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Brazilian pediatric patients with gliomas: treatment characteristics and survival outcomes

Maria Thereza Mansur Starling[1], Allan Andresson Lima Pereira[2], Gustavo Viani Arruda[3, 4], Wellingson Silva Paiva[5], Iuri Santana Neville[5, 6], Felipe Cicci Farinha Restin[1], André Guimarães Gouveia[7, 4], Cecília Félix Penido Mendes de Sousa[1], Marcos Vinícius Calfat Maldaun[8], Felix Hendrik Pahl[8, 9], Samir Abdallah Hanna[1], Fabio Ynoe de Moraes[10, 4], Gustavo Nader Marta[1, 4, 11]

[1]Department of Radiation Oncology, Hospital Sírio-Libanês, São Paulo, Brazil
[2]Department of Clinical Oncology, Hospital Sírio-Libanês, Brasilia, Brazil
[3]Ribeirão Preto Medical School, Department of Medical Imaging, Hematology and Oncology of University of São Paulo (FMRP-USP), Ribeirão Preto, SP, Brazil
[4]Latin America Cooperative Oncology Group (LACOG), Porto Alegre, Brazil
[5]Division of Neurosurgery Department of Neurology Faculdade de Medicina da Universidade de São Paulo São Paulo, Brazil
[6]Instituto do Câncer do Estado de São Paulo, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
[7]Juravinski Cancer Centre, Department of Oncology, Division of Radiation Oncology, Hamilton, ON, Canada
[8]Neurosurgery Group, Hospital Sírio-Libanês, Brazil
[9]DFV Neuro, Brazil
[10]Department of Oncology, Queen's University, Kingston, ON, Canada
[11]Postgraduation program of Departamento de Radiologia e Oncologia, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, Brazil

ABSTRACT

Background: The current study aimed to determine the overall survival (OS) rates of patients diagnosed with pediatric gliomas in Brazil, accounting for the influence of age, treatment modalities, and tumor site, using a population-based national database.

Materials and methods: Patients diagnosed with pediatric gliomas of central nervous system (CNS) from 1999–2020 were identified from The Fundação Oncocentro de São Paulo public database. The Kaplan-Meier and the log-rank test were used for survival analysis.

Results: A total of 1296 patients were included. The most common histologic tumor types were glioblastomas (38.27%; n = 496), pilocytic astrocytoma (32.87%; n = 426), and astrocytoma grade II (20.76%; n = 269). A total of 379 (29.24%) had brainstem tumors. The mean follow-up was 135 months [95% confidence interval (CI) 128–142\. The 1-year, 3-year 5-year OS for pilocytic astrocytoma were 93.72%, 89.98%, and 88.97%; for grade II gliomas, 80.36%, 71.89%, and 68.60%; for grade III gliomas, 53.72%; 31.87%, and 28.33%; and for glioblastoma, 52.90%, 28.76%, 25.20%, respectively. Brainstem tumors had the worse OS compared to no brainstem tumors (p = 0.001). For high-grade glioma (grade III/IV), excluding brainstem tumors (n = 570), young patients had greater median OS (0 to 3 years:22 months; 4 to 18 years:13 months; p = 0.005). Regarding the treatment modalities, combined treatments were associated with higher median survival compared to less intensive therapy (surgery: 11 months; surgery and chemotherapy: 16 months; surgery, radiotherapy, and chemotherapy: 20 months; p = 0.005).

Address for correspondence: Gustavo Nader Marta, Department of Radiation Oncology, Hospital Sírio-Libanês, Brazil, Rua Dona Adma Jafet 91, Bela Vista – Sao Paulo, Brazil 01308050; e-mail: gustavonmarta@gmail.com

Conclusion: In our cohort, low-grade gliomas had favorable prognoses and outcomes. Patients diagnosed with glioblastomas and brainstem gliomas had the worst OS. For high-grade gliomas, undergoing treatment de-intensification in the Brazilian pediatric population is associated with worse survival.

Key words: pediatric brain neoplasia; treatment; prognosis; survival

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Introduction

Central nervous system (CNS) tumors are the most common solid tumors in the pediatric age group, being the second leading cause of cancer death in children 0–14 years of age [1–3]. It affects mainly children between three and seven years old. Symptoms depend on their location, with seizures, headaches, and focal neurologic deficits being the most common [1, 4].

