Pediatr Blood Cancer 2015;62:553–564

CLINICAL PRACTICE GUIDELINES
SIOP PODC Adapted Treatment Recommendations for Standard-Risk Medulloblastoma in Low and Middle Income Settings

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Effective treatment of children with medulloblastoma requires a functioning multi-disciplinary team with adequate neurosurgical, neuroradiological, pathological, radiotherapy and chemotherapy facilities and personnel. In addition the treating centre should have the capacity to effectively screen and manage any tumour and treatment-associated complications. These requirements have made it difficult for many low and middle-income countries (LMIC) centres to offer curative treatment. This article provides management recommendations for children with standard-risk medulloblastoma (localised tumours in children over the age of 3–5 years) according to the level of facilities available. Pediatr Blood Cancer 2015;62:553–564. © 2014 Wiley Periodicals, Inc.

Key words: brain; chemotherapy; pediatric hematology/oncology; tumours

INTRODUCTION

The treatment of malignant childhood brain tumours remains a challenge as it requires a multidisciplinary set up that is not available worldwide, in particular, in countries with limited health care resources. Medulloblastoma is the most common malignant brain tumour in children, accounting for 20–25% of all paediatric brain tumours in high-income countries (HIC). However, data from low and middle-income countries (LMIC) describe large variations in the incidence of medulloblastoma ranging from 6.1% to 49.4% of all diagnosed brain tumours [1–7].

For treatment purposes, patients with medulloblastoma are divided into two prognostic groups: children over 3–5 years of age with non-metastatic disease (Chang stage M0) [8] and minimal residual disease ($<1.5\ cm^2$) post-operatively comprise the standard-risk group. Other patients with a sub-total resection, or metastatic disease and younger patients below 3–5 years of age comprise the high-risk group (Table I). Current 5 year event free survival (EFS) rates are 85% for standard-risk [9]. However, improvements observed in high-income countries (HIC) are not mirrored in LMIC.

There are multiple reasons for poorer outcome of children with brain tumours in LMIC including delayed diagnosis, high rate of advanced disease at presentation, deficiencies in the referral and diagnostic pathways, high rates of nosocomial infection post neurosurgery, significant delays to radiotherapy and discrepancies in socio-economic support services [10]. In a SIOP Africa report [11], massive under-resourcing of child health was noted, leading to poor access to chemotherapy, surgical expertise, supportive care and radiation facilities. The very limited availability of radiation facilities in Africa was highlighted by Levin et al. in 1998 [12] where they reported a total of 155 radiotherapy machines in Africa (Cobalt 62; Linac 93) serving a total population of 500,000,000 [13] Of the 155, 93 were in South Africa or in Egypt. Several countries had no radiation equipment.

However, experience in some MIC reflects promising results in environments where adequate surgery, radiotherapy and chemotherapy resources are available. In a retrospective review of 34 patients with medulloblastoma treated at All India Institute of Medical Science, the 3 year overall survival (OS) was 76%, and both chemotherapy and extent of resection were associated with improved outcome [14]. In a report from Egypt, a combined paediatric-adult cohort [51:16] showed a 89% 5 year OS in paediatric patients. All patients had primary resection, followed by full dose craniospinal radiotherapy and chemotherapy that included carboplatin, etoposide and vincristine in varying sequences [15]. In a report of a twinning initiative between Toronto and Amman in Jordan, 3 year EFS was 100% (CI 57–99%) for children with standard-risk (SR) and 81% (CI 57–99%) for those with high-risk (HR) medulloblastoma, all of whom received chemotherapy in addition to radiotherapy [16]. By contrast, other series suggest significant challenges in the management of patients with

[Author Jeannette Parkes had a misspelling in her name that was corrected on 25 November 2014 after original online publication.]

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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Conflict of interest: Nothing to declare.

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Received 1 May 2014; Accepted 16 September 2014

DOI 10.1002/pbc.25313
Published online 21 November 2014 in Wiley Online Library (wileyonlinelibrary.com).

TABLE I. Risk Stratification of Medulloblastoma

Standard risk medulloblastoma	High risk medulloblastoma
All of the following:	Any one of the following:
>3 years of age	<3 years of age
<1.5 cm^2 residual tumour after resection	Subtotal resection (>1.5 cm^2 residual)
CSF negative for tumour cells on L.P.	CSF positive for tumour cells
MRI spine negative for leptomeningeal spread	MRI shows leptomeningeal spread
Classic or desmoplatic subtypes on pathology	Large cell or anaplastic subtype
Complete staging possible	Incomplete staging

medulloblastoma in limited resources settings. In a series from Tehran, 41% of 66 patients with medulloblastoma underwent only a limited biopsy at the time of diagnosis [17]. A Turkish group reported 5 year OS and EFS of 43.1% and 41.9%, and no benefit in survival from the addition of chemotherapy regardless of the regime used [18]. Studies with smaller numbers of patients from Saudi Arabia (n = 34) and Egypt (n = 17) also failed to show a survival benefit with the addition of chemotherapy [19,20]. Socio-economics certainly impact heavily on survival outcomes in LMIC but there is no documentation on this issue in the existing literature.

This document intends to provide guidelines for health care providers in LMIC for the treatment of childhood with standard-risk medulloblastoma and details the minimal requirements for comprehensive care with intention to cure.

SIOP PODC Recommendations

The International Society of Paediatric Oncology (SIOP) has a committee named Paediatric Oncology in Developing Countries (PODC). The SIOP PODC Adapted Treatment Regimens Working Group produces recommendations for the management of childhood cancers in LMIC as defined by the World Bank and guidelines for their implementation and for continuous quality improvement based on local outcome data [21].

Service levels describing facilities and personnel required for the care of patients with medulloblastoma are defined in Table II. Setting 2 is defined as meeting the minimal requirements for curative treatment. These minimal requirements are detailed below (Table II).

METHODS

A multi-disciplinary writing group was formed of neuro-surgeons, radiation and paediatric oncologists with experience in managing children with medulloblastoma in a LMIC setting. The recommendations were then circulated widely and discussed at SIOP PODC meetings. The guidelines were then ratified by the SIOP board. Online meetings were hosted by the Cure4Kids website (www.cure4kids.org).

In an attempt to explore available resources in LMIC, we conducted an online survey during May and June 2013. There were 104 responses from 47 countries (Table III). A note of caution is that this survey represents countries and centres with some form of oncology service and as a result presents a picture that may not be truly representative of oncology services in LMIC as a whole.

Treatment Guidelines

Presentation. The first and critical step in the management of children with medulloblastoma is diagnosis. Presenting signs and symptoms are largely due to increased intracranial pressure and often non-specific; these include headache, vomiting, occasionally neck pain and blurred vision. Cerebellar deficits (gait disturbances and dysmetria) often occur later in the course of the disease. Although there are no specific studies that have compared the time between onset of symptoms and the diagnosis of posterior fossa tumours in HIC versus LMIC, there are several factors that contribute to delayed diagnosis in countries with limited resources.

The diagnosis of medulloblastoma primarily relies on appropriate imaging studies. Without the minimum availability of CT scanning as well as a surgeon (and facilities) capable of resection of medulloblastoma, pathology services able to make the diagnosis, and the ability to deliver craniospinal radiotherapy, curative treatment of children with medulloblastoma is not possible (Table IV). Imaging characteristics of medulloblastoma have been extensively reported [22]. On CT or MRI imaging, the tumour is predominantly solid, classically arising from the vermis, less commonly from the cerebellar hemisphere. Enhancement following contrast administration is common but absence of enhancement does not exclude the diagnosis. Thus an index of suspicion must be present for most predominantly solid posterior fossa tumours. Spinal MRI prior to surgery should be performed to detect metastatic seeding.

Management at diagnosis. Children with medulloblastoma often present with symptomatic hydrocephalus. This requires definitive surgery or Cerebrospinal fluid (CSF) diversion and/or treatment of cerebral oedema with dexamethasone followed by definitive surgery.

Since the management of children with medulloblastoma is multidisciplinary, early notification of all clinicians involved in the process, in particular the pathologist and the members of the radiation oncology and oncology team, is advocated to facilitate and co-ordinate the diagnostic and treatment process preferably via a multidisciplinary team (MDT) meeting. Informed consent and assent where appropriate must be obtained, including rationale for treatment and an explanation of potential acute and late toxicities of treatment.

Surgery

When children with medulloblastoma can be treated with curative intent, the following is recommended:

Pre-operatively. Pre-operative steroids (dexamethasone 0.1 mg/kg/dose two or three times daily) [23] are beneficial in controlling ICP. Since patients may present with co-morbidities (e.g., malnutrition, malaria), it is essential for the surgeon and anaesthesiologist to review the child and for these co-morbidities to be corrected if possible.

