Medulloblastoma: Management, Radiogenomics and Chemotherapy

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History

- First described by Harvey Cushing and Percival Bailey

- At that time this tumor was described variously – sarcoma, neuroblastoma and neurocytoma.

- Initially described as “spongioblastoma cerebelli” - a soft, suckable tumor usually arising in the vermis of cerebellum

- In 1925, changed name to medulloblastoma – from “medulloblast” - a hypothetical multipotent cell
Epidemiology

- Most common 1° CNS neoplasm in childhood (20%).
- Cerebellum, predominantly neuronal differentiation (WHO-IV)
- 40% posterior fossa neoplasms
- Young age at presentation.
- Bimodal peak between 3-4 and 8-9yrs median 5-8yrs
- Slight male predominance

Fig 5. Sagittal T1 weighted MRI after contrast injection showing a midline cerebellar mass with posterior compression of the brain stem.
Presentation

Increased intracranial pressure:
- headaches, nausea, vomiting

Cerebellar involvement: ataxic gait

In infants: loss of milestones, increased head circumference, head tilt due to CN IV palsy

Clinical exam: papilledema, nystagmus, CN abnormalities (VI most common → "setting sun" sign with downward gaze)

50-75% have <3 months of symptoms
Natural History

Cerebellar vermis (77%)
Fill 4th ventricle
Hydrocephalus above
Brain stem (33%)
CSF spread (33%)
Diffuse subarachnoid seeding, nodular spinal growth
Extraneural spread (<10%)
  bone > lymphnodes > lungs > liver
Histopathology

Small round blue cell tumor
Cell Of Origin: fetal remnant cells in the external granular layers of the cerebellum
Most common embryonal tumor of the CNS (others include PNETs, ATRT)
Molecularly distinct from PNETs
40% have Homer-Wright rosettes
Most stain + for neuron-specific enolase, synaptophysin, and nestin
Histological Variants WHO -2007

- MBEN
  - 3%
  - Infants
  - Good prognosis

- Desmoplastic
  - 7%
  - Adults
  - Better prognosis

- Classic
  - 70-80%
  - Poor prognosis

- LC/A
  - 10-22%
  - Aggressive
  - Early CSF dissemination
  - anaplasia
  - Worst
  - prognosis
Molecular Sub grouping

for a better prognostication and refined risk-stratification.

- Wingless type (WNT) activated
- Sonic Hedgehog (SHH) activated
- Group 3
- Group 4

- These four molecular sub-groups have different
  - developmental origins
  - phenotypes
  - transcription and genetic profiles,
  - diverse biological behaviour
  - markedly variable prognosis and clinical outcomes

WHO 2016 Classification

Embryonal tumours

Medulloblastoma, **genetically defined**
1. Medulloblastoma, WNT-activated
2. Medulloblastoma, SHH-activated and TP53-mutant
3. Medulloblastoma, SHH-activated and TP53-wildtype
4. Medulloblastoma, non-WNT/non-SHH
   - Medulloblastoma, group 3
   - Medulloblastoma, group 4

Medulloblastoma, **histologically defined**
1. Medulloblastoma, classic
2. Medulloblastoma, desmoplastic/nodular
3. Medulloblastoma with extensive nodularity
4. Medulloblastoma, large cell/anaplastic
Medulloblastoma, NOS
## Integrated diagnosis format (WHO 2016)

