12-Cycle of Temozolomide Treatment is not Superior To 6-Cycle of Treatment in Glioblastoma Multiforme

Glioblastome Multiforme'de 12 Kür Temozolomid Tedavisi 6 Kür Tedaviye Üstün Değildir

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Dergiye Ulaşma Tarihi: 31,08,2020 Dergiye Kabul Tarihi: 21.10.2020 Doi: 10.5505/aot.2020.99815

ÖZET

GİRİŞ ve AMAÇ: Grade IV gliom olan glioblastoma multiforme (GBM), yetişkinlerde en sık görülen primer beyin tümörüdür. Biyopsi veya rezeksiyonu takiben, radyoterapi (RT) eş zamanlı ve adjuvan temozolomid (TMZ) kullanımı (6 kür), yeni teşhis edilmiş GBM vakaları için standart tedavi haline gelmiştir. Orijinal tedavi rejimi 6 kür TEMODAL kullanımını içermesine rağmen, bazı merkezler daha iyi sonuç elde etme umuduyla progrese olmayan hastalarda 12 veya daha fazla kür tedavi uygulamaktadır. Butedavi yaklaşımı tartışmalıdır. Çalışmamızın temel amacı, hastalıksız sağkalım (DFS) ve genel sağ kalım (OS) açısından standart kombine tedavi yaklaşımı ile tedavi edilen hastalarda TEMODAL tedavisinin uzatılmasının (6 aydan 12 aya kadar) yararlı olup olmadığını belirlemektir.

YÖNTEM ve GEREÇLER: 2012-2019 yılları arasında retrospektif olarak 180 GBM hastasını analiz ettik ve çalışmaya dahil edilme kriterlerini karşılayan 100 hastayı dahil ettik.

BULGULAR: 100 GBM hastası geriye dönük olarak incelendi. Medyan OS 21 (18.47-23.52) ay iken, 6 kür TMZ alanlarda 24 (18.21-29.78) ay, 12 kür TMZ alan grupta 22 (18.50-25.49) ay ve adjuvan tedaviyi tamamlayamayanlarda 10 aydı. 6 ve 12 kür TMZ tedavisi arasında istatistiksel olarak anlamlı bir fark yoktu ($p = 0.55$). Adjuvan tedaviyi tamamlayamayan hastalar daha düşük sağ kalıma sahipti ve bu grup, 6 ve 12 kür TMZ alan hastalara kıyasla istatistiksel olarak anlamlı bir OS farkına sahipti (sırasıyla $p = 0.04$ ve $p = 0.024$).

TARTIŞMA ve SONUÇ: Çalışmamız, GBM hastalarında adjuvan TMZ tedavisinin uzatılmasının yaş, performans durumu ve tümör özelliklerinden bağımsız olarak ek bir sağ kalım avantajı sağlamadığını göstermektedir.Ayrıca, standart 6 kür adjuvan tedaviyi tamamlayamayan GBM hastalarının hayatta kalma oranları daha düşüktür.

Anahtar Kelimeler: GBM, Temozolomid, Adjuvan Tedavi Süresi

ABSTRACT

INTRODUCTION: Glioblastoma multiforme (GBM), a grade IV malignant glioma, is the most common primary brain tumor in adults. Following biopsy or resection, radiotherapy (RT) and concomitant and adjuvant temozolomide (TMZ) use (6 cycles) have become the standard of treatment for newly diagnosed GBM cases. Although the original treatment regimen involves the use of 6 cycles of TMZ, some centers administer prolonged treatment up to 12 or more cycles in non-progressive patients in the hope of achieving better outcome. This form of administration is controversial. The main purpose of our study is to determine whether prolonging TMZ treatment (from 6 months to 12 months) is beneficial in patients treated with a standard combined treatment approach in terms of disease-free survival (DFS) and OS.

METHODS: Between 2012-2019 years we analyzed 180 GBM patients retrospectively and included 100 patients who met the criteria for inclusion in the study.

