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CLINICAL INVESTIGATION **Brain**

REIRRADIATION OF LARGE-VOLUME RECURRENT GLIOMA WITH PULSED REDUCED-DOSE-RATE RADIOTHERAPY

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Purpose: Pulsed reduced-dose-rate radiotherapy (PRDR) is a reirradiation technique that reduces the effective dose rate and increases the treatment time, allowing sublethal damage repair during irradiation.
Patients and Methods: A total of 103 patients with recurrent glioma underwent reirradiation using PRDR (86 considered to have Grade 4 at PRDR). PRDR was delivered using a series of 0.2-Gy pulses at 3-min intervals, creating an apparent dose rate of 0.0667 Gy/min to a median dose of 50 Gy (range, 20–60) delivered in 1.8–2.0-Gy fractions. The mean treatment volume was 403.5 ± 189.4 cm^3 according to T_2-weighted magnetic resonance imaging and a 2-cm margin.
Results: For the initial or upgraded Grade 4 cohort ($n = 86$), the median interval from the first irradiation to PRDR was 14 months. Patients undergoing PRDR within 14 months of the first irradiation ($n = 43$) had a median survival of 21 weeks. Those treated ≥14 months after radiotherapy had a median survival of 28 weeks ($n = 43$; $p = 0.004$ and HR = 1.82 with a 95% CI ranging from 1.25 to 3.10). These data compared favorably to historical data sets, because only 16% of the patients were treated at first relapse (with 46% treated at the second relapse, 32% at the third or fourth relapse, and 4% at the fourth or fifth relapse). The median survival since diagnosis and retreatment was 6.3 years and 11.4 months for low-grade, 4.1 years and 5.6 months for Grade 3, and 1.6 years and 5.1 months for Grade 4 tumors, respectively, according to the initial histologic findings. Multivariate analysis revealed age at the initial diagnosis, initial low-grade disease, and Karnofsky performance score of ≥80 to be significant predictors of survival after initiation of PRDR.
Conclusion: PRDR allowed for safe retreatment of larger volumes to high doses with palliative benefit. © 2011 Elsevier Inc.

Reirradiation, Transformed glioma, Pulsed reduced-dose-rate radiotherapy.

INTRODUCTION

Combined modality therapy, including maximal safe resection followed by adjuvant radiotherapy (RT) and chemotherapy, is the standard treatment of Grade 4 glioma. The most significant treatment breakthrough in the past decade has improved the median survival from 12.1 months to 14.6 months with the addition of temozolomide given concurrently and adjuvantly after RT (1). Despite aggressive treatment, survival remains poor because of the almost universal recurrence at or near the primary tumor (2, 3).

The efficacy of chemotherapy in the management of recurrent glioma has been limited owing to the poor drug distribution, intrinsic resistance, and systemic toxicity. Reirradiation using conventional and conformal techniques has been associated with modest palliative benefit. Concerns of toxicity have resulted in the reduction of retreatment volumes or reduced doses, potentially reducing the efficacy. In attempt to retreat larger volumes of recurrent disease to greater doses, we explored a new paradigm that allows for enhanced repair of radiation damage in normal tissues while maintaining a therapeutic dose to the tumor.

In conventional RT, a dose of 2 Gy is delivered at a dose rate of 4–6 Gy/min, translating into a daily treatment time of only a few minutes in most cases. Within this interval, the initial radiochemical processes, including the generation of free radicals, occurs. However, this interval is too short for most clinically relevant biologic repair processes to occur. As one increases the interval during which a 2-Gy dose is delivered by lowering the effective dose rate, it becomes possible for repair to occur during RT. The reduction in the dose rate might exploit differences between normal and malignant cells, allowing normal tissues to repair sublethal damage. The

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dose-rate effect is most dramatic between 0.01 and 1 Gy/min (4). A reduced dose rate can be obtained by using continuous reduced-dose-rate aging ^{60}Co sources, which are not readily available clinically, or by dividing a standard treatment fraction into a number of equal subfractions delivered in a pulsed manner separated by a fixed interval (5). Early clinical studies investigating fractionated reduced-dose-rate external beam RT in the curative setting have demonstrated an improved therapeutic ratio in oropharynx cancer (6) and breast cancer (7, 8).

