

Factors associated with one-year survival in post-operative glioblastoma patients

Factores asociados a sobrevida a un año en pacientes postoperados de glioblastoma

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Abstract

Objective: To identify factors associated with one-year survival in postoperative glioblastoma patients at a hospital in north-eastern Mexico. **Material and methods:** Nested case-control study. Patients operated on for glioblastoma between 2016-2019 were included. Information about clinical and surgical factors was obtained, survival was calculated by Kaplan-Meier analysis. Descriptive analysis was performed with medians and ranges, and inferential analysis with χ^2 , Fisher and Student t test, odds ratio and 95% confidence interval. A value of $p < 0.05$ was considered significant. **Results:** Sixty-two patients with glioblastoma were included, 27 (43.5%) women and 35 (56.5%) men, median age 56 years (range: 6-83). Median survival was 3.6 months (1-52), 45 (72.6%) survived less than 12 months. The factors associated with a higher survival were administration of adjuvant treatment ($p < 0.001$), better functional status ($p = 0.001$), and absence of post-surgical complications ($p = 0.034$). **Conclusions:** Most patients with glioblastoma survive less than 12 months and the factors most strongly associated with longer survival are administration of adjuvant treatment, better functional status of the patient and absence of post-surgical complications.

Keywords: Glioblastoma. Survival. Prognosis.

Resumen

Objetivo: Identificar los factores asociados a la sobrevida a un año en pacientes postoperados de glioblastoma en un hospital del noreste de México. **Material y métodos:** Estudio de casos y controles anidado en una cohorte. Se incluyeron pacientes operados de glioblastoma entre 2016 y 2019. Se obtuvo la información sobre factores clínicos y quirúrgicos, se calculó la sobrevida mediante análisis de Kaplan-Meier. El análisis descriptivo se realizó con medianas y rangos, y el inferencial con prueba de χ^2 , Fisher, t de Student, razón de momios e intervalo de confianza al 95%. Se consideró significativo un valor de $p < 0.05$. **Resultados:** Se incluyeron 62 pacientes con glioblastoma, 27 (43.5%) mujeres y 35 (56.5%) hombres, mediana de edad de 56 años (rango: 6-83). La mediana de sobrevida fue de 3.6 meses (1-52), 45 (72.6%) sobrevivieron menos de 12 meses. Los factores asociados a mayor sobrevida fueron: administración de tratamiento adyuvante ($p < 0.001$), mejor estado funcional ($p = 0.001$) y ausencia de complicaciones posquirúrgicas ($p = 0.034$).

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Date of reception: 08-02-2021

Date of acceptance: 12-07-2021

DOI: 10.24875/CIRUE.M21000534

Cir Cir (Eng). 2023;91(3):382-387

Contents available at PubMed

www.cirugiaycirujanos.com

Conclusiones: La mayoría de los pacientes con glioblastoma sobreviven menos de 12 meses y los factores más fuertemente asociados a mayor sobrevida son administración de tratamiento adyuvante, mejor estado funcional del paciente y ausencia de complicaciones posquirúrgicas.

Palabras clave: Glioblastoma. Sobrevida. Pronóstico.

Introduction

Glioblastomas (GBMs) make up 48% of all malignant tumors of the central nervous system.¹ The survival rate described after surgery is ≥ 36 months²⁻⁶; however, despite aggressive treatment, GBM recurrence is inevitable, and the 5-year survival rate remains below 10%⁷⁻¹⁰. Various factors affect the prognosis of GBMs, including clinical and biological patient parameters, tumor characteristics, and treatment received¹¹.

