

# Glioblastoma, Treatment Strategies at the “Hermanos Ameijeiras” Hospital.

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## Abstract

**Objective:** Gliomas are the most common primary malignant tumors of the central nervous system (CNS) and, from them, 45.6 % corresponds to glioblastomas (GB). This work aims to determine the results of treatment for patients with glioblastomas treated at the “Hermanos Ameijeiras” Hospital, Cuba, in the period from January 2015 to December 2020.

**Method:** An observational, descriptive, retrospective cohort assessment was carried out in a population of 45 patients treated at the “Hermanos Ameijeiras” Hospital, Cuba, with a diagnosis of glioblastoma.

**Results:** Male patients aged 40 to 59 years (57.7 %) with white color skin (82 %) were predominant with clinical symptoms of motor deficit syndrome. The survival rate was greater than 12 months in 18 patients (40 %), while for 21 patients (46.7 %) it was between 6 and 12 months.

**Conclusions:** Glioblastoma is a challenge for the multidisciplinary medical team. The best therapeutic results and survival rates are related to the strategies of a multimodal treatment that begins with maximum safe resection of the lesion, followed by radiotherapy, chemotherapy and immunotherapy oncological treatments.

**Keywords:** glioma; glioblastoma; tumors of the central nervous system.

## Introduction

Primary tumors of the central nervous system represent one-third leading cause of cancer mortality and, in adults, account for approximately 1% of all malignant lesions. More than half of these tumors are gliomas with high degree of malignancy, so that patients, invariably, present tumor recurrence<sup>1, 2</sup> Gliomas, accounting 80% of primary Tumors of Central Nervous System, have an annual incidence of 5.55 per 100,000 people in the United States (USA)<sup>3</sup>.

There are, approximately, 11,000 new cases per year of high-grade gliomas in the U.S. From them, 9,000 are glioblastomas, which constitutes 45.6% of all primary malignant CNS tumors. The incidence of the latter is approximately 3.19 per 100,000 inhabitants<sup>4,5</sup>. More cases are reported each year in men than in women, with statistics that show: 7.14 per 100,000 men and 5.06 per 100,000 women worldwide<sup>6</sup>.

Glioblastoma is a fast-growing tumor, composed of a heterogeneous mixture of poorly differentiated astrocytic tumor cells, with cellular pleomorphism, necrosis, vascular proliferation and increased number of mitoses<sup>7</sup>. The median survival rates are from 12.2 to 18.2 months, and the survival rate is inversely proportional to the age<sup>1-3,8</sup>.

In Cuba, for more than three decades, malignant tumors are the second cause of death, only preceded by cardiovascular diseases. In recent years, brain cancer has had an incidence ranging from 300 to 600 new cases per year, for an adjusted rate of 5.2 to 5.8 per 100,000 inhabitants in women and men respectively. Mortality rates remain close to the incidence rates<sup>9,10</sup>.

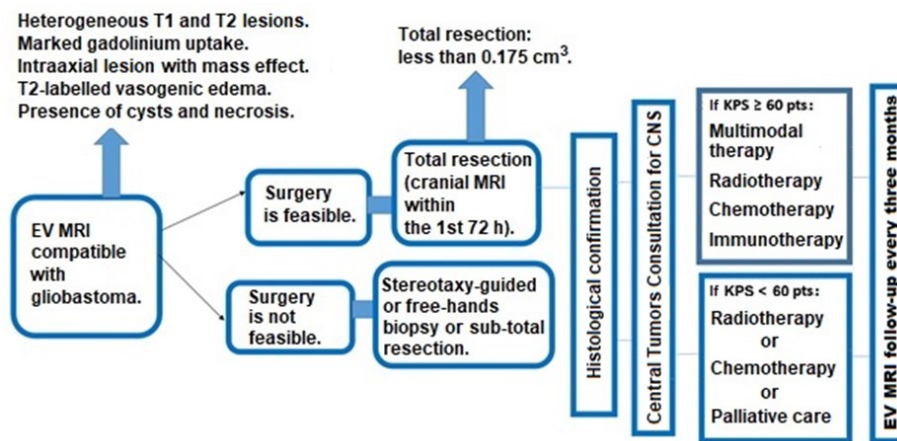
Glioblastoma affects more those patients between 40 and 60 years old, a stage in which people are still in full-intellectual and physical capacity, which represents a health problem if the growing population aging that currently occurs in the country is considered.

