Neuro-Oncology Practice
9(5), 390–401, 2022 | https://doi.org/10.1093/nop/npac032 | Advance Access date 2 May 2022

Clinical outcomes of dose-escalated re-irradiation in patients with recurrent high-grade glioma

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Abstract

Background. Re-irradiation for recurrent gliomas is a controversial treatment option with no clear standard dose or concurrent systemic therapy.

Methods. This series represents a single-institution retrospective review of patients treated with re-irradiation for recurrent high-grade glioma. After 2012, patients were commonly offered concurrent bevacizumab as a cytoprotective agent against radiation necrosis. Kaplan-Meier method was used to estimate overall survival and progression-free survival. Cox proportional hazards regression was used to identify factors associated with overall survival and progression-free survival.

Results. Between 2001 and 2021, 52 patients underwent re-irradiation for a diagnosis of recurrent high-grade glioma. 36 patients (69.2%) had a histologic diagnosis of glioblastoma at the time of re-irradiation. The median BED10 (biological equivalent dose 10 Gy) of re-irradiation was 53.1 Gy. Twenty-one patients (40.4%) received concurrent bevacizumab with re-irradiation. Median survival for the entire cohort and for glioblastoma at the time of recurrence patients was 6.7 months and 6.0 months, respectively. For patients with glioblastoma at the time of recurrence, completing re-irradiation (HR 0.03, $P < .001$), use of concurrent bevacizumab (HR 0.3, $P = .009$), and the BED10 (HR 0.9, $P = .005$) were predictive of overall survival. Nine patients developed grade 3-5 toxicity; of these, 2 received concurrent bevacizumab and 7 did not ($P = .15$).

Conclusion. High dose re-irradiation with concurrent bevacizumab is feasible in patients with recurrent gliomas. Concurrent bevacizumab and increasing radiation dose may improve survival in patients with recurrent glioblastoma.

Keywords

bevacizumab | recurrent glioma | re-irradiation

Treatment options for high-grade gliomas have improved over the past two decades, leading to greater survival times.[1,2] However, this improvement in survival has generally not led to cures but is characterized instead by ultimate tumor recurrence in the great majority of cases.[3] Currently, there is no standard therapy for high-grade glioma recurrence. Cytotoxic chemotherapy, immunotherapy, anti-angiogenic agents, small molecule inhibitors, re-irradiation, and tumor-treating fields

represent several of the available options for treatment after tumor recurrence, with re-irradiation used in patients with a favorable initial response to therapy. However, concern for toxicity often limits its use.[4–9]

Re-irradiation represents an intriguing but often controversial option to treat recurrent high-grade glioma, because the risk of toxicity of radiotherapy is cumulative over a lifetime of multiple courses of treatment.[10] Treatment of high-grade glioma in the upfront setting generally leads to the delivery of radiation doses that approach the thresholds of radiation necrosis.[11] As such, a second course of treatment could exceed this threshold by a substantial amount, preventing safe delivery of a sufficient dose to improve outcomes, as seen in the RTOG 1205 study, where 35 Gy in 10 fractions improved in-field progression but not survival, or the study by Combs et al, which used a median dose of 36 Gy in standard fractionation.[8,12] Both of these regimes are commonly used in practice; however, the biological equivalent dose (BED) is substantially less than those delivered in the first course of radiation therapy.[13] There appears to be a degree of forgiveness of prior radiation damage done to the brain with increased time after the initial treatment, which may allow for further dose escalation, and re-irradiation regimens up to the full initial course have been reported.[14,15] Bevacizumab has been reported as an effective treatment for radiation necrosis.[16] Furthermore, a prior series reported lower risks of radiation necrosis in patients treated with hypofractionated re-irradiation of gliomas.[17] Due to this potential to reduce radiation necrosis, patients in the present series were commonly offered bevacizumab for the purpose of increasing the tolerance of re-irradiation and allowing for higher cumulative doses of radiation.

The present study represents a single-institution series assessing the outcomes of patients with high-grade glioma.

Methods

Data Acquisition

This study was approved by the Institutional Review Board at Wake Forest. Patients who received radiation therapy for primary central nervous system tumors were identified using the record and verify system within the Department of Radiation Oncology at Wake Forest (Mosaiq, Elekta AB, Stockholm, Sweden). Patients who underwent two courses of radiation therapy for a diagnosis of a glioma at least 90 days apart with one course treated within the Wake Forest Baptist Medical Center network from 1998 to 2021 were eligible. Patients with ependymoma and non-glial central nervous system neoplasms for their first course of radiotherapy were excluded. Patients with diffuse disease who were treated with focal radiation for palliative intent with subsequent intent of comfort measures only were also excluded. Electronic medical records were used to determine patient and tumor characteristics, survival times, patterns of progression, and toxicity. For molecular data, if known mutations were present at diagnosis, it was presumed that the same characteristics were present at re-irradiation unless specifically re-tested and found to have changed status.

Re-irradiation

Re-irradiation was offered to patients who had at least 12 months free from local progression within the prior radiation volume after upfront radiation therapy. All patients were treated using photons at re-irradiation. Dose and fractionation scheme for re-irradiation was determined by the treating radiation oncologist but typically based on the volume of disease present. For hypofractionated schedules to be given, patients generally had to have a maximal tumor diameter of 5 cm, and patients with secondary glioblastoma (GBM) who had previously received radiotherapy for a lower grade glioma were generally treated with a more aggressive and protracted radiation course. In the setting of re-irradiation, our institutional philosophy has been to target both the contrast-enhancing and the non-enhancing tumor represented by the growing fluid attenuated inversion recovery (FLAIR) abnormality.

Use of Bevacizumab

Bevacizumab was used as a radiation protective agent in a subset of patients after data began to emerge that patients receiving bevacizumab to lower the risk of radiation necrosis.[17] Bevacizumab was generally prescribed at a dose of 10 mg/m^2 on a schedule of once every 2 weeks. Bevacizumab was continued on that schedule at the discretion of the treating oncologist, and generally discontinued after 4-6 administrations if patients were not requiring steroids. Otherwise, the bevacizumab was gradually tapered to a less frequent schedule once imaging demonstrated a lack of significant treatment-related edema.

Patient Follow-up and Response Assessment

After a course of re-irradiation, patients were followed clinically and with an MRI of the brain at approximately 4 weeks, and then at an interval of every 2 months for the next 6 months. Response assessment was performed using Response Assessment in Neuro-Oncology (RANO) criteria.[18]

Events considered as adverse radiation effects (ARE) included subacute edema with symptoms of mass effect, pseudoprogression, or delayed radiation necrosis. ARE grade was defined using the Common Terminology Criteria for Adverse Events (CTCAE) version 5. Treatment for ARE included corticosteroid administration, surgical decompression, and unplanned administration of bevacizumab.

