Outcomes and prognostic stratification of patients with recurrent glioblastoma treated with salvage stereotactic radiosurgery

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OBJECTIVE Glioblastoma (GBM) is the most malignant form of astrocytoma. The average survival is 6–10 months in patients with recurrent GBM (rGBM). In this study, the authors evaluated the role of stereotactic radiosurgery (SRS) in patients with rGBMs.

METHODS The authors performed a retrospective review of their brain tumor database (1997–2016). Overall survival (OS) and progression-free survival (PFS) after salvage SRS were the primary endpoints evaluated. Response to SRS was assessed using volumetric MR images.

RESULTS Fifty-three patients with rGBM underwent salvage SRS targeting 75 lesions. The median tumor diameter and volume were 2.55 cm and 3.80 cm³, respectively. The median prescription dose was 18 Gy (range 12–24 Gy) and the homogeneity index was 1.90 (range 1.11–2.02). The median OS after salvage SRS was estimated to be 11.0 months (95% CI 7.1–12.2) and the median PFS after salvage SRS was 4.4 months (95% CI 3.7–5.0). A Karnofsky Performance Scale score ≥ 80 was independently associated with longer OS, while small tumor volume (< 15 cm³) and less homogeneous treatment plans (homogeneity index > 1.75) were both independently associated with longer OS ($p = 0.007$ and 0.03) and PFS ($p = 0.01$ and 0.002 , respectively). Based on these factors, 2 prognostic groups were identified for PFS (5.4 vs 3.2 months), while 3 were identified for OS (median OS of 15.2 vs 10.5 vs 5.2 months).

CONCLUSIONS SRS is associated with longer OS and/or PFS in patients with good performance status, small-volume tumor recurrences, and heterogeneous treatment plans. The authors propose a prognostic model to identify a cohort of rGBM patients who may benefit from SRS.

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KEYWORDS recurrent GBM; stereotactic radiosurgery; brain tumor; glioblastoma; Gamma Knife; salvage treatment; oncology

GLIOMASTOMA (GBM) is the most malignant subtype constituting approximately 55% of all glial brain tumors.^{10,31} Despite aggressive management, these tumors tend to recur within 6 months of treatment initiation, and the prognosis remains dismal.^{52,54}

Patients with recurrent GBM (rGBM) pose significant

clinical management challenges, as no standard salvage treatment is currently available for these patients.⁴² Options such as repeat resection,^{57,58} laser interstitial thermal therapy (LITT),^{46,47,60} repeat external-beam radiotherapy (EBRT) alone^{6,40} or in combination with other agents,^{12,28} salvage stereotactic radiosurgery (SRS),^{3,8,32,33,61} various

ABBREVIATIONS EBRT = external-beam radiotherapy; GBM = glioblastoma; GKRS = Gamma Knife radiosurgery; KPS = Karnofsky Performance Scale; LITT = laser interstitial thermal therapy; MGMT = O⁶-methylguanine-DNA methyltransferase; OS = overall survival; PFS = progression-free survival; rGBM = recurrent GBM; RPA = recursive partitioning analysis; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

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chemotherapeutic agents,^{9,13,35,59,65–67} targeted therapies,^{2,7,13,23,38} immunotherapeutic options,^{15,37,41} and tumor treating fields^{53,55,56} have all been utilized with varied success. Salvage radiation with SRS is a well-established treatment modality for a variety of benign^{17,19,24,64} and malignant brain tumors.^{11,16,21,34,39,50,62,68} There is, however, insufficient evidence to either support or refute the use of radiosurgery in patients with recurrent or progressive malignant glioma;⁶³ various salvage SRS series have reported a median overall survival (OS) ranging between 5.3 and 24 months in patients with rGBM.^{3,30,32,33,49} The majority of these series are small retrospective studies with limited and heterogeneous patient populations.

In this study, we present our single-center 20-year experience with salvage SRS in managing 53 patients (75 lesions) with rGBM. We also propose a prognostic model to identify a cohort of patients with favorable factors who may benefit from SRS.

Methods

A retrospective review of the IRB-approved brain tumor database (1997–2016) was performed following IRB approval. Patients with no clinical follow-up or those who were enrolled in another clinical trial at our center investigating dose escalation of SRS in the setting of bevacizumab therapy for rGBM ($n = 9$) were excluded from this study.