The current standard therapy for newly diagnosed GBM consists of maximal tumor resection along with the Stupp regimen¹². This treatment paradigm has improved the median survival from 12.1 months up to 14.6 months¹³. However, at least 50% of the patients with GBMs are resistant to temozolomide (TMZ) therapy¹⁴. Extended administration of the TMZ regimen of up to 12 cycles has improved progression-free survival from 12.8 up to 16.8 months¹⁵. Surgery is the most important modality for establishing diagnosis, as well as improving the patient's prognosis based on their functional status prior to the procedure. The extent of resection is the primary factor determining survival¹⁶⁻¹⁸. Despite the multimodal treatment approaches, the recurrence rate of GBM is nearly 100%¹⁹. Over the years, innovations in neurosurgical oncology have led to strategies for achieving maximal cytoreduction while preserving functional pathways²⁰. However, advances in understanding GBM pathogenesis, and the development of new therapies have not improved prognosis, or survival rates significantly²¹⁻²⁴. Multiple mechanisms contribute to treatment ineffectiveness: complete surgical resection is nearly impossible due to tumor location and its infiltrative nature; the use of fractionated radiotherapy is limited due to the potential damage to normal brain tissue, and the blood-brain barrier blocks most chemotherapy drugs. This study evaluates clinical factors associated with the survival of patients with GBM, which could help identify potential strategies to improve the management of this condition.

Materials and methods

A nested case-control study within one cohort (observational, longitudinal, retrospective, and analytical) was

conducted at the Medical Unit of High Specialization, Specialties Hospital No. 25 of the Mexican Social Security Institute.

Cases were defined as patients who underwent GBM surgery and died within 1 year after surgery. Controls were those who survived one year or more after surgery. Patients of any age and gender who underwent surgery from 2016 through 2019 were included. Patients without health records, lacking postoperative follow-up, and without tumor characteristics in their health records were excluded. Patients without a minimum 1-month postoperative survival period due to a lack of notes in the health records were also excluded.

A total of 62 patients were eventually included, and non-probabilistic convenience sampling was used. Survival was estimated in months from the time of surgery until the end of follow-up. Age, gender, symptoms at presentation leading to the diagnosis of GBM, and the patients' comorbidities were recorded. Tumor characteristics such as volume, location, and degree of midline shift were analyzed as well. The extent of surgical resection was also categorized as total, subtotal, or partial based on the rate of resection: 100%, 90 to < 100%, and < 90%, respectively. Surgical complications, recurrence, and the need for reintervention were evaluated, as well as postoperative functional status according to the Eastern Cooperative Oncology Group (ECOG) scale, and adjuvant treatment received.

Patients with a diagnosis of treated GBM from 2016 through 2019 were identified from the pathology unit databases, and cases confirmed by two pathologists were selected based on the selection criteria. Physical and electronic health records were collected, and an Excel database was created with all the variables for analysis.

One-year survival was calculated for each patient, and patients were categorized into cases and controls. For the descriptive analysis of the results, medians and ranges were used. For the inferential analysis, the chi-square test, Fisher's exact test, and Student's t-test were used. p values < 0.05 were considered statistically significant. One-year survival was calculated using Kaplan-Meier analysis, and the strength of the association was measured using the odds ratio (OR) with a 95% confidence interval (CI).

Table 1. Clinical, surgical, and tumor characteristics of 62 patients with GBMs classified based on whether they survived for more or less than 12 months after surgical resection

