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Chapter 20

Pediatric Neuro-Oncology in Low-/Middle-Income Countries

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Additional information is available at the end of the chapter

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Abstract

Pediatric cancer is becoming increasingly important in low-/middle-income countries (LMICs), due to the improvement in controlling communicable diseases, decrease infant, and early childhood mortalities associated with infection and malnutrition.

Worldwide, although much improvement was encountered in many pediatric tumors particularly acute leukemia that represents the commonest type of cancer in children, this was not so obvious in CNS tumors, the second most common tumor type. Slow advances have been achieved to improve treatment end results in pediatric neuro-oncology. This was largely related to disease under diagnosis, incorrect clinical assessment, improper staging, and lack of the availability of appropriate radiologic, neurosurgical, and radiotherapeutic services in LMICs. Moreover, the need for multidisciplinary team working together to embalmment unified approved management guidelines, highly specific care level within a widely accepted quality control measures are of utmost importance to raise the treatment outcome levels to that of high-income countries (HICs).

Much effort is needed in LMICs to improve the management of pediatric CNS tumors, decrease the gap, and reach good results already attained by the dedicated centers in HICs. There are many international organizations and societies that can and are willing to help in this matter.

In this chapter, an illustration of the obstacles faced by LMIC neuro-oncologists will be discussed. The different ways and procedures are recommended to improve the general situation to attain good results similar to that in HICs.

Keywords: neuro-oncology, children, low-/middle-income countries, LMIC, CNS tumors, brain, late sequelae

1. Introduction

Pediatric central nervous system (CNS) tumors represent the second most common cancer in childhood after leukemias. Pediatric cancer is the leading cause of disease-related childhood mortality in high-income countries (HICs). Furthermore, it is becoming increasingly important in low-/middle-income countries (LMICs) because of the continuing success to decrease the infant and childhood mortality associated with malnutrition and communicable disease. Unfortunately, the 80% cure rate for HIC children suffering from cancer does not apply to many of pediatric patients in LMIC [1]. The barriers to optimize the management of children with cancer in LMICs to reach the same level as that in HICs were investigated in many situations; however, minimal advances have been made to improve the treatment and clinical end results of children especially those with brain tumors. Many factors were identified as responsible for this failure to achieve such an acceptable level of cure. These were underdiagnosis, abandonment of therapy, incorrect assessment, lack of appropriate radiological, histopathologic, neurosurgical, radiotherapeutic, and pediatric oncologic services. More important is the deficiency of the real concept of multidisciplinary care and the team management that definitely contributes negatively to the results of treatment [2]. In many LMICs, a significant portion of pediatric brain tumors remains undiagnosed and the patients subsequently die of their malignancy. Many others abandoned effective treatment due to different reasons: financial, social, long distance from the treating center, or being treated with herbal and unconventional therapy. The identification of these findings will help the development of targeted strategies, such as increased training and tools for neuropathology, improved access to neuroimaging and radiotherapy, improve early diagnosis, and optimal collaborate therapy. Interventions to implement and increase family support may positively contribute on improvement of outcome.

1.1. Magnitude of the PROBLEM

Underdiagnosis, treatment abandonment, improper assessment, lack of appropriate medical imaging, histopathologic, neurosurgical, radiotherapeutic pediatric oncologic services deficiencies, and the deficiency of the multidisciplinary care concept and the team management are well-known barriers that hinder successful neuro-oncologic management that leads to the obtainment of equivalent clinical end results already achieved in HICs. In addition, in many patients, treatment may be negatively affected because of poor general health, with the comorbidity of malnutrition and infections such as human immunodeficiency virus (HIV) and tuberculosis. Furthermore, the lack of adequate supportive drugs and supplements that ameliorate the oncologic treatment side effects and preserve a tolerable general condition may contribute not only in intolerance of therapy but also in lowering the survival rates and quality of life (QoL) of such patients. The applied treatment protocols have to take these factors and conditions into account. Protocols applied in HICs may not be optimum and may be even dangerous in LMICs especially whenever the supportive care is deficient [3]. The aggregation of the necessary facilities and properly trained staff in one referral center serving an LMIC or a large sector of it may be the proper way to serve these children and to raise the stand-

ard of care to reach the acceptable level of cure attained in HICs [4]. It is obvious that it is easier, more convenient, and cheaper to arrange for establishing a referral pediatric neuro-oncologic center to be responsible for the welfare of such children. The tremendous improvements in imaging, surgical approaches, pathological diagnosis, radiotherapy techniques, and chemotherapy drugs in the last three decades have improved survival rates in children with brain tumors and are attained in such referral centers. Innovations in radiation techniques, including the three-dimensional (3D) radiation therapy (RT) and different forms of intensity-modulated radiation therapy (IMRT) such as static IMRT, volumetric modulated arc therapy (VMAT), tomotherapy, cyberknife, and all forms of image-guided radiotherapy, have contributed to the precise and extremely accurate delivery of the radiation dose to the target while reducing the dose to the normal brain tissue. These techniques minimize RT-related toxicities through decreasing the dose to the surrounding functioning structures while increasing tumor control probability [5].

1.2. Diagnosis delay in CNS tumors

Despite advances in neuroimaging, timely diagnosis of CNS tumors remains a problem even in HICs. It is obvious that the issue of late diagnosis of CNS tumors is more obvious and more intense in LMICs. Beyond the usual challenges of nonspecific symptoms, the access to neuroimaging facilities is the main obstacle that patients and families face. The limited number of computerized tomography (CT) or magnetic resonance imaging (MRI) scans in LMICs; prolonged waiting lists, especially in children needing sedation; and high cost of these tests are among the reasons that delay the diagnosis of brain tumor. Furthermore, in many places, the imaging study is limited to the brain, regardless of the state-of-art recommendation. It is exceptional to have preoperative imaging of the spine when a malignant brain tumor such as medulloblastoma is suspected. Most developing countries lack specialized centers presenting the complete multidisciplinary service equipped with the necessary diagnostic and treatment tools in hands of experienced staff [6].

The adoption of unified management protocols represents a major drawback. A single referral neuro-oncologic center in each LMIC that is fully equipped and adequately staffed could serve the patients in a more professional and efficient way that decrease the cost and improve the clinical outcome. Aggregation of the needed staff, equipment, and experience together with standardizing policies, treatment protocols, and managements may be the best way to overcome the difficulties facing LMIC challenges in pediatric neuro-oncology practice [4]. The obstacles of long distance and financial needs to access these specialized centers will remain as a problem that needs effort to be solved. The diagnosis of brain tumor in some LMIC cultures has a negative perception and stigmatization. Families may abundant treatment and even referred to cancer center, for the fear of marginalization associated with brain tumor. Stigma of the false belief that cancer means death or mental and physical disability may influence parental or family decisions including treatment abandonment. Some cultural preferences such as treating boys over girls have to be strongly faced.

Radiotherapy evolved tremendously in the last three to four decades, depending upon the advances in physics, atomic sciences, materials, engineering, computer science, and telecommunication. Linear accelerator-based RT became the backbone technology. This phase represented a megavoltage (MV) power race, which would have skin-sparing properties, while delivering a high dose of radiation at depth. Linear accelerators initiated the new technologies of 3D conformal RT, IMRT, and image-guided radiotherapy including the helical tomotherapy and others [7]. The technique of radiosurgery was developed through combined efforts of multiple specialties, where multiple cobalt-60 sources were fitted into a helmet-like configuration with precision beam collimation to produce remarkably tiny and accurate beams, resulting in the concept of using single-fraction radiation doses for the purposes of target ablation, which expanded the clinical utility beyond neoplasms into the field of benign and functional indications.

1.3. Neuroimaging

Neuroimaging is a key tool in the diagnosis and follow-up of neuro-oncologic patients. MRI and CT are the main imaging modalities involved in neuroimaging diagnosis of these patients. Nevertheless, in pediatric neuro-oncology MRI ranked superior not only due to lack of radiation exposure provided by CT but also due to the more significant details of the brain parenchyma offered by MRI. The standard MRI sequences (T1- and T2-weighted spin-echo in three planes; axial, coronal, and sagittal). Fluid attenuation inversion recovery (FLAIRE) sequences followed by post-contrast are usually adopted. These sequences are usually enough for an accurate differential diagnosis. However, newer sequences and techniques provide additional information for both the diagnosis and treatment management of difficult and/or atypical cases [8]. Although gadolinium-based contrast media is not nephrotoxic yet, it is not advisable for children younger than 2 years [8].

Ideally, post-surgery studies should be performed within the first 48 h after neurosurgical procedure in order to avoid misinterpretations of residual tumor enhancement with blood leakage across the blood-brain barrier. Diffusion study, describing the random thermal motion of the water molecule in tissues, detects the tissue cellularity. It gives a clue about the grade of the tumor and its cellularity. Diffusion tensor imaging (DTI) allows determination of fiber bundle directionality (tractography) study [9].

In neuro-oncology, 3D imaging is used for stereotaxy, a technique creating a coordinate system to guide lesion localization in a surgical procedure or radiotherapy treatment. In order to reduce morbidity in CNS tumor resection, this technique is usually supplemented by other maneuvers and techniques such as functional MRI and direct cortical stimulation [8].

