Outcome and Prognostic Factors in Recurrent Glioblastoma Multiforme Treated with Re-Irradiation: A Retrospective Study from a Tertiary Care Hospital

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Abstract:

Background: Glioblastoma multiforme (GBM) continue to portend a dismal prognosis despite the use of multimodal approaches as nearly all patients will experience relapse. We aimed to determine the outcome and toxicity of re-irradiation (re-RT) for patients with recurrent GBM.

Methods: We retrospectively collected data for 57 patients with locally recurrent GBM who received re-RT from June, 2011 to January, 2018.

Results: The median time interval between primary RT and re-RT was 16 months. The type of recurrences was: "in-field" recurrence (n=41, 71.9%), marginal (n=12, 21.1%) and "out-of-field" (n=4, 7.0%). Of 33 chemo-naive patients, 27 patients (81.8%) received TMZ concomitantly and after re-RT, and 6 patients (18.2%) were medically unfit and received re-RT alone. All patients were treated using 3D conformal radiation therapy with three dose/fractionation schedules: 35 Gy/10 fractions (n=15, 26.3%), 36 Gy/18 fractions (n=34, 59.6%), and 25 Gy/5 fractions (n=8, 14.0%). The median tumor and planning volume at recurrence were 67 cm3 (range: 10 - 170 cm3) and 287 cm3 (range: 28 - 581 cm3) respectively. The median re-RT dose was 36 Gy (range: 31.3 – 39.4 Gy) and the median cumulative doses were 96 Gy (range: 91.3 – 99.4 Gy) for the two irradiation. The median cumulative biologic effective dose (α/β = 10 Gy) was 115.5 Gy (range, 109.5 – 119.3 Gy). The median follow-up duration was 10 months (range: 6 – 31 months). The median Overall and progression free survival was 11 and 8.0 months respectively. Multivariate analysis confirmed that younger age (P=0.022), longer time between primary RT and re-RT (P=0.002), and the combined chemoradiotherapy treatment (P=0.017) at recurrence were predictive for improved survival. All patients completed the planned reirradiation course with manageable toxicity. Only 7 of 57 patients (12.3%) had grade 3 or more toxicities. Late toxicity included radionecrosis in two patients who received 5 Gy per fraction.

Conclusion: Re-RT is tolerable and could be a salvage treatment for selected recurrent GBM patients with younger age, recurrence over a long time, and combined chemoradiation schedule. However, larger randomized studies are required to shed more light on this issue and to establish the optimal management strategy for recurrent GBM.

Keywords: Recurrent glioblastoma, Reirradiation, Survival, Prognostic factors, Toxicity

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Introduction:

Glioblastoma multiforme (GBM) is the most common primary brain tumor, with an incidence of 3-4 cases per 100,000 persons each year [1]. The Stupp protocol [2] is the standard treatment of newly diagnosed GBM which consists of maximal safe resection then concurrent temozolomide (TMZ) and radiotherapy followed by six cycles of adjuvant TMZ. At a median follow-up of 28 months, he reported a median overall survival (OS) of 14.6 months with

concurrent TMZ and radiotherapy compared to 12.1 months with radiotherapy alone [2]. However, most of the patients recur locally despite aggressive management with 85% of recurrences occur in previously irradiated areas of the brain (in-field recurrences) [3]. Surgery offers a local treatment option for recurrent GBM; however, this require further planned salvage therapy as radical resection is unlikely to fully remove the recurrent tumor [4]. Furthermore, the associated surgical morbidity in this population which limit the quality of time remaining. Reirradiation (Re-RT) is another therapeutic option for recurrent GBM and may be delivered using conventionally fractionated radiotherapy (RT), brachytherapy, hypofractionated stereotactic radiosurgery, stereotactic radiosurgery alone, or combination treatment with RT and systemic therapy, and palliative RT [5].

We aim to evaluate the treatment outcome and predictors of survival in patients received re-RT in the management of recurrent GBM at our institute.