Statistics

Time zero for time-dependent variables was considered the last day of re-irradiation. Kaplan-Meier analysis was performed to estimate survival times. Log-rank test was used to compare survival curves between two populations. In order to be evaluable for survival and toxicity, at least one follow-up visit or a decision to halt radiation therapy prior to the end of the prescribed course and transition to palliative therapy was required. At least one MRI of the brain after the second course of radiation therapy was required for a patient to be evaluable for progression.

Cox proportional hazards regression was performed to assess for factors associated with differences in overall survival and progression-free survival. For model selection, we started with relevant predictors (see Tables 2–4) and then used backward stepwise selection using the Akaike information criterion (AIC) as the selection criterion. *P* values less than .05 were considered significant. All tests were two-sided. The results excluded predictors that violated the proportional hazards assumption, determined by Schoenfeld tests. Likelihood of ARE was determined using Fisher's exact tests for categorical predictors and logistic regression models for continuous predictors. All statistics were performed using R version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Population

Patient characteristics are summarized in Table 1. A total of 52 patients were identified who met the inclusion criteria. Among 52 patients, 22 (42.31%) and 36 (69.2%) had a histologic diagnosis of GBM at initial irradiation and re-irradiation, respectively. 11 tumors (21.2%) were known to have MGMT (O^6-methylguanine-DNA methyltransferase) promoter methylation, and 12 (23.1%) were known to have an IDH (isocitrate dehydrogenase) mutation. The median time from the end of the initial course of radiation therapy to the failure that was treated with re-irradiation was 51.9 months, with 40 patients (76.9%) being more than 24 months from the end of the initial course of radiation therapy. 21 patients (40.4%) underwent re-irradiation for the first failure after initial radiation therapy. 11 of 52 patients (21.2%) received 2 or more lines of salvage systemic therapy for recurrence disease prior to the recurrence treated with re-irradiation. The majority of patients had either no surgery or only a biopsy performed for the failure treated with re-irradiation (21 patients, 40.4% and 13 patients, 25%, respectively). The median BED10 at re-irradiation was 53.1 Gy (IQR 47.81-59.47 Gy), delivered to a median planning target volume (PTV) volume of 208.5 cc (IQR 105.3-303.6 cc). Dose-fractionation schemes at initial and re-irradiation are detailed in Supplementary Tables 1 and 2 respectively. 21 patients (40.4%) received concurrent bevacizumab with re-irradiation, and 27 patients received concurrent temozolomide (TMZ, 51.9%), including 9 (17.3%) who received concurrent bevacizumab and TMZ. Forty patients had DICOM format treatment plans accessible for the course of re-irradiation. Of those, 28 (70%) had that T2 FLAIR abnormality intentionally targeted in addition to enhancing disease.

Among patients with GBM at the time of initial radiation, 6 (27.3%) had known MGMT methylation, 3 (13.6%) had a known IDH mutation, and none had a known 1p19q codeletion. The median time from completion of initial radiation therapy to the failure prior to re-irradiation was 42.5 months. Similar to the cohort as a whole, 5 patients (22.3%) had 2 or more lines of salvage systemic therapy prior to the recurrence treated with re-irradiation and the majority of patients had either no surgery or biopsy only prior to re-irradiation (10 patients, 45.6% and 3 patients, 13.6%, respectively). The median BED10 at re-irradiation was 50.74 Gy (IQR 48-53.1 Gy), delivered to a median PTV volume of 174.33 cc (IQR 86.9-257.8).

Among patients with GBM at the time of re-irradiation, 8 (22.2%) had known MGMT methylation, 7 (19.4%) had a known IDH mutation, and none had 1p19q codeletion. The median time from completion of initial radiation therapy to the failure prior to re-irradiation was 41.3 months. Similar to the cohort as a whole, 8 patients (22.2%) received 2 or more lines of salvage systemic therapy prior to the recurrence treated with re-irradiation, and the majority of patients had either no surgery or biopsy only prior to re-irradiation (15 patients, 41.7% and 6 patients, 16.7%, respectively). The median BED10 at re-irradiation was 50.74 Gy (IQR 47.81-53.1 Gy), delivered to a median PTV volume of 214.4 cc (IQR 96.8-299.6 cc).

There were no statistically significant differences between patients who did and did not receive concurrent bevacizumab with re-irradiation in KPS at re-irradiation, PTV volume at re-irradiation, re-irradiation completion rate, histology at re-irradiation (GBM vs all others), BED10 and BED3 at re-irradiation, or standard vs hypofractionation (defined as >2 Gy per fraction). Patients who were treated using volumetric modulated arc therapy (VMAT) or intensity-modulated radiation therapy (IMRT) were more likely to have received concurrent bevacizumab.

Overall Survival and Progression-Free Survival

Kaplan-Meier method was used to estimate overall survival and progression-free survival times. Kaplan-Meier plots for overall survival and progression-free survival are depicted in Figure 1. Kaplan Meier plots for overall and progression-free survival based on patients with glioblastoma at their initial course of radiation are found in Supplementary Figures 1 and 2. Median survival for the entire cohort was 6.7 months (range 5.8-12.2 months). Median survival for patients with GBM at the time of initial and re-irradiation was 5.7 months (range 3.2-10.6 months) and 6.0 months (range 5.1-12 months), respectively. Overall survival for all patients was 55%, 32%, and 8% at 6 months, 12 months, and 24 months, respectively. Overall survival for patients with GBM at initial radiation was 33%, 13%, and 0% at 6 months, 12 months, and 24 months, respectively. Overall survival for patients with GBM at the time of re-irradiation was 47%, 25%, and 0% at 6 months, 12 months, and 24 months, respectively.

Progression-free survival for the entire cohort was 48%, 28%, and 4% at 6 months, 12 months, and 24 months, respectively. Progression-free survival for patients with GBM at the time of re-irradiation was 44%, 19%, and 0% at 6 months, 12 months, and 24 months, respectively.

Median progression-free survival for patients with GBM at initial irradiation was 4.3 months (lower range 3.0 months, no upper range). Progression-free survival for patients with GBM at initial radiation therapy was 50%, 0%, and 0% at 6 months, 12 months, and 24 months, respectively.

