CHAPTER FIVE

Medulloblastoma chapter - past perspectives and future directions

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Abstract

Medulloblastoma, once considered a uniform entity, is now accepted as a complex and heterogeneous group of tumors requiring a nuanced and multidisciplinary approach to diagnosis and treatment. The now four recognized primary subgroups have distinct genetic, epigenetic, and clinical characteristics that influence prognosis and treatment responses necessitating subgroup-specific strategies.

Advances in diagnostics and risk stratification, largely driven by a deeper understanding in tumor biology, has led to an overall improvement in survival (>70 %), through risk-adapted treatment strategies. Contemporary clinical approaches incorporate a multimodality treatment strategy, integrating surgery, radiotherapy and intensive chemotherapy, each of which is associated with significant short- and long-term morbidity.

Novel targeted therapeutics continue to be developed, investigated and explored in vitro, in vivo and through clinical trial design, particularly in the high risk and relapsed settings. As the therapeutic landscape continues to evolve, combining conventional therapies with these approaches holds promise to improve clinical outcomes.

These innovations and developments expanding all disciplines aim to continue to provide precision-based care and enhance survival outcomes across all subgroups whilst mitigating the significant long-term burden of treatment-related sequelae disproportionately experienced by medulloblastoma survivors.

Abbreviations

AAAIR annual age-adjusted incidence rate.
ADC apparent diffusion coefficient.
AI Artificial Intelligence.
ASCR autologous stem cell rescue.
BBB Blood brain barrier.
CAR-T chimeric antigen receptor T.
CCSS Childhood Cancer Survivor Study.
cfDNA circulating cell free tumor DNA.
CMS cerebellar mutism syndrome.
COG Children's Oncology Group.
CSF cerebrospinal fluid.
CSI craniospinal irradiation.
CT Computed tomography.
DWI Diffusion-weighted imaging.
EFS event free survival.
EOR extent of resection.
EVD External ventricular drain.
FLAIR fluid attenuated inversion recovery.
GTR Gross total resection.
HART hyperfractionated-accelerated radiotherapy.
HDAC Histone deacytlase (HDAC).
HDC High dose chemotherapy (HDC).

IHC	immunohistochemistry.
IONM	intraoperative use of neuromonitoring.
LCA	Large cell/Anaplasia.
MB	medulloblastoma.
MBEN	medulloblastoma with extensive nodularity.
MRD	minimal residual disease.
MRI	Magnetic resonance imaging.
NAC	N-acetylaspartate.
ND	desmoplastic nodular medulloblastoma.
NTR	Near total resection.
OS	Overall survival.
PFS	progression free survival.
RAPNO	Response Assessment in Pediatric Neuro-oncology Committee.
rMB	Relapsed medulloblastoma.
SHH	Sonic hedgehog.
SMN	Second malignant neoplasm.
SNHL	sensorineural hearing loss.
STR	subtotal resection.
VEGF	vascular endothelial growth factor.
WHO	CNS5 5th edition of the World health organisation central nervous system classification.
WNT	Wingless/INT1.

1. Introduction

Medulloblastoma (MB) is the most common malignant brain tumor in children and young people aged 0–19 years, accounting for approximately 20 % of all brain tumors and 70 % of all embryonal tumors in this age group, with the average annual age-adjusted incidence rate (AAAIR) (with approximately 6 cases per year in 100,000) (Ostrom et al., 2023; Price et al., 2024). Through integrated genomics, our understanding of MB has radically transformed in the past two decades recognizing tumor heterogeneity with biological, clinical, therapeutic and prognostic implications (Lazow et al., 2022). Diagnosis, treatment strategies and prospective clinical trial design for patients with MB are now heavily influenced by the tumor molecular profile in addition to historic risk-factors including age, stage and morphology such as presence of large cell/anaplasia (LCA). Four consensus molecular subgroups are now accepted– WNT (MB_{WNT}), SHH (MB_{SHH}), Group3 (MB_{Grp3}) and Group4 (MB_{Grp4}) – each with its own genetic profile, presentation and prognosis, the scrutiny of which has led to the understanding of intergroup heterogeneity and recognition of second-generation subgroups (Louis et al., 2021; Sharma et al., 2019).

