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CLINICAL STUDY

Randomized prospective trial of fractionated stereotactic radiosurgery with chemotherapy versus chemotherapy alone for bevacizumab-resistant high-grade glioma

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Abstract

Purpose Outcomes for patients with recurrent high-grade glioma (HGG) progressing on bevacizumab (BEV) are dismal. Fractionated stereotactic radiosurgery (FSRS) has been shown to be feasible and safe when delivered in this setting, but prospective evidence is lacking. This single-institution randomized trial compared FSRS plus BEV-based chemotherapy versus BEV-based chemotherapy alone for BEV-resistant recurrent malignant glioma.

Materials and methods HGG patients on BEV with tumor progression after 2 previous treatments were randomized to 1) FSRS plus BEV-based chemotherapy or 2) BEV-based chemotherapy with irinotecan, etoposide, temozolomide, or carboplatin. FSRS was delivered as 32 Gy (8 Gy × 4 fractions within 2 weeks) to the gross target volume and 24 Gy (6 Gy × 4 fractions) to the clinical target volume (fluid-attenuated inversion recovery abnormality). The primary endpoints were local control (LC) at 2 months and progression-free survival (PFS).

Results Of the 35 patients enrolled, 29 had glioblastoma (WHO IV) and 6 had anaplastic glioma (WHO III). The median number of prior recurrences was 3. Patients treated with FSRS had significantly improved PFS (5.1 vs 1.8 months, $P < .001$) and improved LC at 2 months (82% [14/17] vs 27% [4/15], $P = .002$). The overall median survival was 6.6 months (7.2 months with FSRS vs 4.8 months with chemotherapy alone, $P = .11$).

Conclusions FSRS combined with BEV-based chemotherapy in recurrent HGG patients progressing on BEV is feasible and improves LC and PFS when compared to treatment with BEV-based chemotherapy alone.

Keywords Bevacizumab · Fractionated radiosurgery · Glioblastoma · High-grade glioma · Re-irradiation

Introduction

Glioblastoma (GBM) is the most common and aggressive primary brain malignancy in adults [1]. Tumor control and patient survival have improved significantly with advancements of surgical techniques and the postoperative treatment of concurrent radiation therapy plus temozolomide followed by adjuvant temozolomide; however, these standard of care treatments still deliver a median overall survival of less than 2 years [2]. Patients with World Health Organization (WHO) grade III gliomas (anaplastic astrocytoma and anaplastic oligodendroglioma) treated in a similar fashion have longer median overall survival of approximately 6–8.5 years, but long-term survival is still elusive [3–5]. Despite improvement in combined modality treatment, nearly all patients develop recurrence, generally within 2-cm margins of the resection cavity [6]. This is the area where high-dose

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adjuvant radiation therapy is delivered, which poses a challenge for the treatment of recurrent disease.

Options for salvage treatment include reoperation, chemotherapy, or re-irradiation. Various second-line chemotherapy regimens and targeted agents have been utilized with limited success. Bevacizumab (BEV) alone or combined with chemotherapy has demonstrated efficacy in delaying tumor recurrence, and thus has been widely used as the second line therapy for recurrent GBM [7, 8]. Based on these results, BEV was approved by the FDA for treatment of recurrent GBM; however, the effects of BEV are transient in most patients and malignant gliomas still progress after a median time of 3–5 months and overall survival is about 3–4 months after progressing on BEV [9, 10].

Although most tumors recur at or near the primary site, the infiltrative nature of the disease limits the efficacy of local treatment with radiation or surgery and increases the potential for long-term toxicity [11, 12]. In addition, due to the wound healing side effects of BEV, surgical resections are difficult to perform and can only reduce the tumor burden while not having any major impact on overall survival. As tumor progression and treatment failure on BEV ultimately occurs, there is an urgent need to improve local tumor control in the setting of recurrence.

Contemporary radiation techniques can deliver conformal, high-dose radiation to the irregularly-shaped targets to give an effective dose and limit toxicity. These radiation treatments can be delivered in either a single fraction (stereotactic radiosurgery [SRS]) or in several fractions (fractionated stereotactic radiosurgery [FSRS]). The use of radiosurgery for GBM fell out of favor when the results of RTOG 93–05 showed no benefit of radiosurgery as a boost when used in the setting of initial radiation therapy [13]. Several retrospective studies have evaluated the use of SRS in the treatment of recurrent high-grade glial neoplasms, but prospective or randomized data is scarce [14–17].