RESULTS: 100 GBM patients were retrospectively examined. Median OS was 21 (18.47-23.52) months overall, while it was 24 (18.21-29.78) months in recipients of 6 cycles of TMZ, it was 22 (18.50-25.49) months in the group receiving 12 cycles of TMZ, and 10 months in those who could not complete adjuvant therapy. There was no statistically significant difference between 6 cycles and 12 cycles of TMZ treatment ($p = 0.55$). Patients who could not complete the adjuvant therapy had lower survival and this group had a statistically significant OS difference compared to patients receiving 6 and 12 cycles of TMZ ($p = 0.04$ and $p = 0.024$, respectively).

DISCUSSION AND CONCLUSION: Our study indicate that prolongation of adjuvant TMZ treatment in GBM patients do not provide an additional survival advantage regardless of age, performance status and tumor

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characteristics. Additionally, GBM patients who could not complete standard 6-cycle adjuvant treatment have lower survival rates.
Keywords: GBM, Temozolamide, Duration of Adjuvant therapy

Introduction

Primary tumors of the central nervous system (CNS) include cerebral neoplasms, tumors of the sellar region, cranial nerve tumors, and spinal cord tumors. The World Health Organization (WHO) classification in 2016 covered more than 130 CNS tumor variants **(1)**. Malign gliomas constitute 25% of these tumors. The 2016 classification of diffuse gliomas is based on the combined use of morphological, immunohistochemical (IHC) and molecular test results. The clinical routine evaluation and molecular classification of gliomas includeanalysis of promoter methylation of MGMT, 1p/19q chromosomal deletion, IDH and EGFR mutations and ATRX gene analysis. Glioblastoma multiforme (GBM), a grade IV malignant glioma, is the most common primary brain tumor in adults. Advanced age, poor functional status, and inability to perform a total or near total excision of the tumor are among the reported poor prognostic factors **(2)**.

Following biopsy or resection, radiotherapy (RT) and concomitant and adjuvant temozolomide (TMZ) use (6 cycles) have become the standard of treatment for newly diagnosed GBM cases. This regime has been widely adopted; however,although the original treatment regimen involves the use of 6 cycles of TMZ, some centers administer prolonged treatment up to 12 or more cycles in non-progressive patients in the hope of achieving better outcome. This form of application is controversial. There are studies showing that prolonging treatment after 6 cycles has no effect on progression-free survival (PFS) and overall survival (OS) **(3,4)**. Median OS is around 14 months after standard 6-cycle TMZ treatment **(5)**.The addition of low-intensity alternating electric field (tumor treating fields, TTF) therapy to standard treatment has been shown to increase median OS to 20.9 months. With this treatment method, a statistically significant improvement was observed compared to the 16-month OS of the control group, which received only standard treatment. However, due to its difficulty and high cost, this technique has not been widely adopted yet **(6).**

The main purpose of our study is to determine whether prolonging TMZ treatment (from 6 months to 12 months) is beneficial in patients treated with a standard combined treatment approach (operation, RT, concomitant and adjuvant TMZ) in terms of disease-free survival (DFS) and OS. In addition, another purpose of this study is to examine possible changes inadverse effect profile as a result of prolonging the treatment to 12 months.

Materials and Methods

The data of patients who received adjuvant TMZ treatment with a diagnosis of GBM between 2012-2019 in our hospital's medical oncology clinic were retrospectively reviewed. A total of 100 patients older than 18 years old, who underwent gross or subtotal resection surgery (resection was confirmed by control magnetic resonance imaging after surgery) and who were diagnosed with high grade glioma or GBM were included in the study. Patients who received 6 cycles of the Stupp protocol [RT + concomitant TMZ 75 mg/m^2/day for 7 days + 6 cycles of adjuvant TMZ 150-200 mg/m^2/day, for 5 days every 28 days] and those who received 12 cycles after non-progression with 6 cycles were included in the study. Patients who were scanned by MR-spectroscopy during CRT and in every 3 cycles of adjuvant TMZ and were followed up for hematological toxicity with blood counts in each cycle were included in the study.DFS was calculated according to the recurrence or progress status of the patients, and OS was calculated according to the date of death recorded in the final death notification forms.

