



Guidelines for the management of Medulloblastoma (children >3years of age)

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Guidelines for the management of Medulloblastoma (children >3years of age)

Introduction:

Medulloblastoma is the most common malignant brain tumour in children and is a major cause of mortality and morbidity, particularly in low- and middle-income countries. Up to now, medulloblastoma has been risk-stratified on the basis of clinical (age, metastasis and extent of resection) and histological subtypes (classic, desmoplastic and anaplastic). However, recently medulloblastoma has been sub-grouped by using a variety of different genomic approaches, such as gene expression profiling, micro-ribonucleic acid profiling and methylation array into 4 groups, namely Wingless, Sonic hedgehog, Group 3 and Group 4. This new sub-grouping has important therapeutic and prognostic implications. After acute leukaemia, brain tumour is the second most common malignancy in the paediatric age group. The improvement in outcome of acute lymphoblastic leukaemia in low- and middle-income countries reflects the relative simplicity of diagnostic procedures and management. Unlike leukaemia, the management of brain tumours requires a complex multidisciplinary approach, including neuro-radiologists, neurosurgeons with a paediatric expertise, neuropathologists, radiation oncologists and neuro-oncologists. In addition, the equipment required for the diagnosis (magnetic resonance imaging scan, histological, molecular and genetic techniques) and the management (operating room, radiation facilities) is a limiting factor in countries with limited resources. In Pakistan, there are very few centres able to treat children with brain tumours. The current literature review was planned to provide an update on the management of this tumour.

Key Words: Childhood brain tumours, Medulloblastoma, WNT, SHH.

Eligibility criteria:

Patient Criteria

Age:

Patients must be greater than or equal to 3 years and less than 22 years at the time of diagnosis.

Diagnosis:

The presence of a posterior fossa medulloblastoma as determined by institutional pathologic evaluation.

Preoperative and postoperative cranial MRI with and without contrast must be available. Pre (better) or early postoperative MRI scan of the spine as well.

Assessment must include a pre-operative (within 5 days prior to surgery) or postoperative enhanced MRI of the spine within 28 days after surgery.

Cytological examination of CSF performed after surgery but before the time of enrollment. (minimum 14 days after tumour resection)

False positive cytology can occur within 10 days of surgery. Patients with positive CSF cytology obtained before 10 days after surgery may have cytology repeated to determine eligibility.

Performance Level

Patients must have a Karnofsky performance level of ≥ 50 for patients > 16 years of age or a Lansky performance scale of ≥ 30 for patients ≤ 16 years of age.

Prior Therapy

Patients must have no previous radiotherapy or chemotherapy other than corticosteroids. Organ Function Requirements:

a- Adequate renal function defined as:

- Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73m² OR
- A serum creatinine based on age/gender as follows:
Age Maximum Serum Creatinine (mg/dL)

- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

b- Adequate liver function defined as:

- Total bilirubin < 1.5 x upper limit of normal (ULN) for age, and
- SGOT (AST) or SGPT (ALT) < 3 x upper limit of normal (ULN) for age.

c- Adequate Bone Marrow Function Defined as:

- Peripheral absolute neutrophil count (ANC) $> 1500/\mu\text{L}$
- Platelet Count $> 100,000/\mu\text{L}$ (transfusion independent)
- Hemoglobin greater than 10 gm/dL, (may receive RBC transfusions)

Patient Criteria for Standard Risk Patients

- Patients with brain stem involvement are eligible.
- Presence of minimal volume, non-disseminated disease, as defined by the following criteria:
 - 1) There must be unequivocal evidence that the maximal cross-sectional area of residual tumor is 1.5 cm² or less on MRI, performed with contrast imaging (preferably within 48 hours, and at most 28 days following surgery) upon elimination of the tumor.
 - 2) No evidence of metastatic disease in the head, spine, or CSF.

Patient Criteria for High risk patients:

Newly diagnosed, previously untreated:

- 1) M0 Medulloblastoma with >1.5 cm² residual;
- 2) M+ Medulloblastoma;
- 3) M0 or M+).

Patients with diffusely anaplastic medulloblastoma are eligible regardless of M-stage or residual tumor.

Radiology Guidelines;

Prior to surgery (when possible)

- 1- MRI Brain and Spine
- 2- MRI brain and spine (with contrast) should be done in all patients suspected of having medulloblastoma, who are referred to your center prior to surgery. In case surgery had been done in an outside hospital, all pre-surgery scans should be obtained and reviewed in your center.

Imaging Technique

All patients should undergo brain MR imaging at least at 0.5T.

Following sequences should be obtained: axial and coronal T2 FSE (TR/TE, 2700/100 ms), axial or Coronal FLAIR (TR/TE, 9000/120 ms; TI, 2200 ms), precontrast T1 spin-echo and contrast-enhanced T1 spoiled gradient-recalled echo (TR/TE, 8/3 ms; 1-mm section thickness, 0 skip), 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/mm²; 3 directions; 4-mm thickness, 0 skip)

SWI/GRE/T2* is optional.

Imaging interpretation:

All reports should comment on:

1.tumor location, 2.enhancement pattern,3. cysts/cavities, 4.hemorrhage/ mineralization, 5.intracranial or leptomeningeal seeding, 6.tumor margin, 7.necrosis as suggested by ring-enhancement

“tumor location” should be defined as midline vermian/fourth ventricle, cerebellar hemisphere, or cerebellar peduncle/cerebellopontine angle cistern (CP/CPA).

“Tumor margin” should be characterized as ill-defined if >50% of the margin could not be distinguished from the surrounding cerebellar parenchyma on the basis of all imaging sequences.

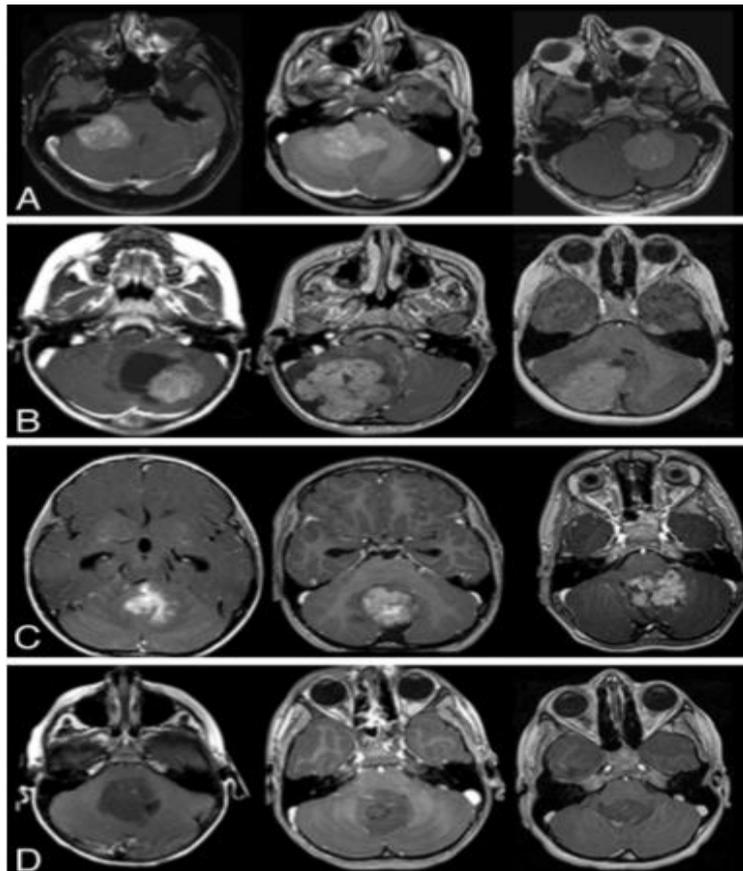
“Enhancement pattern” should be defined as minimal/none if <10% was estimated to enhance, solid if >90% of the tumor volume was estimated to enhance, and heterogeneous if varying degrees of enhancement were seen in 10%–90% of the tumor volume on the basis of radiologist’s visual assessments.

Low signal on 2D gradient recalled-echo or bright on T1W should be used to detect hemorrhage/mineralization.

