The Prognostic Value of the Treatment and Outcome in Patients with Glioblastoma: A Retrospective Cohort Study

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ABSTRACT

The classification of central nervous system (CNS) tumors by the 2021 World Health Organization (WHO) has led to significant changes in tumor taxonomy. One of the most significant changes is that isocitrate dehydrogenase (IDH) mutant forms of glioblastoma multiforme (GBM) have been differentiated into separate entities, no longer allowing entries to be classified as not otherwise specified (NOS). As a result, this entity only comprises the most aggressive adult-type tumors and established prognostic factors no longer apply. Glioblastoma (GBM) IDH-wildtype CNS WHO grade 4 typically presents necrosis and/or microvascular proliferation and molecular alterations. Herein, we aimed to classify glioblastoma cases to establish a patient survival pattern based on age, gender, the number of masses, tumor location, functional localization, presence of shift, the volume of edema and necrosis, extent of surgery, radiotherapy-chemotherapy protocol, and isocitrate dehydrogenase (IDH) presence, affecting overall survival were determined retrospectively. A total of 433 patients >20 years old with primary GBM were treated in a single institution between 1996 and 2019. The median survival was 9±0.62 [95% CI 7.78-10.21] months and the survival rate after diagnosis was 39.4% in 1st year, 17% in 2nd year, and 5% in 3rd year. Statistically, age, tumor location, edema, and necrosis were indicated as independent preoperative predictors of prognosis, and younger age at diagnosis, the left temporal and the right occipital location, maximal tumor resection, and administration of temozolomide adjuvant chemotherapy were revealed favorable prognostic factors.

Keywords: Glioblastoma, Overall survival, Prognosis, Surgery

INTRODUCTION

Glioblastoma (GBM) is the most common and primary malignant neoplasm in adults that progresses quickly and has a poor survival, with a median survival time about 8-10 months.[1-3] GBM can occur at any age; however, it is mainly diagnosed at a later age, with a median age of diagnosis of 65, and is more common in men than women.[2,3]

For planning management strategies of GBM patients, it is essential to understand survival parameters that is helpful to treatment of the patients during decision making and current studies seem to indicate total excision is associated with disease-free survival and overall survival (OS) and the basic principle of standard therapy for GBM, is primarily complete resection of the tumor.[4-7] However, there is still controversy about the type and extent of surgical resection. Although surgeons generally recommend total resection, there is a contradiction in the literature regarding the contribution of aggressive surgery to survival.[7] After all, due to the high local recurrence rate of GBM, adjuvant therapies are still needed even in patients undergoing total surgery.

Based on the literature data, the routine treatment of GBM patients is currently performed as complete surgical resection + simultaneous chemotherapy-radiotherapy (CT-RT) + adjuvant chemotherapy (CT)".[8]

Kandaz et al.[3] analyzed retrospectively the relationship between age distribution and overall survival of a series of 274 patients who were diagnosed with GBM between 2000 and 2016 in our institute. In this study, we analyzed our institutional data of twenty-three years (1996-2019) with GBM of 433 patients >20 years old based on their age, gender, number of masses, tumor location, brain shift, edema, necrosis, the extent of resection and survival to identify the potential prognostic factors for GBM.

PATIENTS AND METHODS

The records of patients treated in our institution between 1996 and 2019 were evaluated. The authors reviewed medical records on patient characteristics and all of the treatment modalities in each patient. Patients diagnosed with radiological or pathological GBM and who received radiotherapy and chemotherapy were included in the study. The incomplete data on medical records were excluded.

Patient Characteristics

Gender, age, number of masses, tumor location in the brain, functional localization, mass effect, the volume of edema, the amount of tumor necrosis, the extent of surgery, and radiotherapy-chemotherapy protocol for 433 patients > 20 years old were reviewed (Table 1). Determination of isocitrate dehydrogenase (IDH) mutation status has been started in our institution since 2015 and only 139 of all patients' IDH status were identified.

Radiological Data

All patients underwent preoperative imaging (contrast-enhanced computed tomography-CECT or magnetic resonance imaging-MRI) and postoperative follow-up MRI available on the institute picture archiving and communication system. The images were analyzed by experienced radiological specialists in neuroimaging. And data evaluation was performed according to institutional guidelines.

Tumor location with regard to proximity to eloquent brain was characterized by functional grade as described by Sawaya, et al.[9] and modified by Noiphithak and Veerasarn[10] (Table 1). Initial tumor location and recurrence location were determined based on T1-weighted sequences on axial and coronal images. The definitions for functional localization are as follows; eloquent brain refers to motor or sensory cortex, visual center, speech center, internal capsule, basal ganglia, hypothalamus or thalamus, brainstem, dentate nucleus and, near eloquent brain refers to tumor locations adjacent to eloquent areas as near motor or sensory cortex, near calcarine fissure, near speech center, corpus callosum, near dentate nucleus, near brainstem and, non-eloquent brain refers to frontal or temporal pole of cerebrum, right parietooccipital lobe, cerebellar hemisphere.

