NARRATIVE REVIEW

# Consensus guidelines for the management of pediatric medulloblastoma in low- and middle-income countries

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## Abstract

The management of medulloblastoma, a pediatric brain tumor, has evolved significantly with the advent of genomic subgrouping, yet morbidity and mortality remain high in LMICs like Pakistan due to inadequate multidisciplinary care infrastructure. This paper aims to establish evidence-based guidelines tailored to the constraints of such countries. An expert panel comprising neuro-oncologists, neurosurgeons, radiologists, radiation oncologists, neuropathologists, and pediatricians collaborated to develop these guidelines, considering the specific challenges of pediatric brain tumor care in Pakistan. The recommendations cover various aspects of medulloblastoma treatment, including pre-surgical workup, neurosurgery, neuropathology, chemotherapy, radiation therapy, and supportive care. They offer both minimum required and additional optional protocols for more advanced centers, ensuring comprehensive patient management with attention to complications and complexities encountered in Pakistan. The paper's consensus guidelines strive for uniformity in healthcare delivery and address significant gaps in diagnosis, treatment, and follow-up of pediatric medulloblastoma patients.

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## Introduction

After acute leukemia, brain tumors are the most common malignancy in the pediatric population. The improvement of outcome s in acute lymphoblastic leukemia (ALL) patients in LMICs reflects the vast benefit achieved through relative affordable and easily accessible diagnostic and management protocols. However, the management of brain tumors requires a complex multidisciplinary and multifaceted approach, with the inclusion of neuroradiologists, pediatric neurosurgeons, neuropathologists, radiation oncologists and pediatric neuro-oncologists. The machinery required for diagnosis (magnetic resonance imaging (MRI), and histological, molecular and genetic techniques) and management (operating rooms (OR), radiation therapy facilities) are a limiting factor in countries with constrained resources. In Pakistan, there are only a few centers capable of properly treating pediatric brain tumors.

Medulloblastoma is the most common pediatric malignant brain tumor and is a significant cause of mortality and morbidity in this age-group, particularly in low- and middle-income countries (LMICs). To date, this disease has been stratified according to clinical and histological subtypes (classic, nodular/desmoplastic and anaplastic/large cell). With the advent of molecular subtyping and signatures identified for specific brain tumors, medulloblastoma can be sub-grouped through gene expression profiling, micro RNA profiling and methylation assay into 4 distinct groups: Wingless (WNT), Sonic hedgehog (SHH), Group 3, and Group 4. This new molecular classification has profound therapeutic and prognostic implications. Outcomes for medulloblastoma have significantly improved within high-income countries (HICs) due to the implementation of evidence-based guidelines and the availability of diagnostic and therapeutic infrastructure.[1, 2]

In light of these circumstances, it is necessary for updated guidelines to be developed and implemented within LMICs such as Pakistan that allow for the differences in infrastructure and gaps in healthcare facilities, while still aiming to improve morbidity and mortality of medulloblastoma cases. The intention of this paper is to provide 'minimum acceptable' guidelines for management as well as recommendations for 'preferable but optional' modalities. There is also a greater need for collaboration within multidisciplinary teams to improve patient care. The goal is to ultimately cover these lapses in care of patients with the necessary specialists in each respective field, and for practical implementation of these guidelines across the spectrum of healthcare facilities.

## Methodology

The literature search of the high-quality data on pediatric medulloblastoma was done in March 2023, on different databases including PubMed, Google Scholar, Scopus, and Embase. The most relevant and high-quality studies were analyzed to develop the evidence-based recommendations. An expert panel was convened consisting of specialists and leading experts within the field of neuro-oncology to identify the gaps in the diagnosis and management of pediatric medulloblastoma within Pakistan. This group was tasked with identifying best-practice recommendations and their application within Pakistan as an LMIC. Recommendations were collated, reviewed and debated regarding utility and evidence-based practices, in a process that has been previously detailed.[3]

## Initial evaluation

**Clinical presentation:** Pediatric patients with medulloblastoma more commonly present with obstructive hydrocephalus and raised intracranial pressure than symptoms due to local mass effect of posterior fossa lesion. Anatomically, medulloblastoma may present acutely with posterior fossa symptoms of headache, nausea, vomiting, and gait abnormalities. Clinicians should be on the lookout for warning signs of obstructive hydrocephalus causing raised intracranial pressure; visual blurring, severe intractable vomiting, and drowsiness are common giveaways. Focal neurological deficits may include rare cranial neuropathy (cranial nerve VI), or lower limb weakness secondary to spinal metastasis. The next step would be for clinicians in the clinic or ER to refer patients for neuro-imaging. Characteristic MR imaging features are shown in Figure 1.