Breaking each fraction into a number of subfractions takes advantage of a second intriguing radiation phenomenon known as low-dose hyper-radiosensitivity (LDHRS), which is increased radiosensitivity to doses <0.3–0.5 Gy. Data are available on the low-dose response of many human cell lines (9), most of which have demonstrated LDHRS (10, 11). Low-dose hypersensitivity might be a product of radiation-damaged G_2 cells entering mitosis prematurely (10). Although most evidence for low-dose hypersensitivity has been demonstrated *in vitro,* analysis of LDHRS in metastatic tumor to skin and subcutaneous tissue has revealed a potential advantage to low-dose ultrafractionated therapy compared with more standard fraction sizes for breast, melanoma, and sarcoma nodules (11). Additionally, Schultz and Geard (12) have provided convincing radiobiologic evidence in glioma cell lines, demonstrating the cytotoxicity of reduced-dose-rate RT and even suggesting the possibility of enhanced cytotoxicity with this approach.

Our reirradiation technique at the University of Wisconsin is pulsed reduced-dose-rate RT (PRDR) (8, 13). A series of 0.2-Gy pulses are separated by 3-min intervals, creating an apparent dose rate of 0.0667 Gy/min (5). The dose rate of the linear accelerator is reduced to 1 Gy/min during each 0.2-Gy pulse. This strategy potentially enhances the therapeutic ratio, taking advantage of the sublethal damage repair of normal tissue and LDHRS of the tumor. In the present study, we have described our experience with PRDR in patients with recurrent glioma who had previously undergone definitive RT. Most of these patients had also undergone salvage chemotherapy or targeted therapy.

PATIENTS AND METHODS

Between December 2000 and September 2007, 103 patients with recurrent primary central nervous system malignancies were treated with PRDR. The median age at PRDR was 45.5 years (range, 23–79). The median age at the initial diagnosis was 43 years (range, 12–78). Of the 103 patients, 41 were female and 62 were male.

At first presentation, 32 patients had undergone initial gross total resection, 53 subtotal resection, and 17 biopsy only; 1 patient had been diagnosed with brainstem glioma with no tissue diagnosis. Table 1 lists the tumor grade at the initial diagnosis and at retreatment. Grade 2 astrocytoma, oligodendroglioma, and oligoastrocytoma were considered low grade for analysis owing to the small number of patients. Also, any patient with an oligodendroglial component was grouped with the astrocytoma patients for that grade. Of the 103 patients, 43 did not undergo a second biopsy or resection before PRDR. Of the 60 patients for whom tissue was available at relapse because of a second neurosurgical intervention, 11 had undergone gross total resection, 44 subtotal resection, and 5 biopsy only.

All patients had previously been treated with definitive RT using the standard dose rate to a median dose of 59.4 Gy (range, 50.4–72.5). A total of 14 patients had also undergone radiosurgery for a previous recurrence; 3 patients had previously been treated with GliaSite brachytherapy (Cytec, Marlborough, MA), and 1 received fractionated stereotactic RT (FSRT). A minimum of 2 months was required from the completion of the initial RT. Patients were evaluated in our multidisciplinary neuro-oncology clinic. According to institutional practice, the triage at recurrence followed the sequence of reoperation, if feasible, followed by evaluation for systemic therapy on protocol. For patients with very localized disease, focal approaches such as radiosurgery, brachytherapy, and/or FSRT were considered. When all such options were exhausted, the cases were discussed again and the patients were then considered for PRDR. Previous systemic regimens included temozolomide, procarbazine, cyclophosphamide, vincristine, carmustine, lomustine, dalteparin, carboplatin, irinotecan, hydroxyurea, high-dose tamoxifen, signal transduction inhibitors, histone deacetylase inhibitors, and antiangiogenic agents. If neurosurgical resection was attempted, 4 weeks of healing were allowed before repeat RT. A contrast-enhanced magnetic resonance imaging (MRI) scan documenting disease progression was used for treatment planning. Each patient or designee gave written informed consent before treatment.

