Will Extended Adjuvant Temozolomide Treatment Confer a Survival Advantage As Compared to The Standard Six Cycles for Newly Diagnosed Glioblastoma Multiforme Patients?

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Abstract

Background: Although concurrent radio-chemotherapy and adjuvant temozolomide (TMZ) treatment for six cycles has been established as a standard of care for newly diagnosed glioblastoma multiforme (GBM) patients, the recommended duration of adjuvant TMZ remains a matter of debate.

Methods: We conducted this historical cohort study to evaluate the survival benefit and toxicity profile of administration of 12 cycles of adjuvant TMZ in patients with newly diagnosed histologically confirmed GBM and compared this data with that of patients who completed the standard 6 cycles without disease progression. After concurrent radio-chemotherapy, TMZ was administered for 6 cycles (group 1) and for 12 cycles (group 2). Univariate and multivariate analysis (using the Cox proportional hazards model) were performed to identify factors affecting progression free survival (PFS) and overall survival (OS).

Results: Between June 2016 and February 2018, 55 patients were eligible. Patients in Group 1 (n=29) had a median PFS of 15 months (95% CI: 10.215-19.785), while those in Group 2 (n=26) had a median PFS of 18 months (95% CI: 16.611-19.389). After a median follow up duration of 20 months (range: 12-41), the median OS was 18 months (95% CI: 13.420-22.580) in Group 1 and 22 months (95% CI: 18.777-25.223) in Group 2. There was no statistically significant correlation between the number of chemotherapy cycles and PFS ($P = 0.513$) or OS ($P = 0.867$). The extent of surgical resection was the only independent prognostic factor for both PFS ($P = 0.015$) and OS ($P = 0.028$) by multivariate analysis. Three grade ≥3 hematologic toxicity were encountered in three patients. One in the six-cycle group (neutropenia), and two in the 12-cycle group (one had neutropenia and the other one developed thrombocytopenia). No statistically significant difference in the toxicity profile between both groups.

Conclusions: Although extending adjuvant TMZ to 12 cycles was not associated with increased toxicities, it did not significantly improve PFS or OS. So we do not recommend any modifications in the six months protocol until further studies are performed. It should be weighed against the compromised quality of life and the cost to the health care system.

Background

Glioblastoma multiforme (GBM), is the most common primary central nervous system tumor in adults with an incidence of 3–4 cases per 100,000 persons each year [1]. The incidence increases with age, with the peak incidence being in the fifth or sixth decade [2]. The prognosis of GBM is generally poor despite advancements in radiation therapy over the years such as decrease in radiation volumes, inverse planning and dose modulation with intensity-modulated radiation therapy which allowed for more-precise targeting and sparing of critical and normal structures in the brain [3].

Currently the Stupp protocol [4] 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 (five days per month). 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. Aiming at improving the survival in patients with GBM, extending the duration of maintenance TMZ for patients without tumor progression after six cycles of adjuvant TMZ has been evaluated by several randomized trials but the results are conflicting [5–12].

In this historical cohort study, we compare between two treatment protocols (12 cycles versus 6 cycles of adjuvant TMZ) as regard to survival and toxicity profile in patients with newly diagnosed histologically confirmed GBM.

Methods

This historical cohort study was conducted from June, 2016 to February, 2018. Patients included in the study where newly diagnosed histologically confirmed glioblastoma multiforme, 18 years or older, performance status (PS) of ≥ 2 according to Eastern Cooperation Oncology Group (ECOG) [13], underwent neurosurgical resection of the tumor [Gross total resection (GTR), subtotal resection (STR) or biopsy], and had magnetic resonance imaging (MRI) and magnetic resonance spectroscopy imaging (MRSI) as a part of treatment follow up evaluation that were available for review by radiologist. Patients with history of previous malignancy, previous treatment with radiotherapy or chemotherapy, recurrent disease, metastatic disease, discontinuation of concurrent radio-chemotherapy for any cause, and tumor progression during first six cycles of adjuvant TMZ, were excluded from the study. Methylation status of O6-methylguanin-DNA methyltransferase (MGMT) and isocitrate dehydrogenase (IDH1/2) mutation status were not available in patients' files as they were not analyzed. This study was approved by the Committee of Medical Ethics of the Faculty of Medicine with IRB no: 17300481. However, the consent was waived.

Treatment Protocols

Surgery

Microsurgical GTR was done for patients with circumscribed GBM, solitary lesion or tumor located in non-eloquent regions. STR was the treatment of choice for multicentric GBM or glioma located in eloquent areas. Stereotactic biopsy was done for lesions located in the thalamic or basal ganglion.

Concurrent radio-chemotherapy

All eligible patients started concurrent radio-chemotherapy within four to six weeks of histologic diagnosis of glioblastoma. Patients who presented with seizures received antiepileptic treatment. Patients presented with neurological deficits, received corticosteroid therapy. Prophylactic antibiotic (400 mg sulfamethoxazole, 80 mg trimethoprim, three times per week) was prescribed to all patients during treatment course.

Radiotherapy

Target volume delineation

Gross tumor volume 1 (GTV1) included T2/ fluid attenuated inversion recovery (FLAIR) abnormality and surgical cavity if present.

GTV2 included T1 contrast enhanced abnormality and surgical cavity if present.

The clinical target volume 1 (CTV1) and CTV2 were generated by adding 2 cm margin to GTV1 and GTV2 respectively. Margin was reduced around natural barriers.

The planning target volume 1 (PTV1) and (PTV2) were generated by adding 5 mm margin around the CTV1 and CTV2 respectively.

Target dose and energy

Fractionated conformal therapy was delivered to,

PTV1: for a total dose of 46 Gy in 23 fractions/ 2 Gy per fraction/ once daily/ five days per week.

PTV2: for boost dose of 14 Gy in 7 fractions/ 2 Gy per fraction/ once daily/five days per week.

All patients were treated using megavoltage linear accelerator and photon energies of 6 MV or more.

Chemotherapy

TMZ (75 mg/m^2/day) was given concurrently with radiation therapy, started from the first day of radiotherapy until the end of radiation.

Adjuvant Chemotherapy

Four weeks after the end of radiotherapy, adjuvant TMZ therapy was stopped either after six cycles (Group 1) or after 12 cycles (Group 2) for patients with no clinical and radiological evidence of disease progression after cycle six of adjuvant course. Initially, patients received up to six cycles of adjuvant TMZ therapy according to Stupp protocol (Group 1). However, survival benefit of long term TMZ administration [5, 7, 8, 9], relative tolerability of TMZ and absence of effective second line therapies, were the important elements supporting physicians' decision to allow up to 12 cycles (Group 2) of therapy in patients with good PS (according to ECOG PS) [13] both after surgery and during follow up, manageable toxicity, stable or responsive disease according to Response Assessment in Neuro-Oncology (RANO) criteria [14]. The dose of adjuvant TMZ was 150 mg/m^2/day for five days in the first cycle and increased to 200 mg/m^2/day for five days in the subsequent cycles if no hematologic toxicity had occurred.

Follow up

Clinical and laboratory evaluations

During radiotherapy, patients were followed up weekly in the clinic, and one month after completion of radiotherapy. During adjuvant TMZ therapy, patients were evaluated before each cycle and every three months thereafter.

