PEDIATRIC MEDULLOBLASTOMAS

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Comité de Neurooncologie Pédiatrique

Mai 2020

BACKGROUND

- Most common malignant pediatric brain tumor
- Treatment is well codified with 60-70% of overall survival at 5 years
- Response to treatment is heterogeneous
- Explosion of knowledge in molecular biology
- Toxicities of radiotherapy and chemotherapy are well known (neurocognitive sequel+++ and secondary malignancies in long survivors)
- Can we limit the morbidities of current treatment to improve quality of life while having a better response to treatment?

HISTORIC

- First described as a cohesive group of tumors by Bailey and Cushing in 1924 using the term of *spongioblastoma cerebelli.*
- Term medulloblastoma was chosen based on their assumption that the tumor derived from a presumed primitive pluripotental cell, the medulloblast.
- In 1983, Rorke proposed including medulloblastomas in the group of tumors called PNETs derived from the transformation of primitive neuroepithelial cells.
- This grouping with PNETs has been widely debated, but it has been adopted by the WHO.
- With the advent of molecular biology techniques the distinctions between cerebellar medulloblastoma and supratentorial PNETs have become better defined.
- WHO Classification 2016: medulloblastoma bellong to the group of embryonnal tumors and molecular features are include

EPIDEMIOLOGY

- Most common malignant brain tumor of childhood, constituting near 20% of brain tumors.
- 30% of all the posterior fossa tumors.
- 80% of medulloblastomas are diagnosed under the age of 15 years.
- Median age of patients is 5 to 7 years.
- 250 to 350 new cases will be diagnosed in USA each year.
- Slight male preponderance.
- Incidence increased in Gorlin's syndrome and in Turcot's syndrome 2.

CLINICAL PRESENTATION (1)

- No symptom or sign is pathognomonic of medulloblastoma
- Generally: history is short
- Patients usually present with signs and symptoms of increased intracranial pressure.
  *Most of the initial symptomatology may be related to the hydrocephalus.
  *In very young children: symptoms initially may be macrocephaly and irritability.
- Additional symptoms may be relate to cerebellar or brainstem compression.
- Rarely: only gastrointestinal symptoms! This lead often to delayed diagnosis ⇒ be carefull!
- Be carefull in cases with easy fall: it can be a first symptom of posterior fossa tumor

CLINICAL PRESENTATION (2)

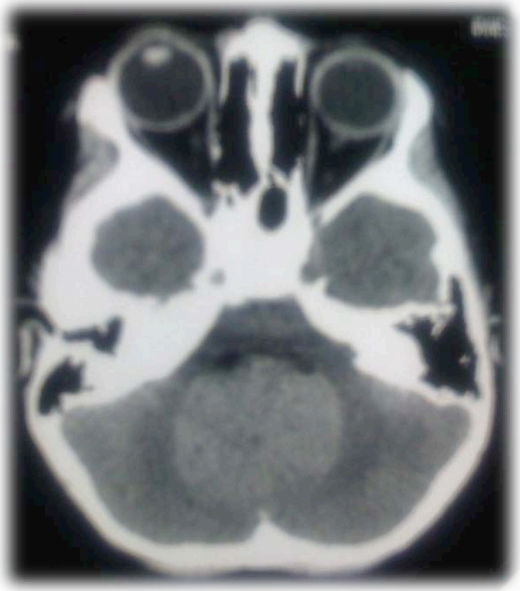
- Because symptoms of medulloblastoma may be quite subtle, many patients have had extensive evaluations before the diagnosis of their tumors. Most of the tumors are large at diagnosis and have resulted in hydrocephalus.

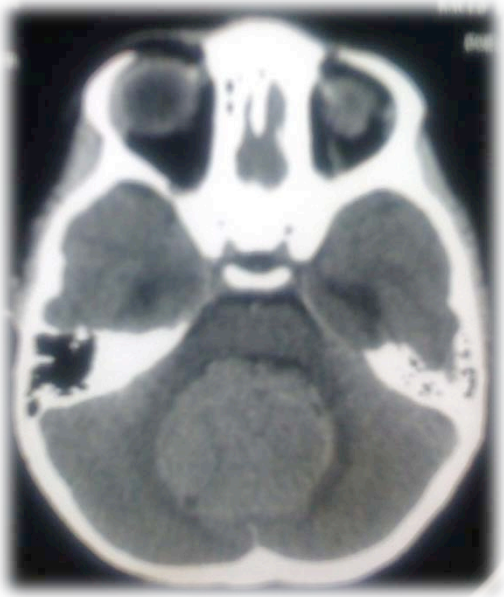
- Medulloblastoma may spread throughout the CSF spaces = symptoms may reflect spinal cord or nerve root involvements.

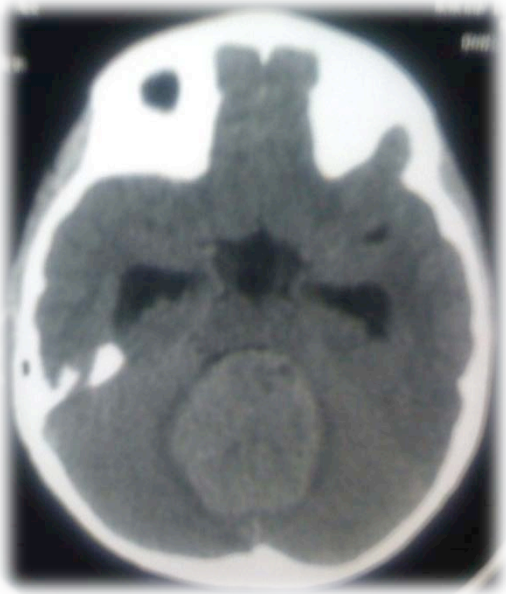
IMAGERIE (1)
TOMODENSITOMETRIE

- Typiquement hyperdenses avec rehaussement homogène après injection de contraste.
- En majorité localisés au niveau de la ligne médiane mais peuvent être latéralisés
- Peuvent être partiellement kystiques.
- Peuvent contenir des petites calcifications.

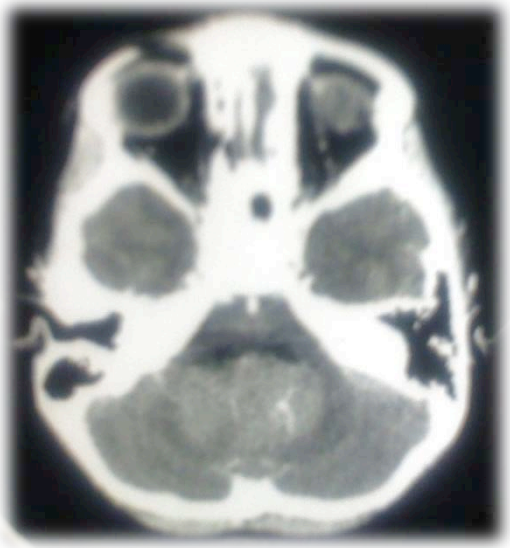
SPC

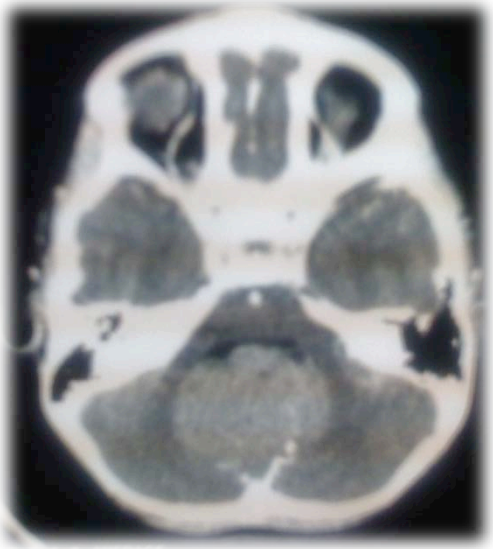


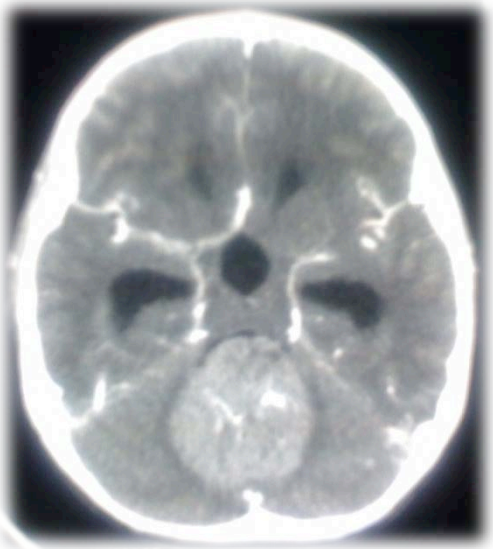


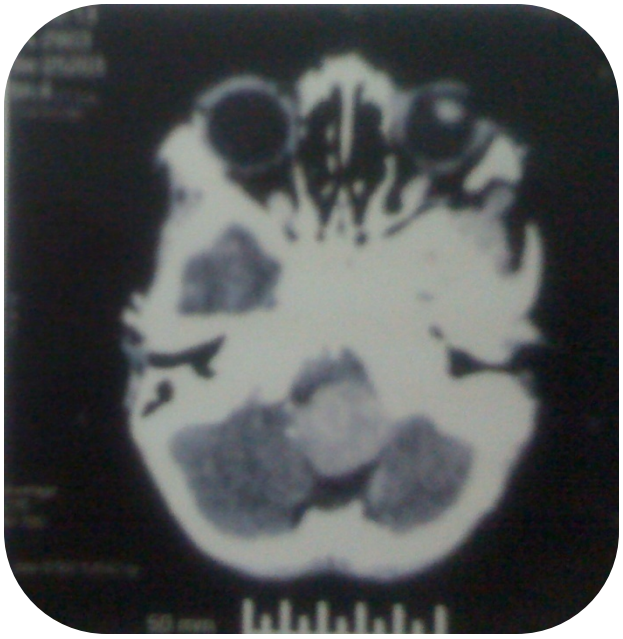
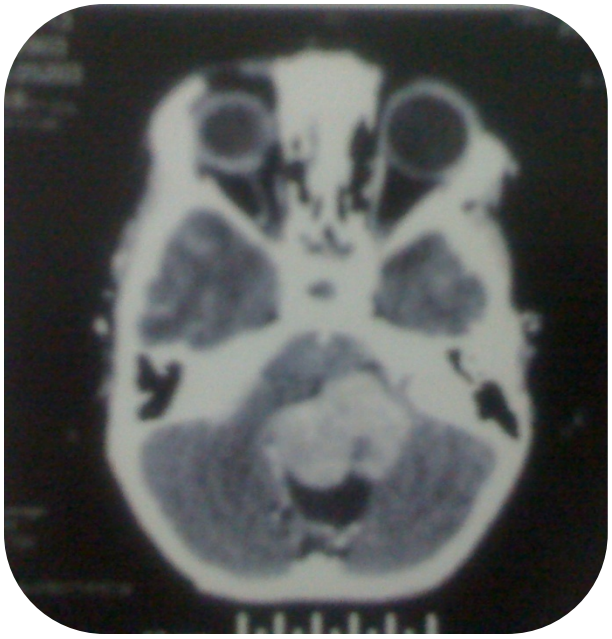
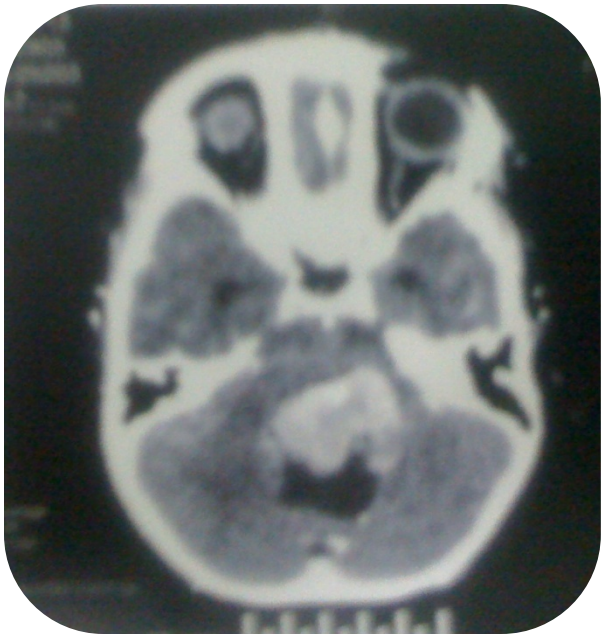
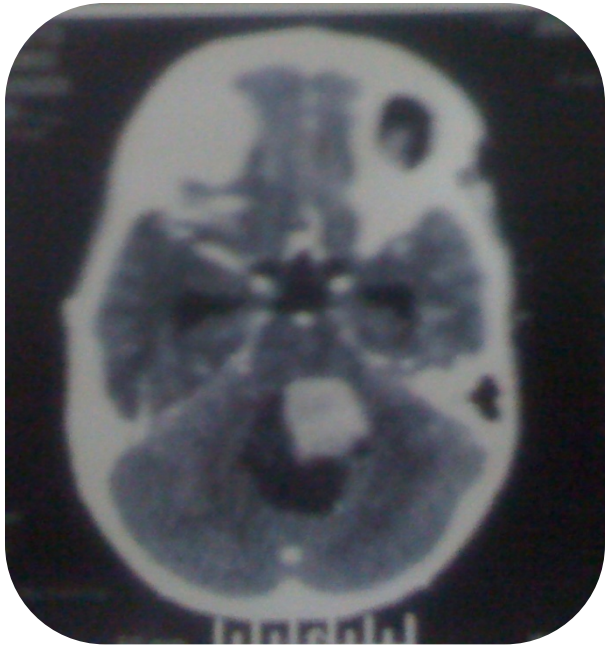
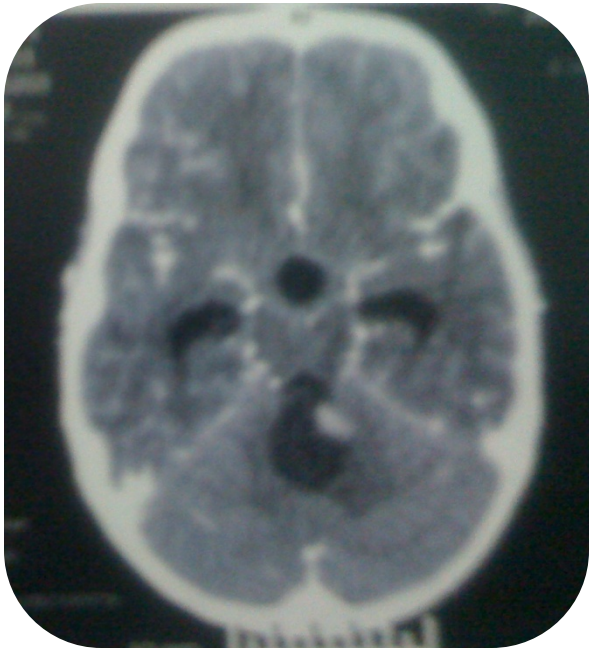


APC



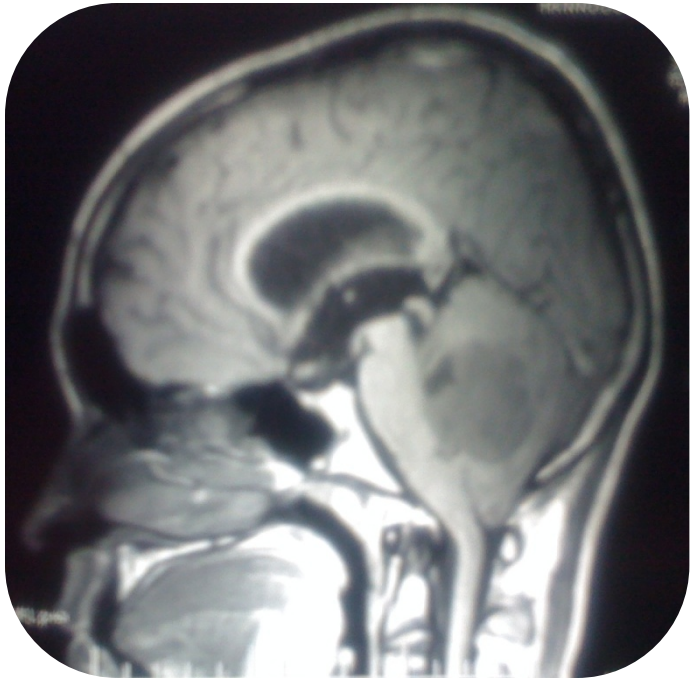


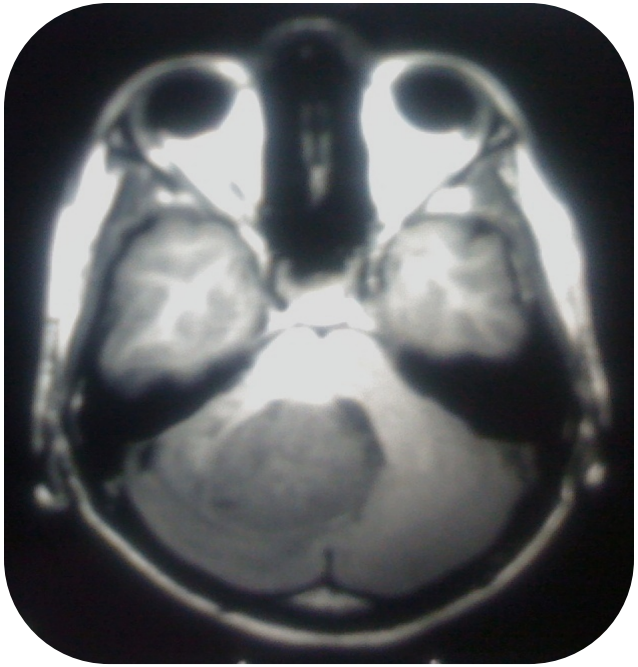


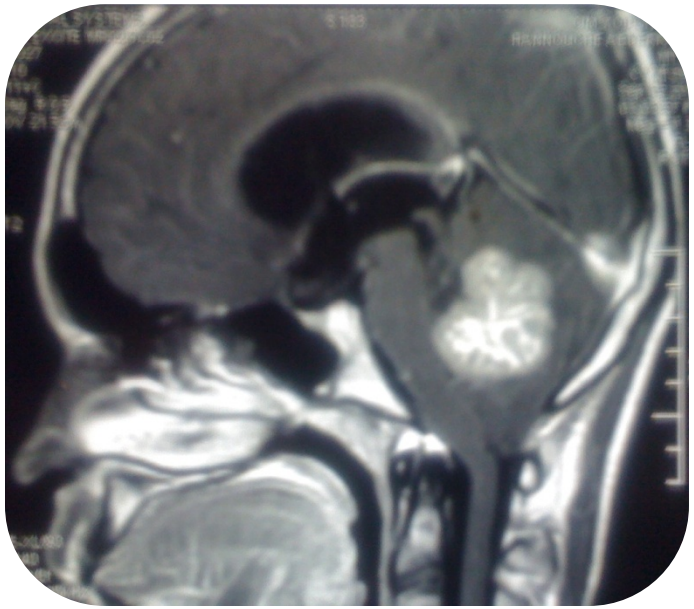






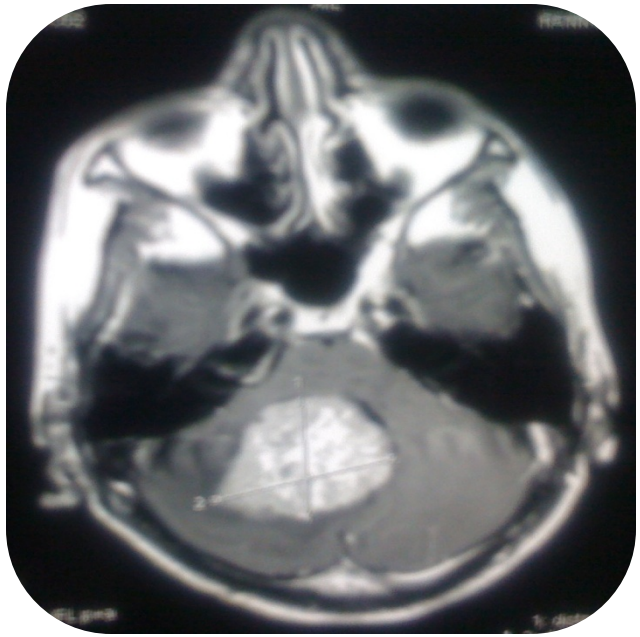
IMAGERIE (2)
IRM

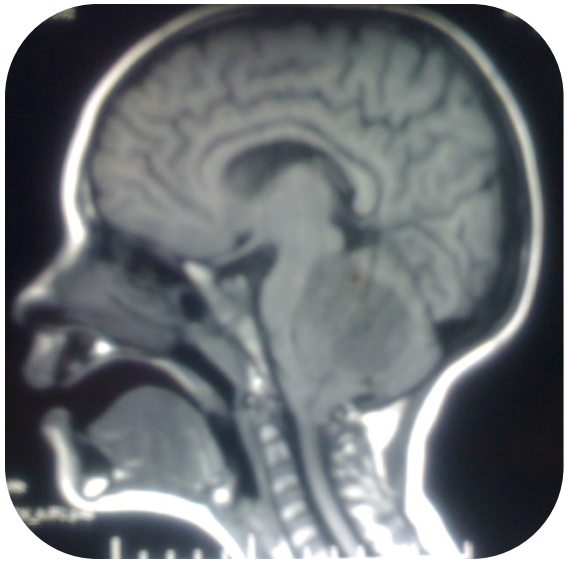
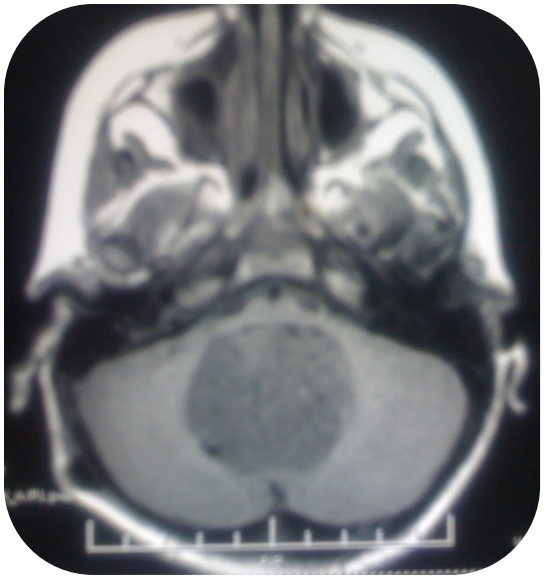
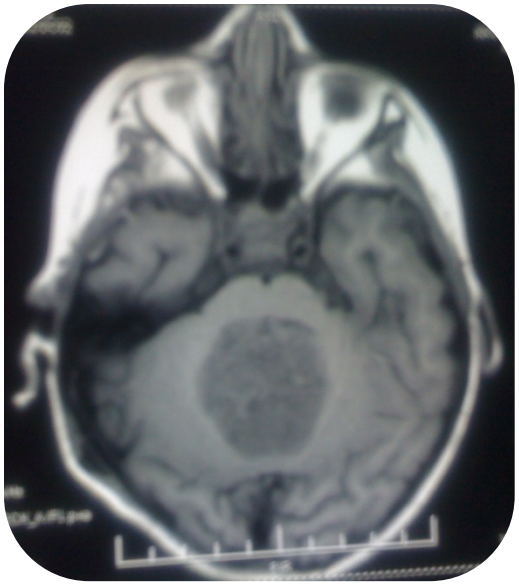
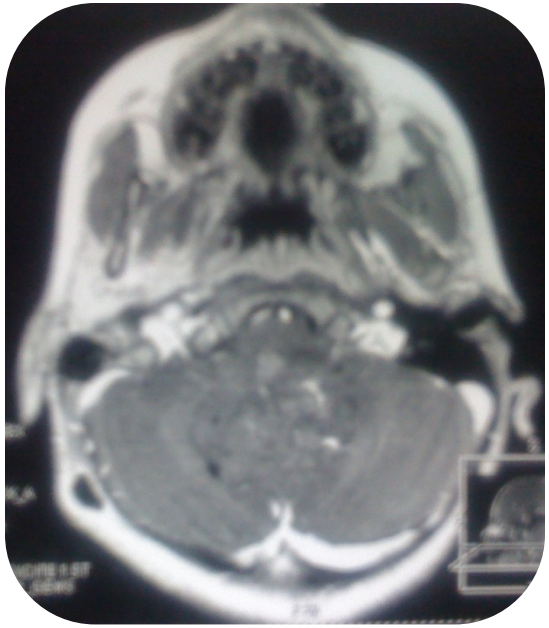
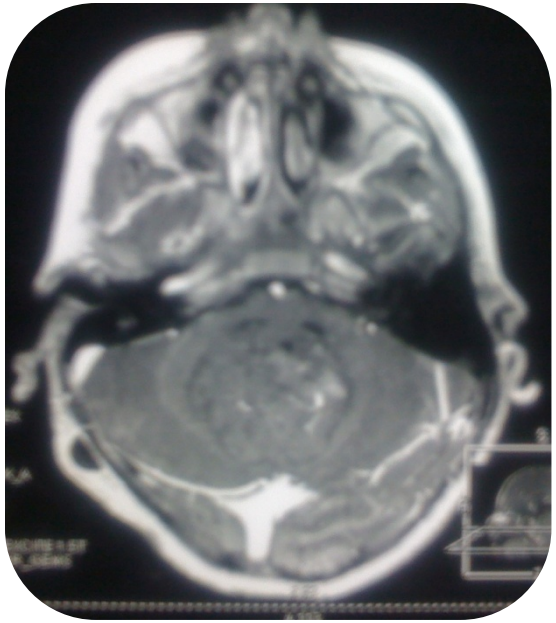
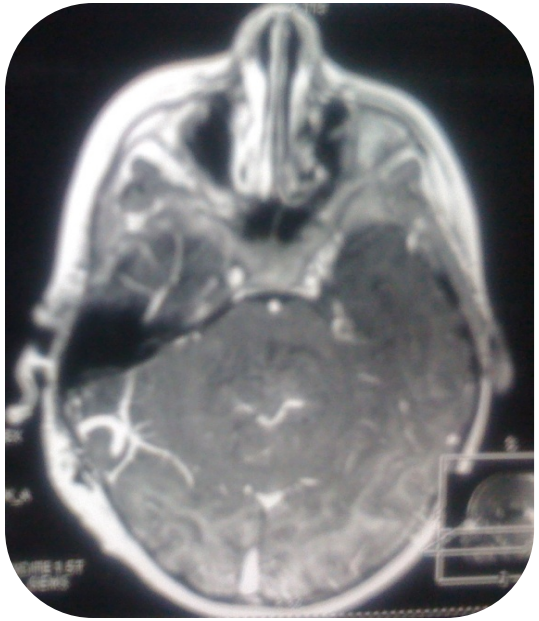
- « The best »
- Images axiales: définissent les rapports avec le plancher du V4 et les pédoncules cérébelleux.
- Images sagittales: extension supérieure et inférieure ainsi que les rapports avec le tronc cérébral.
- Généralement: tumeur hypo à iso-intense en T1, typiquement hyperintense en T2 et rehaussement souvent homogène après contraste.
- 10 à 15%: pas de rehaussement ⇨ difficultés pour l'évaluation de l'envahissement du tronc et du résidu en post opératoire.





