Analysis of the Epidemiological Profile of Glioblastomas in Brazil Between 2012 and 2021: evidence and challenges for public health

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ABSTRACT

Introduction: Glioblastoma is the most common primary malignant tumor of the central nervous system. Furthermore, this tumor has a high morbidity and mortality rate. It is therefore necessary to understand the population that is most affected by this pathology.

Objective: To analyze the epidemiological profile of hospital admissions for glioblastoma in Brazil between 2012 and 2021.

Methods: A retrospective cross-sectional study with a quantitative approach, with data collected from the Hospital Cancer Registry System (SisRHC) database.

Results: 13,764 cases of hospitalization for glioblastoma were found, of which 7,927 were male and 5,756 were female. The approximate prevalence was 6.04 per 100,000 inhabitants. However, the geographical distribution was heterogeneous between the Brazilian Federative Units (FU). Approximately 73.9% of patients with this pathology were over 50 years old.

Conclusion: Brazil has a prevalence similar to that found in other countries. Furthermore, the distribution among the UFs was mainly due to restricted access to neurology and neurosurgery services. Thus, a predominance of male cases was observed to the detriment of female cases. The incidence of glioblastomas increases after the age of 50, with a peak between 55 and 65. In addition, it was found that there is a higher prevalence among white people when compared to other ethnic groups. In terms of pathology, the frontal, parietal and temporal lobes were the most frequent primary locations. As for treatment, the most widely used approach in the country is radiotherapy in monotherapy and the most common outcome was death.

Keywords: Epidemiology; Glioblastoma; Glioma; Neurosurgery; Oncology
INTRODUCTION

Glioblastomas are the most common type of malignant primary brain tumor and are responsible for the majority of deaths among patients with primary brain tumors. Glioblastomas are believed to arise from neuroglial stem or progenitor cells and are characterized by molecular heterogeneity1,2. According to the new World Health Organization (WHO) classification of tumors of the central nervous system, published in 2021, glioblastoma is classified as grade 4, with highly malignant characteristics3. Due to this characteristic, glioblastomas lead patients to death in relatively short periods after diagnosis, especially in the absence of effective therapy4.

The overall age-adjusted incidence of glioblastoma in the United States is 3.22/100,000 people, with a higher incidence in patients who are older at the time of diagnosis and in male patients1. The incidence varies around the world, with recent data showing no trend towards an increase in incidence in the USA or Canada, although data from England pointed to an increase in this country1,3,5. It has also been observed that the incidence of glioblastoma increases after the age of 40 and peaks in adults aged between 75 and 842.

Furthermore, most patients with glioblastoma do not have a family history of brain tumors or cancer predisposition syndromes1,6. As far as the clinical picture is concerned, these tumors have typical features that reflect rapid cell expansion and infiltrative destruction of brain structures1. Thus, the main symptoms observed are epilepsy, focal neurological signs related to the location of the tumor, changes in mental state and progressive headaches, the latter reported in approximately 50% of cases1,2,6. Diagnosis is based on imaging tests, preferably magnetic resonance imaging2. Glioblastomas normally show contrast enhancement on T1-weighted sequences. T2-weighted fluid-attenuated inversion recovery (T2/FLAIR) reveals hyperintense cerebral edema2. Central necrosis and signs of local mass effect may also be present6. However, the diagnosis of glioblastoma can only be confirmed from histological analysis of the tumor tissue1,4.

Currently, in Brazil, glioblastoma is treated according to the EORTC-NCIC (Stupp protocol) in which maximum safe resection is followed by simultaneous chemo-radiotherapy and six cycles of adjuvant chemotherapy with temozolomide (TMZ)7,8. However, elderly patients or those with poor performance status may benefit from hypofractionated protocols or even radiotherapy or temozolomide monotherapy7. Glioblastomas have a low metastasis frequency of 0.5%9.