**Neuroradiology:** Diagnosis would be predicated on

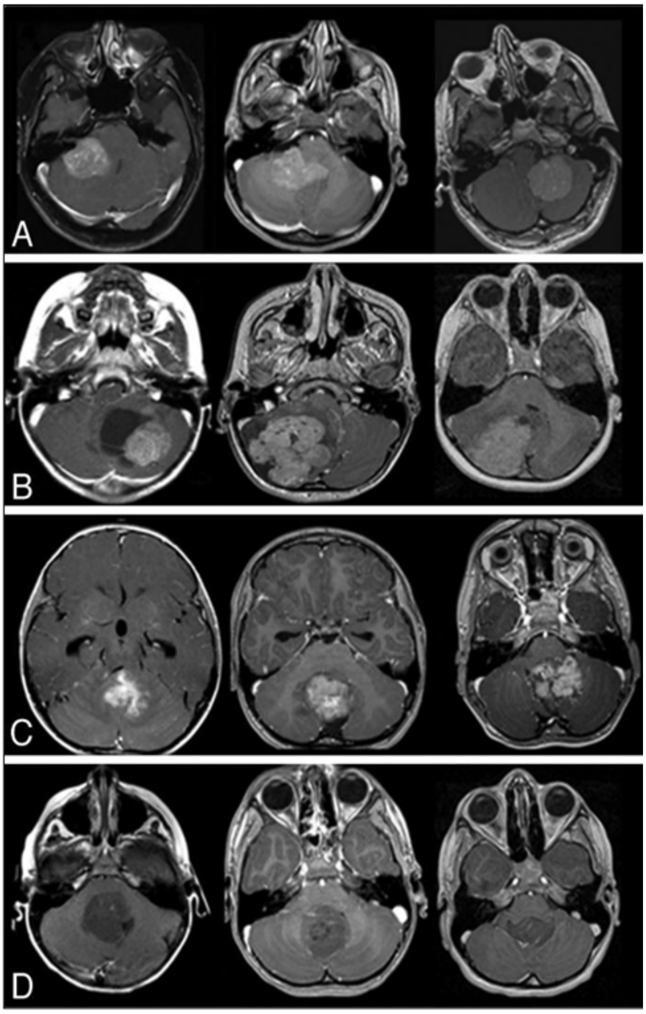


**Figure-1:** Characteristic MR imaging features according to medulloblastoma molecular subgroups. In the top row, characteristic location of WNT tumors in the CP/CPA region is shown. In the second row, SHH tumors are predominantly located in the cerebellar hemispheres. In the third row, group 3 tumors are located in the midline/ fourth ventricle and show enhancement and ill-defined features against the adjacent brain parenchyma. In the fourth row, group 4 tumors are also located in the midline fourth ventricle but tend to show minimal or no enhancement.[11]

MRI scans, preferably MRI brain as well as whole spine to rule out spinal dissemination. These studies should be done on all patients with contrast, with symptoms highly-suspicious for medulloblastoma, or prior imaging that would suggest so. Often, patients will have rudimentary imaging studies done and then referred towards high-volume centers for surgical management. Therefore, the center responsible for the surgery should obtain and review all prior imaging and ensure a full MRI brain and spine study is done. Ideally, assessment for preoperative patients should include scans within 5 days prior to surgery. Given below are our recommendations for minimum required protocols and preferable protocols

**Table-1:** Radiology reporting guidelines for medulloblastoma[11]

| | |
|---|---|
| Tumor Location | Midline vermian/fourth ventricle, cerebellar hemisphere, or cerebellar peduncle/cerebellopontine angle cistern (CP/CPA). |
| Tumor Margin | Ill-defined if >50% of the margin could not be distinguished from the surrounding cerebellar parenchyma on the basis of all imaging sequences. |
| Enhancement Pattern | Minimal/none if <10% was estimated to enhance.Solid if >90% of the tumor volume was estimated to enhance. Heterogeneous if varying degrees of enhancement were seen in 10%–90% of the tumor volume on the basis of radiologist's visual assessments. |
| Tumor Size | Should be given in three dimensions and try best to give volume. Formula for tumor volume is: Tumor volume= length x width2/2, where length represents the largest tumor diameter and width represents the perpendicular tumor diameter.Measurements should be taken on post contrast or T2W/FLAIR. |
| Hemorrhage/ Mineralization | Low signal on 2D gradient recalled-echo or bright on T1W should be used to detect. |
| Other Key Findings | Cysts/Cavities, Intracranial/leptomeningeal seeding, signs of necrosis as suggested by ring enhancement. |

that may be possible at larger centers. However, minimum requirements for neuro-imaging should be met to optimize surgical planning and further management afterwards:

**Minimum required MRI protocol:** All patients should undergo brain MR imaging of at least at 0.5T. Mandatory sequences: Axial T2 and Coronal or axial FLAIR sequence. Pre-contrast T1 spin-echo and contrast-enhanced T1, followed by 2 planes of contrast-enhanced T1 spin-echo (TR/TE, 600–700/20 ms; 5-mm section thickness, 0.5 skip). All, patients should undergo DWI; b-value of 1000 s/mm$^2$; 3 directions; 4-mm thickness, 0 skip)

**Preferable (Optional) protocols:** SWI/GRE/T2

**Reporting guidelines:** In order for accurate radiological reporting, it is essential that radiologists conform to a set pattern for reports, so as to ensure adequate interpretation for any physicians who may require interpretation of the imaging study in the future (Table 1). Tumor location, tumor margins, enhancement pattern, tumor size and presence of hemorrhage and mineralization are features that must be included in a radiological report for medulloblastoma.

