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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

The Effect of Adjuvant Chemoradiotherapy Initiation Time on Prognosis in Glioblastoma Multiforme

Glioblastoma Multiformede Adjuvan Kemoradyoterapi Başlama Zamanının Prognoz Üzerine Etkisi

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Abstract

Objectives: To determine survival and investigate associated prognostic factors in glioblastoma multiforme (GBM) patients receiving adjuvant therapy.

Materials and Methods: The study population comprised patients with isocitrate dehydrogenase wild-type GBM who were enrolled between 1 September 2022 and 1 March 2024. The primary endpoint was overall survival (OS), while the secondary endpoint was progression-free survival. Comparisons between groups were conducted using the log-rank test, and multivariate analyses were performed using Cox regression.

Results: A total of 67 patients were evaluated. The median OS of patients was 19.3 months [95% confidence interval (CI) 15.1 to not reached (NR)]. A total of 60 patients (89.1%) underwent adjuvant treatment. The median OS was 31.1 months (95% CI 19.3 to NR) for patients treated within the first four weeks, 15.7 months (95% CI 15.1 to NR) for those treated within four to six weeks, and 11.3 months (95% CI 9.8 to NR) for those treated after six weeks.

Conclusion: The observed survival rate in our study was comparable to that reported in clinical trials. However, the survival rate was significantly lower in patients who received treatment at a later stage. Therefore, further studies with larger patient populations are recommended to ensure that the guidelines more accurately reflect the timing of adjuvant therapy in GBM patients.

Keywords: Glioblastoma multiforme, stupp protocol, overall survival, time to treatment

Öz

Amaç: Bu çalışmanın amacı adjuvan tedavi alan glioblastoma multiforme (GBM) hastalarında sağkalımı belirlemek ve ilişkili prognostik faktörleri araştırmaktır.

Gereç ve Yöntem: Çalışma popülasyonu, 1 Eylül 2022 ve 1 Mart 2024 tarihleri arasında kaydedilen izositrat dehidrogenaz vahşi tip GBM hastalarından oluşmaktadır. Birincil sonlanım noktası genel sağkalım, ikincil sonlanım noktası ise progresyonsuz sağkalımdır. Gruplar arasındaki karşılaştırmalar log-rank testi kullanılarak yapılmış ve çok değişkenli analizler Cox regresyonu kullanılarak gerçekleştirilmiştir.

Bulgular: Toplam 67 hasta değerlendirildi. Hastaların ortanca genel sağkalımı 19,3 aydı [%95 güven aralığı (GA) 15,1 ila ulaşılamadı (NR)]. Toplam 60 hastaya (%89,1) adjuvan tedavi uygulandı. Ortanca genel sağkalım ilk dört hafta içinde tedavi edilen hastalar için 31,1 ay (%95 GA ila 19,3-NR), dört ila altı hafta içinde tedavi edilenler için 15,7 ay (%95 GA ila 15,1-NR) ve altı haftadan sonra tedavi edilenler için 11,3 ay (%95 GA ila 9,8-NR) idi.

Sonuç: Çalışmamızda gözlenen sağkalım oranı klinik çalışmalarda bildirilenlerle karşılaştırılabilir düzeydedir. Ancak, daha geç dönemde tedavi alan hastalarda sağkalım oranı anlamlı derecede düşüktü. Bu nedenle, kılavuzların GBM hastalarında adjuvan tedavinin zamanlamasını daha doğru bir şekilde yansıtmasını sağlamak için daha geniş hasta popülasyonlarıyla daha fazla çalışma yapılması önerilmektedir.

Anahtar Kelimeler: Glioblastoma multiforme, stupp protokolü, genel sağkalım, tedaviye kadar geçen süre

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Introduction

Glioblastoma multiforme (GBM) represents the most prevalent primary central nervous system (CNS) tumor (1). In accordance with the 2021 World Health Organization (WHO) Classification of CNS tumors, GBM is characterised as isocitrate dehydrogenase (IDH)-wild-type (2,3). The median survival time for this aggressive tumor, with a median age of onset of approximately 60 years, is currently 12 to 15 months, and the 5-year survival rate is 6% (4).

