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ORIGINAL ARTICLE

Radiosurgery reirradiation for high-grade glioma recurrence: a retrospective analysis

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Abstract Despite various treatment strategies being available, recurrent high-grade gliomas (r-HGG) are difficult to manage. To obtain local control, radiosurgery (SRS) reirradiation has been considered as potential treatment. In the present study, a retrospective analysis was performed on r-HGG patients treated with salvage single- (s-SRS) or multi-fraction SRS (m-SRS). The aim of this study was to evaluate the effectiveness of salvage SRS in terms of overall survival (OS); toxicity was analyzed as well. Between 2004 May and 2011 December, 128 r-HGG patients (161 lesions) treated with CyberKnife® SRS reirradiation were retrospectively analyzed. Toxicity was graded according to Radiation Therapy Oncology Group and by Common Terminology Criteria for Adverse Events v.3 criteria. OS from the diagnosis date and OS from reirradiation were estimated using the Kaplan–Meier method. Median follow-up was 9 months (range 15 days–82 months). All patients completed SRS without high-grade toxicity. Radiation necrosis was observed in seven patients (6 %) with large volume lesions. The median survival from initial diagnosis was 32 months. The 1-, 2-, and 3-years survival rates from diagnosis were 95, 62, and 45 % respectively. Median survival following SRS was 11.5 months. The 1-, 2-, and 3-years survival rate following SRS was 48, 20, and 17 % respectively. On multivariate analysis, age <40 years, salvage surgery before SRS, and other post-SRS therapies (second-line chemotherapy and/or surgery) were found to significantly improve survival ($p = 0.03$). SRS represents a safe and feasible option to treat r-HGG patients with low complication rates and potential survival benefit.

Keywords Single-fraction radiosurgery · Multi-fraction radiosurgery · Reirradiation · Recurrent high-grade glioma

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Introduction

A number of treatment options are available for recurrent high-grade gliomas (r-HGG), including surgery, second-line chemotherapy, targeted agents therapy, and reirradiation. All strategies involve the high probability of controversial therapy-related side effects and may be feasible only within a subgroup of patients. Since approximately 80 % of cases of high-grade gliomas (HGG) recur within 2 cm of the primary tumors, where the highest doses of radiotherapy (RT) have already been delivered in the

primary adjuvant or definitive setting [1], reirradiation is often restricted, because of the high risk of radiation toxicity.

To overcome this limitation minimally invasive treatments aiming at local control of disease, such as brachytherapy [2, 3], intermediate-frequency alternating electric fields [4], single-fraction radiosurgery (s-SRS) [5, 6], and multi-fraction radiosurgery (m-SRS) [6, 7] have been proposed. Radiosurgery (SRS) involves a brief, intensified regimen of tightly focused external photon beams targeting one or more discrete intracranial lesions. This peculiarity, together with the improvements in set-up accuracy, may permit a reduction in the prescribed dose volume, and may therefore be advantageous over standard RT. In the attempt to spare adjacent normal brain tissue and organs at risk of therapy-related side effects either s-SRS or m-SRS may be a safe and effective option delivering high radiation doses to small target volumes of previously irradiated tissue [8]. The ability of brain tissue to recover from sub-lethal damage—the principal factor determining the size of the reirradiation dose—was found to be dependent upon the initial biologically effective dose (BED), as well as the time interval between the initial exposure and reirradiation [9, 10]. Although brain, which is considered a late responding tissue, is more likely to be damaged by higher doses per fraction, SRS is more effective in sparing the surrounding tissue, thus counterbalancing the impact of high doses and reducing the grade and the rate of radiation-induced toxicity [11]. Fractionated SRS is more effective in sparing adjacent normal tissue since it exploits the radiobiological mechanism of recovery from sub-lethal damage. Theoretically, this latter modality may permit the safe treatment of larger target areas.

The current study evaluates the clinical results of SRS (both single- and multi-fraction) in 128 patients who had already undergone primary RT as adjuvant or definitive treatment in response to the question of whether different patterns of recurrences and features of treatment may affect survival. The object of the present retrospective study is to evaluate the effectiveness of salvage SRS in terms of overall survival; including an analysis of toxicity.