Intra-operatively. Complete surgical resection is ideal but may not be feasible or safe. Although a residuum greater than 1.5 cm^2 has been associated with a negative prognostic effect [24,25], this must be balanced against anticipated surgical morbidity. It is preferable to leave a small tumour residuum than to risk serious morbidity especially if the tumour is adherent to the brainstem. Second-look surgery is appropriate if there is a large residuum, which can be resected without significant morbidity. Other factors that should be taken into account when planning

TABLE II. Infrastructural and Personnel Service Line Levels for Selection of SIOP PODC Adapted Treatment Regimens for Standard Risk Medulloblastoma

Service	Level 0	Level 1	Level 2	Level 3	Level 4
Paediatric cancer unit description (multidisciplinary team operates at all levels)	Pilot project	Some basic oncology services	Established paediatric oncology program with most basic services and a few state-of-the-art services	Paediatric oncology program with all essential services and most state-of-the-art services	Paediatric oncology centre of excellence with all state-of-the-art services and some highly specialised services (e.g., proton beam radiation therapy, MIBG therapy, access to phase I studies)
Typical settings	LIC in disadvantaged areas	LIC in larger healthcare centres, lower MIC in disadvantaged areas	Lower MIC in larger healthcare centres, upper MIC in disadvantaged areas	Upper MIC in larger healthcare centres, Most centres in HIC	Selected tertiary and quaternary care centres in HIC
Medical facilities					
Ward	No paediatric oncology unit	Basic paediatric oncology service available to some patients	Paediatric oncology unit available to most patients; isolation rooms usually available for infected patients	Paediatric oncology unit with a full complement of fixed staff and available to all patients; isolation rooms always available for infected patients	Specialised paediatric oncology units for particular groups of patients (e.g., transplant, neuro-oncology, acute myeloid leukaemia)
Diagnosis, staging and therapeutic capabilities					
Pathology	None	Microscope, H&E staining, CSF cytology	Limited immunohisto-chemistry panel (disease-specific), Cytospin for CSF samples	Complete immunohisto-chemistry panel, molecular pathology for most diseases	Research diagnostics, whole genome sequencing, molecular pathology for all diseases
Diagnostic imaging	None	Radiographs, ultrasound	CT scan, Bone scintigraphy, Gallium scintigraphy	Magnetic resonance imaging. PET-CT and MIBG may be available	Specialised imaging; advanced nuclear medicine applications, PET-CT and MIBG diagnostic
Antineoplastic availability	Access to a limited selection of oncology drugs	Access to a limited selection of oncology drugs	Access to almost all essential oncology drugs;[35] occasional shortages	Access to almost all commercially available drugs; rare shortages	Access to all approved drugs, plus phase I and phase II studies
Radiation therapy facilities	None	Cobalt source; 2D planning	Cobalt source or Linear accelerator; 2D or some 3D planning. Ability to plan craniospinal radiotherapy and deliver treatment on at least 4 days/week.	Linear accelerator; Full conformal therapy available. Intensity-modulated radiotherapy frequently available	Intensity-modulated radiotherapy. Proton beam facility

(*Continued*)

Pediatr Blood Cancer DOI 10.1002/pbc

TABLE II. (*Continued*)

Service	Level 0	Level 1	Level 2	Level 3	Level 4
Personnel					
Oncology team leader	Primary care physicians care for cancer and many other diseases	Primary care provider with interest in oncology	Primary care provider with paediatric oncology experience or some training, medical oncologist without paediatric expertise	Paediatric oncologist or medical oncologist with significant paediatric experience or training	Paediatric oncologist with highly disease-specific expertise
Oncology unit medical, nursing, and pharmacy staff	A few staff members with basic training	A few oncology personnel with some oncology training; trainees responsible for many aspects of patient care	Generally adequate numbers of oncology personnel; consistent supervision of any trainees involved in patient care	Full complement of oncology physicians; specialised oncology nurses; pharmacists with oncology training	Full complement of oncology personnel, including specialised physician extenders (e.g., nurse practitioners, hospitalists)
Surgery and surgical subspecialties relevant for each cancer	No surgeon	General surgeon or adult subspecialty surgeon (neurosurgeon, ophthalmologist, other)	Paediatric surgeon or subspecialty surgeon (neurosurgeon, ophthalmologist, other)	Paediatric cancer surgeon or paediatric subspecialty surgeon (neurosurgeon, ophthalmologist, other)	Paediatric cancer surgeon or subspecialty surgeon with highly specialised disease-specific expertise
Pathology	No pathologist	Pathologist available for some cases	Pathologist available for all cases	Haematopathologist and paediatric pathologist available	Pathologist with highly specialised disease-specific expertise
Radiation therapy	None	Radiation therapists with adult expertise	Radiation therapists with some paediatric experience	Radiation therapists with paediatric expertise	Paediatric radiation oncologist with highly specialised disease-specific expertise

TABLE III. Online Survey of Available Neuro-oncology Resources in LMIC

Online Survey via www.cure4kids.org in May and June 2013	
Total Responses	104
Responses by Continent	Africa 32% Asia 30% South and Central (S&C) America 33%
Respondents	Oncologists 58% Neurosurgeons 15% Radiation Oncologists 8%Paediatricians 15%
Access to Imaging	CT 93% MRI 82% (Africa 77%)
Access to Pathology	Morphologic diagnosis 96% Subtyping 53% Waiting time longer than 10 days 39%
On site Neurosurgery	76%
VP shunt Insertion	35% of 79 respondents reported that >50% of children had VPS
Access to ICU	80%
Referred to Radiotherapy	Overall: 84% Within 40 days: 74%
Access to CT Planning	89%
Access to Linac	66% (Africa 48%) the rest have Cobalt
Access to Craniospinal XRT	84%
Access to Chemotherapy	79%
Vincristine with Radiotherapy	63%
Chemotherapy pre-XRT	31% (1/3 routinely; 2/3 because of XRT delays)
Venous Access Devices (mostly portocaths)	45% (Africa 21%; Asia 41%; S&C America 64%)
Chemotherapy Drug Access	Lomustine 43% (Africa 44%; Asia 39%; S&C America 64%) Carboplatin 86%All other drugs >89%
Supportive Care	Dedicated paediatric oncology ward 88% Nutritional Support 72% and Dietetics 67% Physiotherapy 78%; Occupational Therapy 47%; Play Therapy 33%
Access to a Combined Clinic	56%

surgery are: involvement of 4th ventricle and peduncles, involvement of the cerebellar hemispheres, age, performance status at presentation and presence of metastatic disease.

CSF diversion. When immediate definitive surgery is not possible hydrocephalus may require urgent placement of an external ventricular drain (EVD). CSF drainage needs to be carefully controlled to avoid upward herniation. An endoscopic third ventriculostomy (ETV) is an alternative to the EVD, but it requires precise training and specific material. However, systematic placement of a ventriculo-peritoneal shunt (VPS) is no longer recommended prior to resection as the majority of these patients will not need a shunt following tumour resection. If hydrocephalus persists following tumour resection, this is usually due to fourth ventricular outlet obstruction. This can be treated by ETV and VPS is indicated only if this fails. Lumbar puncture is contra-indicated in the presence of acute hydrocephalus, unless it is communicating.

Intra-operative. Requirements for neuro-anaesthesia are beyond the scope of this article, these were summarised by Haynes et al. in 2009 [26].

Surgical technique. Various surgical techniques have been described. However, the most common and safest technique is the prone position using a horse-shoe or 3 pin head holder. A suboccipital craniotomy is preferred to a craniectomy and tissue should be harvested for a possible dural graft, especially if synthetic dural substitutes are not available. A key step in the operation is protecting the floor of the 4th ventricle, often with a cottonoid patty. When an operating microscope is not available, loupes are helpful to guide the resection. The use of Cavitron Ultrasonic Surgical Aspirator (CUSA) has proved to be useful but a generous tumour sample is needed prior to CUSA dissection. Intraoperative frozen section pathology services should be utilised if available.

