Original Research Article

Brain re-irradiation for recurrent glioblastoma …. Is it justified?

Abstract

Background: Glioblastoma Multiforme is a grade 4 tumor with high recurrence rates despite of maximum treatment including surgical resection, concurrent chemoradiotherapy and adjuvant chemotherapy. In recurrent tumors, there is no standard treatment available.

Patients and methods: this is a retrospective analysis of patients with recurrent GBM who presented to our department in the period between Jan 2017 to Dec 2018 and received reirradiation at the time of tumor recurrence.Data were collected from patient medical records to assess DFS, OAS and toxicity.

Results: Totally, 33 patients were enrolled. All re-irradiated casees received a total dose of (30 Gy in 15 fractions). The overall survival and progression free survival were significantly better in younger patients with good performance status and small recurrence. Only 2 cases (6.1%) developed radiation necrosis.

Conclusion: brain re-irradiation is a feasible and safe treatment option in patients with recurrent GBM.

Keywords: brain tumor, GBM, recurrence, and re-irradiation.

Introduction

The most common primary CNS tumor in adults is high-grade glioma (HGG, WHO grade III-IV), which is more than 60% of all brain tumors [1]. Nevertheless, the majorityof patients with HGG have bad prognosis after initial treatmentand relapses.Patients with glioblastoma (GBM)Tumor control and survival improved in the last years with radiotherapy (RT) plus concomitant and adjuvant temozolomide (TMZ).

In therecent (EORTC/NCIC) randomized trial, the reported median and 2-year survivals were 14.6 monthsand 27%, respectively; but, the most of tumors recurred locally within a few months [2].Most data suggest that in certain cases re-treatment will improve survival time andstabilization of neurologic deterioration [3,4]. Now, multiple lines are available for the salvagetreatment of recurrent HGG after initial RT, including re-irradiation, surgical re-resection, orsystemic agent(s) administration with chemotherapy which are the most common treatment line, but till now no standard line of treatment.

Due to the risk of toxicity, re-irradiation is generally discussed controversially, but it has benefit after local relapse. Safe and effectivere-irradiation of brain malignancies is challenging. Multiple methods have been undertaken toimprove the therapeutic ratio including {external beam (2DRT) or(3DRT) +/- combined hypoxic cell radiosensitizers, intensity-modulated radiation therapy (IMRT),brachytherapy (BT), fractionated stereotactic radiation therapy (FSRT) andstereotactic radiosurgery (SRS)}. The treatment related toxicity and quality of life still the critical points whenconsidering the therapeutic options asprognosis still bad [5].

Aim of the work: The 1ry end point of this study is the assess PFS and OAS since development of recurrence for this cases with recurrent GBM who received re-irradiation. The 2ry endpoint is assessment of possible toxicities.

Patients and method:

This study is a retrospective one arranged to evaluate the potential of 3DCRT for re-irradiation of cases of recurrent GBM who presented to MansouraUniversity Hospital in the period between Jan 2017 to Dec 2018. All patients had previously undergone a full course of external beam radiotherapy (RT) to a dose of 6000 cGy concurrent with temozolamide followed by adjuvant course of temozolamide for 6 months. Patients who developed recurrence after at least 6 months of ending treatment, age ranged between 40 and 65 years, ECOG performance status 0 to 3 were included in our study. RT was delivered with complex plans designed using fully integrated computed tomography/magnetic resonance imaging (CT/ MRI) tumor volume information, and regions of previous parenchymal treatment were avoided if possible. Composite (initial+ re-treatment) dose-volume histograms (DVH) of dose to non-target brain allowed comparison of alternative plans to select beam orientations which minimized normal brain irradiation. Dose of re-irradiation was 3,000 cGy with normal fractionation.

Statistical analysis

The Statistical Package of Social Science (SPSS) program for Windows (Standard version 24) used to analyze the data. The one-sample Kolmogorov-Smirnov was first testednormality of data

Continuous variables were presented as mean ± SD (standard deviation)whilequalitative data were described using number and percent

For survival analysiswe used Kaplan- Meier test and Log-Rank test used to assessstatistical significance of differences among curves

Level of significance:

The threshold of significance is fixed at 5% level (p-value)for all above statistical tests done.

The results were considered:

- Significant when the probability of error is less than 5% ($p \leq 0.05$).
- Non-significant when the probability of error is more than 5% ($p > 0.05$).

The more significant are the results, the smaller the p-value obtained.

