Chapter

Pediatric Medulloblastoma: A Radiation Oncologist Perspective

Meenu Gupta and Mushtaq Ahmad

Abstract

Pediatric medulloblastomas are radiosensitive and mostly curable tumors if they are non-metastasized. Postsurgery adjuvant radiation therapy remains the cornerstone therapy in the curative intent treatment. In case of children less than three years, pre-irradiation chemotherapy is given to defer radiotherapy till the child is three year old. Introduction of conformal radiotherapy in addition to technical improvements in surgery and radiotherapy, risks definition and molecular analysis of prognostic factors has most likely contributed to the improved survival rates. Children should ideally be referred in time to an appropriate higher center with adequate infrastructure, expertise and radiotherapy facilities for better outcome of the disease.

Keywords: medulloblastomas, radiosensitive, conformal, radiotherapy

1. Introduction

Harvey Cushing and Percival Bailey were the first who described the name medulloblastoma as "Spongioblastoma Cerebelli" in June, 1925 for posterior fossa tumors of preadolescents population**.** They reported 29 cerebellar vermis tumor in children and young adults. Later they renamed as "medulloblastoma" as the term "Spongioblastoma multiforme" was described by Globus and Strauss in 1925 for various adults cerebral tumors in which feature of considerable cellular differentiation was seen. This picture was found absent in tumors of cerebellar origin [1, 2]. World Health Organization (WHO) defined medulloblastoma as "invasive malignant embryonal tumor of the cerebellum with commonest manifestation seen in children". These neuroepithelial tumors have inherent tendency to spread through the cerebrospinal fluid to cranial and spinal subarachnoid spaces [3].

2. Epidemiology

Injuries followed by malignancy are the second leading cause of mortality among children. After leukaemia's, brain tumors are the most common in children accounting for '25%' of all malignancies in children [4]. Most common malignant CNS tumor in children is medulloblastoma (MB) constituting 20% of primary brain tumors and approximately 40% of all tumors of the posterior fossa [5]. The incidence of *medulloblastoma in adults is relatively low as compared to pediatric population. This constitutes 1% of all CNS tumors and this may be the cause of scanty data available in*

adult MB group [6]. U.S data showed the incidence of the medulloblastoma is 1.5–2 cases/100,000 population. Three hundred and fifty new cases in the United States are seen each year. The peak incidence is seen in 1st decade of life and incidence is noted higher in the pediatric age group 3–4 years followed by 8–10 years of age.

CBTRUS (*Central Brain Tumor Registry of the United States*) showed that incidence is higher in males as compared to females (Males: 0.16 vs. Females: 0.12). But this trend is different in children who are less than one year old. There is rising trend of higher incidence (APC: 1.7, 95% CI −0.4, 4.0) and death risk (Hazard Ratio for Survival: 0.74 with p value 0.09) seen in black race compared to whites which is non-significant [7, 8].

3. Clinical presentation

There is rapid initiation of clinical symptoms are secondary to the rapid proliferation of these cellular malignant tumors. Symptoms of medulloblastomas vary with age. Earlier age of onset is associated with behavioral changes. Other symptoms may include listlessness, moodiness or irritability, vomiting, and lack of social interactions. As medulloblastoma is rapidly growing tumor, this results in obstructive hydrocephalus which manifests as raised intracranial pressure (ICP). Children may be seen with macrocephaly, fullness of fontanelle, and delayed developmental milestones. Older children and adults have symptoms of raised intracranial pressure like headache, vomiting, especially upon awakening in the morning hours. Headache usually gets better during the day. As anatomical location of medulloblastoma is cerebellum but symptoms slightly vary within various sites of cerebellum. Truncal ataxia result from tumors located in midline of cerebellum and appendicular ataxia is associated with the hemispheric located tumors [1]. There can be stretching of sixth cranial nerve because of hydrocephalus resulting in double vision. Meningeal irritation causes tilting of head and stiffness of neck due to the tonsillar herniation. Trochlear nerve palsy related to tumor compression is another reason of head tilt. Patients with spinal metastasis had symptoms of backache, weakness of bilateral lower limb and loss of bowel and bladder control. Metastatic disease symptoms depend upon the site involvement [9]. Majority are sporadic cases but there are associated syndromes like *Gorlin syndrome* (*nevoid basal-cell carcinoma syndrome*), *Blue rubber-bleb nevus syndrome*, *Rubinstein-Taybi syndrome* and *Turcot syndrome (glioma polyposis syndrome*) [10].

4. Management

Although radiology is good contributor of diagnosis still detailed history and physical examination remained important and has to be done before proceeding for any investigations. Alteration of child behavior, persistent symptoms and focal neurological deficit are warning signs and should be proceeded with neuroimaging for diagnosis.

4.1 Imaging

4.1.1 Computed tomographic

Computed tomographic (CT) appearance of a medulloblastoma is seen as well-defined vermian cerebellar mass which is hyperattenuated with surrounding

vasogenic edema and sometimes evidence of hydrocephalus is seen. Contrast enhanced images show homogeneous enhancement.

4.1.2 MRI imaging

MRI imaging of the entire neuraxis, brain and spine is recommended for suspected cases. MRI images show "Low-to-intermediate signal intensity" on T1-weighted images and "moderately high signal intensity" on T2-weighted images, compared to cerebellar white matter. Intratumoral haemorrhage, peritumoral oedema, tonsillar herniation, hydrocephalus and calcification are other associated findings. Multivoxel MR spectroscopy (MRS) of the primary tumor can assess the tumor metabolites like 'elevated Choline peaks and decreased Creatine and N-acetyl acetate peaks'. Even without frank necrosis, a small amount of lipid-lactate peak sometimes observed indicating an increase in metabolic activity. Due to densely packed cells within the tumor and nuclear: cytoplasm ratio is higher, MB causes restriction of diffusion. There is restriction of diffusion of water particles in the tumor. So there is high signal of the tumor in diffusion-weighted MR images [11]. As frequency of spine seeding is 35% at diagnosis, to rule out any leptomeningeal metastases, Sagittal fat-suppressed post- gadolinium contrast MRI of the spine should be performed prior to surgery (**Figure 1**). Guang-Yao Wu et al. published data showed that proton *magnetic resonance spectroscopy* (^{1}H-MRS) and Diffusion Weighted Imaging are helpful for qualitative diagnosis of medulloblastoma [12].

Baseline hearing status with tests like Audiometry, IQ Testing and hormonal levels with Serum TSH and GH can be tested.