Patients and methods

Following the approval by Ethic Committee Board a retrospective review was performed. All analyzed patients had signed a written informed consent for the scientific use of medical data.

Between 2004 May and 2011 December, 128 consecutive patients with r-HGG lesions were treated with salvage radiosurgery at our Institute in collaboration with CDI (Centro diagnostico italiano, Milan), using CyberKnife®.

The initial histological diagnosis was glioblastoma (GBM) for 88 patients (69 %), and WHO grade III gliomas for 40 patients (31 %). Based on CT or MRI postoperative imaging, resection type was defined as follows: gross total resection, performed in 30 % of evaluable patients; subtotal resection in 60 %; biopsy in 10 %, while the extent of surgery was unspecified in 11 patients (8 % of global patient population). The 8 % of patients with unspecified extent of resection were excluded from the statistical analysis related to type of resection. All patients received a standard course of RT (mean dose 58 Gy, range 40–60 Gy). After 2004, all GBM patients received concomitant temozolomide as well. Recurrence was defined as the presentation of new or increasingly contrast-enhanced lesions in T1-weighted magnetic resonance imaging (MRI) after standard fractionated RT; recurrence was considered infield when it was within 2 cm of the primary target volume and distant when it was beyond. The median time of progression after initial radiotherapy treatment was 11 months with a range between 2 and 171 months.

Radiosurgery planning and delivery

Patients underwent localizing contrast-enhanced computed tomography (CT) and post-contrast volumetric three-dimensional T1-weighted MRI, in either 1 or 1.5 mm thicknesses, and then were transferred to the planning system. Following image fusion, the target volume was defined by the contrast-enhanced marginless tumor edges. An inverse planning method using non-isocentric technique was used in all cases (Multiplan Accuray Inc., Sunnyvale, CA, USA) (Fig. 1). The median planning tumor volume (PTV) of treatment was 5.2 cm^3 (range 0.14–120 cm^3); the median PTV was 2 cm^3 (range 0.14–83 cm^3) for s-SRS and 10 cm^3 (range 0.63–120 cm^3) for m-SRS. Depending on target volume and proximity to eloquent areas, the treatment was delivered in single- or multi-fractions. The prescribed dose for reirradiation was chosen with respect to prior radiation volume, total dose, and interval between treatments. The prescribed reirradiation dose was evaluated in relation to the final radiation isodose distribution. The median prescription dose was 15 Gy (range 6–22 Gy) for s-SRS; 23 Gy (range 12–28 Gy), with a median number of 3 fractions, for m-SRS. The median prescription isodose was 80 % (range 65–89 %). Ninety-nine patients received SRS once, 25 twice, and 4 patients three times. SRS treatment parameters are summarized in Table 1.

Toxicity

Central nervous system toxicity was defined as any new or aggravated neurological signs or symptoms probably related to radiosurgery treatment.
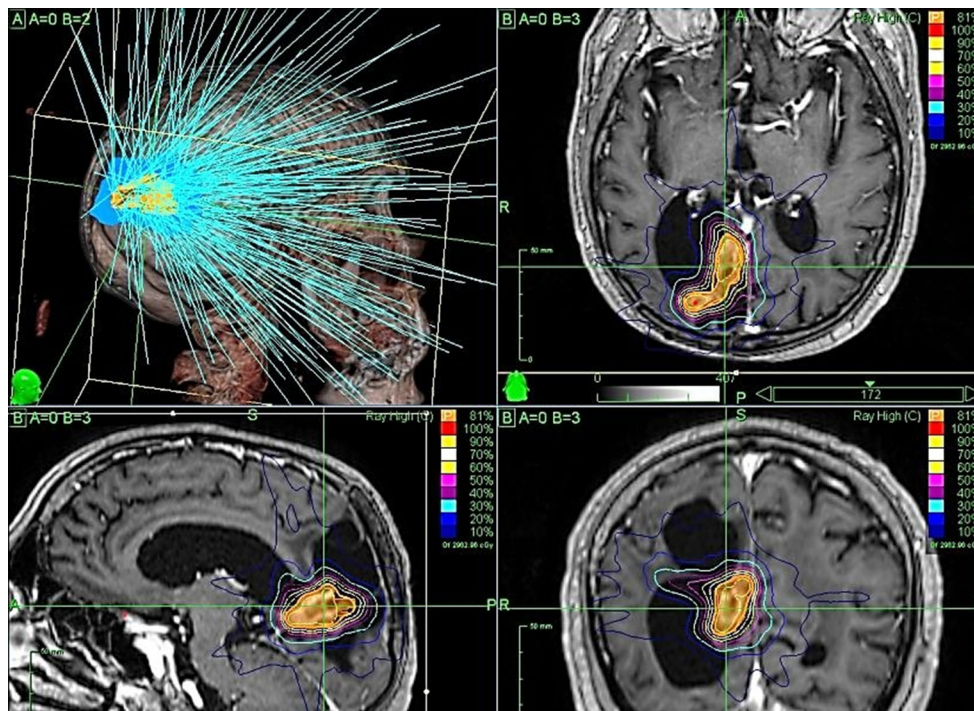
Fig. 1 A CyberKnife three-dimensional rendering of a non-coplanar beam arrangement on T1-weighted magnetic resonance imaging (MRI)