TABLE IV. Approach to Treatment, Overall Multidisciplinary Approach

- Every effort must be made to assign treatment as soon as possible after diagnosis, based on a localized posterior fossa lesion suggestive on imaging of medulloblastoma in a child > 3 years.
- All patients should be discussed by MDT prior to surgery.
- The MDT will vary from a primary care physician and nurse to the full team comprising neurosurgeon, radiation oncologist and paediatric oncologist, but all should be involved at the outset.
- Tumour resection should be undertaken only if CSI is available to the patient

Level 0 – palliate
Level 1 – consider palliation unless the patient can be referred to Level 2 for CSI, which is a requirement for a curative approach. Chemotherapy Regimen 1.
Level 2 – CSI. Chemotherapy Regimen 2.
Level 3 – CSI. Chemotherapy Regimen 2.

TABLE V. Approach to Treatment, Surgery

- Surgery as per guidelines.
- Contact pathologist to expect specimen.
- Pathology confirms medulloblastoma preferably within days.
- Postoperative residuum on imaging $<1.5\,cm^2$.
- Patient fit for further treatment.

Post-operative care. Immediate post-operative care requires close monitoring in an intensive care unit or high dependency setting, as postoperative complications are not unusual. Adequate analgesia must be administered. Post-operative imaging, preferably within 72 hr of surgery should be performed if possible to assess tumour residuum or haematomas requiring re-exploration. In addition, a lumbar puncture should be performed a minimum of 2 weeks after surgery to look for malignant cells (M1 disease). CSF should be submitted for immediate cytospin and microscopy. Dexamethasone should routinely be reduced over no more than 5 days post-operatively unless specific indications for its use remain. Since availability of radiation oncology services may be limited, the patient must be discussed as soon as possible at a multidisciplinary team meeting (MDT) and referred to the radiation oncologist in order to optimize post-operative care and allow initiation of radiotherapy within 4–7 weeks (Table V).

Pathology

Standard-risk medulloblastoma includes the classic and desmoplastic subtypes, large cell and anaplastic pathological subtypes are indicative of high-risk medulloblastoma. Identification of molecular subtypes of medulloblastoma are not necessary to stratify treatment in LMIC. However, due to the excellent survival rates of patients in the Wnt subgroup of medulloblastoma, patients with non-metastatic medulloblastoma and intranuclear beta catenin expression could potentially be treated with reduced dose radiation regardless of the extent of resection [27].

Radiotherapy

In children over the age of 3–5 years, standard treatment of medulloblastoma includes craniospinal (CSI) radiotherapy after tumour resection. This technique has been in widespread use since the 1960s [28] and involves irradiating the neuraxis with a boost to the tumour bed with an adequate margin. CSI is a complex radiotherapy technique to implement due to the need for accurate reproducibility, complicated field matching techniques and the possibility of serious morbidity if not done correctly [29].

Timing of radiotherapy. Radiotherapy planning should start as soon as possible and treatment should commence within 4 weeks and no later than 7 weeks after definitive surgery. Two recent international trials from the SIOP group have shown that delaying treatment after 7 weeks increases the risk of relapse [25,30].

In the context of LMIC, if surgical complications or planning logistics delay the start of radiotherapy, 1–2 cycles of neo-adjuvant chemotherapy may be considered up front. If radiotherapy is commenced >49 days post-surgery, regardless of pre-radiotherapy chemotherapy, then the results of the above SIOP trials suggest that the patient should be considered high-risk and full dose CSI should be given [25,30]. Because of the frequent uncertainty of accurate staging as well as treatment delays in LMIC, many patients whose disease would be deemed "average risk" in HIC require full-dose craniospinal radiotherapy in LMIC. Because of this, both radiotherapy dosage schedules are given in this document. The planning technique is identical.

Planning of CSI. CT-based three-dimensional (3D) planning has become the standard of care in high income countries. This technique requires planning CT and a specialized planning software. CSI can also be planned using an image intensifier or simulator together with a 2D planning system. This technique has been used extensively in the past [28] and is still used in many LMIC. However, this is a difficult and time-consuming process that may increase the dose to the cochlea [31] and skin.

It is standard in HIC to deliver CSI from a linear accelerator (Linac). These machines are sparse in LMIC, where many units still use Cobalt-60 machines. With the latter material, it is more difficult to achieve an acceptable dose distribution and toxicity is greater. However, in many LMIC, unreliable electricity sources, poor maintenance and lack of engineers and physicists mean that reliable Linac functioning can be problematic. Cobalt machines require less maintenance, are easier to operate and require less quality assurance. Since treatment interruptions causing prolongation of treatment beyond 45–50 days are associated with a worse outcome [25,30], Cobalt machines may be a better option in these circumstances [29,32].

Delivery of CSI in supine position has many advantages [33]. However, this requires that the beams enter posteriorly through the treatment couch and head rest, which is not possible for older couches which have metal inserts. In addition supine position is more difficult to set up accurately without adequate portal imaging. Prone treatment is the alternative option that uses a perspex head cast and body foam/shell for patient positioning and immobilization (Fig. 1).

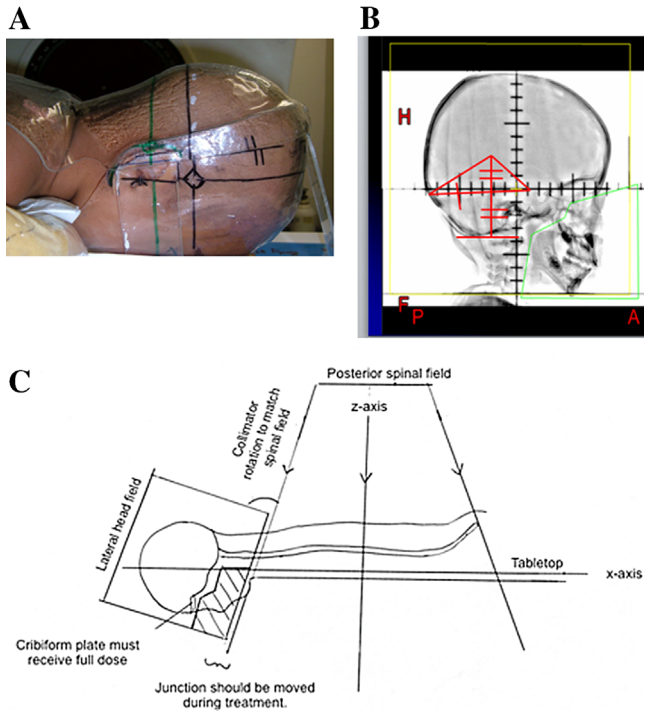

Fig. 1. Radiotherapy. (**A**) Perspex prone cast and body shell (**B**) Lateral head field and face block showing 2-D posterior fossa boost using bony landmarks (**C**) Schematic lateral view of head and spinal beams for CSI.

Patient positioning is critical, as the head and spine must be straight with the head in a slightly extended position and the cervical spine as flat as possible. For children under 5 or 6 years of age or children with posterior fossa mutism, a general anaesthetic or good sedation may be required. Choice of sedative and/or anaesthetic is dependent on local availability and experience; however, play therapy may be effective in helping prepare children for radiotherapy without sedation.

Tumour volumes and fields

The craniospinal axis. CSI involves treatment of the entire brain and thecal sac. Critical areas are the cribriform plate and base of skull [25] and the thecal sac. If no spinal MRI is available, the spinal volume should extend down to the S2/S3 junction [31,33]. Laterally, the widths of the vertebrae, including inter-vertebral foraminae are included [31,33].

Standard beam arrangement uses two lateral head fields and a matching posterior spinal field. The lateral head fields have a small collimator rotation to match the divergent superior beam edge of the spinal field (Fig. 1). The lateral head fields are positioned to cover the whole head and to extend as inferiorly as possible whilst still clearing the shoulders. Face-shielding is accomplished with custom-made lead blocks if MLC (multi-leaf collimator) is not available.

The spinal fields, if not 3D planned, can be simulated with a small couch rotation, alternately clockwise and anti-clockwise, to match the beam divergence of the lateral head fields. The junction between head and spine fields should be shifted at least twice during CSI in order to minimise cold or hot spots caused by the junction/set-up error. This is achieved by extending the spinal field superiorly, and decreasing the head fields inferiorly by 0.5–1 cm with each shift.

The posterior fossa boost. The volume of the boost depends on the planning capability and available quality assurance of the centre. A conformal 3D planned boost to the tumour bed plus margin of 1–2 cm defined on CT [34] has become standard treatment in many centres, but this requires high quality portal imaging for accurate set up [35]. Intensity modulated radiotherapy (IMRT) and proton treatment may offer further limited advantages [36] but are seldom available in LMIC. Alternatively, the boost field will encompass the entire posterior fossa which is either 3D planned to spare the cochleas or defined using bony landmarks on a lateral skull X-ray (Fig. 1), and treated as 2 parallel opposed lateral fields. All CSI and boost fields should be summed and a total Gy plan produced.

