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Standard versus Short Course Radiation Therapy plus Concomitant Temozolamide for Treatment of Glioblastoma Multiforme in Elderly Patients

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Abstract Background: A major challenge concerned with treatment of elderly patients with glioblastoma multiform (GBM) and there is a great controvery about the different treatment modalities. The optimal fractionation schedule of radiotherapy (RT) for GBM is yet to be defined. **Purpose:** The purpose of this study is to assess the efficacy and safety of 2 specific radiation schedules, each combined with temozolamide (TMZ), in patients aged ≥60 years with newly diagnosed GBM. **Patients and Methods**: Forty three patients with GBM, aged ≥60 years, were enrolled during the period from October 2013 to December 2015 at Clinical Oncology Department Tanta University Hospital. All patients had previously undergone surgical resection (total, subtotal or biopsy). After surgery 23 patients patients received standard fractionated RT (60 Gy/30 fractions/6 weeks) and 20 patients received a short course hypofractionated RT (40 Gy/ 15 fractions/3 weeks). All patients received TMZ concomitant with RT at a dose of 75 mg/m^2 daily during RT. This followed or not by adjuvant TMZ with a dose 150 mg/m^2 daily for 5 days and the cycles repeated every 4 weeks for 6-12 cycles. **Results:** The median follow-up time was 5 months, (range, 0-19 months). The median overall survival (OS) time for all patients was 10 months (range, 2-30 months). Median OS time was 11 months (range, 2-18 months) in the standard RT group while it was10 months (range, 7-30 months) in the short course RT group. The 1-year OS rates were 30.4% versus 35% in the standard RT and short course RT groups respectively (p=0.917). Patients in the short course RT group had median PFS 8.5 months compared with 7 months in standard RT group (p=0.447). Short course hypofractionated RT resulted in a comparable rates of toxicity with standard fractionated RT. **Conclusions:** Concomitant RT plus TMZ followed by adjuvant TMZ therapy, is a promising regimen for patients with GBM. The short-course hypofractionated RT can be used for elderly patients with GBM, resulting in comparable OS and toxicity rates with standard fractionated RT and allowing for reduced overall treatment time. To confirm these findings and to determine the optimal RT fractionation for elderly patients with GBM, multicenter trials with a large number of patients are needed.

Key words: glioblastoma multiforme, elderly patients, concomitant TMZ plus RT, short course RT.

1. Introduction

Glioblastoma multiforme (GBM) is the commonest and the most lethal form of glioma in adults accounting approximately 40% of primary CNS malignancies [1]. Glioblastoma multiforme diagnosed at older age and the median age of diagnosis is sixty four years. Hence, GBM represents about fifty percent of primary brain tumors in the elderly patients [2].

Surgical resection followed by concomitant radiotherapy (RT) and temozolamide (TMZ) and adjuvant TMZ is the current recommended therapy aiming at a better local control rate and decreasing the incidence of adverse effects [3, 4].

The optimal RT fractionation schecdule for GBM is still needed to be defined. The current standard RT fractionation regimen for GBM is 60 Gy/30 fractions, 2.0 Gy per fraction/6 weeks [5]. Hypofractionation RT means decreasing the overall treatment time by applying a fewer larger fractions sizes aiming at potential increase cell kill and, limitation of tumor repopulation [6,7]. Although many trials had recommended the use of hypofractionated RT [8-10], the standard conventional RT is still the optimal fractionation schedule for treatment of GBM [5].

In this study we compared the short course hypofractionated RT versus standard conventional fractionated RT as regarda the efficacy and safty profile in elderly patients diagnosed with GBM.

2. Patients and Methods

Forty-three patients with GBM were enrolled during the period from October 2013 to December 2015 at Clinical Oncology Department Tanta University Hospital. All patients had previously undergone surgical resection (total or subtotal) or biopsy. After surgery 23 patients received standard conventional fractionated RT (60 Gy/30 fractions/6 weeks) and 20 patients received short course hypofractionated RT (40 Gy /15 fractions /3 weeks).

All patients received concomitant TMZ during RT treatment.

