RESEARCH ARTICLE

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Comparison between Reirradiation by Stereotactic Body Radiation Therapy and Moderately Hypofractionated Radiotherapy in Combination with Temozolomide for Treatment of Recurrent High Grade Glioma

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Abstract

Objective: High grade glioma (HGG) is considered a lethal disease with a high recurrence rate. There is no standard of care in recurrent HGG. Many treatment options are present, such as resurgery, systemic therapy, and re-irradiation. Re-irradiation seems to be a promising option. In this study, we aimed at comparing the efficacy and toxicity of two re-irradiation protocols. **Methods:** Forty patients with recurrent HGG were randomized equally into two arms. Arm A received 30 Gy/10f/2w, and arm B received stereotactic body radiotherapy (SBRT) 30 Gy/5f/1w. Concurrent temozolamide (TMZ) was given in both arms. Median progression free survival (PFS) and overall survival (OS) were calculated, and brain MRI was done after 2 months of radiotherapy and then every 2 months, with documented toxicity using the Common Terminology of Adverse Events version 5 (CTCAE). **Results:** The median follow-up time after the re-irradiation course was 11 months (range 8-15 months). The median PFS after recurrence was 6.4 months (95% CI 5.3-7.4), the median OS after recurrence was 8.6 months (95% CI 7.5-8.7), and the median total OS form date of diagnosis was 18.5 months (95% CI 17.3–19.8) among the included patients. There was a statistically significant difference in PFS favoring arm B, with a median PFS of 7.3 versus 6.2 months in arm A, with p values of 0.004. There was no statistically significant difference in in median OS (9.3 months in arm B versus 8.4 months in arm A) with p values of 0.088. All patients tolerated their treatment well, and acute and subacute G1-G2 toxicity, consisting of headache, malaise, and nausea, were recorded during and shortly after the end of the re-irradiation course. **Conclusion:** Re-irradiation in recurrent HGG by both protocols is safe and effective, with a significant improvement in PFS in SBRT arm but no significant improvement in OS.

Keywords: HGG- SBRT- Reirradiation

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Introduction

The standard of care in newly diagnosed patients with HGG, is a multi-modal approach with maximally safe resection followed by adjuvant chemo-radiation [60 Gy with concomitant TMZ] followed by 6–12 cycles of TMZ. Despite the variety of modern therapies, including surgery, chemotherapy, and radiotherapy, patients with glioblastoma multiform (GBM) usually have a median survival of approximately 14.6 months, with less than 10% of patients surviving beyond 5 years [1]. Recurrent HGG represents one of the most challenging areas in oncology, despite many treatment options such as resurgery, systemic therapy, and/or re-irradiation. There is no optimal salvage treatment of choice for this group of patients, and nearly all treatment is given with palliative intent [2].

Based on the patient's quality of life and the likelihood of treatment-related toxicity, the optimal treatment is customized for them. Important factors to take into account include the patient's performance status (PS), the location of the recurrence, and the kind of recurrence (diffuse or focal). Reirradiation has become an efficient and increasingly used method to treat recurrent HGG, with encouraging results [3].

Neurological toxicity rates ranging from 5% to 20% and variable median survival times between 6 and 12 months have been documented following stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT). Furthermore, compared to reirradiation alone, survival benefits after reirradiation in conjunction with TMZ or bevacizumab have been confirmed. A meta-analysis and systematic review of patients treated with different SRS reirradiation protocols showed that the PFS was 40% at 6 months and 16% at 12 months, whereas the OS was 70% at 6 months and 34% at 12 months [4]. Different hypofractionated schedules were studied in the setting

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of recurrent GBM. Many trials studied the effect of total doses of 30–45 Gy delivered in 2.5–4.0 Gy per fraction. The median OS time was from 7.5 to 12.5 months [5, 6, 7, 8]. An OS time of 11 months was seen with a dose of 35 Gy in 10 fractions of 3.5 Gy per fraction, as reported by Fogh et al. [9].

