

Short Course versus Standard Course of Radiotherapy in Glioblastoma Multiforme

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Abstract

Background: Six weeks radiotherapy plus concomitant and adjuvant temozolomide (TMZ) is the standard treatment for glioblastoma multiforme (GBM). We are investigating the value of short course radiotherapy (three weeks) in comparison to the standard treatment.

Patients and Methods: Newly diagnosed patients with GBM were randomized to either short course of radiotherapy (40 Gy administered in 15 fractions over 3 weeks) plus TMZ or to standard course of radiotherapy (60 Gy administered in 30 fractions over 6 weeks) plus TMZ. Adjuvant TMZ were given to both groups. The primary end point was overall survival.

Results: 60 patients were randomized, 30 patients to short course and 30 patients to standard course. Median Overall Survival (OS) for short course was 13.7 months (95%CI 10.47-16.92) and for standard course was 15.3 months (95%CI: 8.53-22.06), with no statistically significant difference between the two groups (HR:1.16 (0.64-2.13); P-value 0.613). Median Progression free survival (PFS) for short course was 12 months (95% CI: 8.25-15.74) and for standard course was 12.8 months (95%CI: 7.96-17.63), with no statistically significant difference between the two groups (HR:1.01 (0.57-1.78); P-value 0.969). Six months progression free survival was found 86% of patients in both groups. Assessment of response rate was done within 3 months of adjuvant TMZ. Responder patients, including complete and partial response, were seen in 7 patients (23.3%) in short course group and 6 patients (20%) in standard group. Regarding toxicity profile, there was no significant difference between both groups.

Conclusion: No significant difference between short course radiotherapy and standard course radiotherapy. Short course radiotherapy can be an option for the treatment of GBM.

Keywords: Glioblastoma; GBM; Hypofractionation; Brain tumors; Radiotherapy; Temozolomide

Introduction

Unfortunately, the median survival of patients with GBM, treated with surgical resection followed by six weeks radiotherapy plus concomitant and adjuvant TMZ, is around 14.6 months only [1]. Radiotherapy had an important role in treating GBM, patients with good performance status and age up to 70 years should receive standard six weeks radiation therapy, while the elderly patients (age 70 years or older) can receive short course radiation therapy [2].

Short course radiotherapy has an advantage of reduced treatment time [3]. In older patients (age 60 years or older), short course of radiation therapy is equal in median survival to standard course radiation therapy [3-5], and had a significant better survival in age older than 70 years [4]. In addition, short course radiotherapy was associated significantly with less need to increase corticosteroid dosage after finishing radiation therapy [3]. Many Phase I and phase II trials proved that the addition of TMZ to short course radiotherapy was feasible and safe [6,7]. A large phase III trial over 562 patients proved significant survival improvement for the addition of TMZ to short course radiotherapy than radiation therapy alone [8].

Short course could reduce the burden on medical resources, the patient himself and his relatives. Data on short course radiotherapy on all age groups is limited. In order to know the value of short course in all age groups, our group in Cairo University did a randomized phase II study to compare short course versus standard course in patients with GBM, not only in the elderly, but extending to include all age

groups starting from patients above 18 years old. Both groups received concurrent and adjuvant TMZ.

Patients and Methods

Patient criteria

Eligible patients should fulfill all the following criteria: Pathological diagnosis of GBM, Tumor size ≤ 6 cm, age above 18 years, ECOG performance status 0, 1 and 2 with no previous radiation to brain. Exclusion criteria include patients received previous radiation to brain, Pregnant patients. All patients provided written informed consent, and the study was approved by the ethics committees of Kasr El Aini Center of Clinical Oncology and Nuclear Medicine (NEMROCK).