MR spectroscopy (MRS) is a technique widely used to assess metabolites in the brain parenchyma and lesions. The results of an MRS acquisition are typically displayed in a graphic of metabolite peaks. The assessed metabolites are choline, creatine, N-acetylaspartate (NAA), and lactate. Perfusion technique can be applied with both MRI and CT. Nevertheless, there is a new MRI sequence called arterial spin labeling (ASL) that can be used to study brain perfusion without the use of contrast media [10]. The perfusion images are frequently interpreted

in a color map. The red zones usually demonstrate increased perfusion and the blue zones decreased perfusion. The perfusion technique differentiates between low- and high-grade tumors. It is helpful in the differentiation of radiation necrosis (decreased perfusion) from tumor recurrence (normal to elevated perfusion) and in defining the ideal area for surgical biopsy, avoiding areas of necrosis.

1.3.1. PET scan and future molecular imaging

Positron emission tomography (PET) and molecular imaging are rapidly developing as new techniques to evaluate brain tumor. The results provided by PET and molecular imaging appear to corroborate the findings of MRI studies for decision making in the treatment and follow-up. The use of a PET scan is often carried out together with low-dose CT images or MRI to improve the anatomical localization. Common radiopharmaceuticals applied in brain imaging are fludeoxyglucose (FDG), L-[methyl-11 C] methionine ([11 C]MET), and 3′-deoxy-3′- [18 F]fluorothymidine ([18 F]FLT). However, FDG applicability in clinical practice is low as the normal gray matter also demonstrates increased glucose metabolism, effacing lesions [11].

1.4. Neuropathological services

Experienced pathologists able to differentiate subtypes of pediatric neurological tumors are deficient in many LMICs. Some diagnoses can be promptly made on standard hematoxylin and eosin stains based on classic architectural features alone, while more challenging cases often require ancillary studies including immunohistochemistry, electron microscopy, cytogenetics, and/or molecular studies. The lack of trained personal and inadequate technical equipment is therefore limiting the possibility to achieve an accurate diagnosis in many places. It is likely that a significant number of children are treated without an adequate diagnosis that may lead to inadequate or even improper treatment. Microscopic examination combined with molecular signatures of these tumors continues to identify and define features specific to CNS tumor subtypes mostly of great importance, to reach to the proper diagnosis or the appropriate subtype [12]. Neuro-oncologic telepathology and twinning between centers in both LMICs and HICs can improve the capacity of accurate histopathological diagnosis with little burden on centers shared in these programs [13].

1.5. Radiotherapy services

RT is one of the main critical components of treatment of many pediatric CNS tumors; however, limited radiotherapy machines and personnel in LMICs make them available only at large centers with long waiting lists. Delay in starting radiotherapy has a negative impact on survival. Radiation indications, treatment volumes, and doses are determined according to the extent of disease, magnitude of excision, tumor histology, pattern of spread, and pattern of failure in each tumor type and grade. In malignant CNS tumors such as medulloblastoma and ependymoma, excellent clinical end results have been reported, particularly in patients with

features denoting standard risk (complete resection, absence of metastatic disease, and no anaplastic features). The overall 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 and the number of functioning radiotherapy machines available in most LMICs is the main barrier to optimal patient care. It is obvious that pediatric neuro-oncology programs cannot be implemented in countries, which have no radiation oncology services. Based on World Bank classification, 139 countries are defined in the category of LMICs. Out of these, only four (2.9%) have the requisite number of teletherapy units and 55 (39.5%) have no RT facilities. It is also worth mentioning that LMICs have 0.71 teletherapy units per million population in contrast to 7.62 teletherapy units per million population for HICs [14]. A survey of radiotherapy equipment in Africa reported that 52% (29/56) of their countries had no radiotherapy at all and two-thirds of the MV equipment available in the continent were located in two countries (Egypt and South Africa) [15]. Moreover, many countries rely on machines that are more than 20 years old, which questions their functionality and reliability. The available radiation oncology equipment in the continent represented 18% of the estimated needs, at time of reporting. The needs increased more due to rapid increase in the population in many African countries without simultaneous increase in the facilities. Furthermore, appropriate maintenance of the radiation equipment is a major, problematic issue in countries wherever only one radiotherapy machine is the case. The treatment could get interrupted for an undetermined period of time and the waiting times can be prolonged considerably with the machine going out of service. It was estimated that the LMIC deficit in the teletherapy units was 61.4%, in radiation oncologists 38.9%, radiation physicists 68.4%, and RT technologists was 66.5% to reach the requirement applied in HICs [14]. As a consequence, access to radiation and delay in initiation and/or continuation of radiation treatment are a major problematic issue in most LMICs.

In several situations, pediatric oncologists on trying to overcome the problem of availability of radiotherapy design protocols that offer postoperative chemotherapy prior to radiation, in particular for medulloblastoma patients. Although this is not the sound or ideal option, it may delay or decrease recurrence or dissemination following initial surgery. Another limiting factor in the management is the number of experienced, well-qualified personnel with an experience in CNS radiation techniques. Several medulloblastoma trials showed that the quality of craniospinal radiotherapy (CSI) affects outcome. Therefore, the deficiency of adequate human resources is another major contributing factor for poor RT capacity in LMICs. Most reports on radiation oncology personnel availability and training confirm the unavailability of enough physicians and staff to deal with the number of patients needing radiation treatment. This lack of trained personnel with the high patient volume often leads to long waiting list, disease progression, and poor outcome [16]. In Latin America, a survey reported the major obstacles for provision of adequate RT as insufficient number of specialists, rather than a lack of equipment [17]. The insufficient number of radiation oncologists, medical physicists, and radiation technologists training programs contributed negatively to efficient number of personnel needed for a decent service. To add to the gloomy picture, it is well estimated that within the next 10 years, 70% of newly diagnosed cancer patients will be living in countries that collectively have only 5% of the global resources for cancer control. It is

estimated that approximately 60% of the world's patients with cancer, including the pediatric neuro-oncology patients, do not have access to a complete cancer systemic therapy regimen, and the percentage is higher for radiotherapy [18].

National cancer control programs, large national or international meetings, or even national treatment guidelines though of extreme importance, were not adequate to improve the current situation of neuro-oncology in LMICs. A survey in 167 countries performed by the WHO found that almost half of these countries had a sort of plan for improving treatment, but national guidelines are generally lacking while the accessibility and affordability of treatment remained low in LMICs. In many countries, the national cancer control plans had been designed according to WHO plan without tailoring it to the local conditions, needs, and challenges [19, 20].

Engaging in innovative strategic thinking and finding new ways to mobilize and enforcing local resources to improve the availability and accessibility of cancer care are essential to overall and balanced cancer control in underserved countries. Most LMICs have some local resources; however, they may not be adequately mobilized or used in the appropriate manner. LMICs should not rely entirely on external financial donations. Instead, what is needed is win-win support and adequate assistance from the affluent organizations or countries, as well as the pharmaceutical and radiology industrial companies. Assistance better take the form of technical support for building local capacity, staff training, management guidance, and research cooperation. Other types of support may include provision of information and communication technologies, help with obtaining local funds or international grants, and instructions on how to collaborate on international work in their own countries. (The Win-Win Initiative of ICEDOC's Experts in Cancer Without Borders [21].)

Conducting more clinical trials in LMICs, which have the major bulk of pediatric cancer and neuro-oncologic patients, could shorten the total time needed for conducting clinical trials, may reduce costs, and could enrich the scientific aspects of those trials with more variability. It could also help initiate more cost-effective ways in medical services in LMICs that can be applied even in HICs and could establish a better value cancer care. This may serve double purposes: improve the quality of both health care and research and prevent the brain drain experienced by LMICs when their most highly qualified people immigrate to HICs. Hypofractionation for glioblastoma multiforme (GBM) and diffuse intrinsic pontine glioma (DIPG) are treatment approaches to improve regional tumor control. This has several advantages over conventional RT via increased cell death due to the used higher doses per fraction and reduced tumor repopulation effect consequent to shortening of the overall treatment time. Haas-Kogan et al. [22] assumed that the α/β ratio equals 2 Gy in p53-mutated GBM, and not 7–10 as suggested in other malignant tumor types. Shortened treatment time has additional significant benefit for patients and their families, because patients with GBM or DIPG have a limited survival time after the completion of treatment. Shortening treatment time allows for a better QoL for the patients saving them and their families the burden of prolonged treatment with all its consequent suffering. However, there may be a risk of enhanced radioresistance. Hypofractionated radiation has become a frequent choice in the treatment of GBM and DIPG patients [23–27].

2. Neuro-oncologic treatment modalities

2.1. Neurosurgery

Neuro-oncology multidisciplinary team discussion allows for a non-bias, more appropriate decision, evident-based, and tailored according to local situation. The option between observation, surgical intervention, radiotherapy, chemotherapy, or a combination of these depends on many factors: tumor type, location, invasiveness as well as the patient's age and overall medical condition. Generally, if a tumor is accessible and the morbidity risk is acceptable, resection should be considered. Neurosurgeons should also actively follow up patients even if a nonsurgical approach is preferred since their interference might be required for treating unsuccessful cases or complications of the chosen modality.

