Indian Society of Neuro-Oncology consensus guidelines for the contemporary management of medulloblastoma

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Abstract

Introduction: The high success rate in the management medulloblastoma achieved in the western world is not exactly mirrored in developing countries including India. Socio-demographic differences, health-care disparity, and lack in uniformity of care with resultant widespread variations in the clinical practice are some of the reasons that may partly explain this difference in outcomes. Patients with medulloblastoma require a multi-disciplinary team approach involving but not limited to neuro-radiology, neurosurgery; neuropathology, molecular biology, radiation oncology, pediatric medical oncology and rehabilitative services for optimizing outcomes. Methods: The Indian Society of Neuro-Oncology (ISNO) constituted an expert multi-disciplinary panel with adequate representation from all stakeholders to prepare national consensus guidelines for the contemporary management of medulloblastoma. Results: Minimum desirable, as well as preferable though optional recommendations (as appropriate), were developed and adopted for the pre-surgical work-up including neuroimaging; neurosurgical management including surgical principles, techniques, and complications; neuropathology reporting and molecular testing; contemporary risk-stratification in the molecular era; appropriate adjuvant therapy (radiotherapy and chemotherapy); and follow-up schedule in medulloblastoma. Conclusions: The current document represents a broad consensus reached amongst various stakeholders within the neuro-oncology community involved in the contemporary curative-intent management of children with medulloblastoma. It provides both general as well as specific guidelines and recommendations to be adopted by physicians and health care providers across India to achieve uniformity of care, improve disease-related outcomes, and compare results between institutions within the country.

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Primary central nervous system (CNS) neoplasms are second only to hematologic malignancies as the commonest cause of pediatric cancers,[1],[2], but constitute the single largest source of disability and death from cancer in children and young adults worldwide.[1],[2] Over the years, deeper insights into the understanding of disease biology coupled with advances in diagnosis and therapy have substantially improved the outcomes of several childhood cancers including pediatric brain tumors.[3],[4]

Medulloblastoma, the commonest malignant primary brain tumor in children, has witnessed tremendous biological/molecular [5],[6] and technological advancements [7],[8] in the last decade or so, leading to rapid improvements in outcomes, making it the ideal malignant brain tumor to emulate in contemporary pediatric neuro-oncologic practice. It is generally perceived that the high success rates in the management of medulloblastoma documented in the western world are not exactly mirrored in developing countries.[9],[10] This difference in outcomes could be ascribed to several reasons [10] including but not limited to socio-cultural issues, demographic variations, health-care disparities, and resource constraints that possibly result in delayed diagnosis and referral. The issue is further compounded by a higher morbidity and possibly mortality in the peri-operative setting (advanced stage at presentation, emergency surgery, higher risk of infection) as well as considerable delays in the initiation of post-operative adjuvant therapy (delay in referral, long waiting times for radiation therapy (RT), prolonged course of fractionated RT, and relative lack of specialists adequately trained in administration of systemic chemotherapy), all of which could potentially contribute to inferior outcomes. Even with timely referral and available expertise, there is lack in uniformity of care for these children resulting in widespread variations in clinical practice (neurosurgical, radiotherapeutic, and chemotherapeutic) and resultant outcomes.

Given the potentially high cure-rates in medulloblastoma, the Indian Society of Neuro-Oncology (ISNO), the premier academic forum for promoting and advancing the field of neuro-oncology in the country decided to embark upon this challenging mission to produce consensus guidelines for the management of medulloblastoma (commonest malignant primary brain tumor in children)[11] that would be practical and pragmatic for easy adoption throughout the country, yet remain contemporary in content and direction.

### Methods

An expert multi-disciplinary panel with adequate representation from all stakeholders (neuroradiologists, neuropathologists, molecular biologists, neurosurgeons, radiation oncologists, pediatric medical oncologists, and rehabilitation specialists) involved in the management of medulloblastoma was constituted under the aegis of the Society. Each member of the panel was given the responsibility to collect and analyse the published evidence either individually or in association with other colleagues and peers pertaining to their field of expertise before proposing consensus guidelines in their respective areas of expertise for the management of medulloblastoma. Experts were encouraged to categorize the guideline recommendations as 'minimum desirable' or 'preferable though optional' based on the availability of infrastructure and expertise. The proposed guidelines were then presented by select members of the expert panel in the ISNO Consensus Guidelines Session (Indian Society of Neuro-oncology Annual Conference, ISNOCON, Kochi, March 2015) for wider discussion and debate. All members of the Society were requested to provide their personal views including objections if any, regarding each of the proposed recommendations, either during the meeting or later via e-mail to the ISNO secretariat. Based on the feedbacks provided, the proposed set of recommendations were further revised by the panel of experts to accommodate some of those suggestions, resulting in the current consensus document that was officially adopted by ISNO after ratification at its Executive Meeting (ISNOCON, Hyderabad, April 2016).
Pre-surgical work-up

Clinical presentation

In accordance with its anatomic site of origin, most children with medulloblastoma present acutely or sub-acutely with the classic midline posterior fossa syndrome in the form of headache, nausea, vomiting, and gait abnormalities.[12],[13] Rapid growth of the tumor due to its malignant nature leads to obstructive hydrocephalus resulting in raised intracranial pressure (ICP) that typically manifests as intense headache, projectile vomiting, neck pain, visual blurring, and drowsiness. Persistent and long-standing hydrocephalus can even precipitate blindness due to secondary optic atrophy. Infants and very young children may present with irritability, sometimes associated with macrocephaly and/or fullness of fontanelle, and delayed developmental milestones. Very occasionally, infants may present with torticollis alone. Rarely, cranial neuropathy, especially sixth nerve palsy, may be the presenting sign of medulloblastoma. Specific signs and symptoms pertaining to the cerebellar location of tumor such as truncal or appendicular ataxia, incoordination, and dysmetria occur later in the course of the disease. Patients with spinal dissemination often present with backache, loss of bladder control, and bilateral lower limb weakness. Persistent symptoms and focal neurological deficit(s) should prompt early and appropriate neuro-imaging for diagnosis.