The OS following salvage SRS or hypofractionated RT (HFRT) was marginally ($p = 0.06$) better than that following conventionally fractionated re-irradiation when comparing different fractionation schedules of re-irradiation, most likely from a small target volume [10].

When giving reirradiation, the dose tolerance of the normal brain tissue is the limiting factor. Several factors should be considered in determining the likelihood of radiation necrosis after reirradiation, namely dose, fractionation, irradiated volume, combination with chemotherapy, and interval between radiation courses. There is a confirmed relationship between the cumulative equivalent dose in 2 Gy fractions (EQD2) and the risk of radiation necrosis. After conventional fractionation, the reported risk was about 0–3% at cumulative EQD2 less than 101 Gy [11]. Our aim was to investigate the role of re-irradiation in the setting of HGG, through a comparison between hypofractionated SBRT and moderately hypofractionated radiotherapy in terms of efficacy and toxicity.

Materials and Methods

This is a prospective study that was carried out during the period between January 2021 and January 2023. Forty patients diagnosed with recurrent HGG, with a previous full radiation therapy (RT) course and concurrent TMZ, followed by adjuvant TMZ, were randomized to both treatment arms. Arm A (20 patients) received moderate hypofractionated radiation therapy, with a dose of 30 Gy over 10 fractions, 1 fraction per day, over 2 weeks. Arm B (20 patients) received SBRT with a dose of 30 Gy over 5 consecutive fractions, 1 fraction per day.

TMZ was given concurrently in both treatment arms at a daily dose of 75 mg/m^2, starting on the first day of RT and continuing for the whole treatment. The inclusion criteria were patients who are 18 years of age or older, ECOG PS ≤ 3, pathological confirmation of glioma, previous RT with therapeutic doses, at least 6 months from the end of the previous RT course, the lesion to be at least 1cm away from vital organs, and hemoglobin levels ≥ 10 ng/dl. The exclusion criteria were patients with contraindications to MRI and brainstem gliomas. A written consent was obtained from each patient before recruitment for the study.

Radiotherapy technique

The patient was immobilized using a thermoplastic mask that was fixed to the stereotactic head frame. After being obtained at the CT simulator, planning computed tomography (CT) images with a 1.25-mm slice thickness were sent to the contouring workstation.

The combined CT and MR images were utilized to delineate the gross tumor volume (GTV), planned target volume (PTV), and organs at risk (OARs). GTV was described as the lesion that enhanced contrast, omitting any surrounding edema. The GTV was consistently expanded by 3 mm to create the PTV. OARs were delineated. The volumetric modulated arc treatment (VMAT) technique was used for the planning process, with 3- or 5-mm dynamic multi-leaf collimators (DMLC) and 6-MV photons. A linear accelerator was used to deliver the radiotherapy sessions. The dosage was recommended to cover the PTV up to the 95% isodose line. By comparing reference planning CT images with the online kilo-voltage cone beam CT (kv-CBCT), an accurate set-up verification was carried out.

Follow up and assessment of response

Follow-up visits were scheduled at 2-month intervals, including a complete history and physical examination with neurological status assessments, KPS, and toxicity assessment. A follow-up MRI of the brain was ordered every 2 months with a response assessment in terms of complete remission (CR), partial response (PR), stationary disease (SD), or progressive disease (PD). The patient is considered in progression as follows: 1. A 25% increase in the product of the enhancing lesions' perpendicular diameters. 2. A significant rise in the non-enhancing T2/Flair component. 3. The development of new lesions. 4. Clinical deterioration is not due to other possibilities other than the tumor or a corticosteroid dose reduction.

Outcome parameters

Primary outcome parameters

PFS was evaluated for a maximum of 48 months, starting on the randomization date and continuing until the date of the first recorded progression or death, whichever occurs first. OS was calculated from the date of randomization until death and evaluated for up to 48 months.

Secondary outcome parameters

LC was calculated from the date of randomization until the date of local disease progression and assessed for up to 48 months.

Assessment of toxicity

Toxicity was assessed by the Common Terminology of Adverse Events version 5 (CTCAE) every 2 months, or in the case of patient hospitalization or visit to the emergency room.