Patients and Methods:

This retrospective study was conducted at the Radiation Oncology Department of South Egypt Cancer Institute, in the period from June, 2011 to January, 2018.

Eligibility criteria:

Our institutional database was screened for patients who were primarily diagnosed histologically confirmed GBM; 18 years or older, performance status (PS) of ≥ 3 according to Eastern Cooperation Oncology Group (ECOG) [6], received definitive or adjuvant external beam radiotherapy as a part of their initial treatment, and developed recurrence during treatment follow up.

Exclusion criteria:

Patients with histology other than glioblastoma and those who received either radiation or TMZ or surgery alone were excluded.

Diagnosis of Recurrent disease:

All patients were diagnosed by magnetic resonance imaging (MRI) and/or MR spectroscopy imaging (MRSI) as a part of treatment follow up evaluation (tumor recurrence or progression) that were available for review by radiologists. MRI and/or MRS was performed after primary therapy, at 1 month post adjuvant RT and then after every three cycles of maintenance TMZ followed by every three months after termination of treatment. Tumor recurrence was defined as an increase in the volume of the initial enhanced lesion according to Response Assessment in Neuro-Oncology (RANO) criteria [7] or as appearance of new contrast enhanced lesion. Any progressive contrast enhancement in the 6 months post RT was presumed to be pseudoprogression unless residual tumor proved with MR spectroscopy. Methylation status of O6-methylguanin-DNA methyltransferase (MGMT) and isocitrate dehydrogenase (IDH1/2) mutation status were not analyzed as they are not covered by the public health system.

The medical records of 57 patients were eligible to be retrospectively reviewed to extract the study relevant data. Collected data for the study included the following: patients' age, gender, ECOG PS, tumor location at recurrence, time interval between primary and re-irradiation, size of target volume, type of recurrence and the use of concurrent and maintenance TMZ.

This study was approved by the Committee of Medical Ethics of South Egypt Cancer Institute with IRB no: IORG0006563-579 and deemed not to require patient consent.

Reirradiation technique:

Treatment dosimetry characteristics were recorded for all patients to be reviewed by radiotherapist.

Target volume delineation

Gross tumor volume (GTV) included T1 contrast enhanced abnormality, and the clinical target volume (CTV) were generated by adding 15-20 mm margin to GTV, edema was not included in CTV. Margin was reduced around natural barriers. The planning target volume (PTV) were generated by adding 3 mm margin around the CTV and was encompassed by 95% of the prescribed dose at the isocenter. The organ at risks (lens, optic chiasm, optic nerve, brain, and brainstem) and previously irradiated volumes were contoured to construct cumulative dose volume histograms. The total dose to optic chiasm and brainstem was limited to 75 Gy and 85 Gy respectively. The dose constraint of organ-at-risk were those described by Emami et al. [8] and by the QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) initiative [9].

Target dose and energy:

The treatment dose was prescribed to the isocenter. The equivalent dose in 2 Gy fractions (EQD2) was calculated using an α/β of 10, to compensate for varying dose-fractionation schedules. Re-RT dose was 36 Gy in 18 fractions to the PTV other doses (35 Gy in 10 fractions, and 25 Gy in 5 fractions) were utilized. All patients were treated with 3-D conformal radiotherapy using megavoltage linear accelerator and photon energies of 6 MV or more.

TMZ was given concurrently with radiation therapy if it was not administered during the initial management. TMZ (75 mg/m^2/day) started from the first day of radiotherapy until the end of radiation. Adjuvant temozolomide was started four weeks after completion of re-RT at 150 mg/m^2/day for five days in the first cycle and increased to 200 mg/m2/day for five days in the subsequent cycles if no hematologic toxicity had occurred till disease progression.

Outcome evaluations

Clinical and laboratory evaluations

During radiotherapy, patients were followed up weekly in the clinic, and one month after completion of

radiotherapy and before each cycle for patients who received maintenance TMZ treatment.

