Reirradiation with Proton Therapy for Recurrent Gliomas

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Abstract

Purpose: To evaluate the effectiveness and tolerance of reirradiation with proton therapy (PT) in patients with recurrent gliomas.

Patients and Methods: Between 2005 and 2012, 20 patients with recurrent gliomas were irradiated with proton therapy at the Indiana University Health Proton Therapy Center. Three had low-grade gliomas (LGGs, World Health Organization grade I/II), 4 had grade III, and 13 had glioblastoma (GBM, World Health Organization grade IV). The median time interval between initial radiation and reirradiation was 17.4, 62.8, and 15.3 months for LGG, grade III gliomas, and GBMs, respectively. The median dose delivered was 30, 59.4, and 54 Gy (RBE) for the low-grade, grade III, and grade IV tumors, respectively.

Results: The median follow-up time from reirradiation was 8.3 months (range, 1.4 to 25.3), and 30% of the patients were alive at time of follow-up evaluation. Only 1 patient with an LGG had died. Median overall survival (OS) from the time of the original pathologic diagnosis was 115.9 months and 20.4 months, respectively, for grade III gliomas and GBMs. Median survival from completion of reirradiation was 24.9 months for grade III gliomas and 7.8 months for GBMs. On univariate analysis, significant factors associated with OS from the original pathologic diagnosis included age at retreatment, interval between prior radiation and proton therapy, and extent of surgical resection. Grade and prior radiotherapy dose were borderline significant. Age was the only significant factor associated with OS from retreatment. Most patients tolerated reirradiation well; however, 2 patients experienced radiation necrosis. One was treated surgically and the other with steroids and hyperbaric oxygen therapy.

Conclusion: Proton reirradiation of recurrent gliomas was generally well tolerated and associated with favorable long-term survival in patients with LGGs and grade III gliomas. The 10% rate of radiation necrosis was modest given the high cumulative dose is these patients.

Keywords: proton beam therapy; retreatment; glioma, radiation necrosis, safety

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Introduction

Gliomas, the most common type of primary brain tumors in adults, have an incidence of 4 to 5 per 100,000 [1]. Despite advancements in surgery, medical therapy, and radiation therapy, the prognosis for persons with World Health Organization (WHO) grade III and IV gliomas remains poor, and there is a high rate of locally progressive disease [2]. The great majority of tumor recurrences are in previously irradiated tissue within or adjacent to the tumor bed [1, 3–5]. Maximum surgical resection followed by adjuvant radiation and/or

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Table 1. Patient characteristics.

	Grade before reirradiation		
	Low grade (WHO I/II)	**WHO III**	**WHO IV**
No. of patients	3	4	13
Median age (years)	19.1 (range 11.2 to 30.3)	34.3 (range, 27.3 to 49.4)	56.7 (range, 16.7 to 69.6)
Mean prior RT dose (Gy)	48 (range, 36 to 54)	59.6 (59.4 to 60)	59.4 (range, 54 to 60)
Median interval between RT (months)	17.4 (range, 13.6 to 91.1) Mean, 40.7	62.8 (range, 33 to 152.4)	15.3 (range, 5.3 to 152.6)
Initial surgery type	STR, 2; biopsy only, 1	STR, 3; unknown, 1	GTR, 8; STR, 5
Patients with re-resection between RT courses	0/3	3/4	6/13

Abbreviations: WHO, World Health Organization; RT, radiation therapy; STR, subtotal resection; GTR, gross total resection.

chemotherapy is the standard of care. Treatment for recurrent gliomas includes surgical resection and additional chemotherapy, whereas reirradiation has played a more limited role because of concerns for radionecrosis from the high cumulative dose of radiation. Prior reports have shown that radiosurgery can be safe and effective for small recurrences [6, 7], and hypofractionated stereotactic external beam radiation has been used for somewhat larger target volumes [4, 7–10]; overall survival (OS) after reirradiation is between 7 and 11 months [3, 7, 8, 10, 11]. Given the large cumulative dose, there have been reports of radionecrosis, and incidences vary from 0% to 20% with these techniques [3, 4, 8, 10, 11]; however, few studies have evaluated the safety and efficacy of proton therapy (PT) for recurrent gliomas.

