Revista Mexicana de Neurociencia

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ORIGINAL ARTICLE

Grades 3 and 4 adult-type diffuse gliomas: epidemiology and radiomics in Guanajuato, Mexico

Luis E. Ayala-Hernández[1], Raúl Gómez-Gómez[2], Armando Gallegos[1], and Raúl A. Hernández-Estrada[2]*

[1]*Departamento de Ciencias Exactas y Tecnología, Centro Universitario de los Lagos, Universidad de Guadalajara, Lagos de Moreno, Jalisco;* [2]*Servicio de Neurocirugía, Unidad Médica de Alta Especialidad, Hospital de Especialidades 1 Centro Médico Nacional del Bajío, León, Guanajuato. Mexico*

Abstract

Objective: *The objective of the study is to report epidemiological characteristics and prognostic factors of patients with adult-type gliomas treated in the neurosurgery department of the National Medical Center of Bajío, as well as to evaluate, for the 1st time in Mexican patients, surface regularity (SR).* **Methods:** *Epidemiological and clinical features were statistically compared with international references. Survival was estimated using the Kaplan-Meier method. Kaplan-Meier curves were compared with the log-rank test. SR was obtained by segmenting magnetic resonance imaging.* **Results:** *Median age of patients with glioblastomas was less than that of patients in the United States (p = 0.021). The administration of radiotherapy (RT) and temozolomide (TMZ) prolonged survival (median gain of 35 months). Median SR was 0.6006 and was close to being statistically lower than the value reported in a large cohort (p = 0.09).* **Conclusions:** *Glioblastomas were diagnosed at younger ages and appeared to be more aggressive. The administration of RT and TMZ prolonged substantially survival.*

Keywords: *Central nervous system neoplasms. Glioblastoma. Radiomics. Survival analysis. Age of onset.*

Gliomas difusos de tipo adulto grado 3 y 4: epidemiología y radiómica en Guanajuato, México

Resumen

Objetivo: *Reportar las características epidemiológicas y los factores pronósticos de los pacientes con gliomas de tipo adulto tratados en el servicio de neurocirugía del Centro Médico Nacional del Bajío, así como evaluar, por primera vez en pacientes mexicanos, la regularidad de la superficie.* **Métodos:** *Se compararon estadísticamente las características epidemiológicas y clínicas con referencias internacionales. La supervivencia se estimó mediante el método de Kaplan-Meier. Las curvas de Kaplan-Meier se compararon con la prueba de log-rank. La regularidad de la superficie se obtuvo mediante la segmentación de la resonancia magnética.* **Resultados:** *La mediana de edad de los pacientes con glioblastomas fue menor que la de los pacientes en Estados Unidos (p = 0.021). La administración de radioterapia y temozolomida prolongó la supervivencia (ganancia mediana de 35 meses). La regularidad de la superficie mediana fue de 0.6006 y estuvo cerca de ser estadísticamente menor que el valor reportado en una cohorte grande (p = 0.09).* **Conclusiones:** *Los glioblastomas se diagnosticaron a edades más jóvenes y parecieron ser más agresivos. La administración de radioterapia y temozolomida prolongó sustancialmente la supervivencia.*

Palabras clave: *Neoplasias del sistema nervioso central. Glioblastoma. Radiómica. Análisis de supervivencia. Edad de inicio.*

Correspondence:
Armando Gallegos
E-mail: gallegos@culagos.udg.mx.

