Pediatric Neuro-Oncology in Countries with Limited Resources

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Introduction

Great disparities exist in the care of children with cancer around the world. It is estimated that more than 80 % of all pediatric cancers occur in countries with limited resources and most disparities are related to differences in healthcare resources and organization of healthcare systems. However, in addition to economic barriers, other issues may limit the quality of care delivered to this vulnerable population. In this chapter, we will review the challenges associated with the management of central nervous system tumors in the pediatric population in countries with limited resources and will provide some suggestions and recommendations based on recent successful experiences [1].

Incidence of CNS Tumors in Countries with Limited Resources

There are only few reports on childhood brain tumors in countries with limited resources. Most publications represent single institution experiences rather than collaborative studies [2]. The incidence of childhood brain tumors is difficult to estimate in these countries due to the lack of population-based cancer registries [3]. There are indeed numerous obstacles for the implementation of cancer registries in developing countries. Many of these countries face general problems of poverty, which make cancer diagnosis, treatment, and compliance a low priority. In addition, some low-income countries have large shifts in population due to wars, migration, or rapid changes in incidence of birth or death, which result in inaccurate age-specific population estimates. Infection and malnutrition are major causes of death in children from developing countries; thus, cancer treatment gets little attention from healthcare authorities. Due to the complexity of the care of pediatric brain tumor patients, even when epidemiologic studies are available, these patients are often not included [4]. However, proper cancer registries would be the first step to appreciate the extent of the problem in order to implement cancer programs (Table 27.1).

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Table 27.1 Pediatric brain cancer registration data included in the C15-1X for the period of 1998–2002 by continent

Continent	Countries included/ submitted data	PBCR included/ submitted data	Geographic coverage by continent (%)	Population coverage in millions (%)
Africa	5/14	5/16	31	8.8 (1 %)
Asia	15/18	44/77	57	152.3 (4 %)
Europe	29/30	100/120	83	238.8 (33 %)
North America	2/2	54/58	93	258.5 (80 %)
Oceania	4/6	11/13	85	23 (73 %)
South and Central America	8/11	11/29	38	22.7 (4.3 %)

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PBCR Population based Cancer Registry

Registries may also help to identify unique genetic or environmental risks and allow proper and timely intervention to improve detection and outcome.

Available data suggest a low incidence of CNS tumor in countries with limited resources. While the incidence of pediatric brain tumor in the CBTRUS (Central Brain Tumor Registry of the United States) was 4.92/100,000 person-years for children less than 15 years during the period 2004–2008 [5], Manoharan et al. reported an incidence of 0.9/100,000 in the Delhi Population Based Cancer Registry (PBCR) for the period 2003–2007 [6]. In Colombia, a country with a population of 47,000,000, there is a rough estimate of 400 new pediatric brain tumors per year. Whether this lower incidence is real or related to other factors is unknown. One common proposed cause of lower reported incidence of childhood cancer in general in low-income countries is the high mortality rate in young children (under the age of 5 years) that may lead to early death before the child develops cancer. However, there is no statistical reason that this high rate of premature death should influence the overall incidence of childhood cancer. Using data from the International Agency for Cancer Research (IARC), Howard et al. reported a close correlation between the reported incidence of childhood leukemia and the mean annual per capita gross national income [7]. There is no similar study for childhood brain tumors. However, it is very likely that in many low-income countries, children with brain tumor die before diagnosis.

Delay in the Diagnosis of CNS Tumors

Despite advances in neuroimaging, timely diagnosis of CNS tumors remains a problem in high-income countries. There are no specific studies that have analyzed differences in the delay to diagnosis of CNS tumors between high- and low-income countries. However, the issue of late diagnosis of CNS tumors is obvious for neurosurgeons and oncologists who practice in these countries. Beyond the usual challenges of nonspecific symptoms such as vomiting, failure to thrive, hypoactivity, headaches, or visual disturbance that are usual factors involved in delayed diagnosis [8], access to neuroimaging facilities is the main obstacle that patients and families face. The limited number of CT or MRI scans; long waiting lists, particularly when sedation is needed; and in many places the prohibitive cost of these tests are among the many reasons that delay or prevent the diagnosis of brain tumor in children in these countries. In most places, the imaging study will be limited to the brain and it is exceptional to have preoperative imaging of the spine when a malignant brain tumor such as medulloblastoma is suspected. Once a brain tumor is diagnosed on imaging, then confirmation of the correct diagnosis would mean a referral to a specialized center able to take care of these children.