This research was carried out by scanning data from the hospital database retrospectively. The demographic characteristics, performance scores, diagnosis and recurrence dates, treatment types, duration of treatment, laboratory values before and after treatment, progression, last control and death dates were obtained from the hospital file records. The study was approved by the local ethics committee on 20.02.2020 with decision number: 87.

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Statistical Analysis

Statistical analyses were performed with SPSS 25.0 software (Chicago, IL, USA). While the Mann Whitney U test was used to compare nonparametric data, the Student's T-test was used to compare parametric data. Chi-square test or Fisher's exact test was used to compare categorical data. The Kaplan-Meier method was used for survival analysis and the log-rank test was used for comparisons between groups. A value of $p<0.05$ was considered statistically significant.

Results

100 patients were included in our study, 52 were male and 48 were female, and the median age of these patients was 53 (18-76) years. The most common tumor localization in these patients was the frontal lobe (n = 41), followed by the temporal (n = 23), parietal (n = 21) and occipital (n = 15) lobes. When we evaluated the patients according to tumor size, there were 68 patients with tumor size ≤5 cm and 32 patients with a tumor size>5 cm (*Table 1*). The mean age at diagnosis, gender distributions, tumor localizations, and tumor sizes of the groups receiving 6 and 12 cycles of TMZ treatment were similar.

Table 1: Summary of patientcharacteristics

Characteristics	
Patients	n=100
Gender **Female** **Male**	 42 58
Median Age	53
TumorSize **<5 cm** **>5 cm**	 68 32
TumorLocation **Frontal** **Temporal** **Parietal** **Occipital**	 41 23 21 15
Resection **Gross total resection** **Incompleteresection**	 82 12
RT **60 gray** **40 gray**	 81 16
Adjuvan TMZ **6 ay TMZ** **12 ay TMZ**	 43 30
Not receivingstandardcycles	17
Reoperationafterrelapse	15
Reiiradiationafterrelapse	25

Median PFS was 15 (11.83-18.17) months overall, while it was 16 (11.24-20.75) months in the group receiving 6-cycle adjuvant TMZ, and 14 (11.50-16.49) months in the group receiving 12 cycles of TMZ, but there was no statistically significant difference between the groups (p = 0.088) (*Figure 1*).

Table 2: Baselinecharacteristics of patientsreceiving 6 cyclesversus 12 cycles of adjuvant TMZ

Characteristics	Adj 6 TMZ	Adj 12 TMZ	p
Patients	n=43	n=30	
Median Age	52	49	0,96
Gender **Female** **Male**	 19 24	 9 21	0,38
TumorSize **≤5 cm** **>5 cm**	 32 11	 19 11	0,41
TumorLocation **Frontal** **Temporal** **Parietal** **Occipital**	 18 10 6 2	 14 16 8 2	0,25

According to tumor localizations, median PFS in frontal locations (n = 41) was 18 (13.30-22.69) months, 14 (7.76-20.29) months in temporal locations (n = 23) and 10 (4.33-15.66) months in parietal locations (n = 21). In patients with the tumor located in the occipital lobe (n = 15), median PFS statistically significantly lower compared to patients with tumors located in the frontal (p = 0.009) and temporal lobes (p = 0.043) (*Figure 2*). The median PFS times were 16 (18.72-20.27) months in patients with a tumor size of 5 cm or less, and 10 (5.32-16.68) months in those with tumors greater than 5 cm (p = 0.1).

Median PFS was 16 (12.99-19.00) months in patients who underwent gross tumor resection and 13 months in patients who underwent incomplete resection (p = 0.51). While median PFS was 16 (12.44-19.00) months in patients receiving 60 Gray RT after surgery, it was 9 (6.07-18.92) months in the subgroup receiving 40 gray, and this difference was statistically significant (p = 0.049). The median age of the group receiving 60 gray RT was 50 years, while the group receiving 40 gray RT had a median age of 65 years.

