# Epidemiological characteristics and survival outcomes of children with medulloblastoma treated at the National Cancer Institute (INCA) in Rio de Janeiro, Brazil

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**Abstract**

BACKGROUND: Medulloblastoma (MB), the most malignant brain tumor of childhood has survival outcomes exceeding 80% for standard risk and 60% for high risk patients in high-income countries (HIC). These results have not been replicated in low-to-middle income countries (LMIC), where 80% of children with cancer live. METHODS: Retrospective review of 114 children (3-18 years) diagnosed with MB from 1997 to 2016 at INCA. Data on patients, disease characteristics and treatment information were retrieved from the charts and summarized descriptively. Overall survival (OS) and event-free survival (EFS) were calculated using the Kaplan-Meier Method. RESULTS: The male/female ratio was 1.32 and the median age at diagnosis was 8.2 years. Headache (83%) and nausea/vomiting (78%) were the most common presenting symptoms. Overall survival (5y) was 59,1% and EFS (5y) was 58,4%. The OS for standard-risk patients was 69% and 53% for high-risk patients. Forty-five patients (35%) had metastatic disease at admission. Lower maternal education correlated with lower OS (71.3% versus 49% p=0.25). Patients who lived >40km from INCA fared better (OS= 68.2% versus 51.1% p=0.032). Almost 20% of families lived below the Brazilian minimum wage. CONCLUSIONS: The epidemiological characteristics of this series possibly explain the differences in survival that medulloblastoma patients have in Brazil. Issues related to limited health care resources, poverty, delayed diagnosis, treatment abandonment, and malnutrition are reflected in inferior survival outcomes when compared to high-income countries. Despite the difficulties encountered in an upper-middle income country, it was possible to deliver treatment with good results.

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| | |
|---|---|
| MB | Medulloblastoma |
| HIC | High-income country |
| LMIC | Low-and-middle income country |
| UMIC | Upper middle income country |
| INCA | National Cancer Institute |
| SUS | Brazil Unified Public Health System |
| COG | Children´s Oncology Group |
| GTR | Gross Total Resection |
| STR | Subtotal Resection |
| HR | High risk |
| SR | Standard Risk |
| MRI | Magnetic Resonance Imaging |
| CSI | Craniospinal Irradiation |
| CI | Confidence Interval |
| PFS | Progression Free Survival |
| OS | Overall Survival |
| M+ | Metastatic Disease |
| M0 | Localized disease |
| NOS | Not Otherwise Specified |
| ICE | Ifosfamide, Carboplatin and Etoposide |
| Gy | Gray |

## ABSTRACT

BACKGROUND: Medulloblastoma (MB), the most malignant brain tumor of childhood has survival outcomes exceeding 80% for standard risk and 60% for high risk patients in high-income countries (HIC). These results have not been replicated in low-to-middle income countries (LMIC), where 80% of children with cancer live.

METHODS: Retrospective review of 114 children (3-18 years) diagnosed with MB from 1997 to 2016 at INCA. Data on patients, disease characteristics and treatment information were retrieved from the charts and summarized descriptively. Overall survival (OS) and event-free survival (EFS) were calculated using the Kaplan-Meier Method.

RESULTS: The male/female ratio was 1.32 and the median age at diagnosis was 8.2 years. Headache (83%) and nausea/vomiting (78%) were the most common presenting symptoms. Overall survival (5y) was 59,1% and EFS (5y) was 58,4%. The OS for standard-risk patients was 69% and 53% for high-risk patients. Forty-five patients (35%) had metastatic disease at admission. Lower maternal education correlated with lower OS (71.3%*versus* 49% p=0.25). Patients who lived >40km from INCA fared better (OS= 68.2% *versus* 51.1% p=0.032). Almost 20% of families lived below the Brazilian minimum wage.

CONCLUSIONS: The epidemiological characteristics of this series possibly explain the differences in survival that medulloblastoma patients have in Brazil. Issues related to limited health care resources, poverty, delayed diagnosis, treatment abandonment, and malnutrition are reflected in inferior survival outcomes when compared to high-income countries. Despite the difficulties encountered in an upper-middle income country, it was possible to delivertreatment with good results.