Thorough evaluation of the patient should be performed before a precise neurosurgical opinion including the clinical condition, neuroimaging studies, and case-specific pertinent investigations (e.g., serum hormone levels, tumor markers, genetic syndrome features, etc.). Imaging of the entire neuraxis should be performed, especially for tumors with a tendency for CNS dissemination such as medulloblastomas, germ cell tumors, ependymomas, and primitive neuroectodermal tumors (PNETs).

The main objectives of the neurosurgeons are as follows:

– Maximal safe tumor resection when possible

– Histopathological diagnosis

– Treatment of associated conditions (e.g., hydrocephalus)

2.2. Tumor resection

Maximum safe resection can be performed for a lesion that significant neurological impairments can be avoided after its surgical removal. The patient's prognosis often correlates with the extent of resection.

2.3. Histopathological diagnosis

When pediatric CNS tumors are not amenable to surgical resection, a biopsy is required except in certain situation. Various biopsy techniques have been described and the choice of the appropriate method mainly depends on tumor location.

A) Stereotactic biopsy

Stereotactic coordinates are used for precise guidance of a needle inside the tumor. This is the method of choice for deeply located tumors. Stereotactic biopsy may be performed through a frameless via frameless neuro-navigation device or a metallic head frame-based system. The

coordinates for adequate placement of the burr hole, the angulation, and depth of the needle are determined by preoperative images.

B) Open biopsy

Open biopsy can be performed through a small craniotomy that allows for direct access to the tumor. This method is traditionally used for superficial tumors near or within the cerebral cortex or when leptomeningeal lesions are identified. Neuro-navigation can help in precise localization of the tumor in relation to the skull surface.

C) Endoscopic endonasal biopsy

Anterior skull base, sellar region, and tumors invading sinuses can sometimes be accessed through an endoscopic endonasal approach under general anesthesia.

D) Endoscopic intraventricular biopsy

Tumors located adjacent to or within the ventricular system may be amenable to an endoscopic transventricular approach. This procedure has the advantage of allowing treatment of associated hydrocephalus via endoscopic venticulostomy and obtaining intraventricular cerebrospinal fluid (CSF) sample.

2.4. Treatment of hydrocephalus

Due to the mass effect of the tumor causing partial obstruction of the pathway of CSF, hydrocephalus may develop. The main mechanism of hydrocephalus in the context of CNS tumors is obstruction of the ventricular system by tumors in the posterior fossa and that located around the third ventricle [28].

Unstable patients with clinical evidence of elevated ICP should undergo urgent surgery, inserting external ventricular drain (EVD). The anterior horn of the lateral ventricle is accessed through an inserted catheter through a skull burr hole and CSF flow is ensured. The EVD is connected to an external collecting device and allows the excess CSF to be drained [29]. Endoscopic third ventriculostomy (ETV) is another option in hydrocephalus resulting from posterior fossa or pineal region tumors. An ETV creates a communication between the third ventricle and the interpeduncular cistern under endoscopic guidance within the ventricular system [29, 30]. Many patients need permanent diversion of CSF ventriculoperitoneal shunt (VPS). A proximal catheter is inserted inside the lateral ventricle and is then connected to a distal catheter tunneled subcutaneously till it reaches the peritoneum. A valve is commonly inserted between the proximal and the distal catheter and allows for one-way drainage control. One of the disadvantages of VPSs includes the theoretical risk of intraperitoneal seedling of neoplastic cells.

2.5. Spinal cord neoplasms

Intramedullary spinal cord tumors are rare in the pediatric population, representing around 4% of all CNS tumors. Complete surgical excision if feasible or debulking is the general approach for spinal cord tumors. This procedure often leads to favorable outcome besides providing sufficient materials for histological diagnosis.

2.6. Management of cystic tumors

Many pediatric CNS tumors are composed of a cystic component or having both cystic and solid parts. The potential space of the cystic portion creates an isolated microenvironment that may hinder local treatment (radiotherapy or local chemotherapy). Simple aspiration of the fluid that composes the cyst may sometimes be a sufficient treatment. Moreover, surgical resection can be considered for most cystic tumors. Local treatment may be applied including the insertion of a device in which medical therapy will be administered. Specifically, the use of intracystic radioisotope (radioactive iodine-125 or phosphorus 32) and intracavitary chemotherapy may be used in selected cases [31]. The main advantage of this treatment is the low rate of long-term sequelae. Intracystic chemotherapy has been advocated to delay aggressive treatment such as radical resection or irradiation. This method allows for administration of effective therapy (commonly bleomycin or interferon) and abolishes the systemic toxicity of the systemic chemotherapy and the morbidity of surgical resection. Ommaya reservoir and instillations of single or multiple doses of active drugs remain the method of choice for intracystic chemotherapy.

2.7. Management of tumor recurrence

The decision to reoperate on a recurred tumor must be taken in the light of the patient's life expectancy and QoL, tumor histology, time length between initial resection and recurrence, the risks and benefits of a second surgery, and the potential for adjuvant therapy such as radiotherapy and chemotherapy. Each case should be individually evaluated through multidisciplinary discussion taking into consideration the patient's family opinion and preference. It is worth emphasizing that surgical treatment of recurrent tumors should be seriously considered as reoperation has improved survival for many tumors such as choroid plexus tumors, ependymomas, and cerebellar astrocytomas [32–34].

3. Radiotherapy

RT is an essential treatment for most of the neuro-oncology patients. It is frequently used together with either surgery or chemotherapy or both as a curative treatment. Furthermore, its use in the palliative setting is vital in many situations for symptom relieving [35]. There are two types of RT: 1. teletherapy (external beam therapy) treating patients with MV energy, such as cobalt units and linear accelerators (Linacs), and 2. brachytherapy (internal application of radioactive sources). It is worth noting that providing effective, reliable, and safe RT is a

complex, tedious, and expensive procedure. It requires specialized building structures (bankers) for radiation protection, investment in expensive machinery, dosimetric measurements, and verification devices used by trained staff capable of efficiently using and optimally maintaining such equipment. Furthermore, it requires continuously ongoing quality assurance and training programs for allocated staff. For these reasons, RT infrastructure in general may be poor in LMICs, to the extent that only four countries in Africa treat more than 100 children per year with RT, due to lack of radiation oncology staff, infrastructure, and services [36]. All RT programs require trained medical physicists and technical engineer staff to maintain their machines and to provide quality assurance of the treatment machines and planning programs. Highly trained radiation therapy technicians (RTT) responsible for planning RT treatment and for operating the machines are extremely needed for the appropriate therapy procedures. Unfortunately, skilled staff is frequently attracted away to better-resourced countries providing them with superior payment and better standard of living representing a major issue that needs serious challenge.

Accommodation for the patient and accompanying adult are frequently problematic. In some countries, accommodation and transport for these patients are frequently offered by charity organizations. The major challenge that staff face when dealing with pediatric patients in RT department is the length of time that is needed. Children (and their parents) are more likely to be cooperative when they are not being rushed, and when the team takes the time to explain all the details with patience and when accommodating their fears and anxieties.

In general, it is essential to

1. Allocate sufficient time and experienced staff for the daily workflow.
2. Have all the required clinical information at hand.
3. Get the patient's sedation history from other departments so that it is known beforehand whether the child is likely to cooperate, and how easily they can be sedated.
4. It is always helpful to get the child in for a "play" appointment prior to markup day, so that they familiarize themselves with staff and the machines. A round tour in the departments may be helpful in getting the patient confident that the procedure is not painful.
5. Children of 6 years and older will generally cooperate without sedation, especially if the parents help to prepare them. They should always be told the precise steps of what will happen to them during the process. The best person to convince the child is a colleague child patient who receives RT without anesthesia.
6. Children under 5 years of age usually need sedation. Between 5 and 6 years is variable.
7. Obtaining an anesthetist on a daily basis for radiotherapy treatments may be very difficult in many institutions [37].

Anesthesia may be oral or intravenous. The American Society of Anesthesiologists has proposed a grading system for sedation use as follows: [38].

1. Minimal sedation/anxiolysis.

2. Moderate sedation/analgesia.
3. Deep sedation/analgesia.
4. General anesthesia.

For the two-dimensional (2D) RT, the procedure is a clinical anatomical decision-making process, determining the tumor location as well as the proximity of critical normal tissues. Setting up two orthogonal radiation beam fields on an X-ray simulator with bony anatomy provides the bulk of the guidance. The target was identified on a planar X-ray, and areas not to be treated were blocked, originally with lead or cerrobend alloy, converting a square or a rectangular beam offered by the machine into an irregularly shaped beam, at least in two directions. Bony anatomy visualized on plain radiographs was the primary method of determining field placement using orthogonal, and occasionally oblique or vertex fields. The uncertainty in target determination with this rudimentary method mandated the incorporation of error as a significant element in the radiation field design, generally resulting in large volumes being irradiated [37]. The tremendous advancement in computers and telecommunication allowed more complex treatment planning systems (TPS). Technical advances such as multileaf collimation (MLC), digitally reconstructed radiographs (DRRs), and electronic portal imaging (EPI) greatly contributed to the integration of three-dimensional conformal radiation therapy (3DCRT) effective delivery. The planning process for 3DCRT is significantly more complex than for conventional RT. Therefore, multiple well-coordinated steps are taken by the different categories of radiation oncology team; radiation technologist, dosimetrist, physicist, and radiation oncologist. With the advancement in CT technology, it became possible to incorporate 3D data for both normal organ at risk and tumor into treatment planning systems. This results not only to delineate targets accurately but also to calculate radiation doses efficiently from multiple beams through multiple directions, and to block out (and save) normal tissue more effectively, thus yielding a more conformal 3D radiation plan.