Compared with photon therapy, PT has dosimetric advantages. The Bragg peak of protons causes the dose to fall off to almost zero distal to the target. In treatment of recurrent gliomas, PT can be applied using non-coplanar beams, including vertex beams, to minimize reirradiation of previously irradiated brain tissue; the advantage is that there is no exit dose beyond the target, which further reduces the volume of previously irradiated brain tissue receiving an additional dose.

Patients and Methods

Charts from 127 patients with gliomas treated with PT between 2005 and 2012 were reviewed after approval from the institutional review board. Of these patients, 20 had received prior radiation therapy and had in-field or marginal recurrences. Patient characteristics are outlined in **Table 1**. Because of the small number of patients, those with low-grade gliomas (LGGs; WHO grade I and II) were combined for analysis. Patients with primary brainstem gliomas were excluded from this study, and grade was classified based on the patient's most recent pathology report for all end points. The median age at retreatment was 19.1 years old (range, 11.2 to 30.3) for LGGs, 34.3 years old (range, 27.3 to 49.4) for grade III gliomas, and 56.7 years old (range, 16.7 to 73.3) for grade IV gliomas (glioblastomas [GBMs]).

All patients received neurosurgical intervention before primary radiation therapy. Three patients had LGGs, 4 had WHO grade III gliomas, and 13 had GBMs. The mean dose of prior radiation was 48 Gy (range, 36 to 54) in LGGs, compared with 59.6 Gy (range, 59.4 to 60) in grade III gliomas and 59.4 Gy (range, 54 to 60) in GBMs (**Table 2**). No patients with LGG had additional resection at time of recurrence, compared with 3 of 4 patients with LGGs and 6 of 13 patients with GBMs. Median interval time between last radiation treatment and reirradiation with proton therapy was 17.4 months (range, 13.6 to 91.1; mean, 40.7), 62.8 months (range, 33 to 152.4), and 15.3 months (range, 5.3 to 152.6) for LGGs, grade III gliomas, and GBMs, respectively. None of the patients with LGGs received concurrent or adjuvant chemotherapy for their recurrence compared with 75.0% and 61.5% of patients with LGGs and GBMs, respectively. Tumor recurrence was based on follow-up magnetic resonance imaging (MRI).

All patients were treated with fractionated proton therapy for their recurrence. Standard methods of immobilization were used to ensure accurate simulation and daily repositioning for treatment. Both computed tomography and MRI scans were used for three-dimensional treatment planning. The gross tumor volume was defined as the contrast-enhancing area on T1 weighted MRI, and a planning target volume (PTV) was defined as the gross tumor volume plus a margin designed to compensate for potential uncertainties in proton delivery and variability in patient setup. The median retreatment PTV was 130.0, 131.9, and 84.4 cm^3 for the LGGs, grade III gliomas, and GBMs, respectively.

Treatment planning was performed on either XiO, Elekta CMS (St. Louis, MO), version 4.2.2 or Eclipse, Varian Medical Systems (Palo Alto, CA), version 10.0.39; using one to four schemas, often with alternating daily beams and arrangements. Fields were chosen based on sparing organs at risk (brain stem, optic chiasm, temporal lobes) as well as trying to limit dose to

Table 2. Results.

	Grade before reirradiation		
	Low grade (WHO I/II)	**WHO III**	**WHO IV**
Median dose of PT (Gy [RBE])	54.0 (range, 10.8 to 59.4)	59.4 (range, 37.5 to 60.0)	54.0 (range, 30 to 60.0)
Median PTV (cm^3) of PT	130.0 (range, 71.6 to 190.1)	131.9 (range, 4.0 to 324.7)	84.4 (range, 4.8 to 691.2)
Patients receiving concurrent or adjuvant chemotherapy	1 (16.7%)	3 (30%)	7 (53.8%)
Median time to local progression (months)	N/A[a]	N/A[b]	5.3 (range, 0.5 to 21.9)
Median overall survival from original diagnosis (months)	N/A[a]	115.9	20.4
Median overall survival from reirradiation (months)	N/A[a]	10.2	8.2

Abbreviations: WHO, World Health Organization; PT, proton therapy; PTV, planned target volume; N/A, not applicable.
[a]1 patient from this group died; [b]insufficient data.

previously treated normal brain parenchyma. Beams were shaped with custom brass apertures, and dose depth was modulated with Lucite compensators. Median dose of reirradiation was 54 Gy (range, 30 to 59.4) for LGGs, 59.4 Gy (range, 37.5 to 60) for grade III tumors, and 54 Gy (range, 30 to 60) for GBMs. Chemotherapy was utilized in patients as determined by the patient's medical oncologist as outlined in **Table 3**.