The current gold standard treatment for GBM, a tumor with an adverse prognosis, comprises maximal safe resection and subsequent adjuvant therapy. This consists of temozolomide (TMZ), concurrent chemoradiotherapy (CRT), and six months of maintenance TMZ (5). The Stupp protocol has been demonstrated to enhance overall survival (OS) in patients under 70 with favorable performance status. The treatment regimen entails the concurrent administration of 75 mg/m²/day TMZ in 2 Gy fractions, with a total dose of 60 Gy, followed by six cycles of TMZ monotherapy (6). The long-term results of the trial demonstrated that survival in the TMZ arm remained superior to radiotherapy (RT) alone at both two-year (27% vs. 11%) and five-year (10% vs. 2%) follow-up points (7). In patients of an advanced age and/or with a markedly poor performance status, a supportive care approach may be considered the most appropriate course of action (8).

A number of studies have been conducted in order to ascertain the optimal timing for the commencement of adjuvant treatment in patients with various types of cancer. In patients with non-small cell lung cancer who are to receive adjuvant treatment following a curative resection, commencing treatment after a period of six weeks has been demonstrated to result in a reduction in disease-free survival (9). A study of 24,843 patients who had undergone surgery for breast cancer revealed that those who received adjuvant therapy 91 days or more after surgery exhibited a diminished OS rate [hazard ratio (HR): 1.34, 95% confidence interval (CI): 1.15-1.57] (10).

Despite adjuvant treatment currently being the standard of care, there is no consensus regarding the optimal timing for initiating treatment. The objective of this study was to ascertain the OS of patients diagnosed with GBM who received adjuvant treatment at our center and to evaluate the relationship between treatment approach, clinical characteristics, and time of treatment initiation and survival.

Materials and Methods

The present study is a retrospective cohort study that encompasses patients diagnosed with GBM at our medical center between 1 September 2022 and 1 March 2024. Patients diagnosed with an International Classification of Diseases 10th Revision code C71 (malignant neoplasm of the brain), histologically confirmed (biopsy or resection) GBM IDH-wild-type, CNS WHO grade 4, aged 18 years or older, with no previous chemotherapy or cranial RT, and no active infection, were identified through medical records as meeting the requisite criteria. Patients who did not fulfill the requisite criteria were excluded from the study.

The demographic information of the patients, including diagnosis dates and treatment initiation dates, as well as details of the treatment methods employed (surgery, chemotherapy, RT), the time elapsed between diagnosis and treatment initiation, and survival data (survival time and date of death), were defined. Additionally, data on recurrence and other treatment processes were also determined. The time to diagnosis was defined as the initial pathology date at which the primary brain tumor was identified. The early treatment group was defined as comprising those patients who commenced treatment within the first four weeks of diagnosis, while the delayed treatment group was defined as comprising those patients who commenced treatment six weeks or more after diagnosis (Figure 1).

OS defined as the time elapsed between diagnosis and death or the date of the last visit-served as the primary endpoint in this analysis. The secondary endpoint, progression-free survival (PFS), was operationalized as the time elapsed between the commencement of treatment and the date of the initial observational assessment of relapse, or death/last visit, whichever occurred first.

The time elapsed between surgical intervention and the commencement of CRT was examined as both a continuous variable and a categorical one, based on three defined time