Patients were evaluated during treatment by history, neurological examinations, laboratory investigations (full blood counts and blood chemistry). Assessment of treatment related toxicity was done using common Terminology Criteria for Adverse Events (CTCAE) version 3 [10]. Toxicities were assessed weekly during the re-RT course and every cycle during the adjuvant systemic course and every three months thereafter. During concurrent radio-chemotherapy, treatment was interrupted if neutrophil count was ≥0.5 - <1.5×109/L, platelet count was ≥10 - <100×109/L, or grade 2 non-hematologic toxicity (except for alopecia, nausea, vomiting) was observed. Treatment was stopped if neutrophil count was 0.5×109/L, platelet count was <10×109/L, or ≥grade 3 non-hematologic toxicity (except for alopecia, nausea, vomiting) was observed. During maintenance therapy, reduction of TMZ dose from 200 to 150 mg/m^2 or from 150 to 100 mg/m^2 if neutrophil count was <1×109/L, platelet count was <50×109/L, or grade 3 non-hematologic toxicity (except for alopecia, nausea, vomiting) was observed. Treatment was discontinued if disease progression, patient refusal, and toxicities necessitate reduction of TMZ dose bellow 100 mg/m^2.

Statistical analysis:

Overall survival (OS) was calculated from the date of re-RT to death. Progression free survival (PFS) was calculated from the date of re-RT to recurrence. Kaplan-Meier method was used for survival analysis and prognostic factors were determined by log rank test. Univariate and multivariate analyses were performed using Cox regression analysis. All tests were 2-tailed and differences at P-values < 0.05 were considered statistically significant. Statistical data were performed by Statistical Package for Social Sciences software (version 21, SPSS, Chicago, IL).

Results:

Patients' characteristics:

Of 57 patients of the study cohort, 41 (71.9%) were males and 16 (28.1%) were females. The median age at time of re-RT was 54 years (range: 25– 67 years). All patients were managed primarily with radiation therapy following gross total resection (33.3%), subtotal resection (47.4%) or biopsy (19.3%). The total dose of radiation therapy was 60 Gy, divided into two phases / 2 Gy per fraction/ once daily/ five days per week (n= 46, 80.7%) or 40 Gy / 266.67 Gy per fraction / once daily / five days per week (n = 11, 19.3%). Twenty-four patients (42.1%) received TMZ during and/or after initial radiotherapy. The median time interval between primary and re-RT treatment was 16 months (range: 6 - 63 months). The pattern of recurrences evaluated in 57 patients was: "in-field" recurrence in 41 patients (71.9%), marginal recurrence in 4 patients (7.0%) and "out-of-field" recurrence in 12 patients (21.1%). Of 33 chemo-naive patients, 28 patients (84.8%) received TMZ concomitantly and after re-RT, the remaining 5 patients (15.2%) were medically unfit and received re-RT alone. The median tumor volume treated was 67 cm3 (10 – 170 cm3) and the median PTV treated was 287 (range: 28 – 581 cm3). The median re-RT dose was 36 Gy (range: 31.3 – 39.4 Gy) and the median cumulative doses were 96 Gy (range: 91.3 – 99.4 Gy) for the two irradiation. The median cumulative BED2 (α/β = 10 Gy) was 115.5 Gy (range, 109.5 – 119.3 Gy).

Treatment outcome:

Survival and prognostic factors:

The median follow-up duration for the entire cohort was 11 months (range: 6 – 31 months), with 50 patients died of the disease progression, 2 alive with disease and 5 alive without disease after re-irradiation. Median OS was 11 months [95% confidence interval (CI), 9.594 – 12.406 months]. PFS was 8.0 months (95% CI, 6.876 – 9.124 months).

Potential prognostic variables examined in univariate analyses were gender (female vs. male), age at the time of re-irradiation (≥50 years vs. <50 years), ECOG PS, time interval between primary RT and re-RT (≥16 months vs. <16 months), gross/planned target volume, re-RT schedule (conventional fractionation vs hypofractionation), re-RT dose (≥36 Gy vs <36 Gy), cumulative EQD2 (≥96 Gy vs <96 Gy), and chemoradiation schedule (yes vs no). Univariate analysis of the entire cohort found that younger age, longer time between primary RT and re-RT, and the combined chemoradiotherapy treatment at recurrence were predictive for improved survival. These significant factors were further confirmed by multivariate analysis.

