radiographic response in the treated area (2 with stable disease and 5 with partial response) following re-irradiation. The remaining patients never had any response in their disease on MRI. In patients with a response on MRI, the median time-to-progression from re-irradiation was 5 months (range: 3-8 months) but was 3 months (range: 1-8 months) for those with no response or progressive disease. Patients with an RPA classification of IV had a median TTP and overall survival from SRS of 6 and 9 months, respectively. Patients with an RPA classification of V had a median TTP and overall survival from SRS of 4.5 and 5 months, respectively. There were no significant associations of tumor size, dose or fractionation on TTP and overall survival.

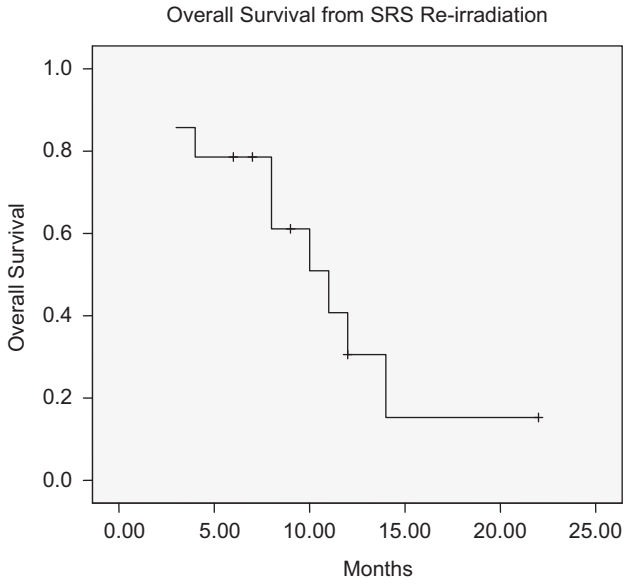

Figure 3: Overall survival from time of re-irradiation with SRS or fSRS (median overall survival of 10 months, overall survival of 30% at 1 year).

Discussion

The treatment of patients with GBM remains a significant challenge, given the high likelihood of local recurrence. Treatment options are often limited due to prior surgical resection and previous radiation. Active treatment is encouraged, as a benefit in progression free and overall survival has been shown (15).

The indications for surgical resection in the setting of recurrence are not well established. Total resection is often not possible and surgical morbidity is common due to the infiltrative nature of GBM. Select patients have been shown to benefit from reoperation. These patients generally have a good performance status, young age, and longer interval since original treatment (5, 16-18). The recursive partitioning analysis (RPA) class similarly helps predict survival in GBM patients and is based on age, tumor location, performance status, and extent of resection (19). Following re-resection, median survival has been shown to range from 3-9 months (5, 16-18). Second-line systemic therapy or enrollment on a

clinical trial is often the chosen treatment for patients with recurrent GBM. The efficacy of bevacizumab for treatment of recurrent GBM was displayed in an abstract presented at the American Society of Clinical Oncology (ASCO) meeting in 2008. This phase II trial showed a 38% response rate and 9-month overall survival with the use of bevacizumab and irinotecan (20).

Re-irradiation using conventional treatment techniques is typically not possible for patients with recurrent GBM due to the high probability of treatment-related side effects. Brachytherapy has been used for re-irradiation in patients with recurrent GBM with moderate success. The largest series in the literature showed a median survival of 49 weeks from time of iodine-125 implant in patients with GBM. The treatment was well-tolerated with only 6% of patients having severe acute toxicity. Long-term, however, 40% of the patients required reoperation for radiation necrosis (21). SRS is a minimally-invasive technique by which highly conformal doses of radiation can be delivered. A German study examined the outcomes of Fractionated Stereotactic Radiation Therapy (FSRT) for recurrent GBM in 59 patients. The median dose delivered was 36 Gy in a median fractionation of 5×2 Gy/week. The authors showed a median overall survival of 8 months and a median progression-free survival of 5 months following re-irradiation (22). Kong *et al*. examined outcomes in 65 patients with recurrent GBM treated with the Gamma Knife using a median dose of 16 Gy prescribed to the 50% isodose line. Median progression-free survival in this group of patients was 4.6 months and overall survival from time of diagnosis was 23 months. The patients who derived the most benefit were those with smaller tumors (<10mL) (23).