Gliomas represent up to 50% of all pediatric CNS tumors. Pediatric low-grade glioma is the most frequent, occurring in around 30–45% of cases of CNS tumors in childhood and adolescence and its main representative is the pilocytic astrocytoma. High-grade gliomas account for around 8–12% of brain tumor cases [1,4]. Gliomas can be sub-classified by World Health Organization (WHO) grades into subependymal giant cell astrocytoma, pilocytic astrocytoma, and pilomyxoid astrocytoma (grade I); diffuse astrocytoma, and pleomorphic xanthoastrocytoma (grade II); anaplastic astrocytoma (grade III), and glioblastoma (grade IV) [5].

Understanding the epidemiology and outcomes for these patients is essential to define future research and help in clinical practice. There is scarce literature regarding treatment patterns and survival outcomes of patients with CNS gliomas in low- and middle-income countries. Therefore, this large retrospective cohort study has addressed the impact of children's age, grade, and treatment modalities on the survival of pediatric glioma patients in Brazil.

Materials and methods

The *Fundação Oncocentro de São Paulo* (FOSP — http://www.fosp.saude.sp.gov.br) was the data source for this study. It is the São Paulo (SP) state populational-based registry with detailed health and socioeconomic information of hospitals and oncology departments. The FOSP is a public institution that generates conditions for improving medical-assistance actions in oncology, constituting a support division of the Secretariat of Health of São Paulo to advise health policies on cancer. FOSP maintains a database of hospital and oncology departments in SP with detailed health and socioeconomic data and has an open-access epidemiology database for public consulting and research.

Pediatric patients (those aged < 18 years) with CNS gliomas treated between January 2000 and April 2020 were included. Patient information, including age, gender, medical practice (public or private insured), and treatment modalities (surgery, radiotherapy, and chemotherapy), was obtained from the FOSP database. Patients' ages were categorized into < 3 years and ≥ 3 years. Regarding the treatment modalities, patients were divided as follows: surgery alone; radiotherapy alone; chemotherapy alone; surgery plus radiotherapy; surgery plus chemotherapy; radiotherapy plus chemotherapy; surgery plus radiotherapy plus chemotherapy; other; no treatment. We also divided the patients according to tumor grade: grade I (pilocytic astrocytoma), grade II (astrocytoma grade II and oligodendroglioma grade II), grade III (astrocytoma grade III and oligodendroglioma grade III), and grade IV (glioblastoma).

The primary endpoint was overall survival (OS), defined from the date of diagnosis to death from any cause.

Statistical analysis

Categorical variables are described as percentages and frequencies. The Kaplan-Meier and the log-rank test were used for survival analysis. For all hypothesis tests, 5% of the significance level was considered. SPSS 23.0 (IBM, Armonk, NY) and RStudio (http://rstudio.com/; R version 3.6.0, https://www.r-project.org/, packages "surviv-

al" version 3.2–7 and "forest model" version 0.5.0) were used for statistical analyses.

Results

A total of 1296 patients were included in the analysis. Gender was balanced in the sample (49.1% male; 50.9% female). The median age was seven years (range 0–17), and 80% of patients were older than three. The most common histologic tumor types were glioblastomas (38.27%; n = 496), pilocytic astrocytoma (32.87%; n = 426), and astrocytoma grade II (20.76%; n = 269). Three hundred seventy-nine patients (29.24%) had brainstem tumors (Tab. 1).

Pilocytic astrocytoma had the highest OS when stratifying for grade and histology; glioblastomas had the lowest (Fig. 1). The 1-year, 3-year 5-year OS for pilocytic astrocytoma were 93.72%, 89.98%, and 88.97%; for grade II 80.36%, 71.89%, and 68.60%; for grade III 53.72%; 31.87%, and 28.33%; and for glioblastoma 52.90%, 28.76%, and 25.20%, respectively. Brainstem tumors had worse OS compared to non-brainstem tumors (p = 0.001). The median OS for brainstem tumors was 14 months [95% confidence interval (CI): 11.48–16.52). For non-brainstem tumors, the median OS was not reached (Fig. 2).