Regarding the evolution of the cases, it can be seen that glioblastoma patients have the worst prognosis of primary tumors of the central nervous system1-3. In this sense, in standard treatment consisting of surgery, RT and chemotherapy with TMZ, the median overall survival (OS) in well-selected patients in clinical studies is approximately 15 to 18 months and 5-year survival is less than 10%1,2,10. In this context, the aim of this study was to identify and characterize the epidemiological profile of hospital admissions in Brazil for glioblastoma from January 2012 to December 2021, as well as to analyze the primary site of the tumours, the main therapeutic approaches offered and the outcomes observed.
METHODOLOGY

This is a retrospective cross-sectional ecological study with a quantitative approach, based on data collected in consultation with the National Cancer Institute (INCA), through the Hospital Cancer Registry System (SisRHC) database. The data was collected in September and October 2023, considering the period from January 2012 to December 2021, the last year available in the database. Data from the Brazilian Institute of Geography and Statistics (IBGE) was also used, referring to the size of populations by state in the middle of the period, 2017.

For the data collected in SisRHC, the cases of glioblastomas related to ICD10: C71- and histological type code M9440/3 registered in hospital systems in Brazil, divided by region and by federative unit (FU) were selected considering the data available for the period from January 2012 to December 2021. The parameters analyzed, compared according to the year of notification, were: tumor location, age group, race/color, gender and case evolution, including deaths related to the diagnosis. Once collected, this data was tabulated in a spreadsheet and used for statistical analysis and construction of graphs in the Microsoft Excel 2017 software.

This study is in line with the Guidelines and Regulatory Norms for Research involving Human Beings, respecting the ethical principles established by Resolution 466/12 of the National Health Council (CNS). Furthermore, since secondary data from anonymized public databases was used, this study is exempt from submission to Research Ethics Committees (RECs).

RESULTS AND DISCUSSION

In the period evaluated, between 2012 and 2021, 13,764 notifications of glioblastoma hospital records were found. As shown in Graph 1, notifications showed continuous growth between 2012 and 2016 – with an average increase of 5.05% per year –, a plateau in the number of notifications between 2016 and 2017, a decrease in 2018 (-4.16%) and a slight increase in 2019 (1.47%). From 2020 onwards, there was a non-linear decrease in the number of notifications. Thus, in 2020 there was a slight drop (-2.9%), followed by a sharp drop in 2021, with -52.37% in the number of records. This evident decrease can be attributed to the decrease in notifications from 2020 onwards due to the COVID-19 pandemic, a period in which there was a general decrease in the number of notifications of all health problems, due to the weakening of health systems.

Furthermore, there was a continuous average increase in cases in both male and female sexes. Males were more affected than females, with an average ratio over the period of 1.37:1, with a total of 7,927 notifications for men (57.93%) and 5,756 notifications for women.

Graph 1. Total of cases and distribution by gender over the period 2012-2021.
for women (42.07%). In a recent article, Carrano et al. pointed out different reasons that may be related to the higher incidence observed in men, among them the stimulating effect of the growth of glioblastomas by the androgen receptor through testosterone, as well as the protective role of estrogen in women with higher levels of this hormone. In addition, dimorphic genetic and molecular differences could also contribute to differences in incidence and outcome.

In this context, when analyzing the total number of cases according to age, shown in Graph 1, it can be seen that the main age groups affected are: 55 to 59 years (2,218 or 16.2%), 60 to 64 years (2,175 or 15.8%) and 65 to 69 years (1,774 or 12.9%). It can also be seen that 73.9% of cases are in patients over 50 years of age. These data suggest that glioblastomas affect Brazilians earlier than North Americans, since in the US the most affected age group is 75 to 84 years old.

More than 90% of notifications (12,511) recorded the location of the case. When analyzing the geographical distribution of these cases across Brazil, it can be seen that the prevalence of cases was heterogeneous between the Federative Units (FU) of Brazil, considering the Brazilian population according to IBGE during 2017. The prevalence per 100,000 inhabitants of each FU was in the following descending order: Santa Catarina with 15.69; Minas Gerais with 11.05; Rio Grande do Sul with 10.51; Paraná with 8.00; São Paulo with 6.70; Distrito Federal with 6.23; Espírito Santo with 6.19; Ceará with 5.72; Mato Grosso with 5.44; Rondônia with 5.40; Sergipe with 4.56; Tocantins with 4.55; Mato Grosso with 4.53; Rio Grande do Norte with 4.14; Piauí with 3.93; Pernambuco with 3.86; Alagoas with 3.80; Maranhão with 3.71; Paraíba with 3.39; Bahia with 2.85; Rio de Janeiro with 2.82; Acre with 2.8; Amazonas with 1.84; Goiás with 1.58; Pará with 1.51; Roraima with 1.27; and Amapá with 1.10. This heterogeneous distribution between the states, also shown in Figure 1, can be explained by the unequal structuring of care for neurosurgery and neurology services, so that the places with the highest incidence are exactly those with the greatest availability of these diagnostic services compared to the states with the lowest prevalence values.