The median PRDR retreatment dose was 50 Gy (range, 22–58) using 1.8–2-Gy fractions. As our experience increased, we shifted to our current fractionation of 54 Gy using 2-Gy fractions. Only 10 patients were treated to a dose <40 Gy. Each daily fraction was delivered using 0.2-Gy pulses separated by 3-min intervals, creating an apparent dose rate of 0.0667 Gy/min. The dose rate of the linear accelerator was reduced to 1 Gy/min during each pulse of 0.2 Gy. Treatment was delivered with 6-MV photons. A customized Aquaplast mask (Aquaplast, Wyckoff, NJ) ensured adequate

Table 1. Initial histologic grade and pattern of change for patients with repeat tissue diagnosis

Initial histologic grade	Patients (*n*)	No rebiopsy or repeat resection	Histologic grade at PRDR	
			Unchanged	Upgraded
Low-grade glioma	25	2	5	18
Grade 3 oligodendroglioma	3	1	2	
Grade 3 oligoastrocytoma	3		1	2
Grade 3 astrocytoma	25	12	7	6
Grade 4 oligoastrocytoma	1		1	
Grade 4 astrocytoma	44	27	17	
Brainstem glioma	1	1		
Previous pineal tumor	1			1

Abbreviation: PRDR = pulsed reduced-dose-rate radiotherapy.

immobilization and reproducibility. The planning target volume was determined using the MRI findings, including the contrast-enhancing lesion and surrounding T_2-weighted or fluid-attenuated inversion recovery abnormality, if present, plus a 2.0-cm margin (T_2-weighted MRI plus 2-cm margin). In the absence of a T_2-weighted/fluid-attenuated inversion recovery abnormality, the target volume included the contrast-enhancing lesion plus a 2.5-cm margin. The treatment plans included opposed lateral fields, wedge-pair fields, or multiple field techniques using three-dimensional conformal planning and the Pinnacle treatment planning system (Philips Medical Systems, Andover, MA). The mean treatment volume was 403.5 ± 189.4 cm^3 (median, 369.2; range, 89.6–1,002.2).

The dose constraints were determined from the PRDR plan only, irrespective of the isodose distributions of the initial RT plan. The lens and cervical spine were shielded from the direct beam at all times. Attempts were made to limit the retreatment dose to the optic chiasm to 54 Gy, the retina of at least one eye to 50 Gy, and the brainstem to 54 Gy. No limitations were placed on the cumulative dose, including the initial treatment dose.

The collection and analysis of data were performed under an institutional review board–approved process for retrospective review. The purpose of the analysis was to determine the estimates of survival over time and the independent predictors of survival. Overall survival was calculated from the date of the initial diagnosis to the last recorded date of follow-up or death, and PRDR survival was calculated from the date of PRDR. The Kaplan-Meier (product-limit) method was used to estimate survival functions, and the log–rank test was performed for categorical variables to reveal differences in survival. On univariate analysis, Cox proportional hazard regression analysis was performed for both categorical and continuous variables to determine the significance and effects of each variable on survival. Additionally, Cox proportional hazard regression analysis using a stepwise selection procedure (entry $p < .3$, stay $p < .05$) was performed for multivariate analysis to determine an overall model of independent predictors of survival. The results were quantified in terms of the hazard ratios and corresponding 95% confidence intervals. Proportional hazard assumptions were satisfied. All statistical analyses were performed using Statistical Analysis Systems, version 9.1, software (SAS Institute, Cary, NC), and Kaplan-Meier plots were created using R 2.5 software for Windows. Statistical significance was defined as a two-tailed $p < .05$.

RESULTS

The PRDR regimen was well tolerated, and no patient discontinued treatment because of associated toxicity (Table 2). The median interval from the initial treatment to the initiation of PRDR was 18.2 months (range, 2–227.6) for the entire cohort.

Table 2. Patient characteristics

Characteristic	Value
Age at initial diagnosis (y)	
Median	42.9
Range	12–78
Age at PRDR (y)	
Median	45.5
Range	23–79
Median previous radiation dose (Gy)	59.4
Median PRDR retreatment dose (Gy)	50
Average cumulative dose (Gy)	106.8
Patients with upgraded histologic grade (*n*)	25
Patients without repeat biopsy (*n*)	43
Patients with repeat biopsy with same histologic grade (*n*)	35
Previous radiosurgery/FSRT (*n*)	15
Previous GliaSite (*n*)	3
Karnofsky performance status (*n*)	
50	3
60	8
70	25
80	39
90	22
100	6
Average number of previous systemic therapies	1.87
Previous systemic therapy (*n*)	
0	8
1	49
2	20
3	10
≥4	16
Brain autopsy	15

Abbreviations: PRDR = pulsed reduced-dose-rate radiotherapy; FSRT = fractionated stereotactic RT.