Variables, Participants, and Data Source

Patients' electronic medical records were retrospectively reviewed to obtain demographic, imaging, and clinical data. Tumor-related variables (maximum tumor dimension, tumor volume, tumor location) and SRS data (prescription dose, maximum dose, conformity index [prescription isodose volume/tumor volume], homogeneity index [maximum dose/prescription tumor dose], gradient index) were also collected. Data from 53 patients (75 lesions) who underwent SRS for rGBM as a salvage therapy were included.

Molecular evaluation from the initial surgical specimens was performed with immunohistochemical staining with antibodies to IDH1 (R132H), Tp53, and Ki-67 to identify the IDH1 mutation and percentage of tumor cells staining positive for Tp53 and Ki-67. The percentages of tumor cells staining positive to Tp53 antibodies were segregated as < 10%, 10%–32%, 33%–66%, and > 66%, as previously described.²⁹ Similarly, tumor cells staining positive to Ki-67 antibodies were classified as < 10%, 10%–30%, and > 30%.⁶⁹ *O*⁶-methylguanine-DNA methyltransferase (MGMT) methylation status was determined using standard polymerase chain reaction (PCR) amplification of a targeted region of exon 1, and methylation of CpG sites was analyzed by pyrosequencing of the amplicons using the PyroMark Q96 ID instrument (Qiagen). The mean percentage of methylation was calculated and used to determine methylation status. Amplification of the *EGFR* gene was evaluated using interphase fluorescence in situ hybridization (FISH) on formalin-fixed, paraffin-embedded tissue sections using epidermal growth factor receptor (EGFR; 7p12) and chromosome 7 pericentro-

meric (7p11.1-q11.1) locus-specific directly labeled probes (Abbott Molecular/Vysis).

Gamma Knife Radiosurgery

SRS was delivered using Gamma Knife radiosurgery (GKRS; Elekta AB) at our center, as described in our previous studies.^{43,44} As the present series spans 20 years, GKRS was performed using different models—B, C, 4C, and Perfexion—during the study period. Since 2007, we have been using the Perfexion model for GKRS. GKRS is performed as an outpatient procedure following acquisition of informed consent. Briefly, on the day of the procedure, a stereotactic contrast-enhanced T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) MRI study (multiplanar reconstruction sequence with 2- to 3-mm-thick slices, no interslice gaps, and isotropic 1.0-mm voxels) was obtained either before or after Leksell frame (Elekta AB) placement. A postframe, stereotactic CT scan was then obtained and coregistered to the volumetric MR image at the planning station.

Target Definition and Clinical Follow-Up

Following satisfactory image coregistration, target tumor volume was defined as the contrast-enhanced tumor margin on the volumetric contrast-enhanced T1-weighted MRI without including the T2-weighted/FLAIR leading edge. A conformal plan was created using a combination of shots. The prescription dose was determined based on the maximum dimension of the tumor, according to the Radiation Therapy Oncology Group (protocol 90-05) guidelines.⁴⁵ Following GKRS, 4–6 weeks after the procedure, patients underwent clinical examination and MRI and then every 3 months thereafter. The median follow-up duration in our study was 10.1 months (range 0.8–51.4 months).

Outcomes and Endpoints

Overall survival (OS) and progression-free survival (PFS) from the date of salvage SRS were the primary and secondary endpoints, respectively. OS and PFS were measured from the time of salvage SRS to death and the first instance of tumor progression/recurrence or death, respectively.

Radiographic response to SRS was assessed using RANO criteria on contrast-enhanced T1-weighted and T2-weighted FLAIR MR images.²⁷ Also, the response to therapy was evaluated using volumetric analysis, after importing the post-SRS MR images into iPlan software (Brainlab AG), and findings were compared to those demonstrated on the pre-SRS MR images. Radiation necrosis was defined based on radiographic findings and our multidisciplinary brain tumor board consensus input, as previously described.^{5,43,44} Additionally, MR perfusion images or short-term follow-up MR images (4–6 weeks) were used to differentiate between radiation necrosis and local tumor progression in certain cases.