Most developing countries lack specialized centers whether due to unavailability of experienced staff or shortage of equipment [9], and even when they have one, families from rural areas

often face difficulties to access these specialized centers due to financial costs and difficulties in transportation, which will also complicate future compliance during treatment and follow-up.

In some countries like Panama, programs have been developed to increase awareness of early signs and symptoms of pediatric brain tumors for primary care physicians. The primary objective is to increase early diagnosis and referral of these patients. Programs like this one are being currently developed in other countries like Colombia, addressing the most common malignancies in childhood.

Cultural Barriers

Cancer is a condition that relates to fate, myths, and beliefs. The diagnosis of brain tumor is a devastating event for the families; often they tend to seek help from local "healers" or use complementary and alternative medicine. As a result, this may affect the natural history of the disease and delay the diagnosis of cancer even more [10]. A classical example is the increased incidence of blindness associated with optic pathway gliomas seen in countries with limited resources.

Brain tumor diagnosis has in some cultures a negative perception and stigmatization. Families may refuse to be referred to a cancer center, trying to avoid the risk of marginalization associated with this condition. Stigma like the belief that cancer equates death or mental and physical disability and cultural myths might also influence parental or family decisions including treatment abandonment. Because the social stigmata of cancer can be so powerful, social barriers must be fully understood before any strategy is implemented in low-income countries.

Some cultural choices, like treating boys over girls, may affect incidence, survival, and mortality data of cancer in some cultural contexts [11]. Other social factors are critical, such as financial and transportation difficulties that have been identified as major sources of abandonment of treatment [12].

Management of Pediatric Brain Tumors in Countries with Limited Resources

Neurosurgery

With a few exceptions, neurosurgical management is generally the first step in the treatment of pediatric brain tumors. Neurosurgeons in low-income countries are overloaded with work and neurosurgical units are generally understaffed. Neurosurgery in these countries faces two main challenges, i.e., quality and quantity in both resources and qualified personnel [9]. The World Health Organization African Subcommittee conducted a survey on African neurosurgical services in the late 1990s. This survey reported a ratio of one African neurosurgeon per 1,352,000 individuals compared to 1/121,000 in Europe and 1/81,000 in North America [13]. Similar figures are described in the South Asian continent.

In addition, there are a limited number of neurosurgeons with a pediatric expertise in low-income countries, and thus, general neurosurgeons, when available, are expected to operate on children. In such conditions, specific knowledge of the principles of pediatric neuro-oncology is important and unfortunately many general neurosurgeons are not familiar with this specialty. As a result, in most places, surgical intervention is limited to the insertion of ventriculoperitoneal shunts for the management of hydrocephalus. Attempt to complete or near complete surgical resection is not a common practice, and surgery is usually limited to a biopsy to allow histological diagnosis. Unfortunately, less than gross total resection greatly impact survival of children with brain tumor like ependymoma or/and would upgrade risk status for some other tumors like medulloblastoma.

Neuronavigation and the use of intraoperative microscope are known to facilitate surgery and to improve tumor resection; however, these equipments are scarce in low-income countries or are only available in selected private practices; trained neurosurgeons with the expertise to use these techniques are limited. A recurrent challenge in this

context is the management of children who underwent incomplete tumor resection. Most often, neurosurgeons consider that there is no role for further surgery and they refer the child to radiation oncologists or pediatric oncologists for adjuvant treatment. While local oncologists are often unsuccessful in trying to convince referring neurosurgeons to proceed to second look surgery in the context of an incomplete resection, telemedicine experiences that involve a contact between neurosurgeons appear to offer a unique opportunity to discuss such technical issues and to optimize the quality of surgical management [14].

Postoperative intensive care with good monitoring of intracranial pressure, fluids, and electrolyte balance is crucial when caring with brain tumor patients especially when hormonal problems are expected like in craniopharyngioma surgery. The lack of such specialized multidisciplinary care will increase perioperative morbidity and mortality.

Another issue identified in some of the twinning programs is the lack of communication between neurosurgeons and pediatric oncologist. Often, these patients are not referred for further adjuvant therapy and frequently a suboptimal surgical resection is the only treatment modality. This seems to be a more prevalent issue, if the surgical management is performed by a non-pediatric neurosurgeon and at an institution where appropriate pediatric oncology or radiation therapy is not available.

