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CLINICAL STUDY - PATIENT STUDY

Salvage gamma knife stereotactic radiosurgery followed by bevacizumab for recurrent glioblastoma multiforme: a case–control study

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Abstract We evaluated the efficacy and safety of gamma knife stereotactic radiosurgery (GKSR) followed by bevacizumab combined with chemotherapy in 11 patients with recurrent glioblastoma multiforme who experienced tumor progression despite aggressive initial multi-modality treatment. Our experience included eight male and three female patients. The median patient age at GKSR was 62 years (range 46–72 years). At the time of GKSR, seven patients had a first recurrence and four had two or more recurrences. The median interval from the initial diagnosis until GKSR was 17 months (range 5–34.5 months). The median tumor volume was 13.6 cm^3 (range 1.2–45.1 cm^3) and the median margin dose of GKSR was 16 Gy (range 13–18 Gy). Following GKSR, bevacizumab was administrated with irinotecan in nine patients and with temozolomide in one patient. One patient was treated with bevacizumab monotherapy. The treatment outcomes were compared to 44 case-matched controls who underwent GKSR without additional bevacizumab. At a median of 13.7 months (range 4.6–28.3 months) after radiosurgery, tumor progression was evident in seven patients. The median progression-free survival (PFS) was 15 months (95% confidential interval (CI), 6.5–23.3 months). Six-month and 1-year PFS rates were 73 and 55%, respectively. The median overall survival (OS) from GKSR was 18 months (95% CI, 10.1–25.7 months) and 1-year OS rate was 73%. One patient (9%) experienced grade III toxicity and one patient (9%) had major adverse radiation effects. Compared with patients who did not receive bevacizumab, the patients who received bevacizumab had significantly prolonged PFS (15 months vs. 7 months, $P = 0.035$) and OS (18 months vs. 12 months, $P = 0.005$), and were less likely to develop an adverse radiation effect (9 vs. 46%, $P = 0.037$). The combination of salvage GKSR followed by bevacizumab added potential benefit and little additional risk in a small group of patients with progressive glioblastoma. Further experience is needed to define the efficacy and long-term toxicity with this strategy.

Keywords Bevacizumab · Gamma knife · Glioblastoma · Recurrence · Sterotactic radiosurgery

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Introduction

The treatment of recurrent glioblastoma multiforme (GBM) is challenging. Although re-irradiation is limited by

the radiation tolerance of the brain, stereotactic radiosurgery can selectively boost the target tissue and the adjacent tumor border where most recurrences develop. Several reports have described the potential efficacy and acceptable toxicity of radiosurgery for recurrent GBM [1–3].

GBMs are innately hypoxic tumors with strong endogenous expression of vascular endothelial growth factor (VEGF) which is a potent mitogen that facilitates migration, proliferation and survival of endothelial cells which are essential for tumor angiogenesis [4]. VEGF is directly correlated with tumor growth rate, metastatic potential and poor outcome [5, 6]. Bevacizumab, a humanized monoclonal antibody to VEGF, inhibits angiogenesis and has been found to be active in several types of tumors such as breast, non-small cell lung cancer and colorectal cancer [7–9]. A series of phase 2 trials employing bevicizumab and irinotecan demonstrated encouraging response rates, as well as improvements in time-to-progression and 6-month progression free survival in patients with recurrent malignant gliomas compared to historical controls [10, 11]. Preclinical studies have demonstrated that radiation induces VEGF expression and angiogenesis in tumors [12, 13]. Bevacizumab may sensitize tumor endothelial cells to radiation by depletion of VEGF and reduction of its pro-survival signaling [12, 14].

Our hypothesis was that radiosurgery and bevacizumab would lead to improved outcome, with radiosurgery promoting endothelial changes for a pronounced bevacizumab response, and bevacizumab ameliorating the radiation induced changes in vascular permeability in the treatment field which are associated with the symptomatic worsening which may be seen after radiosurgery.

In the present study we retrospectively evaluated the efficacy and the safety of re-irradiation using gamma knife stereotactic radiosurgery (GKSR) followed by bevacizumab in a series of patients with recurrent GBM and compared outcomes to a matched cohort who underwent salvage GKSR alone.

Patients and methods

Patient population

Between November 1987 and September 2010, 353 patients with GBM underwent GKSR as an adjuvant or salvage treatment at the University of Pittsburgh Medical Center. Of these, in the most recent 3 year interval, 11 patients with recurrent GBM were treated with GKSR followed by bevacizumab. The case characteristics for this retrospective study were retrieved from the patient charts, and clinical outcomes were assessed at outpatient visits by clinical staff (FL, LDL and DK). At the time of initial diagnosis, all patients had initial biopsy ($n = 4$) or maximal surgical resection ($n = 7$) followed by adjuvant external-beam radiation and temozolomide administration using the Stupp protocol [15]. All patients had radiologic defined progression despite their initial management. Progression was confirmed by pathological examination in two patients and by using neuroimaging criteria (magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and/or positron emission tomography) in nine patients. All patients had a Karnofsky performance status (KPS) of $\geq$70, normal renal, hematopoietic, and liver function. Their estimated survival was $\geq$2 months.