## Materials and Methods

An observational, descriptive, retrospective cohort-type study was conducted in a population of patients diagnosed with glioblastoma and treated at the "Hermanos Ameijeiras" Hospital, from January 2015 to December 2020, who met the following criteria:

- Patients with anatomical pathology diagnosis of glioblastoma.
- Patients that have presented clinical and imaging follow-up in the above-mentioned medical institution.
- Patients older than 18 years old.

All the patients were included in the protocol for treatment of high-grade glial tumors, according to the classification of the World Health Organization and approved in the medical institution where the study was developed (Figure 1). The following diagram shows the behavior followed towards each of the patients<sup>11</sup>.



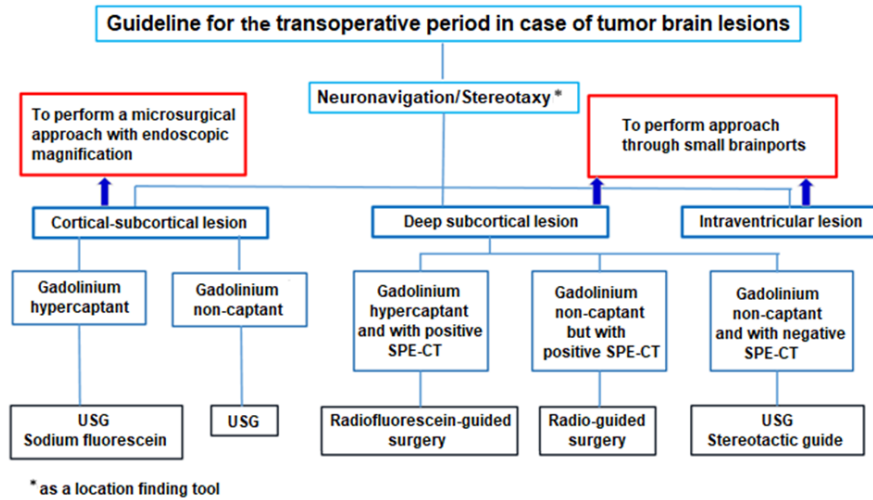
**Figure 1:** Treatment algorithm for patients diagnosed with glioblastomas.

**T1:** T1-weighted image in magnetic resonance; **T2:** T2-weighted image in magnetic resonance; **EV:** Endovascular; **MRI:** magnetic resonance image, **CNS:** central nervous system, **KFS:** Karnofsky functional scale.

The surgeries were carried out following the surgical principles established in the care protocols from "Hermanos Ameijeiras" Hospital, which are:

- ⇒ To perform a detailed analysis of the neuroimaging tests records as part of pre-surgical planning for adequate craniotomy site planning and possible extension of debulking,
- ⇒ Depending on the location of the lesion, to perform a conventional approach with microscopic magnification or through small brain ports (brainport surgery) with endoscopic magnification (Figure 2).

- ⇒ To perform the tumor resection guided by imaging means: Neuronavigation, SPECT-CT (Single Photon Emission Cranial Tomography), USG (ultrasound) and / or by the use of tissue contrasts (Figure 2).
- ⇒ To preserve the hypothetically healthy neurological tissue, to take care of the cerebral vascular structures and perform the maximum safe cytoreduction.
- ⇒ For polar topography tumors, to perform a lobectomy.
- ⇒ In subcortical cortical lesions, to assess the possibility of performing craniotomy with the patient awake.



**Figure 2.** Transoperative action guideline based on the use of neurological tools.

## Results

A total of 45 patients (n = 45) were examined and those aged 40 to 59 years (57.7 %) and white color skin (82 %) were predominant, being the motor deficit syndrome the most frequent clinical form of mainly manifested (see **Table 1**).

**Table 1.** Distribution of samples according to demographic and clinical variables and topographic location of the tumor.

Variables	Frequency	%
Age		
(40-49 Years old)	10	22
(50-59 Years old)	16	35,6
Sex (Male)	26	57,8
Skin color (White)	37	82
Clinical manifestation		
Headache	5	11
ICH Syndrome	8	18
Motor Deficit Syndrome	17	38
Topographic Brain Syndrome	6	13
Seizure Syndrome	9	20
Topographic location		
Frontal	10	22
Parietal	6	13,3
Temporary	8	18
Occipital	3	7
Multilobar	11	24
Other locations	7	16

**ICH:** Intracranial hypertension.

60% of patients (n = 27) underwent a treatment process that included tumor resection supported by adjuvant treatment with radiotherapy, chemotherapy and immunotherapy, according to **Table 2**.

