CHAPTER TWELVE

Management of pediatric brain tumors in low- and middle-income countries

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Abstract

Five-year survival rates exceed 70 % for the 10–20 % children with central nervous system (CNS) tumors in high-income countries (HICs) but are less than 30 % for the 80 % children in lower-middle-income countries (LMICs). The management of CNS tumors is complex and multidisciplinary. It requires a minimum of infrastructure and

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interactive collaboration between the different actors involved in the care of these patients. This chapter addresses the main challenges associated with the management of pediatric CNS tumors in LMIC, and describes examples of successful development, particularly in the context of twinning programs between institutions in HIC and institutions in LMIC.

1. Introduction

Neuro-oncology has witnessed major developments during the last 2 decades. New technologies have emerged with a significant impact on diagnosis, surgical management, as well as on radiotherapeutic and oncological treatments (Ludmir et al., 2018; Sherman et al., 2011). Many neurosurgical units are currently equipped with neuronavigation, intraoperative MRI scans, and electrophysiological monitoring to optimize tumor resection and minimize morbidity. Progress in radiotherapy include the rapid expansion of proton facilities, as well as improvement in radiation techniques. While very few new chemotherapeutic agents have emerged for the treatment of central nervous system (CNS) tumors, the development of targeted therapies has revolutionized the management of many conditions, in particular low and high-grade glioma (Renzi et al., 2025). Certainly, a major development has been the impact of molecular biology on diagnosis, prognosis and therapeutic management of brain tumors (Porter et al., 2023). All these developments have greatly influenced the discipline and contributed to significant improvements in survival as well as quality of survival.

However, 80–90 % of children diagnosed or not diagnosed with a CNS tumor live in low- and middle-income countries where resources are limited, and technological progress is slow (Gupta et al., 2019). This chapter aims to see how we can address this gap in resources and their consequences in terms of diagnosis, management and survival.

2. Incidence of pediatric brain tumors in LMIC

National cancer registries provide the opportunity to compare the incidence of specific conditions in different area of the world. However, pediatric cancer registries are rare in LMIC and there are only few epidemiology studies on childhood brain tumors in this setting. Most publications represent single-institution experiences rather than collaborative

studies. Published rates of pediatric brain tumors are very variable among LMIC registries and show generally a global incidence that is 3 times lower than in HIC.

According to the data of the International Agency for Research in Cancer (IARC, https://www.iarc.who.int/), in HIC, the annual average age-specific incidence rate (ASR) of all malignant and non-malignant CNS tumors in children and adolescents ages 0–19 years is 2.5 per 100,000. Montenegro and the USA show the higheest ASR (3.5. and 3.4 per 100,000 respectively) and Angola is the only LMIC is the top 15 countries. Other data suggest higher rates in HIC: 3.9 in France (Desandes et al., 2014), 4 in Great Britain (Stiller et al., 2019), 4.81 in Finland (Abuhamed et al., 2022), 5.3/100,00 in Canada (Walker et al., 2023), with the highest rates reported in the United States, at 6.38/100,000 (Ostrom et al., 2023). In low-income countries, the ASR for brain tumors in the 0–19-year-old population is 0.56/100,000. It is 0.88/100,000 in lower middle-income countries and 1.6/100,000 in upper middle-income countries (Girardi et al., 2023a; Roach et al., 2023). Such differences may suggest a different epidemiology in different regions of the globe. Another and more plausible explanation is the lack of diagnosis. The diagnosis of a CNS tumour requires a CT and/or an MRI scan. These tests are only available in large urban centres in many LMICs, and their cost is a major obstacle for under-resourced families. Some patients may have an imaging study suggestive a CNS tumor, however no subsequent diagnostic investigation and will not be reported in registries. Other explanations are the lack of registration of tumors diagnosed without pathological confirmation (e.g. diffuse intrinsic pontine glioma, some low grade gliomas, particularly in patients with neurofibromatosis type 1, or secreting germ cell tumors), the lack of registration of low-grade histologies in some registries, or the high mortality rate in young children (under the age of 5 years), which may lead to early death before the child develops cancer. However, there is no statistical reason that a high rate of premature death should influence the overall incidence of childhood cancer. Using IARC data, Howard et al. reported a close correlation between the reported incidence of childhood leukemia and the mean annual per capita gross national income (Howard et al., 2008). There is no similar study for childhood brain tumors. It is very likely that in many low-income countries, most children with brain tumors die before diagnosis. Some tumors may be diagnosed by imaging studies, but the cost of treatment prevents families to proceed any further in the diagnosis and management. In a study of 145 children with a suspected

diagnosis of CNS tumor on imaging seen in Lahore over a one-year period, 38 died before any intervention, and only 45 % underwent surgery (Ul-Ain et al., 2023).

Survival data available from LMIC are scarce. In a systematic review of observational studies that provided estimates of population-based survival by histology for children diagnosed with a malignant or non-malignant primary brain tumor, Girardi et al identified 5 studies that were entirely or partially conducted in LMIC (Girardi et al., 2023b). While in European and North American countries, the 5-year survival in childhood medulloblastoma was 60 % or more, in Tunisia the 5-year survival was less than 27 % in 1997, and it was zero in Uganda in 2007. These survival data only concern patients who were diagnosed, considering that a majority of children with medulloblastoma are not diagnosed in some parts of the world.