Predictive Factors

Cox proportional hazards models for factors associated with overall survival and progression-free survival are

Table 1. Patient Characteristics

Variable	All Patients, n (%)/Median (IQR) (n = 52)	Glioblastoma at Initial Radiation, n (%)/Median (IQR) (n = 22)	Glioblastoma at Re-irradiation, n (%)/ Median (IQR) (n = 36)
Sex			
Male	38 (73.1%)	16 (72.7%)	26 (72.2%)
Female	14 (26.9%)	6 (27.3%)	10 (27.8%)
KPS			
100	0 (0%)	0 (0%)	0 (0%)
90	4 (7.6%)	2 (9.09%)	4 (11.1%)
80	18 (34.6%)	6 (27.27%)	12 (33.3%)
70	7 (13.5%)	4 (18.18%)	5 (13.9%)
60	7 (13.5%)	4 (18.18%)	5 (13.9%)
50	2 (3.8%)	0 (0%)	1 (2.8%)
40	1 (1.9%)	0 (0%)	1 (2.8%)
Unknown	13 (25.0%)	6 (27.27%)	8 (22.2%)
Histology at re-irradiation			
Glioblastoma	36 (69.2%)	21 (95.45%)	36 (100%)
Astrocytoma	7 (13.5%)	0 (0%)	
Oligodendroglioma	4 (7.6%)	0 (0%)	
Mixed oligoastrocytoma	2 (3.8%)	0 (0%)	
Other	3 (5.8%)	1 (4.55%)*	
WHO grade at re-irradiation			
2	6 (11.5%)		
3	9 (17.3%)		
4	37 (71.2%)	22 (100%)	36 (100%)
Molecular characteristics			
MGMT methylation	11 (21.2%)	6 (27.27%)	8 (22.2%)
IDH mutation	12 (23.1%)	3 (13.64%)	7 (19.4%)
1p19q codeletion	2 (3.8%)	0 (0%)	0 (0%)
Surgery prior to re-irradiation			
Gross total resection	7 (13.5%)	6 (27.27%)	5 (13.9%)
Subtotal resection	10 (19.2%)	3 (13.64%)	9 (25%)
Biopsy only	13 (25.0%)	3 (13.64%)	6 (16.7%)
Laser interstitial thermal therapy	1 (1.9%)	0 (0%)	1 (2.8%)
None	21 (40.4%)	10 (45.45%)	15 (41.7%)
Location of recurrence			
In field	23 (44.2%)	11 (50%)	18 (50%)
Out of field	14 (26.9%)	7 (31.82%)	8 (22.2%)
Marginal	1 (1.9%)	1 (4.55%)	1 (2.8%)
Unifocal/multifocal recurrence			
Unifocal	38 (73.1%)	14 (63.64%)	26 (72.2%)
Multifocal	13 (25.0%)	8 (36.36%)	9 (25%)
Initial RT to failure prior to re-irradiation (months)	Median: 51.9, IQR: 116.7 (20.1, 136.8)	Median: 27.63, IQR: 38.73 (10.6, 49.33)	Median: 41.33, IQR: 69.8 (17.8, 87.6)
Re-irradiation at initial failure			
Yes	21 (40.4%)	10 (45.45%)	15 (41.7%)
No	30 (57.7%)	12 (54.55%)	21 (58.3%)
Number of lines of systemic therapy between initial radiation and re-irradiation			
0	28 (53.8%)	13 (59.09%)	19 (52.8%)
1	13 (25.0%)	4 (18.18%)	9 (25%)
2	4 (7.7%)	2 (9.09%)	3 (8.3%)
3	5 (9.6%)	2 (9.09%)	3 (8.3%)
4	1 (1.9%)	1 (4.55%)	1 (2.8%)

Table 1. Continued

Variable	All Patients, n (%)/Median (IQR) (n = 52)	Glioblastoma at Initial Radiation, n (%)/Median (IQR) (n = 22)	Glioblastoma at Re-irradiation, n (%)/ Median (IQR) (n = 36)
5	0 (0%)	0 (0%)	0 (0%)
6	1 (1.9%)	0 (0%)	1 (2.8%)
Median	0, IQR: 1 (0, 1)	0, IQR: 1 (0, 1)	0, IQR: 1 (0, 1)
Re-irradiation BED10 (Gy)	Median: 53.1, IQR: 11.66 (47.81, 59.47)	Median: 50.74, IQR: 5.1 (48, 53.1)	Median: 50.74, IQR: 5.29 (47.81, 53.1)
Re-irradiation BED3 (Gy)	Median: 75.76, IQR: 14.4 (72, 86.4)	Median: 75.69, IQR: 13.48 (72.92, 86.4)	Median: 75.69, IQR: 14.4 (72, 86.4)
Re-irradiation PTV volume (cc)	Median: 208.54, IQR: 198.32 (105.28, 303.6)	Median: 174.33, IQR: 170.94 (86.86, 257.8)	Median: 214.43, IQR: 202.83 (96.79, 299.62)
Re-irradiation technique			
3D CRT	18 (34.6%)	7 (31.82%)	11 (30.6%)
Static IMRT	30 (57.7%)	13 (59.09%)	22 (61.1%)
VMAT	3 (5.8%)	2 (9.09%)	3 (8.3%)
CSI	1 (1.9%)	0 (0%)	0 (0%)
Concurrent chemotherapy at re-irradiation			
None	9 (17.3%)	1 (4.55%)	4 (11.1%)
Temozolomide	18 (34.6%)	9 (40.91%)	15 (41.7%)
PCV	0 (0%)	0 (0%)	0 (0%)
Temozolomide plus bevacizumab	9 (17.3%)	2 (9.09%)	4 (11.1%)
Bevacizumab	12 (23.1%)	8 (36.36%)	10 (27.8%)
Other	4 (7.7%)	2 (9.09%)	3 (8.3%)
Adjuvant chemotherapy following re-irradiation			
None	17 (32.7%)	5 (22.73%)	11 (30.6%)
Temozolomide	10 (19.2%)	3 (13.64%)	6 (16.7%)
PCV	0 (0%)	0 (0%)	0 (0%)
Temozolomide plus bevacizumab	6 (11.5%)	3 (13.64%)	4 (11.1%)
Bevacizumab	11 (21.2%)	7 (31.82%)	9 (25%)
Other	5 (9.6%)	2 (9.09%)	4 (11.1%)
Duration of bevacizumab (patients who received bevacizumab only)	Median: 3.97, IQR: 4.53 (2.23, 6.77)	Median: 2.8, IQR: 3.04 (0.93, 3.97)	Median: 3.97, IQR: 6 (2.35, 8.35)
FLAIR targeted at re-irradiation			
No	12 (23.08%)	7 (31.82%)	10 (27.78%)
Yes	28 (53.85%)	11 (50%)	20 (55.56%)
Unknown	12 (23.08%)	4 (18.18%)	6 (16.67%)
Re-irradiation enhancing volume	Median: 23.34, IQR: 40.59 (13.82, 54.41)	Median: 22.51, IQR: 41.11 (8.08, 49.19)	Median: 34.8, IQR: 61.69 (14.64, 76.33)
Re-irradiation FLAIR volume[a]	Median: 139.62, IQR: 127.6 (62.68, 190.28)	Median: 136, IQR: 148.52 (52.8, 201.32)	Median: 159.06, IQR: 146.34 (59.85, 206.19)
PTV overlap volume	Median: 62.58, IQR: 142.27 (4.79, 147.06)	Median: 62.58, IQR: 138.19 (2, 140.19)	Median: 62.32, IQR: 137.16 (5.19, 142.35)
Percentage of PTV at re-irradiation overlapping Initial Radiation PTV	Median: 0.53, IQR: 0.64 (0.2, 0.84)	Median: 0.36, IQR: 0.62 (0.11, 0.73)	Median: 0.5, IQR: 0.46 (0.2, 0.66)