Neuro-imaging

The initial imaging modality for suspected brain tumors in adults as well as children in some parts of the country is computed tomography (CT). Medulloblastoma is generally seen as a well-defined, solid, hyperdense lesion on plain CT that shows variable contrast enhancement;[13],[14] arises typically from the vermis in the midline posterior fossa and fills the fourth ventricle, causing obstructive hydrocephalus; less commonly, is located laterally in the cerebellar hemisphere with or without extension to the foramen magnum. Magnetic resonance imaging (MRI) with its exquisite anatomic resolution, multi-parametric nature, and ability to image the entire neuraxis (brain and spine) in the same session is the preferred and recommended imaging modality[14],[15] for a suspected medulloblastoma at the initial diagnosis, even in the presence of a recently acquired CT scan. Occasionally, a child may need to undergo neurosurgical intervention for a suspected medulloblastoma based on the CT imaging alone, if the child is significantly symptomatic and needs an urgent or emergency decompressive surgery. [Table 1] summarizes the recommended MRI acquisition protocol in the pre-operative setting for a suspected medulloblastoma. On T1-weighted images [Figure 1]a, a medulloblastoma generally appears hypointense to isointense compared to the surrounding white matter and exhibits contrast enhancement [Figure 1]b following gadolinium administration. It exhibits a variable signal intensity on T2-weighted images [Figure 1]c with densely cellular component of the tumor being hypointense, and the less cellular areas being iso- to hyperintense compared to the surrounding white matter. Intra-tumoral or peri-tumoral cysts, if any, appear hyperintense, while calcification generally exhibits a low signal on T2-weighted sequences. Due to densely packed cells within the tumor, medulloblastoma causes restriction of diffusion [Figure 1]d and has correspondingly low apparent diffusion coefficient (ADC) values. Apart from plain and post-contrast images (acquired in axial, sagittal, and coronal planes), sagittal fat-suppressed post-contrast MRI of the spine is strongly recommended in the pre-operative setting as a screening tool to rule out any leptomeningeal metastases. Leptomeningeal enhancement (representing subarachnoid spread of tumor) seen on the pre-operative MRI is the most specific finding corresponding to dissemination of the disease. Obliteration of the inter-folial, sulcal and cisternal spaces may be an early indicator of leptomeningeal dissemination. More commonly, there may be focal or diffuse leptomeningeal enhancement, with linear and/or nodular appearance, ependymal enhancement, widened tentorial enhancement, and communicating hydrocephalus. [Table 1](Figure 1)

Advanced and specialized MRI techniques [16] such as magnetic resonance spectroscopy (MRS), perfusion imaging, and diffusion tensor imaging are preferable though optional and should be obtained wherever appropriate expertise exists. On MRS, medulloblastoma typically demonstrates the usual tumor spectra with significantly increased choline (Cho), decreased N-acetyl aspartate (NAA) and decreased creatine (Cr). A small amount of lipid-lactate may be observed even without frank necrosis indicating increased metabolic activity. On susceptibility-weighted imaging, medulloblastoma typically shows increased perfusion parameters viz. relative cerebral blood volume (CBV) and relative cerebral blood flow (CBF), that can also be demonstrated using three-dimensional (3D) arterial spin labelling (ASL), a newer MRI technique [17] that measures CBF.

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Neurosurgery

Symptomatic management at the initial diagnosis

Children with medulloblastoma typically present with features of raised ICP due to obstructive hydrocephalus. However, routine pre-operative ventriculo-peritoneal (VP) shunt should generally be avoided [18] as definitive surgical resection readily relieves the obstruction [19] by opening the cerebrospinal fluid (CSF) pathways. Besides the possible morbidity associated with a VP shunt, it can lead to 'reverse herniation' of the superior vermis into the quadrigeminal cistern and occasionally seeding of the tumor into the peritoneal cavity. Occasionally, CSF diversion may be deemed necessary for symptomatic relief if there is anticipated delay in definitive surgery. Such diversion is best achieved by the use of either an external ventricular drainage (EVD) or an endoscopic third ventriculostomy (ETV).[20] Care has to be taken to avoid both rapid decompression of the ventricles and over-drainage. If CSF diversion is not being considered, medical decompressive therapy is recommended in the pre-operative period.[21] The steroid of choice is dexamethasone administered in a loading dose of 0.5-1 mg/kg intravenously (with the maximum dose being 10 mg). Subsequently, dexamethasone (0.25-0.5 mg/kg/day) can be given intravenously or per-oraly in divided doses every 6-8 hours, along with antacids for gastrointestinal protection. Severe hydrocephalus may require the administration of cerebral decongestants (mannitol or frusemide) for a short period. Elevation of the head-end of the bed (by 30 degrees) can help children with symptomatic hydrocephalus who should be monitored closely with periodic recording of vital signs (pulse, blood pressure) and neurologic status. Given the fact that many of the children are likely to be pre-existing comorbidities (malnutrition, infection), their identification and institution of a corrective action can help to reduce the incidence and severity of perioperative complications. Temporary CSF diversion helps to relieve symptoms by facilitating resolution of the hydrocephalus prior to the definitive surgical resection of the tumor. Only a small minority of patients may require a permanent CSF diversion procedure. A VP shunt procedure, however, exposes the patients to a lifetime of shunt dependency and shunt-related complications. The clinical predictors of persistent hydrocephalus [22] are young age, pre-operative severe hydrocephalus, midline tumor location, subtotal tumor resection, presence of leptomeningeal metastases, and post-resection complications.