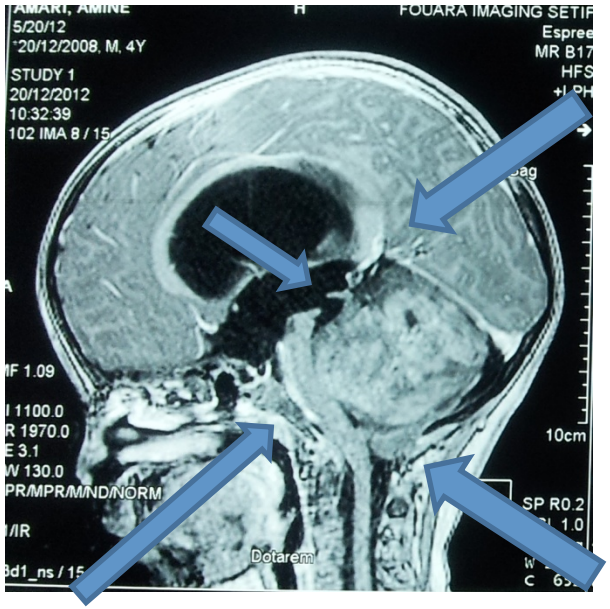


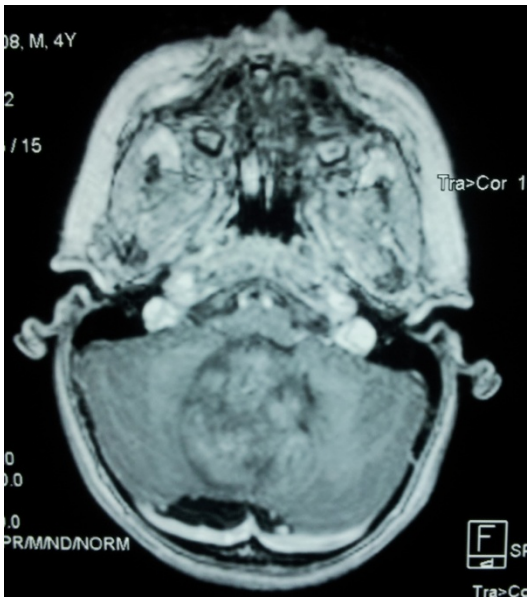


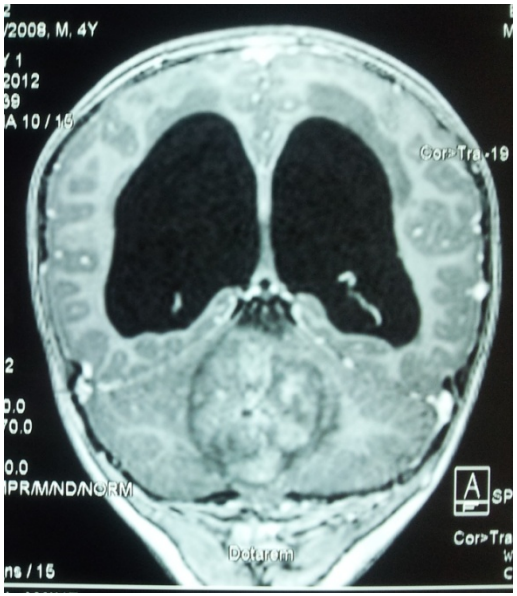







Faible rehaussement après gado

ATTENTION A CE TYPE D'IMAGE







J Neurosurg Pediatrics 11:52–59, 2013

Tumors of the superior medullary velum in infancy and childhood: report of 6 cases

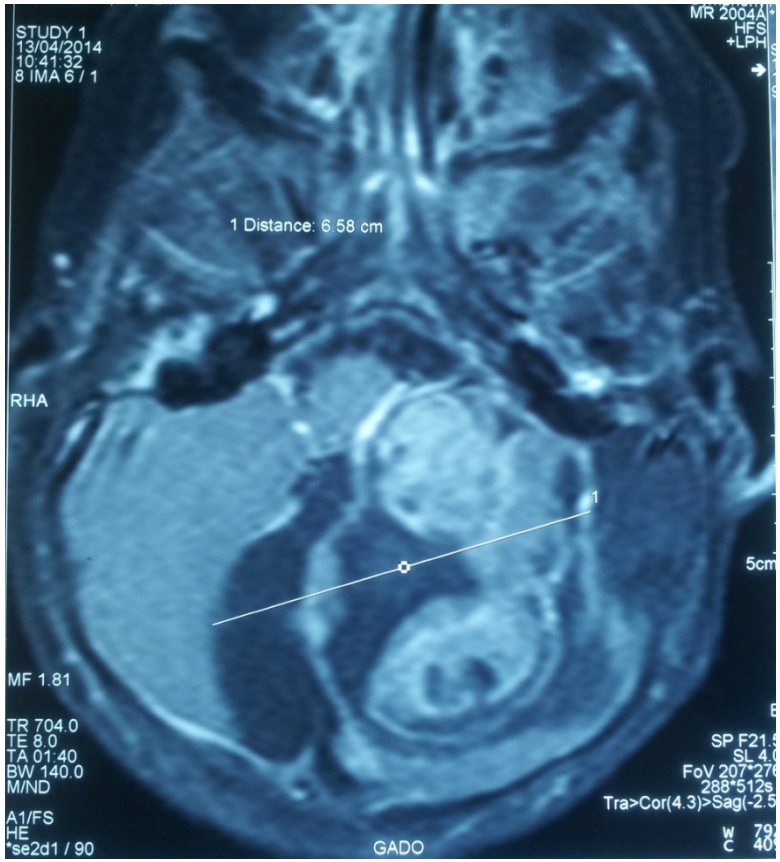
Clinical article

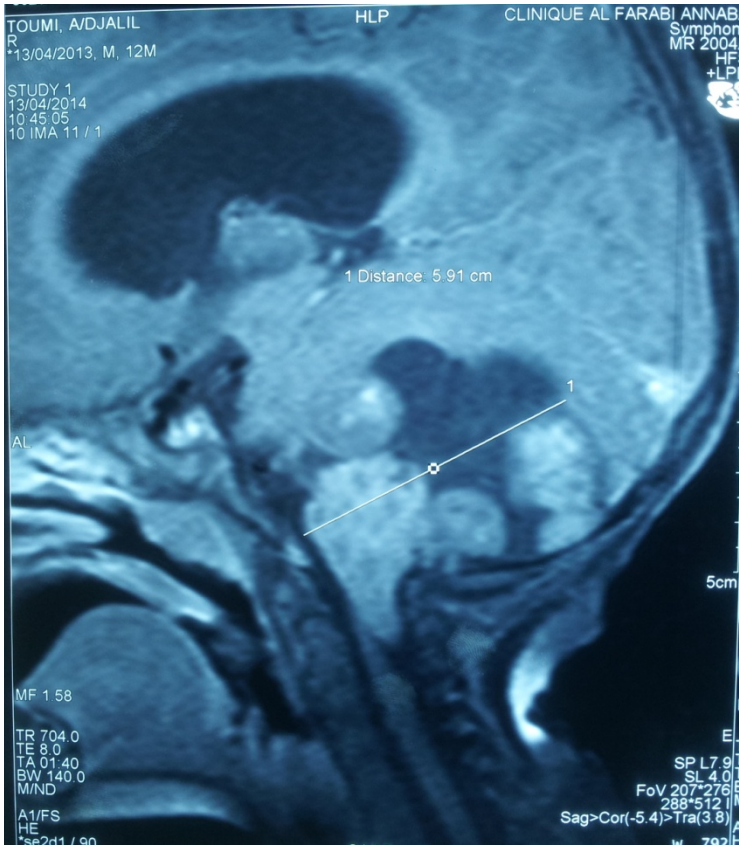
TADANORI TOMITA, M.D., AND PAOLO FRASSANITO, M.D.

Division of Pediatric Neurosurgery, Ann & Robert Lurie Children's Hospital of Chicago; and Northwestern University Feinberg School of Medicine, Chicago, Illinois

Il s'agit de tumeurs du velum médullaire supérieur!

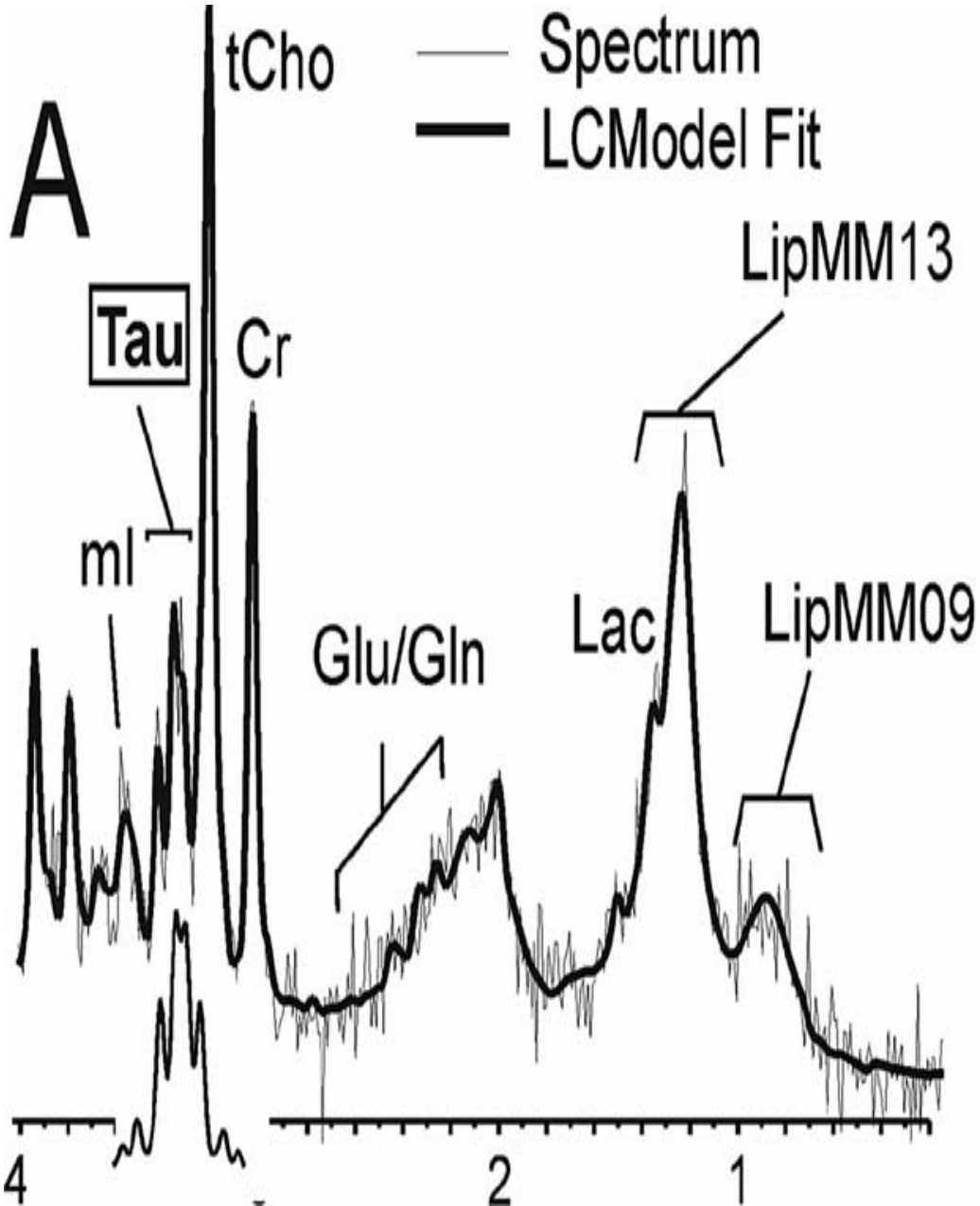
IMAGERIE (3)
Forme particulière des MBEN (médulloblsatomes à extensivité nodulaire ou nodular MB)





IMAGERIE (4)

- Spectroscopie:
  Non spécifique N'est pas effectué systématiquement
  Il semble qu'un pic de Taurine soit souvent objectivé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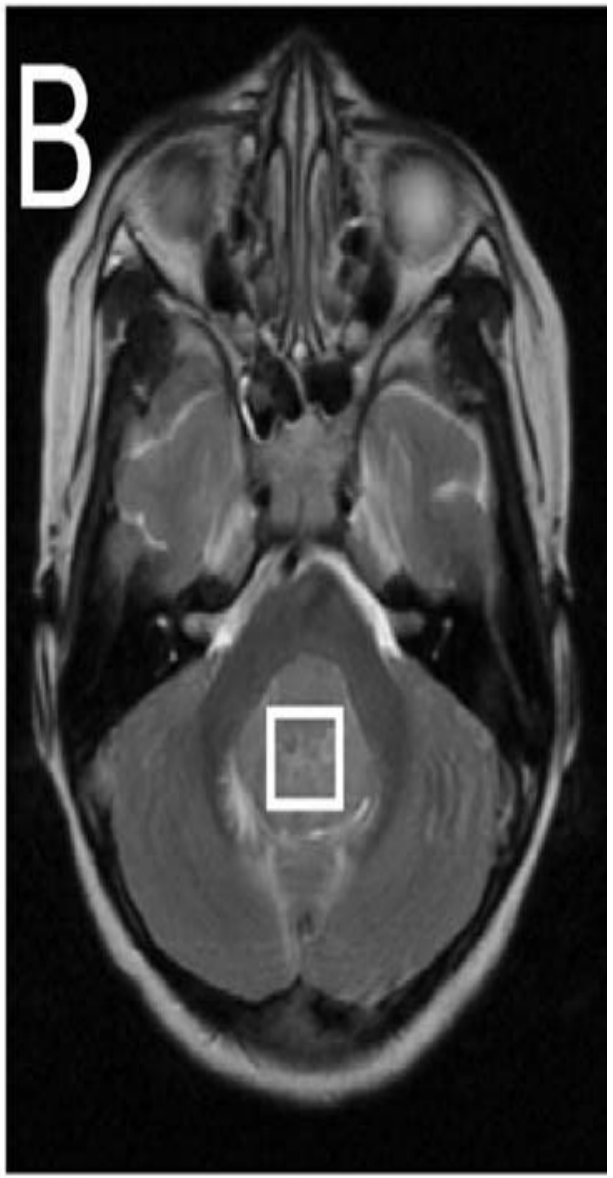
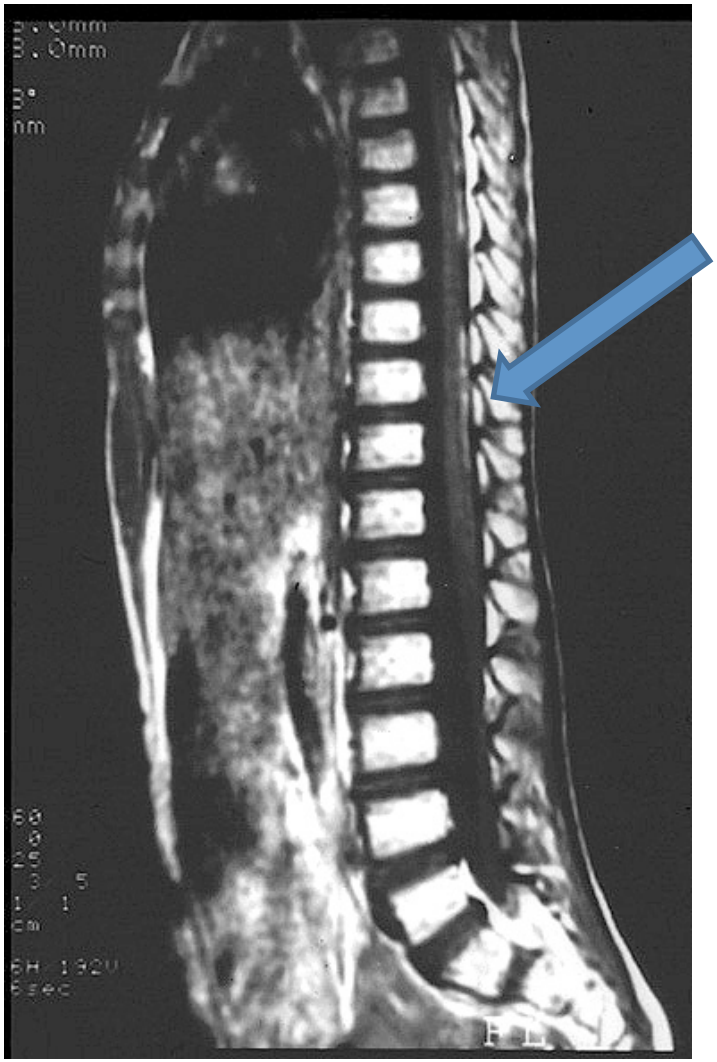
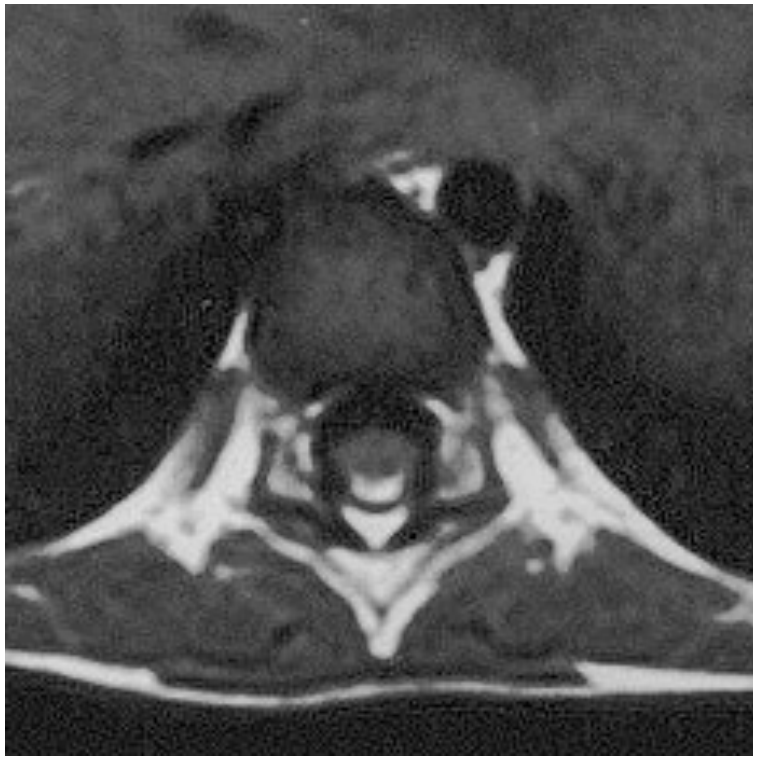

B

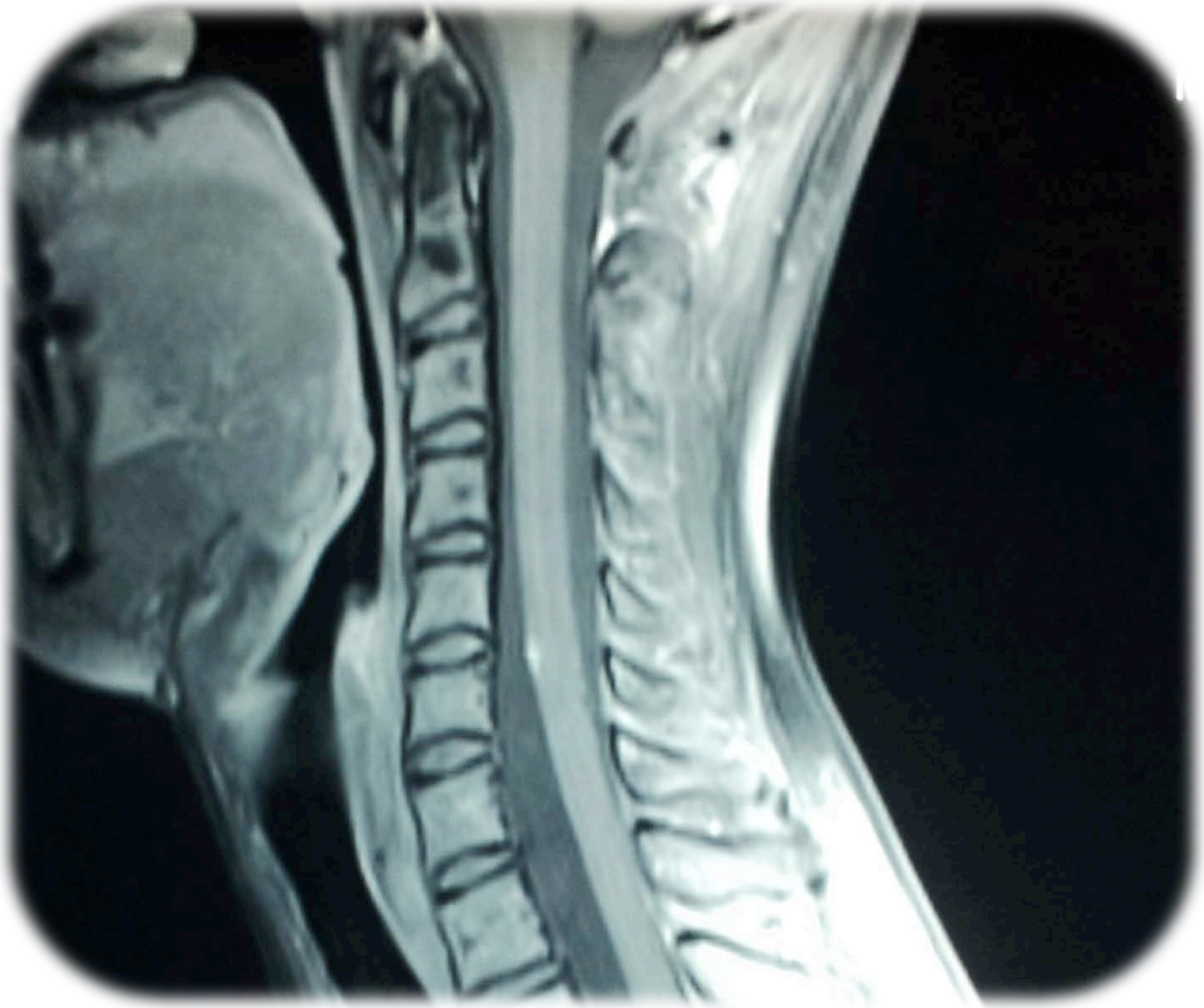
IMAGERIE (5)
AXE SPINAL

- Potentiel élevé de dissémination lepto-méningée (via le LCS).
- IRM de l'axe spinal devant un processus de la FCP évocateur d'un médulloblastome.
- Exploration pré opératoire+++ (artéfacts post opératoires).
- Tout l'axe spinal+++ (trou occipital au cul de sac dural).
- Contraste+++.
- Images axiales+++ (afin d'éliminer des images vasculaires).
- La dissémination peut être dans les espaces sous arachnoïdiens ou intra médullaire

Images en « sugar-coat »





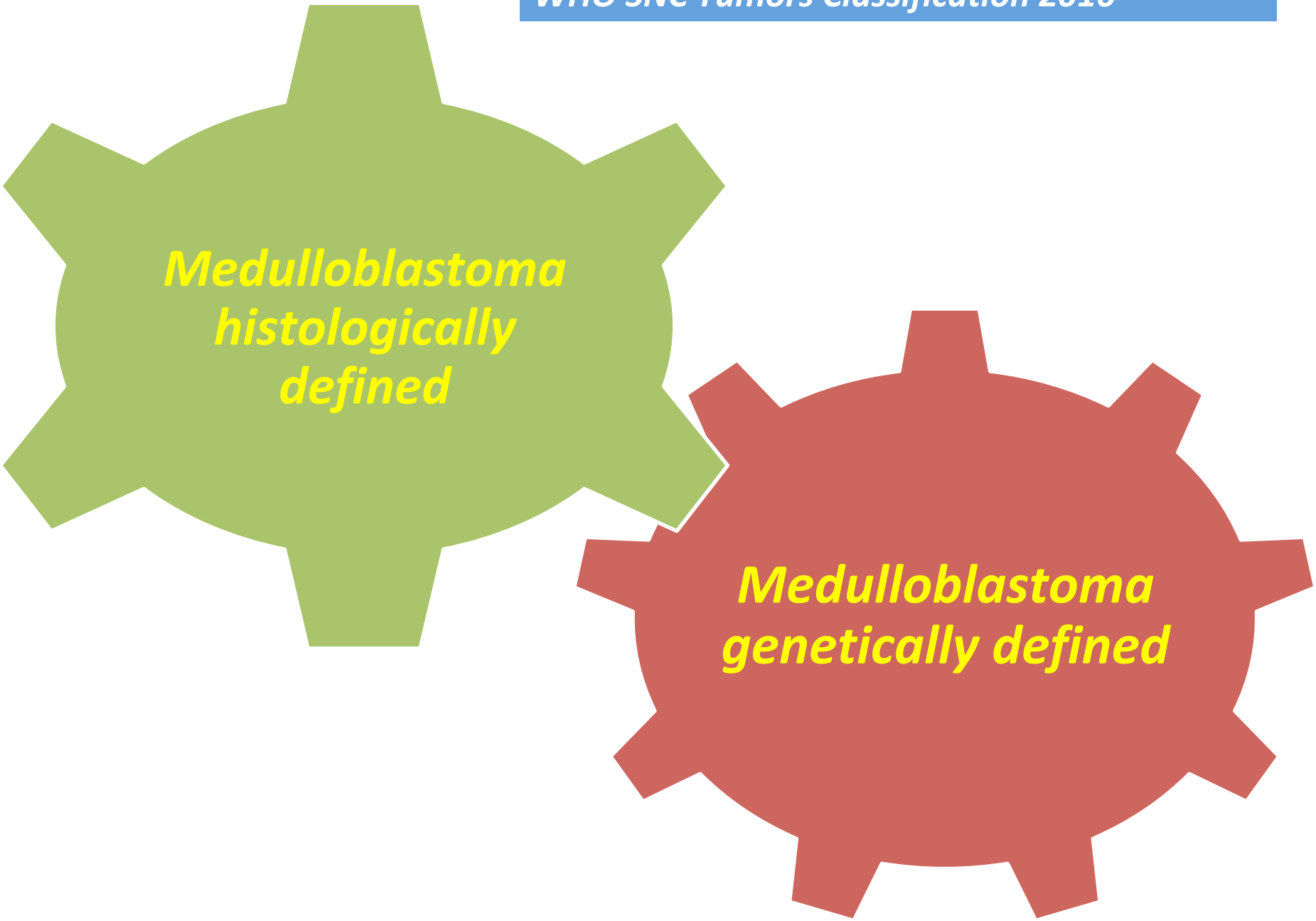


Attention les images peuvent être de très petite taille
Chez ce patient il s'agissait de la seule image qui s'est confirmée par la suite être une métastase

PATHOLOGY (1)

- WHO CNS Tumors 2016 +++
- For the first time inclusion of molecular features

WHO SNC Tumors Classification 2016



PATHOLOGY (2)
WHO CNS Tumors Classification 2016

Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3

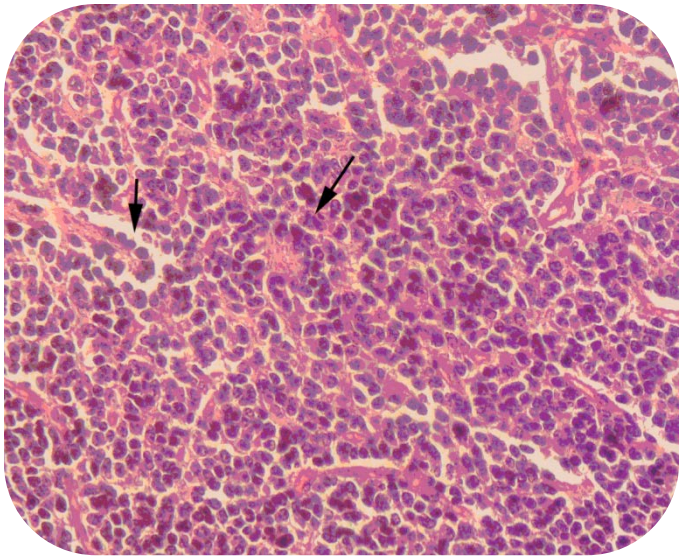
Histologic features and molecular informations ⇒ better selection of patients for treatment et prediction of prognosis (response to treatment)

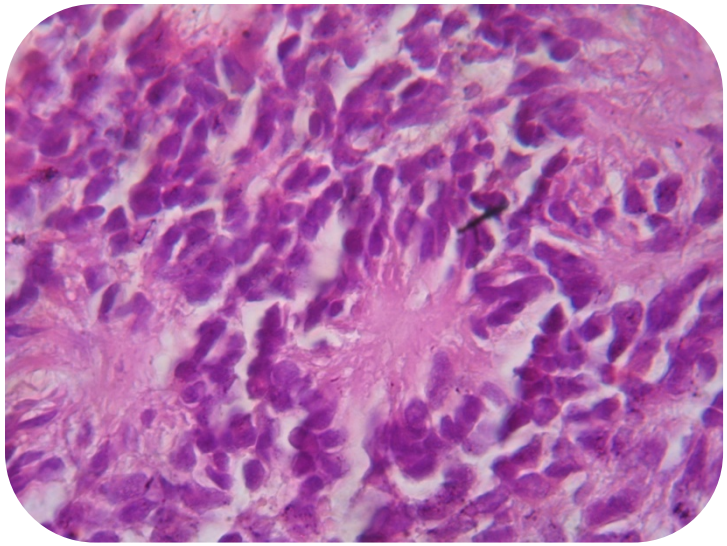
PATHOLOGY (3)

- Macroscopy:
  *Tumor appear as soft, darkish, which appear purplish compared to the surrounding brain.
  *usually located near the fourth ventricule and as such are in proximity to the brainstem and cerebellar peduncle, which they may have invade.