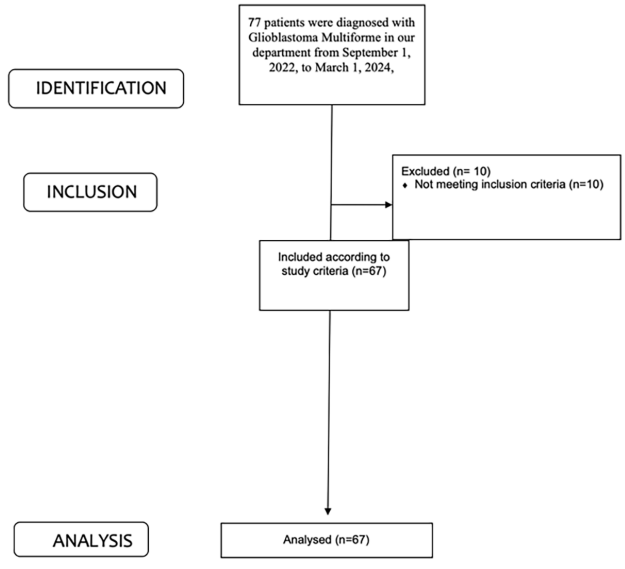

Figure 1: Patient flow diagram

intervals. The intervals were defined as follows: less than four weeks, four to six weeks, and greater than six weeks. This study was approved by the Scientific Research Evaluation and Ethics Committee of Etlik City Hospital (decision no.: AEŞH-BADEK-2024-758, date: 02.10.2024).

Statistical Analysis

In order to facilitate the analysis and presentation of the data, quantitative variables were expressed as means, with accompanying ranges. Similarly, categorical variables were described in terms of percentage frequency distributions. Kaplan-Meier survival curves were employed to estimate survival outcomes. Subsequently, intergroup comparisons were conducted utilising log-rank tests. A Cox regression analysis was employed to conduct multiple analyses. A two-tailed p-value of less than 0.05 was considered statistically significant. The statistical analyses were conducted using the BlueSky Statistics version 10.3.2 software.

Results

The mean age of the 67 patients included in the study was 60 years (range: 42-86 years). Upon analysis of the age distribution, it was observed that approximately half of the patients were under the age of 60. Of the total number of patients, 31 (46.2%) were male. Upon diagnosis, 61.2% of patients exhibited an Eastern Cooperative Oncology Group score of 0 to 1. Among the patients included in the study, 38 (56%) had pre-existing comorbidities. The most prevalent comorbidity was hypertension. A summary of the patient and tumor characteristics is presented in Table 1.

All patients included in the study underwent surgical intervention. A total resection was performed in 41 patients, representing 61.1% of the total number of patients included in the study. Over 90% of the patients were eligible for adjuvant treatment. Of the seven patients who were not eligible for adjuvant treatment, three were excluded due to age and performance status, two patients succumbed to postoperative complications, and two patients refused treatment. Of the total number of patients, 58 (86.5%) received and completed adjuvant. Two patients received only RT due to thrombocytopenia, which precluded the use of chemotherapy. The mean time to commencement of adjuvant treatment was 30 days (range 15-119 days). All patients received the standard doses of RT. During the follow-up period, 22 patients (32.8%) experienced recurrence. The estimated median PFS was 5.3 months (95% CI 3.6 to 12.6) (Figure 2a). During the follow-up period of 9.1 months, 21 patients succumbed to their disease. The estimated OS was 19.3 months (95% CI 15.1 to NR) (Figure 2b) (Table 2).

The Kaplan-Meier curves for PFS and OS were analysed according to the timing of adjuvant treatment initiation among patients. The median PFS was 7.0 months (95% CI 4.4 to NR) for 24 patients (35.8%) who commenced treatment within four weeks, 5.3 months (95% CI 3.5 to NR) for 21 patients (31.3%) who initiated treatment between four and six weeks, and 3.6 months (95% CI 2.8 to NR) for 13 patients (19.4%) who started treatment after six weeks. No statistically significant difference in PFS was observed between treatment groups (p=0.18) (Figure 3a).