Ethical considerations:

- This study protocol will be submitted for approval by (Medical Research Ethics Committee, Faculty of Medicine, Mansoura University).
- This retrospective study will not need informed consent.

Results:

This study is a retrospective one arranged to evaluate the effect of re- irradiation for cases of recurrent GBM. Thirty-three cases were presented to our department from Jan 2017 to Dec 2018. All cases received previous treatment in the form of radical radiotherapy 60 Gy concurrent with chemotherapy temozolamide followed by 6 cycles of temozolamide. All cases develop recurrence after a period of at least 6 months.

As regards patient's characteristics, the mean age was 53.94 (41-63), 18 male and 15 female, most of cases was ECOG score 2 (18 case, 54.5%) followed by ECOG 1(7 cases, 21.2%), ECOG 3 (6 cases 18.2%), ECOG 0 (2 cases, 6.1%). The duration between end of 1ry treatment and development of recurrence was 12.45 months ±2.65. Regarding the size of the recurrence 14 cases (42.4%) had a tumor size less than 3 cm and 19 cases (57.6%) more than 3 cm. 15 cases (45.5%) had peripheral site and 18 cases (54.5%) had central location. Only 5 cases (15.2%) could have surgery before re-irradiation and 27 patients (81.8%) could be re challenged with temozolamide concurrent with radiotherapy. All cases received re-irradiation dose 30 Gy to the growth volume of the disease.

As regards toxicity, only 2 cases (6.1%) developed radiation necrosis with deterioration of neurological symptoms after the course of radiotherapy. Otherwise the course of re-irradiation was tolerable with unremarkable toxicity.

After a period of FU ranged from 9 to 18 months, the PFS was 9.03 months ±2.25 and OAS since the diagnosis of recurrence was 13.48 months ±2.38, as shown in table 1.

Table (1): Patients characteristics:

Patients characteristics	Study group (n=33)
Age/years	
Mean ± SD	53.94±6.57
Min-Max	41-63
sex	
Male	18 (54.5%)
Female	15 (45.5%)
Performance status	
0	2 (6.1%)
1	7 (21.2%)
2	18 (54.5%)
3	6 (18.2%)
Size	
<3	14 (42.4%)
>3	19 (57.6%)
Site	
P	15 (45.5%)
C	18 (54.5%)
Underwent surgery	
Yes	5 (15.2%)
No	28 (84.8%)
Received chemotherapy with radiotherapy	
Yes	27 (81.8%)
No	6 (18.2%)

Radio necrosis	
Yes	2 (6.1%)
No	31 (93.9%)
Duration between end of 1ry ttt and development of recurrence	12.45±2.65
Progression free survival	9.03±2.25
Overall survival / month	13.48±2.38

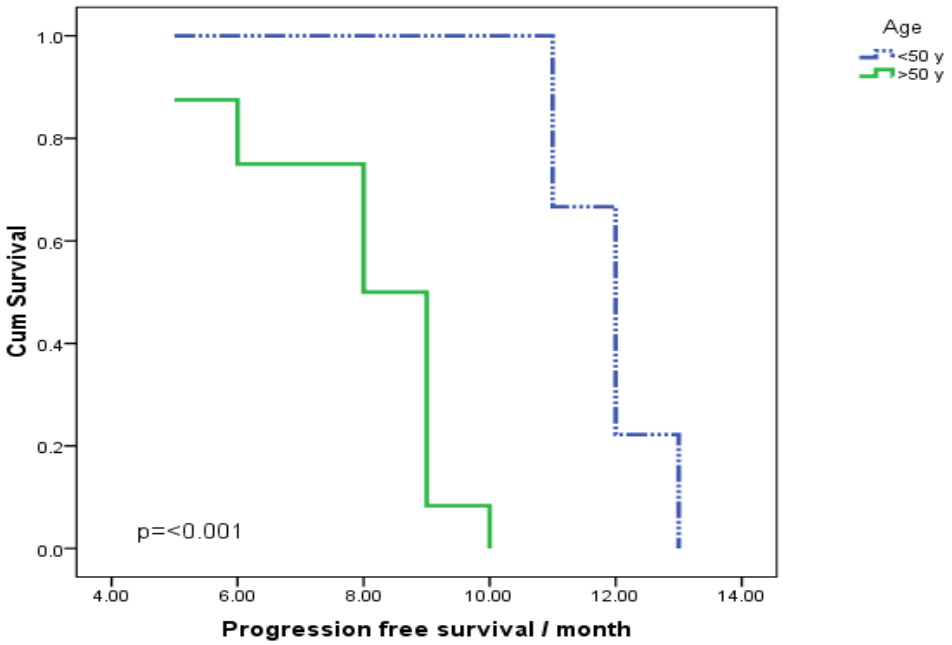
Table 2; show the correlation between different patient's characteristic from one side and PFS and OAS from other side. There was significant difference with higher PFS and OAS in patients aged less than 50 years (PFS 11.88 and OAS 16.44) compared to patients aged more than 50 years (PFS 7.95 and OAS 12.37). Also performance status was found to be strong prognostic factor with significant better survival in ECOG 0 (PFS 13 and OAS 17) and 1 (PFS 11.57 and OAS 16.28) cases compared to score 2 (PFS 8.78 and OAS 13.05) and 3 (PFS 5.50 and OAS 10.33) cases. The site and size of recurrent disease also affect the clinical outcome with significant better survival for tumors less than 3 cm (PFS 10.47 and OAS 15.05) compared to tumors more than 3 cm (PFS 7.07 and OAS 11.36) and for peripheral tumors (PFS 10.80 and OAS 14.4) compared to central lesions (PFS 7.55 and OAS 11.8). Patients who could have surgery before re-irradiation had significant better survival (PFS 12.2 and OAS 16.40) compared to patients who cannot tolerate surgery (PFS 8.4 and OAS 12.96). Also patients who could tolerate chemotherapy with re-irradiation had significant better survival (PFS 9.81 and OAS 14.185) compared to patients who cannot tolerate chemotherapy (PFS 5.50 and OAS 10.333).

