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

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Abstract Background: Treating elderly patients with glioblastoma multiform (GBM) is a major challenge and different treatment modalities are controversial. The optimal fractionation schedule of radiotherapy (RT) for GBM is yet to be determined. **Purpose:** The main 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, age 60 years or older, were enrolled between October 2013 and 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 RT (60 Gy in 30 fractions over 6 weeks) and 20 patients received a hypofractionated short course RT (40 Gy in 15 fractions over 3 weeks). All patients received concomitant TMZ 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, 5 days every 28 days for 6-12 cycles. **Results:** The median follow-up time was 5 months, (range, 0-19 months). The median survival time for the whole population was 10 months (range, 2-30 months). Median survival 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 survival 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 RT resulted in a comparable rates of toxicity with standard RT. **Conclusions:** The hypofractionated short course RT can be used for patients with GBM, resulting in comparable overall survival, comparable rates of toxicity and allowing for a shorter treatment time than standard RT. To confirm this, a multicenter, meta-analysis and a randomized trial with a large number of patients are needed to determine the optimal fractionation for GBM.
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Key words: Glioblastoma Multiforme, elderly patients, concomitant TMZ plus RT, Short course RT.

1. Introduction

Glioblastoma multiforme is the most lethal form, most common glioma in adults and accounts for 40% of primary CNS malignancies [1] Glioblastoma multiforme is primarily diagnosed at older ages, with a median age at diagnosis of 64 years. Hence, GBM constitutes about 50% of primary brain tumors in the elderly patients [2].

Maximal safe resection followed by radiotherapy (RT) with concomitant and adjuvant temozolamide (TMZ0 is the current standard of care aiming at improving the local control rate and reducing the toxic effects [3, 4].

The optimal fractionated RT regimen in GBM remains to be determined. The current standard RT regimen for GBM involves the delivery of 60 Gy in 2.0 Gy per fraction, delivered over 6 weeks [5]. Hypofractionation refers to the use of fewer larger fractions sizes with reduction of the overall time of treatment, limit tumor repopulation, and potentially increase cell kill [6,7]. Despite a number of studies supporting the use of hypofractionated RT [8- 10], the current standard conventional RT regimen is still the standard of care in GBM [5].

Our study investigates the benefits of short course RT in comparison with standard conventional RT in elderly patients diagnosed with GBM.

2. Patients and methods

Forty three patients with GBM were enrolled between October 2013 and December 2015 at Clinical Oncology Department Tanta University Hospital. All patients had previously undergone surgical resection (total, subtotal or biopsy). After surgery 23 patients received standard conventional RT (60 Gy in 30 fractions over 6 weeks) and 20 patients received short-course RT (40 Gy in 15 fractions over 3 weeks). All patients received concomitant TMZ during RT treatment.

Patients eligibility criteria included; biopsy-proven GBM, Karnofsky performance status (KPS) ≥70, age ≥ 60 years, no previous brain irradiation or chemotherapy (CT), adequate hematologic, renal, and hepatic functions, defined as white blood cell count

≥4,000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥10 mg/dl, serum creatinine level ≤1.5 mg/dl, calculated creatinine clearance ≥50 mg/min, liver transaminase levels ≤3 times the upper normal limit, serum bilirubin ≤1.5 mg/dl. Exclusion criteria included; active ischemic heart disease, cerebrovascular disease, congestive heart failure and any previous or concurrent malignancies at other sites.

All patients were informed of the nature of the study and had consented for admission into the study.

The baseline examination included a complete medical history, physical examination, determination of PS, hematological with blood chemistry assessments, and gadolinium-enhanced magnetic resonance imaging (MRI) or contrast enhanced computed tomography (CT) of the brain.

Surgery

Maximum safe resection (total, subtotal) or biopsy was performed by the neurosurgeon and the extent of resection was based tumor location, disease extent, and also on patient characteristics, which included PS, age, and co-morbidities. Presence of residual disease was assessed via postoperative gadolinium-enhanced MRI.

Radiation therapy

Radiation therapy started within 6 weeks of surgery. Patients were immobilized with a thermoplastic mask for simulation and treatment. Patient underwent CT-based planning with 3 mm slices and randomly assigned to standard conventional RT (60 Gy in 30 fractions over 6 weeks) or short-course regimen (40 Gy in 15 fractions over 3 weeks).

