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Pediatric CNS tumors in low- and middle-income countries: expanding our understanding

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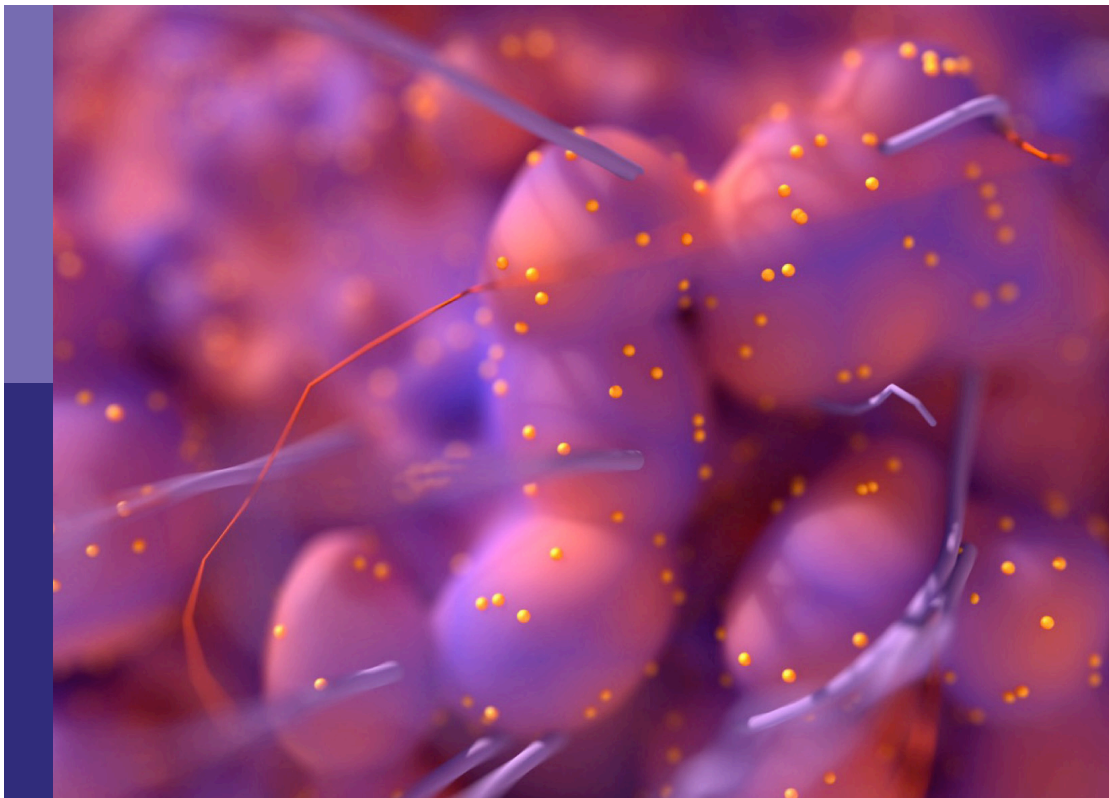

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Pediatric CNS tumors in low- and middle-income countries: expanding our understanding

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Editorial: Pediatric CNS tumors in low- and middle-income countries: expanding our understanding

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Editorial on the Research Topic
Pediatric CNS tumors in low- and middle-income countries: expanding our understanding

Pediatric central nervous system (CNS) tumors are a significant global health burden. These tumors are the second most common childhood cancer and the leading cause of cancer-related death in children (1). Each year, approximately 40,000 children worldwide are diagnosed, with substantial variations in incidence and outcomes between high-income and low- and middle-income countries (LMICs) (2). Many challenges exist, including late diagnosis, limited access to quality care, and lack of specialized treatment facilities (3, 4). Addressing this burden requires international collaboration, improved diagnostic and treatment capacity, all cemented on evidence-based approaches. Between May 2023 and October 2024 *Frontiers in Oncology* opened a Research Topic on *Pediatric CNS Tumors in Low- and Middle-Income Countries (LMIC): Expanding our Understanding*. Twenty-one manuscripts were published that provide insight into the challenges and advances in the care of children with CNS tumors across LMICs.

Pediatric oncologists Diaz-Coronado et al. leaders in their countries, provided an editorial summarizing the challenges contributing to the wide gap in survival outcomes in countries in Latin America. The lack of adequate infrastructure which may include an equipped neurosurgical center and intensive care unit beds, access to radiation, magnetic resonance imaging with timely reports, national treatment guidelines, lack of hospital beds and staff to care for children who may require high-dose chemotherapy or high-level inpatient care. Additional factors such as delays in diagnosis, limited access to medications, lack of a multidisciplinary team approach, higher rates of treatment abandonment, malnutrition, and lack of supportive care measures are common barriers.

Across LMICs, a significant limitation is the lack of pediatric cancer registries to provide real estimation of the burden of disease. However, there are two countries in the forefront of pediatric cancer registries in Latin America. The first and well-established

Registro Oncopediátrico Hospitalario Argentino (ROHA) was started with Dr. Florencia Moreno with the support of the Kaleidos Foundation in 2000 in Buenos Aires, Argentina. ROHA unifies data from the various pediatric cancer centers across the country covering 93% of all national cases and since 2010 it grew to include children up to 19 years of age (5). The systematic collection of patient clinical data paired with diagnosis, pathology findings, institutional affiliation, care migration among other aspects has allowed for various analyses that help devise strategies relevant to the needs of their children and their families at the institutional, provincial and national levels. In Colombia, a Childhood Cancer Clinical Outcomes Surveillance System (VIGICANCER) was established in 2009 and currently obtains data from 27 pediatric oncology centers in ten Colombian cities. Ramirez et al.'s manuscript was able to provide an estimate of the survival outcomes of children diagnosed with a pediatric brain tumor in Colombia. Data captured included mortality, relapse, treatment abandonment and occurrence of second neoplasms including rates of gross total resections. Their data revealed that survival estimates are lower than those of high-income countries.

The first national quantitative assessment of the pediatric neuro-oncology services and resources available in Mexico was undertaken. A total of 33 institutions participated, mostly from the public sector that care for much of the population. They reported that most institutions saw less than 10 new pediatric CNS tumors per year. Mexico reports a total of 850 newly diagnosed patients each year of which 300 deaths occur in children less than 19 years of age. UNICEF estimates there are 39 million children below the age of 18 years as of 2023 in Mexico. The incidence of pediatric brain tumors in the United States reported by CBTRUS in 2022 is approximately 6.3 cases per 100,000 children between 0-19 years of age. This would estimate there is a potential for 2,340 new diagnoses in Mexico between 0-18 years of age, suggesting there are a considerable number of children that are not being accounted for, diagnosed or seeking medical care in time. Of the resources mentioned, ICU bed and services were limited, pathology on average is based on basic histopathological testing, and nearly 20% of institutions did not have access to a neurosurgeon. This effort was published by Arce-Cabrera et al. to bring awareness of the current state of pediatric neuro-oncology resources in Mexico in the hopes to generate interest and amplify the critical components needed to be implemented for effective change in the care of children with CNS tumors.

Neuropathology has become increasingly sophisticated in the recent decade introducing molecular classifications in addition to histopathological analysis to arrive at an accurate diagnosis. In Latin America, it is very common to not have access to the basic immunohistochemical panels required for CNS tumors. Therefore, the likelihood being these rare tumors with great heterogeneity are being reviewed by a general pathologist in a center lacking expertise and equipment on histology alone. Some centers, like the National Children's Hospital Dr. Carlos Sáenz Herrera in San Jose, Costa Rica, as described by Delgado given her additional training in pediatric neuropathology has been able to integrate a broad immunohistochemistry (IHC) panel but is still lacking in molecular studies, such as H3K27 or BRAF fusion studies among others. BRAFV600E is commonly available in Latin America since it is widely used in adult oncology, however, pediatric specific molecular studies are significantly lacking. There is awareness that molecular studies are not always going to help change your treatment management and traditional classifications through IHC are paramount, however, it will become imminent when molecular classification will be an essential component for diagnosis, treatment and prognosis in LMIC as well. Therefore, an excellent proposition by Dr. Nuñez to begin designating locoregional neuropathology centers of excellence and build capacity to review specimens for these highly specialized CNS tumors. It is unrealistic for pediatric cancer centers across LMICs to all become highly specialized in pediatric neuropathology.

Rajagopal et al. from Malaysia collected 50 medulloblastoma samples between 2003 and 2017 and were sent to Heidelberg, Germany for 850K Methylation. In their cohort of 48 patients, seven patients were treated as medulloblastoma, but methylation later revealed some discrepant results such as GBM, ATRT, Ewing sarcoma, MPNST, and pineoblastoma. They highlighted the importance of methylation in being able to subgroup their medulloblastoma samples and more accurately align their patient outcomes with the subgroups and in the future permit subgroup specific therapies, but they also recognize the high cost of this technology.

Amayiri et al. from The King Hussein Cancer Center wrote about their experience outsourcing molecular testing through their twinning program with SickKids Clinical Laboratory in Toronto. Of the 237 patients reviewed, 32 samples were sent for next generation sequencing based on the potential for clinical benefit. From this cohort they found 59% potentially actionable alterations, which included the use of targeted therapies and checkpoint inhibitors, three samples also revealing the suggestion of an underlying germline syndrome later confirmed with formal testing. The ideal would be for future evaluations that all samples be performed upfront rather than at progression.

Recognizing potentially actionable alterations are typically only beneficial if the local providers have access to the targeted medications. The King Hussein Cancer Center retrospectively reviewed their experience using BRAF/MEK inhibitors through a compassionate use program and provide outcomes after treating 20 patients (Laban et al.). Seventeen with 17 low-grade gliomas and three with high-grade glioma. Their experience with dabrafenib/trametinib was favorable with 47% of patients showing a favorable response to therapy vs. 11% for those who received chemotherapy and therefore a significantly longer median progression free survival (PFS) with dabrafenib/trametinib (20.1 months) compared to 7.4 months with chemotherapy. Unfortunately, access to these medications is a significant challenge since the compassionate use program has discontinued and the financial cost of these medications is prohibitive.

The article written by Gilani et al. described how they built neuropathology capacity at their center in Aga Khan University Hospital and Indus Children's Cancer Hospital in Karachi, Pakistan (13). LMIC twinning with Sick Kids in Toronto provided training and mentorship to their pathologists. It also enabled infrastructure development by adopting and validating

new immunohistochemical stains. Molecular diagnostics was undertaken at Sick Kids and their authors pointed out since precision therapies are still largely out of reach for most patients in LMIC, molecular biomarkers remained largely irrelevant for their capabilities as well as other LMIC. Nonetheless, they also found some unresolved cases where molecular techniques were indispensable for diagnosis. Thus, the development of affordable alternative molecular techniques will be important and concluding that select neuro-pathology reference labs in a particular country or region, will improve histopathologic diagnosis for LMIC.

Surgical challenges are vast across LMIC, Haizel-Cobbina et al. performed a large cross-sectional review of 312 patients treated across seven referral centers in Sub-Saharan Africa. She described a significant lack of neuronavigation, intraoperative imaging, and cortical mapping leaving neurosurgeons to depend on anatomical landmarks to perform their resections. Most patients also did not have access to post-operative imaging whether CT or by MRI. Overall, they found approximately one-third of patients indicated for surgery were unable to receive it. And most patients (74%-85%) for whom adjuvant therapy was recommended were unable to receive therapy. For those patients that managed to receive adjuvant care there was discoordination between the oncology and surgical teams leading to delays and missing the optimal window to administer adjuvant therapy.

Access to radiation therapy is also a challenge across LMIC with an insufficient number of radiotherapy machines as per the International Atomic Energy Agency (IAEA) and with technology that is not up to date. Additionally, there can be interruptions in therapy because machines frequently can be down in addition to the same issues with regards to expertise of personnel. Of note, there are some countries without radiation therapy at all. Therefore, LMIC-HIC partnerships and collaborations have proven crucial to address the gap in radiation therapy access. Hernandez et al. understand it is important to explore new, cost-effective radiation therapy technologies that would be more feasible for resource-limited settings. In their manuscript they were able to validate the use of an auto-planning tool for craniospinal radiation therapy planning. They utilized 3D-conformal CSI planning since 84% of resource-constrained clinics utilize this as opposed to more advanced techniques (ie: IMRT, VMAT). The efficiency of the tool has the promise to reduce contouring time and alleviate treatment delays which are known to impact survival outcomes, especially in LMICs.

Survival outcomes and other patient data for LMIC are significantly lacking in the literature. These data provide the pediatric oncology community with a better understanding of the circumstances experienced in the region and the strategies that need to be implemented for effective change. Additionally, it can provide a benchmark for which to measure the clinical impact of such treatment changes. In this series, although mostly retrospective analyses we are provided with clinical outcome data for patients with ependymoma, medulloblastoma, CNS germ cell tumors and optic pathway glioma (OPG) were written by their local pediatric oncologists.

Oigman et al. retrospectively reviewed 72 patients compiled over 20 years of data on pediatric patients with Ependymoma admitted to the National Cancer Institute of Rio de Janeiro, showing an OS for all patients of 67% at 5 years and 50% at 10 and 20 years. However, also demonstrating higher rates of recurrences and long-term quality of survival results inferior to HIC while also highlighting challenges in obtaining post-operative imaging and complete staging. In Peru, Perez-Roca et al. retrospectively reviewed 85 patients over the period of 19 years treated at the National Cancer Reference Center (INEN) in Lima with a 5-year OS for all patients of 55.89% and PFS 37.1%, finding challenges with only 31.76% of patients reported to have a gross total resection. Treatment abandonment was remarkably high in this cohort, as many as 23 patients (27%).

Ramirez-Melo et al. also retrospectively compiled data on 30 patients less than 18 years with newly diagnosed OPG from the Hospital Civil de Guadalajara, Mexico treated over 18 years. They were able to see that although they have the elements needed to provide favorable outcomes for their patients there are still barriers that lead to a poorer quality of survival such as high rates of surgical resections, post-surgical complications, and inability to assess functional outcomes such as vision in two-thirds of their patients. Additionally, they found a higher utilization of radiation therapy in up to 20% of patients contributing to the long-term burden of disease and a 10% rate of treatment abandonment.

Salceda-Rivera et al. compiled a large series of 284 patients treated in 21 pediatric oncology centers throughout Mexico between 1997 and 2017. This included infants and children up to 17 years of age treated with a variety of chemotherapy regimens, predominantly ICE, and up to 75% of patients received craniospinal radiation, including <3 years old. They reported an inferior survival in infants with desmoplastic nodular medulloblastoma of 58% 5-year OS, where in HICs OS is above 95% for non-metastatic non-p53 mutated desmoplastic nodular medulloblastoma utilizing radiation-avoidance chemotherapeutic regimens. However, this study now becomes a benchmark to help homogenize their national protocols and unify treatment strategies to improve survival outcomes, particularly for the most curable entities.

This series also included the Associate of Hematology/Oncology in Central America (AHOPCA) experience treating 48 patients over 20 years gathered mostly from Guatemala and Nicaragua and a few patients from El Salvador and the Dominican Republic. Giron et al. described a different reality where diagnosis is not able to be made with immunohistochemical stains rather relying on histology, serum tumor markers with clinical and imaging characteristics. They included all intracranial germ cell tumors reporting an OS of 68% for germinoma, 50.6% for NGGCT, and 85.7% for unclassified GCT.

Cappellano et al. shared their experience treating a series of complex, high-risk non-germinomatous germ cell tumors (NGGCT) at GRAACC, an experienced children's cancer center in Sao Paulo, Brazil. A total of 15 patients with NGGCT were enrolled in their prospective trial that included all primary intracranial germ cell tumors (GCT). Most patients had pineal or suprasellar tumors and one bifocal. Three of these patients had metastatic disease, one with extra-neural metastasis to the lungs. Twelve patients with BHCG levels over 200 IU/L, seven with combined AFP levels >1000 ng/mL. They reported a 72% EFS and OS at 5 years for this notably high-risk population. This study

also highlighted the risk of hyperhydration in a population of patients afflicted with diabetes insipidus as two toxic deaths occurred.

The therapies we administer are just as important as the supportive care measures we provide. Timely supportive care measures such as infusing antibiotics within 60 minutes of the onset of a fever is incredibly challenging for LMIC. Dassi et al. described the challenges they experienced with invasive fungal infections at GRAACC. An 11-year analysis of 818 children, of which 38 developed invasive fungal infections and concluded that careful evaluation of patient risk factors was the best mitigation strategy for prevention of this highly morbid and potentially fatal infection.

As mentioned, international collaborations between HICs and LMICs are also important to help manage rare, complex diagnoses. Daniel-Abdool et al. described their experience in Trinidad and Tobago caring for a child with WNT-Medulloblastoma and subsequently diagnosed with Turcot Syndrome. The diagnosis was made possible through a collaboration with Sick Kids in Toronto which allowed for the maximization of this child's care.

Moreno et al. reviewed 266 medulloblastoma diagnosed in Brazil, Portugal and Argentina and they noted a higher incidence of hereditary WNT-activated medulloblastomas in the Latin-Iberian population in comparison to the North American and European populations. Interestingly, their Kaplan–Meier analysis revealed patients with WNT-activated medulloblastomas CTNNB1 wild-type had a worse outcome, with 71.4% in comparison to 100% of CTNNB1 mutant cases (p=0.031). Additionally, the WNT-medulloblastomas that are CTNNB1 wild-type cases can harbor APC germline mutations, suggesting that up to 27% of the Latin-Iberian cases of WNT-medulloblastoma may also have familial adenomatosis polyposis contrasting with 10% reported in North America and Europe. s

Robust multidisciplinary collaborations are essential to broaden our understanding of priority interventions and the implementation of successful programs. Over the past decade, we have witnessed a cohesive effort from pediatric oncologists and other pediatric subspecialists across Latin America to overcome the multiple barriers described. Baroni et al. from the Hospital Garrahan in Buenos Aires, Argentina described how they implemented a network and communication strategy through biweekly multidisciplinary meetings across their vast country that has enabled for an early referral system to improve the times to diagnosis and treatment strategies for children with CNS tumors. This effort spans the private and public sector and has proven to be beneficial and is to be implemented as a national health policy. In addition, a multidisciplinary collaboration in Pakistan sought to build pediatric neuro-oncology service delivery capacity by providing education programs, tumor boards, and strengthening of neuro-pathology review in collaboration with The Hospital for Sick Kids in Toronto through regularly scheduled multidisciplinary tumor boards (Mushtaq et al.). They concluded that the importance of establishing treatment protocols, fellowship programs, and regional tumor boards are sustainable opportunities to improve outcomes locally.

Children with CNS tumors in LMICs deserve quality care and should not be neglected as the field continues to advance and evolve. Our ability to cure these children should be constrained solely by our understanding of the disease's biology, not by the availability of care. Ensuring equity in advanced treatments is crucial and probably the largest existing challenge in the field of pediatric neuro-oncology.

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Closing the gap: National Argentinian discussion forum on paediatric brain tumours

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The burden of Central Nervous System (CNS) tumours is further compounded by the fact that they require highly specialised and skilled multidisciplinary care, including access to modern neuroimaging, neurosurgery, neuropathology and molecular biology, radiotherapy and chemotherapy, which may not be widely available in an integrated manner in large parts of low-middle income countries (1–3). Delay in diagnosis and initiation of treatment, the lack of systematic staging and standardised treatment all over the country and the limited access to high complexity medical centres could have a significant influence on outcomes in developing countries (4, 5). In Argentina the incidence of paediatric CNS tumours is approximately 260 new cases (26 cases per million children) per year. Sixty two percent of them needed to migrate to high complexity medical centres for treatment between 2012-2019 (6). About 50% of paediatric brain tumours were treated at "Prof. Dr. Juan P. Garrahan"; a premier reference centre for the care of high complexity child pathologies throughout Argentina. Here the healthcare organisation is based on progressive care with a hierarchy of interdisciplinary activity and an integrated approach supported by the highest technological development (such as 1·5 T Magnetic Resonance Imaging scanners and medical linear accelerators for radiotherapy treatment) and scientific-technical level of its human resources. Although overall survival of brain tumours has improved over the years in this country, it is still lower than in high income countries. Furthermore, considerable mortality reduction was achieved in Hospital Garrahan during the last 10 years, being 61·8 percent of mortality in 2000 vs. 32·4 in 2018. However, this survival improvement was not followed by the rest of the country bringing to light that new strategies were urgently needed.

Since December 2020, a highly qualified multidisciplinary team (including neuro-oncologists, pathologists, radiologists, radiotherapists and neurosurgeons) from Hospital Garrahan has implemented a network and a remote communication strategy for early referral, accurate diagnosis and staging, aiming to provide adequate treatment of children with brain tumours between Hospital Garrahan and other centres in Argentina. Biweekly (twice

per month) interactive multidisciplinary meetings were established between private/public medical centres across the country and Hospital Garrahan. This was set up as a prospective qualitative-quantitative study, with interventions and registration of times of compliance.

The active participation of private and public centres covering approximately 96·6% of the country's population was achieved; being connected up to 40 working groups simultaneously. One hundred twenty five new CNS patients (67 during the first year; 58 during the second year) from 21 provinces (85% of the country) were discussed in a multidisciplinary manner during the first 24 months of this project; 7,2% regarding diagnosis advice, 52% for treatment definition and 40,8% for both. Fifty-three tumour samples required a pathology analysis/review at Hospital Garrahan; 43.39% for initial diagnosis, 50.94% for second review (changing the initial diagnosis in 29.6% cases) and 5.6% for molecular workup. Only 34 patients required a referral to a centre of high complexity; 45% for radiotherapy, 45% for surgical issues and 10% for high dose chemotherapy with stem cells rescue. More than 250 brain and spine MRI scans were reviewed to improve tumour staging and oncology management. After the multidisciplinary meetings, the final treatment plan differed in 47,5% from the initial proposal; 27,6% due to MRI reviewed results and 72,3% regarding oncological discussion. The most frequently implemented therapeutic changes after the discussions were the selection of chemotherapy strategies in 51.3%, followed by neurosurgical intervention in 32.8% and radiotherapy requirement and prescription (field and dose) in 15.7%. Twenty-five patients needed multiple discussions (range 2-4) regarding follow up or after changes in management to guarantee the continued benefit of this recommendation.

On the other hand, we found out the principle barriers for proper diagnosis and treatment in centres of our network. The lack of highly experienced subspecialised neuroradiologists and oncologists in brain tumours and the limited infrastructure, including neurosurgical, pathology and paediatric radiotherapy facilities are the main limitations.

The exponential benefit of this strategy was established, showing to be a useful and fundamental tool to be implemented as a national health policy. The success of the implementation was marked by acceptance, appropriation, feasibility, adherence, coverage and sustainability. Our experience showed that multidisciplinary team management with high level expertise is key in countries with limited resources. Although several years will be needed to see the real survival impact of this strategy on outcomes, it pretends to bridge the gap between high complexity centres and the local community, achieving diagnosis and treatment equity and access opportunity. Furthermore, a gradual gain of knowledge and experience in brain tumour management was shown over these 2 years, changing the main discussion topic from differential diagnosis and proper tumour staging during the first year to treatment strategies and local implementation in the second year.

Finally, we would propose this remote care modality as a state policy in the near future, going up to a higher scale and being expanded into a broader, more far-reaching practice/policy. Actually, a national oncological coordinator centre is being established to be implemented shortly. Importantly, this model may be applied not only to other areas of paediatric cancer care but also to any other area in which a knowledge and skill gap can be identified.

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High frequency of WNT-activated medulloblastomas with *CTNNB1* wild type suggests a higher proportion of hereditary cases in a Latin-Iberian population

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Purpose: Medulloblastomas are the most common primary malignant brain tumors in children. They are divided into molecular subgroups: WNT-activated, SHH-Activated, *TP53* mutant or wild type, and non-WNT/non-SHH (Groups 3 and 4). WNT-activated medulloblastomas are usually caused by mutations in the *CTNNB1* gene (85%–90%), and most remaining cases *of CTNNB1* wild type are thought to be caused by germline mutations in *APC*. So far, the frequencies of *CTNNB1* have been reported mainly in North American and European populations. The aim of this study was to report the frequency of *CTNNB1* mutations in WNT-activated medulloblastomas in a Latin-Iberian population and correlate with their clinicopathological characteristics.

Methods: A total of 266 medulloblastomas from seven different institutions from Brazil (n=211), Portugal (n=38), and Argentina (n=17) were evaluated. Following RNA and DNA isolation from formalin-fixed, paraffin-embedded (FFPE) tumor tissues, the molecular classification and *CTNNB1* mutation analysis were performed by nCounter and Sanger sequencing, respectively.

Results: WNT-activated medulloblastomas accounted for 15% (40/266) of the series. We observed that 73% of WNT-activated medulloblastomas harbored *CTNNB1* mutations. *CTNNB1* wild-type cases (27%) were more prevalent in female individuals and suggested to be associated with a worse outcome. Among the *CTNNB1* wild-type cases, the available analysis of family history revealed two cases with familiar adenomatous polyposis, harboring *APC* germline variants.

Conclusion: We observed a lower incidence of *CTNNB1* mutations in WNT-activated medulloblastomas in our Latin-Iberian cohort compared to frequencies previously described in other populations. Considering that *CTNNB1* wild-type cases may exhibit *APC* germline mutations, our study suggests a higher incidence (~30%) of hereditary WNT-activated medulloblastomas in the Latin-Iberian population.

KEYWORDS

medulloblastomas, WNT activated, *CTNNB1*, APC, Latin-Iberian

Introduction

Medulloblastomas are a group of heterogeneous embryonal tumors considered as the most common primary malignant brain tumor in children, with an annual incidence of 0.4 in 100,000 population in children and young adults aged 0–19 years (1). Histologically, medulloblastomas are divided into classic (40%–45%), desmoplastic nodular (30%–35%), anaplastic/large cell (15%–20%), and with extensive nodularity (10%) (2). These tumors are commonly divided into four molecular subgroups: WNT activated, SHH activated, Group 3, and Group 4 (2, 3). In the 2021 WHO classification, the SHH-activated group is subdivided into *TP53* wild type and *TP53* mutant, and Groups 3 and 4 are merged in a non-WNT/non-SHH subgroup (4). The standard therapy based on surgery, craniospinal irradiation, and chemotherapy may vary according to the molecular subgroup, the patient age, leptomeningeal dissemination status, and the extension of surgical resection (2).

The wingless (WNT)-activated group accounts for 10% of all medulloblastomas, is commonly observed in children older than 4 years, in an equal proportion of boys and girls, and usually shows no metastasis at diagnosis (3). This molecular subgroup is a particular entity with a distinctly better outcome in children, with more than 95% of 5-year overall survival when these children are submitted to standard therapy and displays a distinct molecular pattern of gene expression (5) and methylation profile (6).

The WNT is a conserved pathway that may induce cell proliferation and growth during development via regulation by beta-catenin, which is translocated to the nucleus for binding to transcriptional factors inducing the expression of cyclins and proto-oncogenes (7). In differentiated cells, the WNT pathway is mostly in a non-activated state, in which a disruptive complex comprised APC, AXIN, GSK3, and CK1, enabling beta-catenin phosphorylation, triggering its ubiquitination and degradation (7).

It has been reported that 85%–90% of WNT-activated medulloblastomas harbor hotspot mutations in the *CTNNB1* gene, which encodes beta catenin (8). Hotspot mutations are located at the exon 3, which corresponds to the phosphorylation site of the beta-catenin. These mutations in the exon 3 inhibits the phosphorylation of beta-catenin, triggering escape from degradation, resulting in cytoplasmatic accumulation of beta-catenin, which translocates to the nucleus inducing activation of genes involved in cell proliferation (7, 9). Most of the remaining 10%–15% of WNT-activated (*CTNNB1* wild type) tumors carry germline *APC* variants (8, 10). This later condition is observed in Turcot syndrome, when primary brain tumors such as medulloblastomas may co-occur with multiple colorectal adenomas, observed in families with familial adenomatosis polyposis (FAP) (11).

For patients with WNT-activated medulloblastomas *CTNNB1* wild type, referral for genetic risk cancer assessment and germline *APC* sequencing is recommended. It is reported that 70% of these patients will have the FAP diagnosis, triggering prevention measures such as total colectomy for the patient and germline tests to the relatives (8). Identifying these cases, patients with WNT-activated medulloblastomas and *CTNNB1* wild type have a high

chance of harboring germline mutations in *APC* and should improve the patient's treatment by differentiated surveillance and early cancer detection in patients and relatives resulting in more effective therapy (8).

The incidence of the WNT-activated *CTNNB1* wild type is currently well established for the North American and European population (8), and little is known about the frequency of these mutations in Brazilian and other Latin-Iberian countries. In the present study, we aimed to analyze the frequency of *CTNNB1* mutations in WNT-activated medulloblastomas in a large Latin Iberian medulloblastoma cohort.

Materials and methods

Patient cohorts

In the present retrospective study, we evaluated 266 FFPE medulloblastoma specimens collected between 2001 and 2022 from naive-treated patients from seven different institutions in Brazil, Argentina, and Portugal: Barretos Cancer Hospital, Brazil (n=119); Federal University of São Paulo UNIFESP (n=20), Brazil; AC Camargo Hospital, Brazil (n=15), Ribeirão Preto Medical School, Brazil (n=37); Child Hospital of Brasília, Brazil (n=20); Italian Hospital of Buenos Aires, Argentina (n=17); and Centro Hospitalar Universitário São João, Portugal (n=38). The frequency of molecular subgroups was previously reported in a subset of cohort[5,19]. The patient's clinical and molecular features were collected on medical reports and stored in the Research Electronic Data Capture (RedCap). This study was approved by the institutional review board from Barretos Cancer Hospital (CAAE: 59979816.6.1001.5437). Informed consent was obtained from the patients or familiars before APC germline evaluation.

RNA and DNA isolation

The tumor area was previously marked by an experienced pathologist, ensuring the presence of >80% of tumor cells and the absence of microvascular proliferation and necrosis. For *CTNNB1* gene analysis, DNA isolation from macrodissected formalin-fixed, paraffin-embedded (FFPE) was performed using the QIAamp DNA Mini Kit (Qiagen, Venlo, The Netherlands), following the manufacturer's recommendations. For *APC* gene analysis, DNA was isolated from peripheral blood samples using the QIAamp DNA Blood Mini Kit (Qiagen, Venlo, The Netherlands), following the manufacturer's instructions. The DNA quantification was performed using the NanoDropVR 2000 (Thermo Fisher Scientific, Waltham, USA) (12). The RNA isolation was performed using the deparaffinization solution (Qiagen, Venlo, The Netherlands) and the RNeasy Mini Kit (Qiagen, Venlo, The Netherlands), and the Qubit 2.0 Fluorometer (RNA HS Assay kit, Life Technologies, Thermo Fisher Scientific, Waltham, USA) was applied for RNA quantification following the manufacturer's recommendations (13, 14).

Molecular classification by gene expression

Gene expression assays were performed in the nCounter® FLEX Analysis System available in the Molecular Oncology Research Center of Barretos Cancer Hospital (BCH) using the nCounter® Elements custom panel (NanoString Technologies, Seattle, USA). The panel comprises three reference genes (*ACTB*, *GAPDH*, and *LDHA*) and 22 targets for WNT (*WIF1*, *TNC*, *GAD1*, *DKK2*, and *EMX2*), SHH (*PDLIM3*, *EYA1*, *HHIP*, *ATOH1*, and *SFRP1*), Groups 3 (*IMPG2*, *GABRAS*, *EGFL11*, *NRL*, *MAB21L2*, and *NPR3*), and Group 4 classification (*KCNA1*, *EOMES*, *KHDRBS2*, *RBM24*, *UNC5D*, and *OAS1*) as previously described (15, 16).

CTNNB1 and *APC* sequencing

The *CTNNB1* mutation was evaluated by Sanger sequencing using the following *CTNNB1* primers: forward, GCTGATTTGATGGAGTTGGA; reverse, GCTACTTGTT CTTGAGTGAA as reported (17). The PCR reactions were optimized using 7.2 µL of HotStarTaq Master Mix (Qiagen, Hilden, Germany), 5.6 µL of sterile nuclease-free water, 0.6 µL of magnesium chloride (5 mM), 0.3 µL of each forward and reverse primers (10 µM), and 1 µL of DNA. The PCR was performed in the Veriti 96-well thermocycler (Applied Biosystems, model 9902, Singapore) in the following conditions: 40 cycles of denaturation at 96°C for 45 s, annealing at 53°C for 45 s, and extension at 72°C for 45 s.

APC gene (NM_00038.5) mutations were evaluated by NGS (next-generation sequencing) in patients with a family history of colon cancer and/or polyps who have provided consent for germline molecular analysis. Library construction was carried out according to the Barretos Cancer Hospital Hereditary Rare Cancer Solution kit (Sophia Genetics, Switzerland), which includes the genes *APC*, *BRCA2*, *CEBPA*, *DICER1*, *GATA2*, *SMARCB1*, *MEN1*, *NF1*, *NF2*, *PALB2*, *PTCH1*, *PTEN*, *RB1*, *RET*, *RUNX1*, *SUFU*, *TP53*, *TSC1*, *TSC2*, and *VHL*, according to the manufacturer's protocol. Briefly, DNA fragments were generated using an enzymatic fragmentation step. The three subsequent enzymatic steps, end-repair, A-tailing, and ligation to Illumina adapters, were performed in order to produce NGS libraries. A capture-based target enrichment was carried out on the pooled libraries. The quantitation of the final pool of libraries was performed using Qubit dsDNA HS fluorimetric assays (Life Technologies, USA). Quality control of fragment size was assessed using DNA ScreenTape analysis (4150 TapeStation System, Agilent). Sequencing was achieved with the final library concentration of 10 pM onto a 600-cycle format V3 flow cell, via Illumina MiSeq platform (Illumina, San Diego, CA, USA).

Data analysis was performed in order to detect single nucleotide variants (SNVs), insertions/deletions (indels), and copy number alterations (CNAs). Sequencing FASTQ data were analyzed by the Sophia DDM® platform (Sophia Genetics, Switzerland).

The classification of each genomic variant into five different categories, namely, benign (B), likely benign (LB), variant of uncertain significance (VUS), likely pathogenic (LP), and pathogenic (P), were performed according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

In silico analysis of medulloblastomas molecular subgroups and *CTNNB1* mutation

To access the literature frequency of molecular subgroups and the *CTNNB1* mutation, we downloaded the clinical and molecular information on medulloblastomas from The Cancer Genome Atlas (TCGA) consortium at cBioPortal (https://www.cbioportal.org/). It included five different whole exome and genome datasets from the Pediatric Cancer Genome Project (PCGP) (whole genome, Nature 2012, n=37) (18), the Sickkids (whole genome, Nature 2016, n=46) (19), International Cancer Genome Consortium (ICGC) (whole exome, Nature 2012, n=125) (20), The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) (whole exome, Nature 2017, n=491) (21), and from the Broad Institute (whole exome, Nature, 2012, n=92). We excluded duplicate registers, alterations (mutations, structural variants, and copy number) of unknown significance, and samples not classified in the molecular subgroups, totalizing 617 patients with both information regarding molecular subgroups and *CTNNB1* mutation in the WNT-activated subgroup.

Statistical analysis

The statistical analysis was performed using the software IBM SPSS statistics version 25. The chi-square or ANOVA tests were applied for qualitative variables, and the Mann–Whitney test was applied for quantitative variables, rejecting the null hypothesis with $p<0.05$. For survival analyses, the Kaplan–Meier method and the log-rank test were applied.

Results

Higher frequency of WNT-activated medulloblastomas with *CTNNB1* wild type in Latin-Iberians population

We evaluated 266 Latin-Iberian medulloblastomas from Brazil (n=212), Portugal (n=38), and Argentina (n=16). All cases were molecularly classified into the four main medulloblastomas subgroups, namely, WNT activated (n=40, 15%), SHH activated (n=122, 46%), Group 3 (n=42, 16%), and Group 4 (n=62, 23%) (Figure 1A). The clinicopathological features of WNT-activated medulloblastomas from the Latin-Iberian population (n=40) are outlined in detail in Supplementary Tables 1, 2. Among the 40 WNT-activated, seven cases were inconclusive for *CTNNB1* mutations due to the low quantity and quality of DNA for Sanger sequencing. From the remaining 33 WNT-activated cases (24 from Brazil, seven from Portugal, and two from Argentina), we detected *CTNNB1* mutation in 24 (73%) cases, and nine (27%) medulloblastomas were *CTNNB1* wild type (Figure 1A).

The *in silico* analysis of medulloblastomas from the North American and European (NAM/EU) populations showed that 29% (n=176) was SHH activated, 39% (n=240) Group 4, 24% (n=148) Group 3, and 8% (n=53) WNT activated. In the WNT-activated subgroup, 87% (n=46) showed hotspot mutation in the *CTNNB1*, and 13% (n=7) were *CTNNB1* wild type (Figure 1B).

The frequency of WNT-activated medulloblastomas in Latin-Iberian population (Figure 1A) was significantly higher (15%) compared to the frequency observed in NAM/EU populations of 8% (Figure 1B), ($p=0.000023$).

CTNNB1 variants in the WNT-activated medulloblastomas from Latin-Iberian population

In our Latin-Iberian series of 24 *CTNNB1* mutant medulloblastomas, we found a total of 25 pathogenic variants in the hotspot region of the exon 3, being 24 missense mutations, and one in-frame deletion (Figures 2A, B). More detailed information about the mutational status of *CTNNB1* in WNT-activated medulloblastomas in Latin-Iberian patients is described in Supplementary Table S2. The most frequent *CTNNB1* variant observed was the p.(Ser33Tyr) found in five cases, followed by the p.(Gly34Val) found in three cases, and variants p.(Ser37Tyr), p.(Asp32Tyr), p.(Ser33Cys), and p.(Ser33Phe) were found in two cases each one. The remaining variants were observed only in one case (Figure 2B, Supplementary Table S2). In one case (ID88), we observed two *CTNNB1* variants, p.(Ser33Tyr) and p.(Ala43Thr) (Supplementary Table S2).

The *in silico* analysis of medulloblastomas from the North American and European (NAM/EU) populations reveals 47 *CTNNB1* variants in 46 WNT-activated medulloblastomas, with all variants being located in the exon 3 of the *CTNNB1* gene (Supplementary Figure S1). One case showed two mutations ICGC_MB113, p.(Thr41Ala) and p.(Ser33Cys). Similarly to what was observed in our series, the p.(Ser33Cys) variant was one of the most frequent detected variants (Supplementary Figure S1).

The frequency of WNT-activated medulloblastomas with *CTNNB1* wild type was significantly higher in Latin-Iberian population (27%) (Figure 1A) compared to those observed in NAM/EU populations (13%) (Figure 1B), ($p=0.014769$).

WNT-activated medulloblastomas with *CTNNB1* wild type were prevalent in females and showed worse outcome in the Latin-Iberian population

We further associated the *CTNNB1* mutational status with our patients' clinical–pathological features (Table 1). WNT-activated medulloblastoma patients with *CTNNB1* mutant showed an older median age at diagnosis of 11.3 years, compared with 10.0 years of *CTNNB1* wild type, yet not statistically significant. The *CTNNB1* wild-type cases were prevalent in female individuals ($p=0.04$), and no significant associations were observed regarding histology, surgery extension, and metastasis (Table 1).

Despite not being statistically significant, we observed that *the CTNNB1* mutant had a better outcome, with a 54.6-month median

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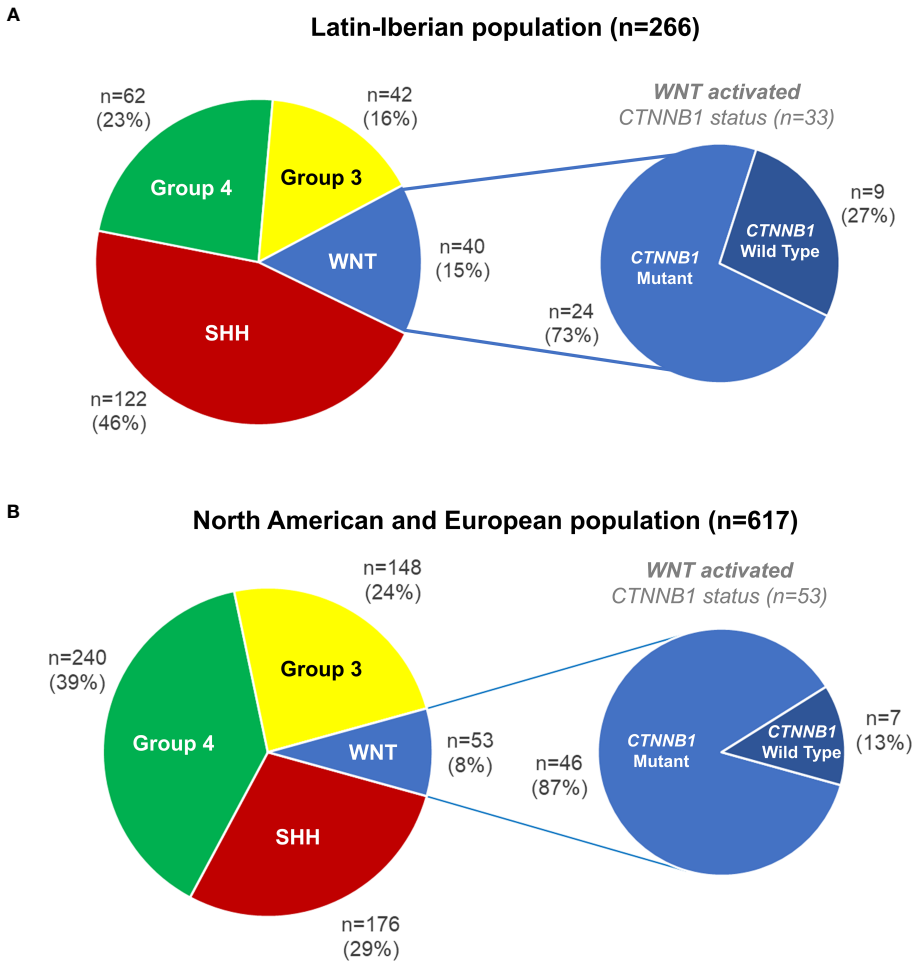

FIGURE 1
Medulloblastomas molecular subgroups and *CTNNB1* mutations in WNT-activated medulloblastomas. **(A)** Latin-Iberian population (n=266, including patients from Brazil, Portugal, and Argentina). **(B)** *In silico* analysis in medulloblastomas from the North American and European populations (n=617).

follow-up, compared with 42.1 months in wild-type cases (Table 1). We observed that 28.6% (2/7) of *CTNNB1* wild-type patients died of cancer, contrasting with *CTNNB1* mutant cases, where any patient died of cancer (p=0.01) (Table 1). Three *CTNNB1* mutants were lost to follow-up (missing: ID97, 197, and 260), and additionally, three patients died due to other reasons (ID94, ID95, and ID96), thus were not included in the survival analysis (Supplementary Table S2).

The Kaplan–Meier analysis showed that patients with WNT-activated medulloblastomas *CTNNB1* wild type had worse outcome, with 71.4% of overall survival compared to 100% of *CTNNB1* mutant cases (log rank: p=0.031) (Figure 3).

APC germline mutation associated with WNT-activated medulloblastomas

We found nine WNT-activated medulloblastomas *CTNNB1* wild type in our Latin-Iberian population. The analysis of the clinical records available showed the existence of two reports of familial adenomatous polyposis, one from Barretos Cancer Hospital (Brazil) (Figure 4) and one from Centro Hospitalar Universitário São João (Portugal).

Of note, the Brazilian case, a germline *APC* c.3183_3147delACAAA-p.(Gln1062Ter) pathogenic variant was detected. The proband of this family is a 7-year-old girl diagnosed with medulloblastoma; her brother was also diagnosed with medulloblastoma when he was 6 years old. Their mother had approximately 100 polyps and developed colorectal cancer at the age of 38, fulfilling the criteria of FAP (also known as Turcot syndrome type 2) (Figure 4).

The Portuguese patient harbored a c.3183_3187delACAAA-p.(Gln1062Ter) *APC* germline variant, similarly to the variant detected in the Brazilian family. The patient was a 9.7-year-old girl diagnosed with WNT-activated, *CTNNB1*-wild type medulloblastoma. At 24 years old, she presented gastrointestinal tumors with hepatic metastasis. Currently, she is 30 years old, and in total remission of the brain tumor.

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FIGURE 2
CTNNB1 variants found in the Latin-Iberian population. **(A)** Electropherogram of Sanger sequencing of the hotspot region in the exon 3 of *CTNNB1* (chr3:41224525 + 41224751), which codes the phosphorylation site of the protein, showing three different *CTNNB1* variants: p.(Ser33Tyr), p.(Gly34Val) and p.(Ser45del). **(B)** Lollipop showing the 25 *CTNNB1* variants observed in the WNT-activated medulloblastomas from the Latin-Iberian population.

Discussion

The origin of the WNT-activated medulloblastomas is attributed to molecular alterations that promote nuclear accumulation of beta-catenin products, inducing cell proliferation and tumor growth (22). Landmark genomic studies have shown that 97% of WNT-driven medulloblastomas can be explained by somatic mutations in the *CTNNB1* gene (~90%) and germline mutations in *APC* (~10%), which are mutually exclusive (8, 10).

In the present study, we report for the first time, the frequency of *CTNNB1* mutations in WNT-activated medulloblastomas in a large cohort of Latin-Iberian patients. The WNT-activated medulloblastoma subgroup in our Latin-Iberian population was of 15% (n=40), which is higher than those reported in North American and European populations (7%–10%) (2). A higher proportion of WNT-activated medulloblastomas were also described in previous Brazilian cohorts, 16.1% (24/149) (5) and 27% (24/92) (23). Another notable distinction observed in our cohort was the higher frequency of 46% for SHH-activated medulloblastomas. A potential reason for these distinct frequencies observed may lay in the methodologies used (24). In our study, we used a robust 22-gene panel assay by nCounter (25). However, DNA methylation assays have been the most recent approach recommended for medulloblastoma classification (26). A comparison study among methodologies showed that up to 10% of WNT medulloblastomas previously determined by nCounter were further classified as high-grade neuroepithelial tumor with BCOR alteration and anaplastic pilocytic astrocytoma by the DNA methylation assay (24). Further studies are needed to understand whether there is methodological issue, a hospital-based bias selection, or true epidemiological differences of medulloblastoma molecular subgroups among populations.

Among the 40 WNT-activated medulloblastomas included in the present study, we successfully evaluated *CTNNB1* mutations in 33 cases and found 73% (24/33) of *CTNNB1*-mutated cases and 27% (9/33) *CTNNB1* wild type. Of note, our frequency of *CTNNB1* wild-type WNT-activated medulloblastomas is significantly higher than that reported in North American and European populations, varying from 6.8% (8) to 13% (*in silico* analysis). Waszak and colleagues performed whole exome sequencing in 66 WNT-activated medulloblastomas and found somatic *CTNNB1* mutations in 89.4% and *CTNNB1* wild type in 10.6% of cases[8]. A recent German study evaluated a large cohort of 191 WNT-activated medulloblastomas and reported 92.2% (176/191) *CTNNB1* mutants and 7.8% (15/191) wild-type cases (10). Our *in-silico* analysis of *CTNNB1* mutations at cBioPortal showed that 13% (7/53) of WNT-activated medulloblastomas are *CTNNB1* wild type.

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TABLE 1 Association of *CTNNB1* status with clinicopathological features of 33 WNT-activated medulloblastomas from a Latin-Iberian population.

Features (n=33)	Variables	*CTNNB1* mutant (n=24)	*CTNNB1* wild type (n=9)	Significance
Age at diagnosis	Median (Range)	11.3 years (5.2-25.9)	10.0 years (7.0-23.5)	p = 0.41
	Pediatric (>4 and ≤ 18 years)	n = 22 (91.7%)	n = 8 (88.9%)	p = 0.81
	Adult (>18 years)	n = 2 (8.3%)	n = 1 (11.1%)	p = 0.83
Gender	Male	12 (50.0%)	n = 1 (11.1%)	**p = 0.04**
	Female	12 (50.0%)	n = 8 (88.9%)	
Histology	Classic	18 (94.7%)	6 (85.7%)	p = 0.85
	Extensive nodularity	0 (0.0%)	1 (14.3%)	
	Anaplastic / large cells	1 (5.3%)	0 (0.0%)	
	Missing	5	2	
Surgery Extension	Total	12 (70.6%)	2 (40.0%)	p = 0.19
	Partial	5 (29.4%)	3 (60.0%)	
	Missing	7	4	
Metastasis at diagnosis	No	17 (89.5%)	7 (87.5%)	p = 0.85
	Yes	2 (10.5%)	1 (12.5%)	
	Missing	5	1	
Status*	Alive	20 (100.0%)	5 (71.4%)	**p = 0.01**
	Deceased by cancer	0 (0.0%)	2 (28.6%)	
	Deceased by other reasons	1	2	
	Missing	3	0	
Follow-up	Median (months)	54.6 (0.03-161.66)	42.1 (1.94-248.13)	p = 0.85
	Missing	2	2	

*In the statistical analysis for status, was included only Deceased by cancer, and 6 cases were not evaluated due to lack of available clinical or died by other reasons.
The bolded entries in Table 1 indicate significant differences ($p < 0.05$).

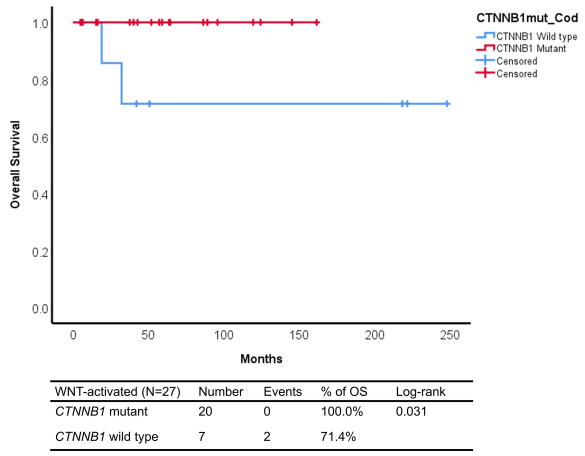

FIGURE 3
Kaplan–Meier curves of *CTNNB1* mutant and *CTNNB1* wild-type WNT-activated medulloblastomas from Latin-Iberian population.

The reason for this discrepancy in the frequency of *CTNNB1* mutations in different populations needs to be clarified. In the present study, we performed Sanger sequencing of the exon 3 of the *CTNNB1* gene, and the studies mentioned above used whole genome or whole exome sequencing (10, 27). Nevertheless, all mutations reported by NGS were located in the exon 3, covered by our Sanger sequencing assay. Moreover, the *CTNNB1* variants identified in our Latin-Iberian study is very similar to the variants reported in the North American and European populations.

We found that patients' *CTNNB1* wild type was more frequent in female individuals and was associated with a worse outcome. Nevertheless, caution should be taken, since these findings are based on a few patients and in a very heterogeneously treated population. Our findings contrast with other North American and European studies that did not observe any association of *CTNNB1* status with WNT-activated medulloblastoma clinicopathological features (8, 10). Therefore, further studies with more extensive series from non-European populations are warranted to explore the clinical impact of *CTNNB1* mutations in WNT-activated medulloblastomas. Moreover, other molecular features, namely, somatic alterations in *TP53*, *OTX2*, and monosomy for chromosome 6, have been associated with prognosis in WNT-activated medulloblastomas (10, 28). Additionally, addressing these alterations is needed to fully characterize the present Latin-Iberian cohort.

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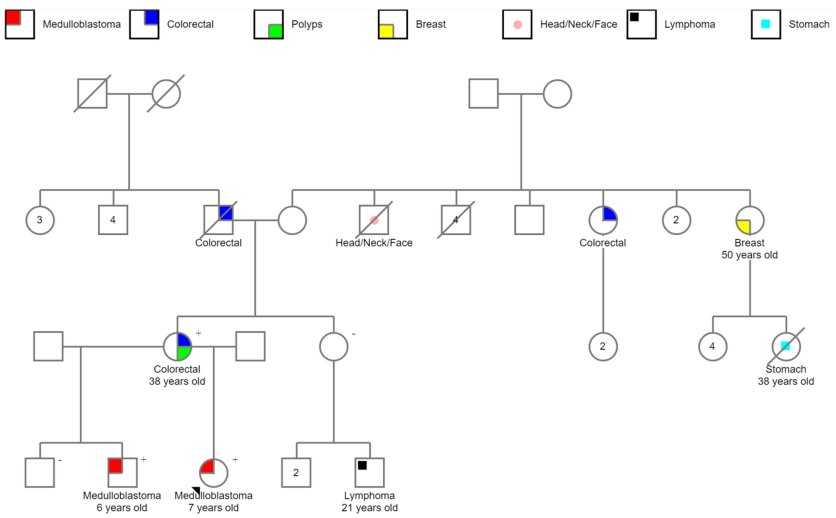

FIGURE 4
Pedigree of familial adenomatous polyposis showing the occurrence of APC-associated WNT-activated medulloblastomas in siblings. The *APC* germline mutation was tested, and the "+" indicates *APC* mutation and "–," *APC* wild type.

Considering that in WNT-activated medulloblastomas, *CTNNB1* wild-type cases can harbor *APC* germline mutations, our study suggests that up to 27% of Latin-Iberian WNT-activated medulloblastomas can occur in the context of FAP, contrasting with the reported approximately 10% in North American and European populations. The rates of germline mutations can vary between different populations (29). A cross-sectional study evaluated the frequencies of germline mutations in *APC* in more than six thousand individuals with a history of colorectal cancer in their families. It showed that *the APC* mutation rate was higher in Asians than in Caucasians (Western/Northern European, Central/Eastern European, and Ashkenazi ancestry), African American, and others (Latin American/Caribbean, Near/Middle Eastern, and Native American) (30).

Disparities in genomic studies due to the under-representation of some populations, such as from South America, were previously demonstrated (31). Consequently, genomic data from North America and the European population may only partially capture the genetic variability range in low- and middle-income countries (32). In this context, the data from our current study may contribute to the characterization of WNT-activated medulloblastomas in a poorly explored population.

It is estimated that germline *APC* mutations are associated with a 92 times higher risk for developing medulloblastomas than in the general population (11). Medulloblastoma was reported to be the most common brain tumor (79%, 11/14) observed in families with FAP[10]. Waszak and coworkers reported that all *APC* mutation carriers with available medical records (n=4) had a family history of FAP and associated cancers. Additional malignancies were observed in three patients with *APC* germline mutations (8).

Based on the available medical records, the present study identified two families fulfilling the FAP criteria. Due to the study's retrospective nature, several clinical records are very omissive in the familiar history description, not allowing for an accurate assessment of the putative hereditary nature of the *CTNNB1* wild-type cases. Nevertheless, an active search of the *CTNNB1* wild-type patients will be done, and genetic counseling and potential confirmation of its germline nature will be offered. Importantly, the possibility of a new or founder *APC* mutation cannot be entirely ruled out (33). These data demonstrate the importance of *CTNNB1* genetic testing and should indicate that patients with WNT-activated medulloblastomas *CTNNB1* wild type must be monitored by a multidisciplinary team, due to possible hereditary nature of the disease and propensity to develop other tumor types.

Interestingly, one of our FAP exhibited a rare co-occurrence of medulloblastomas in siblings. The *APC* variant identified in this family, p.(Gln1062Ter), has been previously detected in families with classic FAP (34–36) and reported founder in Spanish and Greek populations (27, 37). This variant is located in a region of the *APC* gene associated with a higher risk of developing extracolonic tumors (38), which may explain the development of the two reported medulloblastomas. To our knowledge, only one case of siblings with *APC*-associated WNT-activated medulloblastomas was reported, involving an 11-year-old girl and her 19-year-old brother exhibiting both *APC* germline mutation p.(R213*) (10).

In conclusion, the reported higher incidence of *CTNNB1* wild type in our Latin-Iberian patients may be associated with a worse outcome and suggests a higher prevalence of hereditary WNT-activated medulloblastomas in this poorly characterized population. We also reported a rare case of siblings with WNT-activated medulloblastomas associated with *APC* germline mutation in a South American patient.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

This study was approved by the institutional review board from Barretos Cancer Hospital (CAAE: 59979816.6.1001.5437). Informed consent was obtained from the patients or familiars before APC germline evaluation.

Author contributions

DM: data collection, experimental procedures, data analysis, and manuscript writing; MB: experimental procedures, results discussion, and manuscript review. AA: oncogenetic analysis, results discussion, manuscript writing, and review. FP: experimental procedures, results discussion, and manuscript review. LL: experimental procedures, manuscript writing, and review. FG: experimental analysis, medical reports review, manuscript writing, and review. AP: experimental procedures, manuscript writing, and review. GT: pathological review of tumor samples from Barreto's cancer hospital, Brazil, results discussion, manuscript review. IS: pathological review of tumor samples from Barreto's cancer hospital, Brazil, results discussion, manuscript review. FS: pathological review of tumor, results discussion, and manuscript review. LN: pathological review of tumor, results discussion, and manuscript review. EV: patient's clinical data collection, and manuscript review. CS: patient's clinical data collection, and manuscript review. JS: patient's clinical data collection and manuscript review. SM: patient's clinical data collection, and manuscript review; ML: Patient's clinical data collection and manuscript review; GH: patient's clinical data collection and manuscript review; HG-R: Pathological review of tumor and patient's clinical data collection, manuscript review. SC: pathological review of the tumor and patient's clinical data collection and manuscript review. SN: patient's clinical data collection and manuscript review. MG-d-C: patient's clinical data colection and manuscript review. JP: pathological review of tumor and manuscript review. FM: patient's clinical data colection and manuscript review. CJ: medical reports analysis, patients' treatment protocol review, and manuscript review. BM: medical reports analysis, patients' treatment protocol review, and manuscript review. RR: supervisor and project coordinator, results discussion, and manuscript writing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1237170/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Lollipop showing the 47 *CTNNB1* variants observed in the 46 WNT-activated medulloblastomas from the North American and European populations. Data collected at cBioPortal.

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Validation of an automated contouring and treatment planning tool for pediatric craniospinal radiation therapy

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Purpose: Treatment planning for craniospinal irradiation (CSI) is complex and time-consuming, especially for resource-constrained centers. To alleviate demanding workflows, we successfully automated the pediatric CSI planning pipeline in previous work. In this work, we validated our CSI autosegmentation and autoplanning tool on a large dataset from St. Jude Children's Research Hospital.

Methods: Sixty-three CSI patient CT scans were involved in the study. Pre-planning scripts were used to automatically verify anatomical compatibility with the autoplanning tool. The autoplanning pipeline generated 15 contours and a composite CSI treatment plan for each of the compatible test patients (n=51). Plan quality was evaluated quantitatively with target coverage and dose to normal tissue metrics and qualitatively with physician review, using a 5-point Likert scale. Three pediatric radiation oncologists from 3 institutions reviewed and scored 15 contours and a corresponding composite CSI plan for the final 51 test patients. One patient was scored by 3 physicians, resulting in 53 plans scored total.

Results: The algorithm automatically detected 12 incompatible patients due to insufficient junction spacing or head tilt and removed them from the study. Of the 795 autosegmented contours reviewed, 97% were scored as clinically acceptable, with 92% requiring no edits. Of the 53 plans scored, all 51 brain dose distributions were scored as clinically acceptable. For the spine dose distributions, 92%, 100%, and 68% of single, extended, and multiple-field cases,

respectively, were scored as clinically acceptable. In all cases (major or minor edits), the physicians noted that they would rather edit the autoplan than create a new plan.

Conclusions: We successfully validated an autoplanning pipeline on 51 patients from another institution, indicating that our algorithm is robust in its adjustment to differing patient populations. We automatically generated 15 contours and a comprehensive CSI treatment plan for each patient without physician intervention, indicating the potential for increased treatment planning efficiency and global access to high-quality radiation therapy.

KEYWORDS

autoplanning, autocontouring, pediatrics, global health, radiation oncology

Introduction

Each year, 300,000 children are diagnosed with cancer worldwide. Of these, 90% live in low- and middle-income countries (LMICs), where access to proper care may be limited by available resources (1). Globally, the 5-year survival rate for patients with pediatric cancer has increased to over 80% in high-income countries (HIC); however, this trend has not been mirrored in LMICs, where average survival rates remain as low as 20% in some countries (2). Recognizing this issue, the World Health Organization launched the Global Initiative for Childhood Cancer (GICC) program in 2018 aiming to increase global survival from pediatric cancer to 60% (3). Radiation therapy is complex and time-consuming to plan and deliver, yet it plays a critical role in managing cancer in more than 50% of pediatric patients in LMICs, and its use is expected to rise to 78% over the next 10 years (4).

Pediatric brain and CNS tumors constitute the leading cause of deaths associated with pediatric cancer world-wide (5), but even more so in LMICs where access to diagnosis and treatment requires availability of technical and human resources (6). Medulloblastoma is the most common malignant brain tumor in children accounting for 20-25% of pediatric malignancies in HICs with large variations in incidence in LMICs. Patients with this diagnosis (as well as some other pediatric brain tumors) require craniospinal radiotherapy, one of the most technically demanding techniques in a radiotherapy center (7, 8).

Limited personnel create demanding workflows. For example, medical physicists dedicate up to 50% of their time to generating radiation therapy treatment plans (9). To alleviate demanding workflows and increase global access to high-quality radiation therapy, artificial intelligence has been introduced to automate various aspects of the radiation therapy treatment planning process. The Radiation Planning Assistant (RPA) planning team has developed algorithms to automate contouring, treatment planning, and quality assurance for adult disease sites, including the cervix, chest wall, spine, head and neck, and whole brain (10–15). Court et al. recently summarized how the RPA was designed alongside leaders in resource-constrained countries to address the global expertise gap in radiation oncology (16). In short, clinicians import a patient CT scan with a planning prescription into the RPA webpage. The web-based servers of the RPA then automatically generate contours and a corresponding treatment plan using internal algorithms. The contour and plan files are then sent back to the user for download. The RPA was developed with clinical acceptability and safety/risk in mind to ensure successful deployment, and increase global access to high-quality radiation therapy.

Recently, as part of the RPA project, Hernandez et al. introduced artificial intelligence into pediatric radiation oncology to facilitate autosegmentation and planning for craniospinal radiation therapy for pediatric patients with medulloblastoma (17). In addition, Hernandez et al. investigated automatically contouring postoperative GTV volumes using a pediatric dataset (18). Both studies were exclusively trained, validated, and tested on an internal pediatric dataset.

The performance of deep learning models has been shown to decrease when tested on patient populations from different hospitals often due to heterogeneity in medical imaging techniques (19). In addition, models trained only on a single dataset may be susceptible to overfitting, which may further limit the generalizability of the model on different patient populations (20). Chen et al. reported that one of the biggest challenges of incorporating artificial intelligence–based tools into radiation oncology is the generalizability of deep learning models (21). In 2021, the FDA recognized that artificial intelligence may be biased towards the dataset it is tested on. In outlining strategies to mitigate bias in algorithm development, it was highlighted that the algorithms should be tested on diverse patient cohorts to test generalizability (22).

To evaluate the generalizability of our algorithms, we tested our CSI autocontouring and autoplanning tool developed at our institution, on a large dataset from another institution. We recruited three pediatric radiation oncologists from three different institutions to comprehensively evaluate the performance of the autocontouring and autoplanning tool. Automating the contouring

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and planning workflow for pediatric CSI has the potential to increase access to high-quality radiation therapy, as time saved in treatment planning may be allocated to other clinically necessary tasks.

Methods

We tested the CSI autocontouring tool on a dataset from St. Jude Children's Research Hospital, comprising of 63 full-body CSI CT scans. This study was approved by our institutional review board. The dataset was curated such that each patient had been previously treated with photons in the head-first-supine position. Of the 63 scans, 30 had been performed on Siemens machines and 33 had been performed on Philips machines. The median (range) number of slices, slice thicknesses, and tube voltage peaks were 495 (225–780), 1.5 (1–3) mm, and 120 (120–120) kVp, respectively. After evaluating the imaging parameters, all CT images were imported into the Raystation treatment planning system version 11B (Raysearch Laboratories, Stockholm, Sweden) (23).

Autocontouring

Two deep-learning based autosegmentation pipelines were employed to generate the normal tissue contours on the 63 CT scans outside of the treatment planning system. Deep learning uses a series of multi-layer neural networks to learn image features of large training datasets (image and contour pairs) to then automatically segment contours on independent test datasets (images only). To generate the contours in this study, first, a previously validated, adult head and neck autocontouring model was run to generate the brain, brainstem, eye, lens, and cochlea contours (24). Next, a previously validated, pediatric-specific autocontouring model was used to generate the cribriform plate, lacrimal gland, pituitary gland, thyroid, heart, lung, shoulder, mandible, spinal canal, vertebral column, and kidney contours (17). The inputs of both algorithms are a CT scan, and the outputs are a set of autocontours which may then be imported into the treatment planning system for planning.

Autoplanning

Hernandez et al. previously automated the treatment planning process for 3D-conformal pediatric craniospinal radiation therapy (17). The algorithm was written in Raystation using the python-based API and did not use any auto-planning features native to the TPS. In summary (Figure 1), autocontours are first generated using previously-trained deep learning models and then they are imported into the treatment planning system. The autoplanning tool then generates 2 lateral brain fields (gantry at 90 and 270 degrees) matched to a single poster-anterior (PA) spine field (gantry at 180 degrees), an extended spine field (120 cm SSD to couch top), or 2 matched spine fields, depending on the patient's spinal canal length. The MLCs for the brain and spine field(s) conform to a 1 cm uniform expansion of the brain autocontour and a 1 cm lateral expansion of the spinal canal autocontour, respectively. A half-

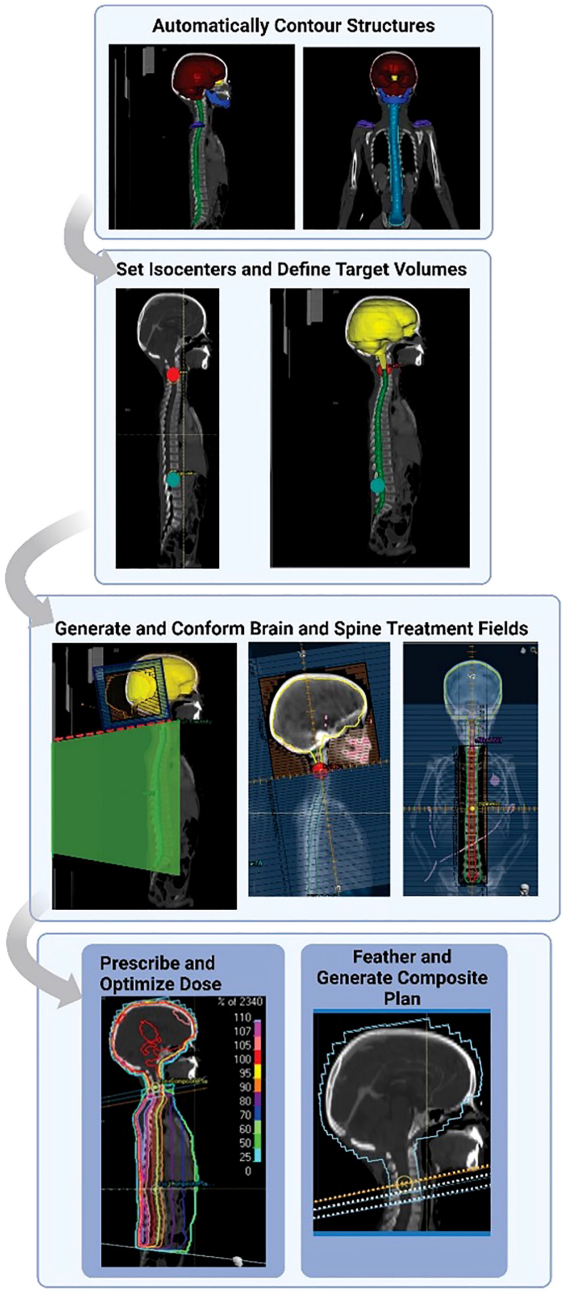

FIGURE 1
Outline of craniospinal irradiation auto-planning workflow. Normal structures and landmark structures are automatically contoured using deep learning methods. The autocontours then guide an autoplanning algorithm scripted in the treatment planning system. Auto-contours are used to automatically set isocenters and define target and prescription volumes. Fields are automatically generated and conformed to the specified targets. The dose is prescribed, and the dose to the spine field is optimized. The original plan is feathered with 2 junction shifts. Finally, a composite plan is generated. Figure reprinted from "Automating the treatment planning process for 3D-conformal pediatric craniospinal irradiation therapy," by Hernandez et al., 2023, Pediatric Blood & Cancer, Volume 70(3), e30164. Copyright 2023 by John Wiley and Sons. Reprinted with permission.

beam block is implemented on the brain field to avoid the need for couch rotations. Spine subfields are then added and iteratively weighted to optimize the spine dose distribution. Finally, feathering is implemented at each match line to yield a composite treatment plan. All beam energies are set to 6 MV. The prescription is set to deliver 23.4 Gy in 13 fractions, normalized to give 95% of the prescribed dose to 100% of the brain volume and 95% of the spinal canal volume using a 5, 5, 3 fractionation scheme. For additional details on the contouring and planning algorithms, we refer the user to our previous work (17).

Prior to generating a treatment plan, the CSI autoplanning algorithm automatically performs a series of checks to ensure that the patient's anatomy is compatible with the algorithm design. First, the algorithm automatically measures the patients' spinal canal and determines whether to implement a single, extended, or multiple spine field configuration. In addition, the algorithm quantifies the amount of space available for junction shifts and decides to implement either 1- or 0.5-cm junction spacing. The algorithm will flag the user if there is <1 cm of space between the mandible and shoulders available for feathering. These patients were omitted from final testing. Finally, the algorithm automatically checks that the patient's anatomy will be compatible with a half-beam block on the brain field by measuring the distance between the most superior slice of the brain contour and the most inferior slice of the mandible contour. A patient with a head tilt would have a higher mandible contour, which decreases the distance between the mandible and the top of the brain relative to that of a patient who is looking straight ahead. Patients with a measured brain-to-mandible distance larger than 20 cm were removed from the final testing set.

After removing the incompatible patients from the final testing set, we ran the autocontouring and autoplanning pipeline to generate CSI treatment plans. Plan quality was evaluated quantitatively with target coverage and dose to normal tissue metrics and qualitatively with physician review.

Quantitative plan evaluation

To quantitatively evaluate the quality of the plans, dose metrics were analyzed across the final test set of patients. Target coverage was quantified using V95% of the prescription dose (23.4 Gy) evaluated for the brain, spinal canal, and cribriform plate. Normal tissue dose was also quantified using the maximum dose to the brain, spinal canal, brainstem, cochlea, eye, lens, and optic nerve autocontours. In addition, the mean dose was reported for the cochlea, heart, kidney, lacrimal gland, lung, pituitary gland, and thyroid autocontours.

Qualitative plan evaluation

Physician review was used to evaluate the quality of the final autocontours and autoplans for each of the patients in the final testing cohort. Three pediatric radiation oncologists from 3 institutions (in the US and South Africa) reviewed the final test set. One patient was reviewed by all 3 physicians, resulting in a total of 53 plans for review. Each physician reviewed and scored each autocontour using a 5-point Likert scale detailed in Table 1 (25). Using the same scale, the physicians reviewed the autoplan of each patient and assigned a clinical acceptability score to the brain and spine dose distributions individually. Autocontours and autoplans scored ≥3 was considered clinically acceptable. For plans that were scored as a 2, we also asked the physician if they would prefer to create their own plan from scratch or edit the plan we presented, as the original Likert scale did not have a metric for plans that required major edits but were still clinically useful.

Results

81% (51/63) of patients met the autoplanning pre-processing requirements. Four patients were automatically removed for having less than 1 cm available to feather junctions and 8 patients were removed for not being compatible with a half-beam block on the brain field. Each flagged case was manually reviewed to verify that it was not compatible with the planning algorithm. Figure 2 shows the variation in junction spacing and required spine field length measured across the dataset. A team of 3 pediatric radiation oncologists from different institutions reviewed and scored the resulting 51 autocontours and autoplans. One patient's case was reviewed and scored by all 3 physicians (total of 53 plans scored). Physician 1 reviewed 16 plans, physician 2 reviewed 19, and physician 3 reviewed 18.

TABLE 1 5-Point Likert scale used to evaluate autocontour and autoplan quality (25).

Score	Acceptability	Description
5	Acceptable, use as-is	Clinically acceptable, could be used for treatment without any changes
4	Acceptable, minor and stylistic edits	Stylistic differences, but not clinically important
3	Acceptable, minor edits that are clinically necessary	Clinically important edits for which it is more efficient to edit the autocontours or autoplans than to start from scratch
2	Unacceptable, major edits	Edits that are required to ensure appropriate treatment and are significant enough that the user would prefer to start from scratch
1	Unacceptable, unusable	Autocontours or autoplans that are so bad that they are unusable (i.e. wrong body area or outside the confines of the body)

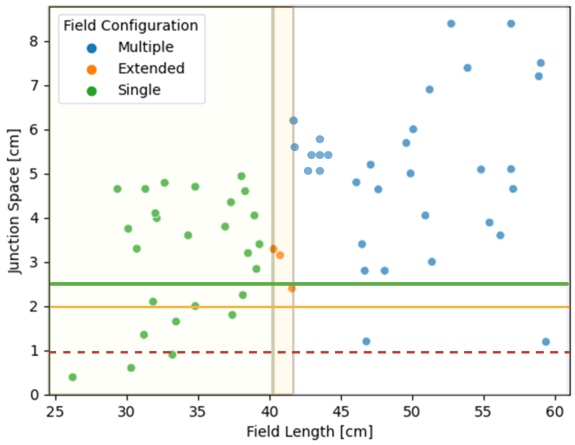

FIGURE 2
Distribution of available junction spacing and required spine field configurations for 63 patients. The green and yellow lines correspond to having enough feathering space for a 1-cm junction. The dotted red line represents the cut-off for a 0.5-cm junction.

Autocontouring

Fifteen autocontours from 51 patients were reviewed by 3 pediatric radiation oncologists, including the eyes, lacrimal glands, lenses, cribriform plate, optic nerves, pituitary, cochlea, brainstem, mandible, brain, thyroid, lungs, heart, kidneys, and spinal canal. Physicians 1, 2, and 3 reviewed and scored 240, 285, and 270 autocontours, respectively. The scores assigned to each contour are summarized in Figure 3. Overall, the autocontouring model's performance was robust across all spine field configurations. Across all physicians, 97% (775 of 795) of autocontours were scored as clinically acceptable, with 92% (733 of 795) of autocontours requiring no edits. Physicians 1, 2, and 3 scored 98%, 95%, and 85% of autocontours, respectively, as requiring no edits (score ≥4).

We evaluated the scores of the target autocontours (brain, cribriform plate, and spinal canal) and found that 85% (45 of 53) of the brain autocontours required no edits and the remaining 15% (8 of 53) required minor, clinically necessary edits because the temporal lobes and cribriform plate had been under contoured. All 51 cribriform plate contours were scored as clinically acceptable, and only 6% (3 of 53) required edits. Physicians 1 and 2 scored 100% of the reviewed spinal canal contours as clinically acceptable (score ≥3). Physician 3 scored 33% (6 of 18) of the spinal canal autocontours as clinically unacceptable (major edits required) because the canal contour was under contoured inferiorly and did not include the distal spinal nerve roots prior to exit from the ventral sacral foramina.