Study design

This prospective randomized clinical study include a total of 60 patients, recruited from Kasr El Aini Center of Clinical Oncology and Nuclear Medicine (NEMROCK) in the period from June, 2014 to

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Received November 12, 2018; Accepted November 23, 2018; Published November 30, 2018

Citation: Gaber MH, Sakr AY, Salama DH, Hashem WB, EL-Zawahry MI (2018) Short Course versus Standard Course of Radiotherapy in Glioblastoma Multiforme. J Nucl Med Radiat Ther 9: 388. doi: [10.4172/2155-9619.1000388](https://doi.org/10.4172/2155-9619.1000388)

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February, 2016, 30 patients in each group. Patients were randomized either to short-course radiotherapy regimen (40 Gy in 15 fractions over 3 weeks) with TMZ, or to standard course radiotherapy regimen (60 Gy in 30 fractions over 6 weeks) with TMZ.

Pretreatment evaluation

All patients underwent baseline complete medical detailed history and physical examination. Laboratory studies include complete blood count, liver function test and kidney function test. Postoperative base line MRI brain evaluation with contrast, chest X-ray, abdomino-pelvic ultrasound. CT scan was done when we have a suspicious lesion in chest X-ray or abdominopelvic ultrasound.

Radiation therapy

Radiation therapy was given within 6 weeks of surgery. Patient treated with three-dimensional conformal radiotherapy, positioning with an immobilization mask system. Continuous 3 mm CT scans of the head was obtained with a 16-slice spiral CT scanner in supine position. The prescribed dose for the standard adjuvant RT is given as a single-phase treatment. Based on postoperative magnetic resonance imaging study, planning target volume (PTV) consisted of the enhancing tumor volume plus 2.5 cm margin around the tumor. Eclipse planning system version 11 was used for planning techniques. Radiation treatment was delivered with Varian unique 6 MV linear accelerator machine.

Temozolomide

TMZ was given concurrently daily during the radiation therapy at a dose of 75 mg per square meter per day starting with the first day of radiation therapy and continue until the last day of radiation. And then as adjuvant after radiation therapy, at a dose of 200 mg per square meter per day for five consecutive days every 28 days for 6 cycles. Adjuvant TMZ started 4 weeks after radiation therapy.

Post-treatment evaluation and follow up

Clinical evaluation was done every week during radiation and then every month during adjuvant TMZ and then every 2-3 months. Contrast-enhanced brain magnetic resonance imaging was done after radiation therapy and then every 3 months or according to the clinical condition of the patient. Second line chemotherapy was given for patients with documented disease progression and with good performance status 0-2. Lomustin 110 mg/m² orally D1 and Vincristin 1.4 mg/m² (Maximum 2 mg) intravenous D1 and D21, cycle repeated every 6 weeks until progression or toxicity.

Outcome parameters

The primary end point of this study was overall survival. The secondary end points were progression free survival, toxicity, and response rate. Progression Free Survival (PFS) was calculated from the date of randomization till the date of documentation of disease progression, last follow up or death. Overall Survival (OS) was calculated from the date of randomization to the date of death or last follow up. Response rate was defined according to the Macdonald criteria [9]. Toxicity was defined according to Common Toxicity Criteria version 4.

Statistical analysis

All data was tabulated and statistically studied by descriptive analysis as well as survival analysis in relation to different clinicoepidemiological factors. Survival analysis was performed using Kaplan Meier method for both overall survival and progression-free survival. Univariate and

multivariate analysis using COX regression module was performed to test the power of relation between the independent variables and overall survival as well as disease free survival. A probability value (P-value) less than 0.05 was considered significant. The statistical calculations were done using computer programs Microsoft Excel version 7 and SPSS (statistical package for the social science) statistical programs.

Results

Median age of all patients was 52 years (range: 18-70 years). Regarding to sex, 41 patients (68.3%) were males and 19 patients (31.7%) were females. The majority of our patients (38 patients; 63.3%) had ECOG performance status 2. At the study enrollment, headache is the most common symptom seen in 41 patients (68.3%) followed by convulsions in 25 patients (41.6%). Parietal region was the dominant tumor site in the MRI images in 19 patients (31.7%). Most of the patients underwent subtotal resection (26 patients; 43.3%) and the mean diameter of postoperative tumor residual size was 3.8 cm. Patients and tumors characteristics were generally well balanced between the two groups of patients as seen in Table 1.