3.1. Immobilization and imaging

The initial step of the planning process is to place the patient in a reproducible position that optimizes treatment of the entire tumor volume while sparing surrounding critical structures. Variable customizable immobilization devices may be used, including thermoplastic facemasks, alpha cradles, and vacuum mattresses. It is important to ensure that these devices are comfortable, reproducible, and sustainable along the whole radiotherapy treatment. Upon the optimal position of the patient, localization (determining points of origin through a laser device) is determined and marks are placed. With the patient in the treatment position, CT images of the area of interest are obtained and the data are transferred to the planning system. At this stage, the clinician will be able to define the target volumes as well as critical structures. Other modalities such as MRI can be co-registered with the CT data for better determination of the target volumes. Two main basic issues are essential for treatment planning: the identification of the topography and geometry of the diseased tissue and the correct segmentation of the anatomy of normal tissues. The International Commission on Radiation Units and

Measurements (ICRU) has defined evolving standard definitions for radiotherapy target volumes. Their recent recommendations [39] include:

- The gross tumor volume (GTV), being gross demonstrable extend and location of the malignant growth, irrespective of the method used for its detection.
- The clinical target volume (CTV), being a volume that contains a demonstrable GTV and/or subclinical malignant disease that must be eliminated.
- The planning target volume (PTV) including the CTV and the surrounding geometrical margin to ensure that the prescribed dose is actually delivered to the CTV with a clinically acceptable probability.
- The organs-at-risk (OAR) tissues that need to be avoided to decrease the morbidity and determine the exact dose to be delivered to each and to be adjusted according to the knowledge of tolerance and normal tissue complication probability (NTCP). This OAR dose determination may influence the treatment planning and/or the dose prescription. An acceptable plan is the one taking in consideration both tumor coverage and OAR dose distribution. Upon target volumes and critical structures definition, each beam geometry and weighting are determined to calculate the final dose distribution. Beam angles selection is performed using either the isodose distribution in axial images or the beam's eye view (BEV). BEV visualizes the relationship of tumor volumes to those of critical OAR, as if looking from the origin of the beam. Once an initial plan has developed, the resulting dose distributions are calculated and evaluated by the clinician. Accurate quantification of radiation doses to the normal structures will allow the choice of the prescribed maximum dose to the target simultaneously with minimum dose to the normal structures to produce a better therapeutic ratio. Consequently, more accurate shielding of normal structures is ensured using MLC. These data are represented graphically on a dose–volume histogram (DVH), presenting information pertinent to the adequacy of tumor dose and maintaining the normal tissue doses below safe thresholds. Conformal RT is the most common treatment used for primary brain tumors; however, the use of IMRT is rapidly increasing. Plans whether conformal or IMRT are evaluated by viewing isodose curves on serial images of a CT scan, as well as by the generation of DVH for tumor volume as well as other normal tissues or organ of interest. This allows the radiation oncologist to evaluate the dose delivered to the total volume (tumor volume and OAR). DVHs are graph percent volume of a given tissue on the *Y*-axis and dose on the *X*-axis allowing the visualization of the percentage of a defined structure receiving a given dose. These data allow plans to be modified as needed to either increase dose delivered to tumor or decrease dose to a nearby critical structure.

Once a satisfactory plan is generated, digital reconstructive radiograms (DRRs) corresponding to the planned radiation fields are obtained. These DRRs typically display field shapes and tumor volumes and the standard radiographic anatomical information. Using a complex 3D plan, MLC allows for rapid change of field shape under computer control, dramatically shortening the time needed to treat a patient. A verification simulation can be performed to check the validity and accuracy of the fields. This can be performed with the use of an electronic

portal-imaging device (EPID) or a cone beam CT (CBCT). CBCT generates an image of the tumor and all surrounding normal structures using the same linear accelerator with which the patient is being treated. Linear accelerators produce the images of CBCT through either the same treating megavoltage beams (MV-CBCT) or built-in kilovoltage device (KV-CBCT). Appropriate adjustments of the exact treatment position can then be made daily to ensure that the tumor is receiving the prescribed dose of radiation, and normal tissues are receiving doses within their tolerance range. Recently, there are different devices for setup accuracy using either ultrasonography, infrared, radiofrequency for verification or setup positioning and to deal with intra-fractional movements.

The major hypothesized benefits of IMRT are a reduction in the dose to normal structures, as well as the potential for dose escalation. In IMRT, radiation beam is subdivided into a very large number of optimized small beamlets each with a unique intensity of radiation, influenced by the patient's anatomy in the path of the beamlet allowing tailored radiation dose distributions, to both the tumor and normal tissues. Three-dimensionally concave or convex shape configuration is one of the important characteristics of IMRT, resulting in a dramatic reduction of high doses of radiation to normal structures near the target. Moreover, it allows for differential doses to be delivered within the same target, giving the component at higher risk of recurrence higher dose while the rest of the target is being treated to a conventional dose. This technique is called simultaneous integrated boost (SIB). This is attractive in certain situations, in that it allows a higher dose per fraction to the target, while giving a lower dose per fraction to normal structures. Biologically effective dose (BED), which is calculated based on the linear-quadratic (LQ) model, is commonly used on trial to relate the unconventional dose to that for the well-known conventional fractionation.

The main disadvantage of IMRT, in some instances, is the increase in low doses to normal tissues leading to increase in the body integral dose (i.e., higher total dose of a large volume). Other challenges of IMRT are the rapid fall-off of dose; therefore, patient immobilization and daily setup verification become critical. Slight motion or setup error may result in a geographic miss; the high dose is deposited in the critical structure designated for avoidance. Therefore, it is always stated that daily setup verification better precedes IMRT especially if proximity of a nearby critical structure is a concern. Fortunately, the brain moves minimally, and standard immobilization devices yield relatively high daily setup accuracy. Because IMRT dose distributions are highly complex, it is not unusual to see unanticipated toxicities in low-dose areas, such as alopecia or mucositis, in the exit-beam regions [7]. Increased incidence of second malignancy was postulated as a serious late side effect. However, it remains unclear whether second malignancies are a real or a hypothetical risk [40]. Intensity-modulated radiotherapy has several potential benefits in specific CNS tumors. Medulloblastoma represents a good example that is treated after surgery with radiotherapy and cisplatin-based chemotherapy, and radiation. Both platinum and radiotherapy significantly contribute to the occurrence of ototoxicity. However, the use of IMRT can spare the auditory apparatus (cochlea) while still maintaining full dose to the target. Reduction in cochlear dose from 54.2 to 36.7 Gy leads to reduction of grade 3 or 4 hearing loss from 64 to 13% with the use of IMRT, compared with

conventional RT [41]. Furthermore, decreasing the cumulative dose of *cis*-platinum or usage of efficient less ototoxic drug is preferable for better hearing integrity.

3.2. Image-guided radiation therapy

Image-guided radiation therapy (IGRT) is the technique of using imaging technology at the time of each treatment to verify accurate positioning.

There are several types of IGRT including CBCT, MV CT (helical tomotherapy), CT-on-rails, the use of electronic portal imaging devices (EPIDs), ultrasound guidance radiofrequency, and fiducial monitoring. Advances in IGRT have allowed selective boost of dose to some targets while at the same time selectively sparing normal structures more aggressively.

3.3. Stereotactic radiosurgery and stereotactic fractionated radiotherapy

The term *radiosurgery* was selected because of its similarity to stereotactic neurosurgery. Radiosurgery technology has become increasingly more available, and its application has widened. Its current indications include arteriovenous malformations, benign brain tumors, malignant brain tumors, and functional disorders. Delivery of radiosurgery is complex and coordination of care by the neurosurgeon, radiation oncologist, and medical physicist is essential. Appropriate coordination leads to improved quality of care, reduction in practice variation, and improved patient satisfaction [42].

Radiosurgery entails a single treatment, whereas conventional RT used multiple treatments. Further, in conventional fractionation regimens, normal brain tissue adjacent to the target receives a considerable dose of radiation. Taking into consideration late toxicity, radiosurgery is able to treat with considerably high-dose gradients adjacent to a nonmobile target that makes its use in the brain ideal. The use of a very large number of beams (significantly modulated beams) ensures that the geometry provides ideal physical dose distribution for targets less than 4 cm in greatest dimension with maximally low dose to surrounding tissues. Beyond this limit, it is difficult to achieve a rapid fall-off in these normal tissues. Radiosurgery can be performed using various devices, including the gamma knife, particle beam devices, or modified linear accelerators (X-knife, cyberknife). With the great technologic advances in software and hardware, there is no clear advantage of one technology over the other [43]. The linear accelerator-based units can serve to treat non-radiosurgery patients.