Tumour size should be given in three dimensions and try best to give volume. Formula for tumour 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 postcontrast or T2W/FLAIR.

Immediate postop scan should be performed in 24-48 hours and should be MRI Brain.



Characteristic MR imaging features according to medulloblastoma molecular subgroups.

- A, In the top row, characteristic location of WNT tumors in the CP/CPA region is shown.
- B, in the second row, SHH tumors are predominantly located in the cerebellar hemispheres.
- C, 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.
- D, In the fourth row, group 4 tumors are also located in the midline fourth ventricle but tend to show minimal or no enhancement.

2- During Surgery

At surgery, every effort should be made to remove the tumor completely. If not possible, then the neurosurgeon should describe, in detail, sites where tumor is believed to remain. Tumor materials from the biopsy, or from materials collected by the surgical vacuum sucker in a sterile trap should be submitted to Pathology for frozen section (if possible) and histopathology.

3-After Surgery and Prior to Radiotherapy

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 must be obtained pre-operatively or within 31 days following surgery. The optimal time for obtaining CSF is 2-3 weeks following surgery. Ventricular CSF (either pre and post-op) may be used only if a post-operative 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).

1. CBC, differential and platelet count
2. Neurological examination

Weekly During Radiotherapy

- ii. Neurological examination including monitoring for signs of vincristine toxicity.
- iii. CBC, differential and platelet count (where bone marrow depletion occurs, these must be carried out more frequently). It is essential that interruptions to treatment are kept as infrequent, and for as short duration as possible.

Four Weeks Post Radiotherapy and Prior to Chemotherapy

- iv. Neurological examination
- v. CBC and differential count, SGOT, SGPT, bilirubin, creatinine and BUN, urine analysis.
- vi. MRI brain (CT of the brain may be used if this was the initial diagnostic tool; consistency of diagnostic examinations during follow up is important).
- vii. MRI spine with gadolinium, only if prior evidence of spinal mets, a positive CSF or new symptoms suggestive of spinal mets.
- viii. CSF should be sampled for cell count, cytology, glucose and protein if previously positive.
- ix. Audiogram before start of chemotherapy and after every other chemotherapy cycle.

Surgical Guidelines:

Presentation of medulloblastoma in pediatric population may be due to local mass effect of the lesion in the posterior fossa, but more commonly it presents with hydrocephalus and raised intracranial pressure.

Medulloblastoma with hydrocephalus:

The hydrocephalus is most commonly due to blockage of the CSF pathway in the fourth ventricle or at the cerebral aqueduct or the outflow foramen. The best strategy would be a definitive procedure with resection of tumor and concomitant opening of the CSF pathway. CSF pathway can be opened up even without gross total resection of the tumor in most of the cases.

A shunt such as ventriculoperitoneal shunt (VPS) should be avoided, if possible. If the patient presents with acute hydrocephalus and logistics do not allow urgent surgery for the tumor, an external ventriculostomy drain (EVD), preferably with long subcutaneous tunnel, can be considered. Alternatively, Endoscopic Third Ventriculostomy (ETV) can also be considered. The problem with VPS is that the child is then committed to a foreign object for the rest of its life. In rare instances, it may lead to reverse herniation or seeding of the abdominal cavity with the tumor. One unique problem seen in Pakistan (probably seen in other LMICs too) is the regression of the parents into denial about the tumor. This happens because treating hydrocephalus leads to remarkable improvement of symptoms. In these cases, the parents tend to ignore the primary disease and fail to follow up. When patient does present back to the oncologist or the surgeon, the tumor is grown tremendously or has seeded into CSF spaces. Therefore, putting VPS is not a good strategy. In rare instances when adequate neurosurgical facility is not within reasonable reach, or nutritional status of the child prohibits tumor surgery, VPS can be considered to avoid any sudden herniation of the brain but then the neurosurgeon has the obligation to keep a close eye on the patient and to ensure that the patient eventually gets definitive surgical treatment. Wherever possible, ETV should be preferred over VPS.

Surgery for Medulloblastoma:

Pre-op screening of the spine for metastases is highly recommended. Pre-op counselling of the patient's parents with pediatric neuro-oncologist is one of the most important steps in preparation of surgery.

The surgery should be performed by a neurosurgeon with experience and expertise in posterior fossa surgery. The misconception that a pediatric neurosurgeon should do the surgery of this tumor needs to be rectified. What is required, is a neurosurgeon with adequate experience in brain tumor surgery and particularly in posterior fossa tumor surgery.

The surgery for tumor should be carried out in institutions that have a suitable team to handle this case in the OR and during post-operative care. The team of anesthesiology should be experienced in pediatric neurosurgical cases to manage volume loss intraoperatively and to use intravenous fluid and blood transfusion prudently. A team of pediatricians should be available to co-manage the patient during post-operative period.

For surgical technique, prone position with head and neck flexed (Concorde position) and a midline incision works reasonably well in most of the cases. Sitting position can be considered based on the experience and familiarity of the surgeon, the anesthesiologist and the OR team with

that position. If a surgeon is meticulous in her/his technique, there is no additional significant benefit of sitting position, but there is definitely a higher risk of air embolism and other risks with the sitting position. Use of Mayfield pins is advisable, and the torque and depth of the pins have to be adjusted based on the age of the child. The surgeon can opt to avoid Mayfield pins and use padded horseshoe, in children 3 years or below.

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.

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.

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 this time.

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 is the primary objective at closure.

Post-Operative Care:

It is best if the patient is extubated in the OR post-operatively and is taken care of in a high dependency unit for 24 to 48 hours. The EVD should be drained at 10-15 cm. It should be pulled out after 48 hours if possible once it is ascertained that there is not much blood in the CSF.

The management of the patient during the post-operative period should be done by the team of neurosurgeon as well as the pediatrician. Pediatric neuro-oncologist, should be involved in the care too.

An MR with contrast should be obtained within first 48 hours. If it is delayed beyond 72 hours then it is best delayed for 3 weeks but should not be delayed more than 4 weeks.

Neuropathology Guidelines:

Medulloblastoma is the most common CNS embryonal tumor and the most common malignant tumors of childhood. Medulloblastoma falls under CNS embryonal tumors and is classified according to molecular characteristics in addition to histopathological features. Histopathological classification has been retained, due to its clinical utility when molecular analysis is limited or not feasible.

Definition

These are embryonal tumors arising in cerebellum or dorsal brain stem, presenting mainly in childhood and consisting of densely packed small round undifferentiated cells with mild to moderate nuclear pleomorphism and a high mitotic count.

Subgroups:

With the advances in genomics, gene expression profiling, and DNA methylation analysis the medulloblastomas have been divided into subgroups. The current integrated classification of medulloblastoma takes into account histological subtype and molecular subgrouping. Following are the subgroups with prognostic implications:

WNT subgroup:

The WNT subgroup represents 10% of all MBs. These are mostly located in the fourth ventricle near the brainstem. Nearly all the medulloblastoma in this subgroup are of classic type. This subgroup has the most favourable outcome and these are rarely metastatic. WNT MBs are characterized by 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.

SHH subgroup:

SHH MBs represent approximately 30% of all MB cases and are characterized by aberrant activation of the SHH signaling pathway. Most SHH MBs are located in the cerebellar hemispheres. Histology in 50% cases is desmoplastic/nodular while most of the rest are classic type. Common alterations in SHH MBs include 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.

Recent studies have identified heterogeneity within the SHH subgroup, further dividing it into four subtypes. The SHH α subtype is enriched in *TP53* mutations, as well as *MYCN* and *GLI2* amplification, and is associated with an extremely poor prognosis. SHH β tumors affect mainly infants and are often metastatic at the time of diagnosis, resulting in poor outcomes. The SHH γ subtype is also found mainly in infants but has a relatively quiet genome and better outcomes. Most MBs with extensive nodularity (MBENs) belong to the SHH γ subtype. The SHH δ subtype is found mainly in adults and frequently contains TERT promoter mutations.

Group 3:

Group 3 MBs account for approximately 25% of all MBs and are the most aggressive of the four subgroups. They mostly have classic or large cell morphology. They are characterized by transcriptional signatures resembling photoreceptors and gamma aminobutyric acid-secreting (GABAergic) neurons. Group 3 tumors are often located in the fourth ventricle near

the brainstem, but nearly 50% of Group 3MB patients exhibit metastatic dissemination at diagnosis.