Median follow up time was 26 months (range 13.5-33.7). All patients completed the specified course of radiation therapy in both groups. Total dose of concurrent temozolomide was given to all patients without need for dose modification and the median dose of TMZ was 100 mg. Four patients (6.6%) didn't receive adjuvant TMZ as they died before start adjuvant treatment and 19 patients (31.6%) received 2nd line chemotherapy.

Response rate

Assessment of response rate was done within 3 months of adjuvant TMZ. Responder patients (complete response + partial response) was seen in 7 patients (23.3%) in short course and 6 patients (20%) in standard course, while controlled patients (complete response+partial response+stable disease) were seen in 19 patients (63.3%) in short course and 22 patients (73.3%) in standard course.

Survival analysis

The estimated median Progression free survival (PFS) for short course is 12 months (95%CI: 8.25-15.74) and for standard course is 12.8 months (95%CI: 7.96-17.63), with no statistically significant difference between the two groups (HR:1.01 (0.57-1.78); P-value 0.969) as seen in Figure 1. Six months progression free survival was found in 86% of patients in both groups. The estimated median Overall Survival (OS) for short course is 13.7 months (95%CI 10.47-16.92) and for standard course is 15.3 months (95%CI: 8.53-22.06), also with no statistically significant difference between the two groups (HR:1.16 (0.64-2.13); P-value 0.613) as seen in Figure 2.

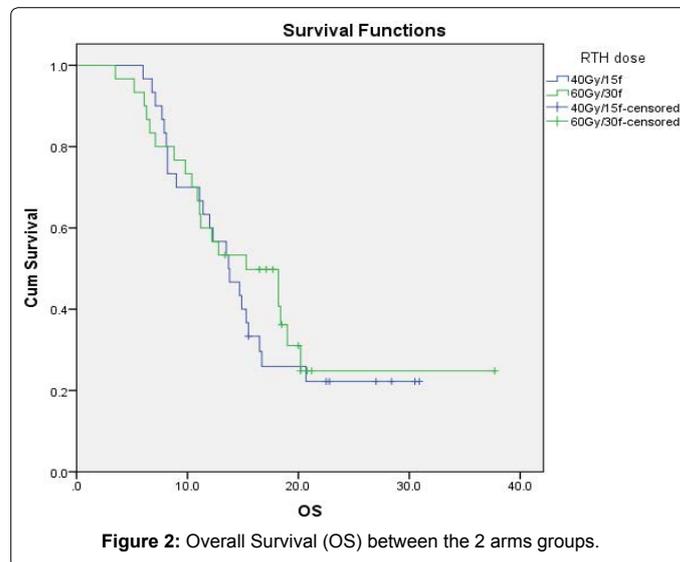
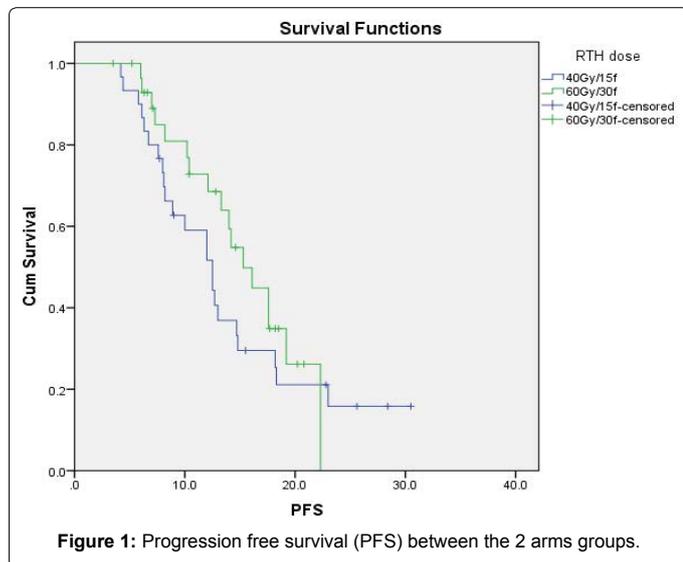
When evaluating the impact of different variables on OS in the two groups. In univariate analysis in the same group, we found longer overall survival with performance status (PS) 1 versus 2 in both groups as 15.3 months versus 11.4 months (p-value=0.038) in short course, and 20.2 months versus 11.1 months (p-value=0.031) in standard course. And for patients underwent total or subtotal resection versus biopsy only as illustrated in Table 2. In multivariate analysis we found no statistically significance in correlating different variables with OS in the two groups as illustrated in Table 3.

