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ORIGINAL ARTICLE

Comparison of Prognostic Factors in Glioblastoma Patients with Short- and Long-term Survival

Berrin BENLİ YAVUZ, Gül KANYILMAZ, Meryem AKTAN

Department of Radiation Oncology, Necmettin Erbakan University Meram Faculty of Medicine, Konya-*Türkiye*

OBJECTIVE

Glioblastoma (GBM) is the most aggressive primary brain tumor. Despite all treatments, very few have long-term survival. This retrospective study aimed to investigate the clinicopathological features, treatment modalities, and factors affecting survival in GBM patients with short- and long-term survival.

METHODS

Data from 217 GBM patients who received radiotherapy (RT) between 2010 and 2021 were analyzed. The patients were divided into two groups: short (<6 months) and long (>2 years) living groups. Treatment, patient, and tumor characteristics were evaluated.

RESULTS

While 37 (17.1%) of 217 patients included in the group lived <6 months, 49 (22.6%) were in the group that lived longer than 2 years. In the long-living group, being under 65 years of age, having better performance, performing total excision, applying conventional RT, and receiving adjuvant chemotherapy (CT) detected more frequently. The regression test showed that young age, good performance, and receiving conventional RT and adjuvant chemotherapy (CT) were independently associated with survival.

CONCLUSION

It was observed that patients who lived longer were frequently young and well-performing ones who underwent wide excision and received conventional RT and adjuvant CT. By estimating the pre-treatment survival, treatment and support plans can be made accordingly.

Keywords: Glioblastoma; long-term survival; prognosis; radiotherapy.

INTRODUCTION

Glioblastoma (GBM) is the most common primary brain tumor encountered in adults.[1] It constitutes 14.3% of all central nervous system tumors and 49.1% of the malignant group.[2] Increasing by age, its incidence is most frequent between the ages of 75 and 84. Today, the standard treatment is maximal surgery and concomitant chemoradiotherapy (CRT), followed by adjuvant temozolomide.[3]

Despite all treatments, the course is fatal, and the average survival is 12–14 months.[4] In GBM patients diagnosed between 2009 and 2015, 5-year relative survival was found to be 7% in the entire group, 3% in the over 65-year age group, and 27% in the 20–39-year age group.[5] Age, performance, localization, surgical resection width, and O (6)-methyl guanine-DNA methyltransferase (MGMT) status are known to affect prognosis.[6] However, the characteristics of the long-lived group are still unclear.[7]

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Dr. Berrin BENLİ YAVUZ
Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi,
Radyasyon Onkolojisi Anabilim Dalı,
Konya-Türkiye
E-mail: berrinyavuz77@gmail.com

The number of people living longer after diagnosis increases depending on advances in treatment and patient management.[8]

Long-term survival refers to those who lived at least 2 years after diagnosis and constitute 13% of GBM patients.[4] However, in the literature, definitional differences exist for long-term survival. It is considered that determining the differences between these groups by comparing the patients with long-term or short-term survivals may help in deciding the type of treatment to be applied to the patient. This study aimed to investigate the clinicopathological features, treatment modalities, and factors affecting survival in GBM patients with short- and long-term survival.

MATERIALS AND METHODS

Selection of Patient

The data of 217 GBM patients who received radiotherapy (RT) in our clinic between January 2010 and October 2021 were analyzed retrospectively. Patient data were acquired from medical and hospital records. Patients over 18 years of age whose diagnosis was confirmed histopathologically, were included in this study. The patients were divided into two groups: those who lived shorter than 6 months and those longer than 2 years. Since the median survival was 14.6 months in the study by Stupp et al.,[9] with the current standard treatment, 2 years and above were accepted as the long-lived group. Patient characteristics (age, gender, and Karnofsky Performance Score [KPS]), tumor characteristics (location and size of the tumor), and treatment characteristics (resection width, RT dose and technique, concomitant and adjuvant chemotherapy (CT) use) were acquired from medical records. In addition, among the group consisting of people who lived longer than 2 years, those who lived for 5 years or more were also examined.

The resection width was acknowledged as in the magnetic resonance imaging (MRI) acquired after the operation, and the tumor size as in the preoperative MRI. Performance was evaluated based on the KPS score. Since those with KPS 80 and above carried out their regular activities and needed no special care, they were considered excellent performance, whereas those 70 and below as poor performance.

Radiotherapy

RT was initiated within the 6th week after surgery. All patients had MRI before RT. CT simulation was performed in the supine position with a thermoplastic head mask. Images were taken in 3 mm sections. Computed tomography (CT) images and MRI were fused. Gross tumor volume was determined as the contrast-enhancing area and surgical bed in MRI. The clinical target volume was created by giving a 1.5–2 cm margin to this volume, and the planned target volume was created by giving it a 0.5 cm margin.