Neuropathology

Experienced pathologists able to differentiate subtypes of pediatric neurological tumors are absent in many developing countries. The lack of trained personnel and inadequate technical equipment are therefore limiting the possibility to achieve a timely and accurate diagnosis in many places. Often, clinicians are faced with long turnover times—sometimes exceeding 1 month—before a diagnosis is proposed [15]. Availability of some important staining techniques may also compromise the possibility to accurately identify tumor types. A classical example is the availability of the BAF47 staining. This staining that has now become part of the standard battery of immunohistochemical staining performed in the context of embryonal tumors of the central nervous system.

In a report on a telemedicine twinning experience between Canada and Jordan in pediatric neuro-oncology between two multidisciplinary programs, the most common recommendation was a review of the neuropathology, resulted in several cases in a change in the initial diagnosis or in the grading of the tumor with significant consequences in term of subsequent management [14]. Those results have been replicated in the ongoing twining program between Canada and Colombia. However, a number of factors are limiting this practice that would greatly benefit pediatric neuro-oncology programs in countries with limited resources. In this context, it is likely that a significant number of children are treated without an adequate diagnosis.

Radiation and Radiotherapy Services

Radiation therapy is a critical component of treatment of many central nervous system tumors in children; however, limited radiotherapy machines and personnel make them available only at large centers with long waiting lists. There is evidence that delay in starting radiotherapy has a negative impact on survival in medulloblastoma and there is no doubt that the extent of neurological recovery will be closely dependent on the time to initiate radiation in patients with diffuse intrinsic pontine glioma (DIPG).

Radiation indications, treatment volumes, and doses are determined by tumor histology, extent of disease, anticipated pattern of spread, and expected pattern of failure. In malignant CNS tumors such as medulloblastoma and ependymoma, excellent survival rates have been reported, particularly in patients with average risk features (complete resection and absence of metastatic disease and no anaplastic features). Survival rates are above 90 % in patients with

pure germinoma, regardless of metastatic stage, with a combination of chemotherapy and radiation. However, access to radiation oncology services is a prerequisite for successful outcome and the number of functioning radiotherapy machines available in most countries with limited resources is the main barrier to optimal patient care. It is clear that pediatric neuro-oncology programs cannot be developed or implemented in countries, which have no radiation oncology services. A survey of radiotherapy equipments in Africa conducted in 1998 reported that 9/56 countries had no radiotherapy at all, 24 had orthovoltage facilities only, and 2/3 of the megavoltage equipments available in the continent were located in two countries (Egypt and South Africa) [16]. The supply of radiation equipments available in the continent represented at that time 18 % of the estimated needs. Appropriate maintenance of the radiation equipment is also an issue in countries where there is only one radiotherapy machine; the treatment could get interrupted for an undetermined period of time or waiting times can increase considerably if the machine goes out of service.

As a consequence, access to radiation is a major issue in most countries with limited resources, and delay in initiation and/or continuation of radiation treatment is a common problem.

In several places, pediatric oncologists are trying to overcome this problem by designing protocols that offer postoperative chemotherapy prior to radiation, in particular for medulloblastoma patients. Although this is not an ideal option, this approach may help prevent early recurrence or dissemination following initial surgery. Another limiting factor in the management is the number of well-qualified personnel with an expertise in CNS radiation techniques and more specifically in pediatrics. Craniospinal radiotherapy (CSI), which is commonly used in the management of medulloblastoma patients, is one of the most complex radiotherapy techniques, and evidence from several medulloblastoma trials has suggested that the quality of CSI impacts outcome. Some groups have started to address specific issues related to the availability of radiation machines. In particular, a group in Cairo has run a randomized trial that has shown similar survival between patients with DIPG treated with normal fractionation (30 sessions at 1.8 Gy each) and hypofractionation (13 sessions of 3 Gy each) [17]. The results of this trial may benefit DIPG patients in countries that face limitations in the access to radiation services.

Ideally, the radiotherapeutic management of children with CNS tumor in countries with limited resources would benefit from a central referral system that would review and validate indications and facilitate timely access to the most appropriate equipment. Hopefully, cooperative groups and support groups will be able to advocate for the development of such process.