PATHOLOGY (4)

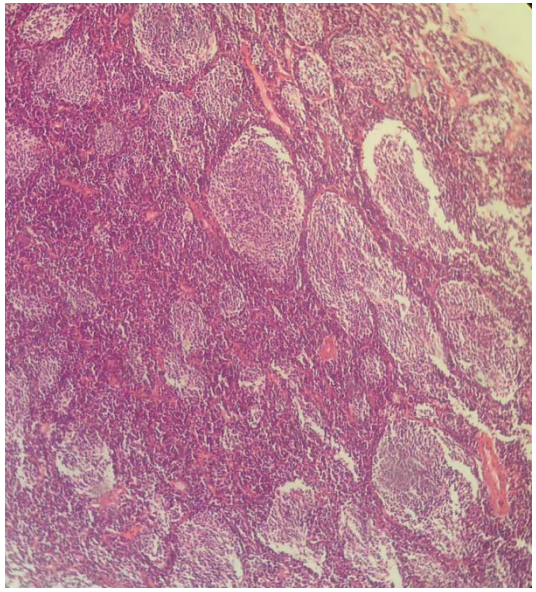
- Classical medulloblastoma: 2/3 of cases
  *Contain sheets of monotonous small cells with a high nuclear: cytoplasmic ratio and round nuclei.
  *Rosettes or palissades are present in some classic tumors.





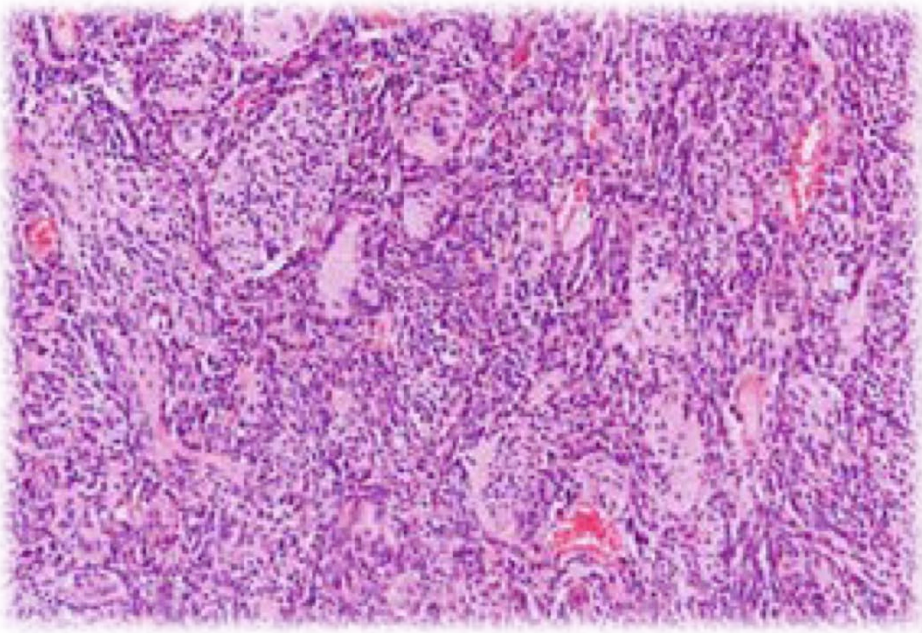
PATHOLOGY (5)

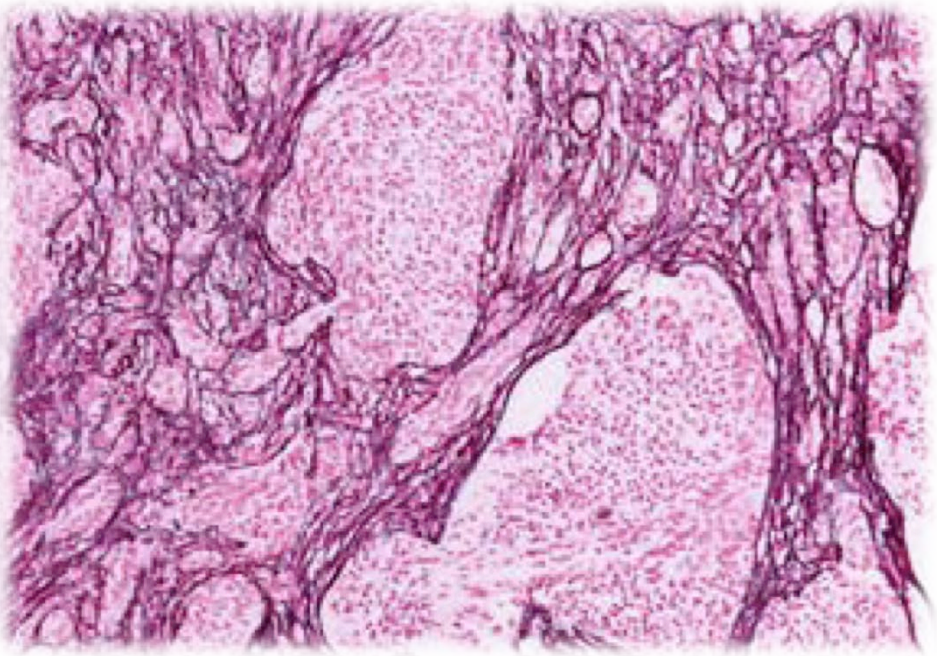
- Desmoplasic medulloblastomas:
  *Characterized by nodules of differentiated neurocytic cells and internodular desmoplasia, which is best demonstrated by reticulin stain.
  *The presence of nodules in desmoplastic tumors can be variable.



PATHOLOGY (6)

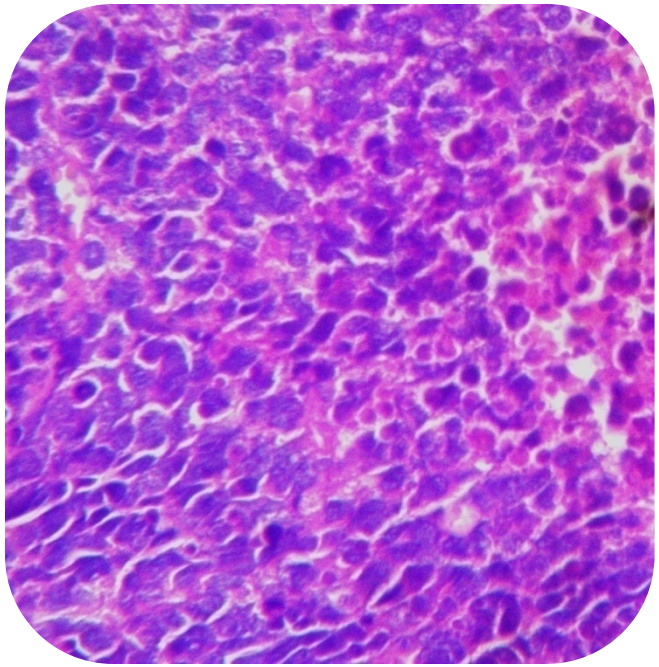
- MBEN medulloblastomas:
  *In MBENs nodules dominate the histopathology and are typically large and irregulary shaped. Internodulary desmoplasia is sparse, but clearly present.



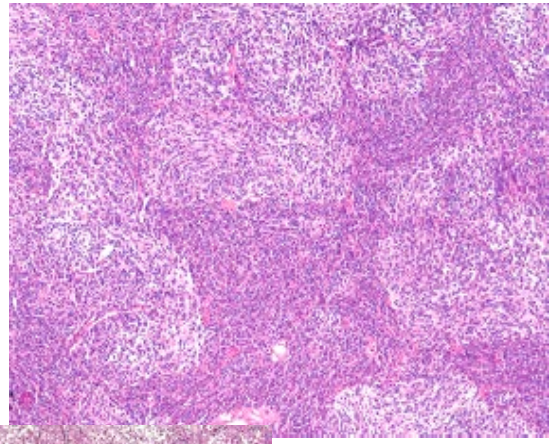


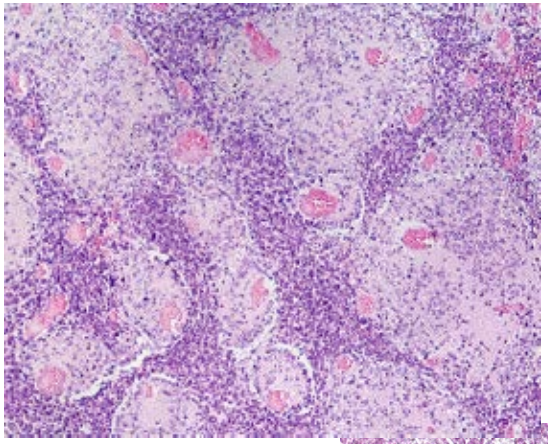
PATHOLOGY (7)

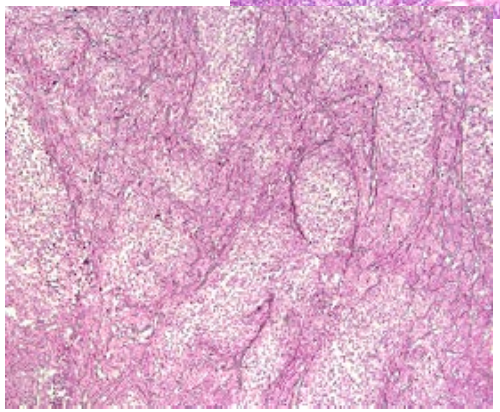
- Large cell / Anaplastic tumors:
  *Cells display significant nuclear pleomorphism, prominent nucleoli, and abundant mitoses.
  *Anaplasia may be difficult to appreciate and subjective.
  *This subset of tumors occurs in approximately 4%.



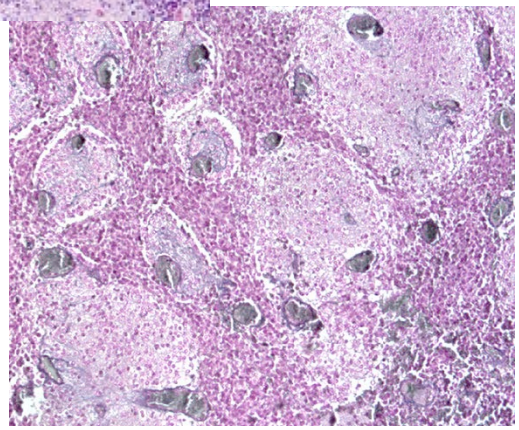
Médulloblastome désmoplasique # Médulloblastome classique avec nodules pales







Réticuline



La confusion entre les 2 types peut avoir des conséquences sur le traitement et le Pc entre les 2 est totalement différent

PATHOLOGY (8)

- Différence entre ATRT et médulloblastome très difficile à faire en l'absence d'immuno-marquage SMARCB1 (INI 1)

- Le problème se pose chez les petits < 03 ans avec variété desmoplasique

BIOLOGY (1)

EXPLOSION DES CONNAISSANCES EN BIOLOGIE MOLECULAIRE

Compréhension de l'hétérogénéité de la réponse au traitement

Emergence de la notion de traitement personnalisé

BIOLOGY (2)

- 1st paper concerning probable biologic subgroups

VOLUME 24 · NUMBER 12 · APRIL 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Genomics Identifies Medulloblastoma Subgroups That Are Enriched for Specific Genetic Alterations

Margaret C. Thompson, Christine Fuller, Twala L. Hogg, James Dalton, David Finkelstein, Ching C. Lau, Murali Chintagumpala, Adekunle Adesina, David M. Ashley, Stewart J. Kellie, Michael D. Taylor, Tom Curran, Amar Gajjar, and Richard J. Gilbertson

BIOLOGY (3)

Acta Neuropathol (2010) 120:305–316
DOI 10.1007/s00401-010-0726-6

REVIEW

Childhood medulloblastoma: novel approaches to the classification of a heterogeneous disease

David W. Ellison

VOLUME 29 · NUMBER 11 · APRIL 10 2011
JOURNAL OF CLINICAL ONCOLOGY

EDITORIALS

Hedgehogs, Flies, Wnts and MYCs: The Time Has Come for Many Things in Medulloblastoma

Michelle Monje, Philip A. Beachy, and Paul G. Fisher, *Stanford University, Palo Alto, CA*

Neuro-Oncology 14(2):203–214, 2012.
doi:10.1093/neuonc/nor196
Advance Access publication November 16, 2011

NEURO-ONCOLOGY

Prognostic classification of pediatric medulloblastoma based on chromosome 17p loss, expression of MYCC and MYCN, and Wnt pathway activation

Ae Kyung Park, Seung-Jun Lee, Ji Hoon Phi, Kyu-Chang Wang, Dong Gyu Kim, Byung-Kyu Cho, Christine Haberler, Sarah Fattet, Christelle Dufour, Stéphanie Puget, Christian Sainte-Rose, Franck Bourdeaut, Jacques Grill, Olivier Delattre, Seung-Ki Kim, and Woong-Yang Park

Published in final edited form as:
Acta Neuropathol. 2011 March ; 121(3): 381–396. doi:10.1007/s00401-011-0800-8.

Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups

David W. Ellison,
Department of Pathology MS# 250, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, USA

Medulloblastoma—translating discoveries from the bench to the bedside

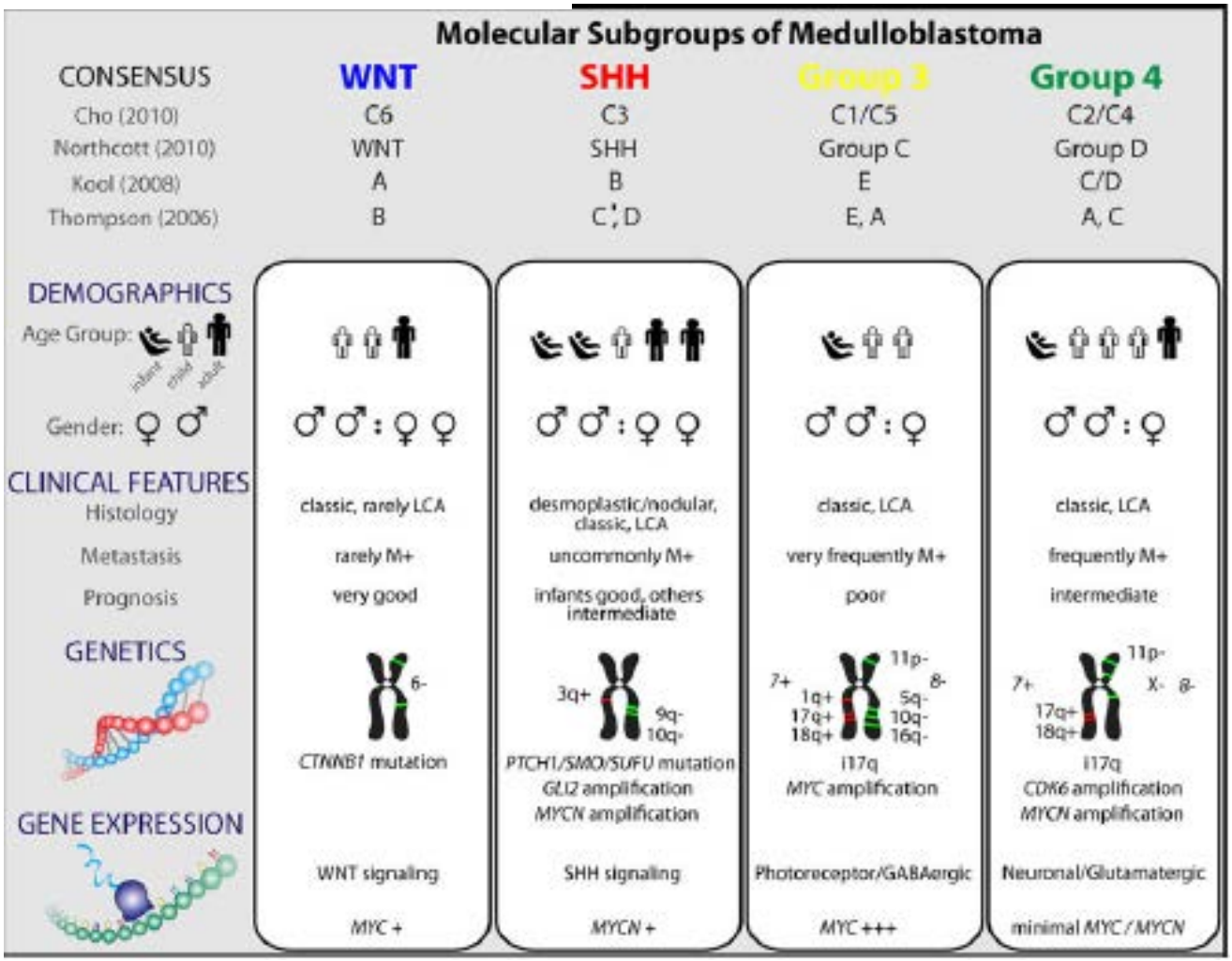
Gajjar, A. J. & Robinson, G. W. *Nat. Rev. Clin. Oncol.* **11**, 714–722 (2014);

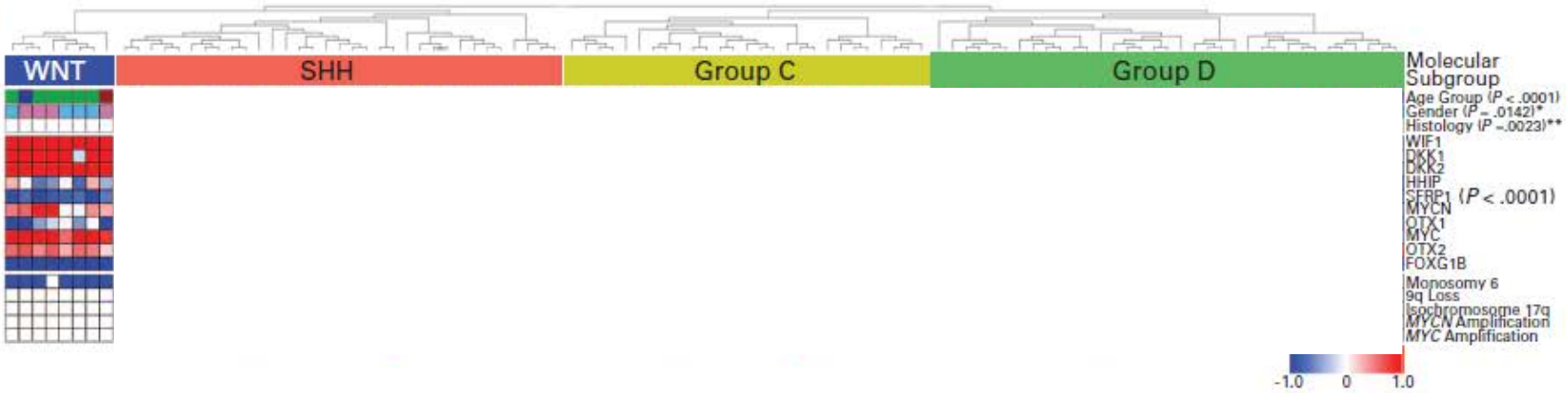
Acta Neuropathol (2012) 123:465–472
DOI 10.1007/s00401-011-0922-z

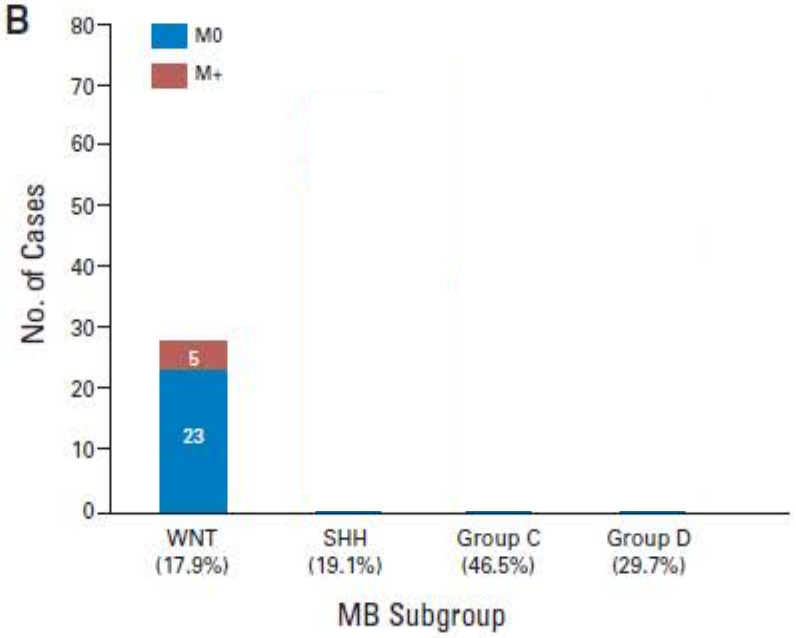
CONSENSUS PAPER

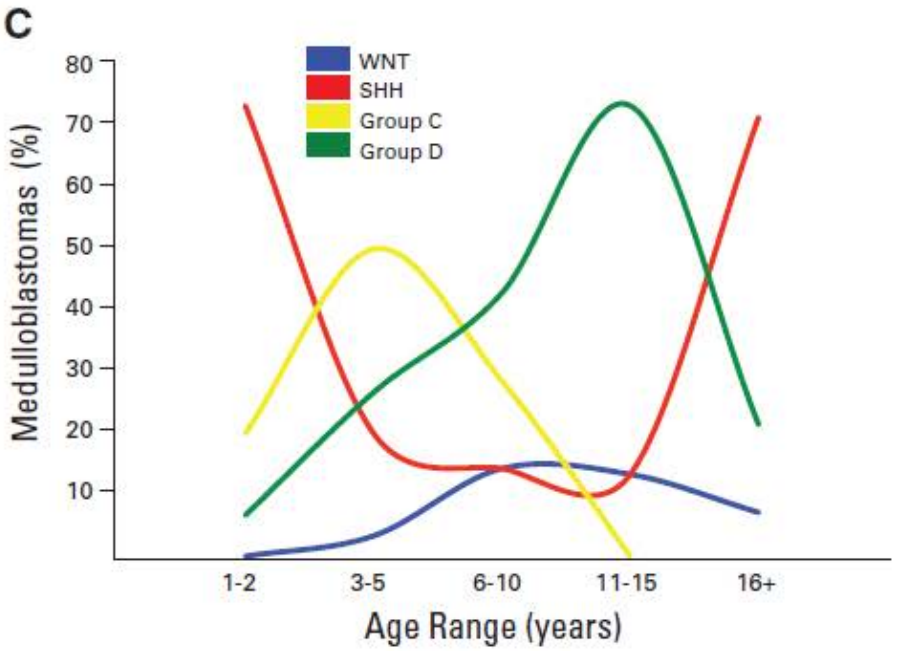
Molecular subgroups of medulloblastoma: the current consensus

Michael D. Taylor · Paul A. Northcott · Andrey Korshunov · Marc Remke · Yoon-Jae Cho · Steven C. Clifford · Charles G. Eberhart · D. Williams Parsons · Stefan Rutkowski · Amar Gajjar · David W. Ellison · Peter Lichter · Richard J. Gilbertson · Scott L. Pomeroy · Marcel Kool · Stefan M. Pfister









Northcott, J Clin Oncol, 2010

BIOLOGIC SUBTYPES (1)
Wnt

- Distributed across ages peak between 5 and 10 years.
- Male to female ratio = 1:1,7.
- Frequency (all ages): 10%.
- Histologic subtype: Classic
- Metastatic disease %: near 0
- Genomic abnormalities: CTNNB1 mutation, monosomy 6
- Elevated gene expression:
  Wnt pathway, n-MYC
- Prognosis: excellent (when classical criteria of standard risk are present).

VOLUME 23 · NUMBER 31 · NOVEMBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

β-Catenin Status Predicts a Favorable Outcome in Childhood Medulloblastoma: The United Kingdom Children's Cancer Study Group Brain Tumour Committee

David W. Ellison, Olabisi E. Onilude, Janet C. Lindsey, Meryl E. Lusher, Claire L. Weston, Roger E. Taylor, Andrew D. Pearson, and Steven C. Clifford

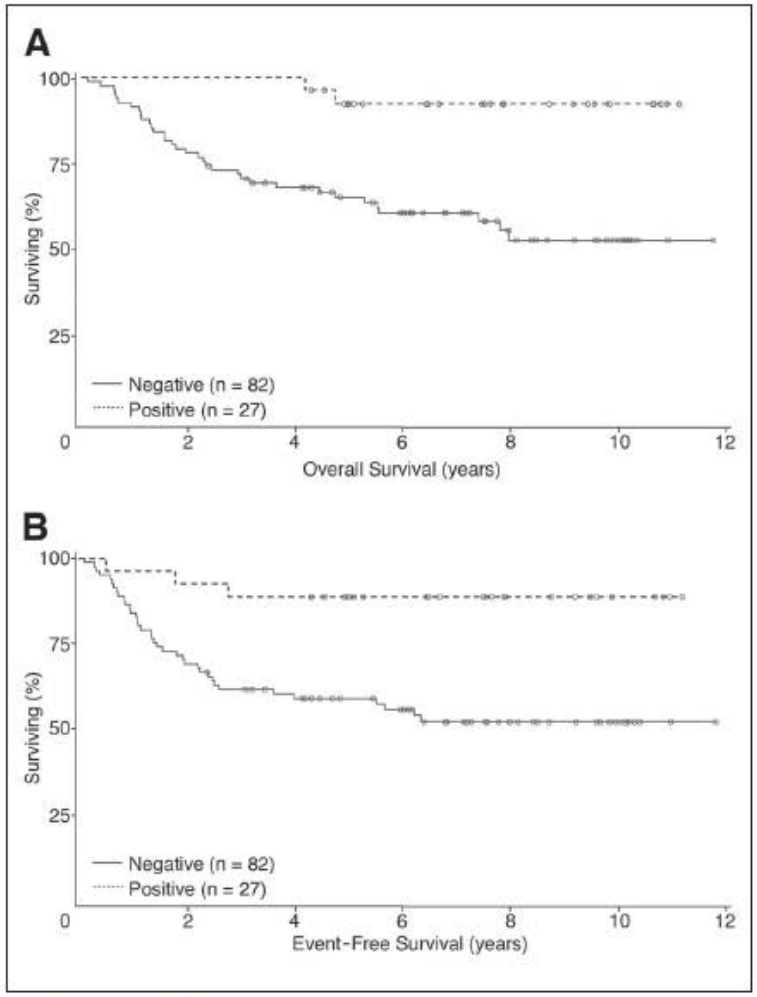


Fig 2. Kaplan-Meier overall (A) and event-free (B) survival curves for children with β-catenin nucleopositive/nucleonegative medulloblastomas (P = .0015 for OS, P = .0026 for EFS; logrank tests).

BIOLOGIC SUBTYPES (2)
Shh

- Primarly in infants < 03 years and adults > 16 years.
- Male to female ratio = 2:1.
- Frequency (all ages): 33%.
- Histologic subtypes: desmoplastic.
- Metastatic disease %: 07.
- Frequent deletion of 9q
- Elevated gene expression:
  Shh pathway, n-MYC
- Frequent mutation of PTCH1 and SUFU
- Prognosis: good in desmoplastic cases in young children.

BIOLOGIC SUBTYPES (3)
Group 3

- Children: 3 -10 years.
- Male to female ratio = 1 : 0,7.
- Frequency (all ages) %: 27.
- Metastatic disease %: 75.
- Histologic subtype: anaplastic / large cell.
- Genomic abnormality: c-MYC and N-MYC amplification.
- Elevated gene expression:
  Photoreceptor pathways, Neuronal differentiation pathways, c-MYC.
- Prognosis: dismal.

BIOLOGIC SUBTYPES (4)
Group 4

- Distributed across ages.
- Male to female ratio = 1 : 0,5.
- Frequency (all ages) %: 28.
- Metastatic disease %: 31.
- Elevated gene expression:
  Neuronal differentiation pathway.
- Prognosis: fair.