Well-accepted multimodal regimens that include maximally safe resection, craniospinal irradiation (CSI) and adjunctive chemotherapy have resulted in a significant improvement in long-term survival, with overall survival rate at 70 %. Unfortunately, despite these improvements in upfront therapy since the 1990's, patients with recurrent/refractory disease continue to a have dismal prognosis with limited curative salvage options (Sabel et al., 2016).

In addition, survivors of MB suffer substantial tumor and treatment-related burdens. Ongoing efforts to mitigate this morbidity remains a necessary component of any future advances.

Through a synthesis of recent research and clinical insights, this chapter aims to provide a comprehensive understanding of medulloblastoma, underscoring its multifaceted nature and the cruciality of a multidisciplinary approach in guiding treatment decisions in this complex and challenging disease entity (Weil et al., 2017).

2. Clinical presentation

Medulloblastoma can manifest very differently depending on tumor size, location, and the patient's age. Symptoms can initially be subtle and develop over weeks to months. In children, symptoms often arise from increased intracranial pressure due to obstructive hydrocephalus caused by the tumor's typical location in the posterior fossa. Most commonly, symptoms include morning headaches, nausea, vomiting, and lethargy. Older children and adults may present with ataxia, gait disturbances, and dysmetria due to cerebellar involvement. Behavioral changes and cranial nerve palsies, particularly involving the sixth nerve, are also common in advanced cases. Prolonged raised intracranial pressure can also result in visual changes from papilledema. Infants may display more nonspecific features such as irritability and developmental delay or regression, making early detection more challenging (NCI, 2018; Franceschi et al., 2019).

2.1 Genetic predisposition

Germline mutations in cancer predisposition genes account for 5–10 % of medulloblastoma diagnoses. Diagnosis of these germline predisposition syndromes can guide surveillance prompting early detection of medulloblastoma particularly in young children. Conversely, when the diagnosis of medulloblastoma is made, detection of germline predispositions can contribute to

risk adapted treatment strategies, in addition to understand potential toxicities and prognosis including the risk of secondary malignancy.

Genome studies have facilitated the association between specific germline variants and the various MB subtypes (Carta et al., 2020). A large, combined retrospective/prospective study reviewing the spectrum and prevalence of genetic predispositions in 1022 patients with MB across international retrospective cohorts and 4 prospective clinical trials, detected damaging germline mutations in 11 % of their patient population in the retrospective component (Waszak et al., 2018).

The gamut of germline mutations in medulloblastoma remain incomplete but a number of germline driver mutations are now well recognised with MB including *APC*, *BRCA2*, *PALB2*, *PTCH1*, *SUFU*, *ELP1, TP53* and the mismatch repair genes *(MLH1, MSH2*, *MSH6*, *PMS1, PMS2).* Germline variants are not equally proportionate across molecular MB subgroups with the highest prevalence seen in MB_{SHH} (20 %), of which *TP53* mutations mark the highest proportion. A more modest prevalence of damaging germline mutations is found MB_{WNT} whilst it is a relatively rare findings in $MB_{Grp3/4}$ subtypes. As such, screening recommendations should be considered standard of care in patients with MB_{WNT} and MB_{SHH} (Carta et al., 2020; Waszak et al., 2018). There is currently no consensus for treatment of MB in children with underlying genetic predispositions. Notably syndromes such as Fanconi Anaemia have been associated with significant systemic radiotherapy and chemotherapy sensitivity resulting in unacceptable toxicities in unmodified regimens.

3. Diagnostics

3.1 Advances in imaging

Magnetic resonance imaging (MRI) remains the cornerstone for the initial diagnosis and surgical planning of medulloblastomas (Fig. 1). The need for meticulous imaging techniques (and reporting) in patients with MB was well demonstrated in the Children's Oncology Group (COG) A9961 clinical trial (Packer et al., 2013). Clinical imaging standards with minimum mandatory sequence acquisition have been published by the Response Assessment in Pediatric Neuro-oncology Committee (RAPNO) to optimize detection of tumor and leptomeningeal spread. Basic characterization with standard MRI protocols including T1-weighted, T2-weighted, and

Table 1 Summary of predisposition syndromes associated with MB.