Date of reception: 04-02-2025
Date of acceptance: 01-07-2025
DOI: 10.24875/RMN.25000005

Available online: 09-09-2025
Rev Mex Neuroci. 2026;27(1):19-26
www.revmexneurociencia.com

Introduction

Adult-type diffuse gliomas represent the bulk of adult neuro-oncology practice[1]. Treatment mainly consists of surgical resection, radiotherapy (RT), and chemotherapy. However, findings in recent years indicate that enrolling patients in clinical trials is now the preferred option[2]. Prognosis varies depending on type of tumor. Glioblastoma IDH-wildtype has the worst prognosis, and oligodendroglioma IDH-mutant and 1p/19q-codeleted have the best prognostic[1,3]. Annual age-adjusted incidence rates for glioblastoma have increased in recent years in the United States and Canada[4,5]. The World Health Organization (WHO) suggests that environmental factors might be responsible for this increase[1]. Recent studies have revealed ethnic variations in incidence, epidemiology, and survival in patients with adult-type diffuse gliomas[6]. In Mexico, there is a lack of studies reporting information on this subject and the few addressing consider mainly patients treated in care centers located in Mexico City[7-10]. Thus, there are regions that have never been explored, such as the State of Guanajuato. This lack of information hinders the practice of neuro-oncology in accordance with the Mexican context.

On the other hand, radiomics is defined as the conversion of medical images to higher-dimensional data and the subsequent mining of these data for improved decision support[11]. Given the central role of medical imaging in diagnosing and managing various diseases, cancer care centers in developing countries are typically equipped with medical imaging equipment. In contrast, other technologies, such as those required to assess molecular profiles, are rarely available in such centers. Hence, there is a growing interest in incorporating radiomics into the clinical management of adult-type diffuse gliomas in developing countries. The glioblastoma surface regularity (SR), a measure describing how much the tumor resembles a sphere, obtained from contrast-enhanced pre-treatment T1-weighted magnetic resonance imaging (MRI), was found to be a predictor of overall survival (OS)[12].

The aims of this study, focusing on grade 3 or 4 adult-type diffuse gliomas, are (1) to report epidemiological and clinical aspects, OS, and prognostic factors of patients treated at the National Medical Center of Bajío (CMNB by its Spanish acronym) and (2) to evaluate SR of the patients with glioblastoma.

Materials and methods

Study design and participating patients

With code R-2023-1001-038, the study was approved by the research ethics committee of the CMNB. No informed consent was necessary. We conducted a retrospective cohort investigation, reviewing the medical records of patients treated in the neurosurgery department between January 2019 and December 2023. 65 glioma diagnoses were identified. To include patients in the study, inclusion criteria were (i) age ≥ 18 years at surgery, (ii) grade of tumor 3 or 4 at diagnosis, (iii) availability of diagnostic histopathological results, (iv) availability of information on treatments received, and (v) availability of information on OS or last follow-up, as applicable. A total of 35 patients satisfied the inclusion criteria.

Histopathological classification

With the histopathological results, tumors were classified, when possible, according to the current WHO classification of central nervous system (CNS) tumors published in 2021 (2021 WHO classification). This classification requires the assessments of the status of *IDH1* and *IDH2* genes and 1p/19q codeletion to assign the type of adult-type diffuse gliomas[13]. When it was not possible to classify tumors according to the 2021 WHO classification due to the lack of molecular information, in most cases, the mutations in *IDH1* and *IDH2* genes other than IDH1-R132H, the term “by pathologist experience” was added to the diagnosis stated in the histopathological reports. Because 4-7% of patients > 55 years only rarely develop a glioma that is IDH-mutant[14,15], and the IDH1-R132H mutation accounts for 89-93% of all IDH1 and IDH2 mutations[14-17], the WHO recommends not testing for non–IDH1-R132H mutations in patients >55 years whose tumors are negative for IDH1-R132H by immunohistochemistry. Thus, patients with a diagnosis of glioblastoma in the histopathological results with a negative test for IDH1-R132H mutation by immunohistochemistry and >55 years at surgery were classified as IDH-wildtype glioblastoma.

Images and SR

From this 35 patient population, the glioblastoma patients with availability of a pre-treatment contrast-enhanced T1-weighted MRI with section thickness ≤ 2.0 mm, spacing between sections ≤ 1.0 mm, gap ≤ 0 mm, and pixel spacing ≤ 1.0 mm, were selected for

a radiomics study. Image inclusion criteria were taken from the work by Pérez-Beteta et al.[12] Figure SM1 in supplementary material (SM) shows a flow chart of the patients included in the study.