## MANUSCRIPT

### Introduction

Medulloblastoma (MB) is the most common malignant brain tumor of childhood (1). The current multimodal therapy in children includes maximal safe resection, radiation therapy, and chemotherapy. In high-income countries (HIC), medulloblastoma survival outcomes are 80% for standard-risk and 60% for high-risk patients (2). These outcomes are largely due to proper risk stratification, surgical expertise, timely radiation therapy, advancements in imaging technology and supportive care, with current strategies focused on lessening the long-term sequelae of treatment (3–6). However, these results have not been replicated in patients living in low-and middle-income countries (LMIC), where almost 80% of children with cancer in the world live (7–9).

Patients with pediatric brain cancers in LMIC have lower survival rates for a multitude of reasons, such as barriers in accessing medical services, shortage of primary care professionals, unawareness of brain tumor presenting symptoms, difficulty in patient referral to complex health care settings, and a lack of availability of sub-specialty care and appropriate expertise (10–13). Data from predominantly HIC have found that delays in care and lack of specialized care can impact outcomes, specifically in pediatric brain tumors (14–16). The most common initial presenting symptoms (ie: headache, nausea, emesis) can simulate many benign conditions in childhood frequently leading to delays in diagnosis. Delays in imaging (due to lack of resources) can also affect staging and risk stratification contributing to under or overtreatment(16). These same factors that negatively impact outcomes are likely present, if not exacerbated, in LMIC.

Brazil is an upper middle-income country (UMIC) according to the World Bank classification in 2018 (17), with a gross national income per capita of US$ 9,140. With a population of more than 209 million inhabitants, Brazil is a country with vast socio-economical disparaties within its five major regions. The National Cancer Institute (INCA) is located in the state of Rio de Janeiro, in southeastern Brazil. INCA is the branch of the Ministry of Health responsible for leading a country-wide policy for prevention and cancer control in the country(18). It is a tertiary care referral center for the treament of adult and children with cancer free of charge within Brazil´s Unified Public Health System (SUS). INCA's pediatric treatment approach is comprised of a multidisciplinary team of pediatric oncologists, neurosurgeons, neuro-radiologists, pathologists, radiation-oncologists, among others. Patients who are identifed to be high-risk for abandoning treatment receive additional support with food, lodging and transportation from the government and nonprofit organizations(19). On average there are 200 new solid tumor pediatric patients registered annually with 40-50 of them being patients with new brain tumors.

The aim of this study is to describe the epidemiological characteristics and provide survival outcome data of children treated for medulloblastoma at a single-institution, public, tertiary care center in Rio de Janeiro, Brazil.

### Methods

*Study population*

We retrospectively reviewed the charts of children ages 3 to 18 years with histopathologically confirmed MB at the INCA in Rio de Janeiro, Brazil. The inclusion criteria was patients with confirmed diagnosis of MB between January 1997 through December 2016, with ages 3-18 years. The sample was limited to patients who received full adjuvant tratement at INCA, therefore we excluded patients who had previously received chemotherapy or radiation therapy elsewhere. Patients with surgeries in other hospitals were included. An initial search revealed 134 patients who met inclusion criteria. After 20 patients being excluded (5 due to missing data; 6 due to lack of any treatment besides surgery, because of clinical conditions; 5 due to treatment in another institution; 4 with admission just for radiation therapy), a total of 114 patients were included for analysis. The study was approved by the Hospital ethics committee.

*Patient Data*

Patient records were examined for relevant demographic and clinical data. Demographic and socioeconomic characteristics that were extracted included age, sex, family income, city of origin, distance from INCA, maternal age, home type, maternal education level, and household services (ie: water, sewage, electricity). Disease and treatment information included initial symptoms, first radiological exam, surgery location (INCA or other hospital), ventricular peritoneal shunt placement, histology report of the tumor and cerebrospinal fluid, risk stratification, surgical outcome, residual tumor volume, Chang modified staging criteria (M0: non metastatic; M+: seeding to the spinal subarachnoid space, to supratentorial compartment or out of the cerebrospinal axis), craniospinal radiation-therapy dose (23,4 or 36Gy) and chemotherapy regimen (Pre Irradiation Regimen, COG 9961, or Head Start 2 modified/ICE).