Normal tissue autosegmentation performed well for all structures but the kidneys due to variation in simulation planning technique. We found that 23% (12 of 53) of the kidney contours were scored as clinically unacceptable. The performance of the kidney autocontouring model was negatively affected by CT scans with contrast administered at the time of simulation. Because the autocontouring model was originally trained on non-contrast CT scans, the model was able to localize the kidneys but failed to accurately contour their shape, which resulted in major edits. The thyroid autocontouring model experienced a similar issue for one patient, when the model mistakenly assigned high-contrast vasculature near the thyroid as thyroid itself, which resulted in a minor, clinically necessary edit.

Quantitative plan evaluation

Of the 51 patients tested, 23, 3, and 25 required single-, extended-, and multiple-field configurations, respectively (Figure 2). The V95% achieved for the target structures across the single, extended, and multiple field configurations are summarized in Figure 4. The whole brain plan was normalized such that 100% of the brain autocontour received the prescribed dose, which was achieved across all three spine field configurations tested. The average V95 ± 1σ% for the spinal canal for single, extended, and multiple fields were 99.3 ± 0.04%, 99.3 ± 0.01%, and 98.6 ± 0.01%, respectively. Finally, the average V95% for the cribriform plate were 96.4 ± 0.01%, 99.5 ± 0.0002%, and 99.5 ± 0.01%, respectively.

The extended- and single-field configurations resulted in better target coverage to the spinal canal than did the multiple-field configuration. Finally, the extended- and multiple-field configurations achieved higher overall coverage to the cribriform plate than did the single-field configuration.

The average maximum doses (Gy) to the brain, spinal canal, and brainstem autocontours across all three spine field configurations were 25.5 ± 0.33 Gy (109% of Rx), 26.4 ± 0.74 Gy (113% of Rx), and 24.7 ± 0.33 Gy (106% of Rx), respectively. The dose to the spinal canal was higher for multiple-field plans (27.3 ± 0.37 Gy) than for single- and extended-field plans (25.6 ± 0.61 Gy and 25.5 ± 0.19 Gy, respectively). The average maximum doses (Gy) delivered to the cochlea, eye, lens, and nerve autocontours were 24.7 ± 0.40 Gy, 14.15 ± 4.03 Gy, and 25.2 ± 0.50 Gy, respectively (Figure 5). The mean doses [Gy] to the cochlea (L/R avg.), heart, kidney, lacrimal gland, lung, pituitary, and thyroid autocontours across all three spine field configurations were 24.0 ± 0.30 Gy, 8.76 ± 1.05 Gy, 1.39 ± 0.27 Gy, 23.7 ± 0.44 Gy, 2.06 ± 0.39 Gy, 22.1 ± 2.30 Gy, and 17.9 ± 1.00 Gy, respectively.

Overall, all spine field configurations resulted in consistent maximum and mean doses to the normal tissues. A dose-volume histogram for the target and normal tissue structures averaged across all spine configurations is summarized in Figure 6.

Qualitative plan evaluation

A total of 51 patients were reviewed and scored for the quality of the composite CSI autoplan. One patient's case was reviewed by all three physicians, resulting in a total of 53 plans. Physicians 1, 2, and 3 reviewed 16, 19, and 18 plans, respectively. For the single-field configuration, 6, 9, and 10 cases were reviewed by physicians 1, 2, and 3, respectively. For the extended-field configuration, 1 and 2 cases were reviewed by physicians 1 and 2, respectively. For the multiple-field configuration, 9, 8, and 8 cases were reviewed by

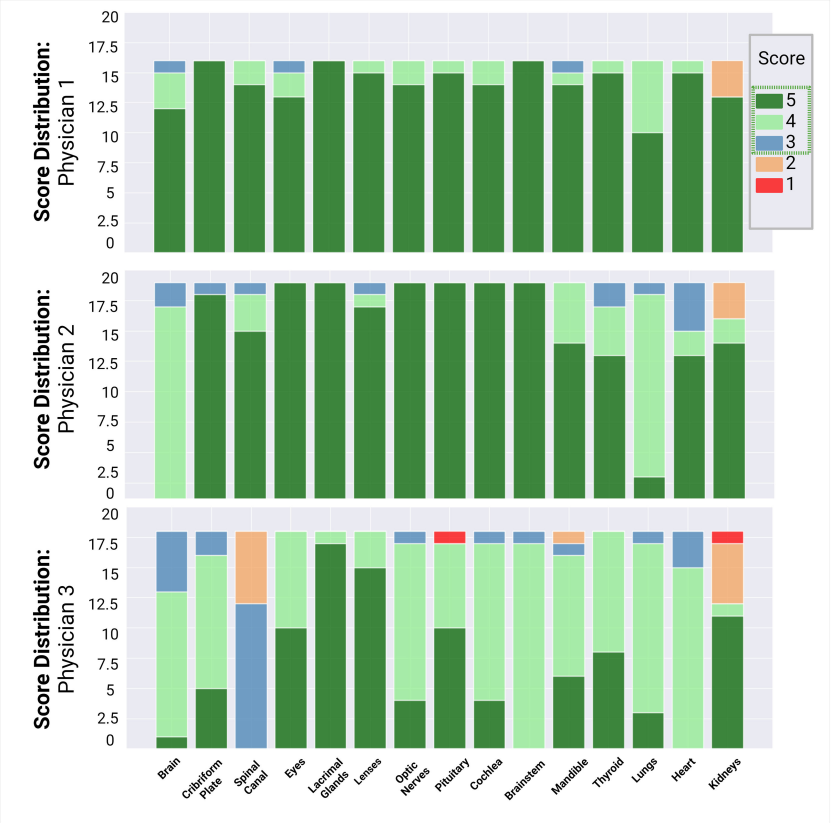

FIGURE 3
Summary of physician review of autocontours. Physicians 1, 2, and 3 reviewed and scored 240, 285, and 270 auto-contours, respectively. A score ≥3 (blue) was considered clinically acceptable.

physicians 1, 2, and 3, respectively. The scores of the autoplans from each physician are detailed in Figure 7. Factors contributing to the scores included the accuracy of the match lines; the dose distribution within the junctions; the target coverage to the brain, cribriform plate, and spinal canal; and the dose to normal tissues, such as the kidneys.

Overall, 100% of the brain dose distributions were scored as clinically acceptable (Likert score ≥3). Of these, 19, 13, and 21 were scored as 5, 4, and 3, respectively. For the spine dose distribution, 92% (23 of 25) of single-, 100% (3 of 3) of extended-, and 68% (17 of 25) of multiple-field cases were scored as clinically acceptable. Most plans required no edits or minor edits. Eight of the 25 multiple-field spine dose distributions were scored as clinically unacceptable, as they required major edits. However, all physicians reported that they would rather edit the autoplan rather than create a new one (Figure 7).

One plan was seen by all three physicians. Physicians 1, 2, and 3 assigned scores of 5, 4, and 3 to the brain dose distributions of the plan and 3, 4, and 4 to the spine dose distributions, demonstrating that while all physicians agreed that the plan was clinically acceptable, each had their own preference as to how they would edit the plan. Across all cases reviewed, all physicians agreed that the coverage to the cribriform plate could be improved on most of the plans, at the expense of an increased lens dose. The physicians had differing preferences on the tradeoff between spinal field coverage and hotspots.

Overall, the autoplanning algorithm worked well. The tool was able to generate composite treatment plans for 51 patients in three minutes per single-field case and eight minutes per multiple field cases. The additional time for multiple field cases was due to running optimization

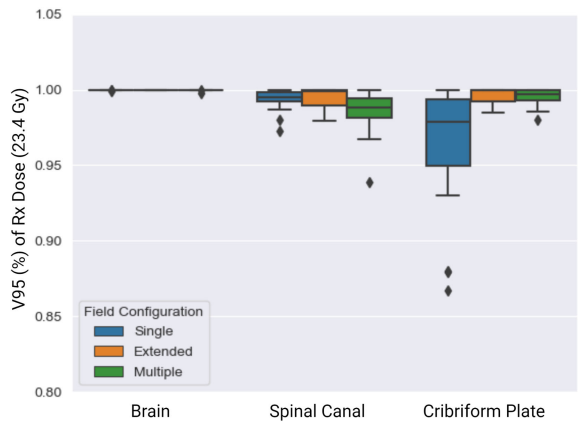

FIGURE 4
V95 (%) of Rx dose (23.4 Gy) across the single (blue), extended (orange), and multiple (green) spine field configurations. The brain field prescription was set to cover 100% of the brain with 95% of the prescription dose, which was achieved.

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Maximum dose averaged across 51 patients		
	Dose ± 1σ (Gy)	% of Rx 23.4 Gy
Brain	25.5 ± 0.33	109%
Spinal Canal	26.4 ± 0.74	113%
Brainstem	24.7 ± 0.33	106%
Cochlea_L	24.7 ± 0.45	106%
Cochlea_R	24.7 ± 0.35	106%
Eye_L	24.3 ± 0.24	104%
Eye_R	24.2 ± 0.23	104%
Lens_L	13.4 ± 4.08	57%
Lens_R	14.9 ± 3.97	63%
OpticNrv_L	24.0 ± 0.26	102%
OpticNrv_R	26.4 ± 0.74	102%

Mean dose averaged across 51 patients		
	Dose ± 1σ (Gy)	% of Rx 23.4 Gy
Cochlea_L	24.0 ± 0.30	102%
Cochlea_R	24.0 ± 0.29	102%
Heart	8.76 ± 1.05	37%
Kidneys	1.39 ± 0.27	6%
Lacrimal Glands	23.7 ± 0.44	101%
Lungs	2.06 ± 0.39	9%
Pituitary	22.1 ± 2.30	98%
Thyroid	17.9 ± 1.00	77%

FIGURE 5
Maximum and mean doses averaged across 51 patients, expressed as a percentage of the prescription dose. Error estimates are standard deviations.

on the upper and lower spinal fields sequentially. It is important to note that the plan generation process does not require user intervention, yielding the potential for high clinical impact, particularly in resource-constrained centers.

Discussion

We validated the performance of an autocontouring and autoplanning pipeline for craniospinal radiotherapy. The algorithms successfully generated 15 autocontours and a comprehensive CSI treatment plan for 51 patients across three spine field configurations. The performance of both tools was comprehensively analyzed using quantitative and qualitative metrics. The autocontouring model successfully generated clinically acceptable normal tissue contours and treatment plans, most of which required no or minor edits. While we observed inter physician variability on spine field scoring, all physicians commented that even if edits (major or minor) were required, they still preferred to edit our autoplans rather than create their own.

The autocontouring tool performed well for each of the 15 structures tested across 51 patients. Since the patients were anonymized prior to testing, we could not directly quantify how the models performed across different age groups. However, the spinal canal length for the 51 patients ranged from 25 cm to 60 cm; thus, we can infer that the model was robust to varying patient anatomy. The autocontouring model also worked well across varying image parameters. For example, the average slice thickness of the scans used to train the autocontouring models was 2.5 mm (1.25-2.5 mm range), and the average slice thickness of the scans from the external dataset was 1.5 mm.

All physicians scored all the brain autocontours as clinically acceptable. We found that the brain autocontouring model could be improved to increase temporal lobe coverage and accommodate patients with post-operative psudomeningoceles. Because the brain autocontour was generated by an adult autocontouring model, it had not been used on pediatric or postoperative cases before. While 2 physicians consistently scored the spinal canal autocontour as requiring no or only minor stylistic edits, one physician noted that the model consistently under contoured the nerve roots and scored the contours accordingly. This physician commented that 5-10 slices of the canal autocontour would require major edits but that it would still be more efficient to edit the autocontour than to create a new contour.

The physicians scored the majority of the normal tissue contours as requiring no or minor, stylistic edits, except for the lung and kidney autocontours. The lung autocontouring model consistently slightly under contoured the true lung volume, and the kidney model failed to accurately contour the kidneys on patients with contrast enhanced CT scans. Despite these errors, the physicians noted that the quality of the lung and kidney contours would not affect the final treatment plan.

Overall, the autoplanning tool performed well for the 51 patients tested across three spine field configurations. The scoring for the brain dose distribution was consistent across the three spine field configurations. The physicians noted that the brain dose distributions could be improved by increasing the cribriform plate coverage at the expense of increased lens dose, but this can be easily achieved by editing the position of the two or three MLCs that are shielding the lenses. Physicians noted that they would prefer to use additional brain sub-fields to reduce the size of the 107% hotspot. While our current CSI approach does not include sub-fields for the brain fields, they could easily be added using a technique that has been separately developed for whole brain radiation (15). Finally, one physician noted that the MLCs could be opened around the back of the skull to ensure that patients with pseudomeningoceles would be treated properly, with no negative effect on the patient.

For the spine field configurations, we found that the single- and extended-field configurations outperformed the multiple configuration plans. Ultimately, the validation of the algorithm proved that the multiple field configuration would need to be improved and further tested prior to clinical implementation. For many of the cases, the physicians were satisfied with the single-field spine dose distributions. They noted that they would adjust the weighting on the spine sub-fields to increase the spinal canal coverage at the expense of increasing the hotspot size. For the multiple-field cases, the match line between the upper and lower spine fields was designed to be placed just anterior to the spinal canal. This worked well for most patients; however, if a patient had an unusually angled spine, the first match point would be in the

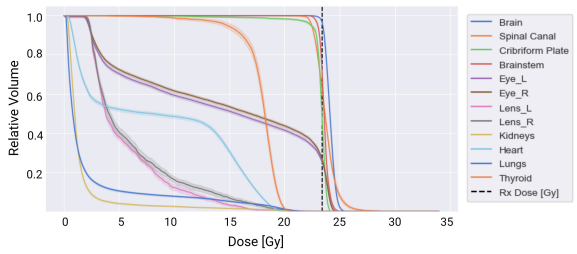

FIGURE 6
Dose-volume histogram summarizing dose delivered to the targets (brain, spinal canal, and cribriform plate) and normal tissues averaged across the 51 treatment plans tested. The solid lines represent the mean dose-volume histogram values, and the shaded portions represent one standard deviation in values across the three spine field configurations tested.

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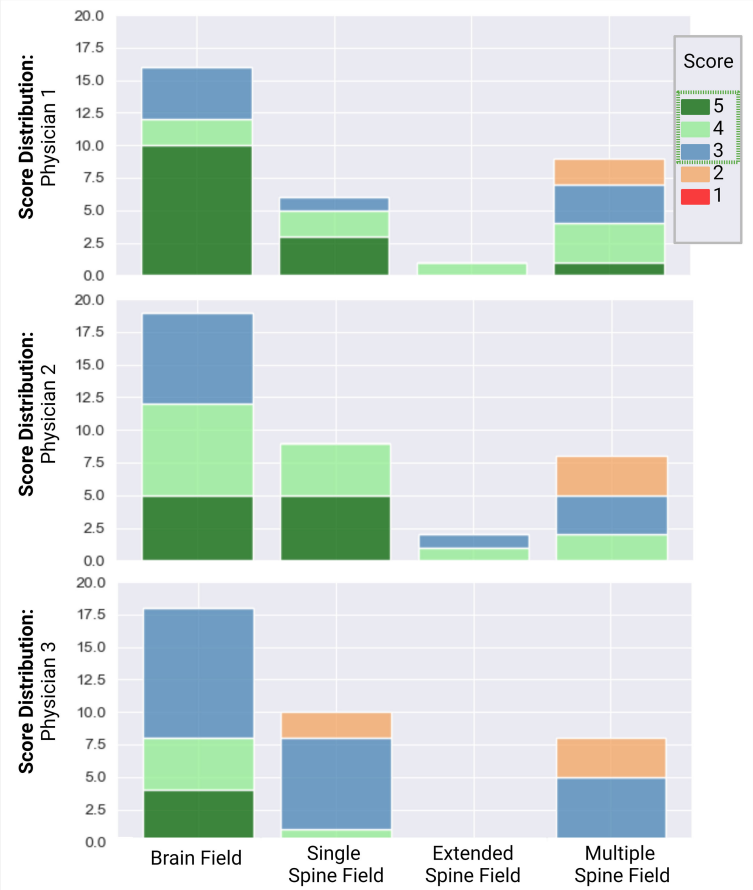

FIGURE 7
Scoring distribution for plans, reviewed by physicians 1, 2, and 3. Physician 1 reviewed 16 plans, physician 2 reviewed 19 plans, and physician 3 reviewed 18 plans. One single-field plan was reviewed by all 3 physicians. Individual scores were assigned to the brain and spine dose distributions. A score ≥3 (blue) was considered clinically acceptable.

correct location and the match point for the latter 2 junctions would start to shift into the canal. The original algorithm was designed to add a single sub-field for single- and extended-field cases and 2 sub-fields for the upper and lower spine fields, respectively, for multiple-field cases. While this technique worked for most patients, physicians noted that they would add additional sub-fields to the multiple field plans to improve the plan quality. In addition, they could adjust the spacing of the spine sub-fields to optimize the dose distribution within the junction.

We identified limitations in our approach after testing it on patients from another institution. First, we encountered variations in clinical practice that the current algorithm was not designed to accommodate (i.e. the addition of sub-fields, patients with required brain fields >20 cm, or different prioritization of target coverage vs. hotspots). Another limitation was that it was not possible to validate our autocontours and autoplans with the clinical plans as we only received the anonymized CT scans and not the corresponding clinical contours and plans. In addition, the planning technique described in this work is currently limited to a single approach to CSI planning based on the recommendations from the SIOP PODC. We opted for 3D-conformal CSI planning as 84% of resource-constrained clinics report using this technique (6). Consequently, patients must have the appropriate setup to be treated with our technique (i.e. having the proper head tilt to achieve a half-beam brain block). Our pre-planning algorithm successfully identified 12 patients that were anatomically incompatible with the original planning design because of insufficient spacing between the mandible and shoulders for junction spacing, and/or insufficient head tilt to fit the brain into a half-beam block (20 cm). To expand the generalizability of our algorithm in the future, we plan to provide user training to ensure appropriate anatomical setup and accommodate couch kicks to treat larger brain fields.

Many institutions in HICs have moved to advanced techniques such as IMRT, VMAT or proton therapy for CSI. However, in LMICs, 3DCRT remains the prevalent technique, where this autoplanning tool would have the potential to produce high quality plans within a very short time. The autocontouring tool generates 15 normal tissue contours in 20 minutes and the autoplanning tool generates a comprehensive CSI plan in less than 3 minutes for the single field configurations and less than 8 minutes for the multiple field configuration. The process does not require any user intervention and both algorithms could be further optimized for time in the future. The efficiency of the tool has the potential to reduce contouring time and alleviate treatment delays which are known to be a major factor impacting survival (26). Additionally, the autocontouring tools are not specific to a single treatment technique or pediatric disease site; thus, they could affect all pediatric patients

requiring radiation therapy. Such a tool could standardize contouring, helping to limit target deviations which impact treatment outcomes for both well-resourced and resource-constrained clinics (7, 27, 28).

The autocontouring and autoplanning tools described in this work will continue to go through rigorous testing before being implemented into the Radiation Planning Assistant. The RPA architecture has been proven to be robust to downtime, thus providing a reliable service to resource-constrained clinics (29). Finally, the RPA aims to provide autocontouring and autoplanning tools at minimal (most likely zero) cost to resource-constrained clinics in LMICs yielding potential for broad impact (16).

Conclusions

In conclusion, we successfully validated an autoplanning pipeline developed at one institution using a large dataset provided by another institution. We automatically generated 15 normal tissue contours and a comprehensive CSI treatment plan for each patient without user intervention. The results indicate that our algorithm is robust in its adjustment to differing patient populations. Although the original algorithm was designed and tested exclusively in pediatric patients with medulloblastoma, we were able to successful generate treatment plans on a dataset that included a variety of disease sites requiring CSI, demonstrating that our algorithm is generalizable. Automating the contouring and planning workflow for pediatric CSI has the potential to increase treatment planning efficiency and global access to high-quality radiation therapy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by MD Anderson Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

All authors have made substantial contributions to the performance and analysis of the work, have helped draft or edit the manuscript, have provided approval of the submission, and have worked to ensure the accuracy of the results presented.

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Conflict of interest

HB is currently employed by the company Varian Medical Affairs, with a sessional lecturing position at the University of Cape Town.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Prognostic significance of molecular subgroups in survival outcome for children with medulloblastoma in Malaysia

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Introduction: Advancements in genomic profiling led to the discovery of four major molecular subgroups in medulloblastoma (MB), which have now been incorporated into the World Health Organization classification of central nervous system tumors. The current study aimed to determine the prognostic significance of the MB molecular subgroups among children in Malaysia.

Methods: We assembled MB samples from children <18 years between January 2003 and June 2017 from four pediatric oncology centers in Malaysia. MB was sub-grouped using 850k DNA methylation testing at German Cancer Research Centre, Heidelberg, Germany.

Results: Fifty samples from patients diagnosed and treated as MB were identified. Two (4%) of the 50 patients' tumor DNA samples were insufficient for analysis. Of the remaining 48 patients, 41 (85%) samples were confirmed as MB, while for 7 (15%) patients, DNA methylation classification results were discrepant with the histopathological diagnosis of MB, with various other diagnoses. Of the 41 MB patients, 15 patients were stratified as standard-risk (SR), 16 patients as high-risk (HR), and ten as infants (age <3 years old). Molecular subgrouping of the whole cohort revealed four (14%) WNT, 11 (27%) SHH, 10 (24%) Group 3, and 16 (39%) Group 4. Treatment abandonment rates for older children and infants were 22.5% and 10%, respectively. After censoring treatment abandonment, for SR patients, the 5-year event-free survival (EFS) and overall survival (OS) were 43.1% ± 14.7% and 46.9 ±

15.6%, respectively, while in HR, 5-year EFS and OS were both 63.6% ± 14.5%. Infants had a 5-year EFS and OS of 55.6% ± 16.6% and 66.7% ± 15.7%, respectively. WNT tumors had the best 5y-OS, followed by Group 3, Group 4, and SHH in children ≥3 years old. In younger children, SHH MB patients showed favorable outcomes.

Conclusion: The study highlights the importance of DNA methylation profiling for diagnostic accuracy. Most infants had SHH MB, and their EFS and OS were comparable to those reported in high-income countries. Due to the relatively small cohort and the high treatment abandonment rate, definite conclusions cannot be made regarding the prognostic significance of molecular subgroups of MB. Implementing this high-technology investigation would assist pathologists in improving the diagnosis and provide molecular subgrouping of MB, permitting subgroup-specific therapies.

KEYWORDS

survival outcome, medulloblastoma, Wingless, Sonic Hedgehog, Group 3, Group 4, abandonment

Introduction

Medulloblastoma (MB), the most common malignant central nervous system (CNS) tumor of childhood, demonstrates high biological and clinical heterogeneity (1, 2). Historically, MB risk stratification was based on age, extent of surgical resection, residual tumor, metastatic status, and histological subtype (3–5). MB was originally classified into four histologic variants predominantly based on features seen on light microscopy and conventional histological stains. These variants were medulloblastoma with extensive nodularity (MBEN), desmoplastic-nodular (DN), classic, and large-cell–anaplastic (LCA).

The standard of care for MB for children ≥3 years old consists of maximal surgical resection, risk-adapted craniospinal irradiation (CSI), and adjuvant chemotherapy. Standard-risk (SR) MB is defined by complete or near total resection with residual tumor < 1.5cm^2 and absence of metastatic disease. Patients with post-surgical residual tumor > 1.5cm^2, metastatic dissemination, and LCA histology in some studies were classified as having high-risk (HR) MB (5). SR MB patients receive CSI of 23.4Gy with a boost up to 54-55Gy to the posterior fossa or tumor bed, followed by adjuvant chemotherapy. Whilst HR MB patients are treated with a higher CSI dose of 36-39Gy with a boost up to 54-55Gy to the posterior fossa or tumor bed, followed by adjuvant chemotherapy (5, 6). Using these approaches, the 5-year overall survival (OS) rate in high-income countries is approximately greater than 80% in SR MB patients and 53-76% in HR MB patients (6–9). For children <3 years old, radiotherapy-sparing approaches have become the accepted standard and the survival outcomes vary based on histology subclass, post-operative residual tumor, and extent of metastasis (10–12). In recent trials conducted in Europe and North America, the 5-year OS rates in children <3 years old who had complete resection, residual tumor, and metastases were 79-93%, 57%, and 38%, respectively (10–12). Based on histology, young children with MBEN/DN, classic, and LCA histologies showed 5-year OS rates of 78-100%, 41-67%, and 33%, respectively (10–12).

Over the past 15 years, through marked advances in genomic studies, our understanding of MB biology has dramatically evolved, culminating in four core distinct molecular subgroups termed: Wingless (WNT), Sonic Hedgehog (SHH), Group 3 (G3), and Group 4 (G4) (1, 13). These molecular subgroups display different genetic, clinical characteristics, recurrence patterns, and survival outcomes (14–17). These subgroups were incorporated into the revised WHO 2016 classification and integrated with the histological variants for improved classification and prognostic correlation (13). In children, G4 is the most frequent MB subgroup representing 40-45% of all MBs, followed by SHH (28-30%), G3 (25-28%), and WNT (10-15%) (2, 18). WNT subgroup patients have an excellent prognosis whilst G3 patients demonstrate worse outcomes (17).

Methylation of the cytosine component of DNA in cytosine-phosphate-guanine (CpG) dinucleotides is a crucial biological mechanism in determining gene expression. Cancers have complex methylation profiles, thus DNA methylation signatures based on thousands of CpG sites can provide robust data for precise diagnosis even when not all histological or molecular features of a tumor are detected. DNA methylation profiling is now considered the gold standard for MB subgrouping due to its unbiased method (19). The German Cancer Research Centre (DKFZ) developed DNA methylation-based CNS tumor classification using a comprehensive machine learning approach to improve the diagnostic accuracy of the clinical decision-making process. This method has been shown to be highly robust and reproducible with a high level of standardization. It reduces the inter-observer variability even from a small sample and poor-quality material (19).

To date, limited data have been reported from low and middle-income countries (LMIC) on pediatric MB patients in relation to the four molecular subgroups (20–22). Indeed, no data exist from

Malaysia. Therefore, we performed a retrospective study of molecular classification of pediatric MB to investigate the subgroup-specific percentage and survival outcomes from the four tertiary pediatric oncology centers in Malaysia using 850k DNA methylation profiling. In addition, we compared the accuracy of histological diagnosis with immunohistochemistry (IHC) and DNA methylation profiling on the diagnostic tumor tissue.

Patients and methods

Children ≤ 18 years old diagnosed with MB at University Malaya Medical Center (UMMC), Penang General Hospital (PGH), Sarawak General Hospital (SGH), and Sabah Women and Children's Hospital (SWCH), Malaysia between January 2003 and June 2017 were reviewed. Archived formalin-fixed paraffin-embedded (FFPE) tumor tissues from these patients were retrieved from the respective pathology departments. The retrieved samples were sent to DKFZ for MB molecular subgroup analysis using the 850k DNA methylation array technique. Clinical data were collected from medical charts, radiological results, and follow-up clinic records. These children were followed up until November 2020 to evaluate the survival outcome.

Statistical analysis

Event-free survival (EFS) was measured from the date of diagnosis to the date of disease recurrence, death, or last follow-up. OS was measured from the date of diagnosis to the date of death or last follow-up. Survival curves were constructed using Kaplan-Meier methods. Statistical significance was defined as a p-value < 0.05. Data analysis was performed using the software IBM SPSS Statistics 27 (IBM Corp., Armonk, NY, USA).

Ethics statement

This study was approved by the Ministry of Health (MOH) Medical Research and Ethics Committee (NMRR-17-991-35677) and UMMC Medical Research Ethics Committee (MREC-2016112-4485).

Results

Comparison between histological diagnosis and 850k DNA methylation profiling results of the whole cohort

A total of 50 samples derived from patients diagnosed and treated as MB were identified. The histological diagnosis and molecular subgrouping were analyzed with 850k DNA methylation profiling. Two (4%) of the 50 patients' tumor DNA samples were insufficient for analysis. Of the remaining 48 patients, 41 (85%) samples were confirmed as MB, whilst for seven (15%) patients, DNA methylation classification results were discrepant with the histopathological diagnosis of MB. These included glioblastoma multiforme (GBM) (n =2), atypical teratoid rhabdoid tumor (n=2), and one each of Ewing sarcoma, malignant peripheral nerve sheath tumor (MPNST) like sarcoma, and pineoblastoma. All seven patients received MB therapy, and six of them died due to progressive disease, except one patient with Ewing Sarcoma survived despite receiving MB treatment (Table 1).

Medulloblastoma patients' demographic data, clinical presentation, and surgery

The demographic and treatment characteristics of the 41 confirmed MB patients were analyzed. The median age at diagnosis was 6 years old (range, 0.25–16 years). A male preponderance was observed with a male-to-female ratio of 2.4: 1. There were 31 children aged ≥3 years old and ten infants (<3 years old). The most common clinical presentations were headache (63.4%), nausea/vomiting (63.4%), unsteady gait (48.8%), and cerebellar dysfunction symptoms/signs (43.9%). The pre-diagnostic symptom interval (PSI) duration varied from 1 week to 16 weeks, and the median duration of PSI was 3 weeks. Data on PSI was unavailable in eight patients. Sixteen patients (39%) had upfront gross total resection (GTR), and another three patients achieved complete resection after second-look surgery. Twelve patients (29%) had near-total resection (NTR) in which three of them underwent second-look surgery to achieve NTR. Radiological subtotal resection (STR) was observed in nine patients (22%) and four of them had second-look surgery. The extent of surgical resection information was missing in one patient (Table 1). A ventriculoperitoneal shunt (VP) was inserted in 24 patients (58.5%). Overall, eight families refused treatment and the abandonment rate for the whole cohort was 19.5%.

Children ≥ 3 years old with medulloblastoma

Medulloblastoma histological variants, molecular subgroup, and risk stratification

Based on histological reports, seven (22.6%) patients had classic histology, DN was reported in three (9.7%) patients and in 21 (67.7%) patients the histological variant was not specified. By methylation, four patients were classified as WNT (12.9%), SHH was identified in four patients (12.9%), G3 in seven patients (22.6%), and 16 patients were stratified as G4 MB (51.6%). Two G3 patients had *MYCC* amplification. For G4, one patient was diagnosed to have *MYCC* and another two patients were found to have *MYCN* amplification with 850k DNA methylation array technique. Radiological imaging and cerebrospinal fluids analysis revealed metastatic disease in 11 patients, 19 patients had localized disease and data was missing in one patient. Sixteen patients (51.6%) were stratified as HR and the remaining 15 patients were stratified as SR (Table 1). The abandonment rate was 22.6% (seven patients) in older children; five HR patients refused radiotherapy

Table 1 Demographic, diagnosis, treatment, and outcome.

Molecular subgroup	Mt	Surgery	Histology diagnosis from local hospitals	Histology subtypes from local hospitals	DNA methylation result from DKFZ	*MYCC*/*MYCN* amp. result from DKFZ	Upfront RT	CTX	Site of relapse	Time to relapse from diagnosis (years)	Outcome (Time from diagnosis to last follow-up/death in years)
Infants and young children (<3 years old)											
SHH-INF (NOS-PQs)	0	STR	MB	Desmo-plastic	MB	N	N	HS II	N	N	Alive (7.75)
SHH-INF (type 2)	0	STR	MB	NOS	MB	N	N	POG Baby brain protocol	Primary site	2.58	Alive (5.83)
SHH-INF (type 2)	NI	STR	MB	MBEN	MB	N	N	Refused CTX	NI	NI	NI (0.33)
SHH-INF (type 1)	0	STR	MB	NOS	MB	N	N	POG Baby Brain protocol	PD-Primary site	1.66	Dead (1.66)
SHH-INF (type 1)	0	STR	MB	Desmo-plastic	MB	N	N	HS II	N	N	Alive (3.4)
SHH-INF (type 3)	0	NTR	MB	MBEN	MB	N	N	ACNS 1221	N	N	Alive (3.66)
SHH-INF (type 2)	0	STR	MB	Desmo-plastic	MB	N	N	ACNS 1221	N	N	Alive (3.25)
G3	0	NTR	MB	Classic	MB	N	N	HS II	N	N	Alive (6.25)
G3	3	NTR	MB	Classic	MB	*MYCC*	N	HS II	Spinal metastasis	1.1	Dead (2.0)
G3	0	NTR	MB	Classic	MB	*MYCC*	N	POG Baby Brain protocol	PD-Primary site, intracranial leptomeningeal and spine	0.51	Dead (0.66)
Standard-risk ≥ 3 years old)											
SHH-AD (type 4)	0	GTR	MB	Desmo-plastic	MB	N	CSI 36Gy, PSB 54Gy	Defaulted after 4 courses of CCNU, Cis, VCR	NI	NI	NI (1.67)
SHH-AD (type 3)	0	NTR <1.5cm^2	MB	NOS	MB	N	CSI 23.4Gy, PSB 56Gy	Recurrence after 4 courses of CCNU/ Cis/VCR	Primary site	1.16	Alive (4.83)
G3	0	NTR <1.5cm^2	MB	NOS	MB	N	CSI 36Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	N	N	Alive (6.25)
G3	0	GTR	MB	NOS	MB	N	No RT ϕ physician decision	No CTX ϕ physician decision	Primary site and spinal metastasis	0.33	Dead (0.33)

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Molecular subgroup	Mt	Surgery	Histology diagnosis from local hospitals	Histology subtypes from local hospitals	DNA methylation result from DKFZ	*MYCC*/*MYCN* amp. result from DKFZ	Upfront RT	CTX	Site of relapse	Time to relapse from diagnosis (years)	Outcome (Time from diagnosis to last follow-up/death in years)
G3	0	GTR	MB	Classic	MB	*MYCC*	CSI 23.4Gy, PSB 54Gy	8 courses of Cis, VCR, Cyclo	Right frontal lobe	2.25	Dead (4.0)
G3	0	GTR	MB	NOS	MB	N	CSI 36Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	N	N	Alive (4.11)
G4	0	GTR	MB	NOS	MB	N	Incomplete RT	N	N	N	Dead (0.5) Surgical infection during RT
G4	0	GTR	MB	Classic	MB	*MYCN*	CSI 36Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	N	N	Alive (14.16)
G4	0	GTR	MB	Desmo-plastic	MB	N	CSI 36Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	*Primary site	4.41	Dead (4.9)
G4	0	NTR <1.5cm^2	MB	Classic	MB	N	CSI 36Gy, PSB 54Gy	Refused CTX	Primary site and spine	2.66	Dead (3.5)
G4	0	NTR	MB	NOS	MB	N	CSI 36Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	N	N	Alive (9.83)
G4	0	GTR	MB	NOS	MB	N	CSI 36Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	N	N	Alive (6.0)
G4	0	GTR	MB	NOS	MB	N	CSI 36Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	N	N	Alive (3.83)
G4	0	GTR	MB	NOS	MB	N	CSI 36Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	Primary site and spinal metastasis	3.16	Dead (4.25)
G4	0	GTR	MB	NOS	MB	N	CSI 36Gy, PSB 54Gy	4 courses of CCNU, Cis, VCR	N	0.91	Dead (0.91) Sepsis after chemotherapy
High-risk (≥ 3 years old)											
WNT	0	NTR >1.5cm^2	MB	Classic	MB	N	CSI 36Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	N	N	Alive (6.67)
WNT	0	STR	MB	Desmo-plastic	MB	N	Refused RT	Refused CTX	NI	NI	NI (0.04)
WNT	NI	GTR	MB	NOS	MB	N	Refused RT	Refused CTX	Primary site	0.33	Dead (0.66)

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Molecular subgroup	Mt	Surgery	Histology diagnosis from local hospitals	Histology subtypes from local hospitals	DNA methylation result from DKFZ	*MYCC/MYCN* amp. result from DKFZ	Upfront RT	CTX	Site of relapse	Time to relapse from diagnosis (years)	Outcome (Time from diagnosis to last follow-up/death in years)
WNT	3	GTR	MB	NOS	MB	N	CSI 36Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	N	N	Alive (5.50)
SHH-INF (NOS-PQs)	3	GTR	MB	Classic	MB	N	CSI 36Gy, PSB 54Gy	4 courses of CCNU, Cis, VCR	*Primary site	0.83	Dead (0.83)
SHH-AD (type 3)	0	STR	MB	NOS	MB	N	CSI 36Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	Primary site	1.42	Death (1.5)
G3	3	NTR >1.5cm^2	MB	NOS	MB	*MYCC*	Refused RT	HS II (1 course then defaulted)	PD-primary site	0.75	Dead (0.75)
G3	NI	GTR	MB	NOS	MB	N	Refused RT	Refused CTX	NI	NI	NI (0.25)
G3	3	NTR >1.5cm^2	MB	NOS	MB	N	CSI 36Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	N	N	Alive (4.0)
G4	1	GTR	MB	Classic	MB	N	CSI 36Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	Primary site	1.75	Dead (2.0)
G4	2	STR	MB	NOS	MB	N	CSI 36Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	N	N	Alive (7.13)
G4	3	NTR >1.5cm^2	MB	NOS	MB	*MYCN*	CSI 45Gy, PSB 54Gy	8 courses of CCNU, Cis, VCR	N	N	Alive (6.58)
G4	0	NI	MB	NOS	MB	N	Refused RT	Refused CTX	NI	NI	NI (0.08)
G4	3	GTR	MB	NOS	MB	N	CSI 36Gy, PSB 54 Gy, spine T2-T9 54Gy	8 courses of CCNU, Cis, VCR	N	N	Alive (5.0)
G4	3	GTR	MB	NOS	MB	*MYCC*	CSI 36Gy, PSB 54Gy	1 course of CCNU, Cis, VCR	*Third ventricle	0.75	Dead (0.83)
G4	3	GTR	MB	Classic	MB	N	CSI 39.6 Gy, PSB 54Gy	POG 9031 (3 courses of Cis/Eto & 7 courses of Cyclo/VCR)	N	N	Alive (4.0)
Discrepancy between local histopathological diagnosis and DNA methylation profiling results											

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Molecular subgroup	Mt	Surgery	Histology diagnosis from local hospitals	Histology subtypes from local hospitals	DNA methylation result from DKFZ	*MYCC/MYCN* amp. result from DKFZ	Upfront RT	CTX	Site of relapse	Time to relapse from diagnosis (years)	Outcome (Time from diagnosis to last follow-up/death in years)
-	**0**	**NTR**	**MB**	**NOS**	**Sarcoma/ MPNST like**	-	**CSI 36Gy, PSB 54Gy**	**Defaulted after 1 course of CCNU, Cis, VCR**	**Primary site**	**10.0**	**Dead (10.5)**
-	**0**	**Biopsy**	**MB**	**NOS**	**GBM**	-	**CSI 36Gy, PSB 54Gy**	**N**	**PD**	**0.83**	**Dead (1.0)**
-	**4**	**STR**	**MB**	**Classic**	**Pineo-blastoma**	-	**CSI 36Gy, PSB 54Gy**	**8 courses of CCNU, Cis, VCR**	**Primary site**	**1.5**	**Dead (1.66)**
-	**0**	**GTR**	**MB**	**NOS**	**Ewing Sarcoma**	-	**CSI 36Gy, PSB 54Gy**	**8 courses of CCNU, Cis, VCR**	**N**	**N**	**Alive (10.5)**
-	**0**	**STR**	**MB**	**NOS**	**ATRT**	-	**N**	**Baby brain protocol**	**PD**	**0.51**	**Dead (0.51)**
-	**0**	**STR**	**MB**	**NOS**	**GBM**	-	**CSI 36Gy, PSB 54Gy**	**PD after 1 course of Cis, CCNU, VCR**	**PD**	**0.58**	**Dead (1.0)**
-	**0**	**STR**	**MB**	**NOS**	**ATRT**	-	**N**	**Refused CTX**	**PD**	**0.5**	**Dead (0.5)**
Samples with insufficient tissue for DNA methylation profiling	**0**	**STR**	**MB**	**NOS**	**Normal tissue**	-	**N**	**N**	**N**	**N**	**Dead (0.25) Post-operative complication**
	0	**STR**	**MB**	**Classic**	**Insufficient tissue**	-	**CSI 36Gy, PSB 54Gy**	**8 courses of CCNU, Cis, VCR**	**N**	**N**	**Alive (9.25)**

amp, amplification; AD, adult; amp, amplification; ATRT, atypical teratoid rhabdoid tumor; CCNU, lomustine; Cis, cisplatin; CSI, craniospinal radiotherapy; CTX, chemotherapy; Cyclo, cyclophosphamide; DKFZ, German Cancer Research Center; Eto, etoposide; G3, Group 3; G4, Group 4; GTR, gross total resection; Gy, Gray; HR, high risk; HS, Headstart; Ifos, Ifosfamide; iHR, young children with high risk group; INF, infant; MB, medulloblastoma; Mt, metastasis; MPNST, malignant peripheral nerve sheath tumor; N, no; NI, no information; NTR, near total resection; NOS, not otherwise specified; PD, progressive disease; POG, Pediatric Oncology Group; PQs, poor quality sample; PSB, primary site boost; RT, radiotherapy; SHH, Sonic hedgehog; SR, standard-risk; STR, subtotal resection; TB, tumour bed; VCR, vincristine; WNT, Wingless.

* Spinal magnetic resonance imaging was not performed at relapse/disease progression.

Φ Physician's decision for conservative treatment after surgery due to poor neurological status.

Color shading signifies certain molecular subgroup in medulloblastoma.

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post-surgery and two SR patients defaulted after surgery and radiation.

Treatment characteristics and relapse pattern

Tables 1, 2 summarize the treatment and relapse patterns. Twenty-five patients (SR MB, n=14, HR MB, n=11) were given up-front radiation with a median interval between surgery and initiation of radiotherapy of 41 days (18-152 days). Six patients (SR MB, n=1, HR MB, n=5) did not receive radiotherapy due to poor neurological status and family refusal.

Clinical course for *standard*-risk MB patients (n=15)

Regarding radiotherapy, eleven patients were treated with a higher CSI dose of 36Gy and primary site boost (PSB) of 54Gy according to physicians' discretion due to difficulties in obtaining magnetic resonance imaging (MRI) of the spine and CSF cytology within the recommended interval for accurate disease staging. In addition, CSF cytology results were unreliable due to technical difficulties in transportation, storage, and interpretation. All but one of these patients (10/11) received radiotherapy within 49 days of surgery, with concurrent weekly vincristine. One patient received radiotherapy at 54 days from surgery due to post-operative infection. Only two patients received a standard CSI dose of 23.4Gy with PSB of 54-56Gy within 49 days of surgery. One G4 patient died from an *Acinetobacter Baumanii* VP shunt infection during radiotherapy. One patient with G3 MB was palliated by the treating physician due to significant neurological impairment post-surgery. Of 13 patients treated with radiation without interruption, nine patients eventually completed eight courses of the A9961 chemotherapy regimen (7), whilst three patients received incomplete courses of adjuvant chemotherapy, and one patient's parents refused adjuvant chemotherapy. Neutropenic sepsis, treatment abandonment, and disease recurrence were the contributing factors to receiving incomplete chemotherapy in the three patients. Out of the nine patients who completed full treatment, six were still in remission at the last follow-up. However, the remaining three patients died due to combined, distant, and local recurrence at 26, 12, and 37.5 months respectively after completing initial treatment. Of these, one patient had G3 MB with *MYCC* amplification, and another two patients had G4 MB. They were referred to the palliative team for the continuation of end-of-life care management. One G4 MB patient who refused adjuvant chemotherapy had primary recurrence with spinal metastasis 30 months following the completion of radiation therapy. He was not salvaged following recurrence (Tables 1, 2).

Clinical course for high-risk MB patients (n=16)

Tables 1, 2 summarize the treatment and relapse patterns. Five families refused radiotherapy. Of these, one G3 MB patient with *MYCC* amplification abandoned the treatment after one course of Head Start II (HS II) chemotherapy and the patient passed away with primary and spinal disease progression (12). The remaining four patients' parents refused treatment after surgery and all these patients died of progressive disease. The remaining 11 patients received CSI at a dose of 36-45Gy with a PSB of 54Gy. Four of these patients received delayed radiotherapy on day 56, day 59, day 77, and day 152 post-surgery due to a limited number of linear accelerators, lack of anesthetists to provide sedation during radiation, and parental phobia of radiotherapy. These patients did not receive chemotherapy as a bridging therapy after surgery while waiting for radiotherapy commencement. Of the 11 patients, ten patients were treated with weekly vincristine during radiotherapy, followed by A9961 chemotherapy (7). One patient received chemotherapy as per the Pediatric Oncology Group (POG) 9031 regimen (9) but without concurrent chemotherapy during radiation. Among those who received delayed radiation, one G4 patient with *MYCC* amplification treated with radiotherapy on day 77 post-surgery had a distant recurrence at the third ventricle after the first course of chemotherapy and died without salvage treatment. Another G4 MB patient with delayed radiotherapy on day 152 post-surgery had primary site recurrence after 4 months of treatment and received palliative care (Tables 1, 2). The remaining two patients with delayed radiotherapy were still in complete remission during the last follow-up.

Survival outcomes

Median follow-up for children ≥3 years old was 4.0 years (range, 0.04-14.16 years). The 5-year EFS rates for SR and HR patients were 37.3 ± 13.3% and 43.8 ± 12.4% respectively. The 5-year OS rates for SR and HR were 40.6 ± 14.1% and 43.8 ± 12.4% respectively. The 5-year EFS rates for non-metastatic and metastatic patients were 35.1 ± 11.4% and 54.5 ± 15.0%. Survival based on molecular subgroups was undertaken only for G3 and G4 patients, as there were too few WNT and SHH patients to generate survival curves. 5-year EFS and OS rates were 42.9 ± 18.7% for G3 respectively. Whilst, the 5-year EFS and OS rates for G4 were 48.2 ± 13.6% and 46.9 ± 13.2% respectively. Of the four WNT patients, all were classified as high-risk based on the presence of either residual tumor >1.5cm^2 and/or metastatic disease. Two of these WNT patients received 36Gy CSI followed by eight cycles of A9961 chemotherapy and are alive disease-free 6 and 5 years from the diagnosis. Treatment was abandoned after a GTR in one WNT patient, who developed a local relapse four months later and died. In another WNT patient, treatment was abandoned after an STR, and the patient was lost to follow-up. Of the four SHH patients, one patient relapsed locally during treatment, was salvaged with focal stereotactic radiosurgery of 15Gy, and remained in remission. Another SHH patient relapsed locally after 2.5 months of treatment and succumbed due to disease progression. The third SHH patient abandoned the treatment after four courses of chemotherapy and was lost to follow-up. Another metastatic SHH patient developed disease recurrence while on treatment and died due to disease progression. After censoring those patients where treatment was abandoned, the 5-year EFS rates for SR and HR were 43.1 ± 14.7% and 63.6 ± 14.5% respectively (Figure 1A). The 5-year OS rates for SR and HR were 46.9 ± 15.6% and 63.6 ± 14.5% respectively (Figure 1B). The 5-year EFS rates for non-metastatic and metastatic patients were 44.4 ± 13.5% and 66.7 ± 15.7%. According to molecular subgroups, G3 MB, 5-year EFS,

TABLE 2 Outcome of relapsed medulloblastoma patients.

Sub groups	Mt	Initial Diagnosis	Site of tumor at diagnosis	Site of recurrence/ progression	TTR/P from the last day of treatment	Surgery during recurrence	Histology during recurrence	Diagnosis at recurrence	MRI spine at recurrence/ progression	CSF cytology	Salvage treatment during recurrence/ progression (No. courses)	Outcome
WNT	Not done	NOS MB, WNT	PF	PF	4 months (after surgery, refused CTX/ RT)	GTR	NOS MB	MB	Neg	NP	Palliative support	Dead
SHH	3	Classic MB, SHH-INF	PF	*PF	Recurrence (during CTX)	NP	NA	MB	NP	NP	Palliative support	Dead
	0	NOS MB, SHH-INF type 2	PF	PF	18 months from EOT	GTR	NOS MB	MB	Neg	Neg	CSI 36Gy and PF 54Gy with 8 courses of CCNU, Cis, VCR	Alive
	0	NOS MB, SHH AD type 3	PF	PF	Recurrence (during CTX)	NP	NA	MB	Neg	Neg	SRS 15Gy	Alive
	0	NOS MB, SHH AD type 3	PF	PF	2.5 months from EOT	PR	NOS MB	MB	Neg	Neg	Palliative support	Dead
	0	NOS MB, SHH-INF type 1	PF	PF	PD (during CTX)	No	No	MB	Neg	NP	Palliative support	Dead
G3	3	Classic MB, G3, c-myc	PF with spinal metastasis	PF with spinal metastasis	3 months from EOT	STR	Classic MB, G3, c-myc	MB	Metastasis	Neg	CSI 35Gy and PF 54Gy	Dead
	3	NOS MB, G3, c-myc	PF with spinal metastasis	PF	PD (Refused RT, defaulted CTX)	NP	NA	MB	Metastasis	NP	Palliative support	Dead
	0	Classic MB, G3, c-myc	PF	Right frontal lobe	12 months from EOT	Biopsy	MB Classic	MB	Neg	Neg	Focal re-irradiation 54Gy Oral etoposide for 1 month	Dead
	0	Classic MB, G3, c-myc	PF	PF, intracranial leptomeningeal & spine	PD (during CTX)	NP	NA	MB	Metastasis	NP	Palliative support	Dead
G4	1	Classic MB, G4	PF	PF	4 months from EOT	NP	NA	MB	Neg	NP	Palliative support	Dead
	0	Desmoplas-tic MB,G4	PF	*PF	37.5 months from EOT	NP	NA	MB	Not done	NP	Palliative support	Dead

(Continued)

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TABLE 2 Continued

Sub groups	Mt	Initial Diagnosis	Site of tumor at diagnosis	Site of recurrence/ progression	TTR/P from the last day of treatment	Surgery during recurrence	Histology during recurrence	Diagnosis at recurrence	MRI spine at recurrence/ progression	CSF cytology	Salvage treatment during recurrence/ progression (No. courses)	Outcome
	0	Classic MB, G4	PF	PF with spinal metastasis	30 months (after RT, refused CTX)	NP	NA	MB	Metastasis	NP	Palliative support	Dead
	3	NOS MB, G4, c-myc	PF with spinal metastasis	*Third ventricle	Recurrence (during CTX)	NP	NA	MB	NP	NP	Palliative support	Dead
	0	NOS MB, G4	PF	PF and spinal metastasis	26 months from EOT	NP	NA	MB	Metastasis	NP	Palliative support	Dead

AD, adult; CCNU, lomustine; Cis, cisplatin; CTX, chemotherapy; CSI, craniospinal radiotherapy; EOT, end of treatment; G3, Group 3; G4, Group 4; INF, infant; MB, medulloblastoma; Mt, metastasis during initial diagnosis; NA, not applicable; NOS, non-otherwise specified; NP, not performed; PD, progressive disease; PF, posterior fossa; RT, radiotherapy; SHH, sonic hedgehog; SRS, stereotactic radiosurgery; STR, subtotal resection; TTR/P, time to relapse/progression; VCR, vincristine; WNT, Wingless.
*MRI spine was not done at recurrence/progression.
Color shading signifies certain molecular subgroup in medulloblastoma.

and OS were both 60 ± 21.9%. G4 MB showed 5-year EFS and OS rates of 55.1 ± 13.9% and 53.6 ± 14.2% respectively (Figures 2A, B).

Children <3 years old with medulloblastoma (n=10)

Medulloblastoma histology subclass, molecular subgroup, and risk stratification

Three (30%) patients had classic histology, two (20%) patients had MBEN subclass, DN was reported in three (30%) patients and histological variant was not specified in two (20%) patients. By methylation, seven patients were classified as SHH subgroups (70%), G3 MB was seen in three patients (30%) and two of these had *MYCC* amplification. Eight patients had localized disease, one patient presented with metastatic disease and staging data was missing in one patient (Table 1).

Treatment characteristics and relapse pattern

Of the ten patients, for one SHH patient, the family declined treatment following surgical resection, whilst the remainder (90%) were treated according to radiotherapy-sparing regimens (n=4 [HS II], n=3 [POG Baby Brain], n=2 [ACNS 1221]) (12, 23, 24). One patient with G3 and *MYCC* amplification had a primary and distant relapse 3 months into treatment. This patient received salvage treatment with CSI of 35Gy and primary tumor boost of 54Gy but succumbed due to disease progression. POG Baby Brain protocol was administered in three patients (two SHH and one G3 with *MYCC* amplification) and all of them had disease progression (24). Of these, one patient with SHH MB was salvaged with a CSI of 36Gy and a primary tumor boost of 54Gy followed by the A9961 regimen and is still in remission 5.83 years from completion of treatment (Tables 1, 2) but the other two patients went on to receive palliative therapy. The extent of surgical resection did not appear to influence the outcome in young children. Overall, the abandonment rate was 10% (one patient) in younger children.

Survival outcomes

The median follow-up was 3.32 years (range, 0.33-7.75 years). The 5-year EFS and OS rates were 50.0 ± 15.8% and 60.0 ± 15.5% respectively. The 5-year EFS and OS rates for SHH patients were 57.1 ± 18.7% and 71.4 ± 17.1% respectively. After censoring the patient who abandoned treatment, the 5-year EFS and OS rates were 55.6 ± 16.6% and 66.7 ± 15.7% respectively for the whole cohort, and 66.7 ± 19.2% and 83.3 ± 15.2% respectively for the SHH group (Figures 1A, B, 3A, B). Numbers were too small to generate survival curves for G3 patients. Of the three G3 patients, two died of progressive disease and both had *MYCC* amplification. The other remains in remission 6.25 years following treatment with HSII.

Discussion

The present study is the first study in Malaysia that reports the molecular subgrouping in childhood MB with clinical descriptions. With the rapid advancement in molecular profiling and

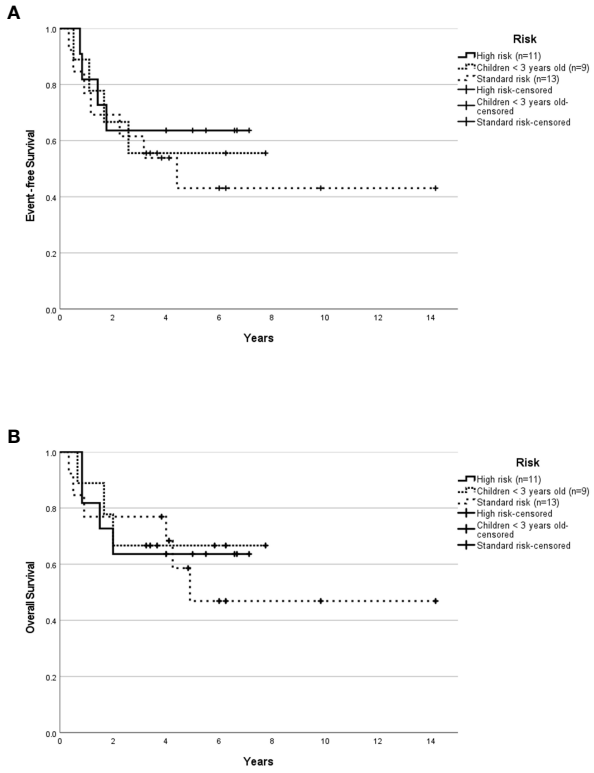

FIGURE 1
Survival outcome of childhood medulloblastoma (excluding the abandonment) based on risk stratification. Event-free survival **(A)** and overall survival **(B)** for the whole cohort according to risk stratification after excluding the abandonment.

incorporation of molecular information into clinical risk stratification, the management of childhood MB has undergone a paradigm shift. However, implementing these strategies in daily practice is challenging for most centers in LMIC due to a lack of expertise and associated high costs. IHC has formed an integral component of histopathological diagnosis for decades, however several reports have shown significant inter-observer variability in the histopathological diagnosis of many CNS tumors (25–27). Capper et al. reported that 129 out of 1104 (12%) CNS tumor cases had discordant histopathological diagnosis based on DNA methylation which resulted in the revision of the original histopathological diagnosis in favor of the DNA methylation classification (19). Consistent with this finding in our study a similar discordant rate of 15% was also observed between local histopathological diagnosis and DNA methylation profiling. The critical importance of an accurate diagnosis in assigning the most appropriate treatment is evident in our series. Patients with GBM, Ewing sarcoma, and MPNST-like sarcoma received more intensive treatment regimens, including craniospinal radiotherapy (CSI) of 36Gy with PSB of 54Gy and intensive chemotherapy than the respective standard of care therapies. This may have resulted in prolonged hospitalization with additional morbidity to the patient and the added socio-economic burden to the family. In the absence of dedicated neuropathologists in many LMICs, DNA methylation would represent an ideal tool for accurate diagnosis, if the costs were not the main limiting factor for its implementation.

The current WHO CNS tumor classification identifies four histopathological subclasses of MB; classic, DN, LCA, and MBEN (28). In our series, tumor histological variants were only reported in 44% of MB patients, highlighting the limited neuropathology expertise that exists in LMIC. Several studies have reported that young children with DN/MBEN subtype showed an excellent outcome, whilst LCA histology demonstrated a dismal prognosis (29, 30). Previous studies in LMIC have used simpler techniques, such as fluorescence *in situ* hybridization (FISH), and specific IHC markers as surrogate methods, to molecularly subgroup MB. GAB1, YAP1, filamen A along with beta-catenin IHC antibodies are used to classify MB into WNT, SHH, and non-WNT/SHH subgroups (31). These techniques are easily applicable and cost-effective (20, 21). For example, specific IHC with positive nuclear beta-catenin and FISH demonstrating monosomy 6 can be used to identify WNT tumors. However, caution has been advised in making a diagnosis of WNT tumors using either nuclear beta-catenin alone as false positives occur or monosomy 6 alone as this marker has been occasionally observed in other subgroups (22, 32, 33). In addition, beta-catenin IHC alone may lead to an incorrect diagnosis of a WNT subgroup due to difficulty in interpreting patchy nuclear accumulation in some tumors (15, 32). Moreover, these specific IHC antibodies are unable to differentiate G3 and G4 tumors. This highlights the importance of DNA methylation profiling method which has a substantial impact on diagnostic precision in CNS tumors across the globe. Hence, DNA methylation testing has

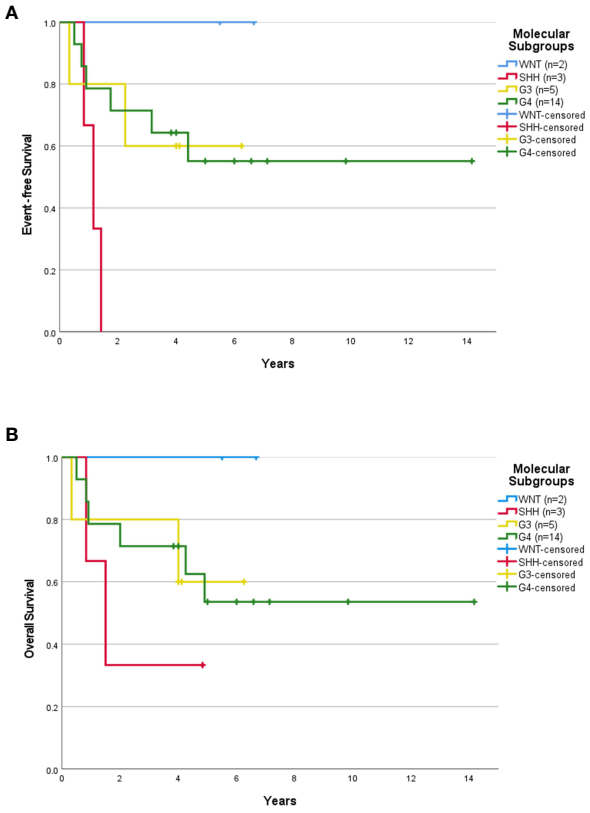

FIGURE 2
Survival outcome of childhood medulloblastoma > 3 years old (excluding the abandonment) based on molecular subgroups. Event-free survival **(A)** and overall survival **(B)** for children > 3 years old according to molecular subgroups after excluding the abandonment.

become an internationally accepted method for accurate molecular identification (19) and has been included in the recently revised fifth edition of the WHO classification of CNS tumors (WHO CNS 5th edition) (28).

MRI is the preferred first-line modality in MB, and traditionally, it has been used for diagnosis, surgical guidance, staging, treatment response evaluation, and surveillance during follow-up. However, recent studies have shown encouraging data regarding radiogenomics features of MB with distinct imaging characteristics (radio-phenotypes) correlating with specific molecular subgroups (molecular phenotypes) (34). It is increasingly recognized that imaging features of MB can reflect the underlying disease biology, which may serve as a helpful tool to predict the molecular subgroups of MB, especially in LMIC (35). Even though there were no specific pathognomonic features for each molecular subgroup, some radiological characteristics were more peculiar and predominant in one subgroup than others (34–38). More work needs to be done to validate these correlations that would benefit clinicians who do not have access to DNA methylation investigation.

For children ≥ 3 years of age, the proportion of WNT, SHH, and G3 patients were consistent with high-income countries (HIC) (WNT 12.9% versus 9-17.4%; SHH 12.9% versus 15%; G3 22.6% versus 21.3-32%) but the proportion was higher for G4 (51.6% versus 44-45.6%) (16, 17). For children <3 years of age, the relative proportions of patients in each of the four molecular subgroups was in keeping when compared with HIC, with a majority of SHH (70% versus 65%), 30% G3 patients and no WNT patients (34, 35). However, in contrast to other studies revealing approximately less than 10% G4 patients, in our cohort there were no G4 patients (29, 30, 39, 40). The age cutoff for infants and young children varies from one cooperative group to another. There is no consensus on the age cutoff for infants and young children with MB. Some infant studies include children up to 3 years old, while others extend the age cutoff to 4 or 5 years old. Hence, the differences in age cutoff in MB treatment protocols exhibit the variances in the proportion of G4 MB in young children. Furthermore, the median age in our study was 6 years old, and G4 MB was most frequently seen in older children. These could be the reasons for the higher proportion of G4 MB in older children and the absence of G4 MB among children < 3 years old in this study, in addition to the racial differences and small sample size. All five patients with *MYCC* amplification in G3 (n=4) and G4 (n=1) passed away with disease progression, whilst patients with *MYCN* amplification in G4 (n=2) were still in remission during the last follow-up. This result is consistent with the SJMB03 trial report where *MYCC* amplification was associated with inferior survival whereas *MYCN* amplification was not associated with G3 and G4 MB outcomes (17).

For children ≥ 3 years of age with HR MB, survival outcomes were comparable with reports from developed countries, after removing patients where therapy was abandoned. In sharp

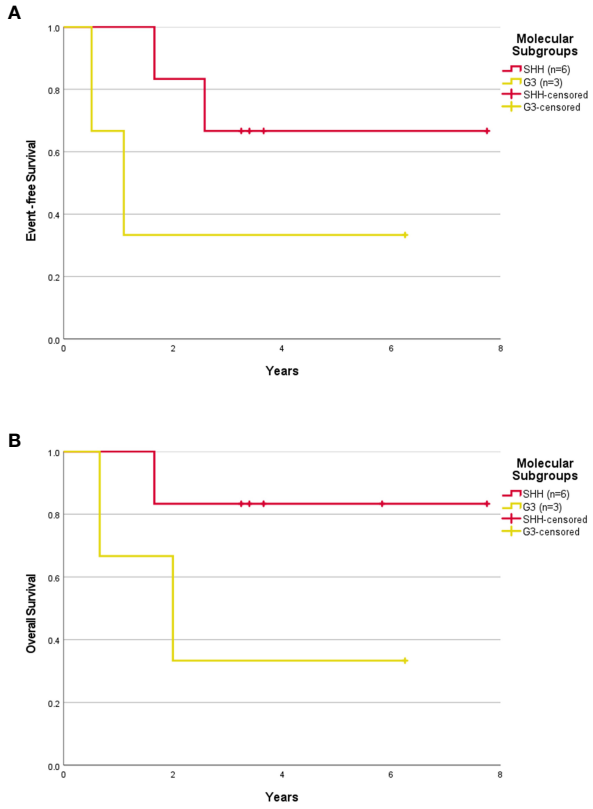

FIGURE 3
Survival outcome of childhood medulloblastoma ≤ 3 years old (excluding the abandonment) based on molecular subgroups. Event-free survival **(A)** and overall survival **(B)** for children > 3 years old according to molecular subgroups after excluding the abandonment.

contrast, the survival for patients with SR MB was dismal (5-year OS 43.1%) despite receiving 36Gy CSI. This was likely due to treatment-related complications such as sepsis and post-surgical mortality. Of note, the 5-year OS outcomes in older patients with G4 MB were inferior when compared to developed countries even after censoring the abandonment cases (53.6% versus 77-95%) (6, 8, 17). The reason for this finding in part is likely related to toxic deaths. The WNT subgroup has been shown to have an excellent outcome, even for the small proportion of patients with high-risk features (6, 8, 17). Consistent with this, both WNT MB patients in our series, who were treated using HR therapy based on the Chang staging system, survived despite having metastatic disease and residual tumor >1.5cm^2. Hence, molecular classification information is important for treatment strategy and disease prognostication. In addition, two G4 patients presented at the age of 3 years, they received upfront radiation and are long-term survivors. This is an important issue in LMIC as radiation in young children is associated with significant neurocognitive deficits when early intervention programs and special education resources are very limited in the community (22).

The 5-year EFS and OS outcomes for children <3 years of age in our cohort were more in keeping with survival from developed countries (12). Young children with SHH clearly had a better outcome than older children in our study consistent with previous reports (28, 39). Using the SJYC07 treatment regimen, Robinson et al. reported a superior outcome for the SHH-II subtype compared with the SHH-I subtype (39). However, the addition of intraventricular methotrexate appears to negate the inferior outcome associated with SHH-I subtype (29). Given the small patient numbers, we did not further analyze the survival outcome for SHH subtypes (SHH-1 and SHH-II). As noted by others, G3 MB did much worse due to the frequent presence of *MYCC* amplification (29, 40). Moreover, aggressive surgical intervention might not be indicated in young children with MBEN and DN histology as the presence of residual tumor was not associated with the dismal outcome in our cohort. MBEN and DN histology variants are known to have excellent outcomes (29, 30).

Treatment abandonment due to cultural beliefs that traditional medicine is superior, lack of awareness regarding childhood cancer trajectory among parents, ideas that cancer is incurable, low socioeconomic status, poor parental education level, long travel time with lack of housing facilities for families from remote areas, painful procedures, and treatment adverse effects and toxicity were well-recognized contributing factors to inferior outcomes (41, 42). The overall abandonment rate in our study was 19.5%. A single-center study on challenges treating pediatric MB in Malaysia reported a treatment dropout rate of 35.3% (42). Similarly, the abandonment rates of MB in other developing countries from Asia ranged from 31% to 36.4% (43–45). In contrast, the treatment refusal rates were only between 0.6% to 5.7% in HIC (6, 17, 39).

Therefore, identifying the risk factors and prioritizing strategies to reduce the incidence of treatment rejection is crucial in LMIC to close the survival gap. Optimal care can be achieved by providing free lodging and food to patients and families, financial support for travel, social support, efficient communication with detailed and repeated counseling, and effective procedural sedation and analgesia. Notably, developing satellite cancer centers for patients living in rural areas and initiating a contact tracing mechanism for defaulters would certainly contribute to mitigating some aspects of treatment abandonments (46). Additionally, organizing regular national campaigns may cultivate health-seeking behavior by creating public awareness about the curability of cancer and its early warning signs (46). Importantly, our study's treatment-related complications, such as septicemic death and post-surgical mortality, were concerning. The critical factors for the dismal outcome were the lack of specialized pediatric neuro-oncology multidisciplinary services, limited human resources and infrastructure, poor supportive care, and deficiency in the internal health delivery system (47). In our cohort, radiotherapy was also delayed in several patients due to a limited number of linear accelerators, frequent machine breakdowns, and a lack of staff to provide sedation or general anesthesia, which resulted in a long waiting list (42). In addition, late parental consent for treatment and post-operative complications contributed to delayed radiotherapy. These factors caused significant barriers to commencing radiotherapy on time, leading to poor adherence to treatment guidelines (42). Hence, building human resource capacity through structured national education and training programs is essential to increase the number of skilled and experienced pediatric neuro-oncology multidisciplinary healthcare professionals to improve the service quality and diagnostic capacity to avoid delays in diagnosis, misdiagnosis, and mistreatment. Furthermore, increasing focus on healthcare financing for catastrophic illness, especially allocating adequate budget, supporting human resource training, establishing specialized diagnostic and treatment cancer centers for childhood CNS tumors, improving the availability of novel drugs and supplies, providing equipment such as radiotherapy and radiology machines, and periodic monitoring of cancer registry should be the priority (46, 47).

This study is the first study reporting on the four molecular subgroups of MB among children in Malaysia. The study's main limitation was that it was a retrospective study with a relatively small sample size. The challenges of small sample size were augmented after patients were divided into four molecular subgroups. Additionally, missing patients' records and incomplete clinical and pathological data limit the analysis and interpretation of the study. Data regarding radiogenomics features of MB to determine the correlation between imaging characteristics and molecular subgroups of MB were not collected for analysis.

In conclusion, the discrepancy between histological diagnoses and DNA methylation profiling highlights the importance of DNA methylation profiling in improving the accuracy of diagnosis. OS for children ≥3 years of age with HR MB was consistent with other reports. However, OS was very poor for those classified with SR. Most infants had SHH MB, and their EFS and OS were comparable to those reported in high-income countries. Due to the relatively small patient cohort and the high treatment abandonment rate with treatment-related mortality, definite conclusions regarding the prognostic significance of the four molecular subgroups of MB cannot be made for children aged ≥ 3 years. Implementing this high-technology investigation would assist pathologists in improving the diagnosis and provide molecular subgrouping of MB as we move toward subgroup-specific therapies. However, treatment abandonment, delayed radiotherapy, and treatment-related complications are the priorities that need to be addressed to maximize the benefits of such technology.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving humans samples were approved by Ministry of Health (MOH) Medical Research and Ethics Committee (NMRR-17-991-35677) and University Malaya Medical Centre Medical Research Ethics Committee (MREC-2016112-4485). The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by- product of routine care or industry. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

RR: Conceptualization, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. AJT: Data curation, Writing – review & editing. VJ: Data curation, Writing – review & editing. OW: Investigation, Writing – review & editing. HM: Investigation, Writing – review & editing. NHAR: Investigation, Writing – review & editing. TY: Data curation, Writing – review & editing. KG: Data curation, Writing – review & editing. AT: Data curation, Writing – review & editing. SY: Data curation, Writing – review & editing. GO: Data curation, Writing – review & editing. HA: Data curation, Writing – review & editing. DJ: Formal Analysis, Investigation, Writing – review & editing. EB: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. NG: Conceptualization, Formal Analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Invasive fungal infections in pediatric patients with central nervous system tumors: novel insights for prophylactic treatments?

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Background and aims: Invasive fungal disease (IFD) poses significant morbidity and mortality risks, especially in pediatric patients with neoplastic diseases. However, there is a notable lack of data concerning patients with central nervous system (CNS) tumors. Considering vulnerability factors to infections such as neutropenia, corticosteroids, chemotherapy, surgical interventions, and others, this study aims to evaluate the incidence of IFD in pediatric patients with CNS tumors and determine appropriate indications for prophylactic measures. This is a single-center, retrospective study conducted between 2011 and 2022 at the Pediatric Institute of Oncology (IOP-GRAACC-UNIFESP).

Results: A total of 38 cases of IFD were diagnosed in 818 children with CNS malignancies (4,6%). The mean age was 3.5 years (0.4-28y), with 22 (57.9%) male patients. Embryonal tumors (18/38, 47.3%) were the most prevalent CNS tumors, followed by low-grade gliomas (13/38, 34.2%). All episodes met the EORTC IFD criteria, and 36/38 (94.7%) were proven. Invasive yeast infections (33/36, 91.6%), predominantly *Candida* (30/33, 90.9%), were the most common diagnosis. In total, 25 patients (25/38, 65.8%) were receiving chemotherapy, with 13 of them having embryonal tumors. A total of 11 infants were in the Head Start scheme, resulting in a high prevalence of IFD in these group of patients (11/58, 18.9%). In total, 13 (13/38, 34.2%) patients underwent neurosurgery, mostly ventricular-peritoneal shunts revisions (10/13, 76.9%). Nine (9/38, 23.7%) were with prolonged use of corticosteroids, eight of them associated with neurosurgery.

Conclusion: Routine systemic antifungal prophylaxis based solely on diagnosis is not recommended for low-risk cases. Evaluating patient- and treatment-specific risk factors is crucial in infants undergoing high-dose chemotherapy with expected neutropenia and in patients requiring prolonged corticosteroid therapy alongside neurosurgical procedures.

KEYWORDS

invasive fungal infections, pediatric central nervous system tumors, infectious diseases, prophylactic treatments, Intracranial tumors

Introduction

Invasive fungal disease (IFD) poses significant morbidity and mortality risks, especially among pediatric patients with neoplastic diseases (1). Furthermore, it is well established that patients with hematologic malignancies and those undergoing allogeneic bone marrow transplantation have a high risk of developing infection and an indication of primary prophylaxis (1, 2). Few studies describe the incidence of these diseases in patients with solid tumors (3, 4) and there is an absence of information regarding pediatric patients with central nervous system (CNS) tumors. Considering other vulnerability factors to infections such as prolonged neutropenia, central venous catheter use, corticosteroid administration, cytotoxic chemotherapy, surgical interventions, and individual comorbidities (2, 5), this study aims to assess the incidence of IFD in pediatric CNS tumor patients. Furthermore, the study seeks to elucidate clinical characteristics, predisposing factors, diagnostic approaches, treatment modalities, outcomes, and indications for prophylaxis within this specific patient population.

Methods

This retrospective, single-center, observational study was conducted on children diagnosed with CNS malignancies and IFD between 2011 and 2022. The study was carried out at the Pediatric Oncology Institute (IOP-GRAACC), affiliated with the Federal University of São Paulo. The Institute operates as a tertiary university hospital and handles approximately 100 new neuro-oncology cases per year. These cases are covered by the Brazilian Unified Health System (SUS), which offers universal access to healthcare for all citizens. Additionally, some patients have private health insurance that covers their treatment costs.

Patient characteristics studied included demographic information, CNS tumor details, treatment modality (such as surgery, chemotherapy, and/or radiotherapy, but excluding the duration of bone marrow transplant), predisposing or risk factors (such as corticosteroid use, prolonged neutropenia, extended hospitalization, presence of central venous catheters, and prior antibiotic usage), IFD diagnosis, antifungal treatment, and clinical outcomes.

The systematic review by Fisher et al. showed that the definitions for some risk factors are not well established. In our cohort, prolonged neutropenia was characterized by an absolute neutrophil count of less than 500 μL for more than 10 days. Lymphopenia was defined as a lymphocyte count of less than 1000 cells/mL. Prolonged hospitalization was categorized as a hospital stay of more than seven days, and prolonged use of corticosteroids was identified as a daily dose of dexamethasone exceeding 0.6mg/m2 for more than 21 days.

Episodes of IFD were categorized as possible, probable, or proven based on the international consensus criteria of the European Organization for Research and Treatment of Cancer (EORTC) (6, 7).

All data were systematically tabulated, and descriptive analyses were employed to report the demographic, clinical, and mycological characteristics of the entire study population. Ethical approval for research involving human subjects was obtained from the study center before the start of the study itself.

Results

Patient characteristics

During the 11-year observation period, 38 cases of IFD were identified among a total of 818 children with CNS malignancies, representing a prevalence of 4.6%. The mean age was 3.5 years, ranging from 0.4 to 28 years, and the majority of cases, 22, were from male subjects (57.9%). The most frequently encountered CNS tumors were embryonal, accounting for 18 out of 38 cases (47.4%), with medulloblastoma being the predominant subtype (11/18, 61.1%). Low-grade gliomas (LGG) followed closely, accounting for 13 out of 38 cases (34.2%).