**Table 2.** Therapeutic modalities.

Variable	Therapeutic modality	
	Frequency	%
Biopsy + R	2	4
Biopsy + R+ C	3	7
Biopsy + R+ C+I	1	2
Tumor resection + R	7	16
Tumor resection + R+ C	5	11
Tumor resection + R+ C+I	27	60
<b>Total</b>	<b>45</b>	<b>100</b>

**R:** radiotherapy, **C:** chemotherapy, **I:** immunotherapy.

The degree of tumor resection<sup>10</sup> behaved in such a way that a total resection was performed in 27 patients, subtotal resection was performed in 9 and partial resection was performed in 3, while in 6 patients only biopsy was performed.

Table 3 shows the score on the Karnofsky functional scale (KFS) in the pre- and postoperative periods. As can be seen, in the latter it got the value of 80 points or more in 75.7% (n = 34) patients.

**Table 3.** Karnofsky (KFS) functional scale for pre- and postoperative.

KFS (points)	Preoperative		Postoperative	
	Fr	%	Fr	%
100	5	11	9	20
90	15	33	17	38
80	11	25	8	17,7
70	9	20	8	17,7
Less than 70	5	11	3	7
<b>Total</b>	<b>45</b>	<b>100</b>	<b>45</b>	<b>100</b>

I

n relation to the overall survival rate, it was observed that 18 patients (40%) had survival rates greater than 12 months, in 21 patients (46.7%) survival rates were between 6 and 12 months, while in 6 patients (13.3%) survival rate were less than 6 months.

A total of 25 medical complications occurred in 12 patients (26.6%), from which 10 were of neurological and 15 extraneurological natures, distributed as follows: surgical bed hematoma 1 patient, cerebrospinal fluid (CSF) fistula 2 patients, obstructive hydrocephalus 5 while urinary tract infection, multiorgan failure and septic shock accounted for by 1 respectively. The last two occurred in the same HIV-positive immunocompromised patients, radionecrosis 2 while urinary tract infection, multiorgan failure and septic shock accounted for by 1 respectively. The last two occurred in the same HIV-positive immunocompromised patients, deep vein thrombosis 2 while urinary tract infection, multiorgan failure and septic shock accounted for by 1 respectively. The last two medical complications occurred in the same HIV-positive immunocompromised patients and bronchopneumonia 10 while urinary tract infection, multiorgan failure and septic shock accounted for by 1 respectively.

The multivariate analysis from **Figure 3** shows a close relationship between the therapeutic modalities, the postoperative Karnofsky functional scale (KFS) and overall survival rate in patients; while the rest of the variables showed no relationship with each other.

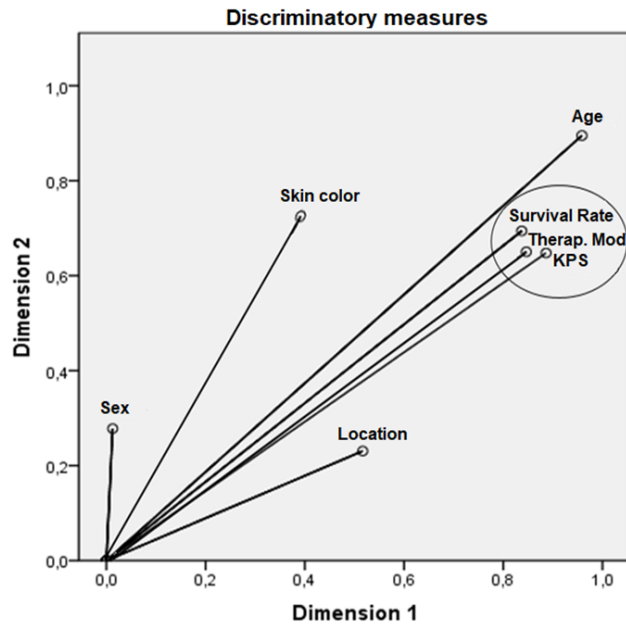


Figure 3. Multivariate analysis.

A statistical analysis performed to the variables related in the previous multivariate analysis and applying Pearson's chi-square statistical test, an association between the therapeutic modality and the postoperative Karnofsky with  $p = 0.014$  is observed, in addition to a statistically significant relationship between the therapeutic modality and survival with  $p = 0.027$ .

## Discussions

The predominant age group was between 40 and 59 years old (57.6%), with an average age of 54.09 years old. In this stage of life these people are still useful to society, with full intellectual and working capacity. If the vertiginous population aging that the society undergoes is taken into account, this represents a current health problem. These results are related to other author's findings, such as Louis et al.<sup>7</sup>, in which the most frequent age of appearance is around 55 years.