Abbreviations: CRT, conformal radiation therapy; CSI, craniospinal radiation; FLAIR, fluid attenuated inversion recovery; IDH, isocitrate dehydrogenase; IMRT, intensity-modulated radiation therapy; IQR, interquartile range; KPS, Karnofsky performance status; MGMT, O^6-methylguanine-DNA methyltransferase; PCV, procarbazine, lomustine (CCNU) and vincristine; PTV, planning target volume; RT, radiation therapy; VMAT, volumetric modulated arc therapy.

[a]For patients where the FLAIR abnormality was targeted at re-irradiation.

* = gliosarcoma.

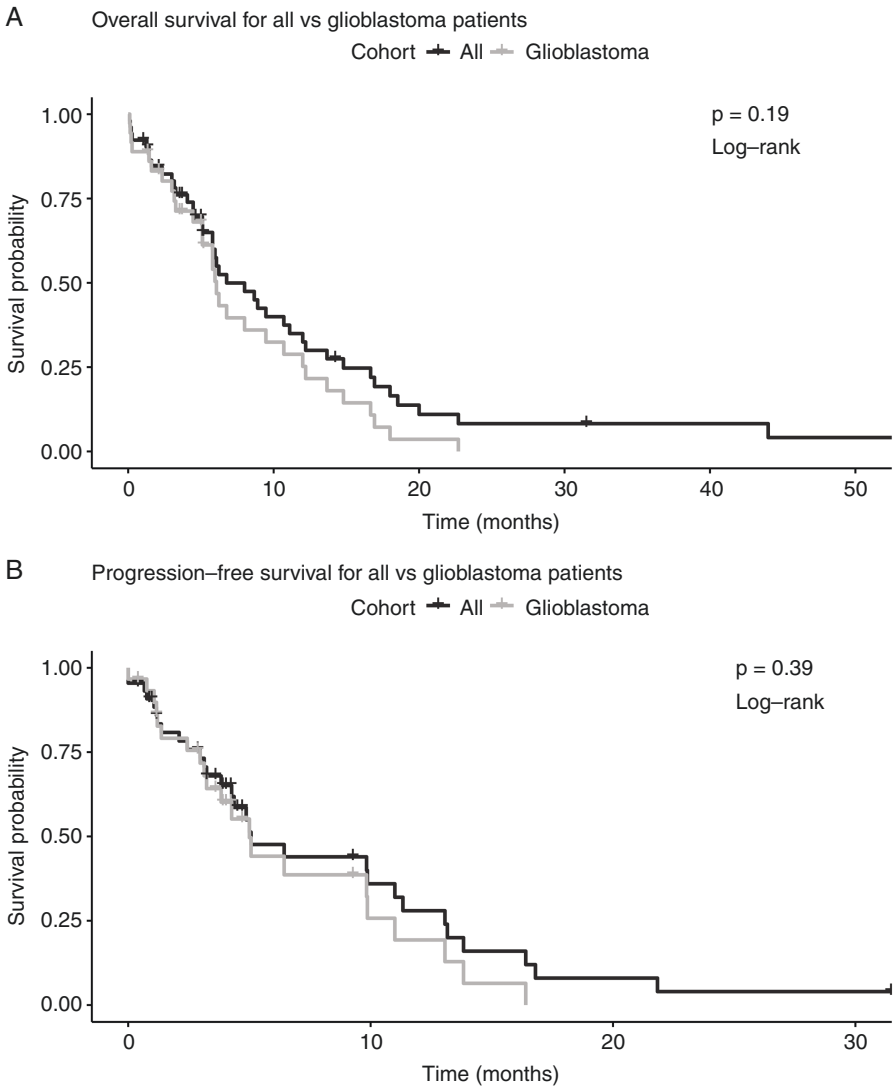

Figure 1. (A) Kaplan-Meier plot for overall survival of the entire cohort and of glioblastoma patients after re-irradiation. (B) Kaplan-Meier plot for progression-free survival of the entire cohort and glioblastoma patients after re-irradiation.

shown in Tables 2–4. For all patients, after adjusting for the patients' status of MGMT promoter methylation and the type of surgery at re-irradiation (GTR vs non-GTR), completion of re-irradiation (HR 0.03, $P < .001$) and the use of bevacizumab concurrently with re-irradiation (HR 0.339, $P = .008$) were associated with improved overall survival. After adjusting for the interval from the end of initial radiotherapy to recurrence, concurrent bevacizumab (HR 0.38, $P = .037$) and completion of re-irradiation (HR 0.14, $P = .022$) were associated with improved progression-free survival. Neither the number of lines of systemic therapy between courses of irradiation nor re-irradiation at first recurrence was predictive of progression-free or overall survival compared with re-irradiation at a subsequent recurrence.

For patients with GBM at the time of initial radiation, multiple predictors of improved overall survival after re-irradiation were identified, including completion of re-irradiation (HR 0.01, $P < .001$), fewer lines of salvage systemic therapy (HR 0.25, $P = .017$), and longer time from the completion of initial radiation therapy to the first recurrence (HR 0.99, $P = .013$). There were also trends toward improved overall survival with increasing BED10 at re-irradiation (HR 0.91, $P = .063$) and younger age at re-irradiation (HR 0.91, $P = .06$).