BIOLOGIC SUBTYPES (5)

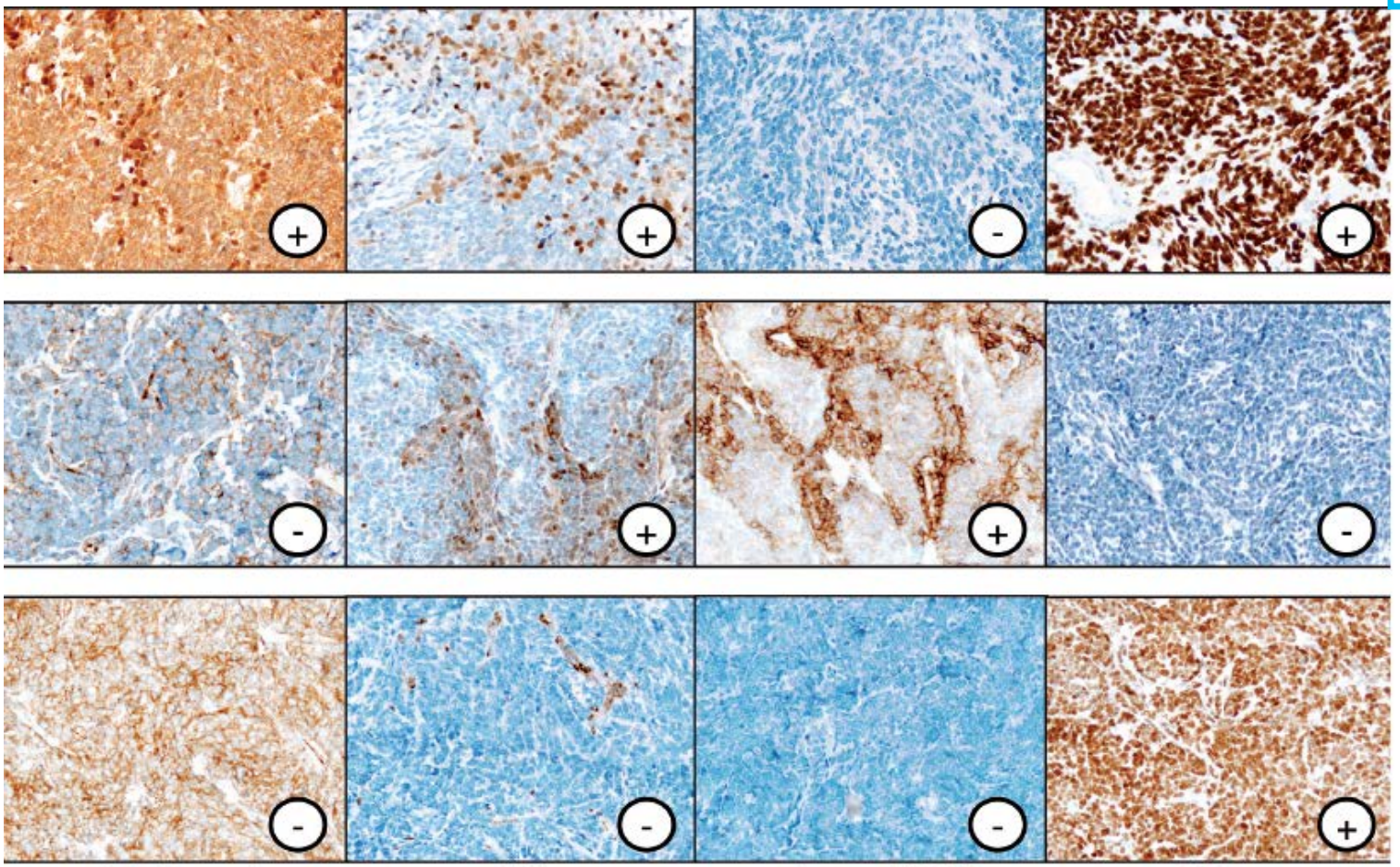
- Diagnosis: techniques of molecular biology
  Fish (Myc amplification)
  CGH array
- Immunohistochemistry can help:
  Difference between Wnt and Shh groups
  No difference can be made between Group 3 and 4
- Radiogenomics can help

Clinical Neuropathology, Vol. 35 – No. 6/2016 (344-352)

Update on the integrated histopathological and genetic classification of medulloblastoma – a practical diagnostic guideline

Torsten Pietsch[1] and Christine Haberler[2,3]

Médulloblastome



→ WNT-activé

→ SHH-activé

TP53 mutée

TP53 wildtype

→ non-WNT/ non- SHH

Childs Nerv Syst (2015) 31:1661–1676
DOI 10.1007/s00381-015-2834-z

SPECIAL ANNUAL ISSUE

Posterior fossa tumors in children: developmental anatomy and diagnostic imaging

Charles Raybaud[1] · Vijay Ramaswamy[2] · Michael D. Taylor[3] · Suzanne Laughlin[1]

Published March 15, 2018 as 10.3174/ajnr.A5578

ORIGINAL RESEARCH
PEDIATRICS

MRI Characteristics of Primary Tumors and Metastatic Lesions in Molecular Subgroups of Pediatric Medulloblastoma: A Single-Center Study

D. Mata-Mbemba, M. Zapotocky, S. Laughlin, M.D. Taylor, V. Ramaswamy, and C. Raybaud

Groupe SHH:
Periphery of cerebellar hemisphere
Strong enhancement

Groupe 4:
4th ventricle
Minimal enhancement
Ependymal metastasis

Groupe 3:
4th ventricle
Spinal metastasis

Groupe WNT:
CPA / 4th ventricle (lateral recessus)

RADIGENOMICS CAN HELP!

TREATMENT (1)

Journal of Multidisciplinary Healthcare

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Medulloblastoma: optimizing care with a multidisciplinary approach

Thomas. A. Journal of multidisciplinary team Healthcare 2019; 12: 335-347

TREATMENT (2)

- SURGERY
- RADIOTHERAPY
- CHEMOTHERAPY
- TARGET THERAPY?
- Multidisciplinary team+++

SURGERY (1)

- Goals of surgery include:

- Establishing diagnosis.
- Resecting as much tumor as safely possible.
- Treating any concurrent hydrocephalus.

SURGERY (2)
HYDROCEPHALUS

- Hydrocephalus is usually responsible for any sudden preoperative deterioration.

- It appears that treatment of significant hydrocephalus before an operation improves the patient's condition and subsequent clinical course.

SURGERY (3)
HYDROCEPHALUS

- Some authors propose to put steroids and do surgery as soon as possible because only 30% of patients will ultimately need a permanent shunt.
- ETV is a good alternative for treatment of hydrocephalus and can permit biobsy of the tumor if aqueduct is open.
- Intermittent, intraoperative drainage through an EVD can be used to help decrease intracranial pressure during surgery for the removal of the tumor.

  It can also be used postopeartively to monitor intracranial pressure and permit intermittent drainage.
- VP Shunt seems to be the worst option
- For EVD and VP Shunts: caution in cases of large tumors because of the risk of upward herniation

SURGERY (4)
TUMOR

- Used of corticosteroids for 24 to 48 hours helps control peritumoral edema.
- Standard pediatric surgical and anesthetic techniques are used in removal of the tumor.
- Tumors can be bloody ⇒ they require adequate venous access, arterial pressure monitoring, and Foley catheter monitoring of urine output during operation.

  Don’t forget: circulating blood volume in a young child is around 70cc/kg. Loss of more than 1.5 volume blood carry the risk of a coagulopathy.

SURGERY (5)
TUMOR

- Positions:
  Prone
  Sitting
  Lateral
  *All these positions requires the head to be pinned in children > 02 years
  *Use of pins in infants (<02 years) can lead to skull penetration producing: depressed fracture, pneumocephalus, dural laceration, hematoma or postoperative abcess

SURGERY (6)
TUMOR

- Prone: and concorde position (variant with neck flexed)
  *Used frequently.
  *For infants: face down on a padded horseshoe headrest. Important to adjust the width of headrest to avoid pressure on eyes. Rest-on foam over the face can avoid pressure on malar eminences and forehead area
  *For children > 02 years: fixation with pins but tightening only 40 pounds/inch. Avoid squamous temporal bone and shunt if present
  *Advantages: better visualisation, better exposure and surgeon comfort. Minimize risk of air embolus
  *Disadvantages: venous congestion which can lead to significant blood loss. Congestion can be improved by elevating head above level of heart.
  Accumulation of blood in the operative field
  Portions of tumor located posteriorly in the aqueduct can be missed

SURGERY (7)
TUMOR

- Sitting position:
  *Generally not under 02 years
  *Advantages:
  Offers a clear operative field
  Some studies showed better lower cranial nerves preservation
  *Disadvantages:
  Cardiovascular instability
  Hypotension
  Air embolism
  Subdural hematoma
  Tension pneumocephalus
  Rapid escape of CSF
  Thermal loss Surgeon discomfort

SURGERY (8)
TUMOR

- Lateral decubitus: (patient is lying on his side)
  Not used frequently
  Anatomy is not centered
  Allow better vizualization of lateral recesses

SURGERY (9)
TUMOR

- Approach: Midline suboccipital approach in most of cases
- Posterior fossa is exposed by a midline incision from just above the inion to approximately the mid-cervical region.
- The incision is deepened in the avascular midline between the strap muscles of the neck.
- It is not necessary to incise across the muscle insertion (so-called T-cut). The strap muscles can be retracted far enough laterally that all tumors, except those in the cerbellopontine angle, can be approached from the midline.

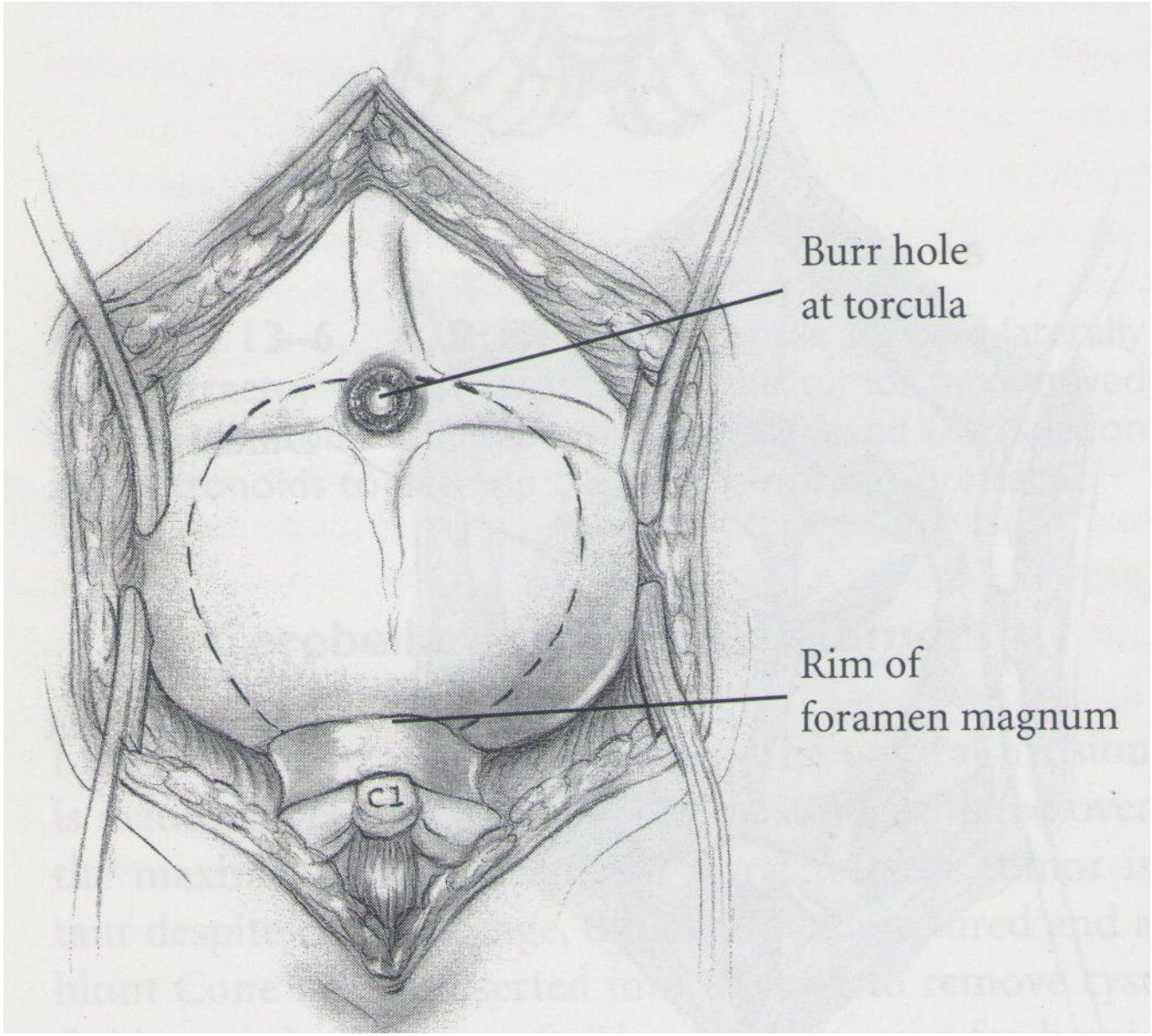
SURGERY (10)
TUMOR

- These muscles are elevated from the cranium and upper cervical laminae (only C1 +++ because risk of spinal instability).
  During exposure of C1: caution with monopolar cautery (superolateral surface+++) to prevent vertebral artery injury
  In young children and infants: C1 is cartilaginous and the dorsal arch does not fuse until age of 3 years

- Most surgeons now perform a suboccipital **craniotomy** rather than a craniectomy.

SURGERY (11)
TUMOR

- There is some evidence that craniotomy can decrease postoperative complications such as a pseudomeningocele and CSF leak.
- Rongeurs are used to widened the exposure as needed.
  Ultrasonography is used to define the adequate exposure.
- The foramen magnum is opened.
- There is no need to open routinely the posterior arch of C1 unless the tumor is located in the cervical canal (rare situation)



Limits of craniotomy

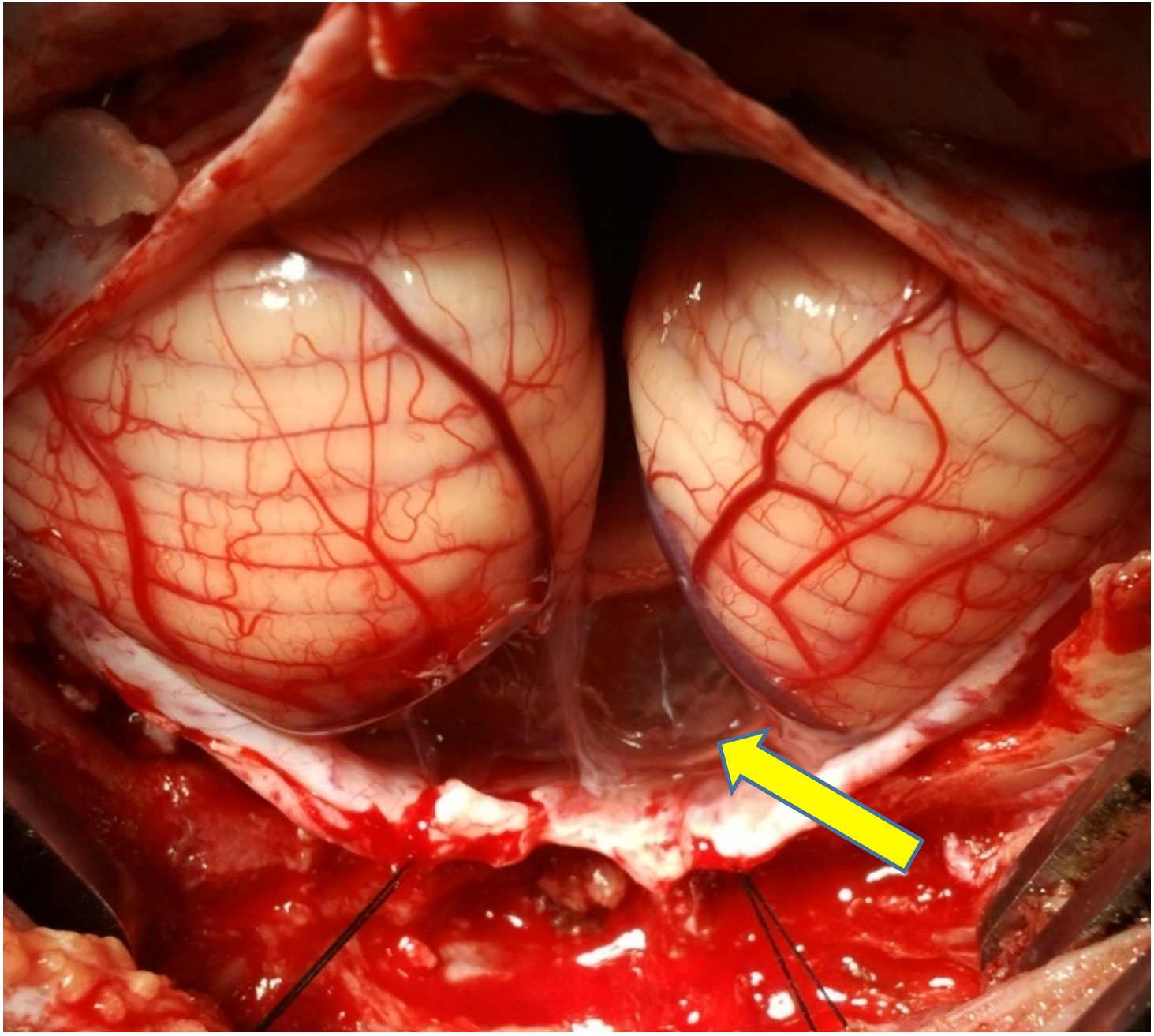
SURGERY (12)
TUMOR

- Dura is opened in Y shape:
  starting from the lateral aspects of the exposure and directed to the midline just above the foramen magnum.
  Special attention must be paid to the circular sinus and **the occipital sinus, which can be large and require careful control** ⟹ The surgeon must be prepared to occlude and ligate these sinuses.
  Suture ligatures are preferable to metal clips

SURGERY (13)
TUMOR

- Medulloblastomas of the fourth ventricle usually involve the vermis, but can involve the brainstem to variable degrees ⟹ identification of the floor of the fourth ventricle and therefore the brainstem is a crucial initial step in the dissection of the tumor.

- The cerebellar tonsils can be separated, exposing the vallecula, entrance to the fourth ventricle, and dorsum of the cervical cord.
  In some cases, tumor is extruding from the fourth ventricle and extending into the cervical canal.



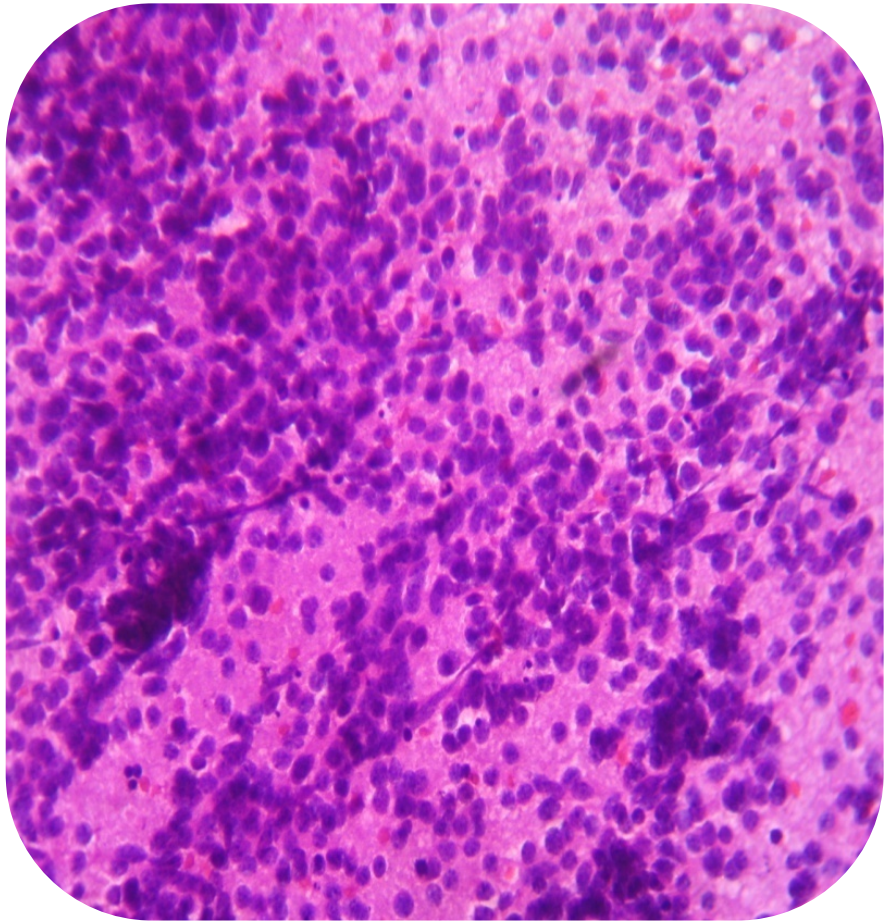
SURGERY (14)
TUMOR

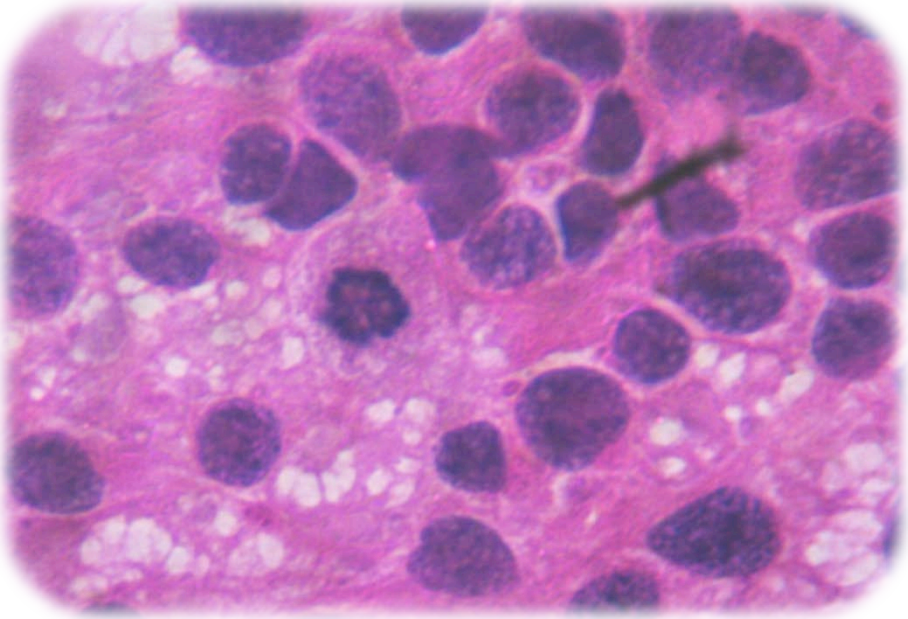
- A cottonoid can be placed along the fourth ventricular floor where it is clear from tumor.
  *This protect the floor and begins to orient the surgeon to the direction of the superior brainstem.
  *Cottonoids should not be inserted into the V4 except under direct vision to avoid injury to the floor (particularly where tumor may have invade it).
- Tumor resection begins with exposure of the dorsal tumor surface and dissection along the usually distinct tumor-cerebellum interface.
  splitting the vermis must be avoided.
  It is usually possible to develop a plane between the vermis and the cerebellar tonsils (and thus not remove any vermis), which may decrease postoperative complications (telovelar approach).

SURGERY (15)
TUMOR

- The PICAs are usually displaced laterally, against medial aspects of the cerebellar tonsils.
- The tumor is usually purplish and can be distinguish from the normal cerebellum.
- After the margins are defined, the tumor is internally debulked, using aspiration or ultrasonic aspirator.
  The internal decompression allows room for further dissection along the tumor margin.
  During this debulking specimens are obtained for pathologic evaluation (Smear….) and investigational studies or tumor banking (frozen specimens).

SMEAR





*Peut être fait en extemporané
*Procure de très bonnes informations sur la morphologie

SURGERY (16)
TUMOR

- Wherever the V4 is entered, the normal tissue should be protected with patties.
- It is usually easiest to enter the V4 from an inferior direction and extend the resection along the lateral walls of the ventricle and cerebellar peduncles.
- The nucleus of the VIth is located in the dorsomedial pons just beneath the floor of V4. Fibers from the VIIth nucleus run dorsomedially toward the floor of the V4, making an acute bend around the VIth nerve so if this area is invaded: caution in manipulation of the tumor to avoid “floor of the fourth ventricle syndrome”.
  Even gentle coagulation with low-current bipolar can produce a partial paralysis with total or near total recovery.

SURGERY (17)
TUMOR

- Likewise entering the floor of the V4 through the midline should be avoided, because the midline should be avoided because the medial longitudinal fasciculus courses just under the ependymal, and disruption of these fibers will lead to permanent intranuclear ophtalmoplegia.

- Irritation of the obex can induce persistent postoperative vomiting

- The tumor can be quite vascular and blood loss must be carefully monitored, particularly in very young children. Hemostasis can be obtained by cotonoids (without using bipolar)

SURGERY (18)
TUMOR

- Tumor attachment at the cerebellar peduncles and along the V4 (15% to 40% of cases) must be carefully isolated.
- The V4 is often free at the superior pole of the tumor near the aqueduct.
- The exposed aqueduct must be occluded to prevent entry of blood into the third ventricle.
- Though gross total resection of the tumor is the goal of surgery, it must be remembered that this a both chemo- and radiosensitive tumor ⟹ so, when tumor invade the brainstem, it is not necessary or advisable to attempt its complete removal.

SURGERY (19)
TUMOR

- Hemostasis is obtained with bipolar coagulation along the cerebellar surfaces.
  On the brainstem and cerebellar peduncles, bleeding is controlled only with gentle pressure or small bits of thrombin-soaked gelatin sponge (bipolar cauterization would transfer an unacceptable amount of energy through the tissue and might injure delicate adjacent structures).
  Valsava's maneuver is performed to confirm hemostasis.
- The cavity is copiously irrigated, and the aqueduct is flushed free of any debris or blood.

SURGERY (20)
TUMOR

- Dural closure is done in a watertight fashion (dural substitutes or sealants as necessary).
- The bone is replaced in cases with craniotomy (held in place either with suture material or plates and screws).
- Subcutaneous tissues are then closed in layers with care being taken to obtain a good fascial closure to decrease the risk of CSF leak.
- Multi-institutional studies indicate that in more than 80% of cases more than 90% of the tumor can be removed.

SURGERY (21)
TUMOR

- What about intraoperative monitoring?
- May be helpful if there is a danger of violating brainstem
- Most common option for direct monitoring of brainstem function is brainstem auditory-evoked potentials (BAEP).
- Evidence of pontomesencephalic transmission of the impulses implies that the brainstem has not been compromized
- Another option is somatosensory evoked potentials (SSEP) but it is less sensitive than BAEP
- It is important to mention that intraoperative monitoring tends to cause the surgeon to leave more tumor behind however the goal is to resect the maximum of tumor in most of cases

SURGERY (22)
COMPLICATIONS

- Nowadays surgical mortality decreased to less than 2%.
- Albright (2000) have shown that surgeons familiar with pediatric brain tumors have the lowest complication rate and achieve the greatest resection rates.
- Patients with the most significant deficits preoperatively had the greatest intraoperative risk.
- Dissection into the brainstem can result in significant cranial nerve deficits.

SURGERY (23)
COMPLICATIONS

- Air embolism remains a risk of any posterior fossa surgery in sitting position.
- Postoperative complications include both permanent and temporary deficits.
- Transient common postoperative findings include nystagmus, ataxia, nausea, vomiting.

SURGERY (24)
COMPLICATIONS

- Vascular injury:
- Injury to major vessels is rare
- Most likely artery to be injured is PICA
- Most patients with PICA injury present with postoperative floculonodular lobe dysfunction with nausea, vomiting, nystagmus, vertigo, and inability to walk or stand without appendicular dysmetria
- Venous infarction is rare even if veins are sacrified. 1 or 2 veins near the tonsils, vermis and inferior roof can be safely sacrified

SURGERY (25)
COMPLICATIONS

- Pneumocephalus:
  - Is not uncommon
  - Can occur in ventricles and/or subdural space
  - Most observed in sitting position
  - Symptomatic postoperative tension pneumocephalus can be treated by burr hole
  - Intraventricular air can cause VP shunt dysfunction due to an air lock within the valve

SURGERY (26)
COMPLICATIONS

- Postoperative pseudomeningoceles:

➢ Affects 15 to 28% of all children with posterior fossa tumors

➢ Normally: small collections are self limited and may respond to serial lumbar punctures

➢ Occasionally collection can enlarge and may produce CSF leak which can increase infectious risk

➢ Can be a manifestation of hydrocephalus and may require permanent CSF diversion

SURGERY (27)
COMPLICATIONS

- Hydrocephalus:

➢ Remember that only 30% of patients will require a permanent CSF diversion.

➢ Currently most of teams use preoperative DVE (as mentioned in chapter of management of HDC)
It can be gradually heighted in postoperative and maintain.
It can be successfully removed within 10 days

➢ Risk factors for shunt dependence are: younger age, larger preoperative ventricle size, more extensive tumors and presence of metastatic disease.

➢ CSF diversion is rarely needed in children > 10 years

SURGERY (28)
COMPLICATIONS

- CSF Leak:

➢ Common complication in posterior fossa surgery

➢ Often secondary to a failed watertight dural closure

➢ Can be treated by lumbar punctions and/or eventually acetazolamide

➢ If a CSF leak is a manifestation of a hydrocephalus then a CSF permanent diversion should be done

CHIRURGIE (29)
COMPLICATIONS

- Infections:

➢ Mainly meningitis

➢ Risk is increased in patients with preoperative shunt

SURGERY (30)
COMPLICATIONS

- "Floor of the fourth ventricle syndrome"

- Etiology is given in chapter of surgical technique
- Includes an ipsilateral palsy of VIth and VIIth cranial nerves and a contralateral hemiparesis
- In most cases patients with temporary facial weakness should be treated with artificial tears to prevent ocular complications. Sometimes a tarsoraphy is performed.
- Permanent weakness can be treated by facial-hypoglossal anastomosis
- VIth palsy is best treated with an eye patch to prevent diplopia (or amblyopia if the patient is under 5 years of age). If it persists beyond 6 months then eye muscle surgery may be appropriate.

