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Prognostic factors in patients with glioblastoma multiforme (clinical research)

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Aim: To define the independent variables that affect the life spans of patients with glioblastoma multiforme (GBM).

Materials and methods: This study was conducted in the neurosurgery clinic of Erciyes University's Faculty of Medicine, lasting from February 2000 to September 2006. A total of 98 patients were diagnosed with GBM after tumor resections. Patients' demographic, neurological, radiological, surgical, and clinical features and adjunct therapies were analyzed retrospectively.

Results: Of the 98 patients, 36 (36.7%) were female and 62 (65.4%) were male. There were 15 patients (15.3%) still alive. The median survival time (MST) of the gross total resection and subtotal resection groups was 12 and 8 months, respectively. The group with postoperative Karnofsky performance scores (KPS) of ≥70 included 56 patients; their survival rate was 19.6% and their MST was 14 months (confidence interval [CI] 95%, 10–18). The postoperative KPS of <70 group included 42 patients; their MST was 4 months (CI 95%, 3–6) and their survival rate was 9.5%. After the radiotherapy, of the 73 patients who underwent chemotherapy, the survival rate was 19.2% and the MST was 14 months (CI 95%, 10–18). The group without chemotherapy had a MST of 2 months (CI 95%, 1–3) and a survival rate of 4%. In a univariate analysis, the MST of age groups I (<45), II (45–59), and III (≥60) were 15 months (CI 95%, 7–23), 10 months (CI 95%, 7–13), and 5 months (CI 95%, 3–7), respectively. The preoperative and postoperative median tumor volume detected was 79 (14–668) and 6 (0–64) mm3, respectively.

Conclusion: Multivariate Cox regression analyses showed that prognostic factors are young age, postoperative KPS, chemotherapy, and postoperative tumor volume.

Key words: Glioblastoma multiforme, prognosis, postoperative tumor volume, Karnofsky performance score

1. Introduction

The prognosis of patients with glioblastoma multiforme (GBM) is not satisfactory and it continues to be expressed in months, despite advancements in the treatment of the disease itself (1). GBM is the most significant and malignant diffuse primary brain tumor. In the literature there is much controversy about the independent variables acting on prognosis; therefore, discrepant conclusions are presented. Major independent variables include surgical resection (1–4), age (3–8), patients' preoperative Karnofsky performance scores (KPS) (1,3–9), tumor localization (1,3,5,7,8), postoperative radiotherapy (RT), and chemotherapy (CT) (5,7,8). Since these variables interact with each other, detection of the primary variables that affect survival requires research of multivariate analyses, together with the other variables. The present study examines the effects on the prognosis caused by variables such as the degree of surgical resection, the localization of the lesion, the age of the patient, preoperative and postoperative KPS, complications, reoperations, preoperative and postoperative tumor volume, RT, and CT. These variables have been studied prospectively using univariate and multivariate statistical analyses.

The objective of this study is to define the independent variables affecting the life span of patients with GBM.

2. Materials and methods

The current study presents correlations of the prognoses with adjunct therapies for 98 patients diagnosed with GBM, based on postcraniotomy tumor resections in the neurosurgery clinic in the Faculty of Medicine of Erciyes University from February 2000 to September 2006. The demographic, neurological, radiological, surgical, and clinical features of the cases were defined retrospectively and were assumed to affect prognosis.

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The material obtained from the surgical resection of each case was studied by an experienced pathologist. Histopathological diagnoses indicated GBM according to the World Health Organization's (WHO) standards (10). The data regarding the patients' radiological and clinical features and their treatment modalities were recorded for safekeeping in tumor follow-up forms specially designed for this study group.

While asymptomatic patients were requested to report back at 3-month intervals, for symptomatic patients clinical and radiological data were recorded in forms specially designed for monitoring tumors. Magnetic resonance imaging (MRI) was conducted at each control session and the results were assessed by an experienced radiologist to determine recurrence and regrowth.