We performed an analysis of the high-grade glioma (grade III and IV), excluding brainstem tumors (n = 570). Young patients had longer median OS (0 to 3 years: 22 months; 4 to 18 years: 13 months — p = 0.005) — Supplementary File — Figure S1. Regarding the treatment modalities, combined treatments were associated with higher median survival compared to less intensive therapy (surgery: 11 months; surgery and chemotherapy: 16 months; surgery, radiotherapy, and chemotherapy: 20 months; p = 0.005) — Supplementary File — Figure S2.

The treatment modalities according to age, histology/grade, tumor site, and period are presented in Supplementary File — Table S1. Children younger than three years old were less likely to receive treatments that included radiotherapy, with only 24% of them receiving it, and were more likely to receive exclusive chemotherapy, which corresponds to about 30% of the database. Surgery alone was performed more in lower-grade tumors, such as pilocytic astrocytoma, astrocytoma grade II, and oligodendrogliomas grade II. Radiotherapy alone was done in 17.7% of glioblastomas. Only 14.1% of the glioblastoma patients underwent surgery with adjuvant radiotherapy and chemotherapy.

We found a significant difference in combined treatment approaches according to time period (p < 0.001). Radiotherapy alone was performed in less than 6% of the patients before 2014, but this increased to 15% between 2014 and 2020.

Table 1. Characteristics of included patients

Characteristic	Patients (n = 1296)	%
Age (years)		
< 3	261	20.14%
≥ 3	1035	79.86%
Gender		
Male	636	49.07%
Female	660	50.93%
Medical practice		
Public insured	557	42.98%
Private insured	102	7.87%
Missing	637	49.15%
Tumor type		
Pilocytic astrocytoma	426	32.87%
Astrocytoma grade II	269	20.76%
Astrocytoma grade III	65	5.02%
Oligodendroglioma II	31	2.39%
Oligodendroglioma III	9	0.69%
Glioblastoma	496	38.27%
Tumor site		
Brainstem	379	29.24%
No Brainstem	917	70.76%
Treatment type		
Surgery alone	471	36.34%
Radiation therapy alone	107	8.26%
Chemotherapy alone	80	6.17%
Surgery + radiation therapy	63	4.86%
Surgery + chemotherapy	133	10.26%
Radiation therapy + chemotherapy	182	14.04%
Surgery + radiation therapy + chemotherapy	138	10.65%
Other	71	5.48%
No treatment	51	3.94%
Period (years)		
2000–2007	424	32.72%
2007–2914	518	39.97%
2014–2020	354	27.31%

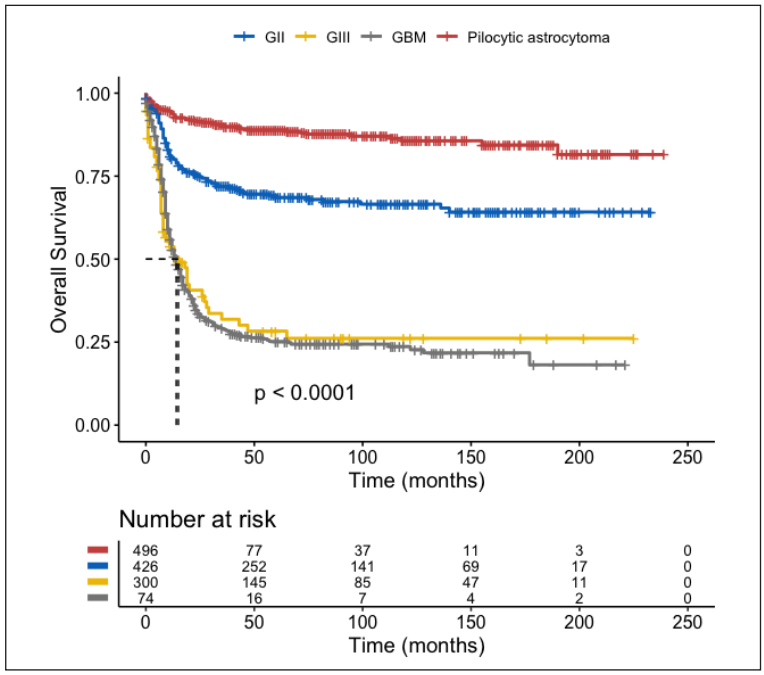
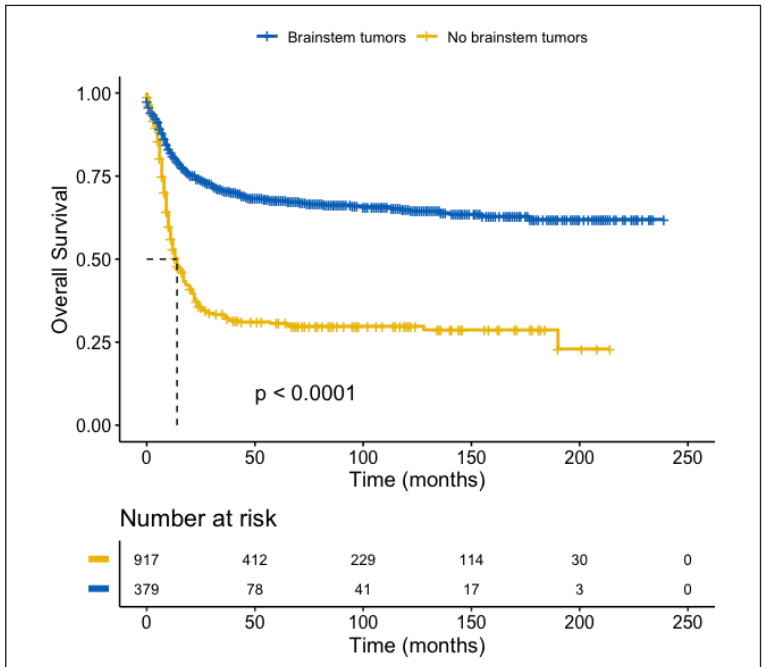