Table 1: Patient, and tumor characteristics	
Age	
Median, (year)	60 (42-86)
Distibution no, (%)	
<60 ≥60	32 (47.7) 35 (52.2)
Sex no, (%)	
Male Female	31 (46.2) 36 (53.7)
ECOG PS no, (%)	
0-1 2 3 4	41 (61.2) 18 (26.8) 7 (10.4) 1 (1.4)
Comorbidty no, (%)	
Yes No	38 (56.7) 29 (43.3)
Comorbidity no, (%)	
HT DM HT + DM	20 (29.8) 8 (11.9) 10 (14.9)
Multifocal no, (%)	
Yes No	8 (11.9) 59 (88.1)
Tumorvolum (cm^3) no, (%)	
<200 200-400 >400	2 (2.9) 34 (50.7) 31 (46.2)

ECOG PS: Eastern Cooperative Oncology Group Performance Status, HT: Hypertension, DM: Diabetes mellitus

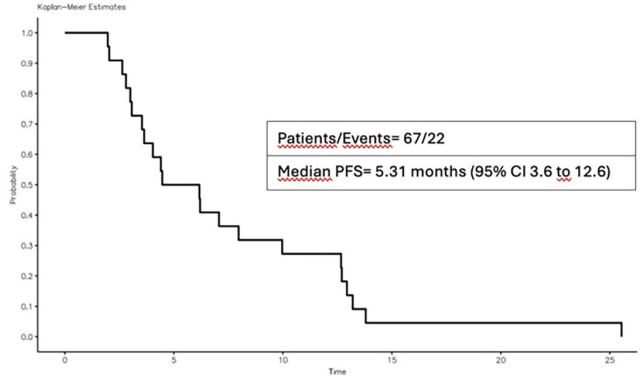

Figure 2a: Kaplan-Meier curve for PFS of the whole population
PFS: Progression-free survival, CI: Confidence interval

The median OS was 31.1 months (95% CI 19.3 to NR) for patients whose treatment was initiated within the first four weeks, 15.7 months (95% CI 15.1 to NR) for patients whose treatment commenced between four and six weeks, and 11.3 months (95% CI 9.8 to NR) for patients whose treatment began after six weeks. The OS time between the groups was statistically significant (p=0.04) (Figure 3b).

The effects of demographic and therapeutic characteristics on PFS were analysed and performance status at diagnosis (p=0.04) and intraoperative resection (total/subtotal) status (p=0.01) were statistically significant in univariate analyses. The only significant effect in multivariate analyses was intraoperative resection (p=0.03) (Table 3).

Univariate and multivariate analyses of OS revealed that performance status (p=0.001), gender (p=0.03) and time of chemotherapy initiation (p=0.03) had a statistically significant effect in univariate analysis. In multivariate analysis, the only significant effect was chemotherapy initiation time (p=0.01) (Table 4). When evaluated as post hoc analysis, a statistically significant difference was seen in all 3 groups 4 weeks/4-6 weeks, 4 weeks/6 weeks later, 4-6 weeks/6 weeks later (p<0.05).

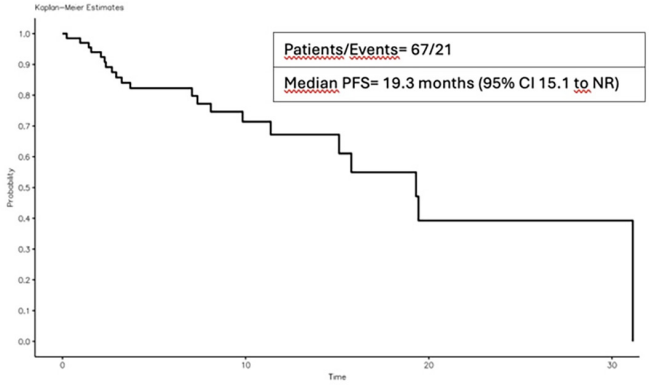

Figure 2b: Kaplan-Meier curve for OS of the whole population
OS: Overall survival, PFS: Progression-free survival, CI: Confidence interval

