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Medulloblastoma:Management, Radiogenomics and Chemotherapy

Dr Shagun Misra
Assistant Professor
Department Of Radiotherapy, SGPGIMS
Lucknow, Uttar Pradesh

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*

Harvey Cushing

Percival Bailey

Epidemiology

- Most common 1º 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

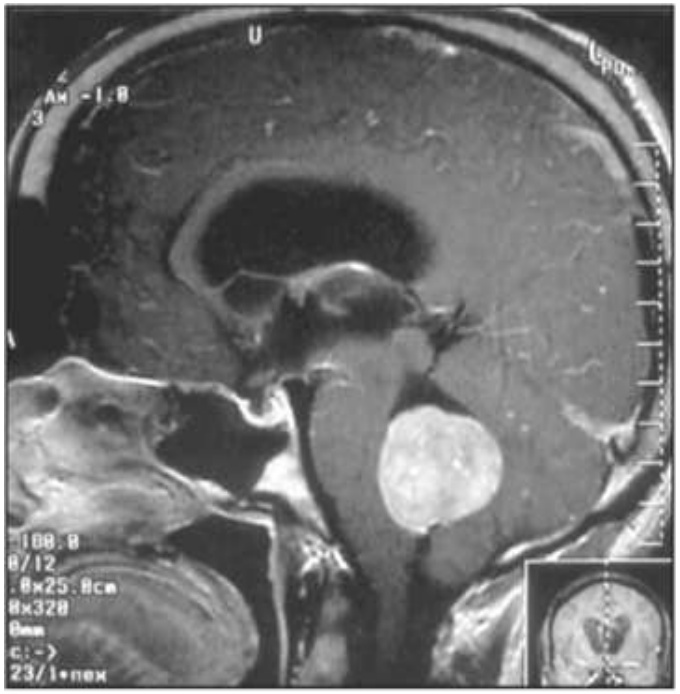


Fig 5. Sagittal T1 weighted MRI after contrast injection showing a midline cerebellar mass with posterior compression of the brain stem.

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 abnormalies (VI most common → "settng sun" sign with downward gaze)

50-75% have <3 months of symptoms

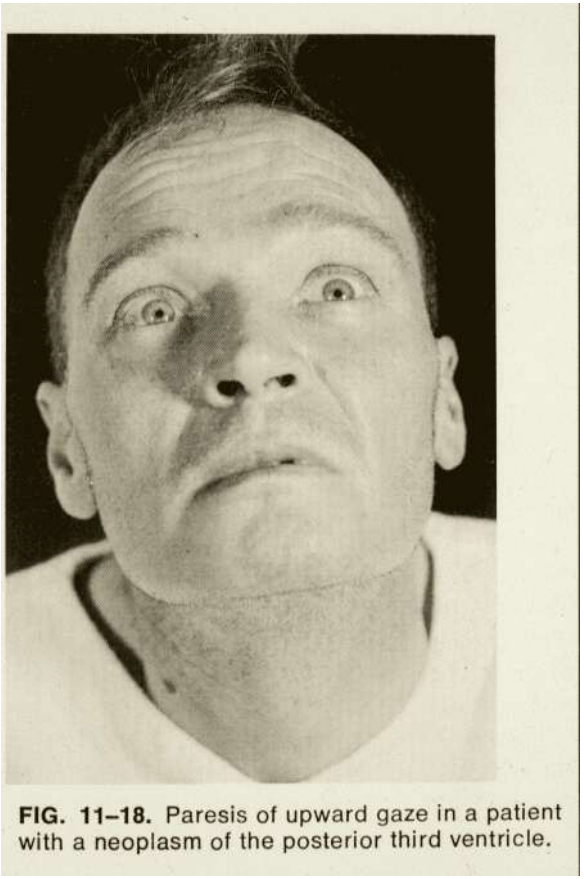


FIG. 11–18. Paresis of upward gaze in a patient with a neoplasm of the posterior third ventricle.

Natural History

Cerebellar vermis (77%)

Fill 4th ventricle

Hydrocephalus above

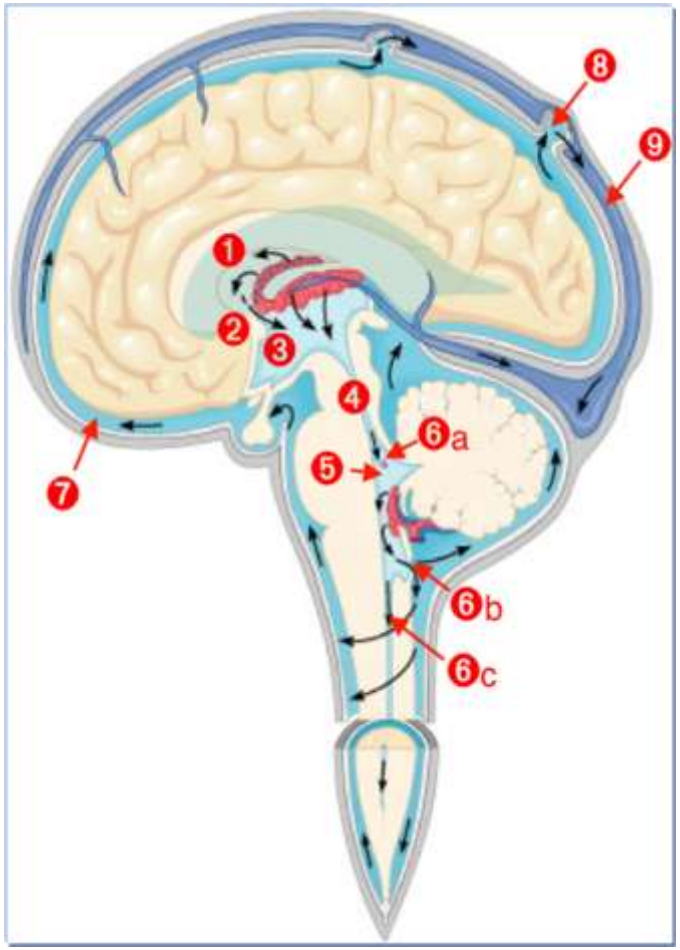
Brain stem (33%)

CSF spread (33%)

Diffuse subarachnoid seeding, nodular spinal growth

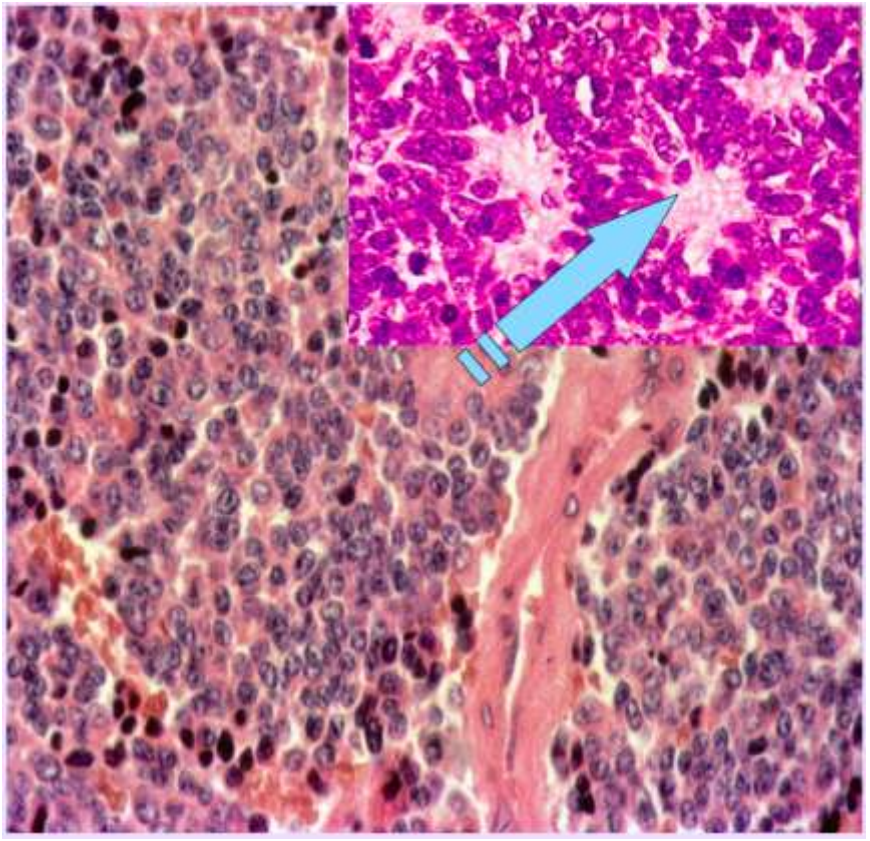
Extraneural spread (<10%)

bone>lymphnodes>lungs>liver

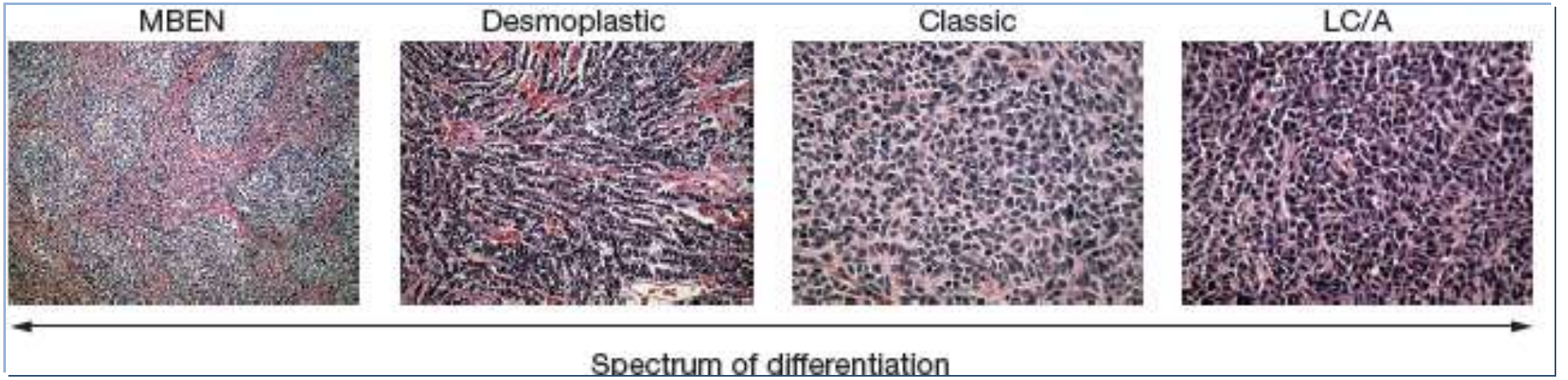


Histopathology

- 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



- 3%
- Infants
- Good prognosis

- 7%
- Adults
- Better prognosis

- 70-80%
- Poor prognosis

- 10-22%
- Aggressive
- Early CSF dissemination
- anaplasia
- Worst
- prognosis

Molecular Sub grouping

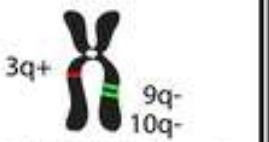
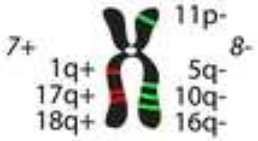
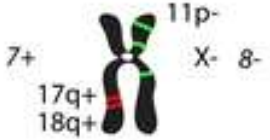
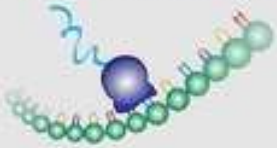
for a better prognostication and refined risk-stratification.