The clinical demographics are shown in Table 1. There were eight male and three female patients. The median patient age at GKSR was 62 years (range 46–72 years). The median KPS at the time of GKSR was 90 (range 80–100). Ten tumors were located in the cerebral hemisphere and one was located in the brain stem. Four patients had already undergone additional salvage therapies that included systemic chemotherapy ($n = 4$) and surgical debulking ($n = 2$) before GKSR. The median fractionated radiation dose delivered at the time of initial diagnosis was 60 Gy (range 54–60 Gy). Seven patients underwent GKSR at the time of first defined progression and four patients had GKSR after the failure of multiple additional therapies. The median duration between the initial diagnosis and GKSR was 17.2 months (range 5–34.5 months). This retrospective study was approved by the University of Pittsburgh Institutional Review Board.

Radiosurgical procedure

Radiosurgery was performed with the Model 4C or Perfexion Leksell gamma knife (Elekta, Inc., Atlanta, GA). After applying the stereotactic frame, high-resolution, volume-acquisition stereotactic MRI were obtained. The target volume was defined as the contrast enhanced tumor volumes defined by high definition MRI. Volumetric GKSR conformal target coverage was performed in all patients. The median tumor volume was 13.6 cm^3 (range 1.2–45.1 cm^3). The median prescription dose delivered to the tumor margin was 16 Gy (range 13–18 Gy), and the maximum dose varied from 26 to 36 Gy (median 32 Gy). The prescription isodose was 50% in nine cases. A median of 11 isocenters (range 2–19) were used for dose planning.

Bevacizumab protocol

At a median of 5 weeks after GKSR (range 4–10 weeks), bevacizumab was administered to all patients at a dose of 10 mg/kg every 2 weeks on a 28-day cycle. Nine patients received irinotecan at a dose of 125 or 340 mg/m^2 (depending on use of enzyme-inducing anti-epileptic

Table 1 Patient characteristics and treatment outcomes

Patients No.	Gender/age	Location	First line therapy			Additional therapy before GKSR	Time between initial diagnosis and GKSR	Tumor Vol. (cm^3)
			Surgery	Concomitant chemoradiation	Adjuvant CTX			
1	M/46	Left T	Resection	TMZ + EBRT	TMZ		5	45.1
2	F/62	Right F	Resection	TMZ + EBRT	TMZ		20.9	5.3
3	F/62	Left F	Resection	TMZ + EBRT	TMZ		22.2	1.2
4	M/56	Left T-P	Biopsy	TMZ + EBRT	TMZ	CTx	19.5	6.9
5	M/57	Left T	Resection	TMZ + EBRT	TMZ	Resection, Novocure, CTx	25.4	8.0
6	M/72	Brain stem	Biopsy	TMZ + EBRT	TMZ		10.2	3.3
7	M/63	Left P–T	Resection	TMZ + EBRT	TMZ	CTx	11.2	40.9
8	F/72	Left P	Resection	TMZ + EBRT	TMZ	Resection, CTx	34.5	19.8
9	M/68	Right F–P	Biopsy	TMZ + EBRT	(−)		6.4	43.1
10	M/57	Left F	Biopsy	TMZ + EBRT	TMZ		12.3	13.6
11	F/57	Left F	Resection	TMZ + EBRT	TMZ		17.3	15.2

Patients No.	KPS at GKSR	Salvage Therapy	Maximal tumor response[a]	Tumor status at last follow up	PFS (months)	OS after GKSR (months)	Additional therapy after GKSR failure	Final patients status
1	100	GKSR + AVA/CPT	PR	Progression	14.9	15.9	GKSR	Alive
2	90	GKSR + AVA/CPT	SD	No progression	17.1	17.1	Resection[b]	Alive
3	90	GKSR + AVA/CPT	PR	No progression	10.2	10.2		Alive
4	90	GKSR + AVA/CPT	SD	Progression	9.5	13.7		Death
5	100	GKSR + AVA/TMZ	CR	No progression	14.2	14.2		Alive
6	80	GKSR + AVA/CPT	PR	No progression	18.2	18.2		Alive
7	90	GKSR + AVA/CPT	PR	Progression	8.9	17.9		Death
8	100	GKSR + AVA/CPT	CR	Progression	20.3	28.3	GKSR	Alive
9	80	GKSR + AVA	PR	Progression	5.9	7.9		Death
10	80	GKSR + AVA/CPT	SD	Progression	5.5	7.2		Death
11	80	GKSR + AVA/CPT	PD	Progression	4.6	6.6		Death

BVZ Bevacizumab, *CPT* irinotecan, *CTX* Chemotherapy, *EBRT* external beam radiation therapy, *GKSR* gamma knife stereotactic radiosurgery, *KPS* Karnofsky performance status, *OS* overall survival, *PFS* progression free survival, *TMZ* temozolomide