T1-weighted MRIs were loaded into 3D Slicer software[18] version 5.6.1 and were manually segmented in the axial plane to identify the tumor region. Once MRIs were segmented, 3D Slicer computed the volume and surface of the tumors. 3D slicer uses two methods to calculate geometric measurements: the "Label Map" method and the "Closed Surface" method. We chose the latter because it is appropriate for calculating surfaces. Following Pérez-Beteta et al.[12] methodology, the surface regularity was then calculated using the mathematical formula

$$S_R = 6\sqrt{\pi}\frac{T_V}{\sqrt{T_S^3}}$$

where T_V corresponds to the total tumor volume and T_S is the total tumor surface. Given the limited number of patients who met image inclusion criteria, an exhaustive radiomic analysis was not feasible. Therefore, we opted not to perform a segmentation reproducibility analysis. Figure 1 shows an example of a segmented tumor with its three-dimensional reconstruction.

Statistical analysis

The statistical analysis was performed in R software version 4.3.2[19]. Using the EnvStats package[20], one-sample sign test was applied to statistically compare a median with a reference value. Once the mathematical assumptions were verified, i.e., expected successes and failures > 5, one-proportion Z test was used to compare a proportion with a reference value. Proportion comparison between two groups was done using the Fisher test. The association between two variables was evaluated with the Spearman correlation coefficient. OS probabilities from the date of surgery were calculated using the Kaplan-Meier method. Patients who were alive until April 24, 2024 (last database revision) were treated as censored events. The function survfit defined in the survival package[21] and the function ggsurvplot in the survminer package[22] were used to calculate OS and plot Kaplan-Meier curves, respectively. Differences between Kaplan-Meier curves were evaluated with the log-rank test. Cox proportional hazards model was used to calculate the hazard ratio (HR) of a variable in the OS analysis. Confidence intervals (CI) for HRs were calculated with the Wald statistic. $p < 0.05$ was considered statistically significant.

Results

Study population and clinical findings

Patient characteristics are detailed in table 1. Astrocytomas were diagnosed at a younger age (median age at surgery 32 years) than glioblastomas (median age at surgery 58 years), the group formed by glioblastoma by pathologist experience and IDH-wildtype glioblastoma (n = 30), and oligodendrogliomas (median age at surgery 47 years). The median age at surgery for patients with glioblastomas was statistically less than that of patients in the United States (p = 0.02), 66 years reported by the Central Brain Tumor Registry of the United States (CBTRUS) in 2023[23]. Due to the few patients with astrocytomas (n = 3) and oligodendrogliomas (n = 2), median ages at surgery for these groups were not statistically compared with those reported by CBTRUS 2023.

Regarding biological sex, most patients with astrocytic tumors (glioblastomas and astrocytomas) were males (67%) and oligodendroglial tumors were diagnosed only in women. The proportion of males with glioblastomas (67%) was not statistically greater (p = 0.18) than that reported by CBTRUS 2023 (58.5%)[23]. The most common initial symptoms for glioblastoma patients were classified, following WHO standards[1], as focal neurological deficits (73%, 22/30), followed by symptoms of elevated intracranial pressure (70%, 21/30). Both seizures and symptoms of elevated intracranial pressure were the most common initial symptoms for astrocytoma patients (67%), and for oligodendroglioma patients, the most common initial symptoms were the same as for glioblastoma patients (Table 1). The median time from symptom onset to surgery was 46 days (range 12-410 days) for glioblastoma patients. For 77% of them, the time from initial symptoms to surgery was < 3 months. No statistical differences were observed when compared to 68% reported by the WHO[1] (p = 0.15). The median time from symptom onset to surgery for astrocytoma and oligodendroglioma patients can be consulted in table 1.