Of the total cases, 94.7% (36 out of 38) met the EORTC criteria (7) for proven IFD, while 5.3% (two out of 38) were categorized as probable, and none met the criteria for possible IFD. Within the subset of proven IFD episodes, the most prevalent diagnosis was an invasive yeast infection, accounting for 33 out of 36 cases (91.6%), with *Candida* infections being the predominant subtype in this category (30 out of 33, 90.9%). Among *Candida* infections, *C. albicans* and *C. parapsilosis* were the most common species, representing 40% (12 out of 30) of cases each. Three out of 36 (8.3%) proven episodes were attributed to molds, specifically *Fusarium oxysporum*. Both probable IFD episodes were identified as suspected invasive pulmonary aspergillosis, supported by positive galactomannan results and characteristic imaging findings.

The sites of infection were distributed as follows: bloodstream infections accounted for the majority, with 32 cases (84.2%), central nervous system (CNS) infections were observed in five cases (13.1%), and pulmonary infections were identified in two cases (5.3%). Additionally, one patient presented with both CNS and bloodstream infections simultaneously.

Cohort characteristics are shown in Table 1.

Risk factors

Of the study participants, 25 out of 38 (65.8%) were receiving chemotherapy. Of these, 13 had embryonal tumors, and 11 were infants enrolled in the *Head Start* backbone scheme (8). Regarding gliomas, 13 out of 14 low-grade gliomas (LGG) were identified, with six of them receiving chemotherapy as follows: three were following the *Roger Packer* protocol (9) as their first-line treatment, one was on vinorelbine (10), and another on temozolomide (11), both irresectable/refractory cases. One case of infant-type hemispheric glioma was treated with the *Baby-POG protocol* (12). Furthermore, neurosurgical interventions had been performed in 13 out of 38 cases (34.2%). Most of these procedures involved ventricular peritoneal shunt revision, accounting for 10 out of 13 cases (76.9%). The other three cases were tumor resections. One patient (one out of 38, 2.6%) with posterior fossa ependymoma received focal radiotherapy, while five patients (five out of 38, 13.1%) were out of treatment/in the follow-up phase.

TABLE 1 Underlying disease and epidemiology of IFD in 38 patients from our cohort.

Central nervous system tumor diagnosis	
Embryonal Tumors	18 (47.4%)
Gliomas	14 (36.8%)
Low-grade glioma	13/14 (92.8%)
High-grade glioma	1/14 (7.2%)
Ependymoma	3 (7.9%)
Plexus Choroid carcinoma	2 (5.3%)
Germ cell tumor	1 (2.6%)
Fungal species	
Yeasts	
C. albicans	12 (31.6%)
C. parapsilosis	12 (31.6%)
C. tropicalis	3 (7.9%)
C. lusitanae	2 (5.3%)
C. pelliculosa	1 (2.6%)
Trichosporon japonicum	1 (2.6%)
Cryptococcus neoformans	1 (2.6%)
Exophialia spp	1 (2.6%)
Molds	
Fusarium oxysporum	3 (7.9%)
Probable Aspergillus	2 (5.3%)
Site of IFD*	
Bloodstream	32 (84.2%)
Central nervous system	5 (13.1%)
Pulmonary	2 (5.3%)

*One patient had both bloodstream and CNS infection.

Among the additional risk factors observed, all patients had central venous catheters. Nine out of 38 patients (23.7%) were identified as having a prolonged course of corticosteroids of more than 21 days. A total of 30 patients (78.9%) were receiving broad-spectrum antibiotics, with eight of them treated for bacterial bloodstream infections. In total, 22 patients (57.9%) had a prolonged hospitalization of more than 7 days, with the majority of these cases exceeding 30 days. Of these patients, 11 were admitted to the intensive care unit (ICU). A total of 10 patients (26.3%) had an absolute neutrophil count of less than 500 cells/mL, while 22 patients (57.9%) had a lymphocyte count of less than 1000 cells/mL. Additionally, four patients (10.5%) were treated for typhlitis, but none had undergone abdominal surgery.

Risk factors associated with IFD are shown in (Figure 1), and their associations are shown in Table 2.

Treatment and outcomes

In our cohort, the primary drugs used in the treatment of IFD were amphotericin, azoles, and echinocandins, as detailed in Tables 3 and 4.

Among the cases involving yeasts, seven out of 33 (21.2%) patients died; however, only two of these deaths were attributed to invasive fungal disease (IFD). One patient with medulloblastoma developed a bloodstream infection with *C. tropicalis*, and another patient with atypical teratoid/rhabdoid tumor (ATRT) developed a bloodstream infection with *C. albicans* and *Klebsiella pneumoniae*, leading to septic shock and typhlitis. Another patient with relapsed leptomeningeal medulloblastoma passed away due to progressive disease and *Cryptococcus neoformans* IFD affecting the CNS and bloodstream. The remaining four patients died in a palliative care context, unrelated to IFD. Regarding molds, two out of five cases (40%) were affected by *Fusarium oxysporum* IFD but ultimately died due to progressive disease. Therefore, within the entire cohort, nine patients (nine out of 38, representing 23.7%) succumbed to various causes, with only two of these deaths attributed to IFD. The other seven patients passed away in a palliative care setting due to progressive disease.

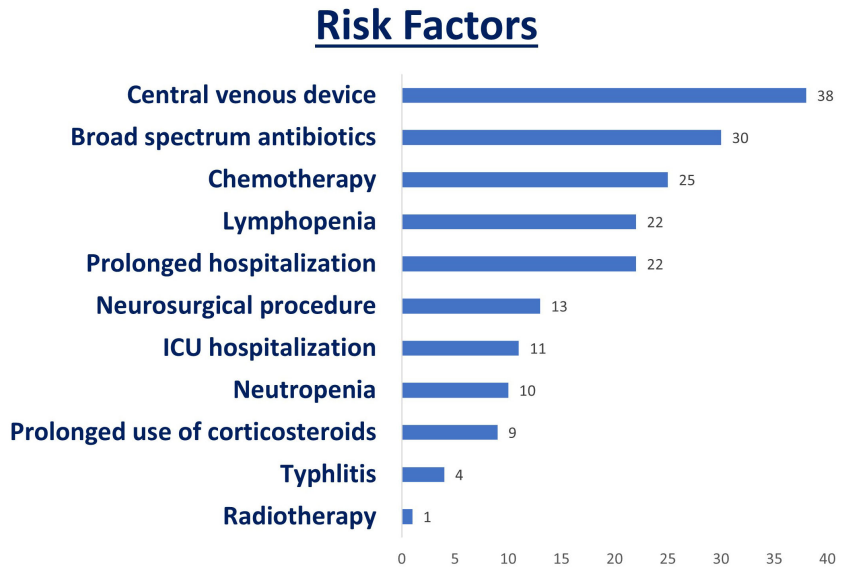

FIGURE 1
Risk factors associated with IFD.

TABLE 2 Correlation between the number of associated risk factors and patients with IFD.

Number of risk factors associated	Number of patients n= 38 (100%)
One risk factor	3 (7.9%)
Two	4 (10.5%)
Three	12 (31.5%)
Four or more	19 (50%)

Discussion

This study provides insight into the epidemiology and treatment of invasive fungal disease (IFD) in pediatric patients with CNS malignancies. Our findings reveal a notable incidence of proven instances of IFD in this patient group, which has traditionally been categorized as low-risk based on their diagnosis alone (13).

The true prevalence of invasive fungal disease (IFD) in children with solid tumors remains underexplored, as highlighted by recent studies by Ruijters et al. (3, 4). Additionally, discussions of IFD cases in the context of CNS tumors are often limited to scenarios involving autologous stem cell transplantation (ASCT) (14). This study aimed to assess the necessity for antifungal prophylaxis in the context of CNS malignancies, excluding the risk associated with ACST that may occur during CNS tumor therapy. This is the rationale behind the exclusion of this specific period from the study.

In the spectrum of fungal infections observed, *Candida* species or invasive candidiasis/candidemia were prevalent in the majority of cases (30/38, 78.9%), a trend consistent with studies in hematological diseases (5). Notably, non-albicans *Candida* species accounted for a significant proportion of these cases (18/30, 60%), consistent with the global epidemiological shift toward an increased prevalence of non-albicans species (15). Specifically, *C. parapsilosis* was the most frequently isolated non-albicans species overall (12/30, 40%), an association first reported in solid tumors by Bartlett et al. (15). However, this study did not specify the subtype of solid tumor in which this association was observed, and CNS tumors represented a minority of cases in their cohort. Given the affinity of *C. parapsilosis* for central venous access devices (15) and the presence of at least this risk factor in most oncology patients, including in our cohort, it is crucial to consider the direction of prophylactic measures.

TABLE 3 Antifungal treatment for yeasts.

Antifungal Treatment (Yeast)	Number of patients n=33 (100%)
Amphotericin	14/33 (42.4%)
Echinocandin	12/33 (36.4%)
Azoles	4/33 (12.1%)
Fluconazole	3/4 (75%)
Voriconazole	1/4 (25%)
Combined antifungal therapy	3/33 (9.1%)

Mold pathogens other than *Aspergillus* are on the rise, constituting 10-25% of invasive mold disease in patients with hematological malignancies or post-hematopoietic stem cell transplantation (HSCT) and carrying a high mortality rate (16). *Fusarium* spp. accounted for 60% (3/5) of the invasive molds identified in our study, despite the small number, which differs from the predominance of *Aspergillus* in hematological cases (17). These patients were previously reported by Carlesse et al. in 2013 (18), due to a hospital outbreak of *Fusarium oxysporum* catheter-related fungemia. This is noteworthy as it deviates from the typical route of infection for this fungal pathogen, which is primarily through the respiratory tract (16). Importantly, we have observed complete clinical recovery following the removal of the central venous device and appropriate antifungal therapy (18). Two patients, one with ependymoma and one with choroid plexus carcinoma, were treated with amphotericin but later succumbed to progressive tumor disease.

Exposure to corticosteroids and antibiotics, central venous devices, prolonged hospitalization (including in the ICU), treatment regimens, and blood counts have all been associated with an increased risk of IFD (2). This is particularly relevant in the context of low-risk based on diagnosis alone. However, determining the precise impact of each factor can be challenging due to their overlapping effects, as demonstrated in our study.

Of the 38 patients, 25 (65.8%) developed IFD after undergoing chemotherapy regimens, with a notable incidence among infants receiving the Head Start backbone chemotherapy regimen, seven of whom had both neutropenia and lymphopenia, and six of whom also required prolonged hospitalizations. During the study period, 58 infants were subjected to this protocol, resulting in a high prevalence of IFD in this patient group (11/58, 18.9%). According to the 2020 guidelines (1), an incidence of ≥10% is typically considered high risk for IFD, and primary antifungal prophylaxis is strongly recommended to reduce morbidity and mortality associated with the disease. Therefore, this group of patients may have benefited from primary antifungal prophylaxis for *Candida* species, given the expected neutropenia, prolonged duration, depth, and/or association with fever following intensive chemotherapy, all of which are highly correlated with IFD. Lymphopenia has also been identified as a risk factor for IFD in adult HSCT recipients (2). In this patient group, these risk factors often overlap, although we describe an additional seven cases with lymphopenia alone, three of which had prolonged hospitalizations.

Exposure to corticosteroids has been associated with an increased risk of IFD in patients with hematological malignancies and those undergoing HSCT (2). When considering only neurosurgical procedures, our study revealed a relatively low rate of fungal infections, accounting for less than 1% of cases during the study period. All the described procedures followed infection control standards, such as a sterile neurosurgical environment and antibiotic prophylaxis. However, it is worth noting that within our study cohort, eight out of nine patients who experienced prolonged corticosteroid use were also associated with neurosurgical procedures, with VP shunt revisions being the most common. Three of these patients developed CNS fungal infections, two of which were caused by *Candida albicans*. These

TABLE 4 Antifungal treatment for molds.

Antifungal Treatment (Mold)	Number of patients n=5 (100%)
Amphotericin	2/5 (40%)
Azoles Voriconazole	3/5 (60%) 3/3 (100%)

factors collectively underscore the significance of this association, as it has been described that *Candida* virulence genes can be upregulated in patients receiving steroids, particularly in cases involving hydrocephalus-related conditions (19). This upregulation may contribute to the mortality rate associated with *Candida* CNS infections, which typically ranges from 10% to 33% (20). In light of these considerations, patients subjected to high doses of corticosteroids due to VP shunt dysfunction are categorized as a high-risk group. For such individuals, we recommend the implementation of primary antifungal prophylaxis for *Candida*, such as fluconazole, during the period of dysfunction and neurosurgery. This prophylactic measure may be particularly important, especially in regions with a high prevalence of VP shunt usage, which is often the case in low- to middle-income countries (21).

The mortality rate associated with IFD in our cohort demonstrated more favorable outcomes compared to many of the previously reported studies, as indicated in the systematic review conducted by Ruijters et al. The mortality rates in these studies varied widely, ranging from 0% to 66.7%. Notably, only one study reported no deaths associated with IFD (4). This difference in mortality rates reflects the substantial improvements in supportive care, diagnostic capabilities, and therapeutic strategies that have been achieved.

Patients undergoing intensive chemotherapy for conditions such as acute myeloid leukemia (AML), high-risk acute lymphoblastic leukemia (ALL), and recurrent acute leukemia are strongly recommended to receive primary antifungal prophylaxis (1, 13). This recommendation is particularly pertinent in cases of AML, where systemic antifungal prophylaxis is advisable for children undergoing treatment that is expected to result in profound and prolonged neutropenia. In the context of ALL, the decision to administer systemic antifungal prophylaxis should be adapted to the specific treatment protocol, taking into account the varying risk of IFD across protocols and treatment phases. Additionally, according to these guidelines, the choice of antifungal agent should consider factors like local epidemiology, potential drug interactions, adverse effects, and cost-effectiveness. Mold-active agents are typically recommended in these cases (1, 13). Conversely, routine prophylaxis is not generally recommended for children with cancer who are at low risk for IFD. Instead, a personalized assessment based on individual risk factors should be conducted (1, 13). According to our cohort profile, for children with CNS tumors, active agents effective against yeasts, particularly *Candida* species, are recommended in two specific scenarios. First, in infants with embryonal tumors undergoing high-dose chemotherapy during the neutropenia phase, and second, when high-dose corticosteroids are used in cases of ventriculoperitoneal (VP) shunt dysfunction. Fluconazole, with its favorable cost-effectiveness, low potential for drug interactions, and manageable side-effect profile, is a suitable choice. However, local epidemiological data should be considered, and prospective analyses should be conducted to inform decision-making.

Given the study design and the substantial heterogeneity among patients with respect to risk factors (such as age, CNS tumor diagnosis, and treatment modalities), it was not possible to perform additional statistical associations. Despite this statistical limitation, we emphasize the importance of describing various risk factors, as they may offer valuable insights for prospective and controlled studies in the future.

In accordance with the guidelines set forth by Lehrnbecher et al., and considering the specific characteristics of our cohort, we have concluded that routine systemic antifungal prophylaxis is not advisable for patients at low risk based solely on their diagnosis. However, it is important to assess individual patients and treatment-related risk factors. In cases involving infants undergoing high-dose chemotherapy with profound and prolonged neutropenia or patients requiring prolonged corticosteroid use alongside neurosurgical procedures, the use of antifungal prophylaxis may provide potential benefits.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics and Research Committee of the Federal University of Sao Paulo - CAAE 67891023.0.0000.5505. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because Data Use Commitment Term (TCUD) was used.

Author contributions

ND, AC, and FC: These authors contributed equally to this work and share first authorship. AS and NS: contributed to conception and design of the study. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Pediatric neurosurgical-oncology scope and management paradigms in Sub-Saharan Africa: a collaboration among 7 referral hospitals on the subcontinent

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Background: Understanding of the epidemiology and biology of pediatric CNS tumors has advanced dramatically over the last decade; however there remains a discrepancy in the understanding of epidemiologic data and clinical capacity between high- and lower-income countries.

Objective: We collected and analyzed hospital-level burden and capacity-oriented data from pediatric neurosurgical oncology units at 7 referral hospitals in Sub-Saharan Africa (SSA).

Methods: A cross sectional epidemiological survey was conducted using REDCap at the 7 SSA sites, capturing 3-month aggregate data for patients managed over a total of 9 months. Descriptive statistical analyses for the aggregate data were performed.

Results: Across the neurosurgical spectrum, 15% of neurosurgery outpatient and 16% of neurosurgery operative volume was represented by pediatric neuro-oncology across the 7 study sites. Eighty-six percent and 87% of patients who received surgery underwent preoperative CT scan and/or MRI respectively. Among 312 patients evaluated with a CNS tumor, 211 (68%) underwent surgery. Mean surgery wait time was 26.6 ± 36.3 days after initial presentation at the clinic. The most common tumor location was posterior fossa (n=94, 30%), followed by sellar/suprasellar region (n=56, 18%). Histopathologic analysis was

performed for 189 patients (89%). The most common pathologic diagnosis was low grade glioma (n=43, 23%), followed by medulloblastoma (n=37, 20%), and craniopharyngioma (n=31, 17%). Among patients for whom adjuvant therapy was indicated, only 26% received chemotherapy and 15% received radiotherapy.

Conclusion: The histopathologic variety of pediatric brain and spinal tumors managed across 7 SSA referral hospitals was similar to published accounts from other parts of the world. About two-thirds of patients received a tumor-directed surgery with significant inter-institutional variability. Less than a third of patients received adjuvant therapy when indicated. Multi-dimensional capacity building efforts in neuro-oncology are necessary to approach parity in the management of children with brain and spinal tumors in SSA.

KEYWORDS

pediatric, neurosurgical-oncology, sub-Saharan Africa, CNS tumor, surgery wait time, postoperative length of hospital stay

Introduction

Central nervous system (CNS) tumors pose a significant public health burden worldwide and is reported to affect 7-11 persons per 100,000 person-years (1, 2). The 2016 global burden of disease collaborative report estimated 330,000 new cases of CNS cancer each year. Moreover, the age-standardized incidence rate of CNS cancers has increased by 17.3% from 1990 to 2016 (2). Pediatric brain and spine tumors are a subset of CNS cancers, representing roughly 17% of all childhood malignancies (3). They are the most common solid tumors of childhood and are the leading cause of cancer-related death in children and adolescents (4–6).

Epidemiological data on burden of pediatric brain and spine tumors has become increasingly available in recent years with a higher incidence reported in high-income countries (HIC) compared to low- and middle-income countries (LMICs) (4, 6–18). This discrepancy can be attributed to poor access to care, lack of imaging resources, inadequate histological diagnostic capabilities, and unreliable or nonexistent tumor registries – all resulting in underreporting in LMIC (11, 17, 19). Over the last two decades substantial resources have been mobilized in HIC for diagnosis, management and research to better understand these tumors (13, 20–22). Advances in managing these tumors are such that most children diagnosed with a CNS malignancy in a well-resourced healthcare system have an option to be enrolled in one or more trials offering cutting edge therapies. This is not the case for children in LMICs where cancer-related mortality is much greater (9, 19).

Before we can begin to invest in the infrastructure to support translational medicine and trial networks in LMICs, understanding the neuro-oncology burden and existing resources is fundamental. To better understand the hospital-level burden of disease and capacity, data was collected across 7 national referral hospitals in Sub-Saharan Africa (SSA) via a cross-sectional survey. In this study, we set out to report the burden of pediatric CNS tumors, their histologic subtype, and the basic resource availability to manage these patients.

Methods

A participatory research approach was employed in our research driven by the need to engage relevant stakeholders involved in pediatric neuro-oncology care in SSA. Potential research collaborators in SSA were identified through professional contacts in the academic neuroscience space. An invitation was extended to the identified neurosurgeons in East Africa, West Africa, and Southern Africa to participate in this study. A study team was assembled based on responses received which included 7 neurosurgeons from 7 referral hospitals in SSA, their respective neurosurgery teams and clinical care coordinators at the study site who assisted with data collection. Three neurosurgeons invited could not participate in the study due challenges related to participatory bandwidth or institutional IRB processes.

A 43-item survey was designed collectively by the study team to assess the hospital-level burden and capacity data from pediatric neurosurgical oncology units at the 7 referral hospitals in SSA (Supplementary File 1).

Institutional review board (IRB) approval was obtained from all 7 SSA sites, as well as the North American coordinating site, Vanderbilt University Medical Center. The seven SSA study sites included: Aminu Kano Teaching Hospital (AKTH), Kano, Nigeria; Komfo Anokye Teaching Hospital (KATH), Kumasi, Ghana; Nelson Mandela Children's Hospital (NMCH), Johannesburg, South Africa; Tenwek Mission Hospital(TMH), Bomet, Kenya; Zewditu Memorial Hospital (ZMH), Addis Ababa, Ethiopia; University Teaching Hospital (UTH), Lusaka, Zambia; and Muhimbili Orthopedic Institute (MOI), Dar es Salaam, Tanzania (Figure 1). Responses to all the survey questions was obtained by retrospective review of aggregate hospital data during the study

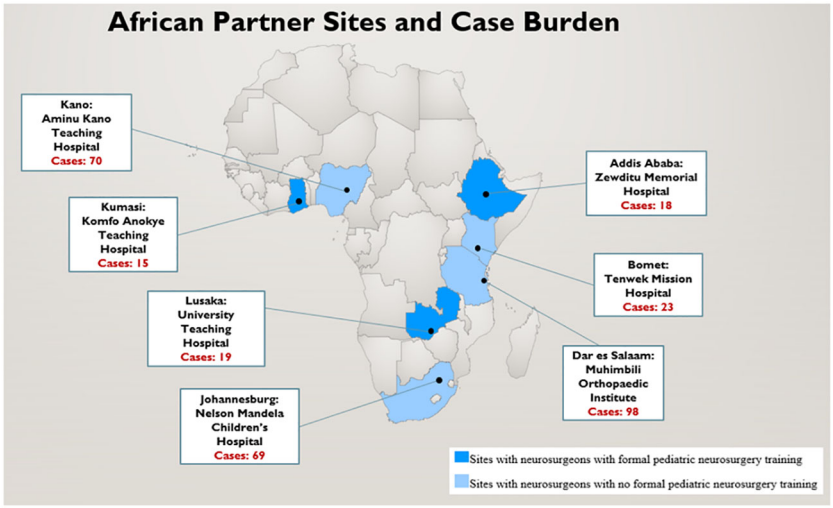

FIGURE 1
Map showing location of study sites in Sub-Saharan Africa and case burden.

period (January 2021 – October 2021). Therefore, identity of patients cannot be ascertained based on information collected by investigators.

The Research Electronic Data Capture (REDCap) tool was used for the cross-sectional epidemiological survey data collection (23). Over the 9-month study period, the REDCap survey was completed by the participating neurosurgeon at each of the 7 sites at three-month intervals to capture aggregate retrospective data of all pediatric CNS tumor cases diagnosed and/or managed over the preceding 3 months. Participating neurosurgeons provided information related to their surgical training, primary hospital and neurosurgical practice. Neuro-oncologic information included that related to tumor location and histopathology, operative details, postoperative management, adjuvant therapy, and follow-up practices. Data was obtained from outpatient and inpatient records, surgical case logs, oncology case logs, and hospital administrative data. The REDCap survey was completed at 3-month intervals for ease of data collection. The complete survey tool is included in the appendix (Supplementary File).

Statistical analysis

Descriptive statistics were pooled across the 7 SSA sites. Continuous data were presented as mean, standard deviation, median and range. Categorical data were presented as frequency and percentage. All statistical analyses were performed using the SPSS version 27 (IBM, Chicago, Inc).

Results

Partner site details and resource availability

Responses were obtained from neurosurgeons at all 7 partnering sites. Each neurosurgeon reported 3-monthly retrospective aggregate pediatric CNS tumor patient data and diagnostic and management capacity at their respective hospitals over the 9-month study period. The three neurosurgeons from UTH, ZMH, and KATH received formal pediatric neurosurgery training. Each site reported a median of 2 neurosurgeons (Range, 1-4) with pediatric neurosurgery practice. During the 9-month window of data collection, a total of 312 patients with pediatric brain or spinal tumors were diagnosed and evaluated in the clinic, emergency department, or ward at the 7 partner sites (Figure 1).

Cumulative across 7 sites, 14.8% of neurosurgery outpatient and 15.8% of neurosurgery operative volume was represented by pediatric neuro-oncology at the partner sites. Computed tomography and/or magnetic resonance imaging was available at all but one site which had no diagnostic imaging modality available. Six sites had a radiologist on site to interpret imaging findings but none of the six had a staff neuroradiologist. One site (TMH) had no radiologist on site even though there is a CT and MRI scanner available, and depended on an international team of radiologists from the United States (US) who provided teleradiology consults. Among patients who underwent a surgical intervention, 86% and 87% of patients underwent preoperative CT and MRI, respectively. Post-operatively, 29% and 37% of patients underwent CT and MRI, respectively, in the immediate/early post-operative period (Figure 2A).

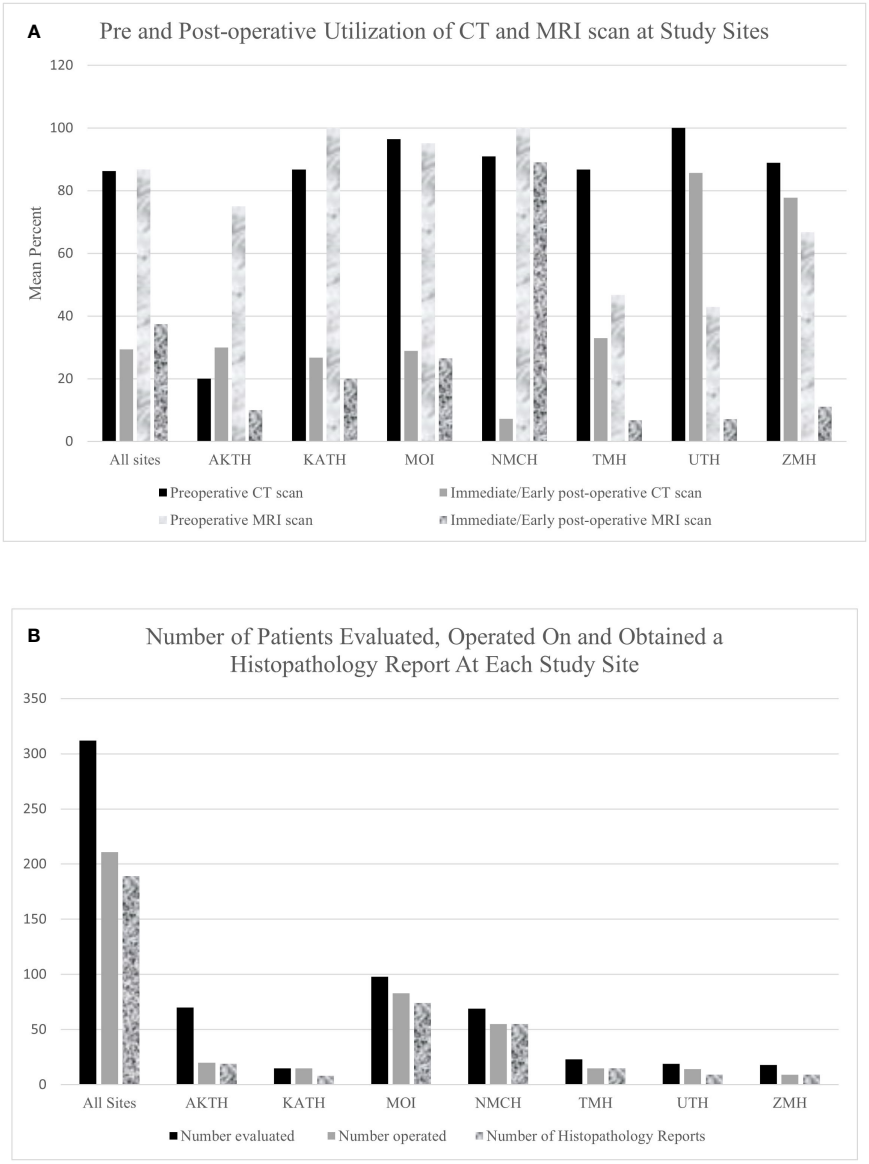

FIGURE 2
(A) Bar graph showing pre and post operative utilization of CT and MRI scan at study sites. **(B)** A Bar Graph showing the number of patients evaluated and operated on and obtained a histopathology report at all study sites.

Surgical management

Of the 312 patients evaluated, 211 (67.6%) patients underwent tumor-directed surgery and 16 (5.1%) were referred to other centers (Figure 2B). There was wide variability in the proportion of patients operated on at each hospital. At KATH, 100% of patients evaluated underwent surgery, whereas only 28% did so at AKTH. Among the 211 patients who underwent surgery, 178 patients (84.4%) underwent resection of tumor, 23 (10.9%) underwent biopsy and for 10 (4.7%) the type of tumor-directed surgery was unspecified. Among all presenting tumors, the most common tumor location was posterior fossa (n=94, 30.1%), followed by sellar/suprasellar (n=56, 17.9%), ventricular (n=29, 9.3%), brainstem (n=22, 7.1%), and spinal (n=22, 7.1%).

The most common tumor location for patients who underwent surgery was posterior fossa (n=72, 34.1%), followed by sellar/suprasellar (n=38, 18.0%), spinal (n=20, 9.4%) and ventricular (n=19, 9.0%) (Figure 3A).

Among 211 patients who underwent tumor-directed surgery, 85 (40.3%) had a CSF diversion either via shunt or endoscopic third ventriculostomy (ETV). Of the 101 patients who did not have tumor-directed surgery, 68 underwent a CSF diversion alone.

Tumor histopathology and adjuvant care

None of the seven partner sites had neuropathology expertise to interpret the histopathology, instead all tissue samples and

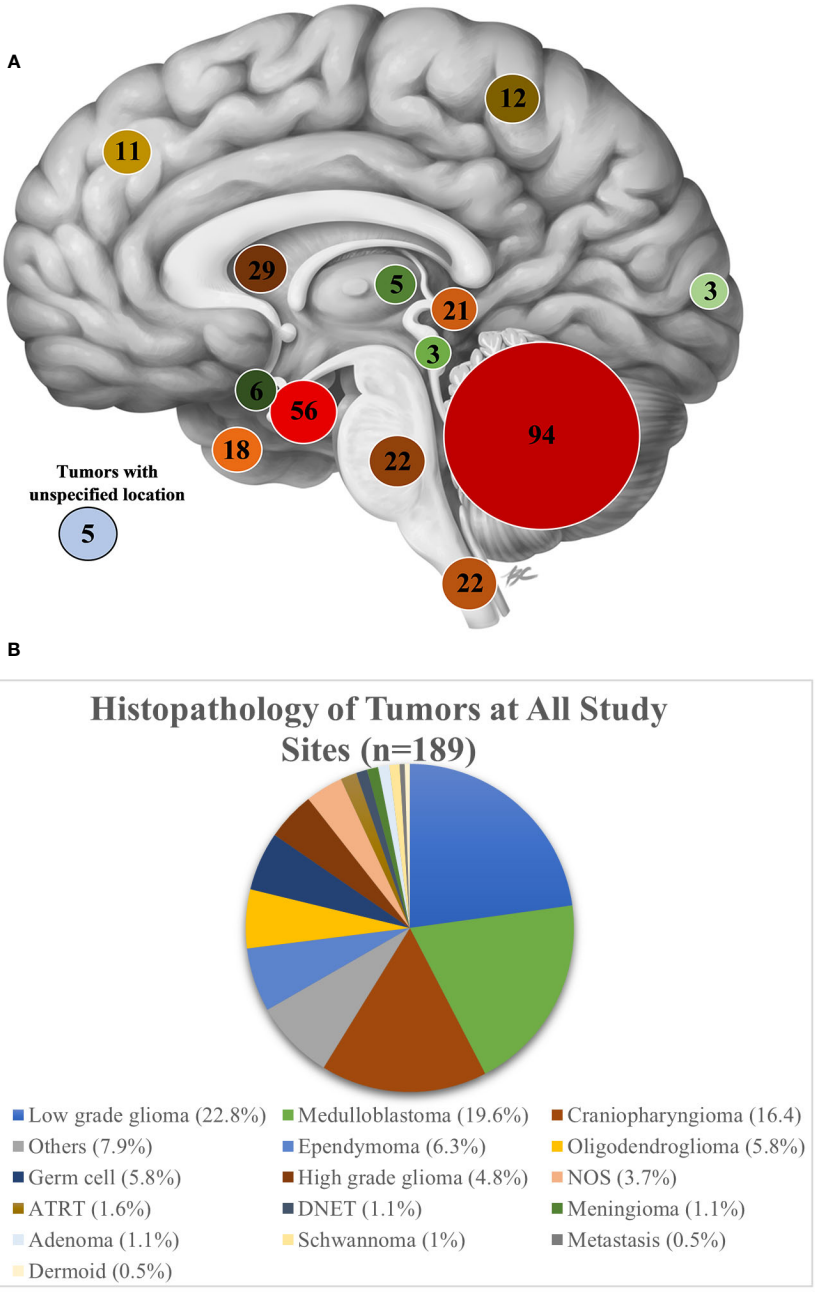

FIGURE 3
(A) A sagittal view of the brain showing the number of patients evaluated on based on tumor location at all study sites. *Image Credit: B Cheung Biomedical Illustration, 2020* (23) **(B)** Histopathology of tumors at all study sites.

histopathology slides were reviewed by a general pathologist. Ten percent of cases did not receive a histopathology report. Of the 90% of cases which received a report, a histopathological diagnosis was made for 88.4%, while for the remaining specimens, the diagnosis was either unspecified neoplasm (NOS) (3.7%) or classified as "other" (7.9%). As an aggregate across all sites, the most common pathologic diagnosis was low grade glioma (22.9%), followed by medulloblastoma (19.7%), and craniopharyngioma (16.5%) (Figure 3B). Among individual sites, however, the proportion of tumor histologies varied. Low grade glioma was the most frequently reported tumor at 4 of the 7 sites (KATH, 62.5%; MOI, 31%; ZMH, 22%; NMCH, 18.2%). Craniopharyngioma was the most common tumor subtype managed at AKTH (31.6%). At NMCH, medulloblastoma (14.5%) was equally as common as craniopharyngioma (14.5%). The sites UTH, ZMH, and TMH noted somewhat equal distribution of tumor pathology.

Among patients for whom adjuvant therapy was indicated, only 26% received adjuvant chemotherapy and 15% received adjuvant radiotherapy. There was variability among partnering sites in aggregate percent of patients who received adjuvant

chemotherapy and radiotherapy. Most sites relied on a pediatric oncologists or medical oncologists to provide adjuvant therapy to pediatric neurosurgical-oncology patients.

Surgery wait times and length of hospital stay

The mean wait time to surgery for patients who initially presented to the clinic was 26.6 ± 36.3 days and median wait time was 17 days (Range, 5-180). For patients admitted to the emergency or ward on initial presentation, the mean wait time to surgery was 18.2 ± 37.9 days and median wait time was 9 days (Range, 3-180). For patients undergoing surgery, the mean preoperative length of hospital stay (LOS) was 10.6 ± 8.4 days and median preoperative LOS was 9 days (Range, 2-30) and the mean post-operative length of hospital stay (LOS) was 10.4 ± 6.0 days and median post-operative LOS was 8 days (Range, 4-28). The mean post-operative ICU stay (LOS) was 3.4 ± 2.4 days and median post-operative ICU stay was 3 days (Range, 0-12).

A mean 26.4% (SD: 29.4%) patients who were candidates for tumor surgery did not undergo surgery due to inadequate resources. This was variable among the partner sites; TMH reported 0% of such patients and AKTH reported 73.7% patients who did not undergo surgery due to inadequate resources. Apart from KATH, all other sites reported having a surgery waiting list. Some of the reasons given for either delays in definitive treatment for CNS tumor cases or patients not receiving surgery reported by sites include lack of ICU beds (86%), lack of operating room space (86%), financial constraints (86%), lack of support system e.g., imaging modalities, blood and blood products (57%) (Figure 4). Twenty-four patients on the waiting list were reported to have died before they could have surgery. AKTH reported the highest number of deaths (8), followed by NMCH (7), MOI (5), ZMH (3), and UTH (1).

Surgical complications, Follow-up, and COVID-19 impact

Twenty-eight (13%) patients who had surgery experienced minor complications such as surgical site infection, wound dehiscence, and minor/transient neurological deficit. Major complications, including hemiparesis, permanent aphasia, or post-op meningitis were observed in 14 (7%). Across the 7 centers and among the 211 surgical patients, the surgical mortality was 2.4%.

Mean 73% (SD:32.1%) of patients received early postoperative follow-up (2-6 weeks post hospital discharge) and 51.7% (SD:34.9%) received mid-term follow-up (>3 months post hospital discharge).

The COVID-19 pandemic had a variable impact on neurosurgical-oncology volume across the 7 sites. UTH reported a 25%-50% reduction, NMCH reported a 25-75% reduction, AKTH reported a 50% reduction, and ZMH reported >75% reduction over the 9-month study period. Three sites (TMH, KATH, and MOI) reported no significant reduction in CNS tumor case volume due to the COVID-19 pandemic. AKTH reported doctors' industrial action (labor strike) as an additional reason for reduction in CNS tumor case volume during which there was cancellation of clinic consultations and non-emergent surgeries. Five treatment centers, KATH, MOI, TMH, UTH, AKTH had either a hospital-based or population-based tumor registry.

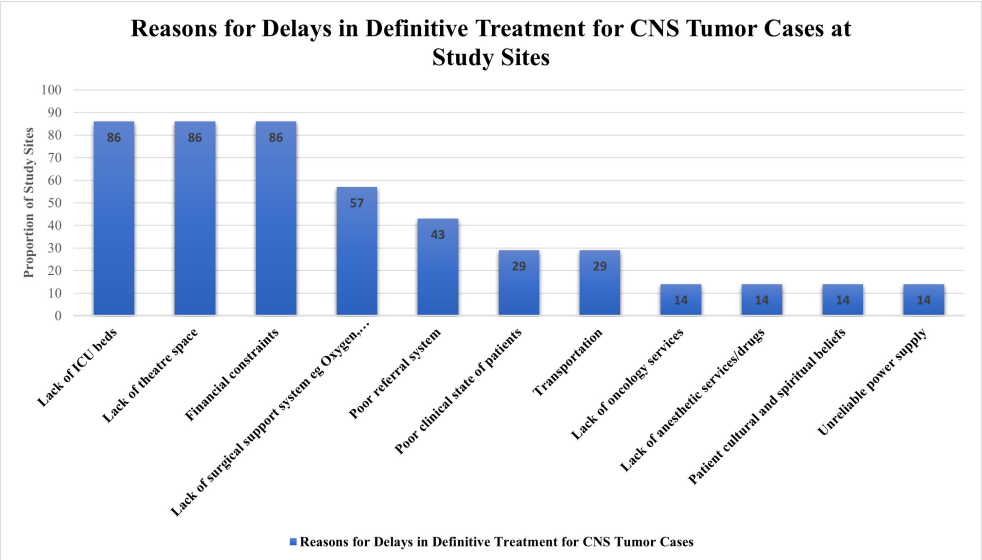

FIGURE 4
A Bar Graph showing the reasons for delay in definitive treatment for CNS tumor cases at study sites.

Discussion

An understanding of the basic epidemiological, clinical, and capacity data is necessary to guide the expansion of pediatric neuro-oncologic services in SSA, where hospital-level data is largely unknown. In this study, we aggregated cross-sectional data from 7 national referral sites in SSA to gain an understanding of the CNS tumor volume, location, and pathology, as well as neurosurgical resource availability and utilization for children with brain and spinal tumors.

Pediatric neuro-oncology forms a considerable proportion of the outpatient and operative volume at the seven national referral sites surveyed. At most sites, these cases are managed by general neurosurgeons due to the lack of fellowship trained pediatric neurosurgeons and neurosurgical oncologists. Despite the increasing burden of cases, pediatric neuro-oncology care is less prioritized in Africa as most treatment centers remain under-resourced.

Pediatric neuro-oncology care is complex and often require multidisciplinary approach. Based on the location radiographic characteristics of the tumor and presenting symptoms, surgical excision or biopsy is indicated for most pediatric brain and spine tumors. In our study, while a majority of the patients underwent preoperative CT or MRI imaging under the auspices of the treating neuro-oncologic team, 10-20% of patients had to arrange imaging elsewhere at a non-affiliated site, likely delaying care. Neuronavigation, intra-operative imaging modalities, and cortical mapping technology are scarce leaving most neurosurgeons in SSA to rely on anatomical landmarks alone to perform tumor surgeries (24). Less than half of patients underwent immediate/early post-operative CT or MRI imaging. Without an objective understanding of extent of resection, advising adjuvant therapy and disease monitoring via surveillance imaging becomes both challenging and speculative (25).

Analogous to prior reports from studies across the globe, a wide spectrum of pediatric brain and spine tumors were managed at the seven national referral sites in SSA (2, 9, 10, 17, 20, 21, 26, 27). Low-grade glioma was the most common subtype followed by craniopharyngioma and medulloblastoma. Similarly, Stagno et al. in a retrospective series of 172 Ugandan patients operated on over a 10-year period, found the most common tumor to be low grade glioma, followed by ependymoma, craniopharyngioma, choroid plexus papilloma and medulloblastoma (17). However, no cases of choroid plexus papilloma were noted in our study. In a multicenter retrospective study from Morocco, medulloblastoma was the most common histopathological subtype followed by low grade glioma, ependymoma and craniopharyngioma (14). The variation in pathological subtypes of tumor might be attributed to the different regional biology, different presentation patterns, or simply a limited dataset. Among the seven referral sites in our study, similar variabilities in histopathological diagnosis was noted. A histopathological diagnosis was unavailable in 12% of tumors after pathologist review. Similar findings were reported in a recent review of neuro-oncology articles from East Africa: 14% of tumors were without a general histologic description and 32% of tumors were reported as unknown or no specified diagnosis (11). Also a fraction of patients (10%) who underwent surgery did not receive a histopathology report despite having their tissue samples sent to the pathologist. Some study sites described delays in receiving histopathology reports taking an average of 4-5 weeks to receive the report post-surgery. The proportion of cases without a histopathology diagnosis indicates areas for improvement in tissue acquisition, processing, analysis, and data storage.

Many patients did not receive standard, comprehensive neuro-oncology care due to poor access or inadequate resources. About a third of cases did not receive surgery and a majority of patients (74%-85%) for whom adjuvant therapy was indicated based on their histopathology diagnosis did not receive adjuvant therapy. In the few patients who are able to receive adjuvant care, dyscoordination between neurosurgery and oncology teams during or following neurosurgical treatment often leads to a delayed start of adjuvant chemotherapy and/or radiotherapy or patients altogether missing the optimal window to receive adjuvant therapy (11, 17). The limited surgical infrastructure and neurocritical care coupled with cost of care contribute to prolonged wait times observed at these study sites relative to well-equipped treatment centers in other countries (28, 29). A meta-analysis evaluating differences in postoperative LOS after brain tumor surgery in HICs and LMICs showed a postoperative LOS in LMICs (10.1 days) similar to what we report in our study (10.6 days) which is longer than the postoperative LOS in HICs (5.1 days) (30). Factors accounting for longer postoperative LOS in LMICs include poorly treated comorbidities, postoperative complications, and lack of adoption of contemporary and/or minimally invasive neurosurgical approaches and techniques due to limited infrastructure (31). While this study does not compare clinical practice in HICs and LMICs, we understand historically and anecdotally there is dramatic inequity in the delivery and reception of care for pediatric CNS tumor patients between these income categories (10, 11). To help address the existing cancer health disparities between HICs and LMICs, the International Society of Pediatric Oncology (SIOP) is currently leading efforts to develop clinical guidelines for different pediatric cancers including CNS tumors based on the resources and facilities available in LMICs (32–34).

Considering the otherwise vast catchment area, the relatively modest burden of cases reported over the 9-month study period also highlights the underdiagnosis and underreporting of neuro-oncologic cases in developing countries (9). Much of this is attributed to limited access to proper neurologic assessments and neuroimaging needed to make a definitive diagnosis (35). As a subcontinental collaborative, we are conducting a follow-up study to better elucidate these and other underlying disparities, and to propose site-derived solutions.

There are several limitations to this study. This is a cross sectional survey and therefore indicates only the neurosurgical practice pattern during the specific 9-month period. As the goal of this study was to determine an epidemiologic profile of tumors managed at these national referral sites, patient-specific details were not captured. These figures represent hospital-level data; population incidence and prevalence cannot be inferred by this methodology. Also, the design of our study did not seek to obtain long-term follow-up data. We used a snowball sampling approach to identify

research collaborators as there is currently no existing catalog of pediatric CNS tumor treatment centers in SSA and details on the types of cancers managed at those centers. Thus, while the 7 sites themselves represent large and diverse catchment areas, these results cannot be generalized to all regions in SSA due to selection bias.

Conclusion

The hospital-level burden, histopathology, and location of pediatric brain and spinal tumors managed at seven referral sites in Sub-Saharan Africa is described. Among patients requiring surgical care, two-thirds received a tumor-directed surgery; less than a third received indicated adjuvant chemotherapy or radiation. Significant healthcare investments are needed to build diagnostic infrastructure, enhance surgical capabilities, and offer adjuvant therapy for children in SSA diagnosed with a CNS neoplasm.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Institutional review board (IRB) approval was obtained from all 7 SSA sites, as well as the North American coordinating site, Vanderbilt University Medical Center. The seven SSA study sites included: Aminu Kano Teaching Hospital (AKTH), Kano, Nigeria; Komfo Anokye Teaching Hospital (KATH), Kumasi, Ghana; Nelson Mandela Children's Hospital (NMCH), Johannesburg, South Africa; Tenwek Mission Hospital(TMH), Bomet, Kenya; Zewditu Memorial Hospital (ZMH), Addis Ababa, Ethiopia; University Teaching Hospital (UTH), Lusaka, Zambia; and Muhimbili Orthopedic Institute (MOI), Dar es Salaam, Tanzania. Written informed consent from the participants was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

JH-C: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Resources, Software, Validation, Writing – original draft, Writing – review & editing. SC: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Resources, Software, Validation, Writing – original draft, Writing – review & editing. JL: Conceptualization, Data curation, Methodology, Writing – review & editing. AB: Conceptualization, Data curation, Methodology, Writing – review & editing. YA: Conceptualization, Data curation, Methodology, Writing – review & editing. HS: Conceptualization, Data curation, Methodology, Writing – review & editing. WC: Conceptualization, Data curation, Methodology, Writing – review & editing. KS: Conceptualization, Data curation, Methodology, Writing – review & editing. MA: Conceptualization, Data curation, Methodology, Writing – review & editing. FN-B: Conceptualization, Data curation, Methodology, Writing – review & editing. MD: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Resources, Software, Supervision, Writing – review & editing.

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Publisher's note

Supplementary material

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Prognostic factors of pediatric ependymomas at a National Cancer Reference Center in Peru

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Background: Ependymomas are central nervous system tumors that significantly impact the quality of life and carry a high mortality rate. Both the disease itself and its treatment cause significant morbidity. At a national level in Peru, there are no reports on clinical characteristics of the disease.

Methods: This retrospective study captured patient aged less than 19 years with a diagnosis of ependymoma from 2012 to 2022 at a tertiary center in Lima.

Results: 85 patients were included with a median follow-up time was 51.6 months. The 5-year overall survival and progression-free survival were 55.89% (95% CI: 44.28 – 65.99) and 37.71% (95% CI: 26,21-49,16) respectively. The main prognostic factors identified were completed treatment (p=0.019), adjuvant chemotherapy (p=0.048), presence of metastasis (p=0.012), and disease recurrence (p=0.02).

Conclusions: The survival of patients with ependymoma is below that reported in high-income countries. Incomplete treatment and treatment abandonment are factors that negatively impact the prognosis. Further studies are needed to identify barriers in the referral and treatment process for patients with ependymoma.

KEYWORDS

pediatric, ependymoma, treatment, prognosis, outcomes, Peru

Introduction

Brain tumors constitute the second most prevalent form of pediatric cancer, with ependymomas comprising 4.6% of them (1). According to Lima's Cancer Registry, a population-based registry that best represents the incidence of different cancers in Peru, between 2013 and 2015, 26 cases of pediatric ependymomas in patients younger than 15 years of age were documented, with a frequency of 8.6 cases per year in the aforementioned time period (2). For patients diagnosed with ependymoma, the disease and its treatment cause significant morbidity, affecting short-term and long-term development (3–7).

Neurosurgical resection and radiation therapy are considered the cornerstones of ependymoma treatment, achieving the highest overall survival (OS) and progression-free survival (PFS) rates (8–10). The role of chemotherapy is still under investigation, as consistent benefits have not been reported (11). Therapeutic alternatives such as adjuvant chemotherapy and radiation therapy or the omission of adjuvant therapy may be valid options for certain patient subgroups, depending on clinical and molecular features that have yet to be characterized (12).

Historically, the classification of ependymomas was based solely on their histological characteristics. Specifically, the anaplastic subtype (grade 3) has been associated with a poorer prognosis, although these findings have not been consistent across different studies. Furthermore, high interobserver variability and low reproducibility limit its application (13, 14). In the last decade, molecular characterization of these tumors has been performed, resulting in a new classification that distinguishes nine subtypes of ependymomas and provides more clinical and prognostic information (15).

Overall survival rates in pediatric patients with ependymomas have been reported to range from 40% to 75% (16–19). In South America, the 5-year overall survival rate for patients with intracranial ependymomas is lower than in many high-income countries, frequently not exceeding 45% (7, 20). Gross total macroscopic resection has consistently been reported as the most significant factor associated with increased survival (8, 14, 17, 21). Other factors such as age, location, histological subtype o treatment have been associated with the prognosis in different studies, but with inconsistent results (8, 14, 21–24). Due to the high variability in reported survival rates, identifying the main prognostic factors for these patients treated in low- and middle-income countries (LMIC) should be a priority.

To date, the available information regarding the characteristics and impact of ependymomas in the pediatric population is still limited in South America and Peru. To describe the clinical and demographic characteristics and survival in pediatric patients diagnosed with ependymoma, a review of medical records was conducted for patients treated at the National Institute of Neoplastic Diseases (INEN) between 2012 and 2022.

Materials and methods

Settings

Peru has a 31 million people, INEN is a national referral center for cancer, belongs to the Ministry of Health, and serves up to 65% of the national pediatric cancer patients. After completing the approvals by the ethics committee, we conducted a retrospective study based on collecting information from clinical records of patients aged less than 19 years with a diagnosis of ependymoma from 2012 to 2022 at INEN in Lima.

Statistical analysis

Treatment status was categorized as abandonment if the treatment was suspended for 30 or more days due to non-medical reasons. Time intervals from symptoms to diagnosis and from diagnosis to outcome were evaluated. The date of diagnosis was considered as evidence of a brain tumor on computed tomography (CT) or magnetic resonance imaging (MRI). Alternatively, the date of the first surgical intervention was used if this was unavailable.

Qualitative variables were described using frequencies and percentages, while quantitative variables were described using measures of central tendency and dispersion. The association of categorized data was determined using the chi-square test, and the magnitude and direction were expressed using relative risks. Survival analysis was conducted using Kaplan-Meier curves, and comparisons were made using the Log-Rank test. Multivariate analysis of prognostic factors was performed using the Cox proportional hazards test. A bilateral p-value of <0.05 was considered significant. Statistical analysis was performed using STATA 17® software.

Results

Epidemiological profile

Ninety-four clinical records were assessed. Nine patients were excluded due to receiving radiotherapy or chemotherapy at another institution (n= 06), incomplete medical records (n= 02) or an incorrect diagnosis (n= 01). Eighty-five medical records were included for the analysis. (Figure 1) The baseline characteristics of the patients and tumors are described in Table 1. The mean age of the patients was 6.94 years (range 1-19 years), and the prevalence was higher in male patients (male-to-female ratio of 1.5:1). The most common location was the posterior fossa (n=54; 63.53%), and the most frequent histological subtype was anaplastic ependymoma (n=45; 52.94%).

Complete disease staging, consisting in a craniospinal magnetic resonance imaging (MRI) and lumbar puncture, was performed for 32 patients (37.64%). For 35 patients (41.17%) only a craniospinal MRI was performed and, for 3 patients, (3.53%) only a lumbar puncture was performed. Staging studies were not documented for 15 patients (17.65%). Ten patients (11,76%) had metastasis, all located in the spine. Patients in whom a lumbar puncture date was recorded (n=35; 41.17%), the median time between the surgical resection and the lumbar puncture was 62 days (IQR 41.5-144; range 27-733). Patients in whom a postoperative MRI was recorded (n=67; 78-8%), the median time between surgical resection and MRI was 64 days (IQR 36.-103.3; range 8-420).

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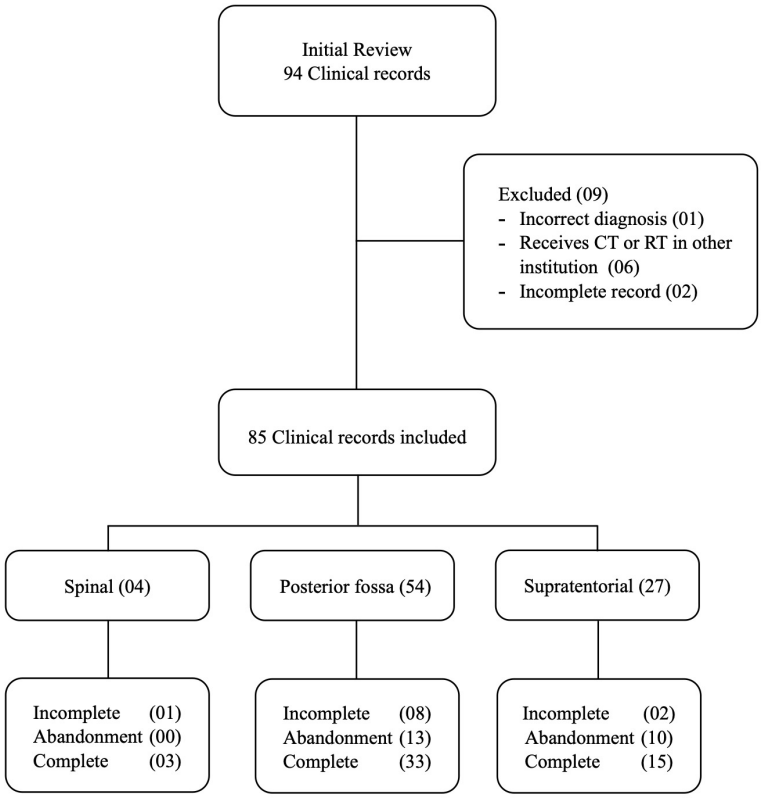

FIGURE 1
Flow diagram of included medical records.

Clinical characteristics

The clinical characteristics are described in Table 2. The median duration of symptoms until diagnosis was 3 months (IQR 2-5; range 0-40). The most common symptoms were headache (n=49; 57.65%), nausea and vomiting (n=40; 47.06%), and ataxia (n=24; 28.24%). Patients with supratentorial ependymoma were more likely to present with hemiparesis (RR=12.88, 95% CI: 1.63-101.85, p=0.0014); those with posterior fossa location had a higher likelihood of ataxia (RR=2.87, 95% CI: 1.07-7.63, p=0.0448), and those with spinal location had a higher likelihood of neck pain (RR=20.25, 95% CI: 3.76-109.01, p<0.0001) and paraparesis (RR=40.5, 95% CI: 4.57-358.43, p<0.0001). Additionally, it was observed that seizures occurred exclusively in the supratentorial location, while dizziness was only reported in the posterior fossa location. There was also an association between age and symptom presence. Headache was more frequently reported in patients aged 3 years or older compared to those under 3 years of age (RR 2.20, 95% CI: 1.10-4.40, p=0.0042). On the contrary, psychomotor development abnormalities were only described in patients under 2 years of age.

Treatment

In Peru, the majority of surgeries are done in General Pediatric Institutes for patients less than 19 years. Complete safe resection and adjuvant focal radiotherapy is the standard of care. Patients less than 3 years old were treated with different approach of chemotherapy until a second look surgery is possible or until they reach 3 years old at which point radiotherapy is administered. At INEN, the decision of administering radiotherapy and the specific radiation dose is contingent upon the tumor's location, histological grade, and the extent of resection.

All patients underwent a neurosurgical procedure (n=85; 100%). The most first surgical interventions in pediatric patients with ependymomas took place in General Pediatric Institutes (n= 57, 67%), followed by General Hospitals (n= 17, 20%) and the remaining at INEN (n= 11, 13%). In the first procedure, gross total resection of the tumor was achieved in 27 patients (31.76%); subtotal resection in 55 patients (64.71%), and only a biopsy was performed in 1 patient (1.18%). The extent of surgery could not be determined in 2 cases due to limited information in the medical records. Among patients with subtotal resection, 7 underwent second-look surgery. In the second procedure, one patient achieved gross total resection, and in a third procedure, two patients did. There was no association between the location and extent of resection (chi-square 4.73, p=0.578).

Adjuvant therapy is described in Table 3. A total of 65 patients received radiation therapy (76.47%). Patients with supratentorial ependymomas received an average dose of 56.81 Gy (SD 2.91; range 53.60-60.00). Those with posterior fossa location received 55.76 Gy (SD 2.73; range 50.00-60.00), and those with spinal location received 46.10 Gys (SD 5.33; range 39.00-50.40). Four patients did not complete radiation therapy due to abandonment (n=3, 4.61%) or death (n=1, 1.53%). One patient with supratentorial

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TABLE 1 Patient baseline characteristics.

	Median	Range
Age at diagnosis (years)	6.94	1-19
	Frequency (n)	Percent (%)
Age		
0-2 years	20	23.52
3-10 years	43	50.58
11-19 years	22	25.88
Gender		
Female	34	40
Male	51	60
Location		
Supratentorial	27	31.76
Posterior Fossa	54	62.35
Spinal	4	4.71
Histology (Grade)		
Myxopapillary (2)	2	2.35
Classic Ependymoma (2)	38	44.71
Anaplastic (3)	45	52.94
Presence of Metastasis		
Yes	10	11.76
No	75	88.24
Extent of resection		
Biopsy	1	1.18
Subtotal	55	64.71
Total	27	31.76
Not specified	2	2.35
Treatment received		
Neurosurgery	85	100
Radiotherapy	65	76.47
Chemotherapy	26	30.29

ependymoma received a limited dose of 40 Gys due to the presence of multiple lesions. The median time between the first surgical intervention and the first radiotherapy session was 151 days (IQR 67-191, range 25-868). The median interval between the first surgical resection and radiotherapy initiation in younger than 3 years was 194.8 days (IQR 95-268, range 47-407), while in patients older than 3 years was 143.65 days (IQR 41-448, range 25-868).

Chemotherapy was administered to 26 patients (30.59%) and the most common regimen consisted of 8 cycles of vincristine and cyclophosphamide alternating with etoposide and carboplatin (n=19, 73.07%). In patients under 3 years of age, chemotherapy was administered as a bridge therapy for a second surgical intervention (n=3, 30%) or radiotherapy (n=7, 70%). Of the latter group, 5 patients abandoned treatment before starting radiotherapy. In patients over 3 years of age, chemotherapy was administered following radiotherapy (n=15, 93.75%) or as a bridge therapy for a second surgical intervention (n=1, 6.25%).

TABLE 2 Clinical manifestations according to tumor location.

Symptoms	Location		
	Supratentorial (n=27)	Posterior Fossa (n=54)	Spinal (n=4)
Headache	15 (55.6)	34 (64.2)	0 (0)
Nausea and vomiting	10 (37)	29 (54.7)	0 (0)
Ataxia	3 (11.1)	19 (35.8)	1 (25)
Hemiparesis	6 (22.2)	0 (0)	1 (25)
Visual problems	3 (11.1)	3 (5.66)	0 (0)
Muscle weakness	0 (0)	4 (7.5)	1 (25)
Neck pain	0 (0)	2 (3.8)	2 (50)
Somnolence	2 (7.4)	1 (1.9)	0 (0)
Paraparesis	0 (0)	1 (1.9)	2 (50)
Psychomotor development alterations	1 (3.7)	2 (3.8)	0 (0)
Dysarthria	1 (3.7)	2 (3.8)	0 (0)
Seizures	2 (7.4)	0 (0)	0 (0)
Dizziness	0 (0)	2 (3.8)	0 (0)
Macrocephaly	1 (3.7)	1 (1.9)	0 (0)
Others	0 (0)	7 (13.2)	3 (75)
Not specified	3 (11.1)	6 (11.3)	0 (0)

A significant association was found between age and the treatment regimen received (chi-square 20.93, p<0.001). Chemotherapy as a sole adjuvant was used exclusively in patients under 3 years of age (n=5, 100%), while adjuvant radiotherapy was used mostly in patients over 3 years (n=30, 88,9%). There was no association between the treatment regimen and histological classification (chi-square 3.97, p=0.86) or location (chi-square 10.50, p=0.31).

Overall, 51 patients (60%) completed treatment, 23 patients (27.06%) abandoned the treatment, and 11 patients (12.94%) did not complete it due to clinical deterioration or death. An association was found between treatment adherence and patient age. Patients aged 3 years or younger were more likely to abandon treatment (RR=2.5, 95% CI: 1.30-4.81, p=0.0083). Additionally, patients under 3 years of age were less likely to complete the treatment (RR 0.64, 95% CI: 0.34-1.06, p=0.0368). There was no association between treatment adherence and location (p=0.515), histological subtype (p=0.432), or province of origin (p=0.31).

Outcome

During the follow-up period, local recurrence was observed in 18 patients (21.18%). One patient with a primary supratentorial location experienced recurrence in the spinal cord (1.18%). The average time

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TABLE 3 Adjuvant therapy.

	Adjuvant therapy			
	RT n (%)	CT n (%)	RT + CT n (%)	None n (%)
Age (years)				
1-2	5 (11.1)	5 (100)	5 (25)	5 (33.3)
3 or more	40 (88.9)	0 (0)	15 (75)	10 (66.6)
Histology (Grade)				
Myxopapillary (2)	0 (0)	0 (0)	1 (5)	1 (6.6)
Classic Ependymoma (2)	22 (48.9)	2 (40)	7 (35)	7 (46.7)
Anaplastic (3)	23 (51.1)	3 (60)	12 (60)	7 (46.7)
Location				
Spinal	3 (6.6)	0 (0)	1 (5)	0 (0)
Posterior fossa	27 (60)	2 (40)	15 (75)	10 (66.6)
Supratentorial	15 (33.3)	3 (60)	4 (20)	5 (33.3)

CT, Chemotherapy; RT, Radiotherapy; RT + CT, Radiotherapy and Chemotherapy.

between the first neurosurgical resection and recurrence was 21.07 months (IQR: 10.43-28.13, range 6.87-54.5 months). No association was found between the treatment received and recurrence (chi-square: 8.41, p=0.209). Sequelae were present in 30 patients. The most frequent sequelae were visual problems (n=10, 33.3%), hemiparesis (n=7, 23.3%), facial paralysis (n=4, 13.3%), gait difficulties (n=5, 16.7%), endocrinological problems (n=2, 6.7%), monoparesis (n=2, 6.7%), nasogastric tube usage (n=3, 10%), and tracheostomy tube (n=2, 6.7%). At the end of the follow-up period, 42 deaths were documented (49.4%).

Survival analysis and prognostic factors

The median follow-up time was 51.6 months. The 5-year OS and PFS rates were 55.89% (95% CI: 44.28-65.99) and 37.71% (95% CI: 26.21-49.16), respectively (Figure 2). In the intracranial ependymoma group, the 5-year OS rate was 56.35%, while in the spinal ependymoma group, it was 50%. In the univariate analysis, histologic subtype (p=0.002), the extension of resection (p=0.019), treatment adherence (p=0.0001) and adjuvant treatment (p=0.03) were significantly associated with the OS (Figure 3, Table 4).

In the multivariate analysis, age less than 3 years (HR=0.17, 95% CI: 0.04-0.64, p=0.009) and completion of treatment (HR=0.25, 95% CI: 0.09-0.72, p=0.010) were significantly associated with higher OS. On the contrary, the presence of metastasis (HR=3.66, 95% CI: 1.47-14.46, p=0.008), adjuvant treatment with chemotherapy alone (HR=4.79, 95% CI: 1.18-34.89, p=0.031), and disease recurrence (HR=4.90, 95% CI: 1.78-13.45, p=0.002) were associated with lower OS (Table 5).

Discussion

Our sample is highly representative of the actual incidence of pediatric ependymomas described by Lima's Cancer Registry 2013-2015 (2). The outcomes of our cohort are similar to what has been reported in the region. A study conducted in Mexico, which included patients under 17 years old diagnosed with ependymoma, describes a 5-year OS of 58.04% (19). In South America, the 5-year OS for patients with intracranial ependymomas has not exceeded 45% (5, 20). In Peru, a study conducted on patients with spinal ependymomas found a 5-year OS of 85.7% (21) in the pediatric subgroup, while a study on pediatric patients with intracranial ependymomas reported a 5-year OS of 70% (22). On the contrary, studies conducted in the United States and Japan report a 5-year OS close to 75% (12, 18).

A lower survival rate in cases of spinal ependymomas compared to other reports (25) is likely due to a small sample size, with only four patients included in our series. A lower survival rate in developing countries compared to developed countries could be attributable to greater difficulty in accessing the healthcare system, longer waiting times, and lower infrastructure and equipment (26).

The diagnosis of pediatric ependymomas pose a significant challenge for healthcare providers as clinical manifestations of brain tumors are nonspecific and often occur in other, more frequent, pathologies (27–32). Additionally, age plays an important role in the identification of these symptoms. For example, in our cohort, headache was less frequently reported in patients under 3 years of age, probably due to the patient's inability to accurately express their discomfort and caregivers' interpretation of the symptom. Psychomotor development disorders were likely limited to patients under 2 years of age, as ataxia or dysarthria may have been interpreted as an inability to walk or speak by primary care physicians.

The classification of ependymomas has undergone multiple changes in the last decade, with a current focus on molecular characteristics. The clinical-pathological utility of histological classification has been contradictory and lacks reproducibility due to high inter-observer variability (14, 33–35). The molecular

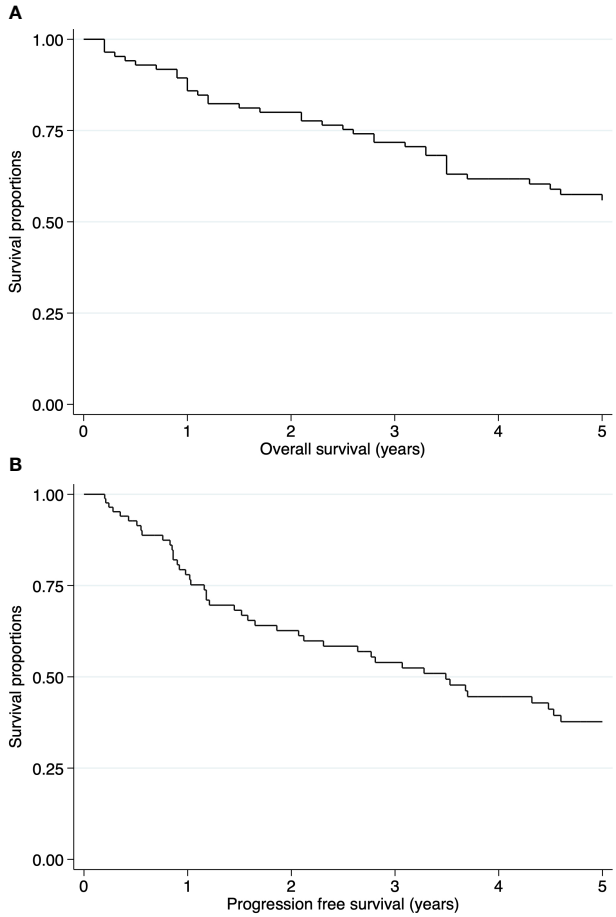

FIGURE 2
Kaplan-Meier curves of pediatric ependymomas treated at INEN. **(A)** Overall survival (OS) of all cases. **(B)** Progression free survival (PFS) of all cases.

component of the current classification can potentially provide prognostic information and contribute to therapeutic decision-making, which is still under investigation. This is reflected in current guidelines, which recommend including molecular characteristics in the classification of ependymomas (36, 37). However, performing this classification requires expensive and less available laboratory techniques, limiting its application in low- and middle-income countries (9).

The standard treatment is considered to be maximal safe neurosurgical resection followed by radiation therapy as they have been associated with improved disease-free and progression-free survival (8, 10, 36, 38, 39). Total macroscopic resection has been identified as the most important independent prognostic factor (21), even considered sufficient in some centers for grade 2 supratentorial ependymomas (40–42). In addition to surgery, postoperative radiation therapy at doses of 54-59.4 Gys is considered the standard treatment for non-metastatic ependymomas to reduce the rate of local recurrence (8). Nonetheless, the benefits of these treatments did not reach statistical significance in our cohort. These results may be due to unmeasured factors such as tumor size at the time of initial intervention and delays in starting radiation therapy.

A study conducted in Peru that included patients of ages 3 to 15 years with the diagnosis of medulloblastoma identified that a delay greater than 30 days in the initiation of radiotherapy after surgery was associated with a poor prognosis (43). In our cohort, only 1 patient commenced radiotherapy in the first 30 days after surgery, which may have limited the statistical significance of this factor. Factors such as insufficient healthcare infrastructure and equipment, lack of appointment availability or socioeconomic factors to attend the appointments for the disease staging could potentially contribute to delays in the initiation of radiotherapy. However, being a retrospective study, the precise factors contributing to the delays in the study timeline cannot be determined with certainty.

In spite of their well described benefits, it's important to acknowledge that complete resection can only be achieved in 50-80% of cases due to inaccessible locations and the risk of neurovascular injury (44). In patients in whom total tumor resection was not achieved, the main limiting factor for reoperation is the risk of increased morbidity. In Peru, the lack of specialized multidisciplinary teams (45), such as pediatric neurosurgeons (46) and pediatric ICU doctors (47), in addition to equipment constraints, or the lack of specialized postoperative care

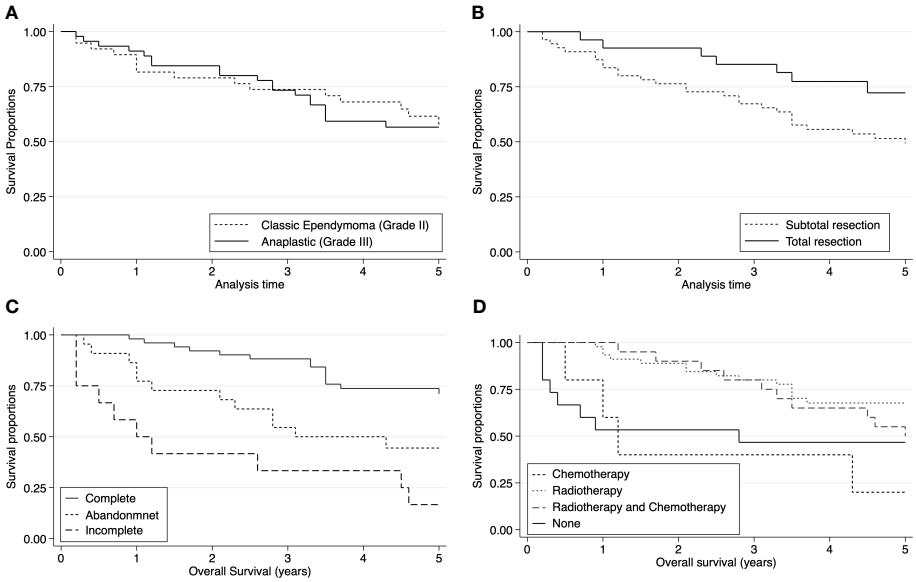

FIGURE 3
Kaplan Meier curves of pediatric ependymomas treated at INEN. **(A)** Histology subtype was not associated with OS (p=0.99). **(B)** Extension of resection was significantly associated with 5-year OS (p=0.03). **(C)** Treatment adherence was significantly associated with 5-year OS (p<0.001). **(D)** Adjuvant treatment was significantly associated with 5-year OS (p=0.039).

such as nutritional support and rehabilitation specialists, could account for the low percentage of total resections performed.

Radiation therapy can cause adverse effects, affecting cognitive development and, in some cases, the growth of patients, which is more pronounced in children under 3 years of age (38). Historically, efforts have been made to limit radiation therapy in children under 3 years by administering chemotherapy to delay the start of radiation therapy or even replace it (8, 11, 38, 48–50). At our institution, patients under 3 years of age were less likely to receive radiation therapy compared to those over 3 years old. This finding was also described in a study conducted by the University of California, San Francisco, which showed that only 30% of patients under 3 years old with intracranial ependymomas received radiation therapy, compared to 82% of patients over 3 years old (18). However, multiple studies that have shown that delaying radiation therapy in children under 3 years results in a worse prognosis (49, 51), as well as replacing it with postoperative chemotherapy (16, 52). Furthermore, radiation therapy has already been safely used in patients as young as one year old (49, 50, 53–55), so there should be no restriction on this treatment in this group of patients.

The evidence regarding chemotherapy usefulness in pediatric ependymomas is still controversial as it has not consistently translated into improved overall survival and is associated with grade III or IV toxicity in various organ systems in many cases (11), limiting its application and long-term adherence.

Various studies support the adjuvant use of chemotherapy in different scenarios, including chemotherapy combined with radiation therapy in patients with subtotal and near-total resection (53), chemotherapy to delay or replace radiation therapy in children under 3 years (11), or as a bridging therapy for a second intervention (52, 53, 56). On the other hand, multiple studies have failed to demonstrate an advantage in administering chemotherapy in different regimens (22, 57–59). In our study, adjuvant chemotherapy alone was associated with significantly lower survival, highlighting the importance of radiotherapy in the treatment of pediatric ependymomas.

Treatment adherence in pediatric oncology patients poses a significant challenge and plays a crucial role in achieving desired outcomes. Despite the heterogeneity in the treatments received, adherence emerged as a significant prognostic factor in our study, with higher survival rates observed among patients who completed the treatment. Factors influencing treatment adherence include but are not limited to, socioeconomical, patient-related and healthcare-related factors. The presence of other siblings, transportations issues or financial constraints are among the factors likely to limit the adherence of cancer patients in LMIC (60). A study conducted in two tertiary referral centers for the treatment of pediatric patients in Peru identified that socioeconomic factors such as living in a rural household or having an informal employment significantly impacted the abandonment rate in pediatric solid tumors (61). Further studies focusing on identifying factors contributing to suboptimal adherence in pediatric patients with central nervous system tumors are needed in order to address this issue with public health strategies.

Delays in the diagnosis of pediatric brain tumors can lead to disease progression; as reported in pediatric low grade gliomas (62), and decreased survival (63). Brain tumors factors, such as the histology and location, influenced the duration of the prediagnostic symptom interval (63–65). Caregiver factors such as the education level of the parents, previous knowledge of the disease and cultural beliefs were identified as factors that impacted the time to diagnosis (66, 67). In LMIC, healthcare factors can significantly contribute to delays in the diagnosis and initiation of treatment of

TABLE 4 Univariate analysis of prognostic factors of Progression Free Survival (PFS) and Overall Survival (OS) at 5-year follow up.