Figure 1. Overall survival according to tumor histology and grade. Grade II — astrocytoma grade II and oligodendroglioma grade II; grade III = astrocytoma grade III and oligodendroglioma grade III



	Overall survival rate		
	1-year	3-year	5-year
Brainstem tumors	53%	33%	31%
No brainstem tumors	81%	70%	68%

Figure 2. Overall survival according to tumor site: brainstem tumors versus no brainstem tumors

There was a significant difference in treatment combination according to localization ($p < 0.001$). Brainstem tumors were more likely to receive radiotherapy alone (17.2 *vs*. 4.6%) or radiotherapy with chemotherapy (33.8% *vs*. 5.9%) and were less likely to receive surgery as a treatment component.

Discussion

To our knowledge, the current study represents a unique attempt to report the treatment modalities and survival outcomes based on a large Brazilian cohort of pediatric patients with CNS tumor glioma diagnosed between January 1999 and April 2020. As expected and consistent with the literature, grade I gliomas had the highest OS, and glioblastomas/brainstem had the lowest OS [6–10].

Pediatric high-grade glioma (grade III and IV) is an aggressive entity, representing a health problem due to morbidity and mortality [4], and it may affect all ages and anatomic compartments. In the new WHO Classification of tumors of the CNS, the high-grade family comprises four types: diffuse midline glioma, H3 K 27-altered; diffuse hemispheric glioma, H3 G34-mutant; diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype; and infant-type hemispheric glioma [5]. Of note, it is essential to emphasize that while the terms "glioblastoma" and "anaplastic astrocytoma" are no longer used in the setting of pediatric-type neoplasm, our study used these terms because our cohort included patients classified before the last revision of WHO. Furthermore, pediatric brainstem gliomas can be divided into focal brainstem gliomas (20%) and diffuse intrinsic pontine gliomas (80%) which are highly malignant and fatal. Glioblastoma was our cohort's most common tumor type, followed by pilocytic astrocytoma, which differs from epidemiology data.

For high-grade gliomas, maximum safe surgical resection is the standard of care unless there are specific contraindications and adjuvant treatment is recommended for high-grade tumors [2, 11]. Various trials have been conducted on pediatric patients utilizing different chemotherapeutic agents. While the response rate of progressive disease in children is significantly less than that reported in adults, the trials failed to show any survival benefit [12]. Indeed, randomized trials have not been performed in the pediatric population. Most centers include temozolomide concomitant with radiotherapy and in the adjuvant setting, thus extrapolating from trials in adult patients with glioblastoma [2, 11, 13, 14]. Based on the data from CCG-945, the most important prognostic factors are tumor grade, age at diagnosis, and extent of resection [15].

