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Re-irradiation with stereotactic radiotherapy for recurrent high-grade glial tumors

Ela Delikgoz Soykut[1], Eylem Odabasi[1], Nilgun Sahin[1], Hatice Tataroglu[1], Ahmet Baran[2], Yildiz Guney[3]

[1]Department of Radiation Oncology, Samsun Education and Research Hospital, Samsun, Türkiye
[2]Department of Medical Oncology, Samsun Education and Research Hospital, Samsun, Türkiye
[3]Department of Radiation Oncology, Memorial Ankara Hospital, Ankara, Türkiye

ABSTRACT

Background: Despite the radical treatments applied, recurrence is encountered in the majority of high-grade gliomas (HGG). There is no standard treatment when recurrence is detected, but stereotactic radiotherapy (SRT) is a preferable alternative. The aim of this retrospective study is to evaluate the efficacy of SRT for recurrent HGG, and to investigate the factors that affect survival.

Materials and methods: From 2013 to 2021, a total of 59 patients with 64 lesions were re-irradiated in a single center with the CyberKnife Robotic Radiosurgery System. The primary endpoints of the study were overall survival (OS), progression free survival (PFS) and local control rates (LCR).

Results: The median time to first recurrence was 13 (4–85) months. SRT was performed as a median prescription dose of 30 Gy (range 15–30), with a median of 5 fractions (1–5). The median follow-up time was 4 months (range 1–57). The median OS was 8 (95% CI: 4.66-11.33) months. Age, grade 3, tumor size were associated with better survival. The median PFS was 5 [95% confidence interval (CI): 3.39–6.60] months. Age, grade 3 and time to recurrence > 9 months were associated with improved PFS. Grade 3 gliomas ($p = 0.027$), size of tumor < 2 cm ($p = 0.008$) remained independent prognostic factors for OS in multivariate analysis.

Conclusion: SRT is a viable treatment modality with significant survival contribution. Since it may have a favorable prognostic effect on survival in patients with tumor size < 2 cm, we recommend early diagnosis of recurrence and a decision to re-irradiate a smaller tumor during follow-up.

Key words: high-grade glial tumors; re-irradiation; stereotactic radiotherapy

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Introduction

High-grade gliomas (HGG) are the most common malignant primary central nervous system tumors in adults, including World Health Organization (WHO) grade 3 and 4 tumors [1]. Maximum surgical resection followed by adjuvant radiation therapy (RT) and/or chemotherapy and/or alternating electric field therapy, as determined by WHO grade, molecular markers, patient's age and performance status, is the current standard treatment [2–5]. Despite intensified treatments, recurrence is unfortunately inevitable. 40% of WHO grade 3 patients and 90% of grade 4 patients develop a relapse within the first 2 years at the initial RT field [2–4]. The patterns of spread of gliomas on imaging have

Address for correspondence: Ela Delikgoz Soykut, Samsun Education and Research Hospital, Department of Radiation Oncology, Samsun, Türkiye; e-mail: eladelikgoz@gmail.com

been classified in several studies [6, 7]. Recently, Piper et al. [7], in their review, which included more than 100 studies in 2018, reported that the progression patterns on imaging for glioblastomas are quite heterogeneous, with the distance determined for definition of local and/or distant progression ranging from 1–5 cm. It can be said that the terminology on this subject is not clear yet.

During the follow-up period, patients should be carefully examined for radionecrosis and treatment-related pseudoprogression that may be confused with recurrent disease. Advanced imaging techniques, such as magnetic resonance imaging (MRI) spectroscopy, MRI perfusion, MRI diffusion, and (18)F-dihydroxyphenylalanine (^{18}F-FDOPA), (18)F-fluoro-ethyl-tyrosine (^{18}F-FET) and (11) C-methionine (^{11}C-MET) positron emission tomography (PET), are very useful in this context, but biopsy may be required in cases where differential diagnosis cannot be made [8–11]. However, the above listed imaging methods may not be available at all institutions.