Patients' follow-up evaluations during treatment included, 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 [15]. Toxicities were monitored weekly during the concomitant course and once every cycle during the adjuvant course and every three months thereafter. During concurrent radio-chemotherapy, treatment was interrupted if neutrophil count was ≥ 0.5 - <1.5×10^9/L, platelet count was ≥ 10 - <100×10^9/L, or grade 2 non-hematologic toxicity (except for alopecia, nausea, vomiting) was observed. Treatment was stopped if neutrophil count was 0.5×10^9/L, platelet count was < 10×10^9/L, or ≥ grade 3 non-hematologic toxicity (except for alopecia, nausea, vomiting) was observed. During adjuvant treatment, TMZ dose was reduced from 200 to 150 mg/m^2 or from 150 to 100 mg/m^2 if neutrophil count was < 1×10^9/L, platelet count was < 50×10^9/L, or grade 3 non-hematologic toxicity (except for alopecia, nausea, vomiting) was observed. Treatment was discontinued if adverse events necessitate reduction of TMZ dose bellow 100 mg/m^2, patient refusal, and disease progression

MRI and magnetic resonance spectroscopy (MRS)

The extent of surgical resection was assessed by conventional MRI within 48 hours after surgical resection because increased enhancement in the wall of the surgical cavity commonly occurs after 72 hours which may be misinterpreted as residual disease. Conventional MRI included axial and sagittal pre-contrast and post-contrast T1-weighted spin echo, axial FLAIR and axial and coronal T2-weighted fast spin-echo images. Diffusion weighted imaging (DWI) helped to determine whether new enhancement developing in the subsequent weeks was a sequelae of ischemia or caused by tumor recurrence. The mean apparent diffusion coefficient (ADC) values were evaluated in areas with contrast enhancement on T1WI or in suspected non-enhancing areas to detect tumor recurrence.

Patients were evaluated for response using MRI and MRS, which were performed immediately before the first cycle, after every three cycles of adjuvant TMZ and every three months after termination of treatment using 1.5T scanner (Achieva, Philips Healthcare; Amsterdam, Netherlands) equipped with the standard head coil. A neuroradiologist with at least 12 years of experience, reviewed the pre-treatment and follow-up MRI scans (blinded to clinical and MRSI data) for all patients. Radiologic response assessment was defined according to response assessment in neuro-oncology RANO criteria [14]. Progression is verified by the presence of steady growth of the enhancing lesion. If progression has occurred, the date of progression was recorded as the date of original suspicion.

MRS was achieved using Point Resolved Spatial Selection (PRESS) at long echo time (TE) 135 msec.. The spectroscopic grid was extended and manually adjusted to include lesion, perilesional edema if present, and normal brain tissue. The mean Choline(Cho)/ N-acetyl aspartate (NAA) and Cho/ Creatine (Cr) ratio were calculated in regions of suspected tumor recurrence where the ADC values were also

measured. Cho/NAA ratio > 2 was considered tumor recurrence while lactate peak with a reduction of all other metabolites was considered treatment-induced necrosis.

Statistical analysis

Patient characteristics between groups were compared using chi square test for categorical variables and Mann-Whitney U test for continuous variables. OS was calculated from the date of surgical resection to the date of death from any cause or last follow up. Progression free survival (PFS) was calculated from the date of surgical resection to the date of progression or date of last follow up or death. Kaplan-Meier methods [16], were used to determine OS and PFS and comparison of survival between treatment groups was determined by log rank test. Univariate analyses was performed to identify the potential prognostic factors for OS and PFS. For multivariable analyses, the Cox proportional hazards model was used and adjusted for age, gender, performance status, tumor location, resection extent, corticosteroid use at initiation of concomitant course, antiepileptic medication use at initiation of concomitant course and number of adjuvant TMZ cycles.

Receiver Operating Characteristic (ROC) curve analysis was used to correlate the results of the spectroscopic metabolite ratios with the results of follow-up imaging. The area under the curve (AUC) was used to calculate the optimal cutoff values of the metabolite ratios for differentiating tumor recurrence from treatment induced changes. 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).

Study end point

Compare survival and toxicity profile of 12-cycle TMZ (Group 2) with the standard six cycle TMZ (Group 1) in postoperative patients with newly diagnosed GBM.

Results

Between June 2016 and February 2018, 121 patients were evaluated for inclusion in the study. Of 121 patients, 66 patients (54.5%) were excluded from the study due to the following reasons:

- Six patients (5.0%) discontinued concurrent radio-chemotherapy as they developed grade 4 neutropenia.

– 13 patients (10.7%) discontinued adjuvant TMZ because of grade 3 pancytopenia during the six-cycle course.

– 42 patients (34.7%) had tumor progression during the six-cycle course of maintenance TMZ therapy

- Five patients (4.1%) lost to follow-up after cycle six of maintenance TMZ.

Overall, a total of 55 patients were eligible for retrospective analysis of treatment outcome and toxicity;

Group 1: consisted of 29 patients (52.7%), received six cycles of maintenance TMZ therapy.

Group 2: consisted of 26 patients (47.3%), received up to 12 cycles of maintenance TMZ therapy.

Patient characteristics

Patient characteristics were matched between the two treatment groups and are summarized in Table 1. There were 41 males (74.5%) and 14 females (25.5%) with median age of 59 years (range: 25–68 years). According to ECOGPS [13], six patients (20.7%) had ECOG PS of 0 in the six-cycle group compared to seven patients (26.9%) in the 12-cycle group. The most frequently reported symptom at presentation was headache in 20 patients (36.4%).There was no statistically significant difference in the median duration of symptoms between the two treatment groups ($P = 0.076$). Early postoperative MRI demonstrated GTR in 38.2% of the patients (12 patients {41.4%} in Group 1 and 9 patients {34.6%} in Group 2). Both treatment groups had a median interval time of one and a half months between diagnosis and surgery.

All 55 patients completed concurrent radio-chemotherapy as planned. The median interval between surgery to the start of concomitant course was 41 days (range: 35–68) in Group 1 and 37 days (28–65) in Group 2. The median total dose of radiotherapy for the entire cohort was 60 Gy (range: 54–66 Gy). Thirty seven patients (67.3%) received corticosteroid at initiation of concomitant course (22 patients {75.9%} in Group 1, 15 patients {57.7%} in Group 2) at a dose of 4 mg, twice daily to alleviate symptoms of increased intracranial tension. Corticosteroid dose was gradually decreased to be stopped when symptoms subsided. Nineteen patients (34.5%) had significant edema during the entire course of treatment therefore, they remained steroid dependent. Of the 17 patients (30.9%) who received antiepileptic medications, eight patients (47.1%) continued their antiepileptic medications throughout the adjuvant treatment course. After four weeks, all patients received at least six cycles of adjuvant TMZ therapy with a median interval of 37 days (range 31–47).

