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Clinical Investigation

Long-term outcome data from 121 patients treated with Gamma Knife stereotactic radiosurgery as salvage therapy for focally recurrent high-grade gliomas

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ABSTRACT

Introduction: We examined patient outcomes after Gamma Knife stereotactic radiosurgery (GKSRS) salvage therapy for recurrent high-grade gliomas (HGGs) to determine whether tumor grade or lesion size affected overall survival (OS) and progression-free survival (PFS).

Methods: This single-center retrospective study assessed radiographic response and clinical outcomes following GKSRS salvage treatment of recurrent malignant gliomas (January 2005–March 2014).

Results: A total of 121 patients (67 female) with 132 tumors were treated. Median (range) PFS was 4.7 (3.9-5.4) months for the cohort, 6.8 (4.6-8.9) months for initial grade 2 tumors, 4.2 (1.9-6.5) months for initial grade 3 tumors, and 4.3 (3.7-4.9) months for initial grade 4 tumors. Patients with small lesions (≤6.7 cm^3; n = 53) had significantly longer median (range) PFS (6.8 [4.8-8.8], P=0.02).

Conclusions: GKSRS offers meaningful salvage therapy with minimal morbidity in appropriately selected patients with focally recurrent HGGs.

Keywords: Gamma Knife; recurrent high-grade glioma; salvage therapy; stereotactic radiosurgery

INTRODUCTION

Glioblastoma (GBM) accounts for approximately 15% of all brain tumors.(1) Because GBMs are highly infiltrative and relatively resistant to radiation and chemotherapy, most patients with GBM experience a recurrence within 1 year. It is considered rare for patients to survive more than 5 years after diagnosis, although reports of long-term survivors have been published.(2) The most recent advance is the addition of tumor-treating fields (TTF), with a reported 20.9-month median overall survival for a cohort of 466 patients treated with upfront TTF in addition to standard resection or biopsy plus radiation and temozolomide.(3) However, even in the best-reported results to date in this large study of 695 patients, the median progression-free survival (PFS) was still only 6.7 months.(3)

Stereotactic radiosurgery delivered by the Gamma Knife (Elekta, AB, Stockholm, Sweden) (GKSRS) or other specialized treatment units offers the ability to treat relatively deep, small areas of focally recurrent high-grade glioma (HGG) in a single-day outpatient setting through a non-surgically invasive approach with a low risk of causing further deficits in the short term. However, this technique has been criticized for its inability to treat the infiltrative nature of HGG and for the risk of post-radiation treatment effect (PRTE).

This study sought to add to the current body of knowledge regarding the outcomes of patients treated with GKSRS as salvage therapy for recurrent HGG to help physicians best determine when GKSRS is an appropriate treatment option. We hypothesized that overall survival (OS) and PFS would decrease as tumor grade increased and that both OS and PFS would decrease as lesion size increased.

MATERIAL AND METHODS

A single-center retrospective study was conducted evaluating radiographic response and clinical outcomes after GKSRS was administered to patients with recurrent gliomas. The institutional review board approved the study and waived informed consent requirements. Data were collected from hospital and medical office records, and all available treatment and surveillance magnetic resonance images were reviewed as described below.

Inclusion Criteria

All adult patients treated with GKSRS for recurrent gliomas between January 1, 2005, and March 31, 2014, were evaluated for inclusion. Patients with initial World Health Organization (WHO) grade 1 tumors were excluded. Patients with WHO grade 2, 3, and 4 gliomas were included based on initial pathologic tissue diagnosis regardless of the time between diagnosis and salvage GKSRS. No patients had GKSRS as a primary treatment. A biopsy was not required before salvage treatment. However, during a weekly review board meeting before patient treatment, a consensus opinion was reached by a neurosurgeon, radiation oncologist, and neuroradiologist that a patient's radiographic change was consistent with focal tumor progression or malignant degeneration of prior lower-grade tumors and was not consistent with PRTE. No patients with diffusely infiltrative or nonenhancing tumors were treated in this series. Previous grade 2 tumors were included because the recurrences were felt to be of high grade due to the presence of enhancing nodules in previously nonenhancing tumors.