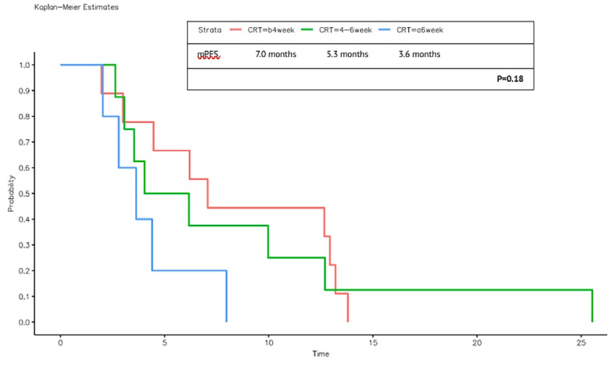

Figure 3a: Kaplan-Meier curves of PFS according to the time of initiation of adjuvant treatment
PFS: Progression-free survival, CRT: Chemoradiotherapy, mPES: Mean pulmonary end systolic

Discussion

Several factors contribute to the poor prognosis of GBM and its resistance to current therapies. The heterogeneity of GBM, the pro-tumorigenic role of the tumor microenvironment, the blood-brain barrier as a barrier to systemic treatment, and the low immunogenicity of GBM, which prevents a strong immunological response, are all factors that contribute to the poor prognosis of GBM and its resistance to current therapies

Table 2: Treatment and survival characteristics

Operation no, (%)	
Total resection Subtotal resection Biopsy	41 (61.1) 21 (31.3) 5 (7.46)
Adjuvant theraphy no, (%)	
Yes No	60 (89.5) 7 (10.4)
CRT no, (%)	
Yes No Only TMZ	58 (86.5) 7 (10.4) 2 (2.9)
RT waiting time, median (days)	30 (15-119)
RT waiting time no, (%)	
<4 weeks 4-6 week ≥6 weeks	24 (35.8) 21 (31.3) 13 (19.4)
RT dose no, (%)	
60 Gy	58 (89.5)
TMZ maintenance no, (%)	
Yes No	54 (80.5) 13 (19.4)
TMZ maintenance no, (%)	
<6 months ≥6 months	22 (40.7) 32 (59.2)
Recurrence no, (%)	
Yes No	22 (32.8) 45 (67.1)
Recurrence no, (%)	
Lokal Mutifocal	20 (90.9) 2 (9.9)
Median PFS (months)	5.3 (95% CI 3.6 to 12.6)
Exitus no, (%)	
Yes No	21 (31.3) 46 (68.6)
Median OS (months)	19.3 (95% CI 15.1 to NR)
Median follow-up (months)	9.1

CRT: Chemoradiotherapy, RT: Radiotherapy, TMZ: Temozolamide PFS: Progression-free survival, OS: Overall survival, NR: Not reached, CI: Confidence interval

(11). Furthermore, studies have demonstrated that patient characteristics (age, comorbidity, performance status), as well as surgical and adjuvant treatment-related factors (total resection, subtotal resection/biopsy), can influence OS (12-14). The tumor- and patient-related analyses, as well as the survival analyses, of our study, are in accordance with the findings of the existing literature on the subject.

The hypothesis that the growth rate of a tumor slows down with increasing tumor size may prove useful as a general rule for all tumors and may also assist in determining the optimal time to commence treatment for GBM (15). Given that radiosensitivity is inversely proportional to tumor growth rate, the commencement of RT at a later stage may result in a reduction in its efficacy (16). Nevertheless, an alternative perspective posits that hypoxia and edema in the vicinity of the surgical site in the immediate postoperative period may result in a reduction in radiosensitivity (17). In fact, the studies conducted support both of these perspectives.