Patient's eligibility criteria included; pathologically proven GBM, Karnofsky performance status (KPS) ≥70, age 60 years or older, no proir brain RT or chemotherapy (CT), adequate hematologic, renal, and hepatic functions. Exclusion criteria included; active ischemic heart disease, cerebrovascular disease, congestive heart failure and any previous or concurrent malignancies at other sites.

All patients were consented for admission into the study.

The initial workup included; medical history, general and local examinations, PS evaluation, hematological with blood chemistry assessments; contrast enhanced computed tomography (CT) and/or gadolinium-enhanced magnetic resonance imaging (MRI) of the brain.

Surgery

Maximum safe surgical resection (total, subtotal) or biopsy was performed and the extent of resection was governed by tumor extent, location, and also based on patient conditions, such as age, PS and general condition. Assessement of presence of residual tumor postoperatively was done by performing MRI and/or CT.

Radiation therapy

Radiation therapy was started within 6 weeks of surgery. Thermoplastic mask for simulation and treatment for patient's immobilization was used. Computed tomography-based planning with 3 mm CT slices was done for every patient and computerized treatment planning was used. All patients were randomized to receive either standard conventional RT or short course hypofractionated RT.

Standard conventional fractionated RT patients group received 60 Gy in two phases: first phase; a dose of 46 Gy/23 fractions was received, and the PTV encompassed the residual tumor with 2 cm margin around the peritumoral edema or 2.5 cm tumor margin if there was no peritumoral edema. Second phase; a dose of 14 Gy/7 fractions was received, and the PTV encompassed the tumor with 2.5 cm margin.

Short course hypofractionated RT patients group received a total dose of 40 Gy /15 fractions /3 weeks and the PTV was the same as applied in the first phase of standard fractionated RT. The PTV was covered by the 95% isodose in most patients.

Photon energy of 6 MeV linear accelerator was used. Treatment plans included opposed wedged lateral fields, or multiple field techniques. Organs at risk including the brain stem, optic chiasm, retina and optic nerves were contoured with respection of their tolerance doses without gross tumor shielding.

Chemotherapy

All patients received 75 mg/m^2 of TMZ during RT daily with or without administration of adjuvant TMZ (150 mg/m^2 daily for 5 consequetive days) and the cycles repeated every 4 weeks for 6-12 cycles.

Prophylactic antiemetic therapy (metoclopramide) was administered during the concomitant and adjuvant phases. Corticosteroids and anticonvulsant were prescribed only as needed.

Patient assessment

During the concomitant phase patients were assessed weekly with complete blood count (CBC), serum electrolytes, liver and renal functions. During adjuvant phase, patients clinically assesseted monthly and CT or MRI of the brain was performed at the end of cycles 3 and 6 for evaluation of tumor response. Acute RT and CT toxicities were recorded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 [11]. Further therapies either with repeat surgery or second line CT in case of development of disease progression was individually descided.

Statistical analysis

The first endpoint was evaluation of the OS time and the second endpoints were evaluation of the PFS time, safety and analysis of the different prognostic factors affecting the survival outcome. Univariate analysis was utelized to assess the impact of the prognostic variables on OS and PFS.

Overall survival was estimated from date of diagnosis to date of death, or last follow-up. The disease progression was defined as residual enhancement progression or appearance of new lesions on radiologic studies. Progression free survival was estimated from the date of treatment initiation until the date of documented disease progression.

Statistical significance of Kaplan-Meier [12] curves was assessed by the log rank test. All analyses were performed using SPSS version 21.0 and p-value ≤0.05 was considered statistically significant.

3. Results

Patient characteristics

Patient's characteristics according the treated group are shwon in Table 1. The mean age ±SD was 63.9 ± 3.67 years, (range; 60-71 years) for all patients and 41.9% of patients aged >65 years. Male patients represented in 58.1% of patients. The majority of patients (51.2%) had KPS >70. The median age of patients in the standard RT group was 66 years and 56.5% of them were presented with KPS ≤70. Extent of peritumoral edema > half hemisphere was represented in 47.8% of patients in the standard RT group whereas it represented in only 20% of patients in short course RT group. One hundred percent of patients in the standard RT group had unifocal GBM

while 10% of patients in short course RT group had multifocal GBM. Subtotal resection was the commonest surgical interference performed for all patients (51.2%); on the other hand, total resection was performed in only two patients (one patient in each studied group). Twenty six (60.5%) patients had received adjuvant TMZ in all series.