Patients receiving standard RT were treated in two phases; prescribed dose of 46 Gy in 23 daily fractions (first phase) and the planning target volume (PTV) was based on preoperative CT and MRI studies and included the enhancing residual disease plus 2-cm margin around the peritumoral edema or a 2.5-cm tumor margin if there was no peritumoral edema. In the second phase, the prescribed dose was 14 Gy in seven daily fractions, and the PTV was defined as preoperative enhancing tumor with a 2.5-cm margin.

Patients who were randomly assigned to short course treatment received a total dose of 40 Gy in 15 daily fractions to a PTV that was identical to that used in the first phase of standard treatment. In most cases, the PTV was covered by the 95% isodose.

Photon energy of 6 MV linear accelerator was used. Treatment plans included opposed lateral fields, wedged pair fields, or multiple field techniques. Computer-aided treatment planning was recommended. Organs at risk including the brainstem, optic chiasm, and optic nerves were contoured. Attempts were made to limit the dose of RT to the optic chiasm (54 Gy), retina (50 Gy), and brainstem (54 Gy), provided this could be accomplished without shielding gross tumor.

Chemotherapy

All patients received concomitant TMZ 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, 5 days every 28 days, for 6 cycles.

During the concomitant and adjuvant regimens, prophylactic antiemetic therapy (metoclopramide or 5-hydroxytryptamine-3 antagonists) was prescribed. Anticonvulsant and corticosteroids were used only as required. The corticosteroids dosage was chosen individually according to the patient's need.

Patient assessment

Patients were assessed weekly during the concomitant phase with blood tests including; complete blood count (CBC), serum electrolytes as well as renal and liver functions. After completion of concomitant phase and during adjuvant TMZ therapy, patients underwent a monthly clinical evaluation and gadolinium-enhanced MRI or contrast enhanced CT of the brain at the end of cycles 3 and 6 for evaluation of tumor response. Acute toxicities from RT and CT reported according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 [11]. If disease progression occurred, further treatment with repeat surgery or second line CT was at the physician's discretion.

Statistical analysis

The primary endpoint of this study was evaluation of the overall survival (OS) time and the secondary endpoints were evaluation of the progression free survival (PFS), safety and analysis of the different prognostic factors affecting the survival outcome. Univariate analysis was used to assess the impact of different prognostic factors on OS and PFS. The effect of prognostic factors on survival was quantified by means of hazard ratios (HRs) with 95% confidence intervals (95% CIs).

Overall survival was measured from date of study entry until date of death, or date of last clinical follow-up visit. The disease progression was defined as progressive residual enhancement or new areas of disease appeared on imaging studies. Progression free survival was measured from the date of study entry until the documentation of disease progression.

Statistical significance of Kaplan-Meier [12] curves was assessed by the log rank test. All P values are two sided and a p-value ≤0.05 was considered statistically significant for all analyses. All analyses were performed using statistical package for the social science (SPSS) version 21.0 (SPSS Inc., Chicago, IL).

3. Results

Patient characteristics:

Patient characteristics according the treated group are summarized in Table 1. The mean age ±SD of all patients was 63.9 ± 3.67 years, (range; 60-71 years) and 41.9% of patients aged >65 years. Twenty five (58.1%) patients were male and 41.9% were female with male to female ratio was 1.4:1. The majority of patients (51.2%) had a KPS of >70. Patients in the standard RT group were older in age, with a median age of 66 years, and had a worse PS. 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 per treatment groups.

Characteristics	Whole group (*n* = *43*)	60 Gy / 30 Fr group (*n* = 23)	40 Gy / 15 Fr group (*n* = 20)	P value
	No (%)	No (%)	No (%)	
Age, years				
Median	64	66	61.5	0.295
Mean±SD	63.9±3.67	64.8±3.84	62.9±3.26	
Range	60-71	60-71	60-69	
≤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	0.019*
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	
≤ 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)	0.120
≤ Half hemisphere	24 (55.8)	11 (47.8)	13 (65)	
> Half hemisphere	13 (34.9)	11 (47.8)	4 (20)	
Extent of surgery				
Biopsy	19 (44.2)	9 (39.1)	10 (50)	0.751
Subtotal resection	22 (51.2)	13 (56.5)	9 (45)	
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 alive. The median duration of follow-up period was 5 months, (range, 0-19 months) for the whole patients.