Tumor necrosis, the degree of mass effect and surrounding edema, and the increase in tumor mass were also measured and recorded using methods described by Hammoud et al.[11] and modified by Noiphithak and Veerasarn.[10]

To define peritumoral brain edema (PTBE), the maximum diameter of the tumor was measured on T1-weighted images (T1WI) and the maximum diameter of the edema band was measured axially on T2-weighted images (T2WI). PTBE was evaluated in terms of the maximum diameter of the edema and classified into 4 grades: no edema, smaller than the tumor, edema of the same volume as the tumor, and edema larger than the tumor. Axial, coronal and sagittal MRI scans were reviewed in all cases and the maximum size of the PTBE was measured using these scans.

Necrosis was defined as non-contrast-enhancing areas within the contrast-enhancing tumor with irregular internal borders on post-contrast T1-weighted images. The diameters of perienhancing and enhancing areas were measured, and the percentage of enhancing areas was calculated. Intratumoral necrotic areas were measured. The amount of tumor necrosis was divided into four grades as follows: no necrosis apparent on the MR images; amount of necrosis < 25% of the tumor volume; amount of necrosis 25-50% of the tumor volume; and amount of necrosis > 50% of the tumor volume (Table 1).

Table 1. Descriptive patient characteristics and their prevalence (%).

Patient Characteristics	n= 433 (100%)		
Gender			
Female	173 (40%)		
Male	260 (60%)		
Age group (year)			
20-29	10 (2%)	**Functional localization**	
30-39	21 (5%)	Non-eloquent brain	43 (11%)
40-49	71 (16%)	Near eloquent brain	180 (41%)
50-59	126 (29%)	Eloquent brain	210 (48%)
60-69	135 (31%)	**Mass effect (brain shift)**	
70-79	56 (14%)	None apparent	328 (76%)
> 80	14 (3%)	Minimal midline shift (≤ 0.5 cm)	78 (18%)
Number of masses		Moderate midline shift (5-1 cm)	22 (5%)
Single	405 (93%)	Significant midline shift (>1 cm), subfalcian or uncal herniation	5 (1%)
Two	25 (6%)	**Edema**	
≥ three	3 (1%)	None apparent	83 (19%)
Tumor location in the brain		Less than tumor volume	7 (2%)
Right frontal	61 (14%)	Approximately equal to tumor volume	292 (67%)
Right occipital	12 (3%)	Greater than tumor volume	51 (12%)
Right parietal	83 (19%)	**The amount of tumor necrosis**	
Right temporal	60 (14%)	No apparent	59 (14%)
Left frontal	69 (16%)	< 25% of the tumor volume	109 (25%)
Left occipital	11 (2%)	25-50% of the tumor volume	193 (45%)
Left parietal	79 (18%)	> 50% of the tumor volume	72 (16%)
Left temporal	52 (12%)	**The extent of resection (EOR)**	
Other	6 (2%)	No surgery	132 (30%)
TMZ treatment		Biopsy	85 (20%)
None	92 (21%)	Subtotal resection	102 (24%)
Yes	341 (79%)	Total resection	114 (26%)

Treatment data

All treatment modalities including surgery, radiotherapy and chemotherapy were reviewed. Patients, eligible for surgery (biopsy/subtotal/total excision), were given postoperative radiotherapy (RT) followed by chemotherapy (CT), while patients, not eligible for the operation, received direct radiotherapy (RT) followed by chemotherapy (CT).

Preoperative and postoperative (72 hours after surgery) MRI findings were assessed to classify the extent of resection (EOR). Based on the maximum area of resection on the images, the EOR was categorized into these three groups accordingly: biopsy (stereotactic only), subtotal resection (residual contrastenhancing tumor mass > 5%) and total resection as anatomical resection beyond the contrastenhancing tumor mass. If the patient is radiologically diagnosed and no surgical intervention has been performed, they were included in the no surgery group. Survival was recorded by determining the final status (alive/dead) of the patients.

Patients with a mass in the brain that was detected radiologically were also treated individually by the multidisciplinary Central Nervous System tumor council. During treatments, radiotherapy, 60 gray dose and simultaneous and 6 weeks, daily, an oral administration of 75 mg/m^2 temozolomide (TMZ)

was applied as simultaneous CT. After RT, at every 28 days, for 5 consecutive days, five cycles of 200 mg/m^2 TMZ were applied. The systemic treatment administered to patients before 2005 when TMZ was introduced as standard treatment was radiotherapy treatment, followed by TMZ decided by medical oncology council or not.