Genetic mutation/ gene	Associated syndrome	Clinical phenotype	MB subtype
APC (Carta et al., 2020)	Familial Adenomatous Polyposis (FAP), Turcot Syndrome Type 2	Numerous colorectal polyps, increased risk of colorectal cancer, medulloblastomas	MB_{WNT}
PTCH1 (Wu et al., 2020)	Gorlin Syndrome (Nevoid Basal Cell Carcinoma Syndrome)	Basal cell carcinomas, jaw cysts, skeletal abnormalities	MB_{SHH}
SUFU (Wu et al., 2020)	Gorlin-like Syndrome	Similar to Gorlin Syndrome, with increased medulloblastoma risk	MB_{SHH}
TP53 (Pandey et al., 2021)	Li-Fraumeni Syndrome	Increased risk of various cancers, including breast cancer, sarcomas, and brain tumors	MB_{SHH}
MLH1, MSH2, MSH6, PMSJ, PMS2 (Hedge et al., 201 4)	Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer), Turcot Syndrome Type 1	Increased risk of colorectal cancer, endometrial cancer, glioblastomas	
BRCA2 (Han et al., 2024)	Fanconi Anemia	Bone marrow failure, physical abnormalities, increased cancer risk	$MB_{Grp3/}$ MB_{Grp4}
PALB2 (Han et al., 2024)	Fanconi Anemia-like Syndrome	Similar to Fanconi Anemia, with increased medulloblastoma risk	$MB_{Grp3/}$ MB_{Grp4}

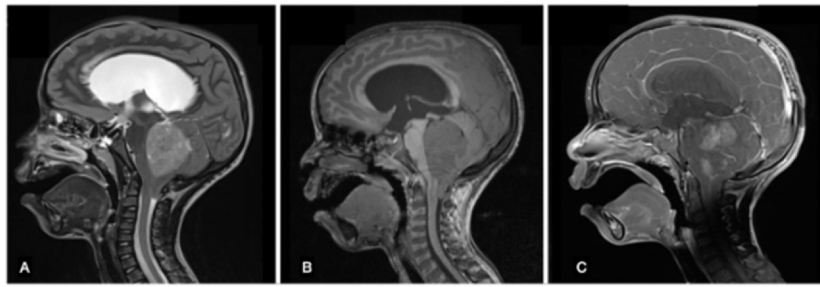

Fig. 1 Brain MRI showing a large, predominantly solid, enhancing midline posterior fossa lesion. There is a marked nodular leptomeningeal enhancement around the caudal brainstem, craniocervical junction and upper cervical spine, concerned for metastasis, with leptomeningeal carcinomatosis. (A) sagittal T2 showing the lesion with hypersignal on the posterior fossa, with herniation of the tonsils through the foramen magnum. (B) sagittal MPRAGE without contrast and (C) sagittal T1 with contrast, showing an irregular enhancement, including brainstem and leptomeninges.

gadolinium-enhanced sequences of whole brain and spine. The group recommended maximum 2D slice thickness acquisition should be ≤4 mm with a small interslice gap (10 % of slice thickness), if required. For post-contrast sagittal T1-weighted imaging of the spine, slice thickness ≤3 mm and minimal gap was recommended. Post contrast T2-weighted fluid attenuated inversion recovery (FLAIR) images are very sensitive in detecting leptomeningeal spread. Post-operative MRI should be performed within 72 h of surgery to assess residual disease (Warren et al., 2018).

Imaging techniques have advanced significantly to predict various histological subtypes. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) are increasingly used to help differentiate tumor cellularity in embryonal tumors and distinguishing MB subtypes and is now routinely recommended. MR spectroscopy (MRS) can aid in distinguishing MB from other tumors by utilising biochemical markers such as choline (Cho) and N-acetylaspartate (NAC), with Cho and cho/NAC ratios being significantly higher in MB when compared to ependymoma. In addition to differentiating tumor entities, Blüml et al. demonstrated a 5-metabolite model which accurately distinguished the metabolic heterogeneity among the MB subgroups with MB_{SHH} from MB_{Grp3} and MB_{Grp4} tumors (Blüml et al., 2016).

Computed tomography (CT) may still be used in emergency settings (Fig. 2) but is less sensitive in delineating soft tissue features compared to MRI. It can detect hydrocephalus, allowing CSF diversion surgery even prior to the brain MRI (NCI, 2018).