2.1. Surgical protocol

After the patients' positions were secured by Mayfield Nail headgear (Brain LAB Surgical Products, Cincinnati, OH, USA) under anesthesia, the patients' positions were matched with neuronavigation. For the correction of surgical deviations due to brain shift, intraoperative ultrasound images were synchronized with navigation images and the navigation systems were fused; this process was continued in real time until the end of each resection as the need arose. Intraoperative ultrasonography recordings were separated, as required, in terms of postresection residual tumors, and the transition to hemostasis was realized when the resection was deemed satisfactory.

2.2. Imaging protocol

Tumor localizations and their proximity to vital areas in the brain were quantified according to the grading system proposed by Sawaya et al. (11) (Table 1). Preoperative and postoperative routine computerized tomography and MRI recordings were obtained with and without a contrast medium, and tumor localization features were determined by a neuroradiologist. Computerized tomography within the first 4 h postoperatively was obtained from each patient to diagnose any asymptomatic complications that might be related to surgery. The extent of surgical resection was determined by the neuroradiologist through T1 MRI images with contrast, which were obtained during the first 72 h postoperatively (≥95%, gross total resection; <95%, subtotal resection). All of the patients were checked postoperatively within the first 72 h.

2.3. Radiotherapy protocol

Of the 98 total patients, 82 patients (83.7%) received RT. The remaining 16 patients were unable to receive RT for social (8 patients) or medical (8 patients) reasons. An effective irradiation area was drawn on the mask in the simulator for each patient. The first stage of the radiotherapy, which was performed by applying 6,000,000 electron volts (MV) with a LINAC teletherapy device (Varian 2300c, USA) device, targeted the area involving pathological contrast consistent with the tumor, the area around with edema, and 2–3 cm of brain tissue beyond this area. A dosage of 40–50 Gy was applied. In the second stage of the therapy, however, the targeted area was narrowed further, and the dosage was increased to 60 Gy. The dosage was limited to 60 Gy in 30 fractions for 6 weeks, which reached the tolerance level of the central nervous system. In both therapeutic stages, the parallel opposed field technique was used. As a prophylactic against cerebral edema, throughout the radiotherapy, each of the patients received 8–16 mg/day dexamethasone, which was tapered and discontinued within 2 weeks after the completion of the therapy.

2.4. Chemotherapy protocol

Following the pathological diagnosis, the first dose of 100 mg/m^2 intravenous fotemustine was administered to 73 patients, together with the first dose of radiotherapy. The same dose was repeated at 3-week intervals to complete 3 cycles (whereas the remaining 25 patients were unable to receive it for economic [11 patients], social [8 patients], and medical [6 patients] reasons). The performance scores (hematological, renal, and hepatic functions) of the patients accepted for CT were monitored closely at regular intervals, and care was taken to keep the scores within normal ranges. When abnormal values were detected, the CT protocol was interrupted until the values were normalized.

2.5. Statistical method

The patients' cumulative life spans, following the dates they were accepted for surgical operations, were determined using the Kaplan–Meier method. Survival time curves for various subgroups were compared by the log-rank test.

Table 1. Grading of malign astrocytomas according to functional localization (11).

Grade	Localization
I: Nonvital area	Frontal or temporal pole, parietooccipital lobe, cerebellar hemisphere.
II: Near vital area	Near motor or sensory cortex, calcarine fissure, speech center, internal capsule, dentate nucleus, and brainstem.
III: Vital area	Motor or sensory cortex, visual and speech center, internal capsule, basal ganglia, thalamus, hypothalamus, dentate nucleus, and brainstem.

The effects of multiple variables on patients' survival times were analyzed with the Cox regression method. Shapiro–Wilk tests were used to evaluate the presences of normal data distribution. If the data distributions were normal, then the parametric test was used. If the data distributions were abnormal, then a nonparametric test was used. The values were given as medians (minimum–maximum) for the nonparametric test results. Crude and processed data in the study were quantified within a confidence interval of 95%. A univariate Kaplan–Meier life analysis and univariate and multivariate Cox regression analyses were used to determine whether the values affecting patient survival times were significant. Values of $P < 0.05$, $P < 0.01$, and $P < 0.001$ were considered statistically significant; values of $P > 0.05$ were considered statistically insignificant. For statistical analyses, SPSS 10.0 (SPSS, Inc., Chicago, IL, USA) was used.

