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Profile of Patients with Central Nervous System Tumors - High and Low Grade Gliomas Seeing Clinical and Histopathological Characteristics in Public Oncological Hospital in Brazil

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ABSTRACT

Introduction: The incidence of neoplasms affecting the Central Nervous System (CNS) has gradually increased worldwide. Malignant CNS neoplasia occupies the 11th position in terms of incidence in Brazil. Brain tumors and other primary CNS tumors are a heterogeneous group of malignant and non-malignant tumors, presenting different signs and symptoms, with variable prognoses. The incidence of brain tumor subtypes varies according to age, with children and adults developing different pathologies. This study aimed to characterize the epidemiological profile of adult patients with low- and high-grade gliomas in a single public health center in Brazil.

Methods: This retrospective, descriptive, analytical, unicentric, quantitative cohort observational study (n = 110). The medical records of patients diagnosed with high- and low-grade gliomas from January/2017 to June/2023 were evaluated.

Results: Multiform glioblastoma (GBM) was predominant (60%), followed by non-GBM high-grade gliomas (20,9%), and low-grade gliomas (19,1%). The predominant sex was male (66.4%). The age group with the highest incidence was 40-64 years (57,3%). Most patients with gliomas did not have relevant comorbidities (46,4%). Most patients were ECOG 1 (Performance Status Scale - 39,1%).

Conclusion: In Brazil, epidemiological data related to malignant primary intracranial tumors are still scarce; therefore, publishing epidemiological data for this challenging pathology can improve the understanding of the disease and treatment of patients.

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Introduction

Epidemiology

Every year, approximately 100,000 people are diagnosed with diffuse gliomas worldwide. Despite representing <1% of all newly diagnosed tumors, diffuse gliomas are associated with high mortality and morbidity. GBM (multiform glioblastoma) is the most lethal glioma, representing approximately 70-75% of all diffuse gliomas, with a median SG between 14-17 months. Due to geographic differences, the incidence of gliomas varies with age, gender, and ethnicity; however, due to histology/grade, survival varies among subtypes, sex and age [1].

The annual incidence of primary malignant brain tumors is approximately 7 per 100,000 individuals, and it increases with age. Five-year survival is approximately 36%. Approximately–49-59% of malignant brain tumors are GBM and 30% are low-grade diffuse gliomas. Symptoms of malignant brain tumors include headaches (50%), seizures (20%-50%), neurocognitive impairment (30%-40%), and focal neurological deficits (10%-40%) [2-5].

The mean age at diagnosis of the CNS (central nervous system) tumors was 59 years. Menigiomas and GBM are primarily diagnosed at more advanced ages [4].

Accurate classification of CNS tumors is important for estimating future prognosis and treatment. For example, astrocytomas with mutations in IDH1 or IDH2 and homozygous loss of cyclin-dependent kinase inhibitor genes 2A and B (CDKN2A/B) are considered grade 4, even if they do not present histological characteristics of a grade 4 tumor (figure 1) [2].

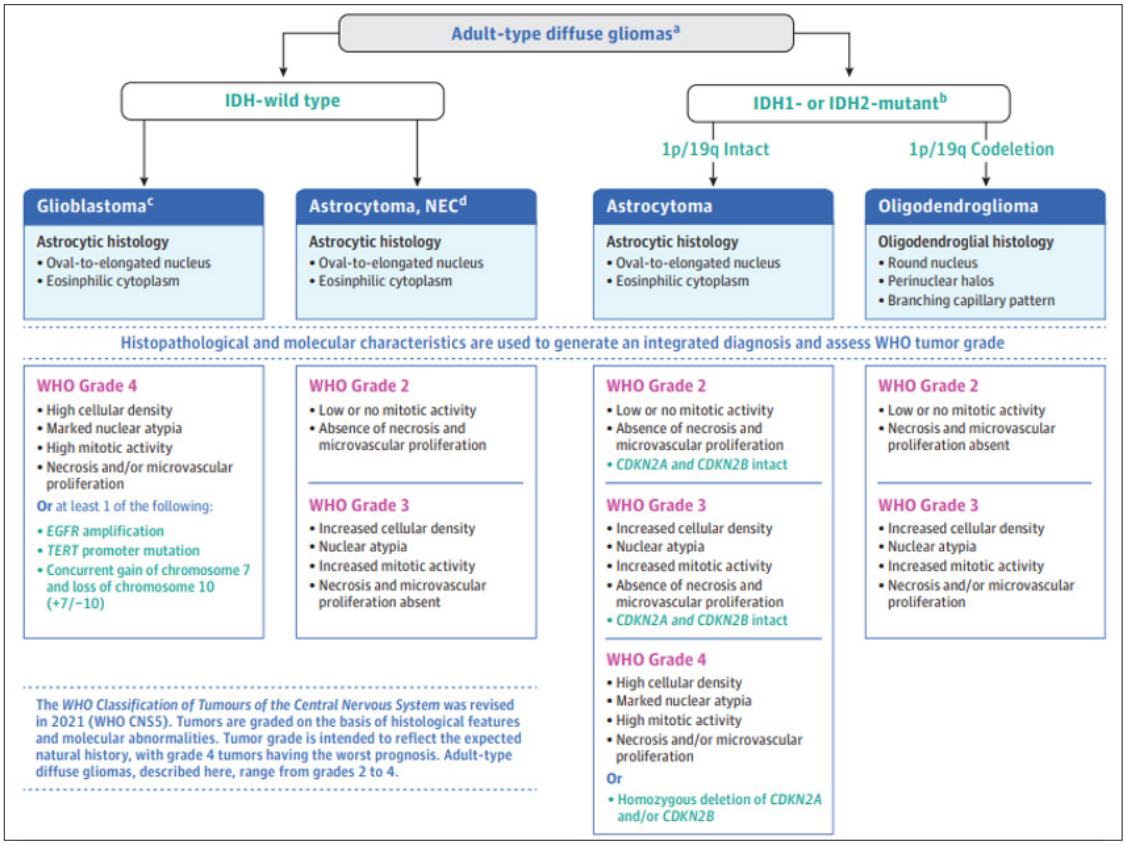

Figure 1: Integration of Histological Characteristics and Molecular Alterations in the Revised WHO 2021 Classification on CNS Tumors