When analyzing the absolute numbers of cases in each state, we can see the following descending order: São Paulo (SP) registered 3,027 cases or 24.2% of the total; Minas Gerais...
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Figure 1. Distribution of cases from 2012 to 2021 in the different states of Brazil, adjusted per 100,000 inhabitants, considering the 2017 population. Model inspired by the hexagonal cartogram of Barreto et al.15.

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(MG) registered 2,311 or 18.5% of the total; Rio Grande do Sul (RS) registered 1,186 or 9.5% of the total; Santa Catarina (SC) registered 1,096 cases or 8.76% of the total; Paraná (PR) registered 902 cases or 7.21% of the total; Ceará (CE) registered 516 cases or 4.12% of the total; Rio de Janeiro (RJ) registered 481 cases or 3.84% of the total; Pernambuco (PE) registered 365 cases or 2.92% of the total; Maranhão (MA) recorded 360 cases or 2.92% of the total; Bahia (BA) registered 421 cases or 3.37% of the total; Mato Grosso do Sul (MS) recorded 148 cases or 1.18% of the total; Rio Grande do Norte (RN) recorded 143 cases or 1.14% of the total; Mato Grosso (MT) recorded 154 cases or 1.23% of the total; Acre (AC) recorded 24 cases or 0.19% of the total; Amapá (AP) recorded 9 cases or 0.07% of the total; and Roraima (RR) recorded 7 cases or 0.06% of the total.

Regarding to race/color, there is considerable incompleteness in the data, with only 65.9% of notifications showing race/color discrimination, which is shown in Graph 3. As a result, it can be seen that there is a greater predominance of white people (5,131 or 56.8%), followed by brown people (3,464 or 38.4%), then, with a large difference in relation to the other ethnic groups, black people (312 or 3.4%), yellow people (94 or 1.0%) and indigenous people (19 or 0.2%). It can therefore be concluded that there was a 1.31:1 ratio of white people affected compared to the other groups. This distribution, according to race/color, follows studies carried out in the United States which indicated that white people are more affected by glioblastomas4,10. However, it is worth noting that racial diversity is an intrinsic characteristic of Brazil and, for this reason, national data may differ from that collected in other countries. Furthermore, as most of the notifications were

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With regard to the primary location of glioblastomas, only 38% of cases (5,262) were discriminated. The predominant location of the tumors was as follows: Frontal Lobe (1,507 or 34.0%); Temporal Lobe (1,292 or 28.5%); Parietal Lobe (996 or 22.4%); Occipital Lobe (270 or 5.3%); Cerebellum (231 or 5.3%); Brainstem (91 or 2.1%); and other locations, including sites such as the Ventricles, Spinal Cord and Cauda Equina (117 or 2.8%). This information is shown in Figure 2. Other findings in the literature corroborate the results found, which indicate that the most affected locations are the Frontal Lobe, Temporal Lobe and Parietal Lobe.\textsuperscript{2,10,16}

Regarding to the therapeutic approach used, only 37.0% of the notifications reported the treatments instituted. Of these, radiotherapy (1,394 or 27.3%), surgery (1,073 or 21%) and chemotherapy associated with radiotherapy (881 or 17.27%) were the main therapeutic approaches chosen. This was followed by surgery associated with radiotherapy (470 or 9.6%), surgery associated with chemotherapy and radiotherapy (398 or 8.2%), chemotherapy (323 or 6.6%), surgery associated with chemotherapy (120 or 2.4%) and other therapeutic approaches (203 or 4.1%).

Graph 3. Distribution of absolute cases according to self-declared race/color.