[a] Treatment responses were evaluated based on the response assessment in neuro-oncology (RANO) criteria [13] which incorporate non-enhancing T2/fluid-attenuated inversion recovery (FLAIR) sequences into standard Macdonald criteria. Complete response (CR) was defined as disappearance of all known disease and stable (or improved) non-enhancing (T2/FLAIR) lesions without corticosteroid administration. Partial response (PR) was defined as 50% or more decrease in tumor size and stable (or improved) non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. Stable disease (SD) was defined as <50% decrease in total tumor size or <25% increase, and stable (or improved) non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids. Progressive disease (PD) was defined as >25% increase in the size of measurable lesion or the appearance of new lesion or significant increasing in T2/FLAIR non-enhancing lesion, or increasing doses of corticosteroids

[b] Resection for radiation necrosis

drugs) every 2 weeks on the same day as the bevacizumab infusion. One patient was treated with bevacizumab plus temozolomide (75 mg/m^2 for 21 consecutive days of a 28-day cycle). One patient received bevacizumab monotherapy. Dose reduction and the schedule modifications were allowed if a patient developed treatment related toxicity. Chemotherapy discontinued for treatment failure, unacceptable toxicity (grade III or IV toxicity), non-compliance of patient, or determination by the clinician that it was no longer safe for a patient to continue therapy. Patients received a median of nine cycles (range: 2–13 cycles) of chemotherapy.

Response and toxicity evaluation

Patients were evaluated every 6–10 weeks after GKSR. Contrast-enhanced MRI scans of the brain were obtained serially in each patient to monitor tumor progression or to detect potential adverse radiation effects (ARE). The median follow-up period was 13.7 months (range 4.6–28.3 months) after GKSR and 11.4 months (range 3.4–26.5 months) after starting bevacizumab based chemotherapy. Treatment responses were evaluated based on the response assessment in neuro-oncology (RANO) criteria [16] which incorporate non-enhancing T2/fluid-attenuated inversion recovery (FLAIR) sequences into standard Macdonald criteria. Toxicity evaluation was performed based on the Common Terminology Criteria for Adverse Events (version 3.0).

Case control group

Of the 353 patients who underwent GKSR for GBM in our center over last twenty-three years, 248 patients were treated with GKSR for recurrent GBM, and were eligible to serve as potential case control matches. Individuals who had GKSR followed by bevacizumab containing chemotherapy ($n = 11$ case cohort) were matched to patients with similar age (difference between groups $\leq$10 years), time interval between initial diagnosis and GKSR (difference between groups $\leq$6 months), follow-up duration after GKSR (difference between groups $\leq$6 months) and KPS at the time of GKSR ($\geq$90 vs. $<$90) who had GKSR alone after failed prior treatment ($n = 44$ control group). The rates of overall survival (OS), progression-free survival (PFS) and adverse effect related with radiosurgery were assessed in both patient cohorts.

Statistical analysis

For statistical analysis we constructed Kaplan–Meier plots for OS and PFS using the dates of diagnosis, GKSR, tumor progression, and death or last follow-up. Log rank tests were performed to compare the survival and PFS experiences for the two treatment groups (case group vs. control group) and to assess factors that influenced the length of patients' survival. The baseline variables of each group were compared using Fisher's exact test and Mann–Whitney *U*-test. All calculations were performed using commercially available statistical software (SPSS, version 15.0; SPSS, Inc., Chicago, IL, USA) and probability values <0.05 were considered statistically significant.

Results

Treatment response and survival

Post-treatment MRI scans were available for review on all 11 patients. The initial MRI at a median of 2 months (range: 1–5 months) after GKSR suggested tumor progression in two patients, stable disease in five patients, and partial response in four patients. Of the two patients with "progression" on the initial images, one was found to have a treatment response at the time of next follow up imaging, thus consistent with pseudoprogression (Fig. 1). The other patient did not undergo subsequent imaging due to clinical deterioration. During follow up after GKSR, the best tumor response was complete response in two patients, partial response in five patients, stable disease in three patients and progressive disease in one patient. Over time, delayed tumor progression was evident in seven patients (63%). Treatment failure occurred within the radiosurgery volume in three patients and at adjacent area close to the margin of the treatment volume in two (Fig. 2). Two patients had a stable or smaller tumor compared with initial imaging but developed additional FLAIR or T2 signal change surrounding the radiosurgery target. The median PFS after GKSR was 14.9 months (95% Confidential Interval (CI), 6.5–23.3 months). The six-month PFS rate was 73% and 1-year PFS rate was 55%. Of the seven patients with progressive tumor, two patients underwent repeat GKSR at 17 and 23 months after initial GKSR. After repeat GKSR, they continued bevacizumab therapy to reduce the risk of ARE.

All six tumors with a volume of 10 cm^3 or more progressed; the median time to progression was 5.9 months (95% CI, 1.8–10.0 months), whereas only single of five tumors with a volume less than 10 cm^3 had tumor progression at 9.5 months after GKSR. Smaller tumor ($<$10 cm^3) at the time of GKSR was associated with longer PFS (log-rank test $P = 0.05$).

