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Stereotactic radiosurgery for glioblastoma considering tumor genetic profiles: an international multicenter study

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OBJECTIVE Molecular profiles, such as isocitrate dehydrogenase (IDH) mutation and *O*^{6}-methylguanine-DNA methyltransferase (MGMT) methylation status, have important prognostic roles for glioblastoma patients. The authors studied the efficacy and safety of stereotactic radiosurgery (SRS) for glioblastoma patients with consideration of molecular tumor profiles.

METHODS For this retrospective observational multiinstitutional study, the authors pooled consecutive patients who were treated using SRS for glioblastoma at eight institutions participating in the International Radiosurgery Research Foundation. They evaluated predictors of overall and progression-free survival with consideration of IDH mutation and MGMT methylation status.

RESULTS Ninety-six patients (median age 56 years) underwent SRS (median dose 15 Gy and median treatment volume 5.53 cm^3) at 147 tumor sites (range 1 to 7). The majority of patients underwent prior fractionated radiation therapy (92%) and temozolomide chemotherapy (98%). Most patients were treated at recurrence (85%), and boost SRS was used for 12% of patients. The majority of patients harbored IDH wild-type (82%) and MGMT-methylated (62%) tumors. Molecular data were unavailable for 33 patients. Median survival durations after SRS were similar between patients harboring IDH wild-type tumors and those with IDH mutant tumors (9.0 months vs 11 months, respectively), as well as between those with MGMT-methylated tumors and those with MGMT-unmethylated tumors (9.8 vs. 9.0 months, respectively). Prescription dose > 15 Gy (OR 0.367, 95% CI 0.190–0.709, p = 0.003) and treatment volume > 5 cm^3 (OR 1.036, 95% CI 1.007–1.065, p = 0.014) predicted overall survival after controlling for age and IDH status. Treatment volume > 5 cm^3 (OR 2.215, 95% CI 1.159–4.234, p = 0.02) and absence of gross-total resection (OR 0.403, 95% CI 0.208–0.781, p = 0.007) were associated with inferior local control of SRS-treated lesions in multivariate models. Nine patients experienced adverse radiation events after SRS, and 7 patients developed radiation necrosis at 59 to 395 days after SRS.

CONCLUSIONS Post-SRS survival was similar as a function of IDH mutation and MGMT promoter methylation status, suggesting that molecular profiles of glioblastoma should be considered when selecting candidates for SRS. SRS prescription dose > 15 Gy and treatment volume ≤ 5 cm^3 were associated with longer survival, independent of age and IDH status. Prior gross-total resection and smaller treatment volume were associated with superior local control.

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KEYWORDS glioblastoma; radiosurgery; isocitrate dehydrogenase; *O*^{6}-methylguanine-DNA methyltransferase; stereotactic radiosurgery

ABBREVIATIONS ARE = adverse radiation event; FRT = fractionated radiotherapy; IDH = isocitrate dehydrogenase; IRRF = International Radiosurgery Research Foundation; MGMT = *O*^{6}-methylguanine-DNA methyltransferase; OS = overall survival; PFS = progression-free survival; RANO = Response Assessment in Neuro-Oncology; RTOG = Radiation Therapy Oncology Group; SRS = stereotactic radiosurgery.

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Glioblastoma is the most common primary malignant brain tumor and accounts for approximately 15% of all brain tumors.[1] The prognosis of patients with glioblastoma is poor; median survival is approximately 15 months, and survival uncommonly exceeds 2 years after diagnosis.[1] First-line treatment typically includes maximally safe resection followed by adjuvant chemotherapy with temozolomide and concurrent fractionated radiotherapy (FRT), and maintenance temozolomide chemotherapy.[2,3]

Molecular profiles of glioblastomas are routinely considered for prognostication and planning.[4] Mutation in isocitrate dehydrogenase (IDH) 1 and 2 is an important prognostic biomarker for glioma patients because IDH-wild type gliomas carry a significantly worse prognosis when compared with IDH mutant gliomas.[5,6] O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is associated with greater benefit from temozolomide chemotherapy.[7,8] IDH mutation and MGMT promoter methylation status have prognostic value as a function of extent of resection of glioblastoma.[9–11]