Prognostic factors		Frequency (%)	5-year		5-year	
			PFS ± SD (%)	P value	OS ± SD (%)	P value
Age (years)	0-2	21	30.3 ± 11.0	0.477	52.0 ± 11.9	0.94
	3-19	64	40.3 ± 7.0		57.0 ± 6.3	
Extent of resection	Total	27	56.0 ± 11.3	0.032	72.3 ± 9.1	0.03
	Subtotal	55	29.7 ± 6.9		49.3 ± 6.9	
Histology (Grade)	Anaplastic (3)	45	33.3 ± 7.8	0.49	56.6 ± 7.6	0.99
	Classic (2)	38	46.7 ± 9.4		57.7 ± 8.5	
Adjuvant therapy	Radiotherapy (RT)	45	49.6 ± 8.5	0.019	67.7 ± 7.2	0.039
	Chemotherapy (CT)	5	20.0 ± 17.9		17.9 ± 0.8	
	RT + CT	20	31.6 ± 11.0		50.0 ± 11.2	
	None	15	26.0 ± 14.2		46.7 ± 12.9	
Adherence	Complete	51	55.4 ± 8.0	<0.001	71.1 ± 55.9	<0.001
	Abandonment	23	15.2 ± 8.1		42.5 ± 10.5	
	Incomplete	11	10.3 ± 9.8		18.2 ± 11.6	
Presence of Metastasis	Yes	10	11.3 ± 10.6	0.046	30.0 ± 14.5	0.083
	No	75	41.5 ± 6.5		59.2 ± 5.9	
Recurrence	Yes	19	N.A.	<0.001	37.5 ± 12.1	0.078
	No	66	52.1 ± 7.1		60.1 ± 6.2	

pediatric patients with brain tumors. The distance to the health center, it's complexity and the availability of specialists have determined the time to diagnosis in different studies (66, 67).

Identifying factors related to patients who were unable to complete treatment due to deterioration in their clinical condition would help in risk stratification and prioritizing the treatment of this group of patients. Unmeasured factors such as the preoperative status of the patient or tumor size at the time of diagnosis may be related to this outcome.

Contrary to various reports, being under 3 years of age was identified as a protective factor in our study population. These findings are most likely to be related to a low sample of patients receiving the standard treatment associated with a high abandonment rate. Studies evaluating a larger sample of patients younger than 3 years should be performed in order to adequately assess prognostic factors in this age group.

TABLE 5 Multivariate analysis of 5-year OS prognostic factors.

Characteristic	Hazard ratio (IC 95%)	*p*
Age less than 3 years	0.17 (0.04-0.64)	0.009
Adjuvant chemotherapy only	6.41 (1.18-34.89)	0.031
Complete treatment	0.25 (0.09-0.72)	0.010
Presence of metastasis	3.66 (1.47-14.46)	0.008
Recurrence	4.90 (1.78-13.45)	0.002

Our study was conducted at a single center convering 65% of the pediatric cancer population diagnosed in Peru. However, some limitations were identified. There is potential for selection bias, given that the majority of patients were insured under the Sistema Integral de Salud (SIS), which primarily serves the underserved population. To obtain a more accurate picture of the reality in our country, it would be necessary to include institutions that serve patients with other types of insurance, corresponding to the remaining 35% of the population. Secondly, being a retrospective cohort based on medical records, the signs and symptoms documented relied entirely on their accurate registration. Problems related to patient follow-up could be avoided as the medical records in our institution are integrated with the National Death Information System (SINADEF). This integration has allowed us to obtain precise information about dates of death and the current status of patients.

Conclusions

The clinical and demographic characteristics of our patient series are similar to those reported in the literature. The main favorable prognostic factor identified was the completion of treatment. On the contrary, adjuvant chemotherapy alone, the presence of metastasis, and disease recurrence were identified as poor prognostic factors. Histological classification did not provide prognostic information in this cohort. Studies incorporating molecular classification will be necessary to determine the epidemiology and assess prognostic

utility. Special focus should be directed to understand the factors influencing a timely diagnosis, early referral, and optimal treatment in patients with ependymoma treated at INEN. Likewise, similar studies must be conducted to assess the prognostic factors of other brain tumors and childhood cancers in our institution.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comité Institucional de Ética en Investigación (CIEI) of the Instituto Nacional de Enfermedades Neoplásicas (INEN). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/ next of kin in accordance with the national legislation and institutional requirements.

Author contributions

EP-R: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. RD-C: Conceptualization, Formal analysis, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. TN: Validation, Writing – review & editing. SC-Z: Validation, Writing – review & editing. LO-M: Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Challenges in treating children with optic pathway gliomas: an 18-year experience from a middle-income country

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Introduction: Patients with optic pathway gliomas (OPG) have good survival rates although their long-term quality of life can be affected by the tumor or treatment-related morbidity. This retrospective study sought to describe the clinical presentation and outcomes of children with OPG at a tertiary center in Mexico.

Methods: Consecutive patients <18 years-of-age with newly diagnosed OPG between January 2002 and December 2020 at the Hospital Civil de Guadalajara Dr. Juan I. Menchaca in Guadalajara, Mexico were included.

Results: Thirty patients were identified with a median age of six years. The most frequent clinical manifestations were loss of visual acuity (40%) and headaches (23%). Neurofibromatosis-1 was found in 23.3% of the patients. Surgery, either biopsy or resection, was done in 20 of 30 patients. Two patients died shortly after initial surgery. The 5-year event-free survival (EFS) was 79.3% ± 10.8% and the 5-year overall survival was 89.5% ± 6.9%. Lower EFS was associated with age less than 3 years, intracranial hypertension at presentation, and diencephalic syndrome. Patients who received surgery as first-line treatment had a 3.1 times greater risk of achieving a performance score of less than 90 points at 6 months after diagnosis (p=0.006). Of 10 patients with vision testing, 5 had improvement in visual acuity, 4 had no changes, and one patient showed worsening.

Conclusion: Our data suggests that favorable outcomes can be achieved with OPG in low- and middle-income countries, although a high rate of surgical complications was described leading to a lower overall survival. These data can be used prospectively to optimize treatment at this institute and other middle-income countries through a comprehensive, multidisciplinary approach.

KEYWORDS

optic pathway glioma, low-grade glioma, global oncology, low-and middle-income countries, visual acuity

Introduction

Central nervous system (CNS) tumors are the second most common cancers in childhood, representing about 20% of cases (1, 2). Among pediatric CNS tumors, 3 to 5% are optic pathway glioma (OPG). OPG are low-grade neoplasms that affect the visual pathway and have a good prognosis, with 5-year overall survival rates frequently reported close to 95% in high-income countries (HICs) (3–5). Nonetheless, OPG have the potential for significant morbidity, from the tumor itself or tumor-directed therapy. Visual deficits and endocrine disturbances frequently affect the quality of life of survivors (6). Poor prognosis has been associated with clinical features, such as young age (less than three years), chiasmatic and hypothalamic invasion, and tumors in patients without neurofibromatosis type 1 (NF-1) (7, 8).

The diagnosis of OPG can usually be made based on neuroimaging and comprehensive clinical examination. Histologic diagnosis is often unnecessary and carries a risk of surgical morbidity, including visual deficits and endocrine dysfunction (9). In patients where treatment is indicated, cytotoxic chemotherapy remains the standard of care, although targeted therapies are becoming more prevalently used as the results of clinical trials are reported (10–13). Radiotherapy can provide better disease control and has better visual outcomes, but due to the long-term side effects, its optimal use remains controversial (14, 15).

About 400.000 children develop cancer worldwide, with 80% residing in low- and middle-income countries (LMICs) (16). The World Health Organization's (WHO) Global Initiative for Childhood Cancer (GICC) aims to achieve at least a 60% survival for pediatric cancer patients worldwide by 2030 (17). Low-grade glioma (LGG) is one of the six index cancers selected by the GICC to demonstrate the impact of increasing access to quality care for children with cancer (18). Importantly, there are few studies describing the outcomes of the treatment of children with OPG in LMICs (19). The aim of this study was to determine the clinical course and outcomes of children with OPG at the Hospital Civil de Guadalajara Dr. Juan I. Menchaca in Mexico.

Materials and methods

Study population

Consecutive patients <18 years-of-age with OPG newly diagnosed between January 2002 and December 2020 treated at the Hospital Civil de Guadalajara Dr. Juan I. Menchaca (HCG) in Guadalajara, Mexico were included. For consideration as an OPG, radiologic characteristics was sufficient, and histologic confirmation was not necessary. The HCG is a regional referral center in the state of Jalisco, on the Pacific coast of Mexico, a middle-income country. The hospital serves approximately 90% of pediatric cancer patients treated with a national health care coverage service in Jalisco. The study was approved by the HCG ethics committee.

Patient data

Clinical information on demographics, treatment, and follow-up were extracted from institutional medical records. A database was created and included sociodemographic data, NF1 status, pathology, clinical manifestations, tumor location, treatment modalities and timing, performance status, and radiographic response assessment. Data collection was completed in December of 2021.

Statistical analysis

Quantitative variables were summarized by measures of central tendency statistics (mean or median), while qualitative variables were summarized with absolute frequencies and percentages. Event-free survival (EFS) was defined as the time from diagnosis to first event (progression or death) or for those who were event-free, the date of last contact. For abandonment-sensitive EFS (A-EFS), treatment abandonment was also considered an event. Overall survival (OS) was defined as the time from diagnosis to death or last contact for those still alive. Patients who had not experienced an event by the end of the study were censored at the time of their last follow-up. EFS and OS analyses were performed using the Kaplan-Meier method and compared by the log-rank test (20). Values of $p < 0.05$ were considered statistically significant. SPSS (version 25) was used for analyses.

Results

Clinical and demographics characteristics

Thirty patients were included, with a median age of 6 years. Patient characteristics are presented in Table 1. The most frequent clinical manifestations were loss of visual acuity (40%) and headaches (23%). Clinical findings consistent with NF-1 were found in 23% of the patients, but genetic confirmation was not available for any of these patients. The criterion for the clinical diagnosis of NF-1 for all patients was the presence of the OPG and at least 6 café-au-lait spots. One child also has a neurofibroma. Nine patients had hydrocephalus at diagnosis. Tissue was obtained in 20 patients (67%), with 2 procedures having non-diagnostic samples.

Surgical approach and outcomes

Neurosurgical procedures were performed in 20 patients: tumor biopsy for 11 patients and resections in 9 cases. None of these patients were evaluated by pediatric oncology before surgery. The acute complications associated with these surgical procedures included two deaths (2/20, 10%): one due to catecholamine-resistant shock, and one patient with meningitis after surgery,

TABLE 1 Patient's characteristics, tumor location, and pathology.

Characteristic	Value, n (%)
Sex (n, %)	
Female	*19 (63.3)*
Age (years)	
Median (SD)	*6.0*
Signs and Symptoms	
Decreased vision	12 (40%)
Headache	7 (23.3%)
Endocrinopathy	*5 (16.7%)*
Seizures	4 (13.3%)
Diencephalic syndrome	5 (16.6%)
Proptosis	3 (10%)
Neurofibromatosis	
No	23 (76.6%)
Yes	7 (23.3%)
Tumor location	
Optic nerve	6 (20%)
Optic nerve/chiasmatic	4 (13.3%)
Chiasmatic	3 (10%)
Chiasmatic/Hypothalamic	15 (50%)
Chiasmatic/Hypothalamic/optics tracts	2 (6.6%)
Histology	
No tissue obtained	10 (33. 3%)
WHO Grade 1	16 (53.3%)
WHO Grade 2	2 (6.6%)
Reactive gliosis	2 (6.6%)

with subsequent shunt failure and septic shock. The patients who died from acute complications related to surgery occurred in 2006 and 2008. Additional features of the patients for whom biopsy or resection was performed are included in Table 2.

Adjuvant treatment and outcomes

Overall, 12 patients (40%) received chemotherapy, all of them with carboplatin: seven as monotherapy and 5 in combination with vincristine. Hypersensitivity to carboplatin was presented in 28.5% of the patients. No severe cases were reported, and patients were able to continue treatment with carboplatin. Three patients started active surveillance at diagnosis because they had no evidence of visual deficit, but after 3, 4, and 5 months respectively visual changes were found, and chemotherapy treatment was started. Two patients had tumor progression while receiving chemotherapy as first-line treatment. Both patients presented progressive disease while receiving carboplatin treatment and therapy was changed to weekly vinblastine with stable disease until the last follow-up. The treatment and outcomes of the 30 patients are included in Figure 1.

Two patients with NF-1 received targeted therapy with sirolimus as first-line treatment. Both patients were asymptomatic at the last follow-up and had stable disease. The combination of chemotherapy and radiotherapy was used as initial treatment in 6 patients (20%). Two patients with unresectable suprasellar tumors, three children with an unresectable thalamic/hypothalamic tumor with quick clinical deterioration, and one patient treated before 2005 without clear indication. Three patients who received chemotherapy and radiotherapy were treated with a chemotherapy regimen based on carmustine, vincristine, and prednisone, all treated before 2007. One patient had surgery and chemotherapy as first-line treatment due to extensive residual tumor.

Survival outcomes

The median follow-up was 5 years (0.3-14.1 years). Three patients abandoned treatment (10%). One patient denied upfront treatment, another patient abandoned the treatment after tumor progression, and one case due to unknown reasons. Five patients died. Two deaths were related to surgery as mentioned above. One death was due to severe post-surgery neurological sequela and aspiration pneumonitis in the sixth year of follow-up. One patient had tumor progression and subsequently died due to *pneumocystis* pneumonia. Finally, one patient with an extensive hypothalamic tumor died due to sodium imbalance and pontine myelinolysis.

The 5-year EFS was 79.3% ± 10.8% (Figure 2A) and the 5-year OS was 89.5% ± 6.9% (Figure 2B). The 10-year EFS was 61.7% ± 19.1% and the 10-year OS was 71.6 ± 16.8%. The 5-year A-EFS 76.7% ± 11.4% and the 10-year A-EFS was 59.6 ± 19.2%. Lower EFS was associated with age less than 3 years (Figure 2C), intracranial hypertension (Figure 2D), diencephalic syndrome (Figure 2E). The first-line treatment used was not associated with EFS (Figure 2F).

Functional outcomes

Ten of 30 patients had a visual assessment available before and after treatment. Five patients had improvement in visual acuity, 4 patients had no changes in visual acuity, and one patient showed worsening (Table 3). At 6 months from diagnosis, the Lansky/Karnofsky performance score was higher in patients who received chemotherapy or targeted therapy compared to those who had a surgical resection. The patients who received surgery as part of first-line treatment had a 3.1 times greater risk of having a Lansky/Karnofsky performance score lower than 90 points ($p = 0.006$).

Discussion

This study of patients with OPG treated in Mexico allows for the evaluation of multiple elements of the care of children with

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TABLE 2 Surgical outcomes.

Patient	Localization	Surgical indication	Degree of resection	Postsurgical complications
1	Chiasmatic, hypothalamic	Intracranial hypertension	NTR	Cerebrospinal fluid fistula, subdural hematoma
2	Optic nerve	Unclear	NTR	Ocular hematoma
3	Chiasmatic, hypothalamic	Differential diagnosis with craniopharyngioma	NTR	Bilateral subdural hematomas, left facial paralysis, left nasal heteronymous hemianopsia, quadriparesis, worse functional status
4	Chiasmatic, hypothalamic	Unclear	NTR	Left facial palsy, unilateral left nasal hemianopsia
5	Chiasmatic, hypothalamic	Intracranial hypertension	NTR	Hypogonadism, hypothyroidism, worse functional status
6	Chiasmatic, hypothalamic	Intracranial hypertension	NTR	None
7	Chiasmatic	Unclear	STR	Catecholamine-resistant shock and death
8	Chiasmatic and hypothalamic	Unclear	STR	Hemiplegia and diabetes insipidus
9	Chiasmatic	Intracranial hypertension	STR	None
10	Chiasmatic, hypothalamic, and optical radiation	Intracranial hypertension	Biopsy	Neurological infection, shunt failure, death due to septic shock
11	Optic nerve and chiasmatic	Unclear	Biopsy	Transfusion for acute bleeding
12	Chiasmatic and hypothalamic	Intracranial hypertension	Biopsy	Neurological infection and intra-abdominal abscess
13	Chiasmatic	Unclear	Biopsy	None
14	Chiasmatic, hypothalamic	Intracranial hypertension	Biopsy	Pneumothorax, cardiorespiratory arrest, wound dehiscence, bone defect, neurological infection, shunt failure.
15	Optic nerve	Unclear	Biopsy	None
16	Chiasmatic, hypothalamic, and optical radiation	Unclear	Biopsy	None
17	Chiasmatic and hypothalamic	Unclear	Biopsy	Decreased visual acuity
18	Optic nerve	Unclear	Biopsy	None
19	Chiasmatic and hypothalamic	Intracranial hypertension	Biopsy	Neurological infection, valvular dysfunction
20	Chiasmatic, hypothalamic	Intracranial hypertension	Biopsy	None

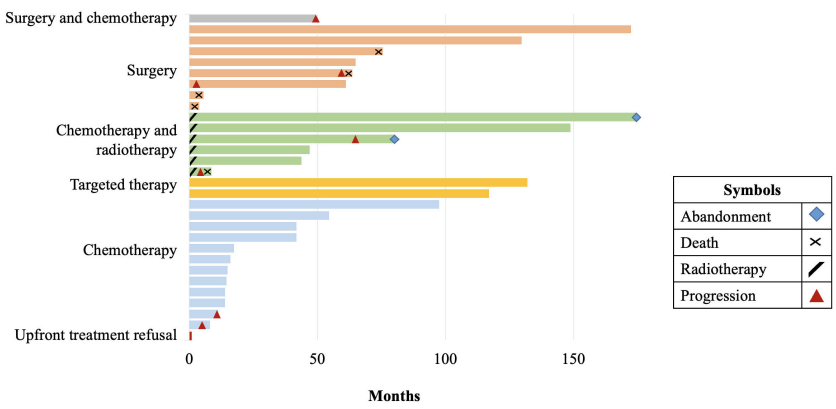

FIGURE 1
Swimmer's plot of cohort.

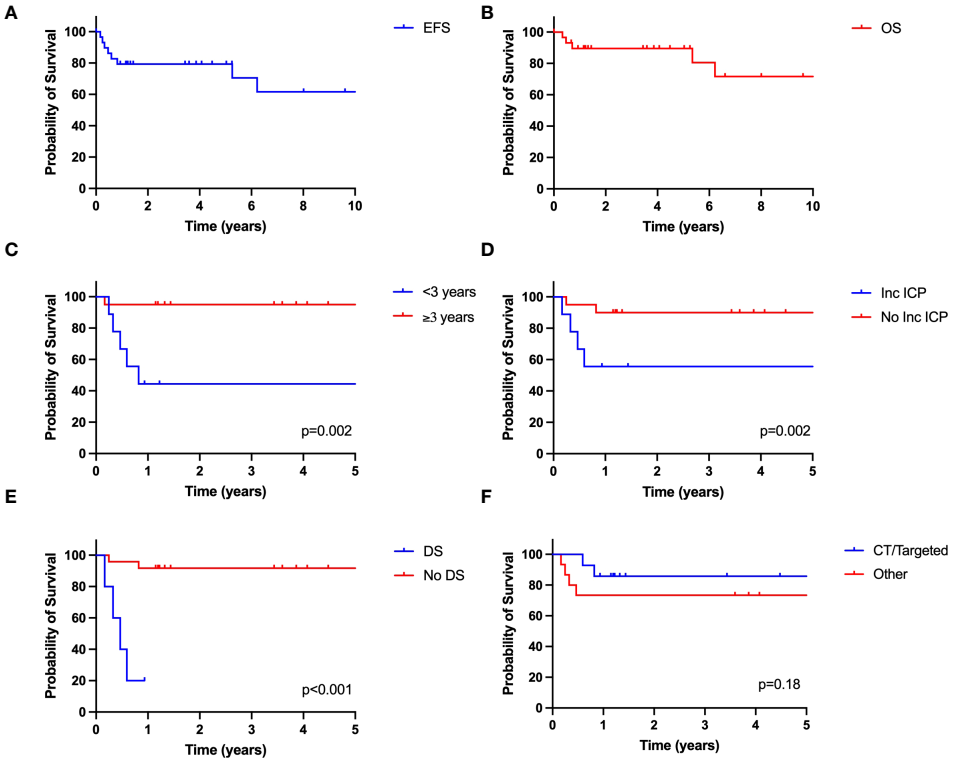

FIGURE 2
Outcome of pediatric OPG in Mexico. **(A)** EFS; **(B)** OS; **(C)** EFS based on age; **(D)** EFS based on presence of increased intracranial pressure (ICP) at presentation; **(E)** EFS based presence of diencephalic syndrome (DS); **(F)** EFS based on treatment. CT, chemotherapy.

these tumors and their outcomes. Our data suggests that favorable outcomes can be achieved with OPG in LMICs, although these are still lower than HICs. Factors such as young age, intracranial hypertension, and diencephalic syndrome continue to portend prognostic significance.

Although LGG are the most common CNS tumor in children, the global burden of LGG is unknown. The comprehensive evaluation of pediatric cancer incidence and mortality rates relies on quality population-based cancer registries (21). Important for LGG, and specifically for OPG, tumors that are not histologically confirmed are inconsistently captured in cancer registries (22). Furthermore, the International Classification of Childhood Cancer, does not segregate pediatric CNS tumors into many clinically relevant groups, such as LGG (23). These factors lead to a limited understanding of outcomes LGGs across the world, making peer-review publications key in describing survival rates.

Consistent with reports from LMICs (10), our study showed inferior outcomes for children with OPG compared to HICs, specifically when considering OS (4, 5). Worse outcomes were influenced by a high rate of post-operative complications. In our study, the complications presented by patients who received surgical resection at diagnosis were frequent and included two deaths. Although surgery can be curative for pediatric low-grade gliomas in other locations, resection of OPG is rarely indicated (10). Furthermore, patients with resection had a greater risk of achieving lower performance scores. As mentioned, none of the patients who had resections were seen by pediatric oncology prior to the surgery. This rate of complications clearly exemplifies the need for comprehensive, multidisciplinary care for children with OPGs starting at the time of diagnosis. A pediatric neuro-oncology program now exists at the HCG, so it is hoped that outcomes for all children with CNS treated at the institution will improve.

Systemic chemotherapy is usually considered the first-line treatment for OPG due to the risk of complications of radiotherapy (10). In our cohort, 20% patients received both radiotherapy and chemotherapy as front-line therapy. This points to an overuse of radiotherapy and the likelihood of an increased burden of long-term morbidity for these patients. Although we sought to evaluate long-term functional outcomes, comprehensive neuro-cognitive testing was not available for the patients of this cohort and other complications of radiotherapy were not captured. Further studies are needed to evaluate if radiotherapy is more prevalently used for OPG in LMICs and what factors could lead to this phenomenon.

In the last years, in HICs, targeted therapies for LGG are being used more frequently to achieve disease control (10). In our study, sirolimus was used in two patients with NF-1 and visual impairment, as this medication is more accessible and less costly than BRAF or MEK inhibitors. The use of mTOR inhibitors has been reported for patients with LGG (11, 24, 25), but may warrant further investigation in contexts where BRAF or MEK inhibitors are not available for patients. Among the challenges for pediatric cancer care in LMICs is the availability and affordability of chemotherapy (26). Although drugs like vincristine, carboplatin, and vinblastine

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TABLE 3 Clinical features and visual outcomes.

Patient	Age	Location and treatment	Test	Baseline	Response
1	4 years	Right ON, Chemotherapy	logMAR visual acuity	OD: counting fingers, 0.5 meters OS: 0.3	OD: counting fingers 1 meters OS: 0.3
			Visual field	Not done	OD: Paracentral scotoma LE: Normal
			Visual potentials	Demyelination and axonal deficit type visual pathway disorder	Not done
			Lansky/ Karnofsky	90	90
2	11 years	Right ON, Chemotherapy	logMAR visual acuity	OD: 1 OS: 0.0	OD: 0.0 OS: 0.0
			Lansky/ Karnofsky	90	100
3	14 years	Chiasm and hypothalamus, Chemotherapy	logMAR visual acuity	OD: VFI 3% OS: VFI 5%	OD: VFI57% OS: VFI31%
			Lansky/ Karnofsky	90	100
4	7 years	Left ON Chemotherapy	logMAR visual acuity	OD: 0.1 OS: no light perception	OD: 0.1 OS: no light perception
			Lansky/ Karnofsky	90	90
5	3 months	Chiasm and hypothalamus, Chemotherapy	logMAR visual acuity	OD: fixes and follows a target OS: fixes and follows a target	OD: fixes and follows a target OS: fixes and follows a target
			Visual potentials	Bilateral and symmetric lesion, more severe in LE	Normal
			Lansky/ Karnofsky	100	100
6	8 years	Right ON Chemotherapy	logMAR visual acuity	OD: 0.1 OS: 0.0	OD: 0.0 OS: 0.0
			Visual field	OD: VFI76% OS: VFI 92%	OD: VFI96% OS: VFI99%
			Lansky/ Karnofsky	90	100
7	4 years	Chiasm and hypothalamus, Chemotherapy	logMAR visual acuity	OD: counting fingers 2 meters OS: no light perception	OD: counting fingers 2 meters OS: no light perception
			Lansky/ Karnofsky	60	100
8	6 months	Chiasm and hypothalamus, Chemotherapy	logMAR visual acuity	OD: fixes, follows, and keeps their vision focused on a target OS: fixes, follows, and keeps their vision focused on a target	OD: fixes, follows, and keeps their vision focused on a target OS: fixes, follows, and keeps their vision focused on a target
			Visual potentials	Bilateral and symmetric lesion, more severe in OS	Normal
			Lansky/ Karnofsky	100	100
9	7 years	Bilateral and Chiasm, Sirolimus	logMAR visual acuity	OD: 0.3 OS: 0.3	OD: 0.3 OS: 0.3
			Lansky/ Karnofsky	90	100

(Continued)

TABLE 3 Continued

Patient	Age	Location and treatment	Test	Baseline	Response
10	9 years	Chiasm and hypothalamus, Surgery	logMAR visual acuity	OD: 0.17 OS: 0.3	OD: 0.3 OS: 0.3
			Lansky/ Karnofsky	90	70

ON, Optic Nerve; OD, oculus dexter; OS, oculus sinister; VFI, Visual Field Index.

are on the WHO essential medicines list, targeted agents relevant for the care of OPG, like MEK inhibitors, are not included (27). These agents could be relevant in LMICs as they have no impact on patient immunity and hence, decrease the need of hospital admissions due to acute complications. Advocacy efforts to increase access to novel agents is imperative to the care of children with LGG across the world. Importantly, a greater use of targeted therapy must align with increase access to the molecular diagnostics needed to identify the patients who would benefit from targeted therapy.

In evaluating the response to treatment of optic pathway gliomas, preservation of visual function is a key goal of treatment. In this series, the most frequent presenting sign was decreased visual acuity and the visual outcomes of 10 patients was included, with improvement in a subset of patients. Data on functional outcomes of pediatric LGG in LMICs are exceedingly sparse (19). Functional outcomes be investigated more in depth in LMICs as this is a key parameter of outcomes for this disease.

We report an abandonment rate of 10%. Treatment abandonment is a complex phenomenon associated with social, economic, and treatment-related factors (28). Importantly, universal healthcare existed for children and adolescents with cancer in Mexico after 2004, timeframe when most of this cohort was treated (29, 30). Additional analyses, including social, economic, and treatment-related factors, are necessary to identify those associated with an increased risk of treatment abandonment for patients with LGG.

This study has limitations to be mentioned. As a retrospective study, all details of diagnosis and treatment was not available for some patients, especially as we sought to extract detailed features of care and outcomes. In addition, although some functional outcomes were included, more robust parameters would be needed to describe the burden of disease in these patients and the impact on quality of life. Furthermore, visual status and follow-up tests was only available in a subset of patients.

The treatment of patients with OPG is focused not only survival but improving the quality of life from both the disease and treatment. The comprehensive, multidisciplinary care of patients during their disease is essential to define the optimal treatment options. Building a robust understanding of the care that exists for patients with OPG in LMICs is needed to define interventions that would lead to improved quality of care for these patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Hospital Civil de Guadalajara ethics committee/institutional review board. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because Written informed consent was waived as this was a retrospective study.

Author contributions

JR: Formal analysis, Visualization, Writing – review & editing, Conceptualization, Data curation, Investigation, Writing – original draft. DM: Formal analysis, Methodology, Writing – review & editing, Visualization. AO: Investigation, Writing – review & editing. FS: Investigation, Writing – review & editing. RN: Investigation, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Methodology, Resources, Supervision, Validation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Next-generation sequencing for pediatric CNS tumors: does it add value in a middle-income country setup?

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Introduction: Advances in molecular diagnostics led to improved targeted interventions in the treatment of pediatric CNS tumors. However, the capacity to test for these is limited in LMICs, and thus their value needs exploration.

Methods: We reviewed our experience with NGS testing (TruSight RNA Pan-Cancer-seq panel) for pediatric CNS tumors at KHCC/Jordan (March/2022–April/2023). Paraffin blocks' scrolls were shipped to the SickKids laboratory based on the multidisciplinary clinic (MDC) recommendations. We reviewed the patients' characteristics, the tumor types, and the NGS results' impact on treatment.

Results: Of 237 patients discussed during the MDC meetings, 32 patients (14%) were included. They were 16 boys and 16 girls; the median age at time of testing was 9.5 years (range, 0.9–21.9 years). There were 21 samples sent at diagnosis and 11 upon tumor progression. The main diagnoses were low-grade-glioma (15), high-grade-glioma (10), and other histologies (7). Reasons to request NGS included searching for a targetable alteration (20) and to better characterize the tumor behavior (12). The median turnaround time from samples' shipment to receiving the results was 23.5 days (range, 15–49 days) with a median laboratory processing time of 16 days (range, 8–39 days) at a cost of US$1,000/sample. There were 19 (59%) tumors that had targetable alterations (FGFR/MAPK pathway inhibitors (14), checkpoint inhibitors (2), NTRK inhibitors (2), and one with PI3K inhibitor or IDH1 inhibitor). Two rare BRAF mutations were identified (BRAFp.G469A, BRAFp.K601E). One tumor diagnosed initially as undifferentiated round cell sarcoma harbored NAB2::STAT6 fusion and was reclassified as an aggressive metastatic solitary fibrous tumor. Another tumor initially diagnosed as grade 2 astroblastoma grade 2 was reclassified as low-grade-glioma in the absence of MN1 alteration. NGS failed to help characterize a tumor that was diagnosed histologically as small round

blue cell tumor. Nine patients received targeted therapy; dabrafenib/trametinib (6), pembrolizumab (2), and entrectinib (1), mostly upon tumor progression (7).

Conclusion: In this highly selective cohort, a high percentage of targetable mutations was identified facilitating targeted therapies. Outsourcing of NGS testing was feasible; however, criteria for case selection are needed. In addition, local capacity-building in conducting the test, interpretation of the results, and access to "new drugs" continue to be a challenge in LMICs.

KEYWORDS

next-generation sequencing (NGS), children, CNS tumors, low-middle-income countries (LMIC), targeted therapy, compassionate access

Introduction

Over the last decade, several advancements, particularly next-generation sequencing (NGS) and DNA methylation profiling, improved our understanding of CNS tumors (1). As a result, a refined classification of CNS tumors leads to the integration of the molecular diagnosis in the recent 2021 WHO-CNS tumors classification (CNS-5) (2). This should help in a better prediction of tumors' prognosis allowing to tailor therapy accordingly. Identifying potentially actionable alterations would, theoretically, result in utilizing targeted therapies for a better control of tumor growth. In the INFORM registry (3), where most tumors were refractory or relapsed solid tumors, 446 of the 519 patients (85.9%) had at least one actionable target. Eventually, 147 patients (28%) received a matched targeted drug whether through clinical trials, off-label use programs, or compassionate use programs. Matched targeted therapy with ALK, NTRK, and BRAF inhibitors showed significantly improved progression-free survival (PFS, $p = .012$) and overall survival (OS, $p = .036$) in comparison with conventional treatment or no treatment (4). These longer PFS and OS were also found in a comprehensive literature review on the clinical impact of NGS tests for the management of adults with advanced cancer (5).

Targeted panel-based NGS, like TruSight, is designed to sequence multiple selected cancer genes to allow for a rapid turnaround time using a small amount of tissue. A negative NGS result either means that the tumor has no detectable molecular alteration or this might be related to low tumor cellularity. Expertise is needed in interpreting the NGS results and integrating them with the histological findings to maximize its diagnostic and prognostic yield (6). This may help personalize the management of individual patients by early introduction of targeted interventions for aggressive tumors. With a more comprehensive DNA and RNA sequencing, germline mutations may be detected with further implications on the care provided to patients through counseling and cancer screening (3, 7).

The addition of the molecular layer of diagnosis to the CNS-5 classification (2) remains a challenge to many low–middle-income countries (LMICs). While surrogate immunohistochemistry (IHC) is relatively available and cheap, it does not cover the full range of the targetable mutations, and its interpretation remains subjective. The use of technologies like NGS and DNA methylation profiling is far more innovative with the need for a technical infrastructure and advanced personnel training. In a Korean pilot study (8) to evaluate the preliminary efficacy and clinical feasibility of NGS-based targeted anticancer therapy in refractory solid tumors, Moon et al. (8) found that 41.7% of patients did not start the targeted therapy due to a decline in their performance status, 20.8% due to stable disease with a previous treatment, and 16.7% due to lack of access to the targeted medication. They encountered several obstacles in their study; NGS was an outsourced test sent to the United States with a turnaround time of 4 weeks, in addition to the lack of insurance coverage for the NGS cost, and the limited access to the targeted medications. Similar data on the NGS utilization from LMICs are limited.

King Hussein Cancer Center (KHCC) is the only cancer-dedicated hospital treating children and adults in Jordan. It has a well-established pediatric neuro-oncology service and multidisciplinary clinic (MDC) team since 2003 with a twinning program with the Hospital for Sick Children (SickKids) in Toronto (9). More than 70% of the Jordanian children with CNS tumors are treated in this service in addition to consultations for non-Jordanians (with a total of 80–110 newly diagnosed cases per year). With the increasing role of molecular and sequencing information in the management of pediatric brain tumors and the implementation of the CNS-5 classification, discussions during the monthly teleconferences between KHCC and SickKids progressively involved the potential benefit of assessing molecular tumor alterations to help us reach the appropriate diagnosis in challenging cases or consider some targeted therapies in some patients. In this context, an outsourcing testing approach was agreed on. We collaborated with the SickKids Clinical Laboratory Improvement Amendments (CLIA) certified laboratory to do TruSight NGS panel for selected tumors based on the KHCC-MDC recommendations based on the potential to add a clinical benefit to the patients.

In the current study, we aim to evaluate our initial experience, namely, the feasibility of outsourcing molecular testing in terms of the turnaround time from shipment of samples to receiving the results back, the cost of testing, and the importance of integrating the NGS results to reach a diagnosis and/or provide options for targeted treatments.

Methods

We retrospectively reviewed our KHCC pediatric Neuro-Oncology experience with NGS testing for pediatric CNS tumors between 01/03/2022, and 01/04/2023. We included all patients who were treated at KHCC whom the MDC team recommended to send their tumors for NGS testing and had sufficient RNA quantity for testing.

The decision to send for NGS testing was clinical and based on the MDC discussions and agreement that it could be of a clinical benefit to the patient. "Clinical benefit" could broadly be categorized as either expecting the NGS result to help confirm further the diagnosis when it was challenging to do so by IHC alone or when the radiological images or the clinical course of the patient were not fully aligned with the pathological diagnosis, or when NGS testing was expected to find a targetable alteration based on the pathological diagnosis (e.g., BRAF alterations in low-grade glioma, LGG) that could support the use of a targeted therapy or contribute to predict prognosis. The decisions to send for NGS testing were made either at the time of the initial diagnosis or upon tumor progression. Integration of the NGS results in the patients' treatment was rediscussed between members of the MDC team and on occasions during KHCC teleconference meetings with SickKids (9), which further helped broaden KHCC's team knowledge on the implications of these results on the patients' care.

NGS testing was performed by the CLIA-certified SickKids laboratory. Specimens underwent pathologic evaluation at KHCC, and then scrolls from the formalin-fixed paraffin-embedded blocks were shipped abroad and RNA was extracted at SickKids. TruSight® RNA Pan-Cancer Panel (10) was used, which represents 1,385 genes implicated in cancer pathways. The resulting report was signed by SickKids neuropathologists with recommendations on the implications of the result. Potentially actionable alterations were defined as those, which may result in altered diagnosis, altered treatment, or indicate a germline syndrome. The cost of NGS testing was US$ 1,000 per tumor sample and was covered by the governmental insurance as it was clinically indicated.

In addition, we reviewed the patients' characteristics, tumor diagnoses, the reason NGS testing was requested, and patient outcome. We assessed the turnaround time and cost needed for this testing in addition to the implications of the results on patients' care.

Statistical considerations

This is a descriptive retrospective study to evaluate feasibility. The median and range were used for continuous variables like patients' characteristics and treatment, whereas counts and percentages were used to present categorical variables. The duration of follow-up was calculated from the time of NGS testing to the patient's last follow-up date.

This study was approved by the KHCC Institutional Review Board.

Results

During the study period, 237 patients were discussed in the weekly pediatric Neuro-Oncology MDC meetings (some were discussed more than once). From these, 36 corresponding tumor samples were planned to be sent for NGS testing. Four samples were excluded from this review due to insufficient RNA quantity for testing.

There were 32 patients (14%) eventually who were included, 16 boys and 16 girls. Their median age at the time of NGS testing was 9.5 years (range, 0.9–21.5 years). The median time between tumor biopsy/resection and NGS testing was 2.4 months (range, 0.1–8.8 years). There were 29 brain and three spinal tumors. LGG was diagnosed in 15 tumors (seven were optic pathway gliomas, three were metastatic), 10 were high-grade gliomas (HGG, two were metastatic), and seven were of other histologies (Table 1).

The selection of tumors to be tested was made through the MDC team discussions and their expectations of a clinical benefit. Generally, this meant choosing rare diagnoses like a mesenchymal tumor (in patient #27), those challenging to reach a specific diagnosis (in patient #29), or tumors that were felt to have a relatively "unexpected behavior" (like in patients #13 and 14). In addition, we tested some tumors based on the expectation to find an alteration (e.g., BRAF fusion or mutation) and an expectation of a lower response to the traditional chemotherapy protocols (like patients #7 and 8). In summary, the reasons behind recommending NGS testing were either to identify a molecular alteration and assess if a targeted therapy is accessible (20 cases) or to help characterize the tumor more and predict its behavior (12 cases). In 21 cases (66%), NGS testing was performed at the time of the initial diagnosis. There were 19 tumors (59%) that had potentially actionable alterations (Figure 1): 14 with FGFR/MAPK pathway inhibitors, two with checkpoint inhibitors, two with NTRK inhibitors, and one with the PI3K inhibitor or IDH1 inhibitor. Two rare BRAF mutations were identified (BRAFp.K601E and BRAFp.G469A) (in patients #13 and 14, respectively). One tumor diagnosed initially as undifferentiated round cell sarcoma harbored NAB2::STAT6 fusion and was reclassified as solitary fibrous tumor (patient #32). This tumor was aggressive and metastatic, and the patient had rapid clinical deterioration. Another tumor (patient #30) initially diagnosed as grade 2 astroblastoma was reclassified as LGG in the absence of MN1 alteration. One tumor could not fit in a specific diagnosis histologically, despite extensive IHC staining, and was diagnosed as small round blue cell tumor and eventually treated as CNS sarcoma (patient #29). NGS did not help characterize this tumor further; however, later, it was diagnosed by DNA methylation as ZFTA ependymoma a with ZFTA: NCOA1/2 fusion (Table 1). NGS results in three tumors (patients #4, 16,

TABLE 1 Tumors' histology with NGS findings, implications on treatment, tumors course, and patients' outcome.

No.	Tumor histology and location	Timing of NGS testing	NGS findings	NGS result used in treatment/duration of use in months	Tumor course till last follow-up*	Patient outcome/ follow-up* (months)
Low-grade glioma						
1	Optic chiasm/ hypothalamic ganglioglioma	Diagnosis	**BRAF v600 mutant** No CDK2A deletion	No	Tumor stabilized with chemotherapy	Alive (10.1)
2	Parieto-occipital pediatric-type diffuse LGG	Diagnosis	MYB::PCDHGA1 fusion		Tumor stabilized with chemotherapy	Alive (13.1)
3	Cervico-medullary pediatric-type diffuse LGG	Diagnosis	**KIAA1549::BRAF fusion transcript**	No, parents refused	Tumor progressed on third-line chemotherapy	Alive (9)
4	Brainstem ganglioglioma	Diagnosis	**FGFR1p.N546K,** PTPN11p.E139D, PIK3CAp.V344G, EGFRp.A289T SNVs	No	Tumor stabilized post surgery	Alive (6.7)
5	Suprasellar ganglioglioma	Diagnosis	**BRAF V600E,** CDKN2A-no loss of expression	Yes, dabrafenib (4.7)	Used following progression on chemotherapy (tumor responded)	Alive (6.7)
6	Frontal glioneuronal tumor	Diagnosis	**FGFR1 tyrosine kinase domain ITD**	No	Tumor stabilized with chemotherapy and surgery	Alive (19.5)
7	Metastatic pediatric-type diffuse OPG	Diagnosis	**KIAA1549(exon15):: BRAF(exon9) fusion**	Yes, trametinib (9)	Used following progression on chemotherapy (tumor responded)	Alive (13.5)
8	Metastatic pediatric-type diffuse OPG	Diagnosis	No reportable SNVs/fusions		Tumor progressed on third-line chemotherapy	Dead (11.3)
9	Spinal pediatric-type diffuse LGG	Diagnosis	**KIAA1549(exon15):: BRAF(exon9) fusion**	No	Tumor responded with chemotherapy	Alive (13.5)
10	Optic pathway pilocytic astrocytoma	Progression	**KIAA1549::BRAF fusion transcript**	Yes, trametinib (9.4)	Used following progression on chemotherapy (tumor stabilized)	Alive (9.5)
11	Optic pathway pilocytic astrocytoma	Progression	No reportable SNVs/ fusions were detected		Tumor shows slow progression	Alive (6.7)
12	Thalamic pilomyxoid astrocytoma	Progression	NF1p.R1276*SNV		Tumor shows slow progression	Alive (7)
13	Tectal pilocytic astrocytoma	Progression	NF1p.A264Qfs*16 **BRAFp.K601E SNVs**	No	Tumor stabilized with chemotherapy	Alive (13.5)
14	Fronto-temporal DIG	Progression	**BRAFp.G469A**	Yes to control variable cystic tumor response and ascites, dabrafenib, and trametinib (4.3)	Tumor stabilized Ascites controlled	Alive (15.4)
15	Metastatic optic pathway pilocytic astrocytoma	Progression	**KIAA1549(Ex16)::BRAF (E09) fusion**	Yes, trametinib (5.7)	Tumor response	Alive (7)
High-grade glioma						
16	Parietal pediatric-type diffuse HGG	Diagnosis	TP53p.R273C, **MSH6p.C687Lfs*10SNVs**	Yes, pembrolizumab (5.1)	Tumor stabilized after surgery and focal radiotherapy and pembrolizumab	Alive (5.9)
17	Cerebellar pediatric-type diffuse HGG H3 wild type	Diagnosis	**NRASp.Q61K** NF1p.V33Sfs*9 SNVs	No	Tumor progressed rapidly despite radio-chemotherapy	Dead (10)

(Continued)

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TABLE 1 Continued

No.	Tumor histology and location	Timing of NGS testing	NGS findings	NGS result used in treatment/duration of use in months	Tumor course till last follow-up*	Patient outcome/ follow-up* (months)
High-grade glioma						
18	Frontal pediatric-type diffuse HGG	Diagnosis	MN1 (exon 1 with pseudoexon in-frame insertion)::PATZ1		Tumor stabilized after surgery and focal radiotherapy	Alive (16.8)
19	Frontal embryonal tumor/ pediatric-type diffuse HGG IDH-1 wild type	Progression	**EGFR overexpression** PTENp.F341V SNV	No,not accessible	Tumor progressed despite surgeries, radiotherapy and chemotherapy/ASCT	Alive (13)
20	Metastatic thalamic midline glioma H3K27M mutated	Progression	**FGFR1p.K656E** PTENp.F341V	Yes, trametinib (13.7)	Initial response to trametinib then progression	Alive (15.6)
21	Spinal diffuse midline glioma H3K27me3 altered	Diagnosis	**SOX10::NTRK3 fusion**	No	Tumor stabilized after surgery and radio-chemotherapy	Alive (9.4)
22	Spinal glioblastoma (initially diagnosed at 1 year old)	Progression	PTENp.F341V TP53p.H95F SNV		Tumor very slowly progressive	Alive (13.5)
23	Frontal pediatric-type diffuse HGG IDH-1 mutant	Diagnosis	TP53p.P152L IDH1p.R132H **MSH6p.R772W**	Yes, pembrolizumab (11.3)	Initial response then progression	Dead (12.4)
24	Frontal diffuse hemispheric glioma H3 G34 mutant	Progression	P53p.M237l ATRXp.K1361 **IDH1p.R132C PIK3R1p.N564D**	No	Tumor progressed rapidly despite radio-chemotherapy	Dead (1.5)
25	Metastatic frontal glioblastoma IDH-1 wild/H3K27 wild	Progression	**SPECC1L(exon11):: NTRK2(exon 14)** fusion transcript	Yes, entrectenib (4.3)	Initial response then progression	Dead (6.5)
Other histologies						
26	Frontal ependymoma	Diagnosis	ZFTA::RELA fusion transcript		Tumor did not recur after surgery and radiotherapy	Alive (10.9)
27	Cervico-medullary mesenchymal tumor (EWSR1 gene rearrangement is positive)	Diagnosis	PTENp.F341V SNV		Tumor stabilized after surgery and radio-chemotherapy	Alive (19.3)
28	Posterior fossa embryonal tumor likely medulloblastoma	Diagnosis	PTENp.F341V SNV		Given intensive chemotherapy/ASCT/ focal radiation	Alive (8)
29	Parietal small round blue cell	Diagnosis	No reportable SNVs/fusions		Tumor did not recur after surgery and radio-chemotherapy	Alive (6.8)
30	Parietal astroblastoma grade 2	Diagnosis	PTEN p.F341V NF1p.Y2487		Tumor did not recur after surgery	Alive (13.1)
31	Pineoblastoma	Diagnosis	No reportable SNVs/fusions		Tumor progression	Dead (10.7)
32	Cerebellar undifferentiated round cell sarcoma with BCOR genetic alteration	Progression	**NAB2::STAT6 fusion transcript** P53 p.L194R SNV		Tumor progressed rapidly	Dead (3.1)

DIG, dysembryoplastic ganglioglioma; HGG, high-grade glioma; LGG, low-grade glioma; NGS, next-generation sequencing; OPG, optic pathway glioma.
*Follow up is calculated from the time of sending NGS test to the last follow-up of the patient.

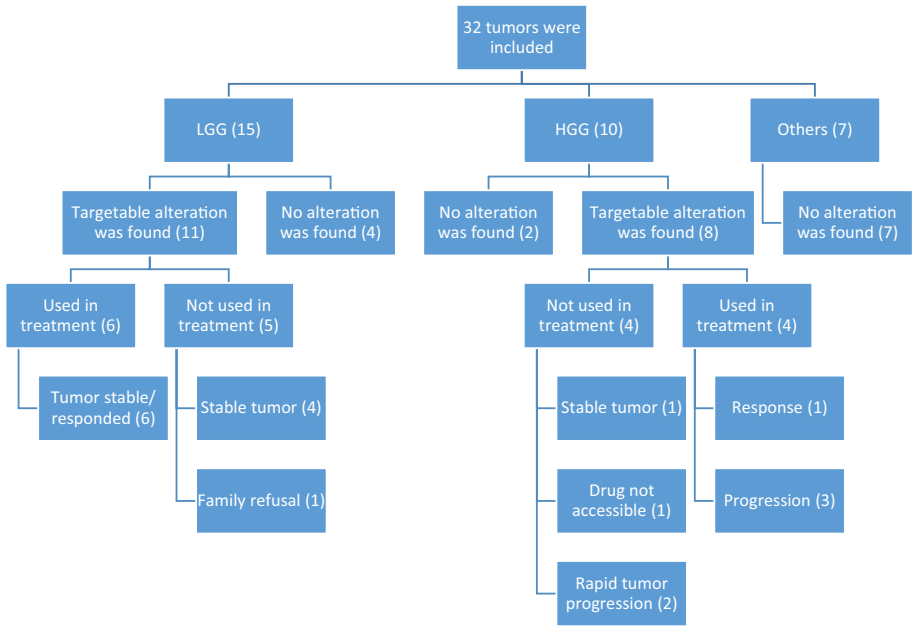

FIGURE 1
Diagram showing distribution of NGS alterations according to histology and effect on treatment. HGG, high-grade glioma; LGG, low-grade glioma.

and 23) suggested an underlying germline syndrome, which was also confirmed by germline testing.

Nine patients (28%) received matched targeted therapy; compassionate dabrafenib/trametinib (6), pembrolizumab (2), and compassionate entrectinib (1). Two patients (# 16 and 23) with biallelic mismatch repair syndrome (BMMRD) had surgical resection then received pembrolizumab during and after radiotherapy without chemotherapy. The remaining seven patients received targeted therapies following tumor progression (they received chemotherapy with or without radiotherapy before). Despite the short duration of using the matched targeted therapy (median 5.7 months, range 4.3–13.7 months), most patients had tumor response, which was sustained when dabrafenib and/or trametinib were used (Table 1). There were 10 patients (53%) who did not receive a targeted therapy: six due to stabilization of the tumor with conventional therapies, two due to deterioration in their clinical condition upon tumor progression, one case in which the targeted therapy was not accessible, and one family who preferred to defer the targeted therapy after consuming all options of conventional chemotherapies. During the short follow-up period after NGS testing (median 10.4 months, range 1.5–19.5 months), seven patients died from disease progression including one patient with HGG despite treatment with entrectinib and one patient with BMMRD-associated HGG who received pembrolizumab.

The median turnaround time to receive the NGS result back calculated from the time of shipment was 23.5 calendar days (range, 15–49 days) and from arrival to SickKids was 16 days (range, 8–39 days). Several challenges were encountered during this experience. Some tumor samples were too small to extract sufficient RNA quantity for testing (four tumors), and one tumor sample was lost in shipment; thus, a new sample was sent causing further delay. The experience of utilizing NGS results to help in the diagnosis and treatment of children with CNS tumors was new to the treating team at KHCC, and the test was not yet validated to be performed locally. Accordingly, self-reading and discussion of some NGS results with the SickKids team helped the local team to gain knowledge about the significance of the genomic alterations and the expected response to targeted therapies if any. Access to the targeted therapy was through the compassionate access from Novartis (dabrafenib and trametinib) and Roche (entrectinib), particularly with the lack of pediatric clinical trials at KHCC. Pembrolizumab use was covered through the governmental insurance due to the beneficial evidence of using checkpoint inhibitors in patients with BMMRD (11–13).

Discussion

Our data demonstrated the feasibility to send out NGS testing in terms of turnaround time and cost for a middle-income country (MIC), with important implications on the diagnosis, treatment, and prognosis for the affected children. Our experience suggests that NGS is not an exclusivity for HIC and our results emphasize the importance of adding molecular diagnostics even in LMICs as an important step to improve the outcome of children with CNS tumors in these countries.

In this initial experience, the selection of the cases was biased toward patients with challenges in diagnosis and/or management. This may explain the high percentage of potentially actionable alterations (59%) reported in this series. In addition, we knew we had access to several special drug access programs with the opportunity to offer some targeted therapies and expect a clinical benefit from the NGS results. In fact, targeted therapy was used in 47% of our patients with an actionable alteration, which constitutes

28% of all tested cases. In the Genome for Kids (G4K) (7), where whole-genome sequencing, whole-exome sequencing, and RNA sequencing were used to test 309 prospectively identified children (85% were newly diagnosed), 86% harbored diagnostic (53%), prognostic (57%), therapeutically relevant (25%), and/or cancer-predisposing (18%) variants. In the MATCH trial (14), where refractory solid tumors, lymphomas, and histiocytic disorders were tested with cancer gene panel sequencing and limited IHC, 109 patients with CNS tumors from the 264 screened (41%) had actionable tumor alterations and 52 patients (48% of those with tumor alteration and 19% of those screened) were enrolled in a trial arm. In this trial, the median turnaround time was 12 days from receiving the sample to completion of testing in this trial, which is shorter compared with ours (16 days).

One would argue that assessing only druggable molecular markers with prognostic value using IHC, FISH, and Sanger sequencing is more realistic in an LMIC setting. This was the conclusion made by Colli et al. (15) from Argentina after they tested 102 pediatric glial and glioneuronal tumors and corelated PFS and OS with several alterations (KIAA1549-BRAF gene fusion, BRAFV600E mutation, H3K27M and H3G34R mutations). While these alterations are the most prevalent, NGS is superior in detecting a wider range of alterations that may change the diagnosis or management. In our experience, two tumor diagnoses were revised based on the NGS finding of NAB2::STAT6 fusion (patient #32) and absence of MN1 alteration (patient #30). In addition, two rare BRAF mutations were identified (BRAFp.G469A, BRAFp.K601E) that would not have been found if a limited test (IHC or FISH) was used to check only for BRAFp.V600E mutation. Furthermore, three tumors (in patients #17, 21, 25) had NRAS and NTRK alterations, respectively, which were unexpected yet targetable alterations. However, even with this wider molecular testing, a proper diagnosis may be difficult to reach without resolving to a more advanced testing, for example DNA methylation profiling, as demonstrated in patient #29. Several studies showed that more extensive testing (e.g., utilizing whole-genome sequencing (WGS), whole-exome sequencing (WES), and RNA sequencing of the tumor) provides clinical data beyond the standard-of-care assays (7, 16).

In the MATCH trial (14),the main reasons for not receiving a targeted treatment for the identified molecular alterations were patients receiving other treatment (32%), poor clinical status (15%), lack of measurable disease (11%), and ineligible diagnosis (10%). The percentage of our patients who did not use a targeted therapy despite having an alteration was similar to the Korean experience (8) (53% vs. 47% respectively) echoing similar reasons, namely, stabilization of tumors, clinical deterioration, or lack of access to the drugs. Practically, these reasons will continue to be the main barriers against performing the tests unless a change in management paradigm is made. The question of whether targeted drugs should be used as a first-line therapy, before conventional chemotherapeutic agents or radiotherapy, is valid especially within the context of the recent FDA approval of the combination of dabrafenib and trametinib as first-line therapy for LGGs and solid tumors with BRAF mutations in children (17). However, this is not easily applicable in countries with limited resources. There is a need for technology transfer and personnel training to establish these molecular tests locally, and a need to have insurance coverage to perform the tests and use of the targeted therapy (1). The high cost of these new targeted drugs remains a significant barrier to their use in LMICs. In fact, this is currently a challenge for our patients with the closure of some special access programs. Efforts to facilitate access to oncology medicines globally and mainly in LMICs were initiated by UICC, the WHO, and Saint Jude Global (18, 19). For this, proper cost-effectiveness studies on the use of targeted therapies in LMICs are needed to balance the current standard of care and poor outcome versus new therapies and their promising results.

Another change in the management paradigm is related to the appropriate timing of performing the molecular tests. Routine upfront testing at the initial cancer diagnosis rather than at tumor progression is more appealing. This may help to better predict the prognosis and allow more time to consider the use of targeted therapies before deterioration in clinical performance occurs. One would argue that the molecular alterations may change with tumor progression and a need for a new biopsy may be preferable in these situations. In addition, the cost–benefit ratio of routine NGS testing needs to be assessed wisely in LMICs settings if access to the targeted drugs is a challenge. It is time to consider MIC participation in molecular clinical trials, considering that 80%–90% of children live in LMICs. Choosing countries with a relatively good infrastructure and centers with trained personnel will not only allow rapid study recruitments and faster results but also enhance the inclusiveness and reduce disparities by allowing wider access to the new technologies and targeted drugs in those communities (1). This should help bridge the survival gap between high- and low-middle-income countries.

In our limited experience, two patients were found to have a cancer predisposition syndrome (namely, BMMRD, patients #16 and 23). This was expected before receiving the NGS results based on their clinical characteristics (consanguinity, family history of cancers, and café au lait spots), and accordingly, a concurrent germline testing was performed, which proved the diagnosis. Several studies that combined tumor and blood NGS testing showed around 7%–18% chance of identifying an underlying cancer predisposition syndrome. This has important consequences on the patient's care (cancer screening and counseling) and in choosing the treatment approach (e.g., use of checkpoint inhibitors in BMMRD). In addition, one patient with brainstem gangliolioma and dysmorphic features (patient #4) had PTPN11 alteration in her tumor, which was confirmed on germline testing to have the heterozygous pathogenic mutation leading to a diagnosis of RASopathy spectrum disorder.

We acknowledge some limitations in our study. The main limitation is its retrospective design and the selection bias of choosing tumors to be tested, which was based on the MDC team clinical judgment. The small number of tumors tested and consequent targeted therapies given make it difficult to compare the effectiveness of this approach on tumor control and survival in the absence of a control group. Nevertheless, this is a feasibility experience in a setting of limited similar reports from LMICs. It emphasizes the importance of MDC members' discussions on how to utilize new cancer advancements selectively. Being a new

experience meant we need to move slowly in order to assess the feasibility and appropriateness of sending samples abroad, in terms of turnaround time and cost, and learn how to interpret the results and integrate them into the patients' care. Moving forward, focused training in molecular pathology was completed by our pathologists and we are now setting the infrastructure to start NGS testing and DNA methylation profiling locally at KHCC, which will have major future implications for our patients. Until then, it is wise to continue to select tumors to be sent abroad for testing, basically tumors with high percentage of expected alterations or tumors that are difficult to diagnose. We would consider the following categories: LGG that are difficult to control by surgical resection and first-line chemotherapy, infant gliomas, HGG, and tumors that are challenging to diagnose by IHC or seem not properly fitting the clinical or radiological picture. Once an alteration is found, the journey of getting access to the drugs starts. It is challenging to find a compassionate access program that will consider applications from LMICs and to consider the shipping challenges as well. Nevertheless, it is worth the journey, and it gets easier with time as the local team gains more expertise and the drug companies' trust increases with ongoing collaboration with the local team.

In conclusion, we demonstrated the feasibility of sending out NGS testing and the ability to use the results to help in patients' diagnosis and treatment. However, to achieve this, a close collaboration between pathologists, molecular biologists, and clinicians is needed ideally in a molecular tumor board format. This is most important for CNS tumors with the rapid advancements and integration of the molecular diagnostics now in their classification. In addition, there is a need to convince governments and insurance bodies of the importance of covering these molecular tests and ultimately to approve the targeted therapies to help improve patients' survival and quality of life.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by KHCC Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the study is retroscpetive in nature and data were de-identified after collection.

Author contributions

NA: Conceptualization, Validation, Writing – original draft, Writing – review & editing. MA-H: Writing – review & editing. BM: Writing – review & editing. SA: Writing – review & editing. QA: Writing – review & editing. AM: Writing – review & editing. AI: Writing – review & editing. NS: Writing – review & editing. MO: Writing – review & editing. CH: Writing – review & editing. EB: Writing – review & editing.

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Conflict of interest

Dr. EB is a member of the advisory board of Novartis and Alexion.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Primary central nervous system tumors survival in children in ten Colombian cities: a VIGICANCER report

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Purpose: Primary central nervous system (CNS) tumors are the second most common cancer in children and adolescents, leading to premature death and disability. Population-based survival estimates aid decision-making in cancer control, however data on survival for primary CNS tumors in Latin America is lacking. We describe survival rates for children with primary CNS tumors treated in ten Colombian cities.

Methods: We analyzed data from children and adolescents newly diagnosed with cancer between 2012 and 2021, participating in the Childhood Cancer Clinical Outcomes Surveillance System (VIGICANCER) in ten cities in Colombia. VIGICANCER collects information on clinical outcomes from twenty-seven pediatric oncology units and conducts active follow-up every three months. VIGICANCER does not register craniopharyngiomas; we excluded intracranial germ cell tumors for this report. We used the Kaplan-Meier method to estimate the overall survival probability, stratified by sociodemographic variables,

topography, WHO grading, receipt of radiation therapy, and type of surgical resection. We analyzed the prognostic capacity of variables using multivariate proportional Cox's regression, stratified by city and year of diagnosis.

Results: During the study period, VIGICANCER included 989 primary CNS tumors in 879 children and 110 adolescents. The cohort median age was 9 years; 53% of patients were males, and 8% were Afro-descendants. Most common tumors were supratentorial astrocytomas (47%), astrocytic tumors (35%), medulloblastomas (20%), ependymomas (11%), and mixed and unspecified gliomas (10%). Five-year overall survival of the entire cohort was 54% (95% CI, 51-58); for supratentorial gliomas, WHO grade I was 77%, II was 62%, III-IV was 27%, respectively, and for medulloblastoma was 61%. The adjusted hazard rate ratio for patients with WHO grade III and IV, for those with subtotal resection, for brainstem location, and for those not receiving radiation therapy was 7.4 (95% CI, 4.7–11.8), 6.4 (95% CI, 4.2–9.8), 2.8 (95% 2.1–3.8), 2.0 (95% CI, 1.3–2.8) and 2.3 (95% CI, 1.7–3.0), respectively.

Conclusion: We found that half of Colombia's children and adolescents with primary CNS tumors survive five years, compared to 70% to 80% in high-income countries. In addition to tumor biology and location, gross total resection was crucial for improved survival in this cohort. Systematic monitoring of survival and its determinants provides empirical data for guiding cancer control policies.

KEYWORDS

central nervous system neoplasms, pediatrics, treatment outcome, prognosis, epidemiology, Latin America, survival, children

Introduction

A wide range of morphologies characterizes primary central nervous system (CNS) tumors in humans, representing about 3% to 4% of all primary cancers (1, 2). Around 12% of all primary CNS tumors occur in children. (<15 years) (1, 2). CNS tumors are the second most common tumor occurring in children (2, 3), after leukemias, with an incidence (per million) displaying wide geographical variations, ranging from 1.7 in Yaoundé (Cameroon, 2004 to 2006) to 53.5 in Nebraska (USA, 1998 to 2012) (4). Differences in disease ascertainment and inclusion of non-malignant tumors partly explain the variations in incidence. In Latin America, the reported incidence of these tumors ranges from 17.9 in Ecuador (based on five population-based cancer registries (PBCR), 1993 to 2013) to 30.2 in Lima, Perú (2010 to 2012). The incidence rate in Colombia from 1992 to 2013 was 25.2, based on data from four PBCR cancer registries (4).

CNS tumors encompass tumors found in the brain, spinal cord, and meninges. Of these, brain tumors are the most frequent (3, 5, 6). In adults and children, tumor types mainly vary because children have a higher frequency of embryonal tumors, with medulloblastoma being the most frequent (7, 8). When planning treatment and evaluating its effectiveness in our era, it is crucial to consider the patient's age, topography, histology, and molecular pathology (7, 9–11). Survival is the most important metric of therapeutic success (12), although life-altering disabilities in long-term survivors should also be considered. Most progress has been made in medulloblastoma, from 1960 to 2010, with five-year overall survival (OS) increasing from 23% to 73% (13).

The World Health Organization is leading the Global Initiative for Childhood Cancer, which aims to improve the survival of children with cancer (14). This initiative requires population-based survival estimates to tailor interventions and measure progress. Regular survival monitoring is crucial for evaluating advances in cancer care for children (15).

However, information about survival of children with CNS tumors in low-and middle-income countries (LMIC) is limited (13). In a recent systematic review of childhood CNS tumors population-based survival only five studies were conducted in LMIC, of which none was from Latin America (13). The Argentinian hospital-based pediatric oncology registry -ROHA- (16) reported (2012 to 2016) a three-year OS of CNS tumors of

64%, and a five-year OS of 52% for medulloblastoma (2005 to 2014). Our aim is to contribute to this knowledge gap by describing the survival of children with CNS tumors treated in 27 pediatric oncology units (POU) at ten Colombian cities.

Methods

Setting and study population

Colombia is located in South America's northwestern region and its population is 51 million inhabitants (17) with 12 million minors under 15 years old. Its 2022 per capita gross domestic product was 6664 US$, ranking 88th in the Human Development Index, with a score of 0.752 in 2021 (18). As of 2021, Colombia was the most unequal country in Latin America, with a GINI index of 0.542 (19), and a poverty rate after the pandemic peak of 39% (20).

VIGICANCER was established in Cali, the third largest city in Colombia, in 2009. VIGICANCER planning, methods, and implementation was previously published (21). VIGICANCER has expanded and currently encompasses 27 POU in ten Colombian cities, including approximately 55% of all childhood cancer cases predicted to occur annually in Colombia. This prediction is based on the estimated incidence of Cali's PBCR (4). VIGICANCER has been approved by the ethics committee of each participating center and by the Universidad del Valle in Cali.

Case definition

VIGICANCER includes individuals under 19 years with a new diagnosis of an invasive malignant neoplasm (5^{th} digit behavior code/3) as classified by the International Classification of Diseases for Oncology, third edition (ICD-O-3) (22). Tumoral behavior benign (/0) or uncertain (/1) are included only for CNS tumors. This benign or uncertain behavior of CNS tumors encompasses low-grade and optic pathway gliomas. The main ICD-O morphologic classification cases of benign or uncertain behavior included were: subependymal, giant cell astrocytoma (9384/1), pilocytic astrocytoma (9421/1), subependymoma (9383/1), myxopapillary ependymoma (9394/1), choroid plexus papilloma (9390/0), atypical choroid plexus papilloma (9390/1), angiocentric glioma (9431/1), choroid glioma of the third ventricle (9444/1), gangliocytoma (9492/0), ganglioglioma (9505/1), desmoplastic infantile astrocytoma and ganglioglioma (9412/1), dysembryoplastic neuroepithelial tumor (9413/0), central neurocytoma (9506/1), extraventricular neurocytoma (9506/1), cerebellar liponeurocytoma (9506/1), papillary glioneuronal tumor (9509/1), rosette-forming glioneuronal tumor of the fourth ventricle (9509/1), pineocytoma (9361/1), meningioma, not otherwise specified (NOS) (9530/0), atypical meningioma (9539/1), hemangiopericytoma, NOS (9150/1), and hemangioblastoma (9161/1). VIGICANCER also includes gliomas of the optic nerve (topographic code C72.3), whereas craniopharyngiomas are not included. As the basis for diagnosis, VIGICANCER uses the guide proposed by the International Agency for Cancer Research, where the most valid basis is microscopic (cytology or histology). However, a non-microscopic-based diagnosis is considered appropriate if a microscopic diagnosis is impossible. Non-microscopic diagnosis can also be based on specific tumoral markers (biochemical and/or immunologic) or by clinical investigation, which includes all diagnostic techniques (22). Clinical diagnosis only (without any diagnostic technique) is not considered sufficient for inclusion in VIGICANCER. Patients with a diagnosis by death certificate are accepted. To be included in VIGICANCER, the patient should also receive treatment in a POU in a participating city. The only exclusion criteria is for patients whose parents/legal guardians decline participation.

For this report, we included information on children and adolescents registered in VIGICANCER from January 1, 2012 to December 31, 2021, with tumors involving the following ICD-O-3 topography coding: meninges (C70.0 to C70.9), cerebrum (C71.0 to C71.4), ventricles (C71.5), cerebellum (C71.6), brain stem (C71.7), overlapping lesion of brain (C71.8), not otherwise specified topography of the brain (C71.9), spinal cord, cranial nerves, and other parts of CNS (C72.0 to C72.5), overlapping lesion of brain and CNS (C72.8), and not otherwise specified tumor in the nervous system (C72.9). The ICD-O-3 morphology codes included are shown in Table 1. WHO grading is used in VIGICANCER as reported in 2007 (23), which is also included in the ICD-O-3 (22).

Variables

VIGICANCER actively collects the information from patients' medical records, pathology reports, nurses administering chemotherapy, and social workers. Although some information is acquired directly from patients' caregivers, in some POUs, access of VIGICANCER clinical monitors to patients' caregivers has been restricted. Pediatric oncologists in each POU help in data quality checks and clarifying information when necessary. Centralized data quality checks are also performed.

We included demographic variables such as: age at diagnosis, sex, place of residence, afro-descendant ethnicity, and health insurance affiliation. We estimated the age of patients at diagnosis using the date of birth and divided it into five-year intervals. Participants who were diagnosed under the age of 15 were considered "children," while those aged 15 to 18.9 were considered "adolescents." VIGICANCER classifies sex and race/ethnicity (Afro-descendants vs. others) based on information from the medical record.VIGICANCER considers "place of residence" where the patient lived for at least six months before being diagnosed with cancer. We categorized the patients' residential areas into those living in the capital city of a department with one or more POUs, those living in municipalities of departments with POU, those without POU, and patients residing abroad. We divided the cities based on the number of reported cases per year: large cities with ≥100 and small cities with <100 cases.

Colombia compulsory health insurance system is divided into contributory (for employees and self-employed) and subsidized categories (informal and low-income self-employed workers) (24, 25). Both insurance plans in Colombia cover 90% of the population.

TABLE 1 International Classification of Diseases for Oncology third edition (ICD-O-3) morphology codes for brain tumors, grouped by the International Classification of Childhood Cancer.

International Classification of Childhood Cancer			ICD-O-3 morphology codes
III.a.	**Ependymomas and choroid plexus tumors**		
	III.a.1.	Ependymomas	9383, 9391-9394, 9396
	III.a.2.	Choroid plexus tumor	9390
III.b.	**Astrocytomas**		9384, 9400-9411, 9420-9424, 9425, 9440-9442; 9380 (including optic glioma)
III.c.	**Intracranial and intraspinal embryonal tumors**		
	III.c.1.	Medulloblastomas	9470-9472, 9474-9478, 9480
	III.c.2.	Primitive neuroectodermal tumors	9473
	III.c.3.	Medulloepitheliomas	9501-9504
	III.c.4.	Atypical teratoid/ rhabdoid tumors	9508
III.d.	**Other gliomas**		
	III.d.1.	Oligodendrogliomas	9450, 9451, 9460
	III.d.2.	Mixed and unspecified gliomas	9380 (excluding optic glioma)
	III.d.3.	Neuroepithelial glial tumors of uncertain origin	9381, 9430, 9431, 9444, 9445
III.e.	**Other specified intracranial and intraspinal neoplasms**		
	III.e.1.	Pituitary adenomas and carcinomas	8158, 8290, 8270-8281, 8300
	III.e.2.	Tumours of the sellar region (craniopharyngiomas)	9350-9352, 9432, 9582
	III.e.3.	Pineal parenchymal tumors	9360-9362, 9395
	III.e.4.	Neuronal and mixed neuronal-glial tumors	9412, 9413, 9492, 9493, 9505-9507, 9509
	III.e.5.	Meningiomas	9530-9539
III.f.	**Unspecified intracranial and intraspinal neoplasms**		8000-8005

People not included in the above categories have health insurance through a government special plan for police, military, teachers, government employees, or private insurers. Around 4% of citizens are uninsured (26).

For CNS tumors we also included specific variables such as WHO grade (I to IV) (23), type of surgical procedure, amount of residual disease after surgery, receipt of adjuvant radiation therapy and/or chemotherapy. Only surgical procedures with diagnostic or oncological intention were registered (including biopsy-only procedures). Medulloblastoma was classified as "high" risk if the age at diagnosis was less than three years and/or gross total resection was not achieved with a residual tumor greater than 1.5 cm.

Follow-up and outcomes

VIGICANCER conducts active follow-up every three months to monitor of the patient's health status and gather information on the outcome variables. If VIGICANCER loses contact with a patient, passive surveillance is started using two different governmental social security information platforms to verify their vital status.

Four outcomes are measured: mortality, relapse, treatment abandonment and occurence of second neoplasms. Mortality is further classified into three categories: resulting from the tumor (caused by relapse or progressive disease), unrelated to the tumor occurring during cancer treatment, and unrelated to the tumor after cancer treatment completion. VIGICANCER uses the definition of treatment abandonment published by the International Society of Pediatric Oncology (27).

Statistical analysis

We followed the group III categorization from the International Childhood Cancer Classification third version (ICCC-3) (28). In addition, we present information on supratentorial gliomas, which we have grouped according to WHO malignancy classification.

Crosstabulations were carried out between tumor groups and each variable. We used the maximum likelihood test or Fisher's exact test to compare proportions, depending on the sample size.

For survival analyses, we estimated the time from the date of diagnosis to either the date of the event of interest or the last contact date for those without an event. The analysis cutoff date was August 31, 2023. We treated patients who abandoned cancer treatment whose vital status could not be verified as informed censorship and assigned an event at the treatment abandonment date. Patients lost to follow-up after cancer treatment were included in the analyses as censored observations if their vital status could not be determined through passive surveillance. Patients who were transferred to a non-VIGICANCER city during follow-up were also censored, however if their vital status was determined through passive surveillance, they were not censored in the analysis.

We used Kaplan-Meier to estimate the observed OS. We stratified survival by each variable and carried out the hypothesis testing of equal survival using the log-rank test.

We used conditional logistic regression to explore the potential association between partial or gross total resection and independent variables. Also, we evaluated whether if the association between brain stem tumors and Afro-descendant ethnicity was independent. We used as the grouping variable the city where the cases were registered. Additionally, we examined the independent prognostic capacity of the included variables by estimating adjusted hazard ratios (aHR) through multivariate proportional Cox's hazards

regression stratified by city and year of diagnosis. We evaluated the proportional hazards assumption for each model (29). We used STATA® v.17.0 and estimated 95% confidence intervals and considered a two tailed p value <0.05 as significant.

Results

During the study period, VIGICANCER registered 7025 patients, including 989 primary CNS tumors, which comprised 879 children and 110 adolescents. Of the 989 CNS tumors registered, 985 had information available for follow-up. The median follow-up period for those still alive was 39 months, with a maximum of 114 months.

Cohort median age was 9 years (IQR 4.8-12.6), 53% of patients were males, 8% Afro-descendants, 41% living in a city with POU, and 47% with subsidized health insurance (Table 2). In Figure 1, we show the flowchart of patients distributed by topography and Table 3 ICCC grouping. The cerebrum (including the diencephalon) was the most commonly involved location (47%), followed by the cerebellum (29%), and brain stem tumors (12%). Cerebellar tumors were more frequent in boys (58% vs. 51% p=0.04) and brain stem tumors most frequent in girls (56% vs. 45%; p=0.02). Afro-descendants presented with more infratentorial tumors (cerebellar 38% and brain stem tumors 27%) compared to others. The frequency of Afro-descendant ethnicity in brain stem tumors was 17% and in the other category of 6% (p<0.01), with an aOR of 2.1 (95% CI, 1.2-3.7).

Overall, 91% of patients had a surgical procedure; patients with the lowest rates of surgical resections were those with brain stem tumors (64%; p<0.01), of which 87% were partial resection or biopsy-only procedures. Gross total resection was attained in 44% of cases included in the cohort, as shown in Table 2, and in 33% of patients under three years of age. Patients with residual tumor >1.5 cm were found in 56% of those with partial resections.

Three and five-year OS of the entire cohort were 57% (95% CI, 54-60) and 54% (95% CI, 51-58), respectively, as shown in Table 4. Children (<15 years) and adolescents (15-18.9 years) had similar 5-year OS (53% vs. 54%). Children under 24 months of age had a lower five-year-OS than older children (43% vs. 55%; P < 0.01). However, after adjusting for other variables, the aHR was 1.3 (95% CI, 0.8-2.0).