Statistical Analysis

The log-rank test (univariable) and proportional hazards model (univariable and multivariable) were used to

analyze the data. Stepwise variable selection, with $p = 0.10$ and 0.05 as the criteria for entry and retention in the model, was used to determine which, if any, provided independent prognostic information. Patients treated in 2005 and earlier ($n = 23$ [43%]) (i.e., prior to the introduction of Stupp's protocol featuring the survival benefit of first-line temozolomide in patients with GBM⁵⁴) had a worse outcome than patients treated after 2005 (median OS 10.0 vs 11.8 months, $p = 0.05$; median PFS 4.1 vs 4.5 months, $p = 0.05$). Therefore, to account for inherent differences related to when the patient was treated, the multivariable models were stratified by the year SRS was performed (2005 and earlier or after 2005). For convenience, recursive partitioning analysis (RPA) was used to find cut-points for continuous variables. Some patients had more than one lesion treated in a single session, and since variables such as maximum dimension, volume, progression, and SRS parameters are specific to the lesion, two analyses were performed. A lesion-specific analysis was performed in which all lesions were considered as separate "cases" and the marginal Cox model approach was used to account for the correlation that might exist between lesions within the same patient.²⁵ However, since most patients had a single lesion, a second, patient-specific analysis was also performed that aggregated lesion and SRS parameters. Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc.).

Results

Participants and Descriptive Data

A majority of patients ($n = 52$, 98.1%) were treated using single-stage SRS and 11 patients (21%) had multiple lesions (4 patients [7.5%] underwent treatment in 2 sessions for different lesions and 1 patient [1.8%] underwent treatment in 3 stages for a single lesion [12 Gy per fraction]). Most of the patients (70%, $n = 34$) had good performance status (Karnofsky Performance Scale [KPS] score ≥ 80). Also, most patients were RPA class 4 (47%, $n = 23$) or classes 5 and 6 (43%, $n = 21$)²⁶ (Table 1). The decrease was $> 25\%$ in 15 of 36 lesions (42%) and $> 50\%$ in 8 of 36 (22%).

Since the series spans 2 decades, molecular analysis was only available for patients treated in the later part of the series (since 2009). The majority (87.5%, $n = 14/16$) of patients with data had wild-type IDH, 35% ($n = 7/20$) had elevated p53 staining ($\geq 33\%$), 41% ($n = 13/32$) had elevated Ki-67 staining ($> 30\%$), and 66.7% ($n = 10/15$) had MGMT-unmethylated GBM.

Lesion Characteristics

The median maximum tumor dimension and volume were 2.55 cm (range 0.25–6.90 cm) and 3.80 cm³ (range 0.01–29.70 cm³), respectively. The median prescription dose was 18 Gy (range 12–24 Gy), and the majority of lesions (46%) were treated at a dose of 15 Gy to the tumor margin. The median conformity index was 1.85 (range 1.35–13.27), and the median homogeneity index was 1.90 (range 1.11–2.02).

Most lesions (74%, 56/75) were initially treated with either gross-total tumor resection (57%, 43/75) or subtotal resection (17%, 13/75) followed by chemoradiotherapy

TABLE 1. Patient, disease, and treatment characteristics, on per-patient basis

Factor (range)	No. (%) or Median (range)
Sex	
Female	17 (32%)
Male	36 (68%)
Age at SRS, yrs*†	58 (19–82)
KPS score*†‡	
50–60	4 (8%)
70	11 (22%)
80	19 (39%)
90–100	15 (31%)
Interval from diagnosis to SRS, mos*†	9.0 (0.07–71.5)
RPA class*	
Class 3	5 (10%)
Class 4	23 (47%)
Classes 5 & 6	21 (43%)
% (+) Tp53*§	
<10%	6 (30%)
10–32%§	7 (35%)
33–66%	2 (10%)
>66%	5 (25%)
IDH mutation*	
Negative	14 (87.5%)
Positive	2 (12.5%)
EGFR amplification*	
No	11 (50%)
Yes	11 (50%)
Percentage of Ki-67-positive–stained cells*	
<10%	5 (15.6%)
10–30%	14 (43.7%)
>30%	13 (40.6%)
MGMT methylation*	
No	10 (66.7%)
Yes	5 (33.3%)

* Missing data: age ($n = 1$); KPS score ($n = 4$); RPA ($n = 4$); interval from diagnosis ($n = 3$); p53 ($n = 34$); IDH ($n = 37$); EGFR ($n = 31$); Ki-67 ($n = 21$); and MGMT ($n = 38$).