A prior study at our institution demonstrated the safety and efficacy of FSRS in the setting of recurrent GBM, using a total dose of 36 Gy (6 Gy × 6 fractions) delivered to the contrast-enhancing lesion. The results showed improved local control, but tumors ultimately progressed in the adjacent margin [16]. We also showed efficacy and safety with the combination of FSRS and BEV [17]. Subsequently, we escalated the therapy with differential doses of 32 Gy (8 Gy × 4 fractions) to the contrast-enhancing lesion and simultaneous delivery of 24 Gy (6 Gy × 4 fractions) to the area of fluid-attenuated inversion recovery abnormality [18]. This regimen showed further improvement, with an increase in local control up to 35% as well as prolongation of progression-free survival (PFS) among the responders.

Based on these findings, we conducted a prospective randomized trial to compare FSRS plus BEV-based-chemotherapy versus BEV-based chemotherapy alone for recurrent BEV-resistant malignant glioma after second-line chemotherapy. Since we invariably see subsequent progression at the initial site of disease, the primary objective of this study was to test the role of adding a local therapy (FSRS) to common systemic therapies used for treatment of recurrent/progressive malignant gliomas with the goal of improving local control and PFS.

Methods

This institutional review board-approved prospective randomized study (HFHS-C # 11–01) was offered to patients with high-grade glioma (anaplastic oligodendroglioma, anaplastic astrocytoma, or GBM) upon tumor progression on BEV and at least one other previous treatment regimen. Starting in January 2012, patients with these characteristics were screened at our academic health system's multidisciplinary central nervous system tumor board. Eligible patients were adults with a Karnofsky performance status (KPS) ≥ 70, recovery from toxicities of prior therapy, and normal hematologic, renal, and liver function. For BEV specifically, eligibility criteria required controlled blood pressure, no proteinuria, and no major surgery within 4 weeks or any other wound healing or gastro-intestinal issues.

Eligible patients were prospectively randomized in a 1:1 fashion to arm 1 (FSRS plus BEV-based chemotherapy) or arm 2 (BEV-based chemotherapy with irinotecan, etoposide, temozolomide, or carboplatin). Chemotherapy drugs were chosen at the discretion of the treating physician recommended by the tumor board. Patients were stratified by KPS (≤ 80 vs > 80).

Radiation treatment

A total dose of 32 Gy (8 Gy × 4 fractions) was prescribed to a gross target volume (GTV), defined as the T1-weighted contrast-enhancing lesion plus the area of diffusion-weighted imaging seen on the co-registered MRI. A dose of 24 Gy (6 Gy × 4 fractions) was prescribed to a clinical target volume (CTV) defined as the area of the new or change in T2-weighted fluid-attenuated inversion recovery abnormality. These doses were planned via a simultaneous integrated boost treatment technique. The dose was prescribed to the highest isodose line encompassing the CTV, which ranged from 50 to 95% of the maximum dose. Planning target volume was equal to GTV or CTV, respectively. There was no limit to the maximum target volume for radiosurgery.

Treatment was delivered using a linear accelerator designed for radiosurgery, with an intensity modulated technique, on both the Novalis Tx™ (Brainlab AG, Munich, Germany) and Varian EDGE™ (Varian Medical Systems, Inc., Palo Alto, CA) platforms. The dose uniformity and

conformity were optimized in the treatment planning process. Treatment was delivered every other day and completed within 2 weeks. Immobilization was achieved using a frameless stereotactic mask and image guidance with orthogonal x-rays or on-board cone-beam computed tomography. Normal tissues/critical structures were kept to minimal doses to decrease toxicity. This was accomplished by assuming that all critical structures had received the maximum point dose in the initial external beam radiation therapy treatment. The dose constraints from the American Association of Physicists in Medicine Task Group 101 (TG101) report of stereotactic body radiation therapy for 3-fraction treatments were used [19]. Coverage to the 32 Gy volume was not compromised based on those constraints. If the TG101 3-fraction dose constraints could not be met, then a constraint that was between the 3- and 5-fraction guidelines was used. All patients received prophylactic oral dexamethasone 8 mg total daily dose during treatment and were tapered off after completing treatment.

