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CLINICAL ARTICLE

# High-grade gliomas in children and adolescents: is there a role for reoperation?

**Marcos Devanir Silva da Costa, MD, PhD,[1,2] Nicole Cavalari Camargo, BSc,[1] Patricia Alessandra Dastoli, MD, PhD,[1,2] Jardel Mendonça Nicácio, MD,[1,2] Frederico Adolfo Benevides Silva, MD,[3] Maria Luisa Sucharski Figueiredo, MD,[4] Michael Jenwei Chen, MD,[4] Andrea Maria Cappellano, MD, PhD,[5] Nasjla Saba da Silva, MD,[5] and Sergio Cavalheiro, MD, PhD[1,2]**

[1]Department of Neurology and Neurosurgery, Universidade Federal de São Paulo; and Divisions of [2]Neurosurgery, [3]Radiology, [4]Radiotherapy, and [5]Neuro-Oncology, Instituto de Oncologia Pediátrica, São Paulo—SP, Brazil

**OBJECTIVE** Tumors of the CNS are the main causes of childhood cancer and have an incidence that exceeds that of leukemia. In addition, they are the leading causes of cancer-related death in childhood. High-grade gliomas account for 11% of such neoplasms and are characterized by aggressive clinical behavior and high morbidity and mortality. There is a lack of studies focusing on the factors that can prolong survival in these patients or guide therapeutic interventions. The authors aimed to investigate the factors related to longer survival durations, with a focus on reoperation for gross-total resection (GTR).

**METHODS** In this retrospective cohort study, the authors analyzed 78 patients diagnosed with high-grade gliomas occurring across all CNS locations except diffuse intrinsic pontine gliomas. Patients 0 to < 19 years of age were followed up at the Pediatric Oncology Institute. Overall survival (OS) and progression-free survival (PFS) were analyzed in the context of various prognostic factors, such as age, sex, histology, extent of tumor resection, reoperation for GTR, adjuvant treatment, and treatment initiation from 2010 onward.

**RESULTS** With a mean age at diagnosis of 8.7 years, 50% of the patients were female and approximately 39% underwent GTR at some point, which was already achieved in approximately 46% of them in the first surgery. The median OS was 17 months, and PFS was 10 months. In terms of median OS, the authors found no significant difference between those with reoperation for GTR and patients without GTR during treatment. Significant differences were observed in the OS in terms of the extent of resection in the first surgery, age, sex, Ki-67 expression, adjuvant treatment, and treatment initiation from 2010 onward. Furthermore, the PFS values significantly differed between those with GTR in the first surgery and Ki-67 expression ≥ 50%.

**CONCLUSIONS** This study demonstrates the importance of GTR for these neoplasms, highlights the role of surgeons in its achievement in the first attempt, and questions the role of reoperation for this purpose. Finally, this study further supports the use of combined adjuvant treatment for the improvement of OS and PFS.

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**KEYWORDS** high-grade glioma; glioblastoma; anaplastic astrocytoma; pediatric neurosurgery; oncology

Tumors of the CNS are the main cause of childhood cancer, the incidence of which exceeds that of leukemia.[1,2] Approximately 5.74 individuals younger than 14 years of age per 100,000 inhabitants are diagnosed with CNS tumors, accounting for approximately 1 in every 2000 individuals in this age group.[2] In addition to their high incidence in the pediatric population, these tumors are also the main cause of cancer-related death in childhood.[1,2] High-grade gliomas account for approximately 11% of all such neoplasms.[1]

According to the WHO, high-grade gliomas are malignant tumors, categorized into grades III and IV, that include glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, and anaplastic xanthoastrocytoma.[3] By definition they are aggressive tumors that are associated with high morbidity and mortality values and a 5-year survival rate of 28.1%.[2] Therefore, treatment is challenging and involves a combination of surgery, radiation, and chemotherapy.[1]

Several studies have investigated the demographic, clin-

**ABBREVIATIONS** GTR = gross-total resection; OS = overall survival; PFS = progression-free survival; STR = subtotal resection.

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ical, and histological factors that affect patient survival in such settings. These prognostic factors, whether clinical, radiological, histological, or genetic-molecular, can be divided into two groups: a group of immutable factors (including age, sex, and histological type), and another group of factors subject to medical intervention (including the time between diagnosis and start of treatment, extent of tumor resection, number of surgeries and, more recently, with new discoveries, biological markers).

Published studies on high-grade gliomas predominantly include adult patients.[4–7] In pediatric populations, the few studies conducted so far have had small sample sizes, with some of them indicating that sex, age, tumor location, and extent of resection affect survival.[8–15]

However, although previous cohort studies have described the prognostic factors in this population, their findings have shown low applicability in the achievement of therapeutic success. Likewise, the formulation of possible interventions in the natural history of the disease for the enhancement of patients' survival or quality of life has been lacking. Therefore, we aimed to investigate the prognostic factors, especially those subject to interventions such as reoperation, that affect survival in a large cohort of pediatric patients.

## Methods

This retrospective study analyzed patients admitted to the Instituto de Oncologia Pediátrica/Grupo de Apoio ao Adolescente e a Criança com Câncer (IOP/GRAACC)/Universidade Federal de São Paulo—(UNIFESP) between 1989 and 2019. The study was approved by the research ethics committee of the institution. No consent was required considering the retrospective nature of the study. The patients' identities were anonymized.

Of 1508 patients with tumors of the CNS, those younger than 19 years with a histological diagnosis of glioblastoma and anaplastic astrocytoma, or high-grade glioma (grades III and IV), were included in the study after meeting the inclusion criteria. The histological diagnosis was defined by the pathologist at the institution even when the patient was initially treated in another institution. All CNS locations were included, except diffuse intrinsic pontine gliomas. Only primary cases of high-grade glioma were included; that is, patients whose results from the first anatomopathological examination did not reveal high-grade glioma were excluded from this series.

The medical records of patients selected based on the inclusion criteria were retrospectively analyzed, and we collected data on the date of diagnosis, age at diagnosis, sex, histological type, location, signs and symptoms, date of recurrence or progression, date of first surgery, extent of resection, occurrence of reoperation, Ki-67 index expression, adjuvant treatment (chemotherapy and radiotherapy), date of treatment initiation, and date of death or the last clinical follow-up.