For patients with GBM at the time of recurrence, completing re-irradiation (HR 0.03, $P < .001$), use of concurrent bevacizumab (HR 0.30, $P = .009$), and increasing BED10 at re-irradiation (HR 0.92, $P = .005$) were predictive of overall survival. Despite the P value being greater than 0.05, the difference in median survival (5.8 months vs 9.47 months) suggested practical significance and improved overall survival in patients treated with re-irradiation courses with doses above a BED10 of 50 Gy, which includes regimens, such as 40.05 Gy in 15 fractions and 45 Gy in 25 fractions. Additionally, all patients surviving for more than 1 year received a BED10 of at

Table 2. Univariate and Multivariate Analysis for Overall Survival for All Patients

Predictors	Univariate Hazard Ratio	*P* value	Multivariate Hazard Ratio	*P* value
Re-irradiation at first or subsequent progression	0.709 (0.369-1.362)	0.302		
Interval from end of initial radiation to recurrence prior to re-irradiation	1 (0.9999-1)	0.436		
Concurrent bevacizumab with re-irradiation	0.687 (0.36-1.311)	0.255	0.291 (0.121-0.699)	0.006
Completed re-irradiation	0.052 (0.018-0.153)	<0.001	0.029 (0.007-0.113)	<0.001
Re-irradiation BED10	0.985 (0.951-1.021)	0.41		
IDH mutation at recurrence				
No	1 (referent)			
Yes	1.062 (0.365-3.092)	0.912		
Unknown	1.383 (0.618-3.098)	0.43		
MGMT methylation at recurrence				
No	1 (referent)		1 (referent)	
Yes	2.037 (0.753-5.506)	0.161	3.939 (1.249-12.424)	0.019
Unknown	1.47 (0.658-3.281)	0.347	1.471 (0.587-3.69)	0.411
Number of lines of systemic therapy between courses of radiation	1.141 (0.846-1.539)	0.387		
Interval from end of initial radiation to first recurrence	0.9998 (0.9997-1)	0.069	1 (0.9996-1)	0.074

Abbreviations: IDH, isocitrate dehydrogenase; MGMT, O^6-methylguanine-DNA methyltransferase.

Table 3. Univariate and Multivariate Analysis for Progression-free Survival for All Patients

Predictors	Univariate Hazard Ratio	*P* value	Multivariate Hazard Ratio	*P* value
Age at re-irradiation (years)	1.003 (0.977-1.029)	0.845		
Re-irradiation at first or subsequent progression	1.131 (0.524-2.442)	0.754		
Interval from completion of initial radiation to recurrence prior to re-irradiation	0.9997 (0.9995-0.9999)	0.008	0.9997 (0.9995-0.9999)	0.011
Concurrent bevacizumab with re-irradiation	0.646 (0.308-1.356)	0.248	0.384 (0.156-0.943)	0.037
Completed re-irradiation	0.181 (0.04-0.818)	0.026	0.14 (0.026-0.75)	0.022
Re-irradiation BED10	0.971 (0.928-1.017)	0.218		
KPS at re-irradiation	0.998 (0.957-1.042)	0.934		
IDH mutation at recurrence				
No	1 (referent)			
Yes	0.465 (0.124-1.746)	0.257		
Unknown	0.938 (0.361-2.434)	0.895		
MGMT methylation at recurrence				
No	1 (referent)			
Yes	0.934 (0.294-2.973)	0.908		
Unknown	0.899 (0.365-2.213)	0.817		
Number of lines of systemic therapy courses of radiation	1.319 (0.972-1.791)	0.075		
Interval from end initial radiation to first recurrence	0.9997 (0.9994-1)	0.038		

Abbreviations: IDH, isocitrate dehydrogenase; KPS, Karnofsky performance status; MGMT, O^6-methylguanine-DNA methyltransferase.

Table 4. Univariate and Multivariate Analysis for Overall Survival for Patients with GBM

Predictors	Glioblastoma at Initial Radiation (n = 22)				Glioblastoma at Re-irradiation (n = 36)			
	Univariate Hazard Ratio	*P* value	Multivariate Hazard Ratio	*P* value	Univariate Hazard Ratio	*P* value	Multivariate Hazard Ratio	*P* value
Age at re-irradiation (years)	0.998 (0.953-1.046)	0.939	0.909 (0.823-1.004)	0.06	1.012 (0.988-1.037)	0.332		
Re-irradiation at first or subsequent progression	0.693 (0.248-1.939)	0.485			1.082 (0.506-2.316)	0.838		
Interval from completion of initial radiation to recurrence prior to re-irradiation	0.9996 (0.999-1)	0.222	1.007 (1.002-1.012)	0.012	1 (0.9998-1)	0.967		
Concurrent bevacizumab with re-irradiation	0.381 (0.12-1.209)	0.102			0.542 (0.248-1.186)	0.125	0.303 (0.124-0.741)	0.009
Completed re-irradiation	0.095 (0.023-0.396)	0.001	0.006 (0.0003-0.139)	0.001	0.054 (0.016-0.187)	<0.001	0.032 (0.007-0.138)	<0.001
Re-irradiation BED10	0.972 (0.912-1.036)	0.377	0.913 (0.83-1.004)	0.063	0.952 (0.906-1.001)	0.055	0.924 (0.874-0.977)	0.005
IDH mutation at recurrence								
No	1 (referent)	0.941			1 (referent)	0.948		
Yes	1.085 (0.123-9.589)	0.166			1.043 (0.289-3.771)	0.371		
Unknown	2.085 (0.738-5.896)				1.525 (0.605-3.842)			
MGMT methylation at recurrence								
No	1 (referent)	0.852			1 (referent)	0.869		
Yes	1.15 (0.266-4.965)	0.057			1.1 (0.353-3.428)	0.102		
Unknown	3.221 (0.967-10.733)				2.057 (0.866-4.886)			
No. of lines systemic therapy between courses of radiation	1.297 (0.829-2.032)	0.255	0.249 (0.08-0.779)	0.017	1.247 (0.911-1.707)	0.168		
Interval from end initial radiation to first recurrence	0.9996 (0.999-1)	0.187	0.993 (0.987-0.998)	0.013	1 (0.9997-1)	0.886		
Concurrent temozolomide with re-irradiation	1.782 (0.629-5.049)	0.277	6.946 (1.646-29.314)	0.008	1.291 (0.593-2.809)	0.52		
Extent of resection (GTR vs non-GTR)	0.723 (0.2-2.613)	0.62	0.192 (0.018-2.024)	0.17	1.167 (0.341-3.996)	0.805		

Abbreviations: GBM, glioblastoma; GTR, gross total resection; IDH, isocitrate dehydrogenase; MGMT, O^6-methylguanine-DNA methyltransferase.