Surgical principles and techniques

Patient positioning

Most surgeons prefer the prone position during surgery.[19],[23],[24],[25] The other positions that may be used are the sitting or the concorde position.[24] The sitting position [26] gives the advantage of a clear operative field due to drainage of CSF and blood. However pediatric patients are not good candidates for this position as there are significant disadvantages associated with this position such as the risk of developing air embolism, hypotension, supratentorial subdural hematoma and pneumocephalus.[26] The concorde position gives a good view of the tumor in the aqueductal region, but this can be achieved even in prone position by positioning the head as described below. The disadvantages of the prone position are venous pooling in the dural sinuses and in the tumor bed, and the associated edema of the face. These are overcome by positioning the head above the level of heart. In children, skull fixation during surgery can be achieved using Mayfield clamps with pediatric skull pins. However, for younger children (<3 years), a well-padded horseshoe shaped cerebellar head rest is recommended. The head is positioned with a slight flexion at the neck with a 'military tuck' (flexion at the atlanto-occipital joint) to open up the space between the foramen magnum and posterior arch of 1st cervical vertebra (C1). This head position aids in visualization of the cerebral aqueduct, which is one of the end points of excision, superiorly. This head position also helps in accessing the dorsal cervical subarachnoid space after C1 posterior arch excision.

Surgical exposure

A standard midline suboccipital craniectomy or craniotomy can be used for access to the tumor.[23],[24],[25] Whatever is the bony exposure used, a good approximation of the deep fascia is the most important aspect in preventing a post-operative CSF leak. This is because, in most of the cases, the dura at the end of the procedure will shrink to an extent that it will be impossible to get a water-tight closure and the bone flap will
not provide any additional support for such a dura. The alternative is to use a pericranial patch from the occipital area, fascia lata or an artificial dural graft. Another advantage of a craniotomy is in the prevention of suboccipital pain, sometimes seen in patients who undergo a craniectomy, that is in all likelihood, precipitated due to the traction caused by the adhesion of dura to the nuchal muscles. Covering the dura with a large sheet of gelfoam usually prevents this type of adhesion and the consequent problem of suboccipital pain. The surgical exposure is started by a vertical midline incision from the inion to the spinous process of 2nd cervical vertebra (C2). In an avascular midsagittal plane, the nuchal muscles are separated subperiosteally. The suboccipital bone from the inion to the foramen magnum is exposed with lateral exposure as wide as the incision allows. The posterior arch of C1 is usually removed, which allows for a proper visualization of the lower end of the herniated tonsils (which is seen with larger tumors) to ensure that medullary compression is relieved. It also aids in releasing the CSF from the dorsal cervical subarachnoid space. The next step of surgery is the dural opening, wherein considerable variation exists. The standard way is to open in a 'Y' shaped fashion. Before opening the dura over the cerebellum, it is mandatory to release CSF from the dorsal cervical subarachnoid space after opening the dura in the midline. This will make the cerebellum lax and fall away from the dura. This part of the dural opening forms the vertical limb of the 'Y'. Then the dura is opened over the right and left cerebellar hemispheres and is extended onto the cervical dura to complete the 'Y'. Care must be taken while dividing the dura at the level of foramen magnum region to prevent torrential hemorrhage from the marginal sinus. This is prevented either by coagulation, dividing between clamps, or by applying small clips. One disadvantage in this Y-shaped dural opening is that the dural edges are splayed apart for a long time during the procedure which makes dural approximation difficult. An alternative way of dural opening is the unilateral C-shaped flap based onto the opposite hemisphere. The cut begins close to midline superiorly and extends on to the paramedian dura and curving back slightly off midline inferiorly to the opposite side on the cervical dura. This provides adequate exposure for the ipsilateral telovelar region and maintains the dural integrity for a water-tight closure.

Surgical technique

Complete surgical resection is ideal, but this may not always be safe or feasible. In such cases, it is recommended to attempt maximal safe resection leaving residual tumor behind rather than aggressive surgical resection that can precipitate significant morbidity.[21],[25] It is common practice to check the plane between the tumor and floor of the fourth ventricle to plan the extent of resection, before initiating tumor decompression. It is prudent to keep a gelfoam and cotton strip over the fourth ventricular floor to prevent an inadvertent injury to the brainstem during tumor decompression. However, this practice is not practically possible sometimes as the tumor may be too large so that it extends beyond the limits of the floor of the fourth ventricle into the cisterna magna. In such cases, tumor decompression should be done before trying to look for the plane between the tumor and the fourth ventricular floor. Tumors which extend through the foramen of Magendie and present in the cisterna magna are generally followed into the fourth ventricle by sequential decompression and dissection. Tumors confined within the fourth ventricle and not visible in the cisterna magna are approached by one of the following two approaches [27] i.e., either the midline transvermian approach or the lateral telovelar approach [Supplementary File S1].[SUPPORTING:1]

Post-operative complications

Complications arising from surgery can be broadly classified as immediate (during and up to 6 hours of the surgical procedure), early (occurring within 72 hours of surgery) or delayed (beyond 72 hours). The expected major post-operative complications include venous air embolism, haemorrhage, wound dehiscence and CSF leak, brainstem dysfunction, cerebellar mutism, and infection.[25],[28] A detailed discussion of all the possible post-operative complications is beyond the scope of this article, but the prevention and management of the expected major complications is briefly summarized [Supplementary File S2].[SUPPORTING:2]

Post-operative neuro-imaging

MRI acquisition parameters in the post-operative setting should ideally be identical to the pre-operative imaging. It is recommended that post-operative MRI of the brain be acquired immediately (within 24-48 hours of surgical resection) to accurately identify the extent of resection and quantify the status of the residual disease. However, whenever immediate post-operative neuro-imaging has not been obtained, it is
recommended to wait for 2–3 weeks (but no later than 4-weeks) to allow resolution of post-operative changes (blood products and surgical debris) for better delineation and characterization of the tumor bed. If screening spinal imaging had not been done pre-operatively, the same should be acquired post-operatively for an accurate spinal staging. Once again, it is recommended to wait for 2–3 weeks after surgery for acquiring the spinal MRI to reduce the chance of erroneous interpretation consequent to post-operative enhancement of spinal leptomeninges. [29, 30]

Practical tips for interpretation of neuro-imaging in the post-operative setting

It is important to appreciate the relationship of the lesion to the brainstem and floor of the fourth ventricle. If the lesion is adherent to these structures, it is highly likely that a sliver of tumor tissue would have been left behind by the neurosurgeon, which should be looked for on post-operative imaging. Some medulloblastomas can have significant non-enhancing infiltrative component extending into the adjoining cerebellar parenchyma that can be mistaken for edema. Occasionally, the entire tumor may be completely non-enhancing; in such cases, the post-operative residual tumor would also be non-enhancing, and in likelihood, be misinterpreted as edema. The relationship of the tumor to the tentorial leaflet also needs to be adequately assessed, as there will be meningeal enhancement following surgery, which may impair proper interpretation. The diffusion characteristics of the medulloblastomas should be defined appropriately on the pre-operative imaging, as ischemic changes can also show restriction of diffusion on post-operative scans, thus interfering with optimal interpretation. The use of packing hemostatic material during surgery can sometimes be erroneously interpreted as residual tumor. Thorough evaluation of the intra-operative notes and communication with the operating neurosurgeon can help to resolve this confusion.