A study conducted at the Henry Ford Health System reported outcomes and radiographic response in 36 patients with recurrent GBM treated with FSRT or SRS. Twenty-six of the patients were treated with SRS to a median dose of 18 Gy and 10 were treated with FSRT with a dose of 36 Gy in six fractions, twice weekly. Median overall survival from time of diagnosis and SRS were approximately 24 months and 8 months, respectively. A response or stable disease was seen on MRI in 33% of the patients. This response correlated with an improved outcome; responders had a median survival of 15.8 months compared to 7.3 months in non-responders (14). The largest series of fractionated stereotactic radiation therapy for recurrent high-grade gliomas followed 147 patients treated to a median dose of 35 Gy in 3.5-Gy fractions. Median overall survival in this study was 11 months and was independent of re-operation or concomitant chemotherapy. Younger age, smaller GTV, and shorter time between diagnosis and recurrence were associated with improved survival (24). Consistent with other studies, FSRT was well tolerated and resulted in excellent responses even in patients with recurrences within 6 months after initial treatment.

A major criticism of re-irradiation is the potential for increased and cumulative late toxicity. Due to the propensity for GBM to recur in previously irradiated fields, the tolerance of normal brain tissue is a major limiting factor in balancing the re-irradiation dose necessary for tumor control and the potential for late morbidity. The Pulsed Reduced Dose Rate (PRDR) method is thought to minimize radiation-related toxicities for re-irradiation, including retreatment of loco-regional recurrence of glioblastoma. In a recent retrospective analysis of PRDR treatment plans compared to conventional treatment plans, it was found the homogeneity indexes were slightly poorer in the PRDR plan, while conformation indexes and normal tissue dose volumes were similar (25). In an analysis of late toxicity in studies utilizing re-irradiation of the brain, it was concluded that the total cumulative dose was the most important factor with regard to the development of radionecrosis, with a tendency to occur at a cumulative normalized total dose (NTD) greater than 100 Gy (12). This study found that SRS and FSRT allowed for higher doses without increasing the probability of normal brain necrosis compared to conventional methods. As the risk of late toxicity is volume dependent, conformal radiotherapy techniques have allowed for reductions in treatment volume while sparing more normal tissue and reducing the risk of late toxicity (26). Re-irradiation, especially with today's modern conformal techniques, is thus a feasible option for palliative therapy of GBM while limiting the potential for late toxicity.

Our results are similar to the outcomes discussed above. The main deciding factors in choosing the dose and number of fractions were tumor volume and location, however patient age, performance status and prior treatment history were also considered. Maximum tolerated doses of single fraction radiosurgery have been previously defined in a population of primary brain tumor patients (27), thus larger tumors received fractionated treatment to avoid unacceptable CNS toxicity. The treatment was well-tolerated in all patients, with no documented acute toxicity. Patients did not require steroids or an increase in steroids (if previously prescribed) due to radiosurgery. Our patients had a median overall survival of 10 months following re-irradiation. We noted a similar response rate on MRI in our patient population (50%). However, there was no statistically significant difference in survival between the responders and non-responders. The limitations of this study, which could account for the minor differences seen, are its small sample size and retrospective nature. Patients included in this study demonstrated radiographic signs consistent with recurrence, but these lesions were not biopsied and could potentially represent radiation necroses. There is also likely a selection bias present, since patients who have a good performance status and small volume of recurrence are more likely to be selected for and benefit from re-irradiation with SRS or fSRS.

Conclusions

In summary, these results support the use of SRS and/or fSRS for recurrent GBM as an option in the management of these challenging patients. It appears to be a safe and effective way to provide a meaningful progression-free survival.

Conflict of Interest

None of the authors have any conflicts of interest to disclose.

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