3. Main obstacles for the development of pediatric neuro-oncology programs in LMIC

Several studies have pointed out the main obstacles to the development of successful pediatric neuro-oncology programs in LMIC (Gupta et al., 2019; Haizel-Cobbina et al., 2021; Syed Ather Enam et al., 2024). Some obstacles are related to insufficient resources in neuroimaging, neurosurgery, neuropathology, radiation equipment or access to chemotherapy or targeted treatment. Some are related to lack of knowledge, lack of training programs and poor organization of care. While money is the bottleneck for the implementation of appropriate equipment, there will be no successful program without a rigorous organization that includes training, team building and multidisciplinary interactions.

3.1 Lack of equipment/technical infrastructure

There is a profound gap in equipment between HIC and LMIC. The ratio of MRI scans between the USA/Germany or Finland and Ghana/Ivory Coast or South Africa is 100 to 1 (WHO data: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/total-density-per-million-population-magnetic-resonance-imaging). Similar differences are seen in the global mapping of CT scans (https://www.who.int/data/gho/data/indicators/indicator-details/GHO/total-density-per-million-population-computed-tomography-units). Surgical neurooncology has witnessed

major innovations and improvements of previous techniques over the last few decades. Although the use of intraoperative microscopes is almost universal, many neurosurgical units in LMIC do not have access to neuronavigation, tractography, brain mapping, electrophysiological monitoring, fluorescence guided tumor resections, and robotic assistance for tumour biopsy, amongst others (Dewan et al., 2019). Intraoperative MRI scan is another example of improvement that has nearly exclusively benefited institutions in HIC. As far as radiation equipment is concerned, global data have repeatedly shown a disparity between HIC and LMIC (https://www.who.int/data/gho/data/indicators/indicator-details/GHO/total-density-per-million-population-radiotherapy-units). In a recent effort to identify available resources for the treatment of childhood cancer in Africa, Geel et al reported that 29 of 54 African countries did not provide access to radiotherapy for children (Geel et al., 2021). In 2022, Laskar et al wrote a review focusing on the challenges associated with accessible and affordable radiation therapy (Laskar et al., 2022). They identified approximately 14,000 teletherapy machines globally. However, 90 % of this equipment is located in HIC, whereas 70 % of the cancer population lives in LMIC. Considering that the treatment of children sometimes necessitates additional resources like anesthesia, and longer treatment time per session, the radiation management of children with CNS tumors is consequently not a priority and often suboptimal in most LMIC.

The disparity is even more obvious concerning the availability of proton facilities. There are nowadays 141 units open (data May 2025, https://www.ptcog.site/index.php/facilities-in-operation-public). Only 18 are located in LMIC, with 15 in upper middle-income countries (China, Russia and Thailand) and 2 in lower middle income countries (India). Thirty-six are under construction, including 10 only in LMIC (7 in China, 1 in Argentina, Kazakhstan and India). There is no proton facility in LICs, which account for 15 % of the world's pediatric population, while 87 % of facilities are located in HICs, which account for 11 % of the world's pediatric population (https://data.worldbank.org/indicator/SP.POP.0014.TO.ZS).

3.2 Lack of human resources

While the lack of equipment is a major challenge to the development of pediatric neuro-oncology programs in LMIC, the lack of human resources is another critical limitation. Dewan et al performed a global mapping survey to identify the number and location of neurosurgeons in the world and correlated this number with the needs of the population in each

country (Dewan et al., 2019). They estimated that 23,3000 additional neurosurgeons are needed to meet the neurosurgical necessities of the population, all in LMIC. For Africa, the estimated deficit of neurosurgeons was 8420 in this survey. There is clearly a need to address this disparity and to increase access to neurosurgical care in LMIC.

A similar survey was conducted and reported by Zhu et al on global radiotherapy demands and available workforces, based on data from the Global Cancer Observatory (GLOBOCAN) in 2022 (Zhu et al., 2024). This survey estimated that only 50 % of patients requiring radiotherapy were able to receive treatment. The authors compared the estimated/ideal radiotherapy workforce to the reported resources in a selection of 32 countries, accounting for 56 % of all cancer cases globally. Twenty-three (71.9 %) of 32 countries did not have enough radiation oncologists to address basic radiotherapy needs. There was no specific information on pediatric brain tumor patients, and this likely reflects the low level of priority that is given to pediatric neuro-oncology in LMIC.

There is no similar study for global oncology workforces. However, the International Society of Paediatric Oncology (SIOP) has launched in 2019 a project entitled "SIOP Global Mapping". Up to now, data on Africa and South America have been collected and published (Geel et al., 2021; Gorostegui-Obanos et al., 2024). In Africa, of 54 countries, there were trained pediatric oncologists in 39 countries, while 15 had none and the proportion of the population < 15 years was negatively correlated with the reported number of pediatric oncologists in the country. All these data demonstrate the profound gap in equipment and human resources between HIC and LMIC. There is no information regarding pediatric neuro-oncology resources. However, with some exceptions, very few institutions in LMIC have developed specific pediatric neuro-oncology programs and children and adolescents with brain tumors are essentially treated by pediatric oncologists with no sub specialization. In some LMIC they are managed by neurosurgeons in neurosurgery units.

While there is abundant material concerning the needs in terms of radiotherapy and neurosurgery in LMIC, and to some extent, less regarding pediatric neuro-oncology, there is limited information regarding the issue of pathology, molecular pathology and access to medications.