- **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

Acta Neuropathol (2012) 123:465–472

Molecular Subgroups of Medulloblastoma

	WNT	SHH	Group 3	Group 4
CONSENSUS				
Cho (2010)	C6	C3	C1/C5	C2/C4
Northcott (2010)	WNT	SHH	Group C	Group D
Kool (2008)	A	B	E	C/D
Thompson (2006)	B	C', D	E, A	A, C
	10%	30%	25%	35%
DEMOGRAPHICS				
Age Group: (infant, child, adult)				
Gender:	♂ ♂ : ♀ ♀	♂ ♂ : ♀ ♀	♂ ♂ : ♀	♂ ♂ : ♀
CLINICAL FEATURES				
Histology	classic, rarely LCA	desmoplastic/nodular, classic, LCA	classic, LCA	classic, LCA
Metastasis	rarely M+	uncommonly M+	very frequently M+	frequently M+
Prognosis	very good	infants good, others intermediate	poor	intermediate
GENETICS				
	CTNNB1 mutation	*PTCH1/SMO/SUFU* mutation *GLI2* amplification *MYCN* amplification	i17q *MYC* amplification	i17q *CDK6* amplification *MYCN* amplification
GENE EXPRESSION				
	WNT signaling	SHH signaling	Photoreceptor/GABAergic	Neuronal/Glutamatergic
	MYC +	*MYCN* +	*MYC* +++	minimal *MYC* / *MYCN*

WHO 2016 Classification

Embryonal tumours

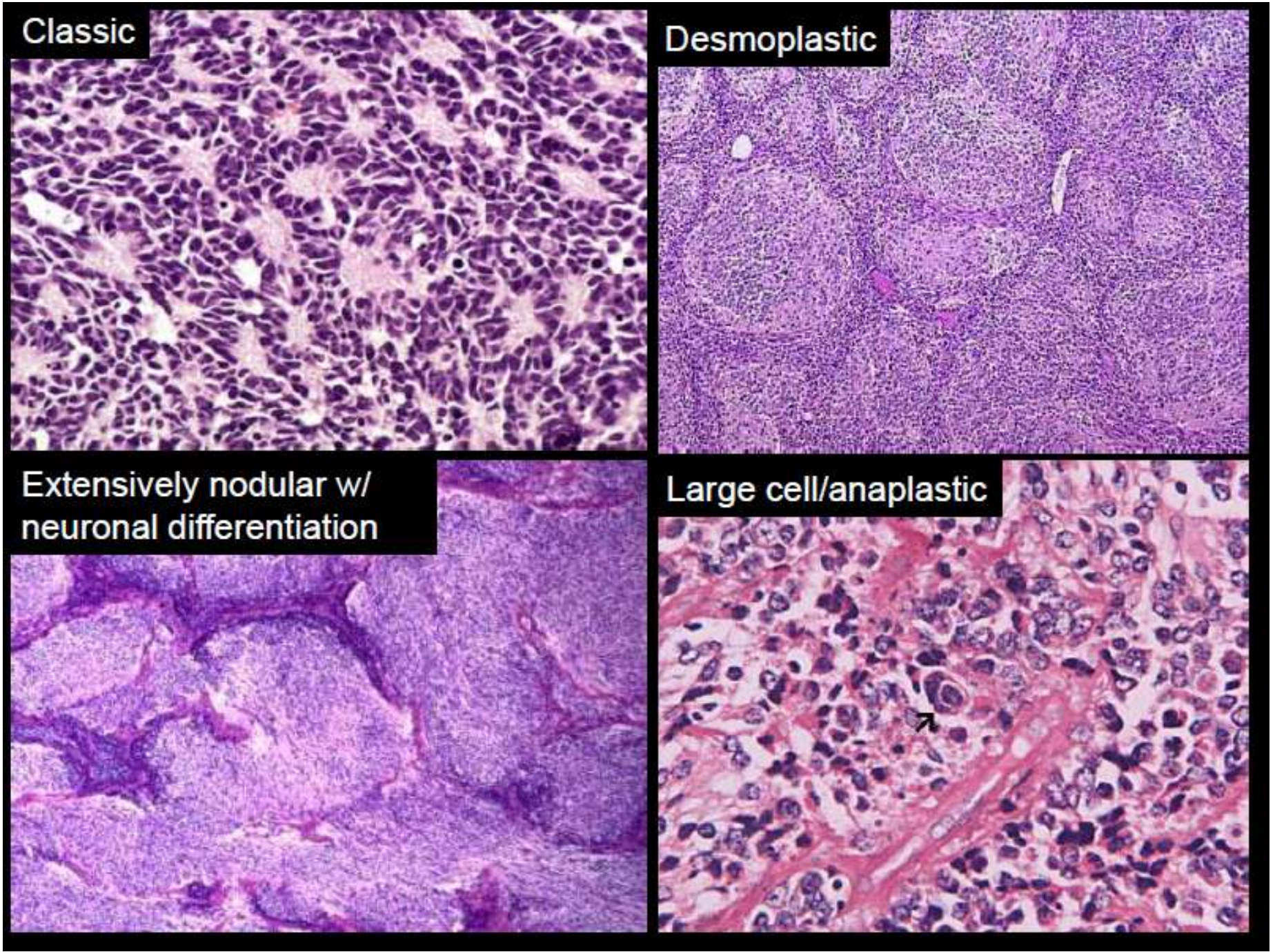
Medulloblastoma, genetically defined

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


Classic
Desmoplastic
Extensively nodular w/
neuronal differentiation
Large cell/anaplastic

Integrated diagnosis format (WHO 2016)

Integrated diagnosis	Medulloblastoma; histological subtype; molecular sub-group; and histologic grade (grade IV)
Histologic diagnosis	Classic, Desmoplastic/Nodular (D/N), Medulloblastoma with Extensive Nodularity (MBEN), or Large-Cell/Anaplastic (LC/A)
WHO grading	Grade IV
Molecular sub-grouping	WNT-activated, SHH-activated (TP53 mutant or wild type), and non-WNT/non-SHH
Genetic alterations (wherever available)	MYC amplification, TP53 status, CTNNB1 mutation, SMO status, PTCH1 status, Isodicentric chromosome 17q, Monosomy 6

Genetic profile	Histology	Prognosis
Medulloblastoma, WNT-activated	Classic	Low-risk tumour; classic morphology found in almost all WNT-activated tumours
	Large cell / anaplastic (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-mutant	Classic	Uncommon high-risk tumour
	Large cell / anaplastic	High-risk tumour; prevalent in children aged 7–17 years
	Desmoplastic / nodular (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-wildtype	Classic	Standard-risk tumour
	Large cell / anaplastic	Tumour of uncertain clinicopathological significance
	Desmoplastic / nodular	Low-risk tumour in infants; prevalent in infants and adults
	Extensive nodularity	Low-risk tumour of infancy
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard-risk tumour
	Large cell / anaplastic	High-risk tumour
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard-risk tumour; classic morphology found in almost all group 4 tumours
	Large cell / anaplastic (rare)	Tumour of uncertain clinicopathological significance

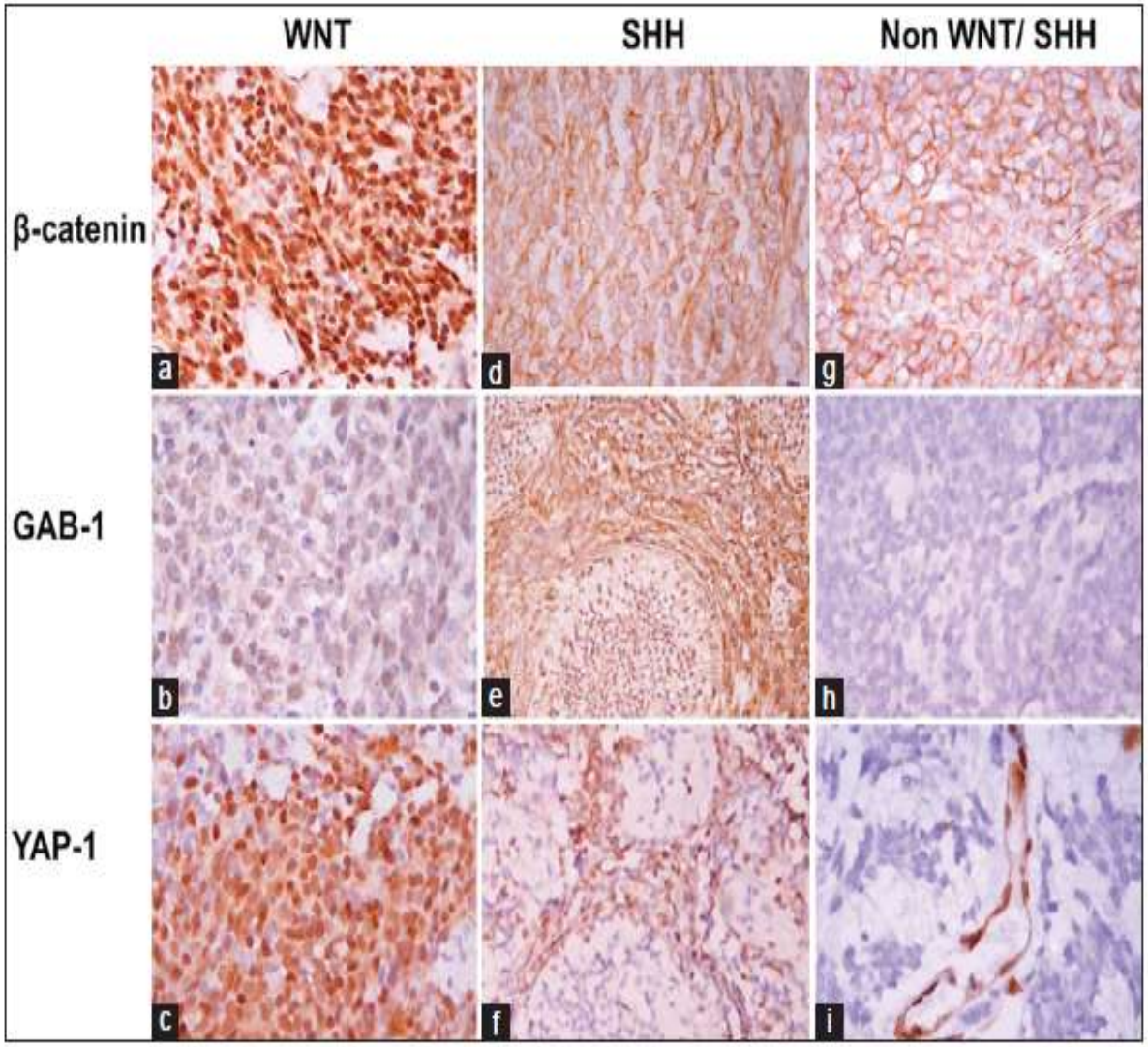
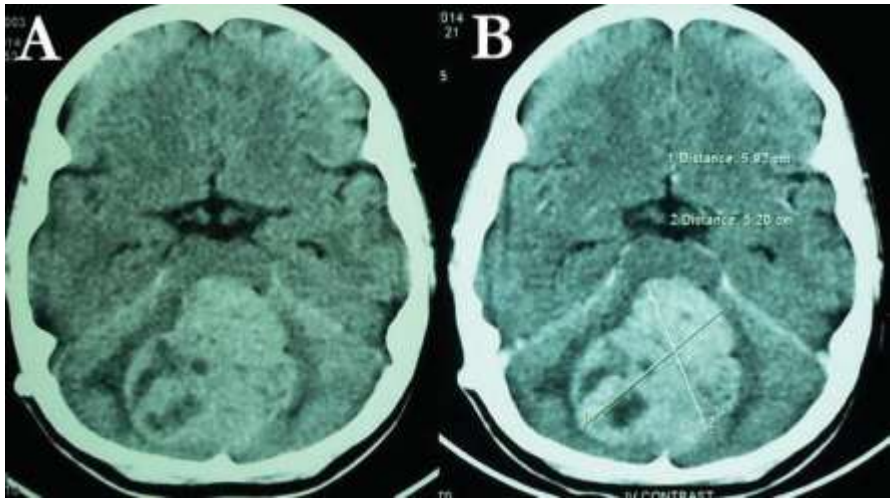
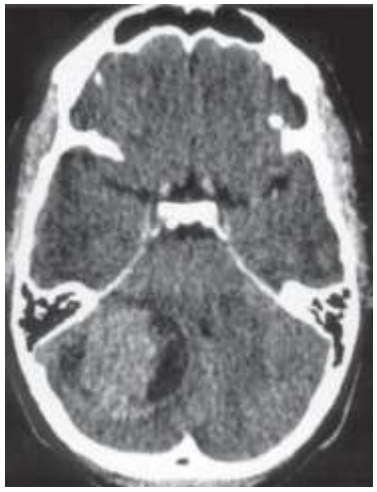