The prognosis of recurrent disease is poor and there is currently a lack of data to establish relapse management. Therefore, appropriate management of recurrent disease should be decided individually for each patient by interdisciplinary evaluation. Possible treatment strategies for recurrent HGG, include resection, re-irradiation (re-RT), systemic chemotherapy, tumor treatment fields, or some combination thereof.

After the diagnosis of recurrent disease is confirmed, surgical resection should be considered as the first choice in the management of recurrent disease, primarily in patients with a good performance status, and surgical feasibility evaluation should be performed [12]. A survival advantage has been demonstrated with gross total resection, but proximity to eloquent tissue may not permit gross total resection in a proportion of cases [13].

There are reasonable options, such as temozolomide, nitrosourea, bevacizumab, that can be used for 2nd series chemotherapy in recurrent disease, but a clearly recommended treatment option has not been defined, unfortunately. Temozolomide can be tried again in patients who did not develop recurrence during the period of temozolomide use, especially in patients with known O6-methylguanine-DNA methyltransferase (MGMT) methylated. Also, nitrosoureas are other preferred alternatives in MGMT methylated patients. The overall survival (OS) contribution varies between 6–12 months [14]. On the other hand, bevacizumab, an antiangiogenic agent, reduces vasogenic edema and leads to improvement in progression-free survival by providing neurological improvement [15]. In a recent review, which included 1400 relapsed HGG, one-third of whom received bevacizumab with re-RT and in two-thirds only re-RT was applied, it was reported that survival was improved and radionecrosis rates were reduced when re-RT was combined with bevacizumab [16]. Possible side effects include thromboembolic events, but due to underreporting of bevacizumab-related adverse events, a clear assessment for adverse outcomes could not be made.

Although there is a concern that it may pose a risk of serious neurologic toxicity, many centers have long practiced re-RT for recurrent HGG. Since the advent of stereotactic radiotherapy (SRT), it has been a preferable alternative with its ability to deliver high-dose radiation accurately and with high precision to target volume, and minimize the dose to normal brain tissues. Depending on the target volume and proximity to sensitive healthy structures, various RT doses and fractionation schedules were used for re-RT. Promising results were obtained with re-RT, with a median OS of 8–10 months, mostly from retrospective series [17–22]. Re-RT remains a viable and effective option that provides survival benefits with acceptable risk, and is a preferable approach in eligible patients. The aim of this retrospective study is to evaluate the efficacy of SRT for recurrent HGG, and to investigate the factors that affect survival outcomes.

Materials and methods

Study design and data collection

A retrospective review of our institutional database was conducted to identify patients with recurrent HGG who were reirradiated with CyberKnife (CK) Robotic Radiosurgery System between September 2013 and March 2021. Inclusion criteria were patients with histologically confirmed HGG at initial diagnosis, over 18 years of age, with recurrent HGG according to the response assessment in neuro-oncology (RANO) criteria [23], and at least 6 months after previous RT. Patients who received more than 5 fractions and had low-grade tumors that had transformed to grade 3 and grade 4

were excluded from the study. Demographic information of patients, including tumor and treatment characteristics, data on initial diagnosis and progression were extracted from patient archive files and electronic medical record system. The study was conducted in accordance with the Declaration of Helsinki and was approved by the medical ethics committee of our institute. Individual approval was waived due to retrospective design. The study was approved by The University of Health Sciences, Samsun Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (No:2021/12/9, Date:23.6.2021)

We identified 59 patients with recurrent HGG and 64 lesions that met the study inclusion criteria. Details on the patients' characteristics can be found in Table 1. Since our department is the only center with CK in the Central and Eastern Black Sea Region of Turkey, there are also patients who received their first RT in the surrounding provinces and were referred to our center for re-RT due to recurrence. Detailed dose volume histogram of the first RT and clinical and pathological information of the cases were requested from the patients who were admitted from another center.

At initial diagnosis, 11 of the patients had WHO grade 3 anaplastic astrocytomas (1 of them was oligoastrocytoma according to the previous classification), and 48 of the patients had WHO grade 4 glioblastomas, surgery was performed in all patients. The patients received a median of 60 Gy (59.4–60 Gy) of postoperative RT, and 51 of them received concomitant and/or maintenance oral temozolomide chemotherapy. Isocitrate dehydrogenase 1 (IDH1) mutations were assessed and found in 13 patients. Molecular markers are not known, since many mutation analyses could not be performed in institutions in our region in the first years of the study, currently available data are presented. MGMT methylation in glioblastoma patients is unknown as the institution cannot provide testing.