## Neurosurgery

**Initial management for hydrocephalus:** Surgical resection of tumor and opening of the CSF pathway is the ideal treatment since it ameliorates symptoms along with emergent symptoms. If there is a delay in surgery, then CSF drainage can be employed initially via an external ventricular drainage (EVD), preferably with a long subcutaneous tunnel or an endoscopic third ventriculostomy (ETV) can be chosen. For both procedures, rapid decompression and over-drainage should be avoided.

Even though ETV and EVD exist as safer drainage procedures, in Pakistan and other LMICs, ventriculoperitoneal shunts (VPS) are often preferred to drain CSF into the abdominal cavity. This may be because it leads to a temporary relief of symptoms. In such instances, parents of these patients tend to ignore the primary disease and fail to follow up. Adversely, this leads to significant tumor growth including seeding into CSF spaces. Moreover, lifelong shunt dependency, reverse herniation of the superior vermis into the quadrigeminal cistern, and seeding of the tumor in the abdominal cavity are concerns for neurosurgeons dealing with such cases. VPS placement in pediatric patients is associated with multiple associated morbidities, especially shunt infection that can delay definitive surgery, and hence should be avoided. In rare circumstances, where lack of neurosurgical facilities and inadequate nutritional status (malnutrition, infection) of the patient prohibit tumor surgery, VPS may be considered. In this case the neurosurgeon must closely monitor the patient and plan for tumor resection soon after the VPS. Ideally, ETV should always be preferred over VPS.

**Pre-operative preparations:** Pre-operative planning is a multi-disciplinary task. Parents' counselling with the pediatric neuro-oncologist is a vital part of surgical preparation. The surgery should be undertaken by an institute with adequate facilities and expert staff for intra- and post-operative care. The neurosurgeon performing the surgery need not be a pediatric neurosurgeon but should have expertise and experience in posterior fossa tumor surgery. Anesthesia team should have experience of handling pediatric neurosurgical cases; management of intra-operative volume loss, intravenous fluid and blood transfusion when required. A team of pediatricians should be appointed for the patient for post-operative management along with the neurosurgery team. Often, it is beneficial for pediatric teams to be taken in consultation pre-operatively so that they may be aware of the preoperative planning and give recommendations where needed. Ideally, extensive laboratory investigations may be done before surgery.[4] However, if there are no overt signs of organ dysfunction seen, surgeons can proceed with baseline investigations (CBC, Creatinine, LFTs).

## Principles of surgery and technique

**Patient positioning:** Surgical excision of the tumor can either be done in a prone, Concorde or sitting position of the patient. Concorde position while the patient is prone provides the best surgical access and view of the tumor in the aqueductal region. The sitting position provides a clear operative field due to CSF and blood drainage. However, it does not provide any additional significant benefits. If the surgeon, the O.R. team including the anesthesiologist are more familiar with sitting position then surgery can be done in this position of the patient. There is a significant risk of air embolism, hypotension, supratentorial subdural hematoma and pneumocephalus; hence the surgical team should be cautious. Even in prone position alone, patient is at risk of associated edema of the face due to pooling of venous blood in the dural sinuses and tumor bed. This can be prevented by putting the patient in a slight reversed Trendelenburg position (head elevated above the level of the heart).

## Surgical procedure

**Surgical exposure:** A standard midline incision with suboccipital craniotomy can be used for ideal access to the tumor. If the CSF diversion was not performed before tumor surgery, a decision to place an EVD temporarily is reasonable. This can be done preferably through Frazier's point in the occipital region. A sample of 20-30 cc of CSF for cytology can be considered at this juncture.

Dissection of the muscle tissue has to be carried out in the midline raphe to avoid excessive blood loss. Every attempt should be made to leave a cuff of muscles at the level of inion extending laterally and avoiding exposing the skull to the point where the aponeurosis ends. This cuff of muscle provides a good closure to prevent post-operative CSF leak or formation of pseudomeningocele. Besides posterior fossa craniotomy, the surgeon should decide about the removal of C-1 arch, depending on the extent of the disease and need of exposure for visualization.