The date of diagnosis was defined as the date of the first imaging tests (CT or MRI) that identified the tumor. Overall survival (OS) was calculated considering the period from the date of diagnosis to the date of all-cause mortality or last follow-up. Progression-free survival (PFS) was considered to be the time interval between the date of diagnosis and lesion recurrence or progression or, in cases with no recurrence or progression, death due to the disease or last follow-up date. Recurrence was defined as the reappearance of the lesion after total resection, and progression was characterized as an increase in the tumor volume > 25% on radiological follow-up.

For the extent of tumor resection three categories were considered: gross-total resection (GTR), subtotal resection (STR), and biopsy. GTR was confirmed on achievement of 100% resection of the preoperative volume of the Gd-enhanced lesion on MRI by using the $(A \times B \times C)/2$ method,[16] which may have been reported by the radiologist, as directly measured by the authors of this article (M.D.S.C., N.C.C.), or described in the medical records by neuro-oncological report. STR was considered when the resection rate, as measured on postoperative MRI, was < 100% of the preoperative volume. Biopsy was considered when only small fragments were removed from the lesion for histological characterization through stereotaxic needle localization or neuronavigation. Postoperative MRI examinations were performed as part of the institution's routine practice within 24–72 hours after surgery, to reduce potential artifacts such as enhancement of blood products. Radiological follow-up was performed according to the institution's routine practice every 2–4 months, using MRI studies, whereas clinical follow-up was dependent on the chemotherapy and radiotherapy routine. Lesion type and histological grade were characterized according to the WHO criteria at the time of diagnosis.

Statistical analysis was performed using Kaplan-Meier survival curves and log-rank (Mantel-Cox) tests to compare the groups. A multivariate analysis was conducted with multiple logistic regression models, in which the variables were selected according to the following criteria: effect and sample size, significance of univariate analysis ($p < 0.05$), and correlation of variables. The qualitative variables were analyzed using a contingency test as well as chi-square and/or Fisher's exact tests, depending on the sample size and the testing for normal distribution for each set of samples. Differences with an $\alpha$ value $\leq 0.05$ were considered to indicate statistical significance. Data were analyzed and graphs plotted using GraphPad Prism 8 for macOS version 8.0.1.

## Results

Of a total of 1508 patients with tumors of the CNS, 78 (5.2%) presented with high-grade gliomas across all locations, excluding diffuse intrinsic pontine gliomas. The case distributions were equal between sexes. The ages at diagnosis were divided into three main groups: 0 to < 3 years, 15 patients (19.2%); 3–11 years, 36 patients (46.2%); and > 11 to < 19 years, 27 patients (34.6%). The mean age at diagnosis was 8.7 years.

The most frequently noted histological type was glioblastoma, which accounted for 54 (69.2%) cases, followed by anaplastic astrocytoma with 24 (30.8%) cases. The most commonly observed tumor location was the supratentorial region, as observed in 62 (79.5%) cases, followed by infratentorial and spinal cord locations with 8 (10.25%) cases each.

Thirty-four (43.6%) patients clinically presented with intracranial hypertension syndrome; 27 (79.4% of this group) experienced headache and 30 (88.2%) had vomiting. The incidence of papilledema in this symptomatic group was not reported. Thirty-three (42.3%) patients presented with focal deficits or focal neurological signs, of whom 26 (78.8%) had paresis, 23 (69.7%) showed cranial nerve alterations, and 10 (30.3%) presented with paresthesia. In 9 (11.5%) patients, the first symptoms were seizures. Two (2.6%) patients were diagnosed incidentally, one of them specifically prenatally (50%).

Sixty-seven (85.9%) patients underwent chemotherapy, 61 (78.2%) radiotherapy, and 53 (68%) both adjuvant treatments. One (1.3%) patient with congenital glioblastoma received an autologous stem cell transplant as part of the treatment. The patients' demographic data are summarized in Table 1.

The median OS of patients was 17 months, and the PFS was 6 months, with 1-, 2-, and 5-year OS rates of 62.7%, 36.35%, and 24.5%, respectively.

In the different age groups, the median overall survival durations in the age groups 0 to < 3 years, 3–11 years, and > 11 to < 19 years were 125, 16, and 14 months, respectively. The female group showed a median survival of 18 months, versus 15 months for males. Considering the different histological types, the median OS durations were 16 months for glioblastoma and 19 months for anaplastic astrocytoma, with a median OS for tumor with Ki-67 expression ≥ 50% of 14 months, in contrast to the expression < 50%, which was 24 months.

Patients with supratentorial tumors had a median overall survival duration of 17 months, whereas those with infratentorial or spinal cord tumors had a median overall survival duration of 12 months. Considering adjuvant treatment, patients who had combined treatment with chemo- and radiotherapy had a median OS of 19 months, whereas those who only underwent radiotherapy had a median survival of 11 months. Patients who underwent surgery without adjuvant treatment had a median OS of 5 months. Patients in whom treatment was initiated before 2010 had an OS duration of 11 months, whereas those treated from 2010 onward had a corresponding value of 23 months. The median OS curves are shown in Fig. 1.

Groups of patients treated before 2010 and from 2010 onward were compared according to the proportions of patients undergoing chemotherapy and radiotherapy, using the Fisher exact test. There was a significant difference between the number of patients who underwent regimens with temozolomide and irinotecan and radiotherapy during these intervals ($p < 0.0001$). However, there were no significant differences in age ($p = 0.77$), sex (0.16), or achievement of GTR during the first surgery ($p = 0.43$) between these groups.

