

Outcomes of Treatment for Glioblastoma Multiforme in Adult Patients: A Single Institution Experience from the Eastern Black Sea Region of Turkey

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ABSTRACT

The aim of the present study was to observe the relationship between age distribution and overall survival in glioblastoma multiforme. A series of 274 glioblastoma patients were analyzed retrospectively. Patients received chemoradiation with temozolomide. For the whole population, median overall survival time was 9.80 ± 1.78 (95% CI, 6.31-13.28) months and 1-, 2- and 3- years survival rates were 38.3%, 16.1% and 8.4% respectively. Median survival time of the patients \leq 5th, 6th, 7th and \geq 8th decade 26.00 ± 7.12 , 14.42 ± 3.07 , 13.65 ± 2.14 and 5.25 ± 0.73 respectively. There were a statistically significant difference in median survival rates among the four groups ($p < 0.001$). GBM remains a poor prognosis and fatal brain tumor despite the availability of multimodal treatment options. Age can be considered as the most important prognostic factor in patients with GBM as elderly patients have an extremely poor prognosis. Further research is thus warranted for the selection of treatment options that can improve the OS as well as ensure quality of life in the adult patients.

Keywords: Glioblastoma Multiforme, Age, Overall survival

ÖZET

Erişkin Hastalarda GBM Tedavisinin Sonuçları: Doğu Karadeniz Bölgesi'ndeki Tek Bir Kurum Tecrübesi

Bu çalışmanın amacı, glioblastoma multiforme'de yaş dağılımı ve genel sağkalım arasındaki ilişkiyi incelemektir. 274 Glioblastoma multiforme hasta retrospektif olarak incelendi. Hastaların hepsi temazolamidli kemoradyoterapi aldı. Tüm hastalar için medyan genel sağkalım süresi 9.80 ± 1.78 (% 95 GA, 6.31-13.28) ay ve 1, 2 ve 3 yıllık sağkalım oranları sırasıyla %38.3, % 16.1 ve %8.4 idi. Hastaların medyan sağkalım süresi \leq 5, 6, 7 ve \geq 8 dekatta sırasıyla 26.00 ± 7.12 , 14.42 ± 3.07 , 13.65 ± 2.14 ve 5.25 ± 0.73 idi. Dört grup arasında medyan sağkalım oranlarında istatistiksel olarak anlamlı farklılık vardı ($p < 0.001$). GBM, multimodal tedaviye rağmen kötü prognozlu ve ölümcül bir beyin tümörüdür. Yaş, GBM'li hastalarda en önemli prognostik faktör olarak düşünülebilir, çünkü yaşlı hastalarda prognoz oldukça kötüdür. Bu nedenle, yetişkin hastalarda yaşam kalitesini artırmanın yanı sıra ortalama sağkalımı artıracak tedavi seçenekleri için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Glioblastoma multiforme, Yaş, Genel sağkalım

INTRODUCTION

More than half of the brain tumors are malignant glioma (WHO Grade III–IV), and approximately 75% of them are glioblastoma multiforme (GBM). GBM is the most aggressive primary malignant tumor of the central nervous system.^{1,2} While it can occur at any age, its prevalence peaks between the sixth and seventh decade of life. The median age at diagnosis of GBM is 64 years in the USA, 63 years in France, and 62 years in the eastern Black Sea region of Turkey. More than one-quarter of the GBM cases occur in patients of age ≥ 70 years. In the recent past, an increase in the brain tumor mortality has been noted with an increase in the occurrence of age-standardized incidences of GBM.³⁻⁵

The standard treatment of GBM is complete surgical excision of the tumor, based on the trial described by Stupp et al.⁶ However, because of its high local recurrence rate, a need has been recognized for adjuvant therapies after surgical treatment. The combined randomized phase III study conducted by Stupp et al.⁶ with the European Organization for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) groups demonstrated that the addition of chemotherapy (CT) with 75 mg/m² temozolomide (TMZ)—which is an oral alkylating agent—and 5 cycles (200 mg/m²) of adjuvant CT simultaneously with the standard conventional radiotherapy (RT) could significantly extend the overall survival (OS) of the patients in comparison with that by administration of RT alone. As a result, the current literature considers “surgery + simultaneous CT-RT + adjuvant CT” as the standard treatment for GBM.⁷

The median OS for patients diagnosed with glioblastoma is approximately 12–15 months.⁶ However, retrospective studies have indicated a median OS of approximately 4–8 months for patients with glioblastoma and age >65 years, inclusive of all treatment modalities.⁸⁻¹⁰ Through this study, we aimed to investigate the effect of age on the OS in GBM cases.