Table 1 Treatment parameters

SRS (radiosurgery) type	*n* (%)
s-SRS (single-fraction SRS)	42 (33)
m-SRS (multi-fraction SRS)	86 (67)
Recurrence pattern lesions	*n* (%)
Total	161 (100)
Infield	117 (73)
Distant	44 (27)
Dose of s-SRS (single-fraction SRS)	Gy
Median	15
Range	6–22
Dose of m-SRS (multi-fraction SRS)	Gy
Median	23
Range	12–28
Planning target volume of s-SRS	cm^3
Median	2
Range	0.14–83
Planning target volume of m-SRS	cm^3
Median	11
Range	0.63–121
Isodose prescription	%
Median	80
Range	65–89

Toxicity was graded according to Radiation Therapy Oncology Group (RTOG) [12] and by Common Terminology Criteria for Adverse Events (CTCAE) version 3 criteria [13].

Other therapies

Prior to radiosurgery, most patients had undergone other salvage therapies: second-line chemotherapy was administered in 60 patients (47 %), while 20 patients (16 %) had undergone surgical resection.

Statistical analysis

Descriptive statistics were calculated by means of absolute and relative frequencies for categorical variables and mean standard deviation, median, and range for continuous variables. The analyzed variables are selected based on literature data. The selected variables are detailed in Table 2.

Overall survival (OS) from the diagnosis date (defined as the time between initial surgery and death) and OS from reirradiation (defined as the time between end of reirradiation and death) were estimated using the Kaplan–Meier

Table 2 Univariate and multivariate survival from diagnosis and reirradiation

Variables	From	Diagnosis			From	Reirradiation		
	Univariate	Multivariate			Univariate	Multivariate		
	p	HR	95 % CI	p	p	HR	95 % CI	p
Age at diagnosis (<40 vs ≥40 years)	**0.0004**	1.90	1.18–3.06	**0.008**	0.1738	–	–	N.A.
Age at reirradiation (<40 vs ≥40 years)	**0.0144**	–	–	N.A.	**0.0460**	1.35	0.86–2.11	0.189
Histology (GBM vs grade III)	**0.0000**	0.89	0.19–4.11	0.883	**0.0103**	0.66	0.15–2.86	0.583
RT dose (<60 vs =60 Gy)	**0.0001**	1.34	0.75–2.41	0.314	**0.0084**	0.80	0.41–1.53	0.510
RPA classes (1–2 vs 4–6–7)	**0.0000**	1.50	0.32–7.03	0.605	**0.0099**	1.32	0.31–5.63	0.705
Other therapies[a] before SRS (no vs yes)	**0.0173**	0.74	0.49–1.13	0.176	0.6135			–
Salvage surgery before SRS (no vs yes)	**0.0278**	0.51	0.30–0.89	**0.019**	0.3813			–
Other therapies[a] after SRS (no vs yes)	0.6165			–	**0.0307**	0.66	0.44–0.98	**0.043**
Frontal site at diagnosis (no vs yes)	0.0503			–	0.4175			–
Frontal site at SRS (no vs yes)	0.0812			–	0.4479			–
Number of SRS fractions (1 vs >1)	0.2750			–	0.8514			–
Number of SRS lesions (1 vs >1)	0.3899			–	0.7964			–
Lesion volume (<7 vs ≥7 cm³)	0.9840			–	0.1335			–