Table 1
Baseline characteristics of 55 patients with GBM

Variables	Group 1 6 cycles 29 (100%)	Group 2 12 cycles 26 (100%)	Total 55 (100%)	*P*-value*
Age	58	60.5	59	0.648
Median	25–68	30–66	25–68	
Range				
Gender	22(75.9)	19(73.1)	41 (74.5)	0.813
Male	7(24.1)	7(26.9)		
Female			14 (25.5)	
ECOG PS	6(20.7)	7(26.9)	13(23.6)	0.855
0	15(51.7)	12(46.2)	27(49.1)	
1	8(27.6)	7(26.9%)	15(27.3)	
2				
Symptoms at presentation	13(44.8)	7(26.9)	20(36.4)	0.168
Headache	12(41.4)	7(26.9)	19(34.5)	0.260
Cognitive deficits	4(13.8)	9(34.6)	17(30.9)	0.070
Seizure	11(37.9)	6(23.1)	13(23.6)	0.234
Motor deficits				
Duration of symptoms	2.5	4.3	3.5	0.076
Median	2-19.5	3–18	2-19.5	
Range				
Tumor location	14(48.3)	8(30.8)	22(40.0)	0.243
Frontal	6(20.7)	10(38.5)	16(29.1)	
Temporal	8(27.6)	5(19.2)	13(23.6)	
Parietal	1(3.4)	3(11.5)	4(7.3)	
Occipital				

Variables	Group 1 6 cycles 29 (100%)	Group 2 12 cycles 26 (100%)	Total 55 (100%)	*P*-value*
Extent of surgical resection	12(41.4)	9(34.6)	21(38.2)	0.812
GTR	12(41.4)	13(50.0)	25(45.5)	
STR	5(17.2)	4(15.4)	9(16.4)	
Biopsy				
Corticosteroid use at initiation of concomitant course	22(75.9)	15(57.7)	37(67.3)	0.126
Yes	7(24.1)	11(42.3)	18(32.7)	
No				
Antiepileptic medications use at initiation of concomitant course	11(37.9)	6(23.1)	17 (30.9)	0.234
Yes	18(62.1)	20(76.9)	38 (69.1)	
No				

GBM; glioblastoma multiforme, **TMZ;** temozolomide, **ECOG PS;** Eastern Cooperation Oncology Group performance status, **GTR;** Gross total resection, **STR;** Subtotal resection. ***Chi-square test was used for all comparisons except age and duration of symptoms (Mann-Whitney U test).

Treatment outcome

Survival

The median follow up period of the 55 eligible patients was 20 months (range: 12–41). Patients received six-cycle course of adjuvant TMZ treatment had median follow up duration of 16 months (range: 12–41), while patients received 12-cycle course of adjuvant TMZ treatment had median follow up duration of 21 months (12–36). There was no statistically significant difference in the median follow up duration between both treatment groups ($P = 0.087$).

A total of 39 patients (70.9%) developed disease progression (20/39 patients were in group 1 and 19/39 patients in group 2). The median time to progression for the entire cohort was 18 months (range: 12–41 months). The median time to progression in Group 1 was 14 months (range 12–41), and in Group 2 was 18 months (range 12–36) with no statistically significant difference between both treatment groups ($P = 0.134$). According to Kaplan-Meier analysis [16], the median PFS was 15 months for Group 1 (95% CI: 10.215–19.785) and 18 months for Group 2 (95% CI: 16.611–19.389) with no statistically significant difference between both groups ($P = 0.513$) (Fig. 1). PFS rates at 12, 18, 24 and 36 months were 82.8%, 40.0%, 22.5%, 22.5% for Group 1 and 88.5%, 48.4%, 22.6%, 22.6% for Group 2 respectively. Treatment of

tumor progression included: best supportive care for most of the patients (n = 25, 64.1%), retreatment with TMZ therapy (n = 9, 23.1%), and 2nd line chemotherapy (n = 5, 12.8%).

Patients with GTR resection who developed tumor recurrence had a significantly higher Cho/NAA and Cho/Cr ratios than patients with treatment induced changes ($P = 0.01$ and $P = 0.02$ respectively). In patients with STR or biopsy who developed tumor progression, the Cho/NAA and Cho/Cr ratios measured at non-enhancing tumor edges were higher on follow up imaging. The cut-off value for Cho/NAA ratio was > 2.2 with 87.2% sensitivity and 76% specificity with area AUC = 0.92 and $P = 0.01$. The cut-off value for Cho/Cr ratio was > 1.88 with 82% sensitivity and 71% specificity with AUC = 0.86 and $P = 0.02$. Regarding DWI, the ADC values were higher in regions of radiation induced changes than in recurrent tumor however, the difference was not significant (Fig. 2).

Pre-concurrent radio-chemotherapy

Pre-concurrent radio-chemotherapy MRI (FLAIR, T1W + Gd, ADC) and MRSI (**A**) showing heterogenous enhancement in the wall of the surgical cavity with low ADC nodule and surrounding edema. The VOI was placed at the site of contrast enhancement and low ADC revealing an elevated choline peak and low NAA with CHO/ NAA ratio = 3.1 and Cho/Cr ratio = 2.7 denoting residual disease. The scan done 9 months after six cycles of adjuvant temozolomide (**B**) shows a heterogenous increase in contrast enhancement surrounding the wall of the surgical cavity with increase in the surrounding FLAIR hyperintensity and hydrocephalus. Metabolite measurement in the surrounding heterogenous enhancement shows Cho/NAA ratio = 2.9 and Cho/Cr ratio = 3.2 denoting progressive disease.

During median follow up duration of 20 months, 34/55 patients (61.8%) died [15/34 patients (44.1%) were in Group 1 and 19/34 patients (55.9%) were in Group 2]. The cause of death was tumor progression during treatment and follow-up period. The median OS estimate by Kaplan-Meier [16], for the entire cohort was 21 months (95% CI: 18.803–23.197). The median OS was 18 months (95% CI: 13.420–22.580) and 22 months (95% CI: 18.777–25.223) for patients enrolled in Group 1 and Group 2 respectively. The OS rates at 12, 18, 24 and 36 months in Group 1 were 86.2%, 48.0%, 38.8%,%and 38.8% respectively, and it was 96.2%, 80.6%, 39.9% and 8.9% respectively for Group 2. There was no statistically significant difference in OS between both groups, ($P = 0.867$)(Fig. 3).

Univariate analysis showed that the extent of surgical resection (EOR) was the only statistically significant variable for PFS and OS. Patients underwent GTR showed a significantly longer PFS ($P = 0.008$) (Fig. 4A) (Table 2) and longer OS ($P = 0.014$) (Fig. 4B) (Table 3) than those who underwent STR, or biopsy. Age, gender, PS, tumor site, the use of corticosteroid medications, antiepileptic medications, and the number of chemotherapy cycles were not statistically significant predictors of PFS or OS. Multivariate analysis confirmed EOR to be associated with both longer PFS ($P = 0.015$) (Table 2) and longer OS ($P = 0.028$) (Table 3).

Patients underwent GTR had longer PFS ($P = 0.008$) and OS ($P = 0.014$) than those underwent STR or biopsy.

Table 2
Univariate and multivariate analysis of factors affecting progression free survival

Variables	Number	survival (months)			Log rank test		Cox regression analysis		
		Median	HR*	95% CI**	χ^2	*P- value*	Exp (B)	95% CI** for Exp (B)	*P-value*
Age	9	22	3.822	14.509–29.491	0.265	0.607			
< 50	46	18	1.064						
≥ 50				15.915–20.085					
Gender	41	19	1.123	16.799–21.201	1.246	0.264			
Male	14	17	1.761						
Female				13.548–20.452					
ECOG PS	13	19	2.359	14.376–23.624	1.332	0.514			
0	27	18	2.339						
1	15	18	0.596	13.416–22.584					
2				16.832–19.168					
Tumor location	22	18	1.756	14.559–21.441	1.107	0.775			
Frontal	16	18	1.428						
Temporal	13	17	2.339	15.202–20.798					
Parietal	4	17	2.750	12.416–21.584					
Occipital				12.110–22.890					
EOR	21	24	2.816	22.863–33.903	9.582	**0.008**	3.970	1.302–12.106	**0.015**
GTR	25	18	1.988						
STR	9	17	1.178	14.104–21.896					
Biopsy				14.962–19.308					
Corticosteroid use* **	37	17	1.591	13.882–20.118	0.304	0.581			
	18	18	0.924						
Yes				16.188–19.812					
No									

Variables	Number	survival (months)			Log rank test		Cox regression analysis
		Median	HR*	95% CI**	χ^2	*P- value*	Exp (B) 95% CI** for Exp (B) *P-value*
Antiepileptic medications* **							
Yes	17	17	1.866	13.342–20.658	1.762	0.184	
No	38	18	0.971	16.097–19.903			
Number of CTH cycles.							
Six cycles	29	15	2.441	10.215–19.785	0.428	0.513	
12 cycles	26	18	0.709	16.611–19.389			

ECOG PS; Eastern Cooperation Oncology Group performance status, **EOR;** Extent of surgical resection, **GTR;** Gross total resection, **STR;** Subtotal resection, ***CI;** Confidence interval, ****HR;** Hazard ratio, ***** At initiation of concomitant course, **CTH;** chemotherapy.