Follow-up

One month after the end of RT, the patients were admitted for their first controls. Complete blood tests and physical examinations were performed. MRI is done in 2-6 weeks after RT and every 2-3 months. Subsequent controls were performed every three months. OS was defined as the time between diagnosis and the last control or date of death.

Survival was recorded by determining the final status (alive/dead) of the patients. Using the tumor registry, the vital status of the patients seen at our institution was identified through the General Directorate of Population Registry and Citizenship, and phone calls to patients and their families.

This retrospective clinical study was performed with the permission of the Karadeniz Technical University Medical Faculty Ethics Committee (December 16, 2019; No: 336).

Statistical Analysis

Statistical analyses were performed using SPSS software (SPSS for Windows, Version 16.0. Chicago, USA). Descriptive analyses of the evaluation results were given as number (n) and percentage (%) for categorical variables and mean, standard error and median values for continuous variables. Survival rates were calculated by the Kaplan-Meier method. Univariate analyses of survival were performed using the long rank test. Independent factors in predicting survival using the possible factors identified in previous analyses were examined using Cox regression analysis in multivariate analysis. Results were presented with 95% confidence intervals. The significance level was set at $p< 0.05$.

RESULTS

Patients

A total 433 patients > 20 years old were included for the prognostic factors (Table 1). 173 (40%) of the patients were female and 260 (60%) were male. The median age of patients was 57.65±12.49 years (age range: 21-89 years). The median age of female patients was 58.08±12.29 years (age range: 22-85 years) and the median age of male patients was 57.36±12.64 years (age range: 21-89 years). 405 (93%) of the 433 patients have single masses and, the tumor is located in the right (n= 83; 19%) and left (n= 79, 18%) parietal region of the brain mostly. 210 of all patients (48%) had a tumor in the eloquent brain and 328 of them (76%) showed no brain shifts. Generally, the edema was approximately equal to tumor volume (n= 292, 67%) and the amount of necrosis was 25-50% of the tumor volume (n= 193, 45%) in patients. The diagnosis was made radiologically in 132 (30%) patients. Biopsy, subtotal resection, and total resection were performed in 85 (20%), 102 (24%), and 114 (26%) patients, respectively (Table 1). These; IDH was wild type in 78 (56%) patients, mutant in 11 (8%) patients, not otherwise specified (NOS) in and non-mutant in 50 (36%) patients.

Survival Outcomes

Overall, the median survival was 9±0.62 [95% CI 7.78-10.21] months (Table 2). The life expectancy is one year for 39.4% of patients, two years for 17%, and three years for 5% (Table 2 and Figure 1a). Statistically revealed that age group, tumor location in the brain, edema, necrosis, and extent of resection were important factors on overall survival while the other tumor characteristics as gender, number of masses, functional localization, brain shifts were not significantly associated with survival and thus, detailed explanation was not given in the following section (Table 2). Also, when the Cox regression analysis of factors affecting survival in patients with GBM was examined, significant factors were found to be age group ($p< 0.021$), tumor location in the brain ($p< 0.025$) and functional localization ($p< 0.023$).

Table 2. Patient characteristics of Log-rank univariate analysis for overall survival