3.3 Neuropathology in LMIC

Appropriate diagnosis is critical for proper allocation of treatment. Errors or discrepancies can have a major impact on outcome. A classic example is the

confusion between low grade and high-grade glioma, due to microvascular proliferation and/or infarct-like necrosis in pilocytic astrocytoma, leading to the disclosure of poor outcome and treatment with radiotherapy with large margins (Collins et al., 2015). Confusion between ependymoma and medulloblastoma is not exceptional, with even more concerning consequences when a patient with medulloblastoma is treated with focal radiotherapy while the standard radiotherapy treatment is based on craniospinal irradiation. Reasons for errors and discrepancies are multiple and may be related to a lack of expertise or a lack of training in pediatric brain tumors. Discrepancies are often the consequence of the lack of expertise in neuropathology (fixation, dehydration, microtome sectioning), the lack of diagnostic techniques, which could be immunohistochemical markers or more sophisticated molecular diagnostic techniques. For example, the lack of INI1 testing will be a major limitation in identifying atypical teratoid rhabdoid tumors. Similarly, the lack of immunohistochemical testing for H3K27M may contribute to an erroneous diagnosis of low-grade glioma. In a retrospective study of histopathology review of 763 pediatric cases referred from outside the United States to Saint Jude Children's Research Hospital, Santiago et al analyzed the rate of concordance between the submitted diagnoses and the reviewed diagnosis at their institution (Santiago & Jenkins, 2013). The level of full concordance was 61 % and in 25.1 % of cases, there was a major disagreement in the diagnosis. The anatomic site that resulted in most of the major disagreements was the central nervous system, with a full concordance rate of 49 % and a 32.8 % rate of major disagreement. Importantly, the change from malignant diagnosis to a final benign diagnosis was three times more frequent than the change from benign to malignant, suggesting that in the context of limited resources or insufficient training, pathologists tend to over diagnose malignancies. In this experience, immunohistochemistry was used in only 45 % of the cases, with an average range of 7.1 antibodies per case.

Another report from Lebanon, a lower-middle income country with a GDP per capita of 2500 USD, analysed 171 cases of second opinions sent to Saint Jude Children's Research Hospital, accounting for 19 % of all cases seen at the American University of Beirut during the period of study 2008–2016 (Merabi et al., 2018). Of a total number of 126 central nervous system tumours seen, 78 (62 %) were sent for review. The percentage of major disagreement was 18 %, while it was 15 % for minor disagreement. Since 48 central nervous system tumors were not sent for review, it is possible that the number of discrepancies would have been higher with a

systematic review of all cases. The most common misdiagnosed entities were pilocytic astrocytoma and ependymoma. The lack of immunohistochemical tests may account for a number of these discrepancies. In this context, there is a need to identify a minimum or a recommended number of immunostains to cminimize diagnostic errors. There is no perfect definition of the type or number of IHC tests. This may include glial fibrillary acidic protein or GFAP (marker of astrocytic tumors), synaptophysin (neuronal marker), EMA and vimentin (ependymoma markers), H3K27M for diffuse midline gliomas, INI1 for atypical teratoid rhabdoid tumours, and LIN28A for ETMR. Some additional tests may contribute to better characterize tumor types: H3k27me3 for PFA ependymoma or some diffuse midline glioma, GAB1 and YAP1 (SHH medulloblastoma), beta catenin (WNT medulloblastoma), TP53 (medulloblastoma, choroid plexus tumours), BRAF V600 (low- and high-grade gliomas). In countries with a high level of consanguinity, testing for mismatch repair deficiency (MMRD) can be helpful (MLH1, MSH2, MSH6, PMS2). However, the benefit of these additional tests remains unproven, particularly in the absence of targeted treatment for low- and high-grade glioma in most LMIC, as well as the unavailability or unaffordable costs of immune checkpoint inhibitors for the management of MMRD related CNS tumors.

3.4 Molecular studies in LMIC

The gap between HIC and LMIC is even more pronounced when it relates to molecular studies (Gupta et al., 2019; Köy et al., 2024). The WHO classification for CNS tumors increasingly relies on molecular information, and recommends adding a NOS suffix that "indicates that the diagnostic information (histological or molecular) necessary to assign a specific WHO diagnosis is not available, providing an alert to the oncologist that a molecular work-up has not been undertaken or failed technically". As a result, most diagnoses of pediatric CNS tumors in LMIC are labeled "NOS" (Louis et al., 2021).

While the unavailability or high cost of targeted treatments makes the relevance of molecular studies questionable in many LMIC, some molecular studies could have an important impact, allowing adaptation of treatment without a need to access expensive medication or sophisticated techniques of treatment. The typical example is medulloblastoma, which includes 4 different subgroups associated with different behavior and outcomes. Gold standard methods recommended by International