Radiosurgery and neurosurgical approaches are often complementary, with the advantage that radiosurgery does not require a craniotomy, nor general anesthesia and patients are usually discharged the same day.

3.4. Charged particles

Proton beam therapy gained great interest in the radiation oncology community especially the pediatric one. This is related mainly to the dosimetric advantages of protons. Proton beam deposits its energy rapidly in what is known as the Bragg peak, a narrow range energy deposition where at the end of its path length the particle slows and. delivers radiation with

a rapid fall-off. This confines the radiation to a smaller volume (clinical tumor volume) and extremely reduces the exit dose. The beam stops at a given depth that depends on their initial energy. Therefore, the possibility of wide low doses of radiation to normal tissues is minimal; different from IMRT. The dose fall-off beyond the Bragg peak is very rapid, reaching zero within a few millimeters beyond the maximum [44–46]. Despite the lack of Level 1 evidence, retrospective studies do exist to support its use in pediatric intracranial lesions. Traditional proton therapy and intensity-modulated proton therapy (IMPT) resulted in more efficient sparing of normal tissue compared to photon-based IMRT [47]. A model was designed to predict neurocognitive dysfunction after RT. The reduction in lower-dose volumes and mean dose afforded by proton therapy might reduce the incidence of late-term sequelae in children with medulloblastomas, craniopharyngiomas, and optic-pathway gliomas [48].

4. Chemotherapy

Chemotherapy is an essential modality in the treatment of many childhood malignancies including brain tumors. A wide variety of chemotherapeutic agents proved to be effective for most types of brain tumors. The role of chemotherapy varies from delaying the RT timing to allow further development of brain functions in the young, stabilizing tumors, reducing radiation doses, or even avoiding RT altogether. Effective agents include many alkylating agents, vinca alkaloids, topoisomerase inhibitors, antimetabolites, and angiogenesis inhibitors.

Chemotherapy for brain tumors can be given by various routes, including orally, intravenously, intrathecally, and via an Ommaya reservoir. Furthermore, chemotherapy may be given as an adjuvant or as concomitant with radiotherapy, improved survival for many pediatric brain tumors including medulloblastoma, germ cell tumor, high-grade astrocytoma, and others. In other conditions, like ependymoma, chemotherapy may be used to increase resect ability of the tumor [49].

The blood-brain barrier is a dynamic interface separating the brain from the circulatory system. The blood-brain barrier regulates the transport of essential molecules from the circulation to the brain, protecting the brain from harmful chemicals. It limits the ability of many chemotherapy agents to penetrate into the CNS. There are mechanisms such as blood-brain barrier disruption, intra-arterial chemotherapy injection, intrathecal chemotherapy administration, or intratumoral chemotherapy administration which were utilized to overcome the blood–brain barrier.

4.1. Intrathecal chemotherapy

Intrathecal administration of chemotherapy is another method of bypassing the blood-brain barrier to deliver chemotherapy within the CNS. Many agents have been investigated for a variety of brain tumors. Intrathecal liposomal cytarabine, mafosfamide, and etoposide were used in children with ependymoma, primitive neuroectodermal tumor, medulloblastoma, and atypical teratoid rhabdoid tumor [50].

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4.2. Intra-ommaya therapy

Ommaya reservoirs were placed directly into the lateral ventricle to prevent repeated lumbar punctures for intrathecal chemotherapy. These provide easy access to the intrathecal space. Ommaya reservoirs have also been placed into the cysts of craniopharyngiomas in order to deliver chemotherapy agents intratumorally. The two agents that have previously been successfully utilized using this method of drug delivery are bleomycin and alpha interferon [51, 52].

5. Supportive care

Supportive care describes the multidisciplinary care required to fulfill the needs of the patient and family in order to meet the physical, informational, psychosocial, emotional, practical, and spiritual needs during all phases of their cancer care [53]. The treatment of pediatric brain and spinal cord tumors is complex and every family is different, with variable needs throughout treatment. This requires a collaborative and multidisciplinary health-care team to effectively assess and address the required supportive care early during the stage of diagnosis or initial therapy [53, 54].

The supportive care needs of pediatric patients and their families include the physical (physiotherapy, occupational therapy, speech pathology, dietician, medical, pharmacy), education/informational (often met by nursing and medical team members), as well as psychosocial (social work, psychology, child life, psychiatry). It is important to reassure the family that the intense emotional reactions (including fear, powerlessness, denial, guilt, sadness, anger, confusion, anxiety, and depression) are normal responses to the child's illness and that the team is there to support and not judge them. Complete family assessment including psychosocial and practical resources, employment, socioeconomic status, as well as an assessment of marital-parental and sibling relationships should be studied and managed [54]. Misunderstanding may influence care [54].

5.1. Informational needs

Good communication by the health-care team, repetition of information, opportunities to ask questions, and written materials are important for assisting families. Gaining information about their child's condition allows parents to feel some control over the situation and regain some peace of mind. Psychosocial providers can assist families to manage feelings of information overload and problem solving according to the demands.

Parents may require guidance from the team regarding how and when to talk to their children, to do it so honestly and at an age-appropriate level, yet in a way that decreases anxiety and increases trust in the treatment process and team.

Normalizing activities as much as possible can be of great help in restoring a sense of safety and normalcy for children. Child life specialists can help to normalize daily activities. Once the child is discharged from the hospital, encourage parents to allow the child to live life as

normal as possible. Social and medical staff have to help the parents to overcome their own fears, and to allow patients to return to pre-illness activities within the restrictions of the illness with no overindulging or overprotecting [54].

5.2. Nutritional support

It is well established that children and adolescents with cancer experience malnutrition due to their underlying malignancy and treatment-related factors. Diminished nutritional status contributes in poor wound healing, increased infection risk, and decreased tolerance to chemotherapy. It is established that poor nutrition affects the QoL, response to treatment, and overall cost of care. This may be attributed to their limited energy stores and increased nutritional requirements to attain their appropriate growth and neurodevelopment [57–58].

Nutritional strategies should be integrated as a fundamental feature of supportive care for all pediatric neuro-oncology patients. The goals of nutritional supportive care include the maintenance of body stores, minimization of weight loss, promotion of appropriate growth, and providing excellent QoL [58].

5.3. Endocrinopathy at diagnosis and during treatment of brain tumor

Tumors of suprasellar and pineal region show various endocrine abnormalities even before the start of any treatment. Endocrinal symptoms in midline tumors include diabetes insipidus; changes in weight, height, and growth velocity; precocious puberty; or delayed sexual development. These symptoms less often lead to diagnosis, despite being present long before diagnosis [59]. Hypothalamic and pituitary endocrinopathies occur commonly in children following ≥24 Gy whole brain or localized cranial RT that included these structures in the radiation field. Hypothalamic-pituitary axis dysfunction gives rise to endocrinal abnormalities. This could be permanent or transient and the pituitary gland may regain its ability to secrete hormones after treatment. Therapeutic modalities, including surgery and radiotherapy, can damage pituitary cells leading to worsening of preexisting hypopituitarism [60]. Careful history and clinical examination, as well as timely reevaluation of children with abnormal body mass index (BMI) or BMI progression, as the presence of other neurological, ophthalmologic, and endocrine signs and symptoms may be indicative of the presence of an underlying hypothalamic-pituitary lesion [59, 60].

6. Long-term sequelae

The high cure rate achieved in pediatric CNS tumors is greatly attributable to refined neurosurgical procedures, the advancement in RT as well as chemotherapy and the multidisciplinary team decisions for treatment. However, with prolonged survival and on reaching adulthood, the incidence of late effects becomes more apparent. A majority of long-term survivors have at least one chronic medical sequelae [61]. These complications include endocrinopathy, osteoporosis, cerebrovascular disease, neurological and neurosensory

dysfunction, secondary neoplasms, as well as psychological consequence and neurocognitive impacts.

6.1. Growth

Radiation-induced growth deficiency is due to damage to either hypothalamus or pituitary gland or local radiation to the spine. Cranial irradiation has an immediate suppressive effect on the hypothalamic-pituitary axis. According to the total cranial dose received, it reduces growth hormone (GH) level and alters the normal pubertal rise in GH secretions. The size and the number of radiation fractions influence growth hormone levels. Early diagnosis of mild hypothyroidism and/or GH deficiency permits early intervention to improve growth velocity and QoL [62]. Craniospinal irradiation and/or disruption of the pituitary-hypothalamic axis can lead to more global changes in physical appearance such as short stature or obesity [62, 63].

Spinal radiation will affect vertebral body growth, especially in the younger ages. Chemotherapy may impair gonadal function, usually more in males than in females. Cyclophosphamide-induced testicular damage is dose dependent. In general, prepubertal patients tend to be more resistant to gonadal adverse effects of RT and chemotherapy than postpubertal patients [62].

6.2. Osteoporosis

Brain radiation, corticosteroids, poor nutrition, restricted weight-bearing exercise, and the developed endocrinopathies interact and all affect bone mineral density (BMD) during a crucial period for bone growth and skeletal growth. Depending on the magnitude of the BMD deficit and the potential for recovery, the pediatric neuro-oncology survivors are at increased risk for osteoporosis that may lead to osteoporotic fractures later in life.