Table 1. Patient's characteristics according to treated group.

Characteristics	Whole group (*n* = 43)	60 Gy / 30 Fr group (*n* = 23)	40 Gy / 15 Fr group (*n* = 20)	*p*
	No (%)	No (%)	No (%)	
Age, years				
Median	64	66	61.5	
Mean±SD	63.9±3.67	64.8±3.84	62.9±3.26	
Range	60-71	60-71	60-69	0.295
≤65	25 (58.1)	12 (52.2)	13 (65)	
>65	18 (41.9)	11 (47.8)	7 (35)	
Sex				
Male	25 (58.1)	16 (69.6)	9 (45)	0.093
Female	18 (41.9)	7 (30.4)	11 (55)	
KPS				
>70	22 (51.2)	10 (43.5)	12 (60)	0.219
≤70	21 (48.8)	13 (56.5)	8 (40)	
Tumor focality				
Unifocal	41 (95.3)	23 (100)	18 (90)	0.210
Multifocal	2 (4.7)	0 (0)	2 (10)	
Tumor size (cm)				
Median	4.5	5	3.1	
Mean±SD	3.87±1.6	4.37±1.56	3.3±1.49	
Range	1-7.8	1.5-7.8	1-6.2	0.019*
≤ 4.5 cm	24 (55.8)	9 (39.1)	15 (75)	
> 4.5 cm	19 (44.2)	14 (60.9)	5 (25)	
Extent of edema				
Non	4 (9.3)	1 (4.3)	3 (15)	
≤ Half hemisphere	24 (55.8)	11 (47.8)	13 (65)	0.120
> Half hemisphere	13 (34.9)	11 (47.8)	4 (20)	
Extent of surgery				
Biopsy	19 (44.2)	9 (39.1)	10 (50)	
Subtotal resection	22 (51.2)	13 (56.5)	9 (45)	0.751
Total resection	2 (4.7)	1 (4.3)	1 (5)	
Adjuvant CT				
Yes	26 (60.5)	11 (47.8)	15 (75)	0.065
No	17 (39.5)	12 (52.2)	5 (25)	

*Significant.

Survival

At the end of the study all studied patients were available for statistical analysis where, 41 patients (95.3%) were died and 4.7% of patients were still alive. The median duration of follow-up period was 5 months, (range, 0-19 months) for whole patients.

The median OS time was 10 months (range, 2-30 months) and the mean ± SD OS time was 11.12 ± 4.20 months for whole patients. The median PFS time was 7 months (range, 1.5-21 months) and the mean ± SD PFS time was 8.31±3.18 months for the whole patients. The median OS time was 11 months (range, 2-18 months) in the standard fractionated RT group and was 10 months (range, 7-30 months) in the short course hypofractionated RT group (p = 0.268). Median PFS time was 7 months in the standard fractionated RT group and was 8.5 months in the short course hypofractionated RT group (p = 0.447).

For all studied patients the 1-year OS rate was 32.6% and the overall PFS was 5.5% (Figure 1&2). The one-year OS rates were 30.4% and 35% (HR: 0.96, 95% CI, 0.52-1.79) in the standard fractionated RT group and short course hypofractionated RT group respectively (p = 0.917, Figure 3). The one-year PFS

rates were 0% and 12.9% (HR: 0.47, 95% CI, 0.24-0.91) in the standard fractionatedRT group and short course hypofractionated RT group respectively (p = 0.026, Figure 4).

As regard the whole patients, our data also showed that the 1-year OS rates were 40% and 22% for patients aged ≤ 65 and > 65 years respectively (p = 0.340, Figure 5) and the 1-year PFS rates were 8.5% and 0% for patients aged ≤ 65 and > 65 years respectively (p = 0.049).

We analyzed the OS and PFS rates for all studied patients in relation to prognostic factors. Univariate analysis showed that, KPS was the most significant independent prognostic factors for OS (p = 0.010, Figure 6), whereas KPS and total RT dose were significantly affected the PFS (Table 2).

As regard patients age, the difference in the OS rate between patients aged ≤65 and >65 years was not significant (p = 0.340) while patients aged ≤65 years had a better PFS rate (p = 0.049).