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Figure-1: Disease Free Survival in patients with GBM by number of TMZ cycles:

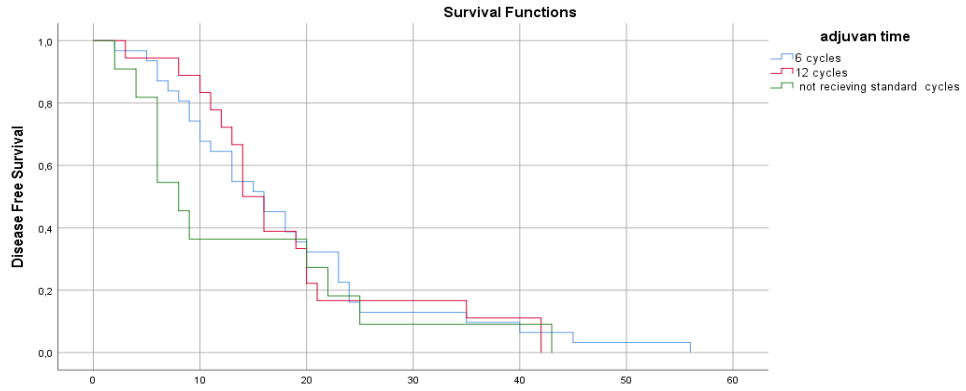

Figure-2: Disease Free Survival in patients with GBM by tumor location

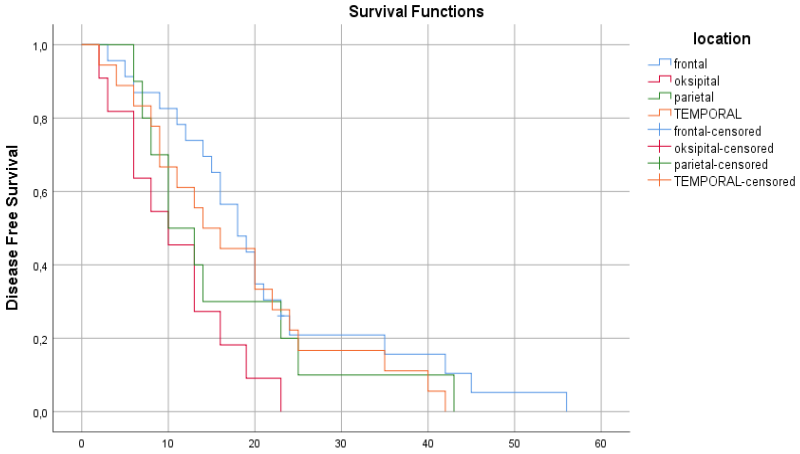

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Figure-3: Overall survival in patients with GBM by number of TMZ cycles:

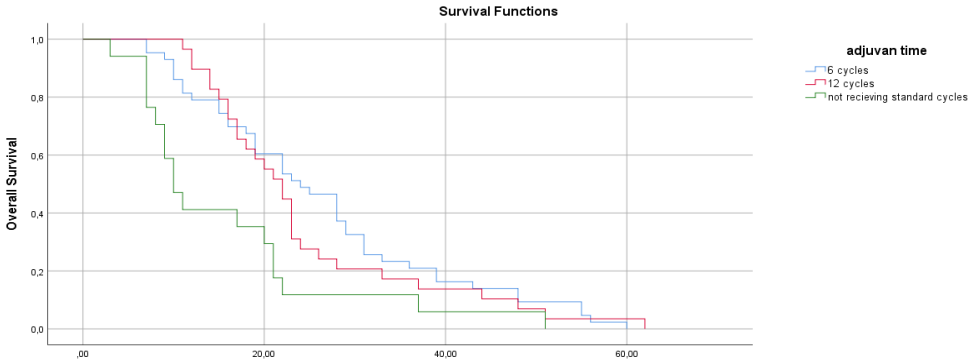

Figure-4: Overall survival in patients with GBM by operation type

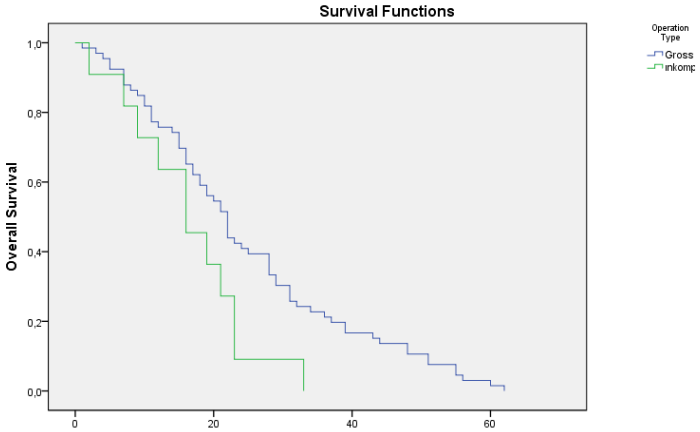

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Figure-5: Overall survival in patients with relapsed gbm by reoperation