Bold values are statistically significant

p p value, *HR* hazard ratio, *CI* confidence interval, *N.A.* not available, *N.S.* not significant, *GBM* glioblastoma multiforme, *RT* conformal external beam radiotherapy, *RPA* recursive partitioning analysis, *SRS* radiosurgery

[a] Other therapies before/after SRS: chemotherapy and/or surgery performed before or after SRS reirradiation

method. Survival for different subgroups was also estimated using the Kaplan–Meier method and compared by means of the log-rank test. All statistically significant variables ($p < 0.05$) obtained by the univariate analysis were included in a Cox proportional hazard rate model.

Results

Patient characteristics

Between 2004 and 2011, a total of 128 patients (161 lesions) received SRS treatment with CyberKnife® and their follow-up was performed at our Institute.

The median time of progression after initial radiotherapy treatment was 11 months with a range of 2 and 171 months. One hundred and seventeen (73 %) recurrent lesions were infield and 44 (27 %) distant. SRS was performed after a median period of 15 months from standard RT (range 6–171 months).

At the time of SRS, the Karnofsky performance score (KPS) was ≥70 for all patients; mean age was 51 years (range 18–79 years). Based on r-HGG classes [14], 18 patients were in RPA 1; 20 in RPA 2; 31 in RPA 4; 41 in RPA 6, and 18 in RPA 7. Disease progression following salvage SRS was treated with surgery in 17 of evaluable patients (13 %) and chemotherapy in 31 (25 %) patients, under different regimens. In 29 (28 %) patients with distant progression, radiosurgery was delivered more than one

time. The characteristics of patients and therapies are summarized in Table 3.

Survival

By the end of study, 91 patients had died of tumor progression and 37 patients were still alive. Median follow-up was 9 months (range 15 days–82 months).

Survival from diagnosis (first surgery)

The median survival for the whole group was 32 months (95 % CI 25–43, SD 3.6) (Fig. 2). Survival rates from diagnosis for 1, 2, and 3 years were 95, 62, and 45 %, respectively. For patients younger than 40 years at the time of diagnosis the median survival was 65 months (95 % CI 35–99, SD ± 1.8); for patients ≥40 years was 25 months (95 % CI 22–32, SD ± 1.6). Median survival for GBM and grade III glioma group was 25 months (95 % CI 22–31, SD ± 1.7) and 65 months (95 % CI 43–111, SD ± 1.8), respectively.

Under univariate analysis, there was a statistically significant improvement in survival for patients <40 years old ($p = 0.0004$), grade III glioma group ($p < 0.0001$), RPA classes 1–2 ($p < 0.0001$), first RT = 60 Gy ($p = 0.0001$), salvage surgery before SRS ($p = 0.028$), and other therapies before SRS ($p = 0.017$).

In multivariate analysis, only age <40 years and salvage surgery before SRS were associated with a

Table 3 Patient and therapy characteristics

Age[a], years	
Median	51
Range	18–79
Gender, *n* (%)	
Female	48 (37.5)
Male	80 (62.5)
KPS[b], *n* (%)	
≤80	118 (92)
>80	10 (8)
Initial WHO grade, *n* (%)	
IV grade	88 (69)
III grade	40 (31)
RPA classes, *n* (%)	
1	18 (14)
2	20 (16)
4	31 (24)
6	41 (32)
7	18 (14)
Prior surgery[c], *n* (%)	
Biopsy	11 (10)
Subtotal resection	67 (60)
Gross total resection	33 (30)
Prior radiotherapy[d], *n* (%)	
<60 Gy	34 (29)
≥60 Gy	84 (71)
Prior chemotherapy[d], *n* (%)	
Yes	84 (72)
No	33 (28)
Salvage surgery (before SRS), *n* (%)	
Yes	20 (16)
No	108 (84)
Second-line chemotherapy (before SRS), *n* (%)	
Yes	60 (47)
No	68 (53)
Salvage surgery after SRS, *n* (%)	
Yes	17 (13)
No	111 (87)
Chemotherapy after SRS, *n* (%)	
Yes	31 (25)
No	91 (75)