Toxicity

All patients completed the planned re-RT course with manageable toxicity. There were no treatment-related deaths. According to the CTCAE version 3, 39 patients (68.4%) developed treatment-related toxicity. The overall treatment related adverse events were higher during the concomitant and adjuvant course than re-irradiation alone. Only 7 of 57 patients (12.3%) had grade 3 or more toxicities; in whom treatment was interrupted and resumed after conservative measures. Steroids were given only to patients who presented with manifestations of increased intracranial pressure. Late toxicity included grade 2 radionecrosis in two patients who received 5 Gy per fraction, and it was proved by MRS. Treatment included dexamethasone.

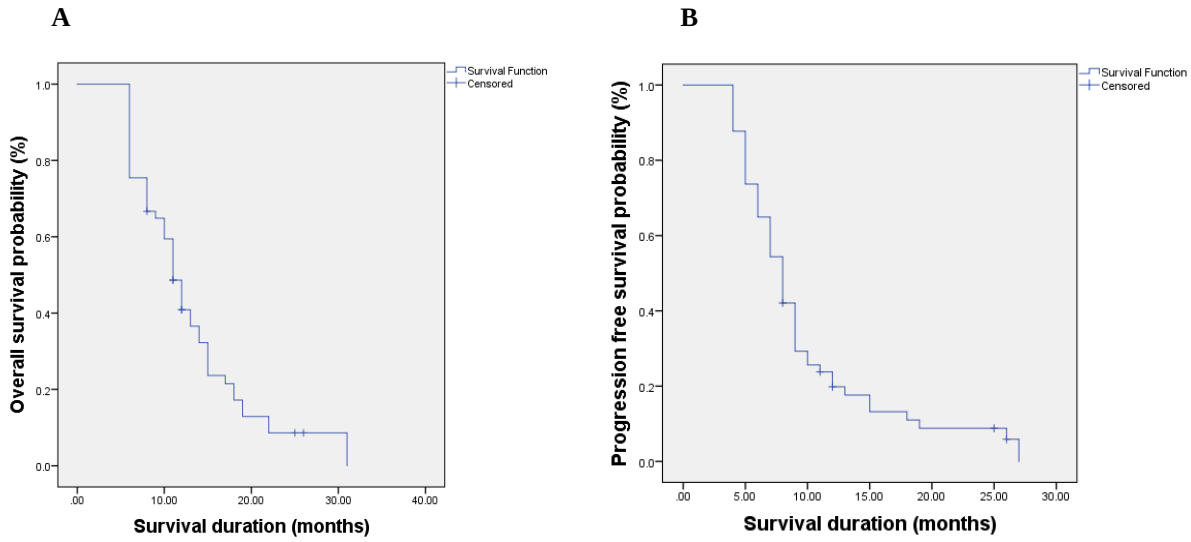

Figure 1: Kaplan-Meier curves showing OS (A) and PFS (B), for recurrent glioblastoma multiforme patients treated with re-irradiation.