Chemotherapy

Both arms of this study had the same general principles of chemotherapy. At progression, BEV was continued and combined with a choice of another chemotherapeutic agent with the best anticipated outcome. Each regimen included BEV combined with irinotecan, temozolomide, carboplatin, or etoposide, which was decided by the treating physician as recommended from the tumor board. If the patient had a prior chemotherapy with BEV and irinotecan, for example, the study regimen was chosen with BEV and temozolomide or carboplatin or etoposide until further tumor progression (Table 1).

Follow-up

After completion of their study treatment, patients underwent follow-up with neurological examination and brain MRI with diffusion-weighted imaging and gradient echo sequence and perfusion to assess immediate vascular changes. Brain MRI was repeated every 2 months thereafter until progression or death. Response to treatment was evaluated according to the Response Assessment of Neuro-Oncology (RANO) glioma response criteria [20]. Throughout the study, neurological examinations were performed and toxicity was evaluated using the National Cancer Institute's Common Toxicity Criteria, version 3.0.

Table 1 Chemotherapy regimen

Chemotherapy	Dosing
Bevacizumab	10 mg/kg IV, days 1 and 15 every 28 days
Temozolomide	75 mg/m^2 orally on days 1–21 every 28 days
Irinotecan	125 mg/m^2 IV on days 1 and 15 every 28 days if not using enzyme-inducing anti-epileptic drugs 340 mg/m^2 IV on days 1 and 15 every 28 days if using enzyme-inducing anti-epileptic drugs
Carboplatin	5 or 6 AUC IV on day 1 of a 28-day cycle or 2 or 3 AUC IV on days 1 and 15 of a 28-day cycle

AUC area under the curve, *IV* intravenously

Statistical methods

The primary endpoints were local tumor control at 2 months and PFS. It was assumed that the FSRS group would have a local control response of 40% compared to a 10% response in the non-FSRS group. Assuming this difference along with alpha of 0.05 and two-sided testing, a sample size of 76 patients (38 patients per treatment arm) was calculated to be required to insure a power of 80%.

Fisher's exact test assessed the difference in local tumor control at 2 months based on MRI results. Median overall survival and PFS were estimated using Kaplan–Meier methods. Logrank tests were used to compare the 2 treatment arms for overall survival and PFS. Primary analysis was intention to treat, where patients were analyzed using the treatment assigned at randomization.

Results

Of the 35 patients randomized to treatment from February 2012 to December 2016, 18 were assigned to receive FSRS plus BEV-based chemotherapy and 17 were assigned to BEV-based chemotherapy alone. The original goal of study accrual was a total of 76 patients, but the study was closed in November 2017 due to slow accrual. All patients were included in the pre-specified intention-to-treat analysis (Fig. 1). No patients were lost to follow-up. Six patients on the chemotherapy alone arm elected to discontinue the trial and receive FSRS at the time of their subsequent progression.

The 35 study patients had a mean age of 55.2 (range 27 to 81) years and median KPS of 80 (range 70 to 100). Twenty-nine patients had GBM (WHO grade IV) and 6 had anaplastic glioma (WHO grade III), of which 4 were anaplastic astrocytoma and 2 were anaplastic oligodendroglioma (Table 2). The median time from initial diagnosis to enrollment was 20.5 months (range 6.7 to 268.4) and the median number of prior recurrences was 3 (range 2 to 6). Twenty-six patients had information available for isocitrate dehydrogenase 1 (IDH1) and methyl-guanine-methyltransferase (MGMT), with 2 patients (8%) positive for IDH1 mutation and 15 patients (58%) with methylated MGMT. No significant differences in age, KPS at enrollment, number of