CSF cytology

It is recommended to test the CSF for malignant cell cytology via lumbar puncture as a part of the post-operative staging work-up. [31] This should be performed at least 2–3 weeks after surgery to avoid false positivity. CSF obtained via a ventricular tap at the time of surgery is not considered appropriate for neuraxial staging. [32]

Other assessments

Given the high cure rates and potential for significant morbidity associated with therapy in childhood medulloblastoma, [33] it is preferable though optional to document post-surgical neurocognitive, endocrinal, and hearing status prior to initiation of any adjuvant therapy so that this baseline assessment is available for future comparisons.

Pathology and molecular biology

Sample processing

It is almost axiomatic that like all other surgical pathology specimens or biopsy samples, medulloblastoma tumor tissues should also be processed timely and appropriately for accurate histological diagnosis and optimal molecular biology testing. For routine diagnostic pathology reporting, it is recommended that medulloblastoma tissues be fixed in 10% neutral buffered formalin for 6-72 hours. [34] For optimal results of immunohistochemical testing, time from tissue acquisition to fixation should preferably be less than 1-hour and time-period of fixation be 12-24 hours. [34] Although some of the profiling studies can be performed on formalin-fixed paraffin-embedded blocks, it is preferable to snap-freeze and store fresh-tissues wherever facilities exist for molecular biology testing. Conventional hematoxylin and eosin staining [35] and reticulin stains are sufficient for a histological diagnosis [Table 2]. Immunohistochemistry (IHC) supplements the histological features [Table 2], with medulloblastomas demonstrating variable immunopositivity for neuronal markers including synaptophysin, neuron specific enolase (NSE), NeuN, class III β-tubulin, and MAP2. [35] MIB-1 labelling index, a marker of proliferative activity, should be calculated in highest proliferating areas (hot-spots) by counting 500 cells. Certain IHC tests may further help in differentiating medulloblastomas from other childhood posterior fossa tumors [Table 2]. {Table 2}
Pathology reporting

Medulloblastomas, originally described as 'small blue round cell tumors' on light microscopy, belong to the family of primitive embryonal malignant CNS neoplasms that are composed of a population of undifferentiated cells with a high nuclear: cytoplasmic ratio and evident mitotic figures. Medulloblastomas are histologically graded as Grade IV tumors by the World Health Organization (WHO) classification [35] that also recognizes different morphologic variants such as classic medulloblastoma, desmoplastic/nodular (D/N) medulloblastoma, medulloblastoma with extensive nodularity (MBEN), and large-cell/anaplastic (LC/A) medulloblastoma [Figure 2].

Classic medulloblastoma is a small round cell tumor with densely packed undifferentiated cells in a syncytial arrangement. Homer-Wright rosettes may be present. Occasionally, nodules of cells showing neurocytic differentiation may be evident; however, intra- or peri-nodular desmoplasia is not seen on reticulin staining. D/N medulloblastoma is characterized by reticulin-free nodules (pale islands) and intervening reticulin-rich areas that are densely packed with undifferentiated cells having hyperchromatic nuclei. Within the nodules, tumor cells showing evidence of neurocytic differentiation (cells with rounded nuclei with perinuclear clearing of cytoplasm) are embedded in a fibrillary matrix, with a streaming pattern. Both, a nodular pattern as well as inter-nodular collagen deposition, are necessary to make a diagnosis of D/N medulloblastoma; one in the absence of the other is insufficient. Mitotic activity and MIB-1 labelling are higher in the inter-nodular areas. MBENs shows an expanded lobular architecture with large reticulin-free nodules of neurocytic cells showing streaming in a fibrillary neuropil-like matrix, and narrow inter-nodular strands of embryonal tumour cells in a desmoplastic matrix. The inter-nodular reticulin-rich component with embryonal cells is a minor element of this variant. Previously categorized as separate histological subtypes, large-cell medulloblastoma and anaplastic medulloblastoma are now combined into one histological entity (LC/A). This variant [36],[37] displays either severe anaplasia with marked nuclear pleomorphism, nuclear moulding, cell wrapping, cannibalism, and frequent mitoses and apoptosis, or large-cell phenotype with large round nuclei having prominent nucleoli over most of the tumor area. Intra-tumoural desmoplasia is not seen in the LC/A variants. In case of inability to classify them into any of the above histological subtypes, the tumor may be reported as medulloblastoma, not otherwise specified (NOS).

Molecular sub-grouping

Genome-wide expression profiling studies have identified four distinct molecular sub-groups of medulloblastoma viz. wingless-type (WNT); sonic hedgehog (SHH), Group 3 and Group 4.[38],[39] These four molecular sub-groups have different developmental origins, distinct phenotypes, unique transcription and genetic profiles, diverse biological behaviour with markedly variable prognosis [40] and clinical outcomes [Table 3]. Molecular sub-grouping of medulloblastomas, in addition to the routine histopathological diagnosis, in centres with appropriate expertise and infrastructure, is therefore, strongly recommended for a better prognostication and refined risk-stratification.