Figure 3: Practical approach to rapid molecular sub-grouping of medulloblastoma using a immunohistochemical panel of three markers viz. β-catenin (1:200, BD Transduction Laboratories), GAB1 (1:100, Abcam) and YAP1 (1: 200, Santa Cruz). WNT-medulloblastomas (a-c) are immunopositive for nuclear β-catenin and YAP1, and immunonegative for GAB1; SHH tumors (d-f) 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

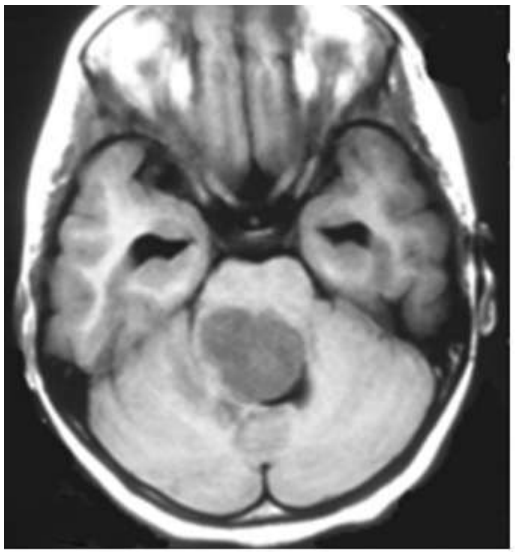
- Hyperattenuated, welldefined vermian cerebellar mass
- Surrounding vasogenic edema
- Evidence of hydrocephalus
- Homogeneous contrast enhancement
- Cyst formation (59% of cases)
- Typically from the vermis – midline, in posterior fossa ; fills fourth ventricle
- Less commonly – in the cerebellar hemisphere,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



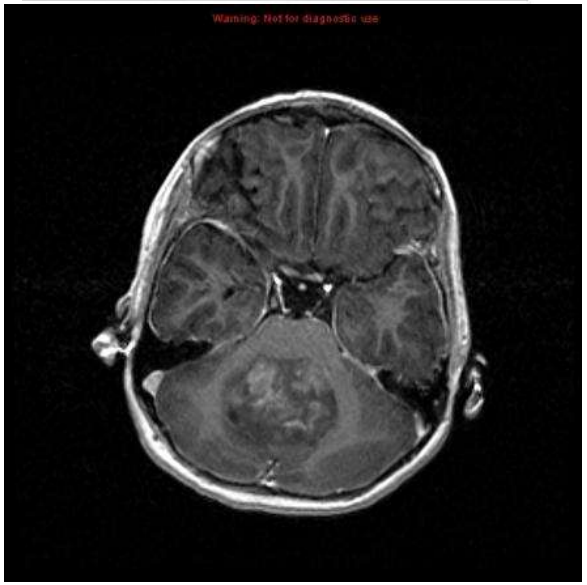


Neuro – Imaging: MRI Brain

- Iso- to- hypointense relative to white matter (T1 images)



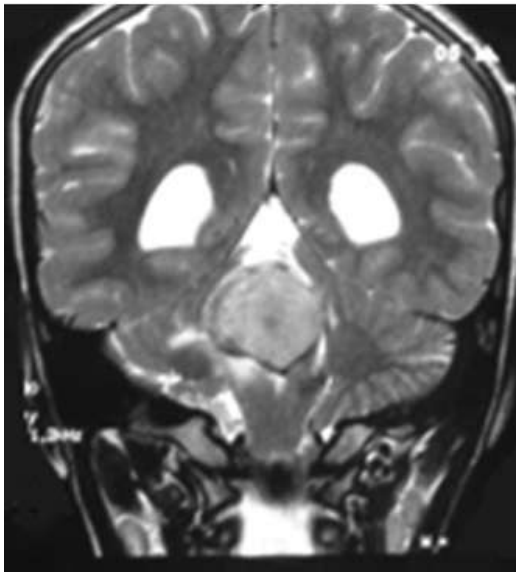
- Enhance following contrast (90%)
- Heterogeneous enhancement.
- Vasogenic edema +



Neuro – Imaging: MRI Brain

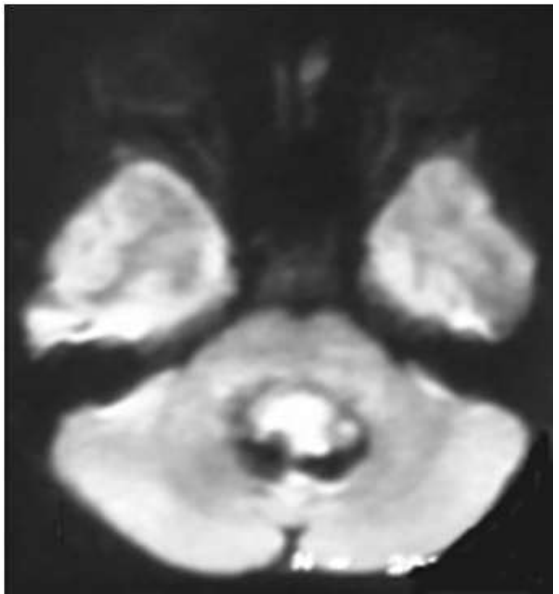
T2-weighted images :

- 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



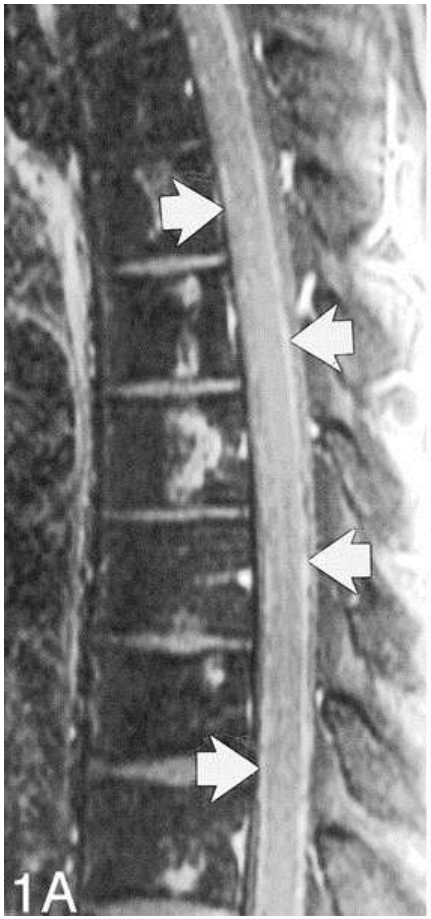
DIFFUSION WEIGHTED IMAGES

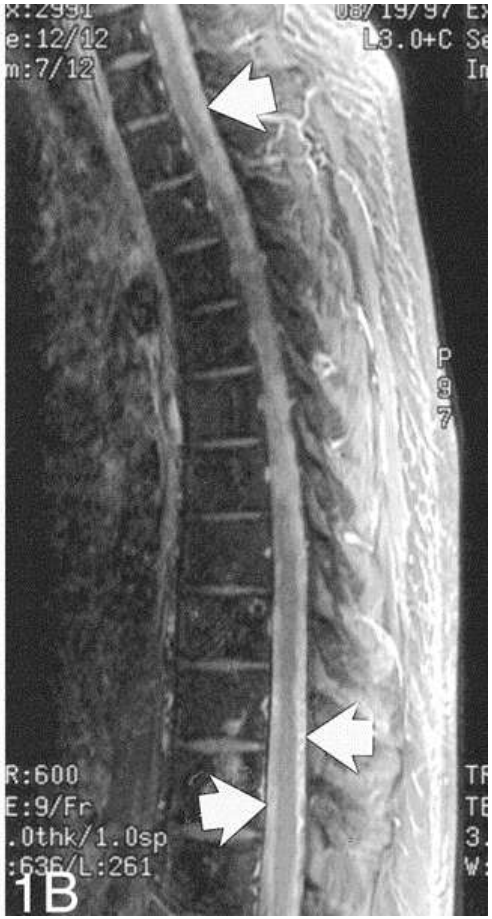
- densely packed cells within the tumor,
- restriction of diffusion : low apparent diffusion coefficient (ADC) values



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

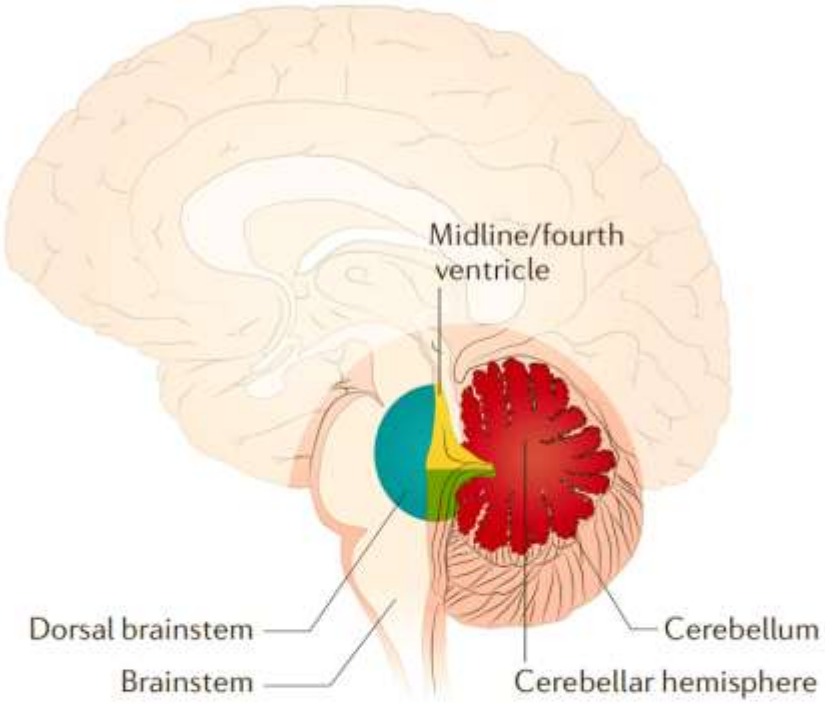


Fig. 1 | **Location of MB.** Sagittal section of the cerebellum and brainstem, with common diagnostic locations of medulloblastoma (MB) indicated on the basis of MRI. MB locations have been colour-coded according to prominent diagnostic locations observed for individual consensus subgroups: WNT (blue);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