Statistical analysis

Statistical analysis was done using SPSS 22nd edition, categorical variables were presented in frequency and percentages, and a Chi2 test was conducted to compare categorical variables between study groups. A survival analysis was conducted to assess time to progression and time to death among study participants. A log rank test was conducted to compare time to event between study groups. Any p value < 0.05 was considered significant.

Results

A total of 40 patients included were diagnosed with

Table 1. Primary Disease Characteristics

		Mean± SD/ Count (%)
Age	Years	46.7± 14.3 (27-67)*
Sex	Female	19 (47.5)
	Male	21 (52.5)
Primary Pathological subtype	Anaplastic	4 (10)
	GBM	36 (90)
Primary surgical resection	Biopsy	15 (37.5)
	Complete	9 (22.5)
	Partial	16 (40)
Baseline Performance status		76.5± 11.9 (60-90)*

*, range; GBM, Glioblastoma multiform

recurrent HGG, with a mean age of 46.6 ± 14.3 years. Males outnumber females, accounting for 21 males (52.5%) versus 19 females (47.5%) of the included patients. GBM represented most of the included patients, which was diagnosed in 36 patients (90%), while anaplastic glioma GIII was diagnosed in 4 patients (10%).

On initial diagnosis, complete resection was performed in 9 patients (22.5%), while partial resection was performed in 16 patients (40%), and biopsy was only done in 15 patients (37.5%) of the included patients (Table 1). Upon recurrence, 27 (67.5%) of the included patients were presented with disease relapse on the left side, and 13 patients (32.5%) on the right side. The frontal lobe was the most common site of relapse in 14 patients (35%). The performance status range on recurrence was 50 to 90%, with a median value of around 70%. The mean value of PTV volume was 31.4±21.2 cc. The mean interval between the end of primary radiation therapy and reirradiation on recurrence was 6.6-11.5 months, with a mean interval of 8.7 months (Table 2). The two treatment groups had well-balanced patient and tumor characteristics, showing no statistically significant P value (Table 3).

Table 2. Relapsed Disease Characteristics

	Count (%)
Side	
Left	27 (67.5)
Right	13 (32.5)
Cerebellum	2 (5)
Frontal	14 (35)
Fronto-parietal	5 (12.5)
Fronto-temporal	5 (12.5)
Site of recurrence	
Occipital	2 (5)
Parietal	4 (10)
Parieto-occipital	1 (2.5)
Parieto-temporal	2 (5)
Temporal	5 (12.5)
Surgical Resection	
Yes	3 (7.5)
No	37 (92.5)
Steroids intake	
No	14 (35)
Yes	26 (65)
PTV (cc)	31.4±21.2 (4.8-80)*
Interval for re-irradiation (months)	8.7±1.5 (6.6-11.5)*
Relapse performance status	68.8± 13.2 (50-90)*

*, Range; PTV, Planning target volume; CC, cubic centimeter

Local control

The local control rate was 100% in arm B after 2 months from the end of the re-irradiation course, versus 95% in arm A. In the 4-month assessment, there was disease progression in 8 (40%) patients in arm A versus no patients in arm B, with a statistically significant P value of 0.008. Eight and ten-month assessment, showed no