On Kaplan-Meier analysis, the median survival time for the whole population was 10 months (range, 2-30 months) and the mean ± SD survival time was 11.12 ± 4.20 months. The median PFS time for the whole population was 7 months (range, 1.5-21 months) and the mean ± SD PFS time was 8.31±3.18 months. The median survival time was 11 months (range, 2-18 months) in the standard RT group was 10 (range, 7-30 months) in the short course RT group (p = 0.268). Median PFS time was 7 months in the standard RT group and was 8.5 months in the short course 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 RT group and short course 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 RT group and short course 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 RT total dose were the most significant independent prognostic factors for PFS (Table 2).

As regard patients age, there was no significant difference in the OS rate between patients aged ≤65 and >65 years (p = 0.340) while patients aged ≤65 years had a better PFS rate (p = 0.049).

Eighteen patients (41.9%) received all concomitant and adjuvant TMZ as planned in the protocol. 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 reasons were mainly administrative (e.g., holidays or technical equipment problems). Only 2 (4.7%) patients discontinued TMZ during the concomitant phase due to grade 3 or 4 hematological toxicity.

Adjuvant TMZ had received 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 reason for not beginning adjuvant TMZ therapy was disease progression. Adjuvant CT was discontinued in 6/26 (23%) of patients (4 patients in standard RT group and 2 patients in short course 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 value	1-year PFS	HR, 95% CI	P value
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%		
RT total 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 RT plus TMZ phase, grade 3/4 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 toxicities

During the concomitant RT plus TMZ phase, grade 3/4 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 short duration of follow-up precludes definitive assessment of late RT toxicity; only 14 (32.6%) patients were alive with a follow-up longer than 12 months.

At the time of progression, 4.7% of patients underwent a second surgery, and 23.3% of patients received salvage CT. The response to salvage CT was not recorded as a part of our study.

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)	
	Grade 3 No (%)	Grade 4 No (%)	Grade 3 No (%)	Grade 4 No (%)	Grade 3 No (%)	Grade 4 No (%)	Grade 3 No (%)	Grade 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

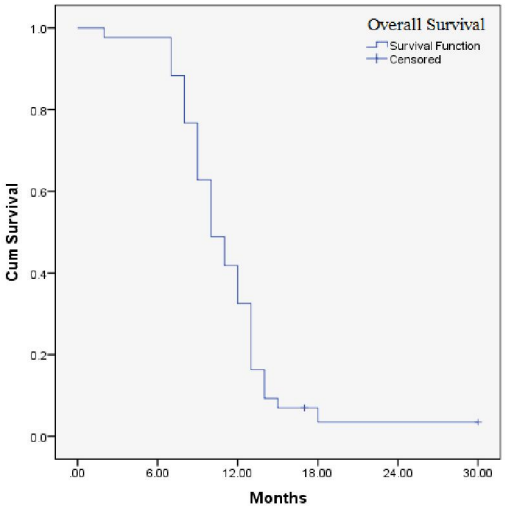

Figure (1): Overall survival for all patients.

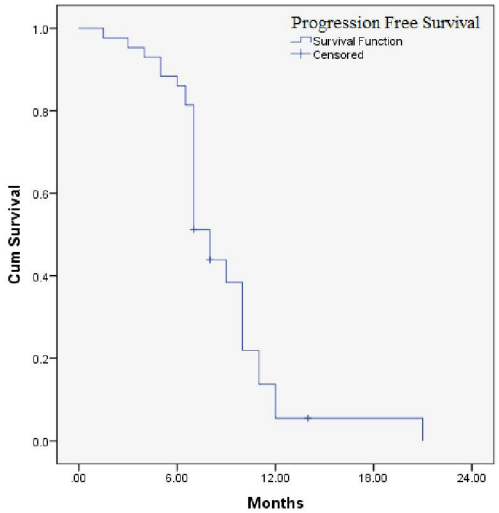

Figure (2): Progression free survival for all patients.