Eighteen patients (41.9%) received the planned treatment protocol of concomitant and adjuvant TMZ. The majority of patients completed their RT within the planned protocol. Unplanned delay in RT were usually brief (median, five days) and interruptions of concomitant TMZ plus RT occurred in only 7 (16.3%) patients due to grade 3 or 4 hematologic toxicities (leucopenia and thrombocytopenia) in 3 patients and the other causes were machines technical problems or holidays. In the concomitant phase only 2 (4.7%) patients discontinued TMZ due to ≥grade 3 hematological adverse effects.

Adjuvant TMZ had administered in 26 (60.5%) patients with total 144 cycles with a median 6 cycles (range, 1-10); 73% (19/26) of them completed 6 cycles. Eleven patients received adjuvant TMZ in standard RT group with a median 6 cycles (range, 1-7) and 15 patients received adjuvant TMZ in short course RT group with a median 6 cycles (range, 1-10). The main cause preventing receiving the adjuvant TMZ therapy was progression of the disease. Adjuvant CT was discontinued in 6/26 (23%) of patients (2 patients in short course RT group and 4 patients in standard RT group) because of progressive disease in 4 patients and in only 2 (7.7%) patients because of grade 3/4 toxic effects.

Table 2. Univairate analysis of prognostic factors affecting OS for all patients.

Prognostic factors	No.	OS			PFS		
		1-year OS	HR, 95% CI	*p*	1-year PFS	HR, 95% CI	*p*
Age, years							
≤65	25	40%	1.35 (0.72-2.55)	0.340	8.5%	1.97 (1.00-3.85)	0.049*
>65	18	22%			0%		
Sex							
Male	25	28%	0.86 (0.49-1.62)	0.646	4%	0.59 (0.49-1.85)	0.874
Female	18	38.9%			9.3%		
KPS							
>70	22	50%	1.54 (1.11-2.13)	0.010*	10.5%	1.69 (1.17-2.44)	0.005*
≤70	21	14.3%			0%		
Tumor focality							
Unifocal	41	34.1%	3.22 (0.72-14.25)	0.123	5.7%	1.82 (0.43-7.83)	0.419
Multifocal	2	0%			0%		
Extent of surgery							
Biopsy	19	31.6%	1.51 (0.90-2.53)	0.110	50%	1.47 (0.87-2.48)	0.152
Subtotal resection	22	27.3%			6.3%		
Total resection	2	50%			0%		
Total RT dose							
60 Gy / 30 Fr	23	30.4%	0.96 (0.52-1.79)	0.917	0%	0.47 (0.24-0.91)	0.026*
40 Gy / 15 Fr	20	35%			12.9%		
Tumor size							
≤ 5 cm	24	37.5%	1.37 (0.74-2.55)	0.312	9.7%	1.51 (0.79-2.89)	0.215
> 5 cm	19	26.3%			0.0%		
Adjuvant CT							
No	17	23.5%	0.73 (0.39-1.38)	0.343	0.0%	0.73 (0.37-1.44)	0.365
Yes	26	38.5%			8.4%		

*Significant.

Hematologic toxicity

During the concomitant phase, ≥grade 3 toxicity was 13% versus 5% in the standard RT and short course RT groups respectively. During the adjuvant TMZ phase, grade 3/4 toxicities were 27.3% versus 26.7%% in the conventional RT and short course RT groups respectively.

Non-hematologic toxicity

During the concomitant phase, ≥grade 3 toxicity was 26% versus 10% in the standard RT and short course RT groups respectively. During the adjuvant TMZ phase, grade 3/4 toxicity was 27.3% versus 20% in the standard RT and short course RT groups respectively (Table 3). The delayed RT toxicity was not definitively assessed due to short follow-up peroid; with a follow-up >12 months only 14 (32.6%) patients were alive.

Repeated surgery was performed for 2 (4.7%) patients as a results of disease progression, and 23.3% of patients received salvage CT. Salvage CT response was not recorded as it is not planned in the treatment protocol.

Table 3. Toxicity per treatment group.