*Study definitions*

High-education status was defined as more than 9 years of education. Distance from tertiary cancer center was separated into two groups: close to INCA ([?] 40 km) and far from INCA (>40km). The histopathologic diagnoses were divided into groups: classic, anaplastic/large cell, desmoplastic/extensive nodularity, and not otherwise specified (NOS). The extent of surgical resection was categorized into two major groups according to the *surgeon's report:* gross total resection (GTR) and subtotal resection (STR) or biopsy, when there was remaining tumor. Patients were classified as high-risk (HR) whether they were metastatic, had residual tumor >1.5cm$^2$ on post-operative MRI. Patients with localized disease, with residual tumor <1.5cm2 or GTR and above 3 years were classified as Standard Risk (SR). Diagnosis date was defined by the date of primary surgery.

Between april/1997 and march/2000, patients received Pre-irradiation Chemotherapy regimen which consisted of 3 cycles of ifosfamide/etoposide and 3 cycles of cisplatin/vincristine, with radiation therapy by week 15, with 36Gy CSI plus boost to posterior fossa). After march/2000, COGA9961 regimen(20) became the standard treatment for children above 3 years. Children were treated with upfront radiation therapy (23.4 Gy CSI for SR and 36 Gy CSI for HR with concomitant vincristine plus boost up to 54Gy to posterior fossa and maintenance chemotherapy with 8 cycles of cisplatin, vincristine and lomustine).

*Statistical analysis*

All data were described using standard summary statistics. Survival estimates were obtained using the Kaplan-Meier method and presented with corresponding 95% confidence intervals (CI). Patients who were less than 3 years old at time of surgery were analyzed separately in the survival analyses, as we considered them a special group with different presentation and outcomes. Progression-free survival (PFS) was defined as time from registry at INCA to the date of first relapse or progression of disease, death, secondary malignancy, or date of last follow-up. Overall survival (OS) was measured as time from registry at INCA to date of death or last follow up. Log-rank tests were used to compare survival between patient groups. P-values were two-sided and those less than 0.05 were considered statistically significant. Statistical analyses were performed in the R statistical package (R Founding for Statistical Computing, Vienna, Austria) using the*survival* and *survminer* packages.

**Results**

*Patient demographic and socioeconomic characteristics*

Data on 114 patients with histopathologically-confirmed medulloblastoma (aged 3-18 years) admitted between 1997 and 2016 were retrieved from medical charts. The male:female ratio was 1.32, the median age at diagnosis was 8.2 years (range 3-17.7). Almost seventy-five percent of children lived in the city of Rio de Janeiro and surrounding areas. The median distance from home to the cancer center was 40 kilometers.

High maternal education was found in 30% (n=34) of the patients, however, this information was only available for 47% of patients (n=53). The median maternal age at diagnosis was 35 years (range: 20-54). Nearly 20% of families lived with a household income of less than 1 minimum wage in this study. The median time between onset of symptoms and surgery was 50.5 days (range: 0-1151 days) (Table 1).

*Clinical characteristics*

Headache (83%), nausea/vomiting (78%), and visual disturbances (37%) were the most frequently reported symptoms described by families. All 114 patients had surgery for their disease, 42% (n=48) of the surgeries occurred at INCA. GTR, as described by the neurosurgeon, was achieved in 65 patients (57%). After MRI imaging 52% (n=59) of the patients showed less than 1.5 $cm^2$ of residual tumor. Regarding histology the majority were non-specific medulloblastoma (86%), followed by desmoplastic/extensive nodularity (4.4%) and classic histology (5.3%). According to the Chang Classification, 35% (n=40) were considered to have metastatic disease (M+) at diagnosis. Fifty-seven percent were defined as HR patients (n=65). One hundred and five patients received chemotherapy (92%) and 109 patients received radiation therapy (95%) (Table 2).