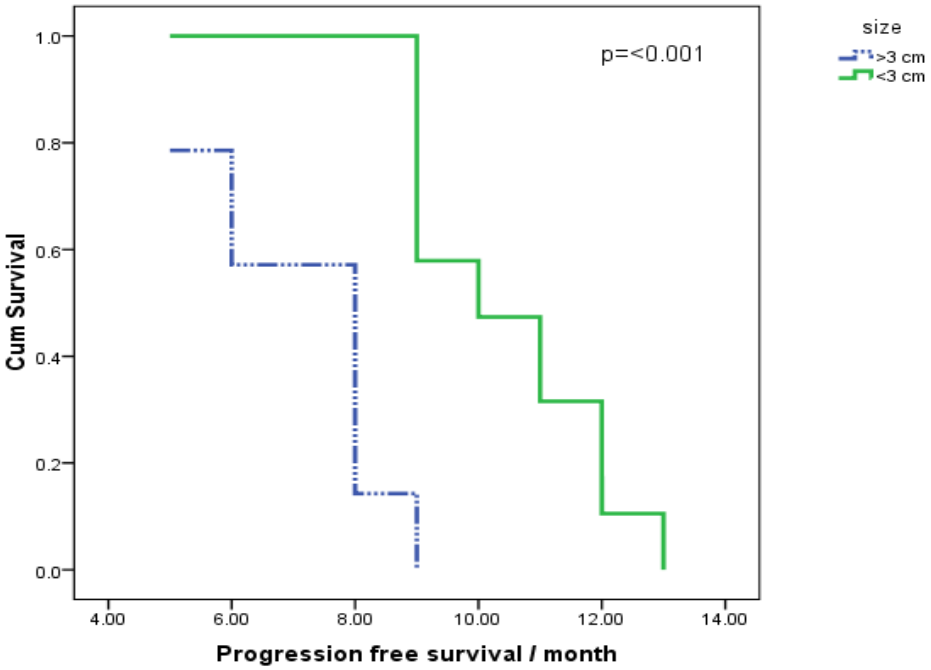
Table (2): correlation between different patient's characteristic and PFS and OAS

Patients characteristics	Progression free survival/month				Overall **survival**/ month			
	Mean	**Std.**	**95% CI**	**P -**	**Mean**	**Std.**	**95% CI**	**P – value**