**Surgical technique:** Every effort should be made to achieve gross total resection (GTR) of the tumor if possible, but in many cases attachment of the tumor to the obex or the floor of the fourth ventricle may prevent GTR, in these cases the strategy should be to attempt Maximum Safe Resection (MSR). It is best to define the extent of the tumor initially, and to temporarily plug the opening of cerebral aqueduct to prevent blood entering into rest of the ventricular system. For very large tumors, defining the extent of the tumor may have to be delayed until significant tumor debulking has been achieved. Microscope should be used with micro-surgical fine instruments. Ultrasonic aspirator, video/Doppler ultrasound may act as adjunct depending upon the availability and individual tumor characters. To minimize the chance of cerebellar mutism, it is best to avoid splitting the vermis and removal of tumor from the roof of the fourth ventricle and the cerebellar peduncles is done with a lot of caution and deliberation. With appropriate positioning of the cranium, the tumor can be excised through the foramen of Magendie, which is usually enlarged by the tumor. Closure of the dura is best done with the help of a patch obtained from the aponeurosis obtained by sub-galeal dissection further cranial to the muscle cuff at the inion. Water-tight closure of the dura minimizes formation of pseudomeningocele and CSF leak.

Operative notes should describe in detail, sites where the surgeon believes the tumor to still remain. Tumor tissue taken as biopsy or collected by surgical vacuum sucker in a sterile trap should be submitted to the pathology lab for frozen section (if facility is available) and histopathology.

**Post-operative complications:** Post-operative complications can occur either intra-operatively or within 6 hours of the procedure (immediate), within 72 hours (early) or after 72 hours (delayed). These include, but are not limited to, hemorrhage, venous air embolism, wound dehiscence, CSF leak, brainstem dysfunction and infection.

**Post-operative care:** The patient should be extubated in the O.R. post-operatively and kept under observation for 24-48 hours in a high dependency unit or pediatric intensive care unit. The EVD should be drained at 15-18 cm and ideally pulled out after 48 hours after ascertaining that the CSF is clear of blood and CSF pressure remains low. Post-operative observation and management of the patient should be under the care of the team of neurosurgery, pediatrics along with pediatric neuro-oncology.

Post-operative Neuroimaging and Testing: Within the first 48 hours post-operatively, a postoperative MRI of the

**Table-2:** Medulloblastoma: Classification based on 2016 WHO Classification of CNS tumors.[7]

| | WNT | SHH | Group 3 | Group 4 |
|---|---|---|---|---|
| **Percentage of MB** | **10%** | **30%** | **25%** | **35%** |
| **Location** | **4th ventricle near brainstem** | **Cerebellum** | **4th ventricle near brainstem** | |
| Pathway of genetic alteration | Aberrant activation of the WNT signaling pathway, often caused by activating mutations in exon 3 of the CTNNB1 gene. They also show loss of chromosome 6. | Aberrant activation of the SHH signaling pathway.Germline or somatic mutations in components of the SHH pathway, such as PATCHED1 (PTCH1) and SUPPRESSOR OF FUSED (SUFU).Focal amplifications of MYCN and GLI2 are also reported.Mutations in the telomerase reverse transcriptase (TERT) promoter are frequently found in adult SHH MBs.Further divided into four subtypes - SHH α, SHH β, SHH γ, SHH δ. | Transcriptional signatures resembling photoreceptors and gamma aminobutyric acid–secreting (GABAergic) neurons.Amplification of the *MYC* oncogene,Unstable genomes, with multiple chromosomal gains and losses. Among these, one of the most common is coordinate loss of chromosome 17p and gain of chromosome 17q—called isochromosome 17q (i17q).Further divided into 3 subtypes -Group 3α, Group 3β, Group 3γ. | Groups 4α and 4γ have focal *CDK6* amplification, chromosome 8p loss, and chromosome 7q gain.Group 4α also exhibits *MYCN* amplification, whereas Group 4γ does not.Group 4β is enriched in *SNCAIP* duplication and *PRDM6* overexpression. |
| Comments | Most favorable outcome; rarely metastatic | | Most aggressive of the four subgroups. Nearly 50% of Group 3MB patients exhibit metastatic dissemination at diagnosis. | Frequently metastatic at diagnosis and have intermediate outcomes. |
| Histology | Mostly classic | Desmoplastic/nodular in 50% of cases with remainder mostly being classic | Classic or anaplastic/large cell | Classic |

patient should be obtained. If MRI is delayed by 72 hours, then MRI should be delayed by 3 weeks but not more than 4 weeks.

MRI brain with contrast (MRI is preferred) and MRI spine with gadolinium if possible these examinations should be performed within 72 hours (if not done before), or between 18-21 days post-op. This is believed to minimize the chances of post-op change being confused with residual tumor. Lumbar CSF cytology examination should be obtained pre-operatively or within 31 days after surgery. The optimal time for obtaining CSF is 2-3 weeks following surgery. Ventricular CSF (either pre- or post-op) may be used if a postoperative spinal tap is contraindicated. CSF should be sampled post-op and prior to starting radiotherapy, for cell count, cytology, glucose and protein (if not already performed at the time of surgery).

