

Introduction: Although the recommended optimal treatment of glioblastoma multiforme (GBM) is adjuvant chemoradiotherapy, trials in GBM have excluded patients older than 70 years. In this study, we aimed to assess overall survival (OS) and prognostic factors in elderly patients (≥ 70 years) with newly diagnosed GBM treated with radiotherapy (RT) \pm concurrent/adjuvant temozolomide (TMZ).

Material and methods: Inclusion criteria were patients ≥ 70 years, pre-RT Karnofsky performance status (KPS) ≥ 60 , and time between diagnosis and start of RT ≤ 2 months. A total of 40 patients aged ≥ 70 years, 12 female and 28 male, treated between January 2004 and December 2012, were evaluated. Median age was 73.5 years (range, 70–83 years). The median RT dose was 60 Gy (range, 30–62 Gy). Twenty-one (52.5%) received concurrent TMZ, and of those 12 (30%) went on to receive adjuvant TMZ.

Results: The median OS was 7 months (95% CI: 5.45–8.54). One- and two-year OS for the whole cohort was 38% and 16%, respectively. Sex, type of surgery, tumor size, and RT dose did not significantly affect the OS. Presence of concurrent TMZ ($p < 0.005$) and presence of adjuvant TMZ ($p < 0.001$) were associated with longer OS in our cohort.

Conclusions: RT \pm TMZ seems to be a well-tolerated treatment in patients ≥ 70 years with GBM. Even though no superiority was found between conventional or hypofractionated RT regimens ($p = 0.405$), the addition of concurrent and adjuvant TMZ to RT increased the OS in our study.

Key words: glioblastoma, radiotherapy, elderly, temozolomide, prognostic factors.

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Radiotherapy with or without temozolomide in elderly patients aged ≥ 70 years with glioblastoma

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Introduction

Glioblastoma (GBM, WHO grade IV) is the most life-threatening primary central nervous system malignancy and represents approximately 20% of primary brain tumors diagnosed in adults. Given the median age of 65 years at GBM diagnosis, a large proportion of cases occur in the elderly population [1, 2]. In the landmark Stupp trial, concurrent oral temozolomide (TMZ) with RT followed by adjuvant TMZ improved survival in patients with GBM compared to postoperative RT alone. This study, however, excluded patients older than 70 years [1].

The treatment for elderly patients affected by GBM is a challenge in geriatric oncology. The standard of care for elderly patients with GBM remains undefined. No randomized trials have compared chemoradiotherapy with other medical alternatives since it has been presumed that elderly patients do not tolerate aggressive therapy [3, 4]. Consequently, clinicians have struggled with management decisions for elderly GBM patients. Nonetheless, with increasing life expectancy and expectations of better quality of life, there is current interest in GBM in the elderly [4–6].

Therefore, in this retrospective cohort analysis we assessed feasibility and outcome in patients ≥ 70 years treated with RT with or without concurrent and adjuvant TMZ.

Material and methods

A retrospective study was performed using patient records, treatment plans and diagnostic imaging for patients who received RT \pm concurrent and adjuvant TMZ. Patients treated with RT for GBM between January 2004 and December 2012 were reviewed. Inclusion criteria were: age ≥ 70 years, proven GBM WHO grade IV histopathology, no prior RT to the head-and-neck region, no prior use of chemotherapy or radiosensitizers, pre-RT Karnofsky Performance Status (KPS) ≥ 60 , and time between diagnosis and start of RT ≤ 2 months.

Patients were treated in the supine position with a 3-point thermoplastic mask. Between 2004 and 2006, RT delivery was based on conventional simulator planning and parallel opposed fields. After September 2006, a 3D-conformal RT approach was introduced, and planning CT scans were acquired with intravenous contrast using 3–5 mm slices. The gross tumor volume (GTV) was outlined as areas of contrast enhancement on T1-weighted images on MRI. The clinical target volume (CTV) was constructed to include the GTV. The median standard planned adjuvant dose was 60 Gy in 30 fractions, and the median palliative dose was 30 Gy in 10 fractions to the planning target volume (PTV). Treatment was delivered with cobalt-60 until 2006, and then with ⁶⁰Co or a linear accelerator.

Patients were given TMZ at a dose of 75 mg/m²/day concurrent with RT, beginning on the day of the first fraction of RT, including weekends and holidays and ending on the day of the last radiation fraction. This was followed by up to 6 cycles of adjuvant TMZ at the dose of 150–200 mg/m² daily for 5 days every 28 days, as per the EORTC/NCIC protocol. All patients received trimethoprim-sulfamethoxazole for prophylaxis against *Pneumocystis pneumonia*.