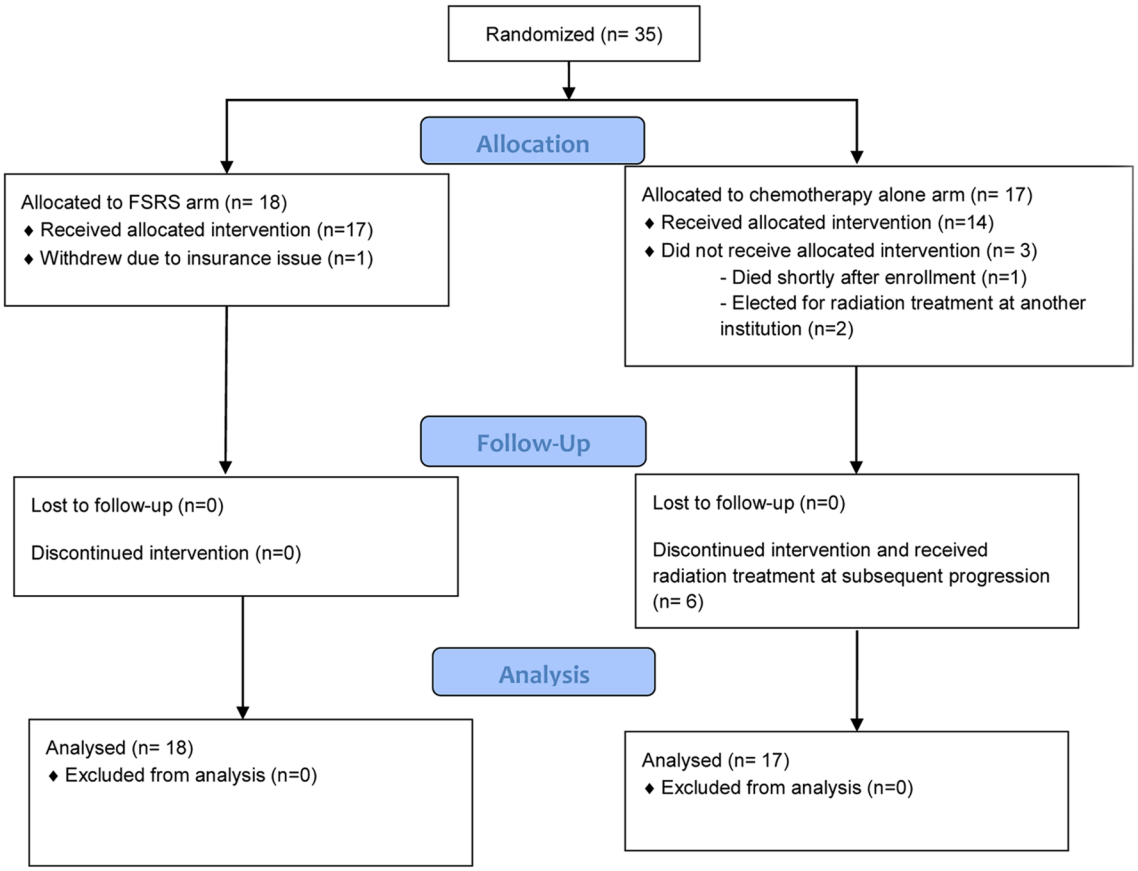


Fig. 1 Study flow diagram. *FSRS* fractionated stereotactic radiosurgery

progressions, initial treatments, and IDH1 and MGMT status were observed between the 2 treatment arms (Table 2).

The FSRS plus BEV group had an improved median PFS compared to BEV-based chemotherapy alone (5.1 months, 95% CI 4.1–6.2 vs 1.8 months, 95% CI 1.2–2.8; $P < 0.001$) (Fig. 2). The FSRS plus BEV group showed a significantly higher rate of local control at 2 months compared to the BEV-based chemotherapy only group (82% [14/17] vs 27% [4/15], $P = 0.002$). Three patients (1 in the FSRS plus BEV group and 2 in the BEV-based chemotherapy only group) who died within 2 months of study enrollment due to tumor progression did not have an MRI available for local control assessment. The median overall survival was 6.6 months (95% CI 5.7–7.5). The FSRS group had a better overall survival compared to the chemotherapy only group, but this difference was not statistically significant (median overall survival: 7.2 months [95% CI 6.1–8.1] vs 4.8 months [95% CI 1.7–7.6]; $P = 0.11$) (Fig. 2).