Stereotactic radiosurgery (SRS) is used for treatment of recurrent glioblastoma and has been shown to offer some survival benefit with acceptable toxicity.[12–20] There is a growing interest in the possible prognostic impact of molecular biomarkers for prognosis of glioblastoma patients treated with SRS.[15,21,22] Single-center series have shown that MGMT promoter methylation can be associated with longer progression-free survival (PFS) and overall survival (OS) as compared with the survival of patients with newly diagnosed and recurrent MGMT-unmethylated glioblastoma treated with SRS.[15,21,22] However, the prognostic value of IDH status is not reported. A recent study of IDH wild-type glioblastoma patients found that a *PTEN* mutation was associated with better prognosis after SRS.[23] Further studies investigating the prognostic value of molecular biomarkers of glioblastoma in patients treated with SRS are warranted for personalized treatment decision-making for this challenging and heterogeneous disease.

The goal of this international multicenter study was to investigate efficacy and safety of SRS for glioblastoma with consideration of IDH mutation and MGMT methylation and status. We hypothesized that SRS would be a safe treatment option for recurrent glioblastoma, which has molecular tumor profiles that affect treatment efficacy.

Methods

Patients

Consecutive patients were identified from institutions affiliated with the International Radiosurgery Research Foundation (IRRF) (protocol no. R-16–10) and agreed to participate in this retrospective observational study. The study inclusion criteria were histologically confirmed diagnosis of WHO grade IV glioblastoma treated with SRS. A database with variables of interest was established by investigators at the University of Virginia and sent to all participating centers. Data collection was approved by the institutional review boards at each of the participating centers. Individual patient data were de-identified and pooled for the analyses.

A total of 96 patients treated with SRS for WHO grade IV glioblastoma were identified from eight institutions participating in IRRF: New York University Langone Medical Center, New York, New York (n = 26), University of Virginia, Charlottesville, Virginia (n = 22), Taipei Veteran General Hospital, Taipei, Taiwan (n = 17), Université de Sherbrooke, Quebec, Canada (n = 11), West Virginia University, Morgantown, West Virginia (n = 9), Jewish Hospital, Mayfield Clinic, Cincinnati, Ohio (n = 4), Post Graduate Institute of Medical Education and Research, Chandigarh, India (n = 4), and Centro Gamma Knife Dominicano and Radiology Department, Santo Domingo, Dominican Republic (n = 3).

Clinical Assessment

We gathered information regarding patient sex, age, functional status (Karnofsky Performance Scale score), tumor laterality and location, medical history, number and extent of pre-SRS resection (gross-total resection, subtotal resection, or biopsy), pre-SRS chemotherapy (agent), and FRT (dose and number of fractions). We also recorded IDH mutation and MGMT methylation status, if available.

SRS Technique

SRS was performed according to standard techniques using Gamma Knife units (models U, B, C, 4C, Perfexion, and Icon, Elekta AB) depending on the available technology at each of the participating centers at the time of SRS. Frame-based stereotaxy was performed using the Leksell Model G Frame (Elekta AB), which was placed under local anesthesia with or without conscious sedation. Frameless SRS using a thermoplastic mask or the Extend bite-block system was used for hypofractionated SRS or when stereotactic frame application was not technically possible due to prior craniotomy. The decision to use single or hypofractionated SRS techniques was made at the discretion of the treating team.

Radiosurgical planning was performed using high-resolution precontrast and postcontrast T1-weighted MRI scans with 1-mm-thick slices and T2-weighted brain MRI. SRS planning was performed by a multidisciplinary team that included a neurosurgeon, radiation oncologist, and medical physicist. At each center, planning was individualized on the basis of the patient's needs and imaging findings. Radiosurgical parameters, including margin and maximum tumor dose (grays), number of isocenters, treatment volume (cubic centimeters), number of fractions, and SRS treatment target (T1-weighted enhancing tumor and/or T2-weighted/FLAIR hyperintense tumor) were recorded for each SRS session, as well as for each SRS target in cases with multiple volumes treated in a single session. In cases involving multiple discrete target volumes per SRS session, we considered average margin and maximal dose and total summation of all target volumes treated in the patient-level analyses. We also recorded treatment with chemotherapy and steroids at each SRS session. Time from completion of prior FRT to SRS was recorded, as well as SRS setting (tumor recurrence or boost after resection).