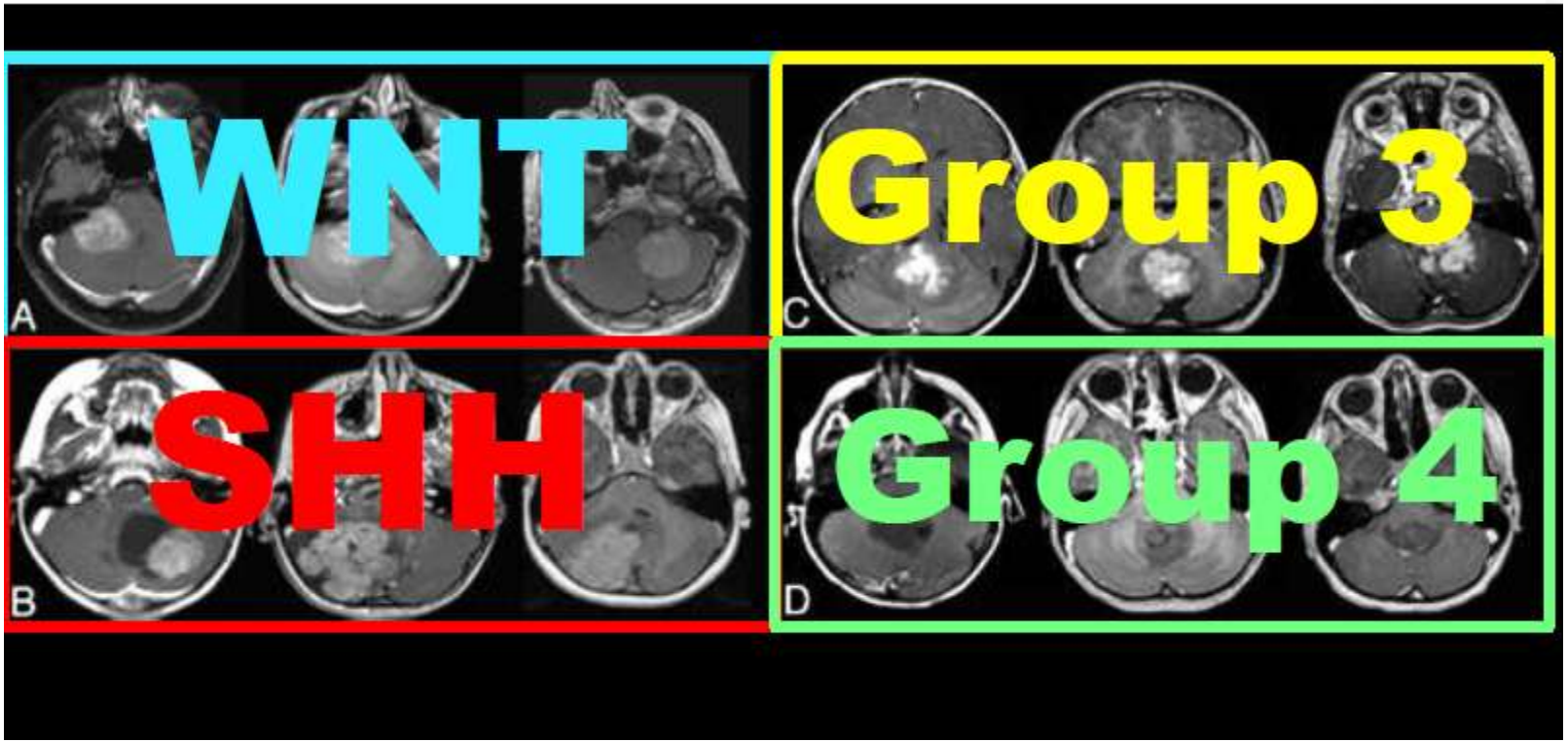
Northcott,2019,Nature Review Disease Primer

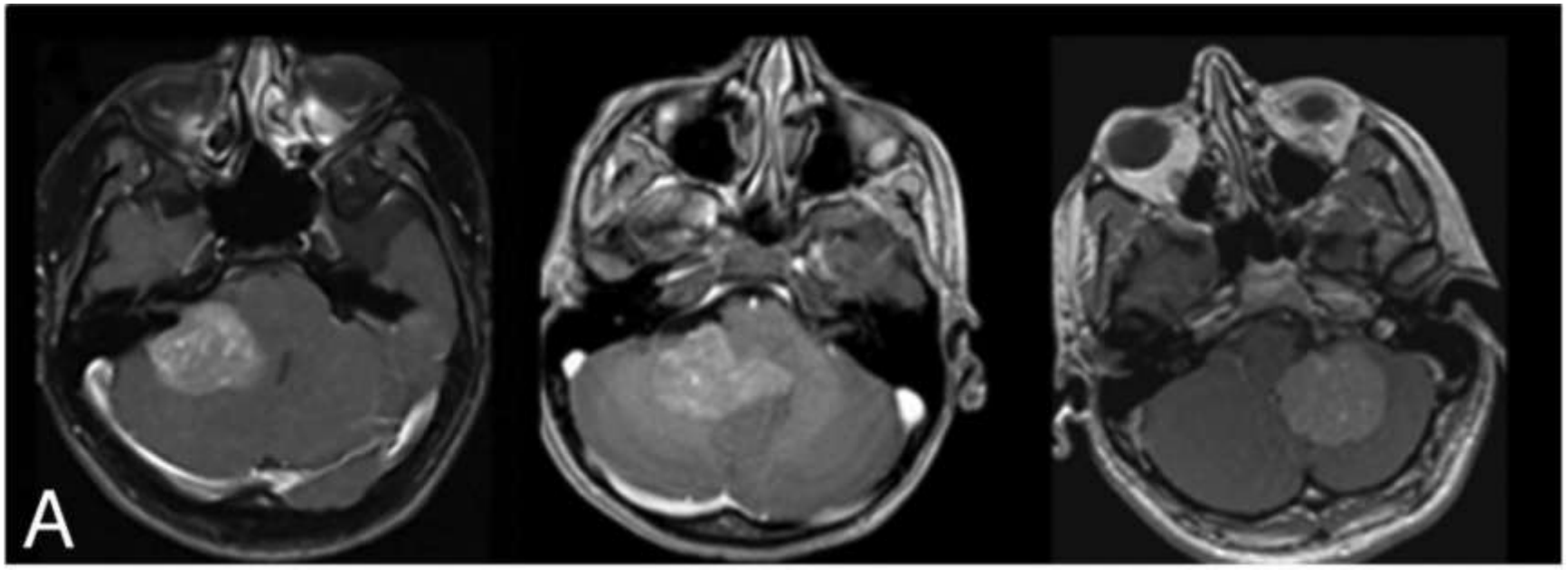
AJNR 2014

EXPEDITED PUBLICATION
BRAIN

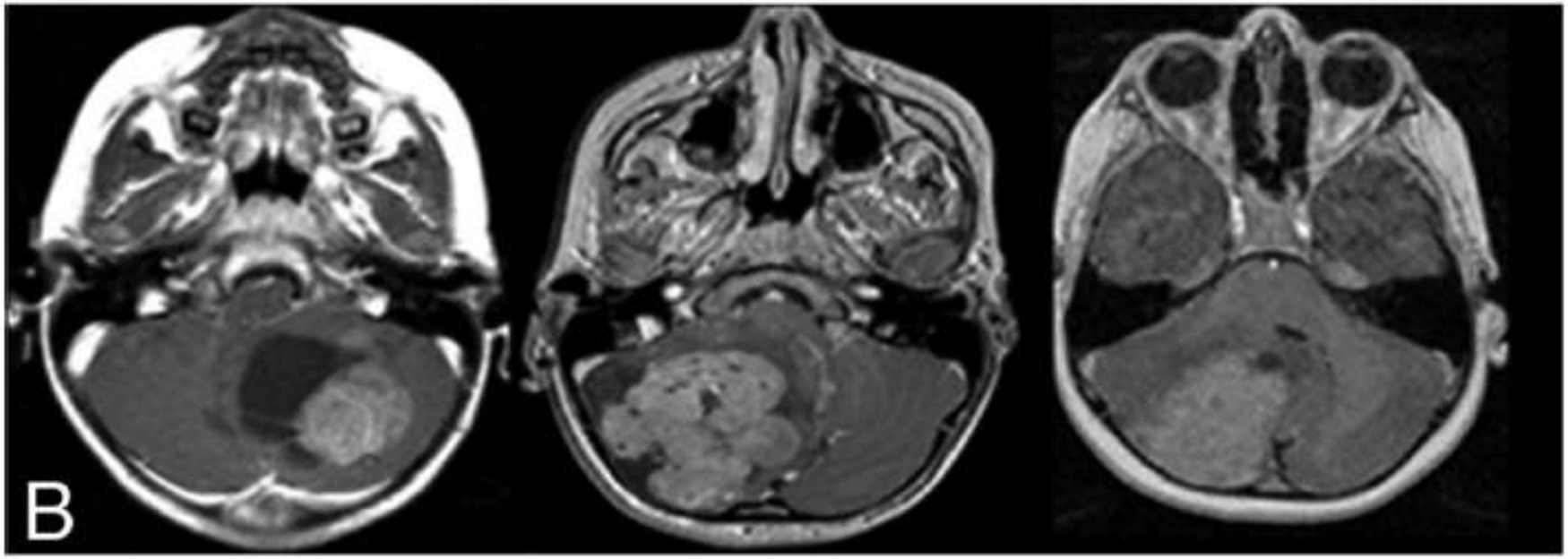
MRI Surrogates for Molecular Subgroups of Medulloblastoma

S. Perreault, V. Ramaswamy, A.S. Achrol, K. Chao, T.T. Liu, D. Shih, M. Remke, S. Schubert, E. Bouffet, P.G. Fisher, S. Partap, H. Vogel, M.D. Taylor, Y.J. Cho, and K.W. Yeom