3. Results

3.1. Demographic features of the patients

Of the 98 patients, 59 underwent gross total resection and 39 underwent subtotal resection. The cases comprised 36 (36.7%) female and 62 (63.3%) male patients. Their ages ranged from 18 to 75 years, with a median of 51 years. The male patients' survival rate was 11.3% (n = 7), with a median survival time (MST) of 10 months, whereas 22.2% (n = 8) of the female patients survived, with a MST of 9 months (Table 2). In univariate and multivariate Cox regression analysis, the sex of the patients was not detected as a statistically significant prognostic factor ($P > 0.05$; Tables 3 and 4).

3.2. Patient age

The ages of the patients ranged from 18 to 75 years, with a median of 51 years. The patients were divided into 3 groups, according to their ages: group I included patients younger than 45 years, group II included patients of 45–59 years old, and group III included patients above 60 years old. In a univariate analysis, the MST for the 35 patients in group I was 15 months (CI 95%, 7–23). For the 34 patients in group II, the MST was 10 months (CI 95%, 7–13). For the 29 patients of group III, the MST was 5 months (CI 95%, 3–7). The findings for groups I and II were statistically significant ($P < 0.01$), and these groups had longer survival times than group III. Group II, in particular, had a statistically significant and longer survival time than group III ($P < 0.05$; Table 2). In a univariate Cox regression analysis, group I's age was detected as a positive prognostic factor ($P < 0.001$), whereas group II's age and group III's age had negative effects on prognosis ($P < 0.001$ and $P < 0.01$, respectively; Table 3). In multivariate Cox regression analysis, there were statistically significant differences between groups I and III ($P < 0.01$ and $P = 0.001$, respectively), but there was no statistically significant difference for group II ($P > 0.05$). For the patients in age group III, the mortality risk was detected as 3.25 times greater (Table 4).

3.3. Functional localization of tumor

The tumors' localizations were grouped according to the method of Sawaya et al. (11) (Table 1). The MST of grades I, II, and III were 18 (CI 95%, 6–30), 11 (CI 95%, 7–16), and 8 (CI 95%, 6–11) months, and their survival rates were 13.3% (2 patients alive), 16.0% (4 patients alive), and 15.5% (9 patients alive), respectively. No statistically significant difference was detected in the tumor localizations' effect on survival times ($P > 0.05$; Table 2). In univariate and multivariate Cox regression analyses, there was no statistical significance related to the localization groups ($P > 0.05$; Tables 3 and 4).

3.4. Preoperative KPS

The group with preoperative KPS of ≥70 included 69 patients whose survival rate was 15.9% (11 patients alive), with a MST of 12 months (CI 95%, 9–15). The preoperative KPS of <70 group included 29 patients, whose survival rate was 13.8% (4 patients alive) with an MST of 5 months (CI 95%, 3–7). The difference between the groups was statistically significant, according to the MSTs ($P < 0.001$; Table 2). In univariate Cox regression analysis, there was a statistically significant difference between the groups' preoperative KPSs ($P = 0.001$; Table 3). In multivariate Cox regression analysis, preoperative KPS was not a statistically significant prognostic factor ($P > 0.05$; Table 4).

3.5. Extent of resection

Of the 59 patients with gross total resection, 12 (20.3%) were alive throughout the follow-up. The MST of the patients in this group was 12 months (CI 95%, 9–15). In the subtotal resection group, 3 (7.7%) of the 39 patients in this group were alive, and the patients' MST was 8 months (CI 95%, 5–11). No statistically significant difference was detected in the effect of tumor resection groups on survival times ($P > 0.05$; Table 2). In univariate and multivariate Cox regression analyses, resection degree was not a prognostic factor, and there was no statistical significance ($P > 0.05$; Tables 3 and 4).