Clinical and Radiographic Follow-Up

Imaging and clinical follow-up were obtained at approximately 3-month intervals and/or as clinically indicated. Imaging follow-up typically included T1-weighted contrast-enhanced and T2-weighted MRI. All follow-up imaging was reviewed by clinicians at the treating institution. The local tumor response of each SRS target was established according to Response Assessment in Neuro-Oncology (RANO) criteria as complete response, partial response, stable disease, or progression.[24] Time from SRS to tumor response (in months) was recorded. Presence, type, grade, timing with regards to SRS, and treatment of adverse radiation events (AREs) were recorded. SRS-related adverse events, including radionecrosis, were categorized according to the CNS toxicity criteria of the Radiation Therapy Oncology Group (RTOG).[25] Radiation necrosis was identified using brain MRI and other imaging modalities, as deemed appropriate by the treating team.

Need for repeated SRS, radiotherapy, resection, or chemotherapy for recurrence of glioblastoma after index SRS, as well as time and cause of death, were recorded. Patients who died of causes other than glioblastoma progression were excluded from analyses of OS.

Statistical Analyses

Statistical analyses were performed with IBM SPSS Statistics for Windows version 25.0 (IBM Corp). For all statistical tests, $p < 0.05$ was considered statistically significant. PFS was defined as the interval (in months) from SRS for glioblastoma to MRI-documented tumor progression or last imaging follow-up, whichever occurred first. OS was defined as the interval (in months) from SRS to tumor-related death or last follow-up, whichever occurred first. First, descriptive statistics were used to present the main clinical, demographic, and SRS treatment data. Next, Kaplan-Meier analyses were used to calculate PFS and OS; patients without an index event were censored at last follow-up. The associations of clinical, molecular, and SRS factors with PFS and OS of patients whose standard of care had failed were first investigated using the Kaplan-Meier method, and then univariate and multivariate Cox regression analyses. Regression models for OS were adjusted for IDH status and patient age. The results of Cox regression analysis are presented as HR, 95% CI, and p value. Finally, the incidence of AREs was analyzed using descriptive statics, and the t-test and chi-square test were used to identify clinical and SRS treatment factors associated with AREs.

Results

Ninety-six patients underwent SRS for recurrent glioblastoma (Table 1). Median patient age at SRS was 56 years, and the range was 13 to 84 years. Laterality distribution was balanced. Before SRS, the majority of patients underwent gross-total (48%) or subtotal (34%) resection, FRT (92%), and chemotherapy that included temozolomide (98%). IDH and/or MGMT status was available for 63 (66%) patients each. The majority of patients harbored IDH wild-type (82%) and MGMT-methylated (62%) tumors.

TABLE 1. Baseline characteristics of the study patients

Characteristic	Value
Sex	
Male	59 (62)
Female	37 (38)
Age at diagnosis, yrs	54.03 ± 14.26 (56 [13–84])
Laterality	
Lt hemisphere	42 (44)
Rt hemisphere	49 (51)
Bilat/other	3 (3)
Data unavailable	2 (2)
Extent of pre-SRS resection	
Gross-total	46 (48)
Subtotal	33 (34)
Biopsy	12 (13)
Data unavailable	5 (5)
No. of pre-SRS resections	
0	2 (2)
1	72 (75)
2	17 (18)
3	4 (4)
5	1 (1)
Pre-SRS fractionated radiation therapy	
Yes	88 (92)
No	8 (8)
Radiation dose, Gy	58.50 ± 8.59 (60 [30–100])
No. of fractions	28.85 ± 5.93 (30 [5–48])
Pre-SRS chemotherapy	
Yes	
Temozolomide	94 (98)
Bevacizumab	30 (32)
Other agent only	1 (1)
No	1 (1)
MGMT status	
Available data	63 (66)
Methylated	39 (62)
Unmethylated	24 (38)
IDH mutation	
Available data	63 (66)
Yes	11 (18)
No	52 (82)

Values are shown as number (percent) or mean ± SD (median [range]).