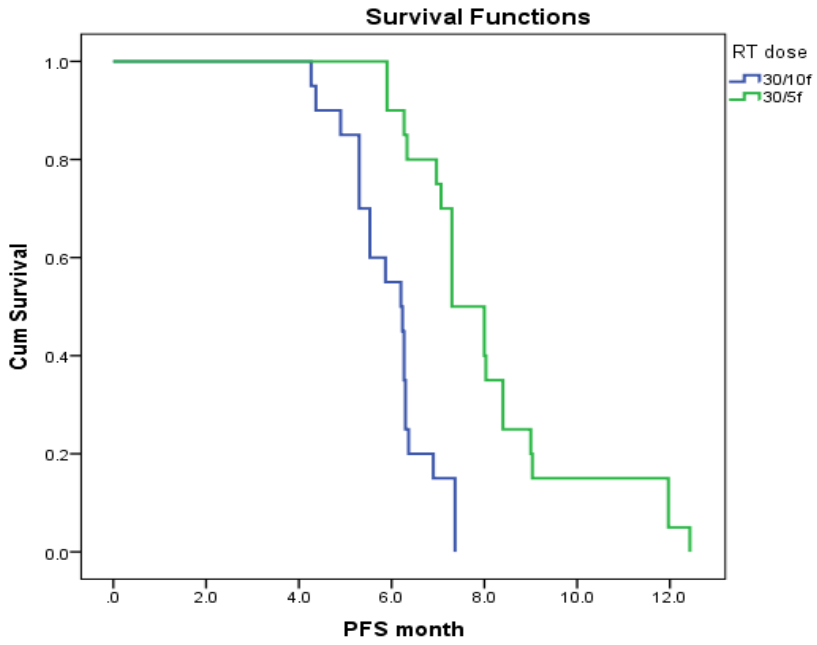

Figure 1. Kaplan Meier Curve Showing PFS among Study Groups. PFS, progression free survival; RT, radiotherapy

Table 3. Comparison of Clinical and Radiotherapy Characteristics among Study Groups

		RT dose		P value
		30 Gy/10 F Mean ± SD (%)	30 Gy/5 F Mean ± SD (%)	
Age	Years	48.6 ± 15.4 (27-67)*	45 ± 13.3 (27-67)*	0.602
Sex	Female	10 (50)	9 (45%)	0.752
	Male	10 (50)	11 (55)	
Primary Pathological subtype	Anaplastic	3 (15)	1 (5)	0.292
	GBM**	17 (85)	19 (95)	
	Biopsy	8 (40)	8 (40)	
Primary surgical resection	Complete	3 (15)	5 (25)	0.251
	Partial	9 (45)	7 (35)	
	Cerebellum	0 (0)	2 (10)	
	Frontal	7 (35)	7 (35)	
	Fronto-Parietal	2 (10)	3 (15)	
	Fronto-Temporal	5 (25)	0 (0)	
	Occipital	0 (0)	2 (10)	0.134
	Parietal	2 (10)	2 (10)	
Site of recurrence	Parieto-Occipital	0 (0)	1 (5)	
	Parieto-Temporal	2 (10)	0 (0)	
	Temporal	2 (10)	3 (15)	
Relapse performance status		73.5± 13.1 (50-90)*	74±11.4 (50-90)*	0.919
Steroids intake	No	8 (40)	11 (55)	0.343
	Yes	12 (60)	9 (45)	
Number of lesions	Single	17 (85)	18 (90)	0.082
	2 lesions	3 (15)	2 (10)	
PTV (CC)		35.9±25.3 (8-80)*	27±15.7 (4.8-57)*	0.445
Interval for re-irradiation (months)		8.2± 1.5 (6.6-11.5)*	9.2±1.3 (7.2-10.9)*	0.401

SD, standard deviation; *, range; GPM, Glioblastoma multiform; PTV, Planning target volume CC, Cubic centimeter

significant difference, while 12-month assessment showed that the death rate was 100% in arm B versus 80% in arm A with a P value of 0.035, while the four (20%) alive patients in arm B showed disease progression (Table 4).

Survival analysis

The median follow-up time after the reirradiation course was 11 months (range 8-15 months). The median PFS after recurrence was 6.4 months, the median OS