Table 3
Univariate and multivariate analysis of factors affecting overall survival

Variables	Number	Overall survival (months)			Log rank test		Cox regression analysis		
		Median *	HR	95% **CI	χ^2 *P value*		Exp (B) 95% **CI for Exp (B)		*P-value*
Age	9	22	1.090	19.863–24.137	0.105	0.746			
< 50	46	20	1.279	17.494–22.506					
≥ 50									
Gender	41	22	1.404	19.248–24.752	0.997	0.318			
Male	14	19	2.235	14.619–23.381					
Female									
ECOG PS	13	16	2.397	14.303–23.697	3.331	0.189			
0	27	21.9	3.780	15.592–30.408					
1	15	19	3.836	12.482–27.518					
2									
Tumor location	22	22	2.195	17.698–26.302	1.172	0.760			
Frontal	16	22	1.345	19.364–24.636					
Temporal	13	18	2.996	12.128–23.872					
Parietal	4	21	1.121	18.803–23.197					
Occipital									
EOR	21	21	1.121	18.803–23.197	8.497	**0.014**	0.291	0.096–0.878	**0.028**
GTR	25	20	3.391	13.355–26.645					
STR	9	18	1.553	14.956–21.044					
Biopsy									
Corticosteroid use***	37	20	1.777	17.693–22.307	1.333	0.248			
Yes	18	22	1.965	18.149–25.851					
No									

Variables	Number	Overall survival (months)			Log rank test		Cox regression analysis
		Median *	HR	95% **CI	χ^2 *P value*		Exp (B) 95% **CI for Exp (B) *P-value*
Antiepileptic medications use***	17	18	1.845	14.384–21.616	1.038	0.308	
Yes	38	22	1.073	19.897–24.103			
No							
Number of CTH cycles.	29	18	2.337	13.420–22.580	0.028	0.867	
Six cycles	26	22	1.644	18.777–25.223			
12 cycles							

ECOG PS; Eastern Cooperation Oncology Group performance status, **EOR;** Extent of surgical resection, **GTR;** Gross total resection, **STR;** Subtotal resection, ***CI;** Confidence interval, ****HR;** Hazard ratio, ***** At initiation of concomitant course, CTH; chemotherapy.

Toxicity

According to the CTCAE version 3 [15], a total of 163 toxicities were encountered in 48 patients (87.3%) out of 55 eligible patients during concomitant and adjuvant TMZ therapy. The overall treatment related adverse events were higher during the concomitant course (n = 30, 54.5%) than during the adjuvant course (n = 21, 38.2%) of TMZ therapy ($P = 0.000012$). Thirty three patients (60.0%) developed hematologic toxicities (22 patients during concomitant course and 14 patients during the adjuvant course). Non-hematologic toxicities were observed in 46 patients (83.6%); 29 patients during concomitant course and 19 patients during the adjuvant course. Forty five patients (81.8%) had grade 1 or 2 treatment related toxicities and 24 patients (43.6%) developed grade ≥ 3 adverse events (Table 4). Neutropenia was the most frequently observed treatment related hematologic adverse events (n = 14, 25.5%). The most frequent non-hematologic adverse events were nausea (n = 27, 49.1%) followed by vomiting (n = 21, 38.2%) and fatigue (n = 21, 38.2%) (Table 5). In most of the patients, nausea and vomiting occurred as a paired adverse events. There was no statistically significant difference in the toxicity profile between six-cycle group and 12-cycle group ($P = 0.289$) (Table 5).

Table 4
Overall toxicity profile of 55 GBM patients treated with concurrent radio-chemotherapy and maintenance TMZ

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4	Total (no = 55)
	No	No	No	No	No (%)
Hematologic					
Anemia	3	1	0	0	4 (7.3)
Neutropenia	6	4	2	2	14 (25.5)
Leukopenia	6	3	1	0	10 (18.2)
Thrombocytopenia	2	5	2	1	10 (18.2)
Non-hematologic					
Alopecia	10	0	0	0	10 (18.2)
Anorexia	3	6	4	0	13 (23.6)
Nausea	7	8	12	0	27 (49.1)
Vomiting	10	8	3	0	21 (38.2)
Constipation	1	2	0	0	3 (5.5)
Diarrhea	0	2	0	0	2 (3.6)
Fatigue	8	11	2	0	21 (38.2)
Insomnia	2	3	2	0	7 (12.7)
Headache	4	6	0	0	10 (18.2)
Dizziness	2	4	0	0	6 (10.9)
Pneumonia	3	2	0	0	5 (9.1)

GBM; Glioblastoma multiforme, **TMZ;** Temozolomide.

Table 5
Comparison of the toxicities between six-cycle treated patients and 12-cycle treated patients

Adverse events	6-cycle (group 1) (n = 29) No (%)	12-cycle (group 2) (n = 26) No (%)	*P*-value
Hematologic			
Anemia	1 (3.4)	3 (11.5)	0.249
Neutropenia	7 (24.1)	7 (26.9)	0.813
Leukopenia	4 (13.8)	6 (23.1)	0.373
Thrombocytopenia	3 (10.3)	7 (26.9)	0.112
Non-hematologic			
Alopecia	7 (24.1)	3 (11.5)	0.226
Anorexia	6 (20.7)	7 (26.9)	0.587
Nausea	11 (37.9)	16 (61.5)	0.080
Vomiting	9 (31.0)	12 (46.2)	0.249
Constipation	2 (6.9)	1 (3.8)	0.619
Diarrhea	0	2 (7.7)	0.128
Fatigue	11 (37.9)	10 (38.5)	0.968
Insomnia	2 (6.9)	5 (19.2)	0.171
Headache	4 (13.8)	6 (23.1)	0.373
Dizziness	2 (6.9)	4 (15.4)	0.313
Pneumonia	2 (6.9)	3 (11.5)	0.550

There was no statistically significant difference in the rate of grade 3 & 4 treatment related toxicities between both groups ($P = 0.851$). During concurrent radio-chemotherapy, 3 grade ≥ 3 hematologic adverse events were encountered in three patients. One of the three patients was in the six-cycle group (developed neutropenia), while the other two patients were in the 12-cycle group (one patient developed neutropenia and the other one developed thrombocytopenia) (Table 6). The concomitant course was interrupted in these patients and it was resumed within 12 days of conservative measures.

During adjuvant TMZ therapy, treatment was delayed in two out of 29 patients (6.9%) enrolled in six-cycle group, because of grade 3 or more hematologic adverse events (neutropenia, one; thrombocytopenia, one) (Table 6). Maintenance TMZ was restarted after improvement of blood cell count with a reduced

dose. Treatment was discontinued in 3/26 patients (11.5%) assigned to 12-cycle group (one patient at cycle 10 of chemotherapy, and two patients at cycle 11 of chemotherapy) because of grade 4 neutropenia in one patient, grade 3 leukopenia in one patient and grade 3 thrombocytopenia in one patient (Table 6).