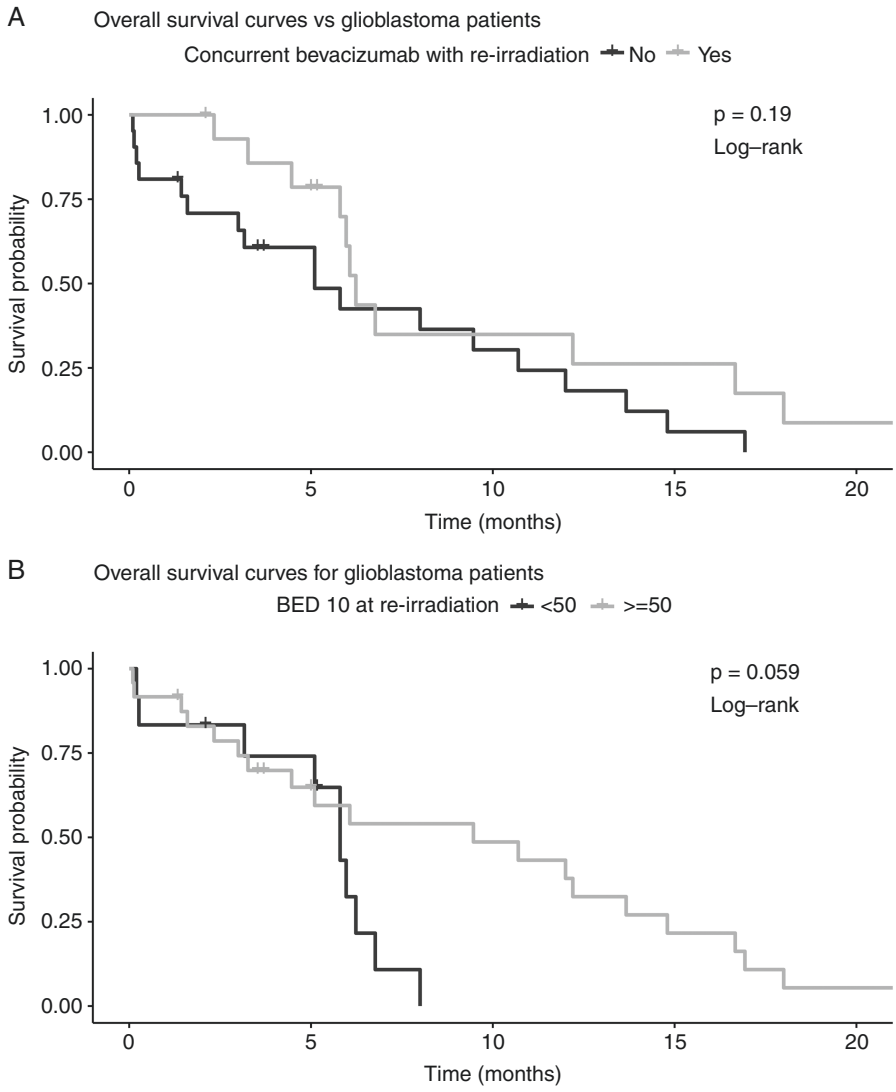

Figure 2. (A) Kaplan-Meier plot for overall survival of patients with concurrent bevacizumab vs patients without concurrent bevacizumab. (B) Kaplan-Meier plot for overall survival of patients with greater than or equal to 50 Gy vs less than 50 Gy.

least 50 Gy at re-irradiation (Figure 2B). Overall survival after re-irradiation did not differ based on the use of bevacizuamb or a BED10 of at least 50 Gy at re-irradiation in patients with glioblastoma at the time of initial radiation (Supplementary Figures 3 and 4). Notably, the interval from the end of the first course of re-irradiation to the recurrence treated with re-irradiation, the number of lines of systemic therapy between courses of radiation therapy, and re-irradiation at initial vs subsequent progression were not predictive of overall survival in patients with GBM.

Toxicity

Of the 46 patients evaluable for toxicity after re-irradiation in this study, 3 developed grade 4 ARE, 2 developed grade 3 neurocognitive decline, 3 developed new-onset seizures, and 4 developed grade 3 neurologic deficits. Two of the nine patients who developed a grade 3 or higher adverse event had received concurrent bevacizumab (one with new grade 3 neurologic deficits and one with new-onset seizures). No patients who received concurrent bevacizumab with re-irradiation developed grade 3 or higher ARE. The overall rate of grade 3 or higher toxicity among those treated with concurrent bevacizumab was 9.5% (2 out of 21 patients), compared with 28% (7 out of 25 patients) who were not treated with concurrent bevacizumab (P = .15). Neither the absolute volume of overlap between the initial and re-irradiation PTV nor the percentage of re-irradiation PTV that overlapped with the initial PTV were predictive of grade 3 or greater toxicity (P = .56 and P = .735, respectively).

The case who developed grade 3 neurologic deficits after re-irradiation with concurrent bevacizumab developed

new-onset right-sided weakness after receiving 50.4 Gy in 28 fractions with concurrent TMZ and bevacizumab for an in-field recurrence of a grade 3 oligodendroglioma approximately 18.5 years after initial radiation. The target at re-irradiation included the left thalamus and cerebral peduncle.

The case that developed new-onset seizures after re-irradiation with concurrent bevacizumab received 36 Gy in 20 fractions with concurrent TMZ and bevacizumab for a recurrent GBM 10.7 years after initial radiation (initial histology was grade 2 mixed oligoastrocytoma). Notably, in this case, the PTV at re-irradiation was 963.3 cm^3 and included all lobes of the right cerebral hemisphere, as well as the corpus callosum and portions of the left cerebral hemisphere.

Discussion

Bevacizumab has been commonly prescribed in the re-irradiation setting for GBM due to its steroid-sparing effects and its use as a salvage therapy for recurrent high-grade glioma.[8,19–22] Recently, it has been posited that bevacizumab may be able to increase the tolerance to a second-course radiation therapy by mitigating the VEGF-mediated radiation necrosis cascade. This theory was validated in two recent studies, one using stereotactic radiosurgery (SRS) at re-irradiation and one using a median dose of 36 Gy in standard fractionation. Both studies showed a decrease in radiation necrosis with concurrent bevacizumab.[8,17] In the present series, there was a trend toward the use of concurrent bevacizumab being protective against ARE in spite of the fact that these patients generally were treated to similar doses and target volumes at re-irradiation compared with those who were not. Interestingly, the amount of overlap between initial and re-irradiation PTVs was not predictive of development of grade 3 or greater toxicity. This may be due to a protective effect of concurrent bevacizumab.