At the last assessment, six patients (55%) were alive. The median OS was 33.2 months (95% CI, 23.7–42.7 months) after initial diagnosis. The median survival from the time of

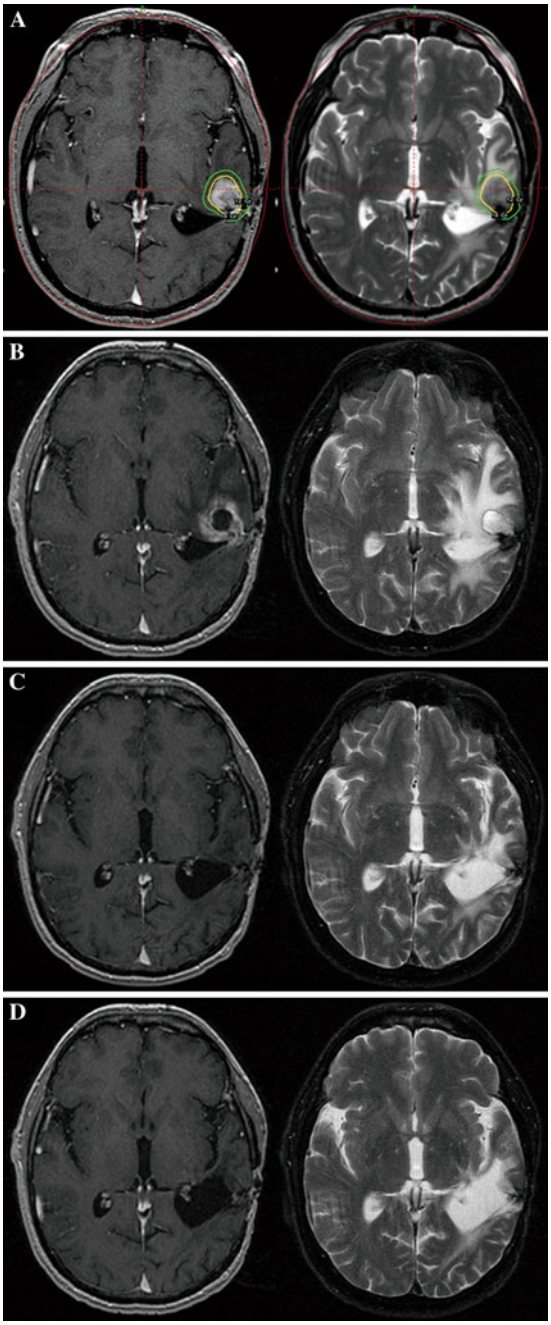

Fig. 1 Magnetic resonance imaging (MRI) of a patient (case 5) with recurrent glioblastoma multiforme who underwent gamma knife stereotactic radiosurgery (GKSR) followed by combination treatment of bevacizumab and temozolomide. In comparison with MRI scan at the time of GKSR (**a**), subsequent MRI scan after first cycle of chemotherapy (**b**) showed progressive changes in T1- and T2-weighted image. Two months later, the contrast enhancing lesion disappeared with improvement of T2 changes (**c**), indicating that the initial MRI demonstrated pseudoprogression. The enhancing tumor was not seen on MRI scan (**d**) at 14 months after GKSR (complete response)

GKSR was 17.9 months (95% CI, 10.1–25.7 months). At 1-year follow up after GKSR the survival rate was 73%, but declined to 42% by 2 years after GKSR.

Treatment-related morbidity

One patient (9%) experienced grade III toxicity after treatment. This patient was initially treated with a combination of bevacizumab and irinotecan, but grade III fatigue and lymphopenia was shown in early post-treatment period. Despite an irinotecan dose reduction by 50% of the initial dose from the 3rd cycle, systemic toxicities persisted. Eventually, the patient discontinued irinotecan but maintained bevacizumab.

Four patients (37%) developed mild (grade I or II) toxicity. Two patients developed diarrhea (grade I and II, respectively), two developed a grade II hypertension, and one showed grade II lymphocytopenia. All such toxicities were transient.

One patient (9%) developed new neurological symptoms. This 62-year-old woman developed increasing hemiparesis and magnetic resonance evidence of an enlarging mass associated with regional edema. Image-guided resection of the mass confirmed the diagnosis of radiation necrosis. The patient continued bevacizumab after resection both as adjuvant for ARE as well as for tumor control.

Comparisons to the matched control series

The demographic and clinical information of the patients with bevacizumab (case series) and those without bevacizumab (matched control series) are summarized in Table 2. There were no significant differences between the two groups in age, gender, time from initial diagnosis to salvage GKSR, KPS, GKSR dose, tumor volume or follow-up time after GKSR. Fifty-three percent of patients who were treated with GKSR alone (control series) had additional tumor treatment that included chemotherapy ($n = 19$), surgical resection ($n = 7$), repeat radiosurgery ($n = 4$), or repeat external beam radiation therapy ($n = 1$).

The matched control group demonstrated a median OS of 12.2 months (95% CI, 8.1–16.3 months) after radiosurgery and 26.7 months (95% CI, 21.8–31.6 months) after initial diagnosis. PFS was 6.7 months after radiosurgery (95% CI, 5.6–7.8 months). Compared to patients who did not receive bevacizumab, the patients who underwent both GKSR and bevacizumab had a significantly prolonged PFS (median 14.9 vs. 6.7 months, $P = 0.035$; Fig. 3a) and OS after radiosurgery (median 17.9 vs. 12.2 months, $P = 0.005$; Fig. 3b).