Conventional RT was determined as 50 Gy and above dose with a 1.8–2 Gy fraction dose, whereas hypofractionated RT (HRT) and whole-brain RT (WBRT) were detected as 30–42.5 Gy in 10–16 fractions. Patients who received WBRT were treated with 3D conformal therapy and those who received hypofractionated and conventional treatment with intensity-modulated radiation therapy or image-guided radiotherapy technique. The clinician determined by which method the patient would receive treatment according to the performance status.

Chemotherapy

Concomitantly, temozolomide (75 mg/m^2/day) was administered daily during the treatment. Adjuvant therapy was applied as 150–200 mg/m^2/day every 28 days, in the 1st and 5th days, for 6–12 months.

Survival

Overall survival was defined as the time passed from diagnosis to the date of death or last control. The primary endpoint of the study was to determine the differences between groups with short- and long-term survival, whereas the secondary endpoint was to determine the prognostic factors affecting survival.

Patient characteristics were given in n (%) for categorical variables and median for continuous variables. Tumor, patient characteristics, and treatment differences between the two groups were evaluated using the Chi-square test and Student's t-test. For survival analysis, log-rank tests and Kaplan–Meier analyses were conducted. Cox proportional hazard models were used for univariate and multivariate analyses. Values in univariate analyzes, $p<0.10$, were included in multivariate analyses. A value of $p<0.05$ was acknowledged as statistically significant. All statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) version 13.

RESULTS

While 37 (17.1%) of 217 patients constituted the group that lived <6 months, 49 (22.6%) constituted the group that lived longer than 2 years. The median follow-up

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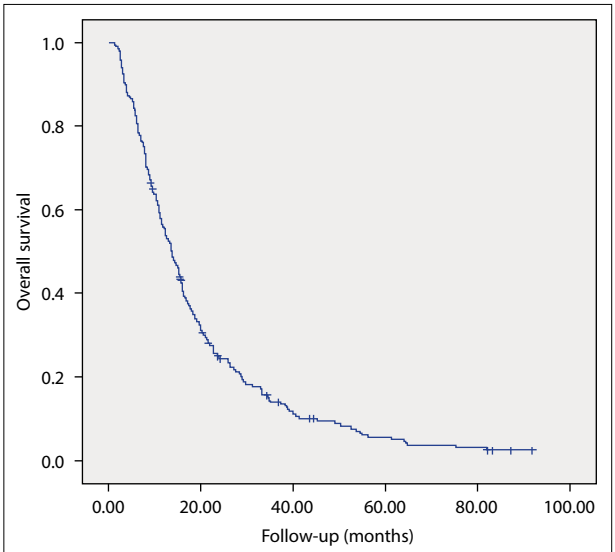

Fig. 1. Overall survival curve for the all group.

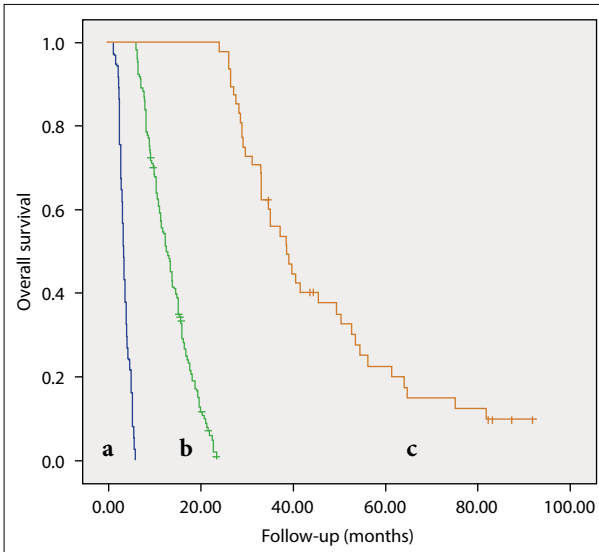

Fig. 2. Kaplan-Meier survival curves based on short (<6 months) (a), medium (6 months-2 years) (b) and long-lived (>2 years) (c) groups.

was 13.56 months. The median age was 65 (41–83) in the short-lived group and 52 (19–72) in the long-lived group. The median OS was 13.79 months in the entire group, 3.25 months in the short-lived group, and 38.73 months in the long-lived group. OS at 1, 2, and 5 years in the entire group was 55.2%, 24.5%, and 5%, respectively (Figs. 1, 2). While 9 (18.4%) of the patients were alive in the long-living group, there was no surviving patient in the short-living group.