Once the patient has been shifted back to the ward, regular interval testing of CBC, differential and platelet count is necessary to watch for postoperative bleeding or infection. A regular neurological examination should be well-documented and reviewed by the surgeon daily. Further monitoring is necessary as management progresses.[5]

## Neuropathology

The microscopic appearance of medulloblastoma often consists of densely packed small round undifferentiated cells with mild to moderate nuclear pleomorphism and a high mitotic count. Morphologic variants of medulloblastoma based on histopathological analysis include classic, desmoplastic/nodular, large cell/anaplastic and medulloblastoma with extensive nodularity (MBEN). A diagnosis of "medulloblastoma, not otherwise specified (NOS)" is appropriate when an embryonal neural tumor is located in the fourth ventricle or cerebellum and the nature of biopsied tissue prevents classification of the tumor.[6]

As previously mentioned, the pathology can be divided into 4 subgroups: WNT-activated, SHH-activated and non-WNT/non-SHH (Group 3 and Group 4). The current integrated classification of medulloblastoma takes into account histological subtype, molecular subgrouping, WHO grading, and genetic information.[7] When molecular analysis is limited or not feasible, histopathological classification can be relied upon due to its clinical utility.

Molecular profiling studies are the gold standard for accurate characterization of medulloblastoma subgroups. Techniques such as real-time reverse transcriptase polymerase chain reaction (RT-PCR), profiling a set of marker genes at the RNA level using nanoString assay, differential expression of a select set of micro-RNAs or surrogate immunohistochemistry (ICH) markers can be used for molecular sub-grouping. However, all of these methods are not available everywhere. Fortunately, surrogate immunohistochemical markers, along with histological types, clinical and radiological data, can be used to subgroup most cases of medulloblastomas.

We recommend an immunohistochemical panel consisting of GAB1, beta-catenin, Filamin A and YAP1 be used as surrogate for medulloblastoma classification.[8] One caveat to using IHC as a surrogate for molecular analysis is that IHC cannot be used to classify Group 3 and Group 4 medulloblastomas. To assess p53 mutation status in cases of SHH subgroup, p53 immunostain can be used as surrogate to molecular studies. Table 2 elaborates on this further.

## Chemotherapy

Chemotherapy is an important component of the multidisciplinary management of medulloblastomas. Its timely initiation can allow for a reduced dose of CSI in average-risk patients and improve survival in high-risk patients. As such, chemotherapy can be administered adjuvant to radiation therapy or surgery, concurrent with radiation therapy, pre-irradiation in infants to defer radiation therapy and as salvage therapy in relapsed or recurrent disease.

Average-risk patients are those who have minimal volume of non-disseminated disease and no evidence of metastatic spread in head, spine or CSF. Patients with brain stem involvement are also eligible to be labelled average-risk. High-risk patients are those with metastatic medulloblastoma or non-metastatic medulloblastoma with >1.5 $cm^2$ residual tumor. Those patient with diffusely anaplastic medulloblastoma are categorized as high-risk regardless of metastatic disease or residual tumor.[9]

We recommend three different chemotherapy regimens for treating patients with medulloblastoma, based on their risk status (Table 3). The chemotherapeutic drugs in use are vincristine, cisplatin, lomustine and cyclophosphamide. Each of these drugs can result in various adverse effects. Vincristine can lead to neurotoxicity, hepatoxicity and jaw pain. Cyclophosphamide and lomustine may cause hematopoietic toxicity, leading to neutropenia and thrombocytopenia. Additionally, hemorrhagic cystitis is a known side effect of cyclophosphamide. Cisplatin may cause nephrotoxicity, manifested by a decrease in creatinine clearance and glomerular filtration rate (GFR), ototoxicity, and hypomagnesemia. Therefore, laboratory monitoring before, during and after the initiation of these chemotherapeutic agents is necessary. A complete blood

**Table-3:** Chemotherapy Regimens for Medulloblastoma[12]

| | Number of cycles and duration | Drugs | Dosage | Days and route of administration | Monitoring |
|---|---|---|---|---|---|
| Regimen IAverage risk Medulloblastoma, during radiation therapy | 6 doses administered at weekly intervals | Vincristine | 1.5 mg/$m^2$ | Day 1 (intravenously) | CBC Comprehensive metabolic panelTotal bilirubinALT and AST |
| Regimen IIAverage risk Medulloblastoma, maintenance chemotherapy for patients aged >5 years | 6 cycles administered at 4 weekly intervals | Vincristine CisplatinLomustine | 1.5 mg/$m^2$ 75 mg/m 275 mg/$m^2$ | Day 1 (intravenously)Day 1 (intravenously)Day 1 (orally) | CBCComprehensive metabolic panelTotal bilirubinALT and ASTSerum creatinineGFRAudiogram |
| Regimen IIIHigh risk Medulloblastoma, maintenance therapy | 6 cycles administered at 4 weekly intervals | Vincristine Cisplatin Cyclophophamide | 1.5 mg/$m^2$ 75 mg/$m^2$ 1000 mg/$m^2$ | Day 1 (intravenously)Day 1 (intravenously)Days 2 and 3 (intravenously) | CBCComprehensive metabolic panelTotal bilirubinALT and ASTSerum creatinine GFR Audiogram |