OS and its prognostic factors

At the time of the final analysis, 18 (75%) glioblastoma patients by pathologist experience, 5 (83%) IDH-wildtype glioblastoma patients, 1 (33%) astrocytoma by pathologist experience patient, and 1 (50%) oligodendroglioma by pathologist experience patient had died after a median follow-up of 5.1 (range 0.16-50.2 months),

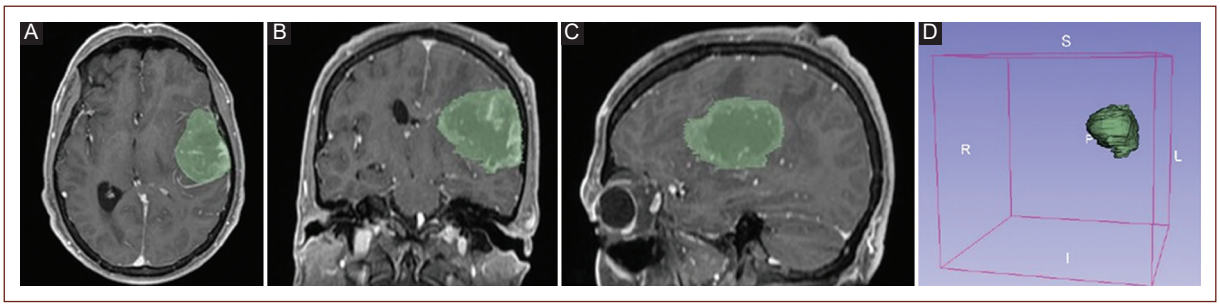

Figure 1. Images showing a segmented glioblastoma included in the study. **A:** axial, **B:** coronal, and **C:** sagittal views of a segmented glioblastoma included in the study. **D:** three-dimensional reconstruction of tumor shape performed by segmenting all the slices with high signal intensity.

3.5 (range 1-10.3 months), 58.7 (range 23.3-59.8 months), and 17.3 (range 0.9-33.8 months) months, respectively.

Due to the few patients in the astrocytoma by pathologist experience and oligodendroglioma by pathologist experience groups, Kaplan-Meier survival curves were only constructed for glioblastoma patients and can be consulted in figure 2. Kaplan-Meier survival curves for glioblastoma patients separated into glioblastoma patients by pathologist experience and IDH-wildtype glioblastoma patients are found in figure SM2 and figure SM3 in SM.

We looked for the age cut-off that best selects patients with a better survival prognosis. Several age cut-offs were tested, 65 years was the cut-off with the less p-value when comparing the Kaplan-Meier survival curves. The obtained p = 0.1 and the HR were 2 with a 95% CI equal to 0.83-4.9 (Fig. 3). This result shows that age at surgery was not a prognostic factor for survival in our cohort. On the contrary, the administration of RT and temozolomide (TMZ) showed substantial survival benefits ($p < 0.001$, HR = 0.1 [0.03-0.33], Fig. 4). To ensure that the improved survival times in the group of patients receiving RT and TMZ were not because this group had, proportionally, more patients with totally resected tumors, the proportions of type of surgery in each group were statistically compared. The proportion differences were not significant (p = 0.78, see Fig. SM4 in SM).

SR

Pérez-Beteta et al.[12] found that glioblastoma SR obtained from high-resolution contrast-enhanced pre-treatment T1 MRI is a predictor of OS. MRIs were available for 23 of the 30 patients with glioblastomas, but only 9 met the imaging inclusion criteria. Imaging characteristics for the 9 patients are summarized in table 2.

With a p = 0.09, median SR (0.6006) was less than that obtained by Pérez-Beteta et al.[12] (0.635), a possible trend suggesting greater tumor aggressiveness in our patients. In addition, Pérez-Beteta et al.[12] found 0.629 as the value of SR that best selects the patients with a better survival prognostic. As shown in table 2, six of the nine patients were in the group with a poor survival prognosis ($S_R < 0.629$). A quantitative summary of the tumor volumes and surface areas obtained for the nine patients is also shown in table 2. On the other hand, age at surgery and SR were not correlated (Fig. SM5 in SM).