Toxicity	60 Gy / 30 Fr group (*n* = 23)				40 Gy / 15 Fr group (*n* = 20)			
	Concomitant CRT (*n* = 23)		Adjuvant TMZ (*n* = 11)		Concomitant CRT (*n* = 20)		Adjuvant TMZ (*n* = 15)	
	G 3 No (%)	G 4 No (%)	G 3 No (%)	G 4 No (%)	G 3 No (%)	G 4 No (%)	G 3 No (%)	G 4 No (%)
Hematological								
Anemia	0	0	1 (9.1)	0	0	0	1 (6.7)	1 (6.7)
Leucopenia	1 (4.3)	0	0	0	0	0	1 (6.7)	0
Neutropenia	0	0	0	0	1 (5)	0	0	0
Thrombocytopenia	1 (4.3)	1 (4.3)	1 (9.1)	1 (9.1)	0	0	1(6.7)	0
Non-hematological								
Nausea &vomiting	1 (4.3)	1 (4.3)	2 (18.2)	0	1 (5)	0	1 (6.7)	0
Infection	1 (4.3)	0	1 (9.1)	0	0	0	1 (6.7)	0
Fatigue	0	2 (8.6)	0	0	1 (5)	0	1 (6.7)	0
Dermatitis	1 (4.3)	0	0	0	0	0	0	0

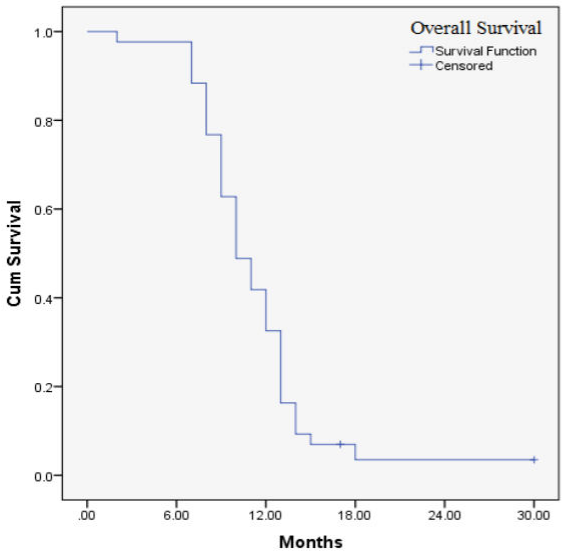

Figure (1): OS for the whole patients.

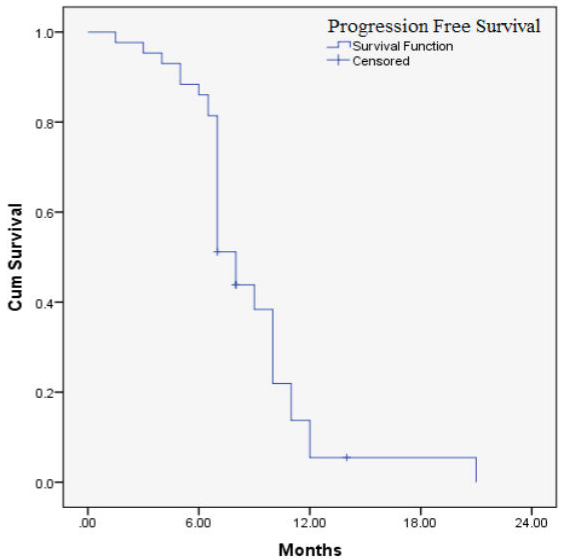

Figure (2): PFS for the whole patients.

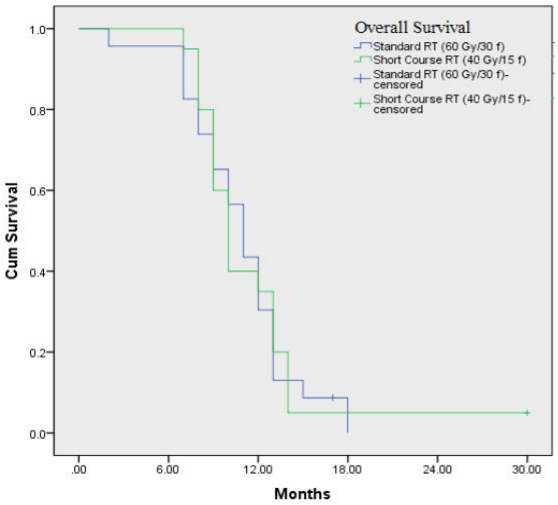

Figure (3): Kaplan Meier curves comparing OS between standard RT (60 Gy) and short course RT (40 Gy) groups.