		Mean OS (Month) (95% CI)	Median OS (Month) (95% CI)	1st year OS (%)	2nd year OS (%)	3rd year OS (%)	p
Patient Characteristics/		12.96±0.70	9±0.62	39.4	17	5	
General		11.57-14.35	7.78-10.21				
Gender	Female	12.96±0.92	10±0.71	40.2	14.8	4.2	
		11.16-14.77	8.59-11.40				0.636
	Male	12.93±1.01	8±0.91	33	14.8	5.8	
		10.95-14.91	6.21-9.78				
Age (year)	20-29	18.04±4.57	11±11.12	48	32	16	
		9.07-27	0-32.80				
	30-39	20.32±2.96	21±1.72	66.7	31	10.3	
		14.52-26.12	17.62-24.37				
	40-49	16.49±2.63	10±1.69	39.7	19.3	11.6	
		11.32-21.66	6.67-13.32				
	50-59	13.15±1	10±0.87	39.6	16.8	2.8	0.0001
		11.19-15.11	8.28-11.71				
	60-69	11.26±1	8±1.16	33	8.6	3.2	
		9.29-13.23	5.72-10.27				
	70-79	8.56±1.49	4±0.57	18.8	11.3	3.8	
		5.64-11.48	2.89-5.13				
	> 80	8.42±2.46	4±1.87	21.4	10.7	–	
		3.60-13.25	0.33-7.66				
Number of masses	Single	13.27±0.74	9±0.64	37,5	15.4	5.1	
		11.81-14.72	7.73-10.26				
	Two	11.97±2.31	7±2.34	36.4	11.4	–	0.627
		7.44-16.51	2.40-11.59				
	≥ three	7.66±2.02	8±3.26	–	–	–	
		3.69-11.64	1.59-14.40				
Tumor location in the brain	Right frontal	10.38±1.14	8±0.60	27.5	10.1	–	
		8.14-12.62	6.80-9.19				
	Right occipital	18.19±5.68	10±3.77	42	42	21	
		7.04-29.33	2.59-17.40				
	Right parietal	14.36±1.82	9±1.44	37.2	20.1	7.6	
		10.78-17.93	6.17-11.82				
	Right temporal	9.52±1.10	6±1.11	27.1	6.3	2.1	
		7.36-11.69	3.81-8.18				
	Left frontal	12.29±1.21	10±1.28	43.3	7.4	2.5	0.039
		9.90-14.67	7.47-12.52				
	Left occipital	10.42±2.34	8±1.30	28.6	–	–	
		5.84-15.01	5.43-10.56				
	Left parietal	11.35±1.26	7±1.29	32.9	13.2	3.8	
		8.88-13.82	4.45-9.54				
	Left temporal	19.73±3.21	13±3.12	52.9	27.4	12.8	
		13.42-26.04	6.87-19.12				
	Other	15.08±5.06	9±8.81	50	25	–	
		5.15-25.01	0-26.28				

Table 2. Patient characteristics of Log-rank univariate analysis for overall survival ***(Continued)***

		Mean OS (Month) (95% CI)	Median OS (Month) (95% CI)	1st year OS (%)	2nd year OS (%)	3rd year OS (%)	p
Patient Characteristics/ General		12.96±0.70 11.57-14.35	9±0.62 7.78-10.21	39.4	17	5	
Functional localization	Non-eloquent brain	13.77±1.11 11.59-15.95	10±0.81 8.41-11.58	38.8	13.4	5	
	Near eloquent brain	12.42±1.09 10.27-14.57	8±1.10 5.82-10.05	34.2	14.7	4.1	0.829
	Eloquent brain	12.11±1.97 8.24-15.97	6±2.07 1.94-10.05	31.7	20.6	10.3	
Mass effect	None apparent	18.86±2.74 13.48-24.24	12±1.78 8.47-15.52	45.7	22.6	9	
	Minimal midline shift (≤ 0.5 cm)	12.71±1.71 9.36-16.06	7±2.03 3.01-10.98	35.1	18.4	7.4	
	Moderate midline shift (5-1 cm)	13.78±2.76 8.35-19.20	10±4.10 1.95-18.04	40.9	14.5	14.5	0.179
	Significant midline shift (> 1 cm), sub falcian or uncal herniation	8.60±4.49 0-17.40	4±1.64 0.77-7.22	20	–	–	
Edema	None apparent	13.57±2.25 9.15-17.99	10±3.19 3.73-16.26	43.5	21.1	7	0.013
	Less than tumor volume	25.47±5.39 14.90-36.04	17±2.12 12.83-21.16	62.8	27.4	16.5	
	Approximately equal to tumor volume	12.49±1.28 9.98-15.01	7±0.98 5.06-8.93	32.8	16.9	6.7	
	Greater than tumor volume	11.37±0.90 9.61-13.14	9	37.5	–	–	
Necrosis	None apparent	22.64±3.85 15.08-30.19	15±3.38 8.35-21.64	53.3	36.9	32.3	
	< 25% of the tumor volume	16.06±2.80 10.57-21.55	9±2.01 5.04-12.95	41.4	22.4	12	
	25-50% of the tumor volume	11.10±1.19 8.76-13.43	8±1.73 4.60-11.4	33.4	9.4	3.5	0.038
	> 50% of the tumor volume	7.58±0.90 5.81-9.35	5±1.65 1.75-8.24	21.9	–	–	
The extent of resection (EOR)	No surgery	11.12±1.79 7.60-14.64	6±1.12 3.78-8.21	34.3	6.8	–	
	Biopsy	11.63±1.50 8.68-14.57	6±1.05 3.93-8.06	34.1	11.5	3.8	
	Subtotal resection	10.63±1.4 7.88-13.38	6±1.44 3.17-8.82	34.9	8.9	4.5	0.040
	Total resection	14.99±1.04 12.94-17.04	10±0.65 8.72-11.27	41.1	19.7	5.6	
TMZ treatment	No	9.8±0.94 7.94-11.66	7±1.3 4.44-9.55	30.3	5.3	1.3	0.010
	Yes	13.81±0.86 12.12-15.5	10±0.67 8.68-11.31	37.3	17.4	6.1	

