Original Research Article

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

Abstract

Background: Glioblastoma Multiforme (GBM) is a grade IV brain tumor with high recurrence rate despite of maximum treatment including surgical resection, concurrent chemo-radiotherapy 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 re-irradiation after tumor recurrence .Data were collected from patient medical records to assess DFS, OAS and toxicity.

Results: Totally, 33 patients were enrolled. All cases were re-irradiated to 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 tumor size. Only 2 cases (6.1%) developed deterioration of neurological symptoms.

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 central nervous system (CNS) tumors in adults is high-grade glioma (HGG, WHO grade III-IV), which is more than 60% of all brain tumors [1]. Nevertheless, the majority of patients with HGG have bad prognosis after initial treatment. However marked improvement in survival was addressed in the last years after administration of radiotherapy (RT) plus concomitant and adjuvant temozolomide (TMZ).

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

Due to the risk of toxicity, re-irradiation is generally discussed controversially; Radiotherapy may facilitate tumor cell-macrophage/microglial fusion-hybridization thus producing highly invasive metastatic cells. Also surgery and radiotherapy disrupt the tightly regulated glutamine-glutamate cycle in the neural parenchyma thus increasing the levels of glutamine and also glutamate, an excitotoxic amino acid that enhances GBM invasion as declared by Thomas et al [5] but many researchers found that re-irradiation has benefit after local relapse includes delay disease progression and improve survival outcome. So safe and effective re-irradiation of brain malignancies is still a challenge and need more justification. Multiple methods have been undertaken to improve the therapeutic ratio of re-irradiation including {external beam (2DRT) or (3D conformal RT) +/- combined hypoxic cell radiosensitizers, intensity-modulated radiation therapy (IMRT), brachytherapy, fractionated stereotactic radiation therapy (FSRT) and stereotactic radio-surgery (SRS)}. The treatment related toxicity and quality of life still the critical points when considering the therapeutic options as prognosis still not good [6].

Aim of the work: The 1ry end point of this study is to assess PFS and OAS since development of recurrence for these 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 3D conformal RT for re-irradiation of cases of recurrent GBM who presented to Mansoura University 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 60 Gy 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 30 Gy with normal fractionation, so a total dose of 90 Gy was given to the growth tumor volume. And according to Mayar et al 2007, a total dose less than 100 Gy is safe and less expected to cause Radiation-induced normal brain tissue necrosis [7]

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 tested normality of data.

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

For survival analysis, we used Kaplan- Meier test and Log-Rank test used to assess statistical 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.

Results:

This study is a retrospective one arranged to evaluate the effect of re- irradiation for 33 cases of recurrent GBM after radical radiotherapy 60 Gy concurrent with chemotherapy temozolamide.

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 (were fit for surgery with ECOG 0 or 1, and had relatively small and peripheral lesions which were accessible for surgeons) while the other 28 cases could not have surgery either due to unfitness with ECOG 2 or 3, or due to large central lesions which were not accessible for surgeons. 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 deterioration of neurological symptoms after the course of radiotherapy. This toxicity is mostly due to development of radiation necrosis after re-irradiation but it may be also due to tumor progression. Radiographic and clinical presentation of radiation necrosis is usually indistinguishable from those of progressive disease, causing a major dilemma. Establishing a reliable diagnosis based on clinical assessment and

conventional MRI is difficult, frequently necessitating a surgical tissue biopsy [8]. As regards our 2 cases, no surgical tissue biopsy was obtained, and MRI was not conclusive, so we consider their toxicities as treatment induced, depending upon clinical assessment after the end of re-irradiation course. Away from this point which needs more advanced research, re-irradiation was tolerable with unremarkable toxicity.

After a period of follow up 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%)