Reports of delivery of re-irradiation doses as high as those delivered in the present study are limited and have not consistently reported radiation necrosis rates. A recent review reported doses of 100-130 Gy EQD2 (equivalent dose in 2 Gy per fraction) being utilized for conventionally fractionated re-irradiation, but the majority of the studies included in this review, especially those treating to higher doses, treated to much smaller target volume than the current series.[23]

The University of Wisconsin published a series of 103 patients with recurrent glioma treated with pulsed reduced dose rate radiotherapy (PRDR) to a median re-irradiation dose of 50 Gy, but this technique can be time-intensive for patients, particularly over a protracted treatment course.[24] This series also did not report radiation necrosis rates for the entire population but instead found that, in a subset of 16 patients for whom autopsy was performed, 4 had pathologic evidence of radiation necrosis, which is consistent with the rate of grade or greater 3 ARE in patients treated without bevacizumab in the current series. PRDR has also been reported in conjunction with bevacizumab, though again, radiation necrosis rates have not yet been reported.[21]

An additional study from Chan et al reported re-irradiation of high-grade gliomas with bevacizumab to large volumes; however, the majority of cases were treated to lower re-irradiation doses, with 67% receiving BED10 of under 50 Gy to slightly smaller volumes than in this series (median PTV 145 cc).[25] A study from Shen et al also reported re-irradiation with concurrent bevacizumab; however, except in cases of out of field failure, doses were limited to no more than 45 Gy in 25 fractions (BED10 = 53.1 Gy) with a median dose of 41.4 Gy in 1.8 Gy fractions (BED10 48.9 Gy). The study did find improved overall survival with doses greater than 41.4 Gy, similar to the current study.[26]

The target volume in the present series also differed from previous reports in that the FLAIR abnormality was intentionally targeted in the majority of cases. The majority of previous series of re-irradiation target the enhancing tumor volume, in some cases with additional margin, but not intentionally targeting FLAIR abnormality.[8,12,20,22,27–30] This is a particularly important distinction in the treatment of IDH mutant tumors (anaplastic glioma or secondary GBMs), as these tumors tend to have large non-enhancing components. Three previous series have intentionally targeted FLAIR abnormality or progression in re-irradiation.[24,25,31] In a series by Kim et al, patients with the FLAIR abnormality included in the target volume had improved local and regional failure.[31] A recent small randomized trial targeted the FLAIR abnormality to a lower dose (24 Gy in 4 fractions, BED10 38.4 Gy) than gross disease in patients with recurrent high-grade glioma concurrently with bevacizumab-based chemotherapy also found improvement in progression-free survival and a trend toward improved overall survival with the addition of fractionated SRS to bevacizumab-based chemotherapy.[32] Recent studies have suggested that progression of non-contrast enhancing disease ultimately leads to patient demise in patients with GBM, and it may have been that insufficient dose to the non-enhancing disease fails to prevent the progression of tumor in that area.[33–35]

The improved outcomes seen with increased radiation dose at re-irradiation for GBM are consistent with data in the initial radiation therapy setting, where a dose-response effect has been shown with improved survival with dose escalation up to 60 Gy.[13] However, some recent series suggest that this dose-response is sensitive to age and performance status.[36] Patients who are offered re-irradiation, in general, are a selected population of patients who have survived for longer with longer disease-free intervals, had lower grade tumors that transform to GBM, and have previously responded to radiation therapy. As such, they represent a population that is enriched for a more protracted disease course and may benefit from the use of concurrent bevacizumab to allow for both radiation dose and target volume escalation.[27]

There are several limitations to the present series. The data are derived from a retrospective single-institution dataset and thus are limited to hypothesis generation. It is also therefore subject to the selection biases of retrospective series, particularly with regards to the physician discretion of re-irradiation

fractionation schemes and the time biases associated with a historical control group treated in a previous era. Additionally, due to the length of the study period, molecular characteristics of the treated tumors were not consistently available. In spite of potential selection biases, patients who were treated with protracted courses were more likely to have greater treatment volumes yet these patients still experienced a greater survival. While the data from the present series will need to be validated, they provide the basis for potential clinical trials of dose-escalated re-irradiation with concurrent bevacizumab delivered as a means to protect against radiation necrosis.

Conclusions

High dose re-irradiation with concurrent bevacizumab is a feasible option in patients with recurrent gliomas even in the setting of large treatment volumes targeting non-enhancing tumor components. GBM patients with the same completion status of re-irradiation appear to have improved overall survival with concurrent bevacizumab use and increasing dose at the time of re-irradiation. These findings require validation in prospective studies.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Practice* online.

Funding

This research was not supported by any grants or funding.

Conflict of interest statement. The authors have no conflicts of interest to declare. The views expressed in this article are those of the authors and do not reflect the official policy or position of Fort Belvoir Community Hospital, the Defense Health Agency, Department of Defense, or the US Government. Reference to any commercial products within this publication does not create or imply any endorsement by Fort Belvoir Community Hospital, the Defense Health Agency, Department of Defense, or US Government.

Authorship statement. Conception and design: C.A.H., C.K.C., and M.D.C. Collection and assembly of data: C.A.H., S.-N.P., and M.D.C. Data analysis and interpretation: C.A.H., S.-N.P., C.K.C., and M.D.C. Manuscript writing: all authors. Final approval of manuscript: all authors.