Twelve patients (21.8%) developed CTCAE grade 3 nausea (Table 6). None of our patients discontinued treatment; only treatment interruption due to grade 3 toxicities and all were resolved by conservative measures. Adjuvant TMZ treatment was resumed in these patients with a reduced dose of 150 mg/m^2 in subsequent cycles. We did not report any morality related to TMZ administration.

Table 6
Grade 3 & 4 CTC that occurred during CRCT and adjuvant course of TMZ

Adverse events	6-cycles (group 1) (n = 29) No (%)	12-cycles (group 2) (n = 26) No (%)	Total (n = 55) No (%)	*P*-value
Hematologic	1(3.4)	1(3.8)	2(3.6)	0.910
Neutropenia	1(3.4)	1(3.8)	2(3.6)	
CRCT	2(6.9)	2(7.7)	4(7.3)	
Adjuvant TMZ				
Total				
Leukopenia	0	0	0	0.286
CRCT	0	1(3.8)	1(1.8)	
Adjuvant TMZ	0	1(3.8)	1(1.8)	
Total				
Thrombocytopenia	0	1(3.8)	1(1.8)	0.489
CRCT	1(3.4)	1(3.8)	2(3.6)	
Adjuvant TMZ	1(3.4)	2(7.7)	3(5.5)	
Total				
Non-hematologic	0	2(7.7)	2(3.6)	0.249
Anorexia	1(3.4)	1(3.8)	2(3.6)	
CRCT	1(3.4)	3(11.5)	4(7.3)	
Adjuvant TMZ				
Total				
Nausea	5(17.2)	0	5(9.1)	0.081
CRCT	4(13.8)	3(11.5)	7(12.7)	
Adjuvant TMZ	9(31.0)	3(11.5)	12(21.8)	
Total				

Adverse events	6-cycles (group 1) (n = 29) No (%)	12-cycles (group 2) (n = 26) No (%)	Total (n = 55) No (%)	*P*-value
Vomiting	0	1(3.8)	1(1.8)	0.060
CRCT	0	2(7.7)	2(3.6)	
Adjuvant TMZ	0	3(11.5)	3(5.5)	
Total				
Fatigue	0	1(3.8)	1(1.8)	0.128
CRCT	0	1(3.8)	1(1.8)	
Adjuvant TMZ	0	2(7.7)	2(3.6)	
Total				
Insomnia	1(3.4)	0	1(1.8)	0.937
CRCT	0	1(3.8)	1(1.8)	
Adjuvant TMZ	1(3.4)	1(3.8)	2(3.6)	
Total				

CTC; Common Toxicity Criteria, **TMZ;** Temozolomide, **CRCT;** Concurrent radio-chemotherapy.

Discussion

Despite the great advances in multimodality approach for high grade glioma, the optimal treatment remains a challenging issue for the oncologist. Extending the duration of adjuvant TMZ therapy has been evaluated in several studies to optimize treatment and to improve survival [5–12]. In our study, 55/121 patients (45.5%) were eligible and retrospectively analyzed. We obtained data from those patients who received up to 12 cycles of adjuvant TMZ chemotherapy (Group 2) and compared them with patients received six TMZ cycles (Group 1). We compared both groups as regard to survival outcome and toxicity profile. The percentage of patients (45.5%) who completed maintenance TMZ treatment in the present study is comparable to what was reported by Skardely et al [12] (75/169 patients {44.4%}). Meanwhile, our figure is higher than what was reported by prospective phase III study of Gilbert et al [18], (35.6% received at least 6 cycles of maintenance treatment, while 19.1% received 12 cycles). TMZ therapy was stopped in 19/121 patients (15.7%) because of toxicity during the first 6 cycles which is consistent with results of prospective phase III study that was conducted by Gilbert et al [17] (16.4%). On the other hand we had lower percentage of patients who discontinued treatment because of tumor progression during the first six cycles compared to what was reported in prospective trials (34.7% vs 39%-49.3%) [4, 17]. In the current study, the median number of cycles in patients received up to 12 cycles of adjuvant TMZ was

11.5 (range: 9–12). This is in accordance to the study conducted by Refae et al [9] (11 cycles, range: 8–23) and by Delion et al [6] (11 cycles, range: 7–13).

Thirty nine patients (70.9%) developed disease progression at a median follow up time of 18 months. Among them, 20 patients (51.3%) were in Group 1 and 19 patients (48.7%) were in Group 2. Patients in whom adjuvant TMZ was stopped at cycle six (Group 1) experienced median PFS of 15 months (95% CI: 10.215–19.785) where as those who received up to 12 cycles of adjuvant TMZ (Group 2) had median PFS of 18 months (95% CI: 16.611–19.389)(P = 0.513). This result is in concurrence with the result showed by Refae et al [9], (The median PFS for more than six cycles arm was 18 .8 months vs. 12.1 months for six cycles arm). However our result is far less than the result showed by Darlix et al [8], it showed PFS of 28.4 months (range 12.8–34.2 months), for patients who received 9 cycles or more. The reason for this contradictory finding was the lower rate of GTR in our study (n = 21, 38.2%) compared to what was reported in the study published by Darlix et al (60.3%) [8]. Hau et al [5], reported a median PFS of 14 months in patients with GBM receiving adjuvant TMZ for a median 13 cycles. This figure is lower than what was reported by our study.

After median follow up period of 20 months (range: 12–41), we reported a median OS of 18 months in patients who received six cycles of adjuvant TMZ (95% CI: 13.420–22.580) and 22 months (95% CI: 18.777–25.223) in patents who received up to 12 cycles of adjuvant TMZ. The 2-year OS rate was 39.9% in the 12-cycle TMZ group versus 38.8% in the 6-cycle TMZ group (P = 0.867). Hau et al [5], reported a median OS of 22.4 months from initiation of TMZ in 73 patients with primary GBM after administration of a median 13 cycles (range 9–40). The present study compare favorably with this report. Although our randomization was done among patients who were progression free after 6 cycles of adjuvant TMZ, patients treated with 12 cycles of adjuvant TMZ had lower median OS than what was reported by Bahandari et al [10], (median OS of 23.8 months and other published series [7, 9, 11, 12], in which median survival for their cohorts who received more than six cycles of adjuvant TMZ therapy ranged from 23.8–30.6 months versus 8–18 months in those who received six cycles of adjuvant TMZ therapy. This might be attributed to the lower number of patients who underwent GTR (n = 21, 38.2%) and this was significantly worsen the OS in our study (P = 0.014). Meanwhile, we reported higher median OS and 2-year OS rate than what was published by Seiz et al [7], (median OS of 15 months and 2-year OS rate of 27.5% in 59/114 patients treated with long term adjuvant TMZ therapy {range 1–57 cycles}).