Dose. The dose used for CSI depends on multiple factors including accurate stratification of patients into standard and high-risk groups (M1,2,3) requiring pre-operative spinal imaging and post-operative CSF cytology (Level 2 setting). If accurate staging is not possible then, the recommendation is to treat the patient as high-risk and consider full dose CSI.

In properly staged standard-risk medulloblastoma, it has been shown that reduced dose CSI, together with adjuvant chemotherapy can safely be used [37]. This approach is beneficial as reduced dose radiation minimises late neuro-cognitive side effects. However, if chemotherapy is unavailable, or the family is unwilling or unable to commit to this, then full dose CSI has shown better long-term efficacy regardless of risk stratification [38].

Full-dose CSI. A dose of 36 Gy given to the craniospinal axis in 20 fractions, delivered 5 times/week. This is followed by a posterior fossa boost of 19.8 Gy given in 11 fractions, 5 times/week. If 3D planning and adequate portal imaging is available, then the boost volume may be reduced as above.

Reduced-dose CSI. If adjuvant chemotherapy is given, then reduced radiation therapy is considered standard of care. A dose of 23.4 Gy is delivered to the craniospinal axis in 13 fractions, followed by a posterior fossa (or tumour bed) boost of 30.6 Gy delivered in 17 fractions [37].

Standard dosing and available data are based on 5 times/week scheduling of radiotherapy. However in some LMIC situations such a schedule is not possible due to logistic constraints. There is some unpublished experience from large LMIC centres with 4 times a week scheduling. This may be considered, provided that the fraction size is increased so that the treatment is delivered in the same overall time with a biologically equivalent dose. It is unclear whether this alternative schedule is associated with an increase in late effects (Table IV). If there is any doubt regarding scheduling, then local or regional radiotherapy experts should be consulted.

Quality assurance. Accurate delivery of radiotherapy is essential for optimal results and several studies have pointed out the negative influence of targeting deviations on outcome [39,40]. Correct positioning of the fields must be checked on a simulator or by portal imaging prior to starting treatment. The position of the axes as well as the face block relative to bony structures must be checked. Lens doses may be measured using lithium fluoride TLDs (thermo-luminesence dosimetry) placed on the lateral canthus of the eye at first or second treatment. This is no longer done in many HIC where cataract surgery is easily accessible but in LMIC, where intra-ocular lenses may be less available, it is desirable to keep the lens dose below 10 Gy if possible whilst adequately treating the cribriform plate.

Treatment checks. During CSI, weekly full blood counts are routinely performed. Treatment breaks should be avoided except for extreme cytopenias, that is, platelets $<50 \times 10^9$/L and white cell count $<2.0 \times 10^9$/L. While a haemoglobin of 10 g/dl is optimal for radiotherapy efficacy, blood transfusion comes with its own risks in LMIC and should be reserved for severe anaemia (below 8 g/dl).

Most patients require anti-emetics during CSI due to the side effects of radiation to the brain and the abdomen. Skin reactions around the pinna and neck are usually treated with moisturizing or hydrocortisone creams. However, zinc-containing creams as well as sun exposure should be avoided. During radiation, many patients suffer from anorexia and nausea with poor intake and consequent weight loss [41]. This can be exacerbated by daily sedation. In this context, weight monitoring is recommended. Based on available evidence, we would suggest the following approach to radiation therapy (Table VI).

Chemotherapy

The place of chemotherapy as adjuvant or neoadjuvant therapy is now well-established in treating children with medulloblastoma. The CCG 942 trial showed survival benefit for patients with metastatic and locally invasive tumours treated with a combination of lomustine, vincristine and prednisone following radiotherapy compared to radiation alone [42]. The SIOP I trial [43] randomised lomustine and vincristine following radiotherapy against radiotherapy alone. This trial initially showed a statistical difference between the arms although this was lost over time. Packer et al. reported a 5-year progression free survival (PFS) of 90% for patients with localised disease with a protocol consisting of weekly vincristine with radiotherapy, followed by a combination of eight 6 weekly cycles of cisplatin 75 mg/m^2, lomustine 75 mg/m^2 and vincristine

TABLE VI. Approach to Treatment, Radiotherapy

- Patients with incomplete staging should receive full dose CSI (36 Gy + Boost).
- Patients unable to attend for adjuvant chemo should receive the full dose CSI protocol.
- CSI should commence within 40 days of surgery. Patients delayed longer than 49 days after surgery, should receive at least one cycle of chemotherapy (but no more than two) and be treated with full dose CSI.
- 3D planning of the boost gives superior cochlea sparing.
- RT should be completed within 50 days.
- Baseline height, weight and endocrine function (as described in the text) should be obtained prior to RT.
- Weekly FBC is required to monitor for myelosuppression during RT.

Indications for CSI in PODC medulloblastoma	Reduced dose CSI –23.4 Gy - Age >3 years - Total macroscopic resection (residual $<1.5\,cm^2$ on post-op imaging) - Spinal MRI clear - CSF clear	Full dose CSI –36 Gy - Spinal lesions on imaging - CSF positive - Incomplete staging ○ No spinal MRI ○ No CSF cytology ○ Unknown extent of resection - Unable to attend for chemo
Dose of large volume (4–5 × 1.8 Gy/week)	23.4 Gy in 13 fractions	36.0 Gy in 20 fractions
Dose of Boost Fractions	30.6–32.4 Gy in 17–18 fractions	18–19.8 Gy in 10–11 fractions

$1.5\,mg/m^2 \times 3$ [44]. Other studies have shown that the radiation dose to the craniospinal axis can be decreased in patients with standard-risk disease from 36 Gy to 23.4 Gy [24] without compromising progression free survival, thus reducing the neurocognitive and endocrine late effects. The combination of eight cycles of cisplatin at the same total dose of $600\,mg/m^2$, cyclophosphamide $1\,g/m^2 \times 2$ in place of lomustine and vincristine $1.5\,mg/m^2 \times 3$ was shown to be equally effective [37]. This regimen has been successfully used in LMIC settings [16] where excellent survival was achieved for standard-risk patients.

A number of trials have looked at pre-radiation chemotherapy. The SIOP III study for M0/1 medulloblastoma [45] compared two cycles each of carboplatin $500\,mg/m^2 \times 2$ with etoposide $100\,mg/m^2 \times 3$ alternating with cyclophosphamide $1.5\,g/m^2$ with etoposide $100\,mg/m^2 \times 3$, followed by radiotherapy with weekly vincristine, to radiotherapy alone (36 Gy + Boost). EFS was superior for the chemotherapy arm (74% vs. 60%, $P = 0.03$) but this difference did not translate into improved overall survival. SFOP [46] utilised two cycles each of 8-in-1 chemotherapy (total cisplatin = $180\,mg/m^2$) and carboplatin with etoposide prior to radiotherapy, achieving an overall survival of 73.8% in standard-risk patients. The GPOH HIT-91 randomised an intensive upfront regimen followed by radiotherapy, against radiotherapy with weekly vincristine followed by 6 weekly vincristine, cisplatin and CCNU [47]. Pre-irradiation chemotherapy was associated with increased myelotoxicity resulting in subsequent radiotherapy interruptions and decreased EFS. There are other reports highlighting high rates of progression on chemotherapy [48] or difficulty completing craniospinal radiation following pre-radiation chemotherapy due to myelosuppression [49]. On the basis of this evidence, the consensus is to recommend radiation upfront. Although vincristine has been traditionally used during radiation, there is emerging evidence [9] that weekly administration during radiotherapy does not improve outcomes.

Cisplatin ototoxicity is significantly related to individual cycle dosage exceeding $100\,mg/m^2$ and total cumulative cisplatin dosage exceeding $300\,mg/m^2$ [50]. Ototoxicity was 15% (grade 2 or higher) in the SFOP trial [46] and was 25–30% for the cisplatin dose of $600\,mg/m^2$ on the Packer regimen [37]. A Canadian study[51] showed that 81% of patients with standard-risk medulloblastoma treated according to the Packer regimen required dose reduction due to ototoxicity and the median dose received was $412.5\,mg/m^2$ instead of a target dose of $600\,mg/m^2$. Much less ototoxicity is reported with carboplatin containing regimens and a number of studies have used carboplatin instead of cisplatin in an attempt to limit the added burden of deafness in children who already have neurocognitive, visual and/or motor problems [52–54]. However, there has been no study comparing these 2 options and the case for the use of carboplatin in children with average-risk medulloblastoma has yet to be made.