The most common genetic alteration is amplification of the *MYC* oncogene, found in approximately 20% of Group 3 MB patients. Group 3 tumors often have 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). i17q is found in 40% of Group 3 MB patients and is associated with poor outcomes.

Recent integrative analysis has suggested that there may be three distinct subtypes within Group 3 MB. Group 3 α tumors are often found in infants and frequently exhibit metastasis at diagnosis. Group 3 β has a high frequency of GFI1 family oncogene activation and orthodenticle homeobox 2 (*OTX2*) amplification. Group 3 γ is also associated with a high incidence of metastasis and often exhibits *MYC* amplification; it has the worst prognosis among the three Group 3 subtypes.

Group 4:

Group 4 is the most common subgroup, accounting for approximately 35% of all MBs. These are mostly classic on histology. Group 4 tumors are frequently metastatic at diagnosis and have intermediate outcomes. Similar to Group 3, Group 4 MB also shows intertumoral heterogeneity. Groups 4 α and 4 γ have focal *CDK6* amplification, chromosome 8p loss, and chromosome 7q gain; however, Group 4 α also exhibits *MYCN* amplification, whereas Group 4 γ does not. Group 4 β is enriched in *SNCAIP* duplication and *PRDM6* overexpression.

Molecular profiling studies are the gold standard for accurate characterization of medulloblastoma subgroups. However these are not available in all regions. Fortunately, surrogate immunohistochemical markers are available which along with histological types and clinical data can be used to subgroup most cases of Medulloblastoma. These include the following immunohistochemical stains.

1. **WNT status**; as defined by presence of nuclear staining for Beta catenin immunostain- For Medulloblastoma, WNT activated
2. **p53 status**; as defined by either diffuse positive staining or complete absence of staining in the tumor cells
3. In laboratories where available, following immunohistochemical panel can be used to a surrogate for medulloblastoma classification.

Immunophenotypes of SHH, WNT, and non-SHH/WNT molecular subgroups

Molecular group	Immunoreactivity			
	GAB1	β -catenin	Filamin A	YAP1
SHH	Cytoplasmic	Cytoplasmic	Cytoplasmic	Nuclear + cytoplasmic
WNT	Negative	Nuclear + cytoplasmic	Cytoplasmic	Nuclear + cytoplasmic
Non-SHH/WNT	Negative	Cytoplasmic	Negative	Negative

The Non-SHH/WNT group can only be separated into group 3 or group 4 based on molecular studies only.

4. Medulloblastoma, 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.

Radiation Therapy Guidelines;

Radiation therapy for medulloblastoma consists of craniospinal axis irradiation (CSI) followed by boost to the primary site. Craniospinal irradiation itself is complex due to multiple fields to irradiate the cranium and spine with matching of these fields to cover the clinical target volume and at the same time avoid overdose to the spine. Three-dimensional image-based radiation therapy treatment planning and computer-controlled delivery systems (conformal radiation therapy) improves disease control and functional outcome for children with brain tumors. The availability of tools necessary to perform conformal radiation therapy with sufficient experience of the centre who treat these patients is required. The allowed treatment methods are restricted to conformal or intensity-modulate radiation therapy using photons.

For treatment planning and delivery, the treating radiotherapy center should have

- Conformal radiation therapy capabilities with adequate hardware and application system
- Quality assurance system which includes peer review of all treatment plan with a site specific team
- General anesthesia and/or deep-sedation capabilities by specialized anesthesia team as needed,
- Customized immobilization that provides for treatment that is both reproducible and safe.

Required Benchmark

Radiation therapy shall be administered using photons. Required photon methods include 3D conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT) and craniospinal radiation therapy. Centers participating in this protocol using 3D-CRT are required to complete the 3D benchmark; those using IMRT must complete the IMRT standards and benchmark on phantom. The QARC craniospinal radiation therapy benchmark form can be used in the absence of national quality standards. Radiation therapy center shall complete the QARC CT/MR image fusion benchmark. Benchmark materials and questionnaires may be obtained from the Quality Assurance Review Center (www.qarc.org) For information regarding the IMRT phantoms, resources like RPC (<http://rpc.mdanderson.org/rpc>) can be used.

Guidelines and Requirements for the Use of IMRT:

Radiation oncologists are required to comply with the ICRU reports (ICRU report 50,63 & 83) guidelines. There is need of a national quality assurance system for recording of treatment setup and accessories, planning and diagnostic imaging used, dose to the targets and normal tissue, dosimetry etc. In our scenario, for the use of IMRT, National Cancer Institute sponsored cooperative group trials guidelines are available through www.qarc.org. These guidelines require that the protocol explicitly state their requirements and methods for localization and immobilization; the use of volumetric imaging; target and organ motion management; nomenclature, definitions and rationale for targets and organs at risk; target volume coverage and normal tissue dose constraints; effects of heterogeneity in tissues; and quality assurance.

1. Timing of Radiation Therapy:

All patients shall receive irradiation to the craniospinal axis followed by a boost to the posterior fossa. Patients shall begin radiation treatments within four weeks of definitive surgery and shall not be delayed beyond 7 weeks. Delay in start of radiotherapy has shown inferior outcome. Patients who start radiotherapy beyond 7 weeks of surgery are considered high risk, requiring higher dose of craniospinal irradiation of 36 Gy.

2. Equipment:

Radiation therapy shall be delivered using photons on Linear Accelerator. CT based planning shall be done on all patients with adequate immobilization devices. If IMRT or VMAT is used, photon energy should be no greater than 10 MV.

a. Modality

X-rays with a nominal energy ≥ 4 MV. Craniospinal axis irradiation is best done with x-rays between 4-6 MV. The boost volume may be treated with a nominal energy ≥ 4 MV, as long as dosimetric Constraints are accomplished.

b. Calibration

The calibration of therapy machines used shall be calibrated and verified by the pertinent authority.

c. Equipment

Patients treated with this study must be treated using conformal radiation therapy treatment planning and delivery techniques at a minimum. IMRT or VMAT shall be used if appropriate quality benchmarks have been attained and maintained as per international standards (QARC, AAPC etc). All patients must be treated on isocentric machines. For treatment to be conformal as per protocol, the following criteria must be met:

- Three-dimensional imaging data (CT or MR) are acquired with the patient in the treatment position. Three-dimensional treatment planning software must be used for planning.
- Double checks of treatment plan shall be done on standardized reporting form e.g. QARC [QARC website (www.QARC.org)]
- Image data are used to delineate and reconstruct a gross target volume, clinical target volume, planning target volume, and normal or critical structures in 3-dimensions.
- All contours and treatment planning volumes shall be peer reviewed by a second radiation oncologist.
- Radiation beams can be freely oriented in 3-dimensions for both the planning and delivery process, and structures traversed by the beam can be visualized with the eye of the beam (beam's eye view – BEV)
- The distribution of dose relative to the target volume or any structure is computable on a point-by-point basis in 3-dimensional space.
- Institutions not equipped to perform conformal radiation therapy according to these guidelines should refer the patient to a center with proven capabilities to comply with the outlined parameters.

3. 3-D Target volume and organ at risk definition

The definitions for the target volumes and treatment dosimetry will adhere as closely as possible to the ICRU Reports 62 and 83. RT volumes for treatment shall be determined by the collective information that delineates the extent of disease at the time of diagnosis and prior to radiation therapy. RT Planning volumes and organ at risk contours shall be peer reviewed with paediatric radiotherapy team of doctors.

These guidelines are meant to be comprehensive and include commonly anticipated treatment scenarios. If for any reason the guidelines do not match the characteristics of a given patient, the treating physicians shall contact colleague from other specialized centers having experience of pediatric CNS radiotherapy.

a. Gross Tumor Volume (GTV)

The GTV includes all gross residual tumor and/or the walls of the resection cavity at the primary site based on the initial imaging examination that defines the tissues initially involved with disease anatomically and the post-operative and pre-irradiation neuroimaging examinations that identify residual disease and the tumor bed.