Contrary to our expectations, we did not find any statistically significant difference in OS (P = 0.513) or PFS (P = 0.867) when extending the duration of maintenance TMZ therapy for 12 cycles. Our data were further confirmed by the recently published manuscript of the GENO-14-01 trial (NCT02209948) [18], 159 patients were randomized according to MGMT status and presence or absence of residual disease to extended cycles (80 patients) vs six cycles (79 patients) of adjuvant TMZ therapy. The author concluded that there was no significant correlation between OS or PFS and extending the duration of adjuvant TMZ beyond 6 cycles. On the other hand, Refae et al [9], conducted a prospective phase II study, in 59 patients with newly diagnosed GBM. Patients were randomized to receive either six cycles of adjuvant TMZ (n = 29) or more than six cycles of adjuvant TMZ (n = 30). There was statistically significant correlation

between median PFS (12.1 months in patients receiving six cycles versus 18.8 months in patients receiving > 6 cycles; *P* = 0.015) and median OS (18.1 months for patients receiving six cycles and 24.1 months for patients with more than six cycles; *P* = 0.048) and the number of adjuvant TMZ cycles. Darlix et al [8], retrospectively reviewed the file of 448 patients with GBM. Eligible patients (n = 58) were randomized to receive Stupp protocol (n = 38) [4], or to receive extended TMZ therapy (n = 20). They found statistically significant improvement in both OS (*P* = 0.01) and PFS (*P* = 0.03) in patients received extended adjuvant TMZ treatment compared to those who received standard adjuvant TMZ. A pooled analysis from 4 randomized trials was conducted by Blumental et al [11], in 2017 for newly diagnosed GBM patients. A total of 624 were eligible for the study and they were randomized to either stop TMZ after 6 cycles (n = 333), or to continue TMZ for 12 cycles or until progression (n = 291). They concluded that extended TMZ therapy was associated with an improved PFS (*P* = 0.03) but without statistically significant improvement in OS (*P* = 0.52).

Several studies [19, 20], have shown that the EOR had a significant impact on survival following adjuvant therapy. Similarly, our present study showed that the EOR significantly correlated with survival; patients in whom GTR was achieved had significantly longer PFS (*P* = 0.015) and OS (*P* = 0.028) than patients underwent STR or biopsy. Contrary to our findings, Michaelsen et al [21], did not find significant correlation between the EOR and survival, although he demonstrated a significant impact of patient age, ECOG PS and use of corticosteroid therapy on survival.

In our study, the overall toxicity profile of adjuvant TMZ therapy was tolerable as most of the patients (n = 45, 81.8%) developed only grade 1 or 2 adverse events and only 3/55 patients (5.5%) discontinued adjuvant TMZ therapy due to toxic effects. This low figure is in accordance with that reported by Stupp et al. [4] in 2005 (only 8% of the patients discontinued adjuvant TMZ treatment due to toxic effects). We reported higher incidence of grade 3 and 4 hematologic toxicity (n = 8, 14.5%) during concomitant and adjuvant course than what was reported in CATNON trial (8–12%) [22]. Although the reason for this is unclear, treatment was discontinued in only 3/26 patients (11.5%) whose adjuvant TMZ extended to 12 cycles. Bahandari et al [10], reported that the incidence of grade 3 and 4 hematologic toxicities was 0% in the six-cycle TMZ group and 5% in the 12-cycle TMZ group during concomitant course. He also reported a higher incidence of grade 3 and 4 hematologic toxicity in the 12-cycle TMZ group compared to six-cycle TMZ group; 15% and 5%, respectively during adjuvant course. Similarly, we observed that 3.4% of the patients in the six-cycle TMZ group and 7.7% of the patients in the 12-cycle TMZ group had ≥ grade 3 hematologic toxicity during concomitant course while during adjuvant course of TMZ, we reported an overall incidence of ≥ grade 3 hematologic toxicity of 6.9% in six-cycle TMZ group and 11.5% in 12-cycle TMZ group. The most frequent hematologic adverse event was neutropenia (n = 14, 25.5%). However, Stupp et al [4], reported that thrombocytopenia (12.0%) was the most common hematologic adverse event of temozolomide.

Nausea (n = 27, 49.1%), vomiting (n = 21, 38.2%) and fatigue (n = 21, 38.2%), were the most frequently reported treatment related non-hematologic adverse events. Our results is in accordance with that reported by Bae SH, et al [23], they analyzed the data of 300 patients with histologically confirmed WHO

grade 3 or 4 glioma who received TMZ therapy as a concomitant, adjuvant, or palliative therapy. They reported that, the most common toxicities were nausea (44.3%) and vomiting (37%). Similarly, we reported high rate of fatigue among treated patients during concurrent and adjuvant course of TMZ (38.2%).

There are several considerations that may limit the potential benefit from extending maintenance TMZ treatment. Prolonged administration of TMZ results in mutational changes in the tumor which in turn leads to resistance to ongoing alkylating therapy [24]. Treatment with alkylating agent resulted in mutation in the mismatch repair (MMR) gene mutS homolog 6 (MSH6) which was found in association with a hypermutator phenotype [25]. Consequently, this hypermutator phenotype may lead to progression to a more malignant tumor phenotype at the time of recurrence [26]. Another limitation is the cumulative toxicities occurred during treatment with TMZ. Momota et al [27], reported an increased risk of myelodysplasia and leukemia with increasing cumulative doses of TMZ therapy. Additionally, prolonged administration of TMZ, may suppress the immune system [28, 29] and prevent the possibility for subsequent salvage therapy at the time of recurrence which subsequently shorten the survival.

The limitations of our study include the small sample size of patients, the lack of assessment of IDH1/2 mutation status and methylation status of MGMT gene and finally, salvage therapy was not uniform in all patients with tumor progression; it included best supportive care for most of the patients (n = 25, 64.1%), retreatment with TMZ therapy (n = 9, 23.1%), and different 2nd line chemotherapy (n = 5, 12.8%) inform of Etoposide/Cisplatin, Bevacizumab as single agent or in combination with irinotecan or carboplatin.

Conclusion

Our study showed that extended duration of adjuvant TMZ does not confer significant PFS or OS advantages as compared to the standard six-cycle course. Meanwhile, we demonstrated a significant impact of the EOR on PFS and OS. Extended cycles of adjuvant TMZ treatment is safe and has comparable toxicity profile as compared to the standard six cycles. Based on our findings we do not recommend extending the duration of adjuvant TMZ treatment beyond six cycles and it needs to be weighed against the compromised quality of life and the cost to the health care system.

Abbreviations

GBM : Glioblastoma multiforme; **TMZ:** Temozolomide; **OS:** overall survival; **PS:** Performance status; **ECOG:** Eastern Cooperation Oncology Group; **GTR:** Gross total resection; **STR:** Subtotal resection; **MRI:** Magnetic resonance imaging **MRSI:** Magnetic resonance spectroscopy imaging; **MGMT:** O6 - methylguanin-DNA methyltransferase; **IDH:** isocitrate dehydrogenase; **GTV:** Gross tumor volume; **FLAIR:** fluid attenuated inversion recovery; **CTV:** clinical target volume; **PTV:** planning target volume; **RANO:** Response Assessment in Neuro-Oncology; **CTCAE:** Common Terminology Criteria for Adverse Events;; **MRS:** Magnetic resonance spectroscopy; **DWI:** Diffusion weighted imaging; **ADC:** Apparent diffusion

coefficient; **PRESS:** Point Resolved Spatial Selection; **TE:** echo time; **Cho:** Choline; **NAA:** N-acetyl aspartate; **Cr:** Creatine; **PFS:** Progression free survival; **ROC:** Receiver Operating Characteristic; **AUC:** Area under the curve; **EOR:** Extent of surgical resection.

Declarations

Ethics approval and consent to participate: This historical cohort study was approved by the Committee of Medical Ethics of the Faculty of Medicine, Assiut University, Assiut, Egypt with IRB no: 17300481. However, given the retrospective nature of the study the need for informed consent from human was waived by the Committee of Medical Ethics of the Faculty of Medicine, Assiut University, Assiut, Egypt with IRB no: 17300481. All methods were carried out in accordance with guideline and regulations. Confidentiality of patient's records was maintained throughout the study.

Consent for publication: Not applicable.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no conflicts of interest.