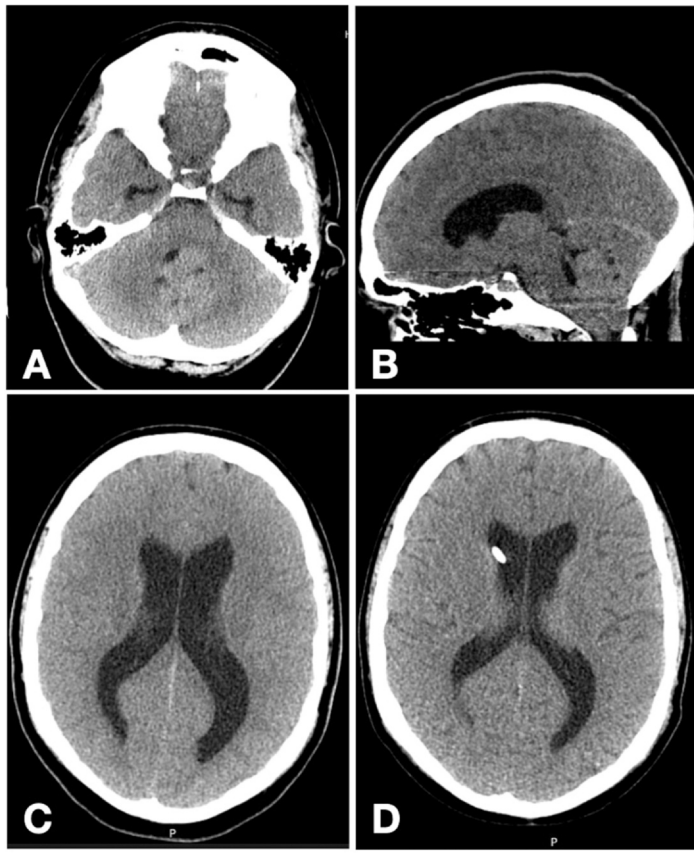

Fig. 2 Head CT scan without contrast shows a large fourth ventricle mass without calcification causing hydrocephalus, with loss of gray-white matter differentiation. (A) Axial view; (B) Sagittal reconstruction; (C) Hydrocephalus with effacement of sulci and gyri (D) Improvement of hydrocephalus after intraventricular drain placement.

3.1.1 Advances in artificial intelligence (AI)

Lee et al., presented the feasibility of an international federated learning platform, FL-PedBrain, designed for the classification and segmentation of pediatric posterior fossa tumors including medulloblastoma. The platform demonstrated less than a 1.5 % decrease in classification accuracy and a 3 % reduction in segmentation performance when compared to centralized data training methods. In addition, this multi-institution study did not compromise on data privacy enhancing the applicability of AI in MRI –based diagnostics (Lee et al., 2024).

Another recent publication by Wang et al., demonstrated an AI system rooted in MR imaging for noninvasive prediction of molecular subgroups which underscored the potential of using AI in presurgical molecular subclassification and facilitating early personalized treatment strategies (Wang et al., 2024). AI can enhance diagnostic precision, accelerate image acquisition, reduce radiation exposure, and improve tumor detection and treatment planning in children (Dalboni da Rocha et al., 2025).

However, several barriers currently limit the full integration of AI into pediatric neuroimaging, including the limited availability of pediatric-specific datasets, the wide developmental variability across age groups, ethical and privacy considerations, and the need for interpretable AI models that clinicians can trust and utilize effectively. Addressing these challenges will require the development of robust, representative datasets, the establishment of multi-institutional data-sharing collaborations, and the design of explainable AI systems that align with clinical workflows and ethical standards.

3.2 Advances in molecular testing

Medulloblastoma is no longer regarded as a single disease but rather a collection of distinct molecular subgroups. In 2012, an international consensus paper reported that medulloblastoma comprises of four molecular subgroups: WNT, SHH, Group 3, and Group 4—each characterized by unique genome-wide transcriptomic and DNA methylomic profiles, signalling pathways, and clinical behaviors (Juraschka & Taylor, 2019; Kumar, Liu & Northcott, 2020).

3.2.1 Histopathology

Histopathological analysis is essential for confirming the diagnosis of medulloblastoma. The 5th edition of the WHO CNS classification (WHO CNS5) released in 2021, emphasized combining molecular and histological features to provide an integrated diagnosis when reporting brain tumors (Louis et al., 2021). The four consensus molecular subgroups defined in WHO CNS5 support the preceding 2016 histopathology-based classification and updated molecular/genetic features.

Medulloblastoma, histologically defined:

- classic
- desmoplastic/nodular,
- medulloblastoma with extensive nodularity (MBEN), and
- large cell/anaplastic.