In accordance with ICRU report, the Gross Tumor Volume (GTV) is defined as the contrast-enhanced tumor in the Brain and the Spine, unless the preoperative tumor is predominantly non-enhancing, in which case this represents the preoperative tumor extent as defined by the most informative MR imaging sequence.

b. Clinical and Planning Target Volumes (CTV and PTV)

The CTV includes the GTV with an added margin that is meant to treat subclinical microscopic disease and is anatomically confined (i.e., the CTV is limited to the confines of the bony calvarium and tentorium where applicable). There are multiple CTVs to be treated.

The Clinical Target Volume₁ (CTV₁) is the entire craniospinal axis. The craniospinal axis Planning Target Volume (PTV₁) is institution-defined according to immobilization techniques and their inherent setup uncertainties. The margin defining the PTV may range from 0.5 cm to 1.0 cm. For the Craniospinal volume, a larger PTV₁ margin should be considered due to inexactness of repositioning for the spinal fields.

CT based or 3D treatment planning for craniospinal axis irradiation offers advantages over conventional simulation methods. A better appreciation of the cribriform plate and middle cranial fossa can be gained with a CT simulation. In most circumstances, the same CT simulation data used for planning the craniospinal axis RT can be used to plan the 3-D conformal boost.

Whole Brain (CTV₁): The whole-brain field shall extend anteriorly to include the entire frontal lobe and cribriform plate region. The volume shall cover the superior orbital tissue (but not the posterior globe as in leukemia protocols). Inferiorly, the CTV₁ shall be at least 0.5 cm below the base of the skull at the foramen magnum. PTV₁ should be defined to account for setup error. The radiation fields to cover this target volume should follow established guidelines for cranial irradiation in medulloblastoma. There will be a junction with the spinal field.

For standard risk patients, the dose prescription for the brain and spine (CSI) will be 23.40 Gy in 13 daily fractions of 1.80 Gy. However, for high risk patients, the dose prescription for CSI will be 36.0 Gy in 20 fractions of 1.80 Gy.

Spine (CTV₁): The spinal target volume will be the entire thecal sac. The field to cover this volume should extend laterally on both sides to cover the recesses of the entire vertebral bodies, with at least a 1 cm margin on either side. The superior border will be the junction with the whole brain field. The inferior border of the treatment volume will be placed after review of the spinal MRI. The border will be 2 cm below the termination of the subdural space. This will extend at least to the inferior border of the second sacral segment (S2-S3 interspace), but may be as low as the inferior border of S4. If this cannot be accomplished in a single field, there will be a junction between the two spinal fields. PTV₁ should be defined to account for setup error as per institution.

For standard risk patients, the dose prescription for the brain and spine (CSI) will be 23.40 Gy in 13 daily fractions of 1.80 Gy. However, for high risk patients, the dose prescription for CSI will be 36.0 Gy in 20 fractions of 1.80 Gy.

Supratentorial Boost (CTVST): This volume refers to children with supratentorial primaries (ST-PNET). The CTVST for a supratentorial boost will be defined using a 1 cm margin around the presurgical MRI defined tumor volume. In the event of proximity to normal tissue structures, this margin may be reduced to 0.5 cm to allow for sparing of critical structures. As the total dose to the optic chiasm and both optic nerves should not exceed 50.4 Gy, these structures should be excluded accordingly. The Planning Target Volume (PTVST) is a 0.3cm to 0.5cm margin around the CTVST to account for day-to-day setup variation.

Limited Target Volume Boost (CTVboost) [for standard risk patients only: 3D-based treatment planning is mandatory for this volume. IMRT or VMAT is allowed for the PTVboost. The Gross Target Volume (GTV) is based upon the T1 signal changes with and without Gadolinium contrast. Identification of the GTV shall be based upon pre-operative extent and anatomic shifts or changes after surgery. The GTV should include any residual enhancing tumor mass and the wall of the resection cavity. The Clinical Target Volume (CTVboost) is defined as the GTV plus a 1.5-cm margin except at bone or tentorial interface (where it remains within the confines of the posterior fossa). The PTVboost margin should be an additional 0.3 to 0.5 cm around the CTVboost. In treatment planning, shielding of critical structures should be attempted, however, coverage of the PTVboost must not be less than 50 Gy. The cumulative dose to PTVboost will be 54.0 Gy. At least 95% of the prescribed dose (54Gy) must encompass at least 95% of the PTVboost as shown by DVH. No part of the PTVboost should receive less than 50 Gy.

Posterior Fossa Boost (CTV_{PF}): 3D-based treatment planning is mandatory for these volumes. IMRT is allowed for the PTV_{PF}. The CTV_{pf} should encompass the entire posterior fossa. The posterior fossa must be defined on the planning CT scan. It is strongly recommended that a sagittal MRI be used to assist in identification of the position of the tentorium. The CTV_{PF} extends inferiorly from C1 vertebral canal through the foramen magnum, laterally to the bony walls of the occiput and temporal bones and superiorly to the tentorium cerebelli. Generally, the sigmoid sinuses define the lateral-superior extent of the bony confines of the posterior fossa that attach contiguously to the tentorium above. The folia of the cerebellum and the anterior border of the brainstem and midbrain bound the CNS contents of the posterior fossa. The Planning Target Volume (PTV_{PF}) is a 0.3cm to 0.5cm (or more depending upon institutional setup error) margin around the CTV to account for day-to-day setup variation. The PTV_{PF} should not extend beyond the external bony confines of the skull except at the foramen magnum to C1-C2. The PTV_{PF} should extend anteriorly to the posterior clinoids (the pituitary is not included) and inferiorly to the C1-C2 junction. In treatment planning, shielding of critical structures should be attempted. At least 95% of the prescription study dose of 55.8 Gy must encompass at least 95% of the PTV_{PF} (the posterior fossa) as shown by DVH. No part of the PTV_{PF} should receive less than 50 Gy. Treatment techniques for the PTV_{PF} may include parallel opposed laterals or other 3D CRT methods to limit dose to the supratentorial brain, hypothalamus, pituitary or middle ear.

Metastasis Site Boost (CTVM): Patients with M1 disease will receive no additional boost. Patients with M2 disease (intracranial subarachnoid disease) will receive boosts to areas of supratentorial or posterior fossa metastatic disease.

Patients with M3 disease (spinal deposits of disease) are subdivided into those with diffuse disease and those with focal disease.

Diffuse spinal disease is defined as radiographically visible multiple sites of disease in each of at least 3 out of 4 spinal regions (i.e., cervical, thoracic, lumbar or sacral). If there is diffuse involvement of the spine, the entire spine will be treated in the boost volume.

The CTV_m margin for boosting metastatic deposits will be 0.5 to 1.0 cm encompassing the lesion within the anatomic compartment. Another 0.3 to 0.5 cm margin will be added for the PTVM. Field shaping may be conformal and consideration may be given for normal organ sparing and abutment of other high dose or boost sites.

c. Organs at Risk (OAR)

The following organs must be defined for 3-D conformal radiation therapy or IMRT planning:

- Supratentorial brain (left and right)
- Cochlea (left and right)
- Hypothalamus/pituitary
- Lacrimal apparatus
- Eyes (left and right) including lens
- Optic nerves (left and right)
- Optic chiasm
- Cervical spinal cord (foramen magnum to C2)
- Skin (non-specified tissues)
- Thyroid gland
- Heart
- Bilateral Lungs
- Bilateral kidneys
- Both ovaries in females
- Vertebral bodies

Details contouring guidelines have been published and illustrated as following:

1. Clinical Oncology Group (COG) atlas for contouring of CSI
<http://www.qarc.org/cog/protocol%20resources/ACNS0331Atlas.pdf>
2. Brain Tumor Study Group of Siop Europe (SIOP-E) guideline on craniospinal target volume delineation for high-precision radiotherapy
[https://www.thegreenjournal.com/article/S0167-8140\(18\)30204-4/fulltext](https://www.thegreenjournal.com/article/S0167-8140(18)30204-4/fulltext)
3. Management of vertebral radiotherapy dose in paediatric patients with cancer: consensus recommendations from the SIOPE radiotherapy working group
[https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(19\)30034-8/fulltext](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30034-8/fulltext)