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Authors' contributions: All authors contributed in the work presented in this manuscript,

Conceptualization A.A., M.A.; methodology A.A., N.A.; software A.A., N.A., H.E.; validation A.E., M.E.; formal analysis A.A., H.E., M.S., N.A.; investigation A.A, N.A., H.E.; resources M.S., H.E., M.E., N.A., M.A., A.E.; data curation A.A, N.A., H.E.; writing—original draft preparation A.A., N.A., A.E.; writing—review and editing A.A., M.S., H.E., M.E., N.A., M.A., A.E.; visualization M.S., A.E.; supervision A.A., N.A.; project administration A.A., M.A., M.E., A.E.; funding acquisition this work was not supported by any grants or companies or institutional funds.

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Figures

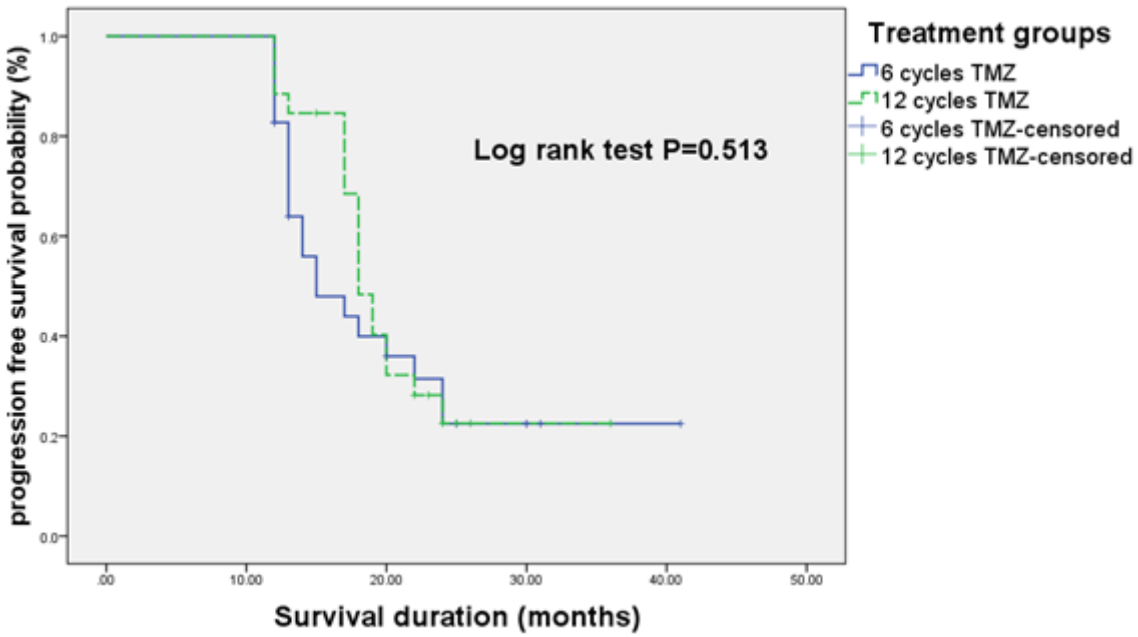


Figure 1

Kaplan-Meier curves showing PFS of GBM patients Patients treated with 12 cycles of adjuvant TMZ compared to those receiving six cycles. P = 0.513

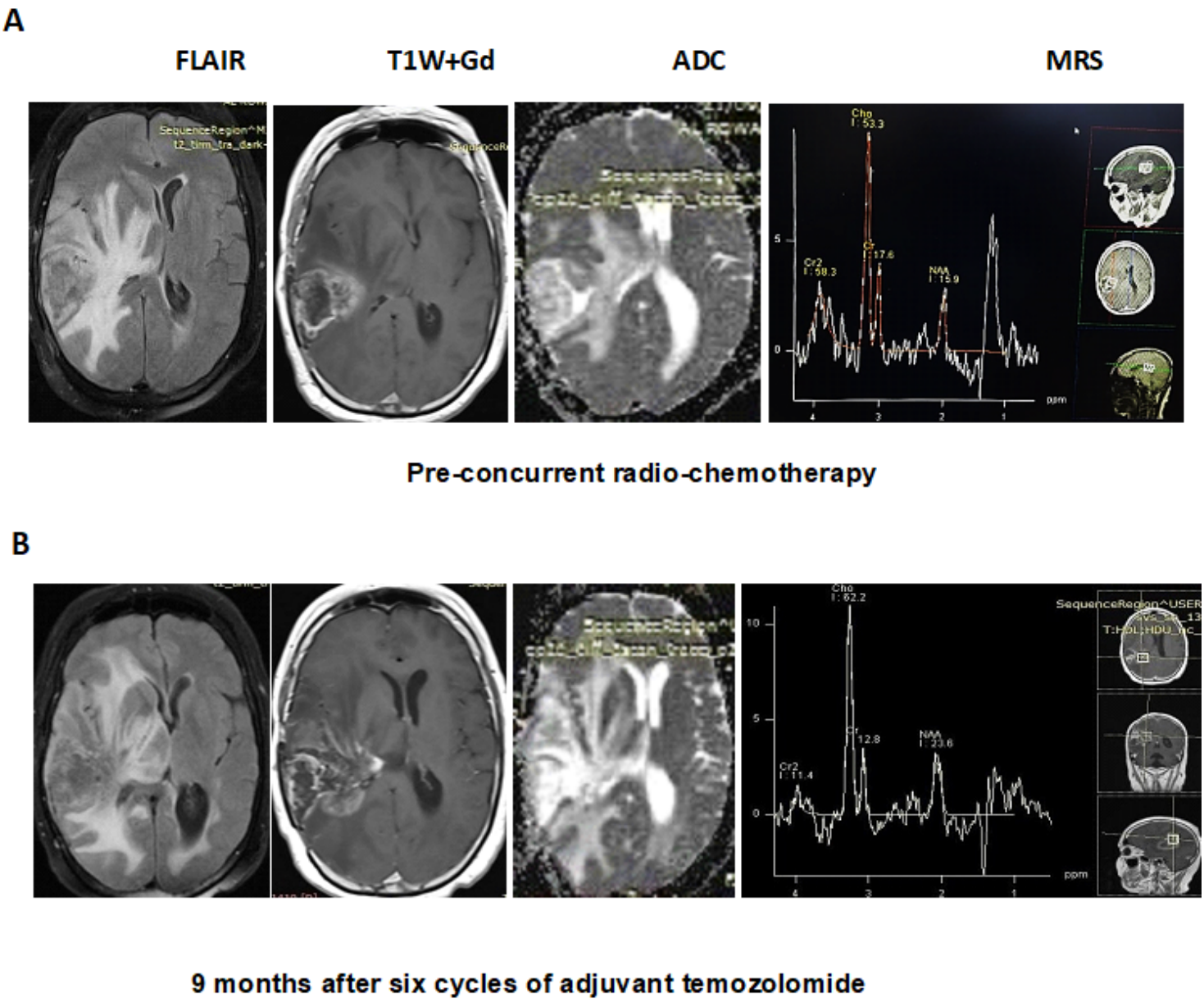


Figure 2

Pre-concurrent radio-chemotherapy and post treatment MRI (FLAIR, T1W+Gd, ADC) and MRSI Pre-concurrent radio-chemotherapy MRI (FLAIR, T1W+Gd, ADC) and MRSI (A) showing heterogenous enhancement in the wall of the surgical cavity with low ADC nodule and surrounding edema. The VOI was placed at the site of contrast enhancement and low ADC revealing an elevated choline peak and low NAA with CHO/ NAA ratio= 3.1 and Cho/Cr ratio=2.7 denoting residual disease. The scan done 9 months after six cycles of adjuvant temozolomide (B) shows a heterogenous increase in contrast enhancement surrounding the wall of the surgical cavity with increase in the surrounding FLAIR hyperintensity and hydrocephalus. Metabolite measurement in the surrounding heterogenous enhancement shows Cho/NAA ratio= 2.9 and Cho/Cr ratio= 3.2 denoting progressive disease.