Grade 4 patients at recurrence

A total of 86 patients were considered to have Grade 4 disease at initiation of PRDR according to the initial tumor, repeat biopsy findings, or radiographic appearance of glioblastoma multiforme (GBM). The median interval from the first RT to PRDR was 14 months, and this breakpoint was used for the secondary analysis. Patients receiving PRDR within 14 months of their initial RT ($n = 43$) had a median survival of 21 weeks, and those treated >14 months after their initial RT ($n = 43$) had a median survival of 28 weeks ($p = 0.004$ and HR = 1.82 with a 95% CI ranging from 1.25 to 3.1). Only 16% of patients were treated at first relapse (with 46% treated at the second relapse, 32% at the third or fourth relapse, and 4% at the fourth or fifth relapse).

When patients initially diagnosed with Grade 4 glioma were compared with those who were initially diagnosed with a lower grade tumor that was confirmed by the biopsy findings to have upgraded to Grade 4, no significant difference was found in survival from the initiation of PRDR (median survival 5.2 vs. 5.9 months, $p = .12$). From the initial diagnosis, the original Grade 4 patients had a median survival of 1.6 years and those with a lower grade tumor that transformed to Grade 4 had median survival of 4.4 years ($p < .001$).

Overall survival from initial diagnosis and initiation of reirradiation

The median overall survival stratified by the initial histologic type from the initial diagnosis was 6.3 years (range, 2.6–22) for low-grade tumors, 4.1 years (range, 0.9–11.1) for Grade 3 tumors, and 1.6 years (range, 0.7–6.6) for Grade 4 tumors (Fig. 1). The 1-, 2-, and 5-year actuarial survival rate was 100%, 100%, and 69.6% for those with low-grade tumors, 94.1%, 76.5%, and 31.5% for those with Grade 3 tumors, and 84.8%, 21.7%, and 2.2% for those with Grade 4 tumors, respectively.

The median survival from the initiation of PRDR was 11.4 months (range, 1–33.8) for those with low-grade tumors, 5.6

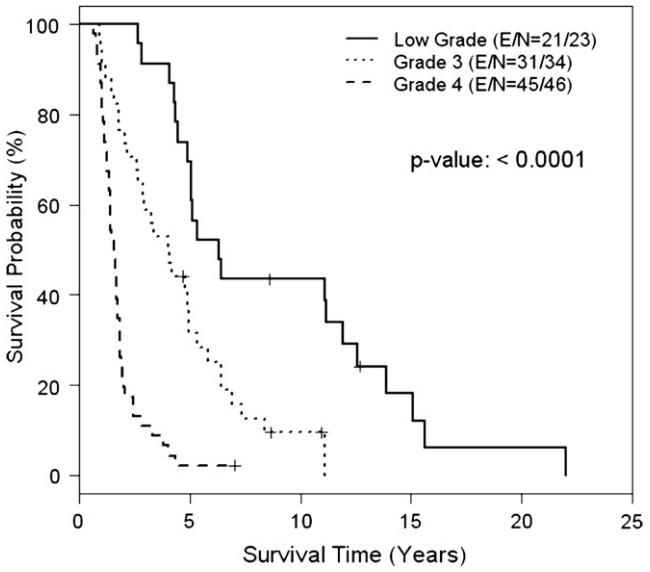

Fig. 1. Survival from initial diagnosis stratified by initial tumor grade. E/N = event/total number.

months (range, 1.2–23.7) for those with Grade 3 tumors, and 5.1 months (range, 1–48.4) for those with Grade 4 tumors according to the histologic findings at the initial diagnosis. The 6-month and 1-year actuarial survival rate after retreatment with PRDR was 73.9% and 47.8% for those with low-grade tumors, 38.2% and 9.7% for those with Grade 3 tumors, and 34.8% and 4.4% for those with Grade 4 tumors, respectively. For the entire cohort, the median survival from the initiation of PRDR was 5.8 months (range, 1–48.4), and the 6-month and 1-year actuarial survival rate was 44.7% and 15.9%, respectively.