*Survival analysis*

Median follow-up was 5 years, and five-year estimated PFS and OS for the entire population was 58.4% (95% CI: 49.4 – 69.1%) and 59,1% (95% CI: 50.5 – 69.3%), respectively (FIG.1). There were no differences observed between males and females in either PFS (53.8% vs 60.1%; p=0.58) or OS (58.3% vs 60.2%; p=0.49). Patients with localized disease [71.0% (95% CI: 60.3 – 83.7%)] had better OS compared to those with metastatic disease [52.9% (95% CI: 38.7 – 72.4%); p=0.019]. SR patients (5-year OS: 69.4%) were observed to have higher OS than HR patients (5-year OS: 53.8%), although this difference was not statistically significant (p=0.063) (FIG.2). Patients that lived >40km from INCA (5-year OS: 68,2%) fared better than those who lived closer (5-year OS 52%; p=0.032) (FIG.3).

Patients treated as per COGA9961 Protocol had better OS (5-year OS: 70.6%) compared to those treated with pre irradiation chemotherapy regimen (5-year OS: 41.7%), however this difference did not reach statistical significance (p=0.16). Sixteen patients initially stratified as SR were treated with higher doses of radiation therapy as per HR regimen because of the delay in starting raditation therapy. The survival outcomes were better, but not statistically significant, than those treated as SR (79.4% vs 67.7%; p=0.22).

## Discussion

Our study sought to describe the epidemiological characteristics and provide survival outcome data of children with medulloblastoma, age 3-18 years in a single, public tertiary-care referral center located in Rio de Janeiro/Brazil.

Five-year event-free survival of this cohort was 58.4% and the overall survival was 59.1%, for patients >3-18 years at diagnosis, and 5-year OS 69.4% for SR and 53,8% for HR patients. In a retrospective study from 1983 to 2001 at the same institution with 101 patients under 18 years, the 5-year OS was 53% and the 5-year Disease Free Survival (DFS) rate was 40%(21). According to staging, our cohort had 5-year OS of 52.9% for M+ and 71.0% for M0 (p=0.019). In previous Brazilian studies, patients M+ had 5-year OS of 43.7% and M0 had 5-year OS of 73.8%(21) and 5-year OS 59% for SR patients and 5-year OS 24% for HR (22).

High-income countries generally have better survival outcomes compared to lower income countries. The COGA9961 trial, conducted in the United States, had 5-year EFS of 81% and OS 87% for standard-risk patients(20). Other reports from Canada(23) (OS: 69.2%) and United Kingdom(24) (OS: 73.4%) show similar survival outcomes. However, some high-income countries show lower survival rates, such as Spain(25,26)

with reported 5-year OS of 55% and EFS of 46%, Singapore(27) with 5-year OS of 51.5% and EFS of 44.5%, and Norway(28) with 5-year OS of 62%. Some upper middle-income countries have reported variable outcomes, such as Taiwan(29) where 5-year OS has been reported 65.9% in one institution and 50% in another institution(30).

The difference in survival among high income (HIC) and low-middle income countries (LMIC) is multifactorial. Late diagnosis with advanced disease presentation, coexisting debilitating conditions (such as malnutrition), treatment abandonment, and inefficient health care systems are some of the barriers of care in pediatric cancer in LMIC(31).

Treatment abandonment has been considered one of the most important causes of cancer treatment failure in LMIC(38) and is defined as the failure to start or complete medically-indicated, possibly curative treatment causing unnecessary mortality and morbidity(39). The causes of treatment abandonment are multifactorial – financial, social, political, health care availability – and are frequently beyond the family's possibility to control. The duration to define abandonment is [?]4 consecutive weeks of missed therapy. Since patient refusals of treatment without resuming therapy are not always recorded, treatment abandonment has been historically underreported and misclassified and the reported rates are variable, ranging from 0 to 74.5%. At INCA, the report from 1139 patients between 2012-2017 was 1.66% for all pediatric solid tumors and 0.7% for pediatric brain tumors(20). The main reasons for abandonment were lack of understanding the need for therapy, followed by transportation and financial difficulties. In this present study there was 2 cases of abandonment of treatment after radiation therapy (1.6%). Both patients are alive and resumed the follow-up without chemotherapy, confirming their result that abandonment was not associated with increased mortality.