**Table-4:** Summary of Recommendations for Pediatric Medulloblastoma.

| | |
|---|---|
| **Radiology** | • Complete MRI brain and whole spine.<br>• 'Minimum required' MRI brain protocol:<br>o Imaging on at least 0.5T.<br>o Sequences: Axial T2 and coronal or axial FLAIR sequence; pre-contrast T1 and contrast enhanced T1.<br>• Tumor location, tumor margins, enhancement pattern, tumor size, and presence of hemorrhage/mineralization.<br>• Postoperative MRI is recommended in the first 48 hours after surgery. If delayed by 72 hours, then MRI should be delayed by 3 weeks but not more than 4 weeks.<br>o To identify the extent of resection.<br>o To have a baseline to compare successive imaging.<br>o Not required after biopsy. |
| **Neurosurgery** | • Surgical goals: Resection of tumor and opening of the CSF pathway.<br>• Gross total resection should be attempted where possible. However, in case of tumor adherence to the surrounding critical structures i.e. obex or floor of the fourth ventricle, maximum safe resection should be performed.<br>• Abstain from the VPS as a temporizing procedure unless there is a significant risk of deterioration due to hydrocephalus. Consider referring the patient to a facility where surgical resection can be done along with CSF diversion if needed.<br>• In case of delay in surgical intervention, CSF drainage (VPS or ETV) should be considered. |
| **Neuropathology** | • There are 4 subgroups (WNT-activated, SHH-activated, and non-WNT/non-SHH [Group 3 and Group 4]) based on histological subtype and molecular subgrouping.<br>• Hematoxylin and Eosin (H&E) slides to assess histological subtype.<br>• Reticulin stain for evaluating the possibility of Nodular/desmoplastic histological type.<br>• Immunohistochemical panel consisting of GFAP, Olig-2, and Synaptophysin to differentiate Medulloblastoma from gliomas.<br>• GAB1, β-catenin, Filamin A, and YAP1 are recommended as a surrogate to molecular studies for differentiating WNT and SHH subgroups from group 3 and group 4.<br>• p53 immunostain is recommended as a surrogate to molecular studies in cases of the SHH group. |
| **Pediatric Oncology** | • Three different chemotherapy regimens are recommended for treating patients with Medulloblastoma (MB), based on their risk status. *<br>Regimen I – Average Risk MB (during radiation)<br>• Vincristine, a total of 6 doses weekly intervals.<br>**Regimen II – Average Risk MB (maintenance)**<br>• Vincristine + Cisplatin + Lomustine, 6 cycles at 28 days intervals.<br>**Regimen III – High-Risk MB (maintenance)**<br>• Vincristine + Cisplatin + Cyclophosphamide, 6 cycles at 28 days intervals. |
| **Radiation oncology** | • Radiation therapy should begin within four weeks of definitive surgery and should not be delayed beyond 7 weeks.<br>• Standard Dose: Reduced dose CSI 23.4 Gy @ 1.8 Gy per fraction followed by a tumor bed boost 30.6 cGy @ 1.8 Gy per fraction to a total dose of 54 Gy.<br>• High Risk: Standard dose CSI 36 Gy @ 1.8 Gy per fraction followed by posterior fossa boost to a total dose of 54-55.8 Gy.<br>• Craniospinal axis irradiation is complex and requires robust quality assurance processes like peer review for radiation treatment planning and delivery. |
| **Follow-up** | • First follow-up at post-op day 10 for wound assessment, stitch removal, discussion related to histopathology, and NOTB recommendations.<br>• Follow-up with serial MRI brain 3 monthly and neuro-axis MRI 6 monthly with a pediatric oncologist. |

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MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, CSF: Cerebrospinal fluid, VPS: Ventriculoperitoneal shunt, ETV: Endoscopic third ventriculostomy, WNT: Wingless and integrated, SHH: Sonic hedgehog, GFAP: Glial fibrillary acidic protein, GAB1: GRB2 Associated Binding Protein 1, YAP1: Yes-Associated Protein 1, CSI: Craniospinal irradiation, Gy: Gray, NOTB: Neuro-oncology tumor board.

count (CBC) with a differential count should be acquired, and an absolute neutrophil count (ANC) of >1000 and platelet count of >100,000 should be observed before initiating therapy. Total bilirubin levels and alanine transaminase and aspartate transaminase levels should be checked, too. Total bilirubin <1.5 mg/dl and AST and ALT <2.5 times the upper limit of normal are needed to begin therapy. Furthermore, serum creatine and GFR should be monitored. Serum creatine <1.5 mg/dl and GFR > 50 ml/min/m2 are required to proceed. An audiogram should also be acquired to assess ototoxicity. A comprehensive metabolic panel can alert the physician to any other metabolic derangements.