4.2 Neurosurgery

Mostly medium and large sized tumors in posterior fossa are associated with hydrocephalus. In routine practice, prior to definitive surgery, ventriculo-peritoneal (VP) shunt should generally be avoided as definitive resection of tumor efficiently relieves the obstruction by opening the CSF pathways. Ideal surgery of any tumor is complete surgical resection, but feasibility and safety is priority. In

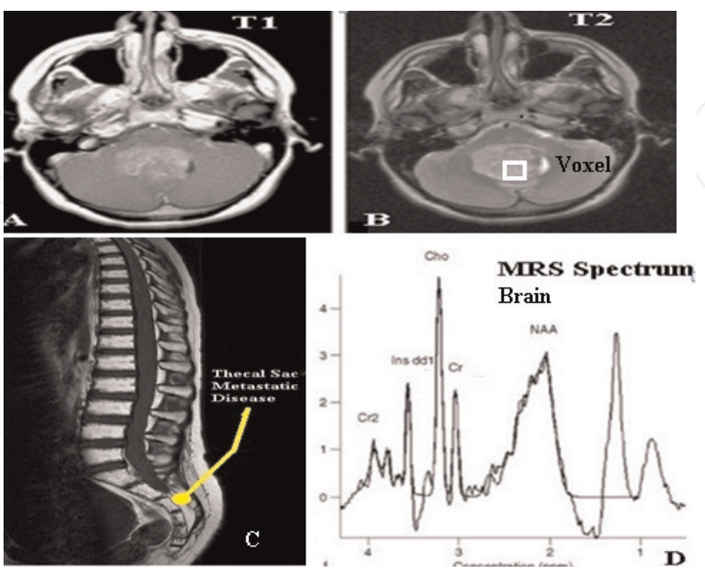

Figure 1.
Showing preoperative MRI. (A) T1 weighted image post- gadolinium with tumor arising from midline of cerebellum. (B) T2 FLAIR with mild hyper intensity and voxel showing the tumor area of interest for spectroscopy. (C) Drop metastasis. (D) Significantly increased choline peaks with decreased NAA and Cr peaks on Spectroscopy.

such circumstances, it is recommended to attempt maximal safe resection and residual disease can be left behind rather than aggressive surgical resection approach that can precipitate significant morbidity. Benefit to risk ratio of complete surgical removal of tumor has to be assessed preoperatively [13, 14].

4.2.1 Post surgery neuroimaging

Ideal timing of post surgery MRI imaging should be obtained immediately, within 24–48 h of tumor resection, for accurately identification of the extent of surgical resection and quantification of the status of the residual tumor. If immediate post surgery MRI imaging has not been obtained, then recommendation is to wait for at least 2–3 weeks, but no more than 4-weeks, for resolution of post surgical changes and this will further prevent false positive results. Recommendations for timing of postoperative CSF analysis for malignant cells are also same, at least 2–3 weeks post surgery to prevent errors like false positive results [15, 16].

4.3 Histopathology

Classification of most of the CNS tumors are still relying on only histopathological features but in medulloblastomas, integration of additional molecular information has updated WHO classification from 2007 to 2016. Medulloblastoma is classified now by an integrative diagnosis including a histologically as well as genetically defined compound as shown in **Table 1** [17].

Molecular classification provides additional clinical and prognostic information which has the potential for identification of innovative strategies and research for the management of this disease (**Table 2**) [18, 19].

4.4 Staging

Medulloblastomas originally were staged only on surgical basis but "Modified Chang Staging" is the current standard and there is addition of imaging [20] explained in **Figure 2**.

Risk stratification based on clinico-radiological analysis is still widely practiced and remains valid for Radiation planning in institutions. COG and SIOP Group accepted the clinical prognostic variables [21] shown in **Figure 3**. Although with the inclusion of molecular sub-grouping and genetic analysis of disease, more robust information about risk stratification and outcome of disease can be concluded to some extent but this required availability of these facilities with expertise in institutions. Incomplete neuraxis staging should be classified as high risk disease.

Histopathologically defined MB	Genetically defined MB
Medulloblastoma, classic	• Medulloblastoma, WNT-activated
Desmoplastic/nodular medulloblastoma	• Sonic Hedgehog (SHH) activated and *TP53*-mutant • Sonic Hedgehog (SHH) activated and *TP53*-wildtype
Medulloblastoma of extensive nodularity	• Non-SHH/Non-WNT
Large cell/anaplastic medulloblastoma	• Medulloblastoma, group 3
Medulloblastoma, not otherwise specified (NOS)	• Medulloblastoma, group 4

Table 1.
WHO 2016 updated classification of medulloblastomas.

	Wingless activated (*WNT*) MB	**Sonic hedgehog (*SHH*) subgroup**	**Group 3**	**Group 4**
Cell of origin	Dorsal brainstem (*lower rhombic lip*) neuronal progenitors	Cerebellar external granular layer, neuron precursors	Ventricular zone neural progenitors	Cerebellum progenitors (*upper rhombic lip*)
Prevalence	10%	30%	25%	35%
Male:female	1:1	1:1	2:1	3:1
Common age	Older children	<3 year and >16 year, adult group	Infants and children <16 year	Infants/children/adults
Histopathology	Classic. In few case, large cell and anaplastic	Nodular desmoplastic histology, classic, large cell and anaplastic	Classic, large cell and anaplastic	Classic, large cell and anaplastic
Genetic aberrations	*CTNNB1 DDX3X SMARCA4*	*MYCN, GLI2, PTCH1, SUFU, MLL2, SMO, TP53, BCOR1, LDB1, GABRG1*	*MYC, PVT1, OTX2, MLL2, SMARCA4, CHD7*	*OTX2, DDX31, CHD7, SNCAIP, MYCN, CDK6 GFI1/GFI1B, MLL2, KDM6A, MLL3, ZMYM3*
Chromosome	−/6	*3q gain, 9q loss, 10q loss*	*1q gain, 5q loss, 10q loss*	*Isochromosome 17q chr X loss, 17p loss*
Molecular markers	Beta-catenin	SFRP1or GAB1	MYC activation in 50% of this subtype	Unknown
Metastasis	Rarely present	Not common	High	35–40% at presentation
Recurrence	Rarely seen	Local	Metastasis	Metastasis
5 year overall survival	95%	75%	50%	75%
Future strategy	Reduction in therapy	SHH pathway inhibitors	Intensified therapy, novel therapeutics	Robust and large data research

Table 2.
Medulloblastoma as a group of molecularly distinct subtypes.

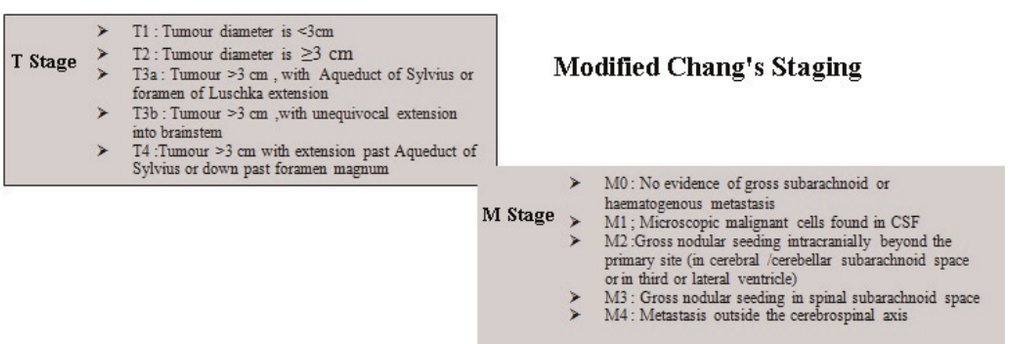

Figure 2.
Modified Chang's staging system.