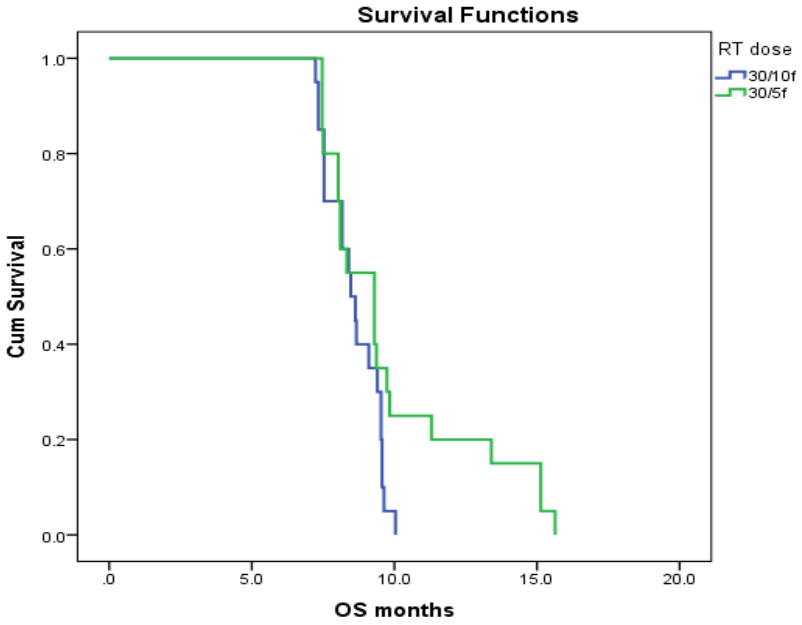

Figure 2. Kaplan Meier Curve Showing Study Specific OS among Study Groups. OS, overall survival; RT, radiotherapy

Table 4. Local Disease Control Rate and Disease Assessment at 2,4, 6, 8, 10 and 12 months

		RT dose		
		30Gy/10f	30Gy/5f	
		Count (%)	Count (%)	P value
2m	PD	1 (5)	0 (0)	
	PR	5 (25)	12 (60)	
	SD	14 (70)	8 (40)	0.063
4m	Died	1 (5)	0 (0)	
	CR	0 (0)	3 (15)	
	PD	8 (40)	0 (0)	
	PR	2 (10)	5 (25)	0.008
	SD	9 (45)	12	
			60%	
6m	Died	6 (30)	2 (10)	
	CR	0 (0)	2 (10)	
	PD	10 (50)	12 (60)	
	SD	3 (15)	4 (20)	0.023
8m	Died	19 (95)	12 (60)	
	CR	0 (0)	2 (10)	
	PD	1 (5)	4 (20)	0.061
	SD	0 (0)	2 (10)	
10m	Died	20 (100)	16 (80)	0.035
	SD	0 (0)	4 (20)	
12m	Died	20 (100)	16 (80)	0.035
	PD	0 (0)	4 (20)	

PD, Progressive disease; CR, Complete remission; SD, Stationary disease

after recurrence was 8.6 months, and the median total OS from the date of diagnosis was 18.5 months among the included patients.

Progression free survival

There was a statistically significant difference in PFS among study groups favoring arm B, with a median PFS of 7.3 versus 6.2 months in arm A, with p values of 0.004. (Figure 1). PFS was not affected by different variables, namely the time of recurrence, age, site of recurrence, performance status, surgical resection, and the interval for reirradiation.

Overall survival

There was no statistically significant difference in OS among study groups, with a median OS of 9.3 months in arm B versus 8.4 months in arm A, with p values of 0.088. (Figure 2). OS was not affected by different variables, namely the time of recurrence as age, site of recurrence, performance status, surgical resection, and the interval for reirradiation.

Total overall survival

There was no statistically significant difference in OS among study groups, with a median OS of 20.4 in arm B versus 17.9 months in arm A with a p value of 0.110. (Figure 3).

Toxicity analysis

All patients tolerated their treatment well and completed their prescribed course as planned. Acute and subacute G1-G2 toxicity, consisting of headache, malaise, and nausea, was recorded during and shortly after the end of the re-irradiation course in 17 patients (42.5%), 20 patients (50%), and 15 patients (37.5%), respectively, with no serious toxicity recorded (Table 5). Three months post radiotherapy toxicity assessment showed that G1-G2 toxicity, consisting of headache, malaise, and nausea, was recorded in 31 patients (77.5%), 29 patients (72.5%), and 16 patients (40%), respectively, with no serious toxicity recorded and no statistically significant difference between