MATERIALS AND METHODS

This retrospective clinical study was conducted with due permission from the Ethics Committee

at the Karadeniz Technical University Faculty of Medicine (2017-107). Between 2000 and 2016 patients records were evaluated. Patients' information about their age, gender, surgical history, and survival were recorded. The patients were grouped by age. Patients who did not receive TMZ treatment were excluded from the study. A total of 274 patients with the diagnosis of GBM by pathology or radiology were included in this study.

Treatment

Computerized tomography was performed before RT. The mass or surgical bed was fused with Magnetic Resonance Imaging (MRG) present before the surgical treatment. The optical nerves, lenses, pituitary gland, optical chiasm, and brain stem were contoured as critical organs. The three-dimensional conformal RT or intensity modulated RT techniques were used for diagnostic purpose. In RT planning, in the absence of edema, the mass or mass bed was described as gross tumor volume-2 (GTV2), while, in the presence of edema, it was described as GTV1. The clinical tumor volume (CTV) was forged with 2-cm margins assigned to GTV1 or GTV2. The CTV was excluded from anatomic barriers in the absence of an extension. The planned target volume (PTV) was forged with 0.5-cm margins assigned to the CTV. Two Gy each for 23 fractions (totaling 46 Gy) were assigned to the PTV1 and 2Gy/7 fractions (totaling 14 Gy) were assigned to the PTV2, resulting in the grand total tumor dose of 60 Gy. For 6 weeks, everyday, an oral administration of 75 mg/m² TMZ was applied as simultaneous CT. After RT, at every 28 days, for 5 consecutive days, five cycles of 200 mg/m² TMZ was applied.

Follow-up

After 2 months of RT, the patients' were clinically examined and their complete blood test and MRG controls were performed. The OS was considered as the time between diagnosis and the last control or death date.

Statistical Methods

The obtained data were subjected to the statistical analysis by using the SPSS (SPSS for Windows,

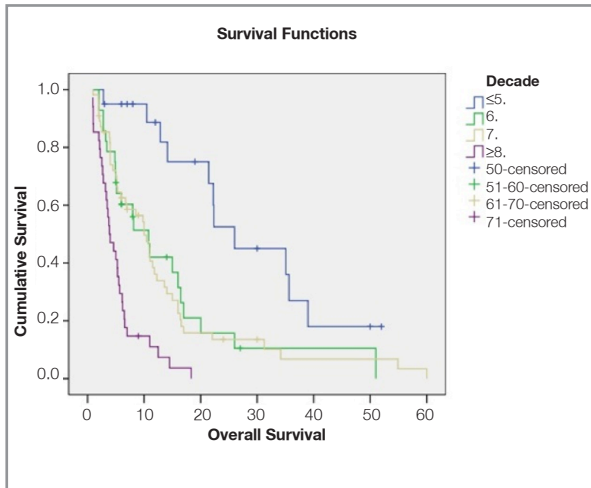


Figure 1: Overall survival of glioblastoma multiforme patients according to age (n= 274)

Version 16.0. Chicago, USA) software. The OS was estimated by using the Kaplan–Meier methods. The survival differences between the groups were examined by using the log-rank test. All tests were considered statistically significant at $p < 0.05$.

RESULTS

Of the 274 patients included in the study, 170 (62%) were men, of which 26 (10%) were in their fifties, 32 (11%) in their sixties, 72 (26%) in seventies, and 40 (15%) were aged >80 years. In addition, 104 (38%) of the patients were women, of which 14 (5%) were in their fifties, 24 (9%) in their sixties, 38 (14%) in their seventies, and 28 (10%) were of age >80 years. The median patient age was 63 years (age range: 7–88 years). Overall, 40 (15%) patients were aged ≤ 50 years, 56 (20%) fell within the age range of ≥ 51 to ≤ 60 years, 110 (40%) were aged ≥ 61 to ≤ 70 years, and 68 (25%) were aged ≥ 71 years.

Among the 86 (31% of total) medically inoperable patients diagnosed radiologically, 8 (3%) were in their fifties, 20 (7%) in their sixties, 30 (11%) in their seventies, and 28 (10%) were of age >80 years. Moreover, from the 106 (39%) patients who underwent operation, biopsy, or subtotal excision, 14 (5%) were in their fifties, 22 (8%) in their sixties, 46 (17%) in their seventies, and 24 (9%) were aged >80 years. Total excision was made in 82

(30%) patients, of which 18 (7%) were in their fifties, 14 (5%) in their sixties, 34 (12%) in their seventies, and 16 (6%) were aged >80 years.