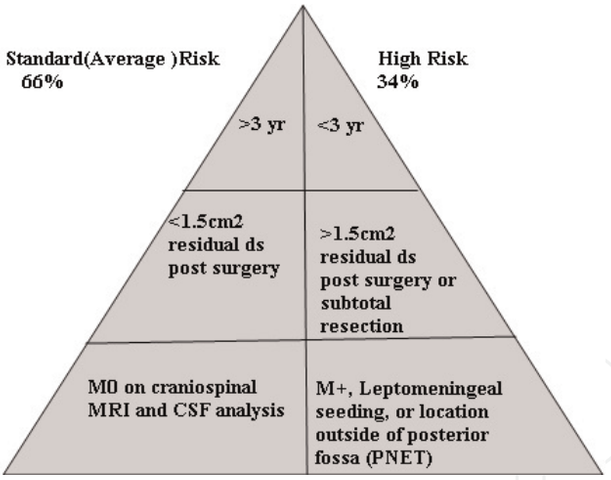

Figure 3.
The stratifying medulloblastoma patients clinically into high risk and standard (average) risk based on variables like age, resection and metastasis.

5. Radiation therapy

Medulloblastoma, the embryonal tumors of the central nervous system, are highly radiosensitive tumors. After 200 cGy, the survival fraction has been reported to be 27%. Although Dargeon in 1948 stated that "medulloblastomas ... have a consistently unfavourable prognosis" but later careful observation of Edith Paterson regarding pattern of disease spread brings hope to this disease. Radiating brain and spinal cord in one undivided volume principle mentioned by Edith Paterson and Farr. was based on the post-mortem findings of brain and spinal cord deposits in untreated cases. In 1953, at the Christie Hospital a five-year survival rate for children who were treated with kV irradiation reported by Paterson and Farr was 41%. Since then the practice to irradiate the entire craniospinal axis is universally adopted [22, 23].

After resection of tumor, entire craniospinal axis irradiation followed by whole posterior fossa or tumor bed boost irradiation is recommended irrespective of clinically detectable disease. Being Radiosensitive, Radiotherapy is curative up to 70% of standard risk patients. For this pediatric age group disease, linear accelerators are better than telecobalt machines and these children should preferably be referred in time to well equipped higher center with radiotherapy facility and infrastructure to prevent unnecessary side effects. As treatment delays beyond 6–7 weeks result in worse outcome, cobalt-60 therapy may be offered in those areas where linacs are not available. To prevent the adverse effects of radiotherapy in the developing nervous system, radiotherapy is avoided initially in children up to 3 years of age. CSI technique required accurate reproducibility and complex field matching techniques. Long and complex shaped target volume homogeneity is a technically challenging process.

Timing of radiotherapy

Improved survival for patients is associated with a shorter interval from surgery to the start of radiation therapy. After definitive surgery, treatment should be started within 4–7 weeks. International Society of Paediatric Oncology (SIOP) trials showed that increase in the risk of relapse is seen if radiotherapy treatment is delivered after 7 weeks [24].

5.1 Radiotherapy planning techniques

Younger brains are much more sensitive to damage caused by radiotherapy. CT based conformal radiation therapy, 3DCRT, is standard of care exists for many

years. Patient can be in the supine or prone position during CSI treatment. Over the years, prone position was used universally. Nowadays supine position is used increasingly.

Advantages of supine position [25]

- Target volume coverage is more easily assured and delivery more reproducible.
- Patient is more comfortable due to stable position.
- Technically, there is better shielding of cribriform plate and inferior temporal lobes.
- For younger pediatric patients who require anaesthesia, there can be better management of airways and cardiopulmonary complications can be reduced.

Limitations of supine position

- Without adequate portal imaging, setup accuracy is difficult.
- Old couches contain metal inserts and beam entrance posteriorly through the head rest and treatment couch is not possible.

Advantages of prone position is the junction between the spinal and cranial fields can be better visualized.

For younger children, good sedation may be required. Expert play therapist may help in treatment for radiotherapy without sedation.

5.1.1 Conventional planning

In 2-dimensional planning, fluoroscopic guidance two-dimensional simulation is done. Immobilization is done with thermoplastic cast and universal prone head-rest is used. CSI board with Lucite base plate having semicircular Lucite structures are available for head rest and chin rest. Various degrees of neck extensions is possible which will prevent the exit of superior border of spinal field through the oral cavity. Chest wall can be supported by thermocols.

This complex 2-dimensional CSI technique fundamentals are:

- Two parallel opposed lateral portals for cranium and upper cervical spinal cord.
- Posterior spinal field matching with the cranial fields.
- In case of adults or larger children, matching of upper posterior spinal field with the separate lower posterior spinal field.

Craniospinal junction can be placed at higher level: C1/C2 interspace or lower level C5-C7. At higher level, overdose to spinal cord is low. Shoulders are excluded from the lateral fields by keeping the craniospinal junction at lower level (C5-C7). Also the exit dose to mandible, thyroid, pharynx and larynx is lowered. Inferior edge of S2 is mostly the anatomical landmark where lower border of spinal field (SF) is set. Single Craniospinal junction is set for smaller children. If length is >36 cm, two junctions are required which are craniospinal and spinal-spinal (SS) junction. Mostly SS junction is place at L2-L3 interspace. Multi-leaf collimators or

custom made lead blocks are utilized for orofacial region shielding. In order to know the divergence of spinal fields, the spinal fields are simulated first.

Various techniques used for matching craniospinal junction are:

- For matching the beam divergence of the lateral head portals with the superior beam edge of SF, Collimator rotation is done 7–10°.
- Couch rotation 6°.
- Half beam blocks
- Asymmetric jaws
- Penumbra trimmers

The craniospinal junction should be feathering/moving weekly during craniospinal irradiation for homogenous dose distribution and further minimizing the hot or cold spots resulted from the gap-junction or set-up errors. With each shift, spinal field can be extended superiorly, and cranial fields can be decreased inferiorly by 0.5–1 cm. Similarly LB (lower border) of "superior spinal field" and SB (superior border) of "inferior spinal" field can be shifted superiorly. This all is done for spread out of dose homogeneity. Still the contribution of human errors is seen in many studies. As there is direct visualization of the optical field light on the skin surface in prone position, verification of beam delivery of CSI is relatively simple (**Figure 4A**) [26, 27].

The posterior fossa (PF) boost volume

Depending on the risk-stratification of the disease, volume of the posterior fossa boost is decided. Those cases which are considered low risk and standard risk medulloblastomas, posterior fossa target volume includes pre-operative tumor bed with adequate margins. Most institutions add 1–1.5 cm margin to the tumor bed. Cases of high risk and very high risk disease require irradiation of the entire posterior fossa. Posterior fossa irradiation can easily be planned based on fluoroscopic imaging in low and middle income countries where there is no availability of multileaf collimators.