Pediatric Neuro-Oncologists

Dedicated pediatric oncologists interested in neuro-oncology are rare. In most of the countries with limited resources, pediatric oncologists are few and usually overworked. Their time is committed to clinical responsibilities and continuous medical education might not be a priority. In the absence of oncologists with specific training in pediatric neuro-oncology, treatment may lean more toward use of radiation rather than chemotherapy. This is particularly the case in the management of low-grade tumors such as low-grade gliomas of the optic pathways, of the brainstem, or of the spinal cord that can be managed with low-dose chemotherapy in most situations.

Absence of properly designed chemotherapy protocols suitable for developing countries, the intermittent supply of chemotherapeutic drugs, and absence of well-trained nurses would also affect the medical management of childhood brain tumors in these conditions. Some of the twinning programs and teleconference tumor boards have attempted to provide modified protocols that can be used in countries with limited resources (Table 27.2).

Table 27.2 Comparison of available resources in high-, middle-, and low-income countries

	DCs ($n=103$) vs. COG ($n=145$)	DCs ($n=103$) vs. HIC ($n=37$)
Centers seeing ≥150 newly diagnosed pediatric oncology patients per year	34 (33 %) vs. 24 (16.5 %) $p=0.004$	34 (33 %) vs. 10 (27 %) $p=0.6$
Centers seeing ≥15 newly diagnosed brain tumor patients per year	42 (40.7 %) vs. 60 (58.2 %) $p=0.9$	42 (40.7 %) vs. 22 (32 %) $p=0.07$
Centers with dedicated NO	NA	48 (46.6 %) vs. 27 (73 %) $p=0.004$
Availability of a general LTFU team	NA	69 (67 %) vs. 33 (89.2 %) $p=0.006$
Dedicated NO LTFU team for children	8 (7.7 %) vs. 43 (29.6 %) $p\leq0.001$	8 (7.7 %) vs. 7 (21.1 %) $p=0.03$
Availability of disease-specific guidelines for the treatment of children with brain tumors	NA	71 (68.9 %) vs. 36 (97.3 %) $p<0.001$
Dedicated NO LTFU team for >21 years	14 (13.6 %) vs. 42 (30 %) $p\leq0.001$	14 (13.6 %) vs. 12 (31.6 %) $p=0.02$
Formal NS evaluation in >50 % of irradiated children	9 (8.7 % vs. 78 (53.7 %) $p<0.001$	9 (8.7 %) vs. 17 (45.9 %) $p<0.001$
Availability of GH	NA	63 (61.2 %) vs. 35 (94.6 %) $p<0.001$

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DC low income country, *COG* Children's Oncology Group, *HIC* high-income countries, *NO* neuro-oncology, *LTFU* long-term follow-up, *NS* neuropsychological, *GH* growth hormone, *NA* not assessed

Multidisciplinary Meetings

In pediatric neuro-oncology, there is a critical need for interaction between disciplines such as neurosurgery, neuroradiology, neuropathology, radiation oncology, and oncology. Optimization of cancer treatment depends on careful orchestration of the different treatment modalities in order to provide patients with maximal benefit. Discussions among team members will allow organizing the treatment plan for each specific patient.

Multidisciplinary meetings are part of the standard of care in many institutions in high-income countries. France and the UK have required for each newly diagnosed pediatric neuro-oncology patient review of the case and the agreement on a treatment plan by a multidisciplinary team of experts. High-income countries have also formed national wide neuro-oncology multidisciplinary groups like the Pediatric Canadian Brain Tumor Consortium, where neurosurgeons, neuro-oncologist, neuroradiologist, and allied healthcare member can share their concerns and experiences and develop a national standard of care treatment approach.

Implementation of multidisciplinary neuro-oncology programs in countries with limited resources is slow. Most physicians in low-income countries still work in silo and are not convinced of the benefit of a dialog between team members, particularly with physicians outside their area of expertise. The role of the pediatric oncologist in this context is critical, even when patients may not require chemotherapy. Multidisciplinary meeting should involve all team members with no exception, in order to discuss every aspect of the care of the patient. In this context, the presence of radiologists, pathologists, neurosurgeons, oncologists, and radiation oncologists at these meetings is critical.