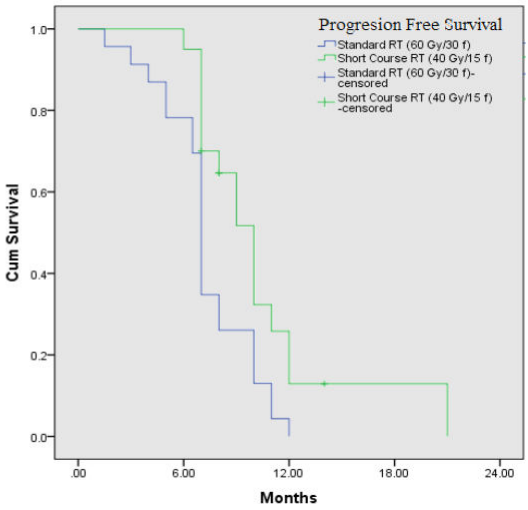

Figure (4): Kaplan Meier curves comparing PFS between standard RT (60 Gy) and short course RT (40 Gy) groups.

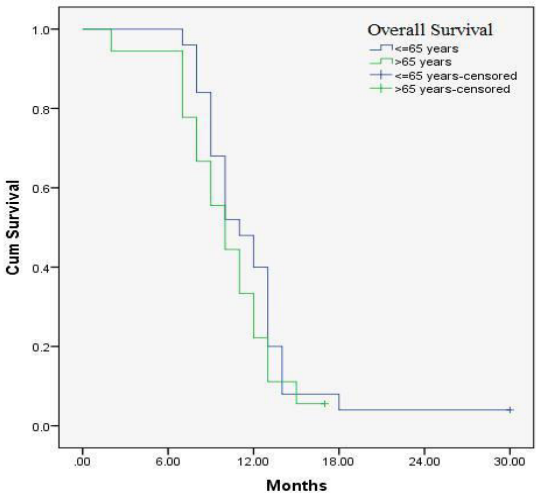

Figure (5): Kaplan Meier curves comparing OS between patients aged ≤65 years and >65 years.

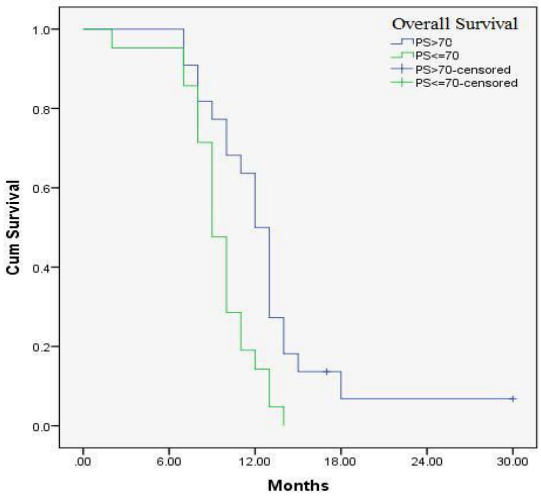

Figure (6): Kaplan Meier curves comparing OS between patients with KPS ≤70 and >70.

4. Discussion

The standard treatment for in elderly GBM patients remains undefined because this population is heterogenous in terms of co-morbidity, PS, and treatment options [13]. Treatment of elderly patients with GBM shouled be made individualized according to PS, age of the patient, patient preferences and O6 - methylguanine-DNAmethyltransferase (MGMT) methylation status [14].

Among GBM patient's age is still the strongest prognostic factor affecting the outcome. At diagnosis about 50% of GBM patients aged ≥65 years [13].

In elderly GBM patients there is an increasing evidence for the use of hypofractionation RT to reduce the overall treatment time and to overcome radioresistance [15]. With using hypofractionation RT there is an increasing rate of cell death as a result of decreased tumor cells repopulation, and higher dose per fraction [7].