Working Groups include gene expression profiling and DNA methylation (Ramaswamy et al., 2016). Both techniques are often not relevant in LMIC, due to availability, cost, lack of technical expertise, bioinformatics complexity and long turnaround times. Gene expression profiling requires fresh-frozen samples and both methods require a sufficient amount of high-quality RNA or DNA. Some reports from LMIC have shown that IHC could be a relatively good surrogate of these techniques (Kaur et al., 2016; Mushtaq, Bashir, et al., 2025; Rajagopal et al., 2023), and contribute to identifying some subgroups, in particular WNT patients (tumors characterised by intranuclear staining for beta catenin) who could benefit from dose reduction of radiation due to their excellent outcome, or SHH patients with important implication for treatment: infants and young children can be successfully treated with a radiation sparing approach; by contrast an older child with a SHH medulloblastoma associated with diffuse TP53 expression should be considered a high risk patient and treated as such, regardless of the result of the staging. Still, these techniques do not allow the implementation of specific approaches that could be lifesaving: the Children's Oncology Group trial ACNS0332 has demonstrated a significant survival benefit of the addition of carboplatin during radiotherapy in high-risk group (Leary et al., 2021). Identification of group 3 patients (versus group 4) requires methylation techniques. Similarly, evaluation of MYC, MYCN status, or presence of isochromosome 17q requires fluorescence in situ hybridisation, RT-PCR, CGH array or copy-number estimates from methylation array. In the absence of these techniques, patients with a group 3 average risk medulloblastoma associated with MYC amplification or isochromosome 17q will be offered treatment with reduced dose craniospinal irradiation and chemotherapy with an 80 % risk of failure (Michalski et al., 2021), whereas the chance of cure will be 2 or 3 times higher with a molecularly adapted treatment using higher doses of radiotherapy and carboplatin during craniospinal irradiation (Leary et al., 2021). This is only one example among many. Efforts should be made to integrate the clinical needs of LMIC patients and their physicians and improve access to molecular diagnosis. This can be achieved by outsourcing samples at a reasonable cost or through compassionate programs. It is also urgent to develop more affordable techniques and/or consider a global effort to identify surrogates of molecular markers using AI, for example. In this context, nanopore sequencing is a promising technique, due to the low capital cost of the device compared to existing

technologies. It is a portable device that does not need sophisticated laboratory equipment and the cost per sample is in the range of 200$ for whole genome sequencing. However, the performance of this technique with FFPE is poor and nanopore requires high-quality DNA from fresh frozen tissue (Filser et al., 2024).

3.5 Access to medications

Availability of cancer medications for curative, supportive and palliative care is critical for comprehensive and holistic management. In many LMIC, access to cytotoxic medicine is a major challenge. Achieving equitable access to affordable medications is a major pillar for successful outcomes. In pediatric neuro-oncology, essential cytotoxic drugs include cisplatin, carboplatin, vincristine, vinblastine, cyclophosphamide, ifosfamide, etoposide and lomustine. The efficacy of temozolomide remains unproven. The use of agents that do not cross the blood brain barrier, such as doxorubicin or actinomycin-D is part of some protocols for patients with atypical teratoid rhabdoid tumors (ATRT) or embryonal tumors with multiple rosettes (ETMR). Unfortunately, although most of these drugs are on the WHO list of essential medicines, access to these medications is not uniform and many institutions lack essential cytotoxic treatments that would allow an appropriate treatment of patients. In addition, drug shortages are frequent and major barriers to providing comprehensive and optimal oncological care (Hantel et al., 2024). Political factors can have a major impact on drug supply. The 2017 US embargo against Iran threatened the life of over 2000 children with leukemia (Ghalibafian et al., 2018). Drug shortage may lead hospitals and patients to seek other alternatives. This includes the disturbing consequences of purchasing counterfeit drugs on the gray market (Mackey & Liang, 2012). The use of alternative protocols is always a challenge for clinicians, due to the potential risk of ineffective treatment or higher risk of recurrences, as well as the risk of potential harm due to toxicity.

In addition to antineoplastic agents, the management of patients with CNS tumor requires access to other medications: steroids are key in the daily management of many conditions; the availability of antibiotics and antifungals is critical for patients who receive intensive chemotherapy protocols. In certain regions of the world, antimalaria and/or HIV medications are also vital. Shortages that affect patients with cancer are not unique to antineoplastic therapies and shortages of antibiotics are also common worldwide (Baraldi et al., 2025).

The use of blood products is not frequent in conditions such as low- or high-grade glioma, as the intensity of chemotherapy is usually mild. However, protocols used for embryonal tumors or germ cell tumors can cause profound neutropenia, thrombocytopenia and anemia. In this context access to blood products is critical and often challenging in the LMIC setting.

Beyond the issue of availability and access to medications, the delivery of anticancer treatments is essential and requires a perfect organisation in terms of storage, prescription, dispensing, and administration. In a recent meta-analysis of medication administration errors in African hospitals, Alemu et al. identified that most errors are related to systemic failures and patient-related factors (Alemu & Cimiotti, 2023). Several factors are involved and can contribute to medication errors, such as understaffing, insufficient skill mix, medical undersupply, poor organization of resources, and inadequate administrative support. In another review of medication errors and adverse drug events, and the factors contributing to medication errors in African hospitals, Mekonnen et al highlighted common recurring problems and contributory factors such as systemic failures and human errors (Mekonnen et al., 2018). The most common errors were related to a prescription and/or an administration of an incorrect dose. Other commonly reported errors included wrong drug combination and/or selection, wrong route of administration, omission errors and wrong frequency and/or duration. Other studies have also highlighted these issues. In a review of 200 randomly selected charts of hospitalized patients admitted to a 200-bed government hospital in Kumasi, Ghana, Koffuor et al. showed that 60.5 % of patients did not receive the correct amount of medication due to illegible handwriting and similar packaging (Koffuor et al., 2012). Studies in the pediatric setting have shown that medication errors are common in LMIC. In a review of 384 pediatric patients admitted at Nekemte Referral Hospital, Ethiopia, Fekadu et al identified medication prescribing errors in 261 patients (67.97 %) (Fekadu et al., 2019). The most common error was a dosing error in 251 (48.6 %), followed by incorrect drug selection in 98 (19.0 %). Studies in the context of paediatric oncology in LMIC are limited. A study involving 286 medical records in Mexico reported that medication errors were common, with 279 (97.6 %) having at least one type of error (Barrios-López et al., 2022). The three most frequent errors were early or delayed administration of chemotherapeutic agents (23.6 %), missing staff signature (20.9 %), and incorrect birthdate (18.3 %). Of all medication errors, 37.2 % had the potential to cause injury.