<table>
<thead>
<tr>
<th>Integrated diagnosis</th>
<th>Medulloblastoma; histological subtype; molecular sub-group; and histologic grade (grade IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histologic diagnosis</strong></td>
<td>Classic, Desmoplastic/Nodular (D/N), Medulloblastoma with Extensive Nodularity (MBEN), or Large-Cell/Anaplastic (LC/A)</td>
</tr>
<tr>
<td>WHO grading</td>
<td>Grade IV</td>
</tr>
<tr>
<td>Molecular sub-grouping</td>
<td>WNT-activated, SHH-activated (TP53 mutant or wild type), and non-WNT/non-SHH</td>
</tr>
<tr>
<td>Genetic alterations (wherever available)</td>
<td>MYC amplification, TP53 status, CTNNB1 mutation, SMO status, PTCH1 status, Isodicentric chromosome 17q, Monosomy 6</td>
</tr>
<tr>
<td>Genetic profile</td>
<td>Histology</td>
</tr>
<tr>
<td>-----------------------------------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>Medulloblastoma, WNT-activated</td>
<td>Classic</td>
</tr>
<tr>
<td></td>
<td>Large cell / anaplastic (very rare)</td>
</tr>
<tr>
<td>Medulloblastoma, SHH-activated, TP53-mutant</td>
<td>Classic</td>
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<tr>
<td></td>
<td>Large cell / anaplastic</td>
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<td>Medulloblastoma, SHH-activated, TP53-wildtype</td>
<td>Classic</td>
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<tr>
<td></td>
<td>Large cell / anaplastic</td>
</tr>
<tr>
<td></td>
<td>Desmoplastic / nodular</td>
</tr>
<tr>
<td></td>
<td>Extensive nodularity</td>
</tr>
<tr>
<td>Medulloblastoma, non-WNT/non-SHH, group 3</td>
<td>Classic</td>
</tr>
<tr>
<td></td>
<td>Large cell / anaplastic</td>
</tr>
<tr>
<td>Medulloblastoma, non-WNT/non-SHH, group 4</td>
<td>Classic</td>
</tr>
<tr>
<td></td>
<td>Large cell / anaplastic (rare)</td>
</tr>
</tbody>
</table>
Figure 3: Practical approach to rapid molecular sub-grouping of medulloblastoma using a immunohistochemical panel of three markers viz. β-catenin (1:200, BD Transduction Laboratories), GAB1 (1:100, Abcam) and YAP1 (1:200, Santa Cruz). WNT-medulloblastomas (a-c) are immunopositive for nuclear β-catenin and YAP1, and immunonegative for GAB1; SHH tumors (d-i) demonstrate diffuse strong positivity for GAB1 and YAP1, but lack β-catenin nucleopositivity; while lack of immunopositivity for all the three markers denotes non-WNT/non-SHH medulloblastoma (g-i).
Neuro – Imaging: CT Brain

- Hyperattenuated, welldefined vermian cerebellar mass
- Surrounding vasogenic edema
- Evidence of hydrocephalus
- Homogeneous contrast enhancement
- Cyst formation (59% of cases)
- Typically from the vermis – midline, in posterior fossa; fills fourth ventricle
- Less commonly – in the cerebellar hemisphere, extending to foramen magnum
Neuro – Imaging: MRI Brain

- Iso- to- hypointense relative to white matter (T1 images)
- Enhance following contrast (90%)
- Heterogeneous enhancement.
- Vasogenic edema +
Neuro – Imaging: MRI Brain

T2-weighted images:

- densely cellular component of the tumor being hypointense
- the less cellular areas being iso- to hyperintense
- Intra-tumoral or peri-tumoral cysts, if any, appear hyperintense,
- calcification generally exhibits a low signal on T2-weighted sequences

DIFFUSION WEIGHTED IMAGES

- densely packed cells within the tumor,
- restriction of diffusion: low apparent diffusion coefficient (ADC) values
**Neuro – Imaging: MRI Spine**

- Most metastases are found along the posterior margin of the spinal cord –
- CSF flow from cisterna magna to posterior margin of spinal cord
- **Sagittal fat-suppressed post-contrast MRI** of the spine is strongly recommended in the pre-operative setting as a screening tool to rule out any leptomeningeal metastases.
Radiogenomics

Fig. 1 | **Location of MB.** Sagittal section of the cerebellum and brainstem, with common diagnostic locations of medulloblastoma (MB) indicated on the basis of MRI. MB locations have been colour-coded according to prominent diagnostic locations observed for individual consensus subgroups: WNT (blue); SHH (red); Group 3 (yellow); Group 4 (green).
MRI Surrogates for Molecular Subgroups of Medulloblastoma