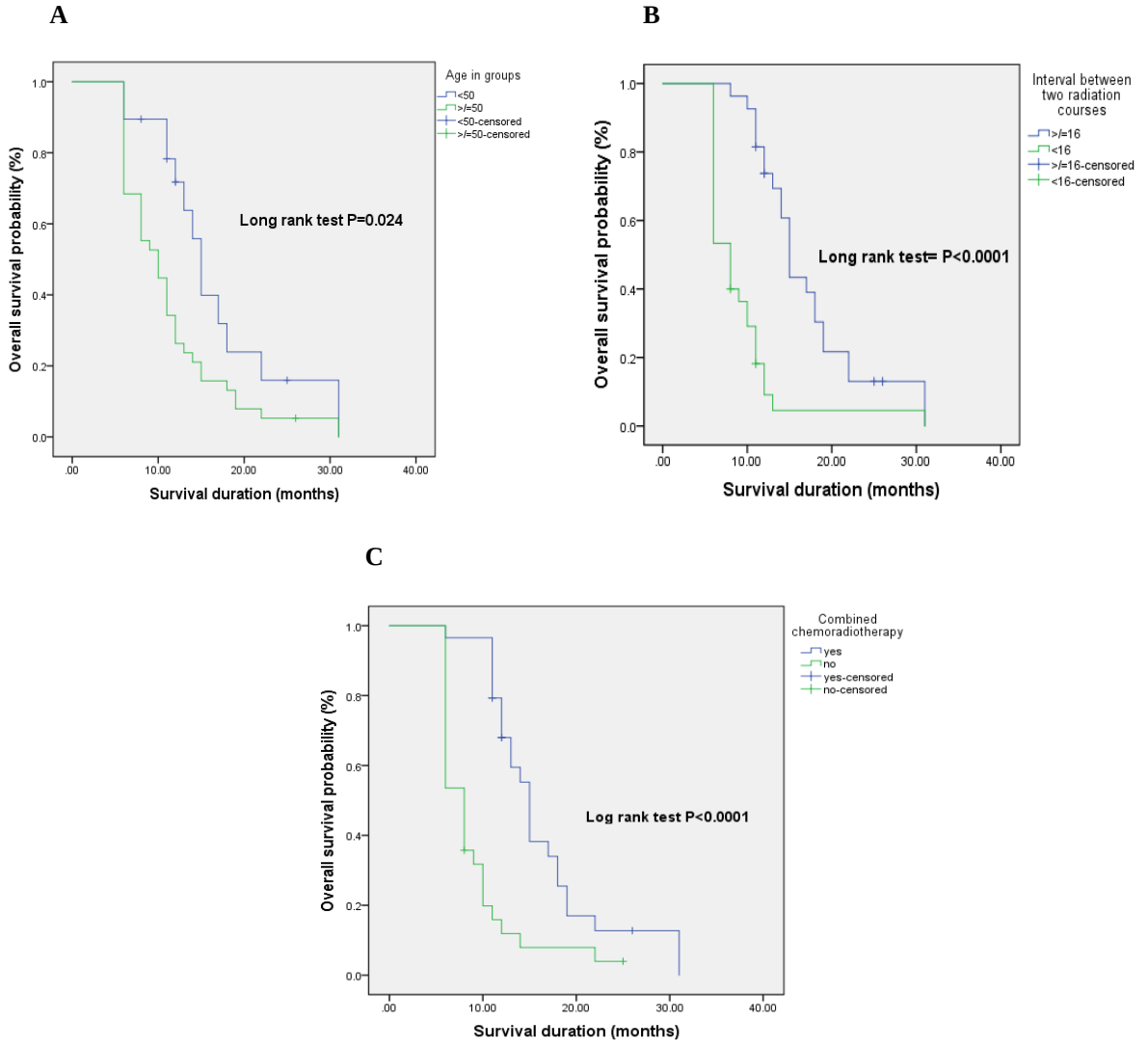

Figure 2: Overall survival after reirradiation by, Age group (A), interval between primary radiotherapy and reirradiation ≥16 months (B), use of combined chemoradiotherapy treatment (C)