In the sample studied, the a predominance of males (57.8%) over females (42.2%) is observed, similar to other researcher's findings, such as Ostrom et al.<sup>4</sup> and Nayak et al.<sup>3</sup>. Nayak et al.<sup>3</sup> shows, furthermore, that this condition is 1.6 times more frequent in men than in women.

This neoplasm was predominant in patients with white skin color in 82% ( $n = 37$ ) of the sample, while mixed -or multiple- ethnic groups represented 11% and black skin color represented 7% only. These findings may be related to what Ostrom and collaborators<sup>4</sup> proposed in their research in the sense that gliomas are more frequent in white skin-color persons, unlike other primary tumors such as meningiomas, which are more frequent in afro-descendants persons. Ostrom and collaborators<sup>4</sup> emphasize, as well, that this may be due to the differences in the access to health services existing between both ethnic groups. However, this research showed a pattern of behavior similar to that previously cited; even though Cuba has a free health service, with equal access to all its citizens.

The most frequent clinical forms of presentation were motor deficit syndrome with 17 (38%) patients, followed by seizure syndrome with 9 (20%) patients and endocranial hypertension syndrome with 8 (18%) patients. In a smaller proportion, the cerebral topographic syndrome and headache -as an isolated symptom- were presented in 6 and 5 patients respectively. These findings correlate with the reports published by other researchers, such as Yuile et al.<sup>12</sup>, in which results the motor deficit syndrome corresponds to 20% of their sample, being the most frequent symptomatology.

Headache, as the only symptom in the series studied, showed a low incidence compared to other authors, who report it up to 77%. But since this symptom is part of the triad of the syndrome of intracranial hypertension that in this research occupies the third place within the forms of debut, the authors of this paper consider that this low incidence may be attributed to underreporting issues. On other hand, the incidence of seizure syndrome in this series behaves similar to that reported by other authors such as Chaichana et al.<sup>13</sup>, which reported an incidence of 24–68%.

As **Table 1** shows, the most frequent location of tumors was multilobar, with 11 patients (24%), followed by the frontal, with 10 patients (22%) and the temporal with 8 cases (18%). These findings correlate with other researchers such as Djililian et al.<sup>14</sup> which suggest that, approximately, more than a half of the GB in adults infiltrate more than one lobe and approximately 5% have multifocal growth.

Other authors such as Ostrom et al.<sup>15</sup> found that the most frequent locations are frontal (25%) and temporal (19.7%). It should be noted that due to the infiltrating and aggressive nature of GB tumors, it is rare that they are located in a single brain lobe. The Karnofsky Functional Scale (KFS) as a pillar and bulwark to decide the behavior, is essential to evaluate the therapeutic response. In the present study a presurgical KPS of 70 points or more was observed in 89% (n = 40) of the sample. Only 5 patients treated presented KPS of 60 points or less, which is related to those who debuted with intracranial hypertension, a clinical state that makes the KFS to decrease greatly, but which could be improved in the postoperative stage.

Authors such as Solomon et al.<sup>16</sup> and Krivosheya et al.<sup>17</sup>; point that, depending of the risk involved for surgeries of patients with low Karnofsky degrees, conduction of the surgical act is only justified if the service is relevant for teaching interests and prior approval of the family. According to these authors it can be justified, as well, in those clinical states with low KFS, but when it could be reversed with a surgical treatment in the first hours.

Postoperative results show a predominance of patients with 70 points or more on the KFS Scale with 42 (93%) patients. 8 patients (18%) improved their scale with respect to admission and 34 (76%) patients maintained it. In general, favorable results comparable with the findings from other authors such as Solomon et al.<sup>16</sup> were achieved, which shows that the higher the preoperative Karnofsky Functional Scale, the better the postoperative results.

The authors of this paper agree in the opinion that careful preoperative planning, in compliance with the "maximum safe resection" principle and the combined and harmonious use of neurological tools, guarantee the tumor resection and the postoperative functionality of the patient.

The present research shows, also, that 18 patients (40%) had survival rates greater than 12 months; in 21 patients (46.7%) survival rates were between 6 and 12 months, while for 6 patients (13.3%) survived for less than 6 months. The best results were seen in those patients who underwent maximum safe tumor resection in relation to those who only underwent biopsy, evidencing a statistically significant relationship with  $p = 0.012$ . This result is justified because when a tumor resection is performed as radical as possible, the cell load is reduced to less than  $0.175 \text{ cm}^3$ , which allows a better action of the adjuvant agents, being significant that the greater survival is achieved when the schemes of Tumor Resection-Radiotherapy-Chemotherapy-Immunotherapy are used.