SRS radiosurgery

[a] Age at the time of reirradiation

[b] KPS at the time of reirradiation

[c] Initial tumor resection (date of diagnosis)

[d] Radiotherapy and chemotherapy treatment at diagnosis

significant improvement in survival. Figure 3 shows Kaplan–Meier curves of significant variables in multivariate analysis.
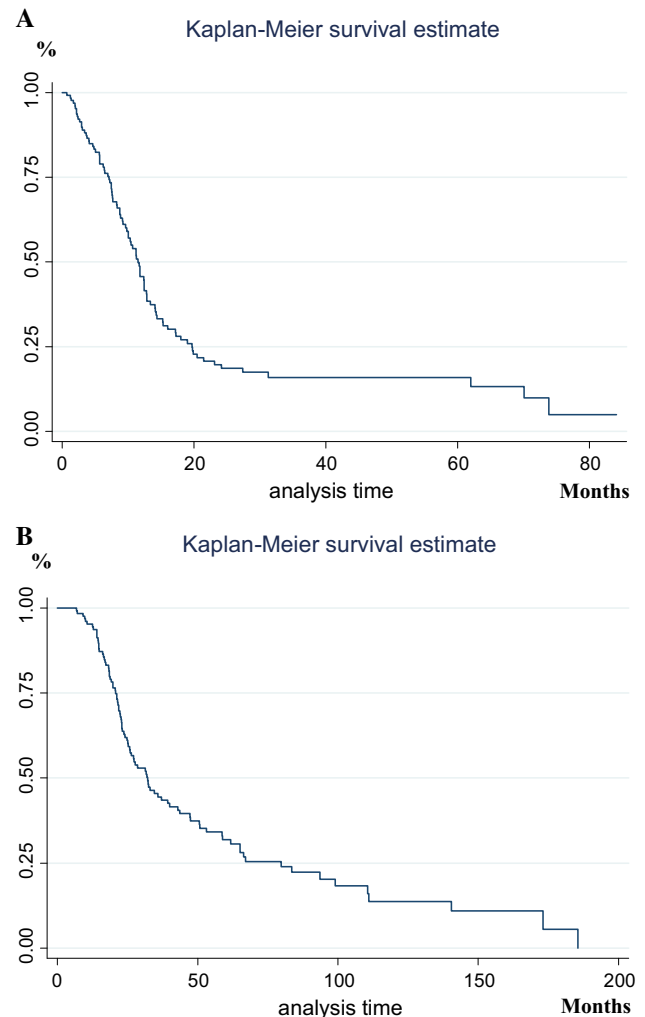
Fig. 2 Kaplan–Meier survival curves. **a** Overall survival for the entire patient population measured from the date of diagnosis to the date of death. **b** Overall survival for the entire patient population measured from the date of radiosurgery reirradiation to the date of death

Survival from reirradiation

Median survival following SRS was 11.5 months (95 % CI 9.8–12.7, SD ± 0.9) (Fig. 2). The survival rate following SRS was 48, 20, and 17 % at 1, 2, and 3 years, respectively. The median survival for patients younger than 40 years at diagnosis was 13 months (95 % CI 10–19, SD ± 0.6) and among patients ≥40 years was 11 months (95 % CI 8–12, SD ± 0.8). GBM and grade III glioma group had a median survival of 10 months (95 % CI 7.5–12, SD ± 1) and 14 months (95 % CI 11–20, SD ± 0.7), respectively.