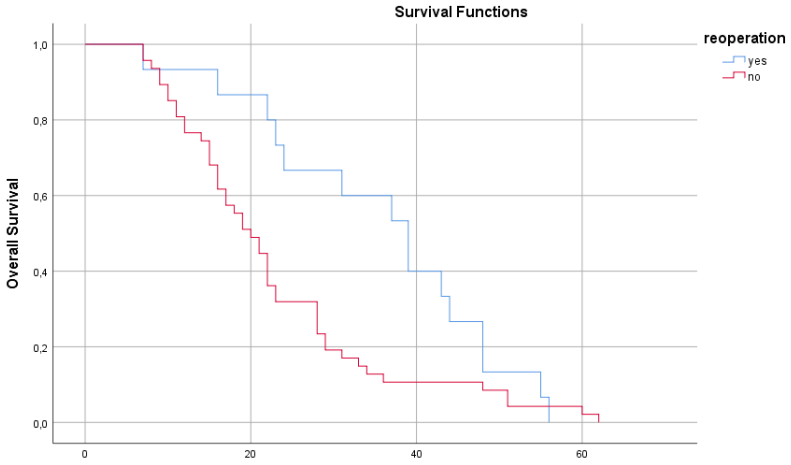
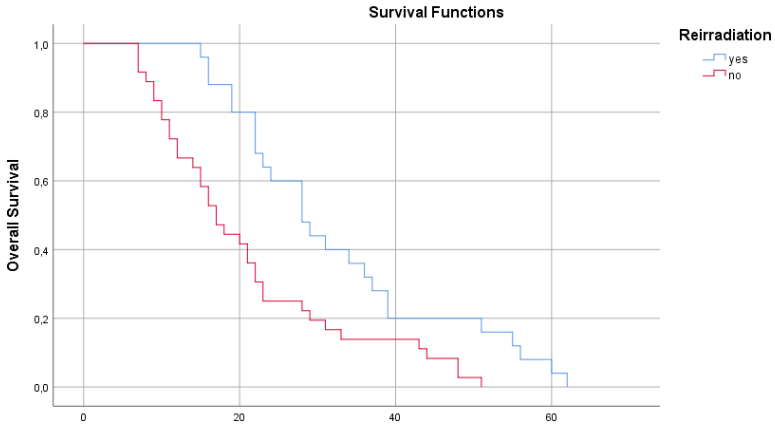


Figure-6: **Overall survival in patients with relapsed gbm by reirradiation**



Median OS was 21 (18.47-23.52) months overall, while it was 24 (18.21-29.78) months in recipients of 6 cycles of TMZ, it was 22 (18.50-25.49) months in the group receiving 12 cycles of TMZ, and 10 months in those who could not complete adjuvant therapy. When Median OS values were compared, there was no statistically significant difference between 6 cycles and 12 cycles of TMZ treatment (p = 0.55). Patients who could not complete the adjuvant therapy had lower survival and this group had a statistically significant OS

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difference compared to patients receiving 6 and 12 cycles of TMZ (p = 0.04 and p = 0.024, respectively) (*Figure 3*). Median OS was 20 (16.35-23.64) months in patients with tumor size of 5 cm or less, and 19 (14.38-23.62) months in patients with tumor size greater than 5 cm (p = 0.82). The median OS was 22 (19.03-24.96) months in patients who underwent gross tumor resection, while it was 16 (8.44-23.55) months in patients who underwent incomplete resection, and this difference was statistically significant (p = 0.041) (*Figure 4*). Median OS was 39 (29.08-48.91, 95% CI) months in patients who underwent surgery after recurrence (n = 15), while median OS was 20 months (16.92-23.08) in patients who did not undergo surgery after recurrence (n = 47) (p = 0.024) (Figure 5). Median OS was 28 (21.88-34.12) months in patients who underwent reirradiation after recurrence (n = 25), and 17 (11.90-22.09) months in patients who did not undergo reirradiation after recurrence (n = 36) (p = 0.001) (*Figure 6*).