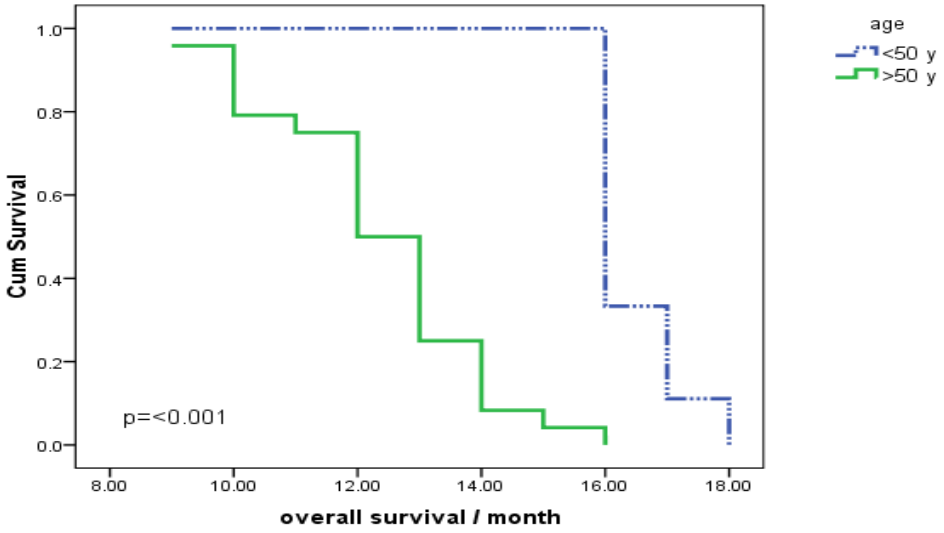
	Survival time	Error		value	Survival time	Error		
Age/years								
<50 y	11.88	0.26	11.4-12.4	<0.001*	16.44	0.24	15.9-16.9	<0.001*
>50 y	7.95	0.32	7.3-8.6		12.37	0.35	11.7-13.1	
Gender								
Male	9.66	0.45	8.77-10.8	0.113	14.00	0.51	13.01-14.9	0.296
Female	8.26	0.62	7.03-9.5		12.86	0.67	11.56-14.2	
Performance status								
0	13.00	0.0	13.0-13		17.00	1.00	15.04-18.9	
1	11.57	0.20	11.2-11.9	<0.001*	16.28	0.18	15.92-16.6	<0.001*
2	8.78	0.15	8.5-9.1		13.05	0.31	12.43-13.7	
3	5.50	0.22	5.06-5.9		10.33	0.42	9.51-11.2	
Size								
>3	7.07	0.39	6.3-7.8	<0.001*	11.36	0.37	10.6-12.1	<0.001*
<3	10.47	0.34	9.8-11.1		15.05	0.37	14.3-15.8	
Site								
P	10.80	0.39	10.03-11.5	<0.001*	15.4	0.40	14.7-16.3	<0.001*
C	7.55	0.38	6.80-8.3		11.8	0.36	11.1-12.5	
Underwent surgery								
Yes	12.2	0.37	11.4-12.9	0.001*	16.40	0.40	15.6-17.2	0.007*
No	8.4	0.36	7.74-9.1		12.96	0.41	12.1-13.8	
Received chemotherapy with radiotherapy				<0.001*				<0.001*
Yes	9.81	0.32	9.2-10.4		14.185	0.38	13.4-14.9	
No	5.50	0.22	5.1-5.9		10.333	0.42	9.50-11.2	
Radio necrosis								
Yes	5.00	0.0	5.0-5.0	<0.001*	10.0	0.0	10.0-10.0	0.001*
No	9.29	0.37	8.5-10.1		13.7	0.41	12.9-14.5	

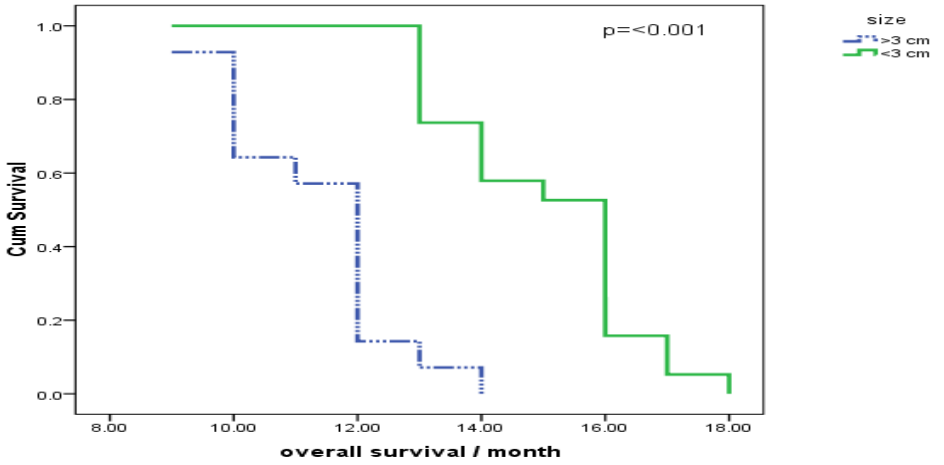
Progression free survival/month	9.03	0.39	8.26-9.8	-	13.48	0.41	12.7-14.3	-