These survivors should be assessed for low BMD and referred for potential bone health assessment and treatment as well as maximizing nutrition, exercise, and calcium and vitamin D intake [64].

6.3. Sleep disorder

Neuro-oncology patients may suffer from sleep disorders including disturbed sleep-wake rhythm, increased sleep duration, disturbed sleep timing, and daytime sleepiness that significantly affect their daily performance and their QoL. Disturbed pattern of sleep is more often experienced in children suffering from hypothalamic, pituitary, or brain stem lesions as well as in those treated with craniospinal radiotherapy. Excessive somnolence and psychosocial functioning with fatigue are common complaints of such patients. Routine evaluation of sleep habits during may help better understanding the mechanisms underlining these disorders and present possible interventions (e.g., melatonin, cognitive therapy, bright light therapy, medications, and/or physical activities) [65].

6.4. Vascular malformations

An increased risk of vascular malformations was noticed with radiotherapy. Radiation can weaken the vessel wall and result in cerebral cavernous malformation, telangiectasias of capillaries, and aneurysms. Radiation is believed to stimulate angiogenesis factors leading to these vascular malformations. Cerebral cavernous malformations were experienced six times higher in those treated with radiotherapy than in the control population. Most of these lesions are asymptomatic, but a subset may be presented with seizures, headaches, and hemorrhages that may require surgical intervention.

Telangiectasias are commonly found in brain tissue obtained from patients treated with radiotherapy, with thin-walled, dilated tortuous vascular channels, associated with perivascular leukocyte infiltration. These abnormalities may become symptomatic after bleeding but are usually considered as benign finding [66].

Small vessel vasculopathy with mineralizing microangiopathy of the basal ganglia and subcortical white matter has also been reported months to years after completion of radiation of the brain [67]. Most patients are asymptomatic, but some investigators have correlated their presence with behavioral disorders, neurological deterioration, and dementia.

Moyamoya vasculopathy was reported in pituitary and chiasmatic tumor patients treated with and without radiation. This vasculopathy is a progressive stenosis of the supraclinoid internal carotid arteries leading to the development of collateral blood vessel formation. Radiation to the circle of Willis and neurofibromatosis type I (NF1) have been identified as risk factors [28].

6.5. Seizures

Childhood Cancer Survivor Study (CCSS) reported the prevalence of epilepsy in long-term survivors of childhood brain tumors as 25%. Many of them had their first seizure more than 5 years after diagnosis of their cancer [68]. Seizures were more frequent in patients treated with RT >30 Gy to any cortical area and more frequent in children treated at young age or who underwent repeated brain tumor excisions. Methotrexate has also been related to late seizure onset, especially with the resulted necrotizing leukoencephalopathy.

6.6. Ototoxicity

High doses of platinum have been reported to cause irreversible early- or delayed-onset hearing loss. Platinum targets the outer hair cells in the organ of Corti and the cochleal wall epithelium. These late complications create hearing affection and hence affect speech development, learning, communication, school performance, social interaction, and overall QoL. Platinum ototoxicity is characterized by a dose-dependent high-frequency sensorineural hearing loss with tinnitus. The magnitude of ototoxicity was influenced by the young age at the start of treatment, the high cumulative doses of platinum compounds (>400 mg/m^2 for cisplatin and carboplatin), and the use of concomitant ototoxic treatments including CNS RT [69]. Genetic polymorphisms in enzymes responsible for platinum metabolism (e.g., gluta-

thione S-transferase, thiopurine methyltransferase, catechol O-methyltransferase) may contribute to the severity of hearing loss [70, 71].

RT to the cochlea or cranial nerve VIII can also cause sensorineural hearing loss. Cranial RT used alone results in ototoxicity when cochlear dosage exceeds 32 Gy. Young age, presence of a brain tumor, and/or hydrocephalus can increase susceptibility to hearing loss. When used concomitantly with platinum, RT can have a synergistic effect and it substantially exacerbates the hearing loss associated with chemotherapy, especially in the high-frequency speech range. RT to temporal lobe (>30 Gy) and to posterior fossa (≥50 Gy) was reported to be associated with an increased risk of tinnitus, and hearing loss.

Early detection of ototoxicity in children is of extreme importance in the prevention of severe hearing impairment that may affect speech recognition. Various strategies have been considered to minimize platinum ototoxicity. Radiation reduction dose to the cochlea has been investigated, including the use of 3D conformal RT, IMRT, and proton therapy [72]. Once treatment is completed, long-term audiometric monitoring should continue.

6.7. Visual affection

CCSS reported in adult survivors of childhood brain tumors, blindness in one or both eyes in 13%, cataracts in 3%, and double vision in 17% [68]. Although cataracts are known complication of RT, prolonged use of corticosteroid such as dexamethasone can also contribute to the development of posterior subcapsular cataracts. Ophthalmologic complications were reported in optic pathway glioma and craniopharyngioma in 20–70% of patients. Poor visual outcome has been frequently reported in the posterior chiasmatic area. Long-standing obstructive hydrocephalus can lead to severe optic atrophy and blindness.

6.8. Secondary neoplasms

The increase in survival in childhood tumors was accompanied with the emergence of secondary neoplasms as a long-term complication of treatment reaching up to 3–4% at 20 years post treatment [73]. Leukemia and primary CNS tumors have a tendency to develop into a subsequent CNS tumor. Armstrong et al. [74] reported 20 (1.1%) second CNS tumors out of 1877 survivors of CNS malignancies. They also observed 171 (9.1%) neoplasms classified as "benign" tumors including 59 meningiomas and 112 nonmelanoma skin cancers in these long survivors. The overall cumulative incidence of a subsequent neoplasm at 25 years was estimated to be 10.7%. Generally, the most common malignancies are malignant astrocytomas, followed by sarcomas and occasionally supratentorial primitive neuroectodermal tumors (sPNET). The cumulative incidence of secondary CNS such as glioblastomas plateaued at 15 years, whereas the cumulative incidence of meningiomas continues to increase beyond 35 years post treatment [75]. Although these secondary tumors have similar histological appearance to the primary tumors, they typically behave more aggressively and are resistant to treatment [76]. Moreover, the meningiomas have also been found to be more often atypical and prone to relapse. The development of secondary CNS tumors is most likely

multifactorial, but RT certainly contributes to this process. The vast majority of secondary malignant neoplasm (SMN) appears within the radiation field. The cumulative incidence of SMNs at 25 years was 7.1% for children who received more than 50 Gy to the cranium compared to 1% for children who did not receive cranial irradiation. A linear dose response could be illustrated with an increased relative risk of 0.33% for gliomas and 1.06% for meningiomas per Gy. The chemotherapy contribution to the development of secondary CNS malignancy is more difficult to assess partly due to the use of combination chemotherapy regimens. Alkylating drugs, especially cyclophosphamide and epipodophyllotoxins, such as etoposide, have been reported to increase the cumulative incidence of second malignancies [77]. The presence of accompanying somatic mutations may predispose for the development of second malignancy. Patients with p53 (Li-Fraumeni syndrome) are more likely to develop SMN including sarcoma, primary brain tumor, and acute lymphoblastic leukemia (ALL).

Therapy may be tailored in order to avoid or reduce the combination of RT and certain chemotherapy agents. Alkylating drugs, especially cyclophosphamide and epipodophyllotoxins, such as etoposide, have been reported to increase the cumulative incidence of second malignancies up to 4% [77]. Other somatic mutations such as the ataxia telangiectasia mutated gene (ATM) known to be involved in DNA repair may possibly play a role. Finally, metabolism and detoxification might also be involved in the development of second malignancy especially in those with acute nonlymphocytic leukemia (ANLL) and acute myeloid leukemia (AML).

7. Palliative care

Palliative care for children has evolved, over the last two decades, as separate specialized entity. Its delivery encompasses the total care of children with life-limiting diseases, regardless of outcome. It is worth noting that palliative care is applicable from the time of diagnosis, through active and curative treatment, and afterwards. Timing is further complicated by the perceived sharp division between curative therapy and palliative care among pediatric oncologists and parents who view palliative care as giving up hope and representing failure.

Palliative care service includes improved communication and continuity of care across different disease and management stages. This care deals with assessment of physical, psychosocial, emotional, and spiritual needs, provision of comprehensive specialized pain and symptom management, and support with complex and ethical decision making. It is also concerned with enhanced awareness of diverse cultural beliefs about dying and death, specialized care of the dying patient, and provision of bereavement care. Education and staff support to improve delivery of care and respond to moral distress are additional important role [78, 79]. Palliative care services must better be organizationally situated within a pediatric oncology program. Without early integration of palliative care, the focus of care then centers on life-prolonging measures, which may result in painful and invasive procedures, additional unnecessary suffering, and futile resuscitation. Care may be missed if not ad-

dressed early in the trajectory of a cancer illness when death is expected. However, the pediatric brain tumor palliative care introduction time remains unclear and controversial, and has little evidence for practice guidelines [78].