Medulloblastoma, molecularly defined.
- WNT-activated,
- SHH-activated and TP53-wildtype,
- SHH-activated and TP53-mutant,
- MB Non-WNT/non-SHH.

Genome-wide transcriptional arrays and/or genome-wide methylation arrays are now the current gold standard for medulloblastoma subgrouping (Ramaswamy et al., 2016). Techniques such as next-generation sequencing, NanoString gene expression profiling, and DNA methylation arrays are now fundamental to the diagnostic workflow but are not universally accessible. In the absence of these techniques, morphology and immunohistochemistry (IHC) assays remain an important tool in the diagnosis of MB and its subtypes.

Hematoxylin and eosin staining are routinely performed to identify classic small, round blue cells with high nuclear-to-cytoplasmic ratios. It is common to find Homer-Wright rosettes and perivascular pseudo-rosettes. IHC stains such as synaptophysin and neurofilament protein N (NeuN) confirm the neuronal origin of the tumor. YAP1, GAB1 and beta-catenin staining continue to be performed to determine MB subtypes but with some limitation (Fig. 3).

Prognostic biomarkers such as c-MYC and n-MYC gene amplifications and the presence of isochromosome 17q, can be performed using fluorescence in-situ hybridization (FISH) or array comparative genomic hybridization. These tools provide valuable information about the genetic

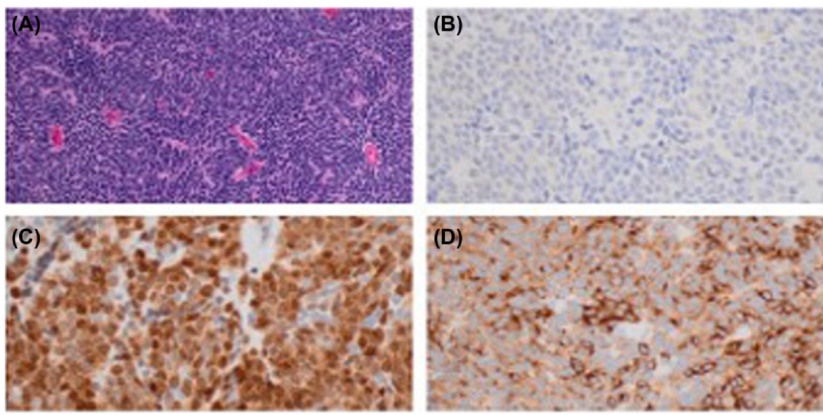

Fig. 3 IHC staining (A) H&E (B) GAB1 (C) YAP (D) synaptophysin.

and epigenetic landscape of the tumor, influencing both prognostic assessments and treatment planning. Some copy number changes are subgroup specific and can help classify tumors into correct molecular categories in settings where more advanced diagnostic techniques are limited or delayed (Bailey et al., 2024).

3.2.2 Tumor-specific biology

Further molecular analysis/DNA methylomic profiles and genome wide transcriptomics has led to the discovery of additional intra-subgroup heterogeneity and further refined these subtypes. Whilst there remain some inconsistencies across different analytical methods, current data supports 4 subgroups in SHH and up to 8 subtypes I-VIII across Group 3 and 4, which have further implications in clinical trial development (Cavalli et al., 2017; Sharma et al., 2019).

In this section, we have provided a broad overview of each molecular subtype.

3.2.3 Wingless/INT1 (WNT) subtype

The WNT subtype accounts for approximately 10 % of cases. They are thought to arise from progenitor cells of the dorsal brain stem so typically appear midline and anatomically close to brain stem. Essential for diagnosis is evidence of activation of WNT signaling pathway and/or corresponding DNA methylation profile. β-catenin nuclear immunoreactivity can be demonstrated throughout the tumor but when focal, can limit the sensitivity of IHC testing. WNT is clearly identifiable and separable across majority of transcriptional and methylation profiling. Approximately 90 % of WNT cases harbor somatic *CTNNB1* mutation and the remaining percent may harbor germline *APC* mutations. Monosomy 6 is also suggestive of the diagnosis and present in majority of WNT cases. Two subtypes have been identified by Cavalli et al.- WNT α and WNT β, with the latter enriched for older patients, who are frequently diploid for chromosome 6 (Cavalli et al., 2017; Cotter & Hawkins, 2022).