GBM is more common among non-Hispanic white individuals than among other races and ethnic groups, and there is a slight predominance in males [2]. Some studies have indicated that in GBM, sex predominance is significantly more common in men. Age is an important factor in cancer development. In GBM, the vast majority of cases occur in people over 40-50 years of age, and the median survival is less than 15 months [3]. It has a prevalence of 3.19 cases per 100,000 inhabitants of the general population and, like most brain tumor, the incidence of glioblastomas grows according to the age of the population: from 65 to 74 years, the incidence is 13.21 per 100,000 inhabitants, and 14.64 per 100,000 for the 75 to 84 year range [4].

Classification

Accurate classification of CNS tumors is important for estimating patient prognosis and requires the integration of histological characteristics and molecular abnormalities. Since 2021, the World Health Organization (WHO) has classified adult diffuse gliomas into three major entities. Astrocytoma, Oligodendrogliomas and GBM [5].

Oligodendrogliomas are defined as gliomas with a mutation in IDH and an unbalanced translocation between chromosomes 1 and 19 (1p/19q co-deleted); they are classified as G2 or G3 based on histological characteristics, such as mitotic activity and presence of microvascular proliferation or necrosis. Mutant IDH gliomas without co-deletion 1p/19q (1p/19q not co-deleted) are astrocytomas and classified as G2, G3, or G4, based on a combination of histological characteristics and molecular markers [2]. Gliomas with wild-type IDH are classified as GBM.

Objectives

Primary Objectives

To evaluate the frequency/incidence of adult patients over 18 years of age diagnosed with high- and low-grade gliomas at the Hospital do Cancer de Londrina (HCL).

To describe the clinicopathological and epidemiological characteristics of the population at a certain time in HCL.

Secondary Objectives

To describe oncological outcomes, such as global survival (SG) and progression-free survival (SLP), at a given time in HCL.

Justification

It is of paramount importance to identify epidemiological data aiming at better knowledge of pathology in the Brazilian population and, above all, in terms of public health, to contribute to the definition of effective prevention and diagnosis strategies. In Brazil, epidemiological data are still scarce; therefore, analyzing risk factors and incidence can contribute to more accurate diagnosis and early treatment.

Methodology

Study Design

Retrospective, Descriptive, Analytical, Single-Center and Quantitative Observational Cohort Study.

Casuistry

Data from patients diagnosed with high- and low-grade gliomas between January 2017 and June 2023 were evaluated using their medical records. Patients were identified using the institutional tool TASY through a search for the International Code of Disease

(CID) C71. Clinicopathological data were collected from the electronic medical records.

Inclusion Criteria

Patients over 18 years of age diagnosed with low-grade gliomas (G2) and high-grade gliomas (G3, G4) were treated at the Hospital do Cancer de Londrina from January/2017 to June/2023.

Exclusion Criteria

Patients evaluated for a second opinion were excluded and, therefore, without treatment/follow-up at the institution; patients with grade 1 neoplasms, meningiomas, neoplasms with central nervous system (CNS) metastasis, embryonic tumors, and clinical-pathological data of oncological outcomes or treatment unavailable in medical records.

Control Variables

The clinical and histopathological characteristics collected for the analysis were: Sex (male or female)

- History of Alcoholism and Smoking
- Comorbidities at Diagnosis
- Date of Birth/Age
- Performance Status According to ECOG Classification
- Family History of Neoplasms
- Other Primary Neoplasms
- Date of Diagnosis
- Histology
- Degree of cell Differentiation (Grades 2, 3, and 4).
- Proliferation Index (Ki-67) Using Immunohistochemistry
- IDH
- OLIG2
- ATRX
- GFAP
- TP53
- Type of Surgery
- Radiotherapy
- Adjuvant Chemotherapy/Time
- Chemotherapy (in Recurrence)
- Date of Recurrence (Radiological Documentation of Disease)
- Date of Death
- Date of Last Assessment and Status.

Statistical Analysis

All statistical analyses were performed using the statistical software STATA® BE 13.0. A significance value of 0.05 was used. For survival analysis, Kaplan-Meier curves were used for graphical visualization, which were tested using the logrank test to determine if there was any statistical difference between the curves. In addition, regression was performed using a univariate Cox Proportional Hazards model for variables such as high-grade gliomas, glioblastomas, and inclusion of Temozolamide (TMZ) in SUS. Exploratory data analysis was performed by constructing multivariate models using Cox regression.

Ethical Aspects

Since this was a retrospective observational study, without interference with treatment or evolution of patients and with guarantee of confidentiality and anonymity of data, we requested exemption from the application of the Free and Informed Consent Form (TCLE). As this was a retrospective observational study, there was no funding from any funding agency relying on the infrastructure already available in the service.

Results

Patients' Characteristics

From July 1, 2017, to June 30, 2023, 110 patients treated at Hospital do Cancer de Londrina, whose International Code of Diseases classified as C71 (malignant brain neoplasm), were analyzed in this study, and their clinical characteristics are listed in Table 1.