Figure 2. Primary locations of glioblastoma-type tumors in the central nervous system according to the percentage in each location.
The individual analysis of each treatment shows: radiotherapy in monotherapy with 30.4% of stable disease, 30.6% of deaths, 17.5% of disease in progression, 8.8% without evidence of disease/complete remission, 7.3% of partial remission and 5.3% out of therapeutic possibility; surgery in monotherapy with 40.2% of deaths, 19.6% of stable disease, 12.3% of disease in progression, 11.6% of partial remission, 9.2% out of therapeutic possibility and 7.1% without therapeutic evidence/complete remission; chemotherapy and radiotherapy with 26.3% of disease in progression, 25.4% of deaths, 25.2% of stable disease, 12.6% out of therapeutic possibility, 5.4% of partial remission and 5% without evidence of disease/complete remission; surgery and radiotherapy with 30.8% of stable disease, 30.6% of deaths, 15.5% of disease in progression, 8.7% without evidence of disease/complete remission, 8.1% of partial remission and 6.2% out of therapeutic possibility; surgery, chemotherapy and radiotherapy with 24.9% stable disease, 23.4% progressing disease, 21.9% deaths, 12.3% partial remission, 10.3% out of therapeutic possibility and 7.3% no evidence of disease/complete remission; chemotherapy in monotherapy with 35.0% deaths, 24.1% progressing disease, 22.9% stable disease, 7.4% out of therapeutic possibility, 7.4% partial remission and 3.1% no evidence of disease/complete remission; surgery and chemotherapy with 30.8% stable disease, 20.8% deaths, 15.8% out of therapeutic possibility, 13.3% disease in progression, 12.5% partial remission and 6.7% no evidence of disease/complete remission; and others with 46.8% partial remission, 22.2% stable disease, 21.7% deaths, 14.3% disease in progression, 6.9% out of therapeutic possibility and 3.9% no evidence of disease/complete remission. The statistics on the use of these approaches are shown in Graph 4.

In comparison, monotherapy radiotherapy (8.8%) and surgery associated with radiotherapy (8.7%) had the best outcomes in terms of complete remission of the disease. As for partial remission and disease stability, the best therapeutic approaches were surgery combined with chemotherapy (12.5%) and surgery combined with radiotherapy (30.8%), respectively. With regard to the number of deaths, surgery in monotherapy (40.2%) achieved more significant results than the other therapeutic approaches, followed by chemotherapy in monotherapy (35.0%), surgery associated with radiotherapy (30.6%) and radiotherapy in monotherapy (30.6%).

Of the 13,764 notifications found, almost half (6,637) had no information on the final stage of the disease, while 16% (2,250) were recorded as “not applicable”. In this sense, only 35% (4,877) had detailed outcomes in the notification records, as shown in Graph 5, of which 1,566 were deaths (31.1%), 1,256 stable disease (25.8%), 897 disease in progression (18.4%), 412 out of therapeutic possibility (8.4%), 409 partial remission (8.4%) and 337 without evidence of disease/complete remission (6.9%). It is known that the most frequent outcome for glioblastoma is death or recurrence, which are inevitable, with a mean progression-free survival of approximately 7 months\(^2,4,17\).
CONCLUSIONS

Over the years, there has been an increase in notifications of glioblastoma cases in Brazil. However, due to the COVID-19 pandemic, as of 2020, the number of notifications has decreased, even though it is expected that the population prevalence has not been impacted by the pandemic.

Thus, this study suggests that the population groups most affected by this type of tumor were: males; people aged between 50 and 69; and self-declared white people, to the detriment of other ethnic groups. Furthermore, the unequal distribution of high-complexity neurosurgery and neurology services shows a heterogeneous prevalence among the Brazilian states. Regarding the primary location of glioblastomas, it can be seen that the Frontal Lobe, Parietal Lobe and Temporal Lobe are the most affected regions. As for treatment, in Brazil, the most widely practiced treatment is monotherapy radiotherapy. In this sense, monotherapy radiotherapy and surgery associated with radiotherapy were the approaches with the best outcomes: complete remission/no evidence of disease, partial remission and stable disease. However, considering that the most frequent outcome at the end of the observed notifications was death, it is recommended not only to carry out new, more detailed studies, but also to build public policies aimed at new research in the area, in order to expand knowledge about the pathology and treatment of glioblastomas.

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