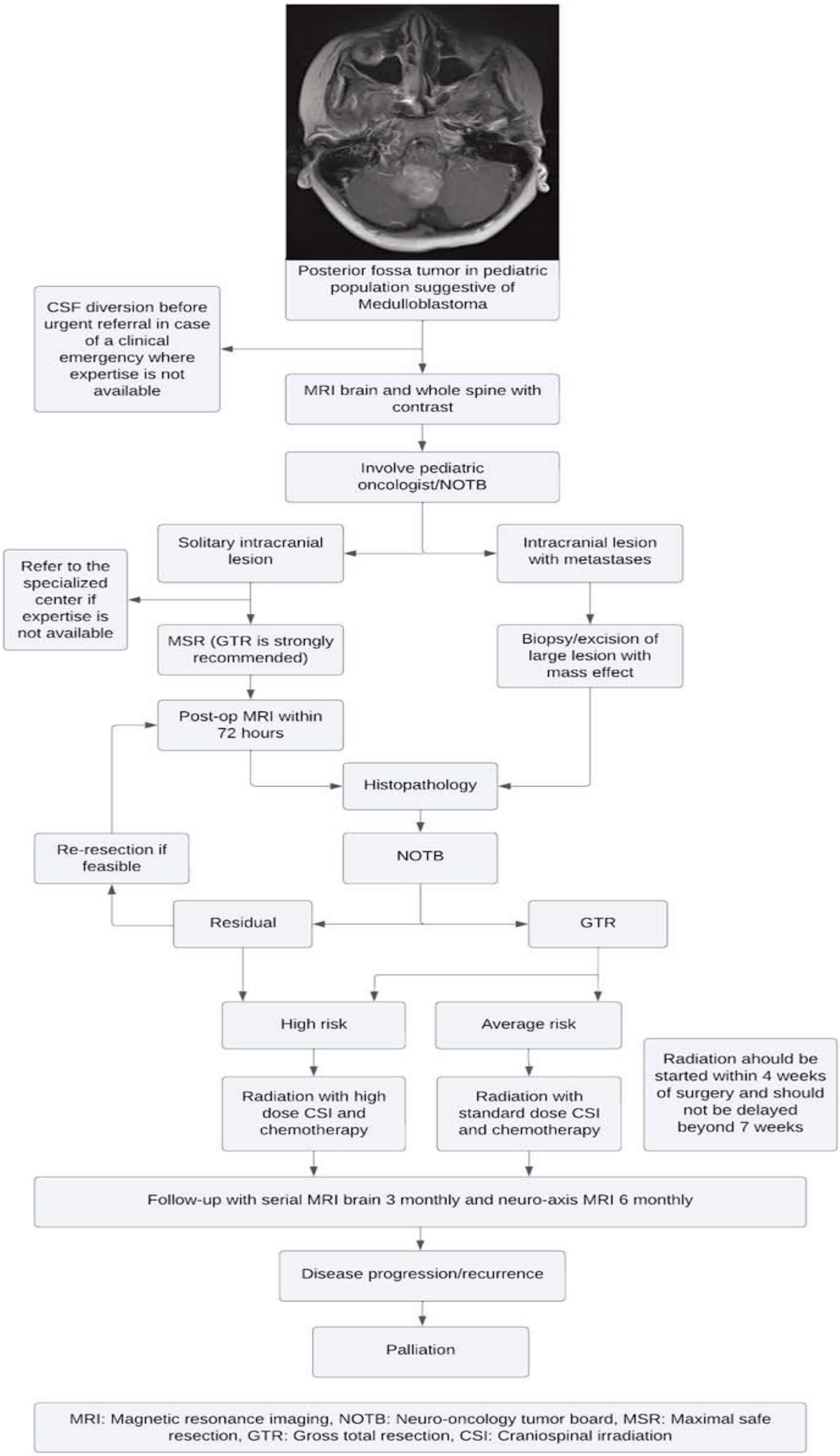


**Figure-2:** Management of Medulloblastoma algorithm.

## Radiation therapy

Radiation therapy (RT) for medulloblastoma consists of craniospinal axis irradiation (CSI) followed by boost to the primary site. 3D image-based RT treatment planning and computer-controlled delivery systems (conformal radiation therapy) improve disease control and functional outcomes for children with brain tumors. Administration methods include 3D conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT) and craniospinal radiation therapy.

## Guidelines and requirements for the Use of IMRT

Radiation therapy should begin within four weeks of definitive surgery and should not be delayed beyond 7 weeks. Patients who start radiotherapy beyond 7 weeks of surgery are considered high risk, requiring higher dose of craniospinal irradiation of 36 Gy.

Radiation therapy should be delivered using photons on Linear Accelerator with photon energy less than 6 MV. CT based planning should be done on all patients. Pre-operative and post-operative MRI scans can be used primarily (co-registered with CT planning data) or adjunctively in the treatment planning process. For cranio-spinal and posterior fossa irradiation, the patient may be treated in a prone or supine position. A supine position is preferred for patients being treated under general anesthesia. Immobilization devices such as head holders or custom molds are also recommended. Deep sedation or general anesthesia is generally encouraged for young children. In treatment planning, shielding of critical structures should be considered.