SURGERY (31)
COMPLICATIONS

- Skewed ocular deviation:

➢ Rare condition observed after fourth ventricle surgery during which the aqueduct is manipulated

➢ Very rare in surgery of medulloblastoma

➢ Usually resolves within weeks after surgery

➢ Can be easily avoid by gentleness when working around aqueduct especially since the superior pole of tumor is generally free and not adherent to aqueduct.

SURGERY (32)
COMPLICATIONS

- Dyspraxia:

➢ Ipsilateral limb ataxia, dysmetria, dysdidokinesis and hypotonia usually result from damage to cerebellar hemisphere especially dentate nucleus

➢ Most injuries to dentate nucleus occur during dissection of a hemispheric tumor

➢ Retraction during dissection of the superior vermis can injure the superior cerebellar peduncle, producing similar symptoms

➢ Most patients recover well within a few months with only a minor residual intention tremor

SURGERY (33)
COMPLICATIONS

- Seizures:

➢ Generalized and focal seizures have been reported in 5.9% of children with posterior fossa surgery

➢ Incidence is higher in faster growing tumors and the presence of EVD or shunt and air embolism

➢ Late-onset seizures may be related to remote hemorrhage, meningitis, or hydrocephalus

➢ Children < 03 years appear to be at increased risk

SURGERY (34)
COMPLICATIONS

- Posterior fossa syndrome
- Over the years, it has been appreciated that a unique delayed postoperative complication can be seen in children undergoing resection of a posterior fossa medulloblastoma.
  Termed *posterior fossa syndrome* or *cerebellar mutism* also called *"pseudobulbar palsy"* but this term is probably not accurate

➢ Debate during long time concerning definition

SURGERY (35)
COMPLICATIONS

New definition of postoperative pediatric CMS: “Postoperative pediatric CMS” is characterized by delayed onset mutism/reduced speech and emotional lability after cerebellar or 4th ventricle tumor surgery in children. Additional common features include hypotonia and oropharyngeal dysfunction/dysphagia. It may frequently be accompanied by the cerebellar motor syndrome, cerebellar cognitive affective syndrome, and brainstem dysfunction including long tract signs and cranial neuropathies. The mutism is always transient, but recovery from CMS may be prolonged. Speech and language may not return to normal, and other deficits of cognitive, affective, and motor function often persist

Board of the Posterior Fossa Society 2015 ⇨ ***International consensus***

Original Article

Cerebellar Mutism Syndrome following Midline Posterior Fossa Tumor Resection in Children: An Institutional Experience

Nand Kishore Gora, Ashok Gupta, Virendra Deo Sinha

Department of Neurosurgery, SMS MC, Jaipur, Rajasthan, India

ABSTRACT

Aim: Cerebellar mutism (CM) syndrome is a well-known and annoying complication of posterior fossa surgery in the pediatric age group. Risk factors such as the type of tumor, size, involvement of posterior fossa structures and

SURGERY (36)
COMPLICATIONS

- Incidence: 8 – 31% but probably more because mild forms are often misdiagnosed
- Symptoms appear 24 to 72 hours postoperatively

SURGERY (37)
COMPLICATIONS

- Symptômes:

➢ Troubles du langage+++

Diminution du flux verbal ⇨ Mutisme

➢ Troubles du comportement

Labilité émotionnelle ⇨ Difficultés cognitives

➢ Troubles moteurs

Fonction executive

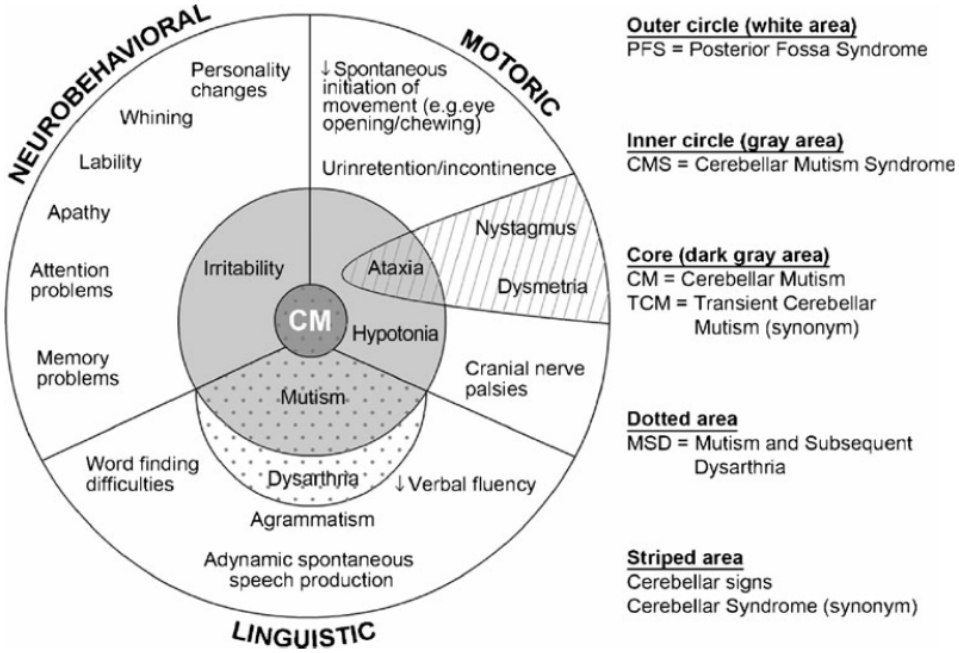
Réduction de la motricité

Ataxie

Hypotonie

Atteinte Nerfs crâniens

Dysphagie

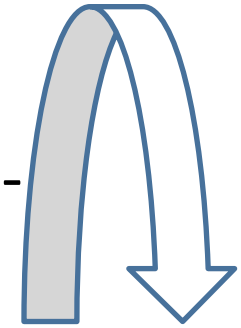


SURGERY (38)
COMPLICATIONS

- Etiopathogénie

➢ Le cervelet a une fonction :
  - Coordination et Contrôle motricité
  - Non motrice

Le circuit cérébro-cérébelleux



➢ Les aires corticales:
  - Pré-motrice
  - Pré-frontale
  - Pariétale

concernées par le comportement cognitif + la fonction motrice

ELSEVIER
Official Journal of the European Paediatric Neurology Society

Review article

Postoperative motor speech production in children with the syndrome of 'cerebellar' mutism and subsequent dysarthria: A critical review of the literature

Hyo Jung De Smet[a], Hanne Baillieux[a], Coriene Catsman-Berrevoets[b], Peter P. De Deyn[c,d], Peter Mariën[a,c,d], Philippe F. Paquier[a,e,f,]*

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Cerebellum and Nonmotor Function

Peter L. Strick,[1,2,3] Richard P. Dum,[2,3] and Julie A. Fiez[2,4]

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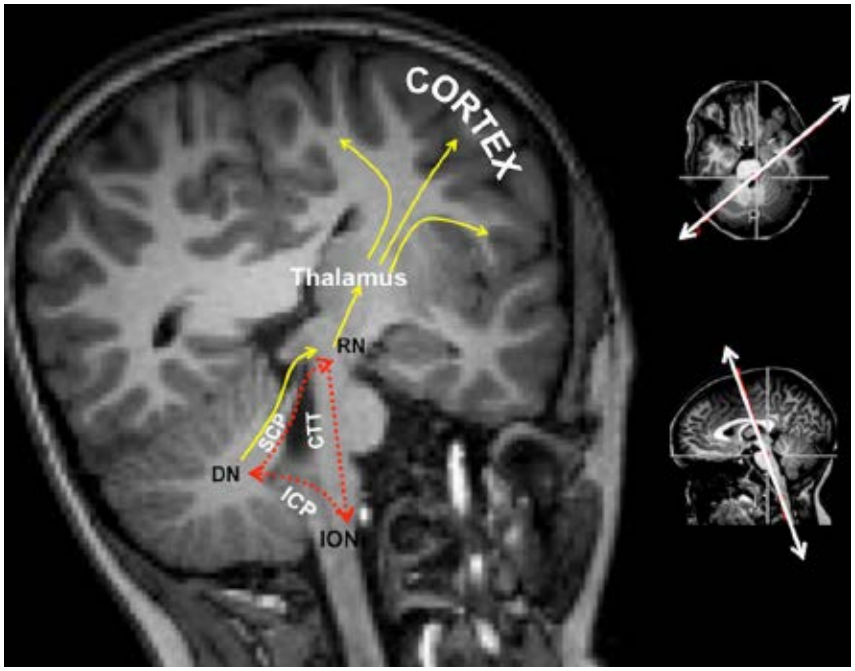
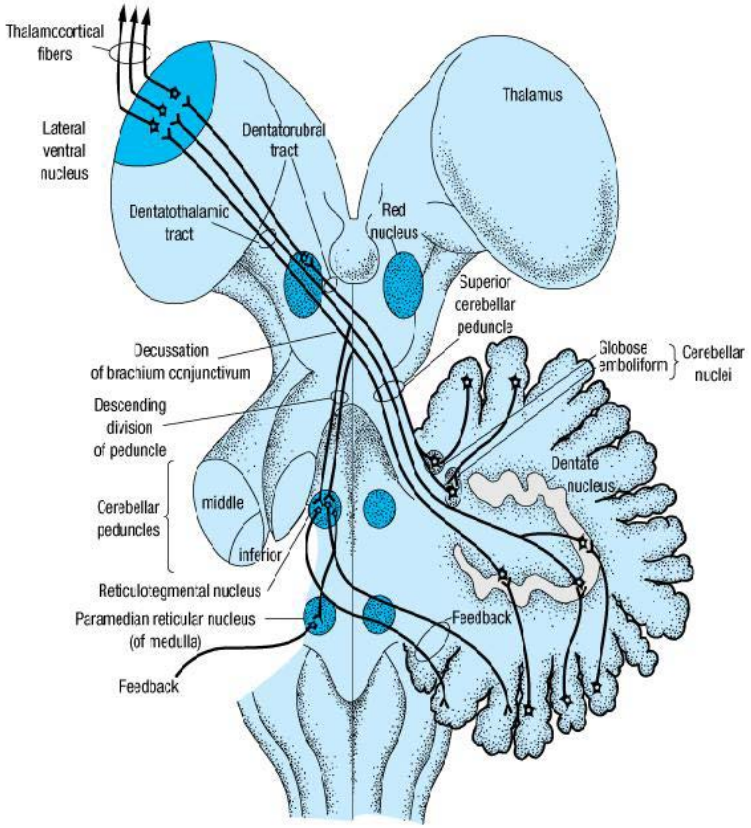
SURGERY (39)
COMPLICATIONS

- Etiopathogénie reste obscure

➢ Interruption de la voie Dentato-Thalamo-Corticale +++ segment proximal?

➢ Circuit cérébro-cérébelleux +++





SURGERY (40)
COMPLICATIONS

- Facteurs de risque:

➢ Les plus incriminés:
  - Localisation médiane de la tumeur
  - Invasion / compression du tronc cérébral
  - Type histologique: médulloblastome +++

➢ Les moins probables:
  - volume tumoral
  - Atteinte du vermis
  - Méthode de debulking tumorale
  - Age au moment de la chirurgie
  - Sexe
  - Hydrocéphalie pré-existante

➢ **La vermiectomie n'est certainement pas en rapport avec la survenue du syndrome**

SURGERY (41)
COMPLICATIONS

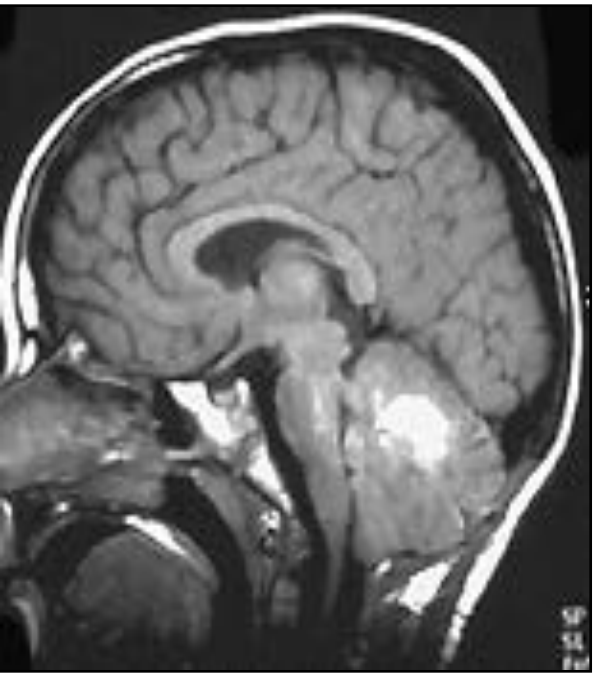
- No available modalities for treatment or prevention
- Some authors use corticosteroids
- Intensive multidisciplinary rehabilitation program is required to manage these patients
- Outcome is variable: recent studies have demonstrated that all children have long-term impairments and emotional problems

POSTOPERATIVE MANAGEMENT (1)

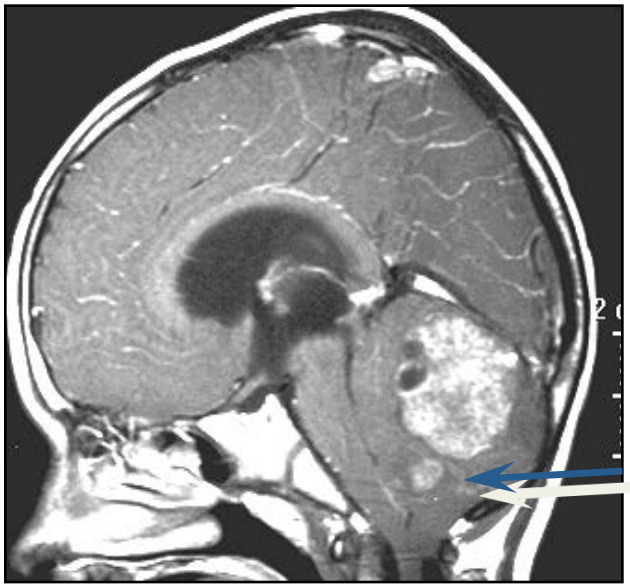
- Postoperative MRI: only validated element to judge the resection +++
  During the 48 first hours if not you have to wait 20 days but tumor may have regrowth!
  Intraoperative datas must be given to radiologist
  Review of preoperative imaging+++

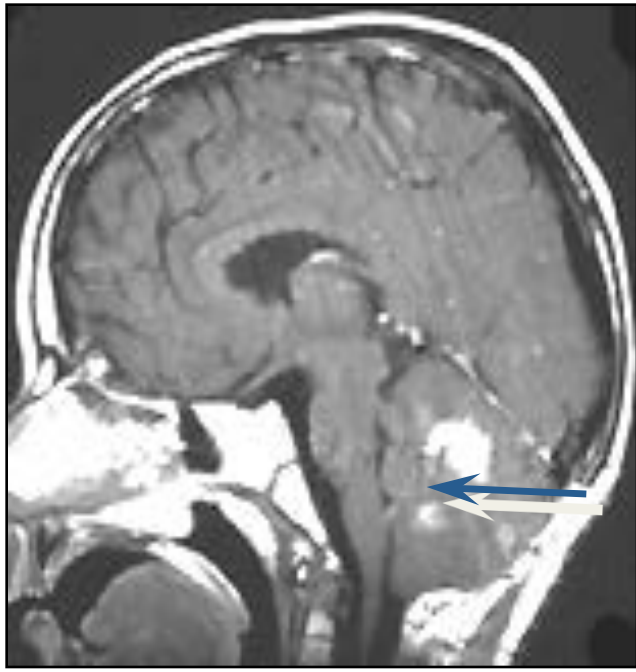
- LP: cytology between 10 and 14 days in post operative.
  Best technique = cytospin

Postoperative MRI / Residual tumor
see preoperative MRI!



postoperative
T1

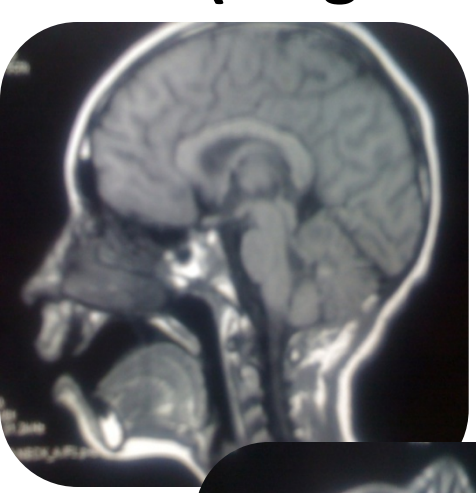
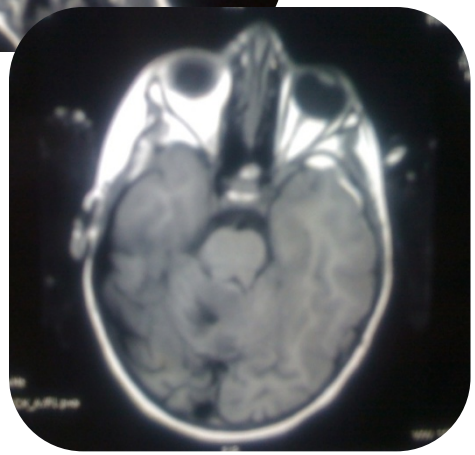
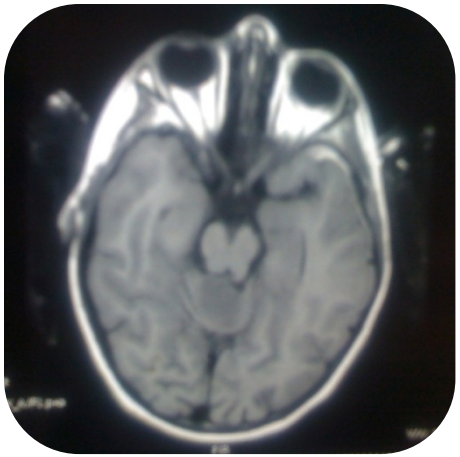
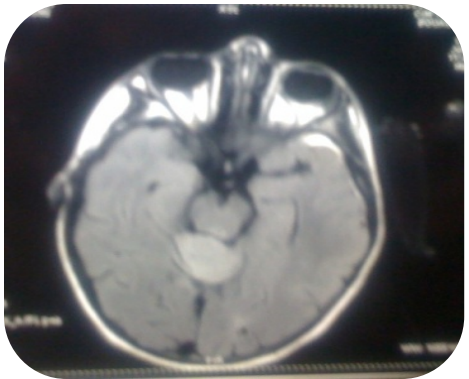
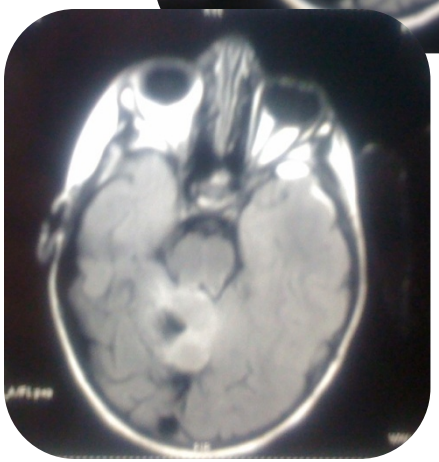
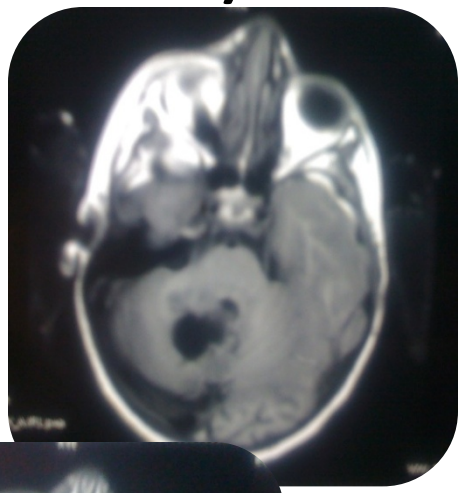


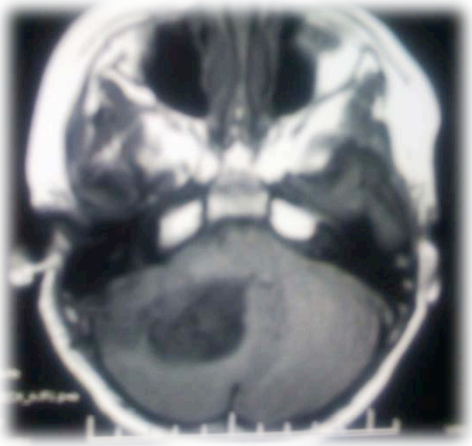
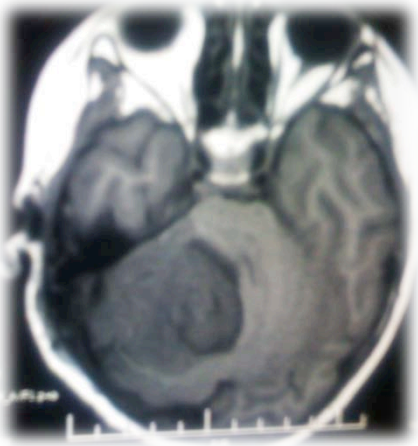
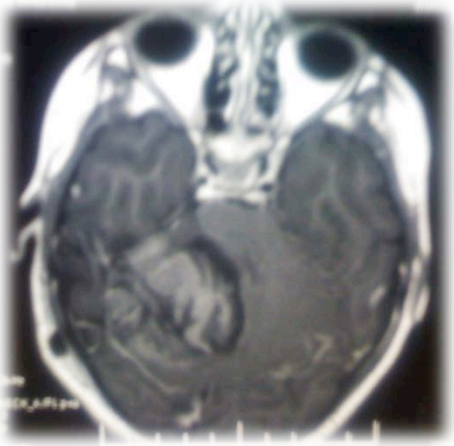
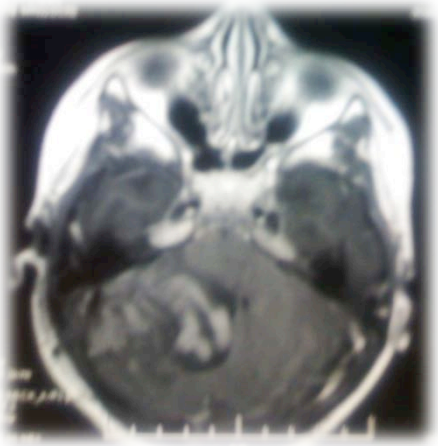


postoperative
T1 + Gd

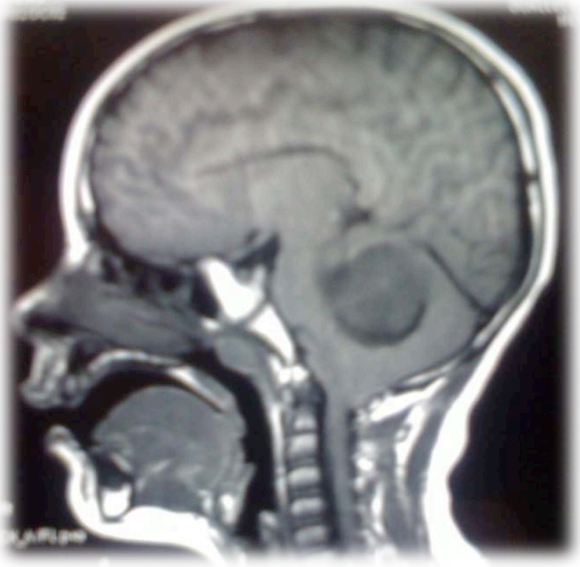
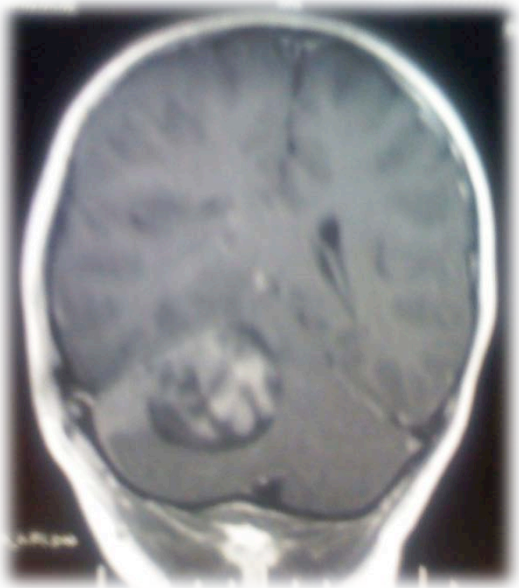
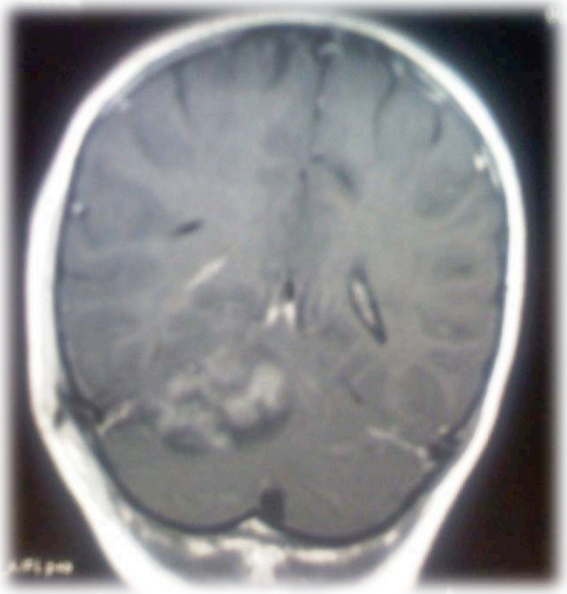
preoperative
T1 + Gd

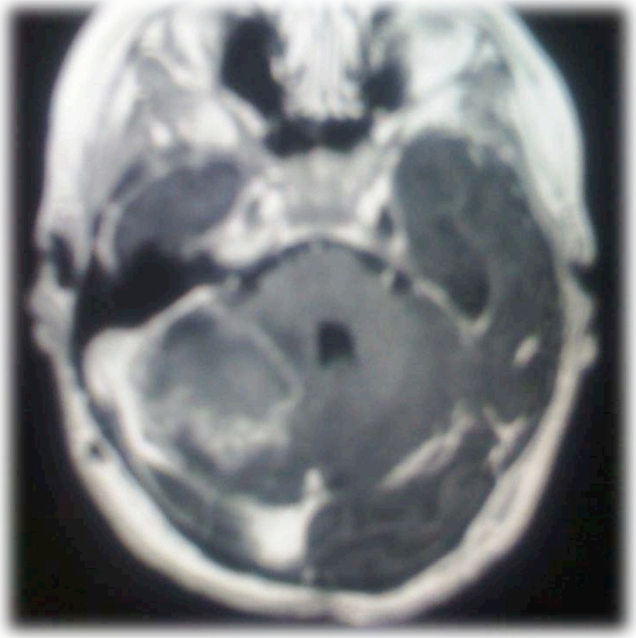
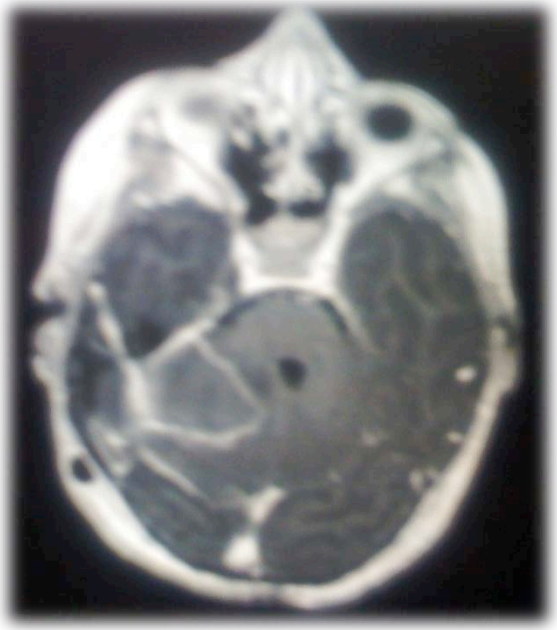
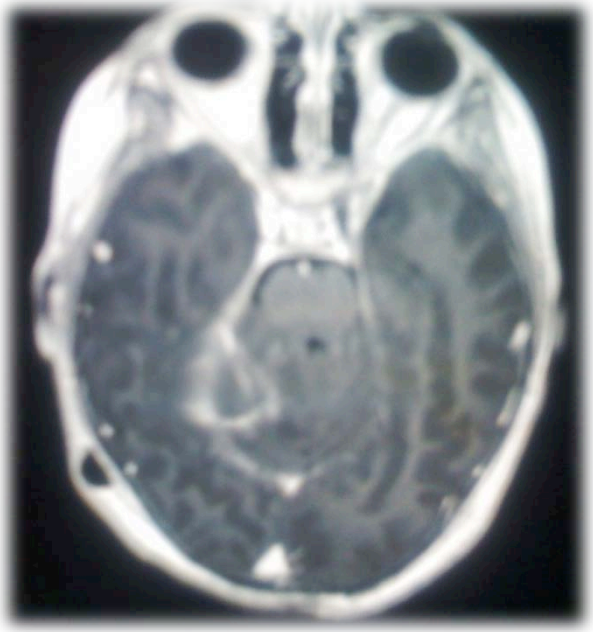
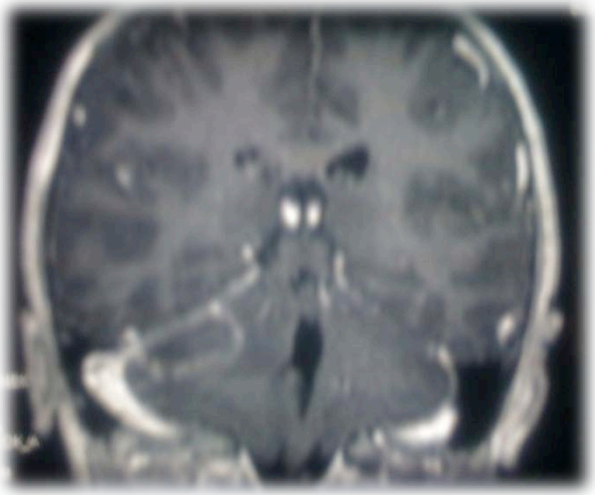
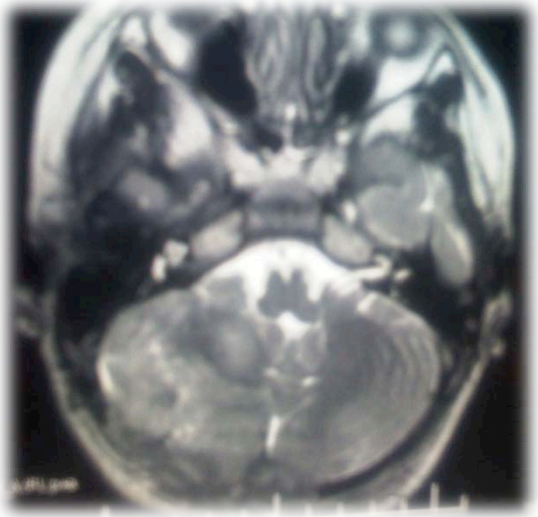
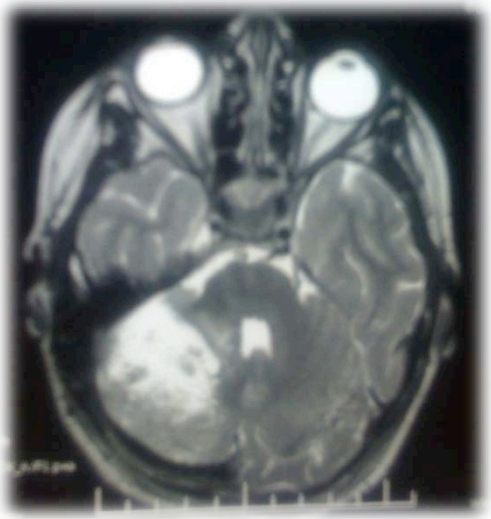
IRM VS OPERATIVE REPORT
(surgeon has mentioned a gross total resection!)