Study Population and Treatment Technique

The decision to treat patients was made on an individual basis and is reported in a retrospective fashion. Per our institutional protocol, all cases suspected to be recurrent HGG were presented and reviewed in a multidisciplinary radiosurgical conference/tumor board before treatment to gain consensus approval for the appropriateness and safety of GKSRS as a salvage therapy. It is important to note that multiple options for therapy, including enrollment in clinical trials, were typically discussed and were chosen many times by patients not included in this study. Additionally, several patients in this study had not responded to therapy after enrollment in various clinical trials, and GKSRS was chosen as their salvage treatment.

All patients were treated with the Leksell Gamma Knife model C (Elekta, Stockholm, Sweden) prior to 2007 and with the Perfexion model (Elekta) thereafter. T-1 weighted SPGR gadolinium-enhanced MR images with 1-mm contiguous slices were obtained. The volume of the enhancing nodule was outlined for treatment using the GammaPlan (Elekta) software. The percentage of the target volume coverage was calculated in all cases with 100% coverage by the 50% isodose line achieved in nearly all cases. Typically, a generous coverage of the target beyond the enhancing margin was performed when the location was deemed appropriate; however, an intentional, specific additional margin beyond the edge of enhancement, as reported in some other series, was not specifically prescribed.(4) The mean and standard deviation for coverage beyond the margin, calculated by subtracting the target volume (mL) from the treatment isodose line volume (mL), was 4.33 ± 6.63 mL. The dose at the 50% isodose line was 12-15 Gy, lower than in other reported series and lower than typically prescribed for metastatic disease, with the goal of avoiding PRTE as all patients had received prior high-dose inten-

sity-modulated radiation therapy (IMRT) near the area of salvage GKSRS.

Overall Survival and Progression-Free Survival Analyses

To retrospectively differentiate tumor progression from PRTE, we applied the Response Assessment in Neuro-oncology (RANO) criteria based on radiographic presentation. Disease progression was defined as greater than a 25% increase in T1-enhanced lesion volume. Progression was then subclassified as either in-field (within 50% isodose margin), marginal (within 2 cm of 50% isodose margin), or distant (greater than 2 cm away from 50% isodose line). For classification as progressive disease, in-field and marginal disease progression criteria must have been met for a minimum of 4 successive imaging dates. If progression was maintained, the first date on which progression was observed was established as the start date of progressive disease. If 4 successive scans did not meet this requirement, no date for progressive disease was assigned. However, if distant disease progression was established at any point in follow-up, the first date at which progression occurred was determined to be the date of progressive disease. When perfusion MRIs were available, focally increased relative cerebral blood volume corresponding to the region of enhancement was confirmatory for progressive disease, and low relative cerebral blood volume was deemed consistent with PRTE. If no imaging follow-up was available, the halfway point between last follow-up and date of death was used to estimate the date of disease progression.

Survival analyses were conducted for OS using the date of death minus the date of initial resection. OS was also computed using the date of death minus date of first GKSRS. PFS was computed using the date of progression minus date of first GKSRS. Kaplan-Meier curves are shown by initial tumor grade and by lesion size. Lesion size was addressed as both a continuous and dichotomized variable using median value to large tumors (above median) and small tumors (at or below median). For patients with multiple lesions, the largest lesion size was used to determine the patient's tumor-size category.

Karnofsky Performance Status

The Karnofsky Performance Status (KPS) score, a physician-assigned value, was used to evaluate patient KPS. The KPS scale provides a score of 0–100 in 10-point intervals, each based on specific criteria, such as the ability to work, care for oneself, and degree of symptoms. A score of zero reflects a deceased patient, and a score of 100 reflects no evidence of disease and normal functional capacity.