The effects of gender, tumor size, and bilaterality on survival could not be demonstrated. In the long-living group, being under 65 years of age, having better performance, having total excision performed, having conventional RT applied, and receiving adjuvant chemotherapy were found to be more frequent. Patient and tumor characteristics are summarized in Table 1. In univariate analyses, being under 65 years of age, having KPS of 80–100, having total excision performed, simultaneous temozolomide use, and having conventional treatment and adjuvant chemotherapy applied were found to have positive effects on OS (Table 2).

In multivariate analyzes, being under 65 years of age, receiving adjuvant chemotherapy, and having total excision and conventional RT applied were effective on OS (Table 2). Among the group consisting of people who lived longer than 2 years, those who lived for 5 years or more were also examined. Compared to those who lived longer than 2 years, patients who lived 5 years or more were observed to be younger (median age 56 and 51, p=0.048). No difference was observed between the treatments received after the relapse and other characteristics.

DISCUSSION

Only a minority of GBM patients have longer survival. Clinical and treatment characteristics of 217 patients diagnosed with GBM and RT with 10 years of single-center experience in terms of long-term and short-survival groups and their relationship with the OS were evaluated retrospectively through this study. No clear consensus exists on the definition of long-term survival in GBMs. Most studies express it as 2, 3, and 5 years.[10–12] In our study, we evaluated those who lived longer than 2 years as long-lived and those who lived 5 years or more as extreme survivors.

This study reaffirmed the factors associated with clinicopathological and therapeutic long-term survival, previously specified in the literature. Both in the literature and in our research, resection width, young age, outstanding performance, conventional RT application, and course of concomitant CRT and adjuvant chemotherapy were found to be associated with survival. In the long-living group, being under 65 years of age, having better performance, having total excision performed, having conventional RT applied, and receiving adjuvant chemotherapy were seen to be more frequent. Jiang et al.[7] exhibited that younger age, better KPS, and better resection width were associated with longer-term survival. In another study with 529 patients, 9% had long-term survival, and 42% had short-term. For patients who lived longer than 2 years, age, performance, resection width, and participation

Table 1 Characteristics of the patient and treatment with respect to survival

Characteristic	All group		<6 months		≥2 years		p
	n	%	n	%	n	%	
Patients	217		37 (17.1)		49 (22.1)		
Age (median)	61 (19–87)		65 (41–83)		52 (19–72)		
Age							
<65	136	62.7	17	45.9	39	79.6	0.001*
≥65	81	37.3	20	54.1	10	20.4	
KPS							
≥80	136	62.7	12	32.4	39	67.6	<0.001*
≤70	81	37.3	25	67.6	10	20.4	
Gender							
Male	145	66.8	22	59.5	34	69.4	0.339
Female	72	33.2	15	40.5	15	30.6	
Type of the operation							
GTR	63	29	3	8.1	24	49	<0.001*
Subtotal/biopsy	154	71	34	91.9	25	51	
Concurrent CT							
None	14	6.5	5	13.5	1	2	0.08
Temozolamide	203	93.5	32	86.5	48	98	
RT fraction							
Conventional	174	80.2	20	54.1	47	95.9	<0.001*
Hypofractionation/whole-brain	43	19.8	17	45.9	2	4.1	
Adjuvant CT							
None	41	18.9	26	70.3	2	4.1	<0.001*
Temozolamide	176	81.1	11	29.7	47	95.9	
Bilaterality							
None	202	93.1	32	86.5	48	98	0.08
Yes	15	6.9	5	13.5	1	2	

*: Statistically significant. KPS: Karnofsky performance status; GTR: Gross total excision; CT: Chemotherapy; RT: Radiotherapy

in clinical trials were found to be independent factors for survival.[10] In the observational study conducted by the Mayo Clinic, young age, female gender, less comorbidity, being non-white, left-sided tumor, and RT treatment were discovered to be factors associated with 5-year survival after multivariate analysis (2249 patients with long-term survival).[13]

We could not display a relationship between gender and tumor size and survival in our study. In the study of Jiang et al.,[7] no connection between tumor size, gender, and survival was found, but good performance, gross total excision, and CRT were the characteristics of long-lived patients. However, in the literature, there are studies showing that the female gender has a longer-term survival.[5]

Tumors crossing the midline were associated with poor prognosis.[14] In our study, the median survival was 7.85 months in patients with tumors displaying bilateral localization, whereas it was 13.89 months in patients without it. However, it was not found to be statistically significant (p=0.069). In multivariate analysis, its relationship with survival could not also be demonstrated. When we compared the short- and long-lived groups, bilaterality was 13.5% in the short-survival group and 2% in the long-survival group. However, it was not statistically significant (p=0.08).