**TABLE 1. Summary of demographic data in 78 patients with high-grade glioma**

| Variable | No. | % |
|---|---|---|
| Age | | |
| 0 to <3 yrs | 15 | 19.2 |
| 3 to 11 yrs | 36 | 46.2 |
| >11 to <19 yrs | 27 | 34.6 |
| Sex | | |
| Female | 39 | 50 |
| Male | 39 | 50 |
| Clinical presentation | | |
| Intracranial hypertension syndrome | 34 | 43.6 |
| Focal deficits or signs | 33 | 42.3 |
| Seizure | 9 | 11.5 |
| Incidental | 2 | 2.6 |
| Histological type | | |
| GBM | 54 | 69.2 |
| AA | 24 | 30.8 |
| Tumor location | | |
| Supratentorial | 62 | 79.5 |
| Infratentorial | 8 | 10.25 |
| Spinal cord | 8 | 10.25 |
| Resection at first surgery* | | |
| GTR | 11 | 17.7 |
| STR | 33 | 53.2 |
| Biopsy | 18 | 29 |
| GTR and tumor location* | | |
| Superficial | 17 | 70.8 |
| Deep | 7 | 29.2 |
| Partial resection or biopsy and tumor location* | | |
| Superficial | 14 | 36.8 |
| Deep | 24 | 63.2 |
| No. of patients with GTR at any point* | | |
| GTR | 24 | 38.7 |
| No GTR | 38 | 61.3 |
| No. of surgeries to achieve GTR* | | |
| 1 | 11 | 45.8 |
| >1 | 13 | 54.2 |
| Adjuvant treatments | | |
| Chemo | 67 | 85.9 |
| RT | 61 | 78.2 |
| Both chemo & RT | 53 | 68 |
| Autologous stem cell transplantation | 1 | 1.3 |

AA = anaplastic astrocytoma; chemo = chemotherapy; GBM = glioblastoma; RT = radiotherapy.

* Data regarding patients presenting with supratentorial tumors. The mean time until first resection or biopsy in patients with supratentorial tumors was 32.42 days.

## Univariate Analysis

The median PFS duration was 17 months in the 0 to < 3 years age group, 5 months in the 3–11 years group, and 6 months in the > 11 to < 19 years group. In terms of the different histological types, the median progression durations were 5 and 7 months, respectively, for glioblastomas and anaplastic astrocytomas. The median PFS durations associated with the different locations were 6 months for infratentorial tumors and 7 months for supratentorial and spinal cord tumors.

The median PFS duration of those who underwent com-

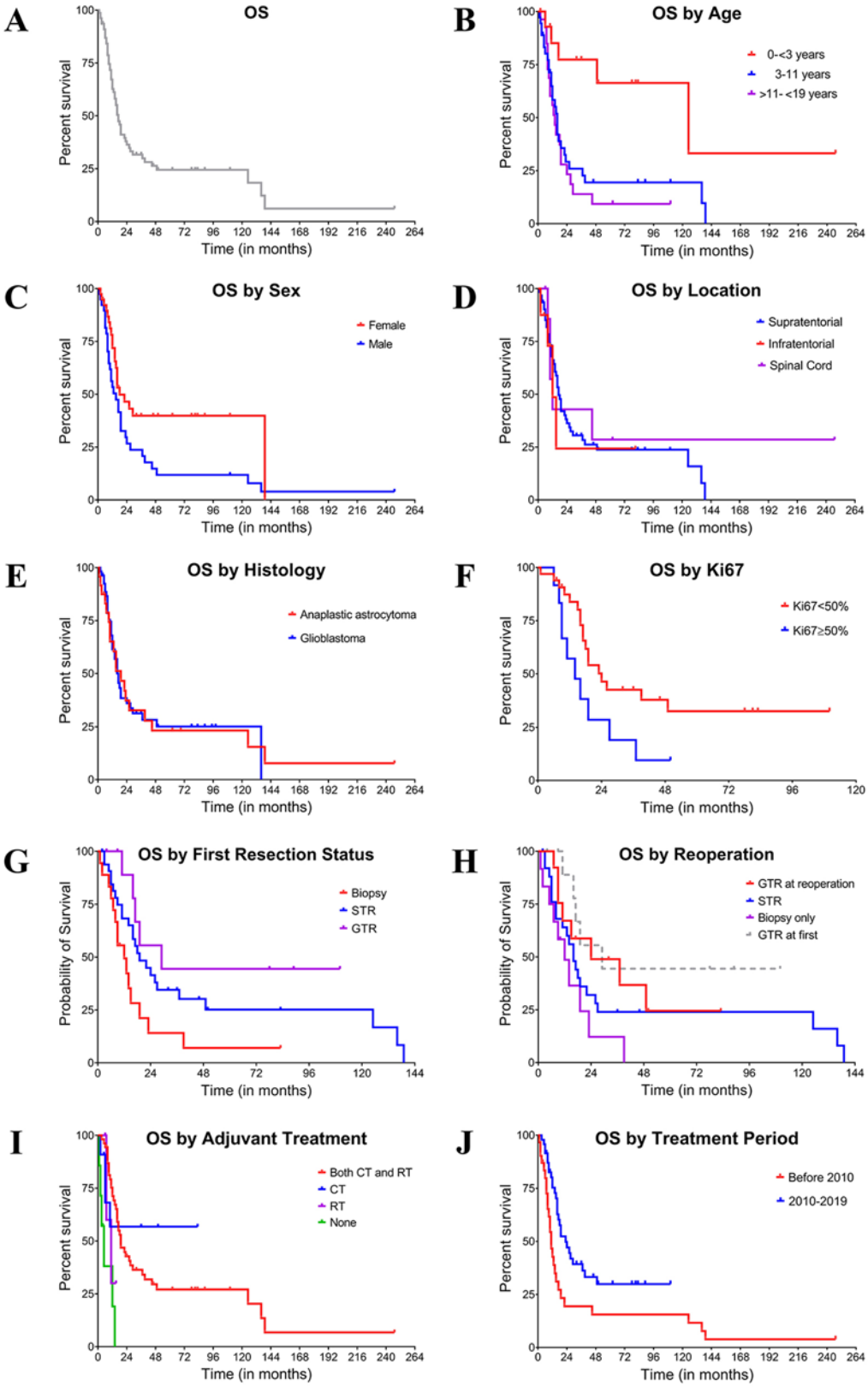


**FIG. 1.** Survival curves demonstrating OS in all patients (**A**), by age (**B**), sex (**C**), tumor location (**D**), histology (**E**), Ki-67 (**F**), first resection status (**G**), reoperation (**H**), adjuvant treatment (**I**), and treatment period (**J**). CT = chemotherapy; RT = radiotherapy. Figure is available in color online only.

bined treatment was 7 months, whereas that of those who underwent surgery and chemotherapy was 10 months. The corresponding values were 4.5 months in those who underwent combined surgery and radiotherapy and 1 month in patients who underwent only surgery. Patients with initiation of treatment before 2010 had a median PFS duration of 5 months, whereas those treated from 2010 onward had a median survival duration of 6.5 months. The median PFS curves are shown in Fig. 2.