Statistical Analysis

Our cohort is described using counts with percentages and means with standard deviations. Kaplan-Meier analyses were used to estimate OS from initial resection and OS and PFS from the time of GKSRS for the entire cohort, by WHO tumor grade, and by lesion volume split at the median to represent large (>6.7 cm^3) versus small (≤6.7 cm^3) tumors. The number of events (deaths), censored cases, and patients exposed to risk at each interval are reported. Mean and median survival estimates are reported with standard errors and 95% confidence intervals. Although standard median survival statistics are reported, we also provide mean survival as an additional statistic to describe patient trajectory. Pairwise log-rank tests were used to assess for statistically significant differences between survival estimates. KPS value differences were compared using a repeated-measures general linear model with follow-up visit as the within-subjects factor and KPS score as the dependent variable. P values <0.05 were considered statistically significant. SPSS version 22 was used for analyses.

RESULTS

Our cohort consisted of 121 patients with 132 tumors who underwent GKSRS for recurrent gliomas. The mean patient age was 49.2±15.7 years, and 67 of 121 (55.4%) were female. Initial tumor grade was missing for 2 patients (Table 1). For the remaining 119 patients, the initial tumor grade for the majority was grade 4 (n=73, 61.3%), followed by grade 3 (n= 27, 22.7%) and grade 2 (n=19, 16.0%). Prior to GKSRS, 100% (n=121) of patients underwent resection, 71.1% (n=86) underwent re-resection, 91.7% (n=111) underwent IMRT, 14.0% (n=17) were treated with carmustine implants, 21.5% (n=26) were participants in a clinical trial, and 28.9% (n=35) were administered BVZ.

Survival and Tumor Grade

Overall Survival after Initial Resection

Survival estimates for the combined cohort and separated by tumor grade are reported in Table 2. The median OS of the combined cohort was 26.0 (95% CI, 18.1-33.9) months and 86.0 (range 39.6-132.4) months for patients with prior grade 2 tumors, 33.0 (range 26.2-40.3) months for grade 3, and 20.5 (range 17.5-23.5) months for grade 4. Patients with small lesions (≤6.7 cm^3) had significantly longer OS with a median OS of 32.3 (range 25.2–39.5) months

Table 1. Characteristics of cohort of 121 patients with 132 glioblastomas

Variable	No. (%)*
Age, mean±SD, yr	49.2±15.7
Sex	
Male	54 (44.6%)
Female	67 (55.4%)
Initial WHO tumor grade (n=119 patients)†	
2	19 (16.0%)
3	27 (22.7%)
4	73 (61.3%)
Location (n=132 tumors)‡	
Frontal	41 (31.1%)
Temporal	24 (18.2%)
Parietal	17 (12.9%)
Cerebellum	8 (6.1%)
Occipital	6 (4.5%)
Corpus callosum	6 (4.5%)
Insula	5 (3.8%)
Pons	4 (3.0%)
Thalamus	3 (2.3%)
Medulla	1 (0.8%)
Atrium	1 (0.8%)
Not available/unknown	16 (12.1%)

*Values are number (percentage) unless otherwise indicated.
†Data on WHO tumor grade were missing for 2 patients.
‡Percentages total >100% due to rounding.

compared to 21.4 (range 17.1–25.8) months for patients with large lesions (>6.7 cm^3) (P=0.04). The overall log-rank test and all pairwise comparisons were statistically significant at P<0.001, suggesting a significant decrease in survival with each increase in tumor grade. Kaplan-Meier curves reported by tumor grade are shown in Figure 1A.

Overall Survival after GKSRS

The median OS calculated from the date of GKSRS for all tumor grades combined was 8.6 (range 6.9-10.4) months. OS was 12.7 (range 7.8-17.5) months for the prior grade 2 cohort, 9.7 (range 5.9-13.4) months for the grade 3 cohort, and 8.2 (range 6.3-10.1) months for the grade 4 cohort. The overall log-rank test resulted in P=0.07, and pairwise comparisons demonstrated a significantly longer survival for the grade 2 cohort in comparison to the grade 4 cohort (P=0.04) (Figure 1B).