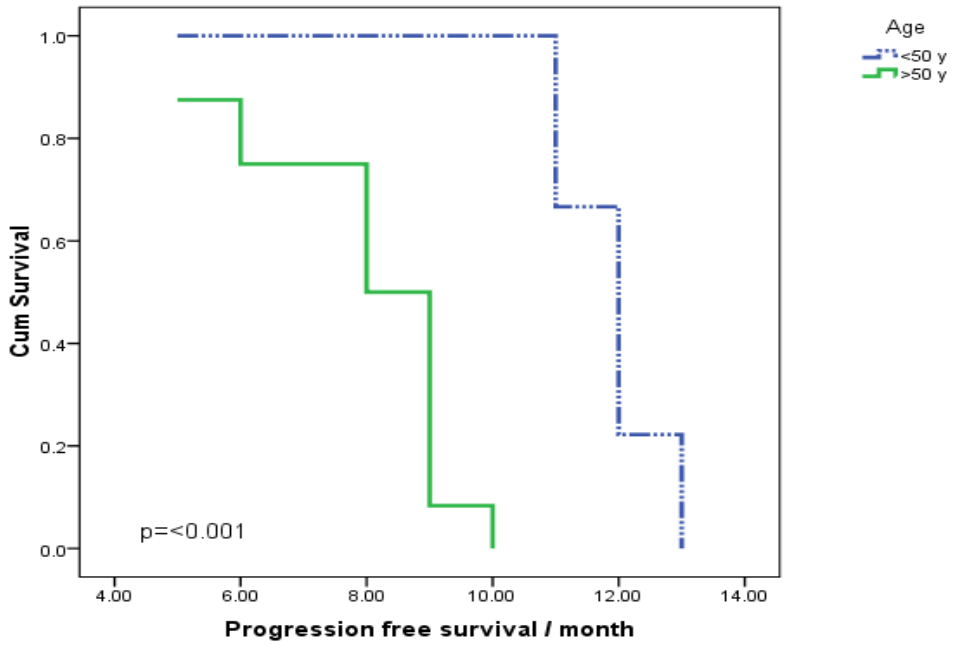
Underwent surgery	
Yes	5 (15.2%)
No	28 (84.8%)
Received chemotherapy with radiotherapy	
Yes	27 (81.8%)
No	6 (18.2%)
Radio necrosis	
Yes	2 (6.1%)
No	31 (93.9%)
Duration between end of 1ry ttt and development of recurrence	12.45±2.65
Progression free survival	9.03±2.25
Overall survival / month	13.48±2.38

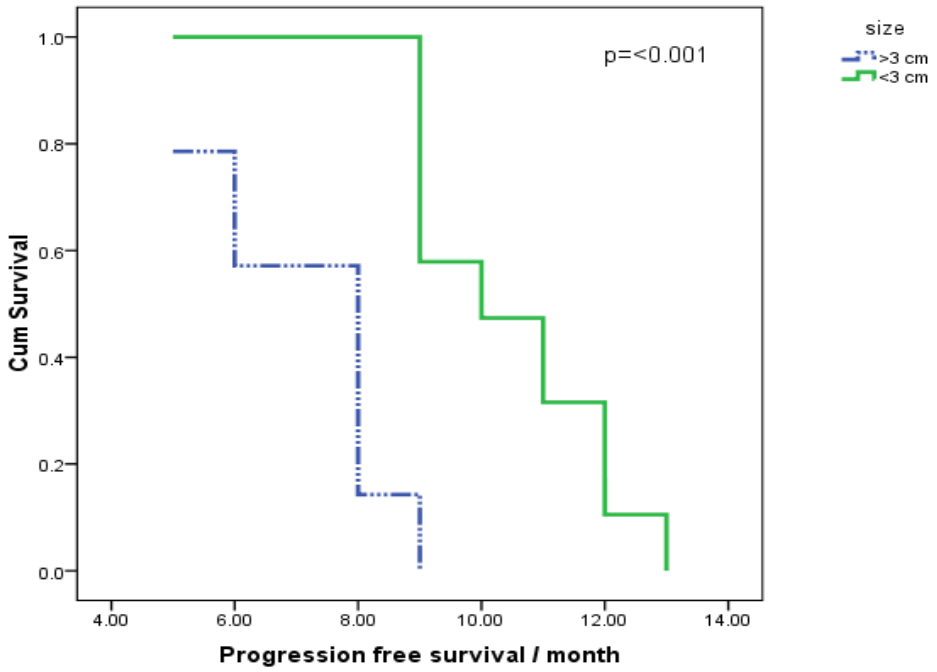
Table 2; show the correlation between different patient's characteristic from one side and PFS and OAS from other side. There was significant difference with higher PFS and OAS in patients aged less than 50 years (PFS 11.88 and OAS 16.44) compared to patients aged more than 50 years (PFS 7.95 and OAS 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