Efforts are made to standardize the organization of pharmacies in LMIC through the International Society of Oncology Pharmacy Practitioners (ISOPP) for example, which aims at advancing oncology pharmacy care for patients throughout the world (Patel et al., 2021. The SIOP Africa Pharmacy technical working group recently developed a pediatric oncology pharmacy curriculum specific to Africa (Wiafe et al., 2025).

4. Training: A major component of capacity building in LMIC

Training is a major component of the building of paediatric neuro-oncology programs in HIC and LMIC. Paediatric expertise is key in each discipline, neurosurgery, radiation oncology and neuro-oncology. Opportunities for training are limited in HIC and often require credentials that preclude hands-on training for potential candidates who will just have the alternative to apply as observers.

4.1 Neurosurgical expertise

In 2016, L. Albright wrote the following statement regarding pediatric neurosurgery in Africa: "There are fewer than 15 fellowship-trained pediatric neurosurgeons in Africa, and there are at least 5 major reasons for that dearth. 1) There are almost no academic pediatric neurosurgeons on African neurosurgery faculties who can offer fellowships. 2) To become a pediatric neurosurgeon requires an additional year of training. 3) Funding for a fellowship year is rarely available. 4) Pediatric neurosurgery pays less than adult neurosurgery. 5) Neurosurgeons prefer—as is true of doctors in general— not to treat disabled people, and many children with pediatric neurosurgical disorders are disabled by hydrocephalus or spina bifida and die within a few years" (Albright, 2016). In addition, specific surgical expertise is required to treat childhood brain tumour due to multiple challenges: the size of the head, the high proportion of tumours in the posterior fossa, which is not a common location in adults, the smaller blood volume compared to adults, the critical role of complete resection in many pediatric brain tumors. Albrights's comments were echoed by Warf who reported his experience in dealing with 172 children with brain tumors in Uganda (Stagno et al., 2014). Several organizations are involved in educational programs in pediatric neurosurgery, including the African Pediatric Neurosurgery Section (*AfPNS*), the Asian Australasian Advanced Course

in Paediatric Neurosurgery, or the CURE Hydrocephalus and Spina Bifida (CHSB) fellowship, amongst others. In addition, retention of trained pediatric neurosurgeons is key, once they have completed their training.

4.2 Training of pediatric neuro-oncologists

The specialty of pediatric neuro-oncology is still young, and, in many countries, pediatric oncologists are dealing with all disciplines without any subspecialization. However, large LMIC institutions with high patient volumes have started to create separate pediatric neuro-oncology programs or sections with a dedicated team. One early experience was at the King Hussein Cancer Center in Amman, where a neuro-oncology-retinoblastoma section was developed in the context of a twinning program with the Hospital for Sick Children for neuro-oncology and St Jude Children's Research Hospital for the retinoblastoma activity (Qaddoumi et al., 2007a, 2008). Eventually, other similar programs were initiated in Pakistan, Egypt or Malaysia (Mushtaq et al., 2022; Rajagopal et al., 2024). These programs benefited from a twinning partnership with institutions in HIC, allowing them to take advantage of frequent contacts and observership opportunities. Observerships are usually offered for a short period of time, 4 to 6 weeks in general. There is no formal structure for these observerships. Usually, observers attend all domains of clinical activities (clinics, ward rounds), tumour boards, team meetings, lectures and grand rounds. The program can also involve an in-depth review of protocols, face to face meetings with each member of the neuro-oncology team, and the sharing of material (articles, PowerPoint presentations). This offers the observer the opportunity to implement in his/her own practice the ideas gathered during his/her stay. The cost of these observerships is usually covered by the host institution. However, some institutions may charge for these experiences – regardless of the country of origin of the observer – limiting therefore the access of physicians from LMIC.

Fellowship opportunities for pediatric neuro-oncologists from LMIC are few. In addition, training in an institution in HICs to acquire necessary skills may have unintended detrimental consequences, with a risk for the LMIC institution to lose a specialist when the trainee does not return to his/her native country to practice. The risk of brain drain seems to be lower when fellowship occurs in the context of a partnership with a collaborating organization from a HIC. New forms of training initiatives need to be considered to avoid the risk of brain drain while offering optimal learning opportunities. Recently the Saint Jude Global Neuro-Oncology program launched 2 initiatives:

- The St Jude Global Academy Neuro-Oncology Training Seminar (NOTS), a hybrid course in pediatric neuro-oncology specifically designed for physicians from LMIC. The first experience took place in 2019. The course started with a target need assessments (TNA), aiming at evaluating the capacity of the team to treat pediatric patients with CNS tumors. Responses from the TNA were used to identify potential areas for improvement in knowledge and team-based approach. Teams that completed the TNA were invited to participate in the NOTS. The NOTS had 2 components, a 9-week online course and an onsite 7-day workshop. Participants from 8 countries were enrolled, including Mexico, El Salvador, Peru, Morocco, Pakistan, China, Malaysia, and the Philippines and involved different disciplines (pediatric neuro-oncology, neurosurgery, radiation oncology, pathology, neurology, radiology). The short-term impact of this experience was reported, and all participants provided positive feedback, acknowledging gains in knowledge and confidence, leading to changes in their clinical practice. Following this experience, the workshop participants created the Global Alliance for Pediatric Neuro-Oncology (GAP-NO), which is still active today with monthly tumor boards where physicians from LMIC present complex cases. Two other NOTS sessions took place in 2022 and 2023. So far, 41 institutions from 29 countries have participated in this program with a total of 191 individuals, including 68 pediatric oncologists, 37 neurosurgeons, 22 radiation oncologists, 19 radiologists, 18 pathologists, and 27 other specialists.
- The Virtual Pediatric Neuro-Oncology Fellowship (VPNOF). This initiative was launched in 2022, with 5 fellows selected from five different countries (Armenia, China, Indonesia, Mexico, and Pakistan) for a virtual training and mentorship program including expert guidance and mentorship in pediatric neurooncology (Moreira et al., 2021). This fellowship included virtual clinical guidance and case-by-case advice, virtual tumor boards and teaching sessions, career mentorship, two one-month rotations at the mentor's institution, clinical research and presentations at international conferences. Fellowship duration is 18–24 months, and VPNO fellows spend most of their time at their local institution while they train. Following a first successful experience, an additional six fellows were selected from China, Costa Rica, India, Romania, South Africa, and Sri Lanka in 2023 and a third generation of 6 VPNO fellows was selected in 2024 (Ghana, Czech Republic, China, Turkey, Brazil, Uganda). The long-term impact of this approach is still

to be demonstrated, as it primarily depends on the commitment and availability of the mentors (each fellow has 2 mentors) during and after the completion of the fellowship.

4.3 Training radiation oncologists

There is a shortage of radiation equipment in LMIC. There is also a shortage of human resources. The International Atomic Energy Agency recommendation for staffing of radiotherapy facilities is one radiation oncologist per program, with one additional radiation oncologist for every 200–250 patients treated annually (Slotman et al., 2005). This recommendation makes no distinction as whether the patient is an adult or a child. Training radiotherapy professionals to deliver quality radiotherapy to all children with brain tumors is a major challenge, even in HIC. Whether LMICs should rely on HIC to provide radiation training is questionable. Differences in equipment and team organization in HIC versus LMICs are obvious. Radiation oncologists from LMIC who train in HIC do not develop the necessary skills to function in a poorly resourced LMIC environment on their return. This may eventually lead to frustration and ultimately to brain drain, compromising the sustainability of LMIC programs. Ideally, the training of radiotherapy professionals should be done regionally. Radiation oncologists in LMIC should be able to use 2D radiotherapy, a technique that was abandoned decades ago in HIC. As units move to more sophisticated techniques, the gaps between HIC and LMIC radiotherapy treatment may decrease, but the difference remains obvious when it relates to human resources.

The Pediatric Radiation Oncology Society Taskforce in Low- and Middle-Income Countries (PROS-LMIC) aims to improve education in clinical pediatric radiotherapy. This includes workshops, visiting trainees, telemedicine, an online curriculum and instruction with region-leading institutions (Parkes et al., 2017). This educational focus on LMIC is critical since the use of HIC clinical trial protocols in LMIC may prove to be inappropriate or dangerous. Major differences between the HIC and LMIC contexts can compromise the anticipated benefits of HIC trials due to differences in nutritional status, infectious control, access to anesthesia, toxicity management, proximity and access to healthcare facilities, and availability of medicines. This does not mean that the status quo is acceptable, and efforts should be made to adapt HIC innovations to LMIC. Pediatric radiotherapy training is still limited in HIC. In a survey of 130 pediatric radiation oncologists from 33 countries conducted in 2019, only 12.1 % did a pediatric

radiation oncology fellowship following residency (Paulino et al., 2020). With > 80 % of the world's pediatric population living in LMIC, there is an urgent need to address the issue of training pediatric radiation oncologists and securing priority access to radiation treatment for this group of patients. In this context, a first successful twinning experience for pediatric radiotherapy has recently been reported between Emory University and Tikur Anbessa Specialized Hospital in Ethiopia (Ali et al., 2024).

5. Telemedicine and twinning, a success story

Technological progress has transformed communication and interaction through computers, smartphones, social media, and instant messaging applications. This change has contributed to the development of telemedicine programs between institutions in high income and low-middle income countries. While these telemedicine program required sophisticated and expensive material in the early 2000s, platforms such as Zoom, Teams, Webex are available at an affordable cost and allow online meetings between participants. The use of telemedicine in paediatric neuro-oncology started in 2004 with the collaboration/twinning between King Hussein Cancer Centre in Amman, Jordan and the Hospital for Sick Children in Toronto, Canada (Amayiri, Swaidan, Abuirmeileh, et al., 2018; Qaddoumi et al., 2007b). The initial connection used a six-channel ISDN telephone line. Each channel transmitted 64 megabytes/sec. At that time, the cost for per channel per 1-hr conference was $60, totalling $360 for each 1-hr conference. With the expansion of international collaboration in pediatric oncology, a web conferencing initiative was developed by St. Jude Children's Research Hospital. Cure4Kids (https://www.cure4kids.org) is a free videoconferencing platform that supports the Saint Jude International Outreach Program partners (Moreira et al., 2022). Over 300 international groups, including brain tumor groups, have used this platform to meet online in web conferencing rooms to discuss clinical cases and share knowledge. One of the limitations was the lack of video program, and the communication was only through narration and uploaded PowerPoint presentations. Progressively, internet platforms such as Zoom, Webex and Teams have become the main way of communication in the context of interaction between institutions in HIC and LMIC.