## Supportive Care during Chemotherapy and Irradiation

CBCs should be obtained weekly. Patients who develop a fever greater than 38.5°C should be evaluated for neutropenia and infection. Patients with an ANC<500/µl or an indwelling catheter require blood cultures and empiric antibiotics. Granulocyte colony stimulating factor (G-CSF) can also be considered according to institutional guidelines. It is recommended that the platelet count be maintained > 30,000/µL. Irradiated and Pall filtered blood products should be used. Transfusions are recommended when hemoglobin falls below 9 gm/dL. The preferred antiemetic is ondansetron. Corticosteroid use as an antiemetic should be avoided if possible. Patients should be started on trimethoprim/sulfamethoxazole (TMP/SMX) at 5mg/kg/day dosed 2-3x/week or per primary care institution's protocol for Pneumocystis carinii prophylaxis. Any patient with greater than 10% weight loss should be provided nutritional support either enterally or via a central venous catheter with parenteral hyperalimentation. All patients should have their magnesium checked prior to each cycle. Endocrine evaluations should be done at diagnosis, completion of radiation therapy, completion of treatment, 6 months following the completion of treatment and then annually unless otherwise indicated.[10]

## Conclusion

These guidelines give recommendations that are needed to fill in the gaps in healthcare when considering pediatric medulloblastoma (Table 4 and Figure 2). Individual practitioners as well as physician groups should remain cognizant of the necessity to properly evaluate and follow up with such patients in order to ensure complete treatment. Guidelines which are "preferred by optional" should be taken into consideration when infrastructure is available. However, our guidelines emphasize crucial recommendations first in order to the bridge the gaps the authors have identified in the care of such patients. With the consensus of all stakeholders, there is greater value in providing these comprehensive recommendations, in order to encourage greater focus on multidisciplinary care with LMICs such as Pakistan

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## References

1. Baqai MWS, Tariq R, Shah Z, Bajwa MH, Shamim MS. Quality of life in survivors of pediatric medulloblastoma: a systematic review and meta-analysis. Childs Nerv Syst 2023;39:1159-71. doi: 10.1007/s00381-023-05886-4.
2. Tariq R, Saeed Baqai MW, Shamim MS. Quality of Life in Paediatric Survivors of Medulloblastoma. J Pak Med Assoc 2022;72:2339-40. doi: 10.47391/JPMA.22-111.
3. Bajwa MH, Shah MM, Mustansir F, Gauhar F, Baig E, Zafar SN, et al. A Guideline On Guidelines – Neuro-Oncology Guideline Standards For Low And Middle-Income Countries. J Pak Med Assoc 2024;74(Suppl 3):s87-92. Doi: 10.47391/JPMA.S3.GNO-10.
4. Mahapatra S, Amsbaugh MJ. Medulloblastoma. Treasure Island, FL: StatPearls Publishing; 2024.
5. Martin AM, Raabe E, Eberhart C, Cohen KJ. Management of pediatric and adult patients with medulloblastoma. Curr Treat Options Oncol 2014;15:581-94. doi: 10.1007/s11864-014-0306-4.
6. Orr BA. Pathology, diagnostics, and classification of medulloblastoma. Brain Pathol 2020;30:664-78. doi: 10.1111/bpa.12837.
7. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-

Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016;131:803-20. doi: 10.1007/s00401-016-1545-1.
8. Ellison DW, Dalton J, Kocak M, Nicholson SL, Fraga C, Neale G, et al. Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups. Acta Neuropathol 2011;121:381-96. doi: 10.1007/s00401-011-0800-8.
9. Ramaswamy V, Remke M, Bouffet E, Bailey S, Clifford SC, Doz F, et al. Risk stratification of childhood medulloblastoma in the molecular era: the current consensus. Acta Neuropathol 2016;131:821-31. doi: 10.1007/s00401-016-1569-6.
10. Heikens J, Michiels EM, Behrendt H, Endert E, Bakker PJ, Fliers E. Long-term neuro-endocrine sequelae after treatment for childhood medulloblastoma. Eur J Cancer 1998;34:1592-7. doi: 10.1016/s0959-8049(98)00212-3.
11. Perreault S, Ramaswamy V, Achrol AS, Chao K, Liu TT, Shih D, et al. MRI surrogates for molecular subgroups of medulloblastoma. Am J Neuroradiol 2014;35:1263-9. doi: 10.3174/ajnr.A3990.
12. Parkes J, Hendricks M, Ssenyonga P, Mugamba J, Molyneux E, Schouten-van Meeteren A, et al. SIOP PODC adapted treatment recommendations for standard-risk medulloblastoma in low and middle income settings. Pediatr Blood Cancer 2015;62:553-64. doi: 10.1002/pbc.25313.