Low-grade gliomas, WHO grade I and II, are usually treated with maximum safe surgical removal, which may be curative with total excision [4, 16]. Still, many authors suggest a conservative course for asymptomatic stable lesions with imaging characteristics suggestive of low-grade gliomas withholding treatment. The prognosis and outcomes are usually favorable, and 5-year OS is approximately 95% [4]. In areas with subtotal resection, adjuvant treatment with chemotherapy and radiotherapy can be discussed in a multidisciplinary tumor board, considering the individual risk factors based on available data from clinical trials, such as primary site outside the cerebellum, histology group other than pilocytic astrocytoma, WHO grade II, age of diagnosis ≤ 2 years old and degree of initial resection (biopsy or no resection) [17].

Children younger than three years old were less likely to receive treatments that included radiotherapy and were more likely to receive exclusive chemotherapy, as radiation is avoided in this population being deleterious in the younger population [7, 11, 18, 19]. As expected, exclusive surgery was performed more in lower-grade tumors in our study.

When analyzing the high-grade glioma cohort exclusively, according to our data, older age was an independent predictive factor of poorer survival; it is consistent with data where younger children have improved survival outcomes even when utilizing radiation-sparing treatment strategies [9, 18]. In an extensive database analysis of The United States Surveillance, Epidemiology and End Results (SEER) that included patients under 20 years of age with confirmed glioblastoma, subjects aged 0–4 years had decreased mortality, with a median survival 2–4 times longer than that of older peers and a significantly higher proportion of 2-year survival [8]. This differs from Sanders et al. who found a more significant hazard of death in children under five years of age in a study with smaller sample size [7]. Finley et al. also demonstrated that younger children have significantly shorter surviv-

al than older children with the same tumor types in the same compartment [10]. Our findings may be biased due to the small number of subjects in this study, and effect estimates could be more statistically precise. Also, the selection bias that could have occurred in this retrospective cohort is worth mentioning. Nevertheless, the literature is ambiguous; there is little data on this topic in the published literature. Moreover, there is still debate if age is a genuinely good prognostic factor or whether the survival differences in younger ages are simply due to the unique biological and molecular characteristics of high-grade pediatric glioma [6. 8, 11, 19, 20].

Our study found that only 14.1% of glioblastoma patients received surgery with adjuvant radiotherapy and chemotherapy. This low percentage may reflect the disparities of an upper-medium-income country such as Brazil, where geographic factors and healthcare heterogeneity jeopardize healthcare access [21, 22]. In the public setting, the lack of access to chemotherapy and radiotherapy can impact the quality of the oncological treatment [20, 23]. In the public setting, temozolomide was only incorporated in 2014, and new interventions and newer radiotherapy technologies, such as modulated treatments, are slowly being adopted. Furthermore, patients may experience treatment delays depending on the center, which hampers adjuvant therapy timing for many of them [24–26].

Apart from the inherent limitations of a retrospective database study, other considerations must be made. These limitations comprise restricted availability of patient data that might influence survival, such as the extent of the resection, the radiation type, volumes, field or dose, the chemotherapeutic agents used, and molecular tumor features. Moreover, the FOSP database reflects patients from the State of Sao Paulo only, making it impossible to generalize our findings to the whole population of Brazil. Nevertheless, this is probably of limited relevance, as São Paulo is the most populous Brazilian state with a representative Brazilian population. We also could not access the molecular information and type of chemotherapy and radiotherapy fractionation of these pediatric patients. Despite these considerations, our data can be useful for guiding the government to incorporate new technologies and interventions in the public setting to mitigate the effects on the survival of oncological patients.

Conclusion

In our cohort, low-grade gliomas had favorable prognoses and outcomes. Patients diagnosed with glioblastomas and brainstem gliomas had the worst OS. For high-grade gliomas, undergoing treatment de-intensification in the Brazilian pediatric population is associated with worse survival.

Conflict of interests

The authors have no relevant financial or non-financial interests to disclose.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by M.T.M.S., A.A.L.P. and G.N.M. The first draft of the manuscript was written by M.T.M.S. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Hospital Sírio-Libanês — Brazil (CAAE 45978821.5.0000.5461).

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