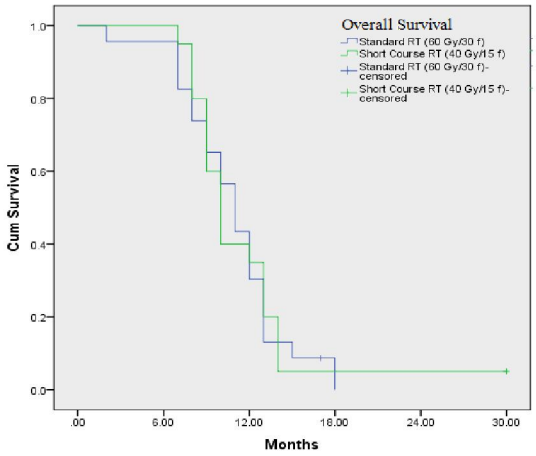

Figure (3): Kaplan Meier curves comparing OS between standard RT (60 Gy) and short course RT (40 Gy) groups.

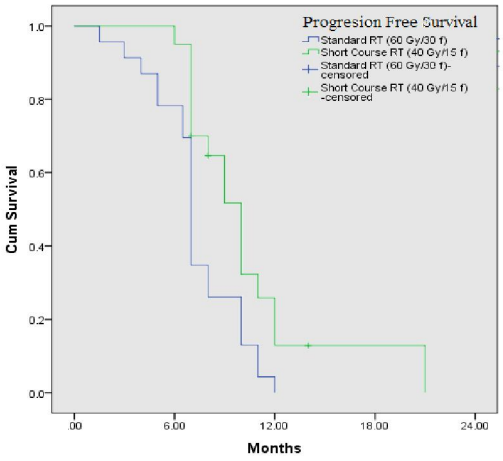

Figure (4): Kaplan Meier curves comparing PFS between standard RT (60 Gy) and short course RT (40 Gy) groups.

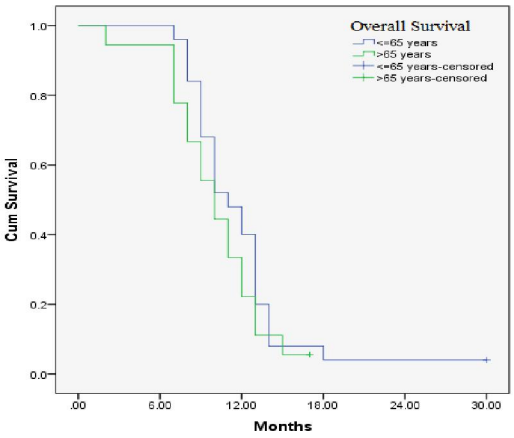

Figure (5): Kaplan Meier curves comparing OS between patients aged ≤65 years and >65 years.

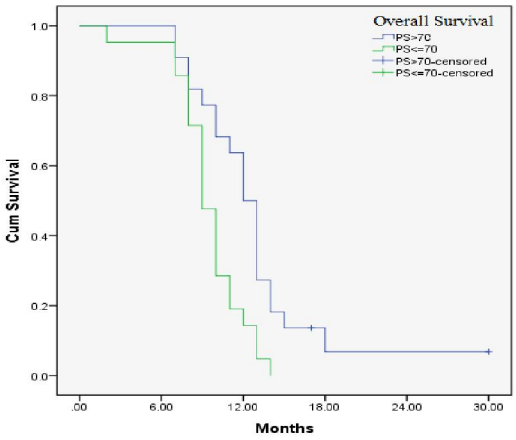

Figure (6): Kaplan Meier curves comparing OS between patients with KPS ≤70 and >70.

4. Discussion

In general, the standard treatment for GBM in elderly patients remains poorly defined due to the heterogeneity of this population in terms of PS, co-morbidity, and treatment options [13]. Management of elderly GBM patients must be made individually according to patient age, O^6-methylguanine-DNA-methyltransferase (MGMT) methylation status, performance score, and patient preferences [14].

