Hypofractionated stereotactic radiosurgery with concurrent bevacizumab for recurrent malignant gliomas: the University of Alabama at Birmingham experience

Grant M. Clark, Andrew M. McDonald, Louis B. Nabors, Hassan Fathalla-Shaykh, Xiaosi Han, Christopher D. Willey, James M. Markert, Barton L. Guthrie, Markus Bredel, and John B. Fiveash

University of Alabama at Birmingham Radiation Oncology, Birmingham, Alabama (G.M.C., A.M.M., C.D.W., M.B., J.B.F.); University of Alabama at Birmingham Neuro-Oncology, Birmingham, Alabama (L.B.N., H.F.-S., X.H.); University of Alabama at Birmingham Neurosurgery, Birmingham, Alabama (J.M.M., B.L.G.)

Corresponding Author: Grant M. Clark, MD, UAB Department of Radiation Oncology. 1700 6th Ave, S. Birmingham, AL 35233 (gmclark83@gmail.com).

Background. Nearly all patients with malignant glioma will have disease recurrence. Our purpose was to define the treatment toxicity and efficacy of concurrent bevacizumab (BVZ) with hypofractionated stereotactic radiosurgery (SRS) of relatively larger targets for patients with recurrent MG.

Methods. A retrospective review of 21 patients with recurrent malignant glioma (18 glioblastoma, 3 WHO grade III glioma), treated at initial diagnosis with surgery and standard chemoradiation, was performed. All patients had concurrent BVZ with hypofractionated SRS, 30 Gy in 5 fractions, with or without concurrent chemotherapy (temozolomide or CCNU).

Results. Median patient age was 54 years, median Karnofsky Performance Status was 80, and median target size was 4.3 cm (range, 3.4–7.5 cm). Eleven patients (52%) had previously failed BVZ. One patient had grade 3 toxicities (seizures, dysphasia), which resolved with inpatient admission and intravenous steroids/antiepileptics. Treatment-related toxicities were grade 3 (n = 1), grade 2 (n = 9), and grade 0–1 (n = 11). Kaplan-Meier median progression-free survival and overall survival estimates (calculated from start of SRS) for GBM patients (n = 18) were 11.0 and 12.5 months, respectively. Concurrent chemotherapy did not appear to show any statistically significant efficacy benefit or have any propensity for toxicity.

Conclusion. BVZ concurrent with hypofractionated SRS was well tolerated by this cohort of patients with relatively larger targets. Ongoing randomized trials with more moderate radiotherapy dosing may help establish the efficacy of this regimen, though intricacies of this approach, including patient selection, radiation target volume delineation/size, and optimal radiation dose, will need further evaluation.

Keywords: bevacizumab, glioblastoma, hypofractionated radiation, radiosurgery, recurrent.

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults,1 and a majority of patients eventually develop recurrence (at a median 8 months) after receiving trimodality therapy.2 In general, patients with recurrent GBM have a poor prognosis and have been treated with various modalities including surgery, chemotherapy, and/or salvage reirradiation.3,4 In 2009 bevacizumab (BVZ), a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), was approved by the FDA as a single agent for recurrent GBM, with rationale for approval based largely on randomized phase II studies showing efficacy (6-month progression-free survival [PFS] of 40%–50%) and corticosteroid-sparing effects.5,6 More recently, 2 prospective clinical trials have reported the safety and efficacy of concurrent stereotactic radiosurgery (SRS) with BVZ for the treatment of recurrent high-grade gliomas.7,8 Both trials reported acceptable toxicity profiles, and the authors concluded that this treatment for recurrent GBM was well tolerated; radiographic responses and survival suggest that this is an active regimen for recurrent malignant gliomas. The results of these trials, combined with the results of a large institutional experience utilizing hypofractionated radiotherapy for recurrent malignant glioma,3 have prompted activation of the Radiation Therapy Oncology Group (RTOG) 1205 study, which is a prospective, randomized phase II trial comparing single agent BVZ versus...
hypofractionated radiotherapy concurrent with BVZ for recurrent GBM.10

Despite these initial reports and the ongoing multicenter randomized trial, a number of clinical questions remain (and will likely persist even after results from RTOG 1205 are reported) due to differences in radiation technique, dose/fractionation, usage of temozolomide, reirradiation sequence (as first versus subsequent salvage therapies), and heterogeneous patient populations between trials. The purpose of this report is to add to the growing body of literature describing the technique, toxicity, and efficacy of concurrent BVZ with SRS for recurrent glioma in an effort to further tailor therapy for those patients most likely to benefit from this treatment. Though the underlying rationale for usage of BVZ concurrent with hypofractionated SRS at our institution is congruent with the rationale for previously reported trials, we have treated a patient population that is slightly more inclusive than those in the aforementioned clinical trials, especially inclusion of patients with larger targets and/or with the addition of chemotherapy (temozolomide or CCNU) with BVZ and SRS.