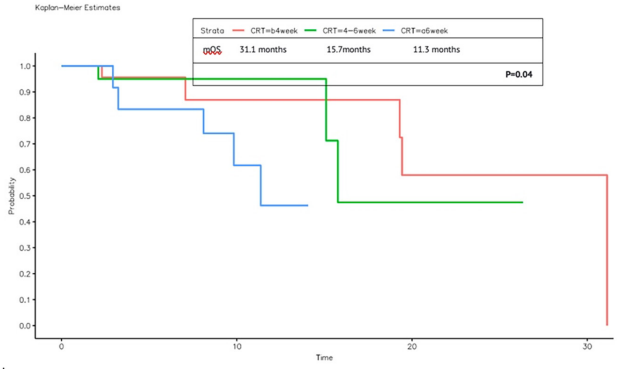

Figure 3b: Kaplan-Meier curves of OS according to the time of initiation of adjuvant treatment
mOS: Mean overall survival, CRT: Chemoradiotherapy

A study conducted in 2007 investigated the efficacy of RT in the early postoperative period. The findings indicated that, contrary to the delay observed at the time of presentation to the RT department, the delay at the time of surgery was associated with a reduction in survival (17). It is important to acknowledge that this study was conducted prior to the establishment of TMZ concurrent RT as the standard treatment. However, a recent retrospective study involving a substantial patient cohort demonstrated that adjuvant treatment initiated within the initial 35 days following total resection was associated with enhanced survival outcomes (18). However, the same improvement was not observed in residual tumors in this study. In a further large patient cohort, the early implementation of the Stupp protocol in patients with high-grade glioma was associated with a notable reduction in survival rates (19). In a separate study, a minimum interval of six weeks between surgery and CRT was associated with superior OS and PFS in patients with GBM (20). Some studies have reached the conclusion that the timing of the initiation of adjuvant treatment has no prognostic significance

Table 3: Univariate and multivariate analysis of prognostic factors for progression free survival

Prognostic factor	Patients /recurrence	Median PFS (months)	Univariate analysis p	HR (95% CI)	Multivariate analysis p	HR (95% CI)
ECOG PS						
0-1 ≥2	40/15 27/7	4.0 12.7	0.04*	0.33 (0.11-0.97)	0.07	0.31 (0.08-1.09)
Age						
<60 ≥60	32/12 35/10	3.8 6.6	0.78	0.88 (0.37-2.09)	0.99	0.99 (0.22-4.31)
Sex						
Male Female	31/11 36/11	4.4 7.0	0.15	1.97 (0.78-4.98)	0.74	1.20 (0.38-3.78)
Comorbidty						
Yes No	38/12 29/10	6.6 3.8	0.28	1.6 (0.66-3.91)	0.86	0.90 (0.30-2.73)
Operation						
Total resection Subtotal resection	41/16 21/5	4.2 13.2	0.01*	0.14 (0.03-0.64)	0.03*	0.14 (0.02-0.84)
RT waiting time						
<4 weeks 4-6 week ≥6 weeks	24/9 21/8 13/5	7.0 5.1 3.6	0.14	1.58 (0.85-2.92)	0.78	1.12 (0.46-2.72)

*Statistically significant
PFS: Progression-free survival, OS: Overall survival, CI: Confidence interval, HR: Hazard ratio, ECOG PS: Eastern Cooperative Oncology Group Performance Status, RT: Radiotherapy

Table 4: Univariate and multivariate analysis of prognostic factors for overall survival						
Prognostic factor	**Patients /exitus**	**Median OS (months)**	**Univariate analysis p**	**HR (95%CI)**	**Multivariate analysis p**	**HR (95%CI)**
ECOG PS						
0-1 ≥2	40/15 27/7	15.0 15.7	0.001*	5.05 (1.83-13.94)	0.17	2.41 (0.67-8.56)
Age						
<60 ≥60	32/12 35/10	15.0 19.3	0.27	1.65 (0.67-4.06)	0.51	1.56 (0.40-6.14)
Sex						
Male Female	31/11 36/11	15.1 15.0	0.03*	3.09 (0.11-8.58)	0.15	3.07 (0.65-14.50)
Comorbidty						
Yes No	38/12 29/10	17.7 15.0	0.53	0.75 (0.30-1.84)	0.17	2.63 (0.64-10.76)
Operation						
Total resection Subtotal resection	41/11 21/9	19.3 9.8	0.08	2.25 (0.90-5.62)	0.26	2.46 (0.50-12.09)
RT waiting time						
<4 weeks 4-6 week ≥6 weeks	24/5 21/3 13/5	31.1 15.7 11.3	0.03*	2.5 (1.04-5.99)	0.01*	3.18 (1.23-8.18)

*Statistically significant
OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, ECOG PS: Eastern Cooperative Oncology Group Performance Status, RT: Radiotherapy

(21,22). The findings of our study indicate that the initiation of treatment within the first four weeks had a significant positive effect on OS.