Patients were followed with repeat MRIs after completion of proton therapy. MRI spectroscopy was also utilized if MRI could not determine progression versus radiation effect. The primary end point of this analysis was survival. Patients were categorized on the WHO grade of most recent pathology before reirradiation. One of the patients with a GBM had a prior diagnosis of a grade III glioma, and one of the patients with a grade III tumor was previously treated for an LGG. Overall survival was calculated from the primary pathologic tissue diagnosis, and survival from reirradiation was calculated from completion of proton therapy using the Kaplan-Meier estimator [12]. Statistical analysis was performed using MedCalc statistical software (MedCalc Software version 15.2, Ostend, Belgium). Influence of prognostic factors on survival was evaluated using the Cox proportional regression model [13]. Factors found to be significant on univariate analysis ($P < .05$) were then included in multivariate analysis.

Results

The median cumulative prescription dose from both initial and reirradiation courses was 84 Gy (range, 64.8 to 95.4) for LGGs, 101.4 Gy (range, 97.5 to 119.4) for grade III gliomas, and 108.2 Gy (range, 89.4 to 185.4) for GBMs. The PT was well tolerated by most patients. Acute toxicities included grade 1 or 2 alopecia, headaches, and skin erythema. In one patient being reirradiated for GBM, treatment was stopped because the patient wanted further neurosurgical intervention. At the time of analysis, all patients with grade III gliomas and GBMs had died of tumor progression. Of the three patients reirradiated for LGGs, one has died; and follow-up for the surviving patients was 66.0 and 9.7 months.

Table 3. Chemotherapy regimens.

	Low grade (WHO I/II)	**WHO III**	**WHO IV**
Chemotherapy with initial RT	2 or 3 - Unknown - Carboplatin/vincristine	3 of 4 - 2 concurrent TMZ followed by bevacizumab - PCV after RT	11 of 13 - All concurrent TMZ
Chemotherapy with reirradiation	None	3 of 4 - Bevacizumab alone - TMZ before RT - CCNU, TMZ, and bevacizumab	8 of 13 - Lenalidomide after PT - PCV after PT - Irinotecan plus Avastin after PT - Irinotecan plus Avastin after PT - 2 receiving concurrent TMZ then bevacizumab - Concurrent imatinib - Bevacizumab - Concurrent TMZ alone

Abbreviations: WHO, World Health Organization; RT, radiation therapy; TMZ, temozolomide; PCV, procarbazine, lomustine, vincristine; PT, proton therapy; CCNU, lomustine.