Variable	Total (n = 62)	Survival < 12 months (n = 45)	Survival ≥ 12 months (n = 17)	OR (95%CI)	p
Sex					
Woman	27 (43.5%)	19 (42%)	8 (47%)	0.820	0.779
Man	35 (56.5%)	26 (58%)	9 (53%)		
Age					
≥ 60 years	26 (42%)	20 (44%)	6 (35%)	1.46	0.575
< 60 years	36 (58%)	25 (56%)	11 (65%)		
Comorbidities	34 (55%)	28 (62%)	6 (35%)	1.35	0.086
Tumor location					
Supratentorial	59 (95%)	42 (93%)	17 (100%)	0.71	0.555
Midline structures	3 (5%)	3 (7%)	-		
Midline shift					
≥ 5 mm	50 (81%)	38 (84%)	12 (71%)	1.30	0.283
< 5 mm	12 (19%)	7 (16%)	5 (29%)		
Resection grade					
Partial (< 90%)	30 (48.3%)	25 (55.5%)	5 (29.4%)	3 (0.90-9.9)	0.059
Subtotal (≥ 90%)	25 (40.3%)	17 (37.7%)	8 (47%)	0.68 (0.22-2.1)	0.351
Total (100%)	7 (11%)	3 (5%)	4 (6%)	0.23 (0.04-1.17)	0.082
Postoperative complications	15 (24%)	14 (31%)	1 (6%)	1.41 (1.10-1.81)	0.034
Tumor recurrence	24 (39%)	11 (24%)	13 (76%)	0.51 (0.32-0.80)	< 0.001
Surgical reintervention	19 (31%)	13 (29%)	6 (35%)	0.91 (0.64-1.30)	0.759
Adjuvant therapy	32 (52%)	16 (36%)	16 (94%)	1.93 (1.35-2.75)	< 0.001
ECOG					
0-2	20 (32%)	9 (20%)	11 (65%)	1.90 (1.15-3.14)	0.001
3-5	42 (68%)	36 (80%)	6 (35%)		

The results are presented as absolute frequencies (percentages).

95%CI: 95% confidence interval; ECOG: Eastern Cooperative Oncology Group Scale; OR: odds ratio.

The present study was evaluated by both the local research ethics committee and the local ethics committee. Procedures fully complied with all ethical standards, institutional regulations, the Regulations of the General Health Act on Health Research, and the Declaration of Helsinki. This study was classified as a non-risk research. Confidentiality was maintained for all participants, as their names, social security numbers, and any other identifying information were not recorded. Additionally, the databases were secured by the researchers. Since this was a retrospective, non-risk study, informed consent was deemed unnecessary.

Results

A total of 62 patients with a diagnosis of confirmed GBM were included. A total of 27 patients (43.5%) were women, and 35 patients (56.5%) were men, with a median age of 56 years (range, 6-83). Comorbidities were present in 34 patients (54.8%). The median time

elapsed between symptom onset and surgical treatment was 3 months (1-42) (Table 1). Patients presented a plethora of symptoms, including seizures in 19 cases (30.6%), headache in 58 (93.5%), altered levels of consciousness in 43 (69.4%), sensory-motor deficits in 46 (74.2%), aphasia in 18 (29%), visual disturbances in 9 (14.5%), cranial nerve involvement in 2 (3.2%), cerebellar syndrome, and urinary incontinence in 1 (1.6%).

Tumor localization included the right cerebral hemisphere in 32 patients (52%), the left hemisphere in 26 (42%), midline structures in 3 (5%), and both the right hemisphere and cerebellum in 1 (2%). In 50 cases (81%) the midline shift was greater than 5 mm, and in 12 cases (19%) it was lower than 5 mm. The median tumor volume in cubic centimeters was 39.8 (6-132). Surgical resection was partial in 30 patients (48%), subtotal in 25 (40%), and total in 7 (11%). Postoperative complications were reported in 15 patients (24%), being severe cerebral edema the most common complication reported in 7 patients

(11%). Other complications included infection in 4 (6%), CSF leaks in 2 (3%), and bleeding and surgical wound dehiscence in 1 (2%). Twenty-four (39%) out of all the patients who underwent surgery experienced relapses, and 19 (31%) required reinterventions. According to the postoperative ECOG classification, 1 patient (2%) was categorized as grade 0, 13 (21%) as grade 1, 6 (10%) as grade 2, 17 (27%) as grade 3, and 25 (40%) as grade 4.

Adjuvant therapy was administered to 32 patients, including radiotherapy to 6 (10%), chemotherapy to 3 (5%), and both to 23 patients (37%). The remaining 30 patients did not receive treatment because 17 (27%) were lost to follow-up, 9 (14.5%) had clinical contraindications (postoperative complications, difficult-to-control epilepsy, and ECOG 4, among others), 2 (3%) due to lacking therapeutic resources, and 2 (3%) because they refused therapy. The median survival of the 60 patients was 3.6 months ($< 1-52$). Only 17 (27%) survived more than 12 months (Fig. 1).