Table 1: Clinical and Demographic Characteristics of the General Population

Characteristics	n = 110
Year of diagnosis	
2017	12 (10.9%)
2018	10 (9.1%)
2019	21 (19.1%)
2020	18 (16.4%)
2021	11 (10%)
2022	29 (26.4%)
2023	9 (8.1%)
Gender	
Male	73 (66.4%)
Female	37 (33.6%)
Age group	
18-39	12 (10.9%)
40-64	63 (57.3%)
>65	35 (31.8%)
Comorbidities	
none	51 (46.4%)
1 to 2	46 (41.8%)
over 2	13 (11.8%)
High blood pressure	41 (37.3%)
Diabetes mellitus	2 (1.8%)
HAS + DM	15 (13.6%)
Another cancer	1 (1%)
Family history of neoplasm	34 (30.9%)
Smoking	
never	73 (66.4%)
active	9 (8.2%)
ex-smoker	28 (25.4%)
Alcoholism	
never	86 (78.2%)
active	12 (10.9%)
ex-alcoholic	12 (10.9%)
ECOG	
0	34 (30.9%)
1	43 (39.1%)
>2	33 (30%)
Histology	
astrocytoma	30 (27.3%)
oligodendroglioma	11 (10%)
glioblastoma	66 (60%)
others	3 (2.7%)

In the general population of patients (Table 1), the highest prevalence of new diagnoses occurred in 2022 (26.4%), 66.4% were male, and 57.3% were age group–40-64 years. Regarding comorbidities, almost half of the patients (46.4%) did not have comorbidities, 41.8% had between 1 and 2, and 11.8% had more than 2. Hypertension was the most common comorbidity (37.3%) followed by hypertension associated with diabetes (13.6%). Only one patient had another type of cancer with a primary etiology of cutaneous basal cell carcinoma. One patient had a family history of primary tumor in the central nervous system.

As for living habits Only 8.2% of the participants were active smokers and 25.4% were former smokers. Regarding alcoholism, most were never alcoholic (78.2%), with 10.9% being active and 10.9% being ex-ethyl alcohol. Regarding the Performance Status Scale (ECOG), 30.9% of the patients were diagnosed with ECOG 0 and 39.1% with ECOG 1. The most prevalent histology was GBM (60%), followed by astrocytoma (27.3%) and oligodendroglioma (10%).

Of all the medical records evaluated, seven patients did not maintain care in this service, went through at least one consultation with a clinical oncologist, and returned to the cities of origin. In addition, seven other patients did not undergo treatment because the diagnosis did not involve radiotherapy or chemotherapy. Only one patient died because of acute myocardial infarction in another hospital in the city of Londrina, which is not related to primary brain neoplasms.

Patients Diagnosed with a Primary Tumor of a Low-Grade Central Nervous System

Table 2 lists 21 patients of low-grade histological type and their clinical and demographic characteristics. This classification includes 38.1% grade 2 oligodendroglioma and 61.9% grade 2 astrocytoma. In this group, 76.2% presented mitotic index below 10%, IDH mutated in 71.4%, Olig2 present in 76.2%, ATRX preserved in 47.6%, GFAP positive in 76.2% and TP53 mutated in 57%. Partial resection was the most frequent in 85.7% of the patients. The vast majority (95.2%) of the patients underwent adjuvant radiotherapy and 80.9% followed with adjuvant chemotherapy. However, 64.7% of patients submitted to adjuvant chemotherapy did it within 6 months (the remainder was performed within 12 months). One patient diagnosed in 2019 received adjuvant chemotherapy with procarbazin and in the progression of disease was exposed to TMZ. Another patient also diagnosed in 2019, received two cycles of the adjuvant protocol based on procarbazin, lomustine and vincristine (PCV), without disease progression and even the analysis of this study, was in clinical follow-up.

Table 2: Histopathological Characteristics, Clinical and Oncological Treatment in Patients with Low-Grade Primary Tumor of the Central Nervous System

Low grade gliomas	n = 21
Oligodendroglioma	
Grade 2	8 (38.1%)
Astrocytoma	
Grade 2	13 (61.9%)
Ki67	
10-30%	1 (4.8%)
31-60%	0
>60%	0
not informed	4 (19%)
IDH	
wild	4 (19%)
mutated	15 (71.4%)
not informed	2 (9.6%)
Olig2	
present	16 (76.2%)
absent	0
not informed	5 (23.8%)
ATRX	
loss	8 (38.1%)
preserved	10 (47.6%)
not informed	3 (14.3%)
GFAP	
positive	16 (76.2%)
negative	0
not informed	5 (23.8%)
TP53	
not mutated	4 (19%)
mutated	12 (57%)
not informed	5 (24%)
Type of resection	
Partial	18 (85.7%)
Total	2 (9.5%)
biopsy only	1 (4.8%)
Adjuvant radiotherapy	20 (95.2%)
Adjuvant chemotherapy	17 (80.9%)
not indicated	2 (9.5%)
not informed	2 (9.5%)
6 months	11 (64.7%)
12 months	6 (35.3%)

Patients Diagnosed with a Primary Tumor of a Low-Grade Central Nervous System

Table 3 describes patients diagnosed with primary tumors in the high-grade histological brain. A total of 89 patients were listed: 7.9% with grade 3 astrocytoma, 14.6% with grade 4, 3.4% with grade 3 oligodendroglioma, and 74.1% with GBM. The most frequent mitotic index was in the range of 10-30% (38.2%), wild type HDI in 77.5% (since most were GBM), Olig2 was present in 79.8%, ATRX was preserved in 74.2%, GFAP in 83.2%, and TP53 not mutated in 51.7%. Regarding the type of neurosurgery, total resection was more prevalent in 59.6% of the patients. Among the 89 patients, 77.5% received adjuvant radiotherapy, and 56.2% received chemotherapy. Of those who received adjuvant chemotherapy, 74% received six cycles of treatment.

Six patients returned to the origin and did not undergo treatment at the Hospital do Cancer de Londrina, and seven patients did not undergo any type of oncological treatment. Regarding drug treatment, two patients received first-line carmustine, both diagnosed in 2022. Only one patient received bevacizumab after disease progression (court order). In the second-line scenario, four patients received carmustine after six TMZ cycles. One patient with a diagnosis of 2017 gliosarcoma histology received two

cycles of TMZ, and by court decision, the medication was stopped. Three patients died before starting onco-specific treatment; one due to acute myocardial infarction.