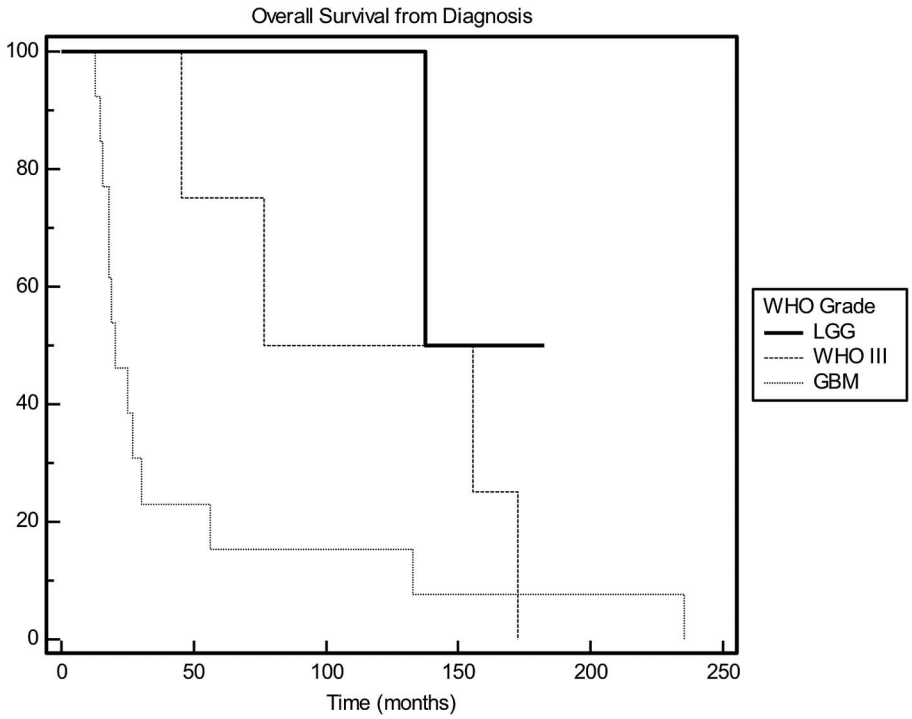

Figure 1. Overall survival (OS) from pathologic diagnosis based on World Health Organization grade of most recent pathology.

There were two cases of radiation necrosis in our cohort of 20 patients. One was a grade 1 radiation necrosis that was asymptomatic; diagnosed radiographically; and treated with steroids, hyperbaric oxygen therapy, vitamin E, and pentoxifylline. The second patient was diagnosed clinically and radiographically and treated with surgical resection, where pathology tests demonstrated radiation necrosis and persistent tumor. The cumulative total dose in the two patients who developed radiation necrosis was 89.4 and 118 Gy, and the interval between the two radiation courses was 8.5 and 63 months. The age in patients developing radiation necrosis was 27.3 and 58.4 years, and the histology differed in each patient; one patient had a GBM and the other an anaplastic (grade III) oligodendroglioma.

In patients with grade III gliomas, the median OS from the original pathologic diagnosis was 115.9 months, whereas median OS for GBM was 20.4 months (**Figure 1**). The median OS from the completion of reirradiation was 10.2 months for grade III gliomas and 8.2 months for GBMs (**Figure 2**). The median time to tumor progression after reirradiation was 5.26 months (range, 0.53 to 21.9) for GBMs. Although most patients with LGGs and grade III gliomas had follow-up imaging after reirradiation, a paucity of progression documented on imaging precluded evaluation of time to local progression for LGGs and grade III gliomas.

On univariate analysis, age at retreatment ($P = .0006$), dose of prior RT ($P = .035$), dose of reirradiation ($P = .014$), RT interval ($P = .014$), and whether the patient received a gross tumor resection at time of original surgery (compared to subtotal resection or biopsy; $P = .050$) were significant factors associated with OS from original pathologic diagnosis. Grade (GBM compared with LGG, $P = 0.0543$) was borderline significant. Other analyzed factors that were not significant in predicting OS from the original pathologic diagnosis on univariate analysis was the use of chemotherapy during the retreatment ($P = .14$), the PTV of the primary radiation treatment ($P = .706$), the PTV for the reirradiation ($P = .904$), and the total dose delivered ($P = .8661$). On multivariate analysis, the dose of prior RT was found to be significant in predicting OS from the original pathologic diagnosis ($P = .036$), while the interval between radiation courses was borderline significant ($P = .069$). Age ($P = .011$) was the only factor that remained significant in predicting OS from the completion of proton reirradiation on univariate analysis, with the interval between RT ($P = .079$), grade (GBM, $P = .0547$), and achieving a gross tumor resection ($P = .077$) being borderline significant.

Discussion

Local recurrence remains a significant problem in gliomas despite aggressive multimodal therapy [1]. Management of recurrent glioma is tailored to the particulars of the patient's case. Surgical re-resection is often preferred in patients whose