While there is a paucity of evidence regarding the optimal timing of treatment initiation, existing studies have yielded conflicting results. Notably, only a handful of investigations have focused on O^6-methylguanine (O^6-MeG)-DNA methyltransferase (MGMT) promoter methylation, which is regarded as a potential predictor of TMZ efficacy. In a study comprising a limited number of patients, univariate regression analysis demonstrated that although MGMT methylation exhibited a borderline significant correlation with OS across the entire population (p=0.048), the initiation of RT within 24 days had a detrimental impact (23). In a separate investigation, MGMT was accessible in approximately half of the patients, and the period of adjuvant therapy exceeding six weeks was linked to diminished survival (24). It was not possible to analyse MGMT in the context of this study. Nevertheless, in the entire cohort of patients, the commencement of treatment after six weeks, irrespective of MGMT methylation status, was associated with a poorer prognosis.

In a 2016 systematic review and meta-analysis of 19 retrospective studies examining the relationship between RT treatment delay and OS in GBM patients, no statistically significant association was identified (HR: 0.98; 95% CI: 0.90-1.08; p=0.70) (25). It is important to note that the study also examined the current standard pretreatment time. The findings of our study indicate that early treatment initiation is a statistically significant predictor of OS, as demonstrated by both univariate and multivariate analyses.

Study Limitations

The study is limited by the absence of investigation into the role of promoter methylation in the pathology slides, the relatively brief follow-up period, and the lack of detail regarding the treatment options employed in the event of recurrence. Furthermore, the lack of information regarding the rationale for the prolonged adjuvant treatment process (e.g., infection or post-operative complications) represents a significant limitation of the study. Nevertheless, it is evident that this study, conducted in a recently established center and clinic, is of significant value and will inform future prospective studies.

Conclusion

A review of the literature and existing guidelines reveals a lack of consensus regarding the optimal timing for initiating adjuvant treatment in patients with GBM. The present study offers significant insights into the subject matter, given the characteristics of the patient population and the results obtained. Further prospective, multicenter studies with larger patient populations are required.

Ethics

Ethics Committee Approval: This study was approved by the Scientific Research Evaluation and Ethics Committee of Etlik City Hospital (decision no.: AEŞH-BADEK-2024-758, date: 02.10.2024).

Informed Consent: Consent was not obtained since it was a retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.E.K., İ.D., G.Y., Concept: E.E.K., G.Y., Design: E.E.K., Data Collection and/or Processing: E.E.K., İ.D., G.Y., Analysis and/or Interpretation: E.E.K., İ.D., Literature Search: E.E.K., Writing: E.E.K., İ.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