4. Dosimetry

a. Prescription Point

The prescription point for the neuroaxis (PTV₁, whole brain and spine) is at or near the center of the targets. For the brain this may be a point other than the central axis. Consideration should be made to using a point midway of the biparietal diameter. The spinal axis dose should be prescribed to the anterior aspect of the spinal canal. In many cases, the depth of the anterior spinal canal will

vary by vertebral level. An average depth may be used that keeps the dose uniformity within the constraints defined below. For the posterior fossa and limited target boost volumes, the doses shall be prescribed in order to have at least 95% of the 54 Gy isodose covers at least 95% of the respective planning target volumes. The minimum dose to the PTV_{PF} or PTV_{boost} shall not be < 50 Gy.

b. Dose Definition

Dose is to be specified in Gray (Gy)-to-muscle.

c. Prescribed Dose and Fractionation STANDARD RISK PATIENTS

23.40 Gy Craniospinal radiotherapy (CSRT) (PTV₁) followed by:

30.60 Gy Local boost (PTV_{boost})

Cumulative Dose: 54Gy

High Risk Patients:

36.0 Gy Craniospinal radiotherapy (CSRT) (PTV₁)

55.8 Gy Posterior fossa boost, cumulative dose (PTV_{PF} or PTV_{ST})

Patients with M1 disease will receive no additional boost.

Patients with M2 disease (intracranial subarachnoid disease) will receive boosts to areas of supratentorial or posterior fossa metastatic disease. (Table below)

Patients with M3 disease (spinal deposits of disease) are subdivided into those with diffuse disease and those with focal disease. Patients with diffuse disease will have their entire spine boosted to 39.6 Gy. (Table below)

Table: Radiation Dose for Craniospinal Axis Radiation Therapy

M-Stage at Diagnosis	CSRT Dose	Metastasis location	Dose to PTV _M	Total Dose to PTV _M	Dose to PTV _{PF} /PTV _{ST}	Total Dose to PTV _{PF} /PTV _{ST}
M0, M1	36 Gy	None	NA	NA	19.8 Gy	55.8 Gy
M2	36 Gy	Intracranial	19.8 Gy	55.8 Gy	19.8 Gy	55.8 Gy
M3	36 Gy	Diffuse	3.6 Gy	39.6 Gy	19.8 Gy	55.8 Gy
		Focal, above terminus of spinal Cord	9 Gy	45 Gy	19.8 Gy	55.8 Gy
		Focal, below terminus of spinal cord	14.4 Gy	50.4 Gy		

*note: if M3 and has intracranial metastatic disease, follow schema for M2 cranial dosage as well

d. Dose Fractionation

Patients will receive one fraction of 1.8 Gy per day, five days per week.

e. Dose Uniformity

The dose variations in each target volume shall be within +10%, -5% of the prescription-point dose. This applies to all photon modalities.

At least 95% of the PTVboost should be encompassed within 95% of the 54 /55.8 Gy isodose surface and no more than 5% of the volume within this isodose surface should receive greater than 110% of the prescription dose as evaluated by DVH. These targets should not receive less than 50 Gy. Treatment should be planned to spare the spinal cord, brainstem, optic chiasm and optic nerves from the highest doses resulting from dose inhomogeneity. An effort should be made to spare the cochlea and middle ear contents.

f. Treatment Interruptions

Treatment will not be interrupted for anemia, leukopenia, or thrombocytopenia unless life threatening. Blood product support should be instituted according to institutional/protocol guidelines. For interruptions of more than 2 treatment days it should be discussed with pediatric oncologist.

5. Treatment Technique

Craniospinal Axis Irradiation

Patient Position

For cranio-spinal irradiation the patient may be treated prone or supine. Supine position is feasible for patients being treated with general anesthesia. The neck should be extended sufficiently to keep the mandible out of the exit beam of the spinal field but not so much as to exceed the dose uniformity specifications of the spinal field. Reproducible setups are critical. Immobilization devices such as head holders or custom molds are highly recommended. Deep sedation or general anesthesia is strongly encouraged for young children. For the posterior fossa boost the patient may be in either the prone or supine position. It is recommended to have a uniform setup through all phases of treatment

Whole Brain Irradiation

Conformal treatment planning is recommended. Regardless, dose from this component of the radiation therapy shall be included in the 3D CRT / IMRT plan of the limited boost volume, including DVHs of the targets and adjacent organs at risk.

Parallel opposed fields may be used. Alternatively, the field center can be placed near the match line with the spinal field and an independent jaw or half-beam block technique utilized. This method decreases overlap at the match line. The collimation of the brain field should be rotated to match the divergence of the spinal field.

If symmetric collimator jaws are used:

$$\text{The angle} = \frac{\tan^{-1} \text{ spine length}/2}{\text{SAD}}$$

If asymmetric collimator jaws are used:

$$\text{The angle} = \frac{\tan^{-1} \text{ upperspine length}}{\text{SAD}}$$

The lateral fields may be angled posteriorly to spare the collateral lens, but, if this is done, great care must be taken to assure adequate coverage of the cribriform plate. Custom divergent blocking of at least 5 HVL should be used to shape the brain field at the base of the skull and around the eyes. The brain field should extend to at least 1 cm beyond the periphery of the scalp.

Spine Irradiation

Preferably, the spinal volume should be treated with a single posterior field. An extended SSD is preferable to the use of adjacent ports. If adjacent ports are necessary, the 50% decrement should cross at the posterior margins of the vertebral body. It is preferable that the match line be placed inferior to the spinal cord (below L2) and should be moved every 900 cGy. Custom blocking may be required at the inferior border of the spine.

Abutting Fields

With the use of collimator rotation and an independent jaw technique, the cranial and spinal fields may be directly abutted (light fields). Many radiation oncologists, though, are more comfortable with a gap between the cranial and spinal light fields. A gap of 0.5 cm is allowed on this protocol. The match line should be moved at least twice during treatment of the cranio-spinal axis (e.g. after each 9Gy). Also, a penumbra broadening “match line wedge” or a dynamic wedge may be used. The match line should never overlap the posterior fossa boost. Therefore, it is recommended that the first match line lie just above the shoulder, and the last 2 cm higher. Alternatively, the first match point could begin at the superior point and end at the inferior point.

Conformal Boost Treatment

Conformal (three-dimensional) planning is required for all phases of treatment. Beam arrangements and treatment techniques should be used that minimize the dose to the auditory apparatus (cochlea), hypothalamic/pituitary unit and supratentorial brain providing that they do not compromise treatment of the intended PTV. Examples of 3-D conformal beam arrangements can be found at the QARC (www.qarc.org) or ITC (itc.wustl.edu) website.

Field Shaping

Field-shaping is required. Shielding shall be at least 5 HVL thick. Multi-leaf collimation may be used.

Example Cases

<http://www.qarc.org/cog/protocol%20resources/ACNS0331Atlas.pdf>

Imaging

CT (3 mm - 5 mm section thickness from the thoracic inlet to the base of the skull, 3 mm for the entire skull) should be performed for treatment planning. Preoperative and postoperative MR is used primarily (co-registered with CT planning data) or adjunctively in the treatment planning process. Surgical guidelines encourage postoperative imaging within 72 hours post-operatively.

6. Normal tissue sparing

Normal tissue dose recommendations are the same for photons

Spinal Cord

No more than 50% of the cervical spinal cord between C-1 and C-2 should receive more than 54 Gy. DVH of this volume shall be submitted.

Tolerance of rest of the spinal cord is to be followed, i.e. <45Gy.

Optic Apparatus

Dose to the bilateral optic nerves and optic chiasm shall be <54Gy

Vertebral Body

Dose gradient over the vertebral body shall be avoided. SIOPE guidelines in this regard is helpful and shall be followed:

[https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(19\)30034-8/fulltext](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30034-8/fulltext)

7. Supportive Care During Irradiation

Hematologic

CBC's should be obtained weekly. If ANC $\leq 500/\mu\text{l}$, either a break in treatment or the use of growth factors may be considered. The option of continuing therapy with the posterior fossa boost field may also be considered in patients who have lowered counts during the cranio-spinal therapy. Cranio-spinal radiation may be resumed when the ANC has risen over 10% on 2 consecutive tests, or is above $750/\mu\text{l}$. If ANC is less than $1000/\mu\text{l}$ and the patient is febrile ($\geq 38^\circ\text{C}$), a break may be instituted while the patient is being evaluated. During this time, the posterior fossa boost may be treated, but cranio-spinal irradiation should be avoided.