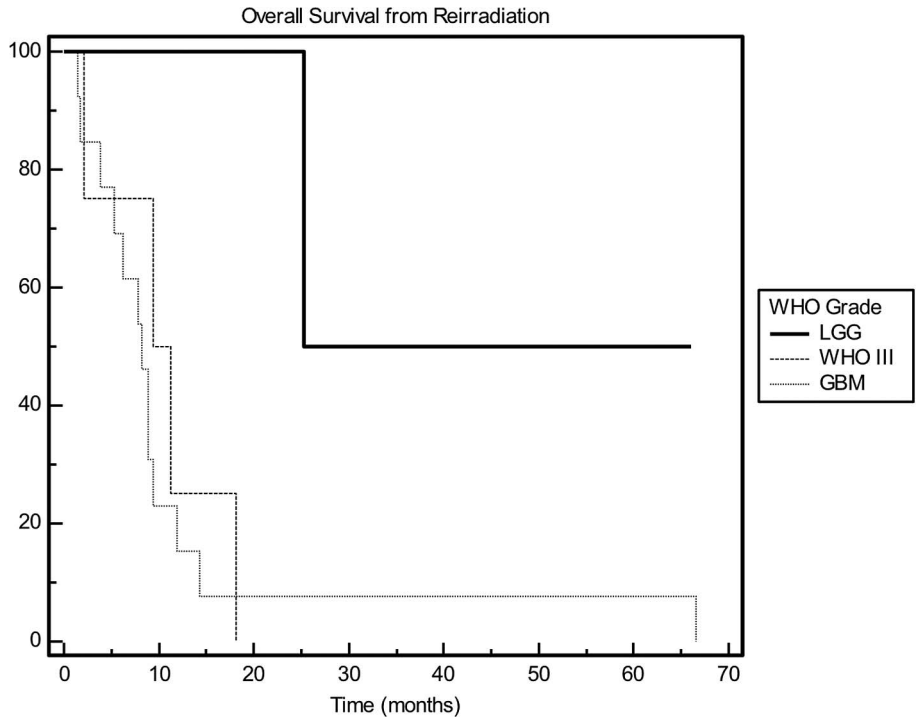

Figure 2. Overall survival (OS) from completion of reirradiation based on World Health Organization grade of most recent pathology.

performance status merits additional surgery and in whom the size and location of recurrence is amenable to resection. Unfortunately, complete resection may not be possible because of the infiltrative nature of glial tumors [9, 14]. One of the few randomized trials involving recurrent GBMs showed that adding carmustine polymers during resection significantly improved median survival compared with a placebo polymer [15].

Another option for salvage is systemic chemotherapy. Even though there have been advancements in chemotherapy agents in recent years, most studies have shown only minimal benefit of using chemotherapy for salvage in malignant gliomas [10, 15–20]. The targeted agent bevacizumab has been shown to prolong 6-month progression free and OS in phase II trials, and it is currently Food and Drug Administration approved for the treatment of recurrent GBMs [10, 21]. However, chemotherapy is not without toxicity. Hypertension and an increased risk of thromboembolic events have been associated with bevacizumab therapy, and the cost of maintenance therapy can be high [22, 23]. Reirradiation with photons is another therapeutic option for recurrent tumors.

Stereotactic radiosurgery (SRS) is an attractive option in patients with small recurrences as toxicity increases with the size of the treatment volume [7, 24, 25]. Fractionating the radiotherapy can minimize the toxicity of the additional radiation by taking advantage of the radiobiologic advantages observed in fractionation [3, 11]. Concurrent chemoradiation has become the standard of care for newly diagnosed high-grade gliomas, but its role in recurrent tumors is less understood. Fractionated stereotactic radiation therapy with temozolomide for recurrent high-grade gliomas is mostly well tolerated but has shown only modest survival benefits [9, 10, 26].

To date, no study has evaluated the efficacy and safety of fractionated proton therapy for recurrent gliomas. Protons have the advantage of having a Bragg peak that drops rapidly to almost zero distal to the target. This allows for the use of vertex beam angles,

Table 4. Analysis of prognostic factors on survival from diagnosis.

	Age at retreatment	Chemotherapy with retreatment	Prior PTV	Prior RT dose	PTV retreatment	Retreatment dose	RT interval	Extent of original surgery	Total dose	WHO grade
Univariate	0.0006	0.1408	0.7063	0.035	0.9041	0.0132	0.0138	STR, 0.2521; GTR, 0.050	0.8661	WHO III, 0.288; GBM, 0.0543
Multivariate	0.3116	-	-	0.036	-	0.2626	0.0694	-	-	GBM, 0.5890

Abbreviations: PTV, planned target volume; RT, radiation therapy; WHO, World Health Organization; STR, subtotal resection; GTR, gross tumor resection; GBM, glioblastoma.