Toxicity

No significant difference between the treatment groups was found. However, we have non-significant more hematological toxicity in

Characteristics	Short course (n=30)		Standard course (n=30)		P-value
	N	%	N	%	
Median Age by (Years)	51 ± 12.84		49.1 ± 11.21		0.408
Age					
<50 Years	13	-43.3	13	-43.3	1
≥ 50 Years	17	-56.7	17	-56.7	
Sex					
Male	22	-73.3	19	-63.3	0.405
Female	8	-26.7	11	-36.7	
P.S					
1	12	-40	10	-33.3	0.592
2	18	-60	20	-66.7	
Surgery Type					
Biopsy	12	-40	13	-43.3	0.428
Subtotal Excision	13	-43.3	13	-43.3	
Total Excision	5	-16.7	4	-15.4	
Pre MRI Size by (cm)	5.9	±1.29	5	±1.43	0.392
Pre MRI Size					
<5 cm	7	-23.3	12	-40	0.165
≥ 5 cm	23	-76.7	18	-60	
Lesion Site by lobes					
Thalamic and Pineal Body	0	0	4	-15.4	0.389
Frontal	8	-26.7	7	-23.3	
Temporal	9	-30	8	-26.7	
Parietal	10	-33.3	9	-30	
Occipital	3	-10	3	-10	

Table 1: Patient and tumor characteristics.



standard course. Also we found more non-significant GIT toxicity in the form of anorexia (12 patient; 40%) and vomiting (12 patient; 40%) in the standard course. Grade 3 fatigue is reported in one patient (3.3%) in short course. The main adverse events of the two groups of patients are summarized in Table 4.

Discussion

The idea of hypofractionation in GBM is very attractive, as the disease is very common and has a poor prognosis with the standard treatment. However, we have only limited number of trials addressing this type of treatment in all age groups. Selected trials are illustrated in

Table 5, the trials mainly started in the elderly with bad performance status. Currently hypofractionation radiation therapy became established in the elderly, especially patients above 70 years old. The concomitant use of TMZ with hypofractionation provided a significant survival advantage. From my prespective, it is very important to test the hypofractionation theory in all age groups as increasing the dose per fraction with concomitant use of TMZ can improve the outcome results and decrease the treatment cost and time.

There are different schedules of hypofractionation, ranging from 2 or 3 up till 4 weeks, with or without TMZ. In our study, we chose the schedule of 40 Gy in 15 fractions over 3 weeks, which is identical to

Variable	Short course (n=30)	Standard course (n=30)
Age		
<50 years	13.7	18.4
≥ 50 years	13.8	12.8
P-value	0.413	0.096
Mass Size		
<5 cm	15.3	18.2
≥ 5 cm	13.5	12.2
P-value	0.549	0.321
Surgery Type		
Biopsy	11.1	8.8
Subtotal Excision	16.7	19
Total Excision	15.5	20
P-value	0	0
Sex		
Male	12.3	12.8
Female	16.5	18.2
P-value	0.089	0.808
P.S		
1	15.3	20.2
2	11.4	11.1
P-value	0.038	0.031
Lesion Site		
Rt	13.8	18.2
Lt	13.5	12.2
Central	NA	8.8
P-value	0.604	0.504
Lesion Site by lobes		
central	NA	6.1
Frontal	15.5	20.2
Temporal	9	12.8
Parietal	13.8	18.2
Occipital	11.4	11.1
P-value	0.183	0.5

Table 2: Correlation with O.S in Same group in univariate analysis.