Multifocal recurrence was seen in 3 patients at the time of re-RT for recurrent disease. 12 of the patients had a second surgery before re-RT. The diagnosis of recurrence was confirmed by MRI, including spectroscopy, perfusion, and diffusion in patients who did not undergo surgery. Amino acid tracers (^{11}C-MET, ^{18}F-FET, and ^{18}F-FDOPA) PET scans could not be used in diagnosis because they are not available in our institution.

Treatment planning

All patients were immobilized with a thermoplastic mask, and underwent simulation computed tomography (CT) with 1 mm slice thickness. A gadolinium contrast-enhanced T1-weighted MRI was acquired with 1 mm slice thickness. Following fusion of CT and MRI, the gross tumor volume (GTV) was defined as contrast-enhanced mass. While planning target volume (PTV) was defined as GTV in the majority of patients, a 1–2 mm margin was added to GTV in some of them for creating PTV. The median target volume was 10.49 cc (1.14–134 cc). While 15–21 Gy stereotactic radiosurgery (SRS) was applied to 4 of 64 lesions, 30 Gy SRT was applied in 5 fractions to 49 lesions and 18–24 Gy SRT was applied to 11 lesions in 3 fractions. The median prescription isodose was 85% (79–92%). The median biologically effective dose (BED_{10}) was 48 Gy (28.8–54.2). Treatment parameters are presented in Table 1.

Treatment was administered in single or multiple fractions depending on target volume, proxim-

Table 1. Clinicopathological and treatment characteristics

Variable	N (%)	Median (range)
Age		54 (20–82)
ECOG		
0–1	26 (44.1)	
2–3	33 (55.9)	
Gender		
Female	24 (40.7)	
Male	35 (59.3)	
WHO Grade		
Grade 3	11 (18.6)	
Grade 4	48 (81.4)	
Size of recurrent tumor [cm]		3.2 (0.8–7)
Volume of recurrent tumor [cc]		10.49 (1.14–134)
Time to recurrence [months]		13 (4–85)
Interval RT to Re-RT [months]		15 (6–145)
Primary RT dose [Gy]		60 (59.4–60)
Chemotherapy		
Yes	51 (86.4)	
No	8 (13.6)	
Re-RT dose [Gy]		30 (15–30)
Re-RT fraction		5 (1–5)
BED_{10} [Gy]		48 (28.8–54.2)
Prescribed isodose		85 (79–92)

BED — biologically effective dose; ECOG — Eastern Cooperative Oncology Group; Re-RT — re-irridation; RT — radiotherapy; WHO — World Health Organization

ity to critical structures, such as brain stem, optic nerves, and optic chiasm, and previous RT dose. Fractionated treatments were preferred in those with high target volume and those close to critical organs. In addition, BED of re-RT was calculated using $\alpha/\beta = 10$ for tumor effects (BED_{10}) and $\alpha/\beta = 3$ for late effects (BED_3). The cumulative dose was calculated using the linear-quadratic model taking an $\alpha/\beta = 2$ to calculate an equivalent total dose in 2-Gy fractions (EQD_2). Radionecrosis in normal brain tissue has been suggested to occur with a cumulative EQD_2 dose of > 100 Gy, and it is aimed not to exceed that level when selecting the re-RT dose [11, 21, 22]. Lastly, cumulative doses of sensitive structures, such as brain stem and optic chiasm, were calculated to avoid increasing toxicity. Doses lower than the prescribed dose for the target were accepted individually in case the tolerance doses were exceeded.

Follow-up

Patients were evaluated at the first follow-up visit 2–4 weeks after Re-RT and by MRI at 2 months. Afterwards, follow-up continued with imaging at 2-month intervals. Response assessment was performed according to the RANO criteria using available imaging datasets of all selected patients, retrospectively.