Roa et al. [16] studied 100 GBM elderly patients received 40Gy/15 fractions/3 weeks or 60Gy/30 fractions/ 6 weeks without concurrent CT. Median OS was 5.6 for abbreviated course and 5.1 months for standard fractionated course. These results were comparable with that reported by Lutterbach and Ostertag [17], who found that hypofractionated RT (42Gy/12 fractions), resulting in a better OS than that with standard fractionation (7.3 versus 5.6 months, respectively).

As the results of treatment of GBM with RT alone without concomitant CT are very poor and aiming at improving the treatment outcome, concomitant RT with several radiosensitizing CT agents has been explored. Temozolomide is oral alkylating agent that has proved antitumor activity as a monotherapy or combined with other CT agents in the treatment of newly diagnosed and recurrent GBM [18-20].

Over at least 15 years the effect of concomitant standard fractionated RT with TMZ for treatment of GBM has been evaluated. In 1993 and 1996 Newlands et al. [21] and O'Reilly et al. [22] had reported the first phase II studies concerned with the use of TMZ for brain glioma. In 1998, Brock et al. [23] recommended the dose of TMZ as 75 mg/m^2 /day and it is continued to be the optimal dose for brain glioma up till now.

In 2002 Stupp et al. [24] reported a very favorable survival outcome with using concomitant RT plus TMZ and recorded 31% two-year-survival rate. In 2005 also Stupp et al. [3] published a randomized trial comparing RT (60 Gy/30 fractions/6 weeks) alone with concomitant RT plus TMZ. Patients treated with concomitant therapy also received adjuvant TMZ for 6 cycles. The OS time was improved with the concomitant therapy compared with RT alone (median survival; 14.6 vs. 12.1 months, respectively). Another randomized trial with smaller number of patients was reported by Athanassiou et al. in 2005 [25] comparing RT alone and concomitant RT plus TMZ. The median OS times were 8.9 vs. 13.6 months and the one-year OS rates were 15.7% vs. 56.3% for RT alone and concomitant RT plus TMZ respectively. Currently it is widely accepted that concomitant RT plus TMZ followed by adjuvant TMZ therapy is the standard treatment for GBM patients [18, 25, 26].

In the present study we defined elderly patients as those aged ≥ 60 years; however most of the GBM trials variably defined the elderly patients as thos ≥60, ≥65, or ≥70 years. **[14].**

In this study, we assessed whether hypofractionated RT given as 40 Gy/15 fractions/3weeks concomitant with TMZ was safe and effictve compared with standard fractionated RT given as 60 Gy /30 fractions/6 weeks concomitant with TMZ among GBM patients aged ≥60 years. As regard the survival outcome of all patients in this study, the median OS was 10 months and median PFS was 7 months.

The median OS and PFS time were 11 and 7 months respectively in our standard RT group. Similarly Combs et al. **[27]** recorded 11 months median survival for GBM patients treaded with concomitant TMZ plus 60 Gy RT. The median OS and PFS time were 10 and 8.5 months respectively in our short course RT group and this results were comparable with the results of other previous studies utilizing TMZ plus short course RT in elderly with GBM such as Fiorica et al. **[28]** and Minniti et al. **[29]** studies (median survival 10.2 and 11.4 months respectively).

Azoulay et al. **[30]** studied 276 GBM patients, 147 patients of them treated with conventional RT (60 Gy/30 fractions), 86 patients treated with 60 Gy/20 fractions, and 43 patients treated with short course RT (40 Gy/15 fractions). Median OS and PFS times were 16 and 9.23 months, respectively in the conventional RT group. This was comparable to outcome in the short course RT group with median OS was 15 months and median PFS was 9.1 months and concluded that, although there was no significant survival benefit from the use of short course RT, the improved quality of life and better coast benefit ratio for patients treated with short course RT should be made in consideration.

In our study, no treatment related death was recorded, concomitant RT plus TMZ was discontinued in only 2 (4.7%) patients due to ≥grade 3 hematological toxicity. Stupp et al. **[3]** reported that TMZ was discontinued in 13% of the patients mainly due to adverse effects. Minniti et al. **[29]** reported only one out of 71 patients discontinued TMZ during RT due to grade 2 thrombocytopenia.