Table 3: Histopathological Characteristics, Clinical and Oncological Treatment in Patients with High-Grade Primary Tumor of the Central Nervous System

High grade gliomas	n = 89
Astrocytoma	
Grade 3	7 (7.9%)
Grade 4	13 (14.6%)
OIigodendroglioma	
Grade 3	3 (3.4%)
Glioblastoma	66 (74.1%)
Ki67	
<10%	15 (16.9%)
10-30%	34 (38.2%)
31-60%	13 (14.6%)
>60%	13 (14.6%)
not informed	14 (15.7%)
IDH	
wild	69 (77.5%)
mutated	14 (15.7%)
not informed	6 (6.8%)
Olig2	
present	71 (79.8%)
absent	1 (1.1%)
not informed	17 (19.1%)
ATRX	
loss	10 (11.2%)
preserved	66 (74.2%)
not informed	13 (14.6%)
GFAP	
positive	74 (83.2%)
negative	0
not informed	15 (16.8%)
TP53	
not mutated	46 (51.7%)
mutated	26 (29.2%)
not informed	17 (19.1%)
Resection	
Partial	29 (32.6%)
Total	53 (59.6%)
biopsy only	7 (7.8%)
Adjuvant radiotherapy	69 (77.5%)
Adjuvant chemotherapy	50 (56.2%)
not indicated	4 (4.5%)
not informed	35 (39.3%)
6 months	37 (74%)
12 months	13 (26%)

Patients Diagnosed with GBM

The clinical and demographic characteristics of patients diagnosed with GBM were evaluated, as described in Table 4. Of this group, 66 patients were analyzed, of which 36.4% had a mitotic index in the range of 10-30%, wild-type IDH in 83.3%, Olig2 in 78.8%, preserved ATRX in 74.2%, GFAP in 80.3%, and unmutated TP53 in 51.5%. Some immunohistochemistry (IHQ) data were not present in the analyzed reports and were described as not informed.

Regarding the type of surgery performed, 57.6% of the patients underwent total resection, followed by partial resection (30.3%). However, 10.6% of these patients underwent biopsy of the CNS lesion. The type of surgical technique was not described in the medical records or the radiotherapy technique used. Regarding cancer treatment, 74.2% received adjuvant radiotherapy and 48.5% received adjuvant chemotherapy, which was indicated for 6 months in 90.6% of the patients (the remainder underwent 12 months). One patient diagnosed in 2019 received only adjuvant radiotherapy and did not receive TMZ because he or she was not released through court decisions. Another patient diagnosed in 2022 was re-exposed to TMZ.

Table 4: Histopathological Characteristics, Clinical and Oncological Treatment in Patients with Primary Tumor of the Central Nervous System

Glioblastoma	n = 66
Ki67	
<10%	9 (13.6%)
10-30%	24 (36.4%)
31-60%	9 (13.6%)
>60%	11 (16.7%)
not informed	13 (19.7%)
IDH	
wild	55 (83.3%)
mutated	4 (6.1%)
not informed	7 (10.6%)
Olig2	
present	52 (78.8%)
absent	1 (1.5%)
not informed	13 (19.7%)
ATRX	
loss	6 (9.1%)
preserved	49 (74.2%)
not informed	11 (16.7%)
GFAP	
positive	53 (80.3%)
negative	0
not informed	13 (19.7%)
TP53	
not mutated	34 (51.5%)
mutated	17 (25.7%)
not informed	15 (22.8%)
Resection	
Partial	20 (30.3%)
Total	38 (57.6%)

biopsy only	7 (10.6%)
not informed	1 (1.5%)
Adjuvant radiotherapy	49 (74.2%)
Adjuvant chemotherapy	32 (48.5%)
not indicated	32 (48.5%)
not informed	2 (3%)
6 months	29 (90.6%)
12 months	3 (9.4%)

Survival Analysis
Progression-Free Survival

General SLP

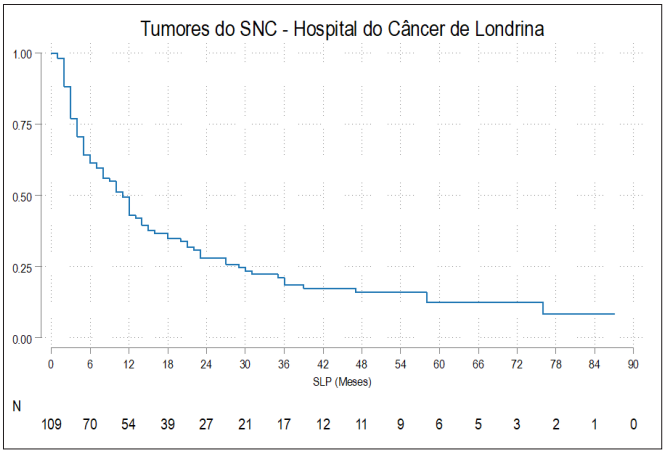

Figure 2: Overall Progression-Free Survival

Considering the entire database (N= 109), we have an 11-month SLPm. One patient missed follow-up after the initiation of radiotherapy.

High Grade/Low Grade Tumors

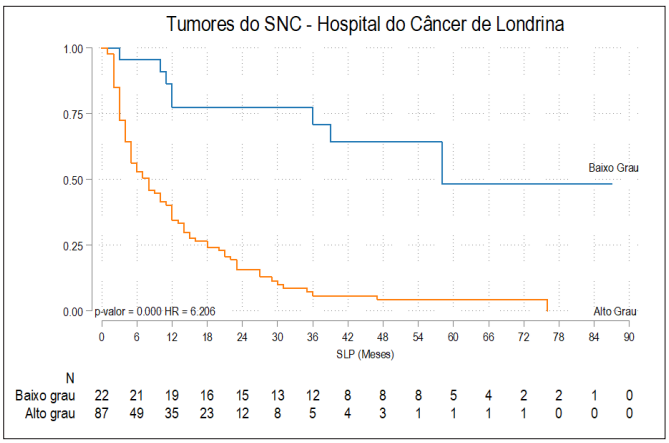

Figure 3: Progression-Free Survival in Low Degree and High Degree

The SLPm for high-grade tumors was 8 months, and that for low-grade tumors was 58 months. In addition, it can be observed that when performing the equity test of Kaplan-Meyer curves through the logrank test, the curves were statistically different (p-value = 0.000 | HR not adjusted = 6.206 [3.008;12.802]).