Survival

For the entire cohort, the median OS time was 9.80 ± 1.78 (standard deviation) months (95% CI, 6.31–13.28) and the 1-, 2-, and 3-year survival rates were 38.3%, 16.1%, and 8.4%, respectively. The median OS and the 1-, 2-, and 3-year survival rates of patients in their fifties were 26.00 ± 7.12 months (95% CI: 12.04–39.95) and 88.7%, 52.5%, and 18%, respectively; for those in their sixties, were 10.80 ± 2.14 months (95% CI: 6.59–15.00) and 42%, 10.5%, and 10.5%, respectively; and for those in their seventies, were 10.00 ± 1.25 months (95% CI: 7.54–12.45) and 33.9%, 13.5%, and 6.8%, respectively. For patients aged >80 years, the median OS was 3.86 ± 0.72 months (95% CI: 2.43–5.29) and the 1-year survival rate was 7.4%, with no patient being alive after 2 years. A statistically significant difference was noted in the median survival rates among the four groups ($p < 0.001$) (Figure 1). On comparing the data from different age groups, a statistically significant difference was noted in the fifth decade of life as compared with that in the sixth ($p = 0.003$), seventh ($p < 0.001$), and eighth ($p < 0.001$) decades. No statistically significant difference ($p = 0.896$) was noted between the patients in their sixth and seventh decades of life, albeit a statistically significant difference ($p < 0.001$) was identified between those in their sixth and eight decades and between those in their seventh and eighth decades of life ($p < 0.001$).

With reference to the gender, the median OS and the 1-, 2-, and 3-year survival rates for men and women were 10.00 ± 2.07 months (95% CI: 5.93–14.06) and 37.4%, 14%, and 11.2% and 8.00 ± 3.03 months (95% CI: 2.04–13.95) and 37.2%, 19.6%, and 5.6%, respectively, with a statistically significant difference of $p < 0.001$.

With reference to the surgery types, the patients diagnosed radiologically showed a median OS of 5.53 ± 0.77 months (95% CI: 4.00–7.05) and their 1-, 2-, and 3-year survival rates were 24.3%, 8.1%, and 6.8%, respectively, with no patient being alive

Table 1. Patient characteristics of Log-rank univariate analysis for overall survival

n (%)		Median (Month) (95% CI)	1 year survival (%)	2 years survival (%)	3 years survival (%)	p	
All patients (274)		9.80±1.78 (6.31-13.28)	38.3	16.1	8.4		
Age	≤5. decade 40 (15%)	26.00±7.12 (12.04-39.95)	88.7	52.5	18	0.001	
	6. decade 56 (20%)	10.80±2.14 (6.59-15.00)	42	10.5	10.5		
	7. decade 110 (40%)	10.00±1.25 (7.54-12.45)	33.9	13.5	6.8		
	≥8. decade 68 (25%)	3.86±0.72 (2.43-5.29)	7.4	-	-		
Surgery	None	Total 86 (31%)	5.53±0.77 (4.00-7.05)	24.3	8.1	-	0.003
		≤5. decade 8 (3%)	14.13	100	50	-	
		6. decade 20 (7%)	8.13± 3.16 (1.92-14.34)	37	-	-	
		7. decade 30 (11%)	4.00±1.64 (0.77-7.22)	25.6	12.8	-	
		≥8. decade 28 (10%)	3.60±1.43 (0.78-6.41)	30	-	-	
		Biopsy-subtotal	Total 106 (39%)	10.00±2.60 (4.89-15.10)	41.3	10.9	
	≤5. decade 14 (5%)	22.33±0.95 (20.45-24.21)	83.3	41.7	20.8		
	6. decade 22 (8%)	4.90±.237 (4.43-5.36)	30	-	-		
	7. decade 46 (17%)	11.03±2.60 (5.92-16.14)	43.3	10.8	-		
	Total	≥8. decade 24 (9%)	3.46±1.44 (0.63-6.29)	25	-	-	0.001
Total 82 (30%)		11.00±0.70 (9.62-12.37)	43.9	27.5	17.6		
≤5. decade 18 (7%)		26.00±4.81 (16.57-35.43)	87.5	43.8	21.9		
6. decade 14 (5%)		16.00±8.95 (0.00-33.54)	62.5	46.9	31.3		
7. decade 34 (12%)	10.40±1.64 (7.17-13.6)	35.3	17.6	17.6			
≥8. decade 16 (6%)	4.60±0.99 (2.66-6.54)	-	-	-			

after 3 years. In patients who had undergone applied biopsy or subtotal excision, the median OS was 10.00 ± 2.60 months (95% CI: 4.89–15.10) and their 1-, 2-, and 3-year survival rates were 41.3%, 10.9%, and 3.6%, respectively. In patients who underwent total excision, the median survival time was 11.00 ± 0.70 months (95% CI:

9.62–12.37) and their 1-, 2-, and 3-year survival rates were 43.9%, 27.5%, and 17.6%, respectively. A statistically significant difference was noted in the median survival rates among the three groups (p< 0.001) (Table 1).