† First SRS if > 1 session.

‡ In the series, 2 patients had a KPS score of 50, 2 had a score of 60, and 2 had a score of 100.

§ This translates into percentage of tumor cells staining positive for Tp53.

prior to salvage SRS. One patient with one lesion (1.3%) had LITT prior to SRS. Most lesions were treated with at least two additional treatment modalities following the index procedure prior to salvage SRS (56%, 42/75). Considering all treatments after the index procedure but prior to salvage SRS, most lesions at some point were treated with EBRT and chemotherapy, with (8%, 6/75) or without (56%, 42/75) additional surgery. Seven percent (5/75) of lesions were treated with whole-brain radiation therapy (WBRT) only, and 5% (4/75) were treated with WBRT and chemo-

therapy with or without additional surgery (Table 2). Also, 3 lesions developed radiation necrosis (3/75, 4%) following SRS during the follow-up period with no focal neurological deficits that could be attributed to radiation necrosis. None of the patients who received EBRT following SRS developed radiation necrosis during the follow-up period. These patients with radiation necrosis were treated using conservative management.

Outcome Data, Main Results, and Other Analyses

Overall Survival

Overall, 83% (44/53) of patients died, and the median OS was estimated to be 11.0 months (95% CI 7.1–12.2). Smaller tumor volume ($< 15 \text{ cm}^3$, $p = 0.03$), low isodose line (≤ 60 , $p = 0.03$), and higher homogeneity index (> 1.75 , $p = 0.09$) were associated with improved OS in the univariable analysis, as was KPS (score ≥ 80 , $p = 0.0007$) and RPA (class 3 vs 4 vs 5 or 6, $p = 0.07$). However, in multivariable analysis, only total tumor volume, KPS score, and homogeneity index (i.e., more heterogeneous plans) were found to be independent predictors of OS ($p = 0.007$, 0.0004, and 0.03, respectively) (Tables 3 and 4 and Fig. 1). Among the subset of patients with molecular data, those with $\geq 10\%$ of cells staining positive for p53 or Ki-67 had longer OS compared to those with $< 10\%$ (13.0 vs 5.4 months for p53, $p = 0.008$; 11.8 vs 5.5 months for Ki-67, $p = 0.04$). However, neither factor was identified as an independent prognostic factor for OS (p53: $p = 0.57$; Ki-67: $p = 0.95$) in the multivariable analysis.

Progression-Free Survival

Six-month survival and median PFS were estimated to be $28\% \pm 6\%$ and 4.4 months (95% CI 3.7–5.0), respectively. Similar to OS, total tumor volume ($< 15 \text{ cm}^3$, $p = 0.03$), low treatment isodose line (≤ 60 , $p = 0.004$), and high homogeneity index (> 1.75 , $p = 0.02$) were significantly associated with improved PFS in the univariable analysis, as was smaller tumor diameter ($< 3 \text{ cm}$, $p = 0.03$). In multivariable analysis, only smaller total tumor volume ($p = 0.01$) and high homogeneity index ($p = 0.002$) were found to be independent predictors of PFS. None of the molecular markers were associated with PFS on univariable analysis ($p > 0.05$) (Tables 3 and 4 and Fig. 1).

Prognostic Groups for OS and PFS

For OS, in addition to tumor volume and homogeneity index, KPS score was also seen to be an independent prognostic factor. By simply counting the number of poor features present (total volume $\geq 15 \text{ cm}^3$, homogeneity index [minimum if > 1 lesion treated] ≤ 1.75 , and KPS score < 80), 4 prognostic groups were possible; however, only 1 patient had all 3 poor prognostic features (OS was 5.2 months), and therefore the last 2 groups were combined. The 3 resulting prognostic groups were labeled “favorable,” “intermediate,” and “unfavorable” and comprised 39% (17/44), 50% (22/44), and 11% (5/44) of patients, respectively. The estimated median OS durations for the 3 groups were 15.2 months (95% CI 7.4–29.0 months), 10.5 months (95% CI 5.2–12.2 months), and 5.2 months (95% CI 0.8–6.3 months), respectively (Table 5 and Fig. 2).