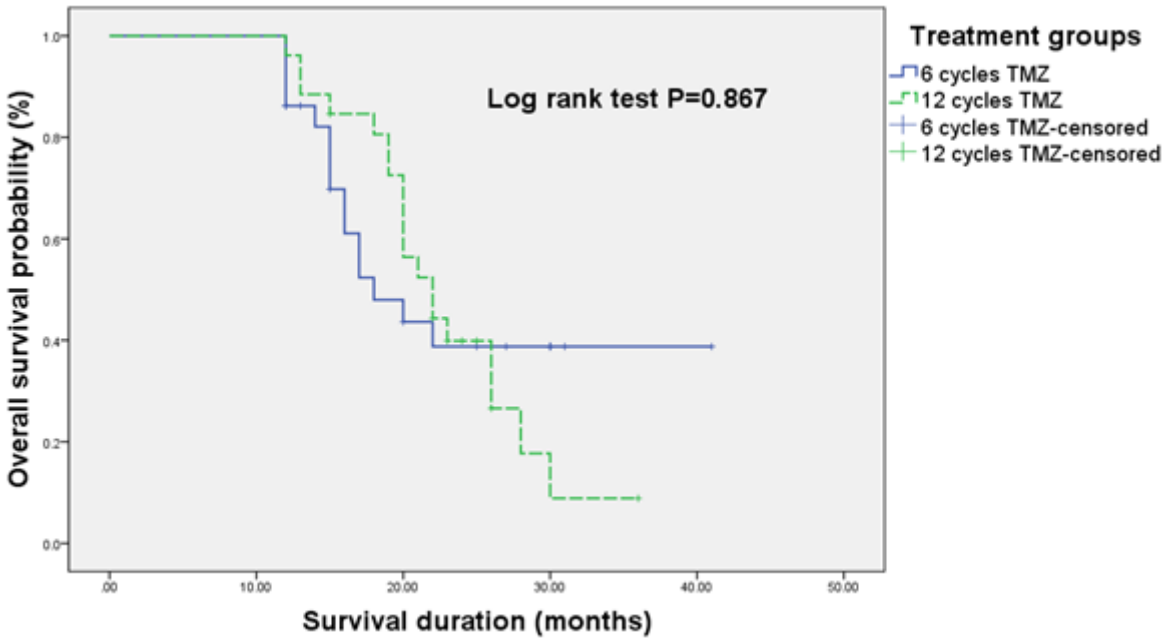
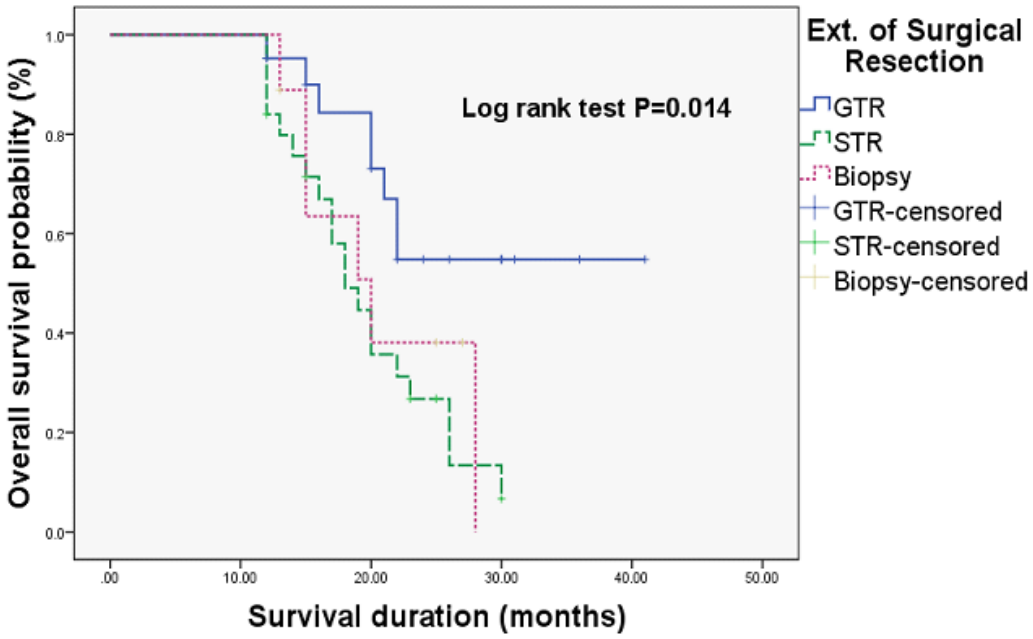


Figure 3

Kaplan-Meier curves showing OS of GBM Patients treated with 12 cycles of adjuvant TMZ compared to those receiving six cycles. P = 0.867

A



B

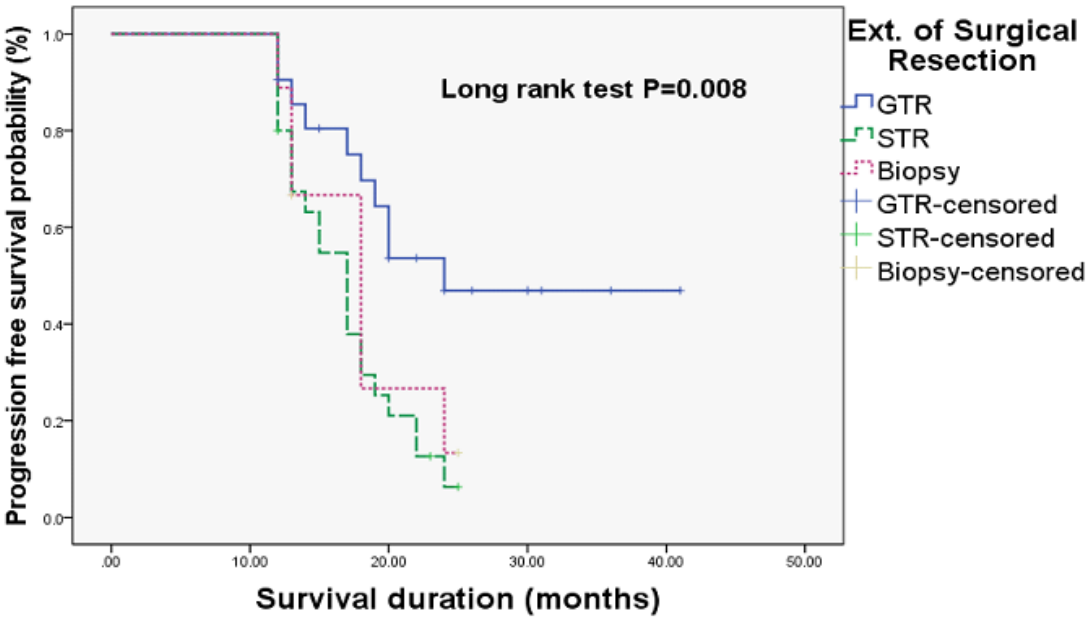


Figure 4

Kaplan-Meier curves of 55 GBM patients showing PFS (A) and OS (B) according to EOR Patients underwent GTR had longer PFS (P = 0.008) and OS (P = 0.014) than those underwent STR or biopsy.