A number of other low intensity regimes have been used with varying success. A Taiwanese study using six cycles of cisplatin $20\,mg/m^2 \times 5$ and etoposide $40–60\,mg/m^2 \times 5$ reported an OS of 64.9% [18]. Two studies from Egypt [19,20] using six cycles of carboplatin at a dose of $500–600\,mg/m^2$/cycle, alternating with six cycles of cyclophosphamide $750\,mg/m^2$, all together with vincristine, both achieved an OS of 70%. The Association of Pediatric Hematology Oncology of Central America (AHOPCA) protocol [55] utilises three cycles of cisplatin at $90\,mg/m^2$ with etoposide $150\,mg/m^2 \times 2$ and three cycles of vincristine $2\,mg/m^2$ with cyclophosphamide $1\,g/m^2 \times 2$. Based on available evidence, we would suggest the chemotherapeutic approach to therapy as described in Table VII and Figure 2.

Supportive Care

The SIOP-PODC committee has produced separate recommendations for supportive care of children with cancer [56]. However, children with brain tumours have specific problems for which supportive care is essential.

Posterior fossa mutism. This post-operative complication is seen in approximately 20–25% of children with medulloblastoma

TABLE VII. Approach to Treatment, Chemotherapy

- No weekly vincristine should be given with radiotherapy—utility is uncertain and it adds a burden when children are being treated at radiotherapy facilities distant to their POUs.
- No lomustine is recommended—access to this drug is limited in many LMIC.
- We recommend hybrid platinum regimens to limit ototoxicity. A carboplatin-only regimen should be used if hearing cannot be monitored or in the event of significant ototoxicity.
- Chemotherapy should be given approximately 28 days post radiotherapy.
- All cycles are delivered every 21 days.
- Each cycle requires [1] Absolute Neutrophil Count (ANC) $>1 \times 10^9$/L and [2] Platelets $>100 \times 10^9$/L.
- Electrolytes and especially magnesium should be monitored as supplementation may be required even after therapy is stopped.

[1] Regimen 1 [alternating cycles to a total of 6]
[2] Regimen 2 [alternating cycles to a total of 8]
[3] Cisplatin-free regimen [alternating cycles to a total of 6 or 8] … *To be used in where hearing loss cannot be monitored, or where nephrotoxicity or ototoxicity precludes the use of further cisplatin*

Toxicity Guidelines

[1] Haematological Toxicity
- If ANC $<1 \times 10^9$/L or platelets $<100 \times 10^9$/L at day 21 then delay chemotherapy by 1 week and reduce the dose of cyclophosphamide, etoposide and carboplatin by 25% for all subsequent courses.
- If the patient requires admission for neutropaenic fever or the platelets fall below 30 at nadir then reduce the dose of cyclophosphamide, etoposide and carboplatin by 25% for all subsequent courses.

[2] Nephrotoxicity
- Check GFR (isotope clearance or modified Schwartz formula (eGFR = k × Height (cm)/serum creatinine (mg/dl). k = 0.413) prior to chemotherapy and before the third course of cisplatin.
- Creatinine clearance <80 ml/min/1.73 m^2: substitute carboplatin andrepeat the GFR prior to the next course of cisplatin.
- Creatinine clearance <60 ml/min/1.73 m^2: substitute carboplatin for all subsequent courses.

[3] Ototoxicity
- Arrange audiogram prior to chemotherapy and before the third course of cisplatin.
- Hearing loss of >40 db in the range of 4–8 kHz: substitute carboplatin.
- Hearing loss >40 db in the range of 1–3 kHz: omit all platinum-based chemotherapy.

[4] Neurotoxicity
- Unexplained seizures or neuropathy: omit next dose of vincristine and then restart at 1 mg/m^2.

Drug Administration and Fluid Regimens

Carboplatin given as an intravenous infusion in 50 ml 5% dextrose water over 1 hr.

Cisplatin given as an intravenous infusion in 0.9% saline up to 120 ml over 24 hr
- Prehydration for 2 hr at 200 ml/m^2/hr with 0.45% saline 1 L + 15% potassium chloride 10 ml (20 mmol) + 10% calcium gluconate 5 ml (1.1 mmol) + 50% magnesium sulphate 2 ml (4 mmol).
- Hydration during cisplatin at 125 ml/m^2/hr with 0.45% saline 1 l+ 25% mannitol 50 ml + 15% Potassium chloride 10 ml (20 mmol) + 10% calcium gluconate 5 ml (1.1 mmol) + 50% magnesium sulphate 2 ml (4 mmol.
- Posthydration for 24 hr after cisplatin at 125 ml/m^2/hr with 0.45% saline 1 L + 25% mannitol 50 ml + 15% Potassium chloride 10 ml (20 mmol) + 10% calcium gluconate 5 ml (1.1 mmol) + 50% magnesium sulphate 2 ml (4 mmol).

Ensure a diuresis of 3 ml/kg/hr for children under 30 kg or 500 ml/m^2 every 6 hr for children over 30 kg. Administer mannitol 0.5 g/kg over 15–30 min intravenously 6 hourly if the urine target is not met.

Cyclophosphamide given as an intravenous infusion in 0.9% saline 200 ml over 1 hr
- Posthydration for 24 hr at 2 L/m^2/day with 0.45% saline 1 L + 15% potassium chloride 10 ml (20 mmol). Check urine for haematuria prior to discharge and continue hydration if present.

Etoposide given as an intravenous infusion in 0.9% saline 200ml–500 ml (maximum concentration 0.4 mg/ml) over 2 hr.

Vincristine given as an intravenous bolus injection.
Please see supplement appendix for details of dose modifications.

[36,57] and includes loss of expressive speech, pseudobulbar palsy, gait apraxia and severe irritability. Most patients will show progressive recovery over time, although postoperative mutism is associated with an increased risk for neurocognitive impairment [36,57]. Radiotherapy should not be delayed as many children, even with profound disability, will improve and delaying radiotherapy may adversely affect outcome [25,30].

Headaches. Mild headaches may be related to surgery, radiotherapy or anaemia but severe headaches, especially when accompanied by vomiting, may be a symptom of raised intracranial pressure and require investigation, particularly if the child has a shunt [23].

Feeding difficulties. Post-operative swallowing problems are not uncommon, particularly in the context of posterior fossa