- **Kaplan-Meier progression free survival/month**





- **Kaplan-Meier overall survival/month**

Discussion:

For locally recurrent GBM,re-RT was used as salvage treatment. Re-RT is used for specific cases in a uncontrolled andnonrandomized manner, using a {fractionated stereotactic radiotherapy (FSRT), single-fraction stereotactic radiosurgery (SRS), intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) technique orthree-dimensional conformal RT (3D-CRT)}. Results have been documented from retrospective analysis.Re-RT role for progressed GBM can be reflected in an analysis of cases enrolled in the (RTOG 0525) trial [6].

In our study as regarding patient's characteristic, there was statistically significant difference with higher PFS and OAS in patients aged less than 50 years compared to older cases also performance status, site and size of the lesion which was similar to a four-categorical Combs' Prognostic Score index (excellent, good, moderate, poor) was firstly generated at Heidelberg in 2013 to distinguish survival after re-RT.

As regarding our results show a significant better survival (p value<0.001) which was similar to The (DIRECTOR) trial of TMZ reused in cases with recurrent GBM whichdescribed a median time to treatment failure of 3.2 vs 1.8 ms and PFS at 6 ms of 39.7% vs 6.9% in patients with and without MGMT promoter methylation, respectively. So, restarting of TMZ could be an option for cases with MGMT promoter-methylation [8].

Although the multiple clinical trials for treatment of recurrent GBM, there are no established standards of care beyond alkylating agent (nitrosourea or TMZ) or BV [9].

In our study the Progression free survival was 9.03±2.25months and Overall survival was 13.48±2.38 months which mostly similar to important radiation results of fractionated re-RT from 10 independent studies published in last 2 decades (1999-2018) [10]. Re-RT was delivered at a median time interval of 11.6 ms (3.5-19 ms) with dose of (24 to 36 Gy) with a daily fractional size of (1.8 - 6 Gy). The median PFS and OS from re-RT were 5.4 ms (4.6- 7.9 ms) and 9.7 months (7.5- 11 ms), respectively.

Studies of re-RT show varying toxicity results with differentcases characteristics and RT techniques, asRT dose, dose/ fractionation, volume of RT, and CCRT. (Shepherd, et al.) [11] found that re-RT doses over 40 Gy for cases who received a median dose of 55 Gy (45–60 Gy) as part of previous RT was a major factor of radiation damage and observed late radiation-related

damage in 13 patients (36%). But (Gutin, et al.) [12] reported no clinical or radiographic radiation necrosis in 25 patients with recurrent glioma who received 30 Gy of hypofractionated re-RT to a recurrent tumor leessthan 3.5 cm, and (Fogh, et al.)[13] reported that only a single patient (0.6%) of 147 with recurrent malignant glioma who received a median 60 Gyas initial RT and a mediandose of 35 Gy re-RT for a recurrent cases with median volume 22 mL, detected late G3 severe headaches. These reports suggested that, with small volumes of irradiation,the RT with more conformalitycan be more tolerable at higher radiation doses than larger volumes which was similar to our result as regards toxicity, only 2 cases (6.1%) developed radiation necrosis with deterioration of neurological symptoms after the course of radiotherapy. Otherwise the course of re-irradiation was tolerable with unremarkable toxicity.

The chemotherapy agents added has survival outcomes similar to re-irradiation alone, but with increased toxicity. (Minnitiet al,) [14] Detected that, 36 cases with recurrent GBM who received 37.5Gy of re-RT/15 fractions with concomitant TMZ, 3 (8%)developed neurological deficit from radiation necrosis but our results show that patients tolerated concurrent chemotherapy and also had significant better survival.

Conclusion:

Our results showed that re-RT of 30 Gy for selected recurrent GBM cases previously treated with 60 Gy feasible and had acceptable complications. Re-surgery before re-RTmay be considered as a salvage management for selected recurrent GBM cases that occurred over a longer period of time and good performance status. Development of new-concept risk groupor prognostic scoring is required to select the cases. Also we recommend use of predictive biomarkers such as (MGMT) promotor methylation to give better result of re-Op/RT, re-RT and re-RT in combination with TMZ/BV.

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