Influence of histologic grade

The histologic grade at the initial diagnosis retained significance ($p = .002$) for survival from the initiation of PRDR for low-grade tumors compared with Grade 3 or 4 tumors (Fig. 2). The effect of an initial low histologic grade remained significant on multivariate analysis. No significant difference ($p = .32$) in survival from the initiation of PRDR was found between initial Grade 3 glioma and initial Grade 4 glioma.

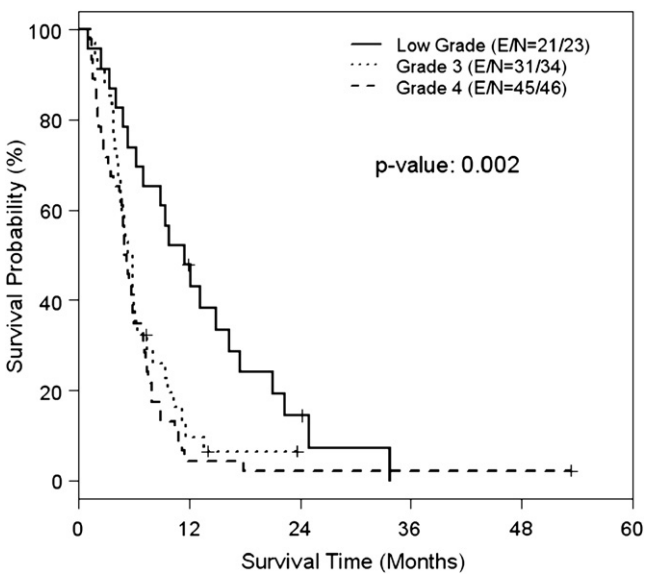

Fig. 2. Survival from initiation of pulsed reduced-dose-rate radiotherapy stratified by initial tumor grade. E/N = event/total number.

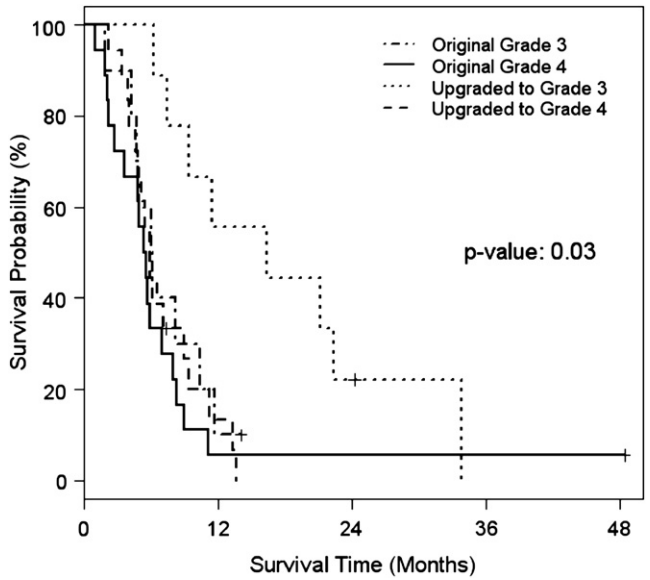

Fig. 3. Survival from initiation of pulsed reduced-dose-rate radiotherapy for patients who had undergone repeat tissue diagnosis before pulsed reduced-dose-rate radiotherapy.

A subset analysis was performed for the 60 patients who had undergone subsequent biopsy or a surgical procedure to establish the histologic diagnosis before PRDR. Of the 60 patients, 55 had either Grade 3 or 4. Of the 36 patients with Grade 4, 18 had originally been diagnosed with Grade 4, 9 had been upgraded to Grade 4 from Grade 3, and 9 had been upgraded to Grade 4 from a low-grade tumor. As shown in Fig. 3, the original Grade 3 and 4 patients appeared to have similar survival from the initiation of retreatment compared with the patients with tumors that were upgraded to Grade 4. Nine patients had tumors upgraded from low grade to Grade 3, and these patients had median survival of 16.3 months compared with median survival of 6.5 months for patients with tumor upgraded to Grade 4 ($p = .03$).