Survival was also assessed by the distance from home to the tertiary cancer center. Patients who lived more than 40km from INCA fared better than those who lived closer, (5-year OS: 68,2% vs 52%; p=0.032). This counterintutive conclusion can be possibly explained by socioeconomic conditions that Brazilian patients face during their treatment. Patients who live far from INCA can stay at housing provided by Ronald McDonald House Charities, which is near the hospital and has transportation at any time of the day and in case of emergencies (such as fever). So even the poorest patients hosted there can access the hospital promptly when needed, reducing the time to get medical support or diminishing absenteeism. Patients often complain about lack of transportation to acess the hospital for outpatient consultations or for emergencies, and while the government provides some resources for patient transportation, it is not widely distributed or utilized.

The use of initial chemotherapy after surgery and delayed radiation therapy has shown worse outcomes when compared to upfront radiation therapy(32). In this cohort, a group of patients (n=12) received pre-irradiation chemotherapy by week 15. Eighty-three patients received upfront radiation therapy post surgery according to the COGA9961 protocol; this group had increased OS when compared to the chemotherapy pre irradiation protocol (70.6% vs 41.7%), which was used until the early 1990s when it was replaced by the COGA9661. Current strategies recommend risk-adapted CSI and adjuvant chemotherapy in children above 3-5 years(1), while infants should receive treatment with either high-dose chemotherapy and stem cell transplant(32) or intraventricular chemotherapy(33), in order to avoid or delay the use of radiation therapy.

The epidemiological characteristics of this series possibly explain the differences in survival that medulloblastoma patients have in Brazil. Issues related to limited health care resources, poverty, delayed diagnosis, treatment abandonment, and malnutrition are reflected in inferior survival outcomes when compared to high-income countries(34).There is a difference in survival between high-income countries treating their patients per COGA9661, with a reported 5-year OS of 87%(20) and the present study where the overall survival was 69.4% for SR patients. Despite the difficulties encountered in an upper-middle income country, it was possible to deliver treatment with good results. Nevertheless many initiatives can hopefully be explored to aid in improving the results and reducing these differences.

The limitations of the study are primarily due to its retrospective nature and the limitations of chart information, with missing data. Patients being operated in other institutions pose also difficulties, because of lack

of information. The strengths of the study are the relatively large number of patients with medulloblastoma from a single institution, and the homogeneous treatment that most patients received. INCA as public reference hospital for cancer pediatric patients registers the vast majority of medulloblastoma patients in the state. Thus, this study is possibly a proxy of the medulloblastoma scenario in Rio de Janeiro.

**Conflict of Interest statement**

All authors declare that there is no conflict of interest.

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**Legend**

FIGURE 1 Overall Survival and Progression Free Survival of the entire cohort

FIGURE 2 Overall Survival according to Risk Stratification

FIGURE 3 Overall Survival according to distance of treatment center

TABLE 1 Demographics and Socioeconomic Information

TABLE 2 Disease and Treatment Information

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`TABLE 1.pdf` available at https://authorea.com/users/377865/articles/494523-epidemiological-characteristics-and-survival-outcomes-of-children-with-medulloblastoma-treated-at-the-national-cancer-institute-inca-in-rio-de-janeiro-brazil

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`TABLE 2.pdf` available at https://authorea.com/users/377865/articles/494523-epidemiological-characteristics-and-survival-outcomes-of-children-with-medulloblastoma-treated-at-the-national-cancer-institute-inca-in-rio-de-janeiro-brazil