Endpoints and statistical analysis

The endpoints of the study were OS, progression free survival (PFS) and local control rates (LCR) after Re-RT. OS was calculated as the time between the date of starting re-RT to the date of death or lost to follow-up. PFS was calculated as the time between the date of starting re-RT to the date of the first occurrence of recurrent disease, suspected clinical progression or death. Local control was defined as the absence of local tumor progression including all cases of stable disease.

Continuous variables are presented as medians after examining with normality tests, and categorical variables are presented as the frequency and proportion (%). Survival curves were estimated with the Kaplan-Meier method and compared using log-rank test, hazard ratios were estimated using Cox regression analysis. All statistical analyses were performed using SPSS 25.0 statistical software (IBM Corp., Armonk, NY, United States). A p-value < 0.05 was deemed to indicate statistical significance.

Results

The median time to first recurrence was 13 (4–85) months. After a median period of 15 months from initial RT (6–145), re-RT was performed. At the time point of re-RT, median age was 54 (20–82). With a median follow-up of 4 months (range 1–57) after re-RT, 11 patients were alive at the last follow-up.

The median OS from initial diagnosis was 27 (95% CI: 23.75–30.24) months. The median OS after re-RT was 8 (95% CI: 4.66–11.33) months, and 1- and 2-y OS were 33.2% and 14.2%, respectively (Fig. 1A). According to WHO grade, the median OS from CK treatment was 6 (95% CI: 3.53–8.46) months for WHO grade 4 gliomas and 17 (95% CI:

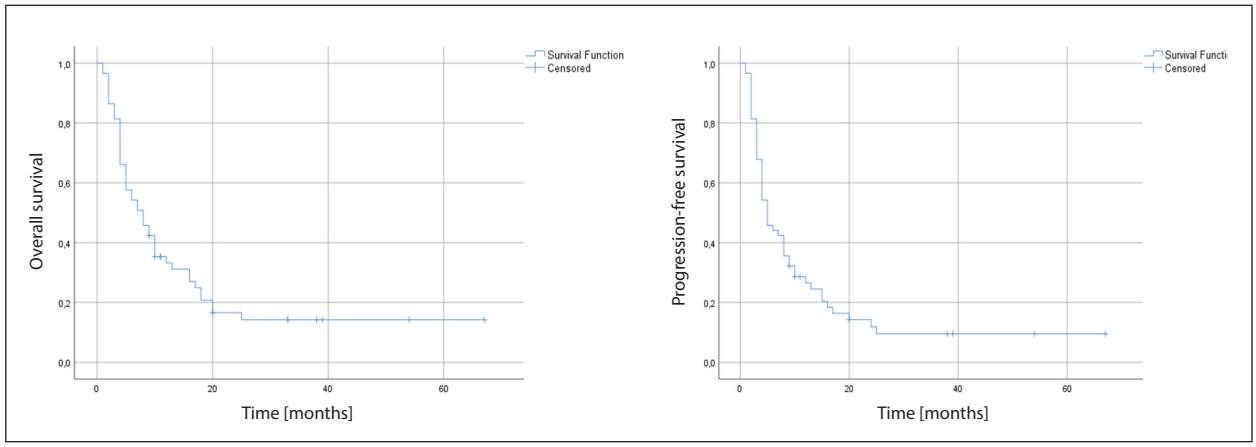

Figure 1AB. Kaplan-Meier graph of overall survival (OS) and progression-free survival (PFS)