Platelets should be transfused as clinically indicated when counts are $< 30,000/\mu\text{l}$. Irradiated and Pall filtered blood products should be used. Cranio-spinal irradiation should be reinstated when platelet counts exceeds $50,000/\mu\text{l}$ or have risen $> 10\%$ on 2 consecutive tests.

Hemoglobin: Transfusions are recommended when hemoglobin falls below 9 gm/dL. Radiated blood

products should be used. Growth factors can also be utilized.

Gastrointestinal

Patients should be weighed weekly. If there is greater than 10% weight loss, aggressive nutritional support, either enteral or parenteral, should be given. Prophylactic anti-emetic therapy, with e.g. a selective 5-HT₃ receptor antagonist, should be considered.

Pneumocystis

Pneumocystis prophylaxis with trimethoprim/sulfamethoxazole (5 mg/kg/d of trimethoprim in two divided doses given 2 consecutive days per week) is recommended for all patients during radiotherapy and should be continued for 2 months after completion of radiotherapy.

Varicella

If patients are seronegative for varicella, VZIG should be administered within 72 hours if history of exposure to chickenpox or zoster is elicited.

8. Dose calculation and reporting

Quality assurance measures, plan parameter and dosimetry record shall be maintained as per international standards both for three dimensional conformal and IMRT / VMAT planning.

The sample Benchmark material can be obtained from the Quality Assurance Review Center (www.QARC.org) Contact the RPC (<http://rpc.mdanderson.org/rpc>), AAPM or IAEA resources.

Prescribed Dose

For standard or 3D conformal techniques: The monitor units required to deliver the prescribed dose shall be calculated and submitted using the standard documentation, like "RT-1 Dosimetry Summary" form. A separate form shall be filled and recorded for each of the planning target volumes.

For IMRT techniques: The monitor units required to deliver the prescribed dose shall be calculated and submitted using the IMRT Dosimetry Summary Form. The monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the plan's fluence distributions can be recomputed for a phantom geometry.

Isodose Distributions

Color hard copies of the isodose distributions must be maintained for each of the treatment sites including the craniospinal axis and primary site boost at the start of radiation therapy. A composite isodose distribution must also be saved. The isodose distributions will display the actual dose to be delivered for a particular phase of treatment (e.g., CSA isodose distributions will show 23.4 Gy, primary site boost isodose distributions will show 30.6 Gy). The cumulative dose (54.0 or 55.8 Gy) will be displayed on the composite isodose distribution. It is understood that some patients may be treated in 2 consecutive phases and have the CSA radiation therapy delivered in a position that is different from the boost radiation therapy (not recommended). While it is sometimes not possible to accurately add radiation doses due to the change in patient shape and position, the institution must submit a plan that closely approximates the cumulative radiation dose that is delivered as part of both the cranial fields from the CSA and the boost treatments. This can generally be done by creating a cranial field in the boost plan that is dose-weighted and shaped similarly to that used in the CSA phase of therapy.

For conformal planning, the following isodose distributions are required by treatment site and for the composite and will include the gross tumor volume, clinical target volume and planning target volume and normal tissue structures listed in section earlier. Axial, sagittal, and coronal isodose distributions through the treatment isocenter will be overlaid on reconstruction of the CT scan in the same plane.

Isodose distributions corresponding to each CT image that shows protocol-specified normal tissue structures or tumor/target volume contours.

The following isodose curves should be shown to determine that the dose distributions conform to the protocol guidelines: dose-maximum, 110%, 105%, 100%, 95%, 90%, 70%, 50%, 30%, 10%.

Dose Volume Histograms

Dose volume histograms shall be calculated and submitted for organs at risk (section 18.3.3) including right and left optic nerves, optic chiasm, right and left cochlea, pituitary/hypothalamus, vertebral bodies, heart, thyroid, kidneys, supratentorial brain, and spinal cord (foramen magnum to top of C2). Dose volume histograms will be calculated and submitted for the GTV, CTV and PTV of each volume treated. Dose volume histograms will be calculated and submitted in composite form whenever technically possible.

9. Quality Assurance and documentation

For quality assurance purpose, the radiation therapy treatment plan should be available in digital format (either Dicom RT, RTOG format or other standard format) if possible. One can see the QARC website (www.QARC.org) for digital data submission information.

It is encouraged to compile the following documents:

Copies of all diagnostic materials and surgical reports used in defining the target volume including (i) preoperative MRI and postoperative cranial MRI with and without contrast; (ii) pre or postoperative spinal MRI with and without contrast; sagittal imaging should be included for both brain and spine; (iii) operative reports.

- Copies of isodose distributions to demonstrate that the dose variation is within specification.
- The target volume, and the prescription point must be clearly shown
- Prescription Sheet for Entire Treatment
- Copies of simulator films and /or digitally reconstructed radiographs (DRR's) for each field.
- Copies of verification (portal) films (or hard copy of real time portal images) for each field.
- Photographs of the patient in the treatment position with the fields marked.
- Beam's Eye Views (BEV's) for all fields and showing the PTV (boost) and critical structures.
- BEV hard copies must be in color to enable reviewers to identify structures.
- A room view display of all fields should be submitted.
- Dose volume histograms as specified in section 18.8.4. If IMRT is used, a DVH shall also be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.
- Documentation of an independent check of the calculated dose if IMRT is used.
- Color copies of isodose distributions to demonstrate that the dose variation is within specification.
- The target volume and the prescription point must be clearly shown.
- Documents verifying peer review and double checks from radiation oncologist, medical physicist and RTTs for all the phases of treatment for each patient.
- RT-1 Dosimetry Summary Form
- RT-2 Radiotherapy Total Dose Record form.

Chemotherapy

a. Average Risk Medulloblastoma concurrent chemotherapy during radiation

PROTOCOL: Vincristine **During Radiation** Therapy (6 cycles of weekly Vincristine)

Allergy: _____	
Weight: _____ KG	Height: _____ CM
Surface Area: _____ M ²	

Lab work: CBC with differential, Chem.18

Parameters: Total bilirubin \leq 1.5 mg/dL, and ALT and AST \leq 2.5 x normal for age, **otherwise contact the oncologist.**

Week 1 (_____), Week 2 (_____), Week 3 (_____)

Week 4 (_____), Week 5 (_____), Week 6 (_____)

- **Vincristine:** 1.5 mg/m² (___%) = _____mg (**maximum dose is 2 mg**)IV in 50 ml N/S over 5 minutes

b. Average Risk Medulloblastoma (Maintenance Chemotherapy)

– for age more than 5 years (Vincristine, Cisplatin and Lomustine CCNU)

Cycle 1 2 3 4 5 6 (Circle one) every four weeks

Allergy: _____	
Weight: _____ kg	Height: _____ cm
Surface Area: _____ m ²	

Lab work: CBC with diff., Creatinine level, chem. 18, audiogram, GFR

Parameters: ANC more than 1000/ μ l, Platelets more than 100,000/ μ l, Creatinine less than 1.5 X baseline ___ or CrCL more than 50 ml/min/m²,

Total bilirubin \leq 1.5 x normal for age, and ALT and AST \leq 2.5 x normal for age, **otherwise contact the oncologist.**

Antiemetics:

- Ondansetron 0.15 mg/kg = _____mg (maximum 8 mg) IV Q 8 hours schedule a dose before chemotherapy for 3 days
- Diphenhydramine 1 mg/kg/dose = _____mg IV PRN every 4 hours for nausea and vomiting.

Day 1 (_____):

Per oral tablet or suspension CCNU (Lomustine) 75mg/m²/day on day one only.