Toxicities attributable to treatment for the patients randomized to FSRS plus BEV included 6 grade 3 (1 pulmonary embolism, 1 headache, 1 nausea/vomiting, 1 new onset weakness, 1 intratumoral hemorrhage, and 1 seizure) and zero grade 4 or 5 toxicities. Toxicities for the patients randomized to chemotherapy alone included four grade 3 (1 cerebral edema, 1 thrombocytopenia, 1 altered mental status, and 1 intratumoral hemorrhage) and zero grade 4 or 5 toxicities (Table 3). There were no documented cases of radionecrosis in any of the patients treated with FSRS, including patients who were treated per protocol or those who crossed over.

The median volume of the 32 Gy GTV was 24.78 cm^3 (range 2.93 to 185.8 cm^3) and the median volume of the 24 Gy CTV was 84.44 cm^3 (range 9.22 to 283.0 cm^3). Of the 17 patients assigned to chemotherapy alone, 12 received BEV plus carboplatin, 2 received BEV plus temozolomide, 1 received temozolomide alone (patient declined study protocol after randomization), 1 received BEV alone, and 1 patient did not receive any chemotherapy. In the chemotherapy only group, the median number of cycles before progression of disease was 1 (range 0 to 6). Of the 18 patients assigned to FSRS plus chemotherapy, 16 received BEV plus carboplatin, 1 received BEV plus temozolomide, and 1 received BEV alone.

Table 2 Age and clinical/treatment information

Variable	Response	All patients (N = 35)	FSRS (N = 18)	Chemotherapy (N = 17)	P^*
Age at study enrollment (years)	Mean ± SD Median (range)	55.2 ± 13.5 58 (27–81)	51.5 ± 16.3 53 (27–81)	59.2 ± 8.3 59 (39–74)	.089
Gender	Female	10 (29%)	4 (18%)	6 (35%)	.470
	Male	25 (71%)	14 (82%)	11 (65%)	
Diagnosis	Anaplastic astrocytoma	4 (11%)	2 (11%)	2 (12%)	.386
	Anaplastic oligodendroglioma	2 (6%)	0 (0%)	2 (12%)	
	Glioblastoma	29 (83%)	16 (89%)	13 (76%)	
Initial resection	Biopsy	7 (20%)	2 (11%)	5 (29%)	.240
	GTR	10 (29%)	7 (39%)	3 (18%)	
	STR	18 (52%)	9 (50%)	9 (53%)	
Upfront RT dose (Gy)	54	1 (3%)	0 (0%)	1 (6%)	.735
	59.4	2 (6%)	1 (6%)	1 (6%)	
	60	32 (91%)	17 (94%)	15 (88%)	
Upfront chemotherapy	TMZ	33 (94%)	16 (89%)	17 (100%)	.485
On trial chemotherapy	BEV + Carboplatin	26 (75%)	15 (83%)	11 (65%)	.357
	BEV + etoposide	1 (3%)	1 (6%)	0 (0%)	
	BEV + irinotecan	0 (0%)	0 (0%)	0 (0%)	
	BEV + temozolomide	3 (9%)	1 (6%)	2 (12%)	
	No trial chemotherapy[a]	5 (14%)	1 (6%)	4 (24%)	
Time from initial diagnosis to enrollment (months)	Median (range)	20.5 (6.7 to 268.4)	16.8 (9.7 to 147.1)	27.7 (6.7 to 268.4)	.387
Progression number	2	16 (46%)	10 (55%)	6 (35%)	.528
	3	11 (31%)	3 (17%)	8 (47%)	
	4 or more	8 (23%)	5 (28%)	3 (18%)	
KPS at enrollment	70	12 (34%)	4 (22%)	8 (47%)	.972
	80	12 (34%)	10 (56%)	2 (12%)	
	90	10 (29%)	4 (22%)	6 (35%)	
	100	1 (3%)	0 (0%)	1 (6%)	
IDH1 status[b]	Positive	2 (8%)	1 (7%)	1 (8%)	> .99
	Negative	24 (92%)	13 (93%)	11 (92%)	
MGMT status[c]	Methylated	11 (42%)	4 (31%)	7 (54%)	.428
	Unmethylated	15 (58%)	9 (69%)	6 (46%)	