There are different formats for these videoconferences. Most have for main objective the discussion of patients in a virtual tumor board. Case presentations are generally done with a PowerPoint presentation. When histology is discussed, it is also generally via PowerPoint. Imaging studies can be shown on slides, but the use PACS or equivalent systems allows a more accurate presentation of the radiology. The conference can involve 2 institutions, it can also have a broader audience with presentations from multiple sites and/or participants from different countries. It is clear that the concept of these teleconferences has evolved and is now an educational tool that can benefit many physicians and other health care professionals (Mushtaq et al., 2024).

For physicians from HIC, these videoconferences may pose some challenges. Language may be a barrier, and imposing English as the only way to communicate may have a negative impact on the attendance. The Latin-American Tumor Board (LATB) was created in 2013 with Spanish as the official language (Rosabal-Obando et al., 2021). The Groupe Franco African d'Oncologie Pediatrique (GFAOP) is having regular neuro-oncology tumor boards in French, with the participation of all pediatric oncology units of 18 French speaking countries of Africa. The time difference can be challenging. There may also be reluctance to provide recommendations due to potential liability issues. Cases presented can be challenging for various reasons, and the expectation from the treating team is to seek an expert opinion promptly. Some experts prefer to review the cases in anticipation of the videoconference, but this may cause important delays due to the sending of the material and the review of the documents. Most conferences will provide case presentations without any preceding review. In this context, the participation of experts from different HIC institutions is an interesting approach that offers participants the opportunity to hear different perspectives.

Documentation of the discussion and decisions is important and allows a critical review of the impact of these interactions. In the Jordanian experience, the review of the minutes could highlight a progressive change in the impact of the teleconference and the evolution of the discussions over time (Amayiri, Swaidan, Abuirmeileh, et al., 2018). While initially, the main issues were the accuracy of the diagnosis and major changes in the surgical, radiation or chemotherapy management of the patients, a retrospective review of cases showed that more recently, the focus was increasingly on molecular typing and access to molecularly targeted treatments. It is the opinion of many physicians in LMIC that the feedback of

these telemedicine interactions to patients and their families increases trust in the team and decreases abandonment (Amayiri & Bouffet, 2021).

One limitation of these telemedicine tumor boards relates to the differences in resources between participants from HIC and LMIC. Unfortunately, some recommendations cannot be followed due to the lack of funding for pathology review or molecular studies. In the collaboration between Aga Khan University Hospital and the Hospital for Sick Children, private funding from a donor provided the opportunity to perform medulloblastoma subgrouping in 33 of 37 patients diagnosed between 2014 and 2020 (Mushtaq, Bashir, et al., 2025). However, in another study on high grade gliomas, only 47 of 84 patients with high grade glioma could be tested for mismatch repair deficiency (MMRD) due to the lack of funding. Sadly also, none of the 15 MMRD patients in this experience could access immune checkpoint inhibitors (Mushtaq, Minhas, et al., 2025). While knowledge sharing is a major benefit of these teleconferences, there are still major obstacles to overcome to close the gap between HIC and LMIC.

Other examples of teleconferences involving participants from HIC and LMIC include the International Pediatric Neuro-Oncology Tumor Board at Washington University in St. Louis School of Medicine (WUSM) that was established in January 2021 (Shatara et al., 2024), the Malaysia-Singapore virtual pediatric neuro-oncology tumor board meeting (Rajagopal et al., 2024) or the GAPNO tumor board (Moreira et al., 2024) among others.

6. Multidisciplinary meetings: A key factor in the development of pediatric neuro-oncology program in LMIC

The development of multidisciplinary programs has contributed to optimize the management of cancer patients, and pediatric neuro-oncology is no exception (Moreira et al., 2024). Organising regular interactions between neuroradiologists, neurosurgeons, neuropathologists, radiation oncologists, oncologists and other experts involved in the care of patients with central nervous system tumors is a critical step in the development of a pediatric neuro-oncology program. The exponential increase of knowledge in each discipline does not allow one individual to make a decision without the contribution of other experts. There is an intrinsic resistance in many places – not limited to LMIC – to accept the concept of multidisciplinarity. The organisation of multidisciplinary meetings may be