References

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352(10):987–996.
2. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA.* 2017;318(23):2306–2316.
3. Taphoorn MJB, Dirven L, Kanner AA, et al. Influence of treatment with tumor-treating fields on health-related quality of life of patients with newly diagnosed glioblastoma: a secondary analysis of a randomized clinical trial. *JAMA Oncol.* 2018;4(4):495–504.
4. Wick W, Gorlia T, Bendszus M, et al. Lomustine and bevacizumab in progressive glioblastoma. *N Engl J Med.* 2017;377(20):1954–1963.
5. Reardon DA, Brandes AA, Omuro A, et al. Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: the CheckMate 143 phase 3 randomized clinical trial. *JAMA Oncol.* 2020;6(7):1003–1010.
6. Vredenburgh JJ, Desjardins A, Herndon JE, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol.* 2007;25(30):4722–4729.
7. Reardon DA, Nabors LB, Mason WP, et al. Phase I/randomized phase II study of afatinib, an irreversible ErbB family blocker, with or without protracted temozolomide in adults with recurrent glioblastoma. *Neuro Oncol.* 2015;17(3):430–439.
8. Tsien C, Pugh S, Dicker AP, et al. Randomized phase II trial of re-irradiation and concurrent bevacizumab versus bevacizumab alone as treatment for recurrent glioblastoma (NRG oncology/RTOG 1205): initial outcomes and RT plan quality report. *Int J Radiat Oncol Biol Phys.* 2019;105(1):S78.
9. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *Eur J Cancer.* 2012;48(14):2192–2202.
10. Greene-Schloesser D, Robbins ME, Peiffer AM, et al. Radiation-induced brain injury: a review. *Front Oncol.* 2012;2. doi:10.3389/fonc.2012.00073.
11. Chan MD, Tatter SB, Lesser G, Shaw EG. Radiation oncology in brain tumors: current approaches and clinical trials in progress. *Neuroimaging Clin N Am.* 2010;20(3):401–408.
12. Combs SE, Thilmann C, Edler L, Debus J, Schulz-Ertner D. Efficacy of fractionated stereotactic reirradiation in recurrent gliomas: long-term results in 172 patients treated in a single institution. *J Clin Oncol.* 2005;23(34):8863–8869.
13. Walker MD, Strike TA, Sheline GE. An analysis of dose-effect relationship in the radiotherapy of malignant gliomas. *Int J Radiat Oncol Biol Phys.* 1979;5(10):1725–1731.
14. Howard SP, Krauze A, Chan MD, Tsien C, Tomé WA. The evolving role for re-irradiation in the management of recurrent grade 4 glioma. *J Neurooncol.* 2017;134(3):523–530.
15. Clarke J, Neil E, Terziev R, et al. Multicenter, phase 1, dose escalation study of hypofractionated stereotactic radiation therapy with bevacizumab for recurrent glioblastoma and anaplastic astrocytoma. *Int J Radiat Oncol Biol Phys.* 2017;99(4):797–804.
16. Levin VA, Bidaut L, Hou P, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int J Radiat Oncol Biol Phys.* 2011;79(5):1487–1495.
17. Cuneo KC, Vredenburgh J, Desjardins A, et al. Impact of concurrent and adjuvant bevacizumab on the risk of radiation necrosis following radiosurgery for recurrent glioma. *Int J Radiat Oncol Biol Phys.* 2012;84(3):S7.

18. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol.* 2010;28(11):1963–1972.
19. Fleischmann DF, Jenn J, Corradini S, et al. Bevacizumab reduces toxicity of reirradiation in recurrent high-grade glioma. *Radiother Oncol.* 2019;138:99–105. doi:10.1016/j.radonc.2019.06.009.
20. Palmer JD, Bhamidipati D, Song A, et al. Bevacizumab and re-irradiation for recurrent high grade gliomas: does sequence matter? *J Neurooncol.* 2018;140(3):623–628.
21. Bovi JA, Prah MA, Retzlaff AA, et al. Pulsed reduced dose rate radiotherapy in conjunction with bevacizumab or bevacizumab alone in recurrent high-grade glioma: survival outcomes. *Int J Radiat Oncol Biol Phys.* 2020;108(4):979–986.
22. Flieger M, Ganswindt U, Schwarz SB, et al. Re-irradiation and bevacizumab in recurrent high-grade glioma: an effective treatment option. *J Neurooncol.* 2014;117(2):337–345.
23. Minniti G, Niyazi M, Alongi F, Navarria P, Belka C. Current status and recent advances in reirradiation of glioblastoma. *Radiat Oncol.* 2021;16(1):36.
24. Adkison JB, Tomé W, Seo S, et al. Reirradiation of large-volume recurrent glioma with pulsed reduced-dose-rate radiotherapy. *Int J Radiat Oncol Biol Phys.* 2011;79(3):835–841.
25. Chan J, Jayamanne D, Wheeler H, et al. The role of large volume re-irradiation with bevacizumab in chemorefractory high grade glioma. *Clin Transl Radiat Oncol.* 2020;22:33–39. doi:10.1016/j.ctro.2020.03.005.
26. Shen CJ, Kummerlowe MN, Redmond KJ, et al. Re-irradiation for malignant glioma: toward patient selection and defining treatment parameters for salvage. *Adv Radiat Oncol.* 2018;3(4):582–590.
27. Krauze AV, Attia A, Braunstein S, et al. Expert consensus on re-irradiation for recurrent glioma. *Radiat Oncol.* 2017;12(1):194.
28. Fogh SE, Andrews DW, Glass J, et al. Hypofractionated stereotactic radiation therapy: an effective therapy for recurrent high-grade gliomas. *J Clin Oncol.* 2010;28(18):3048–3053.
29. Gutin PH, Iwamoto FM, Beal K, et al. Safety and efficacy of bevacizumab with hypofractionated stereotactic irradiation for recurrent malignant gliomas. *Int J Radiat Oncol Biol Phys.* 2009;75(1):156–163.
30. Wick W, Fricke H, Junge K, et al. A phase II, randomized, study of weekly APG101+reirradiation versus reirradiation in progressive glioblastoma. *Clin Cancer Res.* 2014;20(24):6304–6313.
31. Kim EY, Yechieli R, Kim JK, et al. Patterns of failure after radiosurgery to two different target volumes of enhancing lesions with and without FLAIR abnormalities in recurrent glioblastoma multiforme. *J Neurooncol.* 2014;116(2):291–297.
32. Bergman D, Modh A, Schultz L, et al. Randomized prospective trial of fractionated stereotactic radiosurgery with chemotherapy versus chemotherapy alone for bevacizumab-resistant high-grade glioma. *J Neurooncol.* 2020;148(2):353–361.
33. Lasocki A, Gaillard F. Non-contrast-enhancing tumor: a new frontier in glioblastoma research. *AJNR Am J Neuroradiol.* 2019;40(5):758–765.
34. Holmes JA, Paulsson AK, Page BR, et al. Genomic predictors of patterns of progression in glioblastoma and possible influences on radiation field design. *J Neurooncol.* 2015;124(3):447–453.
35. Soike MH, McTyre ER, Shah N, et al. Glioblastoma radiomics: can genomic and molecular characteristics correlate with imaging response patterns? *Neuroradiology.* 2018;60(10):1043–1051.
36. Roa W, Brasher PMA, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. *J Clin Oncol.* 2004;22(9):1583–1588.