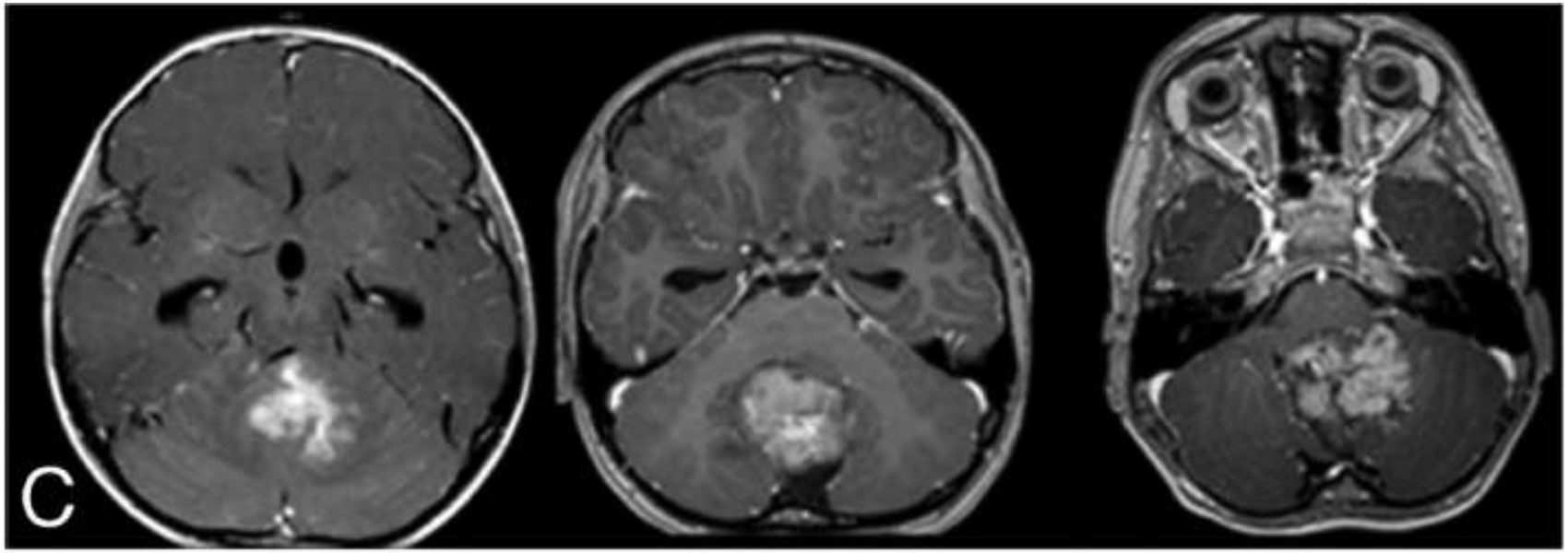




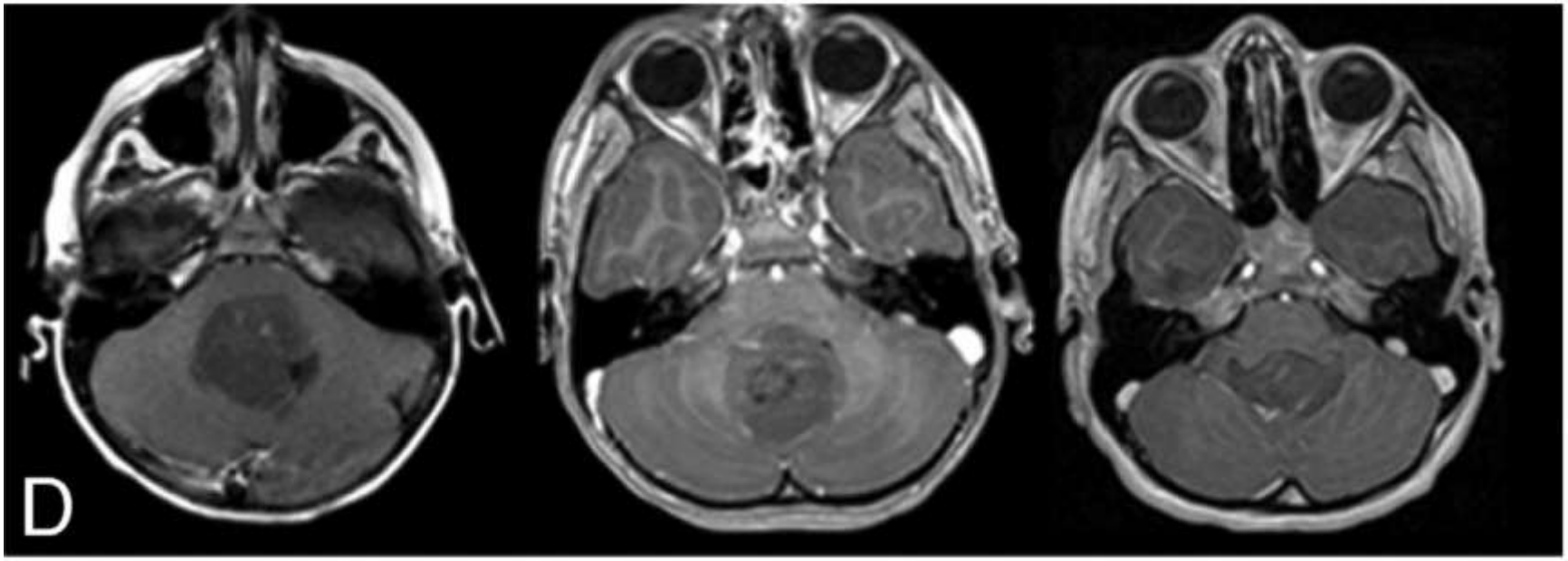
Tumors occur along the CP/CPA:WNT



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

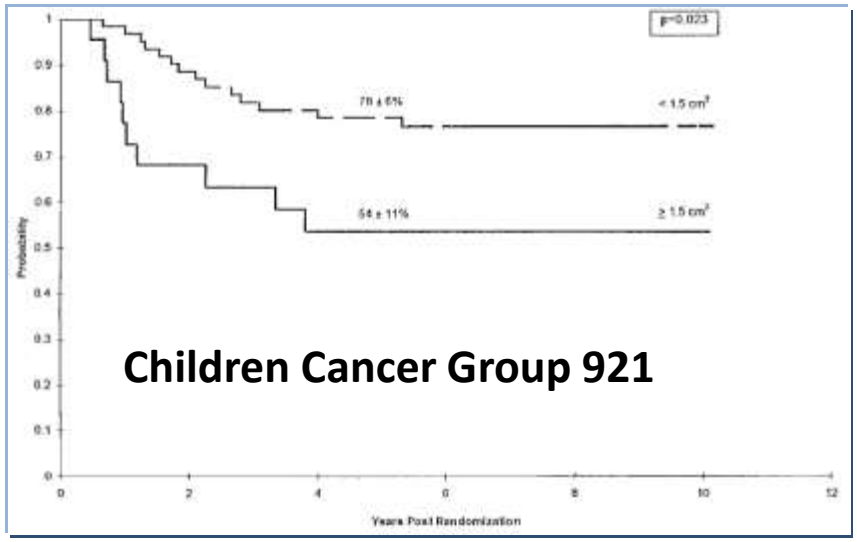
Clinical Pathological staging (Modified chang)

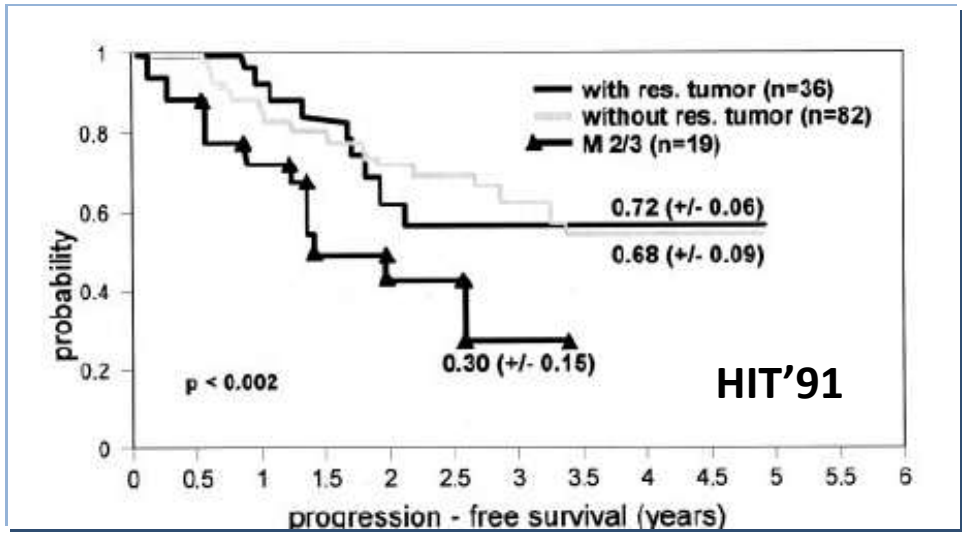
Box 1 Chang staging system.

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*.[4]

Tumor stage	Description
T1	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
T2	Tumor more than 3 cm in diameter, further invading one adjacent structure or partially filling the fourth ventricle
T3a	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
T3b	Tumor arising from the floor of the fourth ventricle or brain-stem cell and filling the fourth ventricle
T4	Tumor further spreading through the aqueduct of Sylvius to involve the third ventricle or midbrain, or tumor extending to the upper cervical cord
Metastasis stage	**Description**
M0	No evidence of gross subarachnoid or hematogenous metastasis
M1	Microscopic tumor cells found in cerebrospinal fluid
M2	Gross nodule seedlings demonstrated in the cerebellar, cerebral subarachnoid space or in the third or lateral ventricles
M3	Gross nodule seedlings in the spinal subarachnoid space
M4	Extraneuroaxial metastasis

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.**

Clinicoradiological Risk stratification

	Average	High
Clinical Age	**> 3 Yrs**	**≤ 3 Yrs**
Residual Tumor	**≤ 1.5x 1.5 Cm**	**Gross residual disease**
Metastases	**M0**	**M+**
Histopathology	Classic or desmoplastic subtypes on pathology	Large cell or anaplastic subtype
Staging	Complete staging possible	Incomplete staging
Prognosis(5yr survival)	**80%**	**40-60%**

Risk stratification – molecular

Table 6: Consensus risk-stratification in the molecular era for medulloblastoma

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

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
    - Ocassional seeding of tumor cells intoperitoneal cavity
    - Lifetime s hunt dependency
    - Shunt related infections

- CSF diversion if necessary
  - External ventricular drainagae (EVD)
  - Endoscopic third ventirculostomy (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 palsies
- Anaesthetic complications