3.6. Postoperative KPS

The postoperative KPS of ≥70 group included 56 patients; their survival rate was 19.6% (11 patients alive) and their MST was 14 months (CI 95%, 10–18). The postoperative KPS of <70 group included 42 patients; their MST was 4 months (CI 95%, 3–6) and their survival rate was 9.5% (4 patients alive). There were statistically significant differences in the MSTs of the 2 groups ($P < 0.001$; Table 2). Univariate and multivariate Cox regression analyses showed a statistically significant difference between the postoperative KPS groups ($P < 0.001$ and $P < 0.05$, respectively), which affected prognosis (Tables 3 and 4).

Table 2. Demographic, characteristics and statistical analyses of the patients with malign astrocytoma.

Variable	Description	%	n = 98	Survival rate	Median survival time (CI 95%)	P
Age group I	<45	35.7	35	25.7	15 (7–23)	<0.01*
Age group II	45–59	34.7	34	14.7	10 (7–13)	<0.05**
Age group III	>60	29.6	29	3.4	5 (3–7)	
Sex	Male	63.3	62	11.3	10(8–12)	>0.05ǫ
	Female	36.7	36	22.7	9(2–16)	
Localization	Nonvital	15.3	15	13.3	18 (6–30)	
	Near vital	25.5	25	16	11 (7–16)	>0.05ǫ
	Vital area	59.2	58	15.5	8 (6–11)	
Preoperative KPS	<70	29.6	29	13.8	5 (3–7)	
	≥70	70.4	69	15.9	12 (9–15)	<0.001∂∂
Gross total resection	>95%	60.2	59	20.3	12 (9–15)	>0.05ǫ
Subtotal resection	<95%	39.8	39	7.7	8 (5–11)	
Postoperative KPS	<70	42.9	42	9.5	4 (3–6)	
	≥70	57.1	56	19.6	14 (10–18)	<0.001ϕ
Postoperative complications	Yes	22.4	22	4.5	4 (1–7)	
	No	77.6	76	18.5	11 (8–14)	<0.01¢
Reoperation	Yes	25.5	25	20	20 (18–22)	<0.01#
	No	74.5	73	13.7	8 (6–10)	
Radiotherapy	With	83.7	82	17.1	11 (8–14)	<0.001ʀ
	Without	16.3	16	6.3	1	
Chemotherapy	With	74.5	73	19.2	14 (10–18)	<0.001ς
	Without	25.5	25	4	2 (1–3)	
Neuronavigation	Yes	83.67	82	17.1	11 (8–14)	> 0.05ǫ
	No	16.33	16	6.3	8 (4–12)	
Median age (range), years			51 (18–75)	15.3	10 (8–12)	
Preoperative median tumor volume			79 (14–668) mm^3			
Postoperative median tumor volume			6 (0–64) mm^3			

* : P < 0.01, age group I versus II and III.

**: P < 0.05, age group II versus III.

∂∂: P < 0.001, preoperative Karnofsky score of ≥70 versus <70.

ǫ: P > 0.05 in the gross total resection versus subtotal resection, localization, sex, and operation with and without neuronavigation groups.

ϕ: P < 0.001, postoperative Karnofsky score of ≥70 versus <70.

¢: P < 0.01, postoperative complication 'Yes' versus 'No'.

#: P < 0.01, reoperation 'Yes' versus 'No'.

ʀ: P < 0.001, radiotherapy group versus group not given radiotherapy.

ς: P < 0.001, chemotherapy group versus group not given chemotherapy.

Table 3. Univariate Cox regression analysis.