Tumors occur along the CP/CPA: WNT
Predominantly located in the cerebellar hemispheres: SHH
Located in the midline/fourth ventricle and show enhancement and ill-defined features against the adjacent brain parenchyma : Group C
Located in the midline fourth ventricle but tend to show minimal or no enhancement: Group D
Risk Stratification Of Medulloblastoma

• Clinicoradiological
• Molecular

• Impetus for stratification
  – Heterogeneity
  – Molecular profiling and classification
  – To escalate/deescalate treatment
Clinical Pathological staging (Modified chang)

**Box 1 Chang staging system.**

The T stage does not demonstrate prognostic significance. The extent of disease progression summarized in the M stage remains a highly prognostic factor. Permission obtained from Lippincott Williams and Wilkins © Halperin EC et al. (2005) *Pediatric Radiation Oncology.*

<table>
<thead>
<tr>
<th>Tumor stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor is less than 3 cm in diameter and is limited to the midline position in the vermis, the roof of the fourth ventricle and less frequently cerebellar hemispheres</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 3 cm in diameter, further invading one adjacent structure or partially filling the fourth ventricle</td>
</tr>
<tr>
<td>T3a</td>
<td>Tumor invading two adjacent structures or completely filling the fourth ventricle with extension into the aqueduct or Sylvius, foramen of Magendie or foramen of Luschka, thus producing marked internal hydrocephalus</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor arising from the floor of the fourth ventricle or brain-stem cell and filling the fourth ventricle</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor further spreading through the aqueduct of Sylvius to involve the third ventricle or midbrain, or tumor extending to the upper cervical cord</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metastasis stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No evidence of gross subarachnoid or hematogenous metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Microscopic tumor cells found in cerebrospinal fluid</td>
</tr>
<tr>
<td>M2</td>
<td>Gross nodule seedlings demonstrated in the cerebellar, cerebral subarachnoid space or in the third or lateral ventricles</td>
</tr>
<tr>
<td>M3</td>
<td>Gross nodule seedlings in the spinal subarachnoid space</td>
</tr>
<tr>
<td>M4</td>
<td>Extraneuroaxial metastasis</td>
</tr>
</tbody>
</table>
Residual Tumor: Important prognostic factor

T stage of the Chang's system did not correlate with survival (possible exception of brain stem invasion) – so replaced by the definition of the post operative residual tumor volume concept.

Children Cancer Group 921

HIT’91
# Clinicoradiological Risk stratification

<table>
<thead>
<tr>
<th></th>
<th>Average</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Age</strong></td>
<td>&gt; 3 Yrs</td>
<td>≤ 3 Yrs</td>
</tr>
<tr>
<td><strong>Residual Tumor</strong></td>
<td>≤ 1.5x 1.5 Cm</td>
<td>Gross residual disease</td>
</tr>
<tr>
<td><strong>Metastases</strong></td>
<td>M0</td>
<td>M+</td>
</tr>
<tr>
<td><strong>Histopathology</strong></td>
<td>Classic or desmoplastic subtypes on pathology</td>
<td>Large cell or anaplastic subtype</td>
</tr>
<tr>
<td><strong>Staging</strong></td>
<td>Complete staging possible</td>
<td>Incomplete staging</td>
</tr>
<tr>
<td><strong>Prognosis (5yr survival)</strong></td>
<td>80%</td>
<td>40-60%</td>
</tr>
</tbody>
</table>
### Table 6: Consensus risk-stratification in the molecular era for medulloblastoma

<table>
<thead>
<tr>
<th>Risk category</th>
<th>WNT</th>
<th>SHH</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk (expected survival &gt;90%)</td>
<td>&lt;16 years</td>
<td>TP53 wild type</td>
<td>All of the following</td>
<td>All of the following</td>
<td>Non-metastatic Chr 11 loss</td>
</tr>
<tr>
<td>Standard Risk (expected survival 75-90%)</td>
<td>TP53 wild type</td>
<td>No MYC amplification Non-metastatic</td>
<td>No MYC amplification Non-metastatic</td>
<td>Non-metastatic</td>
<td></td>
</tr>
<tr>
<td>High Risk (expected survival 50-75%)</td>
<td>One or both</td>
<td>One or both MYC amplification Metastatic</td>
<td>All of the following</td>
<td>Non-metastatic</td>
<td></td>
</tr>
<tr>
<td>Very High Risk (expected survival &lt;50%)</td>
<td>TP53 mutation (metastatic or non-metastatic)</td>
<td>Metastatic</td>
<td>Metastatic</td>
<td>Metastatic</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>Metastatic</td>
<td>SHH</td>
<td>Non-metastatic with MYC amplification; anaplasia; isochromosome 17q</td>
<td>Anaplasia</td>
<td>Melanotic medulloblastoma Medulomyoblastoma Indeterminate between groups 3/4</td>
</tr>
</tbody>
</table>