Age remains the most powerful prognostic factor among GBM patients. Half of all patients with GBM are aged 65 years or older at the time of diagnosis, and the incidence rate of GBM in patients aged over 65 years is increasing rapidly [13].

There is growing evidence for the use of hypofractionation RT in elderly GBM patients to shorten treatment duration and overcome RT resistance [15]. Hypofractionation RT has the dual effects of increasing cell death from a higher dose per fraction, and reducing the effect of tumor repopulation [7].

Roa et al. [16] randomized 100 elderly patients with GBM to receive 60Gy in 30 fractions, over 6 weeks or an abbreviated course (40Gy in 15 fractions, over 3 weeks), with no concomitant CT. Median overall survival time was 5.1 and 5.6 months, respectively for standard fractionated and short course RT. These results were supported by retrospective data from Lutterbach and Ostertag [17], who described a hypofractionated RT (42Gy in 12 fractions, over 2.5 weeks), resulting in overall survival similar to that of traditional RT treatment (7.3 versus 5.6 months, respectively).

Aiming at improving the poor results of RT without CT in treatment of GBM, RT concomitantly with CT has been explored by using several agents with radiosensitizing properties. Temozolomide is oral, second-generation, alkylating agent that has

demonstrated antitumor activity as a single agent or in combination with other chemotherapeutic agents in the treatment of recurrent and newly diagnosed GBM [18-20].

In the treatment of GBM the effect of the combination of standard RT with simultaneous CT using TMZ has been examined for at least 15 years. The first phase II trials were published in 1993 and 1996 [21, 22]. **Brock et al**. in 1998 [23] recommended a dosage of 75 mg/m^2/day which is still regarded to be the standard.

Very favorable survival data after concomitant RT plus TMZ were found by **Stupp et al**. in 2002 [24] who recorded a 2-year-survival rate 31%. In the randomized trial published by the same author group in 2005 [3] the results of RT alone applying a total dose of 60 Gy in 30 fractions within six weeks were compared with the same concomitant RT plus TMZ of 75 mg/m^2/day. The latter patients also received adjuvant CT with six courses of TMZ (150-200 mg/m^2). The combination therapy clearly improved survival (median survival 14.6 vs. 12.1 months, one-year survival rate 61.1% vs. 50.6%). A second randomized trial with fewer patients was published by Athanassiou *et al.* in 2005 [25]. The authors stated a median survival time of 8.9 months for RT alone compared to 13.6 months for concomitant RT plus TMZ resulting in a one-year survival probability of 15.7% vs. 56.3%. Concomitant RT plus TMZ followed by adjuvant TMZ therapy is widely accepted as the current standard care for patients with GBM [18, 25, 26].

In the present study we defined elderly patients as those aged ≥ 60 years; however definitions of the elderly patients vary in the GBM literatures; with most of the randomized trials including patients aged 60, 65, or 70 years and older [14].

In this study, we investigated whether a 3-week hypofractionated course of RT given as 40 Gy delivered in 15 daily fractions concomitant with TMZ was comparable as regard safety and efficacy with standard 60 Gy delivered in 30 daily fractions concomitant with TMZ among GBM patients aged 60 years or older. The median OS and PFS time for our whole population was 10 and the 7 months respectively.

As regard the survival outcome in both studied groups, the median OS and PFS time were 11 and 7 months respectively in the 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 the short course RT group and this results were comparable with other previous studies utilizing TMZ plus short course RT in elderly with GBM reported with Fiorica et al. [28] and Minniti et al. [29] (median survival 10.2 and 11.4 months respectively).

Azoulay et al. [30] studied 276 patients with GBM, including 147 patients treated with conventional RT (60 Gy in 30 fractions), 86 patients treated with 60 Gy in 20 fractions, and 43 patients treated with short-course RT (40 Gy in 15 fractions). Median survival was 16.0 months with a median PFS of 9.23 months in the conventional RT group. This was comparable to outcome in the short-course RT group with median survival 15.0 months and a median PFS of 9.1 months and from this results they concluded that, although there was no significant survival outcome difference between both treated groups, but the reduction of the financial burden and improved quality of life for patients from a shortened course of RT should not be neglected.