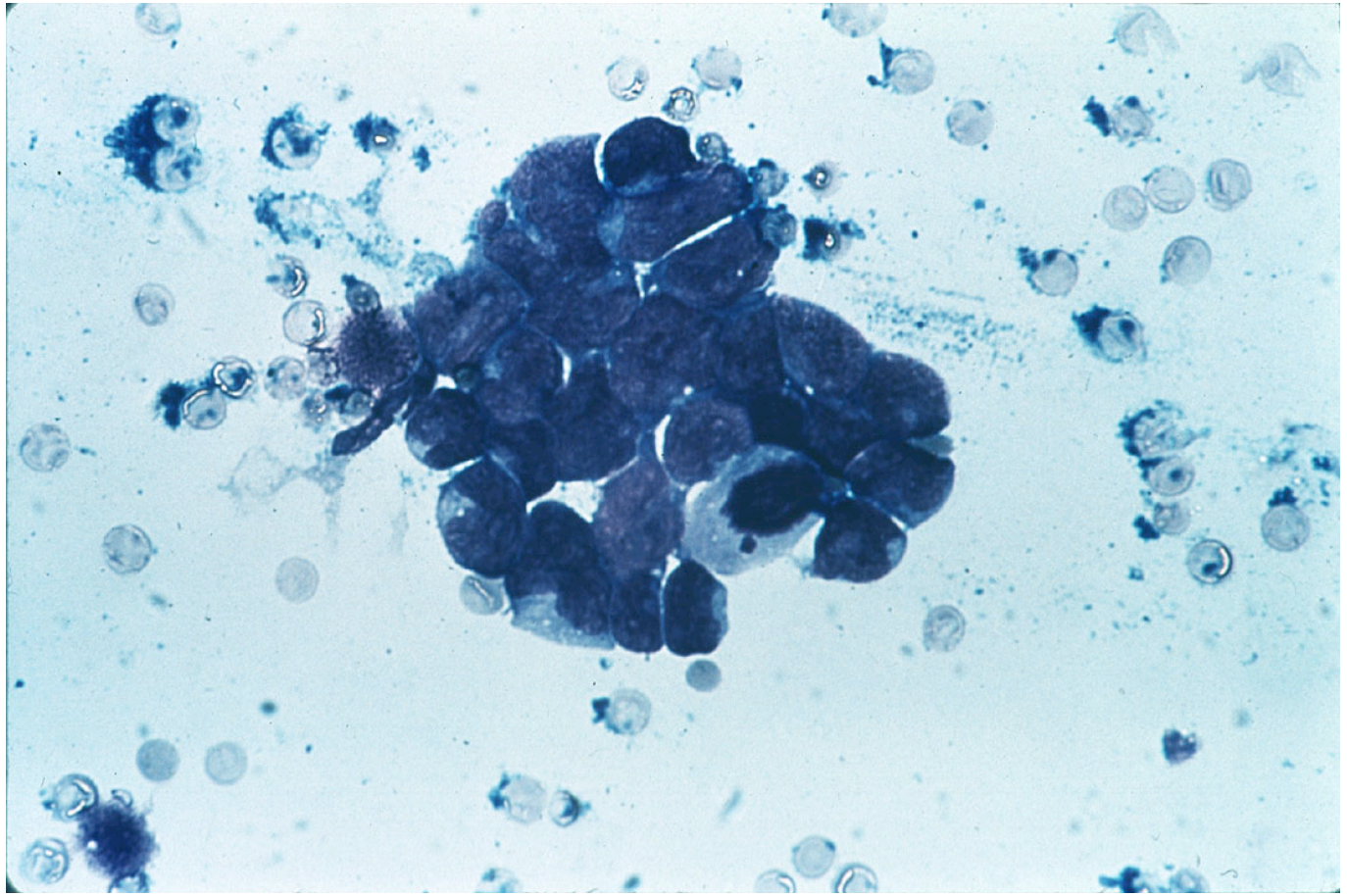
PRE OPERATOIRE

Post op: exérèse totale

CYTOLOGY



Présence de cell tumorales en technique cytospin

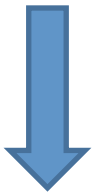
POSTOPERATIVE MANAGEMENT (2) ATTITUDE DU CHIRURGIEN FACE A UN RESIDU (absence de dissémination)

- En cas de résidu important: il est préférable d'envisager un 2ème temps chirurgical à condition de juger qu'il est praticable
  Reprise très précoce +++

POST OPERATIVE MANAGEMENT (3)
PATHOLOGY

- Obtain results in maximum 1 week
- Smear +++
- Use of WHO classification is mandatory +++

Once the postoperative imaging and cytology done and pathology obtained



The multidisciplinary team will classify the patient in a category of risk using a risk stratification

This in order to give adapted adjuvant therapy according to the group of risk

CLASSICAL RISK STRATIFICATION
Used in North America and Australia

- Age > 03 years:
  *Standard risk:
  no metastatic disease (CSF -)
  residual tumor < 1,5cm².
  *High risk:
  metastatic disease
  or
  residual tumor > 1,5 cm².
- Age < 03 years:
  *generally poor outcome

MAY BE **NOT ACCURATE !**

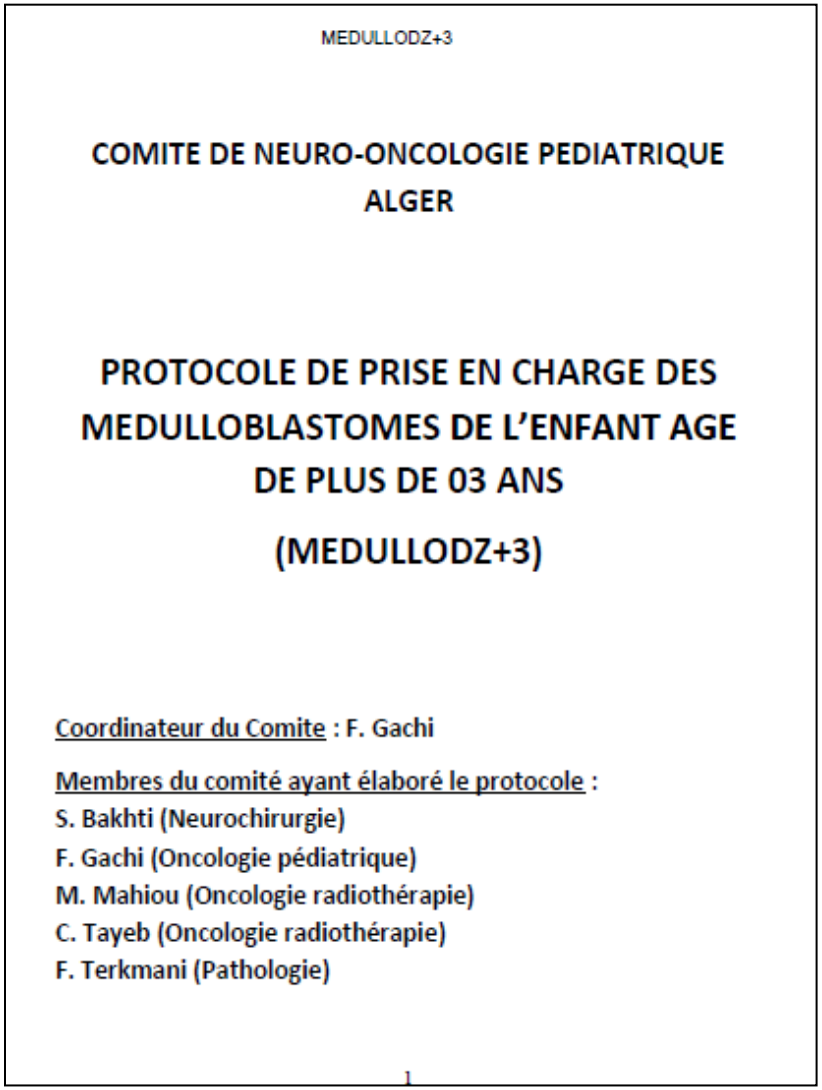
RISK STRATIFICATION with HISTOLOGICAL and MYC GENE CRITERIA Used in Europe

Age > 03

- **Standard risk:**
  Desmoplasic or classic type with:
  Residual tumor < 1.5 cm^2
  AND
  No dissemination M0
- **High risk:**
  *LC/A histological type even with R0 and M0
  *MYC and MYCN amplification even with R0 and M0
  *Desmoplasic or classic type with:
  Residual tumor > 1.5 cm^2
  AND / OR
  Dissemination

RISK STRATIFICATION with HISTOLOGICAL CRITERIA

- Used in Algeria



MEDULLODZ+3

COMITE DE NEURO-ONCOLOGIE PEDIATRIQUE
ALGER

PROTOCOLE DE PRISE EN CHARGE DES MEDULLOBLASTOMES DE L'ENFANT AGE DE PLUS DE 03 ANS

(MEDULLODZ+3)

Coordinateur du Comite : F. Gachi

Membres du comité ayant élaboré le protocole :
S. Bakhti (Neurochirurgie)
F. Gachi (Oncologie pédiatrique)
M. Mahiou (Oncologie radiothérapie)
C. Tayeb (Oncologie radiothérapie)
F. Terkmani (Pathologie)

1

NEW RISK STRATIFICATION Consensus Conference Heidelberg 2015 (1)

Published in final edited form as:
Acta Neuropathol. 2016 June ; 131(6): 821–831. doi:10.1007/s00401-016-1569-6.

Risk stratification of childhood medulloblastoma in the molecular era: The Current Consensus

Vijay Ramaswamy[1,*], Marc Remke[2,3,*], Eric Bouffet[1], Simon Bailey[4], Steven C. Clifford[4], Francois Doz[5], Marcel Kool[6], Christelle Dufour[7], Gilles Vassal[7], Till Milde[8,9], Olaf Witt[8,9], Katja von Hoff[10], Torsten Pietsch[11], Paul A. Northcott[12], Amar Gajjar[12], Giles W. Robinson[12], Laetitia Padovani[13], Nicolas André[14], Maura Massimino[15], Barry Pizer[16], Roger Packer[17], Stefan Rutkowski[10], Stefan M. Pfister[6,8], Michael D. Taylor[18], and Scott L. Pomeroy[19]

NEW RISK STRATIFICATION
Consensus Conference Heidelberg 2015 (2)

Age > 03 years

- Low risk: > 90% survival
  *Non metastatic Wnt in patients under 16 years and R0
  *Group 4 with loss of chromosome 11 and/or whole gain of chromosome 17 with M0 may be can be considered as low risk

- Standard risk: 75-90% survival
  *Non metastatic non-TP53 mutated and non-MYCN amplified SHH
  *non-MYC amplified Group 3
  *Group 4 without chromosome 11 loss and M0

NEW RISK STRATIFICATION
Consensus Conference Heidelberg 2015
(3)

Age > 03 years

- High risk: 50-75% survival
  MYCN amplified SHH regardless of metastases
  TP53 wildtype SHH
  Metastatic group 4

- Very high risk: < 50% survival
  TP53 mutated SHH
  MYC amplified metastatic group 3

ATTENTION

- Cette nouvelle stratification du risque n'est pas encore utilisée de façon routinière
- Utilisée dans les essais thérapeutiques en cours
- Doit être connue pour le Pc

RADIATION THERAPY (1)

- An important part of the treatment.
- Age: 3 or 5 years
- Conformational techniques
- For standard risk:
  CSI of 23.4 Gy in 13 fractions
  Followed by tumor bed boost to reach 54-55.8 Gy
- For high risk:
  CSI of 36-39.6 Gy in 20 to 22 fractions
  Followed by tumor bed boost 54-55.8 Gy
  When appropriate 50 Gy CSI is administrated to local sites of metastases
- Timing = early after surgery (see chapter of prognosis factors)

RADIATION THERAPY (2)

- Proton therapy
- IMRT (intensity-modulated RT)
- Both limit irradiation to normal tissues with acceptable toxicity and survival similar to conventional RT
- Reduced irradiation of normal tissues relieves post-radiation ototoxicity ⟹ preserved hearing and improved quality of life
- Studies needed to assess long term sparing of neurocognitive functions

RADIATION THERAPY (3)
HYPERFRACTIONED RT

Not superior to conventional RT

VOLUME 30 · NUMBER 26 · SEPTEMBER 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Hyperfractionated Versus Conventional Radiotherapy Followed by Chemotherapy in Standard-Risk Medulloblastoma: Results From the Randomized Multicenter HIT-SIOP PNET 4 Trial

Birgitta Lannering, Stefan Rutkowski, Francois Doz, Barry Pizer, Göran Gustafsson, Aurora Navajas, Maura Massimino, Roel Reddingius, Martin Benesch, Christian Carrie, Roger Taylor, Lorenza Gandola, Thomas Björk-Eriksson, Jordi Giralt, Foppe Oldenburger, Torsten Pietsch, Dominique Figarella-Branger, Keith Robson, Marco Forni, Steven C. Clifford, Monica Warmuth-Metz, Katja von Hoff, Andreas Faldum, Véronique Mosseri, and Rolf Kortmann

RADIATION THERAPY (4)
Acute Side Effects

- Anorexia and nausea (attention to nutritional condition)
- Cytopenia must be detected
- Pneumocystis prophylaxis during and the weeks following CSI

RADIATION THERAPY (5)
Late Side Effects of Irradiation

- Neurocognitive sequelae
- Endocrinologic
- Skeletal sequelae
- Secondary malignancies (in long survivors)
- Difference statistically significant between a CSI with 36 Gy vs 23 Gy +++ for sequelea (so good work up before treatment ⟹ risk stratification+++)

CHEMOTHERAPY (1)

- Medulloblastomas are chemosensitive.
- 1990: Evans was the first to report a randomized trial demonstrating the benefits of chemotherapy in conjunction with irradiation versus irradiation alone.
- Various chemotherapy regimens.
- Timing:
  *Concomitant (during irradiation): vincristine??
  *Adjuvant (after irradiation)
  *Neoadjuvant (‘’Sandwich’’) may be interesting in metastatic disease
  *Preoperative after biopsy
  *Most used scheme is chemotherapy after irradiation

CHEMOTHERAPY (2)

- Chemotherapy alone in young children.
- Intensive chemotherapy:
  In children < 03 years
  High risk??
  In some cases of recurrences after CSI.
- Benefit of chemotherapy is establish in high risks (metastases).
- Use of chemotherapy is recommended in standard risks.
- Reduction of the risk of extra neural metastases.

CHEMOTHERAPY (3)
COMITE DE NEURO-ONCOLOGIE PEDIATRIQUE ALGER

- 4 à 6 semaines après l'irradiation.
  Cisplatine et Etoposide les 3 premiers cycles.
  Cytoxan et Vincristine les 3 derniers cycles.

CHEMOTHERAPY (4)
Side effects

- Vincristine induced peripheral neuropathy:
  Affects sensory, motor and autonomic nerves
  incidence: 37% in medulloblastomas
  Symptoms may not resolve
  Chronic peripheral neuropathy favors obesity, diabete type 2, metabolic syndrome and cardiovascular disease
- Cisplatine induced ototoxicity (34%)
- Myelosuppression

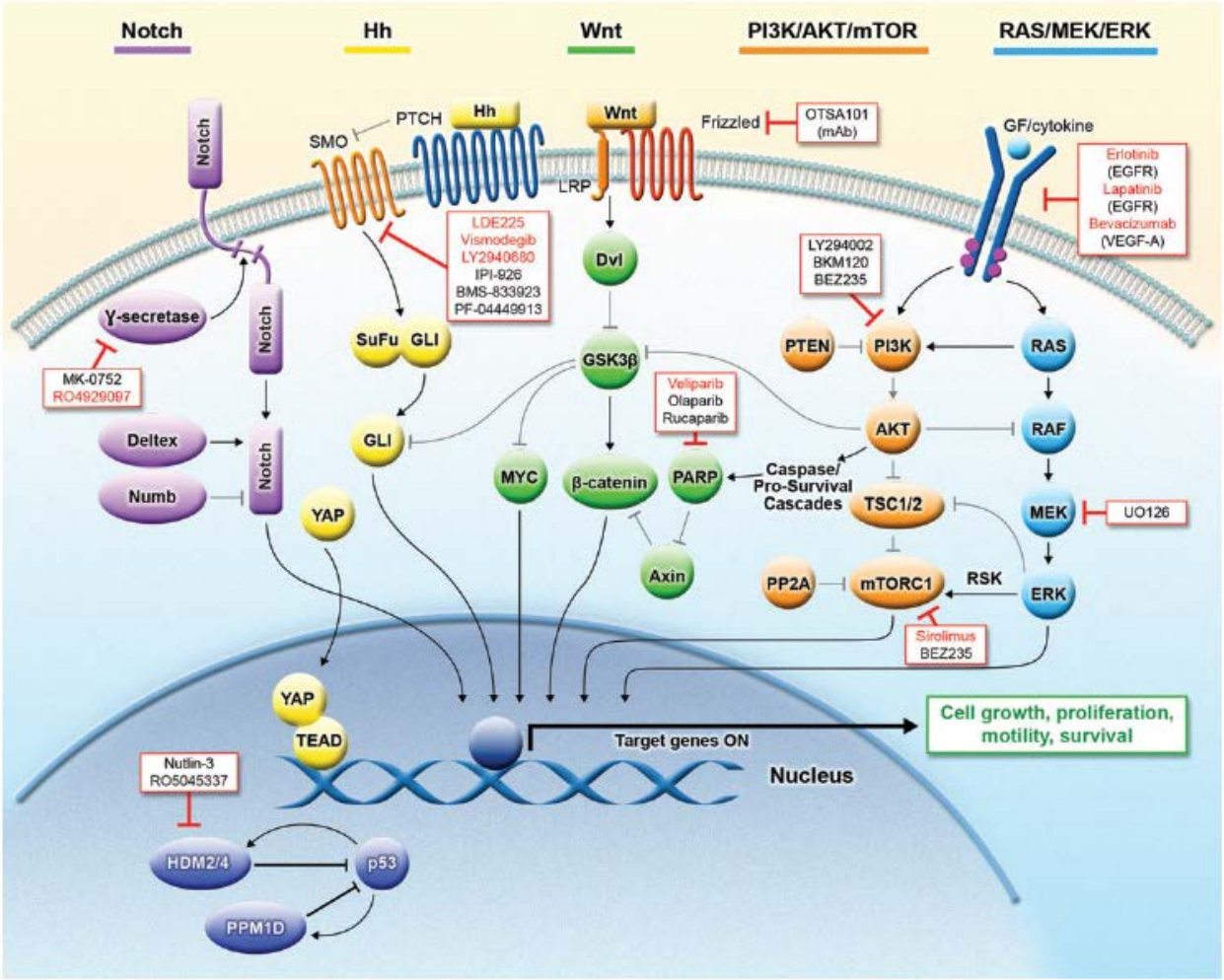
TARGET THERAPY (1)

Neuro-Oncology

Neuro-Oncology 16(1), 9–20, 2014
doi:10.1093/neuonc/not147
Advance Access date 4 December 2013

The rationale for targeted therapies in medulloblastoma

Tobey J. MacDonald, Dolly Aguilera, and Robert C. Castellino



TARGET THERAPY (2)

- Mostly developed for Shh subgroup
- First generation of SMO inhibitors
- Problems of downstream resistance to SMO inhibitors ⟹ new targets ⟹ 2nd generation of SMO inhibitors

TARGET THERAPY (3)

- Not include systematically in the standard current management
- Given in certain circumstances:
  recurrent medulloblastomas (not all)
  refractory medulloblastomas

CALENDRIER D'EVALUATION

- Clinique:
  1 par mois pendant 6 mois
  1 tous les 3 mois durant les 3 années qui suivent
  1 tous les 6 mois durant les 2 années suivantes
  1 par an après 5 ans
- Imagerie:
  IRM crânio-spinale après traitement
  1 IRM tous les 3 mois durant the 2 premières années
  1 TDM tous les 4 mois durant la 3ème année
  1 TDM tous les 6 mois pendant les 2 années qui suivent
  1 TDM par an après 5 ans
- Endocrinologie:
  A partir de 6 mois
- Neuro-psychologique:
  A partir de 20 mois post op

EVALUATION

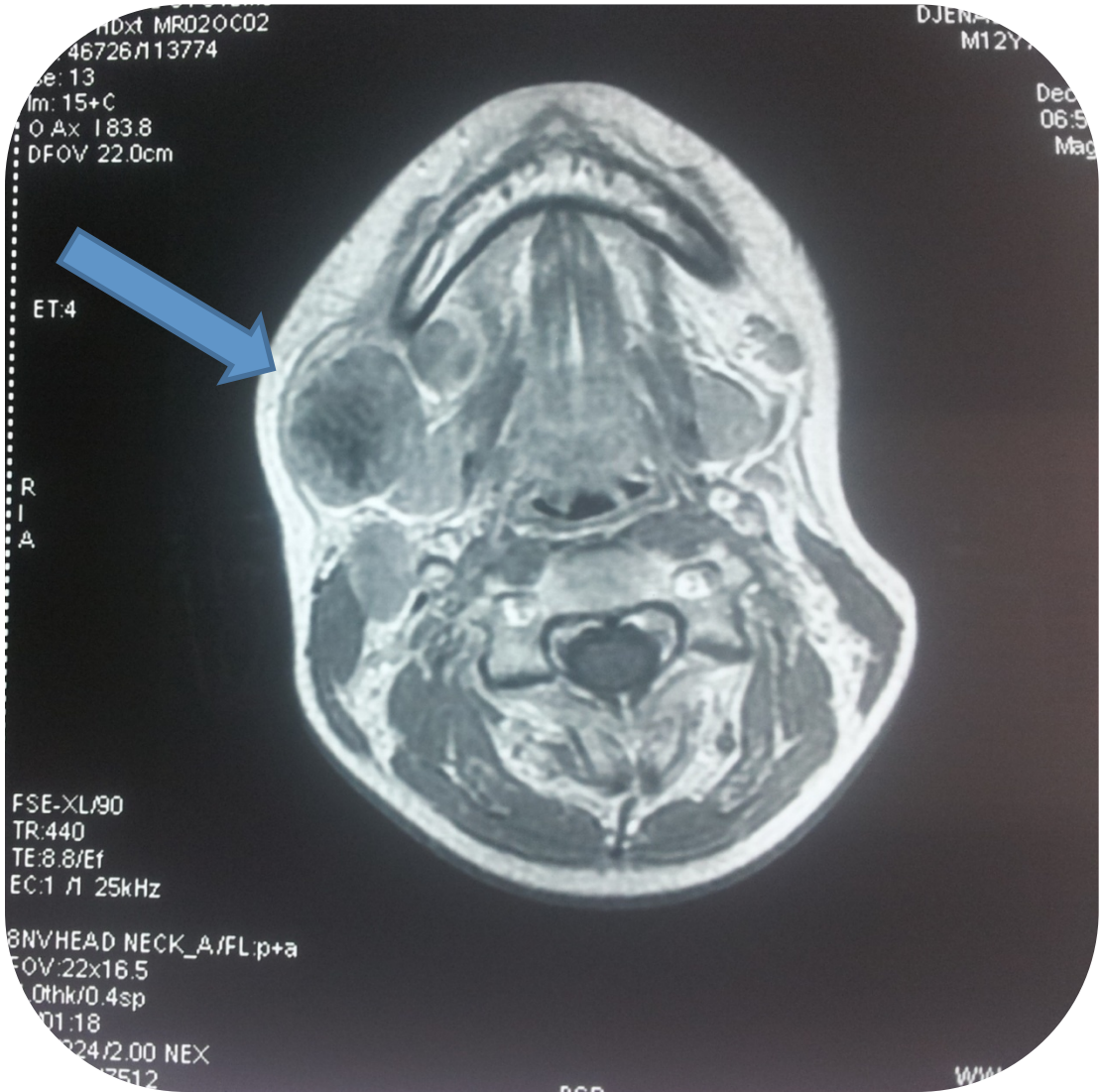
- Le suivi est multidisciplinaire +++

- Les évaluations sont rapportées pendant les réunions de concertation pluridisciplinaire (RCP)

RECURRENCES and METASTASES (1)

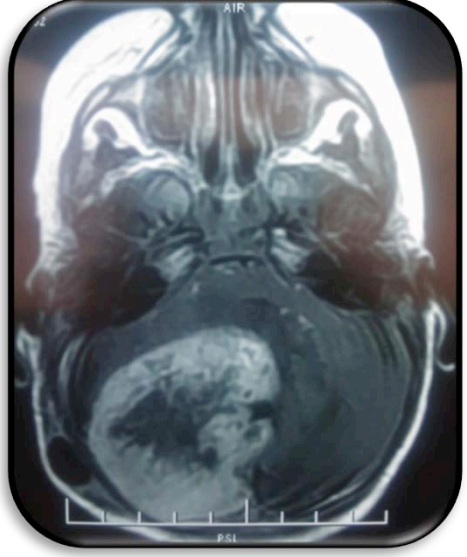
- The majority of patients who had recurrences do so within the first 2 years after presentation.
- Site of recurrence depends on biology: In most instances
  local recurrence in shh
  spinal recurrence in groupe 3
  ependymal metastasis in groupe 4
- High risk biology drive relapse not initial surgery
- Medulloblastoma can rarely spread outside the CNS: 80% of systemic metastases occur in bone or bone marrow, 30% in lymph nodes, 15% in lungs, and 14% in the liver.