Risk stratification – molecular
Surgery

- Symptomatic Mx: *Should VP shunt be performed?*
  - May be avoided for following reasons:
    - Definitive surgical resection will remove the obstruction
    - Reverse herniation of superior vermis into quadrigeminal cistern
    - Occasional seeding of tumor cells into peritoneal cavity
    - Lifetime shunt dependency
    - Shunt related infections

- CSF diversion if necessary
  - External ventricular drainagae (EVD)
  - Endoscopic third ventriculostomy (ETV)

**Steroid of choice**: dexamethasone 0.5-1mg/kg iv (max = 10mg)
Cerebral decongesants: mannitol/frusemide
Extent Of Surgery

• **Maximum safe resection** is recommended
• Leaving behind residual tumor is better than morbidly aggressive surgical resection

- No evidence of residual tumor at surgery and negative postoperative imaging: **Gross total resection**
- > 90%: **Total or near total**
- 51 - 90%: **Subtotal resection**
- 11 - 50%: **Partial resection**
- < 10%: **Biopsy**
Surgical complications

• Cerebellar mutism syndrome (10%-30%)
  – Posterior fossa syndrome
  – Within 48 hrs
  – Mutism + dysarthria + apraxia
  – Behavioural changes
  – Mechanism- controversial (dentate nucleus)
• Meningitis
• Cervical spine instability
• Cranial nerve palsy
• Anaesthetic complications
Post Operative imaging

- To identify extent of resection & quantify residual disease

- Timing – 2 options
  - **Within 24-48 hours post surgery**
  - **2-3 weeks post surgery** (not later than 4 weeks) – to allow resolution of post-op changes (blood products & surgical debris)

- **Spinal screening** if not done prior
  - 2-3 weeks post surgery – erroneous interpretation of post op enhancement of leptomenegis
CSF cytology

- A part of the post-operative staging work up
- To be performed 2-3 weeks post-op to avoid false positivity
- CSF via ventricular tap at the time of surgery is not considered appropriate for neuraxial staging
Adjuvant treatment

- Poor surgical outcome
- Average survival 5-6 months (Bailey and Cushing)
- First cases treated dec.1919 by x-rays and radium
- Improved survival with radiotherapy
- Introduction of chemotherapy
  - Further survival improvement
  - Radiotherapy dose reduction to reduce morbidity
Pre-adjuvant work-ups

• High cure rates but potential for significant morbidity

• Document post-surgical
  ▪ Neurocognitive
  ▪ Endocrinal
  ▪ Hearing status
  ▪ Ophthalmology
Radiotherapy rationale

- Tumor radiosensitivity
- Poor surgical outcome
- PF RT (focal)
- PF + SC RT
- CSI

leptomeningial relapses
supratentorial relapses

Landberg et al reviewed serial treatment results (10 year survival) at Sweden:

<table>
<thead>
<tr>
<th>VOLUME</th>
<th>5YR OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF</td>
<td>5%</td>
</tr>
<tr>
<td>PF + SC</td>
<td>25%</td>
</tr>
<tr>
<td>CSI</td>
<td>53%</td>
</tr>
</tbody>
</table>

Craniospinal radiation is the corner stone in treatment of medulloblastoma
General Guidelines for Radiotherapy

- Children must be referred 7-10 days post surgery
- Adjuvant RT MUST begin at earliest - Preferably within 4 weeks but not more than 6 weeks post op
- Overall treatment time should preferably be within 50 days, and definitely not more than 8 weeks
- Hematological toxicity – start with or switch over to boost phase