Statistical analysis of the factors affecting OS showed significant differences in the following prognostic factors: age ($p = 0.0038$), sex ($p = 0.0245$), and those who received adjuvant treatment ($p = 0.0001$). Significant differences were also found between Ki-67 expression groups ($p = 0.0429$) and between patients treated before 2010 and from 2010 onward ($p = 0.0092$). No significant differences were observed in terms of histology and tumor location. These results are outlined in Table 2.

In terms of median PFS, the analysis revealed significant differences in the Ki-67 expression groups ($p = 0.0135$), whereas no significant differences were found regarding the presence of adjuvant treatments ($p = 0.3423$), or in patients' age, sex, tumor histology, tumor location, and year of diagnosis. These results are summarized in Table 3.

### Multivariate Analysis

In the multivariate analysis for OS, the following variables were included: age < 3 years, female sex, extent of resection in the first surgery of patients with supratentorial tumors, and presence of adjuvant treatment. Although Ki-67 index expression and treatment initiation after 2010 were significant in the univariate analysis, they were not considered in the model because of missing data in the Ki-67 expression group and due to collinearity concerns in the treatment initiation variable. Our results indicated that age < 3 years, female sex, and GTR in the first surgery are predictors of a better chance of survival. Also, the generated model showed high accuracy, with a calculated area under the curve of 0.84 (95% CI 0.73–0.96) with $p < 0.0001$. These results are summarized in Table 4.

Regarding PFS, multivariate analysis could not be generated because there were only two significant predictors, one of which had to be excluded due to missing data.

### Supratentorial Tumors Analysis

Considering only the 62 (79.5%) supratentorial tumors, 24 (38.7%) patients underwent GTR, including 13 (54.2%) who underwent two or more surgeries. Considering the first surgery, 33 (53.2%) patients underwent STR and 18 (29%) biopsy. Thirteen (20.9%) patients underwent reoperation to achieve GTR, with 12 of them (92.3%) undergoing consecutive resections, without adjuvant treatment between surgeries. The mean time from diagnosis to the first resection or biopsy was 32.42 days, in which we did not consider other surgeries such as shunts to treat hydrocephalus.

Among the 24 (38.7%) patients who underwent GTR, 17 (70.8%) had superficially localized tumors, whereas 7 (29.2%) had deeply localized tumors. Of the 38 patients who underwent STR or only biopsy, 24 (63.2%) presented with deeply localized tumors, in locations such as thalamus, whereas 14 (36.8%) were superficial. Testing the difference in proportions of deep and superficial localized tumors between GTR and STR/biopsy groups, the Fisher exact test revealed a significant difference ($p = 0.02$). Demographic data from patients can be seen in Table 1.

Regarding the resection status of the first surgery, those who underwent GTR had a median OS duration of 29 months, whereas those who underwent STR or biopsy showed median survival durations of 19 and 13 months, respectively. Patients who underwent reoperation for GTR had a median OS of 24 months, whereas patients who underwent STR had 16 months and those who underwent biopsy had 12 months of median survival. The curves showing OS by extent of resection and reoperation can be seen in Fig. 1.

In terms of PFS regarding the extent of resection in the first surgery, patients who underwent GTR had a median PFS duration of 12 months, whereas those who underwent STR and biopsy had median PFS durations of 5 and 4 months, respectively. Patients who underwent reoperation for GTR had a median PFS duration of 3 months, whereas patients who underwent STR or biopsy had PFS durations of 5 and 3.5 months, respectively. The curves showing PFS regarding the extent of resection and reoperation can be seen in Fig. 2.

The statistical analysis for OS showed significant differences regarding the extent of resection in the first surgery, with the highest median OS duration observed in those who underwent GTR ($p = 0.0175$). In addition, no significant differences were found between the groups of patients who underwent GTR after reoperation and those who underwent biopsy or STR during treatment ($p = 0.1530$). The 5-year survival rates were 15.4% for the patients who underwent reoperation to achieve GTR, 19.2% for patients who underwent STR, and 8.3% for the biopsy group. The results regarding univariate analysis for OS are summarized in Table 2.

Regarding PFS, the univariate analysis revealed significant differences in first resection status, with GTR presenting the longer PFS ($p = 0.0114$). No significant differences were found between those who underwent reoperation to achieve GTR. These results are outlined in Table 3.

Considering only patients who achieved GTR in the first surgery or after reoperation, there were no significant differences in age, sex, tumor histology, depth of tumor location, adjuvant treatment, or Ki-67 expression. Additional data on patients who underwent reoperation are shown in Table 5.