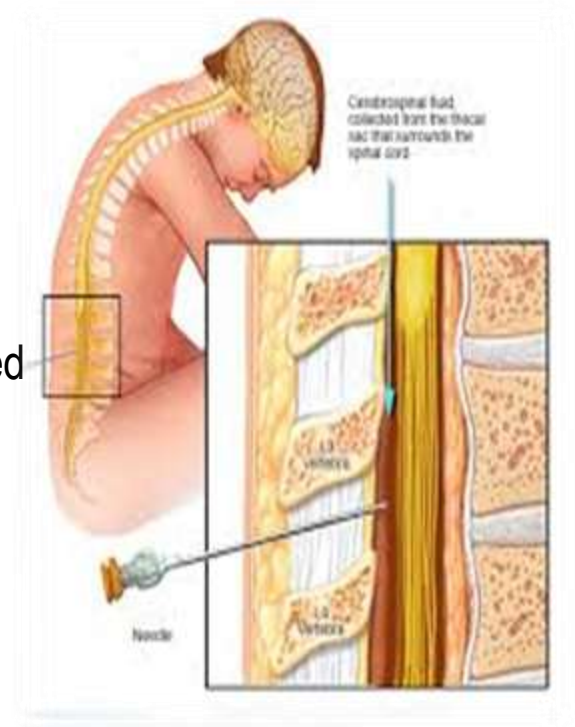
Post Operative imaging

- To identify extent of resection & quantify residual disease
- Timing – 2options
  - **Within 24-48 hours post surgery**

    or
  - **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
  - 2-3weeks 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

  leptomeningial relapses
- CSI

  supratentorial relapses

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

VOLUME	5YR OS
PF	5%
PF+SC	25%
CSI	53%

Craniospinal radiation is the corner stone in treatment of medulloblastoma

General Guidelines for Radiotherapy

- Children must be referred 7-10days 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 50days, and definitely not more than 8weeks
- Hematological toxicity – start with or switch over to boost phase

- Anti-emetic prophylaxis – ondansetron 0.2mg/kg 45-60minutes 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/#

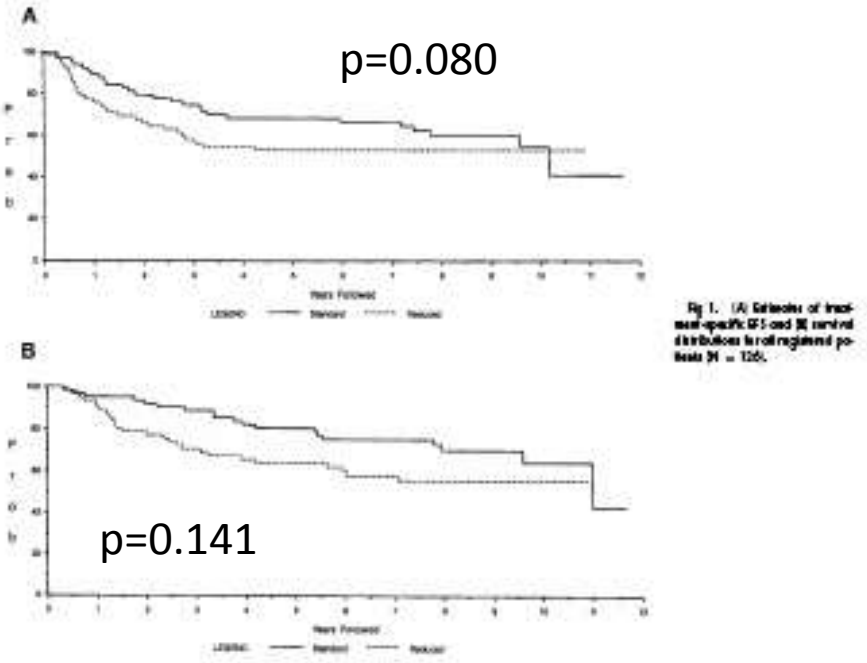
Boost for high-risk disease

- 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



CSI	5yrs EFS	8yrs EFS
Reduced	52%	52%
Standard	67%	67%

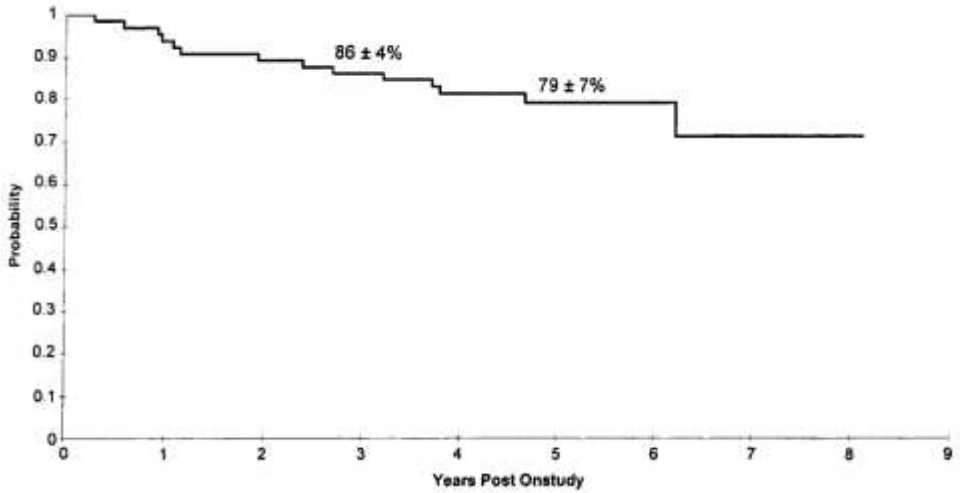
Standard dose (36 Gy CSI; 54 GyPF)
Reduced dose (23.4Gy CSI; 54 GyPF)

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

Thomas,JCO, 2000

Treatment of Children With Medulloblastomas With Reduced-Dose Craniospinal Radiation Therapy and Adjuvant Chemotherapy: A Children's Cancer Group Study

By Roger J. Packer, Joel Goldwein, H. Stacy Nicholson, L. Gilbert Vezina, Jeffrey C. Allen, M. Douglas Ris, Karin Muraszko, Lucy B. Rorke, William M. Wara, Bruce H. Cohen, and James M. Boyett



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

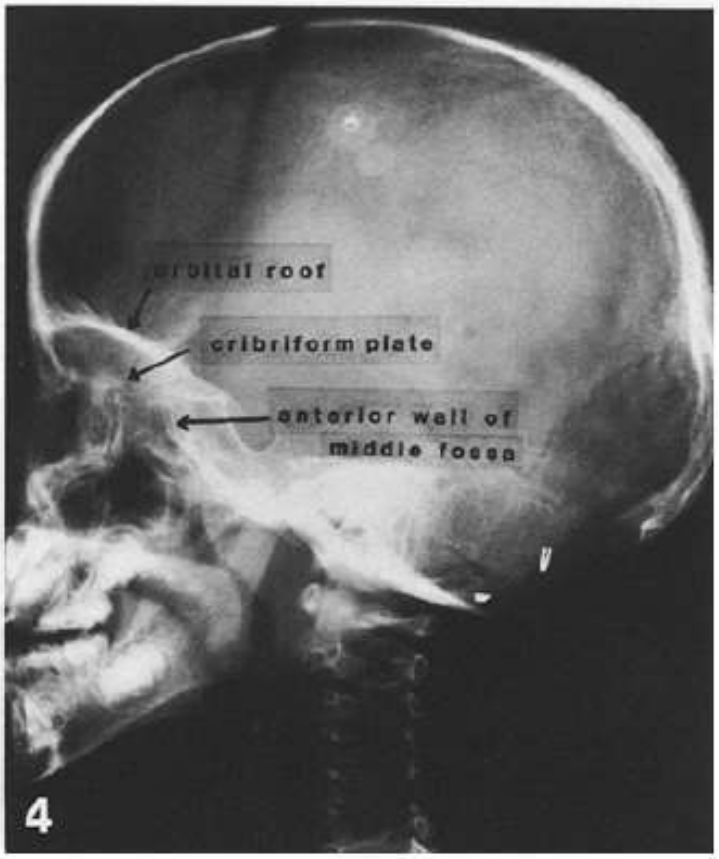
23.4 Gy : Probably YES

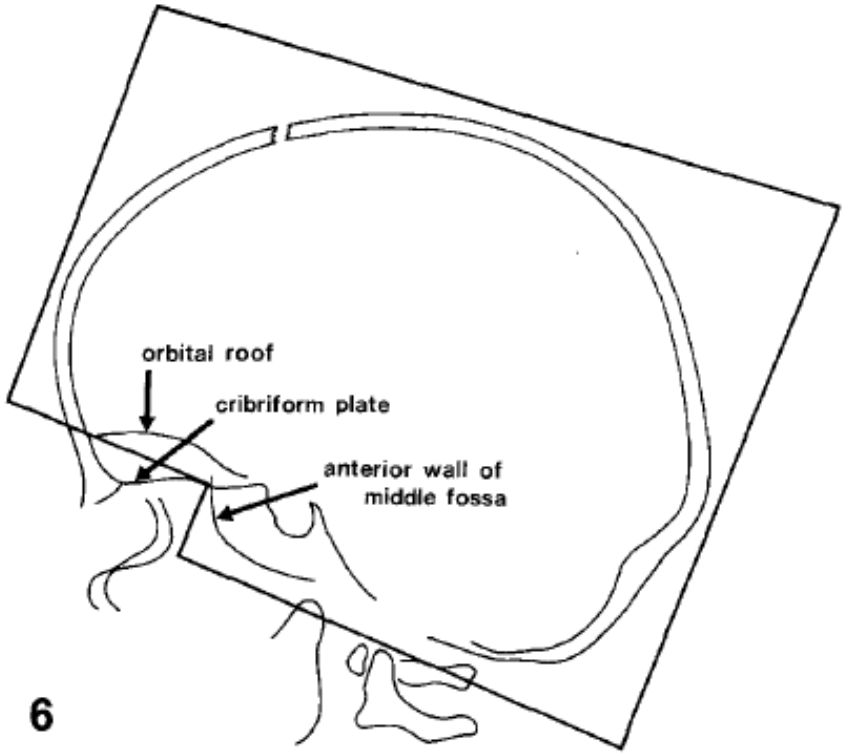
18 Gy : NO

Target Volume

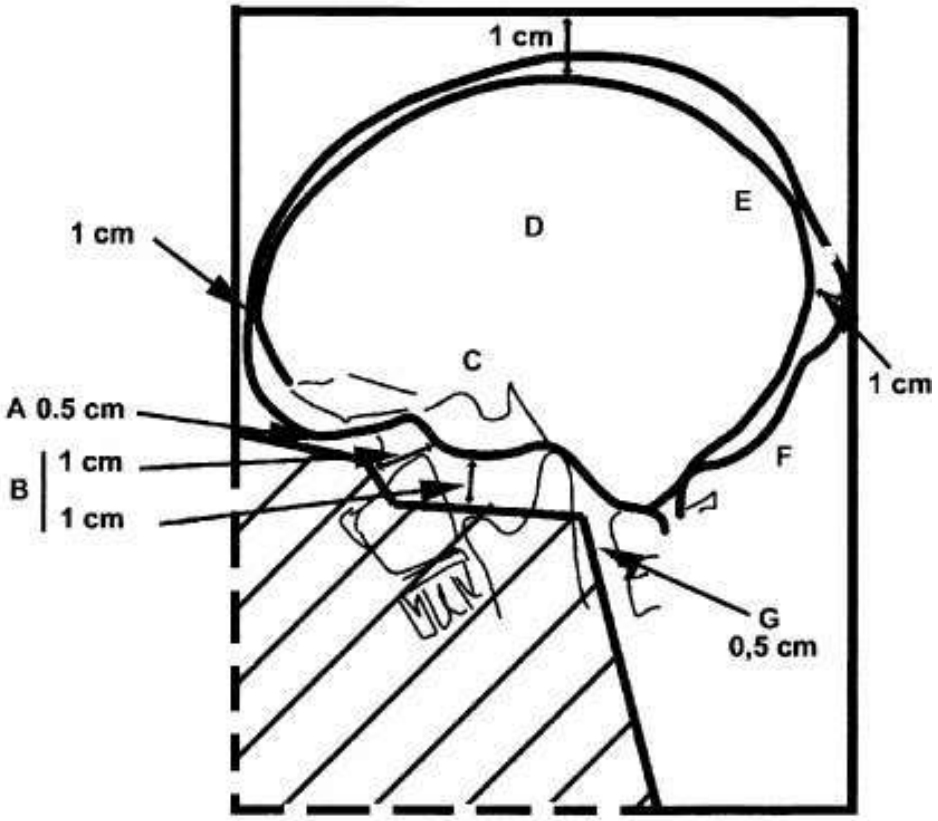
- The intent of CSI is to deliver a cancericidal dose to the primary tumor and any tumor cells distributed in the CSF
- The volume of irradiation thus includes:
  - Entire brain and its meningeal coverings with the CSF
  - Spinal cord and the leptomeninges with CSF
  - Lower border of the thecal sac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