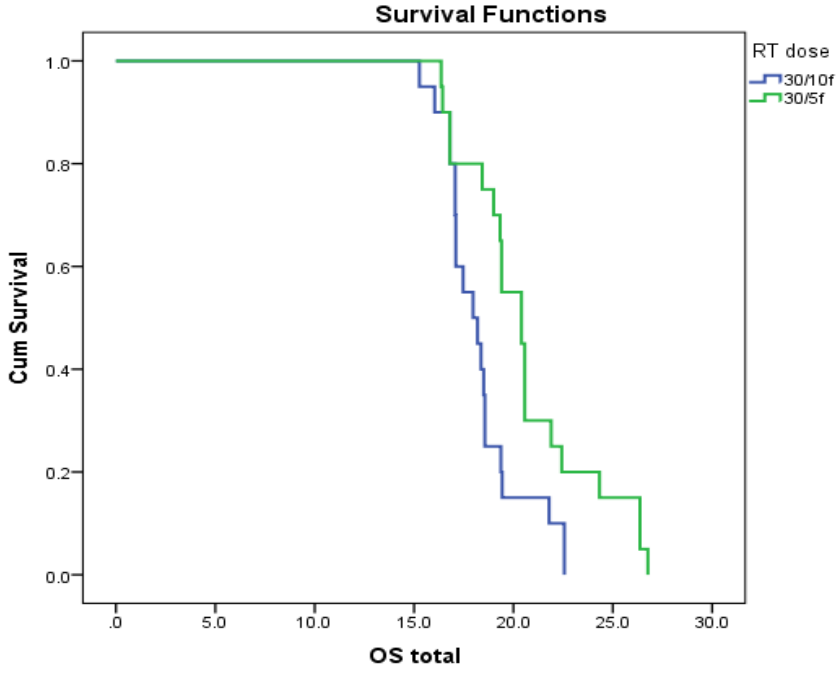

Figure 3. Kaplan Meier Curve Showing Total OS among Study Groups. OS, overall survival; RT, radiotherapy

Table 5. Comparison of Radiation Toxicities and Symptoms Just after the End of Radiation Therapy

	Grade	30Gy/10f Count (%)	30Gy/5f Count (%)	P value
Weakness	G0	14 (70)	16 (80)	
	G1	4 (20)	3 (15)	
	G2	1 (5)	0 (0)	0.939
	G3	1 (5)	1 (5)	
Headache	G0	8 (40)	12 (60)	
	G1	8 (40)	6 (30)	
	G2	2 (10)	1 (5)	0.388
	G3	2 (10)	1 (5)	
Malaise	G0	6 (30)	14 (70)	
	G1	13 (65)	5 (25)	0.03
	G2	1 (5)	1 (5)	
Nausea	G0	10 (50)	15 (75)	0.102
	G1	10 (50)	5 (25)	
Vomiting	G0	14 (70)	16 (80)	0.465
	G1	6 (30)	4 (20)	
Alopecia1	G0	16 (80)	15 (75)	0.705
	G1	4 (20)	5 (25)	
Seizures	G0	17 (85)	18 (90)	
	G1	2 (10)	2 (10)	0.268
	G2	1 (5)	0 (0)	
Disturbed conscious level (DCL)	G0	16 (80)	18 (90)	0.376
	G1	4 (20)	2 (10)	
Blurred vision	G0	18 (90)	20 (100)	
	G1	1 (5)	0 (0)	0.108
	G2	1 (5)	0 (0)	
Dysarthria	G0	16 (80)	19 (95)	0.151
	G1	4 (20)	1 (5)	
Memory	G0	14 (70)	19 (95)	
	G1	5 (25)	1 (5)	0.109
	G2	1 (5)	0 (0)	
Cognitive disturbance	G0	17 (85)	19 (95)	0.292
	G1	3 (15)	1 (5)	

G, grade; F, fractions

the 2 arms. Symptomatic brain necrosis was noticed in only one patient (5%) in each treatment arm after 6 months of reirradiation.