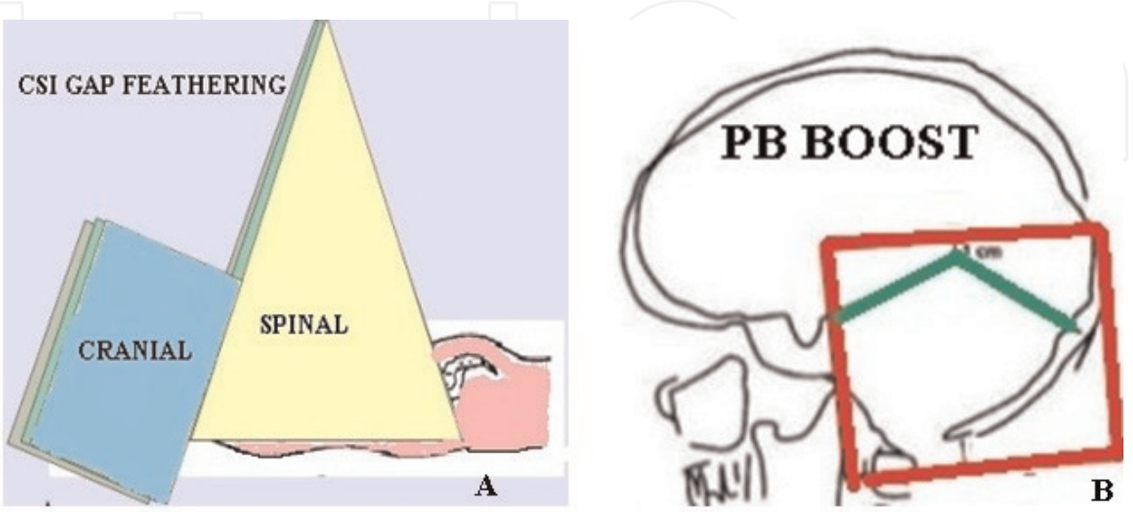

Figure 4.
(A) Gap feathering during craniospinal irradiation (CSI). Junction movement across the long treatment length allows homogenous dose distribution by reducing the overlap hot spot and gapping cold spots. If field length < 35 cm, 100 cm SSD is used and for field length >35 cm, 120 cm SSD is used. (B) Posterior fossa boost volume including whole infratentorial compartment.

Conventional portals for PF boost

The PF boost is given using two lateral opposing fields. Anterior radiotherapy borders are formed by the posterior clinoids, posteriorly by internal occipital protuberance, superiorly extended up to mid-point of *foramen magnum* and *vertex* (or 1 cm above tentorium) and inferiorly extended up to C2-C3 interspace (**Figure 4B**) [28].

5.1.2 Conformal radiotherapy planning

In case of pediatric patients who are potential long term survivors, critical structures are better spared by conformal techniques.

Immobilization is done in supine position and patient is aligned straight keeping neck in the neutral position. A 4-clamp thermoplastic immobilization cast for the head and shoulder region along with appropriate neck rest should be used. A five point orfit for immobilization along with hyperextended head and depressed both shoulders can result in optimal sparing of the upper esophagus and laryngeal structures.

Traditionally, axial planning images of 5 mm thickness on CT simulator from the vertex till the upper thigh region were preferred. But in this era of high precision radiotherapy where CTV accuracy is important for optimal outcome, CT slice thickness is reduced in some anatomical sites of CSI field. Slice Thickness of 1–2.5 mm from the vertex to the inferior border of third cervical vertebrae (C3) and 2–5 mm from the lower border of third cervical vertebrae (C3) to the upper anatomical region of the femur should be obtained. Skull base foramina delineation is of utmost important and for their identification, "1 mm slice thickness at the base of skull" is preferred. To improve better identification of cranial nerves dural sheaths, co-registration of planning imaging CT to MRI can be done [29]. CSF extensions within the dural reflections are better demonstrated by FIESTA (Fast Imaging Employing Steady-State Acquisition) MRI sequences [30].

Treatment volumes

Due to the risk of CSF dissemination, entire arachnoid space is included in the clinical target volume (CTV).

5.1.2.1 Whole brain treatment volume

The frontal lobe and the cribriform plate must be included in the clinical target volume. Inclusion of superior orbital tissue is must in the radiation field for the adequate coverage of the frontal lobe and cribriform plate. As per SIOPE guidelines, "the geometric edge of shielding should extend at least 0.5 cm inferiorly below the cribriform plate and at least 1 cm elsewhere below the base of the skull".

Delineation of $CTV_{cranial}$

a. Brain along with its covering meninges are contoured till second cervical vertebrae (C_2). For outlining the inner table of the skull, CT bony window setting is used with window/level: 1500–2000/300–350 suggested by SIOPE group.

b. The most critical sites are the 'cribriform plate', the 'most inferior parts of the temporal lobes', and the 'whole pituitary fossa'. They all to be included in the $CTV_{cranial}$ delineation. For cribriform plate CT window/level suggested is 3000/400.

c. For inclusion of CSF within the dural sheath of cranial nerves, CTVcranial is modified. For second cranial (optic) nerve, window width 350/level 40 is to be used

Foramina or canals of skull base which are significant for delineation of $CTV_{cranial}$ are cribriform plate, optical canal of sphenoid, superior orbital fissure, foramen ovale, internal auditory meatus (IAM), jugular foramen and hypoglossal canal. Entire components length of the optic nerves in the $CTV_{cranial}$ is included in most institutions where photons are used. But in those institutions where medulloblastomas are treated by protons, for prevention of any potential optical retinopathy risk, only the posterior length components of the optic nerves is included [31, 32].

As CSF flows up to the posterior aspect of eyeball which is better observed in MRI images, it is better to include whole optic nerves in CTV in routine practice of photon beam based radiotherapy in these cases. The cranial nerves which are wrapped without dural cuff are the third, fourth and sixth (oculomotor, trochlear and abducens) nerves. Nobel et al. studied the flow of cerebrospinal fluid beyond the inner table of skull into the IAM (internal auditory meatus), juglar foramen (JF) and hypoglossal canal (HC). Their study (on basis of 96 FIESTA MRI sequences) concluded that the CSF extension was up to '16 mm' in the internal auditory meatus which is not very far away from the cochlea. So the cochlear sparing by CSF exclusion within the internal acoustic canal should not be attempted. Their data also showed that the CSF extension was up to 11 mm in the juglar fossa from inner table of skull. There is no extension of CSF within these dural sheaths outside the outer table of the skull. It is not so easy to delineate dural sheath CSF on MRI but CT images with 1 mm thickness along the base of skull can show skull foramina and canals and they can easily be contoured on bony windows (**Figure 5**) [29].