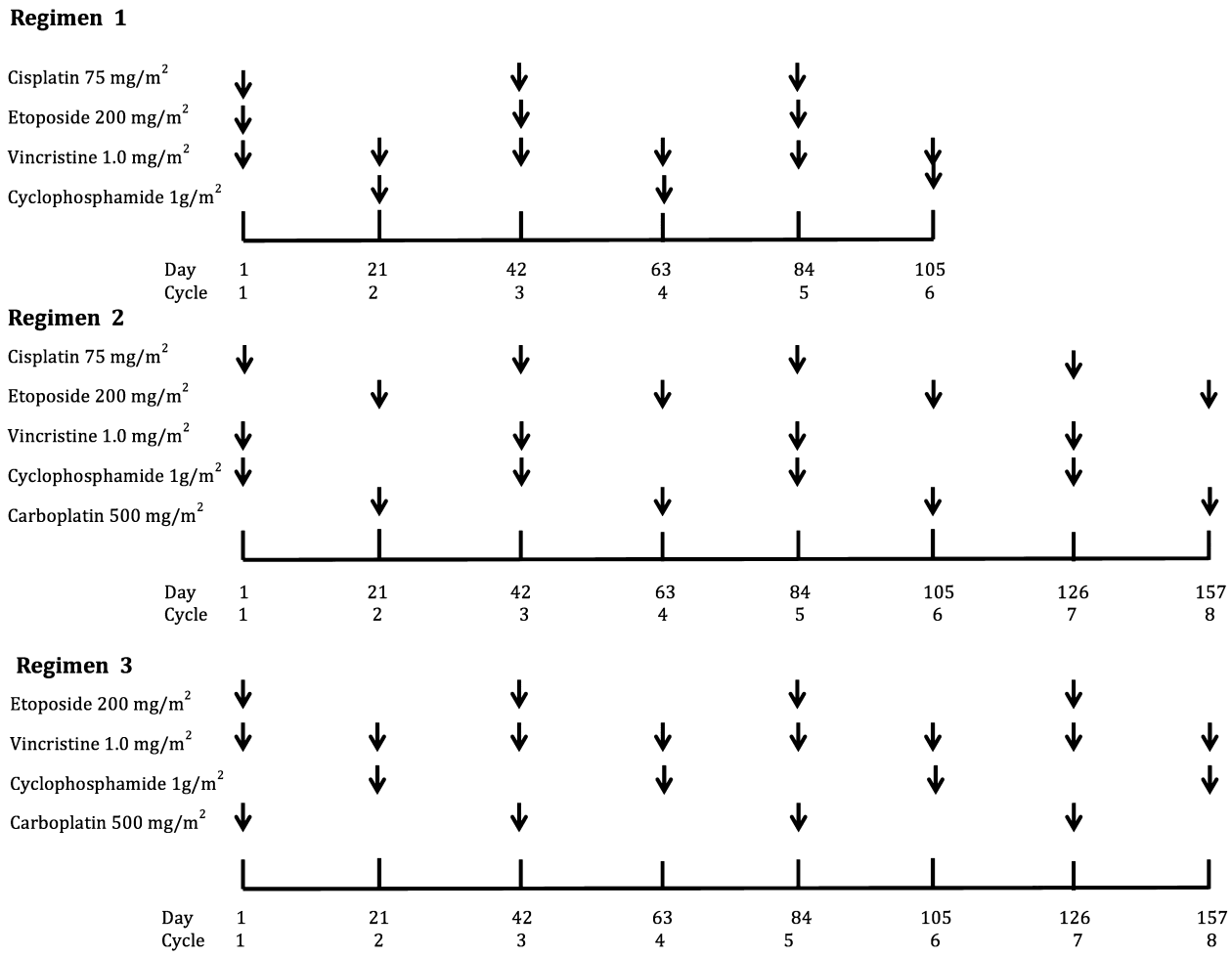

Fig. 2. Approach to treatment, chemotherapy flow diagram.

mutism. Swallowing issues and vomiting may necessitate nasogastric tube feeding. This can be converted to percutaneous gastrostomy if the problem persists, although care needs to be taken with the latter if there is a ventriculo-peritoneal shunt in place [58]. Multimodal treatment often results in significant nutritional morbidity, primarily due to the use of intensive chemotherapy regimens. Nutritional follow-up is essential, and the implementation of enteral feeding in these children can help to improve or reverse their nutritional morbidity.

Mobility problems. Rehabilitation is a critical part of the care of patients with medulloblastoma. Weakness and ataxia require physiotherapy and occupational therapy including in some patients specialised equipment for seating and walking. Speech may be affected especially with posterior fossa syndrome [57]. Many deficits may improve with time, but approximately 50% of children will have long-term problems [59].

Seizures. It is unusual for children with medulloblastoma to develop seizures. These should be treated as per local protocols using available anticonvulsants.

Palliative care. Detailed palliative care recommendations are beyond the scope of this guideline but literature is available [60,61] including a handbook from the International Network of Cancer Treatment and Research (INCTR) (www.inctr-palliative-care-handbook.wikidot.com/).

Late Effects

Late effects and the services required to deal with them should be a factor in treatment decision-making. Late effects can be divided into several categories and may be the result of the disease or its treatment [62,63]. Pro-active surveillance for these late-effects allows early intervention and better quality of life for patients and their families (Table VIII).

Late effects are best managed in a multi-disciplinary setting where access to pediatric endocrine expertise is present. However, in many LMIC this is not possible. Table VIII lists the most common late effects and suggested management. It is always advisable to seek expertise locally, but if not available, one alternative is teleconferencing with a twinning institution abroad.

Disease Specific Follow-up

Because salvage rates are so poor for patients with recurrent medulloblastoma, routine surveillance scans are not deemed essential for follow-up in the context of LMIC. Ideally baseline

TABLE VIII. Late Effects Related to Management of Medulloblastomas

Toxicity	Investigation	Suggested management
Endocrine	Ideally all endocrine disorders should be managed by a paediatric endocrinologist or paediatrician with experience in endocrine disorders of childhood.	
Hypothyroidism [64] Primary (65%) Secondary (23%)	Serum Free T4/TSH	Starting dose 50 μg/m^2. Round off to nearest 12.5 μg. Dose needs to be adjusted according to serum levels.
Growth hormone insufficiency (52–100% of patients) [64]	Growth chart showing crossing of growth centiles, IGF-1 and stimulation testing if possible	Synthetic growth hormone if available. The dose needs to be managed by a paediatric endocrinologist.
Hypoadrenalism (Adrenocorticoid insufficiency) (4–38% of patients) [64]	Early morning (pre-9.30 am) Cortisol Synacthen testing if possible	Hydrocortisone replacement (7–8 mg/m^2/day in three divided doses) Triple if unwell, prednisolone at a quarter of dose can be used if hydrocortisone not available.
Delayed puberty (4–20% of patients) [64]	Clinical examination, serum LH/FSH, testosterone or oestradiol	Should only be managed in discussion with a paediatric endocrinologist
Infertility (depending on total dose of alkylating agent used	Clinical examination, serum LH/FSH, testosterone or oestradiol, sperm testing when required or more specialised testing	Should be managed by endocrinologist or fertility expert.
Neurocognitive dysfunction (memory, concentration and processing speed are usually the predominant features) [65]	Neuropyschometric assessment if available	This is greatest in children treated at <8 years and in children receiving higher dose CSI. Support at school is often required. Specialised schooling is necessary in severe cases.
Hearing loss	Auditory assessment	Sensorineural hearing loss is permanent. Certain patients may benefit from hearing aids
Diplopia	Clinical examination	If persistent, this can be improved with prisms/strabismus surgery
Cataracts	Clinical examination	Cataract surgery
Neurological sequelae including ataxia	Clinical examination	Physio and occupational therapy to advise on management
Secondary tumours	Picked up on routine follow up scans or suspicion on clinical examination.	As per tumour type
Vascular problems, e.g., Arteritis, Moya-moya disease [66]	This usually manifests as a CVA (cerebro-vascular accident). Angiography (either magnetic resonance, CT or formal angiography) is advised.	Management is based on the cause.

imaging of brain and spine if possible should be considered 3 months after the completion of radiotherapy. Recommended clinical follow-up should be planned 3 monthly for the first year, 6 monthly for the next 2 years, and then annually thereafter.

High-Risk and Relapsed Disease

The management of patients with metastatic disease at diagnosis is more complex, requiring intensive treatment with higher doses of radiotherapy and chemotherapy. This will be treated separately. Children with medulloblastoma who relapse after standard treatment have a very poor prognosis. Palliative treatment with oral temozolomide or etoposide may result in a transient response which also allows improved quality of life.

ACKNOWLEDGMENTS

We would like to thank the numerous clinicians who treat children with medulloblastoma and who contributed to this guideline. We would also like to thank Raisa Ioffe at Cure 4 Kids who organised the on-line meetings. Wendy Smith and Sadiq Keraan from the Institute of Child Health Library, Red Cross War Memorial Children's Hospital, Cape Town, South Africa provided invaluable library support in enabling this guideline to be written.

REFERENCES

1. Nasir S, Jamila B, Khaleeq S. A retrospective study of primary brain tumors in children under 14 years of age at PIMS. Islamabad Asian Pac J Cancer Prev 2010;11:1225–1227.
2. Asirvatham JR, Deepti AN, Chyne R, Prasad MS, Chacko AG, Rajshekhar V, Chacko G. Pediatric tumors of the central nervous system: A retrospective study of 1,043 cases from a tertiary care center in South India. Childs Nerv Syst 2011;27:1257–1263.
3. El-Gaidi MA. Descriptive epidemiology of pediatric intracranial neoplasms in Egypt. Pediatr Neurosurg 2011;47:385–395.
4. Katchy KC, Mallik AA, Al-Nashmi NM, Joseph E, Alexander S, Al-Ramadan A. Intracranial tumors in Kuwait: A 15-year survey. J Neurooncol 2011;104:271–277.
5. Harmouch A, Taleb M, Lasseini A, Maher M, Sefiani S. Epidemiology of pediatric primary tumors of the nervous system: A retrospective study of 633 cases from a single Moroccan institution. Neurochirurgie 2012;58:14–18.
6. Karkouri M, Zafad S, Khattab M, Benjaafar N, El Kacemi H, Sefiani S, Kettani F, Dey S, Soliman AS. Epidemiologic profile of pediatric brain tumors in Morocco. Childs Nerv Syst 2010;26:1021–1027.
7. Ahmed N, Bhurgri Y, Sadiq S, Shakoor KA. Pediatric brain tumours at a tertiary care hospital in Karachi. Asian Pac J Cancer Prev 2007;8:399–404.