GBM

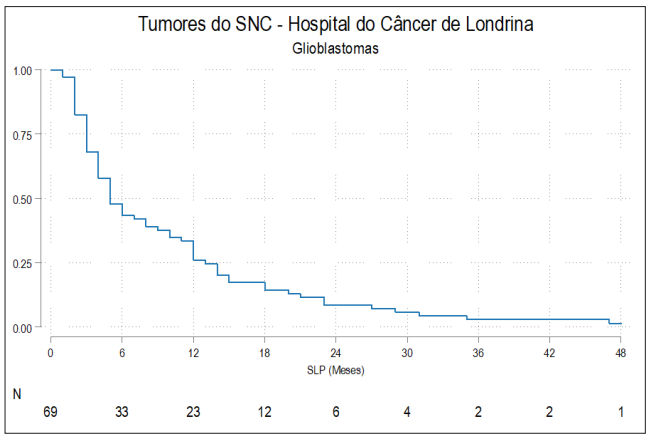

Figure 4: Progression-Free Survival in GBM

The GBM SLPm was 5 months.

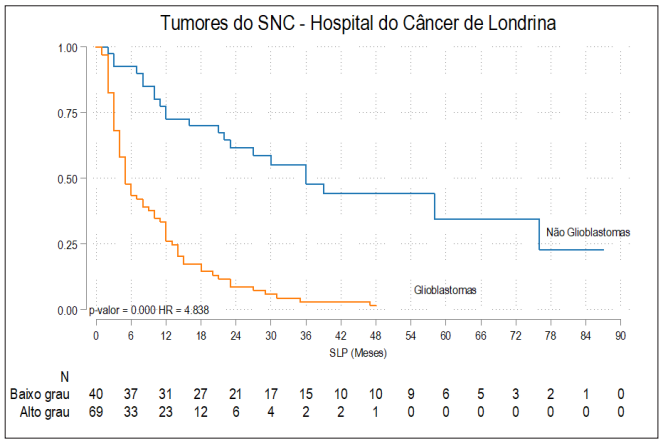

Figure 5: Progression-Free Survival in GBM x Non-GBM

Comparing GBM and non-GBM tumors, the former presented a median SLP of 5 months, whereas the latter had a median SLP of 36 months. Both curves were compared using the logrank test which showed a statistically significant difference (p = 0.000 | HR not adjusted = 4.838 [2.869;8.158]).

Temozolomide

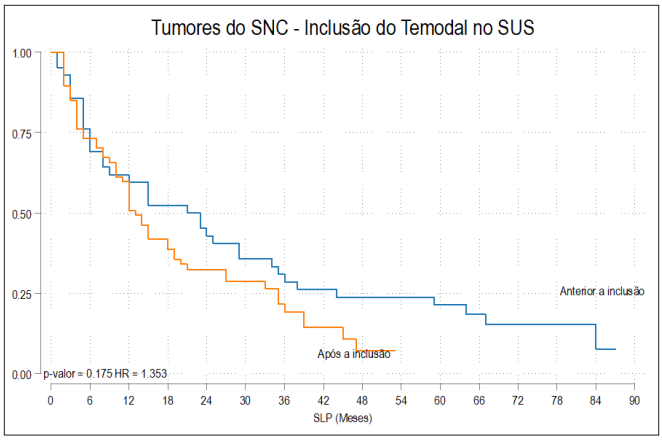

Figure 6: Progression-Free Survival Regarding the Inclusion of TMZ Before and After Jan/2020

Using the date of Jan/2020 as the beginning of TMZ, a total of 69 patients were diagnosed after this inclusion. The SLPm of these patients was 10 months, whereas that of the previous SLP was 14 months. This difference was not statistically significant (p = 0.175, HR not adjusted =1.353 [0.873;2.095]). There was no association between diagnoses of high-grade tumors and diagnoses after the date of Jan/2020 (Chi- square= 0.832; p =0.362).

Multivariate Analysis

Using the Cox proportional hazards regression model with robust standard deviation, it was observed that high-grade tumors, ECOG > 1, are risk factors for disease progression with adjusted HR=5. 953 (p-value= 0.000[2.219 ;15.970;]) and 1.999 (p-value=0.042 [1.025;3.897;]). On the other hand, mutated HDI and the use of TMZ were protective factors for disease progression, with adjusted HR of 0.438 (p =0.005 [0.247;0.777;]) and 0.408 (p =0.002 [0.229;0.728]), respectively. (attachment 1)

Global Survival

Overall SG

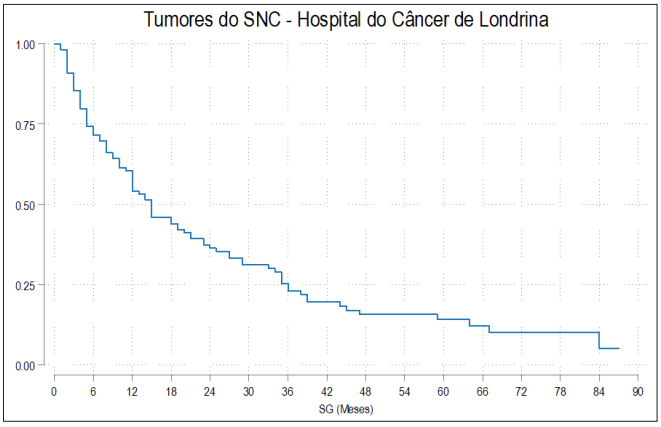

Figure 7: Overall Survival

When considering the entire database (N= 109), we have a 15-month SGm. One patient missed follow-up after the initiation of radiotherapy.