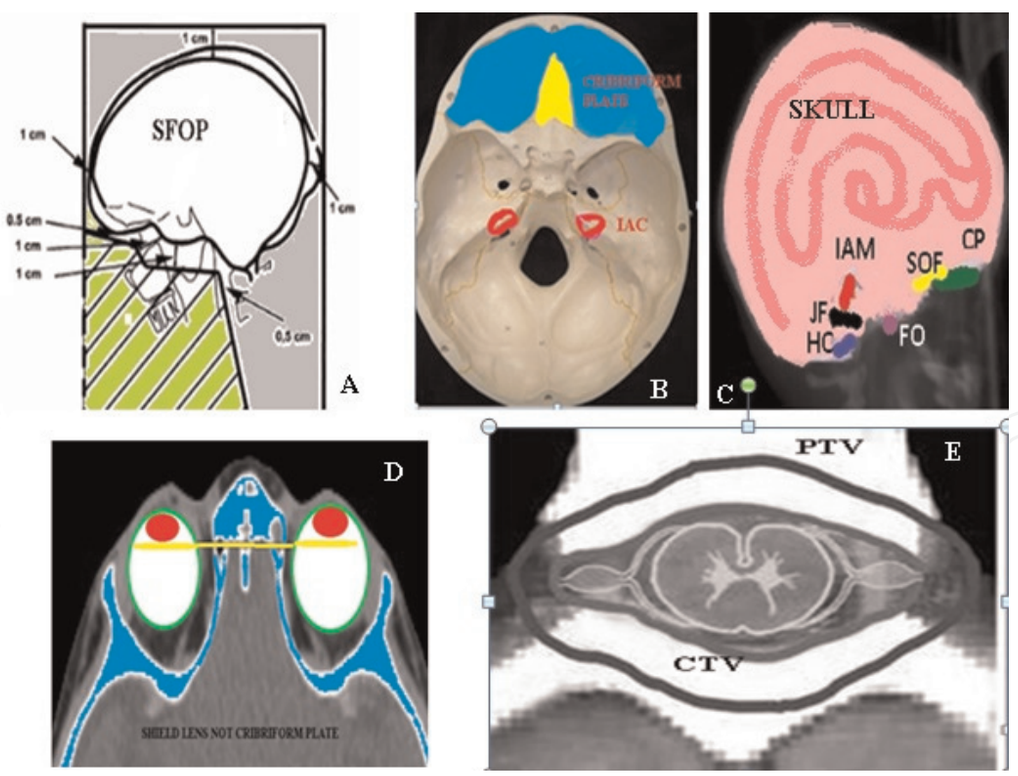

Figure 5.
Showing conformal planning. (A) Cribriform plate is in close proximity to ocular structures. Shielding edge should be at least 0.5 cm below the cribriform plate and 1 cm elsewhere below base of skull to cover the temporal fossa and skull base foramina. (B) The petrous part of temporal bone showing Internal acoustic canal (IAC). (C) Various skull base foramina contoured in $CTV_{cranial}$ including dural cuffs of cranial nerves. (D) Cribriform plate must be in target volume. (E) Entire subarachnoid space, including nerve roots laterally must be included in CTV_{spinal}. SFOP, French Paediatric Oncology Society; CP, cribriform plate; SOF, superior orbital fissure; FO, foramen ovale.

CTV brain: brain and its covering meninges till lower border of C2.
PTV brain: 5 mm isotropic margin around CTV brain.
CTV spine: entire arachnoid space with nerve roots.
PTV spine: 5–8 mm isotropic margin is recommended around the CTV-spine

Issues of the cribriform plate (CP)

According to a 1982 report from MSKCC, 15% of recurrences are subfrontal in medulloblastomas [33]. Hypothesis given by Donnal et al. was that the pooling of cells secondary to gravitational effect of prone position with maximum shielding of eyes can result in the recurrences at the region of cribriform plate [34].

5.1.2.2 CTV_{Spinal}

The CTV_{Spinal} (spinal target volume) includes the complete dural or thecal sac. Lateral extension of delineation is must to cover the intervertebral or neural foramina with their exiting nerve roots from the C2 cervical spine till the lower end of the thecal sac. Lower border of CTV_{Spinal} is appreciated by the latest spinal MRI imaging. Children Oncology Group (ACNS0332, ACNS 0331, ACNS 0122) recommended the inferior border of CTV_{Spinal} is '*2 cm below the termination of the subdural space*' which is usually at bottom of second sacral vertebrae. The other SIOPE group trials recommended that the lower border of CTV_{Spinal} must be determined by the spinal MRI imaging of the termination of the thecal or dural sac. This border should be kep. 1 cm inferior to this. Root canals in the Sacral CTV_{Spinal} can be excluded. This recommendation is based on a MRI study conducted on ten volunteers who were healthy proved that there was no CSF around the nerve roots of sacral segments.

If patients are to be treated by protons, then for skeletally immature patients, CTV_{Spine} should include the vertebral bodies. This will decrease the risk of unequal vertebral growth. In skeletally mature patients, spinal TV should include the sub-arachnoid space of spine with a margin of 3–5 mm is summed up to the body of vertebrae for set up uncertainties/variation (interfraction) [29].

Delineation of posterior fossa boost volume

High Risk and Very High Risk disease: The clinical target volume PF (CTV_{PF}) boost encompassed the whole PF. The boost CTV_{PF} extends superiorly up to the tentorium cerebelli, inferiorly to the foramen magnum, and posterolaterally to the occipital bony walls and temporal fossa. BS (Brain Stem) anterior border and mid-brain cover the components of the posterior fossa anteriorly. The geometric margin of 0.5 cm around the CTV_{PF} is taken for delineation of the PTV posterior fossa (PTV_{PF}). PTV_{PF} is limited to the bony confines of the skull, except at the foramen magnum where it extended to the level of C1. The PTV_{PF} contoured anteriorly up to the posterior clinoids and inferiorly to the C1-C2 junction. PTV is modified at sella and pituitary gland is excluded from anterior extension of PF boost planning.

For low risk and standard risk, tumor bed, as defined on CT images, delineation with a margin of 1–2cm is recommended. For three-dimensional planning, two lateral opposing portals with editing/shaping using the multileaf collimators (MLCs) is recommended. Finally, these craniospinal and boost plans must be summated to produce a composite treatment plan and final dose-distribution is calculated [35, 36].

5.2 Intensity modulated radiotherapy for CSI

Children and adults are two different groups as far as radiotherapy treatment in medulloblastoma is concerned. Proliferating tissues are more in children as

compared to the adults. IMRT for adult population is a used as a routine practice for numerous malignancies but for pediatric patients, IMRT has to be used with great caution in view of low dose volumes. Spinal irradiation during CSI results in increased doses delivered to anterior thoracic and abdominal structures with conventional plans. Parker et al. published data showed that the PTV and dose homogeneity was better for the medulloblastoma CSI, IMRT plans. Dosimeteric analysis showed $V_{95\%}$ for IMRT was 100%, 3D planning was 96% and 2D planning was 98%. Also $V_{107\%}$ for IMRT was 3%, 3D planning 38% and 2D was 37%. The IMRT plans provided better sparing of heart and liver in terms of V (10 Gy) and above. Integral Dose analysis showed the IMRT plans were superior for liver and heart and the 3D plan were better for the body contour. Tomotherapy may be helpful in reducing high dose regions in OAR, but low dose of radiation to a large volume is a concern for pediatric patients [37].

IMRT planning

IMRT for craniospinal irradiation in adult medulloblastomas is delivered after summation of PTV brain plan and PTV spine plan. Usually the spinal PTV planning is done first with 'inverse planning technique' using the 5 posterior fields with 0°, ±20° and ± 50°gantry angles. For the craniocaudal direction, the isocenter is kept at the "geometrical center of the PTV_spine". For the depth and lateral position, it is usually set at the "midline and midplane" at the level of the interphase of second and third cervical vertebral body. Dose prescription and normalization is to the isocenter of the spine. For the cranial target, a separate plan is created. Cranial fields isocenter is set at the inferior most slice of the PTV brain. MLC positions can be modified for dose reduction to the nearby OARs and adequate coverage of the target volume. The geometric center of the PTV_brain is defined as the reference point for dose prescription and normalization. Final composite plan for the whole cranio-spinal axis is obtained after dosimetrically summation of spinal and cranial plans. For taller patients, for upper and lower spine, IMRT plans are created separately [38].

Intensity modulated radiotherapy for posterior fossa boost

Meenu et al. re-planned seven previously irradiated patients of MB with seven field inverse planning IMRT for whole posterior fossa boost. Equidistant gantry angles (0°, 50°, 100°, 150°, 210°, 260°, 310°) were used with step and shoot IMRT on 6MV energy LINAC. Treatment isocenter was set at the geometrical center of the planning target volume. They compared with 3DCRT plan delivered by two lateral opposing beams with multileaf collimators for shaping. Their dosimeteric results showed there were decreased mean dose to most critical organ at risk, cochlea, with IMRT compared to the three dimensional radiotherapy plans with significant p values i.e. 0.032 for the cochlea of right ear and 0.020 for the left sided cochlea (**Figure 6**) [35] Similar results are found in published clinical studies conducted by Huang et al. where 13% of the IMRT group had grade 3 or 4 hearing loss as compared to 64% for the conventional group [39].