Discussion

Due to the lack of a CNS tumor national registry, there is limited epidemiological information regarding gliomas in the Mexican population. Some monocentric studies have reported epidemiological characteristics of patients with gliomas treated in Mexico[7-10,24-31] and most of them were carried out in hospitals located in Mexico City. Only four studies, references[10,25-27], considered patients from regions different to those covered by Mexico City care centers, but none included patients from the State of Guanajuato. This is the first study reporting clinical features and epidemiological information of patients with gliomas treated in a hospital from Guanajuato. CMNB is one of the few institutions in Guanajuato treating glioma patients, thus the Guanajuato population is well represented in our study.

In our cohort, 86% of the patients were diagnosed with glioblastoma, which is consistent with the fact that glioblastoma is the most frequent primary malignant tumor of the CNS[1]. Without leaving aside that for some patients, the mutational status of *IDH1* and *IDH2* genes

Table 1. Summary of characteristics of the patients included in the study by type of tumor

Characteristic	Glioblastoma by pathologist experience (n = 24)	Glioblastoma, IDH-wildtype (n = 6)	Astrocytoma by pathologist experience (n = 3)	Oligodendroglioma by pathologist experience (n = 2)
Patient characteristic				
Age at surgery (years) Median Range	 56 (28-75)	 66 (56-75)	 32 (24-46)	 47 (44-50)
Sex, n (%) Female Male	 8 (33) 16 (67)	 2 (33) 4 (67)	 1 (33) 2 (67)	 2 (100) 0 (0)
Treatment				
Type of resection, n (%) Total Subtotal Biopsy	 17 (71) 6 (25) 1 (4)	 6 (100) 0 (0 0 (0)	 0 (0) 3 (100) 0 (0)	 2 (100) 0 (0) 0 (0)
Radiotherapy administration, n (%) Yes No	 10 (42) 14 (58)	 1 (17) 5 (83)	 3 (100) 0 (0)	 1 (50) 1 (50)
Chemotherapy administration, n (%) Yes No	 10 (42) 14 (58)	 1 (17) 5 (83)	 3 (100) 0 (0)	 1 (50) 1 (50)
Symptoms				
Time from onset of symptoms to surgery (days) Median Range	 50.5 (13-410)	 39 (12-79)	 739 (27-1217)	 34.5 (20-49)
Initial symptoms, n (%) Focal neurological deficits Seizures Symptoms of elevated intracranial pressure Behavioral and neurocognitive changes	 16 (67) 2 (8) 18 (75) 7 (29)	 6 (100) 0 (0) 3 (50) 2 (33)	 1 (33) 2 (67) 2 (67) 0 (0)	 2 (100) 1 (50) 2 (100) 0 (0)

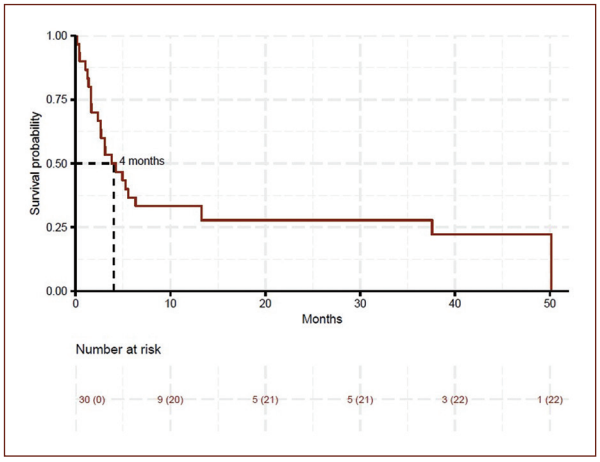

Figure 2. Kaplan-Meier overall survival curve for glioblastoma patients. Survival probability for 1.6, 4, 37.6, and 50.2 months after surgery were, respectively, 73, 50, 22, and 0%.