While there is a worldwide consensus on the four molecular sub-groups, it is increasingly being recognized that significant heterogeneity exists even within the sub-groups,[41] particularly in the subgroup of SHH-associated medulloblastoma.[42] Several platforms/methodologies are now available for molecular sub-grouping of medulloblastoma [Table 4]. These include (but are not limited to) expression profiling of a select set of marker genes at the RNA level using nanoString assay [43] or real time reverse transcriptase polymerase chain reaction (RT-PCR);[44] differential expression of a select set of microRNAs;[45] or expression at the protein level by IHC.[46],[47] The four-antibody based IHC-approach (unique single-protein antibody for each sub-group)[43] could not be replicated in various parts of the world raising questions about its applicability. IHC-based classification into three molecular sub-groups (WNT, SHH, and non-WNT/non-SHH) though relatively simpler and more practical [Figure 3], does not differentiate between sub-groups 3 and 4.[46],[47] Each of the platforms/methodologies has its own unique advantages and disadvantages and it is beyond the scope of this article to recommend one over the other. The choice of the methodology for molecular sub-grouping is left to the judgement and discretion of the treating physician based on the availability of infrastructure and expertise. It is also suggested that the sub-group determination be confirmed by a second orthogonal technique if it is intended to have an influence on therapeutic decision-making.
Updated WHO classification

The 2016 update [49] to the WHO 2007 classification of CNS tumors [35] attempts to enhance the typing and grading of primary brain tumors by incorporating all available tissue-based information. While the histomorphological classification is retained as before, the update now incorporates genetic classification also.

Medulloblastoma, genetically defined

Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated and TP53-mutant
Medulloblastoma, SHH-activated and TP53-wildtype
Medulloblastoma, non-WNT/non-SHH
Medulloblastoma, group 3
Medulloblastoma, group 4.

Medulloblastoma, histologically defined

Medulloblastoma, classic
Desmoplastic/nodular medulloblastoma
Medulloblastoma with extensive nodularity
Large-cell/anaplastic medulloblastoma
Medulloblastoma, not otherwise specified (NOS).

The WHO 2016 update [49] further recommends that diagnoses be layered with histological classification, WHO grading, and molecular/genetic information to provide an 'integrated' diagnosis [Table 5]. While the histological classification remains the same, molecular classification provides clinical and prognostic information beyond that provided by histopathological examination, with distinct associations between the molecular sub-groups, the specific genetic alterations and the clinico-pathological variables. [Table 5]

Risk-stratification

Following surgery, every child with medulloblastoma should undergo risk-stratification for assigning appropriate therapy and predicting outcomes. The traditional risk-stratification schema,[50] though based entirely on clinico-radiological grounds, still remains valid, is widely prevalent in clinical practice, and should be the minimum desirable standard. Children over the age of 3 years with no or small residual tumor (<1.5 × 1.5 cm 2) and absence of leptomeningeal metastases (M0 status) both on neuraxial imaging as well as CSF cytology are classified as having average risk/standard risk disease with >80% long-term survival with standard therapy. Presence of any one or more of the following adverse features such as age <3 years, residual tumor >1.5 × 1.5 cm 2, or metastases (M1-M4 status) makes it a high risk disease with the long-term survival ranging from 40-60% even with intensified therapy. Patients with incomplete neuraxial staging should be classified as high risk. Given the poor outcomes in patients with diffuse anaplasia,[36],[37] it is also recommended that patients with LC/A histology be classified as high risk, irrespective of other adverse features. In addition, in centres with facilities for molecular testing for medulloblastoma, efforts should be made to get all relevant molecular biology and genetic information to arrive at the current consensus risk-stratification schema [Table 6]. This integrates molecular sub-grouping with clinico-radiological features (preferable though optional) to provide a more robust and refined risk-stratification into the low risk, standard risk, high risk, and very high risk categories with distinct survival outcomes.[51] [Table 6]

Radiation therapy

Post-operative adjuvant radiation therapy (RT) remains an integral component and cornerstone of therapy in the curative-intent treatment of medulloblastoma.[12],[13] Given the high propensity of the tumor to develop leptomeningeal dissemination, treatment of the entire neuraxis, i.e. craniospinal irradiation (CSI) followed by boost irradiation of the tumor bed/posterior fossa is recommended to achieve adequate disease control. There is very little doubt that RT for medulloblastoma is preferably delivered using 6MV photons from a linear accelerator. In the case of unavailability of linear accelerators locally, children should ideally be referred in time to an appropriate higher centre with adequate RT facility and infrastructure to prevent unnecessary delays. However, in unavoidable circumstances, it may be more prudent to offer adjuvant RT on a telecobalt machine rather than wait unnecessarily for an unduly long period for appointment on a linear accelerator.

Cranio-spinal irradiation (CSI) planning, delivery, and verification
CSI remains one of the most technically challenging processes in treatment planning, verification and delivery due to the need for a uniform and homogeneous irradiation of a long and complex shaped target volume.

Fluoroscopic two-dimensional (2D) simulation

Traditionally, CSI has been planned in the prone position [52] under fluoroscopic guidance (two-dimensional planning) with the child immobilized in a body shell using thermoplastic cast for the head and shoulder on a universal prone head-rest with customization of head and chin supports to achieve optimal neck extension and flattening of the spinal column. The target volume for CSI includes the entire brain and its covering meninges as well as the entire spinal thecal sac with exiting nerve roots. The standard beam arrangement for conventional CSI is shaped with bilateral cranial fields geometrically matched onto direct posterior spinal field(s) using couch and collimator rotation. The lateral cranial fields are positioned to cover the entire head and upper cervical spine, while still being 2 cm clear of the shoulders (typically lower border at C4/C5 junction). Shielding of the orofacial region is accomplished using multi-leaf collimators (MLCs) or customized lead blocks in case of unavailability of MLCs. Special attention should be given to critical regions such as the cribriform plate, sub-frontal region, temporal lobe meninges, and proximal optic nerves, which may often be inadequately covered due to overzealous shielding of the eyes and the orofacial region. The lower end of the thecal sac should ideally be determined from a sagittal spinal MRI (generally ends at S1). In the absence of such imaging, the spinal volume should be extended till the S2/S3 junction to ensure adequate target volume coverage. The width of the spinal field typically includes the transverse processes to ensure that the nerve root meninges exiting from the intervertebral foramina are adequately covered. Although, theoretically, the craniospinal junction can abut, a gap of 3-5mm is recommended between the brain and spine fields to prevent any overdose on the cord due to accidental overlap. In older children and adults, the use of two adjacent spinal fields with an appropriate gap on the surface to encompass the entire spinal target volume is required. All junctions (craniospinal as well as spinal-spinal, if any) should be shifted periodically throughout the course of irradiation to feather the dose across the junction and minimize hot and/or cold spots. This can be easily achieved by decreasing the spinal field superiorly, and increasing the cranial field inferiorly (by 5mm) during each shift. It is relatively easy and simple to verify delivery of CSI in the prone position due to direct visualization of the field light on the patient's surface.