BEV bevacizumab, *FSRS* fractionated stereotactic radiosurgery, *GTR* gross total resection, *IDH1* isocitrate dehydrogenase 1, *KPS* Karnofsky performance status, *MGMT* methyl-guanine-methyl-transferase, *RT* radiation therapy, *SD* standard deviation, *STR* subtotal resection, *TMZ* temozolomide

[*] *P*-values from two sample t-test for age, Wilcoxon two-sample test for progression number and KPS, and Fisher's exact test for the remaining clinical/treatment variables

[a] Patients were randomized to chemotherapy and decided to forego treatment

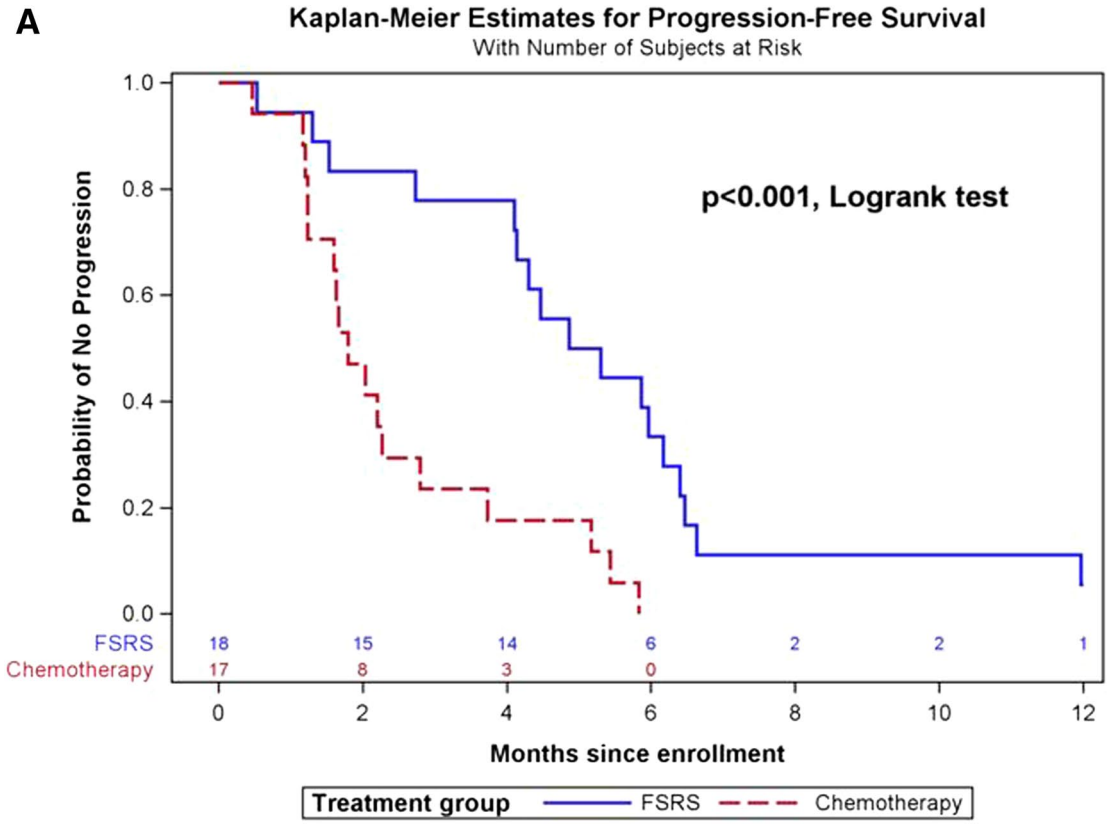
[b] Only 26 patients had IDH1 status available (14 with FSRS and 12 with chemotherapy)

[c] Only 26 patients had MGMT status available (13 with FSRS and 13 with chemotherapy)

Discussion

The findings of this first prospective randomized trial showed that BEV-resistant patients treated with FSRS plus BEV-based chemotherapy had statistically significant improvement in PFS as well as local control at 2 months compared to BEV-based chemotherapy only. The study did not meet accrual goals and therefore was not powered to detect a difference in overall survival, but there was a trend toward higher median overall survival with FSRS.