Progression-Free Survival after GKSRS

Date of progression was documented for 57 patients and calculated as described in Methods for the remaining 62 patients. Median PFS was 4.7 (range 3.9-5.4) months for the combined cohort, 6.8 (range 4.6-8.9) months for prior grade 2 patients, 4.2 (range 1.9-6.5) months for grade 3 patients, and 4.3 (range 3.7-4.9) months for grade 4 patients. PFS was not significantly different by tumor grade (P=0.20) (Figure 1C). Additional analysis using target volume as a continuous variable and adjusting for age, sex, initial KPS, multiple lesions, and initial tumor grade failed to demonstrate a significant difference in PFS (P=0.14). Multiple lesions were found to be the sole significant co-variable in the model (P=0.04). We were able to review imaging data on 81 of the patients who had progression. Of these, 44 (54.3%) were classified as having marginal progression and 37 (45.7%) were classified as having distant progression.

Survival and Lesion Size

Survival analyses were also conducted to compare the association between lesion size and survival. Data on lesion size were missing for 10 patients, resulting in a sample size of 111, as reflected in Table 2. Patients with small lesions had significantly longer OS, with a median OS of 32.3 (range 25.2-39.5) months compared to 21.4 (range 17.1-25.8) months for patients with large lesions (P=0.04). Patients with small lesions also had a longer OS after GKSRS, with a median of 13.0 (range 8.0-18.0) months compared to 7.4 (range 5.1-9.6) months for patients with large lesions (P=0.046). Additionally, patients with small lesions had a longer PFS after GKSRS, with a median of 6.8 (range 4.8-8.8) months for those with small lesions versus 4.2 (range 3.5-5.0) months for those with large lesions (P=0.02). Kaplan-Meier curves comparing survival by size and grade are shown in Figure 2.

Progression-Free Survival and Tumor Grade and Lesion Size

Given the general association between increased lesion size and decreased PFS after GKSRS and the lack of association between PFS and tumor grade, we explored tumor grade and lesion size within a single PFS analysis (Table 2 and Figure 2). The overall log-

Table 2. Summary of progression-free survival from time of GKSRS by tumor grade and size

Variable	Grade 2 Small	Grade 2 Large	Grade 3 Small	Grade 3 Large	Grade 4 Small	Grade 4 Large
N	9	9	11	15	33	34
No. of events	8	9	11	13	30	34
No. censored	1	0	0	2	3	0
Mean survival (SE)	14.9 (7.0)	9.3 (4.1)	13.2 (3.7)	4.1 (1.0)	7.6 (1.6)	5.8 (0.9)
[95% CI], months	[1.3-28.6]	[1.2-17.4]	[6.1-20.4]	[2.1-6.1]	[4.6-10.7]	[4.0-7.6]
Median survival (SE)	8.1 (0.2)	4.7 (0.5)	9.7 (1.4)	3.6 (0.9)	4.7 (1.0)	4.0 (0.6)
[95% CI], months	[7.7-8.5]	[3.6-5.7]	[7.0-12.4]	[1.9-5.3]	[2.7-6.7]	[2.9-5.1]
No. patients exposed to risk						
3 mo	5	3	6	4.5	15	19
6 mo	3.5	1	6	1	7	9
9 mo	2	1	5		6	5
12 mo	1	1	4		2	
24 mo			2		1	
36 mo			1			

rank test was significant, suggesting significant differences in PFS after GKSRS by categories combining tumor grade and lesion size (P=0.03). Within each tumor grade, both mean and median PFS decreased when comparing patients with small tumors to those with large tumors. Pairwise comparisons reflected significantly shorter survival for patients with grade 3 large tumors versus grade 3 small (P=0.005) and grade 2 small (P=0.02). Patients with grade 4 large tumors also had significantly shorter PFS than those with grade 3 small tumors (P=0.02). In Figure 2, for significant values described above, refer to the black dotted survival curve for grade 3 large tumors and black solid curve for grade 4 large tumors.