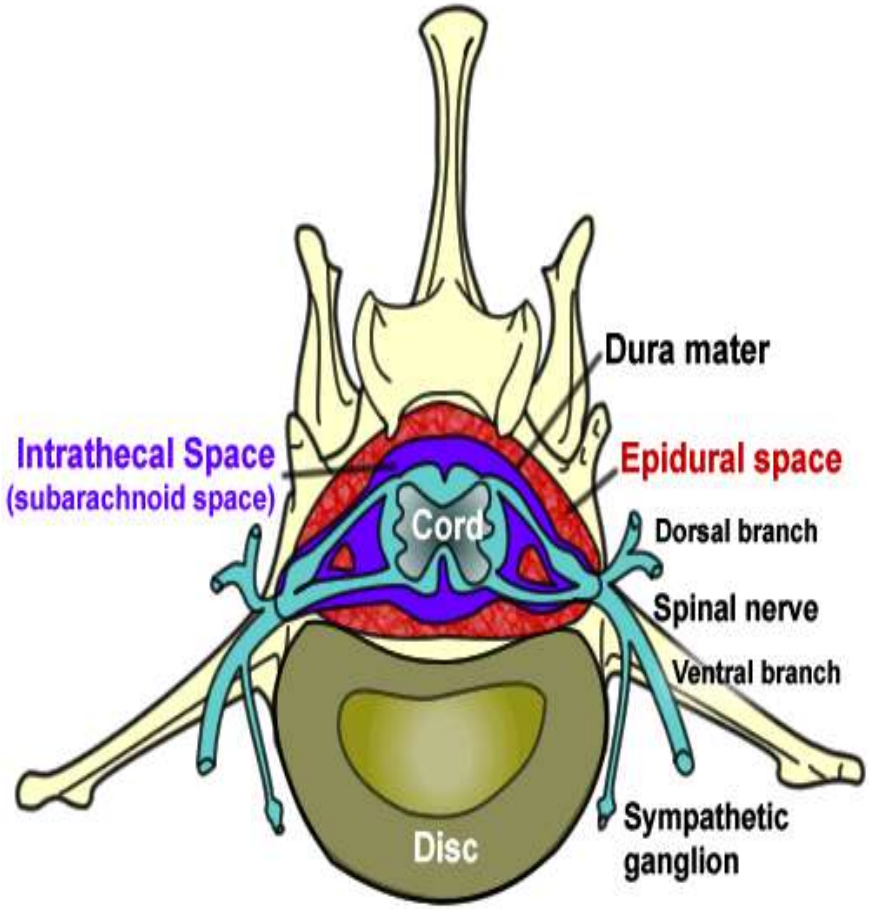
– 1 cm below and 1 cm in front of the lower most portion of the temporal fossa

– 1 cm away from the extreme edges of the calvaria.

– Note the flexion of the head.

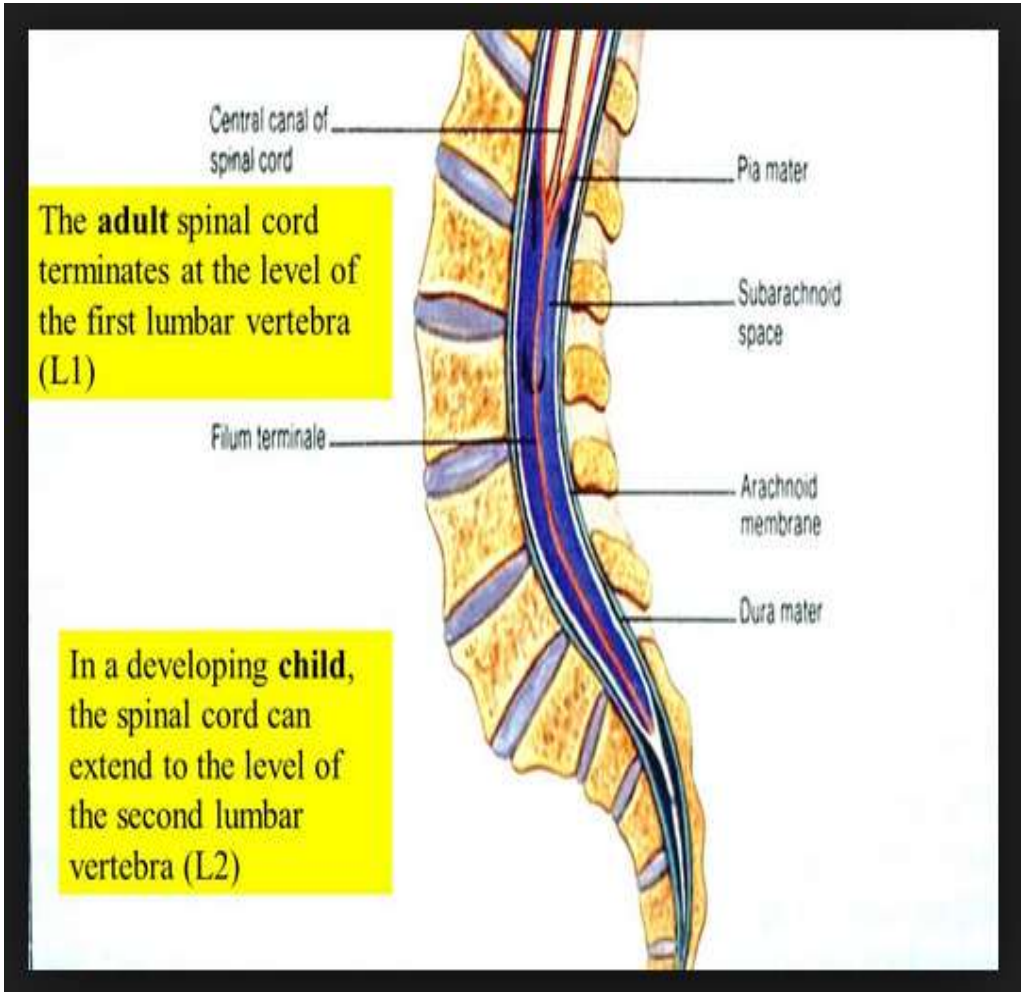
Customized blocks are better than MLCs

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

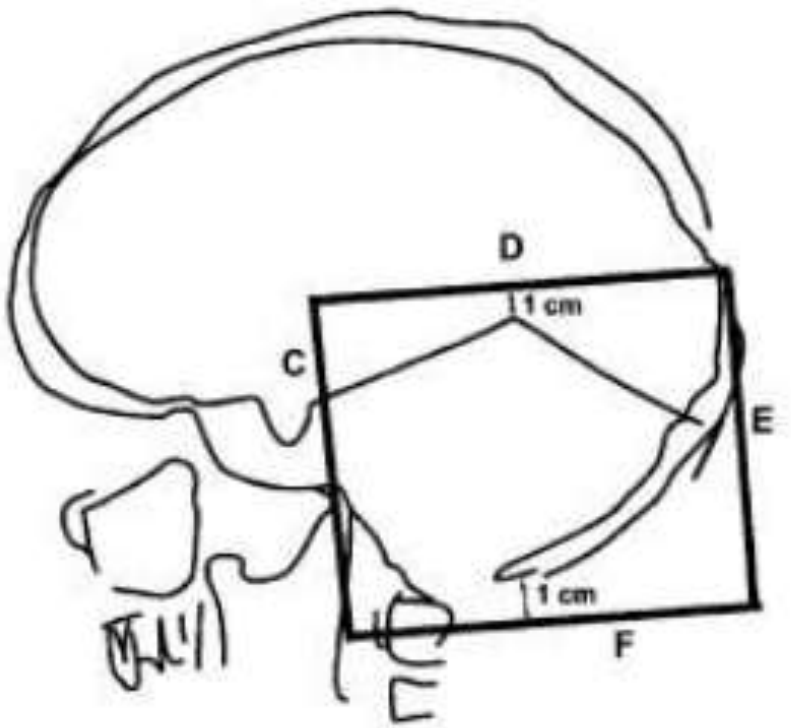


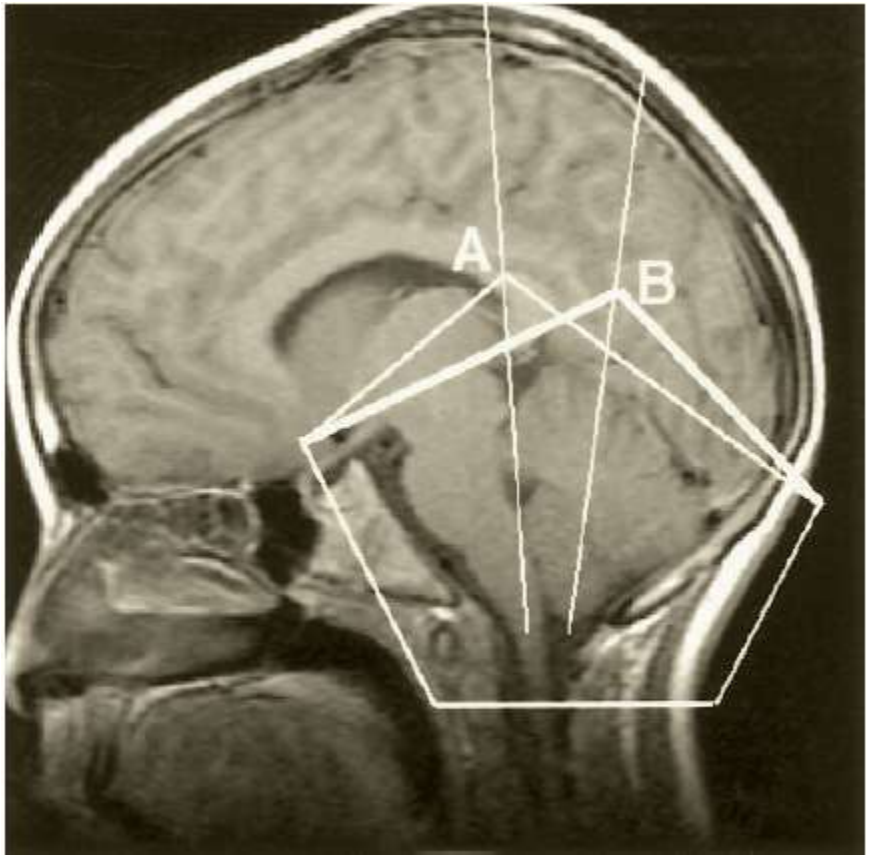
- Sagital MRI
- SA space ends at
  - S2 -66%
  - S1 – 17%
- **Recommendation:**