SRS Treatment Characteristics

The study included 147 SRS treatment targets, with a median (range) number of SRS targets per patient of 1 (1–7) (Table 2). Most patients were treated for tumor recurrence (85%). The treatment targets included only T1-weighted enhancing tumor in 96% of patients and also T2-weighted FLAIR hyperintense lesion in 2% of cases. Ninety-eight percent of patients were treated with single-session SRS. The median (range) treatment volume per patient was 5.53 (0.12–62.4) cm^3. The median (range) margin and maximal doses were 15 (5–24) Gy and 30 (10–55) Gy, respectively. In patients treated with single-session SRS, median treatment volume and prescription dose were 5.16 cm^3 and 15 Gy, respectively. Forty-five percent and 42% of

TABLE 2. SRS treatment characteristics

Characteristic	Value
Patient-level data	
SRS indication	
At recurrence	82 (85)
Boost after resection	11 (12)
Not specified/other	3 (3)
SRS treatment target	
T1-weighted enhancing tumor only	92 (96)
T1-weighted enhancing and T2/FLAIR	2 (2)
Not reported	2 (2)
Total no. of patients	96
Treatment vol, cm^3	9.88 ± 11.81 (5.53 [0.12–62.4])
Margin dose, Gy	15.30 ± 3.19 (15 [5–24])
Maximal dose, Gy	30.45 ± 7.36 (30 [10–55])
No. of isocenters	15.45 ± 17.21 (12.5 [1–151])
No. of fractions	
1	94 (98)
2	1 (1)
5	1 (1)
Chemotherapy at time of SRS	
Yes	43 (45)
No	50 (52)
Not reported	3 (3)
Steroids at time of SRS	
Yes	40 (42)
No	52 (54)
Not reported	4 (4)
Treatment target–level data	
Total no. of SRS targets	147
No. of targets per treatment session	1.85 ± 1.37 (1 [1–7])
Treatment vol, cm^3	6.90 ± 10.85 (1.99 [0.004–62.4])
Margin dose, Gy	16.12 ± 3.28 (16 [5–25])
Max dose, Gy	31.41 ± 7.19 (32 [10–55])
No. of isocenters	11.08 ± 15.44 (7 [1–151])

Values are shown as number (percent) or mean ± SD (median [range]).

TABLE 3. Outcomes

Variable	Value
Imaging follow-up	
Available data	93 (97)
Duration after SRS, mos	12.0 ± 20.32 (6 [1–125])
Local control of SRS target*	
Available data	131 (90)
Complete response	11 (8)
Partial response	28 (22)
Stable disease	50 (38)
Progression	42 (32)
Tumor control	
Available data	89 (93)
Progression	61 (69)
No progression	28 (31)
Clinical follow-up	
Available data	88 (92)
Duration after diagnosis, mos	33.69 ± 28.41 (27 [3–238])
Duration after SRS, mos	12.78 ± 20.03 (8 [1–154])
Death	
Yes	67 (70)
Data unavailable	6 (6)
Post-SRS treatment	
Chemotherapy	62 (65)
Surgery	16 (17)
Radiation therapy	4 (4)
Repeated SRS	4 (4)
ARE	
Any	9 (9)
Post-SRS radiation necrosis	7 (7)
Post-SRS seizure worsening	10 (10)

Values are shown as number (percent) or mean ± SD (median [range]).
* Determined according to the RANO criteria.

patients had received chemotherapy and corticosteroids, respectively, at time of SRS. SRS treatment volume and prescription and maximal doses were similar between patients who received chemotherapy at time of SRS and those who did not ($p \geq 0.234$).

Overall Survival

The median (range) follow-up after initial diagnosis of glioblastoma and after SRS were 27 (3–328) months and 8 (1–154) months, respectively (Table 3). Actuarial 1-year and 2-year post-SRS OS rates were 28% and 6%, respectively. The median (95% CI) survival estimates after diagnosis of glioblastoma and after SRS were 33 (22.68–43.2) months and 9.8 (8.7–11.0) months, respectively. Kaplan-Meier survival of the study patients (n = 92) is presented in Fig. 1. Median (95% CI) survival was not statistically significantly different between patients treated for recurrence and those who received up-front SRS (10.0 [8.9–11.1] months vs 20.2 [4.9–35.5 months], respectively, $p = 0.5$), between patients harboring IDH wild-type tumors and those with IDH mutant tumors (9.0 [7.1–10.8] months vs 11 [4.7–17.2] months, respectively), and between patients with MGMT-methylated tumors and those with MGMT-unmethylated tumors (9.8 [8.6–11.0] months vs 9.0 [2.2–15.8] months, respectively, $p = 0.6$). In Cox regression analyses adjusted for age and IDH status, mortality risk was predicted by prescription dose > 15 Gy (OR 0.367, 95% CI 0.190–0.709, $p = 0.003$) and treatment volume > 5 cm^3 (OR 1.036, 95% CI 1.007–1.065, $p = 0.014$) (Table 4). In multivariate-adjusted regression models, older age (OR 1.039, 95% CI 1.010–1.069, $p = 0.008$) and treatment volume > 5 cm^3 (OR 2.637, 95% CI 1.167–5.962, $p = 0.02$) were associated with greater mortality risk.