Discussion

Re-irradiation is one of several appropriate palliative treatment choices for recurrent HGG. Given their capacity to reduce dosage to nearby tissues, stereotactic techniques might be advantageous. Moreover, fractionated techniques benefit from the biological advantages of fractionation in terms of tumor local control and toxicity. The use of HSRT in this patient population is further supported by recent studies with no acute effects [12]. The risk of symptomatic radiation necrosis was analyzed in many studies. It was mainly related to both the radiation dose and the treated volume and ranged between 0 and 24.4%. The EQD2 was used as a risk predictor. For a median tumor volume of roughly 10 ml of cumulative EQD2 around 120 Gy, the associated risk was < 10%, whereas a higher risk of up to 24% was observed for cumulative EQD2 values > 132 Gy [13].

No brain necrosis occurs when the cumulative radiation dose of the two radiation courses is < 96 Gy as calculated per biological equivalent total dose normalized to 2 Gy/fraction (EQD2) using the linear quadratic model [14]. The rationale for choosing the aforementioned two radiotherapy schedules used in our study is to give the highest possible total biological effective dose (BED) to enhance local tumor control, keeping the EQD2 at a safe limit for radionecrosis. The calculated BED of the initial radiotherapy course that delivers 60 Gy in 30 fractions with an estimated α/β ratio of 10 Gy equals 72 Gy.

Regarding the 30 Gy in 10 fractions schedule, the

BED equals 39 Gy. While the EQD2 equals 32.5 Gy. Therefore, the total BED of the two courses delivered to the lesion, including the initial course on diagnosis and the reirradiation course on progression, is 72 + 39 = 111 Gy. The total cumulative EQD2 for both radiotherapy courses is 60+32 = 92 Gy. Regarding the 30 Gy in 5 fractions schedule, with an estimated α/β ratio of 10 Gy, the BED equals 48 Gy, while the EQD2 equals 40 Gy. Therefore, the total BED of the two courses is 72 + 48 = 120 Gy. The total cumulative EQD2 for both radiotherapy courses is 60+40 = 100 Gy. In the current study, the median PFS after recurrence was 6.4 months, the median OS after recurrence was 8.6 months, and the median total OS from the date of diagnosis was 18.5 months. All patients finished their sessions well and completed their prescribed course as planned, with minor side effects like headache, malaise, and vomiting. Symptomatic brain necrosis occurred in only one patient (5%) in each treatment arm.

In comparison with the retrospective study performed by Demogeot et al., which used a dose of 25 Gy administered to 59 patients in 5 consecutive sessions, there was a comparable median OS after reirradiation (8.8 months); however, the median PFS was significantly lower than our study (3.9 months versus 6.4 in our study). This might be because of the patients chosen, of whom 45 (76%) underwent reirradiation following their first GBM recurrence, 10 (17%) following their second recurrence, 3 (5%) following their third recurrence, and 1 (2%) on the fourth recurrence, with several lines of systemic treatment received before the reirradiation course [15].

On the other hand, the OS in our trial was significantly lower when compared with the OS of a study done by Minniti et al., who used a dose of 30 Gy/6fr. delivered to 54 patients with recurrent HGG concurrent with Temozolomide given during HSRT followed by adjuvant TMZ for a maximum of one year or until disease progression. Median OS after reirradiation by HSRT was 12.4 months, versus 8.6 months in our study. This significant difference was due to the type of patients selected in the study. There were 16 patients with GIII pathology, with a PS median value of 80% (60–100) versus 70% (50-90) and a PTV median volume of 9.7 cm3 (3.1–32.3), including tumors less than 4cm, versus 31.4 cm3 (4.8-80). Another factor is the surgical intervention prior to reirradiation in 12 patients. The PFS was 6 months versus 6.4 months in our study, with Grade 3 neurological deterioration due to radiation-induced necrosis occurring in four patients (7%) at 2, 4, and 10 months after reirradiation [16].

Another study was done by Minniti in 2015, who used a dose of 25 Gy/5fr. delivered to 54 patients concurrent with Bevacizumab or fotemustine (12 anaplastic astrocytomas and 42 GBM). Patients treated with HSRT and bevacizumab experienced a median OS following HSRT of 11 months, whereas patients treated with HSRT and Fotemustine experienced a median OS of 8.3 months. Also, the small PTV irradiated explained these significantly higher results, median value was 12.4 cm3. The median PFS time of patients with GIII was 8 months, compared to 4 months for those with GBM [11].