Karnofsky Performance Status

Mean KPS values are shown in Table 3 for patients before the first GKSRS treatment (initial KPS), the first follow-up visit (mean 1.9±1.0 months), and third follow-up visit (mean 5.3±2.0 months). The repeated measures analysis demonstrated a significant effect of time (P<0.001) with all pairwise comparisons significant at P<0.001 indicating a significant mean drop from initial KPS to KPS at the date of GKSRS treatment and a significant drop from GKSRS treatment to first follow-up. Initial KPS was reported for 86 of 121 patients (71%).

Post-GKSRS Adverse Effects

A total of 29 (24%) of the 121 patients had PRTE at any point following GKSRS salvage treatment as reported by 2 neuroradiologists. Only 2 (1.7%) patients had cerebral edema, and 90 (74.4%) patients had no adverse treatment effect.

DISCUSSION

The prognosis for patients with recurrent disease is even more dismal than that for patients with newly diagnosed disease, prompting the question of whether any salvage treatment is justified. Hau et al.(5) addressed this question in 2003 and reported a superior median PFS rate at 12 months and OS rate at 24 months in the reintervention group (71% and 32%, respectively) compared with a control group who were not re-treated (15% and 5%, respectively). They also reported a stable or even improved KPS after reintervention in the patients selected for treatment. Careful patient selection is important for patients to be considered for reintervention because reports vary widely regarding the benefits of salvage therapy.

Ideally, salvage treatments for GBM would have a low treatment burden to the patient with a minimal recovery time from the treatment because, realistically,