Variable	Short course (n=30)	Standard course (n=30)	P-value	Std. err	HR	Lower 95% CI	Upper 95% CI
Age							
<50 years	13.7	18.4	0.523	0.454	1.401	0.498	3.946
≥ 50 years	13.8	12.8	0.775	0.384	1.116	0.526	2.369
Mass Size							
<5 cm	15.3	18.2	0.682	0.559	1.272	0.403	4.022
≥ 5 cm	13.5	12.2	0.935	0.349	1.03	0.503	2.111
Surgery Type							
Biopsy	11.1	8.8	0.615	0.412	0.541	2.821	1.847
Subtotal Excision	16.7	19	0.736	0.524	0.3	2.342	3.334
Total Excision	15.5	20	0.259	1.168	0.378	36.818	36.818
Resection (subtotal and total)	16.5	20.2	0.36	0.497	0.609	3.833	
Sex							
Male	12.3	12.8	0.44	0.371	1.332	0.644	2.756
Female	16.5	18.2	0.541	0.618	0.685	0.204	2.301
P.S							
1	15.3	20.2	0.601	0.589	1.361	0.429	4.32
2	11.4	11.1	0.746	0.367	1.126	0.548	2.313
Lesion Site							
Rt	13.8	18.2	0.213	0.457	1.766	0.721	4.324

Lt	13.5	12.2	0.61	0.495	0.777	0.294	2.051
Lesion Site by lobes							
Thalamic and Pineal Body	NA	6.1	X	X	X	X	X
Frontal	15.5	20.2	0.87	0.683	0.894	0.234	3.41
Temporal	9	12.8	0.532	0.579	1.437	0.462	4.473
Parietal	13.8	18.2	0.593	0.588	1.37	0.432	4.34
Occipital	11.4	11.1	0.695	0.926	1.437	0.234	8.816

Table 3: Shows correlation with O.S between two arms in multivariate analysis.

	Short course		Standard course		P-value
	N	%	N	%	
Anemia					
Grade 1	7	23.3	9	30	0.824
Grade 2	1	3.3	2	6.7	
Neutropenia					
Grade 1	2	6.7	2	6.7	0.964
Grade 2	0	0	0	0	
Thrombocytopenia					
Grade 1	3	10	5	16.7	0.706
Grade 2	0	0	0	0	
Vomiting					
Grade 1	11	36.7	12	40	0.546
Grade 2	2	6.7	0	0	
Alopecia					
Grade 1	21	70	19	63.3	0.401
Grade 2	8	26.7	10	33.3	
Fatigue					
Grade 1	13	43.3	16	53.3	0.292
Grade 2	3	10	6	20	
Grade 3	1	3.3	0	0	
Insomnia					
Grade 1	1	3.3	3	10	0.569
Grade 2	6	20	7	23.3	
Seizure					
Grade 1	11	36.7	7	23.3	0.368
Grade 2	2	6.7	5	16.7	
Headache					
Grade 1	14	46.7	16	53.3	0.322
Grade 2	4	13.4	7	23.3	
Anorexia					
Grade 1	6	20	12	40	0.095
Grade 2	0	0	1	3.3	

Table 4: Incidence of adverse events post concurrent chemoradiation.

the early American short course schedule published in 2004 [3]. It was also used by Perry and his colleagues in a large multicenter trial for the elderly patients [8]. The Nordic study gives a 2-week schedule. However, it is given without TMZ. The addition of TMZ to the short course of radiation therapy was very safe and effective. A large multicenter phase III trial has proved a significant survival improvement with the addition of TMZ [8]. In our study, the combination was very safe.

In our study, the median overall survival was not statistically different between standard and short course, which makes it consistent with the Canadian data published by Roa et al. However, it is different from the Canadian trial by Azoulay et al, which documented the inferior survival for the three weeks arm (40 Gy in 15 fractions over 3 weeks) relative to the standard course and the four- week course (60 Gy in 20 fractions over 4 weeks). We believe that the difference can be explained

by the fact that it was a retrospective study, with a high percentage of patients (81.4%) \geq 65 years in the three-week group relative to only 22.4% in the standard group. In addition, only 55.8% from the three-week group received TMZ relative to 95.2% in the standard group [10]. We found a relatively high median overall survival than documented in the Nordic, Roa, Azoulay and Perry trials. This may be due to the recruitment of a younger age group, better performance status and the use of concurrent and adjuvant TMZ. That makes it consistent with the overall survival documented in a trial done over all age groups and with the use of TMZ [6,7,11].