CT-based three-dimensional (3D) simulation

Difficulty in administering anaesthesia to young children and the relative lack of comfort in the prone position coupled with widespread availability of CT-simulators within RT departments has heralded the shift to CSI in the supine position [53],[54] in contemporary practice. CT-based three-dimensional treatment planning in the supine position is now being increasingly used and is recommended wherever such facilities are available. Target volume coverage is more easily assured and the delivery is more reproducible with CT planning. For the purpose of CT-based supine CSI planning, it is recommended that the child be immobilized supine and aligned straight in the neutral neck position utilizing an appropriate neck rest using a 4-clamp thermoplastic cast for the head and shoulder region. Axial planning CT images should be acquired from the vertex till the upper thigh region using 5mm slice thickness. The acquired radiological data is transferred to a 3D-treatment planning system via a network for contouring/delineation and optimal treatment planning. The brain and its covering meninges till the C2 cervical spine should be drawn as the clinical target volume (CTV) of the brain. A 5mm isotropic margin is recommended around CTV-brain to create the planning target volume (PTV) of the brain. The spinal thecal sac and exiting nerve roots from the C2 cervical spine till the lower end of the thecal sac should be contoured as CTV-spine. An 8-10mm isotropic margin is recommended around the CTV-spine to generate the PTV-spine. Organs-at-risk (OARs) for CSI should include but may not be limited to eyes, lens, cochlea, mandible, parotids, thyroid, esophagus, lungs, heart, liver, kidneys, bowel bag, rectum, bladder, gonads (ovary/testes), and vertebral bodies plus pelvis (surrogate for red bone marrow). Target volume coverage is more easily assured and delivery more reproducible with CT-planned supine CSI. Although several techniques for supine CSI have been described, it is recommended that the simple fixed-field [53] geometry [Figure 4] be adopted for routine clinical use [Supplementary File S3] [SUPPORTING:3]. Emphasis on calculation of the dose-volume parameters of PTV and OARs has led to progressive improvement in the supine CSI techniques from simple beam geometry to more conformal approaches such as forward planned segmented technique and inversely planned intensity modulated radiation therapy (IMRT) either using...
multiple static/dynamic fields or rotational techniques.[55] However, caution is warranted against the routine use of complex intensity modulated radiotherapy (IMRT) techniques for CSI which should only be practised at higher academic centres with long-standing experience in CT-based supine CSI planning and sufficient expertise in IMRT planning and delivery. {Figure 4}

Boost irradiation planning

The volume of boost irradiation depends on risk-stratification of the disease. For low risk and standard risk medulloblastoma, it is not necessary to treat the entire posterior fossa,[56] and it may be sufficient to treat only the pre-operative tumor-bed with appropriate margins (typically 1-1.5cm around the tumor bed). For high risk and very high risk disease, irradiation of the entire posterior fossa is presently recommended, although increasingly, many centres in the west have shifted to irradiation of the tumor-bed with margins even for these cases with a high risk disease. Posterior fossa irradiation can easily be planned based on fluoroscopic imaging;[57] however, the use of CT-based three-dimensional planning is strongly encouraged for boost irradiation.[58] Whole posterior fossa irradiation can be easily planned based on bony landmarks using simple parallel opposed portals. The availability of 3D-dataset allows the use of multileaf collimators (MLCs) to shield the uninvolved normal tissues as well as wedges to achieve a more homogeneous dose distribution. Boost irradiation should ideally be planned using multi-field three-dimensional conformal techniques [59] with an attempt at cochlear-sparing.[60],[61] Although this is best achieved with IMRT [Figure 5], its routine use for tumor-bed/posterior fossa irradiation should be done only in experienced hands. It is preferred that the CSI and boost plans be summated to produce a composite treatment plan and final dose-distribution. {Figure 5}

Radiotherapy prescription

It is recommended that the total dose to the primary tumor be kept around 54-55Gy delivered over 6-6.5 weeks using conventional fractionation (1.67-1.8Gy per fraction, one fraction per day, 5 fractions per week). The dose prescription for CSI depends on several factors, including an accurate risk-stratification. In rigorously staged standard risk medulloblastomas, reduced dose CSI (23.4Gy in 13 fractions) followed by tumor-bed boost (30.6Gy in 17 fractions) to a total tumor-bed dose of 54Gy in 30 fractions over 6 weeks is currently recommended. Such therapy in conjunction with adjuvant multi-agent systemic chemotherapy results in excellent long-term survival outcomes,[62] but with reduced neurocognitive and endocrinologic sequelae compared to the full-dose CSI. However, if chemotherapy is unavailable, or deemed unacceptable, full-dose CSI (35-36Gy in 20-21 fractions) plus tumor-bed boost (18-19.8Gy in 10-11 fractions) can be offered with nearly equivalent efficacy.[63] If accurate staging is not possible, it is recommended to consider the patient as having a high risk disease and treat with full-dose CSI (35-36Gy in 20-21 fractions) plus posterior fossa boost (18-19.8Gy in 10-11 fractions) to a total tumor dose of 54-55Gy in 30-32 fractions over 6-6.5 weeks.[10] Patients with diffuse leptomeningeal dissemination may be treated with extended dose CSI (39.6-40Gy in 22-24 fractions) plus entire posterior fossa boost (14.4Gy in 8 fractions). An additional boost of 5.4-9Gy in 3-5 fractions to focal nodular metastatic deposits in the brain and/or spine can be planned and delivered concurrently during posterior fossa boost irradiation in appropriately selected patients. The routine use of altered fractionation radiotherapy (e.g., hyperfractionation) is not advocated, but may be applied at the physician’s discretion on an individual basis.[64],[65] Any deintensification (for low risk and standard risk disease) and/or intensification (for high and very high risk disease) of therapy should not be routinely employed in contemporary clinical practice but should be considered only in the context of appropriately designed prospective clinical trials.[48]