Variable	B coefficient	Standard error	OR	OR (95% CI)	P
Sex	−0.016	0.24	0.98	0.62–1.57	>0.05[Δ]
Preoperative Karnofsky score	−0.82	0.25	0.44	0.27–0.72	0.001[C']
Postoperative Karnofsky score	1.13	0.23	3.11	1.97–4.90	<0.001[◊]
Reoperation	−0.76	0.26	0.47	0.28–0.79	<0.01[ǫ]
Radiotherapy	−1.73	0.31	0.18	0.097–0.33	<0.001[Ʀ]
Chemotherapy	−1.83	0.27	0.16	0.093–0.27	<0.001[€]
Complication	−0.68	0.26	1.98	1.19–3.29	<0.01[Ω]
Age group I			-		<0.001[&]
Age group II	−1.32	0.29	0.27	0.15–0.46	<0.001[&]
Age group III	−0.84	0.28	0.43	0.25–0.74	<0.01 [&]
Localization I			-		>0.05[Δ]
Localization II	−0.56	0.33	0.57	0.30–1.08	>0.05[Δ]
Localization III	−0.16	0.26	0.85	0.51–1.43	>0.05[Δ]
Resection	−0.34	0.23	0.71	0.46–1.11	>0.05[Δ]
Preoperative tumor volume	0.000	0.001	1.001	0.99–1.001	>0.05[Δ]
Postoperative tumor volume	0.017	0.008	1.02	1.00–1.034	<0.05[*]

[C']: P = 0.001, preoperative Karnofsky score of <70, which has positive survival advantages.
[◊]: P < 0.001, postoperative Karnofsky score of ≥70, which has positive survival advantages.
[ǫ]: P < 0.01, patient group without reoperation has negative survival advantages in the groups with and without reoperation.
[Ʀ]: P < 0.001, patient group without radiotherapy has negative survival advantages in the radiotherapy group.
[€]: P < 0.001, patient group without chemotherapy has negative survival advantages in the groups with and without chemotherapy.
[Ω]: P < 0.01, in the group developing complications, which has negative survival advantages.
[&]: P < 0.001 and P < 0.01, older age groups have negative survival advantages in the age groups.
[*]: P < 0.01, in the postoperative tumor volume.
[Δ]: P > 0.05, sex, localization, resection groups, and preoperative tumor volume.

3.7. Postoperative complications

The group of patients for whom no complications developed (n = 76) had a survival rate of 18.5% throughout the follow-up, unlike the 4.5% rate for the group of 22 patients with complications. MST was 11 months (CI 95%, 8–14) in the group without complications, while it was 4 months (CI 95%, 1–7) in the group with complications and the difference was statistically meaningful (P < 0.01; Table 2). In univariate Cox regression analysis, complications were detected as a statistically significant prognostic factor (P < 0.01; Table 3); however, this relation was not detected in the multivariate analysis (P > 0.05; Table 4).

3.8. Reoperation

There were 25 patients who were reoperated on, and their MST was 20 months (CI 95%, 18–22). The MST of the patients who had no reoperations was 8 months (CI 95%, 6–10). There were statistically significant differences in the MSTs of the 2 groups (P < 0.01; Table 2). In univariate Cox regression analysis, reoperation was detected as a statistically significant prognostic factor (P < 0.01; Table 3), but this relation was not detected in the multivariate analysis (P > 0.05; Table 4).

3.9. Preoperative and postoperative tumor volume

A Shapiro–Wilk test was used to calculate preoperative and postoperative median tumor volumes as a nonparametric test. The preoperative median tumor volume was detected as 79 (14–668) mm^3, and the postoperative median tumor volume was 6 (0–64) mm^3 (Table 2). In univariate Cox regression analysis, preoperative tumor volume was detected as a statistically significant prognostic factor (P < 0.05). In univariate and multivariate Cox regression analyses, postoperative tumor volume was detected as a statistically significant prognostic factor (P < 0.05), but not preoperative tumor volume (P > 0.05; Tables 3 and 4).

Table 4. Multiple Cox regression analysis.