Influence of patient age

Age (<50 vs. ≥50 years) had a statistically significant ($p < .001$) effect on overall survival for Grade 3 and 4 patients, with a median survival from diagnosis of 2.32 and 1.38 years, respectively. For the entire cohort, age <50 vs. ≥50 years at the initial diagnosis was also statistically prognostic, with a median survival of 4.3 vs. 1.4 years from the initial diagnosis, respectively ($p < .001$). The median survival from PRDR for patients <50 years at the initial diagnosis was 7.0 months compared with 4.3 months for patients ≥50 years ($p < .001$). Age at the initial diagnosis retained significance on multivariate analysis, with a hazard ratio of 2.1 for death after initiation of PRDR for patients aged ≥50 years relative to those aged <50 years ($p < .001$).

Influence of Karnofsky performance status

The Karnofsky performance status (KPS) at the initiation of PRDR was an important factor for survival from the initiation of PRDR. Patients with a KPS of ≥70 had a statistically significant improvement in survival compared with patients with a KPS of <70 (2.4 vs. 6 months, p <.0001). Similarly, patients with a KPS of ≥80 had a statistically significant improvement in survival compared with patients with a KPS of <80 (4.9 vs. 7.1 months, p = .003). The KPS retained significance (p = .013) on multivariate analysis, with a hazard ratio of 0.583 when comparing a KPS of ≥80 and a KPS of <80.

Influence of previous therapy

The use of other therapy before PRDR had little effect on survival from the initiation of PRDR. The cohort of 53 patients undergoing either subtotal or gross total surgical resection before PRDR demonstrated no statistically significant difference in survival relative to the 50 patients who had undergone no additional surgery or biopsy alone (median survival, 6.1 vs. 5.1 months, respectively; p = .17). No significant survival difference from the initiation of PRDR was observed for patients who had previously been treated with no systemic therapy, one previous regimen, two previous regimens, three previous regimens, or four or more previous regimens. Of the patients who were initially diagnosed with Grade 4 or had been upgraded on pathologic examination to Grade 4, no difference was found in survival from PRDR for the 17 patients who were treated before the adoption of temozolomide at our institution and the 47 patients who had receive temozolomide before reirradiation (median survival, 5.4 vs. 5.3 months, respectively; p = .70).

Toxicity

A total of 15 patients had autopsy of the brain, of which 4 had notable necrosis. The retreatment PRDR dose was 50 Gy in 2 patients originally treated to a dose of 54 Gy and 59.4 Gy, with an interval of 12 and 40 months to PRDR. The retreatment PRDR dose was 54 Gy in 2 patients originally treated to 60 Gy, with an interval of 11 and 28 months to PRDR. One patient had also previously been treated with stereotactic radiosurgery to 12 Gy prescribed to the 50% isodose line 25 months after initial RT to 60 Gy. Other patients only manifested punctuate necrosis in the presence of recurrent tumor, usually associated with mitoses or vascular endothelial proliferation. The follow-up MRI scans revealed changes consistent with disease progression, pseudoprogression, or necrosis. Treatment of clinical deterioration consisted of increases in steroid dosage and supportive care. Three patients underwent post-PRDR subtotal resection with the pathologic findings revealing progressive disease without treatment-related necrosis. Although no formal endocrine, neurocognitive, or visual testing was performed, no patient manifested obvious blindness from treatment.

Multivariate analysis

The multivariate analysis for overall survival from the initial diagnosis identified the histologic grade at the initial diagnosis, age at the initial diagnosis, and second surgical intervention to be significant predictors of survival (Table 3). Multivariate analysis for survival from PRDR revealed the histologic grade at the initial diagnosis, age at the initial diagnosis, and KPS at PRDR to be significant predictors of survival (Table 4).

Table 3. Multivariate model for overall survival from initial diagnosis

Variable	HR	95% CI for HR	p	Global p
Histologic grade at initial diagnosis				<.0001
Grade 3 (n = 34; vs. Grade 1-2, n = 23)	2.42	1.23–4.78	.01	
Grade 4 (n = 46; vs. Grade 1-2, n = 23)	7.74	3.70–16.17	<.0001	
Age at initial diagnosis (≥50 y, n = 34; vs. <50 y, n = 69)	2.70	1.66–4.41	<.0001	
Secondary surgery (none/biopsy, n = 50; vs. subtotal/gross, n = 53)	2.02	1.32–3.10	.001	

Abbreviations: HR = hazard ratio; CI = confidence interval.