In another studies, Chen et al.<sup>1</sup>, Roberts et al.<sup>2</sup> and Nayak et al.<sup>3</sup> showed average survival rates of 12.2 to 18.2 months, while research related to treatment modality and survival in patients with glioblastomas, including Stupp et al.<sup>18</sup> and López Piloto et al.<sup>19</sup>, confirm that multimodal treatment provides the best results in terms of survival rate, where the chemotherapeutic agent used is Temozolamide. It is important to point out that Temozolamide, through the Stupp Protocol, is a first-line treatment in the world. This medication, together with radiotherapy, managed to improve, after two years, survival rates to more than double: from 10.4% in the past to 26.5%<sup>18,19</sup> in present times. Another element must, also, be pointed out: the absence of Temozolamide in the Cuban national treatment protocols, what undoubtedly makes the medical team to look for alternatives in the strategies and protocols to treat GB in Cuba.

According to the bibliography, there are several factors that can influence survival rates and age, high score of KFS points, with more than 80 KFS points and the absence of motor or language defect and non-periventricular location are between the most significant. Recent molecular and genetic studies that are also difficult in Cuba due to their high costs, allow medical teams to know which patients would benefit and which would not, with immunotherapy or chemotherapy<sup>20</sup>. The current trend is the personalization of treatments according to the molecular characteristics of each tumor. Determining epidermal growth factor expression allows knowing which patients will actually benefit from immunotherapeutic treatment with nimotuzumab.

A medicine of proven efficacy and that in patients with 1p/19q codeletion, IDH (Isocitrate dehydrogenase) mutation and methylation of MGMT (Methylguanine O6 methyltransferase) together with surgical removal, provides the best benefits. But instead of this, a modification of the PVC scheme (Procarbazine, Vincristina and Cisplatin) is used to replace the Carmustine or Lomustine, the linctus of choice in this scheme, which unfortunately is not available in Cuba and, undoubtedly, influence the survival rates of the patients studied.



The results obtained in this research are in correspondence with both: research and publications related to the national context (Solomon et al.<sup>16</sup>) and to the international context (Krivosheya et al.<sup>17</sup>), which corroborate, as well, that total surgical resection (more than 98% of the lesion or even better, the entire area that heightens with contrast) is the best choice, because it helps to cytoreduce, to improve the mass effect, to take the cells to the same stage of cell division and eliminate necrotic tissue, which is chemo and radioresistant. In this sense, the "maximum safe resection" approach continues to be the predicting factor with the greatest impact aiming to achieve maximal survival benefit with minimal risk, mediated by the strategies for the use of neurological tools (Figure 2) and under the principle of guaranteeing functional neurology.

The degrees of tumor resection of the samples were obtained mostly using endoscopic magnification methods (Vitom Exoscope and Endoscope 0 and 30 degrees) which show the positive effectiveness of minimally invasive neuroncology performed at "Hermanos Ameijeiras" Hospital. As pointed formerly, a total of 25 medical complications occurred in 12 patients (26.6%), from which 10 were of neurological and 15 extraneurological natures. The incidence of patients, compared with the literature reports -which range from 25-32%, according to Michael et al.<sup>20</sup>- is similar. According to Chaichana et al.<sup>13</sup>, among the determining factors reported in the literature, age over 50 years, Karnofsky scale less than 60 points (for another 70 points), infratentorial location, histological grade, size of the lesion, histopathology, as well as the skill and experience of the surgeon are the most representatives.

From the total complications reported (25), 12 patients (48%) with infectious complications are the predominant and which are distributed in such a way that the most representative was bronchopneumonia with 10 cases. Urinary tract infection and septic shock were found to be 1 for each, which is high compared to what is reported in the existing literature<sup>20</sup>, particularly for the bronchopneumonia, to which an incidence of 2% is attributed.

In the same way, obstructive hydrocephalus in 5 patients represented the 20% of the total; which exceeds the reports revised in the literature review, that give an incidence between 0.25–1.5%, according to Michael et al.<sup>20</sup>. This could be related to locations related to the cerebral ventricles or bleeding in the subarachnoid space.

## Conclusions

Glioblastoma represents a challenge for the multidisciplinary medical team. The best therapeutic results are in relation to multimodal treatment strategies that begin with "maximum safe resection", followed by adjuvant oncological treatment (radiotherapy, chemotherapy and immunotherapy) that guarantee maximal survival benefit and quality of life with minimal risk of the patients.

## Conflict of Interest

The authors of this paper declare there is no conflict of interest.

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