DISCUSSION

Brain tumors are rarer than other malignancies; however, they are associated with high mortality rate. GBM is an incurable and a very common primary malign brain tumor. The first priority treatment for this disease is the total excision of the tumor. Because local recurrences are inevitable in these cases, there is an urgent need for an adjuvant treatment option.

Although GBM can occur at any age, its median age of occurrence is 64 years. Over the last 50 years, an increase in the age-standardized incidences of GBM has been noted to be related to an increase in the brain tumor mortality. The mortality rate peaks between the sixth and seventh decades of life.³⁻⁵ In the present study, the median age of the patients was 63 months, which concurs with previously reported data.³⁻⁵ These observations explain why patients in their sixth and seventh decades of life had similar outcomes in our study.

Based on the landmark EORTC/NCIC randomized trial by Stupp et al. in 2005, which demonstrated improved survival with the addition of TMZ to RT, the current standard of care for newly diagnosed GBM patients has been revised to 6 weeks of RT delivered in 1.8–2.0-Gy daily fractions to a total dose of 60 Gy, followed by adjuvant TMZ CT.⁶ However, the Stupp et al. study excluded patients of age >70 years. The alternative treatment for elderly GBM patients primarily includes hypofractionated RT (HRT), in which large fractions of radiation are administered over a short period of time (11). In certain cases, concurrent TMZ combined with HRT has been used despite the lack of established superiority of HRT combined with concurrent TMZ to that of HRT alone.¹² In our study, the patients were treated with a simultaneous application of 75 mg/m² TMZ and 60-Gy RT.

The median OS for patients with GBM is approximately 12-15 months.^{6,13,14} In our study, the median survival time of all patients was found to be 9.8 months, which is in accordance with the literature. In addition, when the patients were divided into age groups, their median OS was 28 months in the fifth decade, with a statistically significant difference in comparison to patients in their sixth, seventh, and eight decades of life.

Age is considered to be the most important prognostic factor in patients with GBM. Elderly patients have particularly poor prognosis and their median OS is also extremely low.¹⁵ The median OS for elderly patients with GBM has been reported to be approximately 4-8 months.^{2,8-10,16,17} No differences in the OS time, progression-free survival time, and quality of life have been noted among patients receiving different RT regimens.^{18,19} In our study, the median survival time of elderly patients was 4 months, which agrees with the reports of some previous studies. However, a statistically significant difference was noted in patients in their eight decade of life as compared to that in younger patients.

Various studies in the literature have revealed that age is the most common and important prognostic variable for GBM.^{20,21} Notably, according to our results, age alone is an important factor in the decision-making for treatment selection. Nevertheless, the most suitable treatment option should not be selected on the basis of the age factor alone, it should, in fact, consider the patient's overall health status, desires, and expectations.

Our study has some limitations. First, it was a retrospective study conducted at a single center, thereby requiring caution while interpreting the results. Second, this retrospective report includes patients treated in 16-year period. During this period, the imaging modalities and RT techniques improved, which may have resulted in a selection bias. Lastly, while we only investigated the chronological age, comorbidities and smoking habits may also be important parameters for patient selection. Moreover, we did not analyze the quality of life. Moreover, neither the methylguanine DNA methyltransferase methylation status nor the IDH1/2 mutation status testing was existing during the study period. Both these markers have been now shown to have significant prognostic and predictive importance in GBM patients.^{22,23} Nevertheless, the findings of the present study are relevant and of significance in analyzing homogenous groups of GBM patients according to age groups.

Conclusion

GBM remains a poor prognosis and fatal brain tumor despite the availability of multimodal treatment options. Age can be considered as the most

important prognostic factor in patients with GBM as elderly patients have an extremely poor prognosis. In addition, the median survival rate was found to be good in patients of age <50 years, although it decreased for patients of age >70 years. Further research is thus warranted for the selection of treatment options that can improve the OS as well as ensure quality of life in the adult patients.

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