Patients who achieved gross total resection had a higher 5-year OS of 76% (95% CI, 70 - 80) than those with a partial resection (48%; 95% CI, 41-54) and than the group with biopsy only [30% (95% CI, 21-39)]. Patients who did not achieve gross total resection had a higher mortality risk with an aHR of 2.8 (95% CI, 2.1-3.8) while those who had biopsy only had an aHR of 4.8 (95% CI, 3.3-7.0). Cases registered as not receiving radiation therapy were independently associated with higher mortality risk with an aHR of 2.3 (95% CI, 1.7-3.0). WHO grading was also associated with increased risk of death with aHR for grade II of 2.7 (95% CI, 1.7-4.4), for grade III of 7.4 (95% CI, 4.7-11.8), and grade IV of 6.4 (95% CI, 4.2-9.8); as shown in Table 5. We did not observe significant differences by sex, ethnicity, place of residence, health insurance type, year of diagnosis, or receipt of chemotherapy. Figure 2 displays survival curves for cerebral, cerebellar, and brainstem tumors, with the worst survival (aHR of 2.1, 95% CI: 1.4-3.0).

TABLE 2 Sociodemographic characteristics of the cohort.

Characteristics	N[a]	n	%
Age (in years)	989		
<1		38	4
1-4		219	22
5-9		322	33
10-14		300	30
15-18.9		110	11
Sex	989		
Boys		528	53
Girls		461	47
Afro-descendant	947		
Yes		72	8
No		875	92
Place of residence	984		
Capital city with POU[b]		400	41
Cities from a department with POU in the capital city		346	35
Cities from a department without POU		231	23
Other country		7	1
City size (cases/year)[c]	989		
≥ 100		764	77
<100		225	23
Health insurance type	972		
Contributory		443	46
Subsidized		456	47
Private insurance		23	2
Special insurance		39	4
Uninsured		11	1
International insurance		0	0
Gross total resection	799		
Yes		349	44
No		450	56

[a]N, Total number of cases; [b]POU, Pediatric Oncology Unit; [c]Number of cases registered per year.

Ependymomas and choroid plexus tumor

During the study period, 106 ependymomas and 13 choroid plexus tumors were registered, representing 12% of all CNS tumors.

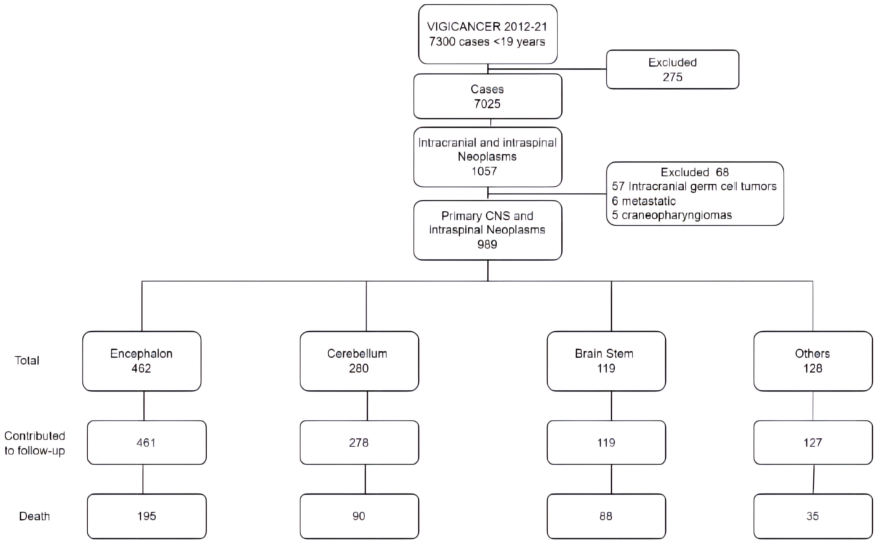

FIGURE 1
Flow chart of patients included in the analyses by topography.

TABLE 3 Distribution of primary CNS tumors in the cohort. The aggrupation is based on the International Classification of Childhood Cancer third version.

International Classification of Childhood Cancer			Total	
			n	%
III.a.	**Ependymomas and choroid plexus tumors**			
	III.a.1.	Ependymomas	106	11
	III.a.2.	Choroid plexus tumors	13	1
III.b.	**Astrocytomas**		357	36
III.c.	**Intracranial and intraspinal embryonal tumors**			
	III.c.1.	Medulloblastomas	201	20
	III.c.2.	Primitive neuroectodermal tumors	31	3
	III.c.3.	Medulloepithelioma	2	
	III.c.4.	Atypical teratoid/rhabdoid tumors	16	2
III.d.	**Other gliomas**			
	III.d.1.	Oligodendrogliomas	21	2
	III.d.2.	Mixed and unspecified gliomas	99	10
	III.d.3.	Neuroepithelial glial tumors of uncertain origin	20	2
III.e.	**Other specified intracranial and intraspinal neoplasms**			
	III.e.1.	Pituitary adenomas and carcinomas	2	0
	III.e.2.	Tumours of the sellar region (craniopharyngiomas)	0	0
	III.e.3.	Pineal parenchymal tumors	22	2
	III.e.4.	Neuronal and mixed neuronal-glial tumors	41	4
	III.e.5.	Meningiomas	9	1
III.f.	**Unspecified intracranial and intraspinal neoplasms**			
	—	Intraespinal neoplasms	26	3
	—	Unspecified intracranial	23	2
		Total	989	100

(Continued)

TABLE 3 Continued

This group of tumors was most frequently diagnosed in children under three years of age vs. older age [21% vs. 11%; aOR 2.3 (95% CI, 1.5-3.8)]. We did not find differences between sex, ethnicity, insurance type, place of residence, or year of diagnosis.

Ependymomas WHO grading II were the most frequent at 49%, followed by grade III at 40%, and grade I at 11%. Out of the 110 cases for which information was available, 109 received a surgical intervention. In 47% of the cases, resection was considered partial, and in 7%, only a biopsy was performed.

The 5-year OS for patients with ependymomas and choroid plexus tumors was 57% (95% CI, 46-67). Table 4 shows survival according to the WHO's scale. Patients under the age of 11 years had a lower 5-year OS rate of 47% (95% CI, 34-59) compared to older patients with a rate of 79% (95% CI, 55-91).

In the group that underwent surgical intervention, those with gross total resection had 5-year OS of 73% (95% CI, 54-85), which was higher than those with partial resection or biopsy only intervention [48% (95% CI, 33-61)].

In the multivariate analysis, patients under the age of 11 years [aHR of 4.4 (95% CI, 1.2-15.7)], those with subtotal resection [aHR

TABLE 4 Overall survival at 36 and 60 months of the most common CNS tumors by WHO grading.

Tumor morphology	Scale	N[a]	n[b]	D[c]	Overall survival			
					36 months		60 months	
					%	(95% CI)	%	(95% CI)
All tumors	—	989	985	408	57	(54 – 60)	54	(51 – 58)
Ependymomas and choroid plexus tumors	**Total**	119	118	44	62	(52 – 71)	57	(46 – 67)
	I	16	16	2	88	(59 – 97)	88	(59 – 97)
	II	59	59	20	65	(49 – 77)	61	(44 – 74)
	III	44	43	22	49	(32 – 64)	40	(23 – 56)
Astrocytic tumors	**Total**	358	355	157	55	(49 – 60)	52	(47 – 58)
	I	157	157	22	86	(79 – 91)	84	(77 – 90)
	II	64	62	25	60	(46 – 72)	57	(42 – 69)
	III	47	47	37	16	(7 – 28)	16	(7 – 28)
	IV	82	81	68	18	(10 – 27)	14	(7 – 23)
	Missing	8	8	5	—	—	—	—
Other gliomas (including gliomas NOS)	**Total**	117	117	67	39	(30 – 49)	29	(15 – 44)
	I-II	51	51	15	68	(52 – 80)	46	(11 – 76)
	III-IV[d]	40	40	35	11	(6 – 25)	—	—
	Missing	26	26	17	38	(20 – 56)	31	(13 – 51)
Embryonal tumors	IV	249	249	101	58	(51 – 64)	56	(49 – 63)
Medulloblastomas	IV	201	201	70	63	(55 – 70)	61	(53 – 68)
Primitive neuroectodermal tumors	IV	31	31	16	49	(30 – 65)	49	(30 – 65)
Neuronal and mixed neuronal-glial	I-III	41	41	10	75	(58 – 86)	75	(58 – 86)
Pineal parenchymal tumors	I-IV	24	24	8	65	(42 – 81)	59	(36 – 77)

[a]. N, Total number of cases; [b]. n, number of cases which contributed to follow-up; [c]. Deaths during the study period; [d]. Twenty-four months survival estimates.

of 2.9 (95% CI, 1.1-7.1)], and those with infratentorial location [aHR of 3.5 (95% CI, 1.1-10.8)], were independently associated with an increased rate of death.

Astrocytoma, oligodendrogliomas, mixed and unspecified gliomas, and neuroepithelial glial tumors of uncertain origin

Astrocytic tumors represented 36% of all CNS tumors, and were classified as WHO grade I in 44%, grade II in 18%, grade III in 13%, grade IV in 23%; and data missing in 2% of cases. Supratentorial astrocytomas represented 47% of all CNS tumors. Two-thirds of astrocytic tumors occurred among children 5 to 14 years of age and were slightly more frequent in boys (53%) than in girls. Total resection was achieved in 36% of cases.

Two percent of CNS tumors were oligodendrogliomas, 10% mixed and unspecified gliomas, and 2% neuroepithelial glial tumors of uncertain origin (Table 3). Oligodendrogliomas were most commonly diagnosed in children over ten years old (71%) and had a similar sex distribution to other patients in the cohort. Additionally, 76% of these tumors were supratentorial, and 60% were classified as WHO grade II. Mixed and unspecified gliomas were most frequent between 5 to 9 years of age (42%). Sixty percent ocurred in girls, which was a higher frequency than for other CNS tumors (40%; p<0.01), with similar distribution between supra and infratentorial locations, and the majority were grade I (63%). Neuroepithelial glial tumors of uncertain origin were found in 90% of patients over five years old, with no sex predominance. Overall, 80% of tumors were supratentorial and 72% were WHO grade I.

Five-year OS for astrocytic tumors and other gliomas is detailed in Table 4, and OS survival curves for supratentorial glioma by WHO grading are shown in Figure 3.

For supratentorial gliomas, the fact of not attaining gross total resection was independently associated with a higher risk of death with an aHR of 3.7 (95% CI, 2.3-5.7).

Intracranial and intraspinal embryonal tumors

Embryonal tumors comprised 25% of all CNS tumors. The majority of these were medulloblastomas at 81%, followed by

TABLE 5 Multivariate Cox's proportional hazards regression models[a].

Variables		Model 1		Model 2	
		HR[b]	(95% CI)	HR	(95% CI)
Gross total resection	Total	**Ref.**		**Ref.**	
	Subtotal	2.7	(2.0 – 3.7)	2.8	(2.1 – 3.8)
	Biopsy-only	5.1	(3.5 – 7.5)	4.8	(3.3 – 7.0)
	Missing	6.3	(2.0 – 19.3)	5.4	(1.9 – 15.8)
Brainstem tumors vs. others		2.1	(1.4 – 3.0)	2.0	(1.3 – 2.8)
WHO grading	I	**Ref.**		**Ref.**	
	II	2.8	(1.7 – 4.6)	2.7	(1.7 – 4.4)
	III	7.7	(4.8 – 12.2)	7.4	(4.7 – 11.8)
	IV	6.5	(4.2 – 10.1)	6.4	(4.2 – 9.8)
	Missing	2.6	(1.2 – 5.7)	2.5	(1.1 – 5.6)
Receipt of adjuvant radiation therapy	Yes	**Ref.**		**Ref.**	
	No	2.1	(1.5 – 2.9)	2.3	(1.7 – 3.0)
	Missing	0.3	(0.0 – 3.2)	0.8	(0.2 – 3.0)
Age <2 vs. ≥2 years old		1.3	(0.8 – 2.0)		
Boys vs. girls		1.1	(0.8 – 1.4)		
Afro-descendant	No	**Ref.**			
	Yes	0.6	(0.4 – 1.0)		
	Missing	0.7	(0.1 – 6.1)		
Other vs. capital with pediatric oncology unit		1.0	(0.8 – 1.3)		
Uninsured vs. insured		0.7	(0.2 – 2.2)		
Receipt of adjuvant chemotherapy	Yes	**Ref.**			
	No	1.1	(0.8 – 1.5)		
	Missing	3.0	(0.4 – 22.7)		

[a]Regression analyses performed over the patients that had any kind of surgical intervention 814 cases. Model 1, saturated model with 780 cases model; Model 2, more parsimonious model with 789 cases; [b]HR, hazard ratio.

primitive neuroectodermal tumors at 12%, atypical teratoid/rhabdoid tumors at 6%, and medulloepitheliomas at only 1%.

We found that one-third of all embryonal tumors were diagnosed in children under five years of age. Among this age group, the most common embryonal tumors were atypical teratoid/rhabdoid tumors (81%), followed by primitive neuroectodermal tumors (47%) and medulloblastomas (25%). Most of these cases occurred in boys (61%), and 10% were found in individuals of African descent.

Median age in children with medulloblastoma was 8 years (IQR, 5-12), 63% were boys and 10% were afro-descendants. Classic medulloblastoma was the most frequent histology (78%), followed by desmoplastic (16%), large cell (4%), medullomyoblastoma (1%), and not otherwise specified (1%). Medulloblastomas were totally resected in 58% of the patients. Children under three years of age had a higher risk of not achieving gross total resection, with an aOR of 3.1 (95%, 1.0-9.2). We did not observe an association between resection and sex, ethnicity, insurance type, city size, or year of diagnosis. Among those who did not undergo gross total resection, 13% underwent biopsy only. A residual tumor greater than 1.5 cm was found in 47% of cases. Radiation therapy and chemotherapy were administered as adjuvant therapy in 76% of patients with medulloblastoma, with radiation therapy given in 59% of high-risk patients and in 29% of cases under three years old.

Table 3 shows the five-year OS for embryonal CNS tumors. Out of the 16 individuals diagnosed with atypical teratoid/rhabdoid tumors, only one has survived after a follow-up of 23 months. Meanwhile, the two patients who had medulloepithelioma have survived for 51 and 108 months since their diagnosis.

Children under the age of three who had medulloblastoma had a lower 5-year OS of 32% (95% CI, 11-55) compared to older children with OS of 65% (95% CI, 56-72) and an increased risk of death with an aHR of 2.6 (95% CI, 1.2-5.7). Those between the ages of 1 and 4.9 had a 5-year OS of 49% (95% CI, 43-63). Patients with contributive health insurance had a 5-year OS of 67% (95% CI, 55-77), while those with subsidized insurance had an OS of 57% (95% CI, 45-67) and an increased risk of death with an aHR of 2.1 (95% CI, 1.1-4.1).

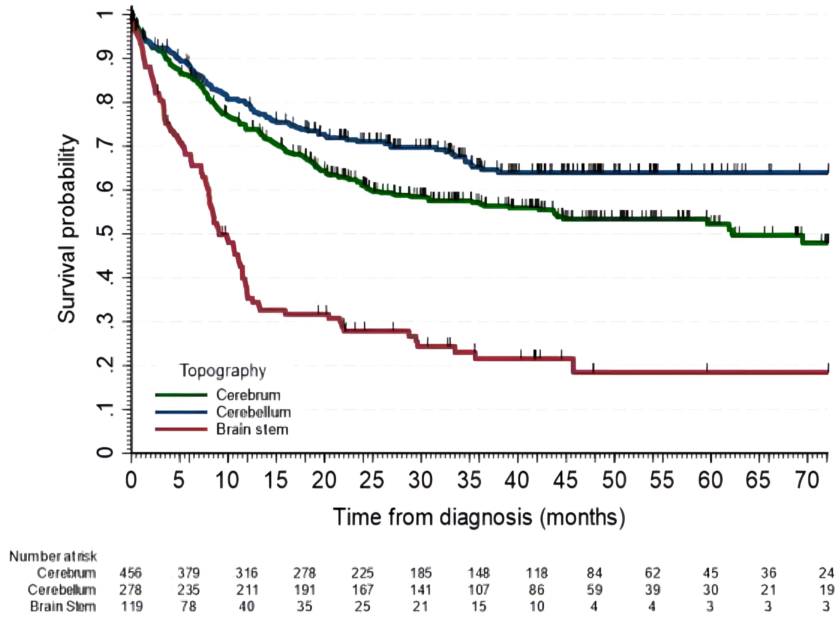

FIGURE 2
Overall survival of patients with cerebral, cerebellar and brain stem tumors. Five-year OS for cerebral tumors was 52% (95% CI, 47-58), for cerebellar 64% (95% CI, 58-70) and for brain stem tumors of 19% (95% CI, 11-28).

Children with classic and desmoplastic types had similar 5-year OS (63% vs. 61%). Eight patients had large cell medulloblastomas, of which only three were alive with a maximum follow-up of 48 months. Five-year OS for children under three years of age was 32% (95% CI, 11-55), lower than the older group [65% (95% CI, 56-72)]. Similarly, for the high-risk group, OS was 40% (95% CI, 26-53) whereas for the standard group it was 70% (95% CI, 61-78) as displayed in Figure 4. Those without gross total resection showed a 5-year OS of 54% (95% CI, 41–65), which was lower than those with total resection of 70% (95% CI, 60-79). Children under fiver years of age and without gross total resection had a 5-year OS of 27% (95% CI, 8-49), compared to those with gross total resection who had an OS of 64% (95% CI, 43-79). High-risk medulloblastomas showed an increased mortality risk with aHRs of 3.9 (95% CI, 2.3-6.8), in

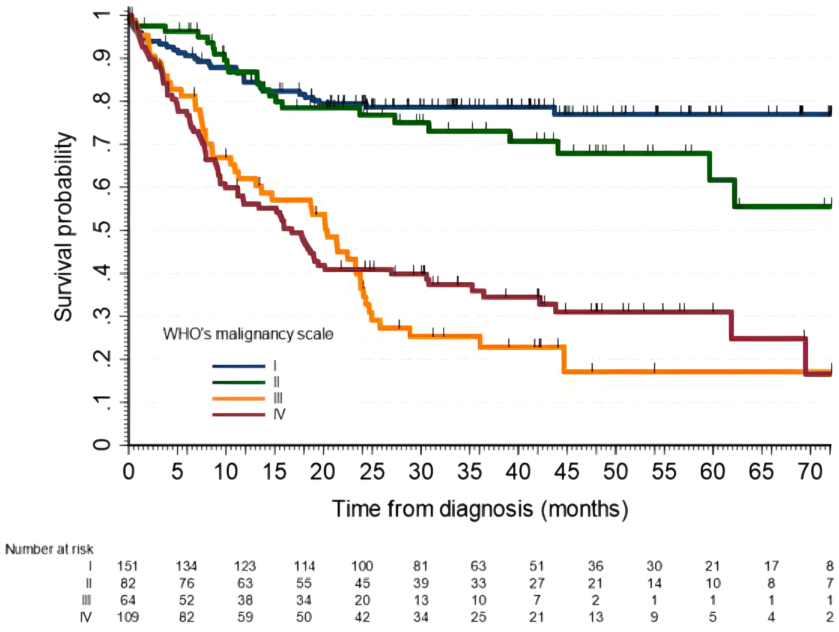

FIGURE 3
Overall survival of patients with supratentorial gliomas by the WHO malignancy scale. Five-year OS for grade I was 77% (95% CI, 69-83), for grade II was 62% (95% CI, 44-75), grade III 17% (95% CI, 7-32) and grade IV 31% (95% CI, 22-41).

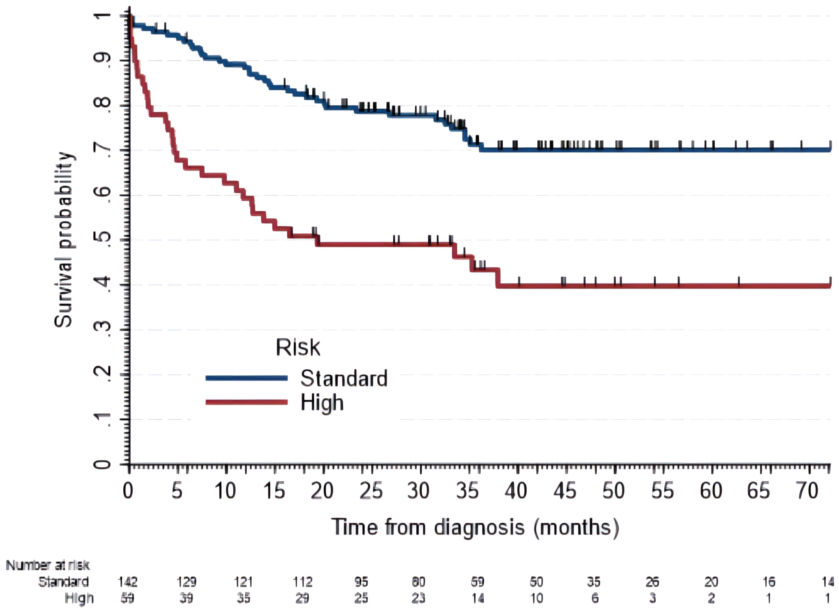

FIGURE 4
Overall survival of patients with medulloblastomas by risk classification. Five-year OS for the standard risk was 70% (95% CI, 60-78) and for high risk was 40% (95% CI, 26-54).

children with subsidize insurance of 2.0 (95% CI, 1.1-3.7) and in those without insurance of 3.5 (95% CI, 1.0-12.0).

Other tumors

Three percent of CNS tumors were spinal cord and cranial nerve tumors, 2.5% were pineal tumors, 1% (13 cases) were optic gliomas, and less than 1% (9 cases) were meningiomas. Pineal tumors showed the lowest 5-year OS in this group at 59% (95% CI, 36-77). All optic gliomas were alive at the end of the study period.

Discussion

In this national multicenter prospective cohort in a Latin American middle-income country, we found that children and adolescents with primary malignant and non-malignant CNS tumors had 54% five-year survival after diagnosis. This survival estimate is lower than estimates reported in high-income countries, which range between 70% and 80% (12), with the Central Brain Tumor Registry of the United States (CBTRUS, cohort 2014 to 2018) estimated at 83% (30). EUROCARE-6 survival for CNS tumors has been reported at approximately 60%, with significant heterogeneity across countries (15).

The CONCORD program for Colombia (2000 to 2014) reported a similar survival of approximately 47% (36% to 58%) based on data from four PBCRs(12). The similarities between VIGICANCER and CONCORD survival estimates suggest that VIGICANCER can approximate population-based survival probabilities. It also indicates that more progress needs to be made in childhood primary CNS tumor survival in our country. According to CONCORD-3 estimates (12), the results are comparable to Ecuador (48%) and Mexico (37%) but lower than Argentina (63%). However, the ROHA reports a five-year OS for CNS tumors of 56%, closer to our estimate (16).

We observed an almost three times increase in risk of death in children not achieving gross total resection. The prognostic role of gross total resection in children is not entirely settled (31–34). Uncertainty about its role increases with the progress into molecular classification and directed therapy (32). The Cross-Border Neuro-Oncology Program (San Diego, California- Tijuana, Mexico) (35) showed an increasing survival trend associated with attaining a higher proportion of patients with gross total resection. In our cohort, we did not find an association between the patient's age and gross total resection.

Ependymomas and choroid plexus tumor

We found that the five-year OS for ependymomas and choroid plexus tumors was 57%, lower than the one reported by EUROCARE-5 of 70% (36), and the one cited by CBTRUS of 89% (30). However, our survival estimates are similar to the ones described by ROHA of 61% (16). Nevertheless, patients with WHO grade I malignancy in our group had a five-year OS of 92%, which is congruent with the 97% reported in EUROCARE-5 (36).

Astrocytic tumors

We found a 52% five-year OS for astrocytic tumors, which is 28% lower than the reported by EUROCARE-5 of 80% (36). The main survival gap in these tumors (EUROCARE-5 vs. VIGICANCER) was for grade I (11% lower in VIGICANCER)

and for grade II (18% lower in VIGICANCER), which are the most curable astrocytic tumors (15). Survival for all supratentorial gliomas was 49%, with OS for high-grade gliomas being approximately half of the one reported by CBTRUS (15% vs. 33%) (30). Patients with astrocytic tumors have a three to four times higher risk of death if they do not achieve a complete gross total resection, regardless of other factors.

Medulloblastoma

For medulloblastoma, the five-year OS was 61%, which is lower than the current estimate of 74% (72-75%) for under 19 years in the United States (2014-2018) (30), and close to ROHA's estimate of 52% (16). We did not find higher survival estimates in children with desmoplastic medulloblastoma, contrasting with published literature. In our cohort, survival outcomes in children with medulloblastoma were significantly influenced by age, with those under three years old having only a 32% five-year OS. The group between one to four years old showed significantly lower OS (49%) compared to the observed survival probability in the United States (30). Children under age five with medulloblastoma who did not attain gross total resection had a five-year OS of only 27%, compared to 64% for those with gross total resection. This is consistent with the survival (64%) reported in the United States for children in the same age group. The difference in survival between our estimates and those of higher-income countries could be, at least, partially explained by the ability to achieve a gross total resection (35).

High-risk medulloblastoma classification includes two strong independent prognostic factors: age and achieving a gross total resection. Patients classified as high-risk had nearly four times the risk of death compared to those classified as standard risk. We also observed a higher risk of death for those without health insurance, underscoring the importance of a universalized health system to improve clinical outcomes (37). Since 2018, we included molecularly defined histopathologies for medulloblastoma in VIGICANCER. Nevertheless, currently the routine application of molecular classification is seldom used in Colombia and, therefore, we do not have enough cases for analysis. We expect that the completeness of this variable will increase in future years.

Other embryonal tumors

Primitive neuroectodermal tumor survival was 49% which is like the figure reported by EUROCARE-5 of 41% (36), but lower than the reported by the CBTRUS of 64% (30). Atypical teratoid/rhabdoid tumor has a dismal prognosis with only 1 patient surviving in our cohort, while survival in EUROCARE (36) and CBTRUS were 23% and 33%, respectively (30).

In conclusion, our survival estimates are congruent with those reported in the German 1990–1999 cohort; with OS for astrocytic grade I-II at 82%, grade III-IV at 24%, medulloblastomas at 53%, and ependimomas at 57% (6). Brainstem tumors had a five-year OS of 19%, which is close to the one reported by ROHA of 22% (16), but much lower compared to reports by CBRTUS of 58% (30).

Our findings support the urgent need to improve treatment for childhood CNS tumors in Colombia. Despite universal health coverage and granted access to childhood cancer treatment, delays in diagnosing CNS tumors persist due to inadequate primary care services and inefficent referral pathways due to several health system organizational barriers. Therefore, strengthening primary care services to quickly detect childhood brain tumors and a straightforward referral to a higher complexity healthcare facility can improve clinical outcomes (38, 39). It is also crucial to enhance diagnostic capacities (number of neuropathologists, centralizing the diagnosis, standardizing reports, including molecular diagnosis), neurosurgical (increasing the proportion of gross total resections and decreasing sequelae), and clinical supportive care capacities, social support services, as well as timely access to radiation therapy. One way going forward is to centralize these patients in specialized centers (38, 40–42). However, in Colombia, this option is currently hindered by the fragmented healthcare system and the dependence of clinical services on unstable insurance contracts.

Study limitations

Our study found that the distribution of tumors based on morphology, topography, and demographics was similar to other reports. However, making direct comparisons with published literature has several challenges. Our study did not include craniopharyngiomas and intracranial germ cell tumors, and we looked at both malignant and non-malignant primary CNS tumors. Our findings were based on pathology reports from treatment centers and did not undergo centralized diagnostic validation. This report is based on 27 POUs, and although those with the highest number of cases diagnosed per year in Colombia are in VIGICANCER, not all POUs are included. Additionally, the population representation of cases decreases as we analyze data from early periods, since the addition of cities to VIGICANCER has been a gradual process over the last decade. Therefore, it is worth noting that our study was not absolutely population-based and cannot estimate the incidence rates of the tumors we examined. In addition, there may be some uncertainty regarding the accuracy of our survival estimates compared to the population estimates. However, as stated previously, our survival estimates fall within the CONCORD (13) population-based survival ranges, indicating that if there was a selection bias, it did not substantially affect our assessments. We consider that VIGICANCER's underestimation of the number of CNS tumors affected mainly adolescents, as its primary data source are POUs. Some adolescents with cancer in Colombia continue to receive treatment from adult oncologists. In Colombia, we have great uncertainty about how many patients with brain tumors are not diagnosed in the country and are contributing to the incidence gap. Statistical modeling has estimated this incidence gap to be 29% for upper-middle-income countries (38). Nevertheless, VIGICANCER's comprehensive geography coverage, high number of participating centers, and low cohort attrition are strengths of this report. We estimate that currently, VIGICANCER covers about 55% of all childhood cancers expected to occur in Colombia.

In summary, this report presents the survival estimates and prognostic factors of primary CNS tumors in Colombian children and adolescents. Overall, age under two years, extent of resection, and WHO's grade were independent prognostic factors. We used data from VIGICANCER, a surveillance system for the systematic monitoring of clinical outcomes of pediatric cancer patients in Colombia. This system provides empirical data that can be used to inform cancer control policies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

OR: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. VP: Data curation, Investigation, Methodology, Project administration, Validation, Writing – review & editing. JA: Funding acquisition, Project administration, Writing – review & editing. CP: Writing – review & editing. EC-B: Writing – review & editing. JL: Writing – review & editing. AS: Writing – review & editing. CP: Funding acquisition, Resources, Writing – review & editing. CN: Writing – review & editing. PR: Writing – review & editing. XC: Writing – review & editing. AC: Writing – review & editing. DE-P: Writing – review & editing. DV: Writing – review & editing. MÁ: Writing – review & editing. JF: Writing – review & editing. PA: Conceptualization, Methodology, Writing – review & editing. LB: Conceptualization, Investigation, Methodology, Software, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Capacity building for pediatric neuro-oncology in Pakistan- a project by my child matters program of Foundation S

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Introduction: Initiated in June 2019, this collaborative effort involved 15 public and private sector hospitals in Pakistan. The primary objective was to enhance the capacity for pediatric neuro-oncology (PNO) care, supported by a My Child Matters/Foundation S grant.

Methods: We aimed to establish and operate Multidisciplinary Tumor Boards (MTBs) on a national scale, covering 76% of the population (185.7 million people). In response to the COVID-19 pandemic, MTBs transitioned to videoconferencing. Fifteen hospitals with essential infrastructure participated, holding monthly sessions addressing diagnostic and treatment challenges. Patient cases were anonymized for confidentiality. Educational initiatives, originally planned as in-person events, shifted to a virtual format, enabling continued implementation and collaboration despite pandemic constraints.

Results: A total of 124 meetings were conducted, addressing 545 cases. To augment knowledge, awareness, and expertise, over 40 longitudinal lectures were organized for healthcare professionals engaged in PNO care. Additionally, two symposia with international collaborators and keynote speakers were also held to raise national awareness. The project achieved significant milestones, including the development of standardized national treatment protocols for low-grade glioma, medulloblastoma, and high-grade glioma. Further protocols are currently under development. Notably, Pakistan's first pediatric neuro-oncology fellowship program was launched, producing two graduates and increasing the number of trained pediatric neuro-oncologists in the country to three.

Discussion: The initiative exemplifies the potential for capacity building in PNO within low-middle income countries. Success is attributed to intra-national twinning programs, emphasizing collaborative efforts. Efforts are underway to establish a national case registry for PNO, ensuring a comprehensive and organized approach to monitoring and managing cases. This collaborative initiative, supported by the My Child Matters/Foundation S grant, showcases the success of capacity building in pediatric neuro-oncology in low-middle income countries. The establishment of treatment protocols, fellowship programs, and regional tumor boards highlights the potential for sustainable improvements in PNO care.

KEYWORDS

pediatric neuro-oncology, capacity-building, multidisciplinary tumor boards, treatment protocols, fellowship program, low-middle income countries, collaborative initiative

Introduction

Pediatric neuro-oncology (PNO), a field dedicated to addressing central nervous system cancers in the 0-18 age group, carries immense significance worldwide. Pediatric brain tumors represent the leading cause of cancer related mortality in high income countries (HICs) (1). However, the gravity of the situation is even more pronounced in lower-middle income countries (LMIC) such as Pakistan, due to the scarcity of resources and facilities dedicated to PNO care.

In Pakistan, a country with the fifth-largest population in the world, healthcare resources are severely limited (1, 2). The doctor-to-patient ratio stands at 1.1:1000 and over 58% of the population must pay for healthcare expenses out of their own pocket, rendering treatment for complex diseases such as pediatric neuro-oncology a privilege for many (3, 4).

At the time of initiation of this capacity building effort, there were 13 Pediatric Oncology centers in Pakistan, 22 pediatric oncologists, and one trained pediatric neuro-oncologist. While there were Pediatric Hematology/Oncology fellowship programs in Pakistan, there was no dedicated fellowship for Pediatric Neuro-oncology. Additionally, there are no specialized pediatric neurosurgeons in the country and no hospitals other than AKUH with dedicated Multidisciplinary Teams (MDT) for managing children with brain tumors.

In Pakistan, nearly 39 percent of the population is under the age of 18 and data on PNO cases is scarce. A recent analysis of the 2020 GLOBOCAN approximated that brain tumors were the most prevalent cause of cancer-related mortality in a majority of the Eastern Mediterranean region (including Pakistan), and that brain tumors had an estimated age-standardized incidence rate of 1.3 per 100,000 patients (5). Studies conducted in single-center settings

have revealed the prevalence of primary brain tumors among pediatric cancers to be around 20-22 percent (6, 7). Additionally, the overall survival rate for these cases remains low, hovering at approximately 25 percent (8). Contributing factors such as delayed diagnoses, inadequate resources, training and a lack of multidisciplinary coordination among healthcare professionals warrants capacity building measures to improve patient outcomes (9).

The initiation of a twinning program in June 2014 marked a significant milestone in the collaboration between the Hospital for Sick Children (SickKids) in Toronto, Canada, and Aga Khan University Hospital (AKUH) in Pakistan. This collaborative endeavor aimed to establish multidisciplinary tumor boards (MTBs) and conduct in-depth reviews of challenging cases at SickKids, ultimately enhancing patient management and prognostication. The program signifies a dedicated effort to improve the overall quality of care through the sharing of expertise and resources between these two institutions. The program's achievements became evident through the adoption of refined and individualized management strategies, increased referrals to tertiary healthcare facilities, and the improved diagnostic facilities within the Pakistani healthcare landscape (10). Building upon the success of the SickKids collaboration, the Aga Khan University Hospital (AKUH) embarked on a mission to expand pediatric neuro-oncological care in Pakistan. This initiative was supported by a grant secured under a My Child Matters/Foundation S call in 2018.

Objectives

The objectives of this initiative were centered on establishing Pediatric Neuro-Oncology (PNO) Multidisciplinary Teams (MDTs), educating medical staff and to develop diagnostic and management guidelines in collaborating children's hospitals across Pakistan for optimal care of pediatric patients with brain tumors. This work aimed to implement National Pediatric NO Tumor Boards and monthly tumor boards in regional centers to facilitate regular discussions among MDT members for the optimization of treatment strategies. A specific focus was placed on educating clinical staff engaged in the care of children with brain tumors, with the objective of elevating the quality of care at regional levels. The overarching goal was to develop and disseminate national protocols and guidelines for various medical specialties, including Nurses, Oncologists, Histopathologists, Neurosurgeons, Radiation Oncologists, and Radiologists, thereby standardizing and improving patient outcomes. Additionally, the research aimed to enhance diagnostic capabilities in Neuroradiology and Neuropathology in regional centers to ensure accurate and timely assessments of pediatric brain tumors, contributing to a comprehensive and standardized approach to pediatric neuro-oncology care in Pakistan.

The initiative aimed to train a significant number of healthcare practitioners, with projections indicating that approximately 85-100 physicians and 40-60 nurses would receive training through workshops. Additionally, around 80-100 healthcare professionals were expected to benefit from regional tumor boards. Furthermore, a one-year fellowship training position would be initiated for specialized training in pediatric neuro-oncology at the Aga Khan University Hospital (AKUH).

Methodology

The Multidisciplinary Tumor Boards (MTBs) were established on a national scale, with at least one MDT in each province.

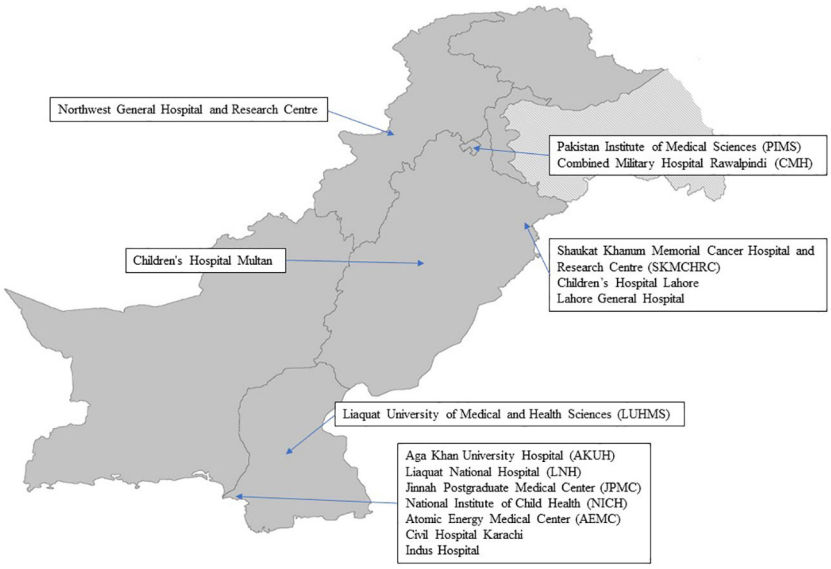

FIGURE 1
PNO Initiative: Hospitals Participating in Multidisciplinary Tumor Boards.

Collectively, these MTBs cover 76% of the total population, equivalent to 185.7 million people. With the onset of COVID-19 pandemic, the intercity MDTs transitioned to videoconferencing for their operations. Outside Karachi MTBs had an online videoconferencing format from the beginning.

The participating hospitals, depicted in Figure 1—a map showcasing all 15 hospitals—originally began with eight hospitals and later expanded to encompass a total of fifteen hospitals across four provinces. The selection criteria for these hospitals were contingent upon their existing infrastructure, requiring the presence of on-site neurosurgery and neuro-oncology departments, as well as convenient access to radiation oncology services.

The tumor boards were initially planned as monthly sessions, featuring multidisciplinary specialists from each participating institution. These sessions, intended to last approximately 60 to 90 minutes, were structured with the flexibility to increase in frequency based on capacity requirements. Notably, the 15 medical centers actively participated in three major tumor boards: Punjab Tumor Board, JPMC Tumor Boards, and LUMHS Tumor Board, each conducted separately. Centers joined the tumor board closest to them geographically for collaboration. To preserve patient confidentiality, cases were anonymized, referring only to the patient's age, gender, and diagnosis. These sessions focused on cases presenting diagnostic or treatment-related challenges, with the overarching objective of formulating comprehensive, individualized, and well-coordinated management plans. Pertinent recent medical literature was scrutinized and subsequently shared among participants to inform specific aspects of clinical decision-making. It is essential to note that all cases underwent rigorous peer review within their respective departments, constituting an additional layer in the patient safety-centered quality management process.

National and international awareness and educational initiatives were initially planned as in-person events, including Pediatric Neuro-Oncology (PNO) symposiums and workshops including workshops for nurses. However, due to the COVID-19 pandemic, these events were transitioned to a virtual format. Despite the initial intent for in-person sessions, the adaptation to virtual platforms allowed for continued implementation, including multiple online lectures, thereby ensuring the dissemination of knowledge, and fostering collaboration.

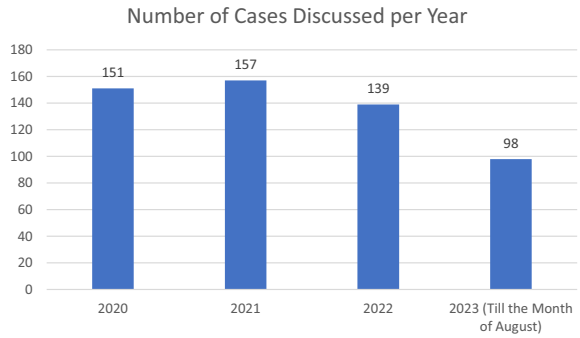

FIGURE 3
Number of Cases Discussed per year.

Results

In total, 124 Multidisciplinary Team (MDT) sessions were conducted from June 19 onwards, persisting to the present day, with the data included up to August '23. These sessions comprised 39 meetings at Jinnah Postgraduate Medical Center (JPMC), 35 sessions at Liaquat University of Medical and Health Sciences (LUMHS) tumor boards, and 50 sessions at the Punjab Tumor board (Figure 2).

The total number of cases deliberated upon amounted to 545, with an average of 4.4 cases discussed per session, spanning a range from 1 to 13 cases. Notably, the majority of cases (66%, n=358) originated from the Punjab Tumor boards, aligning with the higher participation rate of institutions in this particular tumor board. Among the cases discussed, there were 229 female patients and 316 male patients. The mean age of patients discussed was 8.92 years at JPMC, 8.8 years at LUMHS, and 7.37 years at the Punjab Tumor Boards (Figure 3).

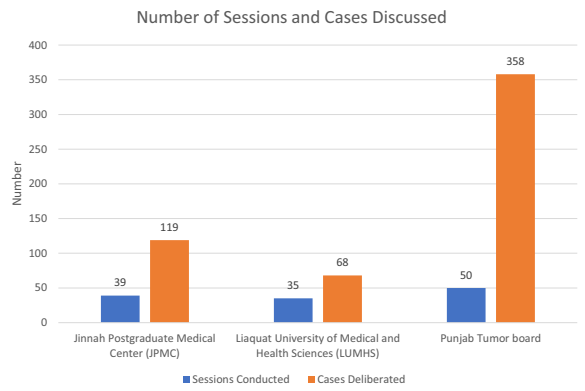

FIGURE 2
Total Sessions and Discussed Cases in Each Tumor Board.

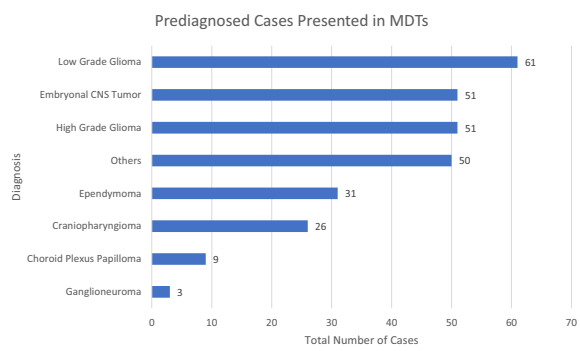

FIGURE 4
Distribution of Diagnosed Cases in Pediatric Neuro-Oncology (PNO) by Tumor Type.

Of the cases examined, 263 patients underwent discussion before receiving histopathological disease confirmation. Among this subgroup, space-occupying lesions within the posterior fossa (33%) and the supratentorial space (22%) comprised over half of the cases. Among cases (n=282) with histopathological diagnoses confirmed before discussion, there was notable heterogeneity, encompassing 48 different diagnostic categories, as shown in Figure 4.

Results of the initiative included the organization of Pediatric Neuro-Oncology (PNO) symposiums aimed at increasing national and international awareness. The inaugural virtual symposium in November 2020 attracted many in the field, bringing together 1126 participants from 58 countries. Themed 'Working Together for Better Outcomes,' it highlighted PNO's significance nationally and globally. Following the inaugural symposium, a second hybrid symposium in November 2021 aimed to establish pediatric neuro-oncology as a vital sub-specialty in lower- and middle-income countries (LMICs). Achievements included 31 international speaker presentations, multiple virtual sessions with 1,007 participants worldwide, and physical sessions with 159 participants (Table 1). These sessions covered challenges in pediatric brain tumor care and the need for multidisciplinary collaboration.

As part of the initiative's outcomes, before the COVID-19 pandemic physical workshops were conducted, engaging a total of 159 participants across four distinct sessions. Commencing in Lahore in 2019 at the Children's Hospital Lahore, the first workshop facilitated discussions on the foremost challenges associated with accessing and upholding the quality of care for pediatric brain tumor patients in resource-limited environments. Subsequent workshops took place at LUMHS in 2019, and AEMC Karachi in January 2020, both delving into the latest diagnostic, pathological, and genetic advancements to enhance the evaluation of children with brain tumors. Additionally, a dedicated physical nursing workshop was conducted in 2021.

The conversion of physical workshops to an online format also led to the development of a longitudinal lecture series, with 41 lectures attracting over 2500 participants from 17 countries. These lectures, lasting 60-90 minutes each, were delivered by subject matter experts and conducted via video conferencing software. Members were also extended invitations to monthly journal clubs organized and led by fellows at Aga Khan University Hospital (AKUH). These journal club meetings have been held monthly, commencing in 2020 and continuing up to the present date, with an ongoing frequency.

Despite a significant burden of pediatric neuro-oncology (PNO) tumors in Pakistan, the country initially had only one trained and dedicated Pediatric Neuro-oncologist. In response to this gap, a 12-month academic and clinical fellowship program was initiated at the Aga Khan University Hospital (AKUH) in 2020. The program currently offers one fellowship position annually, with plans for expansion based on its success. To date, two fellows have graduated from the fellowship program and are practicing in major cities across the country.

Another outcome facilitated by the grant is the formulation of standardized protocols specifically tailored to address various neuro-oncological tumors. These guidelines cover aspects of patient care, including clinical evaluation, imaging techniques, surgical procedures, chemotherapy regimens, and radiation therapy protocols. Furthermore, the guidelines offer insights into the administration of chemotherapeutic agents, dosage considerations, management of adverse effects, and a framework for post-treatment follow-up.

These guidelines have received official endorsement from both the Pakistan Society of Pediatric Oncology (PSPO) and the Pakistan Society of Neuro-Oncology (PASNO), for neuro-oncological

TABLE 1 Number of Participants in The Second Hybrid Symposium.

Country	Number of Participants	Country	Number of Participants
Algeria	1	Malaysia	30
Argentina	2	Mexico	14
Armenia	2	Morocco	5
Australia	8	Nepal	1
Bahrain	5	Netherlands	2
Bangladesh	3	New Zealand	1
Bolivia	1	Nigeria	1
Bosnia & Herzegovina	2	Oman	6
Brazil	1	Pakistan	563
Canada	40	Palestinian Territories	1
China	5	Peru	6
Colombia	5	Philippines	6
Croatia	2	Portugal	2
Croatia	1	Puerto Rico	2
Czech Republic	2	Qatar	4
Ecuador	1	Russia	5
Egypt	26	Saudi Arabia	45
Ethiopia	4	Slovakia	2
Germany	5	Slovenia	5
Germany	4	South Africa	12
Ghana	4	Spain	12
Guatemala	2	Tunisia	1
Honduras	2	Uganda	5
Hong Kong	10	Ukraine	11
India	5	United Arab Emirates	10
Indonesia	10	United Kingdom	15
Jordan	25	United States	45
Kuwait	4	Uruguay	2
Lebanon	3	Yemen	1
Libya	7		

conditions, including medulloblastoma, low-grade glioma, and high-grade glioma. The standardized protocols have been adopted by all 15 participating centers (11).

An additional result that was not planned included the establishment of the Children Brain Tumor Initiative Pakistan (CBTIP): a pediatric neuro-oncological network. This initiative includes the development of an online portal aimed at facilitating case registration and inquiries from patients and healthcare professionals nationwide. The project is considered a unique endeavor in its domain (12).

The dedicated CBTIP website serves as a resource for the early diagnosis and prompt referral of children suspected of or diagnosed with brain tumors. Additionally, a WhatsApp group comprising 90% of pediatric neuro-oncologists (PNO) physicians in Pakistan has been established, with 305 members as of September 2023. This group functions as a platform for knowledge sharing, seeking guidance, and staying updated on institutional developments.

Discussion

A series of studies have demonstrated the effectiveness of telemedicine and twinning programs in improving the quality of pediatric oncology care in developing countries. Al-Jadiry et al. reported significant improvements in diagnoses and management of pediatric cancer in Iraq through a partnership with Sapienza University of Rome, which included teleconsultations and pathology reviews (13). Similarly, Qaddoumi and Bouffet found that e-mail exchanges enhanced a neuro-oncology twinning program between Jordan and Canada, facilitating communication and collaboration (14). Amayiri further supported the sustainability and impact of video-teleconferencing in pediatric neuro-oncology, emphasizing the role of commitment and motivation in maintaining such initiatives (15). These studies collectively highlight the potential of telemedicine and twinning programs in bridging the gap in pediatric oncology care between developed and developing countries.

In terms of the anticipated impact, it was estimated that the initiative benefited up to 1500 pediatric patients over the course of 3 years. Beyond this direct patient impact, it improved practices of health care professionals involved in PNO care. Moreover, it was anticipated that improved clinical outcomes would influence the perspectives and priorities of governmental health authorities, fostering greater attention to the complex and underserved pediatric population with neuro-oncological conditions.

It is worth noting that a pre-tumor board management plan was not established, rendering quantitative assessment of the impact of Multidisciplinary Tumor Boards (MTBs) on altering management plans unfeasible. Nevertheless, based on the collective experience and testimonies of participants, MTBs emerged as a valuable platform for educating participants, optimizing treatment modalities at each center, and fostering the potential for referrals to institutions for further management of complex cases. All participants expressed their enthusiasm for the monthly tumor board sessions and their intent to continue this practice, showing the accrued benefits derived from this collaborative endeavor.

This initiative spans multiple institutions and referral centers, composed of healthcare providers from diverse institutions, helping to address the complex challenges posed by PNO by fostering multidisciplinary relationships. It allows physicians to communicate, coordinate, and streamline patient care across institutional boundaries. This approach recognized and utilized the capabilities of participating institutions, some specializing in radiotherapy while others in chemotherapy, and leverages these strengths to benefit patients in their own regions.

Furthermore, the Principal Investigator (PI) of the grant has played a pivotal role by keeping open lines of communication for PNO physicians to reach out with inquiries, concerns, and requests for insights 24/7. This accessibility to expert guidance has greatly enhanced the quality of care provided to pediatric neuro-oncology patients.

The advent of the website intends to grow connections between patients and physicians in this field. By swiftly connecting parents of affected children to pediatric neuro-oncology centers equipped with the necessary infrastructure, the website will effectively reduce diagnostic delays and ensures timely intervention by trained specialists, ultimately leading to improved patient outcomes. This innovative platform has the potential to make a significant impact in the field of pediatric neuro-oncology care in Pakistan and beyond, underscoring the transformative potential of collaborative initiatives (12).

Looking forward, there is a clear vision of growth in the field of pediatric neuro-oncology in Pakistan. Despite resource limitations, the goal is to equip each pediatric oncology center with dedicated pediatric neuro-oncologists, neuro-radiologists, neuropathologists, neurosurgeons, and radiation oncologists. This growth not only signifies the increasing recognition of the importance of specialized care but also underscores the commitment to providing the best possible outcomes for PNO patients.

One area that requires focused attention and advancement is the generation of pediatric neuro-oncology-related research from Pakistan. While physicians have made substantial progress in offering individualized management of each patient, there is a pressing need to translate this knowledge into published research data.

In addition to the aforementioned priorities, it is essential to emphasize the establishment and significance of a National Cancer Registry. Presently, Pakistan possesses few hospital-based cancer registries at institutions such as AKU, a city-wide Karachi Cancer Registry, and a provincial Punjab Cancer Registry. However, the development of a comprehensive National Cancer Registry is imperative to accurately capture and consolidate data on pediatric neuro-oncological cases. This unified registry will not only provide a more comprehensive and accurate representation of the landscape but also serve as a crucial tool for informed decision-making and strategic planning in the realm of pediatric brain tumor care and ultimately all cancer care.

Our recommendations encompass the establishment of robust pediatric neuro-oncology services in Pakistan, which entail infrastructural enhancements across various domains such as diagnostic imaging, histopathologic analysis, radiation treatment,

oncology services, neurosurgery, and post-treatment rehabilitation. Moreover, fostering collaboration among healthcare providers in these disciplines is crucial to deliver comprehensive multidisciplinary care, guided by locally validated protocols. Central to our approach is the emphasis on the implementation of tumor boards in all cancer hospitals in Pakistan, in alignment with our overarching goal of enhancing pediatric neuro-oncology care in LMICs (10, 16).

By sharing our experiences and successes, we hope to offer valuable insights to not only healthcare professionals and institutions within Pakistan but also to LMICs facing similar challenges in pediatric neuro-oncology care.

Our journey demonstrates the potential to pave the way for improved outcomes in the face of limited resources. We also encourage other institutions within Pakistan to consider joining the cause, contributing their expertise and resources to further strengthen the collaborative effort in addressing the pressing issue of pediatric neuro-oncology care in our region.

In summary, the Foundation S grant has demonstrated considerable success in enhancing the landscape of pediatric neuro-oncology care in Pakistan. It has fostered collaboration, established standardized protocols, and created a supportive network of healthcare professionals. However, there remains an imperative need for more programs of a similar nature to further advance research, standardize care, and ultimately improve outcomes for pediatric neuro-oncology patients in Pakistan and beyond. The data shared above affirms the positive impact of such initiatives and emphasizes the potential for transformative change in healthcare delivery.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

NM: Conceptualization, Funding acquisition, Visualization, Writing – original draft. BQ: Formal analysis, Funding acquisition, Project administration, Writing – review & editing, Supervision. GJ: Writing – review & editing, Funding acquisition, Project administration, Resources, Conceptualization, Supervision. NS: Formal analysis, Writing – original draft, Writing – review & editing. SB: Formal analysis, Writing – original draft, Validation. AL: Investigation, Methodology, Resources, Writing – review & editing, Conceptualization, Validation. SE: Resources, Visualization, Writing – review & editing, Conceptualization, Validation. SA: Investigation, Methodology, Project administration, Writing – review & editing. KH: Investigation, Project administration, Writing – review & editing. AK: Formal analysis, Writing – original draft. AA: Investigation, Methodology, Resources, Writing – review & editing. AG: Investigation, Resources, Writing – review & editing. AM: Investigation, Methodology, Writing – review & editing. AR: Investigation, Methodology, Resources, Writing – review & editing. AM: Investigation, Supervision, Writing – review & editing. MM: Investigation, Writing – review & editing. AK: Investigation, Resources, Writing – review & editing. FB: Data curation, Investigation, Project administration, Writing – review & editing. HH: Investigation, Writing – review & editing. KS: Investigation, Writing – review & editing. KK: Investigation, Project administration, Writing – review & editing. LR: Investigation, Methodology, Resources, Writing – review & editing. MD: Data curation, Investigation, Writing – review & editing. MS: Investigation, Writing – review & editing. MK: Investigation, Writing – review & editing. NS: Investigation, Methodology, Writing – review & editing. NZ: Investigation, Resources, Writing – review & editing. NY: Investigation, Resources, Writing – review & editing. RM: Investigation, Resources, Writing – review & editing. RM: Investigation, Methodology, Writing – review & editing. SK: Investigation, Methodology, Writing – review & editing. SR: Investigation, Methodology, Writing – review & editing. SK: Investigation, Methodology, Writing – review & editing. SR: Investigation, Methodology, Resources, Writing – review & editing. SH: Investigation, Project administration, Writing – review & editing. TG: Investigation, Resources, Writing – review & editing. UI: Investigation, Methodology, Resources, Writing – review & editing. YM: Investigation, Writing – review & editing. ZR: Investigation, Writing – review & editing. EB: Funding acquisition, Supervision, Writing – review & editing. KM: Conceptualization, Formal analysis, Funding acquisition, Resources, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Intracranial non-germinomatous germ cell tumors in children and adolescents: how can the experience from an uppermiddle-income country contribute to the worldwide effort to improve outcomes?

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Background: Non-germinomatous germ cell tumors (NGGCT) accounts for one third of intracranial GCT. While the germinoma group have an excellent overall survival, the standard of practice for children with NGGCT is still under evaluation.

Aims: Describe the results of the of the Brazilian consortium protocol.

Methods: Since 2013, 15 patients with a diagnosis of NGGCT by histopathology and/or serum/cerebrospinal fluid (CSF) tumor markers, βHCG >200mlU/ml and/or positive alpha-fetoprotein were treated with neoadjuvant chemotherapy with carboplatin, cyclophosphamide and etoposide followed by ventricular radiotherapy (RTV) of 18Gy with boost (32Gy) to the primary site. Metastatic patients underwent craniospinal irradiation (CSI) and "slow responders" to the four initial cycles of CT, to autologous stem cell transplantation (ASCT) followed by CSI.

Results: Mean age, 13.1 years. Thirteen males. Primary sites: pineal (n=12), suprasellar (n=2) and bifocal (n=1). Four patients were metastatic at diagnosis. Eight patients had CSF and/or serum alpha-fetoprotein levels > 1,000ng/ml.

Tumor responses after chemotherapy demonstrated complete in six cases and partial in seven, with "second-look" surgery being performed in five cases, and two patients presenting viable lesions being referred to ASCT. The main toxicity observed was hematological grades 3/4. Two patients with metastatic disease, one with Down Syndrome and AFP > 1,000ng/ml and the other with choriocarcinoma and pulmonary metastases, developed progressive disease resulting in death, as well as two other patients without evidence of disease, due to endocrinological disorders. Event-free and overall survival at 2 and 5 years were 80% and 72.7%, respectively, with a mean follow-up of 48 months (range, 7-107).

Conclusions: Despite the small number of patients, in our series, treatment with six cycles of chemotherapy and RTV with focal boost for localized disease (n=11) and ACST for identified slow responders (n=2) seem to be effective strategies contributing to the overall effort to improve outcomes of this group of patients.

KEYWORDS

intracranial germ cell tumors (iGCTs), middle income countries (MIC), reduced radiotherapy, autologous stem cell transplantation (ASCT), non-germinomatous cell tumor

Introduction

Non-germinomatous germ cell tumors (NGGCT) account for one-third of intracranial germ cell tumors (GCT) and encompass various subtypes, including embryonal carcinoma, endodermal sinus tumor, choriocarcinoma, teratoma and mixed tumors (1, 2). Patients in the germinoma group experience excellent overall survival, ongoing research is focused on evaluating treatment strategies to reduce late-effects through less intensive regimens (3). However, the standard of care for children, adolescents and young adults with NGGCT is still under evaluation in order to enhance outcomes.

The objective of this study is to describe a cohort of patients uniformly diagnosed and treated within an upper-middle-income country (UMIC) with chemotherapy and reduced-dose and volume radiotherapy (RTV) followed by autologous stem cell transplantation (ASCT) as a front-line strategy in a subset of patients considered as "slow responders" after initial induction chemotherapy.

Patients and methods

A prospective trial, conducted by a Brazilian consortium, enrolled patients diagnosed with primary intracranial germ cell tumors and treated at the IOP/GRAACC/Federal University of São Paulo (UNIFESP), Hospital Amor de Barretos, and Hospital Santa Marcelina/TUCCA between 2013 and 2021. Data collection and analysis were performed in December 2022. The germinoma stratum was recently published in *JCO Global Oncology* (4).

The primary and secondary objectives of this study were to determine the event-free survival (EFS) and overall survival (OS) at 2 and 5 years of follow-up from diagnosis for patients with intracranial NGGCT; to assess the impact on survival by reducing the RT dose and volume in the proposed treatment group; to examine the impact of ACST on the survival of NGGCT patients identified as "slow responders"; and to implement "second-look" surgery for patients who did not achieve complete radiological response and observe its impact on overall survival.

The diagnosis of NGGCT and staging included cranial and spinal magnetic resonance imaging (MRI) as well as lumbar cerebrospinal fluid (CSF) cytology and tumor marker assessment at baseline, unless clinically contraindicated. In cases where AFP was detectably elevated (usually serum [5-10 ng/dL] or CSF [2-5 ng/dL]) or there was a significant CSF elevation of βHCG exceeding 200 IU/L, NGGCT was considered diagnostic without the need for histological confirmation. However, all patients with negative tumor markers underwent tumor biopsy for histopathological diagnosis. The chemotherapy plan consisted of an outpatient platinum-based regimen administered in six cycles every 21 days. The cycles were as follows: two consecutive days of carboplatin (300mg/m2 on Days 1 and 2) and etoposide (225mg/m2 on Days 1 and 2), alternating with two consecutive days of cyclophosphamide (1200mg/m2 on Days 1 and 2) and etoposide (225mg/m2 on Days 1 and 2). The cycles containing cyclophosphamide required the use of mesna (sodium 2-mercaptoethane sulfonate) and 5-hour hyperhydration at 1500ml/m2 each day. Assessment of disease was conducted after the completion of every two cycles, involving the monitoring of serum and CSF tumor markers and radiological evaluation through craniospinal MRI.

Patients who showed no evidence of progressive disease during the six cycles of induction chemotherapy proceeded to receive adjusted radiotherapy (RTV) as described below. However, if a residual lesion persisted after the fourth cycle of chemotherapy, a second surgical resection was strongly recommended. In cases where residual non-germinomatous (NG) disease was detected and/or positive tumor markers persisted, the recommended course of action was referral for ACST) followed by CSI. For patients with localized disease, radiotherapy comprised whole ventricular field irradiation (WVFI) at a dose of 18 Gy, with an additional 32 Gy administered as a boost to the primary site. Patients diagnosed with metastatic disease received CSI totaling 36 Gy, with a 20 Gy boost to the primary site. Following ACST irradiation included 30 Gy for the craniospinal region, with a 20 Gy boost to the primary site.

Tumor measurements and responses were assessed according to the revised RECIST criteria (Response Evaluation Criteria in Solid Tumors) (5): Complete Response (CR) was defined as no radiological evidence of tumor and normalization of both serum and lumbar CSF tumor markers; Partial Response (PR) as a 50% reduction in the product of the two greatest tumor diameters on imaging and a reduction of previously elevated tumor marker levels in both serum and lumbar CSF; Minor Response (MR) as a 25-50% reduction in imaging and some reduction of previously elevated serum and lumbar CSF tumor markers; Stable disease (SD) as less than a 25% decrease in imaging size, and Progressive disease (PD) as a 25% increase in tumor size or increasing elevations of either βHCG or AFP in either serum or lumbar CSF.

The Common Terminology Criteria for Adverse Events Version 4.0 was used to categorize adverse events.

Event-free survival (EFS) was defined as the duration from the time of study enrollment to disease progression, disease relapse, the occurrence of a second neoplasm, or death from any cause. Overall survival (OS) was defined as the interval from diagnosis to death due to any cause or the last follow-up visit. Nonparametric curves were generated using the product-limit (Kaplan-Meier) estimator, and these calculations were performed using IBM SPSS software for Windows (version 29.0).

Results

Patient characteristics

A total of 58 patients were enrolled in the study, with 15 diagnosed with NGGCT. The median age at diagnosis was 13.1 years, with a range from 5.9 to 16.1 years. Of these patients, 13 (86.6%) were male.

The primary tumor sites were distributed as follows: 12 patients had pineal tumors, two had suprasellar tumors and one had a bifocal tumor. In addition to positive tumor markers, 10 patients received a histopathological diagnosis. Eight patients had AFP levels exceeding 1,000 ng/ml in their CSF and/or serum. Four patients presented with disseminated disease, with three cases located in the ventricular area and one in the thalamus along with extra-CNS involvement in the pulmonary region. Please refer to Table 1 for a detailed presentation of patient characteristics.

Treatment outcomes and toxicities

All patients successfully completed the scheduled induction chemotherapy cycles every 21 days and received radiation therapy (RT) according to the proposed protocol. The mean interval

TABLE 1 Patient's characteristic.

Cases	Age (Y)	Sex	Primary site	Metastasis	Tumor Markers		Pathology
#1	12.6	F	Bifocal	Periventricular	AFP+*	βHCG +**	Germinoma
#2	6.3	F	Suprasellar	No	AFP+	βHCG +	–
#3	13.7	M	Suprasellar	Periventricular	AFP-	βHCG +**	Choricarcinoma
#4	14.1	M	Pineal	No	AFP+*	βHCG +**	Endodermal sinus
#5	8.5	M	Pineal	No	AFP+*	βHCG +**	Germinoma
#6	15.5	M	Pineal	No	AFP+*	βHCG +**	–
#7	10.7	M	Pineal	No	AFP+*	βHCG +**	Choriocarcinoma
#8	14	M	Pineal	No	AFP+	βHCG +**	Germinoma
#9	8	M	Pineal	Periventricular	AFP+*	βHCG +**	Endodemal sinus
#10	5.9	M	Pineal	No	AFP+	βHCG +	–
#11	8.6	M	Pineal	Thalamus/Lung	AFP-	βHCG +**	Choricarcinoma+Embryonal Ca
#12	15.5	M	Pineal	No	AFP+	βHCG +**	–
#13	10.5	M	Pineal	No	AFP+*	βHCG +**	Geminoma
#14	16.1	M	Pineal	No	AFP+*	βHCG +	–
#15	13.3	M	Pineal	No	AFP-	βHCG +**	Geminoma

*AFP> 1000UIml/L **βHCG >200mlU/ml.

between end of chemotherapy and initial RT was 30 days (range, 15-90 days). The patient with the longest interval developed febrile neutropenia and septicemia with prolonged intensive care hospitalization. After the completion of induction chemotherapy, six patients achieved complete responses (three after two cycles and three after four cycles), while seven patients achieved partial responses (PR). Unfortunately, two patients experienced disease progression (PD), one during induction, the other following CSI.

Among the patients who achieved partial responses (PR), five underwent "second-look" surgery. The surgical findings included one case with teratoma, one with both choriocarcinoma and germinoma components, and three with fibrosis without any signs of viable tumor in the sampled tissues. The remaining two patients who achieved PR following induction chemotherapy exhibited negative tumor markers and had minimal unresectable residual lesions.

Two patients underwent ASCT after completing four cycles of chemotherapy, due to persistently elevated tumor markers and the presence of residual non-germinomatous (NG) components (see Figure 1). Both patients initially presented with elevated CSF AFP levels and/or serum levels exceeding 1,000 ng/ml at the time of diagnosis. They are currently alive without disease or recurrence, with event-free survival (EFS) durations of 77 and 107 months, respectively.

Among patients with progressive disease, one had metastatic tumor involvement in the thalamus and lungs, elevated CSF/serum βHCG (>10,000 IUm/L), and a biopsy confirming choriocarcinoma and embryonal carcinoma elements. This patient experienced spontaneous primary tumor bleeding, resulting in neurological deterioration, and progressed despite chemotherapy, ultimately passing away after seven months during the induction chemotherapy (see Figure 2). The other patient, who had Down Syndrome and ventricular dissemination, presented with elevated CSF and serum AFP levels (>10,000 ng/mL). Although achieving a partial response (PR) after chemotherapy with an inoperable scar (negative tumor markers), this patient experienced disease progression locally with positive tumor markers, one month after CSI radiotherapy. Despite receiving additional cancer-directed therapies, he progressed after two cycles of Ifosfamide, carboplatin and etoposide and then two cycles of GEMPOX (6) and passed away 20 months after the initial diagnosis.

Two patients experienced non-disease-related deaths due to electrolyte disturbances attributed to sodium imbalances secondary to diabetes insipidus, after completion of all tumor-directed therapy. EFS for the two patients were nine and 25 months.

Among the eight patients with AFP levels exceeding 1,000 ng/ml in the CSF and/or serum, only one, a patient with Down syndrome, succumbed to disease progression as described above. The other patient deaths were unrelated to disease progression. In the entire cohort, the event-free survival (EFS) and overall survival (OS) rates at 2 and 5 years are 80% and 72.7%, respectively, with a median follow-up of 48 months (range: 7-107) (see Figure 3).

The most prevalent toxicities observed were grade 3/4 hematologic toxicities, primarily anemia (n = 15), neutropenia (n = 49) and thrombocytopenia (n = 34) across all assessable cycles. Febrile neutropenia occurred in twelve episodes, with three cases involving documented bloodstream infections. Additionally, three patients experienced electrolyte disturbances, resulting in two toxicity-related deaths.

Discussion

This study represents the largest prospective trial involving intracranial NGGCT in an upper-middle-income country (UMIC). Our aim is to provide insights into a cohort of patients who received uniform treatment, addressing the challenges posed by social and cancer care disparities while contributing to global efforts to enhance outcomes for this rare group of intracranial tumors.

NGGCT typically occurs in male children during middle school years and predominantly manifests in the pineal region (1, 2), consistent with our series. Bifocal tumors are infrequent in the NG group, and in our series, we identified only one patient with bifocal disease and positive tumor markers. Nevertheless, this underscores the importance of biopsy in such cases, particularly when tumor markers are negative (7, 8).

Primary intracranial germinomas have an excellent overall survival, with the standard approach involving neoadjuvant chemotherapy and reduced-dose whole-ventricular field

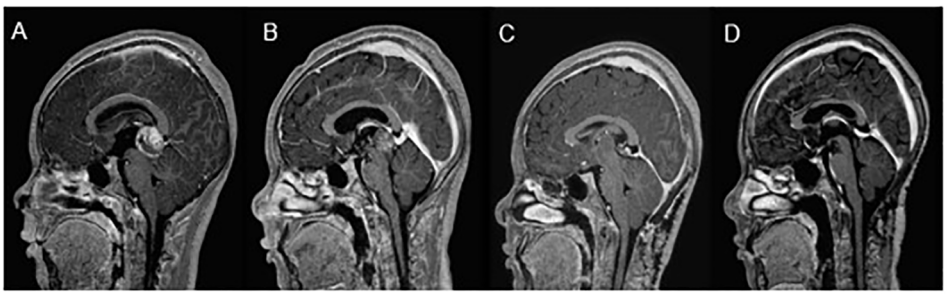

FIGURE 1
NGGCT "slow responder". Patient's journey from diagnosis (CSF βHCG β-10382 mIU/ml; serum-4912 mIU/ml); Biopsy - Germinoma **(A)** to partial response (CSF βHCG 810 mIU/ml) after 2 and 4 cycles of treatment **(B)**, followed by further reduction post second-look surgery (CSF βHCG β- 84 mIU/ml serum-undetectable); Biopsy - Germinoma, **(C)**. Complete response post-autologous stem cell transplantation, disease-free for 8.9 years **(D)**.

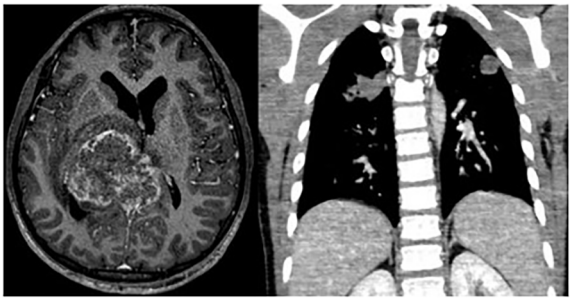

FIGURE 2
Pineal tumor with thalamic and pulmonary metastasis (βHCG> 10.000UI/ml).

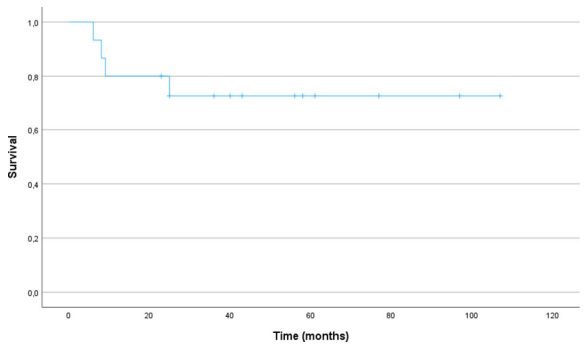

FIGURE 3
Event-free and Overall Survival (n=15).

radiotherapy to minimize late effects without compromising outcomes (9–11). In contrast, historically, NGGCT patients have had a poor prognosis (2). Both radiotherapy-only and chemotherapy-only strategies (12–14) have been deemed inadequate, with platinum-containing combinations as neoadjuvant chemotherapy followed by radiotherapy recognized as an effective treatment (15–17).

Nevertheless, the standard radiotherapy protocol after induction chemotherapy remains a subject of debate. For patients with complete response (CR) and localized disease, several cooperative groups are investigating the ideal radiotherapy field (18–20). For instance, SIOP-96 (18) reported a five-year progression-free survival of 72% for localized tumors (n=116) with local radiotherapy. The Children's Oncology Group (COG) ACNS0122 (19) employed craniospinal irradiation (CSI) of 36Gy and 54Gy boost, achieving a five-year event-free survival (EFS) of 92% (n=102), while subsequent study ACNS1123 (20) used whole-ventricular radiotherapy (WVRT) with 30.6Gy and 23.4Gy focal boost, reducing the CSI irradiation for localized disease, resulting in an 89% two-year EFS (n=107). Notably, the pattern of treatment failure varied among these studies, with local failures being more common in SIOP and ACNS0122, and spinal cord failures occurring in COG ACNS1123. However, a significant pooled analysis suggests that focal/WVI radiotherapy is not associated with an increased risk of metastatic relapse (21).

Despite a small patient cohort, in our series, 18Gy WVRT with a boost for local disease (n=11) yielded positive responses with no relapses over a five-year period. CSI was reserved for metastatic patients. Regarding dose reduction of WVRT, it appears to be feasible as only a few relapses of NGGCT occur in the ventricles after focal RT, and most of them are attributed to the germinoma component. Breen et al. (22) reported three patients with ventricular relapses, all with a germinoma component, and Murray et al. (23) reported three out of five patients with a germinoma component and one with βHCG between 50-200 IU/L, which would be considered a diagnosis of germinoma in our series. In a separate initiative from the recently initiated ACNS2021, which includes whole ventricular and spinal canal irradiation (WVSCI) for all patients, the plan for our next Brazilian protocol will be to assess alternative treatment intensification strategies while retaining WVRT for patients with localized tumors.

While some patients achieved CR after induction chemotherapy, a subset required "second-look" surgery and treatment intensification. Recognizing these "slow responders" is crucial for prognosis. The SIOP-96 trial revealed worse survival for NGGCT patients with end-of-treatment residual disease, even after "second-look" surgery (18). COG ACNS0122 documented two patients undergoing ASCT (19), a strategy supported by subsequent ACNS1123 (20) considering the great number of patients who did not attain complete responses after induction chemotherapy.

The benefit of this approach as part of the initial treatment for NGGCT remains unclear, due to the small number of patients described, necessitating collaborative efforts and consortia to encompass a larger, uniformly diagnosed, and treated patient population. In our series, seven patients exhibited partial responses after four cycles of chemotherapy, with two showing residual viable tumors and positive tumor markers, qualifying them as "slow responders." They underwent ASCT and achieved favorable outcomes, with disease-free survival of 77 and 107 months.

Another established prognostic factor is a serum and/or CSF AFP level >1,000 ng/mL, associated with a negative prognostic impact on survival in the SIOP-96 trial (18). In our series, eight cases had CSF and/or serum AFP levels exceeding 1,000 ng/ml, with only one death related to disease. Due to the limited sample size, our series is unable to establish statistically-significant prognostic correlations.

Notably, the rarity of NGGCT, though linked with Down Syndrome in just one case in our series, warrants careful attention. A recent publication by Harris et al. revealed an increased risk of treatment-related adverse events and long-term neurocognitive sequelae in this patient group, necessitating alternative therapeutic approaches (24). Some innovative cases have been reported, such as ASCT and brentuximab-vedotin for those with CD30-positive embryonal carcinoma (25).

Diabetes insipidus is a common manifestation of germ cell tumors and an important risk factor for complications, especially during chemotherapy infusion using hyperhydration (26). Our two toxicity-related deaths emphasize the importance of education and management of endocrine complications, even in the long-term

follow-up after completion of tumor treatment, to provide the best care for these patients (27, 28).