The survival rate for patients <40 years old was 92 and 51 % at 1 and 2 years, respectively for the grade III glioma subgroup, versus 38 and 19 % for the GBM subgroup.
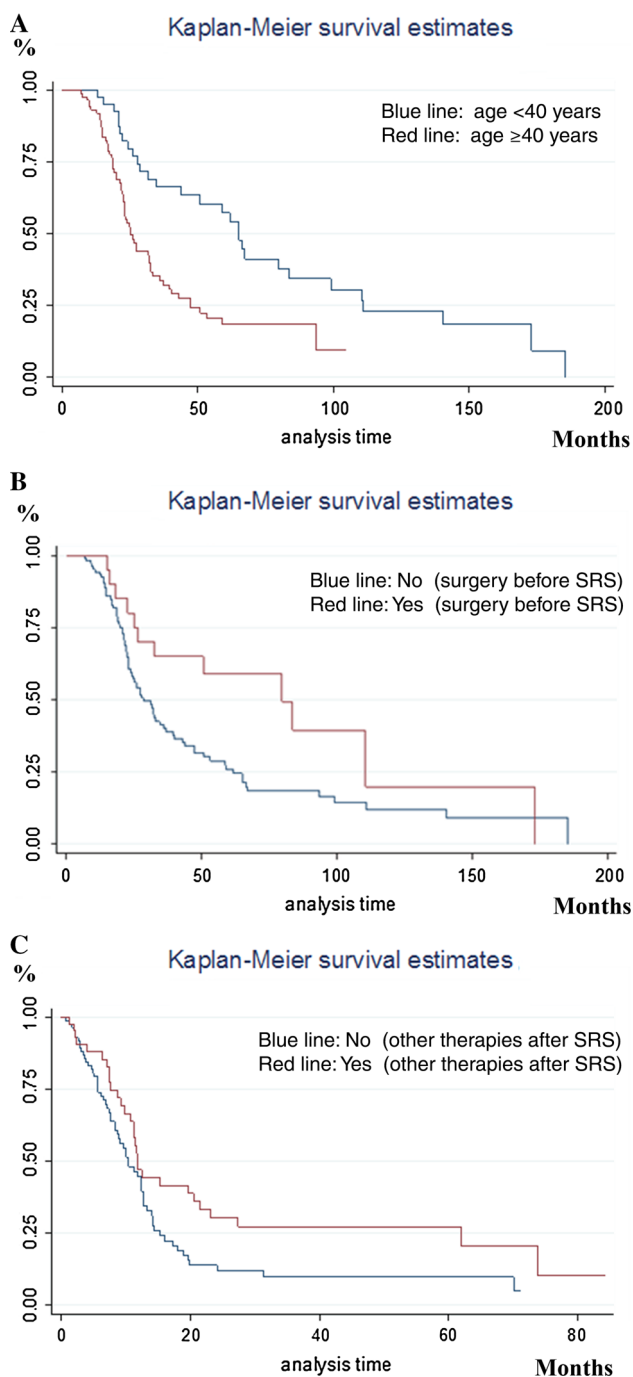
Fig. 3 Overall survival stratified by significant variables. **a** Overall survival from the date of diagnosis stratified by age at diagnosis (age <40 years vs ≥40 years) showing significant dependence (univariate $p = 0.0004$, multivariate $p = 0.008$, HR 1.90). **b** Overall survival from the date of diagnosis stratified by salvage surgery before SRS reirradiation (yes vs no) showing significant dependence (univariate $p = 0.0278$, multivariate $p = 0.019$, HR 0.51). **c** Overall survival from the date of SRS reirradiation stratified by other therapy (chemotherapy and/or surgery) delivered after SRS reirradiation (yes vs no) showing significant dependence (univariate $p = 0.0307$, multivariate $p = 0.043$, HR 0.66)

Univariate analysis showed that age <40 years ($p = 0.046$), grade III glioma group ($p = 0.010$), RPA classes 1–2 ($p = 0.010$), other therapies after SRS ($p = 0.031$), RT = 60 Gy ($p = 0.008$) were associated with a significant improvement in survival. Lesion recurrence site (frontal lobe versus others) and volume had no impact on survival ($p = 0.4$ and $p = 0.13$, respectively).