- **Vincristine** (___%) 1.5 mg/m² = _____ mg (maximum dose 2 mg) IV in 50 ml N/S over 5 minutes
- Hours -2 to 0: Prehydration: D5W 1/2N/S at 250 ml/m²/hour = _____ml/hour +
- mannitol 10 gm/m²= _____gm.
- Hour 0 - 6: D5W 1/2N/S at 125 ml/m²/hour = _____ ml/hour + mannitol 10 gm/m²= _____gm.
- Hour 0 - 6: **Cisplatin** (___%) 75 mg/m² = _____mg IV to be infused over 6 hours in 500 ml N/S
- Hour 6 - 24: Post hydration: D5W 1/2N/S with Magnesium sulfate 1 mEq/kg/day= _____mEq/day at

125 ml/m²/hour= _____ml/hr.

- After finishing post hydration ,start PO magnesium oxide 20 mg/kg/day=_____mg/day divided twice daily for 5 days.
- Strict urine out is required once cisplatin infusion started
- If urine output is less than 3 ml/kg/hr at_____ kg =_____ ml/hr for 2 hours,
- Administer Mannitol 0.5 gm/kg x _____kg = _____ gm in D₅W 10 ml/kg x ___ kg = _____ml over 30 minutes
- If urine output is not increased within one hour, give furosemide 0.5 mg/kg = _____ mg IV push.

Fellow Name _____ Signature _____ Date _____ Time _____

Attending Name _____ Signature _____ Date _____ Time _____

Clinical pharmacist Name _____ Signature _____ Date _____ Time _____

c. High Risk Medulloblastoma (Maintenance Chemotherapy)

– for age more than 5 years (Vincristine, Cisplatin and Cyclophosphamide)

Cycle 1 2 3 4 5 6 (Circle one) every four weeks

Weight: _____kg Height: _____cm Allergy: _____
Surface Area: _____m²

Lab work: CBC with diff., Creatinine level, chem. 18, audiogram, GFR

Parameters: ANC more than 1000/μl, Platelets more than 100,000/μl, Creatinine less than 1.5 X baseline____or CrCL more than 50 ml/min/m²,

Total bilirubin ≤ 1.5 x normal for age, and ALT and AST ≤ 2.5 x normal for age, **otherwise contact the oncologist.**

Antiemetics:

- Ondansetron 0.15 mg/kg = _____mg (maximum 8 mg) IV Q 8 hours schedule a dose before chemotherapy for 3 days
- Diphenhydramine 1 mg/kg/dose = _____mg IV PRN every 4 hours for nausea and vomiting.

Day 1 (_____):

- **Vincristine** (____%) 1.5 mg/m² = _____ mg (maximum dose 2 mg) IV in 50 ml N/S over 5 minutes
- Hours -2 to 0: Prehydration: D₅W 1/2N/S at 250 ml/m²/hour = _____ml/hour + mannitol 10 gm/m²= _____gm.
- Hour 0 - 6: D₅W 1/2N/S at 125 ml/m²/hour = _____ ml/hour + mannitol 10 gm/m²= _____gm.
- Hour 0 - 6: **Cisplatin** (____%) 75 mg/m² = _____mg IV to be infused over 6 hours in 500 ml N/S
- Hour 6 - 24: Post hydration: D₅W 1/2N/S with Magnesium sulfate 1 mEq/kg/day= _____mEq/day at 125 ml/m²/hour= _____ml/hr.
- After finishing post hydration ,start PO magnesium oxide 20 mg/kg/day=_____mg/day divided twice daily for 5 days.
- Strict urine out is required once cisplatin infusion started
- If urine output is less than 3 ml/kg/hr at_____ kg =_____ ml/hr for 2 hours,
- Administer Mannitol 0.5 gm/kg x _____kg = _____ gm in D₅W 10 ml/kg x ___ kg

= _____ ml over 30 minutes

- If urine output is not increased within one hour, give furosemide 0.5 mg/kg

= _____ mg IV push.

Day 2 (_____) and Day 3 (_____):

- Check urine specific gravity, if it is less than or equal to 1.010 continue with cyclophosphamide, otherwise give:
 - Hours -4 to 0: Prehydration: D5W 1/2N/S with KCL 20 mEq/L at 100 ml/m²/hour = _____ ml/hour for 4hours or less until urine specific gravity is less than or equal to 1.010
-

- -15 minutes: Mesna 360 mg/m² = _____ mg in 50 ml D5W over 15 minutes.
-

Hour 0 - 60 minutes: **Cyclophosphamide**(____%) 1000 mg/m² = ____mg IV to be infused over 60 minutes in 100 ml N/S. On Day 2, cyclophosphamide should be given at least 24 hours after CISplatin.

- Hour 3 and 6: Mesna 360 mg/m² = _____ mg IV in 50 ml D5W over 15 minutes.
-

- Hour 0 - 24: Post hydration: D5W 1/2N/S with KCl 20 mEq/L at 100 ml/m²/hour=____ml/hr.

-- must start post hydration concurrently with cyclophosphamide and Continue hydration at the same rate for at least 8 hours on day 3.

- Check urine output and specific gravity Q 8 hours ►

If input more than output by 200 ml, give furosemide 0.5 mg/kg IV =____mg

If specific gravity more than 1.010 give D5W 1/2 N/S 10 ml/Kg =____ml over 30 min.

- Check urine RBCs Q day before cyclophosphamide dose ►

If urine RBCs is, more than 5 / HPF then notify MD on call.

d. Dose Modification for Toxicities

Vincristine Toxicity

Neurotoxicity

For seizures, hold one (1) dose, then reinstitute at 1.0 mg/m² (1.5 mg maximum) while anticonvulsants are continued. If seizures do not recur, then escalate to full dosage. Rule out syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a cause of seizures.

Neurotoxicity Grade 3/4, foot drop, severe paresis, disabling paresthesias or ileus: hold one dose, resume vincristine at 1 mg/m² (1.5 mg maximum) and then escalate to full dosage when symptoms resolve. In children with neuropathies vinblastine at a dose of 4mg/m²/dose can be safely given during radiation and also in combination with cisplatin, CCNU and cyclophosphamide³. This strategy may allow the full dose of vinca alkaloids without the associated peripheral neuropathy.

Jaw Pain

Treat with analgesics (not salicylates). Do not hold or reduce vincristine.

Hepatotoxicity

If total bilirubin is greater than 1.9 mg/dL, hold vincristine dose. If direct bilirubin is 1.5 - 1.9 mg/dL, administer vincristine at 1.0 mg/m².

Hematopoietic Toxicity

If chemotherapy is due and the absolute neutrophil count remains below 750/ μ L or the platelet count is less than 75,000/ μ L, the next cycle of chemotherapy should be delayed. Repeat CBC and platelet count weekly.

If the next cycle of Maintenance is due and ANC < 750/ μ L hold chemotherapy until ANC > 750/ μ L.

- If the patient is due to receive Regimen A, the dose of Lomustine (CCNU) should be reduced to 20mg/m².
- If the patient is due to receive Regimen B, the dose of Cyclophosphamide should be reduced by 50% on Days 1 and 2.

If the next cycle of Maintenance is due and ANC is above 750/ μ L but below 1,000/ μ L or the platelet count is < 75,000/ μ L:

- If the patient is due to receive Regimen A, the dose of Lomustine (CCNU) should be reduced by 50% (38mg/m²)
- If the patient is due to receive Regimen B, the dose of Cyclophosphamide should be reduced by 25% (750 mg/m²/day) on Days 1 and 2.

If the ANC is less than 750/ μ L when the next cycle is due, despite the dose reduction in CCNU, hold chemotherapy until the ANC is greater than 750/ μ L. For the next cycle of Regimen A, reduce Lomustine (CCNU) to 20mg/m².

If a cycle of chemotherapy is delayed for over 2 weeks due to neutropenia, subsequent cycles of chemotherapy should include filgrastim (G-CSF).

If the platelet count is less than 75,000/ μ L for longer than four weeks, perform a bone marrow aspirate and biopsy to differentiate between tumor invasion, marrow hypoplasia, or other causes of thrombocytopenia.

Hemorrhagic Cystitis

For patients with Hemorrhagic Cystitis with Cyclophosphamide, added doses of MESNA postcyclophosphamide and aggressive hydration if urine heme is positive is recommended.