Out of the 45 patients who did not survive more than 12 months, 19 (42%) were women and 26 (58%), men (OR, 0.82; 95%CI, 0.26-2.52; $p = 0.779$). They were divided into two age groups: 20 (44%) were older than 60 years, and 25 (56%) were younger than 60 (OR, 1.46; 95%CI, 0.46-4.65; $p = 0.575$). Comorbidities were reported in 28 (62%) patients (OR, 1.35; 95%CI, 0.96-1.89; $p = 0.086$), being the most widely reported type 2 diabetes mellitus (29%), systemic arterial hypertension (24%), and cardiac arrhythmias (4%). Regarding the clinical presentation, the symptom most commonly associated with shorter survival, observed in 36 (80%) patients, was neurological impairment (OR, 1.76; 95%CI, 1.08-2.89; $p = 0.005$). Other symptoms included headache (93%), sensory-motor deficits (78%), and aphasia (31%). The most common tumor location was the supratentorial region (OR, 0.71; 95%CI, 0.60-0.83; $p = 0.555$). The midline shift greater than 5 mm was reported in 38 (84%) patients and lower than 5 mm in 7 (16%) (OR, 1.30; 95%CI, 0.78-2.15; $p = 0.283$). The extent of surgical resection was partial and subtotal in 42 (68%) patients, and total in 3 (5%) (OR, 1.78; 95%CI, 0.74-4.24; $p = 0.082$). Postoperative complications were reported in 14 (31%) patients (OR, 1.41; 95%CI, 1.10-1.81; $p = 0.048$), relapsed in 11 (24%) (OR, 0.51; 95%CI, 0.32-0.80; $p < 0.001$), and required reoperations in 13 (29%) (OR, 0.91; 95%CI, 0.64-1.30; $p = 0.759$). Among the reoperated patients, 7 underwent reoperation due to recurrence and the rest due to postoperative complications. Adjuvant treatment (radiotherapy,

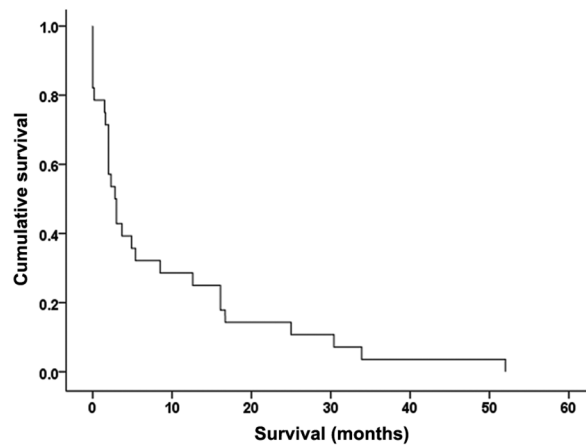


Figure 1. Overall survival curve in months for 62 patients surgically treated of GBMs at a tertiary referral center in Northeastern Mexico.

chemotherapy, or both) was administered to 16 (36%) patients, while 29 (64%) did not receive it (OR, 1.93; 95%CI, 1.35-2.75; $p < 0.001$). Postoperative ECOG grade < 3 (0-2 grades) was reported in 9 patients (14.5%), while > 3 (3-5 grades) in 36 (58%) (OR, 1.90; 95%CI, 1.15-3.14; $p = 0.001$).

Discussion

Despite strategic innovations in the management of GBM, reported survival is often < 36 months²⁻⁶, and the rate of recurrence is nearly 100%¹⁹. For this reason, research continues to investigate potential clinical, radiological, tumor-related, genetic, and treatment strategies that may improve the prognosis and survival of this condition.