Response assessment routinely included clinical and neurological examination, and imaging. Biopsy was considered in the event of clinical or radiological suspicion of progression. Patients were followed up with physical examination every 6–8 weeks in the first year after treatment, every 3 months for an additional 2 years, and every 6 months until death.

Statistical analysis was performed using Statistical Package for Social Sciences software, version 16 (SPSS, Chicago, IL). OS was analyzed using the Kaplan-Meier method. A univariate analysis using Cox proportional regression analysis was used to examine the impact of multiple prognostic factors on OS. Factors identified with a *p* value of ≤ 0.05 on univariate analysis were then analyzed within a multivariate Cox model. All reported *p* values are two-sided and differences were considered statistically significant when *p* was < 0.05 .

Results

Forty elderly patients with GBM, 12 female and 28 male, with a median age of 73.5 years (range, 70–83 years), and a median KPS of 70 (range, 60–90) were treated at the Samsun Education and Investigation Hospital Department of Radiation Oncology between January 2004 and December 2012 using adjuvant RT \pm oral TMZ chemotherapy. Five (12.5%) patients were alive at the median follow-up of 9 (2–43) months. Eleven (27.5%) patients underwent gross total excision. The number of patients with pre-RT KPS = 60 was 13 (32.5%). Patient characteristics

Table 1. Patient characteristics (*n* = 40)

Variables	No.	%
Age at diagnosis – years		
Median	74	
Range	70–83	
Sex – no.		
Male	28	70
Female	12	30
KPS – no.		
60	13	32.5
> 60	27	67.5
Type of surgery – no.		
Gross total resection	11	27.5
Subtotal resection	26	65
Biopsy	3	7.5
Corticosteroid therapy – no.		
Yes	32	81
No	8	9

are summarized in Table 1. Twenty-eight (70%) patients completed ≥ 60 Gy of RT. Twenty-one (52.5%) patients received concurrent TMZ; of these, 12 (30%) patients received adjuvant TMZ. The median duration of RT was 42 days (range, 13–50 days), and the median RT dose was 60 Gy (range, 30–62 Gy) delivered in a median of 30 fractions (range, 10–31 fractions). RT and CT characteristics are summarized in Table 2.

Nineteen (47.5%) patients were treated with RT alone. Twenty-four (60%) patients completed their RT scheme without any interruption. The median number of adjuvant TMZ cycles was 3 (range, 0–6). One patient who was intended to receive 30 Gy in 10 fractions did not finish radiation therapy because of clinical tumor progression. In this case, death occurred after 24 Gy. Median OS was 7 months (95% CI: 5.45–8.54). One and two year OS for the whole cohort was 38% and 16%, respectively. Overall, 35 of 40 patients died (87.5%) with disease progression.

In univariate analysis, no significant difference was found in OS between conventional and hypofractionated RT schedules ≥ 60 Gy vs. < 60 Gy, *p* = 0.405) (Table 3). Younger age (70–75 years vs. ≥ 75 years, MS: 9 months vs. 5 months, *p* = 0.03), presence of concurrent TMZ (yes vs. no, MS: 11.7 months vs. 5 months, *p* < 0.005), and adjuvant TMZ (yes vs. no, MS: 13 months vs. 5 months, *p* < 0.001) were associated with longer OS in Kaplan Meier univariate analysis (Fig. 1). Adjuvant TMZ following concurrent RT+TMZ was found to be a significant predictor of OS on multivariate analysis (exp = 3.758, 95% CI: 1.506–9.376, *p* = 0.005). Univariate and multivariate analyses are summarized in Table 3.

Table 2. Radiotherapy (RT) and chemotherapy characteristics (*n* = 40)

Variables	No.	%
Received > 90% of planned RT dose - no.		
Yes	28	70
No	12	30
RT dose (Gray)		
Median	60	
Range	24–62	
Fraction size (Gray)		
Median	2	
Range	1.8–3	
Number of fractions		
Median	30	
Range	8–31	
Interruption or delay in RT (No.)		
Yes	16	40
No	24	60
Concomitant TMZ		
Yes	21	52.5
No	19	47.5
Adjuvant TMZ		
Yes	12	30
No	28	70