## Discussion

In this study we found that the median OS duration of patients with supratentorial tumors who underwent GTR in the first surgery was longer than that of patients who received STR and biopsy (29, 19, and 13 months, respectively). In addition, we found no significant differences between the survival curves of patients who underwent reoperation for GTR and those with STR and biopsy. This is revealed by the 5-year survival rates of these groups, with 15.4%, 19.2%, and 8.3% of patients alive in the GTR, STR, and biopsy groups, respectively, showing in a long-term comparison of these groups that patients have similar

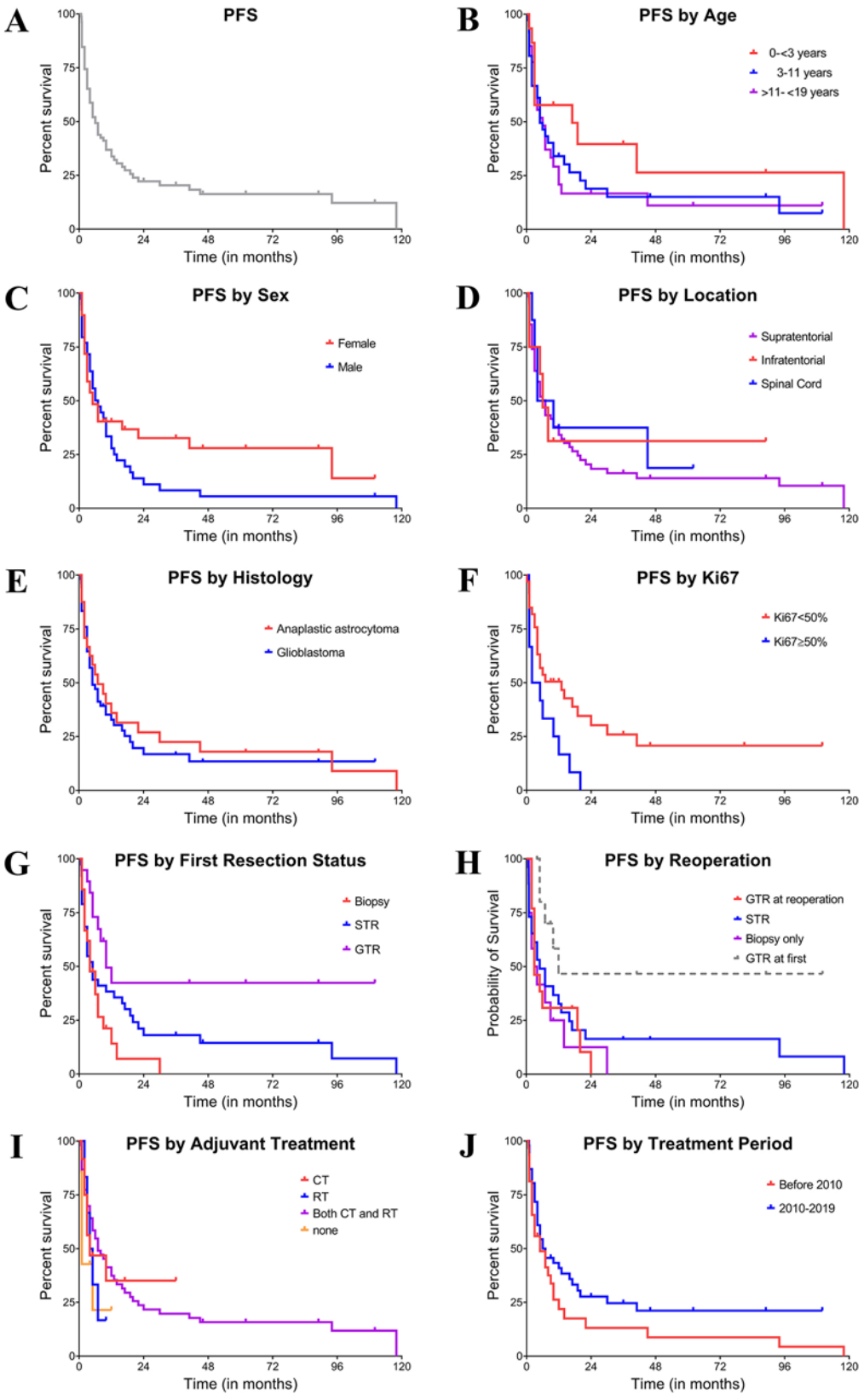


**FIG. 2.** Survival curves demonstrating PFS in all patients (**A**), by age (**B**), sex (**C**), tumor location (**D**), histology (**E**), Ki-67 (**F**), first resection status (**G**), reoperation (**H**), adjuvant treatment (**I**), and treatment period (**J**). CT = chemotherapy; RT = radiotherapy. Figure is available in color online only.

**TABLE 2. Summary of statistical data for OS in 78 patients with high-grade glioma**

| Variable | No. | Median Survival (mos) | p Value |
|---|---|---|---|
| Age | | | 0.0038 |
| 0 to <3 yrs | 15 | 125 | |
| 3 to 11 yrs | 36 | 16 | |
| >11 to <19 yrs | 27 | 14 | |
| Sex | | | 0.0245 |
| Female | 39 | 18 | |
| Male | 39 | 15 | |
| Histological type | | | 0.9904 |
| GBM | 54 | 16 | |
| AA | 24 | 19 | |
| Ki-67 | | | 0.0429 |
| Ki-67 expression <50% | 33 | 24 | |
| Ki-67 expression ≥50% | 12 | 14 | |
| Tumor location | | | 0.7579 |
| Supratentorial | 62 | 17 | |
| Infratentorial | 8 | 12 | |
| Spinal cord | 8 | 12 | |
| Resection at first surgery* | | | 0.0175 |
| GTR | 11 | 29 | |
| STR | 33 | 19 | |
| Biopsy | 18 | 13 | |
| Reop for GTR* | | | 0.1530 |
| GTR after reop | 13 | 24 | |
| STR only | 26 | 16 | |
| Biopsy only | 12 | 12 | |
| Adjuvant treatments | | | 0.0001 |
| Both chemo & RT | 53 | 19 | |
| RT | 6 | 11 | |
| Chemo | 12 | ND | |
| None | 7 | 5 | |
| Treatment period | | | 0.0092 |
| Before 2010 | 32 | 11 | |
| Between 2010 & 2019 | 46 | 23 | |

ND = not done.
* Data regarding patients presenting with supratentorial tumors.