General guidelines for RT

It is strongly recommended that following surgery, children be referred within 7-10 days to an oncologist such that further adjuvant therapy can be planned and instituted in a timely manner. Adjuvant RT should ideally begin as early as is feasible (allowing 2-3 weeks for post-operative recovery and neuraxial staging), preferably within 4-weeks, but definitely within 6-weeks of surgery. The overall treatment time of fractionated course of RT should preferably not exceed 50 days, but definitely not 8 weeks.[66] Treatment interruptions during RT are undesirable and should be avoided as far as practical. In case of significant hematologic toxicity (particularly in children receiving pre-irradiation chemotherapy) precluding immediate CSI delivery, it may be
prudent to either start with or switch over to the boost phase of irradiation and resume CSI after sufficient myelo-recovery. It is also recommended to have good quality assurance for RT including periodic verification of delivery (using either portal imaging or volumetric CT) as the quality of RT has a direct impact upon disease control and survival. The usage of ondansetron (0.2 mg/kg) given per orally 45-60 minutes before CSI is recommended as an anti-emetic prophylaxis. Rescue anti-emetics should be prescribed as and when required. Complete blood counts should be monitored at least on a weekly basis during RT and sometimes even more frequently (particularly in the case of pre-irradiation or concurrent chemotherapy). It is preferable to avoid using prophylactic growth factors during CSI, unless deemed necessary. However, growth factors may need to be administered to maintain an absolute neutrophil count >1 × 10⁹/L to prevent unnecessary treatment interruptions. Similarly, platelet transfusions are not recommended routinely for mild thrombocytopenia, but should be reserved for grade 3 or worse thrombocytopenia to maintain a platelet count >50 × 10⁹/L during CSI. The routine use of steroids (dexamethasone or prednisone) is strongly discouraged unless absolutely necessary (e.g. features of raised intra-cranial pressure or therapy-induced intractable delayed nausea/vomiting).

Chemotherapy

Over the last two decades, the role of chemotherapy has considerably evolved establishing it as an integral component in the multi-modality management of medulloblastoma.[12],[13],[67] There is now consistent and high-quality evidence that chemotherapy allows delivery of reduced-dose CSI in standard risk disease [62],[63] without compromising disease-related outcomes and improves survival in patients with a high risk medulloblastoma.[68],[69] Chemotherapy in medulloblastoma is presently recommended in the following settings:

Adjuvant chemotherapy following RTAdjuvant chemotherapy following surgery in infant medulloblastoma (<3-years)Pre-irradiation chemotherapy in infant medulloblastoma to defer RT (till 3-years)High-dose chemotherapy with autologous stem-cell rescueConcurrent chemotherapy with RTSalvage therapy in relapsed/recurrent medulloblastoma.

Chemotherapy for medulloblastoma (>3-years of age)

General principles

Based on the evidence generated from several clinical trials,[62,63,68,69,70] the following general recommendations apply for the practice of adjuvant chemotherapy (>3-years of age):

Adjuvant chemotherapy should start at least 3 weeks after (preferably at 4-weeks, but definitely within 6-weeks) completion of RT to allow for myelo-recoveryNeuraxial imaging should be done for re-assessment of the disease status prior to initiation of adjuvant chemotherapyA total of 6-8 cycles of adjuvant chemotherapy should be administered generally cycled at 3-6 weekly intervals (depending upon the regimen used)The regimen (drugs, doses, cycling) of adjuvant chemotherapy is largely independent of risk-stratificationBaseline hearing assessment with pure-tone audiometry should be done prior to starting adjuvant chemotherapy. However, in younger children unable to undergo pure-tone audiometry, brainstem evoked response auditory assessment is recommended. Hearing assessment should be repeated after every two cycles of platinum-containing regimenEvery cycle of chemotherapy should be administered only after sufficient myelo-recovery is demonstrated (absolute neutrophil count >1 × 10⁹/L and platelet count >100 × 10⁹/L). Additionally, renal function and liver function tests should also be within normal limits for safe delivery of chemotherapy. Serum electrolytes including sodium, magnesium, calcium and phosphorus should be monitored periodically not only during but even after completion of chemotherapy.

Chemotherapy regimens

The following adjuvant chemotherapy regimens [Table 7] are recommended for treating medulloblastoma in children over the age of 3-years. (Table 7)

Regimen I (Packer chemotherapy)
The Packer regimen [Table 6] consists of 8 cycles of adjuvant chemotherapy administered at 6-weekly intervals with appropriate hydration and anti-emetic prophylaxis. Although this regimen has been used widely, it has resulted in significant ototoxicity mandating dose-reduction of cisplatin and/or its replacement with carboplatin during the course of therapy. The use of this regimen mandates hearing assessment at least at every alternate cycle and even prior to every cycle (if deterioration in hearing is documented). Another difficulty with this regimen remains the poor availability of lomustine in several other parts of the world.

Regimen II

An alternative regimen [Table 7] which has been widely used in many low-middle income countries consists of cisplatin, cyclophosphamide and vincristine, all given intravenously at 3-4 weekly intervals for a total of 6-8 cycles. This regimen is also associated with significant ototoxicity requiring stringent monitoring of hearing status.

Regimen III

A modification of the above regimen [Table 7] has been used in India with good tolerance and reduced ototoxicity. In this regimen, cyclophosphamide and vincristine are given intravenously in all the cycles, but cisplatin is given intravenously only in alternate cycles for a total of 6 cycles of chemotherapy at 3-weekly intervals.