High Grade/Low Grade Tumors

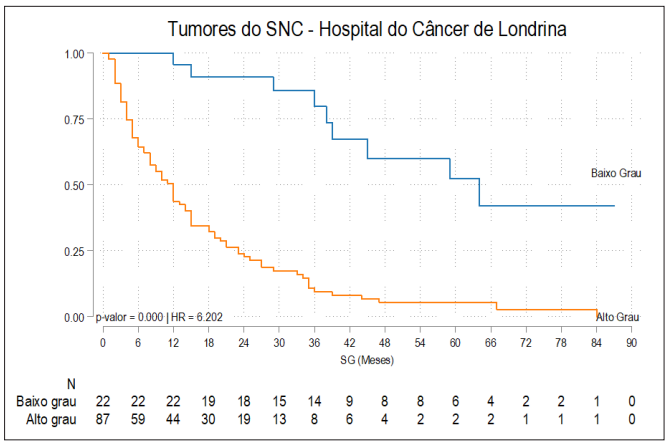

Figure 8: Overall Survival in Low Degree and High Degree

The SG for high-grade tumors was 12 months, and that for low-grade tumors was 64 months. In addition, it can be observed that when performing the equity test of Kaplan-Meyer curves through the logrank test, the curves were statistically different (p= 0.000 | HR not adjusted = 6.202 [3.061;12.566]).

GBM

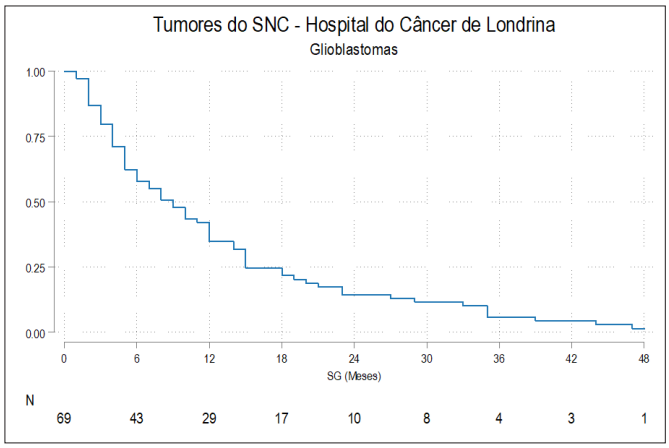

Figure 9: Overall Survival in GBM

SGm of GBM was 9 months.

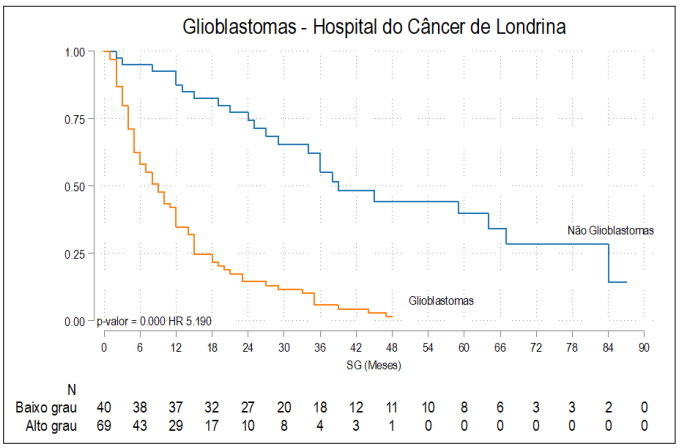

Figure 10: Overall Survival in GBM x non-GBM

Comparing GBM and non-GBM tumors, the first presented an SGm of 9 months, whereas non-GBM presented an SLPm of 39 months. Both curves were compared using the logrank test which showed a statistically significant difference (p = 0.000 | HR not adjusted = 5.190 [3.063;8.795]).

Temozolomide

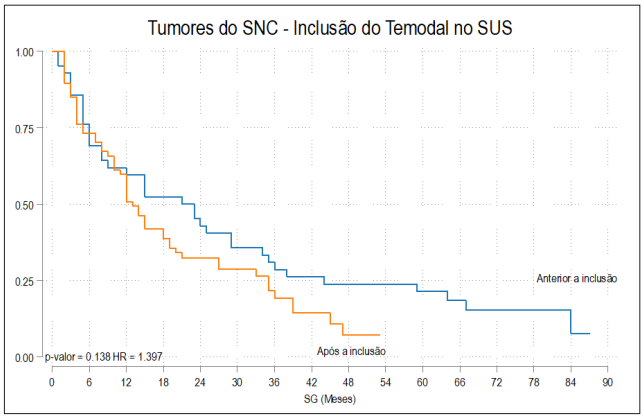

Figure 11: Overall Survival Regarding the Inclusion of TMZ Before and After Jan/2020

Using the date of Jan/2020 as the beginning of TMZ, we identified 67 patients who were diagnosed after this inclusion. The SGm of these patients was 13 months, whereas in the previous SGm, the inclusion was 21 months. This difference was not statistically significant (p = 0.138, HR not adjusted =1.397 [0.897;2.176]).