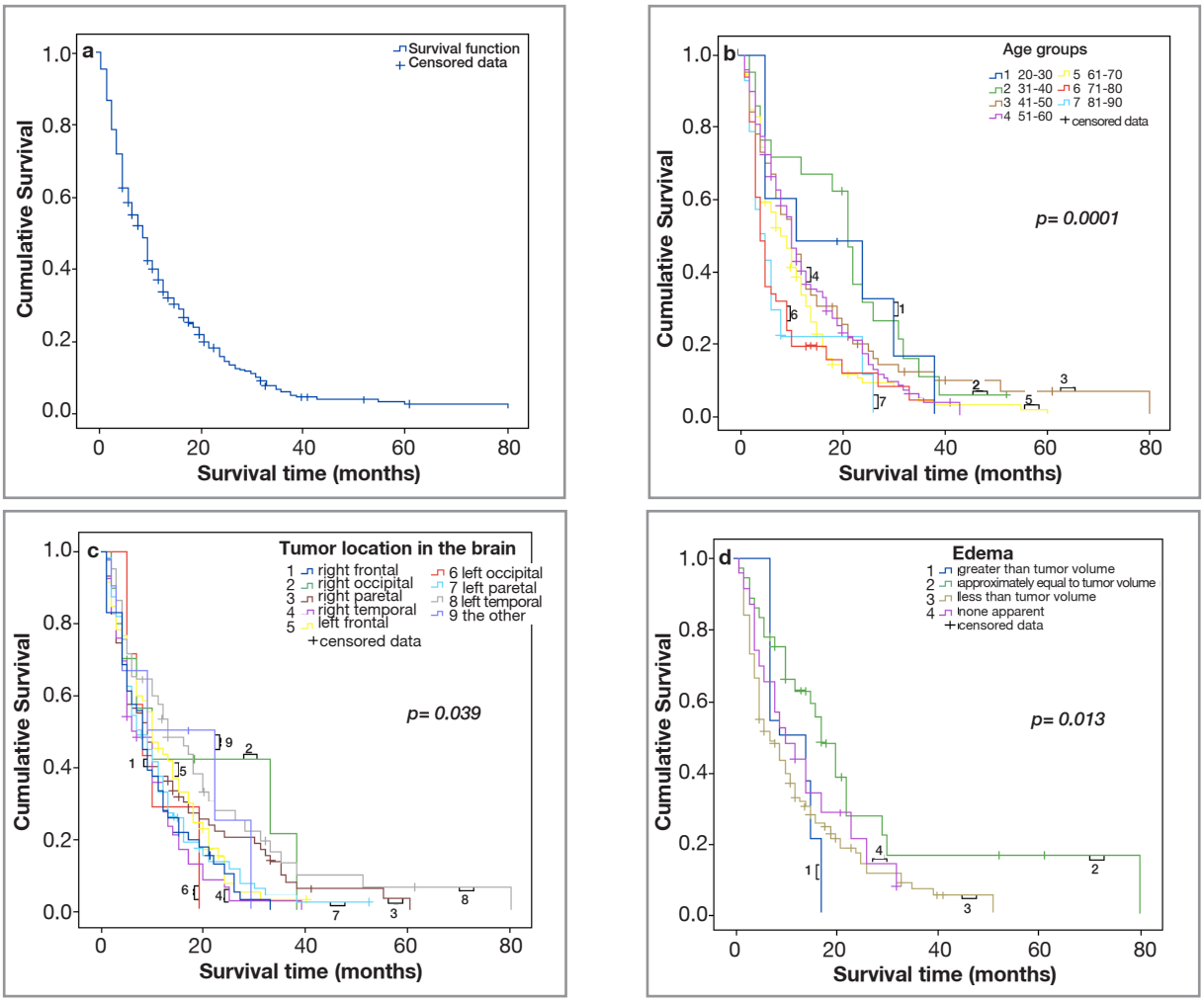

Figure 1. Kaplan-Meier survival curves for the entire cohort **a)** overall survival of patients. Survival curves were plotted according to classifications on the basis of **b)** age groups, **c)** tumor sites in the brain, **d)** edema; none apparent (n= 83), less than the tumor volume (n= 7), approximately equal to tumor volume (n= 292) and greater than tumor volume (n= 51)

Age Group

A difference was found in prevalence between the seven age groups (Table 1) and a statistically significant difference was noted in the mean survival rates (p< 0.0001, Table 2, Figure 1b). In the analyses of age variables at the time of diagnosis, advancing age was associated with shorter survival (Table 2; median survival: 11±1.12 [95% CI: 0-32.80] for ages 20-29, 21±1.72 [95% CI: 17.62-24.37] for ages 30-39; 10±1.69 [95% CI: 6.67-13.32] for ages 40-49; 10±0.87 [95% CI: 8.28-11.71] for ages 50-59; 8±1.16 [95% CI: 5.72-10.27] for ages 60-69; 4±0.57 [95% CI: 2.89-5.13] for ages 70-79; 4±1.87 [95% CI: 0.33-7.66] for ages > 80). GBM occurred most in the seventh decade of life and the longest survival was seen in individuals who were diagnosed in the age range of 30-39 for the first year and then 20-29 for the second and third year.