TABLE 2. Patient, disease, and treatment characteristics based on per-lesion analysis

Factor (range)	No. (%) or Median (range)
Prescription dose, Gy†	18 (12–24)
15	34 (46%)
18	16 (22%)
24	24 (32%)
Isodose line	52 (50–90)
Conformity*	1.85 (1.00–13.27)
Homogeneity*	1.90 (1.11–2.02)
Longest diameter, cm	2.55 (0.25–6.90)
Volume, cm^3 *	3.80 (0.01–29.70)
Initial treatment‡	
Biopsy	5 (7%)
GTR	43 (57%)
STR	13 (17%)
NeuroBlate	1 (1.3%)
SRS	2 (3%)
No. of subsequent treatments prior to salvage SRS§	
1	23 (31%)
2	21 (28%)
3	10 (13%)
> 3 ¶	11 (15%)
Modalities of subsequent procedures	
Any surgery§	16 (21%)
Any EBRT	55 (73%)
Any WBRT	10 (13%)
Any systemic treatment	58 (77%)
Overall procedures**	
EBRT only	4 (5%)
WBRT only	5 (7%)
Systemic only	1 (1%)
EBRT + systemic	42 (56%)
EBRT + systemic + surgery	6 (8%)
WBRT + systemic ± surgery	4 (5%)

GTR = gross-total resection; STR = subtotal resection.

* Missing data: SRS dose ($n = 1$); volume ($n = 1$); conformity ($n = 7$); and homogeneity ($n = 7$).

† The 15-Gy treatment included 2 lesions treated at 12 and 13 Gy; the 18-Gy treatment included 1 lesion treated at 20 Gy; and the 24-Gy treatment included 1 lesion treated at 22 Gy.

‡ Eleven patients (15%) had distant rGBMs with no prior treatment.

§ Excludes biopsies, ancillary surgeries such as shunt placement, and hospice; 10 patients (13%) had no subsequent procedures prior to salvage SRS.

¶ Four patients had 4 subsequent procedures, 5 had 5, and 1 each had 6 and 7.

** Seven patients (9%) had no overall procedures, and 6 patients (8%) had other treatments.

Two factors, total tumor volume and homogeneity index, were seen to be independent prognostic factors for PFS. As with OS, by counting the number of poor prognostic features present (total volume $\geq 15 \text{ cm}^3$, homogeneity index [minimum if > 1 lesion treated] ≤ 1.75), 3 prog-

TABLE 3. Univariable analysis showing factors significantly associated with OS and PFS

Factor	OS		PFS	
	Median (95% CI) or HR (95% CI)*	p Value	Median (95% CI) or HR (95% CI)*	p Value
KPS score				
<80	6.3 (4.7–11.0)		4.1 (1.5–5.0)	
≥80	12.2 (7.4–16.0)	0.0007	4.3 (3.5–5.4)	0.51
RPA class				
Class 3	12.2 (8.1–52.2)		3.9 (1.0–4.6)	
Class 4	12.2 (6.3–14.5)		4.6 (2.0–6.1)	
Classes 5 & 6	5.5 (4.1–11.5)	0.07†	4.0 (2.4–5.0)	0.85†
Maximum tumor diameter				
<3 cm	11.5 (8.1–13.6)		4.7 (3.7–10.1)	
≥3 cm	8.9 (5.2–12.2)	0.28	4.3 (2.6–4.6)	0.03
Total tumor volume				
<15 cm ³	11.7 (7.4–13.8)		4.4 (3.7–6.1)	
≥15 cm ³	5.6 (2.6–11.8)	0.03	3.3 (1.5–4.6)	0.03
p53 staining				
<10%	5.4 (0.8–NA)		4.0 (0.8–11.0)	
10–32%	14.2 (7.4–51.5)		6.9 (1.0–NA)	
33–66%	14.5 (NA)		NA	
>66%	11.2 (8.1–13.0)	0.008‡	3.9 (1.5–13.0)	0.16‡
Ki-67 staining				
<10%	5.5 (4.7–13.6)	0.12	4.6 (1.5–5.4)	0.62
10–30%	12.2 (4.1–16.3)		4.2 (2.5–6.1)	
>30%	11.8 (6.1–14.5)	0.04‡	4.3 (1.5–10.1)	0.36‡
Homogeneity index				
>1.75	0.20 (0.06–0.67)	0.009	0.06 (0.02–0.15)	<0.0001
≤1.75	Reference		Reference	
Isodose line	2.95 (1.14–7.65)	0.03	3.73 (1.65–8.42)	0.002
	1.04 (1.00–1.08)	0.04	1.06 (1.04–1.09)	<0.0001

HR = hazard ratio; NA = not applicable.