Table 2. Survival outcomes

Factors		OS		PFS	
		HR (95% CI)	p	HR (95% CI)	p
Univariate analysis					
Age	< 50 *vs.* ≥ 50	2.34 (1.27–4.47)	0.003	2.06 (1.11–3.80)	0.012
ECOG	0-1 *vs.* 2–3	1.89 (1.03–3.46)	0.037	1.95 (1.07–3.55)	0.028
Gender	Female *vs.* Male	0.77 (0.43–1.38)	0.393	0.79 (0.45–1.39)	0.431
WHO Grade	Gr 3 *vs.* Gr 4	2.52 (1.06–5.97)	0.023	2.35 (1.05–5.26)	0.024
Size of recurrent tumor (cm)	< 2 cm *vs.* ≥ 2 cm	2.09 (1.11–3.93)	0.018	1.77 (0.98–3.20)	0.055
Volume of recurrent tumor (cc)	≤ 10 cc *vs.* > 10 cc	1.82 (1.01–3.29)	0.034	1.70 (0.96–2.99)	0.064
Time to recurrence (months)	≤ 9 *vs.* > 9	0.64 (0.32–1.26)	0.198	0.47 (0.24–0.89)	0.012
Interval RT to Re-RT (months)	≤ 9 *vs.* > 9	1.06 (0.54–2.08)	0.860	0.85 (0.45–1.62)	0.640
First treatment response	Prog *vs.* St	2.31 (0.97–5.48)	0.057	3.77 (1.55–9.21)	0.003
Last treatment response	Prog *vs.* St	1.16 (0.55–2.43)	0.686	1.90 (0.92–3.91)	0.079
BED_{10}	< 45 Gy *vs.* ≥ 45 Gy	0.46 (0.22–0.95)	0.024	0.54 (0.26–1.10)	0.068
Multivariate analysis					
Age		1.58 (0.78–3.21)	0.203	1.67(0.81–3.45)	0.245
ECOG		1.80 (0.96–3.40)	0.067	1.67(0.91–3.06)	0.093
WHO Grade		2.78 (1.12–6.93)	0.027	2.27(0.86–5.99)	0.098
Size of recurrent tumor (cm)		2.51 (1.26–4.97)	0.008	–	–
Time to recurrence (months)		–	–	0.44(0.18–1.12)	0.086
First treatment response		–	–	5.72(2.09–15.65)	0.001
BED_{10}		0.53 (0.25–1.11)	0.095	–	–

BED — biologically effective dose; CI — confidence interval; ECOG — Eastern Cooperative Oncology Group; Gr — grade; HR — hazard ratio; OS — overall survival; PFS — progression-free survival; Prog — progression; Re-RT — re-irradiation; RT — radiotherapy; St — stable; WHO — World Health Organization

11.62–22.73) months for WHO grade 3 gliomas. In the univariate analysis, age < 50 years (p = 0.006), Eastern Cooperative Oncology Group (ECOG) 0–1 (p = 0.037), grade 3 gliomas (p = 0.023), size of tumor < 2 cm (p = 0.018), tumor volume < 10 cc (p = 0.034), BED_{10} < 45 Gy (p = 0.024) were associated with better survival (Tab. 2). Grade 3 gliomas (p = 0.027), size of tumor < 2 cm (p = 0.008) were remained independent prognostic factors for OS in the multivariate analysis (Fig., 2AB).

Recurrence after re-RT was detected in 20 patients, 6 of them belonged to new lesions. 2 patients with new lesion underwent 2nd series of re-RT, 1 patient underwent 2nd surgery. 11 patients received