Multivariate Analysis

Through the Cox proportional hazards regression model, using robust standard deviation, it was observed that High-Grade Tumors, ECOG > 1, and Ki67% were risk factors for disease progression with adjusted HR of 14.393 (p-value = 0.000 [5.857;35.367]), 4.590 (p-value = 0.003 [1.702;12.372]), and 1.400 (p-value = 0.007 [1.097;1.786]), respectively. On the other hand, radiotherapy and the use of TMZ were protective factors for disease progression with adjusted HR=0.295 (p-value=0.000 [0.154;0.563;]) and 0.300 (p-value=0.000 [0.165;0.546]). (attachment 2)

Discussion

In our work, we had an n of 110 patients. One patient soon after starting adjuvant radiotherapy missed the follow-up. In the present study, the most common malignant CNS neoplasm was GBM (66 patients, 60% of the sample). The male sex had the highest incidence (73 patients [66.4%]), and the most affected age group was middle age – 40-64 years (57.3%). Of all our patients, only one had a family member affected by a CNS tumor. Most patients had an ECOG performance status of 1 (39.1%). Considering the number of cases per year, counting the years from 2017 to 2023, one of the years with the lowest incidence/diagnosis was 2021, with only 11 patients, corresponding to 11% of the sample. This might have occurred because of the pandemic COVID19, where the cases were more repressed and there was a delay for these patients to arrive at our service and perform an appropriate onco-specific treatment involving surgery, radiotherapy, and chemotherapy. The year 2023 represented an incidence of only 9 patients (8.1%), which is considered low, but with the justification of our study, we collected the data until July 2023. According to The Central Brain Tumor Registry of the United States (CBTRUS), from 2017 to 2021, the average annual age-adjusted incidence rate (AAIR) of all malignant and non-malignant primary brain tumors and other CNS tumors was 25.34 per 100,000 inhabitants (malignant AAIR = 6.89 and non-malignant AAIR = 18.46). The most common brain malignant histopathology and other CNS tumors were glioblastomas (13.9% of all tumors and 51.5% of all malignant tumors). Glioblastomas are more common in men than in women. Between 2017 and 20216, 87,053 deaths were attributed to malignant brain and other CNS tumors between 2017 and 2021 [6]. Thus, our findings are very similar to the CBTRUS data. In addition, there is a sample difference, since the study of CBTRUS involved all benign and malignant neoplasms, and the present study evaluated only low-grade gliomas (astrocytomas G2 and oligodendrogliomas G2) and high-grade gliomas (astrocytomas G3 and G4 and oligodendrogliomas G3 beyond GBM). The general profile of patients in this study with CNS tumors in which the majority were male and in middle-aged 40-64 years old men was consistent with that reported by the Global Burden of Disease Study 2016, which collected demographic data, among others, as well as from different countries between 1990 and 2016. In 2016, there were 330,000 cases of malignant CNS neoplasms (not only gliomas) and 227,000 deaths globally, and the age-standardized incidence rates of malignant CNS neoplasms increased globally by 17.3% between 1990 and 2016 (standardized incidence rate per age of 2016 4.63 per 100,000 people-year. East Asia had the highest incidence of malignant CNS neoplasms for both sexes in 2016 (108,000 patients), followed by Western Europe (49,000) and South Asia (31,000). The three countries with the highest number of incident cases were China, the USA and India [7]. In Brazil, according to INCA (2023), the most affected sex among CNS tumors is also male. The estimated number of new cases of CNS cancer in Brazil, each year of the triennium from 2023 to 2025, is 11,490 cases, with 6,110 cases in men and 5,380 cases in women. These values correspond to an estimated risk of 5.80 new cases per 100 men and 4.85 per 100 women. Without considering non-melanoma skin tumors, CNS cancer occupies the 11st position among the most frequent types of cancer, with higher incidence rates observed in the southern region for men and women. In terms of mortality in Brazil, in 2020, there were 9,355 deaths due to CNS cancer (4.42 per 100 thousand). Among men, 4,787 deaths (4.62 per 100 thousand), and among women, 4,567 (4.22 per 100 thousand) [8]. In an Australian study in 2017, 2,076 new cases of brain cancer and other CNS cancers were diagnosed, and 1,477 people died of the disease. Although brain cancer and other CNS cancers are the 17th most commonly diagnosed cancers and represent 1.5% of all diagnosed cancers, they are also more common in males and middle-aged patients [9]. In a previous Texan epidemiological study (1976-2013) in the USA (more than 600 patients), most were GBM NOS (not specified elsewhere) and a small portion was classified as classical GBM. The incidence was higher in males (53%), and the majority were 50 years or older, similar to our study [10].

In our study, we divided low-grade gliomas, high-grade gliomas, and GBM in isolation, for a total of 110 patients. In low-grade gliomas, there were four patients (19%) with wild IDH. This may have occurred because of discrepancies prior to 2021 in the molecular classification (before WHO 2021). As in the GBM group, we had 4 patients (6.1%) with mutated IDH, which may have occurred due to molecular classification discrepancies prior to 2021. As it is already known, GBM, by definition are represented by wild IDH, as well as non-GBM CNS tumors such as astrocytomas and oligodendrogliomas are represented with mutated IDH. The discovery of specific mutations in IDH1 and IDH2 genes by large-scale next-generation sequencing (NGS) in glioblastomas, and soon afterwards in low-grade diffuse gliomas, has been an important driver of the classification of diffuse gliomas on a molecular basis. IDH1/IDH2 mutations were found at low or no frequency in glioblastomas but at much higher frequencies in diffuse astrocytomas and oligodendrogliomas [11, 12]. IDH mutations are considered the initial event in oncogenesis of mutant gliomas of IDH [13]. Mutant IDH protein is a tumor-specific immunogenic neoantigen/epitope that may represent a promising therapeutic target, especially the IDH1 R132H mutation, which is responsible for approximately 90% of IDH mutations in gliomas [14]. A study by Zongchao Mo (2022) suggests that in the East Asian population, compared with the white population, there are racial differences in terms of epidemiology and genomic characteristics [15]. A lower incidence of diffuse glioma was observed in East Asian patients than in Caucasians, and patients with GBM had a younger age of onset and a longer SG to whites. In our study, it was not possible to stratify patients by ethnicity due to the lack of data in medical records. In a previous review (2020), the authors reported that astrocytomas with mutations in IDH1/2 demonstrated significantly longer SLP and SG in a grade-by-grade comparison with wild-type HDI equivalents. They can produce an alternative elongation of telomeres phenotype in conjunction with ATRX and TP53 characteristic mutations, which are found significantly more frequently in mutant cases of IDH. Wild-type IDH gliomas with certain molecular characteristics (EGFR amplification, chromosome with 7+/10−, and/or mutation

of the TERT) promoter present particularly aggressive behavior and are therefore currently considered a molecular equivalent of grade 4 compatible with GBM [16]. In our study, in the case of low-grade gliomas (astrocytoma G2 and oligodendroglioma G2), the predominant ki 67 was < 10% (76.2%), the majority was preserved ATRX (47.6%), and the majority had mutated TP53 (57%). In GBM, the predominance of ki 67 was between 10-30% (36.4%), the majority were ATRX preserved (74.2%), and the majority had TP53 not mutated (51.5%). The NGS analysis, as reported above, was not performed due to the cost and not existing in the scope of public health in Brazil.