**TABLE 3. Summary of statistical data for PFS in 78 patients with high-grade glioma**

| Variable | No. | Median Survival (mos) | p Value |
|---|---|---|---|
| Age | | | |
| 0 to <3 yrs | 15 | 17 | 0.2891 |
| 3 to 11 yrs | 36 | 5 | |
| >11 to <19 yrs | 27 | 6 | |
| Sex | | | |
| Female | 39 | 5 | 0.1889 |
| Male | 39 | 7 | |
| Histological type | | | |
| GBM | 54 | 5 | 0.6345 |
| AA | 24 | 7 | |
| Ki-67 | | | |
| Ki-67 expression <50% | 33 | 13 | 0.0135 |
| Ki-67 expression ≥50% | 12 | 3.5 | |
| Tumor location | | | |
| Supratentorial | 62 | 7 | 0.8293 |
| Infratentorial | 8 | 6 | |
| Spinal cord | 8 | 7 | |
| Resection at first surgery* | | | |
| GTR | 11 | 12 | 0.0114 |
| STR | 33 | 5 | |
| Biopsy | 18 | 4 | |
| Reop for GTR* | | | |
| GTR after reop | 13 | 3 | 0.6892 |
| STR only | 26 | 5 | |
| Biopsy only | 12 | 3.5 | |
| Adjuvant treatments | | | |
| Both chemo & RT | 53 | 7 | 0.3423 |
| RT | 6 | 4.5 | |
| Chemo | 12 | 4 | |
| None | 7 | 1 | |
| Treatment period | | | |
| Before 2010 | 32 | 5 | 0.1076 |
| Between 2010 & 2019 | 46 | 6.5 | |

* Data regarding patients presenting with supratentorial tumors.

outcomes as shown in the Kaplan-Meier curve. Therefore, our data indicate the impact of the first surgery on the survival curve of patients, because patients with supratentorial tumors who underwent reoperation do not have longer survival durations than those without GTR.

Perkins et al. found significant differences in the 2-year survival values between those who underwent GTR (60%) and STR or biopsy (25%),[17] and McCrea et al. observed differences in the median OS value of patients treated with GTR (40.8 months) and biopsy (15.6 months).[9] In another cohort of patients, Yang et al. showed differences in the survival values between patients who underwent GTR (45.1 months) and those with STR or biopsy (8.7 and 11.5 months, respectively).[11] None of those studies, however, reported on the impact of reoperation on survival. However, similar to our findings, the results published by those authors highlighted the importance of the first surgery for patient survival.

Another key issue is the extent of resection regarding the tumor location. We found significant differences in the analysis of the primary tumor as deep or superficial and its corresponding extent of resection, without a significant difference on survival durations of those groups when considering only the depth ($p = 0.66$). Patients with lobar tumors more frequently underwent GTR (70.8% vs 36.8%), indicating a greater degree of difficulty in the surgical access to deep tumors. In their cohort, McCrea et al. demonstrated that patients with supratentorial tumors had longer survival durations than those with thalamic, brainstem, or cerebellum tumors (57.6, 31.2, 24, and 45.6 months, respectively).[9]

**TABLE 4. Statistical data from multivariate analysis, considering death as the outcome in 78 patients with high-grade glioma**

| Variable | Median OS (mos) | SR at 1 Yr | SR at 2 Yrs | SR at 5 Yrs | OR | 95% CI | p Value |
|---|---|---|---|---|---|---|---|
| Age <3 yrs | 125 | 80% | 73.3% | 40% | 0.07 | 0.01–0.41 | <0.0001 |
| Female sex | 18 | 64.1% | 38.5% | 23.1% | 0.12 | 0.02–0.5 | |
| GTR at first surgery* | 29 | 82% | 54.5% | 45.4% | 0.12 | 0.02–0.7 | |
| Adjuvant treatment | 19 | 60.6% | 33.8% | 18.3% | 3.06 | 0.25–32.8 | |

SR = survival rate.
* Data regarding patients presenting with supratentorial tumors.

We also found significant differences in terms of age, with the group that was 0 to < 3 years of age showing greater survival values. This may be related to the biology of these tumors; these individuals had a median OS duration of 125 months, whereas those in the group that was > 11 to < 19 years old showed corresponding values of only 14 months, similar to the findings of Lam et al., indicating that younger age is associated with longer survival durations.[10]

Significant differences in the median OS were also noted between adjuvant treatments. The use of chemotherapy and radiotherapy after surgery was associated with a survival duration of 19 months, whereas the OS value related to surgery alone was 5 months, highlighting the effect of adjuvant treatment on the survival curve of these patients. The patients who underwent surgery alone were those who experienced early progression or dissemination a few weeks after surgery, not allowing the use of adjuvant treatment. Boudaouara et al. demonstrated differences in the survival values associated with radiotherapy, with patients who received this treatment showing a median OS value of 30 months, and those who did not receive it showing a median OS duration of 5 months.[18]

The survival of patients treated before 2010 (median OS of 11 months) and from 2010 onward (23 months) may also reflect the effect of the adjuvant treatment. During the first decade of the 2000s, our institution underwent a series of changes reflected also in the treatment of high-grade gliomas. During this period a new radiotherapy device was acquired by our hospital, which reduced the waiting time for radiotherapy. We incorporated protocols using temozolomide combined with irinotecan into our chemotherapy regimens, and our analysis also revealed different proportions of adjuvant treatment regimens from 2010 onward. This hypothesis is in line with the results of the study conducted by Jakacki et al., who favored the use of temozolomide as an adjuvant treatment to resection and radiotherapy.[19] In addition, because younger age is a significant prognostic factor for longer survival durations, another possibility is the presence of a larger number of individuals younger than 3 years in this group, proportionally, compared to those treated before 2010, although no significant difference was found in the chi-square tests.

In this study we found significant differences in the median OS durations between females (18 months) and males (15 months), in line with the findings reported by McCrea et al., who showed higher survival values in girls (57.6 months) than in boys (33.6 months).[9]

Regarding PFS, we found significant differences in the following factors: extent of resection of the first surgery and adjuvant treatment. Patients who underwent GTR (12 months) had greater median PFS than those with STR (5 months) or biopsy (4 months). Patients who underwent adjuvant treatment had greater median PFS (7 months) than those with only surgery (1 month). Jung et al. reported a significant difference in the status of the first resection, with longer PFS noted in patients with GTR than in those with STR and biopsy (15, 7.8, and 8.5 months, respectively).[14] Similarly, Muhammed et al. reported that 30% and 52% of those with total resection and STR, respectively, in the first surgery showed progression in 1 year.[20] Jung et al. demonstrated longer PFS durations in patients who underwent chemotherapy and radiotherapy (10.5 months) than in those who underwent only radiotherapy (4.7 months).