Organ at risk

OAR as demarcated on axial CT images include brain, eyes, lens, optic nerves, optic chiasma, cochlea, parotids, mandible, thyroid, esophagus, lungs, heart, breasts, liver, kidneys, bowel bag, rectum, bladder, gonads (ovary or testes), vertebral bodies, uterus plus pelvis (red bone marrow).

5.3 Radiotherapy doses

Berry et al. reported a five year survival rate of 47% with lesser doses and ten year DFS of 77% once the posterior fossa doses delivered were >52 Gy [40]. Abacioglu et al. showed in adult medulloblastomas, control rate was 33% at 5 year

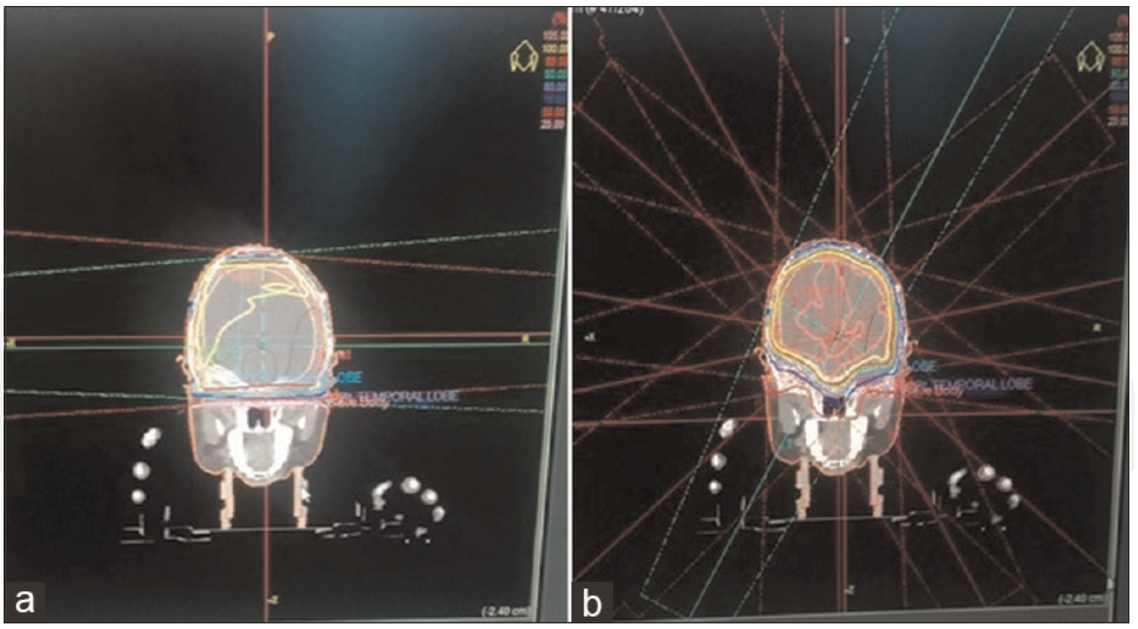

Figure 6.
Coursey JCRT. Meenu et al. mid-axial dose distributions with (a) 3DCRT (b) IMRT for one of the representative case of entire posterior fossa boost. Yellow represents 100%, red 95% and blue 70% of the isodose lines. IMRT is advantageous over 3DCRT for cochlear sparing. 3DCRT, three dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy.

with doses <54 Gy native to 91% in those patients on whom higher doses were delivered [41]. CSI dose reduction is feasible with the addition of chemotherapy as level 1 evidence based data released by Children's Cancer Study Group showed that the reduction of doses from 36- to 23.4 Gy resulted in significantly higher risk of recurrences outside the posterior fossa [42].

Radiotherapy doses to CSI depends upon the risk stratification of the disease at presentation. If risk stratification or accurate staging is incomplete then patient can be treated as high-risk disease. Radiation therapy doses according to the risk stratification are shown in **Table 3** [43]. There are different long term toxicities between the adult and children. CSI dose reduction approach is avoided for adult patients. Still big data is required to justify the addition of adjuvant chemotherapy to radiotherapy in average risk adult patients as data showed that 70–80% of these patients have no progression of disease at 5 years when RT is used as a sole modality. Also there are issues of hematological toxicities in adult patients.

5.4 Proton therapy

Pediatric age is more sensitive to radiation induced carcinogenesis as compared to adults by a factor of at least 10 [44].

As children anatomy is small so critical organs are very much close to the target volume. Also the scatter from the treatment volume is highly significant in children having small body area as compared to large body of adults. Particle beam therapy is a potential powerful tool for improving the therapeutic ratio. Goal of pediatric radiation oncologists is integral dose minimization to whole body and organs at risk. Advantage of protons over the photons is that they can modulate the dose to avoid very close OARs. For CSI, advantages of protons are because of absorption of low dose on tissue entry and the point of maximum dose deposition at the Bragg-peak. This results in the avoidance of dose deposition to anterior organs like thyroid, lungs, heart, gut, liver, esophagus, kidneys and urinary bladder. Also critical brain structures such as the lens, optic chiasma, pituitary, cochleae are better spared.

Various risk stratification	Volume and doses of radiation therapy	Concurrent or adjuvant chemotherapy
High risk and very high risk disease	CSI: 36 Gy/ 20 fractions, 5 days a week Boost to posterior fossa: 19.8 Gy/ 11 fractions, 5 times/week Gross metastatic deposits: Boost dose of 5.4–9 Gy/3–5 fractions	Concurrent carboplatin followed by adjuvant six cycles of systemic chemotherapy
Standard risk	Children <18 year CSI: 23.4 Gy/13 fractions, 5 days a week Boost to whole posterior fossa (or tumor bed): 30.6 Gy/17 fractions, 5 times/week Adults CSI: 36 Gy/20 fractions, 5 days a week Boost to posterior fossa: 19.8 Gy/11 fractions, 5 times/week	Children <18 year Weekly vincristine followed by adjuvant six cycles of systemic chemotherapy
Low risk	CSI: 23.4 Gy/13 fractions, 5 days a week Boost to whole posterior fossa (or tumor bed): 30.6 Gy/17 fractions, 5 times/week	Reduced intensity chemotherapy

Table 3.
Radiotherapy doses according to risk stratification.

In grown up children, sparing the anterior portion of the vertebral body results in minimization of bone marrow dose (**Figure 7**).

Consensus report from the Stockholm pediatric proton therapy conference showed that treatment of choice for medulloblastoma is proton therapy [45]. Based on the review of the existing theoretical and early clinical outcomes evidence, results showed that proton craniospinal irradiation provide similar control of tumor with potentially decreased doses to the normal structures thus reduces the risk of side effects when compared with photon existing data [46]. Spot-scanned intensity-modulated proton therapy (IMPT) is advantageous over the photon therapy in terms of all radiobiological risk estimation [47].