In multivariate analysis, only other post-SRS therapies (second-line chemotherapy and/or surgery) were found to significantly improve survival ($p = 0.03$). Figure 3 shows Kaplan–Meier curve of significant covariates at multivariate analysis. The details of statistical analysis are summarized in Table 2.

Toxicity

All patients completed SRS without interruption. Treatment compliance was good in all patients. Acute toxicity (grade ≤2 for everyone), defined as headache, nausea, fatigue, and alopecia, was noted in 19 patients (15 %).

Radiation necrosis was observed in seven patients (6 %) with large volume lesions (diameter >4 cm) and was associated with neurological deterioration. The median time of radionecrosis presentation was 9 months (range 6–11 months). Three of these patients had surgical intervention with histological validation of radionecrosis.

Discussion

Therapeutic alternative options for r-HGG include surgery, chemotherapy, radiotherapy, and combined modalities. There is no clear evidence as to the superiority of one approach over another due to the absence of randomized studies [15]. Radiosurgery reirradiation has been studied in literature and an evidence-based review of Tsao et al. [16] analyzed his role in HGG recurrence's setting. The authors concluded that there is insufficient evidence to support a survival benefit in the use of SRS for r-HGG compared with competing management strategies such as de-bulking surgery, chemotherapy, or best supportive care. Anyway the conclusions are limited by several biases, such as the wide variation in the employed technologies, lack of homogeneity in patients, and radiation doses. Generally reirradiation of r-HGG is limited by the higher risk of radiation-induced complications. Even when indicated, its application may be problematic due to the paucity of data concerning reirradiation: preferential size for re-treatment volumes, optimal time interval between first and second irradiation (most authors demand an interval of at least 6 months) [17–20], and the lack of reliable dose–volume

Table 4 Recent studies of exclusive radiosurgery in single-(SRS) or multi-fraction (FSRT) for recurrent high-grade gliomas

Authors	Year	Number of patients	PTV contouring	Median target volume (ml)	Median fraction number, prescription dose	mOS after reirradiation (months)	Toxicity
Patel et al. [6]	2009	SRS 26 FSRT 10	c.e.	SRS 10.4 FSRT 51.1	SRS (1 fr), 18 Gy SRS (1 fr), 15 Gy	SRS = 8.4 FSRT = 7.4	Necrosis 7.7 %
Biswas et al. [28]	2009	18	c.e. + 0–1 mm	8.4	4 fr, 20 Gy	5.3	RTOG G4 late 5.5 %
Henke et al. [32]	2009	31	c.e. + 3–10 mm	52.7	10 fr, 30 Gy	10.2	Necrosis 6.4 %
Fokas et al. [19]	2009	53	c.e. + 3 mm	35	10 fr, 35 Gy	9	No ≥ G2
Fogh et al. [7]	2010	147	c.e.	22	1 fr, 15 Gy	G III = 10 G IV = 11	G3 0.68 %
Eliott et al. [29]	2011	26	c.e.	1.22	1 fr, 15 Gy	13.5	Necrosis 7.7 % RTOG G4 3.8 %
Maranzano et al. [47]	2011	SRS 13 FSRT 9	SRS = c.e. FSRT = c.e. + 3–10 mm	SRS = 5.3 FSRT = 44	SRS 17 Gy FSRT 10 fr, 30 Gy	11	Necrosis 23 %
Conti et al. [15]	2012	11	c.e. + margins	n.a.	Vol 10–20 ml = 2fr, 20 Gy Vol > 20 ml = 3–5 fr, 24–25 Gy	7	Corticosteroid dependency 63 %
Skeie et al. [48]	2012	51	c.e.	n.a.	1 fr, 12.2 Gy	12	Complications 9.8 %
Koga et al. [41]	2012	I. 9 II. 9	I. = c.e. II. = c.e. + 0.5–1 cm	I. 15 II. 13	I. 1 fr, 20 Gy II. 1 fr, 20 Gy (max margin dose)	I. 10.5 II. 9	I. Necrosis 6.5 % II. Necrosis 29 %
McKenzie et al. [36]	2013	35	c.e. + 2 mm	8.54	5 fr, 30 Gy	8.6	G3–G4 9 %
MartinezCarrillo et al. [49]	2014	87	c.e. + 0–6 mm	6	1 fr, 18 Gy	10	No toxicity
Anand et al. [50]	2014	16	c.e. + 2–3 mm + 2 cm CC	n.a.	5–6 fr, 30 Gy	9.3	RTOG > G1 6.2 %