When subgroups receiving 6 and 12 cycles of TMZ were compared, similar hematological adverse effect profiles were observed. Anemia developed in 13.4% of patients in the study. Anemia rates of subgroups receiving 6 and 12 cycles of TMZ were 16% and 6.6%, respectively; however, there was no statistically significant difference between these groups (p>0.05). Thrombocytopenia developed in 17.7% of patients. The rate of thrombocytopenia was 14% in the subgroup receiving 6 cycles of TMZ and 13.3% in the subgroup receiving 12 cycles of TMZ, and there was no significant difference between them (p = 0.94). Leukopenia developed in 45.5% of patients. In the subgroups receiving 6 and 12 cycles of TMZ, leukopenia rates were 44% and 33.3%, respectively; and there was no significant difference between them (p = 0.35).

Discussion

In this retrospective study comparing the effectiveness of adjuvant 6 and 12 cycles of TMZ treatment, it has been shown that prolonging the standard treatment does not contribute to OS. As a result of the study published by Stupp et al. in 2005, RT + concomitant TMZ 75 mg/m^2/day for 7 days + 6 cycles of adjuvant TMZ 150-200 mg/m^2/day, for 5 days every 28 days was accepted as the standard treatment in patients with newly diagnosed GBM and this treatment provided a 14-month survival advantage in patients **(5).** In our study, the median OS was 21 months, an increased value comparedto the literature. Age and performance score are important prognostic factors in GBM. In the study conducted by Stupp et al., the median age was 56, and in our study, median age was 51. This indicates that the increased survival may be associated with age. In our study, MGMT promoter methylation of patients could not be evaluated. MGMT methylation occurs in 35-45% of high-grade gliomas. Studies have shown that MGMT methylation is a potent and independent prognostic factor associated with prolonged PFS and OS **(7).** It is possible that our patients may have had higher MGMT methylation rates; thus translating to better OS. Also, none of the patients had been investigated for IDH mutation analysis. The IDH mutation occurs in 6% of primary GBM and is known to be associated with good prognosis **(8**). The frequency of this mutations is therefore likely to be higher in our patient group.Also the study is a retrospective study, it can be explained that the OS is higher than the literature.

In accordance with Stupp data, the median survival in the group whose standard treatment could not be completed was 10 months in our study, and there was a statistically significant decrease compared to the group receiving standard treatment. Previous laboratory studies have suggested that prolonged TMZ therapy has the risk of causing resistance in tumor cells **(9)**. In the analysis of the pooled data of 4 randomized prospective studies, the contribution of prolonged TMZ treatment to increased OS could not be demonstrated. It has also been emphasized that prolonged exposure to TMZ may cause mutations in tumor cells that may develop resistance to alkylating agents and decrease the treatment options after recurrence that may develop in the future **(3**). In addition, in the aforementioned study, prolonged TMZ treatment was shown to provide an advantage of PFS only in the subgroup with MGMT methylation **(3).** Since our study was retrospective and the MGMT data of the patients could not be obtained, it was not determined whether there was a

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similar PFS contribution. In another retrospective study conducted with 37 patients in the literature, significant OS advantage was obtained in the group receiving prolonged TMZ treatment compared to the group receiving the standard treatment (28 vs 8 months, p = 0.001) **(10**). This can be explained by the relatively low number of patients and by the fact that the proportion of patients with positive MGMT methylation was higher in the group receiving prolonged TMZ treatment compared to the standard treatment group (%73.6 vs %27.7) in their study.