Progression-Free Survival

During a median (range) imaging follow-up of 6 (1–125)

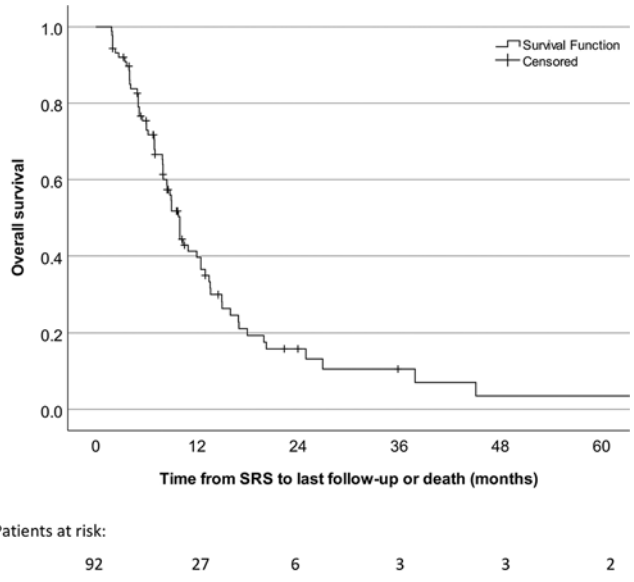

FIG. 1. Kaplan-Meier curve of OS.

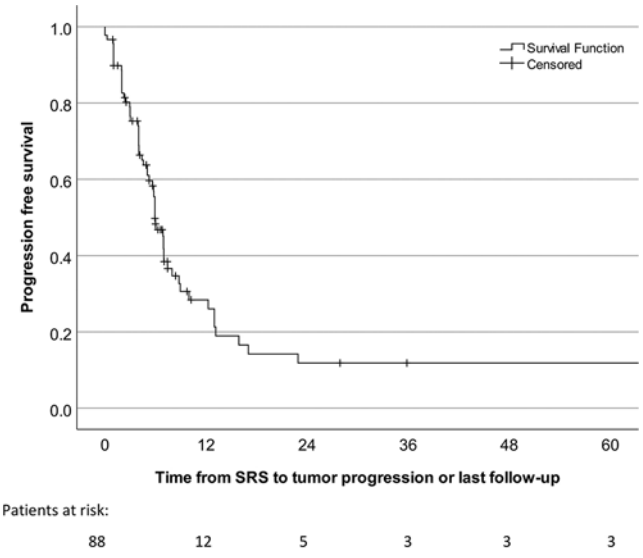

FIG. 2. Kaplan-Meier curve of PFS.

months, local control according to the RANO criteria (complete response, partial response, or stable disease) was achieved in 68% of SRS-treated lesions (Table 3). Forty-two (32%) SRS-treated targets experienced local disease progression. The median (95% CI) post-SRS PFS was 5.9 (95% CI 5.0–6.9) months. Sixty-one patients (69%) with local or remote tumor progression were documented (Fig. 2). One- and 2-year PFS rates were 13% and 6%, respectively. Median (95% CI) post-SRS PFS were similar between patients with MGMT-methylated tumors and those with unmethylated tumors (5.9 [4.8–7.0] months vs 6.0 [2.8–9.2] months, respectively, p = 0.650) and between patients with IDH-mutated tumors and those with wild-type tumors (7.0 [0–16.4] months vs 5.8 [4.3–7.3] months, respectively, p = 0.115).

In Cox regression analysis, only history of gross-total tumor resection was associated with longer PFS (OR 0.446, 95% CI 0.271–0.801, p = 0.006). Subtotal resection or biopsy (vs gross-total resection, p = 0.003), SRS radiosurgical dose ≤ 15 Gy (vs > 15 Gy, p = 0.03), and target volume > 5 cm^3 (vs ≤ 5 cm^3, p = 0.002) were associated with inferior local tumor control of SRS-treated lesions (Table 5 and Fig. 3). In multivariate analyses, treatment volume > 5 cm^3 (OR 2.215, 95% CI 1.159–4.234, p = 0.02) and absence of gross-total resection (OR 0.403, 95% CI 0.208–0.781, p = 0.007) remained associated with inferior local control of SRS treated lesions.