Variable	B coefficient	Standard error	OR	OR (95% CI)	P
Sex	0.39	0.28	1.48	0.86–2.53	>0.05
Preoperative Karnofsky score	−0.52	0.32	0.59	0.32–1.11	>0.05
Postoperative Karnofsky score	−0.73	0.37	0.48	0.23–0.99	<0.0[5K]
Reoperation	−0.44	0.31	0.64	0.35–1.17	>0.05
Radiotherapy	0.76	0.49	2.13	0.82–5.55	>0.05
Chemotherapy	1.45	0.44	4.25	1.78–10.13	0.001[Ω]
Complication	0.28	0.33	1.32	0.69–2.51	>0.05
Age group I			-		<0.01[*]
Age group II	0.39	0.3	1.48	0.82–2.66	>0.05
Age group III	−1.18	0.34	3.25	1.66–6.38	0.001[**]
Localization I			-		>0.05
Localization II	−0.04	0.38	0.96	0.45–2.03	>0.05
Localization III	−0.61	0.4	0.54	0.25–1.19	>0.05
Resection	0.09	0.31	1.1	0.60–2.01	>0.05
Preoperative tumor volume	0.001	0.001	1.001	0.99–1.003	>0.05
Postoperative tumor volume	0.025	0.012	1.025	1.00–1.05	<0.05[V̊]

[K]: P < 0.05, the group that had a postoperative Karnofsky score of <70 had negative survival advantages.
[Ω]: P = 0.001, the patient group treated with chemotherapy had a positive life expectancy.
*: P < 0.01, the youngest age group had a positive life expectancy.
**: P = 0.001, the oldest age group had a negative life expectancy.
[V̊]: P < 0.05, postoperative tumor volume was a prognostic factor.
P > 0.05: there were no statistically significant correlation with life expectancy.

3.10. Radiotherapy/chemotherapy and survival times

Table 2 shows the patient groups with and without RT and CT, their survival rates, and their MSTs. The MST of the patients treated with RT was 11 months (CI 95%, 8–14), and 17.1% of these patients were alive throughout the follow-up. When the MST of this group was compared to the MST of the group without RT, a statistically significant difference was found (P < 0.01). Of the 73 patients who underwent CT, 14 (19.2%) were alive after the treatment with a MST of 14 months (CI 95%, 10–18). The group without CT had a mean survival time of 2 months (CI 95%, 1–3). The differences among the median survival times of the groups were statistically significant (P < 0.001). In univariate Cox regression analysis, RT and CT were detected as statistically significant prognostic factors (P < 0.001). The univariate Cox analysis found a negative correlation between the survival rate and the treatment group without RT and CT (Table 3). CT was a statistically significant prognostic factor (P = 0.001; odds ratio = 4.25), but RT had no statistically significant relation in the multivariate Cox regression analysis (Table 4).

4. Discussion

This study analyzed the possible prognostic factors' effects on prognosis. These factors included extent of resection, age, preoperative and postoperative KPS, functional localization, pathological diagnosis, RT, CT, reoperation, preoperative and postoperative tumor volume, and postoperative complications, which are all among the independent variables acting on survival times.

4.1. The extent of resection and functional localizations

The optimal extent of resection in a patient depends on the size and localization of the tumor, the patient's general and neurological condition, and the surgeon's experience.

Sawaya et al. (11) propounded that the most important variable for determining the neurological deficit risks following a craniotomy is the functional localization of the tumor. When assessing the relationship between

surgical intervention and survival, the appropriate method is consideration of tumor localization and the extent of resection, which may vary depending on tumor localization (3,5,11).

Contrary to the accepted view, this study has revealed, through univariate and multivariate analyses, that resection degree is not a crucial independent factor that determines survival.

The amount of residual tumor, as seen in postoperative MRI, was computed numerically. Numerical studies on tumor size in patients with recurrent malign astrocytoma (MA) report that as the postoperative size of the tumor reduces, the survival time is prolonged significantly (12). In addition, other studies suggested that as the size of the resection grows, the survival time becomes correspondingly prolonged (1–3,5). Other studies reported that the extent of resection had no effect on survival (7,13). Some studies on general prognostic factors have reported that resection size has a favorable effect on survival time (2,3,5,14). Aggressive surgical resection has less to do with prolonging patients' lifespans (15).