Methods

Patient Population

After obtaining approval from the University of Alabama at Birmingham Institutional Review Board, a retrospective review of patients treated with hypofractionated SRS for a diagnosis of glioma was performed at the University of Alabama at Birmingham Department of Radiation Oncology. Inclusion criteria for final analysis comprised all patients who had a histological diagnosis of recurrent WHO grade III or WHO grade IV glioma treated with SRS and concurrent BVZ (10 mg/kg intravenously, administered ≤72 h before the start of radiation). Each case was presented prospectively at a multidisciplinary CNS tumor board, with group recommendation for SRS with concurrent BVZ as the treatment for recurrent glioma prior to undergoing the first SRS fraction. A total of 21 cases were found to be eligible for inclusion into the analysis.

Radiation Technique

Patients underwent a CT-simulation scan with 2 mm slices and 0.8 mm reconstruction. All patients were immobilized with a non-invasive thermoplastic mask for simulation and treatment. CT images were fused with MR images utilizing both the contrast-enhanced T1 series and the T2 fluid-attenuated inversion recovery (FLAIR) series. Gross tumor volume (GTV) was defined as the enhancing tumor on T1 with contrast series (n = 8) or as the contrast-enhancing tumor plus abnormal T2 FLAIR that was progressing as compared with prior scans (n = 13). Of note, progressing T2 FLAIR was considered the GTV in the vast majority of patients (8 of 11) who were considered to have progressed on BVZ prior to SRS. For patients who were BVZ naı¨ve (n = 10), 5 (50%) had GTV defined as T1 plus contrast enhancement only, while the other 5 patients had GTV equal to T1 plus contrast enhancement and abnormal T2 FLAIR. Ultimately, final determination of GTV was at the discretion of the treating physician. The majority of patients (n = 17) had no GTV to planning target volume (PTV) margin (ie, GTV = PTV); 4 patients had a 2–4 mm margin placed around the GTV to create the PTV. Determination of GTV-to-PTV margin was based upon physician preference, taking into account concern for reliability, stability, and reproducibility of patient alignment with the noninvasive thermoplastic mask and image-guidance technique.

All patients had a PTV prescription of 30 Gy in 5 total fractions, delivered via a volumetric-modulated arc radiosurgery plan on a linear accelerator in flattening filter-free high-intensity mode. Attempts were made to normalize plans to 100% of prescription dose (30 Gy) covers 95% of the PTV. Significant inhomogeneity within the plans was allowed in order to achieve conformal prescription-dose distribution and spare adjacent structures at risk. In general, attempts were made to limit maximum brainstem and optic nerve/chiasm dose to <25 Gy in areas that had previously received minimal radiation. However, SRS dose constraints were more stringent for portions of brainstem or optic nerves/chiasm that previously received significant irradiation. Ultimately, final dosimetry and plan approval were at the discretion of the treating physician. Daily image guidance prior to each fraction was performed with orthogonal kV imaging and cone-beam CT scans. All patients were given dexamethasone during their radiotherapy course, either as daily scheduled dosing or as a single dose on the day of each radiotherapy treatment. Median time to radiotherapy course completion was 8 calendar days (range, 5–14 days).

Patient Follow-up and Statistics: Toxicity, Progression Assessment, and Survival Analysis

All patients were evaluated for toxicity during the radiotherapy course and 1 month after completion of the final fraction of radiation, at which time they also underwent MRI plus contrast. Subsequently, patients were evaluated by physicians at 2–3-month intervals and underwent MRI at those times as well. At each physician visit, a history and physical was recorded with medications updated (including steroid usage), and prospective toxicity grading was recorded utilizing the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. All patient MR images were read by neuroradiologists, with progression defined prospectively using the Response Assessment in Neuro-Oncology (RANO) criteria.11 An in-field failure was defined as disease progression on MRI within the high-dose region (volume encompassed by the 80% isodose line). Marginal failure was defined as disease progression within 2 cm of the high-dose region, and distant failure was defined as progression at least 2 cm from the high-dose region.