According to the medical literature currently available, the incidence of malignant glial tumors is higher in men; however, there is no difference in prognosis based on gender, which is consistent with the findings from this study. Although a predisposition toward men was observed in patients who survived < 12 months, no significant p value was ever found in the multivariate analysis between gender and survival. This contradicts the findings of Gorlia et al., who reported that men have a lower survival rate compared to women²⁵.

Recent studies have highlighted the age at the time of diagnosis as an important prognostic factor for the disease. It has been reported that younger patients¹⁶ tend to have significantly longer survival times. Older patients may have more comorbidities, reduced immune function, and resistance to adjuvant therapy, which can contribute to a poorer prognosis.

However, in this study, no significant association was found between age and survival, although there was a p value close to significance for comorbidities associated with lower survival.

The preoperative and postoperative functional status has proven to be a prognostic factor in the survival of patients with GBMs¹⁶. This study found a significant association between preoperative neurological deterioration and survival, and between the postoperative ECOG scale and survival. On the other hand, the midline shift was evaluated, but no association with survival was ever found, despite previous reports suggesting that mass effect and edema from the lesion contribute to a negative outcome¹⁶.

Tumor location is a factor that influences survival. When the tumor is found in eloquent areas, surgical resection is limited, leading to a lower postoperative functional state, and a need for further surgical intervention^{16,25}. However, the present study showed no association between tumor location and prognosis. Buckner et al. found that the extent of resection was the most significant factor in predicting survival²⁶. Lacroix et al. found a significant correlation between aggressive resection (98% or more of the total tumor volume) and a favorable prognosis¹⁶.

Complete macroscopic resection of high-and-low grade gliomas significantly increases the median survival rate by 200% and 160%, respectively, compared to subtotal resection. While complete removal of GBM is unattainable due to residual microscopic infiltrative cells, achieving 90% resection without compromising functional pathways is a realistic goal sought after by neurosurgeons²⁷. In their study, Chaichana et al.²⁸ conducted a study of 259 patients with GBMs and found that a higher degree of resection was associated with longer survival (OR, 0.992; 95%CI, 0.988-0.998; p = 0.0007). They also saw that a minimum resection rate > 70% was associated with longer survival rates (OR, 0.631; 95%CI, 0.462-0.875; p = 0.0006). In the present study, most patients who underwent partial resection did not survive more than 12 months vs those who had subtotal or total resection who eventually had better outcomes. However, the difference approached statistical significance. We should mention that achieving total tumor resection was challenging in many cases, and the extent of resection varied, possibly due to technological limitations at the medical unit where the study was conducted.

Despite multimodal treatment approaches, the 1-year rate of GBM recurrence is nearly 100%¹⁹. In this study, 39% of the patients experienced relapsed,

which may be attributed to the low rate of survival > 12 months. Adjuvant treatment typically involves the administration of fractionated radiotherapy and chemotherapy with TMZ¹², which has proven to improve the median survival of patients¹³⁻¹⁵. The Stupp regimen was administered to the patients included in this study, and some received extended chemotherapy regimens. A significant association was found between the administration of adjuvant therapy and survival, even in those who only received 1 modality, either radiotherapy, or chemotherapy.

Currently, there is no standardized treatment for recurrent GBM. Patients undergoing a 2nd, 3rd, or even 4th intervention show improved survival of 15, 22, and 26 months, respectively²⁹. However, this study did not find a significant association between surgical reintervention and survival, and most reinterventions were performed due to postoperative complications rather than disease recurrence.

Conclusions

Most patients with GBM from this study survived less than 12 months. Factors more significantly associated with longer survival rates included the administration of adjuvant therapy, better patient functional status, and the absence of postoperative complications. Factors that approached statistical significance were total surgical resection and the absence of comorbidities. One limitation of the study was the limited sample size, which may have compromised the statistical significance of some variables, as observed with the degree of resection associated with survival. The results emphasize the importance of early initiation of adjuvant treatment, the need for the appropriate surgical management team, and for prospective research studies with a larger number of patients.

Funding

None declared.

Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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