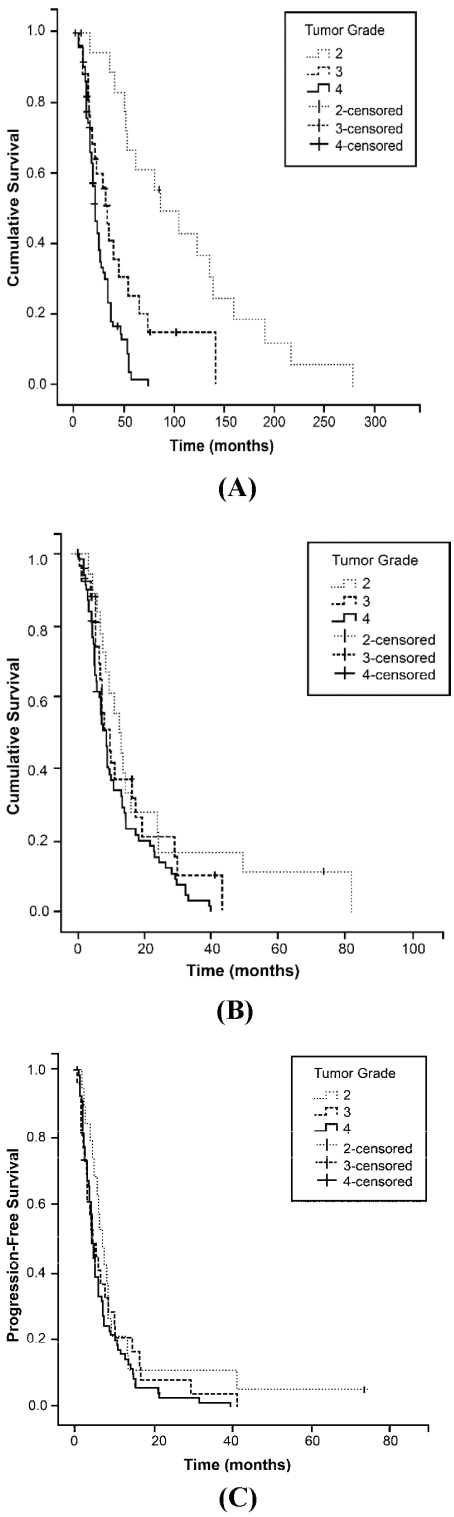

Figure 1. Kaplan-Meier curves showing survival by tumor grade. **(A)** Overall survival from initial resection. **(B)** Overall survival from time of GKSRS salvage therapy. **(C)** Progression-free survival from time of GKSRS salvage therapy. *Used with permission of Barrow Neurological Institute.*

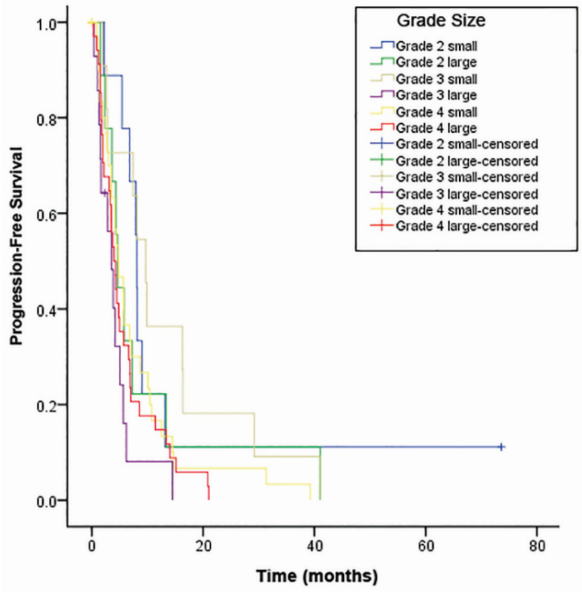

Figure 2. Progression-free survival by tumor grade and size after GKSRS. *Used with permission of Barrow Neurological Institute.*

Table 3. Summary of mean Karnofsky Performance Status scores over time after GKSRS

Time Point	N	Mean value (SE)[§]	95% CI
Prior to GKSRS	86	87.21 (1.17)	84.92-89.50
First follow-up visit*	55	79.27 (1.46)	76.41-82.14
Third follow-up visit[†]	58	67.59 (1.42)	64.80-70.38

*Mean 1.9±1.0 months after first GKSRS salvage treatment.
[†]Mean 5.3±2.0 months after first GKSRS salvage treatment.
[§]All pairwise comparisons significant at P<0.001.

these patients' life-spans are limited and should not be spent in the hospital. Salvage treatment options include (1) possible enrollment in clinical trials; (2) re-resection with or without a carmustine implant; (3) re-irradiation, either after re-resection or as stand-alone salvage treatment with IMRT; (4) brachytherapy seed placement after resection; (5) additional chemotherapy; (6) initiation of TTF; (7) laser interstitial thermal therapy (LITT); and (8) SRS. Each modality exhibits a unique profile of advantages and disadvantages. However, the most efficacious treatment course has yet to be elucidated.

The primary objective of this study was to corroborate the existing literature regarding the outcomes of patients treated with GKSRS as salvage therapy for recurrent

HGG. Several small prospective and retrospective series suggest that SRS may provide a survival benefit in recurrent HGG, with postirradiation OS ranging from 7 to 16 months.(2, 6-16) Moreover, 10 additional reports between 2005 and 2013 for GKSRS for recurrent GBM demonstrated median OS ranging from 9 to 17.9 months after salvage SRS, and the median PFS ranged from 4.6 to 14.9 months.(4, 17-25) Our study, which to our knowledge is the largest series to date, obtained similar results with median OS after GKSRS of 8.6 (range 6.9-10.4) months and a median PFS of 4.7 (range 3.9-5.4) months. These results suggest a meaningful survival benefit to patients that is comparable to other salvage treatments. For example, a recent series of 37 patients found that the median PFS and OS after re-irradiation using IMRT without and with BVZ was 5.1 (range 1.6-17.4) months and 9.0 (range 6.4-17.8) months, respectively.(26) Chan et al.(27) treated 24 patients with recurrent GBM with re-resection followed by GliaSite brachytherapy, resulting in a median survival time of 9.1 months. Another study of permanent brachytherapy showed similar outcomes with a median OS posttreatment of 10.5 to 12.0 months.(6) However, significant symptomatic radiation toxicity was reported, leading clinicians to disfavor this technique.(28)