Treatment Side Effects

During the course of treatment, children with brain tumors are prone to many challenges whether related to their original disease or to the applied

Table 27.3 Comparison of centers from low- and upper middle-income countries regarding center characteristics, availability of resources and follow-up resources

	L-LMIC ($n=45$)	UMIC ($n=58$)	p Value
# of pediatric oncology patients per year			(≥150 cases/year)
<49	11	17	
50–99	5	22	
100–149	4	10	
150–199	4	3	
>200	21	6	
# of brain tumor patients per year			(≥30 cases/year) 0.34
<4	10	9	
5–14	15	27	
15–29	7	11	
30–49	5	7	
>50	8	4	
Dedicated brain tumor team	Yes, 17 (37.8 %)	Yes, 31 (53.4 %)	0.08
Dedicated LTFU clinic for pediatric oncology patients in general	Yes, 28 (62.2 %)	Yes, 41 (70.7 %)	0.2
Availability of follow-up programs for survivors >21 years in the setting	Yes, 18 (40 %)	Yes, 30 (51.7 %)	0.16
Availability of institutional treatment guidelines for the different brain tumors	Yes, 24 (33.8 %)	Yes, 47 (66.2 %)	0.002
Availability of GH	Yes, 22 (48.9 %)	Yes, 41 (70.7 %)	0.02

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L-LMC low- and middle-income countries, *UMIC* upper middle-income countries, *HIC* high-income countries, *LTFU* long-term follow-up, *NS* neuropsychological, *GH* growth hormone

treatment protocols. They may require physical and occupational rehabilitation, mental and psychosocial support, and reintegration programs. When present, visual and hearing deficits need to be assessed, and patients should be directed to specific facilities that will help them to deal with these difficulties. These are generally not a priority in low-income countries, and physicians should be aware that the use of, for example, ototoxic medications can lead to irreversible hearing loss and usually correcting devices are unaffordable.

Supportive therapy during treatment is also a concern in developing countries; appropriate nutritional support during chemotherapy and radiotherapy can be a challenge, and dietitians dedicated to pediatric oncology are not a reality in most of these countries; prophylactic antibiotics and antifungal are part of the practice in some of these countries, but their use is inconsistent due to the lack of treatment protocols.

Many children will also need hormonal supplementation after brain irradiation. Availability of regular endocrine testing and daily administration of hormone replacement, like growth hormone, may be challenging in countries with limited resources. In reality, most children with CNS tumors are very early lost to follow-up in countries with limited resources. A recent international survey showed that the number of aftercare program in countries with limited resources was limited [18]. It is clear that well-designed programs for assessment of aftercare morbidities are difficult to implement in this context (Table 27.3).

Palliative Care

Owing to the delayed diagnosis, many children with brain tumor diagnosed in countries with limited resources present with advanced disease,

and very often in this context, supportive care and palliative treatment would be the most appropriate option. In addition, a number of pediatric brain tumors have a poor prognosis, such as high-grade glioma, DIPG, or atypical teratoid rhabdoid tumors. It is expected that in such context, a majority of patients will eventually succumb to their disease. Pain control and proper palliative care interventions would be important at this stage. Low-income countries are particularly lacking such services [19] and families often perceive palliative care as an abandonment of treatment. Other issues are critical such as access to appropriate pain medications. There is an obvious need to develop palliative care guidelines that address the need of the pediatric brain tumor population in these countries and that also take into account local or regional specificities, either social or cultural or religious. A recent work conducted in families of children diagnosed with DIPG in Jordan suggested that it is possible to address palliative care issues at an early stage and this approach can facilitate the implementation of end of life decisions [20].

Twinning Programs

In the face of the many challenges associated with the management of childhood brain tumor in countries with limited resources, efforts have been developed to implement neuro-oncology programs through twinning initiatives. Support from high-income countries to pediatric oncologists in countries with limited resources provides scientific expertise and can improve management of CNS tumors in these countries. Such initiatives have shown success in the management of childhood leukemia [6], demonstrating that proven treatment regimens can be adapted for use in countries with limited resources.

Previous experience with neuro-oncology twinning programs and teleconference tumor boards [14] have shown that with very little resources, a difference can be made in the diagnosis and therapeutic approaches of these unprivileged children. Although the multidisciplinary care in neuro-oncology requires specific attention, successful twinning initiatives have been described with significant impact on management and outcomes [21, 22].

Conclusion

The concept of pediatric neuro-oncology is still at its infancy in countries with limited resources. Appropriate neuroimaging facilities, neurosurgical units, radiation equipment, and pediatric oncology services are prerequisites for the implementation of such programs. A number of programs have been recently implemented, often in the context of twinning initiatives and teleconferenced tumor boards, attempting to provide expertise and therapeutic approaches adapted to the needs of these countries.

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