DISCUSSION

For patients who have exhausted other therapeutic choices and have achieved a significant disease-free interval after an initial course of RT, reirradiation might represent a potential palliative and life-prolonging option. Biologic differences between normal neural tissue and glial neoplasms for repair of radiation damage and the induction of radiation-induced lethal lesions could potentially be exploited to minimize normal tissue toxicity and maximize tumor control probability. PRDR has been radiobiologically derived to exploit these differences; our institution's experience of reirradiation using PRDR for locoregional recurrence of breast cancer has been previously reported (8).

In the present report, we have presented our outcomes for 103 sequentially reirradiated patients with central nervous system tumors retreated to doses ≤54 Gy. The multidisciplinary neuro-oncology team at our institution believed that no additional options were appropriate for these patients. Of the 103 patients, 8 had received no previous systemic

Table 4. Multivariate model for survival from initiation of PRDR

Variable	HR	95% CI for HR	p
Histologic grade at initial diagnosis (Grade 3-4, n = 80; vs. Grade 1-2, n = 23)	1.74	1.01–3.00	.04
Age at initial diagnosis (≥50 y, n = 34; vs. <50 y, n = 69)	2.11	1.33–3.34	.002
Karnofsky performance status (<80, n = 36; vs. ≥80, n = 67)	1.72	1.13–2.62	.01

Abbreviations as in Table 3.

therapy because of a poor KPS or other co-morbidities, 20 had had disease progression during two previous protocol regimens, and 26 had had treatment failure with at least three previous regimens. A comparison of the patients who had received one, two, three, or four or more systemic regimens revealed no statistically significant difference in survival from reirradiation. Comparing patients who had received previous temozolomide with those who had not, survival after reirradiation for Grade 4 patients was also unaffected.

An analysis by Wong *et al.* (14) had provided a useful comparator for survival at recurrence. These investigators, reviewing eight Phase II drug studies, observed a median survival of 25 weeks (95% confidence interval 21–28) for recurrent GBM and 30 weeks (95% confidence interval 26–35) for the entire cohort of anaplastic astrocytoma and GBM (14). Hence, our experience with large-volume retreatment in GBM patients >14 months from initial RT compares favorably relative to palliative chemotherapy, because these patient had a median survival of 28 weeks and our patients reirradiated within 14 months of previous therapy had a median survival of only 21 weeks ($p = 0.004$). Also, 77% of the patients treated in the Phase II drug studies had received previous chemotherapy, 25% of whom had received at least two regimens. In our series, 92% had received previous chemotherapy, and 45% had received at least two regimens.

As reviewed by others, reirradiation has been commonly used with palliative intent for recurrent glioma patients without other treatment options, although the median treatment volume in major series was not >74 cm^3 (15, 16). The fear of toxicity has led to reduced retreatment volumes or reduced doses. In our series, the mean treatment volume was 403.5 ± 189.4 cm^3 (median, 369.2; range, 89.6–1,002.2). The largest previous series (FSRT) from the University of Heidelberg reported a median planning target volume of 49.3 cm^3 (range, 2.5–636) for 172 patients treated to a median dose of 36 Gy using 2-Gy fractions (15). The substantially larger volume in our series likely reflected both more extensive disease and additional expansion along tumor. The University of Heidelberg used a 1-cm expansion along T_1-weighted MRI-enhancing tumor. In contrast, our volumes consisted of a 2-cm expansion along gross tumor and surrounding T_2-weighted MRI edema.

Radiosurgery is usually reserved for lesions with a maximal diameter of <4 cm, with a median survival of about 10–11 months for GBM patients after a single fraction with a median dose of 13–15 Gy (17, 18). Similarly, GliaSite has been studied for small lesions, with a median survival after retreatment of GBM of 9.1 months at Johns Hopkins (19).