Table 5. Analysis of prognostic factors on survival after reirradiation.

	Age at retreatment	Chemotherapy with retreatment	Prior PTV	Prior RT dose	PTV re-treatment	Retreatment dose	RT interval	Extent of original surgery	Total dose	WHO grade
Univariate	0.011	0.2467	0.663	0.1225	0.2751	0.1762	0.079	STR, 0.633; GTR, 0.077	0.321	WHO III, 0.120; GBM, 0.0547

Abbreviations: PTV, planned target volume; RT, radiation therapy; WHO, World Health Organization; STR, subtotal resection; GTR, gross tumor resection; GBM, glioblastoma.

where the dose build-up region is in an area of the brain that is usually radiation naive. These unique features of proton therapy can spare much of the surrounding normal tissue adjacent to the previously treated lesion. This can be of the upmost importance in reirradiation, as much of the surrounding tissue has been subjected to high doses of radiation during the primary treatment.

This study shows that large targets can be retreated with proton therapy with OS from completion of PT of 10.2 months for grade III gliomas and 8.2 months for GBMs. This is comparable to the studies of reirradiation with single-fraction and multi-fraction SRS [4, 8, 10, 11]; however, the diversity of the patient population in both the referenced and current study makes direct comparison difficult. In addition, larger volumes were treated in the current study, with a median PTVs of 84 to 134.6 cm^3, compared with the published studies on single-fraction and multi-fraction SRS where the median PTV was 22 to 49 cm^3. Of note, Cho et al [7] and Fogh et al [8] also found that smaller PTVs were associated with increase in OS when treating with SRS. In the current study, no correlation was found between OS and size of PTV, indicating that fractionated PT may be less susceptible to increasing the target size compared with SRS. In our cohort, two (10%) patients had radiation necrosis. Despite the larger target size, our findings are similar to those of single-fraction and multi-fraction SRS studies with published rates from 0% to 20% [3, 4, 8, 10, 11]. The incidence of radiation necrosis typically peaks around 1 to 3 years after RT, but this can vary widely [5]. Therefore, although these patients have a high risk of radiation necrosis because of the large cumulative dose received and the large reirradiation target volume, their poor prognosis may prevent them from developing clinically significant necrosis.

In our study, age was the only statistically significant factor predicting OS from reirradiation, while the interval between RT, tumor grade, and extent of initial surgery were borderline significant with **Table 4** summarizing data from diagnosis and **Table 5** summarizing data after reirradiation. It is important to note that all long-term survivors were patients with LGGs, who tended to be younger; therefore, this may confound the data. However, this is in agreement with Fogh et al [8], where younger age also predicted increase in survival after reirradiation with hypofractionated SRS. Interval between RT was borderline significant in our study, a finding previously described by Grosu et al [9] in the article on fractionated SRS using amino acid positron emission tomography/computed tomography/MRI for recurrent gliomas [9]. This phenomenon may reflect the biology of the tumor in that the more aggressive or radioresistant tumors recur more quickly, leading to a worse prognosis after reirradiation compared with those that have a longer disease-free interval. However, this differs from the study by Fogh et al [8], where patients who recurred within 6 months after initial treatment did not have worse OS than those that recurred after 6 months.

The limitations in this study include its retrospective nature, wide patient variation, and low numbers of patients with LGGs and WHO grade III tumors. In addition, the initial radiation dosimetry, while available in paper format, was not merged with the PT plans, so the cumulative dose volume histogram of the combined courses was not available for all patients.

Similar to PT, carbon ions are heavy ions that have a similar Bragg peak that drops rapidly distal to the target. A phase I/II protocol is currently in place by Combs et al [27] at the University of Heidelberg that is comparing carbon ion radiotherapy to fractionated stereotactic radiation therapy in patients with recurrent gliomas.

Conclusion

For recurrent gliomas, PT reirradiation is an effective treatment option. Large treatment volumes are able to be irradiated to high doses with rates of toxicity similar to fractionated stereotactic radiation therapy. Prospective studies are needed for further evaluation, especially in younger patients and patients with longer interval between RT, as these patients may benefit more from reirradiation.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflicts to disclose.

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