Weight changes in medulloblastoma and adaptive proton therapy are coming up but at present there is scanty data available. Patient selection is of utmost important in proton therapy. Limitations of patients with their families to travel in these

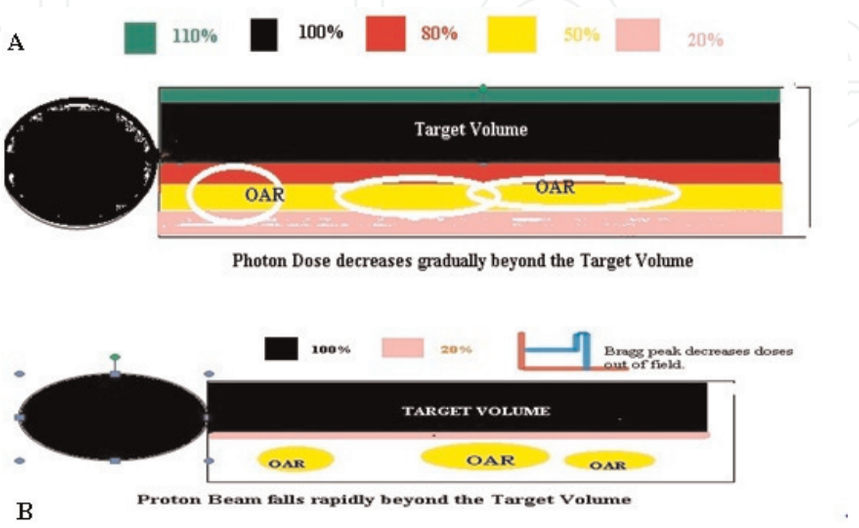

Figure 7.
CSI Schematic Model. (A) Photons are absorbed and secondary electrons have large range in mm resulting in doses beyond the target volume. (B) Advantage of stopping of protons is due to the Bragg peak curve resulting in lower doses to OARs with proton therapy.

centers, the proton center capacity to treat children and the availability of expertise and support structures must be evaluated by the referral physicians.

6. Chemotherapy

Chemotherapy is integral part of treatment and in standard risk cases CSI doses can be reduced. Children less than 3 years, chemotherapy is recommended till the child will attain the age of 3 years. Drugs like carboplatin, cyclophosphamide and etoposide is recommended. There are various regimens recommended (**Box 1**). In a published database analysis of medulloblastoma children (n = 816) age 3–8 years who received adjuvant chemotherapy after surgery, overall rate of RT deferral after surgery was 15.1%. Their practice was associated was decreased overall survival in this pediatric population even in the well-established era of chemotherapy. [48] At present, recommendations of chemotherapy are:

- Following RT as adjuvant settings
- In Infant medulloblastoma, to defer RT, till the age of 3-years
- Autologous stem-cell rescue accompanied with high-dose chemotherapy with
- Concurrent chemotherapy with radiotherapy
- As a salvage therapy in cases of relapsed of recurrent medulloblastoma.

Box 1.
Chemotherapy regimens (adjuvant) in MB children >3 years of age [49, 36].

Packer's Regimen 1	Regimen II	Regimen III
Cisplatin, Lomustine, Vincristine	Cisplatin, Cyclophosphamide , Vincristine	(Days of administration are different from Regimen II) Cisplatin, Cyclophosphamide , Vincristine

A detailed discussion about the chemotherapy and late effects of radio-chemotherapy, management of adverse effects are outside the scope of this chapter. It is recommended and important *to have* multidisciplinary follow-up with pediatric radiation oncologists and endocrinologists.

7. Follow up

Follow up counseling is mandatory prior to initiation of treatment. MRI brain may be performed every three months and MRI spine may be obtained every six months in standard risk category of standard risk patients for the initial two years. These two investigations can be performed every 6 months up to five years, and then repeated every year. In high-risk group, MRI of whole brain and spine may be repeated every three months for the initial two years. Thorough clinical examination with every visit is necessary. In case of pediatric or adolescence groups following radiotherapy, neuroendocrine follow-up with evaluation of serum hormonal levels should be performed every six months.

Acknowledgements

Authors are grateful to Prof. Sunil Saini, Director Cancer Research Institute, Swami Rama Himalayan University for providing motivation and necessary facilities for writing this book chapter.

Conflict of interest

The authors declare that this chapter was written in the absence of any commercial or financial relationships that could elucidate as a potential conflict of interest.

Author details

Meenu Gupta* and Mushtaq Ahmad
Cancer Research Institute, Swami Rama Himalayan University, Dehradun, India

*Address all correspondence to: meenugupta.786@rediffmail.com

References

[1] Millard NE, De Braganca KC. Medulloblastoma. Journal of Child Neurology. 2016;**31**(12):1341-1353

[2] Nelson JS et al. Embryonal tumors of the central nervous system. In: Principles and Practice of Neuropathology. 2nd ed. Oxford University Press; 2003. p. 384

[3] Adesina AM, Yachnis AT. Medulloblastoma Pathology. 2015

[4] Gregory JJ. Overview of pediatric cancer. In: Pediatrics. Merck Manual; Global Medical Knowledge. 2015

[5] Huang MA . Pediatric Medulloblastoma. 2017

[6] Lassaletta A, Ramaswamy V. Medulloblastoma in adults: They're not just big kids. Neuro-Oncology. 2016; **18**(7):895-897

[7] Jallo GI, Osburn BR, Shimony N. Medulloblastoma, 2018

[8] Khanna V, Achey RL, Ostrom QT, Block-Beach H, Kruchko C, Barnholtz-Sloan JS. Incidence and survival trends for medulloblastomas in the United States from 2001 to 2013. Journal of Neuro-Oncology. 2017;**135**(3):433-441

[9] Wilne S, Collier J, Kennedy C, Jenkins A, Grout J, Mackie S, et al. Progression from first symptom to diagnosis in childhood brain tumors. European Journal of Pediatrics. 2012;**171**(1): 87-9310. DOI: 1007/s00431-011-1485-7

[10] Krishna V. The nervous system. In: Text Book of Pathology. Chennai, India: Orient Longman Private Limited; 2004. p. 1035

[11] Koeller KK, Rushing EJ. Medulloblastoma: A comprehensive review with radiologic-pathologic correlation. Radiographics. 2003;**23**(6): 1613-1637

[12] Wu G-Y, Haopeng P, Ghimire P, Liu G. H magnetic resonance spectroscopy and diffusion weighted imaging findings of medulloblastoma in 3.0T MRI: A retrospective analysis of 17 cases. Neural Regeneration Research. 2012;**7**(32):2554-2559

[13] Muzumdar D, Deshpande A, Kumar R, Sharma A, Goel N, Dange N, et al. Medulloblastoma in childhood—King Edward Memorial hospital surgical experience and review: Comparative analysis of the case series of 365 patients. Journal of Pediatric Neurosciences. 2011;**6**(Supp. 1):S78-S85

[14] Spennato P, Ruggiero C, Cinalli G. Medulloblastoma—Surgery. In: Ozek MM, Cinalli G, Maixner W, Sainte-Rose C, editors. Posterior Fossa Tumors in Children. Switzerland: Springer; 2015. pp. 313-332

[15] Meyers SP, Wildenhain SL, Chang JK, Bourekas EC, Beattie PF, Korones DN, et al. Postoperative evaluation for disseminated medulloblastoma involving the spine: Contrast-enhanced MRI findings, CSF cytologic analysis, timing of disease occurrence, and patient outcomes. AJNR. American Journal of Neuroradiology. 2000;**21**:1757-1765