Tumor Location in the Brain

The distribution of GBM by primary tumor sites is shown in Table 1. The most common primary site was in right parietal (19%) followed by the left parietal (18%), left frontal (16%), right temporal (14%), right frontal (14%), left temporal (12%), right occipital, left occipital and other (2%) (Table 1). A statistically significant difference was noted in overall survival among the nine groups (p= 0.039, Table 2, Figure 1c).

The vital status evaluation revealed the highest survival in patients with left temporal region tumors (median survival: 13±3.12 [95% CI: 6.87-19.12]) and the 1st, 2nd, and 3rd-year survival rate was 52.9%, 27.4%, and 12.8%, respectively (Table 2, Figure 1c). Although the median OS for patients with right occipital region tumors (10±3.77 [95% CI 2.59-17.40]) is lower than those with left temporal region tumors, their survival rates were the highest for 2nd, and 3rd-year. The lowest survival rates were found for right temporal region tumors (median survival: 6±1.11 [95% CI: 3.81-8.18]) and the 1st, 2nd, and 3rd-year survival rate was 27.1%, 6.3%, and 2.1%, respectively (Table 2, Figure 1c).

Edema

A difference in prevalence was found between the three groups, and a statistically significant difference in the survival rates (p= 0.013) was revealed. The vital status evaluation revealed the highest OS in people with edema less than tumor volume (median survival: 17±2.12 [95% CI: 12.83-21.16]) and the 1st, 2nd and 3rd- year survival rate was 62.8%, 27.4%, and 16.5%, respectively. The lowest survival rates were revealed for the people with edema approximately equal to tumor volume (median survival: 7±0.98 [95% CI: 5.06-8.93]) but patients with edema greater than tumor were not survived after one year (Table 2, Figure 1d).

Necrosis

When patients are evaluated according to necrosis within four groups; in patients with none apparent necrosis, the median OS was 15±3.38 months [95%CI 8.35-21.64] with the survival rates for 1st, 2nd, and 3rd- year as 53.3%, 36.9%, and 32.3%, respectively. The lowest OS was encountered in the people with necrosis >50% of the tumor volume (median survival: 5±1.65 [95% CI: 1.75-8.24]) and none of the patients was survived after the first year (Table 2, Figure 1e).

The Extent of Resection (EOR)

The Karnofsky Performance Status (KPS) score of our patients was recorded by the operating surgeon and the majority of operated patients for total and subtotal resection had KPS ≥ 70 (functionally independent). Concerning the extent of resection (EOR), the patients diagnosed radiologically (no surgery group) showed the lowest OS (median survival: 6±1.12 [95% CI: 3.78-8.21 months]) with the survival rates for 1st and 2nd- year as 34.3% and 6.8% and no one survived after two years. On the other hand, in patients who underwent total resection, the life expectancy was significantly longer (median survival: 10±0.65 [95% CI: 8.72-11.27 months]) and their 1st, 2nd, and 3rd-year survival rates were 41%, 19.7%, and 5.6%, respectively. A statistically significant difference was noted in the mean survival rates among the four groups (p= 0.040, Table 2). Kaplan -Meier curves display that total resection had the most pronounced effect on overall survival time which was significantly longer than those for patients who underwent biopsy, subtotal resection, and no surgery (Table 2, Figure 1f).

TMZ Treatment

When the patients were evaluated according to concurrent chemotherapy; The median OS in patients without temozolomide was 7±1.3 months [95% CI: 4.44-9.55] and their 1st, 2nd, and 3rd-year survival rates were 30.3%, 5.3%, and 1.3%, respectively. The median OS in patients with temozolomide was 10±0.67 months [95% CI: 8.68-11.31] and 1st, 2nd, and 3rd-year survival rates were 37.3%, 17.4%, and 6.1%, respectively. A statistically significant difference between the two groups was revealed (p= 0.010) (Table 2).