- Anti-emetic prophylaxis – ondansetron 0.2mg/kg 45-60 minutes prior to RT
- Weekly blood counts; avoid GCSF until absolute necessity
- Interrupt RT if
  - ANC <1000
  - Platelets < 50000
Doses and volumes as per risk stratification

CSI for average-risk disease
(age >3 yrs, M0 status, and residual <1.5 cm²)
• Standard dose CSI: 35-36 Gy/21-20#/4 weeks @ 1.67-1.8 Gy/#
• Reduced dose CSI: 23.4 Gy/13#/2.5 weeks @1.8 Gy/# (+ adj CT)

Boost for average-risk disease
• If Standard dose CSI : PF or TB boost: 19.8 Gy/11#/2 weeks
• If reduced dose CSI: Tumour bed boost: 32.4 Gy/18#/3.5 weeks
• Total tumour bed dose: 54-56 Gy/ 30-33#/ 6.6.5 weeks
Doses and volumes as per risk stratification

CSI for high-risk disease
(M+ status, and residual >1.5 cm2)
• Standard dose CSI: 35-36 Gy/21-20#/4 weeks @ 1.67-1.8 Gy/#
• Higher dose spinal RT: 39.6 Gy/22#/4.5 weeks @1.8 Gy/#

Boost for high-risk disease
• Whole posterior fossa boost: 19.8 Gy/11#/2 weeks
• Boost for gross focal spinal deposit: 7.2-9 Gy/4-5#/1 week
How much can the CSI dose be reduced

**Low-Stage Medulloblastoma: Final Analysis of Trial Comparing Standard-Dose With Reduced-Dose Neuraxis Irradiation**

By Patrick R.M. Thomas, Melvin Deutsch, James L. Kepner, James M. Boyett, Jeffrey Krischer, Patricia Aronin, Leland Albright, Jeffrey C. Allen, Roger J. Packer, Rita Linggood, Raymond Mulhern, James A. Stehbens, James Langston, Philip Stanley, Patricia Duffner, Lucy Rorke, Joel Cherlow, Henry S. Friedman, Jonathan L. Finlay, Teresa J. Vietti, and Larry E. Kun

<table>
<thead>
<tr>
<th></th>
<th>5yrs EFS</th>
<th>8yrs EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced</td>
<td>52%</td>
<td>52%</td>
</tr>
<tr>
<td>Standard</td>
<td>67%</td>
<td>67%</td>
</tr>
</tbody>
</table>

Standard dose (36 Gy CSI; 54 GyPF)
Reduced dose (23.4Gy CSI; 54 GyPF)

Trial closed prematurely at N=126
Reduced dose CSI negatively impacts EFS

Thomas, JCO, 2000
N=65 patients
Conc wkly VCR followed by 8 cycles of CCNU, CDDP and VCR
PFS- 86±4% at 3 years , 79±7% at 5 years.
Results better than earlier study using reduced dose CSI alone
Positive impact of adjuvant chemotherapy on EFS

Packer,JCO, 1999
How much can the CSI dose be reduced for average risk medulloblastoma

ACNS0331 trial: 23.4 Gy to 18 Gy CSI in average risk medulloblastoma decreases event free survival and overall survival

23.4 Gy: Probably YES
18 Gy: NO
Target Volume

• The intent of CSI is to deliver a canericial dose to the primary tumor and any tumor cells distributed in the CSF
• The volume of irradiation thus includes:
  – Entire brain and its meningeal coverings with the CSF
  – Spinal cord and the leptomeninges with CSF
  – Lower border of the thecal sac
  – Posterior fossa - boost
Cranial field

The lower border for a conventional cranial field if used with a block will result in a miss of the cribriform plate.
Shielding: SFOP guidelines are less stringent
The recommended placement of block is:
– 0.5 cm below the orbital roof
– 1 cm below and 1 cm in front of the lower most portion of the temporal fossa
– 1 cm away from the extreme edges of the calvaria.
– Note the flexion of the head.
Customized blocks are better than MLCs
Spinal field target volume