[16] Harreld JH, Mohammed N, Goldsberry G, Li X, Li Y, Boop F, et al. Postoperative intraspinal subdural collections after pediatric posterior fossa tumor resection: Incidence, imaging, and clinical features. AJNR. American Journal of Neuroradiology. 2015;**36**: 993-999

[17] Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: A summary. Acta Neuropathologica. 2016; **131**:103-120

[18] Sengupta S, Krummel DP, Pomeroy S. The evolution of medulloblastoma therapy to personalized medicine. F1000Research. 2017;**6**:490

[19] Kijima N, Kanemura Y. Molecular classification of medulloblastoma. Neurologia Medico-Chirurgica. 2016; **56**(11):687-697

[20] Hayat MA, editor. Pediatric Cancer. Diagnosis, Therapy, and Prognosis. Vol. 42013. Springer. pp. 93-95

[21] DeSouza R-M, Jones BRT, Lowis SP, Kurian KM. Pediatric medulloblastoma —Update on molecular classification driving targeted therapies. Frontiers in Oncology. 2014;**4**:176

[22] Paterson E, Farr RF. Cerebellar medulloblastoma: Treatment by irradiation of the whole central nervous system. Acta Radiologica. 1953;**39**(4): 323-336

[23] Paulino AC. Radiotherapeutic management of medulloblastoma. Oncology. 1997;**11**:813-823

[24] Lannering B, Rutkowski S, Doz F, Pizer B, Gustafsson G, Navajas A, et al. Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: Results from the randomized multicenter HIT-SIOP PNET 4 trial. Journal of Clinical Oncology. 2012; **30**(26):3187-3193

[25] Tai P, Koul R, Khanh V, Edwards T, Buwembo J, Teles AR, et al. A simplified supine technique expedites the delivery of effective craniospinal radiation to medulloblastoma—Comparison with other techniques in the literature. Cureus. 2015;**7**(12):e404

[26] Athiyaman H, Mayilvaganan A, Singh D. A simple planning technique of craniospinal irradiation in the eclipse treatment planning system. Journal of Medical Physics. 2014;**39**(4):251-258

[27] Parker WA, Freeman CR. A simple technique for craniospinal radiotherapy in the supine position. Radiotherapy and Oncology. 2006;**78**:217-222

[28] Taqaddas A. Oncological management of medulloblastoma and new viral therapeutic targets. International Journal of Medical and Health Sciences. 2015;**9**(1):27-30

[29] Ajithkumar T, Horan G, Padovani L, Thorp N, Timmermann B, Alapetite C, et al. SIOPE—Brain tumor group consensus guideline on craniospinal target volume delineation for high-precision radiotherapy. Radiotherapy & Oncology. 2018;**128**(2):192-197

[30] Noble DJ, Scoffings D, et al. Fast imaging employing steady-state acquisition (FIESTA) MRI to investigate cerebrospinal fluid (CSF) within dural reflections of posterior fossa cranial nerves. The British Journal of Radiology. 2016;**89**(1067):20160392

[31] Siddiqui JD, Loeffler JS, Murphy MA. Radiation optic neuropathy after proton beam therapy for optic nerve sheath meningioma. Journal of Neuro-Ophthalmology. 2013;**33**:165-168

[32] Ferguson I et al. Risk factors for radiation-induced optic neuropathy: A casecontrol study. Clinical & Experimental Ophthalmology. 2017;**45**: 592-597

[33] Jereb B, Reid A, Ahuja RK. Patterns of failure in patients with medulloblastoma. Cancer. 1982;**50**:2941-2947

[34] Donnal J, Halperin EC, Friedman HS, et al. Subfrontal recurrenceof medulloblastoma. Journal of Neurology Research. 1992;**13**:1617-1618

[35] Gupta M, Kant R, et al. A dosimetric comparison between three-dimensional conformal radiation therapy and intensity-modulated radiation therapy in the treatment of posterior fossa boost in medulloblastoma. Journal of Cancer

Research and Therapeutics. 2017;**13**: 1027-1031

[36] Gupta T, Sarkar C, et al. Indian society of neuro-oncology consensus guidelines for the contemporary management of medulloblastoma. Neurology India. 2017;**65**:315-332

[37] Parker W, Filion E, et al. Intensity-modulated radiotherapy for craniospinal irradiation: Target volume considerations, dose constraints, and competing risks. International Journal of Radiation Oncology • Biology • Physics. 2007;**69**(1):251-257

[38] Sharma DS, Gupta T, Jalali R, Master Z, Phurailatpam RD, Sarin R. High-precision radiotherapy for craniospinal irradiation: Evaluation of three-dimensional conformal radiotherapy, intensity-modulated radiation therapy and helical tomotherapy. The British Journal of Radiology. 2009 Dec;**82**(984): 1000-1009

[39] Huang E, Teh BS, Strother DR, Davis QG, Chiu JK, Lu HH, et al. Intensity-modulated radiation therapy for pediatric medulloblastoma: Early report on the reduction of ototoxicity. International Journal of Radiation Oncology, Biology, Physics. 2002;**52**:599-605

[40] Pierotti MA, van Harten W, editors. European Options and Recommendations for Cancer Diagnosis and Therapy. Vol. 12011. Brussels, Belgium: Organisation of European Cancer Institutes European Economic Interest Grouping c/o Fondation Universitaire (OECI-EEIG); ISBN: 9789080625679

[41] Abacioglu U, OmerUzel MS, SedatTurkan AO. Medulloblastoma in adults: Treatment results and prognostic factors. International Journal of Radiation Oncology • Biology • Physics. 2002;**54**(3):855-860

[42] Thomas PR, Deutsch M, Kepner JL, et al. Low-stage medulloblastoma: Final analysis of trial comparing standard-dose with reduced-dose neuraxis irradiation. Journal of Clinical Oncology. 2000;**18**:3004-3011

[43] Parkes J, Hendricks M, Ssenyonga P, Mugamba J, Molyneux E, Meeterenet A S-v, et al. Clinical practice guidelines SIOP PODC. Adapted treatment recommendations for standard-risk medulloblastoma in low and middle income settings. Pediatric Blood & Cancer. 2015;**62**:553-564

[44] Kutanzi KR, Lumen A, Koturbash I, Miousse IR. Pediatric exposures to ionizing radiation: Carcinogenic considerations. International Journal of Environmental Research and Public Health. 2016;**13**(11):1057

[45] Indelicato DJ, Merchant T, Laperriere N, Lassen Y, Vennarini S, Wolden S. Consensus report from the stockholm pediatric proton therapy conference. International Journal of Radiation Oncology, Biology, Physics. 2016;**96**(2):387-392

[46] Mahajan A. Proton craniospinal radiation therapy: Rationale and clinical evidence. International Journal of Particle Therapy. 2014;**1**(2):399-407

[47] Brodin NP, Munck Af Rosenschöld P, Aznar MC, et al. Radiobiological risk estimates of adverse events and secondary cancer for proton and photon radiation therapy of pediatric medulloblastoma. Acta Oncologica. 2011;**50**:806-816

[48] Kann BH, Park HS, Lester-Coll NH, Yeboa DN, Benitez V, Khanet AJ, et al. Postoperative radiotherapy patterns of care and survival implications for medulloblastoma in young children. JAMA Oncology. 2016;**2**(12):1574-1581

[49] Packer RJ, Gajjar A, Vezina G, Rorke-Adams L, Burger PC, Robertson PL, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. Journal of Clinical Oncology. 2006;**24**: 4202-4208