In the control group 19 of 21 tumors with a volume of 10 cm^3 or more eventually progressed; the median time to progression was 5.1 months (95% CI, 4.0–6.2 months). 21 of 23 tumors with a volume less than 10 cm^3 had tumor progression at a median of 8.3 months (95% CI, 4.2–12.4 months) after GKSR. Smaller tumor volume

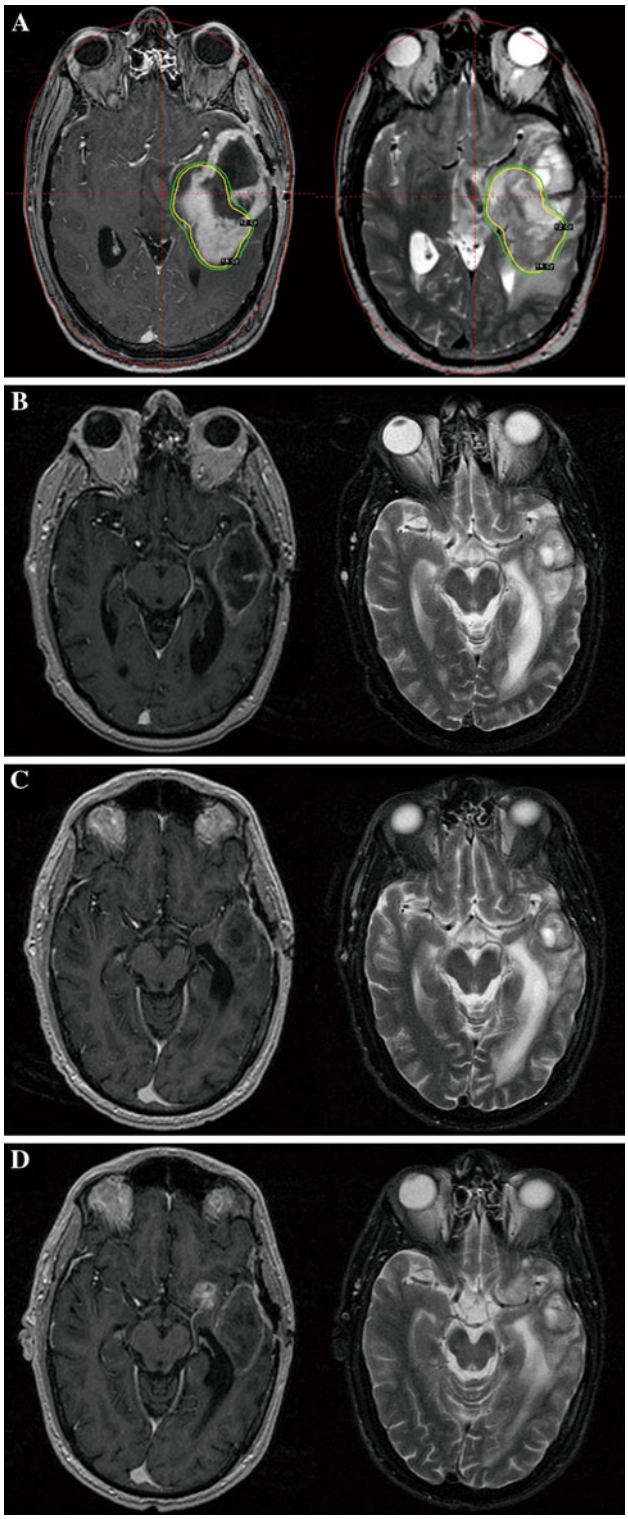

Fig. 2 Magnetic resonance imaging (MRI) of a patient (case 1) with recurrent glioblastoma multiforme who underwent gamma knife stereotactic radiosurgery (GKSR) followed by combination treatment of bevacizumab and irrinotecan. The tumor was significantly smaller after treatment (partial response). MRI scans at the time of GKSR (**a**), 3 months (**b**) and 15 months after GKSR (**c**). However, tumor recurrence was discovered in next follow up MRI scan (**d**). The patient underwent repeat GKSR for the recurrence

significantly reduced the likelihood of early tumor progression ($P = 0.013$) and was associated with longer OS ($P = 0.02$).

ARE related to GKSR was noted in 46% of the control series, and half (23%) also had progression of clinical signs or symptoms that correlated with their radiological findings. Patients who underwent GKSR alone had a greater chance of ARE detection than those who also received bevacizumab ($P = 0.037$). We detected no difference in the rate of symptomatic ARE between the two groups ($P = 0.430$).