- Width: includes the transverse processes
- to ensure that the nerve root meninges exiting from the intervertebral foramina are adequately covered
Spinal field target volume

- Sagittal MRI
- SA space ends at
  - S2 - 66%
  - S1 – 17%
- Recommendation: S2-S3 junction (covers 83%)
BOOST - 2D PLANNING (POSTERIOR FOSSA)

- **Field arrangement**: two lateral opposing fields
- **Anterior**: Posterior clinoid process (avoid pituitary)
- **Posterior**: Internal occipital protuberance
- **Inferior**: C1-C2 interspace
- **Superior**: Midpoint of foramen magnum & vertex or 1cm above the tentorium (as seen on MRI)
Impact of the orientation of the line joining the foramen magnum to the skull on the definition of the posterior fossa boundary. Drayer et al IJROBP1998.
It is possible to treat tumor bed instead of PF in av. risk medulloblastoma hence toxicity reduction.
Boost RT planning

- **Low risk/ Standard risk** – whole posterior fossa need not be treated!
  
  - Pre-operative tumor bed with 1-1.5cm margins
  
  ACNS0331 trial : Involved field equivalent to posterior fossa boost

- **High Risk/Very High Risk** – entire posterior fossa

- Multi –field 3DCRT with cochlear sparing – best achieved with IMRT

- preferred that the **CSI and boost plans be summed** to produce a composite treatment plan and final dose-distribution.
Adjuvant Chemotherapy

Indication for CT:
1. As Adjuvant with Surgery in child <3 yrs to delay/avoid RT.
2. In Recurrent /Progressive disease.
3. In patients with Extra cranial mets.
4. High risk Pt. to improve cure rates
5. In avg. risk group to allow reduced RT dose.

Non-disseminated, totally resected, desmoplastic tumors in children < 3 years showed long-term survival with chemotherapy alone (5Yr EFS: 77-90% and OS: 85-100%).
Adjuvant Chemo in average risk: Toxicity

- 421 patients with non disseminated medulloblastoma
- Cisplatin + CCNU + VCR x 8 cycles
- Cisplatin + Cyclophosphamide + VCR x 8 cycles
- 5 year EFS and OS were 81% and 86% respectively

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3 or 4 Regimen A/B</th>
<th>Grade 4 Regimen A/B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hematologic</td>
<td>97/98</td>
<td>82/90</td>
</tr>
<tr>
<td>Hepatic</td>
<td>12/11</td>
<td>1.7/2.2</td>
</tr>
<tr>
<td>Renal</td>
<td>9.0/5.0</td>
<td>1.1/0.0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3.4/2.2</td>
<td>1.6/1.6</td>
</tr>
<tr>
<td>Nervous system</td>
<td>51/46</td>
<td>5.4/3.8</td>
</tr>
<tr>
<td>Hearing</td>
<td>28/23</td>
<td>5.8/6.7</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>6.2/12</td>
<td>&lt; .10</td>
</tr>
<tr>
<td>Infection</td>
<td>18/30</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Performance</td>
<td>21/14</td>
<td>&lt; .10</td>
</tr>
</tbody>
</table>

Packer, JCO, 2006
General Principles: Adjuvant Chemotherapy

- **Timing of adjuvant CT after radiation**
  - Ideal: 3 weeks
  - Preferably: within 4 weeks
  - Definitely: not beyond 6 weeks

- Every cycle to be given after **sufficient myelo-recovery**
  - ANC > 1000
  - Platelet > 1 lakh
  - RFTT, LFT, s. electrolytes

- **Baseline auditory assessment** is mandatory
  - PTA
Integration of chemotherapy