The impact on the PFS of the reoperation to achieve GTR was not noted either. Although the group who underwent GTR after initial surgery had the shorter survival (3 months vs 3.5 and 5 months for the biopsy and STR groups, respectively), this difference is not statistically demonstrated considering the whole observation period. This is better illustrated by comparison of 1-, 2-, and 5-year PFS rates: the group who underwent reoperation for GTR had rates of 38.5%, 7.7%, and 7.7%, whereas the STR group had rates of 34.6%, 19.2%, and 11.5%. Finally, the biopsy group had rates of 25%, 16.7%, and 8.3% in the 1st, 2nd, and 5th years, respectively. This shows that despite the specific difference at the 2-year follow-up, for example, the final outcome is similar in these groups, which explains the absence of a significant difference ($p = 0.69$).

In contrast to our study, McCrea et al. demonstrated a longer median PFS in females (14.4 months) than in males (6 months).[9]

Regarding Ki-67 expression, we have found significant differences between patients with Ki-67 expression of < 50%, with longer OS and PFS. These results may be due to tumor aggressiveness because Ki-67 is a proliferation marker. In contrast to our study, Alkhaibary et al. found no significant difference between tumors with Ki-67 expression ≤ 27% when analyzing a cohort of 44 patients.[21]

The absence of a unique method to determine lesion size due to the lack of digital images from past patients limited the evaluation of the extent of resection. Alternatively, we defined GTR strictly as a 100% resection of the tumor, which is more rigorous than that reported in other cohorts.[22,23] However, this may also have underestimated the proportion of patients who underwent GTR at our institution.

Our results highlight the role of reoperation, emphasizing the absence of difference on survival curves. No similar studies have been published yet. Further research with larger cohorts may be needed to establish that.

The limitations of our study include its retrospective de-

**TABLE 5. Data from 13 patients with high-grade glioma who underwent reoperation**

| Case No. | Age, Sex | 1st Op | Histology | Immunohistochemistry | Tumor Location | NS | Chemo | RT | OS/PFS (mos) | Death |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 11 yrs 6 mos, F | STR | GBM | H3K27: +; GFAP: +; ALK: −; synaptophysin: +; Ki-67: 20–30%; p53: 50–60%; IDH-1: +; ATRX: +; cyclin D1: +; INI1: +; CD34: + in vessels | Parieto-occipitotemporal | 2 | Irinotecan & temozolomide | 60 Gy | 7/3 | No |
| 2 | 6 yrs 7 mos, M | STR | GBM | GFAP: +; Ki-67: 90%; neurofilament: −; INI1: + | Thalamus | 2 | Irinotecan | 60 Gy & reirradiation w/ 40 Gy | 9/6 | Yes |
| 3 | 8 yrs 9 mos, M | STR | GBM | GFAP: +; neurofilament: −; CD34: + in vessels; Ki-67: 60%; INI1: +; enolasis: −; chromogranin: −; synaptophysin: +; CD56: + | Frontoparietal | 2 | Irinotecan & temozolomide \| vincristine, lomustine, & procarbazine | 59.4 Gy & reirradiation w/ 59.4 Gy | 37/20 | Yes |
| 4 | 15 yrs 7 mos, M | STR | GBM | p53: 10%; IDH-1: −; Ki-67: 10–30%; BRAF: −; GFAP: + | Parietal | 2 | Irinotecan & temozolomide | 60 Gy | 24/24 | Yes |
| 5 | 2 yrs 11 mos, F | STR | GBM | | Parietal | 2 | ND | 59.4 Gy | 11/3 | Yes |
| 6 | 4 yrs 3 mos, F | Biopsy | AA | | Parietal | 2 | ND | 50.4 Gy | 15/2 | Yes |
| 7 | 4 mos, F | STR | GBM | GFAP: +; synaptophysin: −; INI1: +; Ki-67: 25%; p53: 25% | Hemispheric | 3 | Vincristine, etoposide, & cisplatin | ND | 17/17 | No |
| 8 | 16 yrs, M | STR | GBM | | Parieto-occipital | 3 | ND | 60 Gy | 7/5 | Yes |
| 9 | 5 mos, F | STR | GBM | GFAP: +; IDH-1: +; INI1: +; Ki-67: 25–50%; p53: 90% | Hemispheric | 3 | Temozolomide & irinotecan \| cisplatin, cyclophosphamide, etoposide, & vincristine \| methotrexate, cisplatin, vincristine, & etoposide | ND | 32/3 | No |
| 10 | 1 yr 4 mos, M | STR | GBM | GFAP: +; Ki-67: 40%; INI1: +; EMA: +; AE1–AE3: −; enolasis: +; chromogranin: −; myeloperoxidase: + in neutrophils permeating the tumor; LCA: + in typical lymphocytes | Temporal | 3 | Cisplatin, cyclophosphamide, etoposide, & vincristine | 59.4 Gy | 49/19 | Yes |
| 11 | 0, F* | STR | GBM | GFAP: +; EMA: −; S-100: +; enolasis: +; synaptophysin: −; chromogranin: −; neurofilament: −; desmin: −; 1A4: −; CD56: +; Ki-67: 15–20% | Lateral ventricle | 3 | Cisplatin, cyclophosphamide, etoposide, & vincristine | ND | 83/3 | No |
| 12 | 6 yrs 10 mos, F | STR | GBM | Ki-67: 60%; neurofilament: −; CD56: −; GFAP: +; synaptophysin: −; monoclonal enolasis: +; chromogranin: −; vimentin: + | Parietal | 3 | Cisplatin, cyclophosphamide, etoposide, & vincristine \| temozolomide | 594 Gy | 9/2 | Yes |
| 13 | 0, F* | STR | GBM | CD99: −; INI1: +; EMA: −; S100: −; GFAP: +; synaptophysin: −; chromogranin: −; Ki-67: 90%; enolasis: − | Lateral ventricle | 5 | Carboplatin & etoposide \| cisplatin, cyclophosphamide, & etoposide \| irinotecan & temozolomide \| ifosfamide, carboplatin, & etoposide \| vinblastine | ND | 50/2 | No |

NS = number of surgeries to achieve GTR; + = positive; − = negative; | = separates subsequent chemotherapy protocols.
* Diagnosis made at birth or prenatally.

sign and the sample size, although our study included one of the largest cohorts ever reported in the literature. Moreover, the influence of the institutional philosophy and surgeon aggressiveness may limit the study generalizability.