DISCUSSION

Glioblastoma is the most common malignant primary brain tumor in adults.[1] Standard treatment for patients with glioblastoma is surgical resection with adjuvant RT and CT.[12] This study reviewed retrospectively collected data for prognostic variables affecting survival outcomes in patients with GBM. We have documented that overall survival in GBM patients is heterogeneous and influenced by multiple factors. Age, tumor location, the extent of resection, necrosis, and edema extent are strongly related to the length of survival and outcomes for patients with GBM. These findings are extensively supported by other studies in the literature.[13-16]

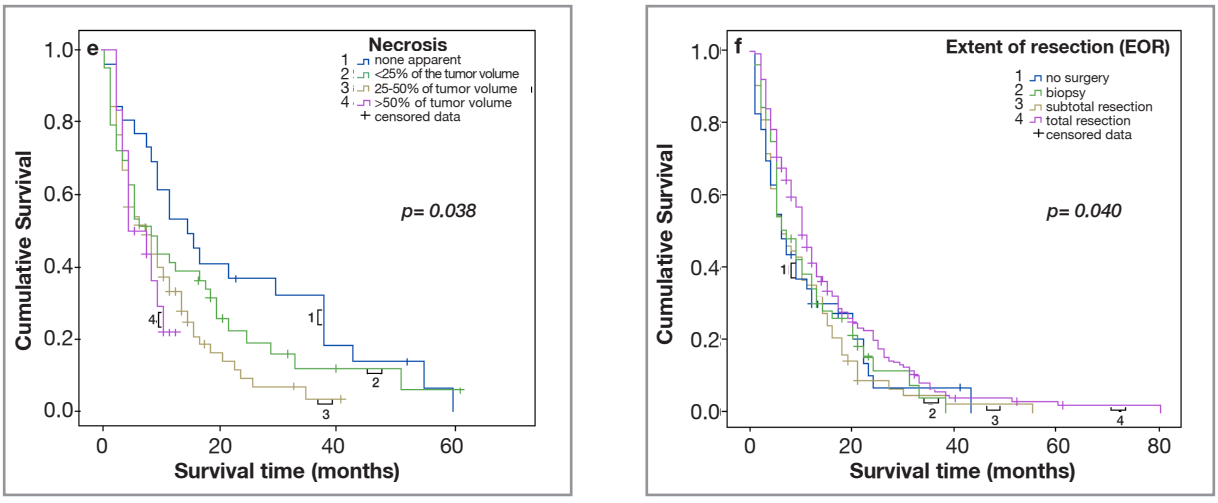

Figure 1 (*Continued*). Kaplan-Meier survival curves for the entire cohort **e)** necrosis; no apparent (n= 59), < 25% of the tumor volume (n= 109), 25-50% of the tumor volume (n= 193), and > 50% of the tumor volume (n= 72), **f)** the extent of resection; total resection (n= 114), subtotal resection (n= 102), biopsy (n= 85) and no surgery (n= 132). Crosses imply censored data.

Ostrom et al.[2] provided a comprehensive summary of the current descriptive epidemiology of primary brain and other central nervous system (CNS) tumors in the United States (US) between 2013-2017. According to their report, the median observed survival in the primary malignant brain and other CNS tumors only was the lowest for glioblastoma (8 months). Kandaz et al.[3] analysis between 2000 and 2016 in our institute indicated 9.80 ±1.78 months (n= 274; 95% confidence interval [CI], of 6.31-13.28 months) median survival time. In the line of previous studies[2,3], the median overall survival time of all GBM cases in this present study was similarly found at 9±0.62 months (n= 433; 95% CI, of 7.78-10.21 months), and survival rates after diagnosis were 39.4% at 1st year, 17% at 2nd year and 5% at 3rd year. Based on our results, increasing age has a negative effect on the prognosis and this effect is more recognizable in the elderly patient. However, the previous studies display that age is an important factor in the case of limited resection, especially for older people but if a safe and large resection can be provided, this effect may be minimized in fit older patients.[14-17]

Previous studies on the survival of GBM patients concerning tumor location have indicated decreasing survival with periventricular involvement and showed possible survival differences between left- and right-sided tumors.[17-19] Recently, Fyllingen et al.[15] suggested differences in OS in glioblastoma patients based on tumor location, not limited to eloquence. According to their research on 215 patients, settlement of tumors in the central location and left temporal lobe pole gave short OS but in the right dorsomedial temporal lobe and white matter region involving the left anterior paracentral gyrus/dorsal supplementary motor area/medial precentral gyrus provided high OS. Besides, they indicated that increasing age may be an important prognostic factor, especially in the case of central tumor locations. Liu et al.'s[18] retrospective research on 253 patients revealed that tumor location in the right occipitotemporal periatrial white matter is predictive of survival, independent of other known prognostic clinical variables, such as patient age and tumor volume. In our cohort, OS of > one year determined in the patients with tumors in the left temporal lobe of the brain favor the high OS but irrelevant to eloquence. However, when second and third-year survival rates are evaluated, patients with right occipital tumors have higher survival rates, similar to those of Liu et al.[18]