8. Conclusion

Although the gap between the neuro-oncology services in HICs and LMICs is still huge, yet the continuous efforts performed by the LMICs assisted by different international organization, medical and scientific societies, and other international medical bodies can decrease and overcome this gap. Pediatric neuro-oncology service is a delicate art and science that is presented by a multidisciplinary team aimed at taking care of pediatric CNS tumors from the day of suspicion of the disease till long way across the adulthood life. The welfare of these patients is the concern of the multidisciplinary team along the journey of diagnosis, treatment, and prolonged extended follow-up. The team is concerned also with dealing with disease and treatment complications together with palliation of the symptoms faced by the patients. Much success was achieved; however, much effort is needed for more improvement of the quality of their life. Very long-term effects 30–40 years after treatment still need to be thoroughly investigated. Cerebrovascular diseases such as stroke, cognitive dysfunction leading to early dementia, secondary neoplasms, and peripheral neuropathy are likely to form real problem in the coming years.

The balance between survival and long-term side effects will certainly be a challenge for several decades. Tailored therapy to reduce and limit the need for radiation and chemotherapy will hopefully lead to improved outcomes with fewer adverse effects and morbidity.

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References

[1] Wagner HP, Antic V. The problem of pediatric malignancies in the developing world. Ann N Y Acad Sci. 1997;824:193–204.

[2] Reutfors J, Kramárová E, Weiderpass E, Monge P, Wesseling C, Ahlbom A. Paediatric central nervous system tumours in children in Costa Rica, 1981-96. Perinat Epidemiol. 2002;16(3):219–25.

[3] Bouffet E, Amayiri N, Fonseca A, Scheinemann K. Pediatric neuro-oncology in countries with limited resources. In Pediatric Neuro-oncology, K. Scheinemann and E. Bouffet (eds.). New York, NY: Springer Science + Business Media; 2015, pp: 299–307.

[4] Zaghloul MS. Single pediatric neuro-oncology center may make difference in low/middle-income countries. Child's Nervous System. 2016;32(2):241–2.

[5] Miyakawa A, Shibamoto Y, Otsuka S, Iwata H. Applicability of the linear-quadratic model to single and fractionated radiotherapy schedules: an experimental study. J Radiat Res. 2013;55(3):451–4.

[6] El Fiki M. African neurosurgery, the 21st century challenge. World Neurosurgery. 2010;73(4):254–8.

[7] Mohan R, Wu Q, Manning M, Schmidt-Ullrich R. Radiobiological considerations in the design of fractionation strategies for intensity- modulated radiation therapy of head and neck cancers. Int J Radiat Oncol Biol Phys. 2000;46:619–30.

[8] ACR Manual on Contrast Media - Version 8. ACR Committee on Drugs and Contrast Media. Reston, VA: American College of Radiology; 2012.

[9] Assaf Y, Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. J Mol Neurosci. 2008;34(1):51–61.

[10] Rao P. Role of MRI in paediatric neurooncology. Eur J Radiol. 2008;68(2):259–70.

[11] Petrirena GJ, Goldman S, Delattre JY. Advances in PET imaging of brain tumors: a referring physician's perspective. Curr Opin Oncol. 2011;23(6):617–23.

[12] Burger P, Scheithauer BW. Diagnostic Pathology: Neuropathology. 1st ed. Salt Lake City, UT: Lippincott Williams & Wilkins and Amirsys; 2011.

[13] Szymas J, Wolf G, Papierz W, Jarosz B, Weinstein RS. Online Internet-based robotic telepathology in the diagnosis of neuro-oncology cases: a teleneuropathology feasibility study. Hum Pathol. 2001;32(12):1304–8.

[14] Datta NR, Samiei M, Bodis S. Radiation therapy infrastructure and human resources in low- and middle-income countries: present status and projections for 2020. Int J Radiat Oncol Biol Phys. 2014;89(3):448–57.

[15] Abdel-Wahab M, Bourque JM, Pynda Y, Iżewska J, Van der Merwe D, Zubizarreta E, Rosenblatt E. Status of radiotherapy resources in Africa: an international atomic energy agency analysis. Lancet Oncol. 2013;14(4):e168–75.

[16] Levin CV, et al. Radiationtherapy services in South Africa. S Afr Med J. 1994;84(6):349–51.

[17] Zubizarreta EH, Poitevin A, Levin CV. Overview of radiotherapy resources in Latin America: a survey by the International Atomic Energy Agency (IAEA). Radiother Oncol. 2004;73(1):97–100.

[18] Grover S, et al. A systematic review of radiotherapy capacity in low- and middle-income countries. Front Oncol. 2015;4: Article 380.

[19] Mellstedt H. Cancer initiatives in developing countries. Ann Oncol. 2006;17:viii24–31.

[20] World Health Organization (WHO). National Cancer Control Programmes: Policies and Managerial Guidelines. Geneva, Switzerland: WHO; 2002.

[21] Available from: http://www.icedoc.org/winwin.htm

[22] Haas-Kogan DA, et al. P53-dependent G1 arrest and P53- independent apoptosis influence on the radiobiologic response of glioblastoma. Int J Radiat Biol Phys. 1996;36:95–103.

[23] Reddy K, Damek D, Gaspar LE, Ney D, Waziri A, Lillehei K, Stuhr K, Kavanagh BD, Chen C. Phase II trial of hypofractionated IMRT with temozolomide for patients with newly diagnosed glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2012;84:655–60.

[24] Chen C, Damek D, Gaspar LE, Waziri A, Lillehei K, Kleinschmidt-DeMasters BK, Robischon M, Stuhr K, Rusthoven KE, Kavanagh BD. Phase I trial of hypofractionated intensity- modulated radiotherapy with temozolomide chemotherapy for patients with newly diagnosed glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2011;81:1066–74.

[25] Floyd NS, Woo SY, Teh BS, Prado C, Mai WY, Trask T, Gildenberg PL, Holoye P, Augspurger ME, Carpenter LS, Lu HH, Chiu JK, Grant WH 3rd, Butler EB. Hypofractionated intensity-modulated radiotherapy for primary glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2004;58:721–6.

[26] Zaghloul MS, Eldebawy E, Ahmed S, Mousa AG, Amin A, Refaat A, Zaky I, Elkhateeb N, Sabry M. Hypofractionated conformal radiotherapy for pediatric diffuse intrinsic pontine glioma (DIPG): a randomized controlled trial. Radiother Oncol. 2014;111(1):35–40.

[27] Zaghloul MS. Has hypofractionated radiotherapy become the standard of care in pediatric DIPG? Child's Nervous System. 2015;31(8):1221–2.

[28] Ullrich NJ, Robertson R, Kinnamon DD, Scott RM, Kieran MW, Turner CD, Chi SN, Goumnerova L, Proctor M, Tarbell NJ, Marcus KJ, Pomeroy SL. Moyamoya following cranial irradiation for primary brain tumors in children. Neurology. 2007;68(12): 932–8.

[29] Maher CO, Raffel C. Neurosurgical treatment of brain tumors in children. Pediatr Clin North Am. 2004;51:327–57.

[30] Crawford JR, MacDonald TJ, Packer RJ. Medulloblastoma in childhood: new biological advances. Lancet Neurol. 2007;6:1073–85.

[31] Kobayashi T, Kageyama N, Ohara K. Internal irradiation for cystic craniopharyngioma. J Neurosurg. 1981;55(6):896–903.

[32] Lapras C, Patet JD, Mottolese C, Vitale G. Cerebellar astrocytomas in children. Prog Exp Tumor Res. 1987;30:128.

[33] Winn HR, editor. Youman's Neurological Surgery. Philadelphia, PA: Elsevier; 2011.

[34] Obaid S, Champagne P, Mercier C, Crevier L. Neurosurgery. In Pediatric Neuro-Oncology, K. Scheinemann and E. Bouffet (eds.). New York, NY: Springer Science Business Media; 2015, pp: 31–39.

[35] Sullivan R, Kowalczyk JR, Agarwal B, Ladenstein R, Fitzgerald E, Barr R, Steliarova-Foucher E, Magrath I, Howard SC, Kruger M, Valsecchi MG, Biondi A, Grundy P, Smith MA, Adamson P, Vassal G, Pritchard-Jones K. Improving cancer care for children and young people 4. New policies to address the global burden of childhood cancers. Lancet Oncol. 2013;14(3):e125–35.

[36] Magrath I, Steliarova-Foucher E, Epelman S, Ribeiro RC, Harif M, Li CK, Kebudi R, Macfarlane SD, Howard SC. Paediatric cancer in low-income and middle-income countries. Lancet Oncol. 2013;14(3):e104–16.

[37] Parkes J, Wetter J. Pediatric radiotherapy. In Pediatric Hematology-Oncology in Countries with Limited Resources: A Practical Manual, D.C. Stefan and C. Rodriguez-Galindo (eds.). New York, NY: Springer Science Business Media; 2014, pp: 181–206.

[38] Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists. An Updated Report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Anesthesiology 2002;96: 1004–1017.

[39] Gregoire V, Mackie TR. State of the art on dose prescription, reporting and recording in intensity-modulated radiation therapy (ICRU report No. 83). Cancer Radiother. 2011;15 (6–7):555–9.

[40] Hall EJ. Intensity-modulated radiation therapy, protons, and the risk of second cancers. Int J Radiat Oncol Biol Phys. 2006;65:1–7.