A challenging factor in treating recurrent GBM is the inherent difficulty of differentiating true tumor progression from pseudoprogression or PRTE using modern imaging techniques.(29-31) In many cases, the patient has a mixture of both tumor recurrence and PRTE simultaneously. One study found that tumor recurrence or a mixture of tumor recurrence and PRTE was twice as likely as PRTE alone after radiation therapy for primary brain gliomas.(32, 33) This confounding variable can result in inappropriate treatment because prescribing any form of additional radiation for patients with PRTE results worsens PRTE.

An important distinction should be drawn between symptomatic and nonsymptomatic PRTE. Asymptomatic small areas of necrotic tissue within the margins of treatment are in many regards a desired treatment response after salvage SRS. It is only considered a negative response to treatment when the PRTE extends beyond treatment margins with evidence of associated symptoms due to edema and mass effect on adjacent viable tissue. The incidence of patients experiencing symptomatic PRTE following SRS has been reported in multiple series, ranging from 6 to 24%, which is similar to that found in our series (24%).(22, 34-37) Post-SRS PRTE appears to be relatively less problematic than PRTE reported after brachytherapy, likely due to smaller overall volumes of treatment.

Inherent limitations of a nonrandomized, retrospective, single-institution study with a heterogeneous sample of patients include selection bias. In general, our patients were selected for salvage GKSRS when they exhibited relatively small areas of nodular tumor recurrence, which did not induce significant mass effect that would have required surgical resection, or when the recurrence was in a deep and relatively difficult location for surgical access. Patients with larger tumor burdens requiring surgical decompression or with diffuse disease and declining clinical status were not chosen for GKSRS salvage therapy and were typically referred for hospice care. Multifocal nodular disease was not a contraindication for GKSRS, and its presence may have skewed the decision toward salvage GKSRS because multifocal surgical approaches were felt to be contraindicated or excessively burdensome to these patients.

Our retrospective long-term outcome data from a large cohort of select patients, with focal nodular areas of presumed recurrent disease, suggest that salvage GKSRS offers an effective means of adding modest, but meaningful, increased survival in these patients with minimal treatment burden or recovery time and minimal long-term risk of adverse events. We do not suggest that GKSRS is the best or even the first option for these patients. We encourage enrollment of these patients into well-designed clinical trials, ideally with tissue confirmation and molecular profiling-guided targeted therapies in the hope of gaining improved outcomes for these and future patients with this disease. However, salvage therapy with low-dose, low-volume GKSRS is an acceptable treatment option for patients with recurrent GBM who are unwilling to undergo invasive surgery or enroll in clinical trials of experimental therapies.

COMPLIANCE WITH ETHICAL STANDARDS

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Ethical Approval: Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

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Authors' disclosure of potential conflicts of interest

The authors have nothing to disclose.

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Symbols and Abbreviations

BVZ, bevacizumab; GBM, glioblastoma; GKSRS, Gamma Knife stereotactic radiosurgery; HGG, high-grade glioma; IMRT, intensity modulated radiation therapy; KPS, Karnofsky Performance Status; LITT, laser interstitial thermal therapy; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; PRTE, post-radiation treatment effect; RANO, Response Assessment in Neuro-oncology; SRS, stereotactic radiosurgery; TTF, tumor-treating fields

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