EXTRA NEURAL METASTASE
Lymph nodes

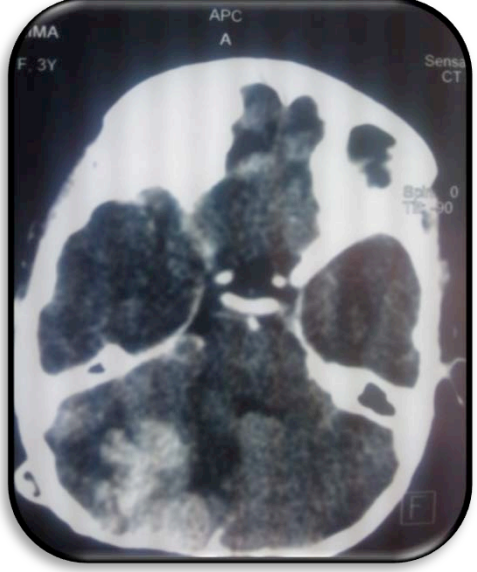


RECURRENCES and METASTASES (2)

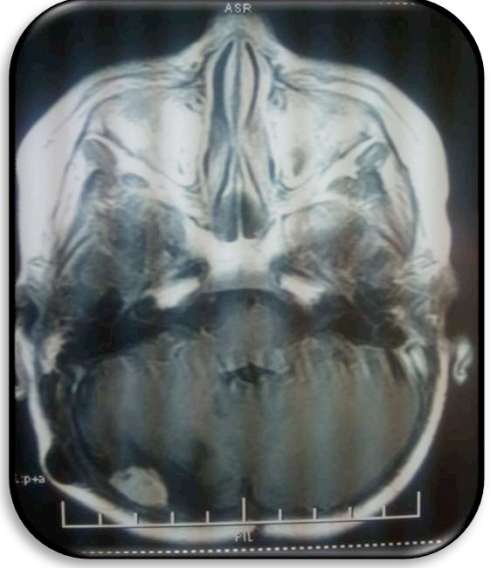
- Are the major barrier to therapeutic success
- Disease recurrence is responsable for 95% of deaths
- Patients who relapsed after upfront RT rarely survive (salvage 10%)
- Group 4 patients seem recur later comparing to other subgroups
- Molecular subgroup affiliation seems to remain stable between tumor at diagnosis and recurrence
- However the genetics is often different (clone seen at diagnosis is different than the one observed at recurrence) ⇒ this may explain the resistances to therapy (target therapy+++) at recurrence



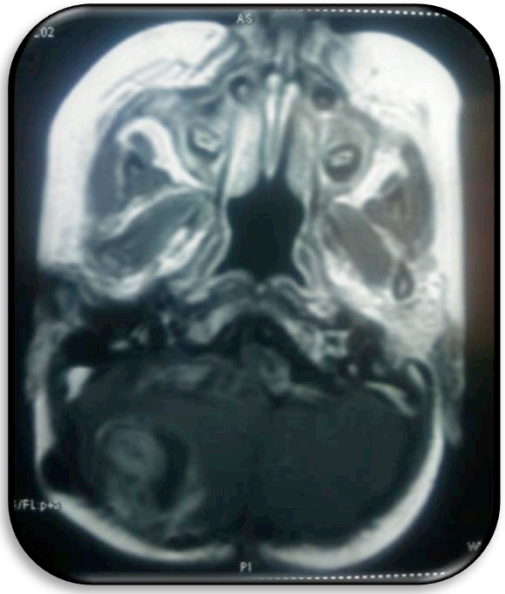
05/2007



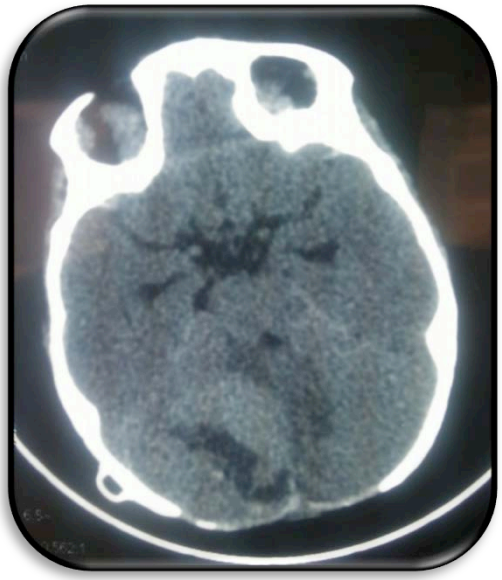
10/2008



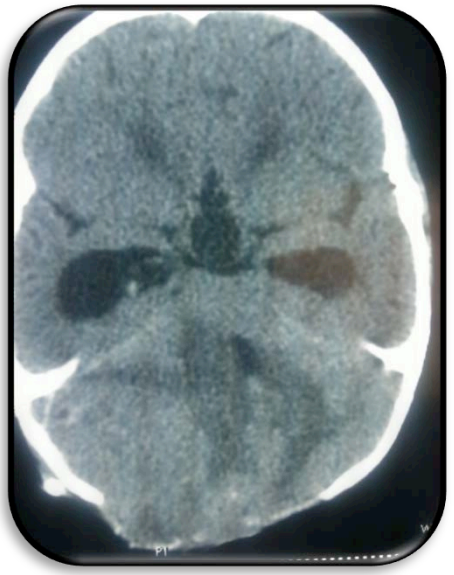
01/2010



05/2010



09/2010



10/2010

Cas personnel avec récidives de plus en plus rapprochées témoignant probablement d'accumulation d'aberrations génomiques pendant les récidives

RECURRENCES and METASTASES (3)

- Treatment of recurrences is still a matter of debate.
- Surgery can be used in local recurrences
- Treatment with a variety of chemotherapeutic agents
- High-dose chemotherapy with stem cell rescue and even bone marrow transplantation have been used with moderate success.
- Target therapy is also used but resistances are often observed (explanation has been given above)
- Conference consensus of Heidelberg:
  recurrent tumors should be biopsied before giving target therapy or if 2 years beyond initial diagnosis to rull out radio-induced malignant glioma

RECURRENCES and METASTASES (4)

- Difficulty of managing recurrent / refractory / progressive medulloblastoma is reflected in the number of clinical trials dedicated to this population
  Current number of trials is 80 (2/3 are still in early phase

OUTCOME

- Standard risk:
  PFS at 5 years = 60 to 80%
  OS reach 95%

- High risk:
  PFS at 5 years = 40 to 70%

PROGNOSIS FACTORS

CLINICAL FACTORS

- Survival correlates strongly with : age at diagnosis, extent of dissemination at the time of diagnosis, and extent of resection.
- Children younger < 3 years have been shown to have a worse outcome; probably because they can’t receive irradiation.
- Duration of symptoms, severity of hydrocephalus, size of tumor, and even invasion of the brainstem have not been shown to correlate with final outcome.

EXTENSION OF SURGERY (1)

- The extent of resection was also found to have an influence on survival.
- It is generally accepted that complete resection is a significant prognosis factor for posterior fossa control.
- Padovani 2007 and Rutowsky 2005 found no adverse impact of postoperative residual tumor in both children and adults??
- It is thought that there is no statistical difference in outcome between a resection of 100% and of 90%
- The limit of 1.5 cm^2 has been fixed at the era of CT but it is till now used??

Published in final edited form as:
Lancet Oncol. 2016 April ; 17(4): 484–495. doi:10.1016/S1470-2045(15)00581-1.

Prognostic Value of Medulloblastoma Extent of Resection After Accounting for Molecular Subgroup: An Integrated Clinical and Molecular Analysis

*First study of extent of resection in era of biology

*No statistical difference between group of GTR and NTR/STR for PFS and OS in Wnt, Shh and group 3

*Statistical difference only in group 4

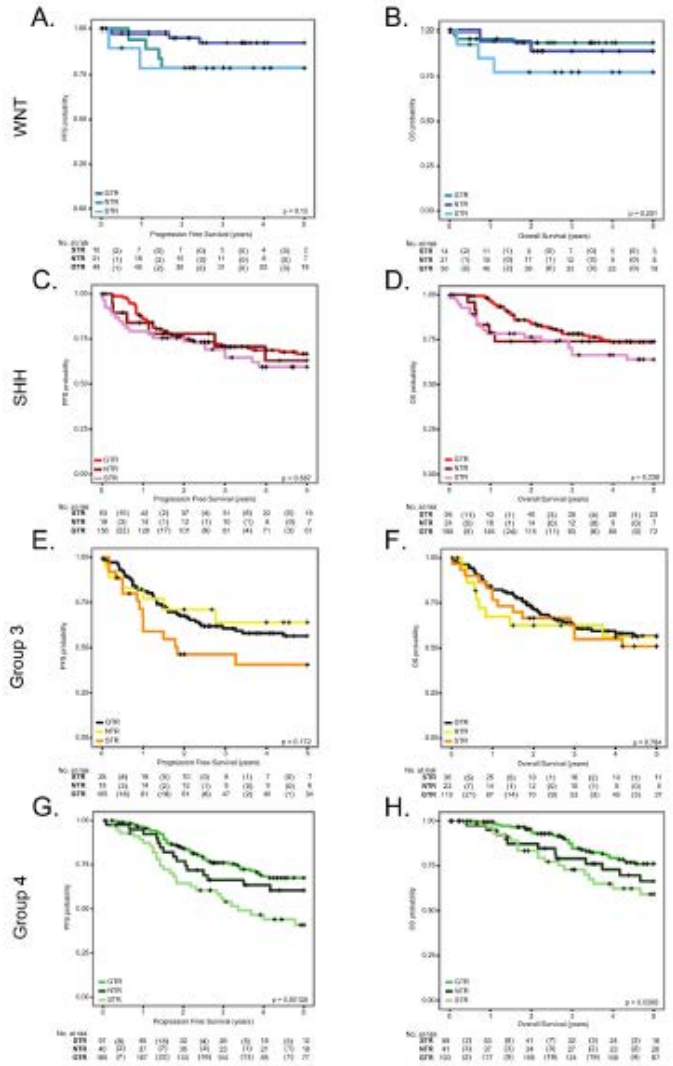
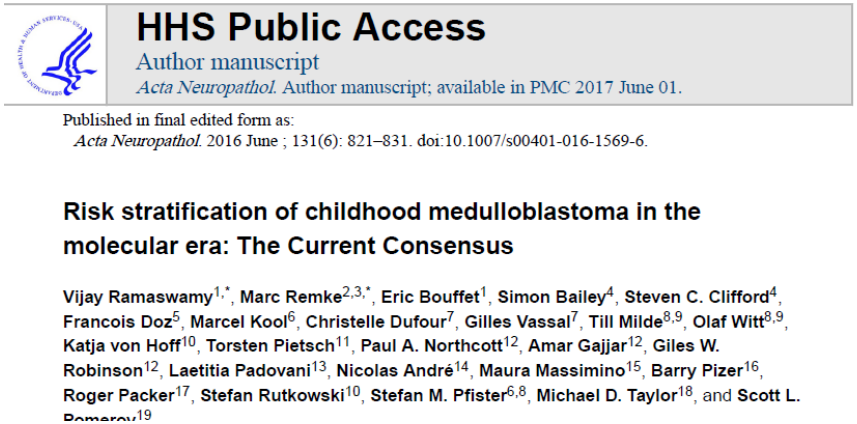


Fig 2.
Five-year PFS and OS survival curves for EOR by subgroup. There was not a significant PFS or OS advantage of those patients that had NTR or STR compared to GTR for the WNT group (A and B), the SHH group (C and D), or Group 3 (E and F). There was an association of increased EOR and both PFS and OS for Group 4 (G and H).

EXTENSION OF SURGERY (2)

- Maximal resection is still a standard

But



Published in final edited form as:
Acta Neuropathol. 2016 June ; 131(6): 821–831. doi:10.1007/s00401-016-1569-6.

Risk stratification of childhood medulloblastoma in the molecular era: The Current Consensus

Vijay Ramaswamy[1,*], Marc Remke[2,3,*], Eric Bouffet[1], Simon Bailey[4], Steven C. Clifford[4], Francois Doz[5], Marcel Kool[6], Christelle Dufour[7], Gilles Vassal[7], Till Milde[8,9], Olaf Witt[8,9], Katja von Hoff[10], Torsten Pietsch[11], Paul A. Northcott[12], Amar Gajjar[12], Giles W. Robinson[12], Laetitia Padovani[13], Nicolas André[14], Maura Massimino[15], Barry Pizer[16], Roger Packer[17], Stefan Rutkowski[10], Stefan M. Pfister[6,8], Michael D. Taylor[18], and Scott L. Pomeroy[19]

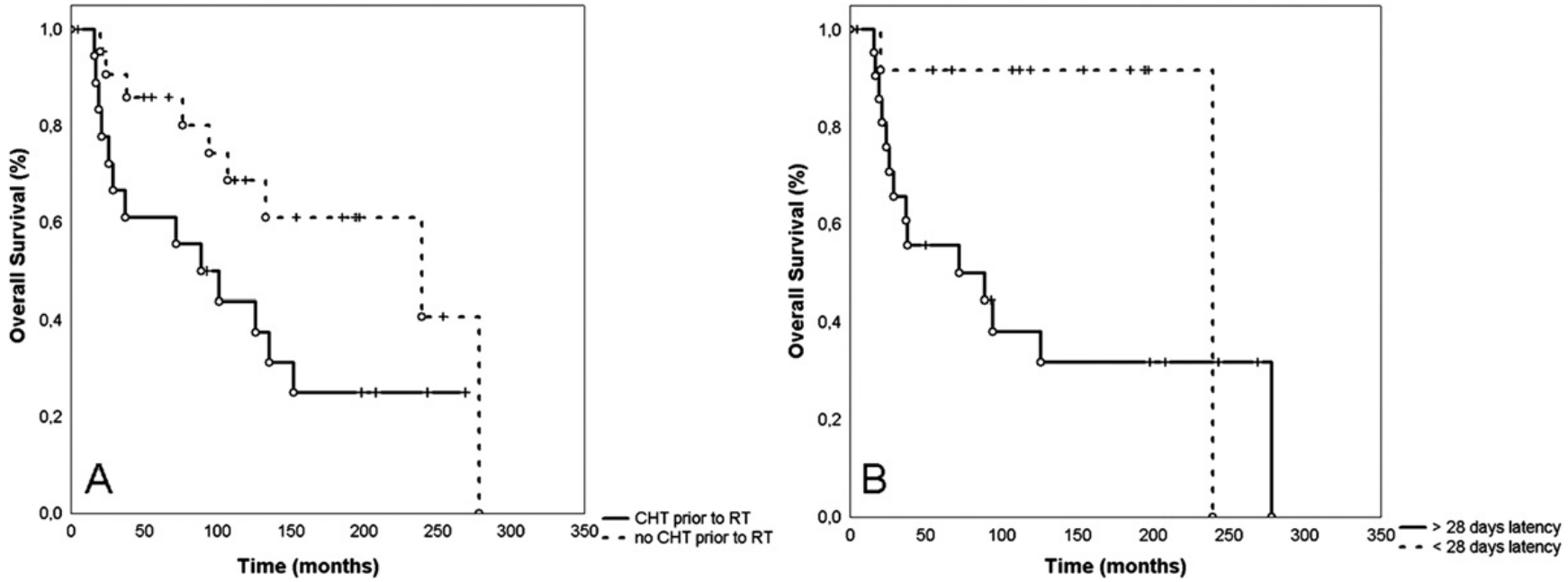
- Without increasing moribidity

- No benefit of GTR (100%) over NTR (near total resection

TIMING OF RADIOTHERAPY (1)

- Early radiotherapy is associated with improved outcome (Rieken 2011).

TIMING OF RADIOTHERAPY (2)



Neoadjuvant preirradiation chemotherapy.
(A) Overall survival is significantly reduced in children after preirradiation chemotherapy (CHT; p = 0.04).
(B) Overall survival is significantly reduced if more than 28 days elapse between surgery and initiation of radiotherapy (RT; p = 0.02).

TIMING RADIOTHERAPY (2)

Neuro-Oncology

20(8), 1133–1141, 2018 | doi:10.1093/neuonc/noy001 | Advance Access date 4 January 2018

Survival impact of postoperative radiotherapy timing in pediatric and adolescent medulloblastoma

Alexander L. Chin,* Everett J. Moding,* Sarah S. Donaldson, Iris C. Gibbs, Scott G. Soltys, Susan M. Hiniker,# and Erqi L. Pollom#

- Early RT ≤ 03 months is associated with decreased of OS at 5 years

- No adverse outcome on OS when RT initiated after 5 weeks but within 90 days

BIOLOGIC FACTORS (1)

- Ellison 2010, 207 samples of medulloblastomas
  *Wnt activation pathway, monosomy 6 marked a subset of tumors with excellent prognosis
  *c-MYC amplification was found in subset of patients with poor event free and overall survival.
- Cho 2010, 194 samples
  *Wnt pathway-active = excellent prognosis
  *Hh pathway-active = good prognosis
  *c-MYC-amplification = poor prognosis
- Northcott 2009, 103 samples
  Wnt subtype = excellent outcome
  Hh subtype = good prognosis
  c-MYC amplification = metastatic disease and poor prognosis
  fourth subtype = fair prognosis

BIOLOGIC FACTORS (2)

- Northcott identify a specific molecular marker – a signature gene- for each subgroup;
- P53 expression correlated with poor outcome.
- Worse survival with 50% c-erb-2-positive tumor cells.
- HER 2 et HER 4 coexpression correlated with improved survival.

BIOLOGIC FACTORS (3)

- Possibilité d’une accumulation des aberrations génomiques durant la progression clinique

QUALITY OF LIFE (1)

- Significant concerns regarding the quality of life following treatment are now being addressed.
- Neurocognitive, endocrine, and skeletal sequelae have been well documentated.
- Children < 7 years of age have substantially greater loss of intellectual function and drop in IQ scores.
- As many as 80 to 90% of children who survive their tumors have serious neurocognitive sequelae discovered upon psycometric testing.
  Similary, pituitary dysfunction occurs and most children require endocrine replacement therapy.

QUALITY OF LIFE (2)

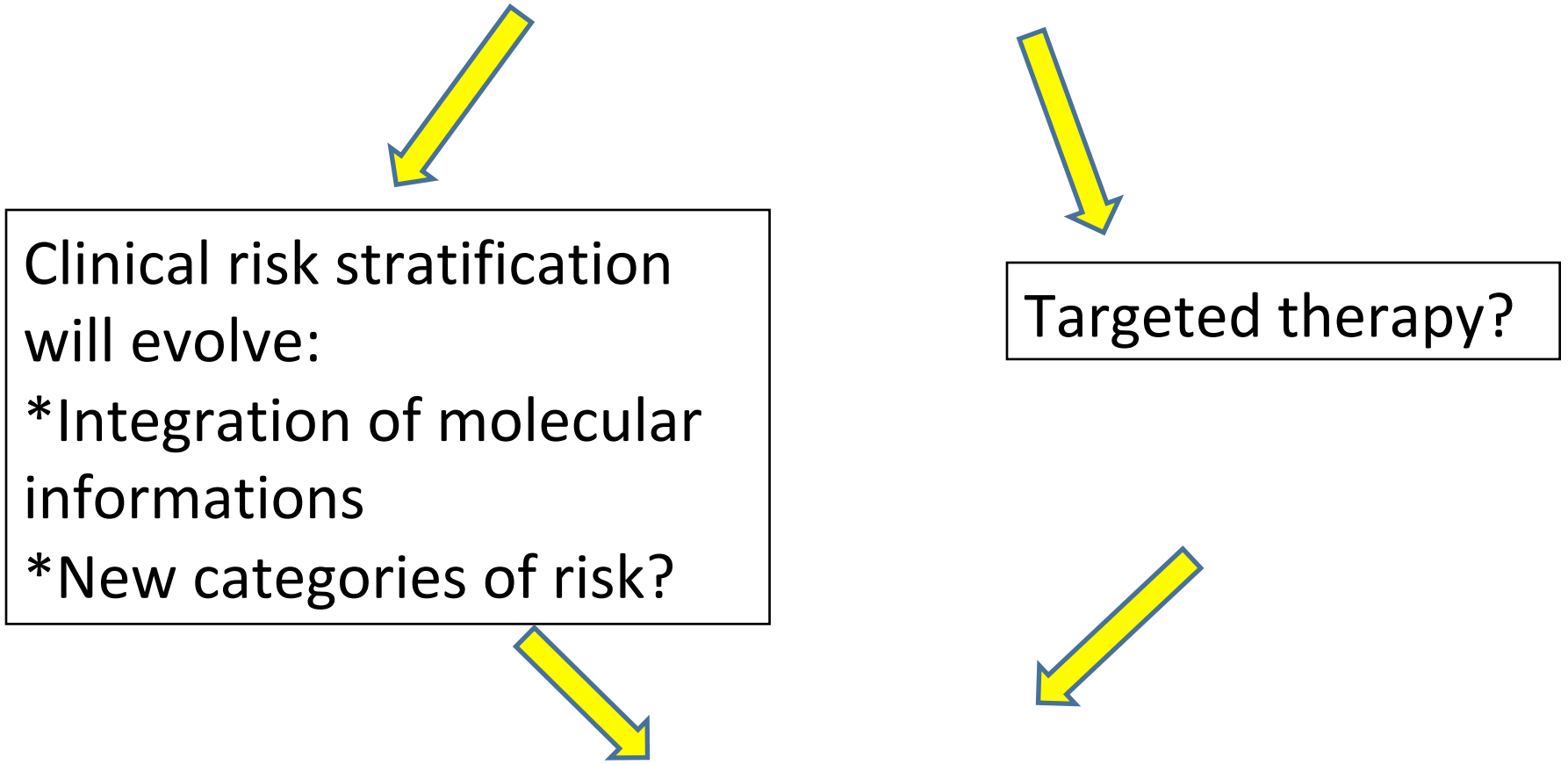
- Otoxicity, neurotoxycity, and leukoencephalopathy have also reported with chemotherapy.
- Studies suggest that psychometric testing would best assess the long-term cognitive effects of all therapy.
- There is some indication that children treated with chemotherapy alone had significantly less decline in neurocognitive function than those treated with radiation therapy, though their scores still remained bellow age-matched controls.

QUALITY OF LIFE (3)

- Clinical trials over last 20 years did not include functional and quality of life measures
- Most of studies include suboptimal and inconsistant evaluations
- Early evidence suggests that quality of life may be related to tumor clinico-biological features

PERSPECTIVES

Implications of Advances in Molecular Biology



- Medulloblastomas with good prognosis are probably over treated ⇨ may be patients could be spared from certain complications by reducing their treatment.
- Medulloblastomas with poor prognosis die in spite an agressive treatment ⇨ reduction of therapies may improve quality of life without modification of prognosis.

Pediatr Blood Cancer 2014;61:1300–1304

De-escalation of Therapy for Pediatric Medulloblastoma: Trade-Offs Between Quality of Life and Survival

PERSPECTIVES
Risk Stratification (1)

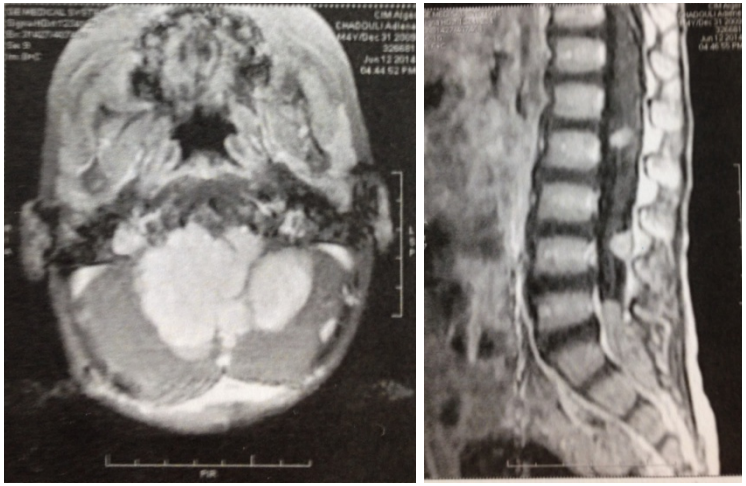
- The classic system of staging is anachronic.
- Bio-pathologic criteria must be integrated in the classification of patients.
- The first protocol who integrated bio-pathologic criteria is European protocol PNET 5 LR and SR.

PERSPECTIVES
Risk Stratification (2)

- Current ongoing trials use the risk stratification proposed by the consensus conference of Heidelberg
- The use of > 1.5 cm^2 as a marker for high risk requiring intensified craniospinal irradiation clearly needs to be questioned and re-evaluated in future clinical trials (conference of Heidelberg)

PERSPECTIVES
Extension of Resection

- Will we operate all medulloblastomas samely?
- Probably not! May be new paradigms of surgery
- Limit of 1.5 cm^2??
- May be some tumors will benefit of limited resection (preservation of quality of life)? But nothing is validate till now!

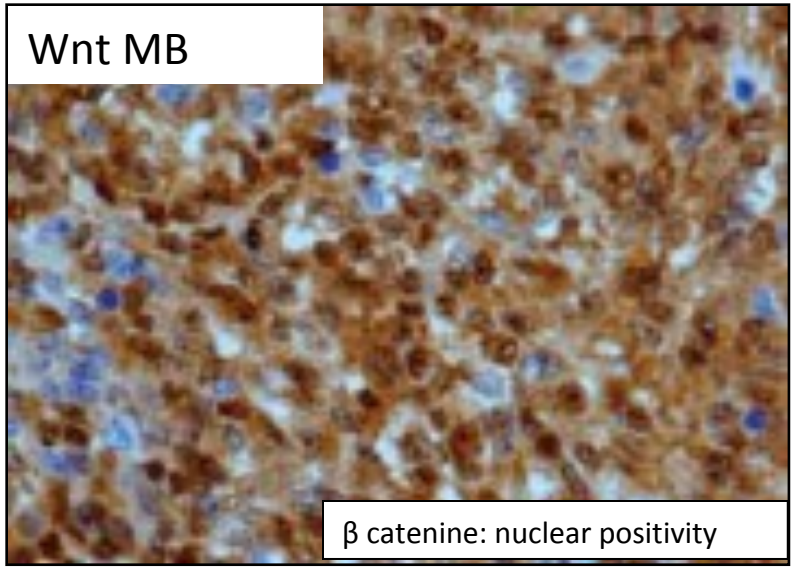


Bouyoucef et coll. Minimally invasive skull base surgery Principles and Practice Ed Berhouma M Nova Science Publisher 2013: 311-324

PERSPECTIVES
Reducing Doses of Irradiation?

Étude PNET 5 : étude de phase 2-3, randomisée et multicentrique évaluant le taux de survie sans événement chez des enfants de plus de 5 ans ayant un médulloblastome de risque standard avec un profil biologique de faible risque (PNET 5 MB-LR) ou de risque moyen (PNET 5 MB-SR).

Étude internationale concernant les enfants de plus de 5 ans atteints de médulloblastome de risque standard avec profil biologique de faible risque (PNET 5 MB-LR) ou de risque moyen (PNET 5 MB-SR).



Arms	Assigned Interventions
Experimental: PNET 5 MB-LR (low-risk) Radiotherapy and reduced-intensity maintenance chemotherapy. Total treatment duration is 39 weeks.	Radiation: Radiotherapy without Carboplatin Brain - 23.40 Gy in 13 daily fractions of 1.80 Gy Spine - 23.40 Gy in 13 daily fractions of 1.80 Gy Primary tumour boost - 30.60 Gy in 17 daily fractions of 1.80 Gy Total dose - 54 Gy Duration of radiotherapy 6 weeks LR Arm after Amendment (Protocol version 11- 17 Nov 2014): Brain - 18.0 Gy in 10 daily fractions of 1.80 Gy Spine - 18.0 Gy in 10 daily fractions of 1.80 Gy Primary tumour boost - 36.0 Gy in 20 daily fractions of 1.80 Gy Total dose - 54 Gy Duration of radiotherapy 6 weeks Drug: Reduced-intensity maintenance chemotherapy Starts 6 weeks after radiotherapy. 6 cycles alternating Regimen A and Regimen B. Regimen A (cycles 1, 3, 5): cisplatin 70 mg/m2 day 1, CCNU 75 mg/m2 day 1, vincristine 1.5 mg/m2 days 1, 8 and 15, Regimen B: (cycles 2, 4, 6): cyclophosphamide 1 x 1000 mg/m2 days 1-2, vincristine 1.5 mg/m2 day 1. Interval after cycle A: 6 weeks, after cycle B: 3 weeks, for a total duration of 27 weeks. Cumulative doses of chemotherapy drugs: cisplatin 210 mg/m2, lomustine (CCNU) 225 mg/m2, vincristine 18 mg/m2, cyclophosphamide 6 g/m2. Other Names: • Cisplatin • Lomustin (CCNU) • Vincristine • Cyclophosphamide

PERSPECTIVES
Chemotherapy alone as adjuvant therapy?