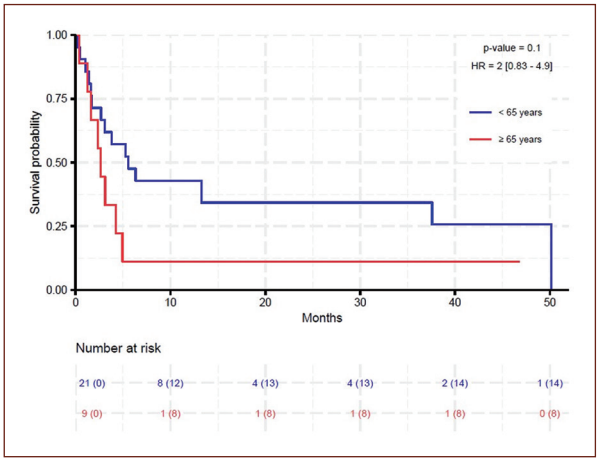

Figure 3. Kaplan-Meier overall survival curves for glioblastoma patients by age at surgery (≥ 65 vs. < 65 years at surgery). No statistical differences were observed. In brackets, the 95% confidence interval for the Hazard ratio.

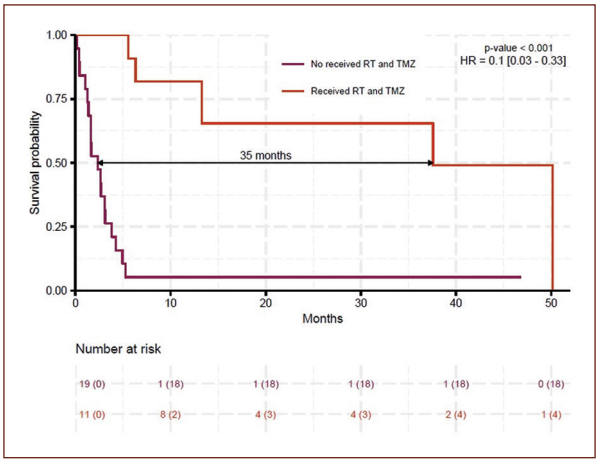

Figure 4. Kaplan-Meier overall survival curves for glioblastoma patients by administration of radiotherapy and temozolomide. Large statistical differences were obtained. In brackets, the 95% confidence interval for Hazard ratio.

Table 2. Summary of contrast-enhanced T1-weighted magnetic resonance imaging parameters and geometric measurements for the nine glioblastoma patients who met imaging inclusion criteria

Parameter	p
MR imaging parameter	
Pixel spacing (mm)	0.44 (0.43-0.49)
Section thickness (mm)	1.11 (1-2)
Spacing between sections (mm)	1 (1-1)
Gap (mm)	−0.11 (−1-0)
Geometric measurement	
Tumor volume (cm^3)	61 (31-106)
Surface area (cm^2)	150 (65-367)
Tumor regularity*	0.6006 (0.1027-0.6874)
Number of patients below the best regularity threshold reported by Pérez-Beteta et al. [12], 0.629	6 (67%)
Number of patients above the best regularity threshold reported by Pérez-Beteta et al. [12], 0.629	3 (33%)

Unless otherwise specified, values are means with ranges in parentheses.
*Median.

was unknown, and the few patients with grade 3 tumors, astrocytomas, and oligodendrogliomas were diagnosed mostly in young adults and glioblastomas at older ages. Several studies mention that glioblastomas affect the Mexican population at significantly younger ages, i.e., the ages of Mexicans at glioblastoma diagnosis are significantly less compared to other ethnicities[6,7,9,30,32]. Our results are in complete agreement with these findings (median age 58 years and significant p-value when compared to patients in the United States). Similar to other studies[6,8,10,23,31,33], gender distribution in astrocytomas and glioblastomas showed a male preponderance in our cohort (68%). Clinical features and time from symptom onset to diagnosis were presented similarly to the WHO report[1].