The combination of FSRS plus BEV-based chemotherapy was well tolerated overall. The total rate of grade 3 toxicities was 29% and there were no grade 4 or 5 toxicities. These toxicities were a combination of the symptoms of the disease as well as effects from treatment. Cabrera et al., in a prospective pilot study of 15 patients with recurrent



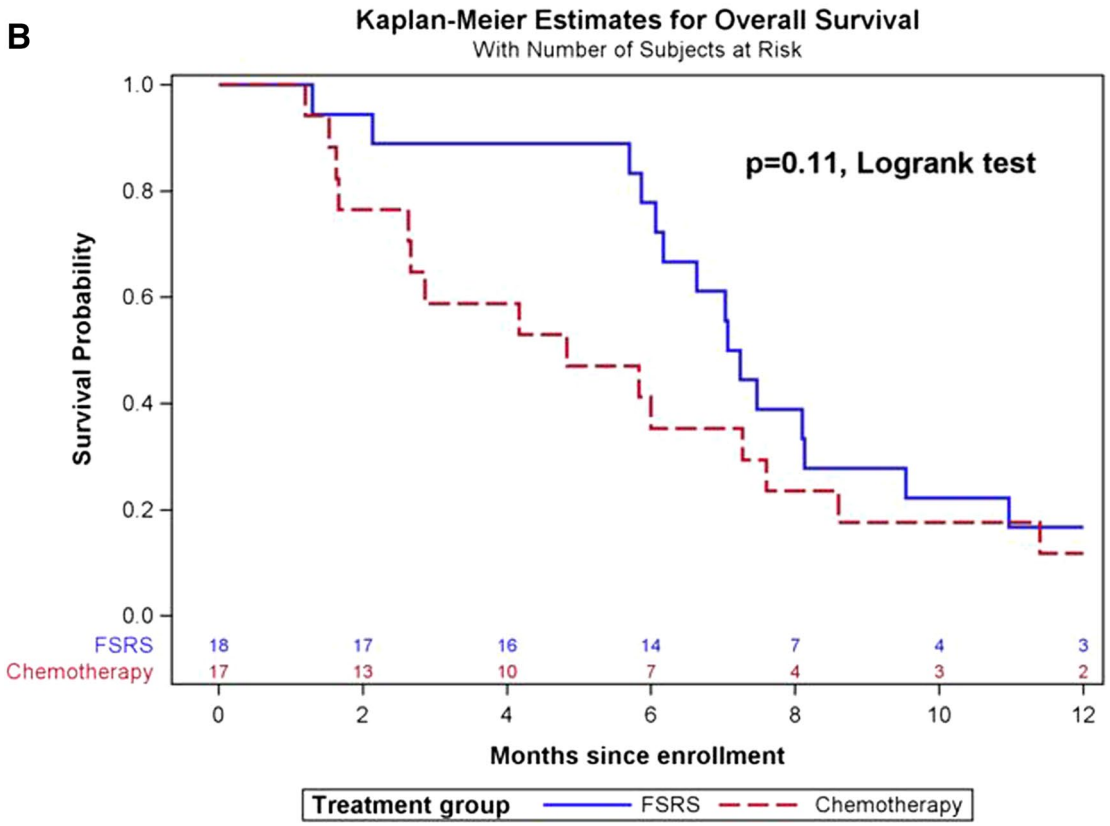


Fig. 2 **a** Progression-free survival per protocol. **b** Overall survival per protocol. *FSRS* fractionated stereotactic radiosurgery

Table 3 Overall toxicity

Toxicity	Grade 3	Grade 4
Hematologic		
Thrombocytopenia	1	
Pulmonary embolism	1	
Neurologic		
Intratumoral hemorrhage	2	
New deficit	1	
Altered mental status	1	
Headache	1	
Seizure	1	
Cerebral edema	1	
Other		
Vomiting	1	
Total	10	0