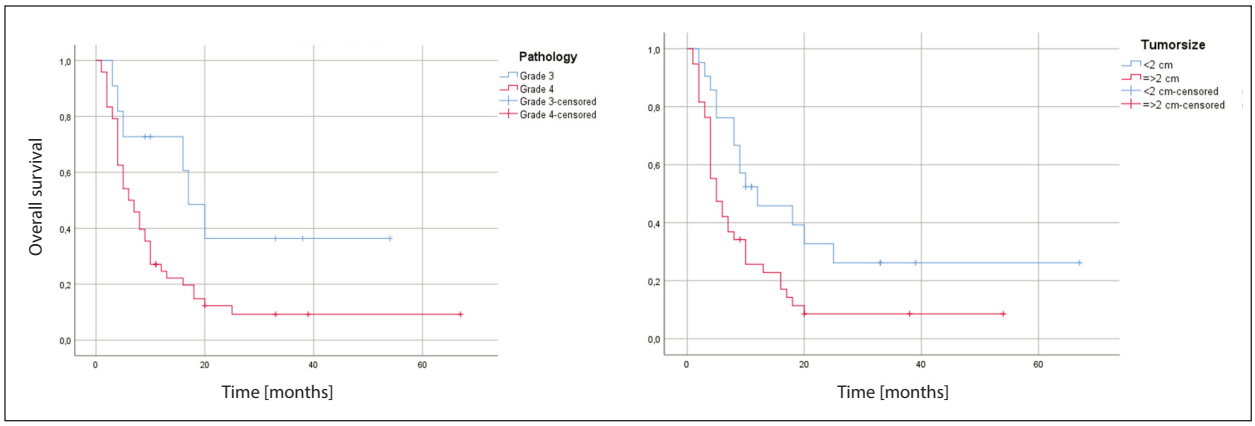

Figure 2AB. Kaplan-Meier graph of overall survival (OS) according to grade and tumor size

2nd series chemotherapy, the rest received best supportive care. LCRs were 62.7% and 33.9% at the first and last follow up. The median PFS after re-RT was 5 (95% CI: 3.39–6.60) months, and 1- and 2-y PFSs were 24.5% and 9.5%, respectively (Fig. 1B). In the univariate analysis, age < 50 years (p = 0.012), ECOG 0-1 (p = 0.028), grade 3 gliomas (p =0.024), stable response at first evaluation with imaging (p = 0.003), and time to recurrence > 9 months (p = 0.012) were associated with improved PFS survival (Tab. 2). Stable response at first evaluation after CK (p = 0.001) remained to be a prognostic factor for PFS in the multivariate analysis.

Discussion

In our single-center retrospective study, we investigated the efficacy of SRT in the treatment of recurrent HGG and evaluated the factors affecting survival outcomes. We determined the median OS after re-RT as 8 months for the entire group. Age, WHO grade and tumor size were found to be effective on OS in univariate analysis. In our study, we noticed that factors such as grade and tumor size, which we found to be associated with survival, were in agreement with the literature [24–28].

Re-RT remains a viable and effective option that provides survival benefits with promising results. Among the different re-RT methods, we wanted to compare our data with the results reported with CK. In a meta-analysis conducted by de Maria et al. [24], in which they included 12 studies involving 398 HGG patients who underwent SRS and/or SRT with CK, they found a median survival of 8.6 months (95% CI: 6.65–10.47) after re-RT. In our series, we found the median OS of 8 months for the entire group. Our result for OS was also comparable to that obtained from this meta-analysis.

It is known that HGG tumors differ in terms of both survival and recurrence rates with respect to the WHO grade. In this context, the effect of grade was also investigated in re-RT studies [25, 26]. In the study which included 300 patients with recurrent glioma the median survival of 12.2 *vs.* 8 months was better in grade 3 patients than in grade 4 patients (p < 0.01) [25]. Pinzi et al. [26] reported that the median survival was increased by grade (14 months for grade 3 *vs* 10 months for grade 4). Finally, in a meta-analysis published in 2021, it was reported that the median survival was improved in grade 3 patients compared to grade 4 patients [11 months (95% CI: 5.12–16.88) *vs.* 8.3 months (95% CI: 6.35–10.45)] [24]. Similarly, in our study, WHO grade was found to have an effect on OS.

Regarding the analyzed variables, age is also known to be a predictor of OS in glial tumors. Patient frailty and susceptibility to treatment toxicity are also associated with increasing age, and treatment failure may occur accordingly. Different age groups were taken as thresholds by several authors and a significant relationship was reported [25–27]. Our study also showed the link between age and survival in terms of OS and PFS. It was found in the univariate analysis that the survival deteriorated with increasing age, especially above 50.

Previous studies have shown a significant association between survival with those with low tumor volume and/or size prior to re-RT. A pooled analysis of recurrent high and low grade glial tumors was published in 2018, many of which were reirridated with fractionated RT (FSRT) [27]. An established prognostic score validation was performed. Tumor volume was used as a parameter of this score, and tumor volume over 47 cc was determined as a poor prognostic factor. In another series of 116 patients, most of whom were treated with SRS, it was reported that OS was adversely affected when PTV was greater than 6.4 cc [28]. In our study, we found that survival was adversely affected if the tumor diameter was over 2 cm and the tumor volume was over 10 cc. An inverse relationship was found between tumor size and OS in multivariate analysis, which was consistent with other series of re-RT.