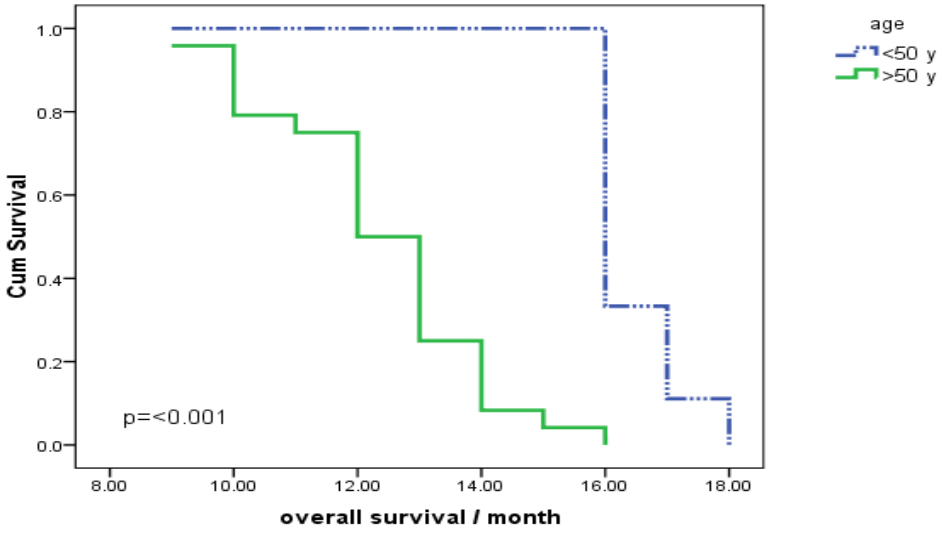
Patients characteristics	Progression free survival/month				Overall **survival**/ month			
	Mean Survival time	**Std. Error**	**95% CI**	**P - value**	**Mean Survival time**	**Std. Error**	**95% CI**	**P – value**
Age/years								
<50 y	11.88	0.26	11.4-12.4	<0.001*	16.44	0.24	15.9-16.9	<0.001*
>50 y	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*

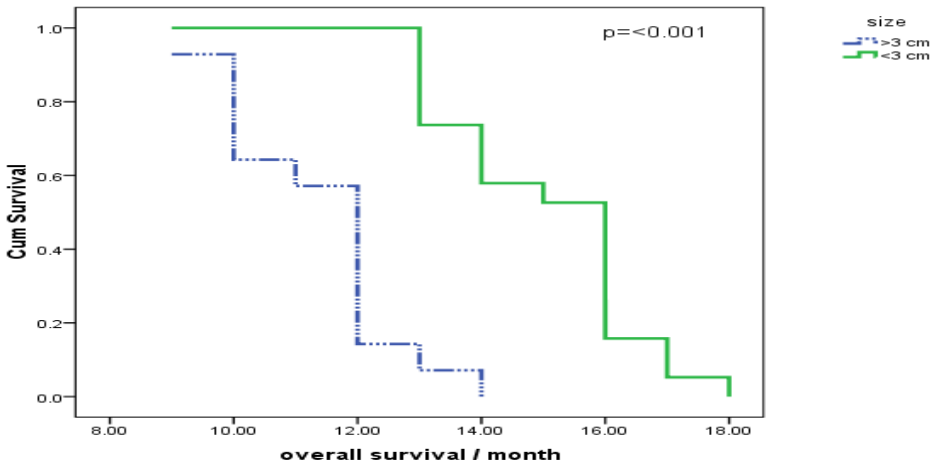
Yes No	9.81 5.50	0.32 0.22	9.2-10.4 5.1-5.9		14.185 10.333	0.38 0.42	13.4-14.9 9.50-11.2	
Radio necrosis Yes No	 5.00 9.29	 0.0 0.37	 5.0-5.0 8.5-10.1	 <0.001* 	 10.0 13.7	 0.0 0.41	 10.0-10.0 12.9-14.5	 0.001*
Progression free survival/month	9.03	0.39	8.26-9.8	-	13.48	0.41	12.7-14.3	-





- **Fig 1 : Kaplan-Meier progression free survival/month**





- **Fig 2 : Kaplan-Meier overall survival/month**

Discussion:

For recurrent GBM, re-irradiation was used as salvage treatment. Re-irradiation is used for specific cases, using a {fractionated stereotactic radiotherapy (FSRT), single-fraction stereotactic radio-surgery (SRS), intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) technique or three-dimensional conformal RT (3D-CRT)}. In our study, we assess the effect of re-irradiation with 3DCRT.

There was statistically significant difference with higher PFS and OAS in patients aged less than 50 years compared to older cases also survival was better in cases with good performance status, peripheral site and small size of the lesion. This results were similar to a four-categorical Combs' Prognostic Score index (excellent, good, moderate, poor) which was firstly generated at in 2013 to distinguish survival after re-irradiation [9].

In our study the Progression free survival was 9.03±2.25months and Overall survival was 13.48±2.38 months which were more or less similar to results of fractionated re-irradiation from 10 independent studies published in last 2 decades (1999-2018) [10]. Re-irradiation 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).

Studies of re-irradiation show varying toxicity results with different cases characteristics and RT techniques, as RT dose, dose/ fractionation, volume of RT, and CCRT. Shepherd, et al [11] Found that re-irradiation 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 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-irradiation to a recurrent tumor less than 3.5 cm, also Fogh, et al [13] Reported that of 147 with recurrent malignant glioma who received a median 60 Gy as initial RT and a median dose of 35 Gy re-irradiation for a recurrent cases with median volume 22 mL, only one patient (0.6%) developed late G3 severe headaches. These reports suggested that, with small volumes, small dose, re-irradiation with more conformal techniques is more tolerable which is similar to our results.