Lamborn et al. (4) divided patients into 4 risk groups, and they found that the lowest risk group contained patients younger than 40 years old with tumors localized in the frontal region. The authors stressed, in light of these observations, that localization should be considered as a prognostic factor in future studies.

Li et al. (1), in their study of 116 patients, reported that frontal lobe involvement is a statistically significant marker of the delayed progression of postoperative disease. Furthermore, they concluded that the involvement of a vital area or deep structure is linked with poor prognosis. The favorable effect of the degree of surgical resection is statistically significant in univariate analyses, unlike the multivariate analyses, in which no such effect has been verified.

The desire to preserve neurological functions has engendered a tendency to remove the tumors proximal to the vital areas of the brain through biopsy or partial resection, whereas those in nonvital areas are usually removed through more aggressive resection (3).

In this study, the effect of the tumor's functional localization on survival time was not found to be statistically significant in univariate and multivariate analyses. Although some studies (1,3,4,7,8,11) reported that localization is a crucial and effective factor in prognosis, others (6,14) reported the absence of a relationship between localization and prognosis.

Although tumors with localizations in functional areas are associated with shorter survival times (1,3,8), this study found that functional localization has no effect on survival times in univariate and multivariate analyses. This discrepancy is ascribed to the boundaries of surgical resection and vital areas being determined through navigation. For the obtainment of optimal tumor resection, it is necessary to use navigation technology, together with the surgical microscope and ultrasonography compatible with that technology.

4.2. Patient age

This study detected a strong association between younger ages and survival. The patients in age groups I (below 45 years) and II (45–49 years) had a statistically significant advantage over the patients in group III (60 years and above).

There is significant evidence of the relationship between patients' young ages and longer survival times in adult patients with MA (3–8). Consequently, patient age is an independent variable that determines the choice of surgical method and hence the survival time.

As age increases, so does mortality risk. Aggressive therapies administered to old patients are less effective, whereas they prolong survival times in young patients (5,15).

The incidence of MA in old patients is important, and it may rise with advancing age (16). Uzuka et al. (17) suggested that maximal safe resection is an optimal treatment followed by radiochemotherapy using temozolomide (TMZ), regardless of age and KPS, for patients with GBM.

In summary, there is strong evidence of the relationship between adult patients' young ages and longer survival times (3,5–7). Therefore, when medical professionals assess the effect of aggressive surgical intervention on the patients' survival, they should consider the age factor (18).

4.3. Preoperative functional state

Although the scoring system developed by Karnofsky (19) is frequently used in the literature, researchers use different scoring systems when assessing patients' performance levels. This, in turn, produces different results (7,13). In general, when the preoperative functional state is studied as an independent variable, patients with elevated Karnofsky scores have more favorable results (1,3,4,6–9,13). These studies, however, have an important limitation: although low preoperative KPS (which is significantly correlated to high mortality rates) is included in a statistical assessment, the extent of surgical resection (which is a crucial prognostic factor in multivariate analyses) is not (13). Chang et al. (7) reported that both preoperative KPS and the type of surgery are significantly correlated with survival time.

This study's univariate analyses showed that patients' elevated preoperative KPSs influence survival as an independent variable, and low KPSs affect survival adversely. These results are consistent with those of previous studies (1,3,6–9).

4.4. Postoperative functional state

There are 2 other clinical variables that determine the reaction of radiation in cases with GBM: pre-RT KPS and the degree of surgical resection applied (5). The mechanism of the correlation between KPS and radiation response is unknown. In malignant gliomas in patients with low KPSs, high tumor metabolism can be observed through 18-fluorodeoxyglucose positron emission tomography (PET scanning) (20).

In the present study, univariate and multivariate analyses have shown that a high postoperative KPS is associated with a considerable increase in the rate of survival, which is consistent with the findings from previous studies (1,5,13). Wang et al. (21) reported that the only independent prognostic factors for a longer overall survival were gross total resection and higher KPS in multivariate analysis.