Median OS after surgery for glioblastoma patients was 4 months (Fig. 1). Survival information of each patient is required to statistically compare survival times of our cohort of glioblastoma with those obtained in other studies. Unfortunately, that information is not usually available and patient survival is strongly influenced by the presence of IDH1 or IDH2 mutations[16], thereby precluding a rigorous comparative analysis of survival times of our glioblastoma patients. To obtain a general, although imprecise, indication of how long or short the survivals of our patients is, median survival can be compared. McCormack et al.[32] in patients with glioblastomas from the Mexican Institute of Neurology and Neurosurgery obtained a median survival of approximately 15 months and a median survival of approximately 16 months in patients from the United States. On the other hand, Beltrán et al.[8] in patients from the General Hospital of Mexico obtained a median survival of 24 months. However, this study contains a few glioblastoma patients; therefore, this value is a rough estimate. Comparing our median of 4 months with the medians in these studies, it seems that the survivals of our patients are lower.

Several studies in different countries, including one in Mexico[9], have found that younger patients have longer survival times. Our survival analysis for age (Fig. 3) reflects this result, with a p-value close to statistical significance. We believe that significance for age would be achieved with a larger cohort. On the other hand, as observed in seminal clinical trials[34], the administration of RT and TMZ significantly prolonged OS for glioblastoma patients in our cohort (Fig. 4). However, in our study, the survival gain (difference in medians equal to 35 months) was substantially greater. A similar result was found by Wegman et al. in patients from the Mexican Institute of Neurology and Neurosurgery[9]. Although more studies are needed to determine the exact survival benefits provided by RT and TMZ in Mexican patients, huge efforts should be made to ensure all Mexican patients with good performance status receive RT and TMZ.

Inspired by a mathematical model[35], the shape of the tumor in the pretreatment contrast-enhanced T1 MRI has been studied as a survival prognostic factor in glioblastoma patients[12,36]. SR was found to positively correlate with OS[12]. Consequently, the more irregular

the tumor, the more aggressive it is. We found that glioblastomas were, in general, more irregular than the patients of the study where SR was found to predict OS[12] (0.6006 vs. 0.635 in median SR) and a statistical trend was observed (p = 0.09). This means that our results of SR suggest an even more aggressive tumor behavior in glioblastoma patients treated at CMNB, indicating potential clinical relevance. This should be interpreted with caution because of the small sample size in the radiomic subanalysis. A larger cohort of patients treated at CMNB with pre-treatment MRIs meeting imaging inclusion criteria is needed to obtain conclusive results. Due to this is the first study evaluating SR in Mexican patients with glioblastoma, it was not possible to compare our results with patients from other medical institutions in Mexico.

This study shows the current clinical management of patients with adult-type diffuse gliomas at a reference care center in Mexico. Although our results cannot be generalized to the Mexican population because of the small number of patients, this study provides valuable information that can help guide future research involving larger cohorts of Mexican patients and reveals the limitations that must be addressed to improve the clinical management of these patients.

Future perspectives

A natural extension of this work would be to include additional patients treated at CMNB from 2024 and repeat the analysis performed here.

Multicenter studies in Mexico with rigorous inclusion criteria that control clinical variables affecting patient survival, i.e., tumor diagnosis according to 2021 WHO classification, administration of RT and chemotherapy, type of surgical procedure, and extent of the resection evaluated with a post-operative MRI, among others, are needed to confirm whether glioblastomas exhibit increased aggressiveness in the Mexican population.

Funding

The author L.E.A-H wishes to thank SECIHTI for the financial support granted through scholarship 779584.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

Supplementary data

Supplementary data are available at DOI: 10.24875/RMN.25000005. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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