TMZ – temozolomide

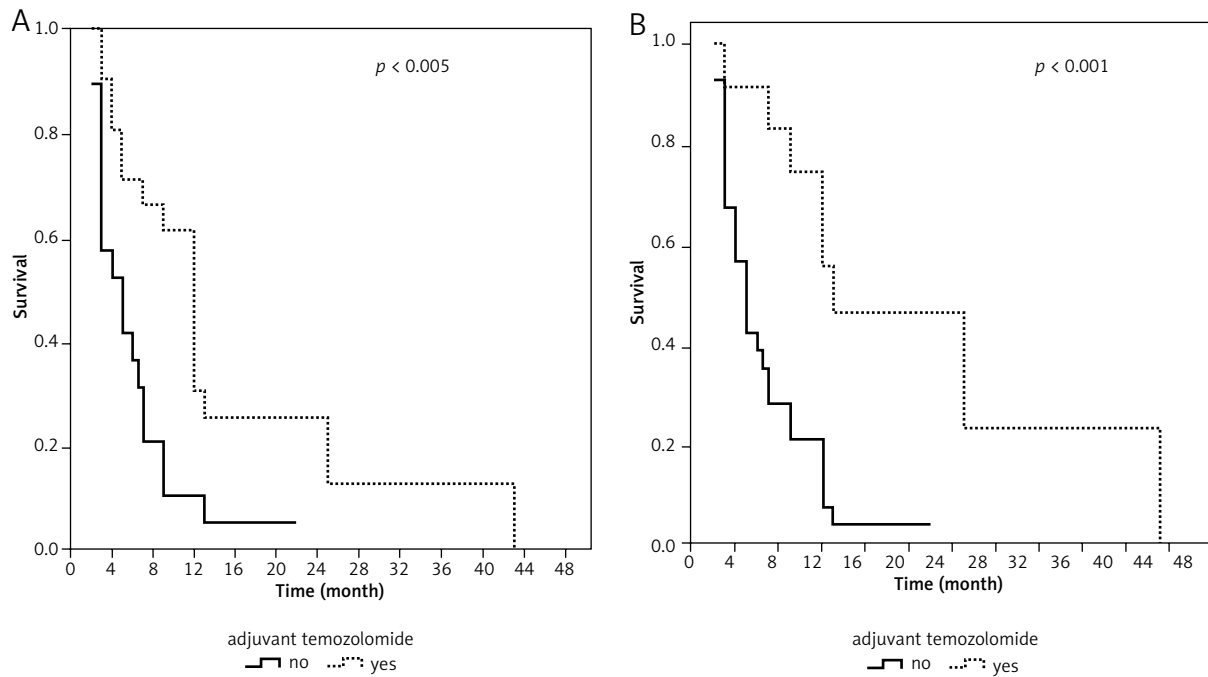


Fig. 1. Kaplan-Meier plots are shown relationship between overall survival (OS) and temozolomide (TMZ) in elderly patients with glioblastoma multiforme (GBM): A) Kaplan-Meier plot comparing OS in only radiotherapy (RT) vs. RT plus concurrent TMZ groups ($p < 0.005$). B) Kaplan-Meier plot comparing OS in adjuvant TMZ vs. follow-up after RT+TMZ groups ($p < 0.001$)

Table 3. Univariate and multivariate analysis of prognostic factors for overall survival (OS)

Variable	Univariate (Kaplan Meier)			
	OS (week)	95% CI ¹	SE ²	p value
KPS ³				
60	7.6	5.3–9.9	1.18	
> 60	8.8	6.2–11.4	1.31	0.648
Extent of resection				
Gross total resection	8.1	4.1–12.2	2.08	
Subtotal resection	9.1	6.6–11.7	1.30	
Biopsy	5.5	4.1–6.9	0.70	0.407
RT dose groups				
≥ 60 Gy	9.2	6.6–11.9	1.37	
< 60 Gy	7.2	4.6–9.8	1.93	0.405
Concurrent TMZ ⁴				
Yes	11.7	8.7–14.7	1.56	
No	5.1	3.8–6.4	0.67	< 0.001
Adjuvant TMZ				
Yes	14.9	10.6–19.2	2.21	
No	5.9	4.6–7.2	0.66	< 0.001
Variable	Multivariate (Cox regression)			
	Exp β (SE)	95% CI ¹ for exp β	SE ²	p value
Adjuvant TMZ YES vs. NO	3.758	1.506–9.376	(0.466*)	0.005

¹Confidence interval

²Standard error

³Karnofsky performance status

⁴Temozolomide

Discussion

This study shows that addition of adjuvant TMZ followed by concurrent TMZ with either short course (< 60 Gy) or long course (\geq 60 Gy) RT prolongs overall survival in patients with newly diagnosed GBM who are 70 years of age or older. OS in this small cohort of patients was comparable to patients treated with current standard of care therapy.