Veninga *et al.* (20) retreated patients with various histologic types to a median reirradiation dose of 46 Gy at a median of 46 months after the first course of RT. The median survival time was 6.1 months after reirradiation (20). Voynov *et al.* (21) reported on 10 patients treated with intensity-modulated RT to a median dose of 30 Gy using 5-Gy fractions with a median survival time of 10.1 months. Bauman *et al.* (22) reported on 30 patients with various histologic types, 10 of whom had high-grade glioma. The median survival of the 11 patients with malignant glioma was 2.8 months (22).

Regarding the outcome after PRDR, no significant difference was found between patients initially diagnosed with Grade 4 and those whose disease was transformed to Grade 4. Furthermore, patients with initial Grade 3 tumors appeared to have similar survival to those with initial Grade 4 tumors and transformed Grade 4 tumors. In contrast, the University of Heidelberg series found that Grade 3 glioma patients continued to have an intermediate median survival after retreatment (16 months) relative to those with low-grade glioma (22 months) and those with Grade 4 glioma (8 months). The grade at primary diagnosis was the strongest influencing factor on survival after reirradiation with FSRT. The interval between the primary RT and reirradiation in the University of Heidelberg series was similar to the intervals for our series for all, except for Grade 3, which was 32 months, compared with 43.5 months in our series (15). A longer interval likely allowed many of our initial Grade 3 tumors to transform to Grade 4 by PRDR.

The natural history of low-grade tumors seems to continue to influence survival even after failure of systemic treatment. Our patients with initial low-grade tumors demonstrated statistically significant improved survival after reirradiation compared with the patients with Grade 3 and 4 tumors. Shepherd *et al.* (23) similarly found that initial low-grade astrocytoma was prognostic, representing the only favorable prognostic factor for survival in a series of recurrent glioma patients undergoing hypofractionated stereotactic RT.

Age has been demonstrated to be a strong prognostic factor for malignant glioma in recursive partitioning analysis of patients treated in Radiation Therapy Oncology Group trials, with a marked distinction between patients <50 years and ≥50 years (24). In our series, age at the initial diagnosis correlated significantly not only with overall survival from the initial diagnosis but also with survival from retreatment. Age <50 years at the primary diagnosis predicted for significantly improved survival for Grade 3 or 4 patients and for the entire cohort of patients. The University of Heidelberg series found age at the initial diagnosis to be significant for overall survival, but age did not retain significance as a prognostic factor for survival after reirradiation (15). The University of Minnesota series found age as a continuous variable to predict for longer survival on univariate analysis for recurrent high-grade glioma patients treated with stereotactic radiosurgery or FSRT (25).

The KPS at retreatment was a significant predictor for survival after retreatment with PRDR on multivariate analysis. The KPS when analyzed as a continuous variable was prognostic of longer survival in the University of Minnesota series of either single-dose RT or FSRT for recurrent Grade 3 or 4 glioma (25). Recurrent GBM patients at Johns Hopkins treated with GliaSite demonstrated a marked difference in survival on subgroup analysis for patients with a KPS of ≥70 vs. a KPS of <70 (median survival, 9.3 vs. 3.1 months, respectively; $p < .003$) (19).

Our study had the limitations associated with any retrospective series. Patients with unfavorable characteristics might have been referred to hospice rather than to radiation oncology for consideration of retreatment, influencing patient

selection. Although our patients had had multiple treatment failures, the patients who had received more therapy might have had more favorable tumor biology. Only 15 patients had a pathologic examination of the brain after death, limiting our ability to fully assess for treatment-related necrosis. We did not perform a correlative analysis of survival with biomarker expression. It is possible that patients with superior survival might have had associated biomarkers of improved survival, which would dilute the claims of therapeutic benefit. Additional analysis of this resource is ongoing. We did not formally evaluate visual, auditory, neurocognitive, and endocrine deficiencies after PRDR, and the effect of high doses on these functions cannot be adequately assessed.

CONCLUSION

Pulsed reduced-dose-rate RT is a reirradiation strategy that is well tolerated, allowing for safe retreatment of larger target volumes to high doses with palliative benefit. Cumulative doses >100 Gy were well tolerated. For Grade 4 patients at recurrence, an interval from initial RT of >14 months predicted for longer survival after PRDR. Age at the initial diagnosis, the KPS at retreatment, and the initial tumor grade were also prognostic for survival after retreatment on multivariate analysis. An expanded prospective study is needed to further delineate the toxicity and efficacy of PRDR.

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