In our study, no treatment related death was reported, concomitant RT plus TMZ was terminated prematurely in only 2 (4.7%) patients due to grade 3 or 4 hematological toxicity. Stupp et al. [3] recorded an early discontinuation of TMZ application in 13% of the patients, the main reason was side 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 and 4 leucopenia were noticed in 2.3% and grade 3 and 4 thrombocytopenia in 4.7% and this results were nearly similar to that reported with Newlands *et al.* [21] (3.5% and 5.2% for grade 3 and 4 thrombocytopenia and Leucopenia respectively). Minniti et al. [29] reportd hematotoxicity grade 3 and 4 were noticed in 9.3% of the patients, mainly neutropenia and thrombocytopenia. Stupp et al. [3] reported that, hematological toxicity grade 3 and 4 were noticed in 7% of the patients, mainly neutropenia while Athanassiou et al. [25] found a myelosuppression in 8.7% of their patients. Also, Becker-Schiebe et al. [31] observed grade 3/4 anemia, leucopenia and thromobocytopenia in 5.8%, 7.2% and 8.6% of cases respectively.

In 2013 Gupta et al. [32] published a study reviewing randomized trials evaluating severe TMZ induced toxicities and according to this data the overall incidence of grade 3/4 thrombocytopenia and neutropenia was 5 to 15.5% using the standard dose-schedule of TMZ in the Stupp protocol [3]. Conclusively, the authors stated a rate of leucocyte toxicity grades 3 and 4 in the range of 3% to 15% and a frequency of thrombocyte toxicity grades 3 and 4 in the range of 0 - 15% of their patients [28, 33, 34, 35, 36, 37].

In the present study during the concomitant RT plus TMZ phase, grade 3/4 toxicity was recorded in 13% versus 5% in the standard RT and short course RT groups respectively. Fiorica et al. [28] recorded

23.8% myelotoxicity (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% myelotoxicity in the patients treated with concomitant TMZ plus 60 Gy RT.

In the present study, as regard hematological toxicity during the adjuvant TMZ phase, grade 3/4 hematological toxicity was recorded in 16.3% of all patients while grade 3/4 toxicities were recorded in 27.3% versus 26.7% in the standard RT and short course RT groups respectively. Also TMZ discontinued in 7.7% due to grade 3 or 4 hematologic toxicity. Results from a meta-analysis that included 12 randomized trials [38] demonstrated among the 3,004 patients included in this analysis, during adjuvant TMZ less than 10% of patients developed grade 3 or 4 hematologic toxicity, and less than 2% of patients had to suspend the drug due to side effects.

In the present study there was no statistical significant difference in the 1-year OS between patients treated with standard 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.

Advanced age is the most significant prognostic factor for elderly patients with GBM. For all patients with GBM the median survival is around 15 months only, regardless of age, even when treated aggressively with surgery, RT and CT [3]. Arvold and Reardon [14] had reported that, beyond patient age, PS, extent of resection and, methylation status of the MGMT promoter appear to be an important prognostic factor.

Lichtman et al. [39] observed worse prognosis include higher number of co-morbid conditions, drug interactions and higher toxicity from systemic therapy such as myelossupression, mucositis and cardiotoxicity, all leading to higher mortality. Approximately 40%–60% of GBM among the elderly exhibit MGMT promoter methylation [40,41,42] and methylation of the MGMT gene promoter does remain both predictive and prognostic among elderly patients. [43]

Recent data have suggested that prognosis of patients with GBM is also determined by a complex interaction between age and several genetic alterations such as, mutation p53, deletion CDKN2A/p16 as a poor prognostic factors [44], deletion 1p36 and amplification EGFR as good prognostic factor [45].

5. Conclusions:

This study demonstrated concomitant RT plus TMZ followed by adjuvant TMZ therapy, is a promising regimen for patients with GBM, nevertheless, the challenge remains to improve the treatment outcome. The hypofractionated short course RT can be used for patients with GBM, resulting in comparable overall survival, comparable rates of toxicity and allowing for a shorter treatment time than standard RT. To confirm this, a multicenter, meta-analysis and a randomized trial with a large number of patients are needed to determine the optimal fractionation for GBM.

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