Previous studies have reported that OS improves with longer intervals between the two radiation treatments or longer intervals between initial diagnosis and recurrence [29, 30]. Unlike the studies by Klobukowski et al. [30] and by Combs et al. [16], the time from primary RT to re-RT was not prognostic for OS in this study. In our study, only the time from initial diagnosis and recurrence > 9 months were associated with improvement in PFS.

Another clinical prognostic factor in the literature is MGMT promoter methylation [16, 20]. As in primary treatment, re-RT studies have shown that the results are more promising in patients with MGMT methylation. However, this evaluation could not be made because the MGMT status was

not known in our patient group as the institution cannot provide testing.

The radiobiological efficacy of each dose and fraction combination varies. Therefore, many studies have investigated the effect on survival by calculating the BED_{10}. Navarria et al. [25] reported that the BED_{10} threshold > 43 Gy had been proven to affect survival. The present data similarly showed that BED_{10} > 45 Gy had an impact on OS.

However, there is no standard recommendation regarding fractionation and dose. When the literature is reviewed, it is seen that fractionated therapies are preferred by clinicians due to treatment-related toxicity concerns, especially in order to reduce the risk of radionecrosis development. SRS is mostly preferred in small targets. Doses between 10–20 Gy were prescribed to a median volume of 10 cc. In our study, SRS was applied to only 4 lesions. Doses of 15–21 Gy were administered to 4 lesions with a median tumor volume of 7 cc. Since SRS was preferred in a small number of patients in our study, we could not obtain statistically significant results when compared with SRT. A systematic review evaluating OS and radionecrosis in reirradiated HGG tumors included 3302 patients from 70 studies [22]. The adjusted mean OS was found to be better in patients treated with SRS than in patients treated with fractionated SRT and conventional RT [12.2 months (95% CI: 11.8–12.5); 10.1 months (95% CI: 9.7–10.5) and 8.9 months (95% CI: 8.4–9.4) ($p < 0.0001$)]. In fact, in 13 of the 27 fractionated SRT studies included in this review, daily doses ranging from 2.2-3.8 were administered in 8-15 fractions. We think that the difference in OS when fractionated SRT is compared with SRS is due to the inclusion of moderately hypofractionated RT studies, thus giving less radiobiological doses. Considering all studies, the mean rate of radionecrosis was found to be 4.6%. When compared with the RT technique, the adjusted mean radionecrosis rate was found to be lower with conventional RT [1.1% (95% CI: 0.5–1.7) for conventional RT; 7.1% (95% CI: 6.6–7.7) for fractionated SRT; 6.1% (95% CI, 5.6–6.6) for SRS]. In addition, the authors emphasized that the risk of radionecrosis increases with increasing EQD_2 and decreasing interval between initial RT and re-RT ($p < 0.0001$). Unfortunately, due to its retrospective nature, we could not state the radionecrosis rates in our study. During the follow-up period, MR spectroscopy, MR perfusion and MR diffusion images were not available in some patients because they applied to our center for follow-up after only having MRI scans in the institutions in their cities. Therefore, we had to evaluate the response assessment of these patients with conventional MRI alone.

This study adds to the growing literature demonstrating the efficacy of re-RT with CK for HGG tumors. However, some limitations of this study must be acknowledged; one is the relatively small sample size with a heterogeneous dose and fractionation of SRT from a single institution. The data were collected retrospectively, so it could be potentially biased. Due to its retrospective nature, it was difficult to accurately determine the treatment related toxicities. Despite the limitations of the present study, survival rates are consistent with other series of re-RT. Robust studies with high levels of evidence for SRS and/or SRT in the setting of recurrent HGG are still needed.

Conclusion

SRT is a viable treatment modality with significant survival contribution in recurrent HGG. Since it may have a favorable prognostic effect on survival in patients with tumor size < 2 cm, we recommend early diagnosis of recurrence and a decision to re-irradiate to a smaller tumor size during follow-up.

Conflicts of interest

None declared.

Funding

None declared.

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