Overall survival (OS) and PFS were calculated for patients with GBM (n = 18) from the date of the first fraction of radiation delivery. Death was confirmed by the Social Security Death Index. For PFS, patients were censored from the analysis at the time of last follow-up. Survival estimates were generated by the Kaplan-Meier method and compared with the log-rank test. Of note, 2 patients had death as their first event because they elected to have follow-up MRIs at an outside institution or no follow-up imaging was available for this analysis; they were thus censored from the PFS analysis at the time of their last follow-up. For OS analysis, patients were censored from the time of last clinical follow-up. The effect of various parameters on PFS were estimated by univariate Cox proportional hazards modeling, and binomial logistic regression was used to test the effect of parameters on the development of grade 2 or worse toxicity at any time. Factors analyzed...
were age, KPS, target size, target delineation method (contrast enhancement or FLAIR), usage of concurrent chemotherapy, months between radiotherapy courses, or total radiation dose to SRS target (prior radiotherapy plus SRS). To investigate the effect of overall treatment time on toxicity, a binary logistic regression analysis was performed, with the presence of grade 2 toxicity as the endpoint. Statistical analysis was performed using SPSS version 22.0 software.

**Results**

**Patient Characteristics**

A total of 21 patients met inclusion criteria for the analysis, with eligible patient treatment courses spanning the time period from August 8, 2010 to July 7, 2013. Median follow-up time was 8.5 months after the start of SRS (range, 1 week to 31 months). Table 1 presents patient characteristics. The majority of patients (n = 18) had GBM as their histological diagnosis. The median number of prior salvage therapies (i.e., re-resection, chemotherapy, BVZ monotherapy or in combination with chemo) was 2. The median between first and second radiotherapy course was 24 months (range 9–124 months). Just over half of the patients (n = 11) had previously failed a BVZ-based regimen at the time of their SRS. All patients had concurrent BVZ during radiotherapy, with 10 patients (48%) having additional concurrent chemotherapy (temozolomide n = 8 or CCNU n = 2) in combination with the BVZ and SRS. Usage of concurrent chemotherapy was at the discretion of the treating neuro-oncologist, largely based upon prior tolerance of temozolomide, and was utilized in both patients who had previously failed BVZ (n = 5) and those who were BVZ naïve (n = 5).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 21)</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (48%)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (52%)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>54.1 (30–82)</td>
</tr>
<tr>
<td>Karnofsky Performance Status, n (%)</td>
<td></td>
</tr>
<tr>
<td>70–80</td>
<td>14 (67%)</td>
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<tr>
<td>90–100</td>
<td>7 (33%)</td>
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<tr>
<td>Prior low-grade glioma, n (%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Most recent histological diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>18 (86%)</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Median prior salvage therapies (range)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>Median months from initial radiotherapy (range)</td>
<td>24 (9–124)</td>
</tr>
<tr>
<td>Course to SRS</td>
<td></td>
</tr>
<tr>
<td>Median prior radiotherapy dose to SRS target (range)</td>
<td>60 Gy (10–60)</td>
</tr>
<tr>
<td>Reirradiation of previous target volume, n (%)</td>
<td>16 (76%)</td>
</tr>
<tr>
<td>Previously failed bevacizumab, n (%)</td>
<td>11 (52%)</td>
</tr>
<tr>
<td>Median PTV cc (range)</td>
<td>20.0 (3.6–85.6)</td>
</tr>
<tr>
<td>Median diameter of PTV cm (range)</td>
<td>4.3 (3.4–7.5)</td>
</tr>
</tbody>
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*Common Terminology Criteria for Adverse Events, version 4.0.

The median PTV diameter was 4.3 cm with range of 3.4–7.5 cm. Median PTV was 20.0 cc with range of 3.6–85.6 cc. All patients completed all 5 radiosurgery fractions. All patients were planned to go on to receive adjuvant systemic therapy with a BVZ-based regimen, with the majority (n = 18) receiving at least one additional cycle of adjuvant BVZ +/- additional chemotherapy following the last fraction of radiotherapy.