[41] Huang E, Teh BS, Strother DR, Davis QG, Chiu JK, Lu HH, Carpenter LS, Mai WY, Chintagumpala MM, South M, Grant WH 3rd, Butler EB, Woo SY. Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. Int J Radiat Oncol Biol Phys. 2002;52:599–605.

[42] Larson DA, Bova F, Eisert D, Kline R, Loeffler J, Lutz W, Mehta M, Palta J, Schewe K, Schultz C. Task force on stereotactic radiosurgery, American Society for Therapeutic Radiology and Oncology. Current radiosurgery practice: results of an ASTRO survey. Int J Radiat Oncol Biol Phys. 1994;28:523–6.

[43] Stieber VW, Bourland JD, Tome WA, Mehta MP. Gentlemen (and ladies), choose your weapons: gamma knife vs. linear accelerator radiosurgery. Technol Cancer Res Treat. 2003;2:79–86.

[44] Hug EB, Slater JD. Proton radiation therapy for pediatric malignancies: status report. Strahlenther Onkol. 1999;175(Suppl. 2):89–91.

[45] Hug EB, Sweeney RA, Nurre PM, Holloway KC, Slater JD, Munzenrider JE. Proton radiotherapy in management of pediatric base of skull tumors. Int J Radiat Oncol Biol Phys. 2002;52:1017–24.

[46] Khuntia D, Tomé WA, Mehta MP. Radiation techniques in neuro-oncology. Neurotherapeutics 2009;6(3):478–499.

[47] MacDonald SM, Safai S, Trofimov A, Wolfgang J, Fullerton B, Yeap BY, Bortfeld T, Tarbell NJ, Yock T. Proton radiotherapy for childhood ependymoma: initial clinical outcomes and dose comparisons. Int J Rad Oncol Biol Phys. 2008;71:979–86.

[48] Merchant TE, Hua CH, Shukla H, Ying X, Nill S, Oelfke U. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. Pediatr Blood Cancer 2008;51:110–7.

[49] Lee J, Johnston DL. Chemotherapy. In Pediatric Neuro-oncology, K. Scheinemann and E. Bouffet (eds). New York, NY: Springer Science + Business Media; 2015, pp: 207–215.

[50] Lassaletta A, Lopez-Ibor B, Mateos E, Gonzalez-Vicent M, Perez-Martinez A, Sevilla J, Diaz MA, Madero L. Intrathecal liposomal cytarabine in children under 4 years with malignant brain tumours. J Neurooncol. 2009;95:65–9.

[51] Dastoli PA, Nicácio JM, Silva NS, Capellano AM, Toledo SR, Ierardi D, Cavalheiro S. Cystic craniopharyngioma: intratumoural chemotherapy with alpha interferon. Arq Neuropsiquiatr. 2011;69:50–5.

[52] Mottolese C, Stan H, Hermier M, Berlier P, Convert J, Frappaz D, Lapras C. Intracystic chemotherapy with bleomycin in the treatment of craniopharyngiomas. Childs Nerv Syst. 2001;17:724–30.

[53] Kerr LM, Harrison MB, Medves J, Tranmer JE, Fitch MI. Supportive care needs of parents of children with cancer: transition from diagnosis to treatment. Oncol Nurs Forum. 2004;31(6):E116–26.

[54] PDQ Supportive and Palliative Care Editorial Board. Pediatric Supportive Care (PDQ®): Health Professional Version. PDQ Cancer Information Summaries [Internet]. Bethesda, MD: National Cancer Institute (US); 2002–2016.

[55] Lanskowksy P. Manual of Pediatric Hematology and Oncology: Psychosocial Aspects of Cancer for Children and their Families. 5th ed. Burlington, VT: Elsevier; 2011.

[56] Co-Reyes E, Li R, Huh W, Chandra J. Malnutrition and obesity in pediatric oncology patients: causes, consequences, and interventions. Pediatr Blood Cancer. 2012;59(7): 1160–7.

[57] Pizzo PA, Poplack DG. Principles and Practices of Pediatric Oncology: Nutritional Supportive Care. 6th ed. Philadelphia, PY: Lippincott Williams & Wilkins; 2011.

[58] Bauer J, Jürgens H, Frühwald MC. Important aspects of nutrition in children with cancer. Adv Nutr. 2011;2(2):67–77.

[59] Taylor M, Couto-Silva AC, Adan L, Trivin C, Sainte-Rose C, Zerah M, Valteau-Couanet D, Doz F, Chalumeau M, Brauner R. Hypothalamic-pituitary lesions in pediatric patients: endocrine symptoms often precede neuro-ophthalmic presenting symptoms. J Pediatr. 2012;161(5):855–63.

[60] Jorsal T, Rorth M. Intracranial germ cell tumours. A review with special reference to endocrine manifestations. Acta Oncol. 2012;51(1):3–9.

[61] de Boer AG, Verbeek JH, van Dijk FJ. Adult survivors of childhood cancer and unemployment: a meta-analysis. Cancer. 2006;107(1):1–11.

[62] Turner CD, Rey-Casserly C, Liptak CC, Chordas C. Late effects of therapy for pediatric brain tumor survivors. J Child Neurol. 2009;24(11):1455–63.

[63] Nathan PC, Jovcevska V, Ness KK, Mammone D'Agostino N, Staneland P, Urbach SL, Barron M. The prevalence of overweight and obesity in pediatric survivors of cancer. J Pediatr. 2006;149(4):518–25.

[64] Cohen LE, Gordon JH, Popovsky EY, Sainath NN, Feldman HA, Kieran MW, Gordon CM. Bone density in post-pubertal adolescent survivors of childhood brain tumors. Pediatr Blood Cancer. 2012;58(6):959–63.

[65] Verberne LM, Maurice-Stam H, Grootenhuis MA, Van Santen HM, Schouten-Van Meeteren AY. Sleep disorders in children after treatment for a CNS tumour. J Sleep Res. 2012;21(4):461–9.

[66] Burn S, Gunny R, Phipps K, Gaze M, Hayward R. Incidence of cavernoma development in children after radiotherapy for brain tumors. J Neurosurg. 2007;106(Suppl. 5): 379–83.

[67] Price RA, Birdwell DA. The central nervous system in childhood leukemia. III. Mineralizing microangiopathy and dystrophic calcification. Cancer. 1978;42(2):717–28.

[68] Packer RJ, Gurney JG, Punyko JA, Donaldson SS, Inskip PD, Stovall M, Yasui Y, Mertens AC, Sklar CA, Nicholson HS, Zeltzer LK, Neglia JP, Robison LL. Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: childhood cancer survivor study. J Clin Oncol. 2003;21(17):3255–61.

[69] Whelan K, Stratton K, Kawashima T, Leisenring W, Hayashi S, Waterbor J, Blatt J, Sklar CA, Packer R, Mitby P, Robison LL, Mertens AC. Auditory complications in child-

hood cancer survivors: a report from the childhood cancer survivor study. Pediatr Blood Cancer. 2011;57(1):126–34.

[70] Mukherjea D, Rybak LP. Pharmacogenomics of cisplatin- induced ototoxicity. Pharmacogenomics. 2011;12(7):1039–50.

[71] Ross CJ, Katzov-Eckert H, Dubé MP, Brooks B, Rassekh SR, Barhdadi A, Feroz-Zada Y, Visscher H, Brown AM, Rieder MJ, Rogers PC, Phillips MS, Carleton BC, Hayden MR; CPNDS Consortium. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. Nat Genet. 2009;41(12):1345–9.

[72] Paulino AC, Lobo M, Teh BS, Okcu MF, South M, Butler EB, Su J, Chintagumpala M. Ototoxicity after intensity modulated radiation therapy and cisplatin-based chemotherapy in children with medulloblastoma. Int J Radiat Oncol Biol Phys. 2010;78(5): 1445–50.

[73] Inskip PD, Curtis RE. New malignancies following childhood cancer in the United States, 1973–2002. Int J Cancer. 2007;121(10):2233–40.

[74] Armstrong GT. Long-term survivors of childhood central nervous system malignancies: the experience of the Childhood Cancer Survivor Study. Eur J Paediatr Neurol. 2010;14(4):298–303.

[75] Hijiya N, Hudson MM, Lensing S, Zacher M, Onciu M, Behm FG, Razzouk BI, Ribeiro RC, Rubnitz JE, Sandlund JT, Rivera GK, Evans WE, Relling MV, Pui CH. Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukemia. JAMA. 2007;297(11):1207–15.

[76] Sobowale OA, McCabe M, Pal P, Soh C, Karabatsou K. Radiotherapy-induced supratentorial primitive neuroectodermal tumour in a 17-yearold female: a case report and review of the literature. Acta Neurochir. 2011;153(2):413–7.

[77] Borgmann A, Zinn C, Hartmann R, Herold R, Kaatsch P, Escherich G, Möricke A, Henze G, von Stackelberg A; ALL-REZ BFM Study Group. Secondary malignant neoplasms after intensive treatment of relapsed acute lymphoblastic leukaemia in childhood. Eur J Cancer. 2008;44(2):257–68.

[78] Waldman E, Wolfe J. Palliative care for children with cancer. Nat Rev Clin Oncol. 2013;10(2):100–7.

[79] Epelman CL. End-of-life management in pediatric cancer. Curr Oncol Rep. 2012;14(2): 191–6.

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