* Hazard ratios > 1 (< 1) indicate that the prognosis decreases (increases) as the value of the factor increases.

† Trend test (class 3 vs 4 vs 5 and 6).

‡ < 10% versus ≥ 10%.

TABLE 4. Multivariable analysis showing factors significantly associated with OS and PFS

Factor	HR (95% CI)	p Value
PFS		
Total tumor volume (<15 [ref] vs ≥15 cm ³)	2.96 (1.24–7.07)	0.01
Homogeneity index (>1.75 [ref] vs ≤1.75)*	3.73 (1.65–8.42)	0.002
OS		
Total tumor volume (<15 [ref] vs ≥15 cm ³)	3.78 (1.44–9.94)	0.007
KPS score (≥80 [ref] vs <80)	5.18 (2.09–12.87)	0.0004
Homogeneity index (>1.75 [ref] vs ≤1.75)*	2.95 (1.14–7.65)	0.03

Analyses were stratified by year of SRS.

* If > 1 lesion was treated in a session the minimum homogeneity index was used.

nostic groups emerged; however, similar to OS prognostic categories, only 1 patient had both total volume ≥ 15 cm³ and a homogeneity index ≤ 1.75 (PFS was 1.5 months), and therefore patients with 1 or 2 poor features were

combined. The two resulting prognostic groups, labeled “favorable” and “unfavorable,” comprised 60% (27/45) and 40% (18/45) of patients, respectively. The estimated 6-month PFS and median PFS of the favorable group were

FIG. 1. Kaplan-Meier curves showing the percentage of PFS and OS in patients following SRS for rGBM.

45% $\pm$ 10% and 5.4 months (95% CI 4.0–8.4), and those for the unfavorable group were 6% $\pm$ 5% and 3.2 months (95% CI 1.8–4.4), respectively (Table 5 and Fig. 2).

Discussion

In our study, based on total tumor volume ($< 15 \text{ cm}^3$), homogeneity index (> 1.75), and KPS score ≥ 80 , 2 prognostic groups were identified for PFS, while 3 were identified for OS. The estimated median OS durations for the 3 groups were 15.2 months (95% CI 7.4–29.0 months), 10.5 months (95% CI 5.2–12.2 months), and 5.2 months (95% CI 0.8–6.3 months), respectively. The estimated median PFS of the favorable group was 5.4 months (95% CI 4.0–8.4 months), and that for the unfavorable group was 3.2 months (95% CI 1.8–4.4 months), respectively.

In 2004, Radiation Therapy Oncology Group (RTOG) protocol 93-05 investigated the use of a postoperative SRS boost to any residual tumor followed by EBRT and BCNU versus EBRT and BCNU without the SRS boost in patients with newly diagnosed GBM.⁵¹ The median OS in

the SRS arm was 13.5 months compared to 13.6 months in the non-SRS arm ($p = 0.5711$).⁵¹ Since publication of the negative results of this randomized study and those reported by Stupp et al.⁵⁴ in 2005, the role of SRS in patients with newly diagnosed GBM has not been clearly established. However, the utility of SRS in patients with rGBM was not addressed in these studies. Our previous phase I trial of radiosurgery dose escalation in combination with bevacizumab therapy in patients with rGBM has shown that a single dose of bevacizumab administered about 1 week prior to SRS permitted safe SRS dose escalation of up to 22 Gy for rGBM, with a maximum linear tumor diameter of 2.58 cm.¹

Factors Predictive of Outcomes

Niranjan et al.³⁰ reported that younger age (< 60 years) and smaller tumor volume ($< 14 \text{ cm}^3$) were associated with improved OS and that smaller tumor volume ($< 14 \text{ cm}^3$) was associated with improved PFS (4.9 months vs 4.0 months, $p = 0.011$). SRS margin dose was identified as a prognostic factor affecting time to progression in a study in which a low margin dose of 6 Gy was used as a salvage therapy.³⁶ Elliott et al.⁸ identified a higher performance score (KPS score ≥ 90), smaller tumor volume, and increased time to recurrence as factors predictive of longer OS. Kong et al.²² also identified smaller tumor volume ($< 10 \text{ cm}^3$) as predictive of OS. In the present study, we similarly identified smaller tumor volume ($< 15 \text{ cm}^3$) and KPS score (≥ 80) as independent predictors of improved OS.