High-dose chemotherapy

Given the logistics and resource implications associated with delivering high-dose chemotherapy with autologous stem-cell rescue, the routine usage of such intense regimens in a resource-limited setting is not recommended despite its proven efficacy.[69]

Chemotherapy for Infant Medulloblastoma (<3-years of age)

The treatment strategy for medulloblastoma in infants and very young children (<3-years) continues to evolve. Therapeutic approaches have included strategies to either delay radiotherapy or sometimes even eliminate it completely [71],[72] to avoid the deleterious effect of radiation on the immature nervous system. It is now becoming increasingly evident that there are two major subgroups of infant medulloblastoma: (i) nodular desmoplastic (including MBEN), which can be cured with intense adjuvant chemotherapy alone; and, (ii) anaplastic or classic medulloblastoma, which has poor outcomes with chemotherapy alone strategy.[72] The role of focal conformal irradiation of the tumor bed alone, without CSI in this subgroup is also highly debatable. Therapeutic regimens for infant medulloblastoma have included multi-agent chemotherapy including carboplatin/cisplatin, etoposide, cyclophosphamide, vincristine with or without the use of systemic high dose methotrexate and/or intrathecal methotrexate.

Based on previously published data,[71],[72] it is recommended that children under the age of 3-years at time of establishment of the initial diagnosis of medulloblastoma receive adjuvant systemic chemotherapy following appropriate surgical resection for at least 12-months or until they attain the age of 3-years, whichever occurs earlier. CSI with boost to the primary tumor bed and sites of metastases if any, should be administered after the child attains the age of 3-years. In case of localized high-risk disease (either defined by anaplastic histology or molecular testing), focal conformal radiotherapy to the primary site can be considered on a case-to-case basis after discussion in a multi-disciplinary tumor board. The following chemotherapy regimen [Table 7], administered intravenously at 4-weekly interval for a maximum of 12 cycles is recommended for infant medulloblastoma.

Concurrent chemotherapy with RT

Concurrent weekly vincristine (1.5mg/m 2) given as an intravenous bolus [62] throughout the course of RT is recommended (as in the original Packer’s regimen) for children with standard risk disease being treated with reduced dose CSI. For children with high risk medulloblastoma, the use of daily concurrent carboplatin
(35mg/m²) as a short intravenous infusion throughout the course of RT has demonstrated very promising outcomes [73] with manageable acute toxicity and it is left to the discretion of the treating physician whether or not to employ concurrent carboplatin in routine clinical practice.

Chemotherapy dose-modification guidelines

Hematological toxicity

If absolute neutrophil count is <1 × 10⁹/L and/or the platelet count is <100 × 10⁹/L on day 21 from the last cycle of chemotherapy, the dose of carboplatin, etoposide or cyclophosphamide should be reduced by at least 25% for all subsequent courses. If patient develops febrile neutropenia and requires hospital admission for the same, the dose of carboplatin, etoposide or cyclophosphamide should be reduced by at least 25% for all subsequent courses.

Ototoxicity

Hearing assessment should be done at baseline and prior to every alternate cycle of cisplatin. In the case of hearing loss of 15-30 decibels at lower speech frequencies (1-2 KHz) or >40 decibel loss at 4-8 KHz (higher speech frequencies), cisplatin should be substituted with carboplatin for all subsequent cycles. In the case of hearing loss >30 decibels at 1-2 KHz (lower speech frequencies), all forms of platinum should be stopped completely.

Nephrotoxicity

Renal function has to be assessed prior to every cycle of cisplatin by calculating the creatinine clearance. If creatinine clearance is <80ml/min/1.73m², cisplatin should be replaced with carboplatin for that particular cycle followed by re-assessment prior to the next planned cycle of cisplatin. If creatinine clearance is <60ml/min/1.73m² at any point in time, cisplatin should be replaced with carboplatin for all subsequent cycles. If creatinine clearance is <50ml/min/1.73m², platinum should be stopped completely.

Neurotoxicity

In the case of severe vincristine-induced neuropathy (severe constipation, peripheral motor weakness, paraesthesia or sensory loss), it should be omitted from the present cycle and restarted at 1mg/m² from the next cycle. However, if the neuropathy worsens, vincristine should be omitted completely.

These dose-modification guidelines can help but should not supplant the clinical judgement and expertise of the treating physician.

Follow-up and rehabilitation

It is recommended that following completion of therapy, children with a medulloblastoma be followed up periodically (3-monthly for the first 2-years, 6-monthly till 5-years, and annually thereafter) both for disease control as well treatment-related toxicity. Follow-up assessment should include a detailed physical examination including evaluation of the neurological status and a pro-active surveillance of the treatment-related late effects.[33],[74] Contrast-enhanced MRI of the brain and spine is recommended at 6-12 weeks after completion of all therapy to serve as a baseline for future comparison. Children with a medulloblastoma who relapse/progress after standard therapy have a very dismal prognosis [75] with no potentially curative, salvage therapy options available. Routine imaging surveillance is, therefore, not recommended, but should be ordered only if neurologic worsening occurs, recurrence/progression of disease is suspected, or as a part of any study-specific protocol. Radiological detection of asymptomatic failures and early institution of salvage therapy has not shown to translate into any meaningful survival benefit. A detailed discussion about the late effects of therapy and its management is beyond the scope of this article. However, it is recommended that management of late effects in long-term survivors of childhood medulloblastoma be discussed in a multidisciplinary joint clinic in conjunction with pediatric endocrinologists and rehabilitation specialists.
Conclusions

The current document, containing the 'minimum desirable' as well as 'preferable though optional' recommendations, represents a broad consensus reached amongst various stakeholders within the neuro-oncology community involved in the contemporary curative-intent management of children with medulloblastoma. It provides both general as well as specific guidelines and recommendations to be adopted by physicians and health care providers across India to achieve uniformity of care, improve disease-related outcomes, and compare results between institutions within the country.

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Conflicts of interest

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