Post-SRS treatment included chemotherapy (65%), surgery (17%), radiation therapy (4%), and repeated SRS (4%) (Table 3).

Adverse Events

Nine (9%) patients experienced AREs after SRS that included radiation necrosis (n = 7), hyponatremia (n = 1), and vomiting (n = 1). Ten patients experienced seizure worsening after SRS. Radiation necrosis was diagnosed from 59 to 395 days after SRS and required surgical treatments in 4 patients. The risks of AREs and radiation necrosis were not associated with IDH mutation and MGMT methylation status, prescription and maximal dose, and treatment volume (all p ≥ 0.634).

Discussion

Our international multicenter study provides evidence

TABLE 4. Predictors of overall survival

Characteristic	Univariate*	Multivariate
Older age		**1.039 (1.010–1.069) (0.008)**
IDH mutation		0.480 (0.167–1.382) (0.174)
Karnofsky Performance Scale score before SRS	0.989 (0.964–1.016) (0.422)	
Prescription dose >15 Gy (vs ≤15 Gy)	**0.367 (0.190–0.709) (0.003)**	0.669 (0.312–1.436) (0.302)
Treatment vol >5 cm^3 (vs ≤5 cm^3)	**1.036 (1.007–1.065) (0.014)**	**2.637 (1.167–5.962) (0.02)**
Bevacizumab w/in 30 days of SRS	1.685 (0.717–3.961) (0.231)	
Extent of resection	1.387 (0.875–2.1980 (0.164)	

Values are shown as HR (95% CI) (p value). Boldface type indicates statistical significance (p < 0.05).
* Adjusted for age and IDH status.

TABLE 5. Predictors of PFS

Characteristic	Univariate	Multivariate
Patients (n = 88)		
Older age	1.006 (0.987–1.024) (0.551)	
Karnofsky Performance Scale score before SRS	0.998 (0.973–1.024) (0.883)	
IDH mutant	0.435 (0.149–1.269) (0.128)	
SRS prescription dose >15 Gy (vs ≤15 Gy)	1.013 (0.595–1.727) (0.961)	
SRS treatment vol >5 cm^3 (vs ≤5 cm^3)	1.126 (0.673–1.884) (0.652)	
Bevacizumab at time of SRS	0.800 (0.288–2.222) (0.668)	
Gross-total resection	**0.446 (0.271–0.801) (0.006)**	
SRS-treated lesions (n = 119)		
Older age	1.005 (0.985–1.026) (0.632)	
IDH mutant	0.352 (0.116–1.069) (0.065)	
SRS prescription dose >15 Gy (vs ≤15 Gy)	**0.515 (0.280–0.947) (0.03)**	0.841*
SRS treatment vol >5 cm^3 (vs ≤5 cm^3)	**2.676 (1.456–4.919) (0.002)**	**2.215 (1.159–4.234) (0.02)**
Bevacizumab at time of SRS	0.040 (0.001–3.008) (0.145)	
Gross-total resection (vs biopsy or subtotal resection)	**0.368 (0.191–0.710) (0.003)**	**0.403 (0.208–0.781) (0.007)**

Values are shown as HR (95% CI) (p value). Boldface type indicates statistical significance (p < 0.05).
* The p value is shown.

regarding the efficacy and safety of SRS for glioblastoma. OS and PFS after SRS were similar in patients stratified as a function of IDH mutation and MGMT promoter methylation status. SRS prescription dose > 15 Gy and treatment target volume ≤ 5 cm^3 were predictors of longer survival of glioblastoma patients, independent of patient age and IDH status. Prior gross-total resection and smaller treatment volume were associated with superior local control.

Treatment volume ≤ 5 cm^3 was an independent predictor of longer OS and PFS after SRS. Treatment volume included contrast-enhancing areas on T1-weighted brain MRI in all cases. The association of smaller SRS treatment volume with better post-SRS prognosis was previously reported by most[12,13,17,26] but not all authors.[14] For example, in the University of Pittsburgh experience with 297 glioblastoma patients treated over 20 years, tumor volume < 14 cm^3 was associated with longer OS and PFS.[13] A group from the Cleveland Clinic reported that glioblastoma volume ≥ 15 cm^3 was associated with superior OS and PFS in a series of 43 recurrent glioblastoma patients.[17] Imber and colleagues noted that they typically consider Gamma Knife radiosurgery for small (< 5 cm^3) nodular/focal deep tumors.[14] However, the molecular signatures of glioblastoma that are now routinely used for patient counseling and treatment decision-making in contemporary neuro-oncology were not considered in prior studies. Our findings suggest that smaller SRS treatment volume is associated with longer survival, independent of IDH status