Discussion

Re-irradiation using a conventional fractionated radiotherapy technique, either alone or combined with chemotherapy potentially is associated with a higher risk of ARE on the surrounding brain [17]. Stereotactic radiosurgery, however, utilizes image guidance and precise target immobilization. Highly conformal radiation delivery significantly reduces the dose delivered to brain adjacent to the imaging defined target volume [18]. This technique achieves a powerful radiobiological effect through the use of accurate focused radiation delivery in a single procedure with sparing previously irradiated tissue by a steep dose fall-off outside the target volume. During the last 15 years several trials have investigated the survival benefit of radiosurgery for recurrent GBM. Kondziolka et al. [19] showed a median OS of 30 months in 19 patients with GBM who were treated with GKSR at the time tumor progression, demonstrating an improved survival benefit in comparison to historical controls. Kong et al. [20] compared the survival of 65 patients who underwent radiosurgery for recurrent GBM as salvage treatment with the survival of 264 historic controls treated at the same institution. They noted that the median OS was longer in patients who received radiosurgery compared to the survival time of patients who did not undergo radiosurgery (23 vs. 12 months, $P < 0.001$). In contrast, Larson et al. [21] reported the outcomes of a trial of radiosurgery and marimastat in patients with recurrent grade IV astrocytoma. Median survival for these patients was reported as being worse than historical controls for grade IV tumors. In the recent study of evidence-based review, Tsao et al. [22] concluded that there is insufficient evidence to support a survival benefit in the use of radiosurgery at the time of progressive or recurrent malignant glioma as compared with competing strategies of management such as debulking surgery, chemotherapy, or best supportive care. Such analyses are limited by the wide variation in technologies, targets, patient selection, and doses that are used to administer boost radiation to patients who have failed initial GBM management.

Table 2 Comparison of outcomes between group of patients who had gamma knife radiosurgery followed by bevacizumab treatment and control group who underwent radiosurgery without bevacizumab therapy

	Case (GKSR with BVZ, $n = 11$)	Control (GKSR without BVZ, $n = 44$)	P value
Characteristics			
Age (median, ranges)	62 years (46–72)	64 years (41–77)	0.541
Gender (male/female)	73%/27%	64%/36%	0.730
Interval time between initial diagnosis and GKSR	17.2 months (5–34.5)	16.8 months (3.8–38.5)	0.825
KPS at GKSR	90 (80–100)	90 (70–100)	0.739
GKSR margin dose (median, range)	16 Gy (13–18)	15 (10–20)	0.295
Tumor volume	13.6 cc (1.2-45.1)	9.5 cc (1.5–48.9 cc)	0.697
Follow up period after GKSR	13.7 (4.6–28.3)	12.1 (2.5–27)	0.141
Presence of additional treatment after failure of GKSR	2 (18%)	23 (52%)	0.051
Outcomes after GKSR			
PFS after GKSR (median, 95% CI)	14.9 months (6.5–23.3)	6.7 months (5.6–7.8)	0.035
6 month PFS rate	73%	58%	
12 months PFS rate	55%	22%	
18 months PFS rate	41%	8%	
OS after GKSR (median, 95% CI)	17.9 months (10.1–25.7)	12.2 months (8.1–16.3)	0.005
6 month OS rate	100%	89%	
12 months OS rate	73%	55%	
18 months OS rate	42%	10%	
OS after Diagnosis (median, 95% CI)	33.2 months (23.7–42.7)	26.7 months (21.8–31.6)	0.048
18 month OS rate	91%	75%	
24 months OS rate	72%	52%	
36 months OS rate	45%	20%	
Adverse radiation effect (including asymptomatic)	1 (9%)	20 (46%)	0.037
Symptomatic adverse radiation effect	1 (9%)	10 (23%)	0.430

BVZ Bevacizimab, *CI* confidential interval, *GKSR* gamma knife stereotactic radiosurgery, *KPS* Karnofsky performance status, *OS* overall survival, *PFS* progression free survival

The finding that some tumors overexpress VEGF has led to the development of targeted anti-VEGF therapies. Recently bevacizumab, a humanized monoclonal antibody to VEGF, has shown promising results in delaying tumor progression. A phase 2 trial of single-agent bevacizumab at tumor progression in recurrent GBM patients who underwent conventional fractionated radiotherapy and temozolomide chemotherapy reported that the median PFS and OS was 3.7 and 7.2 months, respectively [23]. This anti-angiogenic agent has been noted to increase bioavailability of chemotherapy agents by normalizing tumor vasculature and decreasing interstitial fluid pressure [24, 25]. This finding has led to the application of bevacizumab combined with a cytotoxic agent such as irinotecan which has excellent central nervous system penetration, making it a logical cytotoxic therapy for GBM [7, 26]. Vredenburgh et al. [27] reported that recurrent GBM patients who received both bevacizumab and irinotecan had a median PFS of 4.7 months and a median OS of 9.3 months. The patients with combination therapy of bevacizumab and irinotecan had slightly longer survival than those treated with bevacizumab monotherapy.