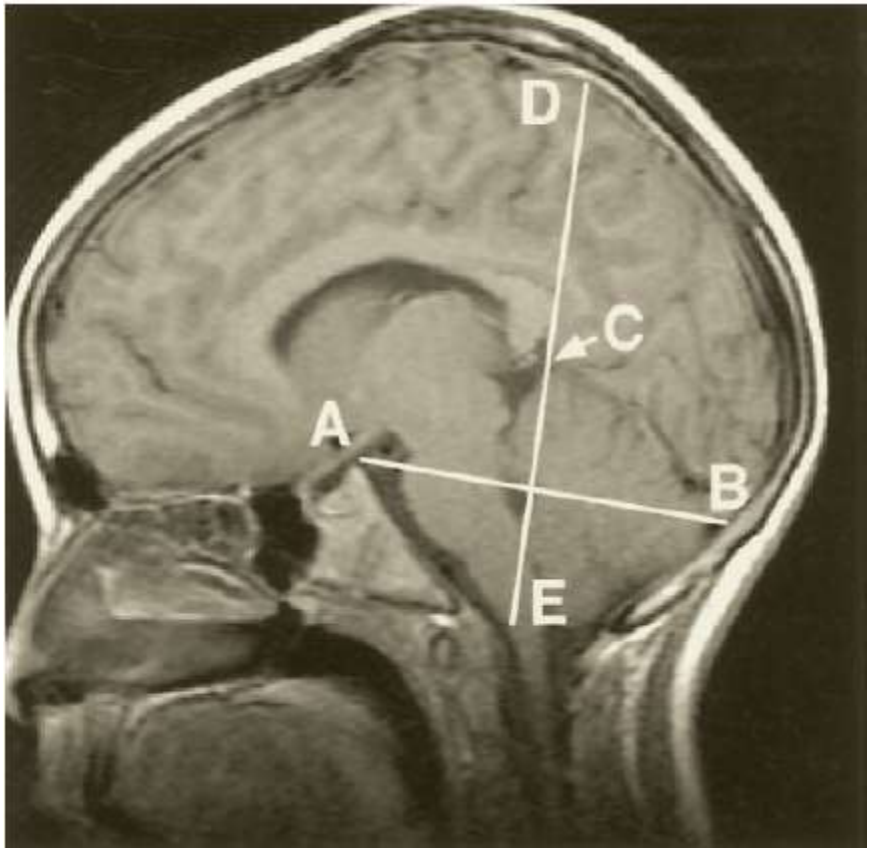
  S2-S3 junction (covers 83%)

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)

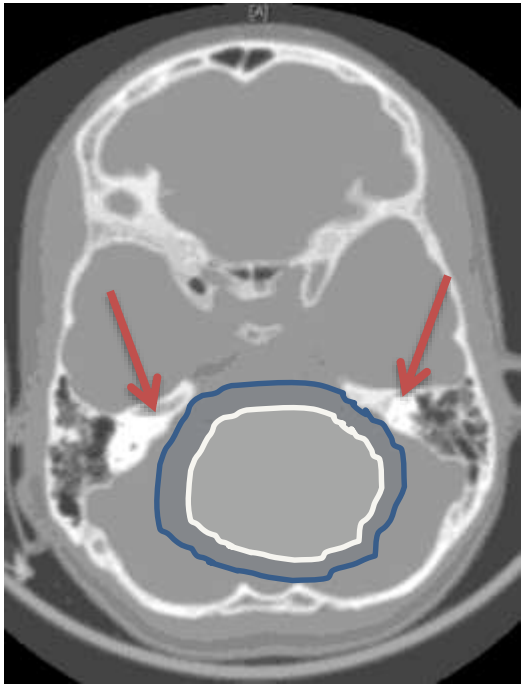


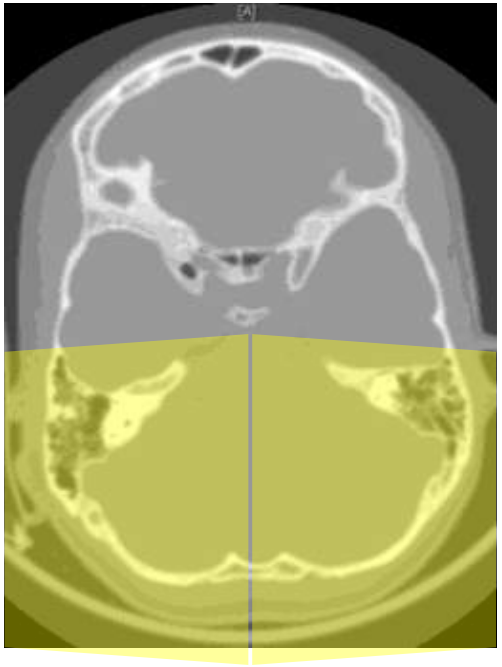




Impact of the orientation of the line joining the foramen magnum to the skull on the definition of the posterior fossa boundary. Drayer et al IJROBP1998.

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 summated** 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 4. Cumulative Toxicity Rate

Toxicity	Grade 3 or 4 Regimen A/B %	*P*	Grade 4 Regimen A/B %	*P*
Hematologic	97/98		82/90	< .01
Hepatic	12/11		1.7/2.2	
Renal	9.0/5.0		1.1/0.0	
Pulmonary	3.4/2.2		1.6/1.6	
Nervous system	51/46		5.4/3.8	
Hearing	28/23		5.8/6.7	
Electrolytes	6.2/12	< .10	1.7/3.9	
Infection	18/30	< .01	1.6/6.9	< .05
Performance	21/14	< .10	4.9/4.8	

Packer, JCO,2006

General Principles: Adjuvant Chemotherapy

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

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

- **Baseline auditory assessment** is mandatory
  - PTA

Integration of chemotherapy

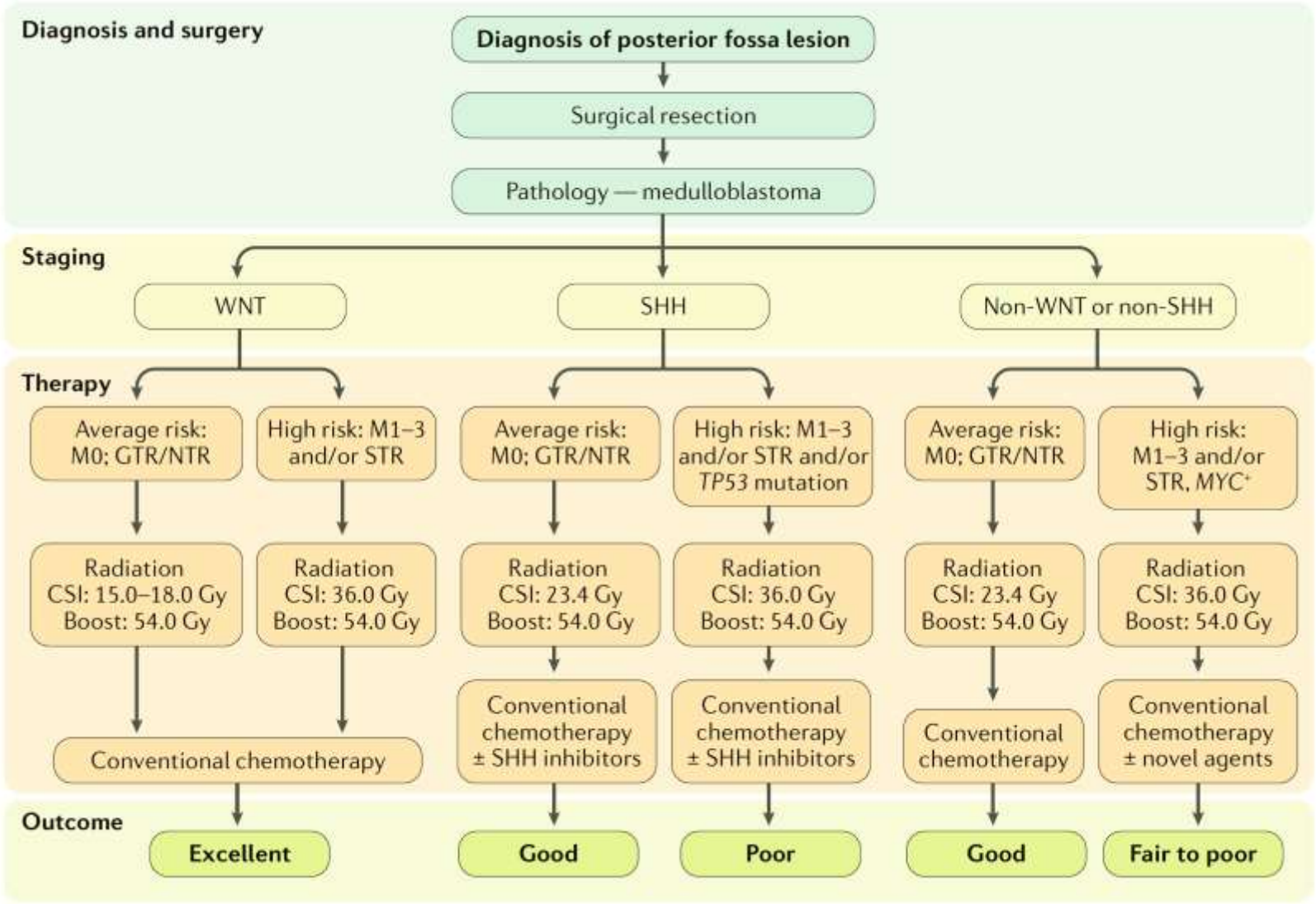
- Delay in starting RT results in inferior outcome: Halperin
- Prolongation of RT duration negatively impacts upon survival: Del Charco & SIOP PNET 3
- Pre RT CT inferior to post RT CT: CCG 921 and HIT 91
- Pre RT CT does not improve survival compared to RT alone: SIOP II & SIOP PNET 3
- Pre RT CT followed 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/m^2	Day 1 only (intravenously)
Lomustine	75 mg/m^2	Day 1 only (per orally)
Vincristine	1.5 mg/m^2	Days 1, 8 and 15 (intravenously)
Regimen II		
Cisplatin	75 mg/m^2	Day 1 only (intravenously)
Cyclophosphamide	1000 mg/m^2	Days 1 and 2 (intravenously)
Vincristine	1.5 mg/m^2	Days 1, 8 and 15 (intravenously)
Regimen III		
Cisplatin	75 mg/m^2	Day 1 only (intravenously) in cycle 2, 4 and 6 only
Cyclophosphamide	1000 mg/m^2	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/m^2	Days 1 and 8 (intravenously) in all 6 cycles
Adjuvant chemotherapy regimen for infant medulloblastoma (<3 years of age)		
Carboplatin	600 mg/m^2	Day 1 only (intravenously)
Cyclophosphamide	1000 mg/m^2	Day 1 only (intravenously)

Molecular risk-adapted management



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