The homogeneity index (maximum dose/prescription tumor dose) evaluates the uniformity of the dose distribution in the target volume, with a higher number indicative of a heterogeneous dose distribution that is associated with a greater number of hot spots. Interestingly, we found that a higher homogeneity index (> 1.75 ; i.e., a more heterogeneous plan) was also an independent predictor of both PFS ($p = 0.002$) and OS ($p = 0.03$). Moreover, since the radiation dose is relevant in the management of GBMs, and as Chan et al.⁴ noted, the majority (91%) of tumor recurrences occurred within the central portion of the tumor volume region (i.e., 95% of the tumor volume region). These findings of high homogeneity index as an independent, favorable prognostic factor are novel and noteworthy, but they need to be investigated in a large cohort of patients with rGBM managed with salvage SRS.

TABLE 5. Prognostic groups significantly associated with PFS and OS following salvage SRS

Prognostic Group	No. of Patients (%)	Median (95% CI)
PFS (n = 45)		
Favorable (homogeneity index > 1.75 & total volume $< 15 \text{ cm}^3$)	27 (60%)	5.4 (4.0–8.4)
Unfavorable (homogeneity index ≤ 1.75 &/or total volume $\geq 15 \text{ cm}^3$)*	18 (40%)	3.2 (1.8–4.4)
OS (n = 44)		
Favorable (no poor prognostic factor)†	17 (39%)	15.2 (7.4–29.0)
Intermediate (1 poor prognostic factor)†	22 (50%)	10.5 (5.2–12.2)
Unfavorable (2 or 3 prognostic factors)†	5 (11%)	5.2 (0.8–6.3)

* Only 1 patient had both a homogeneity index ≤ 1.75 and volume $\geq 15 \text{ cm}^3$; the PFS for this patient was 1.5 months.

† Poor prognostic features: KPS score < 80 , total volume $\geq 15 \text{ cm}^3$, and homogeneity index ≤ 1.75 .

FIG. 2. Kaplan-Meier curves showing PFS (left) in patients stratified into prognostic groups (favorable: homogeneity index > 1.75 and total volume $< 15 \text{ cm}^3$; unfavorable: index ≤ 1.75 and/or total volume $\geq 15 \text{ cm}^3$) and OS (right) in patients stratified into prognostic groups (favorable: 0 poor prognostic features; intermediate: 1 poor prognostic feature; unfavorable: 2 or 3 poor prognostic features) following salvage SRS for rGBM. The poor prognostic features were KPS score < 80 , total tumor volume $\geq 15 \text{ cm}^3$, and homogeneity index ≤ 1.75 .

We also found that patients treated after 2005 had a better outcome than patients treated prior to 2005 (median OS 10.0 vs 11.8 months, $p = 0.05$; median PFS 4.1 vs 4.5 months, $p = 0.05$). This may be attributed to the standardization in the management of patients with newly diagnosed GBM following the introduction of Stupp's protocol, which led to improvement in median OS, from 12.1 months to 14.6 months.⁵⁴ However, the difference in our study may also be attributed to higher median prescription dose to a smaller median tumor volume after 2005 (21 Gy to a 0.2-cm^3 tumor volume) compared to the era prior to 2005 (15 Gy to a 10.4-cm^3 tumor volume, $p = 0.01$). Based on these predictive factors, we have created prognostic groups (favorable, intermediate, and unfavorable), which may help guide the selection of patients who are likely to benefit from salvage SRS for rGBM.