- Delay in starting RT results in inferior outcome: Halperin
- Prolongation of RT duration negatively impacts upon survival: Del Charco & SIOP PNET 3
- Pre RT CT inferior to post RT CT: CCG 921 and HIT 91
- Pre RT CT does not improve survival compared to RT alone: SIOP II & SIOP PNET 3
- Pre RT CT followed by reduced dose CSI inferior: SIOP II
# Chemotherapy regimen

| Adjuvant chemotherapy regimens for childhood medulloblastoma (>3 years of age) |
|---|---|---|
| **Drugs** | **Dosage** | **Days and route of administration** |
| Regimen I (Packer’s regimen) | | |
| Cisplatin | 75 mg/m² | Day 1 only (intravenously) |
| Lomustine | 75 mg/m² | Day 1 only (per orally) |
| Vincristine | 1.5 mg/m² | Days 1, 8 and 15 (intravenously) |
| Regimen II | | |
| Cisplatin | 75 mg/m² | Day 1 only (intravenously) |
| Cyclophosphamide | 1000 mg/m² | Days 1 and 2 (intravenously) |
| Vincristine | 1.5 mg/m² | Days 1, 8 and 15 (intravenously) |
| Regimen III | | |
| Cisplatin | 75 mg/m² | Day 1 only (intravenously) in cycle 2, 4 and 6 only |
| Cyclophosphamide | 1000 mg/m² | Days 1 and 2 (intravenously) in cycle 1, 3 and 5 |
| | | Days 2 and 3 (intravenously) in cycle 2, 4 and 6 |
| Vincristine | 1.5 mg/m² | Days 1 and 8 (intravenously) in all 6 cycles |
| Adjuvant chemotherapy regimen for infant medulloblastoma (<3 years of age) | | |
| Carboplatin | 600 mg/m² | Day 1 only (intravenously) |
| Cyclophosphamide | 1000 mg/m² | Day 1 only (intravenously) |
Molecular risk-adapted management

**Diagnosis and surgery**
- Diagnosis of posterior fossa lesion
  - Surgical resection
  - Pathology — medulloblastoma

**Staging**
- **WNT**
- **SHH**
- Non-WNT or non-SHH

**Therapy**
- **Average risk:**
  - M0: GTR/NTR
  - Radiation CSI: 15.0–18.0 Gy
    - Boost: 54.0 Gy
  - Conventional chemotherapy ± SHH inhibitors
  - **Outcome:** Excellent
- **High risk:** M1–3 and/or STR
  - Radiation CSI: 36.0 Gy
    - Boost: 54.0 Gy
  - Conventional chemotherapy ± SHH inhibitors
  - **Outcome:** Good
- **Average risk:**
  - M0: GTR/NTR
  - Radiation CSI: 23.4 Gy
    - Boost: 54.0 Gy
  - Conventional chemotherapy ± SHH inhibitors
  - **Outcome:** Good
- **High risk:** M1–3 and/or STR and/or TP53 mutation
  - Radiation CSI: 36.0 Gy
    - Boost: 54.0 Gy
  - Conventional chemotherapy ± novel agents
  - **Outcome:** Poor
- **Average risk:**
  - M0: GTR/NTR
  - Radiation CSI: 36.0 Gy
    - Boost: 54.0 Gy
  - Conventional chemotherapy
  - **Outcome:** Good
- **High risk:** M1–3 and/or STR, MYC+
  - Radiation CSI: 36.0 Gy
    - Boost: 54.0 Gy
  - Conventional chemotherapy ± novel agents
  - **Outcome:** Fair to poor

**Dose decrease of RT and CT**

- SMO inhibitor (vismodegib)
- BET inhibitors
- CDK4/6 inhibitor (ribociclib)
- MET inhibitor (foretinib)
Long-term sequelae of RT

- Neurocognitive & neurophysiological dysfunction
- Endocrine abnormalities & hormonal imbalance
- Growth retardation - spinal component
- Ototoxicity- particularly with platinum based adj CT
- Cerebrovascular accidents
- Gonadal toxicity & reduced fertility
- Second malignant neoplasms
Recommendations for Follow up

- 3 monthly - first 2 years
- 6 monthly - next 5 years
- Annually thereafter

- Contrast-enhanced MRI of the brain and spine
  - 6-12 weeks after completion of all therapy
  - to serve as a baseline for future comparison.

- Routine imaging surveillance should be ordered only if neurologic worsening occurs, recurrence/progression of disease is suspected