Nephrotoxicity

If the creatinine clearance or GFR is less than 50% of baseline value, then the cisplatin should not be administered. It should be held until the creatinine clearance rises above 50% of baseline value.

If the creatinine clearance or GFR is less than 75% of baseline value, then the cisplatin dose should be reduced by 50% of the calculated dose.

If the creatinine clearance or GFR does not rise above 30 ml/min/1.73 m², the cisplatin should be deleted from treatment.

Following transient renal dysfunction, as defined above, the cisplatin should be reinstated at 50% dosage until the creatinine clearance or GFR has maintained above 50% of baseline value for two cycles of chemotherapy. After two cycles of therapy with acceptable creatinine clearance, cisplatin should be given at full doses.

Ototoxicity

An audiogram or BERA should be done before the start of chemotherapy and repeated after every other chemotherapy cycle. For a decrease in auditory acuity of \geq 30 decibels at 4,000 – 8,000 Hz, a 50% reduction in cisplatin dosage should be made. For a \geq 20 decibel loss at 500-3,000 Hz, a 50% reduction in cisplatin dosage should be made. For Grade 4 ototoxicity, cisplatin should be held and not restarted unless follow-up audiograms show an improvement in hearing function. We recommends the addition of sodium thiosulfate, at a dose of dose of 20 g per square meter, administered intravenously over a 15-minute period, 6 hours after the discontinuation of cisplatin

resulted in a lower incidence of cisplatin-induced hearing loss among children without jeopardizing overall or event-free survival

Hypomagnesemia

As a consequence of renal tubular wastage of magnesium caused by cisplatin, hypomagnesemia can develop. It may become symptomatic manifested by paresthesias, muscle cramps, weakness and occasionally disorientation seizures. If this occurs, magnesium should be given orally or intravenously.

Supportive Care Guidelines

Supportive Care Guidelines during Chemoradiotherapy.

Venous Access:

Patients are required to have an indwelling central venous access catheter prior to Maintenance Chemotherapy to facilitate chemotherapy and the use of sedation/anesthesia in young children.

Antiemetics:

The preferred antiemetic for cisplatin is ondansetron (0.15-0.20 mg/kg) given ½ hour prior to infusion and every 4 hours thereafter for a total of 3 doses. Corticosteroid use as an antiemetic should be avoided if possible.

Filgrastim (G-CSF):

Granulocyte colony stimulating factor (G-CSF) will be used to maintain treatment schedule if there is a 2 week delay in initiation of chemotherapy due to low white count. Filgrastim will be discontinued when the ANC is greater than 1500/µl.

Fever and Neutropenia:

Patients who develop a fever greater than 38.5°C should be evaluated for neutropenia and infection. If the patient has an indwelling catheter or has an ANC < 500/µl blood cultures should be drawn and antibiotics should be administered per institutional policy. Aminoglycosides should be avoided if possible to decrease the chance of ototoxicity. Filgrastim can be administered according to institutional guidelines.

Prophylactic Antibiotics:

Patients who receive chemotherapy should be started on trimethoprim/sulfamethoxazole at 5mg/kg/day dosed 2-3x/week or per primary care institution's protocol for Pneumocystis carinii prophylaxis. TMP/SMZ can be discontinued 3 months after chemotherapy has discontinued. Patients with TMP/SMZ allergy should be considered for treatment with dapsone or pentamidine.

Recommendations

1. All patients without a contraindication should receive TMP/SMX 5mg/kg/day divided bid on Mondays and Tuesdays.
2. Dapsone 2mg/kg/day should be used as second line prophylaxis for the following groups:
 - Patients with TMP/SMX allergy or intolerance
 - TMP/SMX failure
 - Patients in whom a transient drop in hemoglobin would place them at significant risk should receive Pentamidine.

3. Pentamidine can be given IV or aerosolized and is generally efficacious once monthly. Pentamidine should be considered prophylaxis for the following groups:
- Patients without prescription plans who are unable to afford TMP/SMX or Dapsone,
 - Patients who are non-adherent with oral TMP/SMX or Dapsone,
 - Patients with TMP/SMX and Dapsone allergy or intolerance,
 - Patients for whom a mild hemolytic anemia would not be tolerated.

Blood Products:

Platelets

Patients will be transfused as necessary with platelets. It is suggested that the platelet count be maintained $> 30,000/\mu\text{L}$. All blood products will be irradiated to prevent graft-versus-host disease. Filters to remove leukocytes should be used to prevent WBC sensitization. CMV seronegative patients should receive CMV negative blood products.

Red Blood Cells

Therapy-induced anemia and reticulocytopenia are expected with this protocol. Patients will be transfused as necessary with irradiated packed red blood cells to maintain a hematocrit $> 20\text{-}25\%$. Blood products will be irradiated to prevent graft-versus-host disease. Filters should be used to prevent WBC sensitization.

Nutritional Support:

Any patient with greater than 10% weight loss should begin nutritional support. Aggressive nutritional support will be provided either enterally or via a central venous catheter with parenteral hyperalimentation. All patients should have their magnesium checked prior to each cycle and be supported with magnesium supplementation if necessary in a minimum dose of 3 mEq/m²/day p.o. or IV in three divided doses to maintain serum levels in the normal range.

Endocrine Guidelines:

Obtain endocrine evaluations at diagnosis, completion of radiation therapy, completion of treatment, 6 months following the completion of treatment and then annually unless otherwise

indicated.

Evaluation	Diagnosis	Completion of RT	Completion of treatment	6-months following the completion of treatment	Annually	2 years post start of treatment
Height, weight, BMI and percentiles ¹	X		X	X	X	
Growth Hormone stimulation test						X ²
T4, TSH, and thyroid exam for nodules	X	X	X	X	X	
Perform ROS for failure to thrive, dehydration, hypoglycemia					X	
8 AM Cortisol			X	X	X	
Low Dose ACTH Stimulation test						X ²
Tanner stage (See Appendix IV)	X		X	X	X	
LH, FSH, Estradiol or Testosterone					X	
If precocious puberty Bone age, LH, FSH, Estradiol or Testosterone, Bone age and pelvic ultrasound	X		X	X	X	
If delayed puberty obtain Bone age, LH, FSH, Estradiol, testosterone, and DEXA scan	X		X	X	X	
Serum sodium ³	X					

¹ If abnormal patterns obtain Bone age annually

² Obtain 2 years off therapy and as clinically indicated

³ If the patient is DDAVP check serum sodium at each visit

Required Evaluations Following Completion of Protocol Therapy

Evaluation	3 mos	4 mos	6 mos	8 mos	9 mos	12 mos	15 mos	16 mos	18 mos	20 mos	21 mos	2.0 yrs	2.5 yrs	3.0 yrs	3.5 yrs	4.0 yrs	Annually	At Relapse Disease Progression
History, Physical with Neurologic Exam	X		X		X	X	X		X		X	X	X	X	X	X	X	X
Liver Function, BUN, Creatinine, Electrolytes (Ca, Mg), CBC	X		X		X	X	X		X		X	X	X	X	X	X	X	
MRI of head (with contrast)	X		X		X	X	X		X		X	X	X	X	X	X	X	X
Spinal MRI (with contrast)*	X§		X§		X§	X§	X§		X§		X§	X§	X§	X§	X§	X§	X§	X
Lumbar CSF Cytology		X§		X§		X§		X§		X§		X§	X§	X§		X§	X§	X
Audiogram			X			X			X			X		X		X	X	
Thyroid Function Evaluation (Free T ₄ and TSH)			X			X						X		X		X	X	
LH, FSH, estradiol or testosterone						X						X		X		X	X	
Serial Measurement of Height (Stature)%			X			X						X		X		X	X	

* Spinal MRI should include complete spine (cervical, thoracic, lumbar and sacral)
 % Refer to endocrinologist if a growth below the 3rd percentile, drop in height percentile on growth grid, growth velocity <4-5cm/yr in childhood or lack of pubertal growth spurt
 § Obtain if initially positive. Patients with M1-M3 disease require the more frequent scans.

References

“These guidelines are drafted on treatment strategy of Clinical Oncology Group based upon the findings of ACNS0331 & ACNS0332 prospective studies.

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