challenging in places where neurosurgery, radiotherapy and chemotherapy are not performed in a single location, but the development of platforms such as Zoom, Teams, WebBex and other have transformed the classical format of tumor boards and distance should not be an excuse nowadays. There is evidence that poor communication between specialists has a detrimental impact on survival and quality of survival. Delays in referral can lead to tumor regrowth, more advanced disease, increased costs of treatment, higher doses of radiotherapy and poorer survival. Ideally, a team meeting at the time of diagnosis will allow to address all challenges and anticipate issues that may arise from the decision of one person only. For example, the importance of having a preoperative MRI scan of the spine in case of posterior fossa tumour suspicious to be a medulloblastoma, an ependymoma or an atypical teratoid rhabdoid tumor; or the value of germ cell tumor markers in an adolescent with a suprasellar or pineal tumor that may contribute to achieving a diagnosis an initiating treatment immediately without proceeding to surgery. An early postoperative multidisciplinary tumor board, ideally within a week of surgery will review pre and post-operative scans of each patient seen during the period of time, review the pathology, discuss the patient's condition, plan the staging if needed, and discuss treatment options. The conclusions of the tumor board should then be shared with the parents. One common comment is the multidisciplinary meetings are time-consuming. However, the benefits of a multidisciplinary approach have been demonstrated, and the implementation of multi-disciplinary paediatric neuro-oncology programs has shown a major impact on survival and quality of survival both in HIC and LMIC. At these meetings, sharing information is critical: background on the patient and family can contribute to identify specific risk factors or a cancer predisposition condition, some imaging features can help neurosurgeons in their operative strategy, interaction with the neuropathologist will allow a comprehensive review of all aspects of the case and identify possible discrepancies that do not fit with the proposed diagnosis. Treatment options will be discussed based on all information collected and in the best interest of the patient. The absence of one or several members of the team at these multidisciplinary meetings will be detrimental in terms of management, and team members should make every effort to attend these discussions. At these multidisciplinary meetings, all team members should have an equal voice. When the meeting makes a recommendation, the recommendation must be followed. Multidisciplinary meetings are not about seniority and authority. If one senior member dominates the discussion or if junior

members are intimidated and afraid to voice their opinion, it becomes impossible to discuss the pros and cons of different treatment options, and patients will receive suboptimal management. MDT should take place at regular intervals (weekly, biweekly, monthly) with a pre-assigned agenda to allow preparation for all participants in the meeting.

7. Targeted treatments

Although the WHO Global Initiative for Childhood Cancer (GICC, https://www.who.int/initiatives/the-global-initiative-for-childhood-cancer) has included pediatric low-grade glioma as one of the 6 index diseases, global access to targeted treatment for this condition and other pediatric brain tumors in LMIC is still a utopia. Some isolated experiences have been reported. Mustansir et al (Pakistan) described a child with a BRAF V600E mutated low grade glioma of the optic pathway who received compassionate dabrafenib after failure of first line treatment with vinblastine (Mustansir et al., 2020). According to the authors, it took over one year to access the medication. Despite this delay, the patient showed spectacular visual improvement and significant tumor shrinkage. Amayiri et al (Amman, Jordan) described a patient with pleomorphic xanthoastrocytoma (PXA) associated with BRAF V600E who was treated with compassionate dabrafenib in the context of disseminated relapse (Amayiri, Swaidan, Al-Hussaini, et al., 2018). The patient experienced a dramatic response. Eventually, she showed progression that was temporarily controlled with the addition of trametinib. More recently, Abu Laban et al (Jordan) reported on a cohort of 20 patients (15 pLGG, 3 HGG and 2 PXA) treated with BRAF and or MEK inhibitors (Abu Laban et al., 2024). This experience demonstrates the feasibility and safety of targeted treatment in limited-resource countries when the treating team has gained experienced in using these new therapies. Similarly, Chinnaswamy (Mumbai, India) et al described a series of 22 evaluable pLGG patients treated with trametinib, including 5 patients without histological diagnosis (Chinnaswamy et al., 2024). The drug was provided through the financial support of a Childhood Cancer Foundation. Twenty patients experienced tumor control, and the authors mentioned that school attendance increased, and hospital visits decreased during treatment. These experiences are still anecdotal, and efforts are needed to expand access to targeted treatment to more children in LMIC. Interesting, the randomized trial FIREFLY-2 of tovorafenib versus standard chemotherapy in pLGG patients requiring first line systemic treatment recently opened in

Jordan (https://clinicaltrials.gov/study/NCT05566795) with the prospect to open in other MICs such as Argentina.

8. Long term follow-up of survivors of CNS tumors in LMIC

Multiple reasons explain the lack of interest in long-term follow-up neuro-oncology programs in LMIC. Poor survival, lack of awareness of long-term side effects of treatments, limited resources to build a comprehensive long-term follow-up clinic, lack of rehabilitation programs are all obstacles, despite the evidence that this population is at risk for long-term morbidities. In a survey of 103 LMIC institutions, Qaddoumi et al identified long-term follow-up programs in 8 institutions only (Qaddoumi et al., 2011). Integration of these aftercare programs as well as rehabilitation in the scope of the pediatric neuro-oncology activity is critical and should be planned as soon as possible during the course of treatment.

9. Conclusions

Overall, this review only addresses a limited number of challenges associated with the care of children with brain tumors in LMIC. The needs are obvious and the gap between HIC and LMIC is unacceptable. The ongoing WHO GICC has triggered hope and optimism regarding the future of pediatric oncology around the world. However, the field of pediatric neuro-oncology is complex, and progress needs to address multiple challenges. In addition to the equipment's needs and requirements in terms of the workforce described in this chapter, universal health care coverage (UHCC) is a major obstacle to equitable access to treatment (Indraswari et al., 2021). UHCC should include all aspects of the management (imaging, surgery, pathology services, radiotherapy, medical treatments, rehabilitation and long-term follow-up). As long as these services have a financial impact on families, there will be treatment abandonment. Some initiatives have already demonstrated that it is possible to successfully develop pediatric neuro-oncology programs in countries with limited resources. The role of governments in providing essential services such as radiotherapy facilities is critical. This includes allocating specific resources for pediatric cancer and passing laws such as UHCC laws. Additionally, governments play a crucial

role in fostering international cooperation. More international collaboration, particularly between HIC and LMIC is needed to reduce the current gap between these two worlds.

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