Our study's limitations include the small patient cohort, underscoring the importance of collaborative efforts, particularly in countries with diverse populations like Brazil. Additionally, financial constraints prevented us from conducting biological studies, such as the recent discovery of 12p gain as a possible poor prognostic marker (29).

Despite these limitations, our study represents the largest series of NGGCT patients uniformly diagnosed and treated in an UMIC. It offers valuable insights into radiotherapy field strategies for localized disease and the ASCT approach for "slow responders." Such feasible strategies in a collaborative setting contribute to global efforts aimed at improving outcomes for these patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee Federal University of Sao Paulo. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

AC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. ND: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. BM: Data curation, Writing – review & editing. SE: Data curation, Writing – review & editing. DA: Conceptualization, Data curation, Writing – review & editing. SC: Conceptualization, Data curation, Writing – review & editing. PD: Conceptualization, Data curation, Writing – review & editing. MA: Conceptualization, Data curation, Writing – review & editing. JN: Conceptualization, Data curation, Writing – review & editing. MCo: Conceptualization, Data curation, Writing – review & editing. FS: Conceptualization, Data curation, Writing – review & editing. SA: Conceptualization, Data curation, Writing – review & editing. MF: Conceptualization, Data curation, Writing – review & editing. MCh: Conceptualization, Data curation, Writing – review & editing. NS: Conceptualization, Data curation, Investigation, Writing – review & editing. JF: Conceptualization, Investigation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1308128/full#supplementary-material

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Case report: Turcot syndrome type 2 in a developing country within the Caribbean

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Medulloblastoma is the most common malignant pediatric brain tumor and has been linked to known cancer predisposition syndromes. We report a case of medulloblastoma of a 12-year-old Indo-Trinidadian female with a strong family history of colorectal carcinoma. In collaboration with the SickKids-Caribbean Initiative (SCI), her tumor was confirmed to be a WHO grade 4 medulloblastoma – Wnt subtype. Genetic testing further confirmed the presence of a pathogenic APC gene variant [c.3183_3187del (p.Gln1062*)] which led to a diagnosis of Turcot syndrome type 2. The index patient received multimodal therapy which included surgery, radiation and chemotherapy and is currently post end-of-treatment and in remission. This case report aims to highlight the complexity of diseases and the need for expertise in identifying them in low-and-middle income countries, the need for access to specialized testing and the benefits of collaborating between low-and-middle income and high-income countries when managing complex oncology patients.

KEYWORDS

medulloblastoma, Turcot syndrome, cancer predisposition syndromes, colorectal carcinoma, APC, low-and-middle-income countries, Caribbean, pediatrics

1 Introduction

Cancer is a major leading cause of disease-related deaths for children worldwide, with an increasing trend in recent decades. Despite this prevalence, the five-year survival rate of these patients exceeds 80% – largely due to improvements in diagnostic imaging, technology and multi-drug regimens (1). However, outcomes vary between high-income countries (HICs) and low-middle income countries (LMICs) due to multiple factors which include constraints to equitable health due to inadequate funding; shortages in appropriately trained healthcare professionals; limited and/or unreliable access to specialized testing and essential medicines; and lack of registries and case tracking to

facilitate appropriate resource planning and policy generation (2). The most common type of pediatric solid tumors are brain tumors classified as supratentorial or infratentorial in location. Medulloblastomas are the most common malignant pediatric brain tumors and are defined to occur infratentorial within the posterior fossa (3).

The etiology of childhood cancer is multifactorial with both intrinsic and extrinsic factors contributing to its development. Intrinsic factors involve a genetic predisposition that increases the risk of specific diseases regardless of environmental factors.

To date, a variety of genetic predisposition syndromes are associated with primary brain tumors. Common syndromes are Neurofibromatosis type 1 and 2, Tuberous sclerosis, Li Fraumeni syndrome, Gorlin's syndrome (nevoid basal cell carcinoma syndrome), familial adenomatous polyposis and its associations with Turcot syndrome (TS) and Gardner syndrome, rhabdoid tumor predisposition syndrome and retinoblastoma germline syndrome or hereditary retinoblastoma (1, 4).

In this article, we focus on familial adenomatous polyposis (FAP) and TS. TS was originally described by Canadian surgeon Jacques Turcot in 1959. Turcot reported on two consanguineous siblings with a combination of colon polyposis and primary brain tumor. Anecdotally, the brother presented with a case of polyposis, sigmoid colon adenocarcinoma and medulloblastoma and the sister presented with glioblastoma and pituitary adenoma (5). TS can be further classified as TS type 1 (TS1) (primary central nervous system tumor secondary to mismatch repair [MMR] gene variant) or TS type 2 (TS2) (primary central nervous system tumor secondary to adenomatous polyposis coli [APC] gene variant). Colorectal carcinoma (CRC) is often associated with TS and is divided by hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP), each associated with MMR and APC gene variants respectively.

We aim to highlight the role of international collaborations between HICs and LMICs in identifying and managing complex diagnoses which ultimately leads to more superior outcomes. In our index case, we specifically highlight the collaboration between The Hospital for Sick Children (SickKids) in Canada and Eric Williams Medical Sciences Complex, Trinidad and Tobago, made possible through the SickKids-Caribbean Initiative (SCI). The aim of SCI is to improve the outcomes and quality of life for children with cancer and blood disorders throughout six partnering Caribbean countries — The Bahamas, Barbados, Jamaica, St. Lucia, St. Vincent and the Grenadines and Trinidad and Tobago — that may not have the resources to maximize care (2).

2 Case history

The index case is a 12-year-old Indo-Trinidadian female who presented to the emergency department with a four-day history of intermittent vomiting and one instance of decreased consciousness. She was noted to have a five-month history of headaches and myopia prior to presentation, and a three-week history of persistent fatigue and progressive gait unsteadiness. One week prior to presentation, the patient complained of diplopia, bilateral tinnitus, throbbing lateral and frontal headaches, had decreased appetite and periodic vomiting. She had a history of congenital right-sided hemi-hypertrophy and Melker-Rossenthal syndrome that was monitored with routine follow-up care, but otherwise exhibited normal physical and psychosocial development throughout childhood.

Her initial assessments included neuroimaging scans which showed a cerebellar mass with obstructive hydrocephalus and diffuse effacement of the sulci, resulting in raised intracranial pressure (ICP) (Figure 1). A ventriculoperitoneal shunt was sited and she was referred to the Eric Williams Medical Sciences Complex where the primary neurosurgeon and pediatric hematologist/oncologist were based. On initial examination, the patient had an inability to ambulate without support, combined with left-sided weakness, a right convergent squint and aphasia – all in keeping with posterior fossa syndrome. On initial consultation

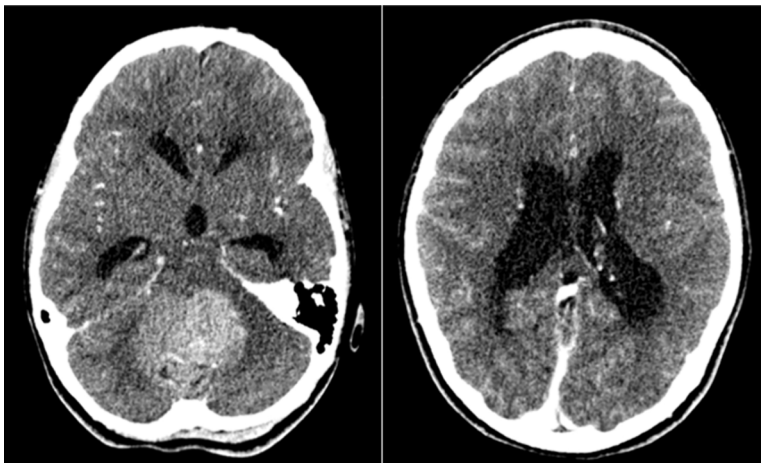

FIGURE 1
Axial post-contrast CT images demonstrating a large heterogenous mass arising from the posterior fossa (left image) and obstructive hydrocephalus secondary to the mass (right image) in our index case at time of initial presentation.

with the pediatric oncologist, a family history of CRC and clinical FAP (Figure 2) was elicited. Her paternal grandfather was diagnosed with CRC at 53-years-old and this prompted subsequent investigations into the patient's father and paternal aunt via colonoscopy. They were both identified as having multiple colonic polyps and thus, both were clinically diagnosed with FAP. They each underwent prophylactic total colectomies at ages 37 and 32, respectively, in an effort to reduce the risk of developing CRC in the future. There are two other paternal 2nd degree relatives with a history of malignancy, including CRC while two maternal 2nd degree relatives have a history of malignancy including breast and lung cancer. Both of the patient's paternal and maternal great-grandfathers developed prostate cancer, indicating a strong, multi-generational family history of cancer.

To identify a potential genetic link, the patient underwent focused genetic testing locally and a pathogenic variant in the APC gene was detected, confirmed as variant c.3183_3187del (p.Gln1062*). The patient and her family were counseled on the mode of inheritance of this variant and its likely link in developing medulloblastoma. Subsequent cascade testing was done for her first-degree relatives which included her father, brother and paternal aunt. All three relatives were found to have identical pathogenic variation in the APC gene, confirming the clinical suspicion of the genetic cancer predisposition of FAP.

Meanwhile, the patient underwent neurosurgery for attempted gross total resection shortly after her initial pediatric oncology consultation. A subtotal resection was achieved given the complexity of the tumor and high risk of post-surgical morbidities. The resected tumor was sent to both our local pathology laboratory and SickKids in Canada, facilitated through the SCI. Pathology report at both centers confirmed a WHO grade 4 medulloblastoma while molecular categorization conducted at SickKids identified Wnt-activated subgroup. Microscopic findings showed a cellular neoplasm with mid-size hyperchromatic, round, clear nuclei, fine chromatin and some distinct nucleoli. A subtle nodular pattern was noted within the neoplasm, in addition to Homer-Wright rosettes. The patient had staging workup completed including postoperative MRI brain, spine and cerebrospinal fluid analysis which was negative for malignant cells and hence stage M0. However, due to a residual tumor volume being greater than 1.5cm^2, the patient was deemed high risk.

Subsequently, our index patient was managed with cranio-spinal radiation (CSI) with a posterior fossa boost as part of standard medulloblastoma treatment with weekly intravenous vincristine chemotherapy. Due to incomplete resections and associated high risk, she received 30 fractions of radiation therapy over the course of six weeks (36Gy in 20 fractions followed by a posterior fossa boost 18Gy in 10 fractions to a total of 54Gy in 30 fractions over a six-week period). After which, the patient started chemotherapy following the Children's Cancer Intergroup Study with Pediatric Oncology Group, Regimen B Maintenance Chemotherapy, A9961. This protocol consists of eight 42-day cycles consisting of vincristine, cyclophosphamide, cisplatin and G-CSF. To date, the patient has regained the ability to walk short

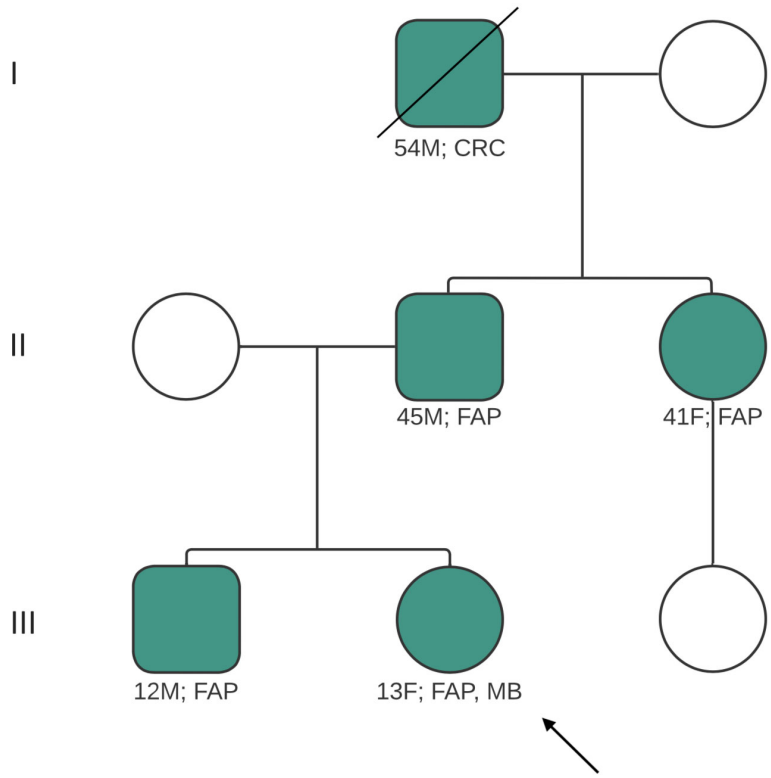

FIGURE 2
Pedigree of patient's family, illustrating family members affected and/or diagnosed with FAP, CRC. Index case indicated by arrow. Diagonal line indicates deceased relative. CRC, colorectal carcinoma; FAP, familial adenomatous polyposis; MB, medulloblastoma; M, male; F, female.

distances with assistance, fine motor skills (legible penmanship and utilizing an electronic tablet), moderate speech and communication abilities and is able to feed herself. She has maintained a positive disposition and plans to continue her secondary education. Her end-of-treatment MRI scans show no active tumor and continues with her multidisciplinary post-treatment management which includes speech therapy, physiotherapy and both she and her brother have been referred to the paediatric gastroenterologist for colonoscopy follow-up. As part of post end-of-treatment follow-up, this patient will be closely monitored for late effects to the multimodal therapy that she received. This includes complete annual endocrine screening and neuropsychological assessment to evaluate her ability to integrate back into school and determine if special aids are needed. As expected, extensive exposure to cisplatin has affected her hearing and caused high-frequency sensorineural hearing loss, which was identified by recent audiometry screening. She has been referred to the otolaryngologist for monitoring and management, in addition to the aforementioned therapies.

3 Discussion

Central nervous system tumors comprise approximately 23% of primary pediatric malignancies (1) (Table 1). Moreover, tumors can be caused by various factors such as genetic variants or infections. For example, gliomas are categorized by low-grade or high-grade gliomas. Individuals with tuberous sclerosis or neurofibromatosis type 1 have predisposition to developing low-grade gliomas, in addition to complex germline variants in the *BRAF* gene or mitogen-activated protein kinase (MAPK) signaling pathway (such as *NF1* and *RAF* varaints) (4, 10). High-grade gliomas involve abnormalities in multiple pathways such as the phosphatidyl-inositol 3-kinase (PI3K), p53 and retinoblastoma tumor suppressor pathways, and variants of the receptor tyrosine kinase (*RTK)* gene (4, 11). Diffuse intrinsic pontine gliomas involve variants in histone genes such as H3K27M, H3F3A or HIST1H3B (1). Ependymomas may arise from infection with simian vacuolating virus 40 (SV40), neurofibromatosis type 2, Li-Fraumeni syndrome or Turcot syndrome type B/Turcot syndrome 2 (1, 10–12).

Turcot syndrome (TS) is a rare inherited disorder of colorectal cancer (CRC) with primary brain tumors, as defined by Canadian surgeon Jacques Turcot (13). It can be further classified as TS1 (primary CNS tumor secondary to MMR gene variants) or TS2 (primary CNS tumor secondary to APC gene variants). HNPCC and FAP, each associated with MMR and APC gene variants respectively, are associated with TS (13). Further associations include HNPCC with Lynch syndrome and FAP with Gardner syndrome. With these syndromes and malignancies, the relationship between cancer and genetics is significant such that patients with TS2 and FAP have a 92% relative risk of developing medulloblastoma. TS1 patients tend to be associated with glioblastomas. Additionally, patients with FAP have a nearly 100% relative risk of developing CRC. Nevertheless, TS remains an incredibly rare but life-altering condition. Approximately 30% of CRC patients have a family history of CRC and of these cases, only 3-5% include a genetic component (11, 13–18). To date, there are over 150 cases of TS accounted for in literature. Recordings of the actual number of the cases have been limited by prevalence, the need for genetic testing and the use of various alternative terms such as the more recently suggested substitution of TS with brain tumor polyposis syndrome (BTPS) (13, 17, 19).

TABLE 1 Cancer predisposition genes and associated brain tumor characteristics.

Syndrome	Gene abnormality	Characteristics of CNS lesions	Additional findings	References
Neurofibromatosis Type 1	*NF1*	Low-grade gliomas (optic pathway and brainstem)	Café-au-lait spots, lisch nodules, axillary/ inguinal freckling	(4, 6)
Neurofibromatosis Type 2	*NF2*	Bilateral acoustic schwannomas, meningiomas, ependymomas	Increased risk of cataracts and seizures	(2)
Tuberous Sclerosis	*TSC1*; *TSC2*	Subependymal giant cell astrocytoma (SEGA)	Increased risk of skin and renal growths	(2, 3)
Li Fraumeni Syndrome	*TP53*	Malignant glioma, choroid plexus carcinoma	Numerous cancers at younger ages (breast, sarcoma, adrenal cortical carcinoma)	(7)
Gorlin's Syndrome (nevoid basal cell carcinoma syndrome)	*PTCH*	Medulloblastoma	Basal cell carcinoma	(4, 8)
Familial Adenomatous Polyposis (Gardner/Turcot)	*APC*	Medulloblastoma and malignant glioma	Multiple colonic polyps and increased risk of colorectal carcinoma	(4)
Rhabdoid Tumor Predisposition Syndrome	*SMARCB1*; *SMARCB4* (*INI-1*)	Atypical teratoid rhabdoid tumor (AT/RT)	Rhabdoid tumors in kidney, schwannomatosis; typically < one years of age at diagnosis	(4, 9)
Retinoblastoma (germline)	*RB1*	Trilateral retinoblastoma (unilateral or bilateral retinoblastoma + pineoblastoma)	Pineoblastoma is usually diagnosed after retinoblastoma but often prior to five years of age	(3, 4)

Medulloblastomas are the most common brain malignancy of childhood, accounting for 15-20% of all neoplasms of the CNS (20). Histologically, four variants of medulloblastoma can be classified: classic (68-80%); large cell/anaplastic (10-22%), desmoplastic (7%) and extensive nodularity (3%) (12, 21, 22). Our patient has a histological type of vague nodular pattern.

There are also four molecular sub-groups of medulloblastoma which has been classified as: MB-Wnt, MB-Shh (Sonic Hedgehog [Shh]) and Group 3 and 4, of which our patient had MB-Wnt subgroup (12, 19). Turcot syndrome type 2 is associated more commonly with MB-Wnt subtype. This accounts for approximately 10% of diagnoses and is found mainly in girls with peak incidence between 10-12 years of age, as seen in our patient. MB-Wnt has a low tendency to metastasize and patients under 16 years of age have an excellent prognosis due to its prognostic status in comparison to other subgroups (8, 17, 19, 21, 23).

Medulloblastoma are mostly sporadic in nature, however there is an inherited predisposition in TS2 (17, 21, 23). In TS2, the primary brain tumor of medulloblastoma is associated with a germ line variant in the APC gene which is a tumor suppressor gene associated with CRC due to FAP (17, 21). There can be inactivation of the second copy of the gene when there is a germline variant of APC, which appears to be a brain tumorigenesis factor. However, the variant is not always identified in the second copy of the APC gene in brain tumors, and this may be attributed to the difficulty in detecting alterations of the APC gene itself (19). This serves as a point of interest for future research in an effort to increase genetic diagnostic sensitivity in patients with medulloblastoma.

In terms of management, the most illuminating and time-efficient investigation for a primary care provider is the patient's family medical history. Patients often present with adenomatous polyps at an early, atypical age and most importantly, there is a strong family history of early-onset CRC. In patients with primary CNS tumors and an absence of polyps, any family history of CRC should still raise prompt investigation into genetic syndromes. An understanding that TS1 has autosomal recessive inheritance and TS2 has autosomal dominant inheritance can also be helpful in identifying affected or at-risk individuals in a family tree, as in our case. In our index case, the family history highlighted the autosomal dominance pattern and strong inclination of FAP. By initiating molecular testing and genetic counselling, early diagnosis and preventive management within family members can be maximized.

Due to collaboration with SickKids, facilitated through SCI, our patient had the ability to have a more detailed pathological review of her biopsy tissue, including molecular studies (2). This allowed for her identification of Wnt subtype which is associated with almost all cases of TS2. In addition, multidisciplinary review with the neuro-oncology team was done which helped in guidance of therapeutic approaches for our patient such as considering de-escalation of radiation doses and long-term surveillance screening. As such, this case also highlights the benefits of LMICs collaborating with HICs to facilitate management of complex patients, aid in improving local systems to become more sustainable and eventually enhance the standard of care, particularly highlighting the positive impact that SCI has had on the pediatric oncology landscape within the Caribbean.

3.1 Navigating management and surveillance

Genetic counseling in TS is imperative in the management of the patient and their family. Families with confirmed FAP can benefit extensively from counseling due to the risk of developing various tumors. There are no established guidelines for screening, diagnosis and genetic counseling of pediatric patients for rare cancer predisposition syndromes, such as TS (12, 13). When evaluating due to suspicion, gaining details of family history as well as maintaining high vigilance for clinical signs is of utmost importance. In any case, pediatric patients who have 1st degree relatives diagnosed at an early age with CRC with or without associated cancer predisposition syndromes should be screened for pre-cancerous polyps and may require genetic testing. In this case, a pre-adolescent female who developed medulloblastoma and had a family history of CRC prompted genetic testing. This allowed for subsequent identification of identical gene variants in multiple relatives and will provide the basis for surveillance for the patient and her sibling beginning in pre-adolescence.

Confirmation of a cancer predisposition syndrome by molecular diagnosis can impact how the patient and relatives aremanaged, alter when cancer screening may be initiated to detect the syndrome and its manifestations and prevent possible complications by implementing treatment in earlier stages. There has been expansion of pediatric genetic research by the use of molecular testing and analyzation of germlines, as a result of the practice of next generation sequencing (NGS) in evaluating cancer predisposition syndromes in adults.

The panel of multi-gene testing allows the advantage of testing high, moderate and even low penetrance genes associated with the patient's diagnosis and possible genes of unknown risks. This added benefit may allow for the identification of pathogenic variants of germline variants that are not typically tested for. In this case, our patient had a SMARCE1 mutation which is a variant of uncertain significance, unknown in its associations with TS and whether it may have added to her pathogenicity of disease.

It remains that the mainstay of early evaluation of family members with evidence of FAP, HNPCC-associated APC or MMR gene variants should be early serial colonoscopies and family members of the patient would benefit from genetic analysis. An annual sigmoidoscopy with the goal of identifying colonic polyps is the recommendation to at-risk family members with the APC gene variant. This screening would start from the early ages of 10 to 12 years. Genetic testing of children and adolescents would determine those that will require clinical screening (8, 17, 24). However, in regard to screening of brain tumors, there are no guidelines and proves to be arduous (11).

We suggest that the detection of early CRC and signs of FAP, via colonoscopy and biopsy, should highlight the need for genetic testing on samples. Identifying genetic variants can serve as screening for primary brain tumors. With identification of a primary brain tumor, detecting genetic variants may be imperative, allowing for screening and prevention of CRC. The discovery of a genetic variant associated with cancer predisposition

syndromes will allow patients with an increased risk, and their families, to be monitored for developing manifestations (11).

Overall, the diagnosis and management of our index case illustrates a few key learning points. Firstly, it highlights the importance of taking a thorough history, particularly focusing on family history to identify potential cancer predisposition syndromes. It also highlights the need for expertise in linking a family history, a cancer predisposition syndrome and navigating testing to validate these complex diagnoses. In our index case, identifying two generations of colonic disease in the setting of medulloblastoma helped identify a potential germline FAP which prompted genetic testing. This case illustrates the presence of complex disorders that exist in low-and-middle income countries and the need for highly specialized testing such as molecular and genetic studies to facilitate more accurate diagnoses. That being said, the number of these rare cases will be substantially lower and discussions of incorporating such highly specialized testing will have to be further assessed based on financial feasibility of institutions. However, collaborative initiatives such as SCI are crucial in facilitating highly specialized testing to be done in high-income countries to help diagnose these very rare cases and aid in precision medicine.

4 Conclusion

Although TS2 has been documented in literature, albeit a rare syndrome, this case highlights a few essential points in ensuring the holistic care of children with cancer. It must be appreciated that some childhood cancers are due to cancer predisposition syndromes which are familial. As such, a detailed family history may be the only information needed to identify a predisposition syndrome, which is essential to all clinicians.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

Ethics statement

Ethical approval was not required for the study involving human samples in accordance with the local legislation and institutional requirements because no human samples were utilized in this study. Written informed consent for participation in this study was provided by the participants' parents/legal guardians. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MD-A: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. BG: Writing – review & editing, Writing – original draft, Conceptualization. UB: Writing – review & editing, Investigation. CB: Writing – review & editing, Investigation. KD: Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Pediatric neuro-oncology in Latin America and the Caribbean: a gap to be filled

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KEYWORDS

pediatric, brain tumors, LMIC, gap, LATAM

1 Childhood cancer and disease burden

From the estimated 400,000children and adolescents who develop cancer each year, 80% live in low-middle income countries (LMIC) and are, unfortunately, responsible for 90% of the deaths in this age group (1, 2). The global outcome disparities are influenced by several factors mostly related to the availability of resources, with underprivileged patients placed "on the wrong side of a pediatric oncology 'death canyon'", with less than 5% of global resources for cancer dedicated to this group of patients (3–9).

Caring for children with central nervous system (CNS) tumors is a significant challenge due to the number of resources required, ranging from infrastructure to specialized staff. Frequently, the availability of resources is the difference between success and failure and should move pediatric oncologists worldwide to action (10).

2 CNS tumors overview in Latin America (LATAM) and the Caribbean

Latin America and the Caribbean is a diverse region, with countries varying in culture, language, and health systems strength. In 2020, based on GLOBOCAN data, there were 2,585 incident cases of pediatric CNS tumors in Latin America and the Caribbean. Brazil (791), Mexico (702) and Colombia (179) had the most cases. In terms of age-standardized incidence rates, there is a considerable variability in the region, with Guatemala (0.47), Bolivia (0.73), and Panama (0.89) having the lowest rates, while Mexico (2.2), Uruguay (2.3) and Guadeloupe (3.2) having the highest (11).

Data on survival, is a challenge mainly due to the lack of pediatric cancer registries. Despite this, Girardi et al, reported a survival analysis from 2000 to 2014 for LGG, that turns to be uniform between High income countries (HIC) ranging from 90 to 100%

compared to a LATAM countries reaching almost 70%.; for medulloblastomas there are variable survival rates ranging from 30 in LMIC, compared to over 80% in HIC. Although we know that there is an under representation for countries classified as LMIC, the real gap is still difficult to calculate so far, but we can imply is wide larger. A preliminary results of a multicenter study on medulloblastoma survival on 4 centers belonging to LMIC (Peru, Pakistan, Philippines and Uruguay) reports a 75% 5-year overall survival and 35% Event-free survival, this example depicts the existent gap in the second most common tumor globally (12, 13).

In pediatric brain tumors, despite the epidemiological distribution of LMIC being seemingly similar to HIC, the well-known vulnerabilities and dismal outcomes are particularly true (14). As the second most common malignancy in childhood and the leading cause of death related to cancer is still a therapeutic challenge (15–18). The cause of high mortality in LMICs is multifactorial, with factors like delayed diagnosis, misdiagnosis, late presentation, late referrals, delay in starting proper treatment, high rates of treatment abandonment that can exceed 20% in LATAM, and comorbidities are contributing elements like high rates of malnutrition that can have adverse effects of treatment tolerability and lower survival. Other causes include limited access to supportive care, including palliative care, essential medications, continuous medical education, and multidisciplinary approach (7, 9, 19–21).

Lack of pediatric cancer registries in LMICs limits the estimation of the real burden of childhood cancers and how each of these factors contribute to the trends in survival and mortality in each country, thus preventing identification of effective interventions. The implementation of a quality registry, an adequate hospital infrastructure with a surgical center equipped for neurosurgery, intensive care unit prepared for highly complex cases and an appropriate multidisciplinary team requires financial resources, time, and expertise (22). In addition, recent advances in the molecular characterization of cancer have promoted considerable changes in diagnosis, prognosis, and outcome for our patients. Thus, the resources and expertise that an institution in a LMIC would need to allocate to characterize such tumors are indeed limiting and not always justified since targeted therapies are also not readily available (23, 24).

3 Regional and international interventions

Over the past years, pediatric cancer has gained momentum in the context of cancer control and non-communicable diseases. The World Health Organization (WHO) member states passed a resolution on May 31, 2017, to add cancer prevention and control initiatives for all age ranges (25). In 2018, the WHO launched the Global Initiative for Childhood Cancer (GICC) aiming to achieve at least a 60% survival for pediatric cancer patients by 2030. Importantly, a CNS tumor, low-grade glioma, is included one of the six index cancers selected by the GICC to demonstrate impact of the interventions. The goal achievements will occur through governmental support for awareness of childhood cancer at national and global levels and promoting the capacity expansion of countries to perform best practices in care for these patients (26). Furthermore, the GICC has gained a lot of traction in Latin America with many activities ongoing to improve care capacity (27). In Peru, thanks to the GICC, a multicenter team was created to map the baseline on LGG, the results showed a survival of 80%, and recognized the importance of long-term effects of treatment, information that is not available due to the loss of follow up, and the lack of long term follow up programs (28).

To provide comprehensive cancer care for children with CNS tumors, a strong health system needs to exist, with robust referral networks and specialized centers. In Brazil, a unified national health system (SUS) was implemented in 1990 subsidizing most cancer treatments and the creation of high-complexity cancer centers (CACON). In Mexico, social health insurance was established in 2006, and combined with standard treatment protocols and accreditation of childhood cancer, the treatment abandonment was reduced from 35% to 5% (15, 16). It is anticipated that the GICC will continue to help strengthen pediatric cancer in national cancer control plans in Latin America.

Prompt diagnosis, referral, multidisciplinary approach, and local capacity are important tasks where interventions can improve the outcomes. An example of success due to the effort of well-structured services was the protocol for the treatment of intracranial germinoma, a recently published Brazilian consortium that demonstrated with a median follow-up of 44.5 months, overall and event-free survivals of 100% (29, 30).

Another process to be filled in the task of diagnosis and treatment of pediatric brain tumors is to organize the referral pathways and the length during treatment. Diaz-Coronado et al, described that a child with medulloblastoma starting radiotherapy more than 30 days after surgery showed a negative impact on their survival (29).

An important element to provide comprehensive, context-related care is the existence of cooperative research groups. In Central America, the AHOPCA (Central American Association of Pediatric Hematology and Oncology) for the last 20 years which has unified countries and applied risk-adapted protocols and established patient registries. In addition, the Latin American Pediatric Oncology Group (GALOP) that have supported the conduct of local clinical trials in solid tumors (Ewing sarcoma, retinoblastoma, osteosarcoma). These are initiatives needed to narrow the treatment gap (7, 17).

Quantitative needs assessments for institutions in Brazil, Paraguay, and Chile were performed to provide an understanding of their strengths and their challenges. These play an important role to develop guidelines or policies that can help reduce the gaps in terms of resources (31–33). In the context of the molecular transformation to the field of pediatric neuro-oncology, access to an optimal pathology service is key to inform optimal treatment strategies (34). A comprehensive evolution of neuro-pathology services in Latin America, unfortunately does not exist. For children with CNS tumors, access to timely radiotherapy is essential to achieve optimal outcomes. In Latin America and the

Caribbean in 2018, 30% (12/40) of countries did not have any radiotherapy centers, and only 7.5% (3/40) of countries (Antigua/Barbuda, Curacao and Uruguay) met the International Atomic Energy Agency's (IAEA) recommendation of 1 megavoltage machine (MVM) per 250,000 inhabitants (35).

The expertise advisory programs, such as in surgical procedures, or web-based tumor boards, can dramatically change a patient's survival. The LATB (Latin American Brain Tumor Board) reviews patients weekly with multidisciplinary teams from South and Central America, providing timely therapeutic recommendations, and continuous education, while also recognizing the institutional resource limitations across the different regions (14, 33, 36). Also, The Global Alliance for Pediatric Neuro-Oncology (GAP-NO), built from a pediatric neuro-oncology course focusing on LMIC needs, is another step forward in education of professionals, creating a network, and building capacity through research and national policies (37).

Developing and implementing policies that prioritize palliative care for pediatric brain tumors is an ongoing effort. Advocacy for policy changes at the national and regional levels is important to ensure sustainable and widespread access to palliative care services. It's important to recognize the progress being made in Latin America while acknowledging the need for continued efforts to enhance palliative care services for children with brain tumors and other life-limiting conditions. Increased awareness, education, and collaboration are key factors in improving the overall quality of care for affected children and their families in the region (27, 38–40).

The importance of recognizing the educational gap in pediatric neuro-oncology among healthcare providers was described in a global cross-sectional survey demonstrating the importance of raising professional awareness on knowledge about clinical presentations of CNS tumors (41). Since 2020 an expert panel from Hospital Garrahan in Argentina aim to improved treatment in almost all centers in the country reaching to 96% of patients with brain tumors. This local intervention through monthly multidisciplinary virtual meetings between private and public hospitals has the aim to reduce mortality and improved survival (42).

Global educational initiatives like the Neuro-Oncology Training Seminars launched by St. Jude Global in 2018 are helping to cultivate an understanding of the importance of a multidisciplinary approach to the management of children with brain tumors; in 2022 the program enrolled from 20 countries (43). Another example is the Pediatric Neuro-Oncology Virtual Fellowship which started in 2022 by St. Jude Global and has partnered 5 pediatric oncologists with local and international experts from pediatric neuro-oncology centers of excellence who mentor them and provide individualized training with a set curriculum. This ambitious project tries to reduce the knowledge gaps by providing access to sub-specialty training in pediatric neuro-oncology not otherwise offered locally.

Increasing educational knowledge capacity to improved diagnosis of brain tumors can be challenge, needs of a well structure and sustainable curriculum to be adopted by the health care workers on each country, meanwhile WHO and PAHO, implemented a virtual and free material on their web page to improved early diagnosis. In Peru there is a mobile application, called ONCOPEDS, that aims to facilitate early diagnosis and education not only to health care providers, but parents and teachers. ONCOPEDS has promising results so far improving the referral time and education in Peru (44).

There are undoubtedly challenges ahead to narrow the gap between HIC and LMIC of pediatric oncology and specially neuro-oncology, but certainly, with joint efforts, the survival disparity will be narrowed. Initiatives in Latin America are already being implemented and paving the way to inform other regions of optimal strategies to build care capacity to improve outcomes for children with CNS tumors.

Author contributions

RD-C: Conceptualization, Validation, Visualization, Writing – original draft, Writing – review and editing. RC-V: Validation, Visualization, Writing – original draft, Writing – review and editing. AC: Conceptualization, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing.

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Impact of treatment and clinical characteristics on the survival of children with medulloblastoma in Mexico

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Introduction: Data on medulloblastoma outcomes and experiences in low- and middle-income countries, especially in Latin America, is limited. This study examines challenges in Mexico's healthcare system, focusing on assessing outcomes for children with medulloblastoma in a tertiary care setting.

Methods: A retrospective analysis was conducted, involving 284 patients treated at 21 pediatric oncology centers in Mexico.

Results: High-risk patients exhibited markedly lower event-free survival than standard-risk patients (43.5% vs. 78.3%, p<0.001). Influential factors on survival included anaplastic subtype (HR 2.4, p=0.003), metastatic disease (HR 1.9, p=0.001); residual tumor >1.5cm^2, and lower radiotherapy doses significantly impacted event-free survival (EFS) and overall survival (OS). Platinum-based chemotherapy showed better results compared to the ICE protocol in terms of OS and EFS, which was associated with higher toxicity. Patients under 3 years old displayed notably lower OS and EFS compared to older children (36.1% vs. 55.9%, p=0.01).

KEYWORDS

medulloblastoma, survival, clinical characteristics, low and middle income countries, CNS tumors, childhood, brain tumor

1 Introduction

Brain tumors are the most frequent solid tumors in children and adolescents, and they represent the major cause of cancer-related mortality in childhood. Medulloblastoma is the most common malignant brain tumor of childhood (1). However, there is very little data available in low- and middle-income countries (LMIC) regarding the outcome and, more importantly, the experience (2). Cancer registries in Latin America cover only 21% of the cases, compared to 99% in the USA and 86% in Canada (3). This demonstrates a problem in MIC, where implementing a national cancer registry system is challenging.

In Mexico, our closest data comes from single institutions or collaborations among a few hospitals, and in the best-case scenario, from one health system. In 2015, the incidence of intracranial neoplasms among children under 18 years treated with Popular Medical Insurance, which covers 55% of childhood cancer, was 10.3 cases per million/year (4, 5).

The healthcare system in Mexico, like other middle-income countries, faces several difficulties in delivering quality care (6, 7). In general, oncologists and patients struggle with the lack of accessible imaging resources such as MRI or CT scans, difficulties in initiating timely radiotherapy, limited availability of equipment like linear accelerators and 3D programming, saturated neurosurgery services, and a shortage of neurosurgeons trained in pediatrics (2, 8). Additionally, there are other important co-morbidity problems such as malnutrition, a high rate of infections that delay treatments, and the remote distances that some patients must travel to access oncology centers (9).

The improvement in the cure and quality of survival of children with medulloblastoma relies not only on chemotherapy protocols but also on multidisciplinary management, diagnostic technologies (such as MR imaging), radiation therapy, skilled neurosurgeons, radiotherapists, and board-certified pediatric oncologists.

The purpose of this study is to assess the outcomes of patients with medulloblastoma and their characteristics, as treated in a tertiary care setting in a middle-income country.

2 Methods

We conducted a retrospective analysis of the data from 284 patients who were treated between 1997 and 2017 at 21 pediatric oncology centers in Mexico.

For risk stratification, patients were divided into two prognosis groups, we used Chang Staging System to classify them as standard- and high-risk, as shown in Table 1 (6). Treatment modalities included surgery, radiotherapy, the timing of treatments, the modality (cobalt vs. linear accelerator) used for radiotherapy, and the type of chemotherapy.

TABLE 1 Risk stratification of Medulloblastoma.

Standard risk (All of the following)	High risk (Any one of the following)
≥3 years of age	<3 years of age
Residual tumor <1.5cm^2	Residual tumor >1.5cm^2
Non-metastatic disease	Metastatic disease
Classic or desmoplastic histology	Large cell-anaplastic histology
Complete staging	Incomplete staging

2.1 Statical analyses

Descriptive data was presented in terms of frequencies and percentages, while quantitative data was described using mean, standard deviation, minimum, and maximum values. P-values less than 0.05 were considered significant. The prognostic value was assessed through multivariate analysis using the Cox regression model and the log-rank test. Nonparametric overall survival (OS) and event-free survival (EFS) were computed using Kaplan-Meier curves, and the log-rank test was employed to compare survival differences according to different variables. EFS was defined as the interval between the time of diagnosis and relapse or death. Data management and analysis were performed using SPSS version 23.0.

3 Results

A total of 284 patients from 21 pediatric oncology centers in Mexico, ranging in age from 1 month to 17 years old, were included in the study, with an average age at diagnosis of 6.7 ± 4.05 years old. Among the patients, 17.6% (n=50) were less than 3 years old. The male-to-female ratio was 1.6:1, and there was no significant difference in age or prognosis based on gender.

Among all the patients, the most common pathology subtype was classic medulloblastoma (53.9%, n=153), followed by desmoplastic (12.7%, n=36), large cell-anaplastic (8.5%, n=24), and extensive nodularity (3.2%, n=9). However, in 21.8% (n=62), the pathology report did not specify the subtype. All patients with anaplasia were in the high-risk group, and in the rest of the different histologic groups no significant differences were found between high- and standard-risk patients (p >0.05). Survival analysis indicated that pathology subtype played a role in predicting survival, as children with anaplastic subtype had a 2.4 times higher risk of death or relapse compared to other subtypes (p=0.003). The 5-year EFS rates were 60.7% for classic type, 75% for extensive nodularity, 47.8% for desmoplastic, and 27.9% for anaplastic (p=0.005), as depicted in Figure 1.

Regarding the risk stratification of medulloblastoma, we found that 74.3% (n=211) of the patients were classified as high risk, while only 25.7% (n=73) were categorized as standard risk. Patients with high-risk demonstrated significantly lower EFS compared to patients with standard risk (5-year EFS 43.5% vs. 78.3%, p<0.001), as shown in Figure 2. Furthermore, having high-risk characteristics increased the risk of death or relapse by 3.7 times (p<0.001, 95% CI 2.11-6.72). Table 2 describes the chemotherapy protocols that were used in high- and standard-risk patients, and Table 3 describes the doses of radiotherapy used in both groups of patients.

Based on the approach for metastasis, utilizing cerebrospinal fluid cytology and MRI, 54.9% (n=156) of the patients did not show metastasis at diagnosis (M0). Microscopic evidence of tumor cells in cerebrospinal fluid (M1) was observed in 15.8% of cases, while 9.9% showed intracranial metastasis (M2), 11.3% had gross nodular seeding of spinal metastasis (M3), and 1.8% had metastasis outside the central nervous system (M4). Patients with metastatic disease had a 1.9 times higher risk of death (p=0.001, 95% CI 1.29-2.89).

Since residual tumor after surgical resection is considered part of the risk stratification, we performed an analysis of the surgical results. Based on post-operative CT or MRI, residual tumor less than 1.5cm^2 was achieved in 46.1% (n=131) of the patients, and gross tumor resection was accomplished in 29.6% (n=84) of the cases. Survival analysis revealed that patients with a residual tumor less than 1.5cm^2 and gross tumor resection had significantly higher EFS compared to those with residual tumor >1.5cm^2 (5-year EFS 72.1% vs. 33.6%, p<0.001). Further statistical analysis showed that a residual tumor >1.5cm^2 increased the risk of death or relapse by 3.6 times (p<0.001). Within the first 48 hours post-surgery, a CT or MRI was obtained in 62.7% (n=178) of the cases. Interestingly, only

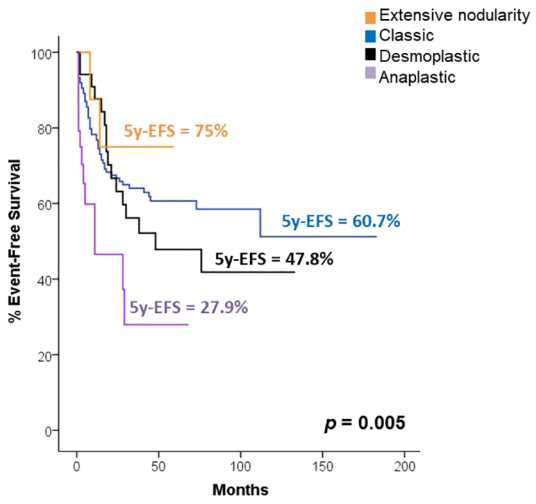

FIGURE 1
Survival according to risk classification.

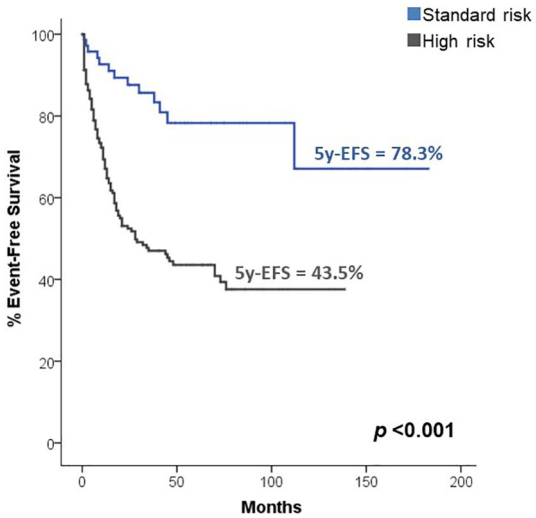

FIGURE 2
Survival according to histology.

TABLE 2 Chemotherapy protocol according to risk group.

	High risk n= 211	Standard risk n= 73	*p* value
Chemotherapy			
ICE protocol	130 (61.6%)	24 (32.8%)	<0.001
Carboplatin + VP-16 + VCR ± CPM	11 (5.2%)	17 (23.2%)	<0.001
Cisplatin + VCR ± VP-16 ± CPM	33 (15.6%)	26 (35.6%)	0.001
Other regimens	9 (4.3%)	2 (2.7%)	0.461
Without chemotherapy	17 (8.1%)	3 (4.1%)	0.303
Unknown	11 (5.2%)	1 (1.3%)	0.308

8.5% (n=24) of the children displayed clinical data of cerebellar mutism syndrome.

In the entire cohort craniospinal radiotherapy (CSI) was administered to 75% (n=213) of the patients; conformal, intensity-modulated and, in some centers, cobalt-based radiotherapy was used; all patients received posterior fossa boost. Table 3 provides an overview of radiotherapy doses based on different clinical characteristics. We found that the dose to posterior fossa radiation impacted OS, with a 3-year OS of 81.8% for patients who received >50Gy and 60.2% for those who received <50Gy (p=0.04). The mean age at which patients received radiotherapy was 7.4 ± 3.6 years, ranging from 1 to 17 years old. Notably, 9.7% (n=20) of the patients who received CSI were less than 3 years old. Of the cohort, 60 patients did not receive radiotherapy for various reasons such as lack of resources, age of the patient, or early death due to complications. Of this group of patients, 26 were younger than three years, and the mean age was 5.2 years. The patients who did not receive radiotherapy had a 1-year OS of 36.7% and a 3-year OS of 19.3%.

In 31.3% (n=89) of the cases, radiotherapy was applied after surgical resection, and in 21.8% (n=62) of the children was initiated within the first 6 weeks after surgery. No significant differences in the risk of death or relapse were found between those who initiated radiotherapy within 6 weeks and those who had a delay of more than 6 weeks (p=0.717). In the case of patients who took more than 6 weeks to receive radiotherapy after surgery, this was due firstly to infectious or post-surgical complications, and secondly to administrative problems such as availability, equipment failure or economic issues.

TABLE 3 Radiotherapy doses based on clinical characteristics.

Characteristic	Posterior fossa Mean ± SD	Craniospinal Mean ± SD
All patients	52.1 ± 6.2 Gy	29.1 ± 7.8 Gy
High risk	51.7 ± 7.1 Gy	30.4 ± 7.6 Gy
Standard risk	53.01 ± 3.6 Gy	26.5 ± 7.4 Gy
>3 years old	53.1 ± 3.9 Gy	29.05 ± 7.7 Gy
<3 years old	43.8 ± 13.4 Gy	29.8 ± 8.3 Gy

Because of the wide variability among healthcare systems in Mexico, this study found that different chemotherapy regimens were used. The most frequently used regimen was the ICE regimen (ifosfamide, carboplatin, and etoposide), with a median of 7 cycles, followed by protocols based on cisplatin such as the Packer protocol (10), or based on carboplatin protocols (11). In a very low frequency, other regimens such as irinotecan, temozolomide, or nitrosoureas-based protocols were utilized.

Some patients were reported as not receiving chemotherapy. This was either due to their arrival in precarious health conditions that led to death before any treatment could be administered or due to expiration resulting from post-surgical complications. Figure 3 provides an overview of the frequency and percentage of the different chemotherapy regimens used.

The platinum-based regimens demonstrated superior OS and EFS compared to the ICE protocol, with 5-year OS rates of 73.6% vs. 59.7% (p = 0.029) and 5-year EFS rates of 63% vs. 53.6% (p=0.040), respectively, as is shown in Figure 4. Through multivariate analysis to predict the risk of death or relapse, we found that the use of the ICE protocol was associated with a 1.7 times higher risk of death or relapse compared to the use of any other chemotherapy regimen (p=0.032), mainly explained by toxicity complications.

Regarding the survival analyses of the entire cohort, the 5-year OS and EFS rates were found to be 59.9% and 52.6% respectively. Table 4 presents the results, highlighting significant differences in OS and EFS based on various patient characteristics, including age, histology, and risk. Table 5 provides a description of the factors that influenced death or relapse.

The group of patients under 3 years old, exhibited significantly lower OS and EFS compared to older patients (5-year EFS 36.1% vs. 55.9%, p=0.01). The type of chemotherapy they received is described in Table 6, with the ICE protocol being the most used. Only two patients received autologous stem cell transplant, both with minimal residual disease. One of them is alive with 17 months of follow-up and received focal radiotherapy, while the other one did not receive radiotherapy and passed away after 21 months of diagnosis.

4 Discussion

Medulloblastoma is a tumor that predominantly occurs in pediatric age, with most cases diagnosed between 5 and 10 years (12). Our study found a similar median age of 6.0 years (SEM 0.24), aligning with previous findings.

Similar to a study conducted by Akyüz et al. in Turkey (13), we observed a male-to-female ratio of 1.6. The relationship between gender and survival has been a subject of discussion. Unlike the results reported by Curran et al. from the U.S. Surveillance Epidemiology and End Results (SEER-9) registry (14), we did not find a difference in OS or EFS based on gender.

In our study, we observed the following frequencies of histological variants: classic medulloblastoma 53.9%, desmoplastic 12.7%, large cell-anaplastic 8.5%, and extensive nodularity 3.2%.

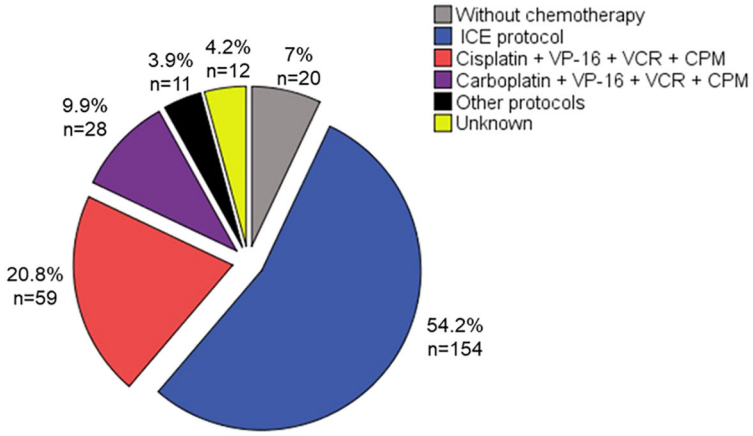

FIGURE 3
Chemotherapy regimens used.

These findings are very similar to the report by Louis DN et al., who found 72% classic, 14% desmoplastic, 11% large cell/anaplastic, and 3% extensive nodularity (12).

Regarding survival, one unexpected result was observed in desmoplastic/extensive nodularity histology, which is known for its nodular architecture and excellent prognosis (15–17). Even without radiotherapy as adjuvant treatment, children younger than 3 years with desmoplastic histology showed a 10-year progression-free survival of 85%, compared to classic histology with 34% (18). However, in our study, the survival of the desmoplastic variant was similar to the classic variant (5-year OS 58.7% vs. 52.2%). The patients with extensive nodularity variant showed an excellent outcome with a 5-year OS of 83.3%, which is similar to the prognosis reported for this histological variant in other studies (19). Another unexpected result was the lower frequency of desmoplastic/extensive nodularity histology of 24% among our 50 patients under three years old, while other series reported a frequency of approximately 44% for the desmoplastic variant in patients under three years old (20). We believe that these results can also be explained by a recurring issue we encountered wherein: 21.8% of our patients, the histological variant was not reported in the pathology results. Additionally, since we do not routinely perform molecular studies, we are unaware of the frequency of mutations that confer a worse prognosis to the sonic hedgehog subgroup, such as TP53 mutations or specific chromosomal aberrations (19).

Regarding the large cell-anaplastic histological subtype and survival, we found that it is a risk factor for death or relapse, with a hazard risk of 2.4, which is consistent with the findings of Eberhart et al., who reported that severe anaplasia alone is associated with worse clinical outcomes (p=0.002) (21). Other reports suggest that the anaplastic subtype is related to an inferior prognosis when certain biological characteristics are present, such as c-myc amplification (22). Unfortunately, we do not have information on

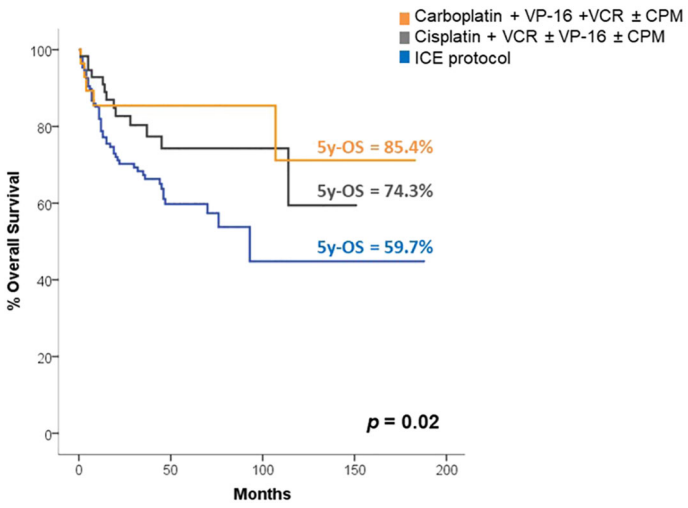

FIGURE 4
Survival according to chemotherapy regimens.

TABLE 4 Survival according to different characteristics.

	3y-OS	5y-OS	*p* value	3y-EFS	5y-EFS	*p* value
High risk	56.9%	52.6%	<0.001	47%	43.5%	<0.001
Standard risk	85.7%	80.6%		85.7%	78.3%	
<3 years old	47.3%	47.3%	0.04	36.1%	36.1%	0.011
>3 years old	68.3%	62.5%		61.5%	55.9%	
Anaplastic	52.2%	52.2%	0.011	27.9%	27.9%	0.001
Other histology	68.1%	63.9%		63%	58.7%	
Residual tumor >1.5cm^2	46.6%	44.7%	<0.001	37.3%	33.6%	<0.001
Residual tumor <1.5cm^2	82.5%	77.4%		76.9%	72.1%	
Metastatic disease	53.6%	50.9%	0.001	45%	42.4%	<0.001
Non-metastatic disease	73.6%	67.4%		67.2%	61%	

the molecular markers of our patients, this is due to the fact that these studies are not available in our country.

In our cohort, the median dose for the posterior fossa radiotherapy boost was 52.1 ± 6.2 Gy, which is not significantly different from the recommended dose of 54 Gy (23). Comparing survival between patients who received less than 50 Gy and those who received more than 50 Gy, we found a significantly lower survival in the group that received a lower dose (5-year OS 52.6% vs. 76.7%, p=0.04). Similar reports by Silverman CL et al. (24) have associated the dose of radiotherapy received with survival, and another study by Santos MA et al. found a correlation between lower doses and poorer survival (5-year OS 80% vs. 58%, p=0.02), although they used a censored dose of 44 Gy (25). This underscores the importance of radiotherapy as a fundamental part of medulloblastoma treatment, as the tumor is known to be radiosensitive.

Among our 50 patients under 3 years old, 20 of them underwent irradiation. Of those, five patients underwent surgery, followed by radiotherapy and then chemotherapy, resulting in a 5-year OS of 80%. Fifteen patients after surgery received chemotherapy and then radiotherapy, with a 5-year OS of 83.1%. In contrast, those who did not receive radiotherapy had a significantly lower 5-year OS of 25.7% (p < 0.001). These results differ from a study by Rivera-Luna R. et al. (26), conducted with Mexican patients from different hospitals. In their series of 49 patients under 3 years old, 100% of those who received only chemotherapy died, while those who received chemotherapy and radiotherapy had a 5-year progression-free survival of 66%. It is crucial to explore other treatment strategies for these patients, such as intraventricular therapy or high-dose chemotherapy with hematopoietic progenitor cell rescue (18, 27, 28), to improve survival rates in Mexico. Although medulloblastoma is radiosensitive, CSI should be avoided in children under 3 years of age, due to its adverse effects that can be catastrophic at this age (29–31), other treatment strategies should be used for patients in this age group, especially when patients have desmoplastic nodular histology (17, 27, 32), since the objective of pediatric oncology is not only to cure but to achieve the best possible quality of life.

In our entire cohort, 17.6% (n = 50) of the patients were under 3 years old, and among them, 27 patients experienced death or relapse, resulting in a 5-year EFS of 36.1%. This finding is comparable to several reports that associate being under 3 years of age with a poor prognosis (26, 27). One of the reasons for this is the preference to avoid or delay radiotherapy in these patients due to the side effects associated with it (18).

In the analysis of survival according to chemotherapy regimen, we found that those based on carboplatin had the highest OS and EFS in our patients, with a 5-year OS of 85.4% and 5-year EFS of

TABLE 5 Characteristics related to death or relapse by multivariate regression.

Factor related to death or relapse	Hazard ratio (risk)	*p* value	95% CI
ICE protocol	1.7	0.032	1.04-2.81
Metastatic disease	1.9	<0.001	1.33-2.8
Anaplastic	2.4	0.003	1.35-4.36
Residual tumor >1.5cm^2	3.6	<0.001	2.35-5.53
High risk	3.7	<0.001	2.11-6.72

TABLE 6 Chemotherapy used in children under 3 years.

	High risk n= 211	Standard risk n= 73	*p* value
Chemotherapy			
ICE protocol	25 (50%)	24 (32.8%)	<0.001
Carboplatin + VP-16 + VCR ± CPM	4 (8%)	17 (23.2%)	<0.001
Cisplatin + VCR ± VP-16 ± CPM	10 (20%)	26 (35.6%)	0.001
Other regimens	2 (4%)	2 (2.7%)	0.461
Without chemotherapy	4 (8%)	3 (4.1%)	0.303
Unknown	5 (10%)	1 (1.3%)	0.308

68.1%. These results are very similar to the findings in pediatric patients in Cairo, where the regimen of carboplatin, etoposide, and vincristine led to a 5-year OS of 89% and disease-free survival at 5 years of 78% (33).

In our study, the regimens based on cisplatin showed the second-best survival, with a 5-year OS of 74.3%. This is consistent with results from a study in Turkey, a middle-income country, conducted by Akyüz et al., who reported an 8-year OS of 60% with the cisplatin plus etoposide regimen [16]. They transitioned to this regimen in an effort to improve survival and decrease the toxicity associated with their previous lomustine-based regimen, which showed an 8-year OS of 41.1%. However, our study's survival with cisplatin-based regimens differs significantly from that reported in high-income countries. Such as Packer et al. reported a 5-year OS of 87% in standard-risk patients treated with the Children's Oncology Group trial A9961, which included CSI therapy followed by adjuvant chemotherapy with cisplatin, vincristine and cyclophosphamide (10). Similarly, in high-risk patients treated with platinum-based chemotherapy, Tarbell et al. reported a 5-year OS of 76.1% (34).

Analyzing one of the reasons why the ICE protocol in this study is significantly associated with lower OS than other protocols, we found that it is associated with a high rate of toxicity, as described by Kanamori M et al. (35, 36). They reported adverse effects of ICE combination chemotherapy in the treatment of various brain tumors, including grade 4 neutropenia in 81.4% of cases, grade 4 thrombocytopenia in 35.4%, and infection in 26.8%, among other toxicities such as grade 4 anemia and elevated alanine and aspartate aminotransferases. These findings suggest that the high rate of adverse effects requires close follow-up or dose reduction.

One early complication observed within the first two days after surgical resection of medulloblastoma in children is cerebellar mutism syndrome. In our population, we found a low frequency of 8.5%, compared to the 24% reported by Robertson et al. (37). This difference in rates can be explained by our lack of intentional use of a diagnostic tool. In their study, Robertson et al. used a questionnaire aimed at identifying the presence and severity of cerebellar mutism syndrome.

In our total cohort, patients with standard-risk characteristics have been successfully treated, while the prognosis for children with high-risk characteristics remains poor. Table 7 compares our survival rates with treatment protocols that use similar resources to those currently available in our country.

TABLE 7 Comparison of 5y-EFS according to risk.

Standard Risk		High Risk	
Mexico (this study)	78.3%	Mexico (this study)	43.5%
Gajjar et al., 2006 (SJMB96) (28)	83%	Gajjar et al., 2006 (SJMB96) (28)	70%
Packer et al., 1999 (CCG9892) (38)	79%	Zeltzer et al., 1999 (CCG921) (39)	63%
Packer et al., 2013 (COG A9961) (10)	81%	Jakacki et al., 2012 (40)	71%

5 Conclusion

This study has several strengths, including the collaboration of twenty-one pediatric oncology centers and a significant sample size from different regions of Mexico. However, it is important to note that this is a retrospective study, and future multi-institutional prospective clinical trials are needed to further define survival, risk factors, and outcomes in Mexico.

Managing medulloblastoma poses challenges in low and middle-income countries. Nevertheless, this study identifies characteristics that increase the risk of death in our patients. With feasible changes, we can improve staging and better guide treatment decisions, such as requesting histopathological subtyping and establishing direct communication with the radiotherapy team to discuss and determine the appropriate radiation dose for each patient, avoiding CSI in young children.

One of the most important aspects that we need to improve is our infrastructure in all cancer care centers for children with cancer, such as access to conformal radiotherapy, magnetic resonance imaging, neuronavigation, or microscopes for neurosurgery, to mention a few examples that would make significant improvements in survival. In addition, given the crucial role of genotype knowledge in medulloblastoma treatment worldwide, countries like Mexico should implement this important tool as part of routine practice to ensure accurate treatment for these children.

Implementing twinning programs, which have shown success in improving survival rates in low and middle-income countries, could also be a valuable strategy to consider (8, 41).

Additionally, it would be beneficial to develop unified national treatment guidelines and explore new treatment strategies for patients with high-risk disease and young children and consider using the least toxic chemotherapy protocols whenever possible, aiming to heal with the best possible quality of life.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

VS-R: Conceptualization, Data Curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. IT-R: Data Curation, Investigation, Validation,

Visualization, Writing – original draft, Writing – review & editing. DO: Data Curation, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. RB-M: Data Curation, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. AL-F: Data Curation, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. SA-A: Data Curation, Investigation, Validation, Writing – original draft, Writing – review & editing. DO-M: Data Curation, Investigation, Writing – original draft, Writing – review & editing. RR-L: Data Curation, Investigation, Validation, Writing – original draft, Writing – review & editing. ER-G: Data Curation, Investigation, Writing – original draft, Writing – review & editing. RR-G: Data Curation, Investigation, Writing – original draft, Writing – review & editing. LV-H: Data Curation, Investigation, Validation, Writing – original draft, Writing – review & editing. DC-A: Data Curation, Investigation, Writing – original draft, Writing – review & editing. SL-A: Data Curation, Investigation, Writing – original draft, Writing – review & editing. FA-G: Data Curation, Investigation, Writing – original draft, Writing – review & editing. AB-R: Data Curation, Investigation, Validation, Writing – original draft, Writing – review & editing. SC-G: Data Curation, Investigation, Writing – original draft, Writing – review & editing. EP-R: Data Curation, Investigation, Writing – original draft, Writing – review & editing. GG-F: Data Curation, Investigation, Writing – original draft, Writing – review & editing. JL-E: Data Curation, Investigation, Writing – original draft, Writing – review & editing. JD-S: Data Curation, Investigation, Writing – original draft, Writing – review & editing. CL-C: Data Curation, Investigation, Writing – original draft, Writing – review & editing. CS-G: Data Curation, Investigation, Writing – original draft, Writing – review & editing. TL-F: Data Curation, Investigation, Writing – original draft, Writing – review & editing. NM-G: Data Curation, Investigation, Writing – original draft, Writing – review & editing. AG-E: Data Curation, Investigation, Writing – original draft, Writing – review & editing. FG-M: Data Curation, Writing – original draft, Writing – review & editing. PC-T: Writing – original draft, Writing – review & editing. OG-R: Data Curation, Investigation, Writing – original draft, Writing – review & editing.

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Conflict of interest

Author DO was employed by ICON PLC.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Pediatric neuropathology practice in a low- and middle-income country: capacity building through institutional twinning

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Background: Accurate and precise diagnosis is central to treating central nervous system (CNS) tumors, yet tissue diagnosis is often a neglected focus in low- and middle-income countries (LMICs). Since 2016, the WHO classification of CNS tumors has increasingly incorporated molecular biomarkers into the diagnosis of CNS tumors. While this shift to precision diagnostics promises a high degree of diagnostic accuracy and prognostic precision, it has also resulted in increasing divergence in diagnostic and management practices between LMICs and high-income countries (HICs). Pathologists and laboratory professionals in LMICs lack the proper training and tools to join the molecular diagnostic revolution. We describe the impact of a 7-year long twinning program between Canada and Pakistan on pathology services.

Methods: During the study period, 141 challenging cases of pediatric CNS tumors initially diagnosed at Aga Khan University Hospital (AKUH), Karachi, were sent to the Hospital for Sick Children in Toronto, Canada (SickKids), for a second opinion. Each case received histologic review and often immunohistochemical staining and relevant molecular testing. A monthly multidisciplinary online tumor board (MDTB) was conducted to discuss the results with pathologists from both institutions in attendance.

Results: Diagnostic discordance was seen in 30 cases. Expert review provided subclassification for 53 cases most notably for diffuse gliomas and medulloblastoma. Poorly differentiated tumors benefited the most from second review, mainly because of the resolving power of specialized immunohistochemical stains, NanoString, and targeted gene panel next-generation sequencing. Collaboration with expert neuropathologists led to validation of over half a dozen immunostains at AKUH facilitating diagnosis of CNS tumors.

Conclusions: LMIC-HIC Institutional twinning provides much-needed training and mentorship to pathologists and can help in infrastructure development by adopting and validating new immunohistochemical stains. Persistent unresolved cases indicate that molecular techniques are indispensable in for diagnosis in a minority of cases. The development of affordable alternative molecular techniques may help with these histologically unresolved cases.

KEYWORDS

Low- and lower-middle-income countries, diagnosis, brain tumor, pathology, precision medicine, precision diagnostics, next generation (deep) sequencing (NGS), targeted therapy

Introduction

The World Health Organization (WHO), classification of central nervous system (CNS) tumors has traditionally relied on the morphologic appearance of the tumor under the light microscope. In recent years, however, molecular information has increasingly been used for diagnostic classification. The 4th revised edition of the WHO released in 2016 introduced the concept of "layered integrated diagnosis," according to which reporting of molecular alterations was made a formal part of the essential diagnostic criteria of several tumor entities (1, 2). This conceptual leap in diagnosing CNS tumors was made possible by the wide availability of next-generational sequencing (NGS) technologies. This led to the adoption of genetic sequencing as a routine clinical test in most academic centers in North America and Europe. This trend reached its zenith with the introduction of the 5th edition of WHO classification in 2021 (CNS5), in which several tumor entities are now defined by their genomic or epigenomic signatures (3, 4). Several studies demonstrate that a multiomic approach improves diagnostic precision (5).

Molecular diagnostic techniques such as NGS and DNA-methylation profiling remain out of reach for most LMICs. Pathologists in the LMIC are either insufficiently aware of the recent diagnostic guidelines or their implementation remains outside their practical experience. As a result, there is a widening gap in diagnostic and patient management practices between LMICs and high-income countries (HICs). CNS5 criteria allow for the use of the suffixes "Not Otherwise Specified (NOS)" for cases in which the necessary diagnostic molecular tools are not available; however, this can result in many cases being assigned to these waste-basket categories (embryonal tumor, NOS; infiltrating glioma, NOS, and so on). The WHO classification purports to providing a shared vocabulary for communication and practice guidelines to pathologists worldwide. However, the utility and relevance of the CNS5 in LMIC remain to be demonstrated.

Various approaches have been implemented to enhance the diagnostic capacity in LMICs and to bring pathologists in these regions up to date with current diagnostic practices. One such approach is Institutional twinning, which refers to the collaboration and sharing of expertise and resources between institutions in LMICs and HICs. Here, we describe the impact of a 7-year-long twinning experience between Aga Khan University Hospital (AKUH) in Karachi, Pakistan, and the Hospital for Sick Children (SickKids) in Toronto, Canada, on histopathologic diagnosis. The twinning program had two components: a multidisciplinary tumor board (MDTB) meeting between AKUH and SickKids and a pathological review of biopsy material of selected cases at SickKids. Previously, we demonstrated the impact of twinning on neurooncological services (6). The results of the histopathological review of biopsy material at SickKids are described in more detail in this paper.

Methods

The pediatric neuro-oncology twinning program between the Hospital for Sick Children (SickKids) in Toronto, Canada, and several hospitals in Pakistan began in June 2014. Pakistani partners included the Aga Khan University Hospital (AKUH) and Indus Children's Cancer Hospital (ICCH) in Karachi as significant partners. The partnership was later expanded to include several private and public sector hospitals. Tissue biopsy and initial histopathologic processing were conducted locally at each hospital, but all pathology was later reviewed at the AKUH. At AKUH, the pathology department does not follow a subspecialty practice model for pathology. This means that any of the approximately 25 histopathologists available can review a CNS tumor case. However, most cases are reviewed by KM at some point. It is important to note that subspeciality fellowship training in neuropathology is currently unavailable in Pakistan.

A total of 460 cases were reviewed and discussed in the virtual (video-conferenced) multidisciplinary tumor board (MDTB) meetings during the study period (2014–2020). Typically, the meetings were arranged once every month and were attended by specialists from both countries. The Pakistani side was represented by neuro-oncologists, neurosurgeons, radiation oncologists,

neuroradiologists, and neuropathologists, whereas one or more neurooncologists and neuropathologists represented SickKids in these meetings. The pathologists in Pakistan shared photomicrographs of *H&E* and immunohistochemical stains for each case. The case was then discussed and recommendations given for further treatment or pathology review. Select cases (n = 141 included in this study) were sent to SickKids for review. Inclusion criteria for such cases included the following: (1) cases in which a precise histopathologic diagnosis was not reached at AKUH; (2) cases requiring demonstration/ruling out of specific molecular alterations such as *IDH1/2*, histone 3 genes, and *BRAF* mutations; (3) unusual cases that required expert review for confirmation of the AKUH diagnosis; (4) any case for which the treating clinician requested a consult; and (5) consult was requested by the team during MDTB meetings. Patients who were 19 years old or younger at the time of biopsy were considered pediatric and included in this study. Typically, one to two blocks were sent for review and additional testing. Specimen shipping times typically varied from 7 to 10 calendar days, and preliminary diagnosis was typically rendered within 5–7 calendar days of receipt by the consulted pathologist.

Histologic processing conducted at the referring institutions followed standard guidelines in compliance with those of the College of American Pathologists (CAP). At the initiation of the study, both AKUH and Indus Hospital labs were in the process of acquiring CAP accreditation, receiving CAP accreditation in 2018 and 2023 respectively. Formalin-fixed paraffin-embedded (FFPE) blocks or unstained sections on glass slides, along with clinical information and official histopathologic reports, were sent along for review to SickKids. These cases were logged into the SickKids system and treated like any other referral case. H&E examination, immunohistochemical staining, and any relevant molecular test were then conducted at the discretion of the consulting neuropathologist (CH).

Molecular testing included fluorescent *in situ* hybridization (FISH), NanoString (7), or a TruSight Assay. Methodological details of the NanoString assay have been published before (7, 8). Briefly, custom panels (pediatric low-grade glioma panel, medulloblastoma panel, or the ependymoma fusion panel) were developed and tested using NanoString nCounter system (NanoString Technologies, Seattle, WA). RNA was extracted using the RNeasy FFPE kit ((QIAGEN, Valencia, CA). Probes designed to detect expression of three different housekeeping genes were included to assess RNA quality. For the medulloblastoma panel, probes were designed to detect gene transcripts enriched in specific groups including the following: WNT signature genes: *WIFI, TNC, GADI, DKK2*, and *EMX2; SHH* signature genes: *PDLIM3, EYAI, HHIP, ATOHI*, and *SFRPI*; Group 3 signature genes: *IMPG2, GABRA5, EGFL11, NRL, MAB21L2*, and *NPR3*; Group 4 signature genes: *KCNA1, EOMES, KHDRBS2, RBM24, UNCSD*, and *OASI*. Oligonucleotide probes were obtained from Integrated DNA Technologies (Coralville, IA), and the Elements tag sets were supplied by NanoString Technologies (Seattle, WA). A PAM class prediction algorithm was used to predict subgroup based on the expression levels of the above signature genes. The subgrouping was subsequently confirmed by visually inspecting the expression levels of the 22 signature genes. Pediatric LGG fusion gene analysis used probes designed to detect fusion transcripts in several genes most notably *BRAF*, *FGFR1*, and *FGFR3* genes. Similarly, the ependymoma fusion gene detection probes were designed to detect fusion transcripts including *C11orf95-RELA* and *YAP1-MAMLD1*.

Later in the course of the study, cases were tested using the TruSight pan Cancer RNA panel (Illumina, San Diego, CA) using FFPE tissue. NGS and Automated Fusion Calling RNA-derived NGS libraries are enriched using the TruSight Pan-Cancer 1385 gene panel. The TruSight Pan-Cancer-targeted gene list can be found at https://www.illumina.com/content/darn/illumina marketing/documents/products/genelists/genelistTruSight pan cancer.xlsx). Libraries were sequenced on an Illumina MiSeqDx, with a minimum library size of two million reads. Sequence was aligned to the hg19 human genomic scaffold, and fusions are called using the Illumina STAR aligner (v2.5.0b) and the Manta structural variant caller (v1.5.0). The following genes were manually checked for fusions using IGV: *FGFR1, FGFR2, FGFR3, BRAF, RAF1, NTRK1, NTRK2, NTRK3.*

MMR testing by immunohistochemistry was performed in a subset of cases based on clinical suspicion or histomorphological features. MSH2, MSH6, MLH1, and PMS antibodies were used.

Since the study was conducted prior to the release of the 2021 World Health Organization (WHO) classification system, the official diagnoses used the WHO 2016 nomenclature.

For this study, each case was described as *concordant, subtyped, discordant*, or *deferred*. Cases were descried as discordant when there was a significant change in diagnosis often involving a change of grade, tumor cell lineage, etc. In subtyped cases, there was no change in diagnosis, but a tumor subtype was provided by the consulted pathologist. Cases in this category most commonly included glioblastoma and medulloblastoma. In concordant cases, there was either no change in diagnosis or a more specific diagnosis was provided without a change in the diagnostic class, for example when the expert diagnosis was a diffuse astrocytoma, IDH mutant instead of a referring diagnosis of diffuse glioma. In two cases, only a descriptive diagnosis was rendered by the expert neuropathologist.

Results

The referring and consulted pathologists were in general agreement regarding the diagnosis in 102 cases (72.3%). Expert consultation provided subtyping without a change of diagnosis in 53 cases (*subtyped* cases). The rest, described here as *concordant* cases, often showed refinement of the diagnosis upon expert review.

Good concordance was seen for tumors, such as pleomorphic xanthoastrocytoma (PXA), choroid plexus tumors, pineoblastoma, and medulloblastoma. In these tumors, the expert opinion provided confirmation of the diagnosis and identification of molecular alterations. In 23/49 concordant cases, the consult identified or ruled out common driver genetic alterations in the diagnosed tumor type (Table 1, Supplementary Table 1). Of the 32 patients that were diagnosed with diffuse glioma, i.e., astrocytoma, anaplastic astrocytoma, glioblastoma, or high-grade glioma (HGG), histone

TABLE 1 Molecular alterations identified upon consultation at SickKids.