For all our patients ≥grade 3 leucopenia was recordrd in 2.3% and ≥grade 3 thrombocytopenia was recordrd in 4.7% of the patients and this results were nearly similar to that reported with Newlands et al. **[21]** (3.5% and 5.2% for ≥grade 3 thrombocytopenia and Leucopenia respectively). Minniti et al. **[29]** reported ≥grade 3 hematotoxicity (mainly neutropenia and thrombocytopenia) were recorded in 9.3% of the patients. Stupp et al. **[3]** reported that, ≥grade 3 hematological toxicity (mainly neutropenia) was recorded in 7% of the patients while Athanassiou et al. **[25]** observed ≥grade 3 hematological toxicity in 8.7% of the patients. Also, Becker-Schiebe et al. **[31]** found that ≥grade 3 thromobocytopenia, leucopenia and anemia were noticed in 8.6%, 7.2% and 5.8% of patients respectively.

In 2013 Gupta et al. **[32]** conducted a study reviewing randomized trials evaluating high grades TMZ adverse effects and reported that the rate of ≥ grade 3 neutropenia and thrombocytopenia were ranged from 5% to 15.5%. Conclusively, the authors found the incidence of ≥grade 3 leucopenia in the range from 3% to 15% and from 0 - 15% for ≥grade 3 thromobocytopenia [28, 33, 34, 35, 36, 37].

In the present study ≥ grade 3 adverse events during the concomitant phase was recorded in 13% versus 5% in the standard RT and short course RT groups respectively. Fiorica et al. **[28]** recorded 23.8% hematological toxicity (only 7% grade 3) and Minniti et al **[37]**. recorded 4% grade 3/4 hematological toxicity

in the patients treated with concomitant TMZ plus 40 Gy RT while Combs et al. [27] recorded 9% hematological toxicity in the patients treated with concomitant TMZ plus 60 Gy RT.

In the present study, as regard hematological toxicity for all patients during the adjuvant TMZ phase, ≥ grade 3 adverse events was recorded in 16.3% of patients while it recorded in 27.3% versus 26.7% of patients in the standard RT and short course RT groups respectively. Also TMZ discontinued in 7.7% due to grade 3 or 4 hematological toxicity. A meta-analysis that included 3,004 GBM patients in 12 randomized trials [38] revealed that during adjuvant TMZ <10% of patients developed ≥grade 3 hematologic toxicity, and <2% of patients had discountiued TMZ due to its toxicity.

As regard the one-year OS rate in this study there was no significant difference between patients treated with standard conventional RT and short course RT (30.4% and 35% respectively, p=0.917). Univariate analysis of different prognostic factors revealed that, KPS was the only parameter significantly affected the OS.

The most powerfull prognostic factor for GBM in elderly patients is the advanced age. For all GBM patients regardless they age, even when aggressively treated with multimodality therapy the median OS time is only around 15 months [3]. Arvold and Reardon [14 reported that, in addition to patient age, there are many other parameters significantly affecting the outcome such as; extent of surgical resection, PS and methylation status of MGMT promoter.

Lichtman et al. [39] reported that, poor prognostic factors of GBM leading to high mortality rate include; presence of multiple comorbid conditions, high grade systemic therapy adverse effects such as hematologic toxicity, cardiotoxicity and mucositis and also drug interactions. Approximately 40%–60% of GBM among the elderly patients express [40, 41, 42] methylation of MGMT gene promoter which is still considered as a very strong prognostic and predictive parameter for GBM in elderly patients. [43]

Molecular studies have proposed that prognosis of GBM patients is affected by interaction between patients age and many genetic abnormalities such as, tumor suppressive gene p53 mutation, CDKN2A/p16 deletion which consider as a poor prognostic factors [44], epidermal growth factor receptors (EGFR) amplification and 1p36 deletion which consider as good prognostic factor [45].

5. Conclusions:

Concomitant RT plus TMZ followed by adjuvant TMZ therapy, is a promising regimen for GBM patients. The short course hypofractionated RT can be used for elderly patients with GBM, resulting in comparable OS and toxicity rates with standard fractionated RT and allowing for reduced overall treatment time. To confirm these findings and to determine the optimal RT fractionation for elderly patients with GBM, multicenter trials with a large number of patients are needed.

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