As with previous studies over GBM, performance status and resection of the tumor were found to be the most important factors for the overall survival. Several clinical studies have indicated that O6-methylguanine-DNA methyltransferase (MGMT) promoter

Author	Trial Type	Age	Schedule	N	OS	Finding
Roa [3]	Phase III	≥ 60	SRT 60 Gy/30 fr/6 wks	47	5.1	No difference in survival
			HRT 40 Gy/15 fr/3 wks	48	5.6	
Malmström [4]	Phase III	≥ 70	Temozolomide	93	8.3	Poor outcome with standard radiotherapy.
			SRT 60 Gy/30 fr/6 wks	98	7.5	
			HRT 34 Gy/10 fr/2 wks	100	6	
Reddy [6]	Phase II	All	HRT 60 Gy/10 fr/2 wks+TMZ	24	16.6	HRT+TMZ is safe
Jastaniyah [7]	Phase I	All	HRT 54.4 Gy/20 fr/4 wks+TMZ (76%)	25	15.6	HRT+TMZ is feasible and safe.
			HRT 60 Gy/22 fr/4.5 wks+TMZ (76%)			
Azoulay [10]	Retrospective	All	SRT 60 Gy/30 fr/6 wks+TMZ	147	16	HF60 is equal to SRT, both are significantly better than HF40.
			HF60 60 Gy/20 fr/4 wks+TMZ	86	15	
			HF40 40 Gy/15 fr/3 wks+TMZ (55%)	43	8	
Carlson [11]	Randomized phase II	All	HRT 60 Gy/10 fr/2 wks+TMZ	26	16.3	No survival benefit for the addition of BEV.
			HRT 60 Gy/10 fr/2 wks+TMZ+BEV	30	16.3	
Perry [8]	Phase III	≥ 65	HRT 40 Gy/15 fr/3 wks	281	7.6	Survival benefit for the addition of TMZ
			HRT 40 Gy/15 fr/3 wks+TMZ	281	9.3	
Current Study	Randomized phase II	All	SRT 60 Gy/30 fr/6 wks+TMZ	30	15.3	No significant difference
			HRT 40 Gy/15 fr/3 wks+TMZ	30	13.7	

SRT: Standard Radiation Therapy. HRT: Hypofractionated Radiation Therapy. TMZ: Temozolomide. HF: Hypofractionated. BEV: Bevacizumab. N: Number of patients. OS: Overall Survival (in months).

Table 5: Selected trials of hypofractionation in GBM.

methylation is associated with improved overall survival [4,8]. However, we did not assess MGMT due to a financial issue and as all the patients were planned to receive TMZ as concomitant and adjuvant with radiation.

Regarding pseudoprogression, which has been reported in variable incidence, we believe that it may be related to the timing of the imaging post radiation as the later the imaging, the fewer the incidents of pseudoprogression. We usually do the imaging 3 months post radiation, therefore, we did not find any cases with pseudoprogression. All the cases were true progression.

Short course treatment is relatively associated with less hematological and non-hematological toxicity as a result of half-time treatment duration of TMZ (3 weeks versus 6 weeks). There were no side effects documented from increasing the dose per fraction of radiotherapy from 2 Gy up to 2.66 Gy.

In countries with moderate to low income and a relatively low health budget, the cost of the treatment is very important, specifically when we deal with a fatal disease that has dismal prognosis like GBM. In those cases, the short course schedule is very essential as it decreases the time of radiation therapy and the dose of adjuvant TMZ by 50%.

In conclusion, short course radiotherapy is comparable to the standard course in the treatment of GBM. Accordingly, three weeks radiation therapy concomitant with TMZ followed by adjuvant TMZ can be an option for the treatment of GBM, especially in countries with limited resources.

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