Table 1: Characteristics of patients received re-irradiation for recurrent GBM

Variables	Patients (%)
Gender	
Male	41 (71.9)
Female	16 (28.1)
Age	
Median (range)	54 (25-67)
ECOG PS	
0	5 (8.8)
1	20 (35.1)
2	24 (42.1)
3	8 (14.0)
Site of recurrence	
Frontal	24 (42.1)
Parietal	12 (21.1)
Temporal	20 (35.1)
Occipital	1 (1.8)
Type of recurrence	
In-field	41 (71.9)
Marginal	12 (21.1)
Out-field	4 (7.0)
Interval between primary and re-RT (months)	
Median (range)	16 (6 -63)
Number of recurrences before re-RT	
1	33 (57.9)
2	24 (42.1)
Salvage chemotherapy before re-RT	
TMZ	17 (29.8)
Etoposide	7 (12.3)
Initial radiotherapy dose	
60 Gy/30#	46 (80.7)
40 Gy/15#	11 (19.3)
Chemotherapy with re-RT	
None	29 (50.9)
Concomitant +/- adjuvant TMZ	28 (49.1)
Re-RT dose	
35 Gy/10	15 (26.3)
36 Gy/18	34 (59.6)
25 Gy/5	8 (14.0)
Re-RT tumor volume in (cm^3)	
Range	10 – 170
Median	67
Re-RT PTV in (cm^3)	
Range	28 - 581
Median	287
Re-RT dose (Gy)*	
Range	(31.3- 39.4)
Median	36
Cumulative dose (Gy)*	
Range	(91.3 – 99.4)
Median	96
Cumulative BED (Gy)*	
Range	(109.5 – 119.3)
Median	115.5

GBM, Glioblastoma multiforme. ECOG, Eastern Cooperative Oncology Group - performance status. Re-RT, Re-irradiation. TMZ, Temozolomide. PCV, procarbazine, lomustine, vincristine. PTV, Planning target volume. *The equivalent dose in 2 Gy fractions (EQD2) was calculated using an α/β of 10. BED, biologically effective dose.

Table 2: Predictors of overall survival after reirradiation by univariate and multivariate analyses using COX regression

		Univariate analysis*			Multivariate analysis*		
Variables	Number	**HR**	***P*- value**	**95% CI**	**HR**	***P*- value**	**95% CI**
Age (years)							
< 50	19	ref			ref		
≥ 50	38	2.083	**0.024***	1.103 – 3.935	2.548	**0.022***	1.143 – 5.676
Gender					Not included in the model		
Male	41	ref					
Female	16	1.313	0.391	0.704 – 2.449			
ECOG PS					Not included in the model		
0	5	ref					
1	20	1.614	0.394	0.536 – 4.860			
2	24	2.297	0.140	0.761 – 6.937			
3	8	1.599	0.464	0.455 – 9.623			
Tumor location					Not included in the model		
Frontal	24	ref					
Parietal	12	0.773	0.523	0.351 – 1.704			
Temporal	20	0.681	0.243	0.358 – 1.298			
Occipital	1	1.795	0.572	0.236 – 13.657			
Interval between primary and re-RT							
≥ 16	27	ref			Ref		
< 16	30	3.790	**< 0.0001***	2.036 – 7.053	3.829	**0.002***	1.647 – 8.901
The size of GTV (cm^3)					Not included in the model		
<67	35	ref					
≥67	22	1.403	0.270	0.767 – 2.560			
The size of PTV (cm^3)					Not included in the model		
<287	35	ref					
≥287	22	1.403	0.270	0.767 – 2.560			
Combined CRTH							
Yes	29	ref			ref		
No	28	3.254	**<0.0001**	1.783 – 5.939	3.352	**0.017**	1.239 – 9.068
Re-RT schedule					Not included in the model		
Conventional	34	ref					
Hypofractionated	23	1.494	0.169	0.844 – 2.647			
Recurrence type					Not included in the model		
In-field	41	ref					
Marginal	12	0.902	0.784	0.433 – 1.882			
Out-field	4	0.592	0.337	0.203 – 1.724			
Re-RT dose (EDQ2)					Not included in the model		
≥36 Gy	38						
<36 Gy	19	0.737	0.322	0.403 – 1.348			
Cumulative dose (EDQ2)					Not included in the model		
≥96 Gy	39	ref					
<96 Gy	18	1.052	0.868	0.580 – 1.907			

***** Cox regression model with significant *P* value of <0.05. CI, confidence interval. HR, hazards ratio. ECOG-PS, Eastern Cooperative Oncology Group - performance status. GTV, Growth tumor volume. PTV, Planning tumor volume. CRTH, Chemoradiotherapy. Re-RT, reirradiation. EDQ2, equivalent dose in 2 Gy fractions (EQD2) was calculated using an α/β of 10.