8. Harisiadis L, Chang CH. Medulloblastoma in children: A correlation between staging and results of treatment. Int J Radiat Oncol Biol Phys 1977;2:833–841.
9. Gajjar A, Chintagumpala M, Ashley D, Kellie S, Kun LE, Merchant TE, Woo S, Wheeler G, Ahern V, Krasin MJ, Fouladi M, Broniscer A, Krance R, Hale GA, Stewart CF, Dauser R, Sanford RA, Fuller C, Lau C, Boyett JM, Wallace D, Gilbertson RJ. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): Long-term results from a prospective, multicentre trial. Lancet Oncol 2006;7: 813–820.
10. Baskin JL, Lezcano E, Kim BS, Figueredo D, Lassaletta A, Perez-Martinez A, Madero L, Caniza MA, Howard SC, Samudio A, Finlay JL. Management of children with brain tumors in Paraguay. Neuro Oncol 2013;15:235–241.
11. Kruger M, Hendricks M, Davidson A, Stefan CD, van Eyssen AL, Uys R, van Zyl A, Hesseling P. Childhood cancer in Africa. Pediatr Blood Cancer 2014;61:587–592.
12. Levin CV, El Gueddari B, Meghzifene A. Radiation therapy in Africa: Distribution and equipment. Radiother Oncol 1999;52:79–84.
13. Parkes J. Developing paediatric radiotherapy services in Africa. SIOP Africa 2012;9–10.
14. Awasthy BS, Das Gupta C, Singh R, Patel AK, Julka PK. Medulloblastoma–a retrospective analysis. Indian J Pediatr 1997;64:693–697.
15. Khalil EM. Treatment results of adults and children with medulloblastoma NCI, Cairo University experience. J Egypt Natl Canc Inst 2008;20:175–186.
16. Qaddoumi I, Musharbash A, Elayyan M, Mansour A, Al-Hussaini M, Drake J, Swaidan M, Bartels U, Bouffet E. Closing the survival gap: Implementation of medulloblastoma protocols in a low-income country through a twinning program. Int J Cancer 2008;122:1203–1206.
17. Mehrvar A, Faranoush M, Hedayati Asl AA, Tashvighi M, Fazeli MA, Qaddoumi I, Mehrvar N, Sobuti B, Jafarpour A, Ravan Parsa R, Zangooei R, Alebouyeh M, Vossough P. Childhood central nervous system tumors at MAHAK's Pediatric Cancer Treatment and Research Center (MPCTRC), Tehran, Iran. Childs Nerv Syst 2014;30:491–496.
18. Akyuz C, Varan A, Kupeli S, Akalan N, Soylemezoglu F, Zorlu F, Kutluk T, Buyukpamukcu M. Medulloblastoma in children: A 32-year experience from a single institution. J Neurooncol 2008;90: 99–103.
19. Nasr A, Al-Ghamdy H. The prognostic impact of additional chemotherapy to radiation therapy for postoperative management of pediatric medulloblastoma. J Egypt Natl Canc Inst 2004;16:195–201.
20. Salama MM, Ghorab EM, Al-Abyad AG, Al-Bahy KM. Concomitant weekly vincristine and radiation followed by adjuvant vincristine and carboplatin in the treatment of high risk medulloblastoma: Ain Shams University Hospital and Sohag Cancer Center study. J Egypt Natl Canc Inst 2006;18:167–174.
21. Howard SC, Metzger ML, Wilimas JA, Quintana Y, Pui CH, Robison LL, Ribeiro RC. Childhood cancer epidemiology in low-income countries. Cancer 2008;112:461–472.
22. Tortori-Donati P, Danieli D, Meli S, Fondelli MP, Rossi A, Curri D, Garre ML, Gullotta F. Langerhans cell histiocytosis presenting as a lumbosacral intradural-extramedullary mass. Pediatr Radiol 1996;26: 731–733.
23. Bailey S. Oxford Handbook of Paeditric Haematology and Oncology. Oxford: Oxford Medical Publication 2010;510.
24. Packer RJ, Goldwein J, Nicholson HS, Vezina LG, Allen JC, Ris MD, Muraszko K, Rorke LB, Wara WM, Cohen BH, Boyett JM. Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: A Children's Cancer Group Study. J Clin Oncol 1999; 17:2127–2136.
25. Lannering B, Rutkowski S, Doz F, Pizer B, Gustafsson G, Navajas A, Massimino M, Reddingius R, Benesch M, Carrie C, Taylor R, Gandola L, Bjork-Eriksson T, Giralt J, Oldenburger F, Pietsch T, Figarella-Branger D, Robson K, Forni M, Clifford SC, Warmuth-Metz M, von Hoff K, Faldum A, Mosseri V, Kortmann R. Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: Results from the randomized multicenter HIT-SIOP PNET 4 trial. J Clin Oncol 2012;30:3187–3193.
26. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AH, Dellinger EP, Herbosa T, Joseph S, Kibatala PL, Lapitan MC, Merry AF, Moorthy K, Reznick RK, Taylor B, Gawande AA. A surgical safety checklist to reduce morbidity and mortality in a global population. N Engl J Med 2009;360:491–499.
27. Ellison DW, Dalton J, Kocak M, Nicholson SL, Fraga C, Neale G, Kenney AM, Brat DJ, Perry A, Yong WH, Taylor RE, Bailey S, Clifford SC, Gilbertson Medulloblastoma: RJ. Clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. Acta Neuropathol 2011;121:381–396.
28. Bloom HJ, Wallace EN, Henk JM. The treatment and prognosis of medulloblastoma in children. A study of 82 verified cases. Am J Roentgenol Radium Ther Nucl Med 1969;105:43–62.
29. Dobbs HJ, Parker RP, Hodson NJ, Hobday P, Husband JE. The use of CT in radiotherapy treatment planning. Radiother Oncol 1983;1:133–141.
30. Taylor RE, Bailey CC, Robinson KJ, Weston CL, Ellison D, Ironside J, Lucraft H, Gilbertson R, Tait DM, Saran F, Walker DA, Pizer BL, Lashford LS. Impact of radiotherapy parameters on outcome in the International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 study of preradiotherapy chemotherapy for M0-M1 medulloblastoma. Int J Radiat Oncol Biol Phys 2004;58:1184–1193.
31. Breen SL, Kehagioglou P, Usher C, Plowman PN. A comparison of conventional, conformal and intensity-modulated coplanar radiotherapy plans for posterior fossa treatment. Br J Radiol 2004;77: 768–774.
32. del Charco JO, Bolek TW, McCollough WM, Maria BL, Kedar A, Braylan RC, Mickle JP, Buatti JM, Mendenhall NP, Marcus RBJ. Medulloblastoma: Time-dose relationship based on a 30-year review. Int J Radiat Oncol Biol Phys 1998;42:147–154.
33. Parker WA, Freeman CR. A simple technique for craniospinal radiotherapy in the supine position. Radiother Oncol 2006;78:217–222.
34. Merchant TE, Happersett L, Finlay JL, Leibel SA. Preliminary results of conformal radiation therapy for medulloblastoma. Neuro Oncol 1999;1:177–187.
35. Carrie C, Hoffstetter S, Gomez F, Moncho V, Doz F, Alapetite C, Murraciole X, Maire JP, Benhassel M, Chapet S, Quetin P, Kolodie H, Lagrange JL, Cuillere JC, Habrand JL. Impact of targeting deviations on outcome in medulloblastoma: Study of the French Society of Pediatric Oncology (SFOP). Int J Radiat Oncol Biol Phys 1999;45:435–439.
36. De Braganca KC, Packer RJ. Treatment Options for Medulloblastoma and CNS Primitive Neuroectodermal Tumor (PNET). Curr Treat Options Neurol 2013;15:593–606.
37. Packer RJ, Gajjar A, Vezina G, Rorke-Adams L, Burger PC, Robertson PL, Bayer L, LaFond D, Donahue BR, Marymont MH, Muraszko K, Langston J, Sposto R. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 2006;24:4202–4208.
38. Thomas PR, Deutsch M, Kepner JL, Boyett JM, Krischer J, Aronin P, Albright L, Allen JC, Packer RJ, Linggood R, Mulhern R, Stehbens JA, Langston J, Stanley P, Duffner P, Rorke L, Cherlow J, Friedman HS, Finlay JL, Vietti TJ, Kun LE. Low-stage medulloblastoma: Final analysis of trial comparing standard-dose with reduced-dose neuraxis irradiation. J Clin Oncol 2000;18:3004–3011.
39. Miralbell R, Bleher A, Huguenin P, Ries G, Kann R, Mirimanoff RO, Notter M, Nouet P, Bieri S, Thum P, Toussi H. Pediatric medulloblastoma: Radiation treatment technique and patterns of failure. Int J Radiat Oncol Biol Phys 1997;37:523–529.