In 2009, the combination of stereotactic radiotherapy and bevacizumab was described by Gutin et al. [28] in the management of 25 patients with recurrent malignant glioma. For 20 patients with GBM, the overall tumor response rate was 50%, and median PFS and OS of the patients were 7.3 and 12.5 months, respectively. The rationale for combining bevacizumab and radiotherapy is based on the potential radiosensitizing benefit of bevacizumab. The potential for such synergistic effects has been proposed both for the ability of anti-angiogenic agents to normalize blood vessels (thereby reducing tumor hypoxia), and for its ability to counteract the effects of radiation-induced VEGF secretion from tumor cells [25, 29–33]. More recently, Cuneo et al. [34] analyzed the outcomes of 49 patients with recurrent GBM. Thirty three patients received bevacizumab before or after linear accelerator based radiosurgery and 16 patients underwent radiosurgery without bevacizumab. They demonstrated that patients who underwent radiosurgery followed by

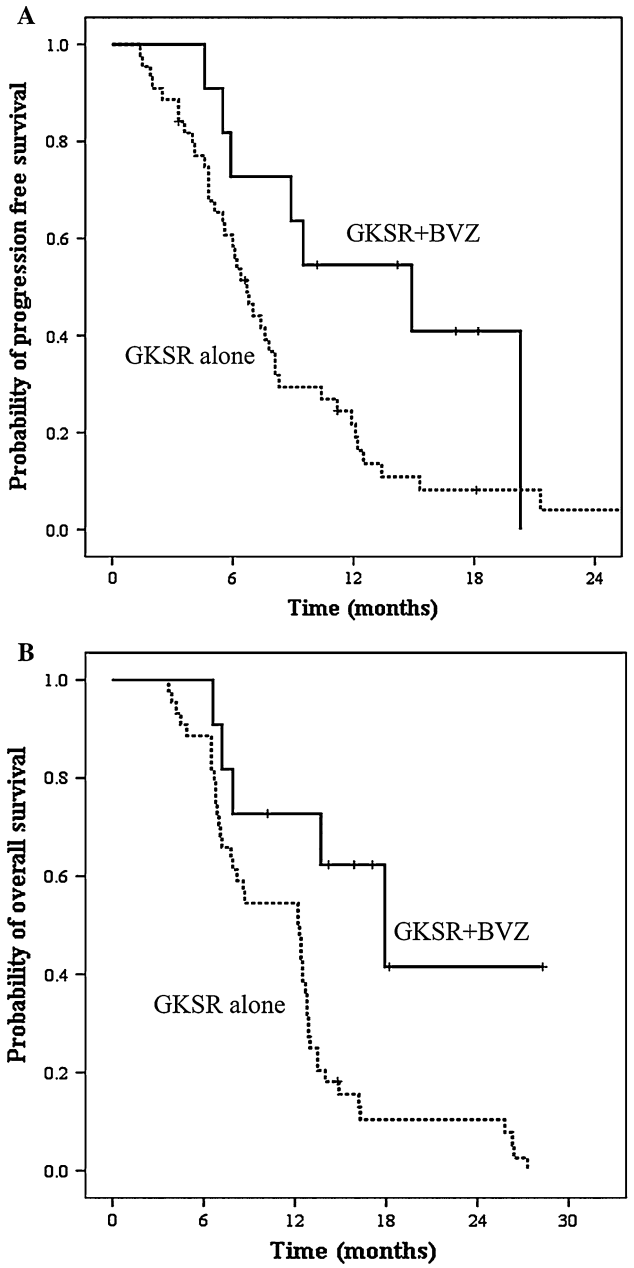

Fig. 3 Kaplan Meir curve showing progression-free survival (**a**) and overall survival (**b**) from the time of salvage gamma knife stereotactic radiosurgery (GKSR) in patients with a recurrent glioblastoma multiforme who did (*solid line*) or did not (*dotted line*) receive bevacizumab containing chemotherapy. Patients who were treated with GKSR plus bevacizumab had longer PFS (median 14.9 vs. 6.7 months, $P = 0.035$), and OS (median 17.9 vs. 12.2 months, $P = 0.005$)

bevacizumab administration had significantly longer PFS and OS compared with patients who had radiosurgery without bevacizumab (median PFS 5.2 vs. 2.1 months; median OS 11.2 vs. 3.9 months). In the current study, follow up imaging demonstrated radiographic improvement (either complete response or partial response) in seven patients (64%). The median PFS after GKSR was 14.9 months. The six-month and 1-year PFS rate were 73 and 55%, respectively. The median survival from the time of GKSR was 17.9 months, and 1- and 2-year survival rate after GKSR were 73 and 42%, respectively. The OS after initial diagnosis was a median of 33.2 months. We believe that our initial experience using GKSR and bevacizumab compares favorably with the results reported from other centers using a similar patient selection process [1–3, 28, 34–42] (Table 3). The survival benefit observed in our series may in part reflect selection bias, since our patients had a favorable performance status at the time of treatment and had already shown an initial response to the first line treatment. Additionally, the case–control groups were not matched by year in which radiosurgery was applied. All patients with case group were treated within last 3 years, whereas majority of patients in control group were treated in pre-bevacizumab era. Enhanced survival in patients with bevacizumab group may be attributed in part by application of relatively modern surgical and radiosurgical technology during their treatment course.