Molecular alteration	Method of detection	Number of positive cases
BRAF V600E	IHC	**13**
***BRAF* fusion (KIAA1549 - BRAF)**	**NanoString assay**	**10**
BRAF (ex16 - ex9)		6
BRAF (ex15 - ex9)		3
BRAF (ex16 - ex11)		1
BRAF duplication	FISH	1
Histone mutations	**IHC**	**10**
H3 K27M		9
H3 G34R		1
***IDH* mutations**		6
IDH1 R132H	IHC	4
IDH1 R132S	NanoString	2
Mismatch repair deficiency	**IHC**	**5**
***c11orf95-RELA* fusion**	**NanoString assay**	**3**
***MYB-QKI* fusion**	**NanoString assay**	**1**
***MYCN* amplification**	**TruSight assay**	**1**
***KRAS* p.Q61K mutation**	**TruSight assay**	**1**
FGFR3 mutation	**TruSight assay**	**1**
***EWSR1-CREM* fusion**	**TruSight assay**	**1**
***EGFR* mutation**	**TruSight assay**	**1**
***DICER 1* mutations**	**TruSight assay**	**1**
***NF1* mutations**	**TruSight assay**	**1**
***SMARCB1* loss**	**IHC**	**1**
Total		**57**

alterations were found in a little over a third (nine cases of H3K27M, one case with *EGFR* ex 20 mutations, and one case of *H3 G34R* mutation), and IDH1 mutations in six (four with *IDH1 R132H* and two with *IDH1 R132S* mutations (Table 1, Figure 1).

Of the 29 medulloblastoma, 28 had been called accurately by the referring pathologists; in one case, the diagnosis was deferred. Expert consultation, however, provided molecular subclassification in these cases using an assay based on the NanoString nCounter system (8). In most cases of medulloblastoma, the consulted pathologist conducted histologic review in addition to molecular testing, providing an opportunity for the referring pathologist to compare their histologic diagnosis for WNT-activated subtype and desmoplastic/nodular subtype for which the immunohistochemical (B-catenin) or special histologic (reticulin) stains were available at AKUH. The results (Figure 2) show variable degrees of concordance for histologic subtypes of medulloblastoma. Discordant cases were due to differences in interpreting reticulin stain, not performing reticulin stain, and not recognizing patchy and often rare B-catenin nuclear positivity. GAB1 immunostain was validated at AKUH at the conclusion of the study and is now routinely performed to enable identification of SHH-activated subtype of medulloblastoma.

Seven cases were deferred to expert opinion or were diagnosed descriptively as malignant neoplasms, high-grade gliomas, or embryonal tumors. These eventually yielded a variety of low and high-grade tumors including an angiomatoid fibrous histiocytoma with *EWSR1::CREM* fusion, a pleomorphic xanthoastrocytoma, and a DICER 1 associated sarcoma.

A disagreement in diagnosis was seen in 30 cases (referred here as *discordant* cases). Discordant cases included changes in diagnoses with limited clinical impact such as a change from a Pilocytic astrocytoma to ganglioglioma and vice versa; as well as cases with major clinical impact such as change in tumor grade (high-grade to low-grade or vice versa), change from neoplastic to non-neoplastic or vice versa, or change of tumor type/lineage (such as a switch between embryonal, ependymal, glial categories). Notable cases including two cases which were deemed non-neoplastic were diagnosed as a germinoma, and a sarcoma (Supplementary Table 1). Both these specimens featured heavy inflammatory reaction, demonstrating the difficulty of accurately diagnosing cases where rare neoplastic cells are present alongside a majority of reactive or normal cells.

Seven out of 10 patients who were initially diagnosed with ependymal tumors at AKUH were called as such on expert consultation (Figure 1 and Supplementary Table 1). The remaining three were astrocytomas (a GBM, a glioma with an *H3 K27M* mutation, and a pilocytic astrocytoma). Conversely, one patient diagnosed with a posterior fossa "CNS Embryonal tumor with rhabdoid features" was eventually diagnosed with ependymoma by the expert. These discrepancies could be avoided by recognizing the histologic features and immunohistochemical profiles of particular CNS-tumor types. To enable astrocytoma-ependymoma differentiation, Olig2 was validated and incorporated in the immunohistochemical repertoire at AKUH. Subtyping was provided in four ependymoma patients with identification of *RELA* fusion in three supratentorial ependymoma cases and posterior fossa-A designation in a fourth ventricular tumor.

Not unexpectedly, poorly differentiated tumors diagnosed as embryonal tumors often changed diagnosis upon expert review with the final diagnosis being a glioblastoma with *IDH1* mutation, an ependymoma (mentioned above), and a peripheral nerve sheath tumor. These cases show the inability of histologic examination to distinguish between ependymoma, astrocytoma, and embryonal tumors in poorly differentiated, highly malignant cases.

Another tumor type with a high degree of discordance in this series is oligodendroglioma. Six specimens diagnosed as oligodendroglioma or likely oligodendroglioma were eventually diagnosed as (*IDH1* mutant astrocytoma, two cases; one DNET and two pilocytic astrocytoma and a diffuse glioma). Two cases showed a major change in grade between low-grade and high-grade, whereas two additional cases showed a change between diffuse vs. circumscribed glioma.

Apart from providing confirmation, refining diagnoses, and correcting some diagnoses, institutional twinning helped with diagnostic capacity building at AKUH. Several new immunohistochemical stains to aid with

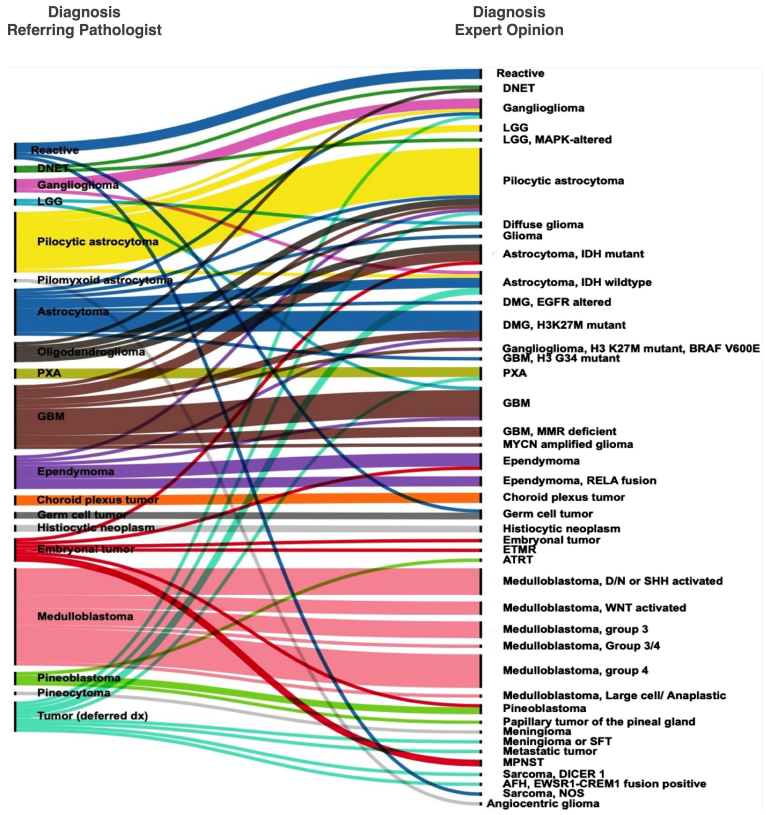

FIGURE 1
Concordance and discordance in histopathological diagnosis between the referring pathologists and the expert opinion.

the diagnosis of CNS tumors were validated at AKUH and incorporated in the clinical laboratory's testing menu. For this purpose, SickKids shared protocols and cases already tested at SickKids were used for validation. Newly introduced stains included stains used for differentiation between cell lineages (Olig2), surrogate markers for molecular alterations (IDH1 R132H, ATRX), markers of specific tumor types (Lin28 for ETMR and L1CAM for supratentorial ependymoma, RELA/ZFTA fusion-positive), and markers for tumor subtyping (including GAB1 for SHH-activated tumor and H3 K27me3 for ependymoma, posterior fossa-A/posterior fossa-B distinction). Introducing these stains developed in-house capacity to resolve additional cases, thus reducing dependency on expert review at SickKids for such cases toward the conclusion of the study. IDH1 R132H stain was incorporated in 2019. In the beginning, a few cases showed differing interpretation of this stain between AKUH and SickKids Pathologist; since then, there has been good concordance. Immunohistochemical stains for identifying mismatch repair deficiency (MMR) were introduced at AKUH in 2019 and were performed in a few cases in this cohort with concordant results on retesting at SickKids Hospital. Additional immunostains are in the validation process (including immunostains for *H3 K27M*, *H3 G34 R/V*, and *BRAF V600E*).

Discussion

We describe the impact of expert opinion and mentorship provided during institutional twinning on histopathology diagnosis. We also show the types of unresolved cases and those with the most discordant diagnosis between the referring LMIC pathologists and HIC expert opinion.

The relevance of molecular diagnostics-based criteria like the CNS5 for LMICs has been called into question, and it has been suggested that, increasingly, these criteria are unlikely to be of significant benefit to most patients in LMICs (9). Several authors have pointed out that precision therapies are still largely out of reach of most patients in LMICs. Hence, the identification of molecular biomarkers and diagnostic criteria heavily based on molecular alterations is largely irrelevant to LMICs.

Molecular testing and identification of oncogenic drivers and prognostic and therapeutic markers have also intensified the search for surrogate markers that can be obtained using traditional diagnostic techniques. Surrogate biomarkers for molecular alterations in central nervous system (CNS) tumors are less expensive than other forms of molecular testing. Still, they are also faster and easily integrated into the usual surgical pathology workflow. These biomarkers can be diagnostic, prognostic, and/or predictive (e.g., provide biological targets for treatment). We also note that in rare instances, successful targeted therapies have been conducted in LMICs, including by our group (10, 11).

We show that most cases will likely be resolved by careful histopathologic analysis and the use of immunohistochemical stains, including surrogate stains for histone 3, *IDH1* and *BRAF* mutations, and subtype-specific stains for ependymoma and

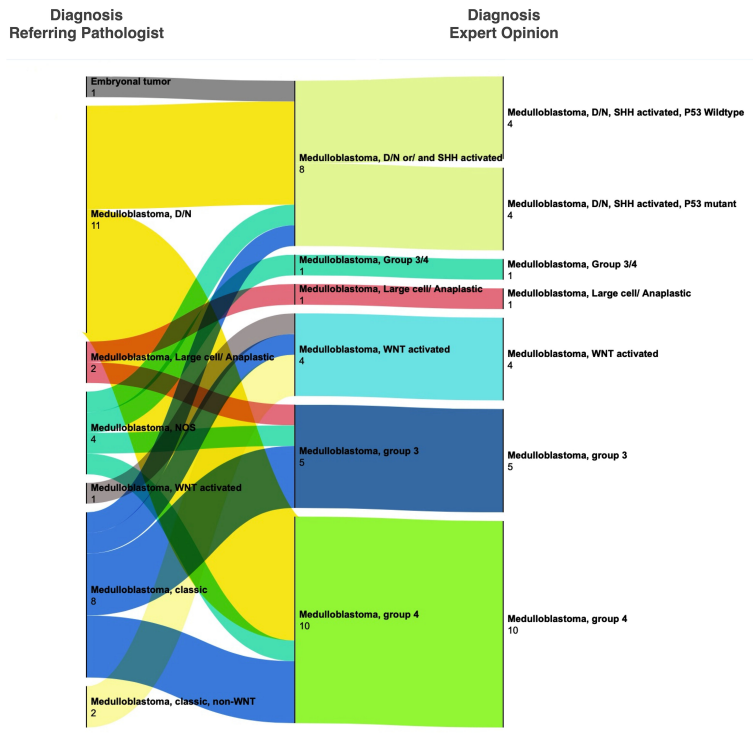

FIGURE 2
Change in histopathological diagnoses after expert consultation for medulloblastoma. Most cases were given a histologic diagnosis by the referring pathologist. Upon review at SickKids, cases received either molecular testing alone (by NanoString assay) or both molecular testing and histologic review. Significant discordance was seen in the interpretation of B-catenin immunohistochemistry and desmoplastic nodular histology (also see Supplementary Table 1).

medulloblastoma. Out of a total of 57 genetic alterations identified in the cases in this study, only 10 cannot be identified by IHC stains. Half of all medulloblastoma consisted of WNT-activated or SHH-activated groups, which can be diagnosed based on immunohistochemical stains. The remaining unresolved cases (10 cases with non-*BRAF*/non *RELA/ZFTA* fusions and 16 non-WNT/non-SHH medulloblastoma) can then be subjected to NanoString, NGS, or other advanced molecular testing methods.

As shown in this and previous studies, *BRAF-KIAA1549* fusions and mutations such as *BRAF V600E*, *IDH1 R132H*, and *H3 K27M* are among the most common types of genetic alteration mutations in pediatric gliomas, and the immunostains for these alterations should be part of the immunohistochemistry (IHC) repertoire of reference labs in LMICs. These stains should be used in combination with Olig2 (to identify H3 G34R/V mutant tumors), ATRX, and P53 stains. Therefore, in many cases, the likely diagnosis can be achieved by using surrogate immunohistochemical markers in the context of the clinical features. This approach will miss a small minority of IDH mutant tumors, namely, those with non-canonical *IDH* mutations (enriched in specific clinical scenarios such as the infratentorial diffuse gliomas (12) and Li-Fraumeni patients) (13).

Although morphological features alone can be used for diagnosis of CNS tumors in a vast majority of cases; in reality, pathologists often use the identification of molecular biomarkers to substantiate their histologic impression. For example, the identification of a *BRAF* fusion can lend credence to a diagnosis of histologically ambiguous pilocytic astrocytoma, or the presence of *BRAF V600E* mutation and deletion of *CDKN2A/B* gene by FISH or DNA testing can confirm the diagnosis of PXA. Similarly, although not strictly required, identification of *MYB-QKI* fusion can confirm a diagnosis of angiocentric glioma, which can be confused with other LGGs such as pilomyxoid astrocytoma, as evident in this series. Limited access to molecular testing places additional demands on the clinical and diagnostic acumen of both pathologists and oncologists who ought to recognize each tumor's standard, expected behavior, and treatment response, so that if a particular patient deviates from that pattern, advanced, more costly diagnostic tests are obtained to rule out alternative diagnoses.

Our data show that in a significant subset of cases, the correct diagnosis could have been arrived at by careful study of the patient's clinical picture, astute histologic examination, and greater awareness of the published diagnostic criteria. This is exemplified by the diagnosis of oligodendroglioma in six patients; none of them was eventually substantiated as an oligodendroglioma. According to 2016 and 2022 WHO diagnostic criteria, this diagnosis should only be given to tumors that are IDH mutant and 1p/19q co-deleted. Furthermore, oligodendroglioma will be exceedingly uncommon in the pediatric age group. Knowledge and expertise gaps were therefore at least partially responsible for this discrepancy. We expect that this issue will be partly resolved by subspecialty-based practice by virtue of which a pathologist specializes in providing

CNS tumor diagnosis either after a structured fellowship training or by learning on the job. IDH1 R132H immunohistochemical and ATRX stains are now available at AKUH and at least two other laboratories in the country and will hopefully facilitate the diagnosis of oligodendroglioma. 1p/19q co-deletion testing, the other requirement for oligodendroglioma diagnosis, is currently available in only two laboratories in Pakistan, namely, AKUH and Shaukat Khanum Memorial Cancer Hospital (SKMH), Lahore. The cost of this fluorescent *in situ* hybridization (FISH)-based test is borne out of pocket by the family/patient and, at approximately 100 $, is often considered prohibitive unless strongly advised by the treating physician.

In a minority of cases, advanced molecular testing for identification of the characteristic molecular alteration was required for the diagnosis. This includes a case of angiomatoid fibrous histiocytoma with *EWSR1-CREM* fusion, an angiocentric glioma with *MYB-QKI* fusion, a glioma with *MYCN* amplification, two patients with non-canonical IDH mutations (both with *IDH1 R132S*), and a patient with a *KRAS* mutation (Table 1).

At the beginning of the study, AKUH did not provide any molecular testing for the diagnosis of CNS tumors. In recent years, testing for *IDH1/2* hotspot mutations has been incorporated, but gene fusion testing, mutation testing for *BRAF* or histone genes, and copy number testing for *CDKN2A* deletion are still not available. We also note that the diagnostic criteria for CNS tumors have undergone significant revision since the conclusion of this study. The WHO 2021 classification of CNS tumors has increased the utility of NGS and DNA-methylation assays in the diagnosis of CNS to the extent that a significant number of tumors, particularly gliomas, cannot be classified on histology or IHC alone.

We believe that subspecialty practice for neuropathology, at least in a handful of reference labs in a particular country or region, will improve histopathologic diagnosis. This mirrors our experience that developing a subspecialty caregiver team in which the caregivers become experts in their respective fields improves patient outcomes for CNS tumors (6). Pediatric neuropathology is complex by its very nature. Tumors are histologically and molecularly diverse. The field is rapidly growing with frequent advances and changes to diagnostic criteria. In addition, the incidence of these tumors is low; hence, a general pathologist will see only a small number of cases in a certain month or year. It, therefore, stands to reason that a general pathologist cannot be expected to master the intricacies of this field. Sub-specialization is needed. The case volumes in many reference laboratories (such as AKUH and SKMH) can sustain this model. Such sub-specialization has already taken place in other aspects of pediatric neuro-oncology care where specialized pediatric neuro-oncologists, pediatric neurosurgeons, and often pediatric neuroradiologists now care for cases of CNS tumors in children. Studies have shown improved patient outcomes due to the development of subspecialty caregiver teams in which the caregivers become experts at their respective fields (6).

We previously showed that discordance in clinical plans between AKUH and SickKids decreased from around 30% at the beginning of the twinning to 16% at the end of the 7-year study period (2014–2020, both inclusive) (6). In contrast, the number of cases with discordant diagnoses remained high throughout the study period, perhaps reflecting the role of molecular testing in reaching an integrated diagnosis (6). Stated another way, whereas additional training and subspeciality focus will solve some of the problems, they are unlikely to improve the discrepancies further, as even the most experienced neuropathologist will render a somewhat descriptive diagnosis without molecular results.

Our study supports the findings of several previous studies showing the role of second review in improving diagnostic accuracy. A retrospective review of pediatric tumor cases received at St. Jude Children's Research Hospital (SJCRH) from international institutions showed major disagreement in approximately 25% of cases overall and 33% in the CNS (14). The rate of major disagreement at US institutions was lower than that for international institutions at. A switch from malignant to less aggressive (GBM to PXA, for example) was three times more common than vice versa. This study, which compiled data from 2009 to 2011, identified lack of the availability of immunohistochemistry as a major cause for the discrepancy (14). Whether the problem of inadequate tools leading to diagnostic inaccuracy has further aggravated in the molecular era remains to be seen. Another major cause identified by the study was deficient training of pathologists in the diagnosis of pediatric neoplasms. Another study by the same investigators focused on training of a general pathologist in the diagnosis of pediatric neoplasms, implementation of a basic IHC panel in a pathology laboratory in a developing country, and inclusion of the pathologist in a multidisciplinary team. These measures dramatically improved the diagnostic accuracy of pediatric neoplasms (14). This group showed that brief, focused training in pediatric cancer histopathology improved diagnostic accuracy (15). Similarly, a study from Lebanon identified the unavailability of immune and molecular stains as the primary cause of diagnostic discrepancy, accounting for 12/14 cases. The remaining two were due to differences in interpretation (16)..

We demonstrate the utility of remote/virtual twinning between an LMIC and an HIC. While most twinning programs involve physical exchanges of personnel between the participating institutions—a time-consuming and costly proposition—we show the feasibility of virtual twinning in combination with the mailing of pathology specimens. Similar results were shown by Qaddoumi and colleagues achieving successful outcomes using telemedicine-based twinning between King Hussein Cancer Center, Amman, Jordan, and SickKids (17). Interestingly and of particular relevance to this discussion, the most common recommendation was a review of the neuropathology, which was suggested in 10/23 patients. This resulted in a change in the initial diagnosis or the grading of the tumor with significant consequences in terms of subsequent management. As a result, six patients were recommended observation instead of radiation, thereby saving resources and long-term treatment-related toxicity for those patients (17). In a follow-up paper in 2018, the authors presented a 10-year review of

their experience (18). These authors noted that during the study period, there were suggestions for molecular testing, including BRAF fusion/mutation, medulloblastoma subgrouping, and genetic testing. Six cases underwent such testing (18). In one case of disseminated recurrence of a pleomorphic xanthoastrocytoma, identifying *BRAF* mutation at the SickKids laboratory led to the administration of BRAF inhibitor therapy (11).

Recently, important initiatives have been launched to improve access to high-quality medicines and technologies in LMIC by strengthening training programs and developing centers of excellence. One such initiative is the World Health Organization's Global Initiative for Childhood Cancer. Established in 2018, this initiative brings together stakeholders from around the world with the joint goal of increasing the survival rate of children with cancer globally to at least 60% by 2030 while reducing their suffering and improving their quality of life (19). We hope that histopathologic and molecular diagnostics will not be neglected in this and other similar initiatives. We also note that this study was concluded in 2020 before the widespread adoption of DNA methylation-based classification for diagnosing challenging cases. None of the cases in this cohort were tested on that assay. It is conceivable that some of the cases unresolved by traditional histologic and immunohistochemical stains and NGS studies will be resolved using DNA methylation array-based testing. Similarly, several cases were diagnosed as glioblastoma, which is no longer a favored term in the pediatric and young adult age groups. In short, in 2024 as compared with the study period, the diagnostic requirements have become even more complicated and resource intensive.

While this paper only describes in detail the neuropathology infrastructure at AKUH, Karachi, we note that other leading laboratories in Pakistan face similar limitations. A large chunk of all CNS tumors in Pakistan are eventually reviewed at a handful of laboratories in the three major metropolitan cities in Pakistan. These laboratories include AKUH in Karachi, Shaukat Khanum Memorial Cancer Hospital (SKMH) and Chughtai Lab in Lahore, and Shifa International Hospital in Islamabad. AKUH currently offers the most extensive immunohistochemical panel of these institutions. SKMH has recently validated an NGS-based DNA mutation panel, hopefully leading to better identification of key diagnostic, therapeutic, and prognostic markers for CNS tumors in Pakistan. A fusion panel is currently not being offered at any institution in Pakistan.

One possible limitation of LMIC-HIC twinning programs is that it may result in overreliance on second opinion. Pathologists in LMIC should diagnose cases as best as possible based on available tools rather than relying solely on HIC experts or molecular tests. Twinning between LMIC and HIC institutions is maximally beneficial when aiming to build capacity in LMIC. A second opinion from an HIC expert cannot replace local experts.

In conclusion, this study identifies persistent gaps in diagnosing CNS tumors in LMICs due to unavailability of specialized immunohistochemical stains, molecular diagnostic tools, and deficiencies in pathologists skill and knowledge. Twinning between LMIC and HIC institutions can mitigate these deficiencies, help in capacity building, and, therefore, greatly benefit patients. Previously, we showed the role of twinning in improving the care of patients with pediatric CNS tumors in Jordan and Pakistan (6, 16). We now show its impact on histopathologic diagnosis.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by The Aga Khan University - Ethics Review Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

AG: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. NM: Data curation, Funding acquisition, Investigation, Methodology, Project administration, Writing – review & editing. MS: Formal analysis, Writing – review & editing. AA: Writing – review & editing, Data curation, Formal analysis. ZS: Writing – review & editing, Data curation, Formal analysis, Visualization. EB: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing. UT: Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – review & editing. CH: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Writing – review & editing. KM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1328374/full#supplementary-material

SUPPLEMENTARY TABLE 1
Clinicopathologic information and summary of diagnosis rendered by the referring pathologist and the expert neuropathologist at SickKids.

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Resources for the practice of pediatric neuro-oncology in Mexico: a cross-sectional evaluation

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Background: The evaluation of existing resources and services is key to identify gaps and prioritize interventions to expand care capacity for children with central nervous system (CNS) tumors. We sought to evaluate the resources for pediatric neuro-oncology (PNO) in Mexico.

Methods: A cross-sectional online survey with 35 questions was designed to assess PNO resources and services, covering aspects including number of patients, infrastructure, human resources, and diagnostic and treatment time intervals. The survey was distributed to the members of the Mexican Association of Pediatric Oncology and Hematology (AMOHP) who belong to the nation's many different health systems.

Results: Responses were obtained from 33 institutions, distributed throughout the country and part of the many health systems that exist in Mexico. Twenty-one (64%) institutions had less than 10 new cases of pediatric CNS tumors per year. Although 30 (91%) institutions saw pediatric patients up to the age of 18 years, 2 (6%) had a cutoff of 15 years. Twenty-four (73%) institutions had between 1 and 3 pediatric oncologists providing care for children with CNS tumors. Six (18%) institutions did not have a neurosurgeon, while 19 (57%) institutions had a pediatric neurosurgeon. All centers had a pathology department, but 13 (39%) institutions only had access to basic histopathology. Eleven (33%) institutions reported histopathological diagnoses within one week, but 3 (9%) took more than

4 weeks. Radiotherapy for pediatric CNS tumors was referred to outside centers at 18 (55%) institutions. All centers had access to conventional cytotoxic chemotherapy, but only 6 (18%) had access to targeted therapy. Eighteen (55%) respondents estimated a survival rate of less than 60%. Fifteen (45%) centers attributed the main cause of mortality to non-tumor related factors, including infection and post-surgical complications.

Conclusions: This is the first national assessment of the resources available in Mexico for the treatment of CNS tumors. It shows disparities in resource capacity and a lack of the specific and efficient diagnoses that allow timely initiation of treatment. These data will enable the prioritization of collaborative interventions in the future.

KEYWORDS

LMIC, pediatric neuro-oncology, pediatric brain tumors, care capacity, resource availability

Introduction

Central nervous system (CNS) tumors are the second most common pediatric cancer globally (1). Importantly, CNS tumors in children and adolescents have high mortality and morbidity rates (2). In low- and middle-income countries, late presentation and limited infrastructure for comprehensive care lead to significantly lower survival rates. Although historically the study of pediatric CNS tumors has not been prioritized, recent attention has been brought to the disparities in care available and outcomes (3–5).

In Mexico, each year, approximately 850 cases and 300 deaths occur for CNS tumors in children and adolescents less than 19 years-of-age (6). Mexico is an upper-middle-income country in North America with 37 million inhabitants under the age of 18 years (7). In the country, numerous public and private healthcare systems exist in parallel (8). The public sector is primarily funded through the government, providing services at no direct cost to the patient, and includes organizations such as the Mexican Social Security Institute (IMSS) and the Institute for Social Security and Services for State Workers (ISSSTE). Only approximately 5% of Mexicans have private health insurance. Since the early 2000s, Mexico has sought to have universal health coverage through government funded initiatives (9). In 2020, Mexico implemented the Institute of Health for Well-being (INSABI) to expand free healthcare coverage, replacing the Seguro Popular that was established in 2003.

The nation's federal programs have recognized childhood cancer as an important part of child health and offered access to treatment for children with cancer by covering the cost of therapy. Despite these efforts, the systems often struggle with underfunding and inequality in service quality (10). Specifically, the 5-year net survival of pediatric CNS tumors in Mexico is estimated to be approximately 37% (2). Recent publications suggest that poor outcomes are associated with high rates of surgical morbidity, treatment-related mortality, and abandonment (11, 12).

There are approximately 70 pediatric cancer units in Mexico, with varying infrastructure and resources (13). The care of children with CNS tumors requires access to complex infrastructure and the availability of numerous pediatric subspecialists (14). The evaluation of existing resources and services is key to identify gaps and prioritize interventions to expand care capacity for this vulnerable patient population. Efforts to describe the resources for pediatric neuro-oncology have been made in countries in Latin America, but these have not included Mexico. An analysis from Chile demonstrated access to basic services to provide care for children with CNS tumors, while one from Paraguay described more limited available infrastructure (15–17). In this study, we sought to evaluate the resources for the practice of pediatric neuro-oncology (PNO) in Mexico.

Methods

Study design and participants

A cross-sectional online survey with 35 questions was designed to assess pediatric neuro-oncology resources and services (Appendix 1). Survey questions were initially created by the first author and subsequently revised by the research team. The questions covered aspects including number of patients, infrastructure, human resources, and diagnostic and treatment time intervals. Survey questions were created as multiple-choice and open-text field questions. The survey was distributed to the members of the Mexican Association of Pediatric Oncology and Hematology (AMOHP) and was open from February 1st to 16th, 2023. Participation in the survey was voluntary and no personal identifying information was collected.

Statistical analysis

Descriptive statistics were used to analyze all results. For these analyses, SPSS® version 22 was used.

Results

Responding institutions

Overall, responses were obtained from 33 institutions distributed throughout Mexico (Figure 1). Institutions are part of the many health systems that exist in Mexico (Table 1). Twenty-one (64%) institutions had less than 10 new cases of pediatric CNS tumors per year. In addition, although 31 institutions (94%) saw pediatric patients up to the age of 18 years, 2 (6%) had a cutoff of 15 years. In 14 (42%) centers, the initiation of the diagnostic approach for children with CNS tumors was carried out by a pediatric oncologist. In 12 (36%) centers, it was carried out by neurology or neurosurgery teams, while in 6 (18%) centers it was carried out by general pediatrics.

Infrastructure and resources

Twenty-four (73%) institutions had between 1 and 3 pediatric oncologists providing care for children with CNS tumors (Table 2). Although 2 (6%) institutions did not have a neurosurgeon, 19 (57%) institutions had a pediatric neurosurgeon. Twenty-three (70%) centers performed second-look surgeries to achieve larger tumor resections.

Four (12%) institutions had no pediatric intensive care unit (PICU). Where such a unit was available, the number of beds was scarce and only 16 (48%) centers had 24-hour specialist coverage in the PICU. Twenty-one (63%) centers reported that children who undergo surgery for CNS tumors have priority access to the PICU.

All centers had a pathology department, but 13 (39%) had only basic histopathological testing. At 15 (45%) institutions, radiation oncologists with expertise in pediatric radiotherapy were available. Furthermore, radiotherapy for pediatric CNS tumors was referred to outside institutions in 18 (55%) institutions.

All centers had access to conventional cytotoxic chemotherapy, but only 6 (18%) had access to targeted therapy. Furthermore, 17 (58%) centers relied on non-governmental organizations (NGOs) and foundations to offset the cost of cancer-directed medications. Although 29 (88%) centers had a blood bank and access to blood products, there were 4 (12%) centers without these services. Nineteen (58%) centers had a pediatric palliative care service, while the remaining 14 (42%) did not, with pediatric oncologists providing these services or through other solutions.

Timelines for diagnosis and treatment

The diagnostic and treatment intervals are included in Figure 2. At 29 (88%) institutions, imaging for the diagnosis and follow up of CNS tumors could be obtained within 1 week. When a resection was needed, this could happen in less than a week at 6 (18%) centers. Furthermore, radiotherapy planning could occur in less than a week at 22 (67%) institutions. Although 11 (33%) centers had a histopathological diagnosis in one week, 3 (9%) did not have pathology reports available until more than 4 weeks.

Outcomes

Understanding that most centers did not have comprehensive hospital-based cancer registries, respondents were asked to estimate

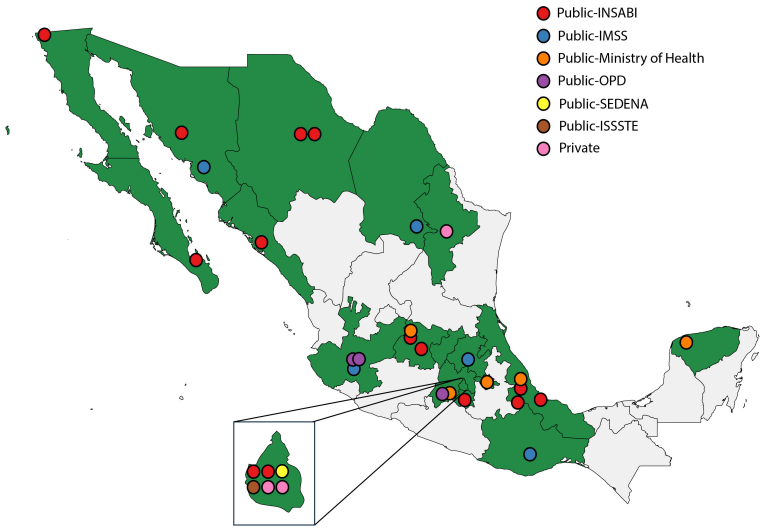

FIGURE 1
Geographic distribution of responding institutions and health systems.

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TABLE 1 Hospital characteristics.

Characteristic	n (%)
Region	
North	3 (9)
Northeast	1 (3)
Pacific coast	3 (9)
Bajío	5 (15)
West	2 (6)
Central	11 (33)
Gulf	7 (21)
South	1 (3)
Healthcare system	
Public-IMSS	5 (15)
Public-ISSTE	1 (3)
Public-Ministry of Health	5 (15)
Public-INSABI	14 (42)
Public-SEDENA	1 (3)
Public-OPD	3 (9)
Private	4 (12)
New pediatric CNS tumors per year	
<10	21 (64)
10–20	7 (22)
21–30	2 (6)
>30	3 (9)
Maximum age of pediatric services	
15 years	2 (6)
18 years	30 (91)
21 years	1 (3)

TABLE 2 Hospital resources and infrastructure.

Characteristic	n (%)
Pediatric oncologists per hospital	
1–3	24 (73)
4–5	5 (15)
>5	4 (12)
Neurosurgeons per hospital	
Only adult neurosurgeon	8 (24)
Pediatric neurosurgeon	15 (45)
Adult and pediatric neurosurgeon	4 (12)
None	6 (18)
Radiation oncologists per hospital	
Adult radiation oncologists	18 (55)
Pediatric radiation oncologists	15 (45)
ICU bed availability	
None	4 (12)
1–3	2 (6)
4–6	10 (30)
7–9	7 (21)
>10	10 (30)
Imaging availability	
CT at facility	29 (88)
CT at outside facility	1 (3)
MRI	18 (55)
MRI at outside facility	13 (39)
Pathology	
Basic histopathology	13 (39)
Basic histopathology and immunohistochemistry	13 (39)
Basic histopathology, immunohistochemistry, and basic molecular testing	7 (21)
Radiotherapy	
At the center	15 (45)
Referred to another center	18 (55)

5-year overall survival for children with CNS tumors. Eighteen (55%) respondents estimated a survival of less than 60% (Table 3). Furthermore, when asked about the causes of mortality, 15 (45%) centers attributed the main cause of mortality to non-tumor related factors, such as infection and post-surgical complications.

Discussion

This study sought to evaluate the elements that lead to comprehensive pediatric neuro-oncology care in Mexico. Our data suggest significant limitations and disparities in resources, prolonged timelines in key elements of care, and poor outcomes.

Ideally, hospitals that treat children with CNS tumors should have all the necessary resources to carry out comprehensive

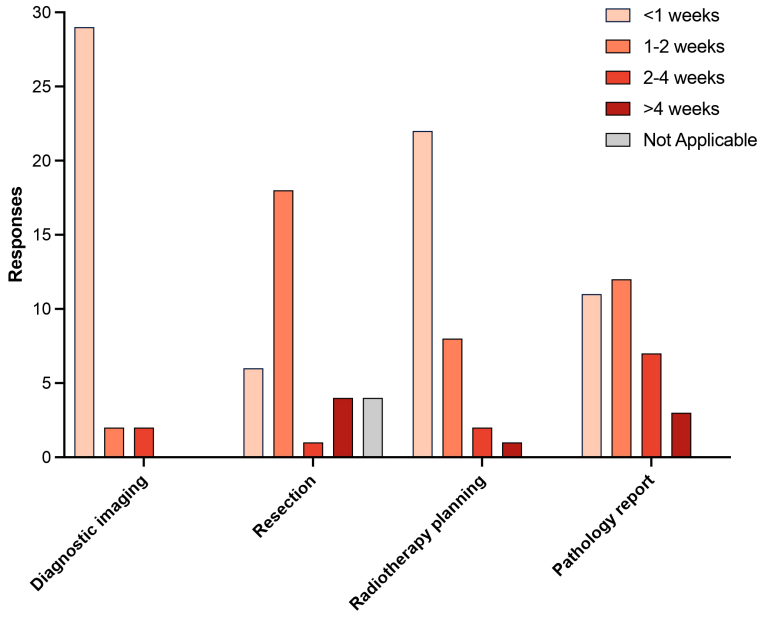

FIGURE 2
Diagnostic and treatment intervals.

diagnosis and treatment, including not only cancer-directed therapy, but also supportive and palliative care. Furthermore, these resources need to be integrated into functioning, efficient pediatric neuro-oncology services (18). Our data suggest that, for many institutions, key elements of care are lacking. Moreover, the evaluation of time intervals of care, with delayed times for some of the core elements of diagnosis and treatment, suggests that optimization of service integration is a priority.

The fragmented healthcare system in Mexico translates into unequal resources and different packages of coverage for patients. This is reflected in our data based on the variability in described resources. For example, in 12% of the centers there was no PICU available for patients, as well as limited specialists for the postoperative care of children with CNS tumors. This care context increases the risk of postoperative complications, one of the most common causes of mortality described by respondents. Investments in post-operative care and infection control may be one of the priority interventions to improve outcomes for many centers in Mexico. These represent immense areas of opportunity to reduce mortality, in many cases with limited investment (19).

In the era of a rapidly evolving field of pediatric neuro-oncology based on molecular characterization and risk-stratification, strategies to expand diagnostic capacity are essential (20). Many of the included centers have only basic pathology and incur in important delays in reporting. The regionalization of pathologic evaluation for pediatric CNS tumors would be a strategy to optimize the available resources (21). With a more comprehensive diagnostic infrastructure, novel approaches and treatment would become more relevant. Importantly, only a small number of centers had access to targeted therapies, so it is also necessary to implement strategies to expand access to novel therapeutics for all centers.

The included centers had limited capacity to estimate survival for children with CNS tumors. The World Health Organization has encouraged the development of cancer registries as a step toward pediatric cancer control (22). Cancer registries provide invaluable information about disease burden and help establish priorities for cancer in low-resource settings. Expanding hospital-based cancer registries would establish a framework for more data on clinical characteristics and outcomes, helping define evidence-based strategies to improve services.

This study has multiple limitations. Firstly, data was collected from less than half of the institutions caring for children with cancer in Mexico. Although we captured data on institutions in different geographic areas and health systems, there may be additional insight that was not elucidated. Secondly, although we sought to evaluate the multiple elements that are needed to provide care for children with CNS tumors, a more in-depth evaluation would be needed to define detailed strategies to expand access to quality care for children treated at these institutions. In addition, the existence of tumor boards and collaborations focused on PNO were not collected in the survey. Finally, although elements of perceived survival and outcomes were collected, patient-level data was not collected. Retrospective or prospective data collection would be needed to provide more reliable survival estimates.

This study represents the first description of the resources for PNO care in Mexico, generating a vision of the essential needs to provide comprehensive, quality care for children with CNS tumors. The work has galvanized the integration of a group of Mexican

TABLE 3 Perceived outcomes.

Characteristic	n (%)
Estimated 5-year survival	
≤50%	6 (18)
51–60	12 (36)
61–70	7 (21)
>70	2 (6)
Unknown	6 (18)
Main cause of mortality	
Tumor	16 (48)
Infections	9 (27)
Post-surgical	6 (18)
Unknown	2 (6)

pediatric oncologists especially invested in strategies to expand quality care for children with CNS tumors. Progress must be made in the development of innovative methods of diagnosis, treatment, and long-term follow-up with the aim of improving survival rates and reducing treatment-related toxicity.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

DA: Data curation, Software, Writing – original draft. GE: Conceptualization, Data curation, Investigation, Writing – original draft. MN: Investigation, Writing – original draft. RN: Conceptualization, Investigation, Writing – original draft. MO: Conceptualization, Investigation, Writing – original draft. FP: Conceptualization, Writing – original draft. FA: Conceptualization, Data curation, Investigation, Writing – original draft. IZ: Conceptualization, Investigation, Writing – original draft. JL: Conceptualization, Investigation, Writing – original draft. DS: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. AM: Conceptualization, Formal analysis, Validation, Writing – original draft. DM: Supervision, Validation, Writing – review & editing. AB: Formal analysis, Methodology, Supervision, Visualization, Writing – original draft, Project administration, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/fonc.2024.1330705/full#supplementary-material

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Primary central nervous system germ cell tumors in Central America and the Caribbean Region: an AHOPCA 20-year experience

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Background: Primary central nervous system germ cell tumors (GCT) are rare neoplasms in pediatrics. Treatment depends on the histological subtype and extent of the disease. Overall survival (OS) is above 90% for germinomas and 70%–80% for nongerminomatous GCT (NGGCT) in high-income countries (HIC) while data are usually lacking for patients in Low-Middle Income country (LMIC).

Objective: This study aims to describe the experience of treating patients with CNS GCT in four of eight countries, members of the Asociación de Hemato-Oncología Pediátrica de Centro América (AHOPCA), and determine their 5-year OS.

Design/methods: We conducted a retrospective chart review of patients treated for CNS GCT. Epidemiological and clinical characteristics, histology, treatment modalities, and outcomes were analyzed.

Results: From 2001 to 2021, 48 patients were included: 22 from Guatemala, 18 from Nicaragua, three from the Dominican Republic, and five from El Salvador. Thirty-one (64.6%) were boys; the median age at diagnosis was 10.2 years (range: 1 to 17 years). Presenting symptoms were headaches (*n* = 24, 50%), visual disturbances (*n* = 17, 35.4%), vomiting (*n* = 12, 25%), nausea (*n* = 8, 16.7%), and diabetes insipidus (*n* = 7, 14.6%). Two patients with NGGCT presented with precocious puberty. Biopsy or tumor resection was performed in 38 cases (79.2%): 23 (88.4%) germinomas, 11 (78.6%) NGGCT, and four (50%) CNS GCT. Eight patients were diagnosed and treated based on CSF tumor marker elevation; four germinomas (BHCG 11.32–29.41 mUI/mL) and four NGGCT (BHCG 84.43–201.97 mUI/mL or positive AFP > 10 UI/mL). Tumor locations included suprasellar (*n* = 17, 35.4%), pineal (*n* = 13, 27.1%), thalamus/basal ganglia (*n* = 5, 10.4%), other (*n* = 12, 25%), and one bifocal. Four (8.3%) had metastatic disease, and six had positive CSF; staging data were incomplete in 25 patients (52%). Patients were treated with varied chemotherapy and radiotherapy

modalities. Nine patients had incomplete data regarding treatment. Five-year OS was 65% (68% for germinoma, 50.6% for NGGCT, and 85.7% for unclassified GCT).

Conclusions: Germinoma was the most common histology, and there was a male predominance. More than half of patients had incomplete staging data and treatment was variable across the region. OS is lower compared to HIC. Standardized treatment protocols will aid in adequate staging and treatment planning, prevent complications, and improve survival.

KEYWORDS

primary central nervous system germ cell tumors, chemotherapy, radiotherapy, survival rate, children, CNS tumors LMIC

Introduction

Central Nervous System Germ Cell tumors (CNS GCT) are a rare group of tumors in children (1). The 2021 WHO classification identifies GCT histology types as germinoma, teratoma (mature, immature, with somatic-type malignancy), yolk sac tumor, embryonal carcinoma, choriocarcinoma, and mixed germ cell tumors (2). The latter harbor different histology types. Usually, CNS GCT is classified into two groups, germinoma and nongerminomatous germ cell tumors (NGGCT; including all other histologies and mixed tumors) (2, 3). The histologic identification of these two groups and the extension of disease are fundamental for treatment planning and prognosis (4).

Incidence varies across different populations; North America reports < 3% of all CNS tumors, and parts of Asia report up to 16% in some regions (5–7).

For germinomas, 5-year survival rates are now reported above 90%, and for NGGCT, from 70% to more than 80%, in high-income countries (HIC) (8–11). In middle- and low-income countries (LMIC), survival varies, with reports of 5-year OS of 75%–88% for germinoma and 53%–75% for NGGCT (12, 13). In Latin America, Argentina reported 100% 5-year OS for localized germinoma and 75% for NGGCT. Brazil reported 100% 5-year OS for localized germinoma with chemotherapy, low-dose whole ventricular irradiation (WVI 18 Gy), and low-dose local boost (12 Gy) (14, 15).

Treatment modalities have changed through the years for the two GCT groups. Combination modalities with chemotherapy and reduced-field and reduced-dose radiotherapy in later studies demonstrated survival rates above 90% (10, 11). For localized germinoma showing complete response to chemotherapy, reducing whole ventricular (18 Gy) with boost to a total of 30 Gy or WVI (24 Gy) alone shows excellent OS, produced results similar to CSI radiotherapy alone, and is the most recent approach to treatment (15, 16). Bifocal germinoma is also treated as a localized disease and not metastatic, with excellent results (17). For metastatic germinoma, chemotherapy plus reduced-dose CSI radiotherapy and local boost to primary and metastatic lesions can also achieve survival rates similar to localized tumors. This approach has allowed to further reduce radiation dose and fields, and it is intended to reduce toxicity related to higher doses of radiotherapy (10, 11, 17, 18).

Improvement in survival for NGGCT has involved multimodality treatment that includes intense chemotherapy, CSI, and local radiotherapy with or without aggressive tumor resection (19–22). Recently, efforts have been made to stratify patients into different risk groups according to histology, tumor markers, and response to treatment and thus evaluate a possible dose reduction in radiotherapy (23).

The Asociación de Hemato-Oncología Pediátrica de Centro America (AHOPCA) group was formed in 1998 in collaboration with St. Jude Children's Research Hospital and other institutions in North America and Europe in order to promote multidisciplinary care and education and to develop shared clinical guidelines applicable for the region. Participating members include institutions from Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, Panamá, the Dominican Republic, and Haiti. Since 2000, several treatment guidelines have been developed for different cancers, but not for brain tumors such as CNS GCT (24). At the moment, no data are published on the treatment and outcome for these tumors in the AHOPCA group. In this study, we conducted a retrospective review of 48 patients with CNS GCT treated in four participating countries across five institutions with the purpose of determining OS rates, identifying diagnostic and treatment challenges in our region, develope strategies to improve them.

Patient and methods

Patient selection

A retrospective review of patients diagnosed with CNS GCT was conducted from January 2001 to December 2021 in four

participating countries across five institutions in Guatemala, Nicaragua, El Salvador, and the Dominican Republic (Table 1).

Patient charts were reviewed, and data were collected on variables such as age, gender, tumor location, symptoms at diagnosis, histology, cerebral-spinal fluid (CSF) and serum tumor maker levels, the extent of resection if performed, chemotherapy and radiotherapy administered, follow-up time, delays in treatment, abandonment, and date of death.

Diagnosis

The diagnosis was determined by neuroimaging, that in some centers was limited to computer tomography (CT) when access to magnetic resonance imaging (MRI) was limited, especially of the spine, for complete staging. Histological confirmation and/or serum and/or CSF markers from the time of diagnosis, when available. Pathology confirmation was performed by morphology alone with H&E due to the lack of immunohistochemistry across the region. When pathological diagnosis was not available, surgery was not performed, or tissue was not diagnostic, patients were diagnosed with levels of tumor markers. Guatemala was the only country where CSF tumor markers were able to be performed. They applied the same techniques and reagents used for serum markers. In the Dominican Republic, it can occasionally be done in private laboratories. Germinoma was considered a diagnosis if serum or CSF beta-human chorionic gonadotropin (βHCG) markers were between 5.3 and 50 mUI/L and negative for alpha-fetoprotein (AFP). Patients with serum and CSF βHCG values above 50 IU/L and/or positive for AFP (above 10 UI/mL) were considered NGGCT (25–27).

Metastatic disease was assessed with a postoperative spine MRI and CSF cytology, when available.

Treatment

Surgery

In general, after a lesion was identified, surgery was attempted, typically at an adult center, by general neurosurgeons. Neurosurgeons often made the decision to refer patients for radiation therapy or to the referral pediatric oncology centers where patients received the remainder of their treatment. The extent of resection was generally determined by a postoperative image (MRI or CT) or by surgical report when available.

Chemotherapy

Different chemotherapy regimens were administered as the region did not have unified guidelines, and treatment strategies have also evolved over the last 20 years. The predominant chemotherapy regimens used were platinum-based, and regimens were not necessarily chosen based on GCT type. Since 2012, chemotherapy has been administered as per the International Society of Pediatric Oncology (SIOP) CNS GCT 96 protocol for germinoma and COG ACNS0122 for NGGCT in Guatemala. It was also used in other centers, but frequently treatment was decided case-by-case, based on consultations and case presentations with

TABLE 1 Patient demographic and clinical characteristics.

	Total	
	N	%
Total	**48**	100
Sex		
Female	**17**	35.4
Male	**31**	64.6
Age		
Median [Q1–Q3]	**10.2 [8.0–12.8]**	
< 10 years	**20**	41.7
≥ 10 years	**28**	58.3
Symptoms		
Headache	**24**	50.0
Vision disturbances	**17**	35.4
Vomit	**12**	25.0
Nausea	**8**	16.7
DI	**7**	14.6
Precocious puberty	**2**	4.2
Other (e.g., seizures, hemiparesis)	**9**	18.8
Histopathology		
Germinoma	**26**	56.2
NGGCT	**14**	29.2
Not specified	**8**	16.7
Primary site		
Suprasellar	**17**	35.4
Pineal gland	**13**	27.1
Third ventricle	**4**	8.3
Thalamus	**4**	8.3
Posterior fossa	**4**	8.3
Bifocal	**1**	2.1
Basal ganglia	**1**	2.1
Not specified	**4**	8.3
Metastasis		
Yes	**4**	8.3
No	**35**	72.9
No data/Incomplete staging	**9**	18.8
Cerebro-spinal fluid		
Positive	**6**	12.5
Negative	**20**	41.7
Not performed/No data	**22**	45.8

(Continued)

TABLE 1 Continued

	Total	
	N	%
Biopsy/Resection		
Yes	**38**	75.0
No	**9**	18.8
No data	**1**	6.2

collaborative specialists and groups. In a group of patients from Nicaragua, the chemotherapy regimen is not specified (Tables 2, 3).

Radiotherapy

Patients received a range of radiation therapy doses and fields independent of the GCT type. Treatment was based on their resources, availability, experience, and information at that time (Table 3). Similarly, radiation therapy doses and fields were decided following the SIOP CNS GCT 96 protocol for germinoma and COG ACNS0122 for NGGCT in a group of patients since 2012 or on a

TABLE 2 Treatment.

	Total		Germinoma		NGGCT		GCT not specified	
	N	%	N	%	N	%	N	%
Total	**48**	100	**26**	100	**14**	100	**8**	100
Overall therapy								
Surgery only	**3**	6.2	**0**	0	**3**	21.4	**0**	0
Radiotherapy only	**5**	10.4	**5**	19.2	**0**	0	**0**	0
Combined therapy (chemo + radiotherapy ± surgery)	**19**	39.6	**12**	46.1	**5**	35.7	**2**	25
Chemotherapy/No data on radiotherapy	**9**	18.7	**2**	7.7	**3**	21.4	**4**	50
Chemotherapy/ No radiotherapy[a]	**11**	23	**8**	30.7	**3**	21.4	**1**	12.5
Treatment not specified	**1**	2.1	**0**	0	**0**	0	**1**	12.5
Surgery	**38**	79.2	23	88.4	11	78.6	4	50
Complete resection	**6**	12.5	**1**	2.1	**5**	10.4	**0**	0
Partial resection/Biopsy	**29**	60.4	**20**	41.6	**6**	12.5	**3**	6.25
Extent of surgery not specified	**3**	6.2	**2**	4.1	**0**	0	**1**	2.1
Chemotherapy								
Yes	**39**	81.2	**21**	80.8	**11**	78.6	**7**	87.5
No	**9**	18.8	**5**	19.2	**3**	21.4	**1**	12.5
Radiotherapy								
Yes	**24**	50.0	**17**	65.4	**5**	35.7	**2**	25.0
Focal only	**3**	6.2	**3**	11.5	**0**	0	**0**	0
Focal and CSI	**6**	12.5	**3**	11.5	**3**	21.4	**0**	0
Focal and WV	**6**	12.5	**5**	19.2	**1**	7.1	**0**	0
Focal and cranial	**1**	2.1	**1**	3.8	**0**	0	**0**	0
WV and CSI	**3**	6.2	**2**	7.7	**1**	7.1	**0**	0
WV only	**1**	2.1	**0**	0	**0**	0	**1**	12.5
Cranial only	**4**	8.3	**3**	11.5	**0**	0	**1**	12.5
Radiotherapy dose								
Total focal < 50 Gy	**5**	10.4	**4**	15.4	**1**	7.1	**0**	0

(Continued)

TABLE 2 Continued

	Total		Germinoma		NGGCT		GCT not specified	
	N	%	N	%	N	%	N	%
Radiotherapy dose								
Total focal ≥ 50 Gy	**10**	20.8	**7**	26.9	**3**	21.4	**0**	0
Cranial only < 50 Gy	**1**	2.1	**1**	3.8	**0**	0	**0**	0
Cranial only ≥ 50 Gy	**3**	6.2	**3**	11.5	**0**	0	**0**	0
WVI ≤ 24 Gy	**8**	16.7	**6**	23.1	**2**	14.3	**0**	0
WVI > 24 Gy	**2**	4.2	**1**	3.8	**0**	0	**1**	12.5
CSI < 36 Gy	**3**	6.2	**2**	7.7	**1**	7.1	**0**	0
CSI = 36 Gy	**6**	12.5	**3**	11.5	**3**	21.4	**0**	0

[a]Eight patients died; two abandoned before radiation treatment.
WVI, whole ventricular irradiation; CSI, cranioespinal irradiation.

TABLE 3 Chemotherapy regimens.

Tumor type	Chemotherapy administered	*N*
Germinoma	Carboplatin/VP 16 (CNS GCT 96)	12
	No chemotherapy	5
	PEB	5
	Cisplatin/VP 16 with ifosfamide/ VP 16	1
	Cisplatin/VP 16	1
	Carboplatin/Vincristine	1
	Chemotherapy regimen not specified	1
NGGCT (mixed and by markers)	Carboplatin/VP 16 alt ifosfamide/VP 16 (COG ACNS0122)	4
	PEB	2
	Chemotherapy regimen not specified	1
Germinoma with mature teratoma	Carboplatin/VP 16 × 4 (CNS GCT 96)	1
Immature teratoma	Cisplatin/VP 16	1
	PEB	1
Mature teratoma	None	3
	Chemotherapy regimen not specified	1
GCT without histologic subclassification		
Suprasellar	Chemotherapy regimen not specified	2
Pineal	PEB	2
	Chemotherapy regimen not specified	1
Thalamic	Chemotherapy regimen not specified	1
Posterior fossa	PEB	1
Unknown	None	1

VP 16, etoposide; PEB, cisplatin/etoposide/bleomycin.

case-by-case basis after consultation with international experts in the field (Table 2).

Statistical analysis

The outcome was estimated using the Kaplan–Meier method with Greenwood standard error (SE) and compared with the log-rank test if needed. The estimates included the following: abandonment-sensitive event-free survival (as-EFS), defined as the time from the beginning of treatment until the first event: death (related to treatment); treatment abandonment (if the patient was absent ≥ 4 consecutive weeks during therapy); progressive disease (PD); relapse; and second tumor. The overall survival (OS) was estimated as the time from the beginning of treatment until death (from any cause) or date of abandonment (assuming that patients who did not complete therapy succumbed to their disease).

Results

This retrospective analysis examined data for 48 patients diagnosed with CNS GCT over a 20-year period (between January 2001 and December 2021). The majority of patients (22) were from Guatemala and received treatment at the Unidad Nacional de Oncología Pediátrica (UNOP). Eighteen patients were from Nicaragua and treated at the Hospital Escuela La Mascota. Five patients from El Salvador received treatment at the Hospital Nacional de Niños Benjamín Bloom, and two patients were from the Dominican Republic and treated at either the Hospital Infantil Regional Dr. Arturo Grullon or Hospital Infantil Robert Reid Cabral.

The median patients' age was 10.2 years, ranging from 1 to 17 years. Boys made up 64.6% (28), while girls made up 35.4% (17).

The most frequent presenting symptoms were headache in 24 patients (50%), visual disturbances in 17 (35.4%), vomiting in 12 (25%), followed by nausea in eight patients (16.7%), and diabetes insipidus in

seven patients (14.6%, five suprasellar tumors, one bifocal, and one pineal location). Two patients presented with precocious puberty; one tumor was located in the right thalamus, and the other was a suprasellar tumor. Both of these patients were diagnosed with an NGGCT. A 1-year 11-month-old patient presented with a regression of milestones. Other presenting symptoms included seizures, hemiparesis, conduct alterations, and ataxia.

The tumor was located in the suprasellar region in 17 patients (35.4%). Thirteen patients (27.1%) had a pineal tumor, and one patient (2.1%) had a bifocal tumor. Other tumor locations were the thalamus, third ventricle, and posterior fossa, with four (8.3%) patients in each of those locations, one located at the basal ganglia, and four patients without data. Of the four posterior fossa tumors, two were mature teratomas, one was an immature teratoma, and one GCT was not subclassified.

The tumor marker data available were from the initial diagnosis. Tumor marker level ranges included serum: βHCG 0.2–325.7 mIU/mL, with four patients having levels above 50 mIU/mL, and CSF: βHCG 11–201.97 mIU/mL, with three patients having levels above 50 mIU/mL. Serum AFP levels: 0–1,399 mIU/mL, and CSF AFP: 0–0.52 mIU/mL. Some results for both CSF and serum markers were reported only as negative. Serum tumor markers were done in 26 patients, and CSF tumor markers in 19 and all were performed at diagnosis. Four patients with positive BHCG levels below 50 mIU/mL were diagnosed as germinomas; three patients with BHCG levels greater than 50 mIU/mL and one with positive AFP were diagnosed as NGGCT; and this last patient had histologic confirmation with surgery after chemotherapy. Tumor marker data were not available for 22 patients (45.8%).

Staging

Tumor staging was incomplete, with either CSF cytology (22 patients, 45.8%) and/or spinal MRI (25 patients, 52%) not done or data were not available. Three patients had neither CSF nor spinal MRI done (one mature teratoma, one immature teratoma, and one germinoma).

A total of four patients (8.33%) had metastatic ventricular lesions evidenced on brain imaging (all germinoma); six had CSF cytology positive for malignant cells, three of which had metastatic lesions on brain imaging.

Event survival (EFS) and OS at 5 years for this group of patients are 63% and 65%, respectively (Figure 1).

Treatment

Germinoma treatment and outcome

In total, 26 patients (54.1%) were diagnosed with germinoma, four of those based on tumor marker results. Twenty-three patients had surgery: 11 had a biopsy, 10 had a partial resection, one had a total resection, and one had surgery with unknown results due to a lack of data. One patient who had a partial resection and was diagnosed with CNS GCT was later classified as having a germinoma with tumor makers. Monotherapy with radiation was used in five (19.2%) patients; three had focal radiation, and doses were 50 to 59.4 Gy total; one patient had CSI at 36 Gy and completed 54 Gy of focal radiation; and one had a total of 54.5 Gy focal and the same dose whole ventricular (WV). Twelve patients had combination therapy with radiation and chemotherapy, with a carboplatin/VP 16 (etoposide) regimen used, one in combination with ifosfamide/VP 16, usually four cycles. Other chemotherapy regimens were used in three patients, including one patient treated with PEB (cisplatin, etoposide, and bleomycin). Different radiation modalities were used; four patients received 24 Gy WV with a focal boost that completed 40 Gy in three patients and 50 Gy in one. Two patients received 24 Gy WV and 36 Gy CSI radiotherapy. Three patients received focal therapy with 50 to 60 Gy. Two patients received focal (50.4 Gy) and CSI (30.6 Gy), and one patient was treated with 30.6 Gy cranial radiation with a focal boost of

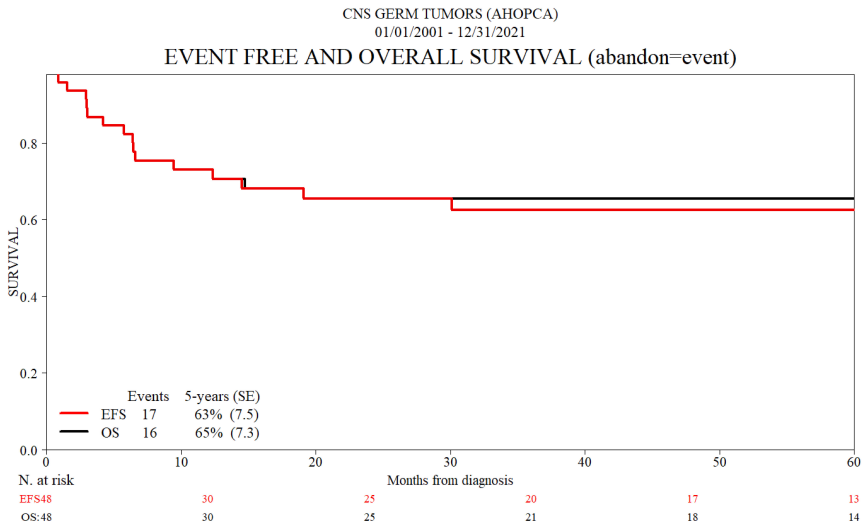

FIGURE 1
Event-free and overall survival (abandon = event).

19.8 Gy. Six patients died during chemotherapy before radiotherapy, and one abandoned treatment and did not receive radiation therapy. Two patients received chemotherapy, but no data on radiation are available for these two patients. One patient who relapsed received rescue treatment and is currently alive. A total of eight patients died, and the causes of death include the following: intracranial hemorrhage after a car accident (one patient), sepsis due to *Candida tropicalis* (one patient), complications following VP shunt replacement with ventriculitis (one patient), complications from diabetes insipidus (one patient), complications after surgery (one patient), and disease progression (three patients). The 5-year OS rate for patients with germinoma was 68% (Tables 2, 4; Figure 2).

NGGCT treatment and outcome

Fourteen (29.1%) patients were diagnosed as NGGCT, four based on tumor marker results. Eleven patients underwent surgical resection, including one patient initially diagnosed with tumor markers after five cycles of chemotherapy who had a complete resection. Six patients had a partial resection. One patient with confirmed germinoma and teratoma histology received combined treatment with carboplatin/VP-16 for four cycles and radiation therapy (24 Gy WV and 40 Gy total focal). Two patients were treated with the PEB regimen. One received radiation therapy (25 Gy CSI and 50.5 Gy total focal) but died of progressive disease. Data on radiation treatment for the other patient are unavailable. One patient died of sepsis after one cycle of chemotherapy with carboplatin/VP-16 regimen. Two patients have no data on chemotherapy or radiation treatment and both died of progressive disease. Five patients had a complete resection, including three with mature teratoma; one abandoned treatment after five cycles of chemotherapy (carboplatin/VP-16 alternating with ifosfamide/VP-16); and one received combined treatment with the PEB regimen and radiation with 36 Gy CSI and 24 Gy WV. Of the three patients who had no surgery, two were treated with combined chemotherapy with carboplatin/VP-16 alternating with ifosfamide/VP-16 for six cycles total and radiation with 36 Gy CSI and 54 Gy total focal. Three patients with mature teratoma had no chemotherapy and appropriately did not proceed with radiation

TABLE 4 Last status.

	Germinoma		NGGCT		GCT nonclass		Total	
	N	%	N	%	N	%	N	%
Enrolled	**26**	100	**14**	100	**8**	100	**48**	100
Dead	**8**	30.8	**5**	35.7	**1**	12.5	**14**	29.2
Abandoned treatment	**1**	3.8	**1**	7.1	**0**	0.0	**2**	4.2
Alive	**17**	65.4	**7**	50.0	**7**	87.5	**31**	64.6
Lost to follow-up	**0**	0.0	**1**	7.1	**0**	0.0	**1**	2.1
Median follow-up time (months)	18.3		33.9		17.9			

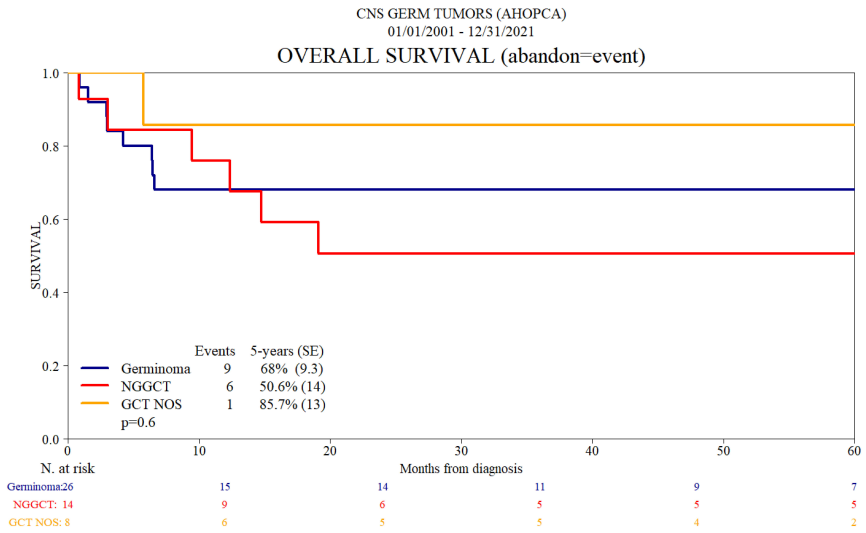

FIGURE 2
Overall survival (abandon = event).

therapy. Five patients died; three had disease progression as the cause of death, one due to diabetes insipidus and complications from sepsis after three cycles of chemotherapy, and one after one cycle of chemotherapy due to sepsis. Five-year OS for NGGCT is 50.6% (Tables 2–4; Figure 2).

Germ cell tumors without histologic subclassification treatment and outcome

Eight (16.6%) patients from Nicaragua were diagnosed with CNS GCT without histologic subclassification. None of the eight patients had tumor marker results in either CSF or serum. Four patients had surgery, two had a partial resection, one had a biopsy, and one had no data on the extent of surgery. All patients had chemotherapy, but the regimen was not detailed, and only one had data on receiving focal radiation at a dose of 59.4 Gy. Three patients had no surgery and received chemotherapy with regimens that were not detailed, and there were no data available on radiation therapy. One patient did not receive chemotherapy and has no data on surgery and radiotherapy. One patient died, but the cause of death is not reported. For this group, the 5-year OS survival is 85.5% (Tables 2–4; Figure 2).

Radiation therapy availability

In Nicaragua, prior to 2019, radiation therapy was administered with a cobalt machine. Only more recently they have the ability to perform intensity-modulated radiation therapy (IMRT). IMRT has been available in Guatemala since 2009, in El Salvador since 2018, and is also available in the Dominican Republic, but we do not know the date they started using it.

Discussion

This retrospective study helps us gain some insight into the treatment approach and outcomes for patients diagnosed with CNS GCT in Central America. We can also appreciate in this study how the resources can vary across the four Central American countries that form part of AHOPCA. They have similar challenges and limited resources as other LMICs within the LATAM region, such as the lack of pediatric neuro-oncology-trained subspecialists, pediatric neurosurgeons, multidisciplinary team meetings, access to resonance imaging prior to surgery, complete staging (spine MRI and CSF markers), and diagnostic pathology techniques beyond morphology (29). Although the patient characteristics and symptom presentation are expectedly similar to those of other HIC and MIC countries in the region, it is notable that the survival outcomes and treatment approach have great variability (12–15).

There are evident limitations to the diagnosis of patients with CNS GCT, as noted in our results. Diagnostic imaging and surgeries are usually performed based on CT imaging. Postoperative imaging can include MRIs, but they are not performed within a 24–72-h window after surgery. We do not have the data for this study, but the images for this review were usually performed a few weeks after surgery, when patients were transferred to the pediatric oncology units. The ability to determine the degree of leptomeningeal involvement or metastasis was difficult to ascertain in a very important percentage of patients since spine MRIs were generally not performed and the degree of metastases (presence of additional lesions or presence of leptomeningeal disease) was designated based on the brain imaging findings. Treatment planning and treatment response cannot be performed with incomplete and inadequate staging, as it is the standard of care to evaluate with a preoperative MRI at diagnosis and perform subsequent evaluations with routine resonance imaging and tumor markers (serum/CSF) (23, 27, 30, 31).

In Latin America, serum tumor markers are more commonly standardized and readily obtained compared to CSF tumor markers. Even though the reagents and laboratory techniques are similar for both serum and CSF markers, in Nicaragua, for example, they have been unsuccessful in obtaining CSF tumor markers, even after approaching privately funded laboratories. In Guatemala, the instructions on the labels of the reagents used do not specify they can be used for CSF. However, after further discussion with the chemical biologist and chief of the laboratory, they were able to overcome this barrier and provide CSF tumor marker results. Therefore, training for these laboratory techniques on CSF would be useful across the region for other countries to overcome this barrier.

Tumor values for diagnostic purposes were only available for a small group of patients since they were not routinely done before surgery. The cutoff level to define germinomas (βHCG < 50 mUI/mL) did not change over this period of time, even though there is evidence that germinoma can produce βHCG levels above 50 mUI/mL. This might have led to the overtreatment of patients with germinoma. The consensus on cutoff levels for tumor marker values varies around the world. The SIOP study defined germinoma with βHCG < 50 IU/L and NGGCT with serum or CSF AFP level of 25 ng/mL or higher and/or βHCG ≥ 50 IU/L (20, 27). The Children's Oncology Group (COG) defined NGGCT with the level of 10 ng/mL for AFP and βHCG > 100 IU/L (23, 27). In a study in Brazil, cutoff levels for germinoma were undetectable levels of AFP and βHCG ≤ 200 mIU/L; NGGCT was defined as serum βHCG > 200 mIU/L and AFP > 5–10 ng/dL (9). Japanese studies have shown elevated βHCG levels above 200 mIU/L in germinomas and NGGCT with negative tumor markers; thus, they consider necessary histology confirmation as well as marker levels (28, 32, 33).

In this group of patients, tumor markers for follow-up were rarely taken, even though it is usually standard of care to evaluate treatment response and tumor recurrence (27, 28, 30, 31).

Local pathology still has limitations in that the diagnoses are carried out without immunohistochemical staining and are, to this day, based on histology and morphology alone. Therefore, it also puts into question which of the patients in this cohort may have a different diagnosis, particularly those patients who were tumor marker-negative.

Surgery was largely performed by neurosurgeons without pediatric subspecialty training. The region, as with other LMICs, has limitations in regards to trained neurosurgeons, instrumentation, and no data on complications (34). Since the majority of patients initially arrive at the neurosurgery unit and tumor markers are not done in these centers, a subgroup of patients with secreting GCT

undergo surgery that can otherwise be spared, which can diminish complications after major surgery procedures (35, 36).

The chemotherapy regimens administered were mainly platinum-based, and the regimens varied among patients even from the same center. Some of the regimens used include cisplatin, bleomycin, and etoposide (PEB), cisplatin and etoposide, and carboplatin and etoposide with or without ifosfamide. Regimens sometimes were used independent of tumor histology and the regimen used in some patients is not specified. In some centers, since around 2012, as a result of the case-by-case consultation with international experts in pediatric neuro-oncology who provided timely feedback, chemotherapy regimens have been used as per the SIOP CNS GCT 96 protocol for germinoma and COG ACNS0122 for NGGCT for a number of patients (9, 23). Unfortunately, data on toxicity are not available, but one patient with germinoma died due to sepsis during chemotherapy treatment, and in the NGGCT group, two patients died also of sepsis after three and one cycles of chemotherapy. Challenges in supportive care are also mentioned in other publications that affect patients with GCT survival in LMICs (13).

Similar to chemotherapy administration, the approach to radiation treatment varied and was not always adapted to histology diagnosis, and no data are available on changes made based on tumor response to chemotherapy. IMRT has been available in Guatemala since 2009 and since 2019 in Nicaragua. Monotherapy with radiation was done in five patients with germinoma, with different doses and fields. Radiation alone, cranial, and CSI produce good outcomes in germinomas (8). As of 2012, many patients were treated with SIOP CNS GCT 96 protocol for germinoma and COG ACNS0122 for NGGCT (9, 23); others depended on recommendations after case-by-case consults. This collaboration allowed the reduction of dose and fields of radiotherapy, but new studies and protocols now approach treatment with an even greater reduction of radiation dose without compromising survival outcomes (14, 15). Therefore, there was not one single treatment approach across this region over this 20-year period and varied based on the treating physician's criteria and/or resources available (Table 3).

We recognize that the diverse treatment approach demonstrated across the patients has very likely impacted our patient's overall survival outcomes. Even though data on toxicity and complications are missing, two patients died due to diabetes insipidus and three due to sepsis, which reflects limitations in supporting treatment. As mentioned before, we share difficulties with other LMICs that can contribute to lower survival rates in these tumors, but we also have an

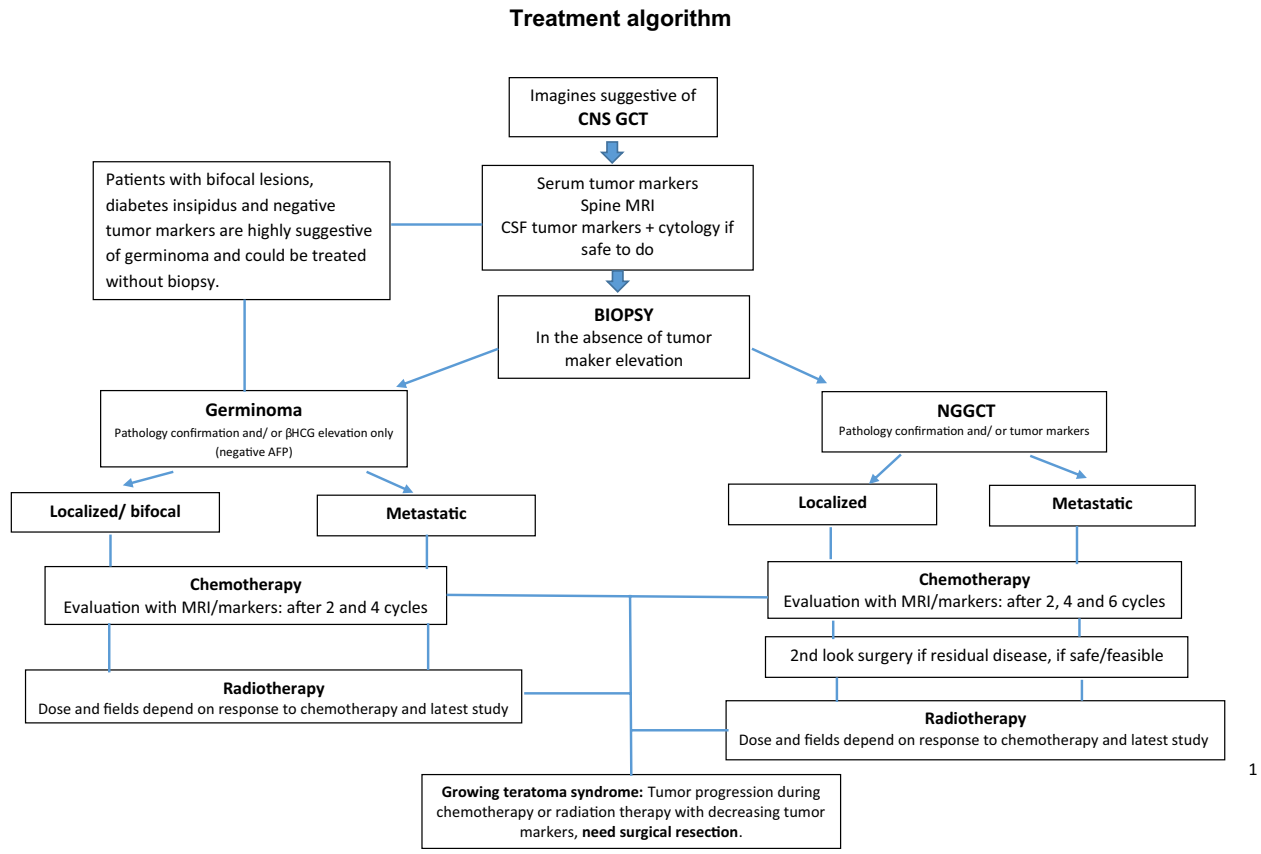

FIGURE 3
Treatment algorithm.

example of a group in LATAM, such as Brazil, with a well-organized multidisciplinary team that has elaborated treatment protocols with excellent outcomes (15).