In 1997, Kondziolka et al.²⁰ reported an overall median survival of 30 months for salvage SRS when performed at the time of recurrence versus 20 months when performed upfront as a part of initial treatment in patients with GBM. Recently, Hsieh et al.¹⁴ reported an improved median OS of 16.7 months when salvage SRS was performed at the time of tumor progression compared to 10 months when GKRS was performed as an upfront adjunct treatment in 26 patients with GBM using a median margin dose of 12 Gy. This difference in SRS responsiveness in primary versus recurrent GBMs may simply be attributable to selection bias toward patients with good overall performance status for salvage SRS and small local tumor recurrences. Alternatively, perhaps some yet-to-be elucidated factors or features intrinsic to the recurrent tumors contribute to enhanced radiosurgical responsiveness in rGBMs. Further studies regarding optimal timing, SRS dosing, and combination of SRS with other chemotherapeutic/radio-sensitizing agents to achieve maximum efficacy for rGBMs are required.

In our study, patients with a larger number of cells staining for p53 or Ki-67 showed prolonged OS compared to patients with a lower number of cells staining positive, with no impact on PFS. This finding may be attributed to

the fact that focal tumors with rapidly dividing cells are perhaps more likely to respond to SRS than otherwise. Of note, while there was no correlation between the molecular status and overall outcome in our study, due to the small number of patients with available molecular information, the associated statistical power is acknowledged to be low, and we believe further research in this area is needed.

Recently, minimally invasive techniques such as LITT have been shown to be efficacious in managing patients with rGBM.^{46–48,60} The minimally invasive nature of this treatment modality makes it a useful tool, particularly in patients with deep-seated recurrent tumors. In our series, only one patient with one lesion was treated with LITT prior to SRS. The impact of LITT in combination with SRS still needs to be elucidated in cases of rGBM. Similarly, various immunotherapeutic agents^{15,37,41} have been tried in patients with rGBM, and the results have varied. The impact of these agents on SRS outcomes in patients with rGBM could not be evaluated in our study due to heterogeneous treatment modalities and the small sample size. However, this question can be addressed and answered in future studies.

Our finding of a median OS of 11 months after salvage SRS in patients with rGBM appears comparable to the 11.8 months observed following a combination of the newer treatment modality of tumor treating fields and chemotherapy in patients with rGBM.¹⁸ Moreover, the median OS of 15.2 months in our patients with favorable prognostic factors is very encouraging given that SRS is a well-established treatment modality with the convenience of a single treatment session. Our work suggests that SRS is an effective treatment modality in patients with rGBM and may be considered earlier and more often in carefully selected patients (Fig. 3).

Limitations and Future Directions

The retrospective design, heterogeneous management strategies, potential for selection bias, and lack of control

FIG. 3. Illustrative case of a 61-year-old man who presented with rGBM following standard concurrent chemoradiotherapy and 3 cycles of adjunct chemotherapy. He exhibited a good response to salvage SRS (22 Gy at 50% isodose line; homogeneity index 2.005) at the 9.4-month follow-up (pretreatment axial [A] and sagittal [B] postgadolinium T1-weighted MR images and postgadolinium axial [C] and sagittal [D] T1-weighted MR images at last follow-up). Figure is available in color online only.

groups are potential limitations of our study. Also, the effects of ongoing systemic treatment cannot be segregated from that of local control offered by SRS on follow-up imaging (as in other studies). However, our study confirms the utility of SRS in managing patients with rGBM and identifies prognostic groups. The defined prognostic groups may be a useful tool for clinical decision-making, treatment planning, resource utilization, and clinical trial design.

Conclusions

Good performance, smaller tumor volumes, and treatment at higher homogeneity indices were associated with longer OS and/or PFS despite multiple prior treatments for

rGBM. SRS for rGBM is a reasonable salvage treatment option for these patients.

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Disclosures

Dr. Barnett is a consultant for Elekta. Dr. Mohammadi is a consultant for Monteris Medical.

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Conception and design: Angelov, Sharma. Acquisition of data: Sharma, Schroeder, Meola. Analysis and interpretation of data: Sharma, Elson. Drafting the article: Sharma. Critically revising the article: Angelov, Sharma, Barnett, Vogelbaum, Suh, Chao, Mohammadi, Stevens, Murphy. Reviewed submitted version of manuscript: Angelov, Sharma, Schroeder, Meola, Barnett, Vogelbaum, Suh, Chao, Mohammadi, Stevens, Murphy. Approved the final version of the manuscript on behalf of all authors: Angelov. Statistical analysis: Elson. Administrative/technical/material support: Angelov, Barnett. Study supervision: Angelov, Barnett.

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