Resection width is one of the primary factors affecting the prognosis of GBMs.[6] Today, if surgical resection is more than 98%, overall survival rates are reported as 52–86 weeks. However, no consensus exists about the optimal resection width to increase survival, and counselors recommend maximum safe resection.[15] Maximal resection has a positive effect on both progression-free survival (PFS) and OS.[16] While the median OS was reported as 15.5 months after gross total resection (GTR), it was 11.79 months

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Table 2 Analysis of univariate and multivariate factors affecting overall survival in the all patient group

Variances	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
Age						
<65	1	1.261–2.255	<0.001*	1	1.031–1.944	0.032*
≥65	1.680			1.416		
KPS						
≥80	1	1.337–2.390	<0.001*	1	0.971–1.857	0.075
≤70	1.788			1.343		
Gender						
Male	1	0.817–1.472	0.540	–	–	–
Female	1.079					
Type of the operation						
GTR	1	1.388–2.612	<0.001*	1	1.197–2.275	0.002*
Subtotal/Biopsy	1.904			1.650		
Concomitant CT						
Yes	1	1.399–4.205	0.002*	1	0.621–2.214	0.624
None	2.425			1.172		
Adjuvant CT						
Yes	1	2.903–6.017	<0.001*	1	2.622–5.595	<0.001*
None	4.180			3.830		
RT fraction						
Conventional	1	1.669–3.343	<0.001*	1	1.099–2.500	0.016*
Hypofractionation	2.362			1.657		
Bilaterality						
None	1	0.956–2.851	0.072	1	0.912–2.913	0.099
Yes	1.651			1.630		

*: Statistically significant. HR: Hazard ratio; CI: Confidence interval; KPS: Karnofsky performance status; GTR: Gross total excision; CT: Chemotherapy; RT: Radiotherapy

after subtotal resection and 5.9 months without resection.[17] In our study, while the median OS was 19.94 months after total excision, it was 10.80 months after subtotal excision/biopsy (p<0.001). While the total excision was applied to 49% of the patients in the group that lived longer than 2 years, this rate was 8.1% in the short-lived group (p<0.001). In the meta-analysis, the relative risk for the relationship between total resection and OS was found to be 1.25 for 12 months and 1.58 for 226 24 months.[15]

The use of combination CRT is one of the significant components of GBM treatment. In the results of the EORTC/NCIC study of 2005, the best results were obtained after adding temozolomide to RT.[9] In the 5-year follow-up, the survival rate was 1.9% in the single RT, whereas it was 9.8% in the combined form.[3] In a study comparing 154 long-term patients and 622 control populations, undertaking CRT was more frequent in the long-living group (94% vs. 40%, p<0.001). When the predictors for long-term survival were evaluated, young age and undertaking GTR and CRT were found to be meaningful.[4] In our study, undertaking concomitant CRT and adjuvant chemotherapy was significant in univariate analysis, but the application of adjuvant chemotherapy was seen to be effective on OS in multivariate analysis.

HRT regimens are desired, especially in the elderly patients with poor performance.[18] In the meta-analysis of four randomized controlled trials, no difference was observed in OS and the side effects between hypofractionated and conventional RT. However, longer OS has been shown with HRT in patients over 70 years.[19] HRT, HRT + temozolomide, and standard RT + temozolomide were compared in the study, in which 104 patients over 70 years of age were evaluated. While there was no difference between the factions receiving temozolomide, OS was found to be shorter in the faction receiving single HRT (3.9 months vs. 5.9 months,

p=0.018). However, in the study, this faction had older patients with worse performance.[20] In the retrospective review of Azoulay et al.,[21] they evaluated 276 adult GBM patients; 147 patients undertook conventional RT, 86 patients 60 Gy in 20 fractions, and 43 patients 40 Gy in 15 fractions. While the median OS was 16 months and PFS was nine months in the conventional group, it was eight months and 5.4 months in the 40 Gy HRT faction, respectively. In the HRT faction, there were older patients who had lower KPS and had more biopsies performed. In our study, undertaking conventional RT in univariate and multivariate analyzes had a positive effect on OS. Conventional RT application was more frequent in the long-living group. In our cohort, patients in the HRT arm had lower KPS were older and had more biopsies.

The most obvious limitation of our study was its retrospective nature. Since molecular subtyping could not be performed routinely in our center during the data collection process, the MGMT and IDH status of all patients could not be evaluated. In addition, the cognitive and functional situation of the long-living group could not be assessed in this study.

CONCLUSION

Despite all treatments, the proportion of patients who live long is still low. It was observed that long-lived patients were more often young, had good performance, underwent wide excision, and received conventional RT and adjuvant CT. This study can help us plan treatments and supportive care by predicting long-term survival at diagnosis. More comprehensive studies should be conducted in times to come, incorporating molecular markers and quality of life.

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Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the Necmettin Erbakan University Pharmaceutical and Non-Medical Research Ethics Committee (no: 2022/3698, date: 18/03/2022).

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