GBM treated with SRS and BEV, had only 1 patient with grade 3 central nervous system toxicity and no grade 4 or 5 toxicities [21]. This study's reported toxicity is similar to that reported by Gutin et al. in a prospective pilot study of 25 patients with recurrent malignant glioma treated with FSRS and BEV [22]. Similar to their study, our patients did not develop any documented cases of radiation necrosis. A recent meta-analysis of radiosurgery treatment for GBM recurrence showed that 5.9% of patients developed radiation necrosis, while 3.3% suffered from major neurological deficits [23]. The reason for the low rate of radiation necrosis seen in these patients may be due to the short median survival, as the delay of asymptomatic or symptomatic radionecrosis after stereotactic radiotherapy varies from 10 to 16 months [24]. Use of BEV may also contribute to the low rates of radionecrosis, as BEV is part of treatment regimens for radionecrosis [25].

This study is the first prospective randomized evidence to show a benefit with the inclusion of FSRS plus BEV-based chemotherapy to the treatment paradigm for patients with recurrent BEV-resistant malignant gliomas. This finding occurred despite the cross-over of 6 patients in the BEV-based chemotherapy alone arm receiving FSRS at the time of subsequent progression. These 6 patients had a median PFS of 2 months, which is similar to the median PFS of the BEV-based chemotherapy alone group. However, the median overall survival from study enrollment for these 6 patients was 7.5 months, which is similar to the median overall survival for the FSRS plus BEV-based chemotherapy group. The PFS in patients treated with salvage SRS/FSRS and BEV reported in retrospective case series ranges between 3.9–14.9 months [21, 22, 26, 27]. Our PFS of 5.1 months and overall survival of 7.2 months in patients treated with BEV plus FSRS is better than the 3.6 months that has been reported in patients progressing on BEV treatment. Considering that there is no rescue treatment for patients with HGG progressing on BEV, our study suggests that FSRS might be a valuable option to extend PFS and increase local control in this challenging patient population. While there was no significant improvement in overall survival, patients had increased PFS, better local control and low rates of toxicity.

The major limitations of the study are that it failed to meet the accrual goal, it was performed at a single institution, there were several WHO grade III patients included, and there were different chemotherapy regimens utilized. Of note, due to the low number of patients per arm, no corrections for potential inclusion bias by subgroup analysis can be accomplished. Accrual to this type of study is challenging, given the poor prognosis and performance status of this patient population. Additionally, our study lacks quality of life data, which would have been beneficial for patients and their families to make confident treatment decisions and should be included in any future studies.

Conclusions

Given the findings of this first prospective randomized trial and the increasing amount of retrospective data, it is reasonable to conclude that FSRS is a safe and effective treatment option for BEV-resistant patients with recurrent malignant glioma. The question of the benefit for re-irradiation with BEV in recurrent GBM is currently being evaluated in the large, cooperative group study RTOG 1205. This randomized phase II study randomized 182 BEV-naïve patients between BEV plus re-irradiation (35 Gy in 10 fractions) and BEV alone. Preliminary findings suggest that the overall survival in that study did not change with the addition of radiation while the PFS rate at six months improved from 29 to 54% [28]. It is important to note that the RTOG study was treating patients who were BEV- naïve while our study was specifically for patients who are BEV- resistant. Other important differences include the radiation dose (35 Gy in 10 fractions vs 32 Gy in 4 fractions) as well as our study including other chemotherapy agents with BEV. However, the preliminary results of this large randomized phase II trial for patients with recurrent high-grade glioma suggest similar to our study that the combination of BEV and radiation might not extend overall survival but might help to increase progression free survival for patients with otherwise limited treatment options.

Author Contributions: Study design and oversight: SR, MSS, TW, TM. Manuscript composition and editing: DB, TW, SR, TM. Statistical analysis: LS. Collection of data: DB, AM, MS, MSS. Data analysis: TW, JS, SR, DB, AM. Approval and review of submitted manuscript: DB, AM, LS, JS, TM, MS, SR, MSS, TW.

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Data availability Data will be available from the authors upon request.

Compliance with ethical standards

Conflict of interest: The authors declare there are no conflicts of interest. ICMJE forms have been signed by all authors.

Ethical approval: This study was approved by our institutional review board (HFHS-C # 11–01).

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