One (9%) of 11 patients experienced grade III toxicity related to the use of irinotecan, which lead to discontinuation of this cytotoxic agent. When we compared the outcomes of these 11 patients with those of matched patients who underwent radiosurgery without receiving bevacizumab, we found that patients who were treated with GKSR plus bevacizumab had longer PFS and OS. Our results support the results published by Cuneo et al. [34] who also noted a positive role for bevacizumab in selected patients with recurrent GBM.

Although radiosurgery is regarded as a relatively safe modality to boost the radiobiological effect of GBM radiation, ARE occurs in 14–31% [3, 36, 37, 42]. In the current experience we encountered a single patient who developed surgically confirmed radiation necrosis after administration of bevacizumab therapy and radiosurgery. Of interest the incidence of ARE in patients who received bevacizumab was significantly lower than our patients who did not receive bevacizumab (9 vs. 46%, $P = 0.037$). These findings may support the potential benefit of bevacizumab as a means to reduce tumor related edema and to reduce the incidence of ARE [43].

The patterns of recurrence following radiosurgery for GBM are similar to those reported for conventional radiation, with local recurrence eventually noted in 85–92% of patients [1, 36]. Tumors tend to progress within 2 cm of the contrast-enhancing edge. In our study, five (71%) of seven patients with delayed progression either progressed within the GKSR treatment volume or within 2 cm of the target margin. One potential reason for delayed tumor progression is the difficulty presented by adequate definition of the tumor target itself. Most centers select the target volume as

Table 3 Literature review of stereotactic radiotherapy for recurrent glioblastoma multiforme

Study	Patient No.	Treatment	Age (years)	KPS	Tumor volume (cm^3)	RTX dose (Gy)	Time between initial diagnosis and salvage RTX (months)	PFS (months)	OS from salvage RTX (months)	OS from initial diagnosis (months)	Radiation necrosis
Hall et al. [36]	26	SRS (LINAC)	47	70	28	20	10	NR	6.5	18	14%
Sheirive et al. [42]	86	SRS (LINAC)	46	80	10.1	13	10.3	NR	10.2	NR	16%
Combs et al. [2]	32	SRS (LINAC)	56	NR	10	15	10	5	10	22	0%
Hsieh et al. [37]	26	SRS (GK)	58	70	21.6	12	NR	NR	10	16.7	31%
Mahajan et al. [38]	41	SRS (LINAC)	54	NR	NR	NR	11	NR	11	26	NR
Vordermark et al. [41]	14	HFSRT	50	90	15	30	19	4.6	7.9	NR	0%
Kong et al. [3]	65	SRS (GK)	49	100	10.6	16	NR	4.6	13	23	24.4%
Patel et al. [39]	26	SRS	53	80	10.4	18	12.5	NR	8.4	24.4	7.6%
Patel et al. [39]	10	HFSRT	44	90	51.1	NR	14.9	NR	7.4	24.1	NR
Biswas et al. [1]	18	SRS (LINAC)	58	NR	8.4	15	12.1	3.4	5.3	17.4	NR
Pouratian et al. [40]	26	SRS (GK)	61	80	21.3	6	NR	7.1	9.4	17.4	0%
Gutin et al. [28]	20	HFSRT + BVZ	56	80	34	30	14.5	7.3	12.5	NR	0%
Fogh et al. [35]	105	HFSRT	53	NR	22	35	8	NR	11	23	NR
Cuneo et al. [34]	42	SRS (LINAC) + BVZ	47	80	4.5	15	21	5.2	11.2	47	5%
Present series	11	SRS (GK) + BVZ	62	90	13.6	16	17.2	14.9	17.9	33.2	9%

BVZ Bevacizimab, *GK* gamma knife, *HFSRT* hypofractionated stereotactic radiation therapy, *KPS* Karnofsky performance status, *LINAC* linear accelerator, *OS* Overall survival, *PFS* progression free survival, *RTX* radiation therapy, *SRS* stereotactic radiosurgery, *NR* not record

that volume defined by the contrast enhanced T1-weighted MRI. Pathological data confirm that tumor cells migrate up to 4 cm away from the tumor edge, spreading down white matter tracts [44]. Determination of the appropriate radiosurgical target volume (including the contrast enhancing volume and the adjacent border zone) may be essential to improve the efficacy of GKSR for GBM patients.

The North American gamma knife consortium is currently planning a Phase 2 multicenter prospective study to investigate the safety and efficacy of salvage GKSR plus bevacizumab for recurrent GBM. We hypothesize that treatment volume escalation will be successful at improving OS in patients with GBM when appropriate targeting and precision dose delivery is performed in a single treatment session. The 'border zone' of the tumor will be targeted for radiosurgery (defined as a combination of the MRI volume of gadolinium enhancement plus up to 2 cm of the surrounding T2 volume). In this trial, the border zone will be determined using MRI and MRS. We hypothesize that the addition of bevacizumab will reduce radiation toxicity in the volume treated by GKSR and will improve therapeutic effect to the solid tumor itself.

Conflicts of interest Drs. Lunsford, Kondziolka, and Niranjan are consultants with AB Elekta. Dr. Lunsford is a stockholder in AB Elekta.

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