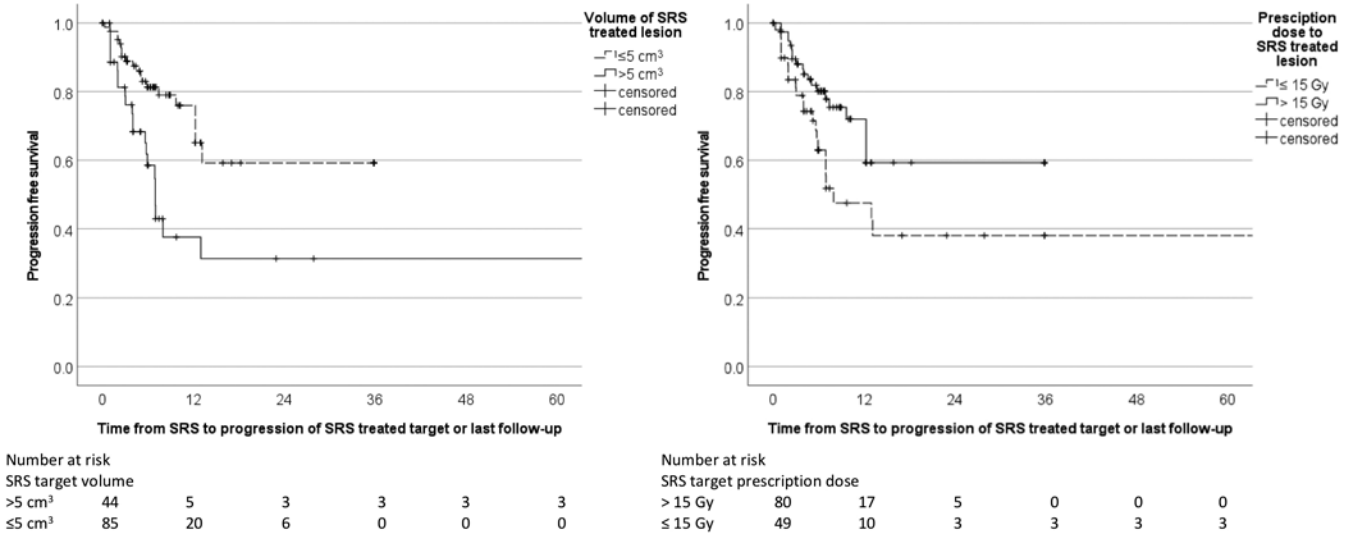

FIG. 3. Kaplan-Meier analysis of local control of SRS-treated lesions as a function of tumor volume (> 5 cm^3 vs ≤ 5 cm^3; log-rank = 11.034 and p = 0.001) (**left**) and prescription dose (> 15 Gy vs ≤ 15 Gy; log-rank = 4.801 and p = 0.028) (**right**).

and patient age, which are well-established prognostic indicators of glioblastoma patients. Volume of contrast-enhancing tumor should be carefully considered when selecting patients for SRS because patients harboring smaller tumors may benefit more from SRS than patients with more extensive disease.

SRS prescription dose > 15 Gy was associated with longer OS, independent of IDH status and patient age. However, the association was not statistically significant after adjustment for tumor volume. SRS prescription dose > 15 Gy was also associated with better local tumor control in univariate Cox regression analysis. These findings are in line with those of the study by Imber and colleagues, in which prescription dose > 15.5 Gy was associated with longer OS in 174 glioblastoma patients.[14] Adequate SRS treatment dose (possibly 15 Gy or more) should be considered to maximize local control and prognosis of glioblastoma patients.