**Toxicity and Steroid Usage**

Table 2 presents all treatment-related toxicities. The most common toxicities were mild-to-moderate headache and fatigue. One patient had grade 3 toxicities (grade 3 seizure and grade 3 aphasia) that required inpatient admission and acute medical management with intravenous steroids and antiepileptics; both of these toxicities resolved with inpatient care and the patient was discharged home. All other patients had ≤ grade 2 toxicity. No intracranial hemorrhages, thromboembolic events, clinical or radiographic radionecrosis, or wound complications were observed. Treatment-related toxicities included one grade 3 toxicity, nine grade 2 toxicities, and eleven grade 1 toxicities. No pretreatment or treatment parameters were found to be statistically significant predictors of grade ≥ 2 toxicity. No statistically significant relationship between time to radiation course completion and grade ≥ 2 toxicity was noted (HR = 0.8, P = .638). All patients were treated with steroids (dexamethasone) during their radiotherapy course. Four patients (19%) were already on steroids prior to the initiation of the BVZ and SRS course. Of patients still alive and available for follow-up clinic visit after 1 month post SRS, 2 out of 17 (11.7%) were still on steroids.

**Survival and Patterns of Failure**

Figure 1 displays Kaplan-Meier PFS curves for patients having a pathological diagnosis of GBM, with median PFS of 11.0 months. Figure 2 displays Kaplan-Meier OS curves for GBM patients, with median OS 12.5 months. At the time of data analysis (median follow-up time was 7.4 months), 12 patients (57%) were still alive, and 6 patients were still alive more than 18 months after
the radiosurgery course. Of the 6 longer-term survivors, 5 had a most recent pathological diagnosis of GBM and one patient had anaplastic astrocytoma. Concurrent BVZ with SRS was the first salvage attempt in half of these longer-term survivors, while the other 3 patients had BVZ with SRS as their second salvage therapy. Five of the 6 patients had concurrent temozolomide with BVZ during their SRS course.

Patients who underwent concurrent chemotherapy with BVZ and SRS had a longer Kaplan-Meier estimated median PFS (11.7 vs 6.3 months) and OS (19.3 vs 8.3 months), although these differences were not statistically significant (PFS \( P = .26 \) and OS \( P = .21 \)). Although it did not reach statistical significance (P = .70), there was also a numerical difference in median Kaplan-Meier PFS estimates for those GBM patients who had previously failed BVZ (\( n = 11; \) PFS, 6.2 months) versus those who were BVZ naïve (\( n = 7; \) PFS, 19.9 months) as visualized in Fig 3. On Cox regression analysis, SRS target size or GTV delineation method (T1 plus contrast or T1 plus contrast in addition to T2 FLAIR) did not correlate with PFS, OS, or incidence of grade ≥ 2 toxicity.

Patterns of first site(s) of failure (19 patients total available for this analysis) were as follows at the time of analysis: no failure (\( n = 8 \)) and RANO progression (\( n = 11 \)). Of those who progressed, sites were as follows: in-field (\( n = 4, 36\% \)), marginal (\( n = 1, 9\% \)), distant (\( n = 5, 45\% \)), and combined local plus distant (\( n = 1, 9\% \)). Two patients had death as their first event because they elected to have follow-up MRI at an outside institution or no follow-up imaging was available for this analysis. Local in-field failure at any point in follow-up (as first or subsequent site of failure) occurred in 11 of 19 patients (58%).

Discussion

In this institutional experience, hypofractionated SRS concurrent with BVZ was well tolerated for selected patients with recurrent high-grade glioma, including a substantial number of patients in our cohort who had relatively larger targets than those reported in prior prospective trials. The overall number of patients in this report is larger than the previously reported prospective trial from Duke (\( n = 15 \)) and just smaller than the Memorial Sloan-Kettering (MSK) trial (\( n = 25 \)).7,8 Our Kaplan-Meier estimates of PFS (11.0 months) and OS (12.3 months) for GBM patients in this report are similar to median PFS and OS estimates from these 2
prospective trials (Duke PFS = 3.9 months/OS = 14.4 months and MSK PFS = 7.3 months/OS = 12.5 months [GBM] and 16.5 months [anaplastic glioma]). The toxicity profiles in our report also compare favorably with previous reports.

There are some important differences to note about the patients in this report and those enrolled in the prior trials utilizing SRS and concurrent BVZ. The median target diameter in this study was 4.3 cm, with 17 patients (81%) having PTV diameters >3.5 cm and 7 patients (33%) having PTV diameters >5 cm. In contrast, the MSK series excluded patients with enhancing tumors >3.5 cm, and the Duke trial excluded lesions >5 cm (with the Duke trial also using a lower SRS dose — 25 Gy in 5 fractions for targets from 3–5 cm). Both of the prospective clinical trials included only the T1 contrast-enhancing tumor plus 1 mm (Duke) or 5 mm (MSK) of planning margin to delineate the SRS target, whereas in our experience the slight majority of patients (n = 13, 62%) were treated with target volume encompassing both the contrast-enhancing T1 tumor and expanding/changing T2 FLAIR while typically using no GTV-to-PTV margin.