Considering GBM, which had the highest incidence, we had a median SLP of 5 months and a median SG of 9 months. Furthermore, it should be considered that in the public health field in Brazil, we do not have access to TMZ concomitantly with RT (radiotherapy). There are still public oncological centers in Brazil where TMZ is not yet available. At our center (HCL), TMZ was only available from January/2020 (chart in the "results" section). Before that date, we had to litigate the TMZ medication, which sometimes took time to arrive and, in fact, the patient began to use it or sometimes the patient did not have access. In the chart shown in the "results" we had no statistical difference in SGm and SLPm before and after January/2020, very likely due to our n (small), and the discrepancies in the arrival of TMZ to the patient in fact (could have reached the medication in a month for example, as well as could not even have the medication arrived and the patient died more quickly).

For example, a study by Stupp et al. (2005) had a follow-up of 28 months, 14.6-month SGm (RT + TMZ) x 12.1 months with isolated RT. SLPm was 6.9 months (RT + TMZ) × 5 months, with isolated RT [17]. The overall survival and progression-free data were very similar to those of our study, indicating that it is a very aggressive neoplasm with low survival. However, one question remains: How important is it to carry out TMZ in conjunction with RT? Would we not add more adverse effects to patients in this first phase of treatment at the expense of very little gain in survival? In this scenario, we did not conduct randomized GBM studies. In this same line of reasoning as the CATNON study, a 2 × 2 multifactorial designs, only in astrocytomas G3 (1p19q not co-deleted), seems to have no benefit of TMZ in conjunction with RT, and here the total adjuvant was for 12 months [18]. In our study, we have no charts in this scenario because only seven patients (8%) had high-grade gliomas. But what surprised even in terms of global survival (with numbers never before achieved) in GBM was the study of Stupp et al (2017), placing TTFields to maintenance chemotherapy with TMZ, which statistically improved overall survival, with the highest level of survival of 20.9 months in the TTFields group – TMZ x 16 months in the isolated TMZ group [19].

Low-grade gliomas are grade 2 WHO tumors that mainly affect adult patients, and include diffuse astrocytomas and oligodendrogliomas. New diagnostic criteria based on histology and molecular characterization with IDH mutation status and 1p/19q co-deletion status provided additional categorization of these tumors and additional insights into prognosis and response to treatment [20]. In a previous Swiss study, Ohgaki H reported that the SGm in this type of diffuse glioma (WHO G2), was 5.6 years. In oligodendrogliomas (WHO G2), the SGm was 11.6 years. In astrocytomas, the most common mutation was TP53 [21]. An important previous study in 2012 (RTOG 9802) on low-grade gliomas concluded that SLPm was positive, and the SGm (after 2 years in who was alive) was also positive one as well. This study compared RT + PCV (procarbazine, lomustine, vincristine) × RT alone in a low-grade glioma scenario [22]. In Brazil, it has been difficult to access the drugs lomustine and procarbazine for a few years. For this reason, in some scenarios, we do not use the PCV scheme but rather TMZ. A previous study, a little newer by Buckner JC, et al (2016), in low-grade gliomas (astrocytomas and oligodendrogliomas G2), in patients who received PCV + RT had an SGm of 13.3 years x RT isolated, which had a 7.8-year SGm [23]. The data were positive, and chemotherapy actually made a difference in this scenario, which had a better prognosis. In our study, we did not have such a robust n for low-grade gliomas (only 21 patients, corresponding to 19.1% of the sample). Fifteen patients (71.4%) had mutated IDH and four patients had wild-type IDH. This may have occurred because of discrepancies in the molecular analysis prior to 2021 (WHO 2021). As for TP53, most had this mutation (57%). Most of the patients underwent partial resection (85.7%). In low-grade gliomas, we observed a 58-month SLPm and 64-month SGm. These results were different from the literature for reasons that may involve the follow-up time, n, which was low in this type of glioma (n= 21 patients), and incomplete data in medical records.

Our study had some limitations. The retrospective observational model is prone to information bias, which can be somewhat limited regarding the demographic data collected. Because it was retrospective with data collection from medical records, some risk factors could not be fully evaluated, such as smoking, alcohol consumption, disease volume, location, clinical signs to diagnosis, and medications in use, among others. Another limitation is that the medical records were incomplete, harming the collection, in addition to being performed in a single center. However, we had a considerable n, even more, with the pandemic year of 2021, a low number was obtained in incidence (and in data collection). A greater number of studies are necessary in this epidemiological field/molecular profile, which is scarce for malignant neoplasms of the CNS.

Conclusion

In this study, we observed the predominance of the histological subtype GBM and the prevalence of male sex, middle age (40-64 years), and wild IDH. Most of the data corroborate those reported in the literature. In this context, knowledge of the epidemiological profile of patients with CNS tumors may be useful in the implementation of public policies, with associated risk factors, preventive methods, and targeted treatment, since GBM is the most common malignant neoplasm of the CNS in patients and a more aggressive subtype with a worse prognosis.

Ethical Compliance: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of Interest Declaration: The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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