- Shh Medulloblastomas with desmoplastic histological type treated before age of 3 years
- Intrathecal chemotherapy


VOLUME 28 · NUMBER 33 · NOVEMBER 20 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Survival and Prognostic Factors of Early Childhood Medulloblastoma: An International Meta-Analysis

Stefan Rutkowski, Katja von Hoff, Angela Emser, Isabella Zwiener, Torsten Pietsch, Dominique Figarella-Branger, Felice Giangaspero, David W. Ellison, Maria-Luisa Garre, Veronica Biassoni, Richard G. Grundy, Jonathan L. Finlay, Girish Dhall, Marie-Anne Raquin, and Jacques Grill

Medulloblastoma—translating discoveries from the bench to the bedside

Gajjar, A. J. & Robinson, G. W. *Nat. Rev. Clin. Oncol*. **11**, 714–722 (2014);

PERSPECTIVES
Chemotherapy alone as adjuvant therapy ? (2)

26 Neuro-Oncology
20(8), 1026–1033, 2018 | doi:10.1093/neuonc/nox222 | Advance Access date 15 November 2017

Desmoplastic nodular medulloblastoma in young children: a management dilemma

Mohamed S. AbdelBaki, Daniel R. Boué, Jonathan L. Finlay, and Mark W. Kieran

German HIT trial showed good results in desmoplastic nodular treated without intensive chemotherapy and without radiation
BUT
ACNS 1221 clinical trial initiated in 2013 has been closed regarding high incidence of recurrences

Analysis of 188 patients enroled in 11 prospective trials: it seems that we are in need of further trials to validate the need or not of irradiation in desmoplastic nodular medulloblastomas

PERSPECTIVES
TARGET THERAPY (1)

- SMO inhibition with vismodegib: seems to be efficient only in Shh medulloblastomas with mutations in PTCH1
- SMO inhibitors could lead to premature fusion in children
- Shh medulloblastomas with SUFU or GLI1 mutations do not respond to vismodegib

PERSPECTIVES
TARGET THERAPY (2)

- Recent therapeutic approach refers to epigenetic treatment with bromodomain (BET) inhibitors
- BET inhibitors have been shown in vitro and in vivo to decrease cell viability and proliferation in Shh meduloblastomas
- MET inhibitor foretenib: strong rationale for its clinical evaluation in Shh metastatic medulloblastomas (for which MET kinase is a marker)

PERSPECTIVES
TARGET THERAPY (3)

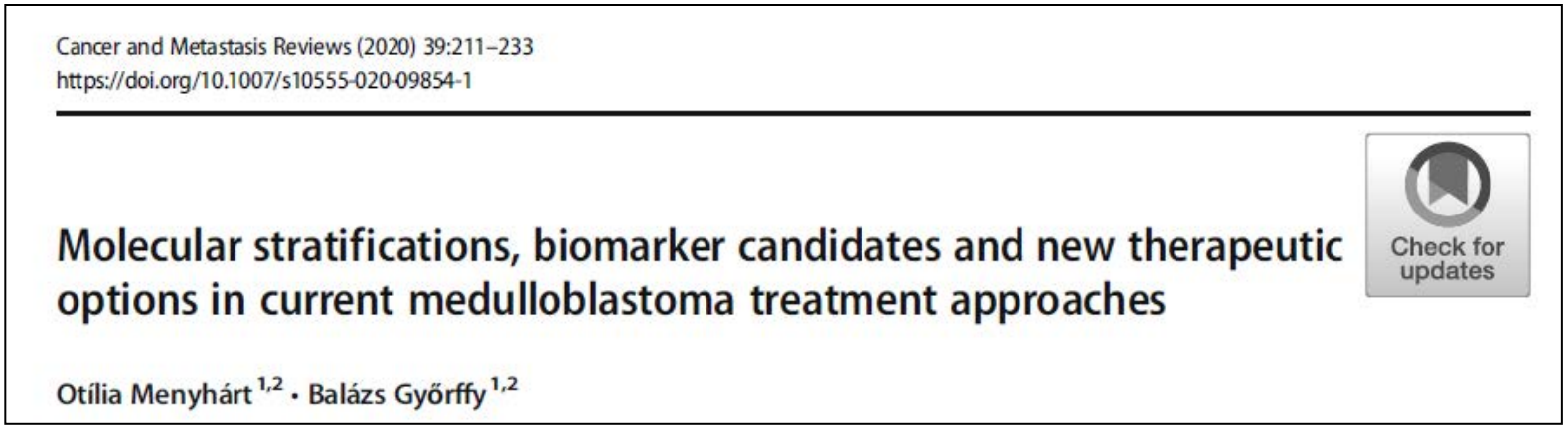
- For group 3:
  Efforts have been made concerning MYC inhibition but no direct MYC inhibitor could successfully be finalized
  A clinical trial showed the efficacy of using HDAC with P13K inhibitor in group 3 with MYC amplification
  BET inhibitors also represent a significant therapeutic approach

PERSPECTIVES
TARGET THERAPY (4)

- Other ongoing therapeutic approach = targeting medulloblastoma stem cells
- Medulloblastoma stem cells are a subpopulation of cancer cells largely responsible for medulloblastoma initiation, maintenance, dissemination, and relapse

PERSPECTIVES
Immunotherapy

- Proportion of targeted and immunotherapies in recurrent and refractory medulloblastomas is increasing comparing to cytotoxic strategies
- Immune therapies utilize a wide range of options:
  Immune check point inhibitors
  CAR-T therapies
  NK-cells
  Oncolytic viruses


Cancer and Metastasis Reviews (2020) 39:211–233
https://doi.org/10.1007/s10555-020-09854-1

Molecular stratifications, biomarker candidates and new therapeutic options in current medulloblastoma treatment approaches

Otília Menyhárt [1,2] · Balázs Győrffy [1,2]

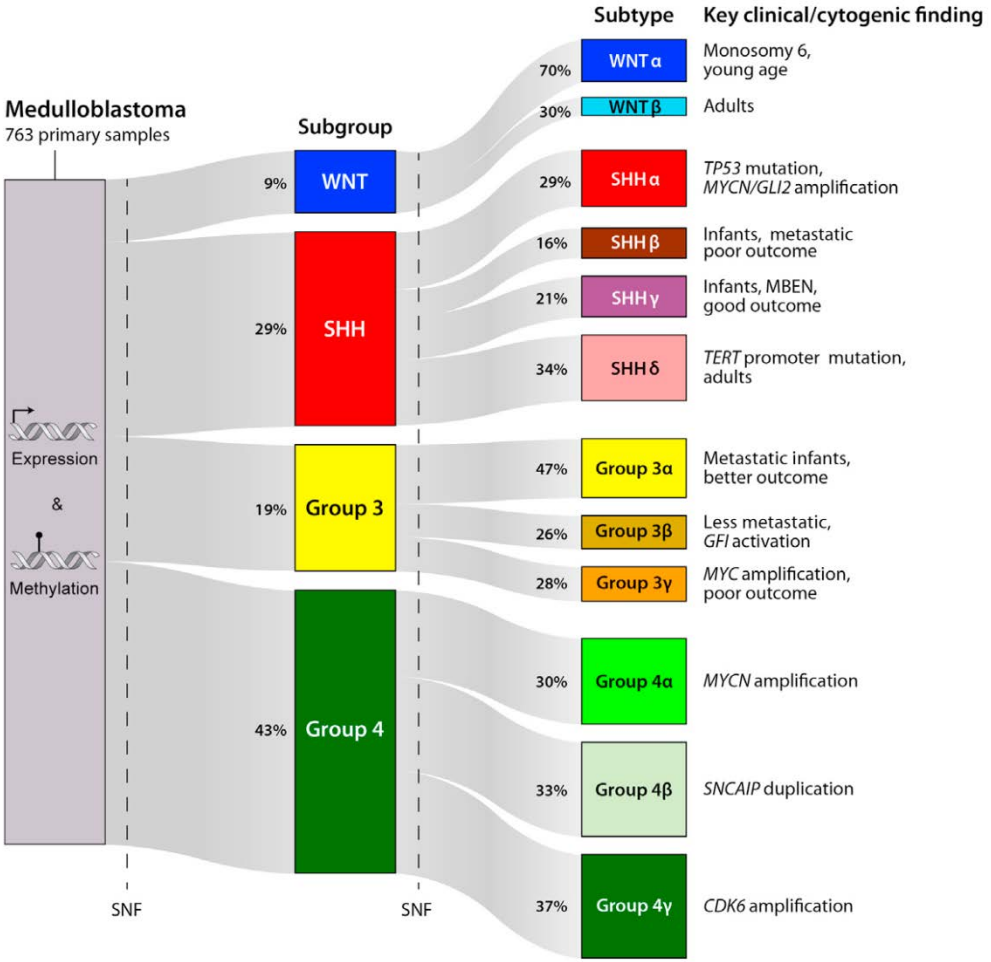
Check for updates

Things Get More Complicated
12 subgroups!

Article

Cancer Cell

Intertumoral Heterogeneity within Medulloblastoma Subgroups



PERSPECTIVES

Medulloblastomics revisited: biological and clinical insights from thousands of patients

Volker Hovestadt[1,2], Olivier Ayrault[3,4], Fredrik J. Swartling[5], Giles W. Robinson[6], Stefan M. Pfister[7,8,9] and Paul A. Northcott[10]*

Nat Rev Cancer 2020; 20 (1): 42-56

PERSPECTIVES

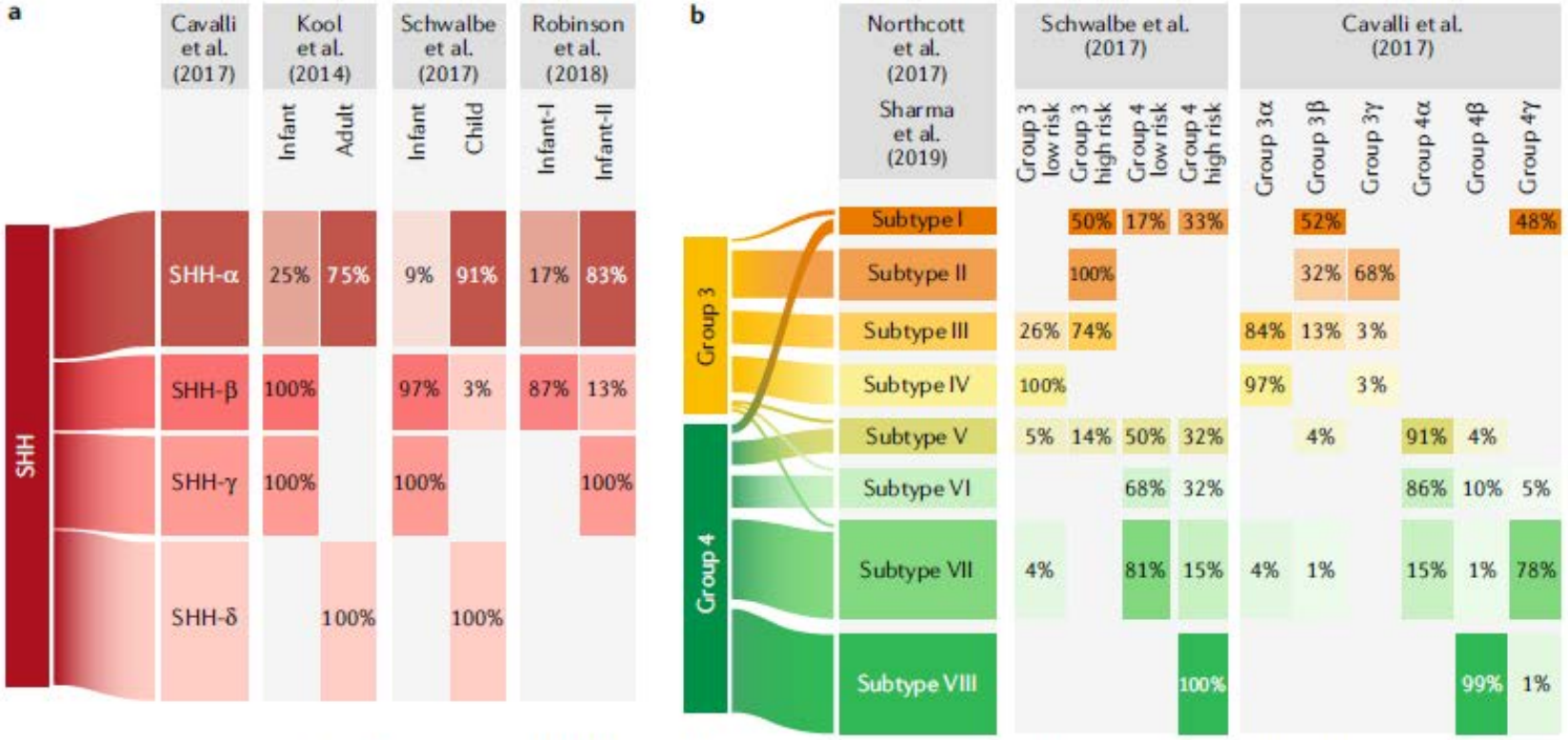
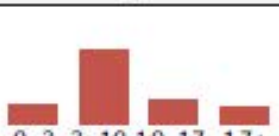
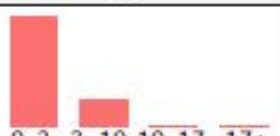
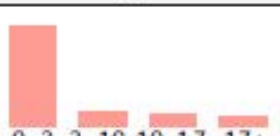
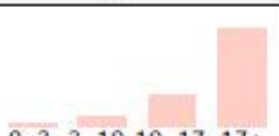
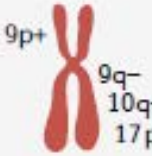
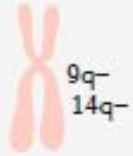
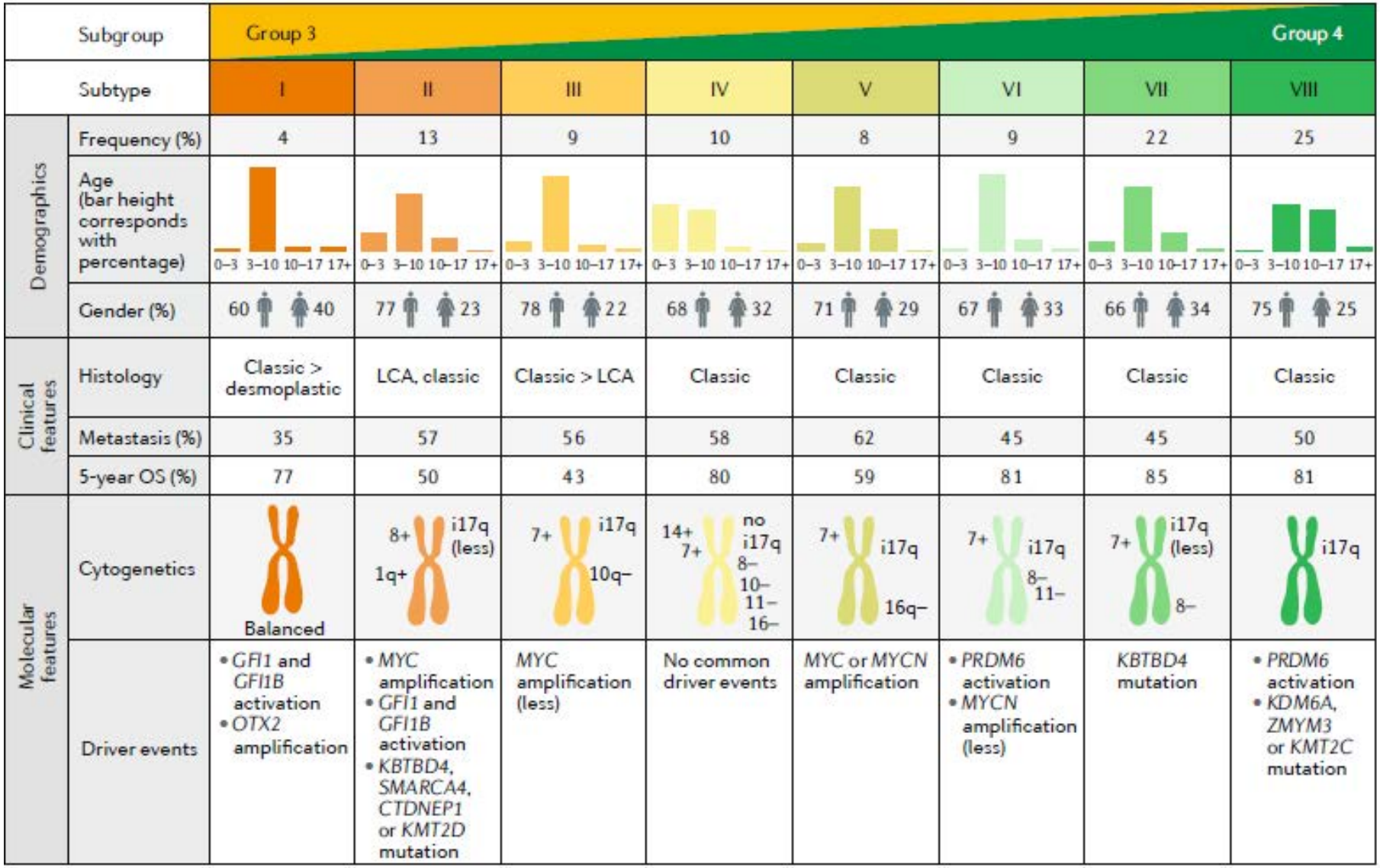


Fig. 1 | **Comparison of MB DNA methylation-derived subtypes described across recent studies. a** | Correspondence between the four molecular subtypes of the Sonic hedgehog medulloblastoma (SHH-MB) subgroup, described by Cavalli et al.[29] ($n = 223$ samples) and the subtypes described in three additional studies (Kool et al.[38], $n = 129$ samples; Schwalbe et al.[31], $n = 103$ samples; Robinson et al.[44], $n = 82$ samples). DNA methylation profiles from all samples of each additional study were used to classify patients into the four molecular subtypes using a machine-learning approach. The height of each row corresponds to the fraction of samples per subtype in the Cavalli et al. study[29] (SHH-α = 29%; SHH-β = 16%; SHH-γ = 21%; SHH-δ = 34%). Percentages indicate overlap of the predicted subtypes with the original subtype annotations in each additional study. The samples from the study by Robinson et al.[44] were not predicted as SHH-δ, consistent with the study including only patients under the age of 6 years. **b** | A similar comparison of the eight molecular subtypes of Group 3 and Group 4 MB described by Northcott et al.[30] and Sharma et al.[134] ($n = 1,370$ samples; subtype: I = 4%, II = 13%, III = 9%, IV = 10%, V = 8%, VI = 9%, VII = 22%, VIII = 25%) and the subtypes described in two additional studies (Schwalbe et al.[31], $n = 273$ samples; Cavalli et al.[29], $n = 470$ samples). The line widths between the two consensus subgroups (Group 3 and Group 4) and the eight DNA methylation subtypes indicate the fraction of samples per subtype that were originally classified as Group 3 or Group 4 MB.

PERSPECTIVES

	Subgroup	WNT	SHH			
	Subtype		α	β	γ	δ
Demographics	Frequency (%)	100	29	16	21	34
	Age (bar height corresponds with percentage)					
	Gender (%)	45 55	63 37	47 53	55 45	69 31
Clinical features	Histology	Classic	Classic > desmoplastic > LCA	Desmoplastic > classic	Desmoplastic > MBEN classic	Classic > desmoplastic
	Metastasis (%)	12	20	33	9	9
	5-year OS (%)	98	70	67	88	89
Molecular features	Cytogenetics					
	Driver events	*CTNNB1*, *DDX3X* or *SMARCA4* mutation	• *MYCN* or *GLI2* amplification • *TP53* mutation • *PTCH1* mutation (less)	• *PTCH1* or *KMT2D* mutation • *SUFU* mutation/ deletion • *PTEN* deletion	• *PTCH1*, *SMO* or *BCOR* mutation • *PTEN* deletion	• *PTCH1* mutation • *TERT* promoter mutation

PERSPECTIVES



PERSPECTIVES

- Some are against use of such complicated molecular classification
  - BUT
- It can reduce the health cost (toxicities of treatment) for a subset of patients

PERSPECTIVES

Cancer and Metastasis Reviews (2020) 39:211–233
https://doi.org/10.1007/s10555-020-09854-1

Molecular stratifications, biomarker candidates and new therapeutic options in current medulloblastoma treatment approaches

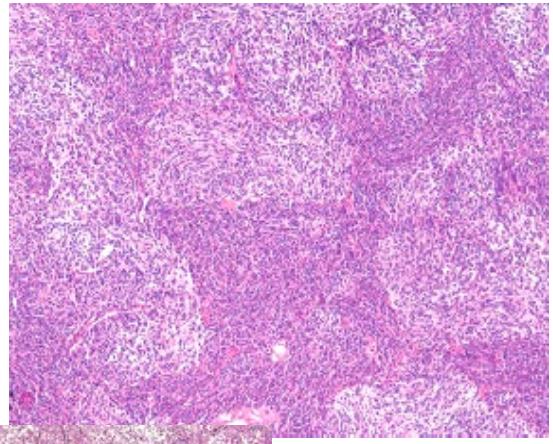
Otília Menyhárt [1,2] · Balázs Győrffy [1,2]

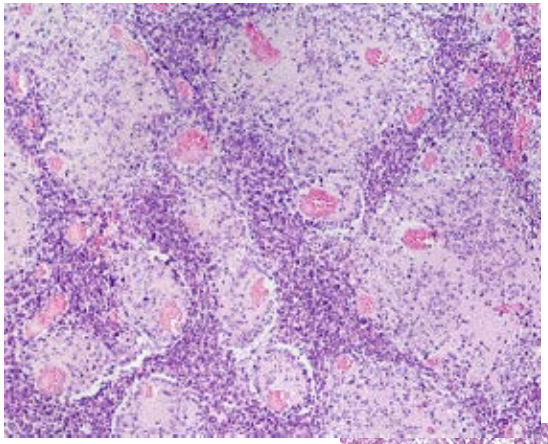
Check for updates

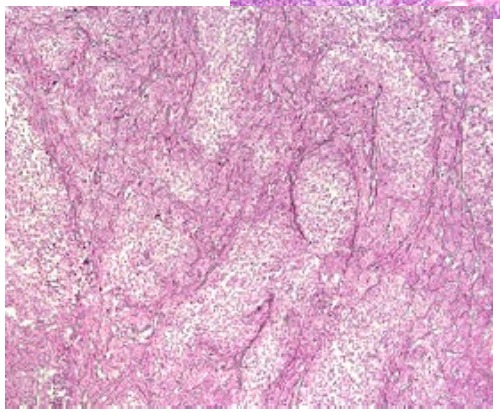
In this article are summerized all trials with new protocols of treatment based on molecular stratification

SITUATION ACTUELLE EN ALGERIE

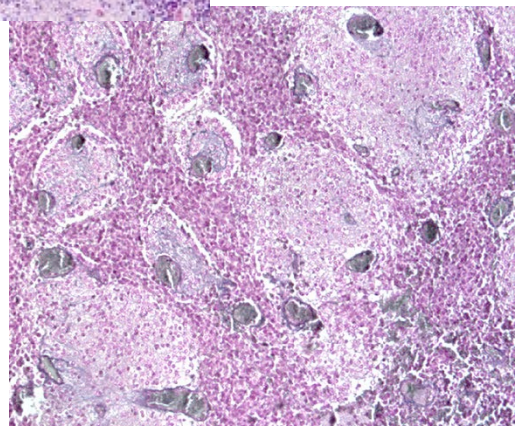
Médulloblastome désmoplasique # Médulloblastome classique avec nodules pales







Réticuline



Actuellement pas de coloration au sel d'argent en Algérie!!!
La différence est importante à faire car les pronostics sont totalement différents

CURRENT SITUATION IN ALGERIA

Immunohistochemical markers needed

- β catenin
- GAB1
- Yap1
- P53
- p-77NGFR

Immunohistochemical markers available

- β Catenin
- GAB1
- Yap1
- P53

Genetic Profile

non WNT/ non SHH # groupe3 / groupe4

FISH (amplification MYC), CGH array are not available for medulloblastoma

CHALLENGES FOR ALGERIA

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LES MEDULLOBLASTOMES A L'ERE DE LA BIOLOGIE MOLECULAIRE : UN CHALLENGE POUR L'ALGERIE ?

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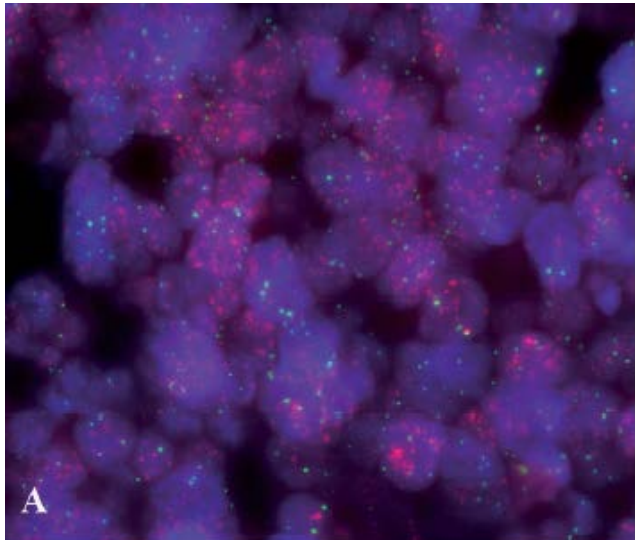
Il est impératif que les techniques de biologie moléculaire soient totalement intégrées dans le diagnostic des médulloblastomes

SINON

Nous serons dans l'incapacité de traiter nos patients selon les protocoles basés sur les données moléculaires!

Les choses évoluent rapidement et nous devons nous adapter dans le but de traiter correctement nos patients!



TAKE MESSAGE HOME (1)

- Medulloblastomas are a heterogeneous disease.
- Most frequent malignant brain tumor in children
- Diagnosis requires histologic confirmation using WHO CNS tumors classification 2016
- Spinal MRI is better performed in preoperative
- Management needs a multidisciplinary team+++

TAKE MESSAGE HOME (2)

- Use of pre operative ETV is helpful BUT keep in mind that only 30% of patients will require a permanent internal CSF diversion
- Preoperative EVD with maintaining in postoperative period is a good option
- Large resection is very important
- If tumor invades crucial structures do not attempt GTR

TAKE MESSAGE HOME (3)

- Position assise vs position ventrale?
- Craniectomie vs craniotomie? Tendance actuelle = craniotomie
- Ouverture de C1? Absolument pas nécessaire
- Pas de désinsertion musculo-aponévrotique au-delà de C1 (risque d'instabilité rachidienne après irradiation spinale).
- Abord télo-vélaire vs vermiectomie (syndrome de la FCP?). Aucune confirmation que la vermiectomie est la cause du syndrome de la FCP

TAKE MESSAGE HOME (4)

- Possterior fossa syndrome is not rare and probably underdiagnosed currently

TAKE MESSAGE HOME (4)

- A second surgery should be considered if large, accessible residual tumor is found on postoperative scanning, which should be done within 48 hours of surgical resection.
- Tumor banking has important implications for future treatment protocols and should be done as much as possible as part of cooperative trials.

TAKE MESSAGE HOME (5)

- Use of WHO CNS Tumors Classification 2016
- Medulloblastoma vs ATRT +++
- Molecular subgroups+++
- Risk stratification before adjuvant therapy+++

TAKE MESSAGE HOME (6)

- Standard adjuvant therapy = Irradiation + Chemotherapy
- Infants < 03 years are treated by chemotherapy given high side effects of irradiation
- Close monitoring after treatment is mandatory to detect side effects and potential recurrence and/or metastases

TAKE MESSAGE HOME (7)

- Age at time of diagnosis, extent of resection, tumor dissemination, histology, and biologic parameters are the factors that correlate with long-term survival from medulloblatoma.
- Trend is towards personalized treatment +++.
- In the futur treatment will focus on:
  Tumor itself for Wnt group
  Tumor and local recurrence for Shh group
  Tumor and metastases for group 3
  Tumor, recurrence and metastases for group 4

TAKE MESSAGE HOME (8)

- Big attention is given to develop target therapy and immunotherapy in hope to reduce the cytotoxic treatment (irradiation and chemotherapy)
- Neurosurgeons must know exactly the biology of medulloblastomas because it has a major impact on outcome of patients and it may in the future guide the extension of resection
- Neurosurgeons who are dealing with medulloblastomas (or other tumors) are neurooncologists as the other specialists such as medical oncologists, radiotherapists etc…..

TAKE MESSAGE HOME (9)

- The current challenge for neurooncologists is precision medicine
- Iatrogenic morbidity is a matter of concern
- We must avoid the overtreatment of patients with good pronosis
- Agressive treatment should be reserved to patients with worse prognosis factors
- New therapeutic approaches must be developed to improve survival rates in treatment patients

TAKE MESSAGE HOME (10)

- Keep in mind that OS at 5 years reach 95% in standard risk
- Prognosis is excellent in Wnt group

- We should pais attention to quality of life+++

MULTIDISCIPLINARITY IS MANDATORY!