Table 3. Overall acute toxicity profile of 57 GBM patients treated with re-irradiation

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4	Total (no=57)
	No	No	No	No	No (%)
Hematologic					
Anemia	3	1	0	0	4 (7.0)
Neutropenia	6	4	1	0	11 (19.3)
Leukopenia	6	3	1	0	10 (17.5)
Thrombocytopenia	2	5	1	0	8 (14.0)
Non-hematologic					
Alopecia	8	0	0	0	8 (14.0)
Anorexia	3	4	2	0	9 (15.8)
Nausea	6	5	2	0	13 (22.8)
Vomiting	9	8	1	0	18 (31.6)
Fatigue	8	9	2	1	20 (35.1)
Headache	4	6	0	0	10 (17.5)
Weakness	1	1	1	0	3 (5.3)
Dermatitis	3	2	0	0	5 (8.8)

Discussion:

This retrospective study reports the results of 57 GBM patients treated primarily with conventional chemo-radiation therapy and who underwent re-irradiation for their tumor recurrence. The principal focus of our analysis is to evaluate the outcome and safety of re-irradiation at tumor progression.

Most studies [12-20] reported a median OS of 7 to 12 months which concurred with the results of our study (median OS of 11 months).

An appropriate patient's selection is essential to choose re-RT as a treatment option, and to avoid treatment where the benefit could be limited. We identified age ≥ 50 years, the time interval between the first to the second irradiation of < 16 months, and re-irradiation without systemic treatment, as prognostic factors which were negatively impacted on survival.

Our findings regarding the negative correlation between gender and survival on multivariate analysis were in line with most published studies [21-23]. However, a study reported by Scholtyssek et al [24], revealed a positive impact of female gender on OS by multivariate analysis.

In our study, young age positively influenced OS and this finding is in agreement with the literature [18,19,22,25,27]. Nevertheless, some authors did not find the positive prognostic value of young age [27,28].

With regard to the time interval between the first to the second irradiation, we found a statistically significant correlation between longer interval (≥ 16 months) and survival after re-RT. Similar observations were reported in two studies on both univariate and multivariate analysis [27,29]. Contrary to our findings, six studies reported negative prognostic value of the time interval between initial radiotherapy and re-RT [14,16,19,22,28,30].

Several trials found that the type of local recurrence in relation to the radiation fields ("in field", "marginal" or "out-field" recurrence) was associated with poor prognosis [3, 31-35]. The median survival was 17.3, 14.8 and 26.1 months in patients with recurrence inside, at the margin and outside the irradiation field respectively [33]. However, in our cohort, we did not find statistical significance on survival between patients with regional, marginal and distant recurrences. Similar findings were reported by Ciammella et al [36].

In our cohort, the size of the target volumes was not associated with survival differences. Similarly, we identified four studies that confirmed the lack of association between the size of the target volumes and survival [26,27,37,38]. Meanwhile, one study reported a significant positive correlation between smaller gross/planned target volumes and survival on multivariate analysis [18].

In our cohort concomitant +/- adjuvant TMZ was associated with longer OS in univariate and multivariate analysis. This is consistent with the findings of Grosu et al [27], in which 29 patients (66%) had received one to two cycles TMZ before and four to five cycles after reirradiation. The author concluded that TMZ was associated with better survival in the univariate and multivariate analysis. Fogh et al [18], re-irradiated 147 recurrent high-grade gliomas, of which 48 patients received different regimes of concomitant chemotherapy. In contrast to our finding, Fogh et al [18], found no significant benefit of chemotherapy in this population when analysis was controlled for other prognostic factors.