4.5. Complications

This study detected that complications developing within the first postoperative month have an adverse effect on survival. Patients without complications have higher survival rates.

Previous studies have not significantly considered the effects of postoperative complications on MA patients' survival times, but this issue has gained importance in today's studies owing to the complications' crucial adverse effects. Almost all previous studies observed patients during the postoperative weeks and months, without presenting surgical mortalities and mortality rates. Such an approach may produce false results concerning the effects of surgical operations (15).

4.6. Radiotherapy

It has been propounded that younger GBM patient age correlates with a better reaction to RT. Other important clinical variables that point to better reactions to radiation are high postoperative KPSs and extensive surgical resection (5). Theoretical tumor models indicate that tumors with smaller diameters can display greater radiosensitivity (22). In this study, small postoperative tumor volume was revealed as a prognostic factor. According to this result, small postoperative tumor volume might increase the response to the RT and hence improve the prognosis.

Recent studies suggest that differences in the molecular pathology of GBM tumors might be related to sensitivity to therapy. Yount et al. (23) found that GBM cells in which p53 functions are missing undergo less apoptosis after ionizing radiation therapy. GBM cells interacting with the p53 function undergo more prolonged cell cycles arrested by apoptosis (24). However, the p53 mutation is most common in GBM cases in young patients. That indicates the presence of a correlation between other molecular defects and radiation reaction assessed radiographically in GBM (25). GBM in older patients tends to display the deletion of the tenth chromosome, and it is probable that the genes that are important in terms of radiosensitivity in gliomas are located on this chromosome (26). Some studies report that radiation reactions are visually evaluated more accurately in patients with malign gliomas who have shown favorable performances and undergone more comprehensive resections (21). The cause of the correlation between KPS and radiation reaction is unknown. However, in some studies, PET has shown that malign gliomas in patients with low KPSs have higher tumor metabolisms (20). Tanaka et al. (27) reported that a patient with lower KPS who underwent resection appeared to benefit from radiotherapy. When a patient underwent biopsy, he or she did not benefit from RT. The KPS was improved after RT in the resection group.

This study found that RT is an independent variable that is statistically significant in both Kaplan–Meier life analysis and univariate Cox regression analysis. RT lost its statistical significance in multivariate Cox regression analysis, however, when CT was added to the analysis. These conclusions indicate that RT has prognostic value in MAs during the postoperative period, and they verify the literature findings (2,4,6,8,27)

4.7. Chemotherapy

Patients who received CT had longer survival times in both univariate and multivariate analyses. When RT was ignored in multivariate Cox regression analysis, CT had no effect on survival time; this demonstrates the effect of CT on survival after RT. It was also observed that CT application following RT was an important independent variable affecting survival.

Filippini et al. (8) found, in a study of 676 patients, that CT is statistically significant with respect to survival. In addition, making references to the literature, the authors stressed that in patients with recurrent glioblastoma, second-line CT has statistically significant effects on survival. Barker et al. (16) reported that when TMZ is given concomitantly with RT, the survival of elderly patients with GBM may be improved. Kaur et al. (28) reported that chemotherapy was not a prognostic factor in the multivariate analysis, nor was localization of the tumor. On the other hand, age and extent of resection were significant prognostic factors in the multivariate analysis.

Iwadate et al. (29) reported great GBM chemosensitivity in the absence of a mutation in p53, the tumor-repressing gene. SongTao et al. (30) reported that the best chemosensitivity was associated with isocitrate dehydrogenase mutation and O-(6)-methylguanine DNA methyltransferase promoter methylation, but p53 expression was not.

In conclusion, all independent variables interact with each other. Even though surgical resection degree is

not a prognostic factor, according to the univariate and multivariate analyses, postoperative tumor volume was revealed as a prognostic factor in the multivariate analysis. Therefore, surgical resection is an important prognostic variable, along with age, chemotherapy, postoperative KPS, and postoperative tumor volume. Extensive surgical resection is an important variable because small tumor volume has a significant effect on prognosis.

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