The optimal management of GBM in the elderly remains an area of controversy. Most studies demonstrate OS increases of several months among elderly GBM patients who receive surgery, RT, and/or TMZ. It is not clear whether the increased survival reflects treatment efficacy or better patient performance status. The NCCN guidelines currently include a category 2B recommendation for combined RT and TMZ in patients with GBM aged > 70. Previously published non-randomized data suggest that either TMZ or RT alone results in similar overall survival rates in elderly patients with GBM. Although there is concern that chemotherapy causes excess toxicity and is less efficacious in this population, a previous phase II study published by Chinot *et al.* showed that TMZ is a well-tolerated oral chemotherapeutic agent. This study evaluated patients with GBM aged > 70 years treated with TMZ alone as first line therapy, and reported a median overall survival of 6.4 months. Based on these data, in subsequent studies, the authors treated elderly GBM patients with TMZ alone or with RT [7–9].

The other area of contention for elderly patients with GBM is RT fractionation and total dose. Data from several prospective but nonrandomized studies have suggested that survival in patients receiving shorter-course RT is similar to that of historical controls treated conventionally. In the study by Roa *et al.*, 100 patients with GBM aged > 60 years were randomized to receive either hypofractionated RT (40 Gy in 3 weeks) or standard dose RT (60 Gy in 6 weeks). The authors observed no significant difference in OS between the two study groups [10]. In another study by Keime-Guibert *et al.*, 85 patients with GBM aged 70 years or older were randomized to receive either RT (50 Gy in 6 weeks) or supportive care alone [11]. This trial was closed early after an interim analysis showed a significant OS improvement in the RT group (HR: 0.47; 29.1 weeks vs. 16.9 weeks, $p = 0.002$). There were no severe toxicities related to RT, and quality of life did not differ significantly between the treatment groups [11]. Brandes *et al.* evaluated patients with GBM aged > 65 years treated with high-dose radiotherapy (60 Gy in 6 weeks) with concomitant TMZ. They reported a median OS of 13.7 months [12].

Results from our cohort showed that conventional and hypofractionated RT schemes were comparable in terms of OS (\geq 50 Gy vs. < 50 Gy, $p = 0.158$; or \geq 60 Gy vs. 30–60 Gy vs. \leq 30 Gy, $p = 0.405$). In another recent study, patients aged 70 years and older with GBM and KPS \geq 70 were randomized between RT in 1.8 Gy daily fractions to a total dose of 50 Gy plus supportive care, or supportive care alone. Analysis of preliminary results demonstrated the efficacy and safety of this hypofractionated accelerated

regimen, which compared favorably with classically fractionated treatments [13]. Hypofractionated RT offers the advantage of a shorter treatment period, which is important in this group of patients with limited life expectancy [12–15].

Gzell *et al.* determined the outcome of 109 elderly patients with GBM with hypofractionated (40 Gy) or long-course (60 Gy) external beam RT. Patients aged > 60 years diagnosed with GBM managed with RT were identified as to ECOG performance status, RT dose and use of TMZ. Median OS of patients was 12 months, with age distribution from 61 to 88 years (63%, 65–75). For age groups 65–75 and > 75, the survival was 12 and 9 months, respectively ($p = 0.001$). They found an association between longer survival and the use of 60 Gy (15 vs. 9 months, $p < 0.0001$), and use of TMZ (13 vs. 7 months, $p < 0.0001$). They concluded that improved OS is possible in the elderly population when TMZ is added to RT. Those in the age group 65–75 may benefit from long-course RT with TMZ [16]. Similarly to this study, we found superiority of concurrent and adjuvant TMZ usage on OS in our patients with median age of 73.5 years (range, 70–83), even though there was no significant difference for OS between RT schemes.

Several studies have investigated the treatment patterns and outcomes among elderly GBM patients over the last 20–30 years. In the current literature, age remains one of the most powerful prognostic factors among GBM patients. More than 50% of 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. The standard of care for elderly GBM patients remains controversial. Although the historical standard for GBM management has been surgery followed by adjuvant RT, many studies have recommended concurrent and adjuvant chemotherapy. Assessment of RT duration and toxicities is increasingly popular among researchers, and longer treatment schemes may be considered onerous in many clinics if not associated with significantly prolonged survival. The landscape of treatment options for elderly GBM patients has changed substantially over the past decade and even in the past 2 years. Based on the available evidence, Arvold and Reardon have outlined suggested management options based on patient age and KPS. Thus, as treatment decisions are made regarding elderly patients with GBM, honest discussions between physicians and patients and their families are crucial in terms of survival outcomes and quality of life and patient preferences [17].

In conclusion, our experience in this retrospective study with a small number of elderly patients with GBM will need to be considered in the planning of future studies. TMZ appears to be an effective treatment concurrently with and following RT for elderly patients with newly diagnosed GBM. The RT scheme for elderly patients requires careful consideration, and future randomized multicenter trials will be necessary to evaluate the role of hypofractionated RT with TMZ in the treatment of patients \geq 70 years with newly diagnosed GBM.

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