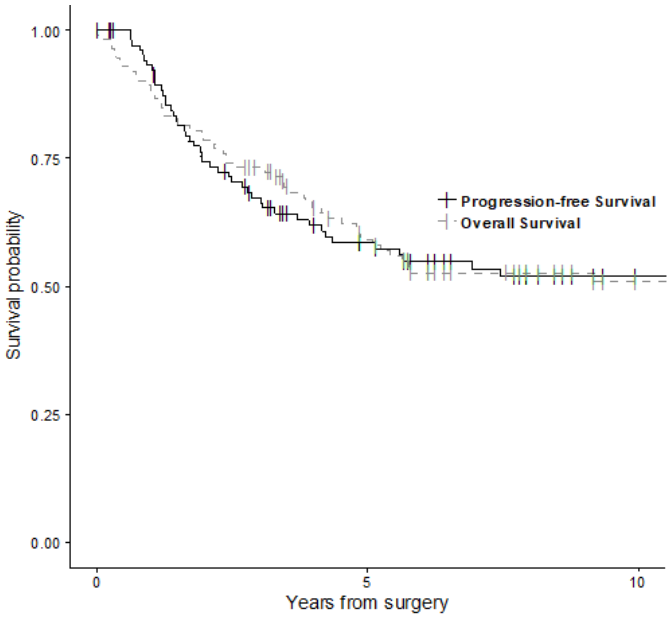


FIGURE 1 Overall Survival and Progression Free Survival of the entire cohort

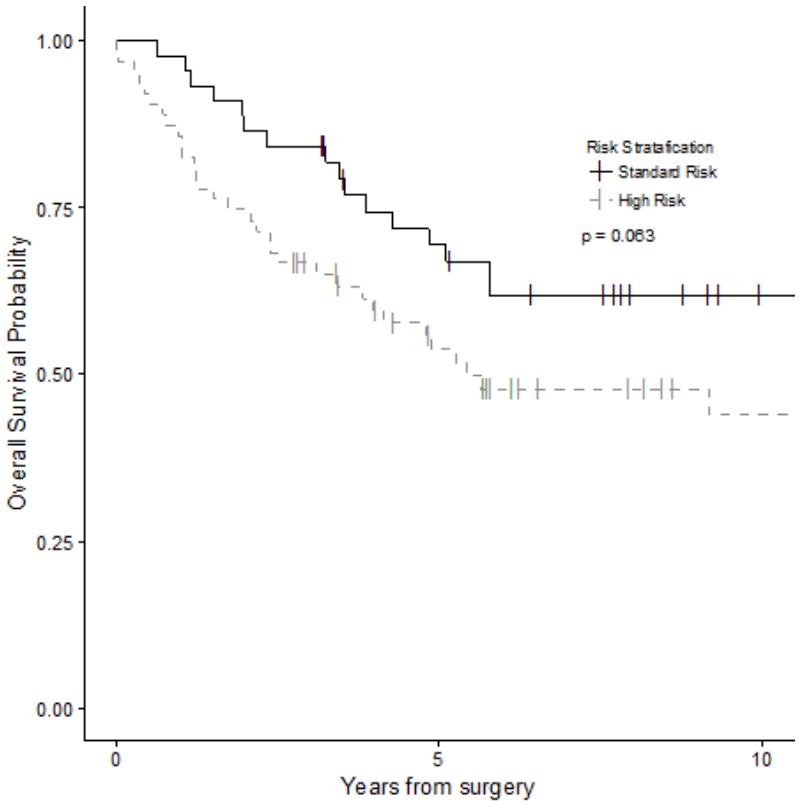


FIGURE 2 Overall Survival according to Risk Stratification

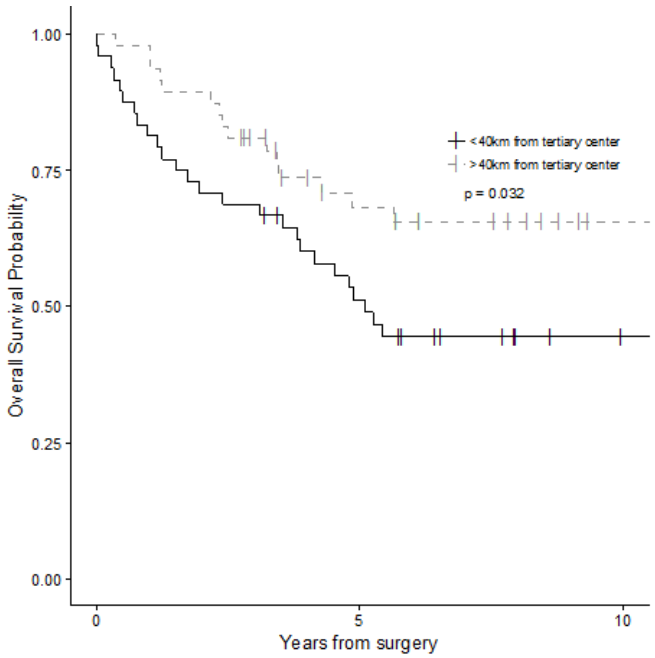


FIGURE 3 Overall Survival according to distance from treatment center