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References

1. Miller KD, Ostrom QT, Kruchko C, et al. Brain and other central nervous system tumor statistics, 2021. CA Cancer J Clin. 2021;71:381-406.
2. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol. 2021;23:1231-1251.
3. Molinaro AM, Taylor JW, Wiencke JK, et al. Genetic and molecular epidemiology of adult diffuse glioma. Nat Rev Neurol. 2019;15:405-417.
4. Skaga E, Skretteberg MA, Johannesen TB, et al. Real-world validity of randomized controlled phase III trials in newly diagnosed glioblastoma: to whom do the results of the trials apply? Neurooncol Adv. 2021;3:vdab008.
5. Sulman EP, Ismaila N, Armstrong TS, et al. Radiation therapy for glioblastoma: American Society of Clinical Oncology clinical practice guideline endorsement of the American Society for Radiation Oncology Guideline. J Clin Oncol. 2017;35:361-369.
6. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352:987-996.
7. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009;10:459-466.
8. Weller M, van den Bent M, Hopkins K, et al. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. Lancet Oncol. 2014;15:e395-403.
9. Ürün M, Sezgin Y, Uysal E. The impact of timing adjuvant therapy on disease-free survival among patients with stage iib-iiia non-small cell lung cancer receiving platinumbased treatment. Turk J Clin Lab. 2023;14:639-644.
10. Chavez-MacGregor M, Clarke CA, Lichtensztajn DY, et al. Delayed initiation of adjuvant chemotherapy among patients with breast cancer. JAMA Oncol. 2016;2:322-329.
11. Ius T, Somma T, Pasqualetti F, et al. Local therapy in glioma: an evolving paradigm from history to horizons (Review). Oncol Lett. 2024;28:440.
12. Abacıoğlu U, Çetin İ, Akgün Z et al. Treatment results and prognostic factors for adult patients with diagnosis of glioblastoma multiforme after radiotherapy. Turk J Oncol. 2004;19:112-118.
13. Gilbert MR, Wang M, Aldape KD, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. J Clin Oncol. 2013;31:4085-4091.
14. Benli Yavuz B, Kanyılmaz G, Aktan M. Comparison of prognostic factors in glioblastoma patients with short- and long-term survival. Turk J Oncol. 2023;38:392-398.
15. Benzekry S, Lamont C, Beheshti A, et al. Classical mathematical models for description and prediction of experimental tumor growth. PLoS Comput Biol. 2014;10:e1003800.
16. Burnet NG, Jena R, Jefferies SJ, et al. Mathematical modelling of survival of glioblastoma patients suggests a role for radiotherapy dose escalation and predicts poorer outcome after delay to start treatment. Clin Oncol (R Coll Radiol). 2006;18:93-103.
17. Blumenthal DT, Won M, Mehta MP, et al. Short delay in initiation of radiotherapy may not affect outcome of patients with glioblastoma: a secondary analysis from the radiation therapy oncology group database. J Clin Oncol. 2009;27:733-739.
18. Pollom EL, Fujimoto DK, Han SS, et al. Newly diagnosed glioblastoma: adverse socioeconomic factors correlate with delay in radiotherapy initiation and worse overall survival. J Radiat Res. 2018;59(suppl_1):i11-i18.
19. Nathan JK, Brezzell AL, Kim MM, et al. Early initiation of chemoradiation following index craniotomy is associated with decreased survival in high-grade glioma. J Neurooncol. 2017;135:325-333.
20. Zur I, Tzuk-Shina T, Guriel M, et al. Survival impact of the time gap between surgery and chemo-radiotherapy in glioblastoma patients. Sci Rep. 2020;10:9595.
21. Han SJ, Rutledge WC, Molinaro AM, et al. The effect of timing of concurrent chemoradiation in patients with newly diagnosed glioblastoma. Neurosurgery. 2015;77:248-253.
22. Wang TJ, Jani A, Estrada JP, et al. Timing of adjuvant radiotherapy in glioblastoma patients: a single-institution experience with more than 400 patients. Neurosurgery. 2016;78:676-682.
23. Adeberg S, Bostel T, Harrabi S, et al. Impact of delays in initiating postoperative chemoradiation while determining the MGMT promoter-methylation statuses of patients with primary glioblastoma. BMC Cancer. 2015;15:558.
24. Spratt DE, Folkert M, Zumsteg ZS, et al. Temporal relationship of post-operative radiotherapy with temozolomide and oncologic outcome for glioblastoma. J Neurooncol. 2014;116:357-363.
25. Loureiro LV, Victor Eda S, Callegaro-Filho D, et al. Minimizing the uncertainties regarding the effects of delaying radiotherapy for Glioblastoma: a systematic review and meta-analysis. Radiother Oncol. 2016;118:1-8.