A group at the Henry Ford Health System has shown safety in utilizing a hypofractionated SRS approach (6 Gy in 6 fractions) without concurrent BVZ for larger radiosurgery target volumes (median target volume 51 cc) in the treatment of both enhancement and rapidly changing FLAIR in a small cohort of patients (n = 10) with recurrent malignant glioma. In their series, one patient had a mixed residual tumor and necrosis on post-hypofractionated SRS biopsy. They subsequently reported improved PFS for patients who had failed BVZ and then received reirradiation SRS concurrent with BVZ compared with those who did not have reirradiation. The SRS target volume in this comparison also encompassed rapidly evolving FLAIR as well as enhancing tumor.

Bevacizumab can markedly reduce contrast enhancement, and patients may exhibit progression without marked increase in T1 contrast enhancement. It has become apparent that a subset of patients on anti-VEGF therapy, who initially experience reduction in tumor contrast enhancement, subsequently develop progressive increase in nonenhancing T2 or FLAIR signals, suggestive of infiltrative tumor. Thus, given these imaging characteristics, patients at our institution who failed a BVZ-containing regimen and were deemed appropriate candidates for hypofractionated SRS with concurrent BVZ have often had SRS targets that included the worrisome T2 or FLAIR changes indicative of tumor progression. Our experience, combined with the Henry Ford report, suggests that this treatment-planning technique may still be safe and efficacious.

The optimal radiotherapy dose for this treatment regimen remains unknown. The current randomized RTOG trial for recurrent malignant glioma excludes patients with tumor >5 cm and is comparing a more moderate dosing schedule of 35 Gy in 10 fractions concurrent with BVZ versus BVZ monotherapy without irradiation. Previous reports have shown a wide range of radiosurgery doses for recurrent malignant glioma in the reirradiation setting ranging from a single fraction of 24 Gy to 25 Gy delivered in 5 total fractions. Other reports have utilized a more standard fractionation approach of 2 Gy per fraction to 36 Gy total. A current phase I dose-escalation trial is underway at MSK and will attempt to determine the maximum tolerable SRS dose concurrent with BVZ for recurrent malignant glioma. Despite our patient cohort having relatively larger targets than some prior reports, the overall toxicity profile still seems favorable, and patient outcomes (including PFS and OS) mirror the more selective prospective trials.

It is notable that the addition of concurrent temozolomide with BVZ and SRS was utilized in 5 of the 6 patients who survived more than 18 months, even though direct comparison of PFS and OS estimates for the cohort of GBM patients who had concurrent BVZ and chemotherapy with SRS versus those who had BVZ monotherapy with SRS did not show statistical significance. However, with such a small number of patients for this subgroup comparison, the lack of statistical significance is not surprising. It is possible, however, that treating physicians may have selected only the most robust patients for further escalation of therapy with additional radiosensitizing chemotherapy. Nevertheless, for highly selected patients, and especially those who showed excellent tolerance and/or tumor response to temozolomide in the past, there may be a benefit to the addition of reintroducing radiosensitizing temozolomide during BVZ and SRS therapy for recurrent malignant glioma. Further studies will need to clarify the role of temozolomide in this setting. Though all patient data were collected prospectively, the retrospective chart review nature of this study lends itself to the inherent limitations of any retrospective analysis. Though the number of patients in this analysis is essentially as large as the 2 largest prospective trials, the overall number is not large enough to make many definitive subgroup comparisons. It is likely that patients were highly selected for an aggressive salvage attempt with SRS and were felt to have a high enough life expectancy and functional status to tolerate therapy.

In conclusion, we have presented our institutional experience of concurrent BVZ with hypofractionated SRS for the treatment of recurrent malignant glioma and included patients with larger target volumes than previously reported. Our results show that this was a well-tolerated treatment for selected patients, and PFS and OS estimates suggested that this is also an active regimen, even for patients who had previously failed BVZ or other salvage therapies. The ongoing randomized trial with more moderate radiotherapy dosing may help establish the efficacy of this regimen, although some intricacies of this approach, including patient selection, the role of concurrent temozolomide, radiation target volume delineation, target size, and optimal radiation dose schedules, will need further evaluation.

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References