The AHOPCA group has continued collaboration with partners from HIC pediatric neuro-oncology experts. Additionally, the Latin America Brain Tumor Board (LATB) provides opportunities for expert neuro-oncology feedback in real-time and confirms the diagnoses of our patients with second pathology reviews and weekly individual case presentations (37). Also there is an effort from the St Jude Children's Research Hospital, through the Global Alliance for Pediatric Neuro-Oncology (GAP-NO), to provide training and education to specialists in the region (38).

We hope that as future collaborations continue to occur across our region, we will be able to harmonize not only our treatment approaches but also our ability to share patient data in the hopes of improving the overall care and outcomes for children with brain tumors.

Additionally, we find this study demonstrates the need for unified, resource-based diagnostic and treatment guidelines for the region based on experts' recommendations (Figure 3).

Limitations

Our study lacks data due to several factors, such as data from patients treated many years ago that are no longer retrievable, challenges in obtaining data from outside institutions such as neurosurgery and radiotherapy units, and the lack of resources and support for data management and such personnel. Data on treatment toxicity and postsurgical complications is also not included for the same reason and should be a priority to be included in future studies.

Another limitation of our study was the lack of involvement of additional AHOPCA institutions across Central America, which were not able to share or obtain the data for this study and provide us with an even broader overview.

Conclusions

This paper represents the first description of the overall treatment approach and outcome of patients with CNS GCT in Central America. Given the limitations described herein, it helps us understand the differences in OS compared to those of a HIC. We also believe that the early involvement of pediatric oncologists in the diagnosis of brain tumors will aid our local subspecialists in ensuring better treatment planning with more adequate staging and imaging. Furthermore, adapted chemotherapeutic regimens and standardized protocols may prevent complications and improve survival. Continued collaboration with the weekly LATB and GAP-NO is also of importance as the neuro-oncology field continues to advance in diagnostics and therapeutics.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

AG: Supervision, Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. JB-L: Writing – review & editing, Software, Formal analysis. PC: Writing – review & editing, Data curation. RJ: Writing – review & editing, Data curation. EP: Writing – review & editing, Data curation. MM: Writing – review & editing, Data curation. YL: Data curation, Writing – review & editing. UB: Writing – review & editing, Supervision, Methodology, Conceptualization. DO: Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Conceptualization, Writing – review & editing, Data curation.

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Conflict of interest

DO was employed by the company ICON PLC, a clinical research organization.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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BRAF/MEK inhibitors use for pediatric gliomas; real world experience from a resource-limited country

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Introduction: Most pediatric low-grade-gliomas (LGG) and some high-grade-gliomas (HGG) have alterations in the RAS/MAPK pathway. Promising high tumor response rates were achieved using BRAF/MEK inhibitors, however data on their use in low-middle-income-countries (LMICs) are limited.

Methods: We retrospectively reviewed our Jordanian experience of using compassionate BRAF/MEK inhibitors in treating children with gliomas. We reviewed patients' clinical characteristics, tumor response, and side effects.

Results: Twenty patients (13 males, 7 females) were identified. Median age at diagnosis was 8.3 years (0.3-18.9years). There were fifteen LGGs, three HGGs and two grade-2 pleomorphic xanthoastrocytoma (PXA-2). Fifteen tumors were supratentorial, three posterior fossa/brainstem, one diffuse-glioneuronal tumor (DLGNT) and one spinal. Five tumors were metastatic. Except for one patient with neurofibromatosis, ten patients underwent partial resection and nine had biopsy. All patients, except three, received BRAF/MEK inhibitors after initial standard chemo/radiotherapy. Seven LGGs had BRAF-mutation, six had BRAF-fusion, and two were empirically treated (one neurofibromatosis and one DLGNT). Fourteen LGGs were treated with 1-4 chemotherapy regimens before BRAF/MEK inhibitors' use; all had partial/stable response on targeted therapy at a median of 1.9 years (0.5-5.4years). Two patients with *BRAFv600E*-mutated/*CDKN2A* deleted PXA-2, had progression following resection, and experienced stable/partial response at 9 months of dabrafenib use. Two patients with HGGs had *BRAFv600E*-mutation, and one had an FGFR-mutation. All three patients with HGG had temporary stable/partial response, two with significant clinical improvement. At a median of 2.7 years (1.3-3.2years), all patients experienced tumor progression, and two died. Eight patients (40%) developed acneiform rash, three (15%) paronychia, and one had significant panniculitis and fatigue. Six patients (30%) needed dose-reduction. Nine patients had temporary drug

interruptions [due to side effects (5) and drug shortage (4)]. Two patients who stopped trametinib due to side effects (significant acneiform rash/paronychia and intracranial bleeding) did not experience progression.

Conclusions: Our experience with BRAF/MEK inhibitors' use was positive achieving response in all LGGs and provided sustained response with good quality of life for patients with HGG. Cost effectiveness analyses and patients' satisfaction comparisons with chemotherapy are needed to evaluate the routine use of these drugs in LMICs.

KEYWORDS

BRAF/MEK inhibitors, dabrafenib, trametinib, low-middle-income countries (LMIC), targeted therapy, glioma, off-label/compassionate

Introduction

Gliomas are the most common pediatric CNS tumors with low-grade glioma (LGG) being more prevalent than high-grade glioma (HGG). LGGs are usually cured with gross tumor resection (GTR), however this is not achievable at every neuroaxis location, nor it is enough when the tumor is metastatic. The decision to treat or not incompletely resected or unresectable LGGs and with what modality depends on many factors including the child's age, neurofibromatosis (NF1) status, size of the residual tumor, the anticipated neurological compromise with further tumor progression, and the availability of treatment modalities (chemotherapeutic agents or radiotherapy) (1). Several chemotherapeutic protocols (vincristine/carboplatin, vinblastine, TPCV) are considered as first, second and third lines of treatments for unresectable or progressing LGGs achieving a 5-year progression free survival (PFS) of 30-50% (2–4). While radiotherapy achieves higher PFS rates >70% (5, 6), its long-term neurocognitive and neuroendocrine side effects preclude its use as a frontline therapy in young children. While overall survival (OS) of patients with LGG is high (>80%) (2–4), PFS is low (<50%) highlighting the importance of preserving the best quality of life (QoL) for these children who may require multiple lines of treatment. In comparison, HGGs have poor prognosis (3year-OS < 30%) (7)despite surgery, radiotherapy, and chemotherapy, therefore maintaining a decent QoL during this short survival is integral.

Most LGG (>80%) harbor a driver alteration in the RAS/MAPK pathway signaling which makes this a plausible target for medical intervention (8). The type of this alteration plays a major role in the tumor trajectory, response to therapy and the risk of transformation to HGG. The presence of *BRAFv600E* mutation in a LGG (which occurs in 15-20%) was associated with a worse PFS and a higher risk of transformation to HGG even in the absence of radiotherapy (9). On the other hand, BRAF mutations are uncommon in pediatric HGGs (5-10%) (10) where the most frequent alteration is the *H3K27M* mutation (11). Integration of the molecular diagnosis with the histologic features is now required for several tumor types according to the WHO-CNS-5 classification (11). While this approach provides a more accurate diagnosis and a better understanding of the tumor's behavior, it also helps in utilizing some targeted drugs for treatment. Several publications have demonstrated the efficacy of BRAF/MEK inhibitors in treating progressive LGGs (12–15) and HGGs (16–18) leading recently to the FDA approval of the dabrafenib and trametinib combination for the first line treatment of *BRAFv600E* mutated LGGs (19).

In a resource-limited setting, access to "new drugs" is challenging. These countries barely participate in international clinical trials and most families are not able to afford the high cost of these new drugs. On occasions, temporary access through off-label and compassionate drug access programs may be available to some institutions. This is not an ideal situation, however increasingly, off-label and compassionate use prescriptions are becoming common in the pediatric oncology world with the limited approved treatments for children and the scarce number of pediatric clinical trials (20, 21). There are very few publications on the use of compassionate targeted drugs in treating pediatric CNS gliomas in low-middle-income countries (LMICs) (22, 23).

Jordan is a LMIC according to the World Bank classification (24) with an estimated population of 10.3 million (including 37.7% are children aged 0-17 years old) (25). King Hussein Cancer center (KHCC), is the only cancer-dedicated hospital in Jordan to treat children and adults. Most children (> 80%) with CNS tumors are treated at KHCC. All Jordanians are insured through the Jordanian government for cancer therapy, while most non-Jordanians are covered through charities or self-paid.

In this study, we report on the compassionate use of dabrafenib and/or trametinib in pediatric patients with gliomas at KHCC. We demonstrated its feasibility, efficacy, and plausibility for the patients. In addition, this experience displayed the challenges encountered particularly in relation to the sustainability of access to these drugs.

Methods

We retrospectively reviewed the medical charts of all children <18 years old at the time of diagnosis of gliomas at KHCC who received dabrafenib and/or trametinib before December 2023. The earliest child received therapy was in 2015. Targeted therapies were provided through a compassionate drug access program from Novartis. The decision to request and start the drugs was made by the multidisciplinary pediatric neuro-oncology team (MDT) and approved by the pharmacy and therapeutics committee at KHCC. We reviewed our patients' clinical characteristics, tumor pathology and molecular alterations. We assessed the indication behind using dabrafenib/trametinib, drugs' side effects and any clinical or radiological responses achieved.

Tumor diagnosis was extracted from the pathology reports issued by the KHCC neuropathologists. BRAF mutation was confirmed by immunohistochemistry (IHC), mutation analysis or TruSight next generation sequencing (NGS) (26). BRAF fusion was tested either by nanoString or NGS testing; both were performed at the laboratory of the Hospital for Sick Children (Sickkids) in Toronto. Not all gliomas were tested for molecular alterations. The decision to do so was based on the MDT discussions after weighing the likelihood of finding an alteration, the clinical condition of the patient, response of tumor to previous therapies (if previous treatment was given) and the expectations to have access to the targeted therapy. Once an alteration was found and compassionate access was available, the case was discussed again in the MDT to review if targeted therapy was needed immediately. This would be mostly in the context of tumor growth/progression despite previously administered chemotherapy and/or radiotherapy.

Tumor characteristics on MRI were reviewed for tumor location, presence or absence of metastasis, and response. GTR was considered if no residual tumor could be appreciated on the postoperative MRI, subtotal resection (STR) when a residual tumor is present, and a biopsy was considered if reported as such by the neurosurgeon. MRI scans just before and after the use of dabrafenib/trametinib were reviewed by the KHCC radiologist (D.A) according to the RANO criteria (27). These were reported as complete response (CR) in the absence of a residual tumor, partial response (PR) if the sum of the perpendicular diameter of the mass improved by 50% or more, stable disease (SD) if sum of the perpendicular diameter of the mass remained unchanged, improved by < 50% or increased by <25%. Progression was considered if the perpendicular diameter of the mass increased >25% or if new lesions appeared.

Drugs' side effects that were suspected to be related to the use of dabrafenib/trametinib were extracted from the medical charts. A need for drug dose reduction, steroids use, or interruption/discontinuation of therapy was documented. For this study, parents, and children (older than 12-year-old) were asked to fill a one-time short questionnaire (Supplementary Table S1) on their opinion on the use of dabrafenib/trametinib; what they like, and dislike of this treatment option compared to chemotherapy (if it was previously prescribed). The questionnaire was administered between June and December 2023.

This study was approved by the Institutional Review Board at KHCC.

Results

Twenty patients were identified, 13 males and 7 females (Table 1). The median age at diagnosis was 8.3 years (range, 0.3-18.9 years). The oldest patient (Table 2, #4) was originally treated for posterior fossa pilocytic astrocytoma (PA) with partial resection followed by vincristine and carboplatin. Then he was observed regularly with a stable residual tumor for 7 years. At 18.9 years, significant tumor progression upon transformation to glioblastoma was noted (Supplementary Figure S1). The retrospective analysis of the initial tumor identified a *BRAF V600E* mutation associated with *CDKN2A* deletion. There were 3 patients with HGG, two with pleomorphic xanthoastrocytoma (PXA, WHO grade 2) and 15 with LGG. Fifteen tumors were supratentorial, three were in the posterior fossa/brainstem, one diffuse leptomeningeal glioneuronal tumor (DLGNT) and one primary spinal LGG. Five tumors were metastatic at time of initiation of the targeted therapy: two HGG, one DLGNT, one posterior fossa PA and one suprasellar desmoplastic infantile astrocytoma (DIA). Except for one patient with NF1, all patients had tissue proven diagnosis. Ten patients underwent STR and nine had tumor biopsy. All patients, except three, received dabrafenib and/or trametinib after the standard treatment protocol (chemotherapy with/without radiotherapy). Summary of patients' and tumors' characteristics, treatment

TABLE 1 Summary of patients' and tumors' characteristics, treatment received and response to targeted therapy.

Diagnosis	LGG	PXA	HGG
Number of patients	15	2	3
Molecular tumor characteristics			
BRAF fusion	6	0	0
BRAF mutation	7	2	2
CDKN2A deletion	NA	2	1 (2 NA)
FGFR mutation	0	0	1
Empirical therapy	2	0	0
Tumor metastasis at start of targeted therapy	3	0	2
Treatment received			
Dabrafenib alone	6 (then 3 had trametinib added)	2	1 (then trametinib was added)
Trametinib alone	8	0	1
Combination	1	0	1
Initial radiological response	10 PR, 5 SD	1 PR, 1 SD	3 PR
Progression	0	0	3
Median follow up	1.9 years (range, 0.5-5.4)	9 months	2.7 years (range, 1.3-3.2)
Death	0	0	2

NA, not available; PR, partial response; SD, stable disease.

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TABLE 2 Characteristics of patients with low grade glioma and their treatment.

#	Diagnosis and Molecular alteration	Initial treatment	Tumor status before targeted therapy	Targeted therapy / Response & duration (months)	Further therapy	Response	Progression	Total duration of targeted therapy (year)	Patient outcome /duration of survival (year)
1	Suprasellar PA, *BRAFv600E* mutation (IHC)	VCR/Carboplatin (15 cycles) then vinblastine (51 weeks)	Local progression	Dabrafenib / progression (6)	Trametinib was added	Partial response	No	5.4	Alive / 12.9
2	Suprasellar PA, *BRAFv600E* mutation (IHC)	VCR/Carboplatin (14 cycles) then vinblastine (42 weeks) then TPCV (8 cycles)	Local progression with visual decline	Dabrafenib /stable (12)	Trametinib was added to control side effects	Partial response & resolution of panniculitis/ fatigue	No	4.8	Alive /9.5
3	Suprasellar PA, *BRAFv600E* mutation (IHC)	VCR/Carboplatin (15 cycles) then vinblastine (70 weeks)	Local progression with visual decline	Dabrafenib/ progression (6)	Trametinib was added	Partial response	No	3.9	Alive /11.1
4	Suprasellar PA, *KIAA1549_Ex15-BRAF_Ex9* fusion (NGS)	VCR/Carboplatin (15 cycles) then vinblastine (70 weeks) then vinorelbine (7 cycles)	Local progression with visual decline	Trametinib/ partial response			No	1.9	Alive /7.3
5	Suprasellar PA, *KIAA1549::BRAF* fusion (NGS)	VCR/Carboplatin (13 cycles) then vinblastine (10 weeks)	Local progression with risk on residual vision	Trametinib/ stable			No	1	Alive /4.6
6	Suprasellar PA, *KIAA1549 (exon15)::BRAF (exon9)* fusion (NGS)	VCR/Carboplatin (7 cycles)	Local and metastatic progression with diencephalic syndrome	Trametinib/ partial response with weight gain			No	0.9	Alive /1.4
7	Suprasellar PA, *KIAA1549 (Ex16)::BRAF (Ex09)* fusion	VCR/Carboplatin (12 cycles), then vinblastine (68 weeks) then TPCV (7 cycles)	Local and metastatic progression with risk on residual vision	Trametinib/ partial response			No	0.6	Alive /12.1
8	Suprasellar ganglioglioma, *BRAF V600E* mutation, *CDKN2A*- no loss of expression (NGS)	VCR/Carboplatin (2 cycles)	Symptomatic local progression	Dabrafenib/ partial response with significant clinical improvement			No	0.6	Alive /0.8
9	Suprasellar metastatic DIA, *BRAFv600E* mutation (IHC)	—	Developed ascites following ventriculo-peritoneal shunt insertion	Dabrafenib /partial response with resolution of ascites without VA insertion			No	0.9	Alive /1
10	Suprasellar and thalamic/basal ganglia PA, (NF1)	VCR/Carboplatin (7 cycles), then surgery then vinblastine (57 weeks)	Local progression	Trametinib/ Stable disease (stopped therapy later)			No (off trametinib 4 months)	3.6	Alive /8.9

(Continued)

TABLE 2 Continued

#	Diagnosis and Molecular alteration	Initial treatment	Tumor status before targeted therapy	Targeted therapy / Response & duration (months)	Further therapy	Response	Progression	Total duration of targeted therapy (year)	Patient outcome /duration of survival (year)
11	Metastatic posterior fossa PA, *KIAA1549_Ex15-BRAF_Ex9* fusion (NGS)	VCR/Carboplatin (6 cycles) Then vinblastine (52weeks) then TPCV (5cycles) then vinorelbine (17 cycles) and surgery	Symptomatic local and metastatic progression with significant pains	Trametinib/ stable disease (stopped therapy later)			No (off trametinib 9 months)	2.9	Alive /11.7
12	Frontotemporal DIG, *BRAFp.G469A* (NGS)	Baby POG protocol (6 cycles)	Variable tumor growth and developed ascites	Dabrafenib and Trametinib/ stable disease with resolution of ascites without VA insertion			No	0.5	Alive /2.1
13	Cervico-medullary ganglioglioma, *BRAFv600E* mutation (PCR)	VCR/Carboplatin (7 cycles), then surgery, then vinblastine (50 weeks)	Symptomatic local progression	Dabrafenib/ partial response			No	4.3	Alive /8.7
14	DLGNT, tumor RNA quantity not enough for NGS	VCR/Carboplatin (3cycles), and focal spinal radiotherapy (cord compression)	Intracranial metastatic progression	Trametinib/ Partial response in brain, stable in spine			No	1.9	Alive /2.1
15	Spinal fibrillary astrocytoma, *KIAA1549_Ex15-BRAF_Ex9* fusion (NGS)	Vinblastine (52weeks) then VCR/Carboplatin (10 cycles)	Symptomatic local progression	Trametinib/ stable disease			No	1.5	Alive /11.5

DIA, desmoplastic infantile astrocytoma; DIG, desmoplastic infantile ganglioglioma; DLGNT, diffuse leptomeningeal glioneuronal tumors; F, female; IHC, immunohistochemistry; M, male; NF1, neurofibromatosis type 1; NGS, next generation sequencing; PA, pilocytic astrocytoma; PCR, polymerase chain reaction; POG, pediatric oncology group; TPCV, thioguanine/ procarbazine/ lomustine/ vincristine; VA; ventriculo-atrial shunt; VCR, vincristine.

received, response to targeted therapy and duration are demonstrated in Table 1 and Figure 1.

Patients with LGG

We identified 15 patients with LGG (Table 2); nine males and six females at a median age of 5.4 years (range, 0.3- 13.1 years) at diagnosis. Ten patients had optic hypothalamic pathway gliomas (OPG). Three tumors were metastatic. Ten patients underwent tumor biopsy and five had STR. Nine tumors were PA, two DIA/ DIG, two gangliogliomas, one fibrillary astrocytoma, and one DLGNT. Seven tumors had BRAF mutation (one was a rare mutation: *BRAFp.G469A*), six had BRAF fusion, and two were empirically treated; one (#10) had NF1 and one (#14) with DLGNT had small tumor biopsy insufficient for NGS testing. Tumors with BRAF mutation were treated with dabrafenib and trametinib was added after tumor progression, while tumors with BRAF fusion, NF1 or DLGNT were treated with trametinib. Six patients were started on dabrafenib alone and later trametinib was added in three of them; two due to tumor progression and one to help control the side effects. After adding trametinib, this patient (#2) could be weaned off opioids and steroids that were used to control his panniculitis and fatigue. Eight patients were initially started on trametinib, and one patient (#12) was started on the combination of dabrafenib and trametinib due to his rare mutation (*BRAFp.G469A*). All patients except one used dabrafenib/trametinib after tumor progression following chemotherapy use. This one patient (#9), who was previously reported, underwent a ventriculoperitoneal shunt insertion and biopsy of his metastatic DIA, and later developed ascites. Dabrafenib achieved significant tumor response and ascites resolved without a need for permanent shunt diversion. All patients, except two (#10 & #11), are continuing treatment. All tumors showed SD or PR at a median follow up of 1.9 years (range, 0.5-5.4 years) from starting dabrafenib/trametinib. Figure 2 demonstrates the tumor response to targeted therapy in two patients with LGG. The two patients who stopped trametinib (#10 & #11) had no tumor progression on follow-up MRI scans at 4 and 9 months, respectively.

Patients with PXA and HGG

Two patients with supratentorial PXA-2 underwent STR and GTR, respectively (Table 3). On histology, their tumor exhibited high risk features. Both patients had tumor progression within 3 months. Because further surgical resection was felt to achieve less than GTR, and to avoid giving radiotherapy, a trial of medical therapy was felt reasonable. Both had *BRAFv600E* mutation and *CDKN2A* deletion. Dabrafenib was started and during the first 9 months SD and PR were achieved respectively.

Three patients had HGG (Table 3); one had multiple recurrent BRAF mutated aPXA [#3, previously published (23)] was treated with dabrafenib then trametinib was added upon progression, one had posterior fossa BRAF mutant PA transformed to HGG after 7 years without prior radiotherapy use and was started on combined dabrafenib and trametinib, and the third had K27M altered HGG with *FGFR1p.K656E* and ependymal metastatic lesions who received trametinib and still alive with disease. All tumors underwent STR followed by radiotherapy and temozolomide, then upon further tumor progression they received dabrafenib and/or trametinib. In addition to the radiological response, two patients (#3 & 4) had significant symptomatic improvement. In two patients, hydroxychloroquine was tried to overcome the drug resistance; this was temporarily successful in one patient. With a median of 2.7 years (range, 1.3-3.2 years) from starting dabrafenib and/or trametinib, all tumors progressed, and two patients died.

BRAF/MEK inhibitors side effects

Eight patients (40%) developed acneiform rash; six were on trametinib alone. Three patients (15%) developed paronychia, and one had panniculitis (needing opioids and systemic steroid use) with fatigue. Six patients (30%) needed dose reduction in addition to the supportive measures. Panniculitis and fatigue resolved with addition of trametinib in patient (#2 in Table 2). Ophthalmic and cardiac toxicities were not reported on our regular assessments. One patient (#11 in Table 2) with a difficult to control metastatic LGG, stopped trametinib after 2.2 years despite significant clinical response (became off multiple analgesics including opioids). She had repeated acneiform rash and significant paronychia needing multiple surgical debridement despite the medical care and drug interruptions. Nine months off trametinib, she was asymptomatic with no evidence of radiological tumor progression. One patient (#10 in Table 2) developed significant intracranial bleeding and trametinib was held. Four months later, his tumor did not re-grow. Nine patients had temporary drug interruptions: five due to drug-related side-effects and four due to periods of drug shortage. Three patients developed significant neurological symptoms coinciding with radiological tumor progression within 3 weeks of drug interruption.

Parents and children's opinions on using BRAF/MEK inhibitors

Eleven of 17 parents of patients with PXA or LGG answered the questionnaire (Supplementary Table S1) in addition to 5 of their children. Children had similar responses to their parents. Except for the patient who stopped trametinib due to side effects (#11 in Table 2), all others were very satisfied with the drugs and felt they were better than chemotherapy. They mainly liked the oral route of these drugs, less frequent hospital visits, the minimal hematological toxicity and lack of hair loss. They disliked the dermatological side effects, particularly those patients who had severe symptoms, and the drugs' risks on the heart and retina. The risk of tumor progression with drug interruptions and the need to continue these drugs for long time was of a significant concern to the families.

Discussion

We report for the first time on a series of children with gliomas treated with BRAF/MEK inhibitors in a resource-limited country. The compassionate drug access program allowed us to prescribe these drugs and achieve an excellent tumor control in LGGs and a temporary prolonged control in HGGs. Though most families were very satisfied using these new drugs, there are several challenges encountered.

Treating pediatric LGGs is an art that requires to balance tumor control with the treatment's side effects. The discovery of the molecular landscape of pediatric LGGs and the integral role of the RAS/MAPK pathway signaling in tumorigenesis led to the introduction of BRAF/MEK inhibitors in their management. Many case series demonstrated their efficacy in the recurrent setting achieving reasonable tumor control with a favorable side effects' profile. This triggered a still ongoing debate as whether targeted therapies should replace chemotherapy (28). A recently published phase II trial (29) on 110 children with *BRAFv600E*-mutated LGG randomized in a 2:1 ratio to receive dabrafenib and trametinib or standard chemotherapy (carboplatin and vincristine), led to the FDA approval of this combination as a frontline therapy (19). In this trial, and at a median follow-up of 18.9 months, overall tumor response occurred in 47% of children treated with targeted therapy compared to 11% for those given chemotherapy, with observed clinical benefit of 86% and 46% respectively. This resulted in a significantly longer median PFS in the dabrafenib/trametinib arm (20.1 months) compared to 7.4 months in the chemotherapy arm. Currently, the type II RAF inhibitor tovorafenib, is being investigated in a randomized phase 3 trial (30) as a frontline therapy compared to standard chemotherapy in children with BRAF-altered LGG. Type II RAF inhibitors result in tumor response regardless of the BRAF alteration type (mutation or fusion) without a risk of paradoxical activation.

In comparison, the outcome of pediatric HGG is significantly lower despite surgery, radiotherapy, and chemotherapy. *BRAFv600E*-mutated HGGs are a clinically distinct subtype, and most are secondary to transformed LGGs (10). Nobre et al (31) reported on eleven HGGs previously received radio-chemotherapy; four responded to targeted therapy (36%) with all but one tumor progressed in 18 months. Forty-one children with relapsed/refractory *BRAFV600E*-mutated HGG received combined dabrafenib and trametinib in a phase II trial (17) had overall response rate of 56% with a median duration of response of 22.2 months. At a median follow-up of 25.1 months, 51% of patients

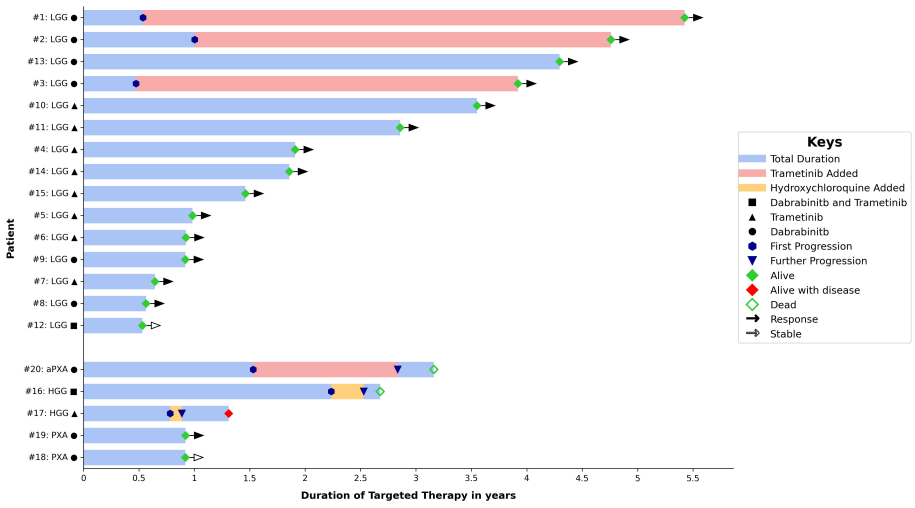

FIGURE 1
Change from baseline in tumor measurement and duration of response.

remained on treatment. This is exceptional in recurrent HGGs which rarely respond to chemotherapy resulting in OS of only few months. This raises the question of whether upfront use of BRAF/MEK inhibitors (32–34) is superior in children with HGGs to optimize their management and try to delay radiotherapy use with its deleterious neurocognitive side effects. One of our patients (#5, Table 3) had the unique entity of K27M altered HGG with FGFR1 mutation. His tumor response to trametinib and prolonged survival despite disease progression was previously described in the literature (35).

The use of dabrafenib/trametinib in our setting was encouraging. All gliomas showed tumor control, and though it was temporary in HGGs the duration was of the longest reported (1.3-3.2 years). Importantly, many patients experienced significant control of their symptoms; two children experienced dramatic improvement in their neurological function and were able to practice normal daily activities (Table 1 patient # 8 & Table 3 patient # 3), two patients were spared from a CSF diversion procedure for their ascites (Table 1 patients # 9 &12) (36), one patient with significant sleep apnea became off night BiPap (Table 1 patient #13), one patient became off pain control medications including opioids (Table 1 patient #11), and one child with diencephalic syndrome gained weight (Table 1 patient #6). These symptoms were not previously controlled despite the use of multiple lines of chemotherapy. We would argue whether the earlier introduction of dabrafenib/trametinib, with their rapid tumor response, would have saved some patients from the morbidities of recurrent tumor progressions, particularly on vision, and resulted in a better overall functional outcome. None of our patients with LGG had visual decline while using dabrafenib/trametinib, but several patients had dropping vision with previous tumor progressions. While we did not easily have the option of upfront use of dabrafenib/trametinib through the compassionate drug access program, it is clearly an FDA approved indication now for BRAF-mutated LGGs. This further supports the opinion that every CNS tumor should be tested molecularly as this can make a huge impact on the child's management and outcome.

Our experience echoes the published data on the side effects' profile of dabrafenib/trametinib. While most side effects are dermatological, mild, and manageable (17, 29) they can be very distressing to the patients particularly the adolescents. Meticulous skin care is needed to help control these side effects which can be very demanding and challenging to the patients. Emollients and sunscreens were regularly prescribed to our patients and most reported compliance using them. One patient (Table 1, #11), and despite the great control of her neuropathic pains, she could not tolerate the recurrent paronychia and acneiform rash. She eventually stopped trametinib despite her awareness of the risk of rebound and the possible need for radiotherapy. This is a well reported risk when stopping the targeted therapies (37). Fortunately, her tumor is still under control 9 months after discontinuation of treatment. Recently, experts from Canada developed a consensus algorithm for discontinuation of targeted therapies in children with *BRAFV600E* gliomas (38). One patient (Table 1, #10) developed significant intracranial bleeding while on trametinib. This rare event was previously reported in the literature (39). We did not notice cardiac dysfunctions or ophthalmic side effects in our cohort despite regular assessments. These risks were one of major drawbacks of using targeted therapies according to the families. In addition, the uncertainty on the duration of using these drugs, and the high risk of rebound tumor growth with drug interruptions were stressful to the families. This is still a medical challenge. There are anecdotal data on successful rechallenge after stopping BRAF inhibitors (31), or shifting to a selective BRAF inhibitor (40), or combining it with chemotherapy. Despite these risks, most of our patients preferred the use of targeted therapies over chemotherapy.

With the use of the compassionate drug access program, we provided new targeted drugs to our patients however this is not without a challenge. We had times with drugs interruptions related

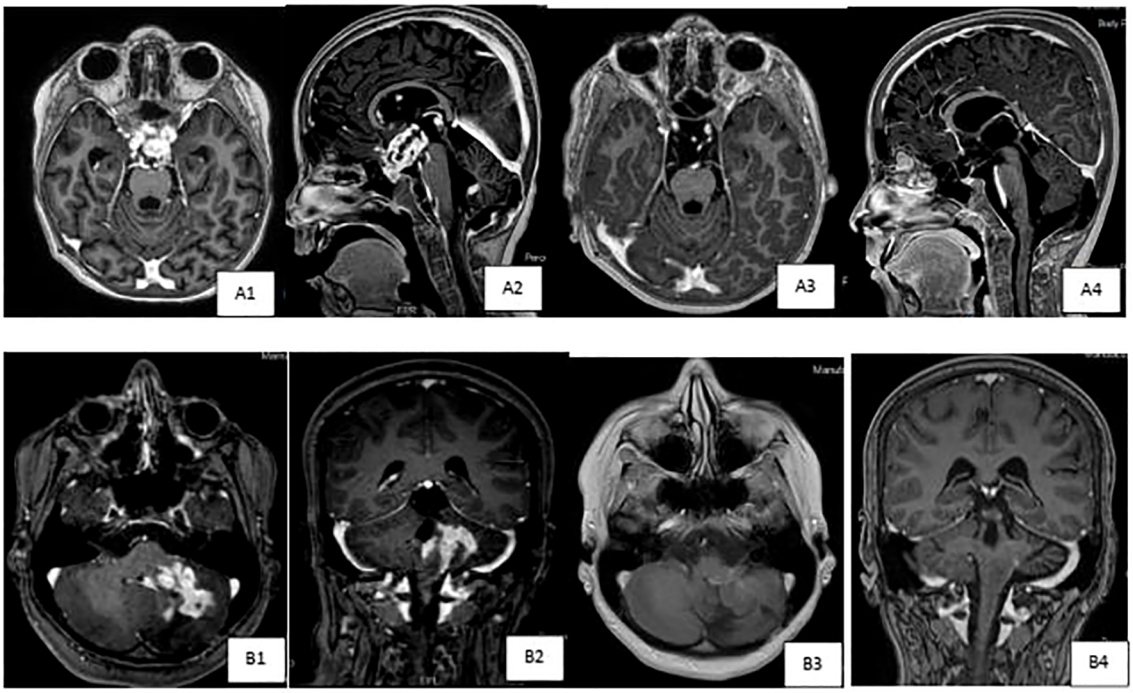

FIGURE 2
Brain MRI scans demonstrating tumor response to targeted therapy in two patients with low grade gliomas. **(A)** Axialand sagittal T1-weighted post IV contrast brain images of patient # 14 with diffuse leptomeningeal glioneuronal tumor (DLGNT),demonstrating pretreatment (A1& A2) large contrast enhancing mass in the suprasellar cistern,inseparable from the optic chiasm,extending to the floor of the third ventricle. Subependymal, intraventricular enhancing nodules are also noted, seen onlower row images. Marked interval tumor response {A3 & A4) with resolution of cortrast enhancement with almost resolution of previously seen subependymal enhancing nodules,currently much smaller and nonenhancing, as seen in upper row images. **(B)** Axialand coronal T1-weighted post IV contrast brain images of patient # 13 with cervico-medullary gangiloglioma, demonstrating pretreatment (B1 & B2) heterogeneous contrast enhancingmass in the left cerebellar hemisphere,with the involvement of the brain stem,particularly l eft hemi medulla,and leptomeningealenhancement extending to the left foramen of Luschka.Marked interval tumor response (B3 & B4) in the tumoral component within theleft cerebellar hemisphere, with almost resolution of mass like contrast enhancement,development of leukomalacia, improvement in the expansion of the left hemi medulla and contrast enhancement.

to drug importation and during the COVID era. This route of drug access is used globally particularly in children with cancer where there are limited drug approvals or clinical trials access (20). It may be more "justified" in a LMIC setting where access to new drugs will take long time, if ever. The high cost of the targeted drugs is a challenge for routine clinical use even after the accumulating evidence of efficacy in the literature. We are now working on a cost effectiveness analysis and specific indications to use dabrafenib/trametinib at KHCC after closure of the compassionate drug access program in Jordan following the FDA approval of the combination of trametinib and dabrafenib for pediatric patients with BRAF mutated LGGs in March 2023. It is important as well to consider the participation of LMICs in international clinical trials of new targeted medications. Most of these drugs are orally administered and need less frequent monitoring which makes the idea of using them is more plausible in a resource-limited setting. This hopefully would result in less abandonment of therapy or a need to use alternative choices with shorter duration of therapy, like radiotherapy, with its detrimental neurocognitive side-effects particularly on young children. In addition, most targeted drugs act rapidly which help decrease the morbidities associated with tumor growth (e.g. visual loss or neurological deficits) which are more difficult to "tolerate" in a resource-limited setting. On the other hand, inclusion of LMICs in the international clinical trials will help advance the whole health system in these countries.

The present study is limited by the fact it is a retrospective review of a single center experience in a resource-limited setting. KHCC is a relatively advanced center for a LMIC and has excellent infrastructure and trained staff. Furthermore, KHCC has a long-standing twinning program with SickKids hospital. This has contributed to facilitate the interaction with the team involved in the Novartis compassionate program, to build a strong relationship with this team and to be granted approvals for compassionate use for this entire cohort of patients. This makes our experience unique, as reports on targeted treatment in children with brain tumors in LMICs remains anecdotal (22). The response rate observed in our experience appears to be higher than in clinical trials of targeted therapies (29). This may be related to a selection bias in our MDT. However, discrepancies between institutional evaluation and central reviews were noted in several trials (29, 41), with higher response rates reported by investigators. Capturing toxicity data was limited by the retrospective nature of this review and the toxicity may appear lower than in prospective trials of targeted treatments. However, only significant side effects were captured particularly those resulted in dose reductions or interruptions. The positive insight

TABLE 3 Characteristics of patients with pleomorphic xanthoastrocytoma and high grade glioma and their treatment.

#	Diagnosis/ Molecular alteration	Initial treatment	Tumor status before targeted therapy	Targeted therapy	Response & duration (months)	More therapy	Response /duration	Progression	Total duration of targeted therapy (year)	Patient outcome /duration of survival (year)
1	Tempero-parietal PXA, *BRAFv600E* mutation (FISH) and CDKN2A deletion	STR	Asymptomatic local progression	Dabrafenib	Stable	——	—	No	0.9	Alive / 1.3
2	Tempero-parietal PXA, *BRAFv600E* mutation (FISH) and CDKN2A deletion	GTR	Asymptomatic local progression	Dabrafenib	Partial response	——	—	No	0.9	Alive / 1.2
3	Tempero-parietal aPXA *BRAFv600E* mutation (IHC)	STR/focal rads with TMZ then TMZ 10 cycles then STR followed by Procarbazine /CCNU/ Vincristine (1 cycle)	Symptomatic local and leptomeningeal metastasis	Dabrafenib	Partial response (15) with significant clinical improvement	Partial resection/ added Trametinib	Stable (15 months)	Local and lepto-meningeal metastasis	3.2	Dead /6.7
4	Posterior fossa high grade glioma *BRAFv600E* mutation (IHC) and CDKN2A deletion *	STR/focal rads with TMZ then TMZ (7 cycles)	Symptomatic local progression	Dabrafenib and Trametinib	Partial response (24)	HQC was added upon lepto-meningeal progression	Partial response (2 months)	Lepto-meningeal metastasis	2.7	Dead / 3.7
5	Metastatic thalamic DMG, *H3K27M* altered NGS: *FGFR1p.K656E* and *PTENp.F341V*	PR/WBR with TMZ then TMZ 7 cycles	Asymptomatic leptomeningeal metastasis	CSI then Trametinib	Stable (9)	HQC was added upon lepto-meningeal progression then stopped in 2 months due to limited response	Progression	Lepto-meningeal metastasis	1.3	Alive with disease / 2.4

aPXA, anaplastic pleomorphic xanthoastrocytoma; CSI, craniospinal radiotherapy; DMG, diffuse midline glioma; F, female; FISH, Fluorescence in situ hybridization; GTR, gross tumor resection; HCQ, hydroxychloroquine; IHC, immunohistochemistry; M, male; PXA, pleomorphic xanthoastrocytoma; STR, subtotal tumor resection; TMZ, temozolomide.

*This patient was originally treated for posterior fossa pilocytic astrocytoma with partial resection followed by vincristine and carboplatin. Then he was observed with regular MRI scans showing stable residual tumor for 7 years before his tumor transformed to high grade glioma.

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provided by the parents and children on using dabrafenib/trametinib is encouraging and rarely documented in LMICs.

In conclusion, our experience demonstrates the feasibility of using new targeted drugs in a resource-limited setting and the effectiveness in achieving good tumor control with excellent patients' satisfaction. Questions remain to be answered regarding the duration of using these drugs and their long-term toxicity in children. The current ethical challenge facing LMICs is to balance the affordability of using these drugs in routine clinical practice. Moving targeted drugs to the frontline can save children several morbidities and be more cost effective on the long-term even in a resource-limited setting. Well-designed global studies that combine patients' reported outcome, families' perspective, tumor response and cost effectiveness are needed.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving humans were approved by The Institutional Review Board at KHCC. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because it is a retrospective data review.

Author contributions

DA: Data curation, Writing – review & editing. AA: Writing – review & editing. MA-H: Writing – review & editing. MO: Writing – review & editing. BM: Writing – review & editing. QA: Writing – review & editing. AM: Writing – review & editing. SJ: Writing – review & editing. RR: Writing – review & editing. KK: Writing – review & editing. AI: Writing – review & editing. NS: Writing – review & editing. EB: Writing – review & editing. NA: Conceptualization, Data curation, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

EB is a member of the advisory board of Novartis and Alexion.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1417484/full#supplementary-material

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Current situation of neuropathology in Central America

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The present situation of neuropathology practice in the Central American region has not been addressed in the past. These are low middle-income countries, and therefore, many do not have a basic immunohistochemistry panel. Cytogenetics and molecular studies are not available in most of Central America. Pediatric brain tumors are diagnosed either by anatomical pathologists or by pediatric pathologists. Access to a weakly Latin American Tumor Board is available to consult cases, but most countries do not participate in these expert meetings. The most recent World Health Organization brain tumor book has a very broad molecular classification of pediatric brain tumors. All these factors make it very difficult to properly diagnose pediatric brain tumors in the region, and this impacts the treatment and overall survival of children with brain tumors.

KEYWORDS

neuropathology, brain tumors, pediatric, Central America, immunohistochemistry

1 Background

As the lead pediatric pathologist who has been involved in the diagnosis of pediatric brain tumors for Costa Rica for over 15 years, I have found the evolution of the molecular classification of these tumors to have become overwhelming in a system which does not have all the proper diagnostic tools. The WHO classification of central nervous system tumors has changed three times since I first started practicing. The most recent 2021 WHO fascicle has increased its molecular pediatric brain tumor classification compared with 2016. This has caused a more integrated categorization of pediatric brain tumors, which in previous WHO editions were mostly described along with adult central nervous system tumors. This new classification is important because it considers the great variety of tumors in the pediatric population and how these are unique morphologically as well as from an immunohistochemical and molecular perspective. This is worrisome because in our region, most pathologists are still making diagnosis based on histological patterns alone, which is no longer admissible. All these advances in molecular classification and the lack of proper immunohistochemistry and molecular tools make pathologists feel uncomfortable making a diagnosis of brain tumors in children. Although there is access to weekly meetings with experts from Canada, United States, and Spain through the Latin American Tumor Board

where cases are presented and recommendations are given to the treating oncologist, there is a very low participation of pathologists in these meetings. Moreover, although this group also receives a selected number of pathology samples for second review, this is not enough to address the needs of the region.

At Costa Rica's National Children's Hospital Dr. Carlos Sáenz Herrera, a broad immunohistochemical panel is available but a series of essential molecular studies are still required. For example, for the classification of gliomas and glioneuronal and neuronal tumors, BRAF V600E is available, but we still lack molecular tools such as BRAF fusions, fusions between MYB or MYBL1 and a partner gene necessary for the diagnosis of MYB- or MYBL1 altered diffuse astrocytoma, as well as deletions and amplifications at the MYB locus on 6q23.3 for the diagnosis of angiocentric glioma and MAPK pathway-activating abnormalities needed in the diagnosis of both polymorphous low-grade neuroepithelial tumor of the young and diffuse low-grade glioma, MAPK pathway-altered (1).

For the proper diagnosis of pediatric-type diffuse high-grade gliomas, such as diffuse midline glioma, diffuse hemispheric glioma, and infant-type hemispheric glioma, H3 K27 and H3 G34 mutations and RTK fusions (NTRK, ROS1, and MET) are required, respectively. DNA methylation profiling is not available and is the only method for establishing a diagnosis of high-grade astrocytoma with piloid features and other tumors such as diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters, as well as rosette-forming glioneuronal tumor, and for the molecular subgrouping of pineoblastoma (1).

We do not have MN1 alteration for a proper diagnosis of astroblastoma, PRKCA fusion needed for papillary glioneuronal tumor, or dinucleotide mutation in the PDGFRA gene required to make the diagnosis of myxoid glioneuronal tumor (1).

For the proper categorization of ependymal tumors, we still require ZFTA and YAP fusions, and for the adequate classification of medulloblastoma, although we have N-MYC and C-MYC (by FISH), we are still lacking DNA methylation analysis, as well as immunohistochemistry for YAP1 and GAB1 (1).

To date, no study or publication has been carried out on the current situation of pediatric neuropathology in developing countries such as Central American countries. It is worrisome because in these countries as well as in the rest of the world, brain tumors in the pediatric age are the most common solid tumors and continue to cause high morbidity and mortality.

It is important to consider that in Central America, most of the population can only access public medicine for economic reasons, so we will only refer to this and not to private medicine where other studies may be available.

Most pediatric brain tumors are diagnosed by general pathologists and pediatric pathologists. In some cases, consultations with adult neuropathologists are carried out because there are no formally trained pediatric neuropathologists in the region.

I carried out a short survey to other participating Central American hospitals who participate in AHOPCA (Asociación Hemato-Oncológica Pediátrica de Centro América) to get a sense of their resources. The main findings where that 40% of the countries do not have immunohistochemistry in general in their Pathology Departments or do not have basic immunohistochemical markers used in the diagnosis of brain tumors and base their diagnosis on morphology alone. The countries that have immunohistochemistry available are Panamá, Costa Rica, Guatemala, and San Salvador. Moreover, for example, although Guatemala has access to some immunohistochemical stains, these are not used for the diagnosis of pediatric brain tumors. The markers available include S100, GFAP, ATRX, olig-2, EMA, enolase, neurofilament, IDH1, p53, and IN1-1, but most countries with immunohistochemistry are still lacking stains such as GAB-1 necessary for proper classification of medulloblastoma and YAP-1 useful in both medulloblastomas and ependymomas, ZFTA which is used in the diagnosis of supratentorial ependymomas, and H3 K27 which is important in diffuse midline gliomas.

More than 85% of the countries do not have access to special tools such as cytogenetics and molecular studies. Those that are available are of very limited use in the diagnosis of brain tumors. For example, Costa Rica has studies such as IDH1, IDH2, 1p/19q codeletion, PTEN, and EGFR which are more useful in the diagnosis of adult brain tumors. N-MYC and C-MYC (FISH) are also available and helpful in embryonal brain tumors in the pediatric population. N-MYC has been available for over a decade because of its implications in the prognosis of neuroblastoma.

It is important to mention that no other publications were found addressing the current situation of neuropathology in Central America. This is the first scientific paper that seeks to analyze the reality this region faces.

In Costa Rica, between 2000 and 2014, the incidence of childhood cancer in children under 15 years of age was 2,396 cases; of these, 13.9% were malignant tumors of the central nervous system, which represents 19.4/million. The highest incidence rates are in children aged 1–4 (22.2/million) and 5–9 years (22.0/million). The incidence of malignant CNS tumors in infants varied between the regions from no cases to 20.8/million. Lower malignant CNS tumor incidence rates were found for most solid tumors, including malignant CNS tumors (4). For medulloblastoma, between the years 2009 and 2015, a total of 31 cases were diagnosed with a 5-year OS rate of 61.3% (3).

It is very challenging to gather outcome data without the existence of pediatric cancer registry in some countries of the region. Most countries in Central America are low middle-income countries and therefore cannot afford to assign staff to keep record of cancer data. Without this information, it is difficult to estimate survival data and mortality in the region (2).

2 Conclusions

In summary, there is still a lot that can be done for this region. One option is establishing an outreach program between a specialized center and Central American countries specifically focused on pathology review. Pediatric brain tumors of this region could be presented in a weekly brain tumor board and specific cases, in which the pathology report is unclear, there is a clinical pathologic discrepancy, or if the case requires more immunohistochemical stains or molecular studies for a proper diagnosis, it could be sent out for a second review. This can benefit the patient's treatment and outcome. Also, it is important for pathologists in this region to have access to proper training in pediatric neuropathology.

I also envision one highly specialized neuropathology center for the diagnosis of pediatric brain tumors located in one country in Central America with at least two trained neuropathologists, and centralization on immunohistochemistry and molecular studies would be more feasible because these are developing countries and the resources and infrastructure required to have the highly specialized equipment and expertise are not feasible to have in most centers. With a project of this nature, all pediatric brain tumor blocks could be sent to one center which would specialize in the diagnosis of pediatric brain tumor of the region. This would be of great benefit for the patients because biopsy results would be more accurate and prompter. Also, specific cases could still be sent out for a second pathology review and to perform specific molecular studies that are only available in highly specialized centers.

Costa Rica has a socialized healthcare system, and the government invests in this health system. This has made it possible for us to have access to more diagnostic tools. It has been a long journey finding providers that are willing to bring the immunohistochemical stains necessary for the diagnosis of pediatric brain tumors because these are not so widely, and the economic cost is high. Countries in Central America could partner with developed countries in the diagnosis of brain tumors and invest in one large center in the region where the expertise, a broad panel of immunohistochemical markers, and molecular studies would be available.

Central America is a region that definitively would benefit from an outreach program with a highly specialized center in the United States, Europe, or Canada, and this would be of high impact in making treatment decisions and in the overall outcome of children with brain tumors in the region.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Author contributions

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Conflict of interest

The authors declare that the article was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Survival of pediatric patients with ependymoma in a tertiary cancer center in Rio de Janeiro, Brazil

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Introduction: Ependymoma is the third most frequent central malignant nervous system tumor in the pediatric age group. There is scarce data in the literature on survival of these patients, especially in upper and lower middle-income countries. We aimed to describe the clinical and demographic characteristics, treatment, and outcome of pediatric patients with ependymoma admitted to a public cancer hospital.

Methods: Retrospective analysis of medical records of patients with ependymoma, admitted to the Pediatric Oncology department (0-20 years) during the period of 2000-2022. Data on patient, disease characteristics, and treatment were analyzed. Overall survival (OS) was calculated using the Kaplan-Meier method.

Results: Seventy-two patients were evaluated; median age at diagnosis was 6.5 years (range: 1-20), 63% were male, 54% of the tumors were in the posterior fossa (PF-EPN), 45% were classified as WHO grade 3, and 68% were operated on in other institutions before referral. Regarding treatment, 72% underwent radiotherapy and 33% of patients underwent chemotherapy. Almost 70% percent of the patients had relapses. The median follow-up time was 5.2 years (Range: 0,1-21,4). The OS in 5 years was 67%. Totally resected tumors had OS in 5 years of 88% (p: 0.028).

Conclusion: The results achieved in this series show a survival gap between UMIC and HIC. Relapses occurred mainly in the first ten years and then reached a plateau, with the majority of patients experiencing endocrinological and neurological sequelae.

KEYWORDS

childhood cancer, ependymoma, survival analysis, low-and-middle-income country, epidemiology

1 Introduction

Ependymoma is the third most frequent pediatric malignant brain tumor and the most common tumor in spinal cord and cauda equina. Patients can often experience multiple recurrences and poor long-term overall survival (OS) (1, 2). According to CBTRUS (the Central Brain Tumor Registry of the United States), the average annual age-adjusted incidence rate is 0.29 per 100,000 for children and adolescents (0-19 years), and is higher among younger children (0-4 years old) at 0.46 per 100,000, lowering with increasing age to 0.26 per 100,000 (15-19 years) (2). High-income countries (HIC) report 5-year OS of 80-85%, while there is scarce information on survival outcomes in low-to-middle income countries (LMIC), but reports range from 40-60% (3–5). Delayed diagnosis, lack of specialized professionals, toxic death, shortage of chemotherapies, and limited infrastructure are some of the barriers that LMIC have been facing.

Historically, treatment of Central Nervous System (CNS) tumors has been neglected because of the complexity required for diagnosis and treatment. Health systems are required to have optimized referral systems from primary care or emergency departments to cancer centers where patients can be assisted by a specialized team (6).

Standard treatment has not changed much over the years whereby a maximal, safe surgical resection is still considered the most important prognostic factor in ependymoma followed by the administration of focal radiation for a large number of cases, even in young children (7–9). Chemotherapy remains a controversial option because of the questionable chemosensitivity of ependymomas. In the context of post-operative residual disease, it can be delivered pre-irradiation, although with contradictory results (10–12). The role of maintenance chemotherapy (after surgery and radiation) was investigated by COG ACNS 0831 protocol, the final publication of which is pending (13).

Our retrospective review aimed to describe the clinical and demographic characteristics, treatment, and survival outcomes of pediatric patients with ependymoma admitted to a LMIC public cancer hospital over 20 years.

2 Material and methods

2.1 Study population

A retrospective study was conducted at the National Cancer Institute (INCA), located in Rio de Janeiro, Brazil. Demographic, clinical, disease, and treatment characteristics were retrieved from medical records of pediatric patients with ependymoma, admitted to the Pediatric Oncology Department during the period of 2000-2022. We included any patient less than 20 years of age at admission with a confirmed diagnosis by histopathology of ependymoma from any location within the central nervous system in the newly diagnosed and recurrent setting. Patients previously operated on and treated with chemotherapy outside of INCA were eligible.

2.2 Statistics

The median and interquartile range were used to summarize the quantitative variables, and absolute and percentage values were used for the categorical variables. Survival curves were generated using the Kaplan-Meier method and statistically compared using the log-rank test. All analyses were performed using the statistical software R, version 3.6.3 (2020-02-29). Patients with myxopapillary ependymoma were excluded from the survival analysis because they are a distinct histology. Patients not seen at the institution for more than two years were considered lost to follow up and were censored. Analysis was performed on December 12, 2023.

2.3 Setting

According to the World Bank, Brazil is an UMIC (upper middle-income country), with a population of 215 million inhabitants and a Gross Domestic Product (GDP) per capita of US$ 8,900 (14). INCA is a tertiary cancer center and accounts for the treatment of most pediatric CNS tumors in Rio de Janeiro with free care, provided by Brazil´s Unified System of Care (SUS). The Ministry of Health is responsible for the development and coordination of integrated actions in the prevention and control of cancer (15). Today it is equipped with a pediatric inpatient ward with 22 beds, an intensive care unit (since 2002), an emergency department (since 2009), and a radiation therapy center with 3D conformal technique (since 2002). There is a large team of professionals dedicated to pediatric care: pediatric oncologists, pediatric neurosurgeons, pathologists, radiologists, radiation oncologists, physiotherapists, speech therapists, nutritionists, an abandonment prevention team, and a clinical research team, among others. Pediatric supportive care is available from the pediatric emergency and pediatric intensive care unit. Around 40 new patients with CNS tumors are treated annually at INCA.

2.4 Study definitions and treatment

Ependymomas were divided into supratentorial ependymomas (ST-EPN), posterior fossa ependymomas (PF-EPN), and spinal ependymomas (SP-EPN). The extent of surgical resection was evaluated by MRI and/or CT of brain or spine within 48-72 hours postoperatively, according to exam availability at the institution. The extent of resection was categorized into two major groups based on the surgeon's report and/or MRI performed at time of patient registration at the institution: gross total resection (GTR) and subtotal resection (STR)/biopsy. Metastatic disease was defined by disease outside of the primary location as seen on brain and spinal MRI and/or cerebrospinal fluid (CSF) cytology. The histopathological diagnosis was divided according to WHO grading (1, 2, and 3) and specific histological subtypes (classic, anaplastic, myxopapillary, clear cell, tanycytic, and papillary) and immunohistochemistry using EMA (epithelial membrane antigen), S100, Olig2, and GFAP (glial fibrillary acidic

protein). The pathological diagnosis did not include newer immunohistochemistry and molecular studies to classify the tumors in this cohort. Patients operated on outside INCA had their histopathology confirmed at our institution. During this long period, many treatment regimens were used. Most PF-EPN received focal RT after surgery. Radiation therapy was indicated for rade 3 ST-EPN, irrespective of their extent of resection, and all grade 2 partially resected ST-EPN. Intracranial tumors were treated with different doses: anaplastic tumors were treated with 59.4Gy in 33 fractions of 1.8Gy and other grades received 54Gy in 30 fractions of 1.8Gy. Spinal tumors were treated with doses between 45 and 50.4 Gy, in 25 to 28 fractions. Multiple chemotherapy regimens were used during the period, with different intents: to bridge infants to radiation therapy (Baby POG) and for patients with residual disease pre-irradiation (CCG 9942). In the first ten years, ICE Protocol was the chemotherapy used in the recurrent setting. Currently the COG ACNS 0121 has been used to attempt to minimize residual disease before second-look surgery, while oral etoposide is still used for palliative treatment.

At recurrence, re-operation was attempted when feasible and re-irradiation was performed in some cases, even when surgery was not possible. OS was measured as the time from registry at INCA to the date of death or last follow-up. OS was calculated using the Kaplan-Meier method.

3 Results

From 2000-2022, 82 patients were admitted with ependymoma. Patients were excluded from the study due to lack of data (n=9) and change of diagnosis according to the pathology review at the institution (n=1). In total, 72 patients were eligible for analysis. Patient characteristics are described in Table 1. Median age at diagnosis was 6,5 years (range: 1-20), with a male predominance (62%). Sixty-eight percent of patients were primarily operated on in other institutions before referral to INCA. Four patients were registered at recurrence. There were 39 patients with PF-EPN (54%) and 24 patients with ST-EPN (33%). Eight patients had SP-EPN primaries (11%), with four myxopapillary, one clear cell, one tanycytic, one anaplastic, and one without histological subtype. Grade 3 was the histology in 45% of patients. Regarding histopathology of ST-EPN, four were WHO grade 2 and 13 were WHO grade 3 and all but two were localized. PF-EPN was localized in 23 patients (58%); 16 patients had WHO grade 2 and 13 patients were WHO grade 3.

Only two patients received a brain MRI within 48h post-operative, with the remaining patients being submitted to post-operative CT scan. Only 54% of patients had craniospinal MRI (pre- or post-operatively). Of these, 26% had spine MRI within one month of surgery. Cerebrospinal fluid (CSF) was assessed for neoplastic cells in 38 patients (52% of cases) with positivity in three patients (8%). Resection grade reports (either by MRI reports or surgeons report) were available in 70% of patients, namely 38 patients with gross total macroscopic resection. After first surgery, 52 patients received focal radiation. One other patient received craniospinal radiation at recurrence. Eleven patients were not submitted to RT at any moment. Of these, four patients remained alive.

Only 22 patients (30%) received CT: 15 PF-EPN (68%), six ST-EPN (27%), and one SP-EPN (5%). Eleven patients received CT for adjuvant treatment (including three infants treated with bridge therapy, as per Baby POG and BB SFOP), and four patients before second-look surgery, as per COG ACNS 0121), six patients received ICE protocol, and five patients received oral chemotherapy with palliative intent (oral etoposide). Radiation therapy after surgery was administered in 52 patients: 19 ST-EPN (36%), 27 PF-EPN (52%), and six SP-EPN (12%). Five ST-EPN patients were initially just observed.

Fifty patients (70%) had relapses: 17 patients with ST-EPN (34%) and 27 patients with PF-EPN (54%). Salvage treatments included at least one additional re-resection in 20% of patients and re-irradiation in 15% (all focal and one craniospinal).

At the time of analysis, 28 patients were alive and 22 of these had some degree of long-term sequelae (78%). Only six patients (22%) did not present any sequelae. The most common were neurological, in 67% of patients, with the following symptoms: cerebellar ataxia, intellectual deficit, epilepsy, facial palsy, dysphagia, hypotonia, and strabismus. Twenty-five percent of patients also had endocrinological symptoms, with growth hormone and thyroid deficiencies being the most common.

The median follow-up time for this cohort was 5.9 years (Range: 0,1-21,4); 14 patients were lost to follow up. The OS in 5, 10, and 20 years was 67%, 50%, and 50% respectively with 34, five, and two patients surviving 5, 10, and 20 years respectively (Figure 1). The OS in 5 years for patients with totally resected tumors was 88% and for partially resected was 57% (p: 0.028) (Figure 2). Regarding tumor location, OS in 5 years for ST-EPN was 78%, PF-EPN 61%, and SP-EPN was 75% (Figure 3). The OS in 5,10, and 20 years for patients submitted to surgery at INCA was 62%, 54%, and 54%, and for patients with surgery elsewhere was 69%, 44%, and 51%, respectively (p: 0.77) (Figure 4).

4 Discussion

Although the overall survival rate at 5 years of 67% was satisfactory, the long-term results were poor and the rate of recurrences higher than in HIC. This highlights that current treatment in LMIC settings should be improved. Table 2 shows the comparison of OS and EFS in countries of different economic status according to the World Bank. There are a few Brazilian papers, and the newest one, focusing on posterior fossa tumors, showed an OS in 5 years of 49% (23); other Brazilian studies in intracranial ependymomas reported OS of 60% and 33% (24, 25). HIC show OS around 82% (10, 26), whereas UMIC have similar survival rates to the present cohort (4, 27).

Treating pediatric CNS tumors in low- and middle-income countries can be very challenging, as they require complex care with multidisciplinary teams comprising pediatric oncologists, pediatric neurosurgeons, neuropathologists, neuroradiologists, radiation therapists, and technology and clinical support, which is not always accessible (28). With epidemiological transition, chronic diseases such as cancer have become leading causes of death. CNS tumors are the first cause of disease-related mortality in pediatric solid tumors in Brazil, with specific adjusted mortality rate of 10,26 per million of

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TABLE 1 Disease and treatment information.

N: 72	n (%)
Age (median and range)	6,5y (1-20)
Sex	
Male	45 (62)
Female	27 (38)
Surgery location	
INCA	23 (32)
Other hospitals	49 (68)
Tumor location	
ST-EPN	24 (33)
PF_EPN	39 (54)
SP-EPN	8 (11)
NI	1 (2)
Extent of disease	
Local	48 (66)
Disseminated	9 (13)
NI	15 (21)
WHO Grade	
Grade I	4 (6)
Grade II	24 (33)
Grade III	32 (45)
NI	12 (16)
CSF	
Positive	3 (4)
Negative	33 (46)
Not performed	34 (47)
Inconclusive	2 (3)
Extent of resection	
GTR	28 (38)
STR	23 (32)
NI	21 (30)
Radiotherapy	
Sim	52 (72)
Não	20 (28)
Chemotherapy	
Yes	23 (32)
N	47 (66)
NI	2 (1)
Recurrence/progression	
Sim	50 (70)
Não	22 (30)

CSF, Cerebrospinal fluid; GTR, Gross total resection; STR, Subtotal resection; RT, radiation therapy; CT, chemotherapy; NI, not informed.

children/adolescents, according to INCA (29). Barriers to care, such as delayed diagnosis, treatment abandonment, malnourishment, and low parental education, explain the survival gap faced by children in this setting (30, 31). Currently, pediatric neuro-oncology experts have been addressing how to bridge the gap with interventions, for instance, twinning programs, optimization of available resources, and establishment of multidisciplinary teams (20, 32).

Ependymomas are surgical tumors, with questionable response to current chemotherapy protocols (33). Also, the prognosis is related to the extent of resection (34), with patients with totally resected tumors having better survival than patients with residual tumors (35). Ependymomas are sharply demarcated tumors, usually rising from the fourth ventricle, but specific locations (cerebellopontine angles and eloquent areas, for example) may eventually be a deterrent to gross total resections. The shortage of subspecialized pediatric neurosurgeons can directly impact the grade of resection in brain tumors and, therefore, the survival (36). According to Brazilian pediatric neurosurgery society (SBNPed), there are 143 Brazilian pediatric neurosurgeons (37) for a population of around 62 million children/adolescents under 19 years (22). Of those, 84 pediatric neurosurgeons are concentrated in the southeast region (comprising Rio de Janeiro, Sao Paulo, Minas Gerais, and Espirito Santos). In Rio de Janeiro, where INCA is located, there are 19 pediatric neurosurgeons for a population of 4,6 million children/adolescents under 19 years (16), with a pediatric neurosurgeon for every 245,000 children, which is higher than other LMICs with one pediatric neurosurgeon for every 3.6 million children (17). In the present study, 68% of patients had first tumor surgery outside INCA, including emergency hospitals, and were than referred for adjuvant treatment. It is not possible to identify if they were operated on by pediatric neurosurgeons, however it is described that pediatric neurosurgeons are more prone to remove above 90% of the tumors (36). Therefore, we encourage the transfer of brain tumor patients to INCA and all our efforts are towards reoperation in case of residual tumor on imaging.

Although long-term OS for patients operated on at INCA was superior, it was not statistically significant. Due to the small cohort numbers, it was not possible to accurately assess this difference.

In this series, only 51 patients had reports on extent of resection, and of these, 28 patients had gross total resection (54%) with the following locations: 11 supratentorial tumors, 12 posterior fossa tumors, and five spinal tumors. Extent of resection was significant to survival. Other studies show similar results (19, 38).

Adequate pre- and post-operative imaging with brain and spinal Magnetic Resonance Imaging (MRI) is the gold standard imaging

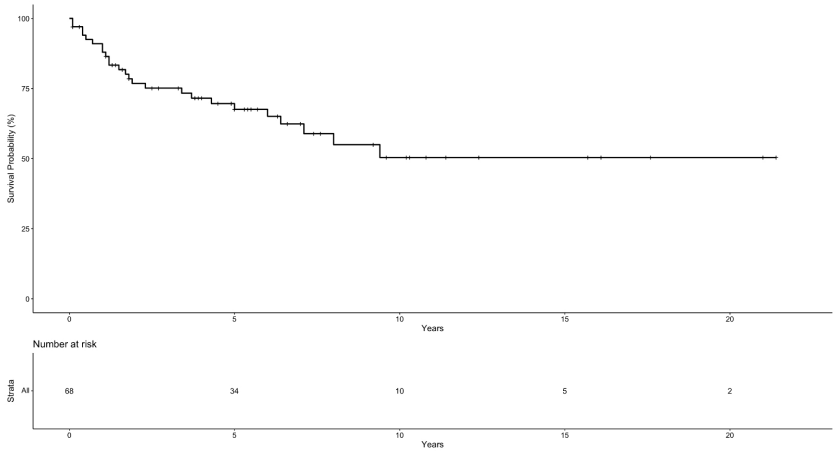

FIGURE 1
Ependymoma Overall Survival Probability.

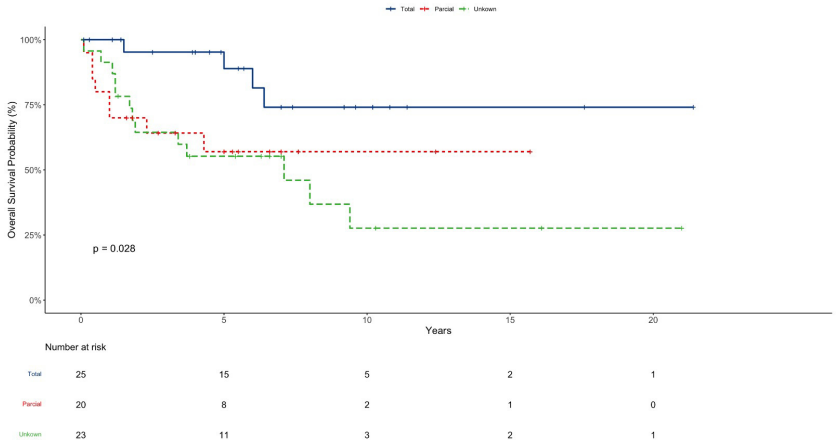

FIGURE 2
EP OS according to resection grade.

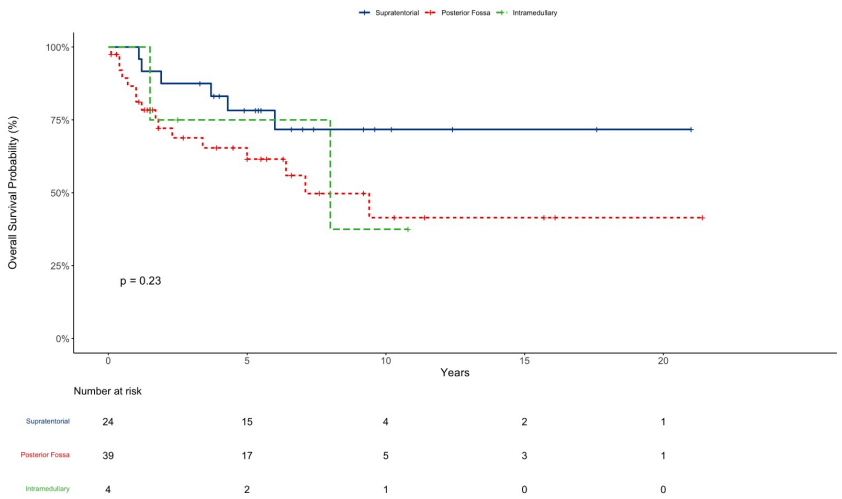

FIGURE 3
EP OS according to tumor location.

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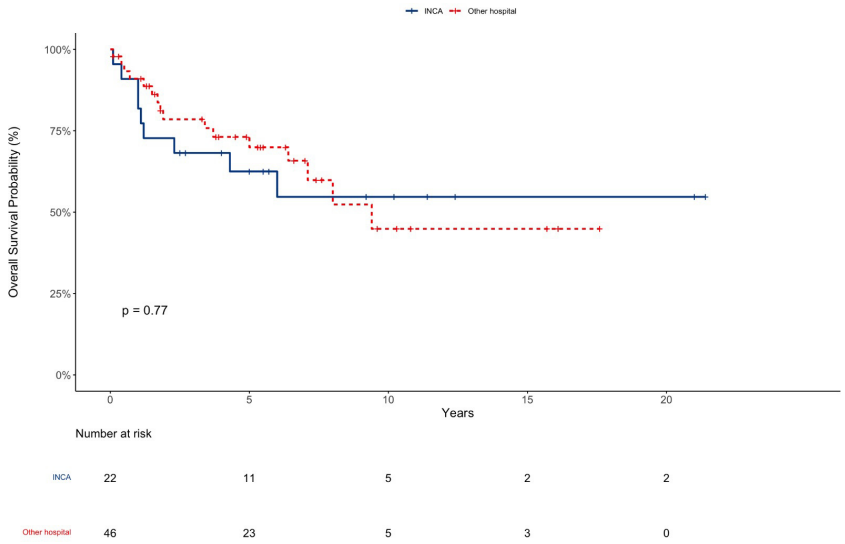

FIGURE 4
EP OS according to place of surgery.

evaluation for these tumors. Postoperative imaging guidelines for brain tumors recommend that brain and spine MRI should be performed within 48-72h hours to define the extent of resection (18). Unfortunately, not every hospital in our setting has an MRI and some children in our study were registered without appropriate post-operative imaging tests. In this series, only two patients had brain MRI within 48h post-operative, and the remaining patients were submitted to post-operative CT scans. Twenty-six percent had spine MRI within one month of surgery. Instituting imaging protocols (early post-operative brain MRI) in intensive care units is mandatory to

TABLE 2 Comparative survival.

Citation	Country	Economic status	Number of patients	Population	Tumor location	OS (%)	EFS (%)
De Andrade (2009) (16)	Brazil	Upper middle income	34	Ped and adults	Intracranial/ spinal	60 (5y)	
De Araujo (2011) (17)	Brazil	Upper middle income	8	pediatric	Intracranial	33 (5y)	
Godfraind (2012) (18)	USA	High income	146	pediatric	Intracranial	82	69
Tashvighi (2018) (5)	Iran	Lower middle income	73	pediatric	Intracranial	61 (3y)	59 (3y)
Wang (2018) (19)	China	Upper middle income	55	Ped and adults	Intracranial	64 (5y)	49 (5y)
Das (2018) (3)	India	Lower middle income	20	pediatric	Intracranial		35 (3y)
Ruangkanchanasetr (2019) (4)	Thailand	Upper middle income	24	pediatric	Intracranial	75	56
Shah (2020) (20)	Saudi Arabia	high income	22	pediatric	Intracranial	44	18
Hammad (2021) (21)	Egypt	Low income	47	pediatric	Intracranial	43 (3y)	43 (3y)
Ritzmann (2022) (8)	UK, Ireland, Spain, Denmark, Sweden, Netherlands	high income	72	pediatric	Intracranial	69 (5y)	49,5 (5y)
Da Costa (2023) (22)	Brazil	Upper middle income	55	pediatric	Intracranial (Posterior fossa)	49 (5y)	

OS, Overall survival; EFS, Event free survival.

properly define grade of resection and to program further surgery in order to have no residual tumor.

Interventions to achieve better surgical results, besides the pediatric neurosurgical specialization, are technological improvements like intraoperative neurophysiological monitoring. This technique assesses the integrity of cranial nerves, allowing safer surgeries and larger resections with less neurological morbidities, but are rarely available in LMIC settings because of the high cost (21).

This series reports more than 20 years of treatment with different treatment strategies. Patients received several chemotherapy protocols (10, 11, 39–41): to delay radiation therapy, before second-look surgery, and for palliation. Currently, patients above one year have been receiving focal radiation therapy after surgery, instead of chemotherapy, since it improves survival (42). For recurrent disease there is no standard salvage treatment. Regarding re-irradiation, all patients received focal radiation therapy, except one who received CSI. Currently, CSI re-irradiation has shown improvement in survival in recurrence (43, 44).

Ependymomas are tumors with high recurrence rates, and even with standard therapies one third of patients fail treatment (43). In this series, 70% of patients recurred once, with multiple salvage treatments in different combinations: surgery, irradiation (or reirradiation), and chemotherapy,. Although there were more relapses than described in the literature, the overall survival of this series was similar to other upper middle-income countries.

Long-term sequelae were found in 80% of ependymoma survivors in this study, with neurological and endocrinological alterations being the most common. Hormone replacement was indicated when necessary. Patients with neurological deficits were followed by pediatric neurologists, speech therapists, physiotherapists, and occupational therapists. These numbers highlight the need to improve not only treatment, with the aim of increasing survival, but also paying attention to patient quality of life. Vulnerable patients such as ependymomas survivors in countries with limited resources must be submitted to neuropsychological assessments. Initiatives such as The European Society of Paediatric Oncology Ependymoma-II program Core-Plus model for an internationally accepted test battery for follow-up of pediatric ependymoma patients has been developed (45, 46).

Study limitations include the retrospective nature of the study, long period of inclusion of patients with different treatment strategies, lack of neuropsychological data, and lack of imaging results in some patients, mostly in the early years. The strength of the study is a cohort of patients from the same institution.

In conclusion, with a multidisciplinary approach, survival outcomes were similar to those described in literature for upper-middle-income countries, but still less than those achieved in HIC. Relapses occurred mainly in the first ten years and then reached a plateau, with the majority of patients experiencing endocrinological and neurological sequelae. There is still a need for improvement, with earlier referral to specialized hospitals, more imaging studies to define grade of resection, more reoperation, and timely adjuvant treatment, when indicated.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study of human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

GO: Writing – original draft. YG: Data curation, Writing – review & editing. MC: Conceptualization, Writing – review & editing. DM: Conceptualization, Writing – review & editing. VM: Conceptualization, Writing – review & editing. DO: Supervision, Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. SF: Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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