Some authors reported that chemotherapy added to re-irradiation has survival outcomes similar to re-irradiation alone, but with increased toxicity. Minniti et al [14] Detected more toxicity in the form of development of neurological deficit (8% of cases) when adding temozolamide to re-irradiation of 36 cases with recurrent GBM who received 37.5Gy over 15 fraction compared to cases received re-irradiation alone. But our results show that patients tolerated concurrent chemotherapy and also had significant better survival. This could be explained by the good performance status of most of our cases (about 82% ECOG 0-2) and so could tolerate combined treatment without marked compilications.

Conclusion:

Our results showed that re-irradiation with 30 Gy for selected recurrent GBM cases previously treated with 60 Gy is feasible and had acceptable complications. Development of new-concept risk group or prognostic scoring is required to select the cases with more predicted benefit from this protocol.

Ethical Approval

This study protocol was approved by (Medical Research Ethics Committee, Faculty of Medicine, Mansoura University).

Consent :

It was a retrospective study, so there was no need for informed consent from the cases.

Reference:

1. Wen, P.Y.; Kesari, S. Malignant gliomas in adults. N. Engl. J. Med. 2008, 359, 492-507.
2. Stupp, R.; Mason, W.P.; van den Bent, M.J.; Weller, M. Fisher, B.; Taphoorn, M. et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N. Engl. J. Med. 2005, 352, 987-996.
3. Nieder, C.; Adam, M.; Molls, M.; Grosu, A.L. Therapeutic options for recurrent high-grade glioma in adult patients: Recent advances. Crit. Rev. Oncol. Hematol. 2006, 60, 181-193.
4. Butowski, N.A.; Sneed, P.K.; Chang, S.M. Diagnosis and treatment of recurrent high-grade astrocytoma. J. Clin. Oncol. 2006, 24, 1273-1280.
5. Thomas N. Seyfried, Laura Shelton, Gabriel Arismendi-Morillo, Miriam Kalamian, Ahmed Elsakka, Joseph Maroon . Provocative question: should ketogenic metabolic therapy become the standard of care for glioblastoma?. Mukherjee Neurochemical Research volume 44, pages2392–2404(2019)
6. Patel, M.; Siddiqui, F.; Jin, J.Y.; Mikkelsen, T.; Rosenblum, M.; Movsas, B. et al. Salvage reirradiation for recurrent glioblastoma with radiosurgery: Radiographic response and improved survival. J. Neurooncol. 2009, 92, 185-191.
7. Mayer R, Sminia P. reirradiation tolerance of human brain.International Journal of Radiation Oncology, Biology, Physics, 26 Nov 2007, 70(5):1350-1360DOI: 10.1016/j.ijrobp.2007.08.015.
8. Sebastian F Winter, Franziska Loebel, Jay Loeffler, Tracy T Batchelor, Maria Martinez-Lage, Peter Vajkoczy. treatment induced brain tissue necrosis: a clinical challenge in neuro-oncology.Dietrich*Neuro-Oncology*, Volume 21, Issue 9, September 2019, Pages 1118–1130, https://doi.org/10.1093/neuonc/noz048

9. Combs SE, Edler L, Rausch R. Generation and validation of a prognostic score to predict outcome after re-irradiation of recurrent glioma. ActaOncol. 2013;52:147–52.

10. Seystahl K, Wick W, Weller M. Therapeutic options in recurrent glioblastoma: an update. Crit Rev OncolHematol. 2016;99:389–408.

11. Shepherd SF, Laing RW, Cosgrove VP, Warrington AP, Hines F, Ashley SE, et al. Hypofractionated stereotactic radiotherapy in the management of recurrent glioma. Int J RadiatOncolBiol Phys. 1997;37:393–398.

12. Gutin PH, Iwamoto FM, Beal K, Mohile NA, Karimi S, Hou BL, et al. Safety and efficacy of bevacizumab with hypofractionated stereotactic irradiation for recurrent malignant gliomas. Int J RadiatOncolBiol Phys. 2009;75:156–163.

13. Fogh SE, Andrews DW, Glass J, Curran W, Glass C, Champ C, et al. Hypofractionated stereotactic radiation therapy: an effective therapy for recurrent high-grade gliomas. J ClinOncol. 2010;28:3048–3053.

14. Minniti G, Armosini V, Salvati M, Lanzetta G, Caporello P, Mei M, et al. Fractionated stereotactic reirradiation and concurrent temozolomide in patients with recurrent glioblastoma. J Neurooncol. 2011;103:683–691.