40. Carrie C, Muracciole X, Gomez F, Habrand JL, Benhassel M, Mege M, Mahe M, Quetin P, Maire JP, Soum F, Baron MH, Clavere P, Chapet S, Gaci Z, Kolodie H, Maingon P, Vie B, Bernier V, Alapetite C, Hoffstetter S, Grill J, Lafay F. Conformal radiotherapy, reduced boost volume, hyperfractionated radiotherapy, and online quality control in standard-risk medulloblastoma without chemotherapy: Results of the French M-SFOP 98 protocol. Int J Radiat Oncol Biol Phys 2005;63:711–716.
41. Bakish J, Hargrave D, Tariq N, Laperriere N, Rutka JT, Bouffet E. Evaluation of dietetic intervention in children with medulloblastoma or supratentorial primitive neuroectodermal tumors. Cancer 2003;98: 1014–1020.
42. Evans AE, Jenkin RD, Sposto R, Ortega JA, Wilson CB, Wara W, Ertel IJ, Kramer S, Chang CH, Leikin SL, Denman Hammond G. The treatment of medulloblastoma. Results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine, and prednisone. J Neurosurg 1990;72:572–582.
43. Tait DM, Thornton-Jones H, Bloom HJ, Lemerle J, Morris-Jones P. Adjuvant chemotherapy for medulloblastoma: The first multi-centre control trial of the International Society of Paediatric Oncology (SIOP I). Eur J Cancer 1990;26:464–469.
44. Packer RJ, Sutton LN, Elterman R, Lange B, Goldwein J, Nicholson HS, Mulne L, Boyett J, D'Angio G, Wechsler-Jentzsch K, Reaman G, Cohen BH, Bruce DA, Rorke LB, Molloy P, Ryan J, LaFond D, Evans AE, Schut L. Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy. J Neurosurg 1994;81:690–698.
45. Taylor RE, Bailey CC, Robinson K, Weston CL, Ellison D, Ironside J, Lucraft H, Gilbertson R, Tait DM, Walker DA, Pizer BL, Imeson J, Lashford LS. Results of a randomized study of preradiation chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: The International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study. J Clin Oncol 2003;21:1581–1591.
46. Oyharcabal-Bourden V, Kalifa C, Gentet JC, Frappaz D, Edan C, Chastagner P, Sariban E, Pagnier A, Babin A, Pichon F, Neuenschwander S, Vinchon M, Bours D, Mosseri V, Le Gales C, Ruchoux M, Carrie C, Doz F. Standard-risk medulloblastoma treated by adjuvant chemotherapy followed by reduced-dose craniospinal radiation therapy: A French Society of Pediatric Oncology Study. J Clin Oncol 2005;23:4726–4734.
47. Kortmann RD, Kuhl J, Timmermann B, Mittler U, Urban C, Budach V, Richter E, Willich N, Flentje M, Berthold F, Slavc I, Wolff J, Meisner C, Wiestler O, Sorensen N, Warmuth-Metz M, Bamberg M. Postoperative neoadjuvant chemotherapy before radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the treatment of medulloblastoma in childhood: Results of the German prospective randomized trial HIT '91. Int J Radiat Oncol Biol Phys 2000;46:269–279.
48. Hartsell WF, Gajjar A, Heideman RL, Langston JA, Sanford RA, Walter A, Jones D, Chen G, Kun LE. Patterns of failure in children with medulloblastoma: Effects of preirradiation chemotherapy. Int J Radiat Oncol Biol Phys 1997;39:15–24.
49. Mosijczuk AD, Nigro MA, Thomas PR, Burger PC, Krischer JP, Morantz RA, Kurdunowicz B, Mulne AF, Towbin RB, Freeman AI, Nigro ED, Friedman HS, Kun LE. Preradiation chemotherapy in advanced medulloblastoma. A Pediatric Oncology Group pilot study. Cancer 1993;72:2755–2762.
50. Li Y, Womer RB, Silber JH. Predicting cisplatin ototoxicity in children: The influence of age and the cumulative dose. Eur J Cancer 2004;40:2445–2451.
51. Lafay-Cousin L, Purdy E, Huang A, Cushing SL, Papaioannou V, Nettel-Aguirre A, Bouffet E. Early cisplatin induced ototoxicity profile may predict the need for hearing support in children with medulloblastoma. Pediatr Blood Cancer 2013;60:287–292.
52. Sirachainan N, Nuchprayoon I, Thanarattanakorn P, Pakakasama S, Lusawat A, Visudibhan A, Dhanachai M, Larbcharoensub N, Amornfa J, Shotelersuk K, Katanyuwong K, Tangkaratt S, Hongeng S. Outcome of medulloblastoma in children treated with reduced-dose radiation therapy plus adjuvant chemotherapy. J Clin Neurosci 2011;18:515–519.
53. Heideman RL, Kovnar EH, Kellie SJ, Douglass EC, Gajjar AJ, Walter AW, Langston JA, Jenkins JJ, Li Y, Greenwald C, Sanford RE, Kun LE. Preirradiation chemotherapy with carboplatin and etoposide in newly diagnosed embryonal pediatric CNS tumors. J Clin Oncol 1995;13:2247–2254.
54. Lopez-Aguilar E, Sepulveda-Vildosola AC, Rivera-Marquez H, Cerecedo-Diaz F, Santacruz-Castillo E, Valdez-Sanchez M, Arias-Gomez J, Quintana-Roldan G. Survival of patients with medulloblastoma treated with carboplatin and etoposide before and after radiotherapy. Arch Med Res 1998;29:313–317.
55. Arambu IC, Carrasco LF. AHOPCA Protocol for Standard-risk Meduloblastoma (modified from COGA9961 and POOG 9031).
56. Israels T, Renner L, Hendricks M, Hesseling P, Howard S, Molyneux E. SIOP PODC: Recommendations for supportive care of children with cancer in a low-income setting. Pediatr Blood Cancer 2013;60: 899–904.
57. Gudrunardottir T, Sehested A, Juhler M, Schmiegelow K. Cerebellar mutism: Review of the literature. Childs Nerv Syst 2011;27:355–363.
58. Gassas A, Kennedy J, Green G, Connolly B, Cohen J, Dag-Ellams U, Kulkarni A, Bouffet E. Risk of ventriculoperitoneal shunt infections due to gastrostomy feeding tube insertion in pediatric patients with brain tumors. Pediatr Neurosurg 2006;42:95–99.
59. Robertson PL, Muraszko KM, Holmes EJ, Sposto R, Packer RJ, Gajjar A, Dias MS, Allen JC. Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: A prospective study by the Children's Oncology Group. J Neurosurg 2006;105:444–451.
60. Baker JN, Hinds PS, Spunt SL, Barfield RC, Allen C, Powell BC, Anderson LH, Kane JR. Integration of palliative care practices into the ongoing care of children with cancer: Individualized care planning and coordination. Pediatr Clin North Am 2008;55:223–250, xii.
61. van de Wetering MD, Schouten-van Meeteren NY. Supportive care for children with cancer. Semin Oncol 2011;38:374–379.
62. Benesch M, Spiegl K, Winter A, Passini A, Lackner H, Moser A, Sovinz P, Schwinger W, Urban C. A scoring system to quantify late effects in children after treatment for medulloblastoma/ependymoma and its correlation with quality of life and neurocognitive functioning. Childs Nerv Syst 2009;25:173–181.
63. Frange P, Alapetite C, Gaboriaud G, Bours D, Zucker JM, Zerah M, Brisse H, Chevignard M, Mosseri V, Bouffet E, Doz F. From childhood to adulthood: long-term outcome of medulloblastoma patients. The Institut Curie experience (1980–2000). J Neurooncol 2009;95:271–279.
64. Laughton SJ, Merchant TE, Sklar CA, Kun LE, Fouladi M, Broniscer A, Morris EB, Sanders RP, Krasin MJ, Shelso J, Xiong Z, Wallace D, Gajjar A. Endocrine outcomes for children with embryonal brain tumours after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. J Clin Oncol 2008;26:1112–1118.
65. Palmer SL, Armstrong C, Onar-Thomas A, Wu S, Wallace D, Bonner MJ, Schreiber J, Swain M, Chapieski L, Knight S, Boyle R, Gajjar A. Processing speed, attention, and working memory after treatment for medulloblastoma: an international, prospective, and longitudinal study. J Clin Oncol 2013;31:3494–3500.
66. 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 tumours in children. Neurology 2007;68:932–938.