The tumors of the patients in our study were most frequently localized in the frontal lobe (41%) and the least in the occipital lobe (15%). Statistically, tumors localized in the occipital lobe were found to have worse prognosis, as demonstrated by shorterPFS. Previous studies have shown that tumors localized in the frontal lobe showbetter prognosis than other localizations **(11).** Therefore, the relatively better OS values in our study may also be attributed toa higher number of patients with tumors localized in the frontal lobe.The functional separation in different anatomical regions of the brain and the different glial tissue density in these regions explain the difference in GBM development rate in different anatomical regions **(12).** Studies have emphasized that poor prognosis in the occipital, parietal and temporal lobes may be associated with neuroanatomy and underlying tumor biology. This relationship needs to be clearly determined by the analysis of molecular mutations **(13).**

We have found that OS data were statistically better in patients who underwent gross tumor resection compared to those who underwent subtotal resection (22 vs. 16 months). Gross-total resection was defined as the absence of solid enhancing tissue on postoperative MRI. GBM is an infiltrative tumor and the quality of resection is directly related to the localization of the tumor. Although there is no randomized study showing whether gross total resection provides a survival advantage than subtotal resection, in most of the observational studies, extent of resection has been shown to directly affect prognosis **(14).** In our study, patients who receivedpost-operative adjuvant standard treatment with 60 Gray RT were found to have longer PFS than those receiving 40 Gray RT.Our results support the literature in showing that RT (60 gray, for 6 weeks) combined with TMZ isbeneficial as the standard treatment to increase survival time **(15).** However, it is a given that 40 Gray RT is often preferred in patients older than 70 years of age with lower performance than younger patients**(16).** In our study, the mean age of the group receiving 40 Gray RT was higher (65 vs. 50 years) and the PFS values of these patients were lower in accordance with the literature.

Only 15 (24%) of our patients who developed recurrence had a chance for re-surgery and had a longer survival than those who could not be operated (39 vs 20 months). Studies have found that only 20–30% of patients are suitable for a second operation in cases who develop recurrence **(17)**.Although it has not been exactly determined to whom surgery should be performed, the median survival has been shown to vary between 8–12 months in patients undergoing surgery after recurrence **(18)**.In 25 patients who underwent reirradiation after recurrence, longer survival was achieved than those who could not be re-irradiated (28 vs. 17 months). The role of reirradiation in patients with recurrent glioblastoma is uncertain. According to retrospective studies, patients with small tumors and good performance can benefit from reirradiation**(19)**.Conventional radiotherapy in the form of whole brain radiation treatment is not possible during reirradiation, since most patients already receive the maximum tolerable dose during adjuvant RT. Thus,focal irradiation is preferred in these cases**(20).**

Patients receiving TMZ are at risk for hematological toxicity. In our study, hematological adverse effects were observed at similar rates in patient groups receiving 6 and 12 cycles of TMZ. Thrombocytopenia is the most common hematologic adverse effect, occurring in approximately 10 to 20 percent of patients **(21).**Thrombocytopenia was found to be present in17.7% of the patients in our study, similar to the literature data.In the literature, TMZ-induced moderate or severe lymphopenia and neutropenia can be seen in at least 15% of patients and it was reported that the frequency of lymphopenia increased especially in RT + concomitant TMZ treatment**(22).** There is also literature data on the increased risk of myelodysplasia and leukemia secondary to

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prolonged use of TMZ, although it was not detected in our study **(23).** Additionally, it must be kept in mind that the increase in the risk of infection, especially due to the increased frequency of lymphopenia, may create additional risk for morbidity and/or mortality.

This study has some limitations.The main limitation of our study is that it is a retrospective study.The duration and effectiveness of adjuvant TMZ therapy can be better assessed with a prospective multi-centered study.Another limitation of our study is that there is a risk of bias in some results due to missing data, even though the majority of characteristics were well-recorded throughout the patient group.The third limitation of our study was that, since molecular analyses could not be performed, the effects of MGMT mutation and other mutations, which have been reported to reflect good response to TMZ treatment could not be determined.

This study has shown that prolongation of adjuvant TMZ treatment (over 6 cycles)in GBM patients did not provide an additional survival advantage regardless of age, performance status and tumor characteristics.In addition, in this study, it was found that GBM patients who could not complete standard 6-cycle adjuvant treatment had lower survival rates.Prospective and more comprehensive studies in the future may provide us with more precise information on this issue.

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