## Conclusions

Our cohort study reiterates how challenging the approach to these neoplasms is and highlights the role of the surgeon in the achievement of GTR right from the first surgery, because this factor is subject to intervention and alters the duration of survival. In addition, reoperation for GTR does not appear to have a significant impact on OS in patients with supratentorial high-grade gliomas, further reinforcing the role of the first surgery. Finally, the importance of combined chemotherapy and radiotherapy is reinforced through the increase observed in the survival values of these patients.

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## References

1. Ostrom QT, Gittleman H, Truitt G, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011-2015. *Neuro Oncol*. 2018;20(suppl_4):iv1–iv86.
2. Ostrom QT, de Blank PM, Kruchko C, et al. Alex's Lemonade Stand Foundation infant and childhood primary brain and central nervous system tumors diagnosed in the united states in 2007–2011. *Neuro Oncol*. 2015;16(suppl 10):x1–x36.
3. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol*. 2016;131(6):803–820.
4. Gerges N, Fontebasso AM, Albrecht S, et al. Pediatric high-grade astrocytomas: a distinct neuro-oncological paradigm. *Genome Med*. 2013;5(7):66–77.
5. El-Ayadi M, Ansari M, Sturm D, et al. High-grade glioma in very young children: a rare and particular patient population. *Oncotarget*. 2017;8(38):64564–64578.
6. Chamdine O, Gajjar A. Molecular characteristics of pediatric high-grade gliomas. *CNS Oncol*. 2014;3(6):433–443.
7. Paugh BS, Qu C, Jones C, et al. Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. *J Clin Oncol*. 2010;28(18):3061–3068.
8. Tamber MS, Rutka JT. Pediatric supratentorial high-grade gliomas. *Neurosurg Focus*. 2003;14(2):e1.
9. McCrea HJ, Bander ED, Venn RA, et al. Sex, age, anatomic location, and extent of resection influence outcomes in children with high-grade glioma. *Neurosurgery*. 2015;77(3):443–453.
10. Lam S, Lin Y, Zinn P, et al. Patient and treatment factors associated with survival among pediatric glioblastoma patients: a Surveillance, Epidemiology, and End Results study. *J Clin Neurosci*. 2018;47:285–293.
11. Yang T, Temkin N, Barber J, et al. Gross total resection correlates with long-term survival in pediatric patients with glioblastoma. *World Neurosurg*. 2013;79(3-4):537–544.
12. Walston S, Hamstra DA, Oh K, et al. A multi-institutional experience in pediatric high-grade glioma. *Front Oncol*. 2015;5:28.
13. Nikitović M, Stanić D, Pekmezović T, et al. Pediatric glioblastoma: a single institution experience. *Childs Nerv Syst*. 2016;32(1):97–103.
14. Jung TY, Lee JY, Kim DS, et al. Pediatric supratentorial high-grade glioma: multicenter retrospective observational study of the Korean Society for Pediatric Neuro-Oncology. *J Neurooncol*. 2015;121(2):413–419.
15. Finlay JL, Boyett JM, Yates AJ, et al. Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen. *J Clin Oncol*. 1995;13(1):112–123.
16. Sreenivasan SA, Madhugiri VS, Sasidharan GM, Kumar RV. Measuring glioma volumes: A comparison of linear measurement based formulae with the manual image segmentation technique. *J Cancer Res Ther*. 2016;12(1):161–168.
17. Perkins SM, Rubin JB, Leonard JR, et al. Glioblastoma in children: a single-institution experience. *Int J Radiat Oncol Biol Phys*. 2011;80(4):1117–1121.
18. Boudaouara O, Charfi S, Bahri M, et al. Pediatric high grade gliomas: Clinico-pathological profile, therapeutic approaches and factors affecting overall survival. *Neurochirurgie*. 2019;65(2-3):63–68.
19. Jakacki RI, Cohen KJ, Buxton A, et al. Phase 2 study of concurrent radiotherapy and temozolomide followed by temozolomide and lomustine in the treatment of children with high-grade glioma: a report of the Children's Oncology Group ACNS0423 study. *Neuro Oncol*. 2016;18(10):1442–1450.
20. Muhammed A, Gaber MS, Elbeltagy M, et al. Risk stratification of pediatric high-grade glioma: a newly proposed prognostic score. *Childs Nerv Syst*. 2019;35(12):2355–2362.
21. Alkhaibary A, Alassiri AH, AlSufiani F, Alharbi MA. Ki-67 labeling index in glioblastoma; does it really matter? *Hematol Oncol Stem Cell Ther*. 2019;12(2):82–88.
22. Bloch O, Han SJ, Cha S, et al. Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. *J Neurosurg*. 2012;117(6):1032–1038.
23. Wisoff JH, Boyett JM, Berger MS, et al. Current neurosurgical management and the impact of the extent of resection in the treatment of malignant gliomas of childhood: a report of the Children's Cancer Group trial no. CCG-945. *J Neurosurg*. 1998;89(1):52–59.

### Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

### Author Contributions

Conception and design: Silva da Costa, Camargo, Saba da Silva, Cavalheiro. Acquisition of data: Silva da Costa, Camargo. Analysis and interpretation of data: Silva da Costa, Camargo. Drafting the article: Silva da Costa, Camargo. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Silva da Costa. Statistical analysis: Silva da Costa, Camargo. Study supervision: Saba da Silva, Cavalheiro.

### Correspondence

Marcos Devanir Silva da Costa: Universidade Federal de São Paulo, Brazil. marcoscostaneuro@gmail.com.