mOS median overall survival, *SRS* radiosurgery, *FSRT* fractionated stereotactic radiotherapy (multisession radiosurgery), *c.e.* contrast-enhancement tumor area on T1-weighted MRI, *RTOG* radiation therapy oncology group, *G* toxicity grade, *n.a.* not available, *CC* craniocaudal

constraints. However, SRS is characterized by set-up accuracy and rapid radiation dose fall-off at the margins of treatment. SRS therefore reduces the radiation exposure of adjacent normal tissue. Several retrospective studies have demonstrated a median survival range of 7–17.9 months, although a selection bias in favor of patients who are amenable to SRS cannot be excluded [21–30]. Moreover, recent studies have described the effectiveness of salvage reirradiation for HGG recurrence or progression [1, 7, 9, 22, 31–37], while also supporting the use of m-SRS in this patient population with minimal acute toxicity [33–35].

The present study analyzed a rather wide population of HGG high-dose reirradiation by means of single or multi-fraction radiosurgery. Two authors [33, 7], reporting on similar series, observed improved survival after HGG reirradiation, despite most patients received lower doses per fraction (<4 Gy). With regard to SRS as salvage therapy, our analysis confirmed these encouraging findings in terms of median survival and survival rate at 2 years. We found a median OS similar to that generally reported in the recent literature (Table 4): 32 months from diagnosis and 11.5 months after reirradiation (Fig. 2). With respect to analyzed variables, several authors found tumor grade, age at primary diagnosis, extent of resection, and volumes of reirradiation fields, to be predictors of OS [19, 38–41]. Our study confirmed statistically significant differences in survival only for patient's age. The tumor grade did not impact on survival ($p = 0.883$) most likely due to the fact that biomolecular characteristics could have a major impact on HGG patient's survival than basic histology. However, age ≤40 years at diagnosis (initial surgery) affected survival from diagnosis. It is worth noting that to analyze the impact of age on survival we initially chose 50 years of age as a cut-off, as well as it was usually what literature referred. This value did not impact on survival. Finally, salvage surgery before SRS also improved survival from diagnosis ($p = 0.019$) as well as other therapies (second-line chemotherapy and/or surgery) delivered following SRS improved survival from SRS ($p = 0.043$) (Fig. 3).

These findings differ from our previously published results [42]: the cohort of analyzed patients could not be compared, as they also included outpatients with longer follow-up.

Several authors have found that the volume of reirradiated tumor correlates with survival [6, 21, 29, 43, 44]. Although we have considered three different cut-offs for tumor volumes (of an ideal spherical tumor volume): 7 cm^3 (corresponding to 2.4 cm in diameter), 14 cm^3 (corresponding to 3 cm in diameter), and 33.5 cm^3 (corresponding to 4 cm in diameter), neither tumor volume nor the number of lesions and their location were found to be significantly related to survival. With respect to toxicity, the radionecrosis data reported in the literature indicate an average of 5–14 % [16, 45, 46]. Otherwise, Fokas et al. [19] did not report high toxicity despite the fact that median tumor volume (35 cm^3) was double than the volumes reported in previous studies, at a higher dose than the average reported in the literature. We also observed a low overall toxicity: only 7 (6 %) grade 3–4 neurological adverse events could be related to large s-SRS irradiated volumes. This may support the hypothesis that m-SRS could be a suitable option in difficult reirradiations, such as lesions larger than 4 cm or in the eloquent cortex.

Thus, the high dose delivered by reirradiation SRS (single- and multi-fraction) involves a low toxicity profile and an encouraging outcome.

Conclusions

In our study, the large tumor volumes and number of lesions represented no obstacle for radiosurgical treatment as long as the dose was fractionated in order to prevent toxicity.

The question should no longer be whether or not reirradiation is a valid treatment option, but when and which salvage treatments should be administered in prospective trials.

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