OS of glioblastoma patients treated with SRS was similar as a function of IDH mutation and MGMT promoter methylation status. It has been demonstrated that radiation dose escalation may have a therapeutic advantage for malignant glioma patients.[27,28] Omuro and colleagues suggested that hypofractionated stereotactic radiotherapy (36 Gy in 6 fractions) combined with concomitant/adjuvant temozolomide and bevacizumab can overcome the negative prognostic impact of MGMT status.[29] However, a prospective dose escalation study by Azoulay and colleagues, who used 5-fraction SRS with concurrent temozolomide to treat newly diagnosed glioblastoma, did not confirm these findings because OS remained significantly shorter in patients harboring MGMT unmethylated tumors than those with methylated tumors (11 vs 20 months, respectively).[21] Other single-center retrospective series also reported shorter survival in patients with MGMT-unmethylated tumors than those with methylated or hypermethylated glioblastomas treated with SRS.[15,22] Studies that have explored the potential prognostic value of IDH mutation status for glioblastomas treated with SRS are lacking. Further studies are warranted to better understand if radiation dose escalation with SRS can overcome the adverse prognostic roles of IDH wild-type status and MGMT unmethylation status in patients with recurrent glioblastomas. Other genomic alterations of glioblastoma, such as the *PTEN* mutation, were shown to have prognostic significance in glioblastoma patients treated with SRS, and their prognostic value for post-SRS prognosis warrants further investigation.[23]

Bevacizumab administered at the time of salvage SRS was shown to improve OS and PFS of glioblastoma patients.[16,30] However, others have failed to demonstrate the benefit of concurrent chemotherapy administered at the time of SRS for glioblastomas.[14,31] In our study, bevacizumab administered at the time of SRS was not associated with OS and PFS. These findings can be partially explained by our study's retrospective design and the heterogeneity of patient selection for SRS and concurrent bevacizumab therapy across the participating centers. Thus, randomized prospective trials are warranted to clarify the potential benefit of administering concurrent bevacizumab and/or other chemotherapeutic agents at the time of SRS for glioblastoma patients.[32]

Median OS was longer in patients treated with boost SRS after resection (20 months) than those treated with salvage SRS at disease recurrence (10 months). However, the difference did not reach statistical significance ($p = 0.5$). These findings can be explained by the fact that the patients in the boost arm were treated earlier in their disease course, as opposed to the patients treated after failure of initial treatment. An RTOG trial (no. 93–05) that included 203 glioblastoma patients failed to demonstrate an advantage in survival or patient-reported outcomes in those who received postoperative SRS (15–24 Gy) followed by FRT (60 Gy) plus carmustine chemotherapy when compared with those who received FRT and carmustine alone.[33] Retrospective series have indicated beneficial therapeutic effects of SRS delivered after FRT (i.e., boost SRS).[34,35] However, another study demonstrated longer survival of glioblastoma patients treated with SRS at progression when compared with the survival of patients treated after FRT.[36] Prospective studies that evaluate the optimal timing of SRS for glioblastoma patients are encouraged.

Limitations and Strengths

Our study has limitations to be considered. First, one-third of patients did not undergo IDH and MGMT assessment, thus decreasing the statistical power of the study to detect the potential prognostic value of these molecular signatures. We did not perform a central pathology review; however, detailed information was provided. Technological advancements of SRS devices and planning software, increasing experience of participating centers, and increasing number of treatment options for recurrent glioblastoma may contribute to intrainstitutional and interinstitutional variations in treatment plans and outcomes.[37] However, the majority of our patients underwent standard first-line treatment according to the Stupp protocol, and all patients were managed at high-volume SRS centers and according to the prevailing guidelines at the time of treatment. Furthermore, we did not include a historical control of patients treated with other approaches for recurrent glioblastoma. However, treatment at time of recurrence is typically limited and determined on a case-by-case basis. Further studies that prospectively compare the treatment results of SRS with those of other modalities used for recurrent glioblastoma are strongly encouraged. Our results should be extrapolated with caution for patients treated with fractionated SRS because the majority of our patients were treated with single-session SRS. On the other hand, this multiinstitutional series provides real-world evidence of the effectiveness and safety of SRS for glioblastomas with consideration of tumor molecular signatures.

Conclusions

In our multiinstitutional series, OS and PFS after SRS were similar as a function of IDH mutation and MGMT promoter methylation status, suggesting that molecular profiles of glioblastoma should be considered when selecting candidates for SRS. SRS prescription dose > 15 Gy and treatment target volume ≤ 5 cm^3 were associated with longer survival of glioblastoma patients, independent of

age and IDH status. Prior gross-total resection and smaller treatment volume were associated with superior local tumor control. Further larger studies that evaluate the genetic profiles of glioblastoma patients treated with SRS are encouraged to better inform treatment decisions for this challenging and heterogeneous disease.

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