There were comparable results between our study and the study done by Dincoglan et al., which included 28 patients receiving HSRT for recurrent GBM with a median KPS of 80% who received 25 Gy delivered in 5 fractions over 5 consecutive days. The median OS calculated from reirradiation was 10.3 months vs. 8.6 months in our study, while the PFS was 5.8 months vs. 6.4 months in our study. PTV was 36.5 cc vs. 31.4 cc for recurrent disease [17].

In comparison to our study, there is a relative improvement in the OS and PFS shown by the cohort study of Greenspoon et al., which enrolled a total of 31 patients. Depending on the maximum tumor diameter, patients receiving robotic radiosurgery were treated with three dose/fractionation protocols ranging from 25 to 35 Gy in five fractions. The median OS was 9 months vs. 8.6 months in our study, and PFS was 7 months vs. 6.4 months in our study. This mild increase in survival may be attributed to a small PTV volume with a median value of 12.1 cm3 and a different radiotherapy technique delivered using robotic radiosurgery [18].

Patient heterogeneity remains one of the drawbacks of many studies. This may be evident in the study of Mckenzie et al., which included 35 patients with heterogenous pathological behavior (two patients had grade II tumors at first, but they later developed high grade lesions; four had grade III and twenty-nine had grade IV tumors). A median of five fractions and a total dose of 30 Gy were administered to treat 47 recurring lesions.

This heterogeneity may explain the significant increase in the OS to be 7.9 for multifocal recurrence versus 10 months for unifocal recurrence, while it was 8.7 months in our study. Furthermore, a large number of patients underwent further systemic therapy, either in addition to or following salvage SRT [19]. In another trial, fifty-one patients received different treatment schedules. Single dose (range 12-20 Gy) in 4 patients (8%), hypofractionated (20-25 Gy) in 36 patients (70%), and normo-fractionated (30-50 Gy) in 11 patients (22%), delivered to the PTV with a median value of 55.1 cm3 by 3DCRT in 22 patients (43%), and IMRT in 29 patients (57%). After re-irradiation, survival approached statistical significance in favor of the hypofractionation group (median OS was 10.7 months) and the single-dose group (median OS was 10.0 months). The patient who received standard fractionation survived a median of 7.5 months after reirradiation (P = 0.06). Bevacizumab was used in 12 patients concomitant with reirradiation, which may be the reason for the increase in survival results in comparison to our study, in addition to being a retrospective study [20].

The older studies devoted to this issue were flawed by many factors, like heterogeneous management approaches, PS selection, and the size of the recurrent lesions. In our prospective study, we tried to overcome these drawbacks by recruiting a higher number of homogeneous populations with no selection bias, almost one histology, and two treatment schedules for the patients. The median PTV volume in our study is relatively larger compared with other studies. The patients included are presented on the first progression to purely investigate the role of reirradiation in recurrent high-grade glioma without regard to their performance status because of other lines of treatment.

This study enhanced the role of reirradiation in recurrent high-grade glioma concurrently with temozolomide. It explored two different radiation protocols: SBRT and the moderately hypofractionated protocol, and our results revealed that both protocols are safe and effective, with a significant improvement in PFS in the SBRT arm but no significant improvement in OS.

Author Contribution Statement

Ehab Saad: supervision of patients' recruitment, randomization, treatment plan acceptance, monitoring early radiation toxicity, management of radiation toxicity and review of literature, and methods section writing. Mahmoud Abdelwahed: recruitment, data collection, data processing, and patient follow up, statistical analysis and discussion section writing. Rania Moussa: treatment planning, dose calculation, IGRT. Mohamed Abdulla: senior supervisor.

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Approval

The study was approved by the scientific and ethics research committee of the faculty of medicine, Cairo University. (Ref: MD-49-2019).

Availability of data

Statistical analysis output is available upon request, however, raw data can't be shared because of participants confidentiality of data.

Conflict of Interest

The authors declare no conflict of interest.

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