Gamburg et al.[19] retrospectively evaluated the influence of midline shift during the initial presentation on the survival of patients with GBM in the context of other known prognostic factors. In their study, 80% of patients with a midline shift underwent decompressive resection before irra-

diation, the presence of midline shift at diagnosis was defined as an independent prognostic factor influencing OS due to decompressive surgery. In our study, we could not detect a statistically significant relationship between the sizes of brain shifts and OS. However, our institutional experience provides the knowledge that increases in brain shifts in GBM patients require urgent surgical intervention and therefore, resection of the tumor has a positive effect on OS as expected. Furthermore, we would rather replace the bone flap at the end of the procedure to avoid postoperative complications.

Neuroncologists have been discussing the consideration of tumoral components such as contrast enhancement, peritumoral edema, and central necrosis.[11,14,20] The impact on GBM prognosis for preoperative volumetric radiological features may represent a potential marker for the OS. Necrosis which is a histopathological term, used to generally describe tissue death resulted from extensive tissue hypoxia serving as the initial trigger, is likely due to rapid growth of the tumor outstripping vascular supply.[21] It was reported that necrosis is a common feature and poor prognostic predictor and is a diagnostic hallmark as well as positively correlates with tumor aggressiveness and poor outcomes in GBM.[11,16,22]

Glioblastoma is often associated with peritumoral brain edema (PTBE) and, if left untreated, can lead to increased intracranial pressure and devastating neurological sequelae. In clinical practice, surgeons use their clinical judgment to decide whether PTBE tissue should be resected. The standard surgical approach is to maximally resect the tumors while retaining maximum neurological function. Qin et al. revealed that GBM is associated with PTBE when surgically treated, and can lead to a delay in relapse rates.[23] On the other hand, Wu et all.[24] indicated that edema and necrosis were negative prognosis indicators for OS. Kandaz et al.[25] investigated the relationship between peritumoral edema and overall survival in glioblastoma multiforme (GBM) in a total of 101 patients with radiologically or pathologically GBM in our institute. The patients were divided into two groups as patients without edema and with edema and the volume of edema undifferentiated. Their results indicate that the presence of edema lowers the OS. In our report, we statistically proved that a moderate degree of peritumoral edema as smaller than the size of the tumor provided higher OS in patients with GBM. Our surgical experience in our clinic has shown that surgical resection is easier when the patient has edema smaller than the size of the tumor compared to no edema. This is because the margins of the tumor are more identified. This may indirectly have a positive effect on OS as it positively affects the extent of resection. Our study also supported a significant impact of necrosis and edema, preoperatively identified radiological features on OS. Without necrosis or a very limited amount as well as a moderate degree of peritumoral edema provided higher OS in patients with GBM.

Based on our findings, the extent of resection on glioblastoma patients is an important criterion and impacts widely on OS. Specifically, our result also suggested that patients with total resection have an increased survival rate of 10±0.65 [95% CI: 8.72-11.27 months] median OS (month), and their 1st, 2nd, and 3rd-year survival rates were 41.1%, 19.7%, and 5.6%, respectively. This result is consistent with the finding from previously published retrospective studies that the removal of 70-78% of the tumor volume is the ideal resection goal that will benefit survival.[14,26,27] The importance of the EOR threshold in OS of GBM patients was first introduced by Sanai et al.[28] and Ius et al.[14] highlighted that the best survival rate in patients with an EOR higher than 96% with an estimated 1st year OS of 92%. However, one should remember to provide an optimum balance between a maximal resection and a safe resection via neurosurgical methods available as frameless navigational systems, intraoperative imaging, ultrasonography, and functional mapping. On the other hand, the Cox regression analysis of factors affecting survival in patients indicated tumor location in the brain and functional localization as also important factors consistent with previous reports.[29]

Perry et al.[30] evaluated the addition of temozolomide to short-course radiotherapy in elderly patients with glioblastoma and indicated in longer survival term than short-course radiotherapy alone. Our study also reveals that the addition of TMZ to standard treatment positively affects overall survival in all patients older than 20 years.

The identification and validation of these prognostic variables in our cohort add strength to this study, indicating that our cohort is representative of patients with GBM and our results are not unlikely to be restricted to this patient cohort. However, the usual limitations of a retrospective analysis especially in terms of selection bias still apply. First of all, the data were collected from only one hospital and might not reflect the broad population. But taking into consideration that the hospital which data collected is the main university hospital of the region and number of the patients, this obstacle might be minimized.

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