The recommended dose-fractionation schedule for re-RT has not yet been well established. Although conventionally fractionated RT has been commonly used, hypofractionated RT (HFRT) has been also used to reduce overall treatment time and enhance the tumoricidal effects, with encouraging results. Fogh, et al [18], demonstrated that 35 Gy in 10 fractions was well tolerated and resulted in a median survival time of 11 months. In our study, no statistically significant difference was seen in survival of patients treated by HFRT or conventionally fractionated schedule. Our results are similar to what was published by Kataria et

al [39], for 25 patients with recurrent glioma. Kataria et al [39], in their study had suggested that no statistically significant difference was seen in survival of patients treated by HFRT or conventionally fractionated stereotactic radiotherapy (CFSRT). In contrast, Dong et al [40], reported that fractionated radiotherapy should be prescribed to large sized tumor and tumor located near to critical structure while SRS should be considered for small sized and unifocal tumor.

The optimal dose of re-RT has yet to be established. Our study did not demonstrate a significant difference in survival when doses of at least 36 Gy were delivered. Similarly, Other studies have

not shown a relationship between dose and OS [41,42]. In contrast, Rades et al., reported significant difference in survival when doses of 30 Gy were delivered and a trend toward improved survival by multivariate analysis.

The majority of glioma recur within 2 cm of the original tumor. Therefore, radiation toxicity is a concern due to irradiation of normal brain tissue that was previously irradiated. Acute grade 3 or more toxicity in our cohorts occurred in 7 patients (12.3%). Similar observations were reported in a study conducted by Kataria et al [39], for 25 patients with recurrent glioma in which patients were treated by RT (+/−TMZ). Re-RT showed acute toxicity of grade ≥ 3 in 3 out of 25 patients (two had neurological toxicity and one had headache). While HFRT to doses of 35 Gy in 3.5-Gy fractions associated with low risk of radionecrosis, doses greater than 40 Gy and/or 5 to 6 Gy per fraction are associated with an increased risk of radionecrosis [12,13,18,43]. Similarly, we found radionecrosis in two patients who received HFRT (5 Gy per fraction).

Our study has some limitations including, the retrospective nature, the small sample size of patients, the lack of assessment of methylation status of MGMT gene and IDH1/2 mutation status as it is not covered by public health centers, and finally, patients were treated by different RT schedules.

Conclusion:

Our study demonstrated the safety and feasibility of re-RT. Younger age, longer time between primary RT and re-RT, and the combined chemoradiotherapy treatment at recurrence were predictive for improved survival after salvage treatment. However, larger randomized studies are required to shed more light on this issue and to establish the optimal management strategy for recurrent GBM.

List of abbreviations:

HGG High grade glioma
TMZ Temozolomide
Re-RT Reirradiation
RT Radiotherapy
ECOG PS Eastern Cooperation Oncology Group Performance status
MRI Magnetic resonance imaging
MRSI Magnetic resonance spectroscopy imaging
RANO Response Assessment in Neuro-Oncology
MGMT O6 -methylguanin-DNA methyltransferase
IDH ½ Isocitrate dehydrogenase
GTV Gross tumor volume
CTV Clinical target volume
PTV Planning target volume
QUANTEC Quantitative Analyses of Normal Tissue Effects in the Clinic
EQD2 Equivalent dose in 2-Gy fractions
OS Overall survival
PFS Progression free survival
CTCAE Common Terminology Criteria for Adverse Events
SPSS Statistical Package for Social Sciences software
HFRT Hypofractionated RT
CFSRT Conventionally fractionated stereotactic radiotherapy

Conflict of interest

The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Author Contributions

Conceptualization: A.A. Data curation: A.A., A.F. Formal analysis: A.A., A.F. Methodology: A.A., A.F., N.A., B.F. Resources: A.A., A.F., N.A., B.F. Writing—original draft: A.A., A.F., N.A., B.F. Writing—review & editing: A.A., A.F., N.A., B.F. Approval of final manuscript: A.A., A.F., N.A., B.F

Conflicts of Interest:

The authors declare that they have no potential conflicts of interest.

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