MB-WNT demonstrates the most favorable prognosis, with 5-year survival rates exceeding 90 %. Given the favorable outlook of WNT medulloblastoma, several studies have looked at reducing therapy in this group.

3.2.4 Sonic Hedgehog (SHH) subtype

Representing about 30 % of cases, SHH tumors are linked to aberrations in the Sonic Hedgehog signalling pathway leading to uncontrolled cell

growth and proliferation. Activation is due to genetic alterations, including loss of function mutations or deletions in *PTCH1* and *SUFU*, activating mutations in *SMO*, and amplifications of *GLI1, GLI2*, and/or *MYCN* (Kumar, Liu, & Northcott, 2020).

MB_{SHH} is more common in infants and adults and exhibits an intermediate prognosis. Four subtypes have been identified SHH-α, SHH-β, SHH-γ and SHH-δ, which correspond to the WHO 2021 classification 3,1,2 and 4, respectively. SHH-1 (SHH-β) and SHH-2 (SHH-γ) are dominated in the infant population, whilst SHH-3 is found in children and adolescents and SHH-4 in adults. SHH-3 tumors are often enriched with *MYCN* amplifications, and *GLI2* amplifications. The presence of *TP53* mutation carries a distinct high risk in SHH tumors, which has led to WHO CNS5 defining SHH-activated TP53 mutant tumors as a distinct category.

3.2.5 Group 3/4 (Non-WNT/Non-SHH)

The non-WNT/non-SHH subgroup encompasses Group3 and Group4 consensus molecular variants of medulloblastoma. No convergent pathway that defines group 3 and 4 subgroups has been detected. Accounting for 25 % of cases, **Group 3** is frequently characterized by *MYC* amplification occurring in 15–10 % of patients and has the worst prognosis due to a high rate of metastatic disease at diagnosis. It primarily affects young children and often presents with large, midline tumors. **Group 4,** the most prevalent subtype, makes up about 35 % of cases, but is less well understood. It is associated with isochromosome 17q and mutations in genes involved in neuronal differentiation. Although often metastatic, its prognosis is slightly better than Group 3.

In 2017, three independent studies investigated the MB subgroups at higher genome resolution, with eight subtypes (I-VIII) within Group 3 and 4 now strongly supported. Each second-generation subtype has been classified with its own cytogenetic signatures, clinicopathological and survival correlates (Cavalli et al., 2017; Cotter & Hawkins, 2022; Northcott et al., 2017) (Table 2).

3.2.6 Tumor microenvironment

The cerebellar microenvironment is integral to the development, progression and spread of medulloblastoma, with interactions between tumor cells and their surrounding stroma, vasculature, blood brain barrier (BBB) and immune cells significantly influencing tumor behavior and response to therapy.

Table 2 Summary of four consensus subgroups.

Molecular subtype	Frequency	Second-generation Subtypes	Key genetic features	Somatic vs germline	Typical age group	Metastatic risk	Prognosis OS rate
WNT	~10 %	WNT-α, WNT-β	CTNNB1, DDX3X, SMARCA4, TP53, Monosomy	Mostly somatic; APC may be germline (Turcot II)	Children & young adults	Low	Excellent 95 %
SHH	~30 %	SHH-α, SHH-β, SHH-γ, SHH-δ	PTCH1, SUFU, SMO, GLI2, MYCN, TP53	PTCH1, SUFU, TP53 may be germline (Gorlin, Li- Fraumeni)	Bimodal: Infants and adults	Moderate	Intermediate 75 %
Group 3	~25 %	Subtypes II, III, IV	MYC amplification, SMARCA4, CTDNEP1, KMT2D, KBTBD4	Mostly somatic	Infants & children	High	Poor 50 %
Group 4	~35 %	Subtypes V—VIII	Isochromosome 17q, KDM6A, KBTBD4, ZMYM3, KMT2C	Mostly somatic; ZMYM3 sometimes germline	Primarily school-age children	Moderate	Intermediate 75 %

Angiogenesis, a critical process in tumor growth, is often exploited by medulloblastomas, with vascular endothelial growth factor (VEGF) playing a central role in increasing vascular density within the tumor. This enhanced vascular network supports the rapid proliferation of tumor cells and is a potential target for therapeutic intervention (Eisemann & Wechsler-Reya, 2022).

The BBB plays a critical role in the behavior and treatment responsiveness of medulloblastomas by modulating drug permeability based on tumor subtype.[24] In addition to biologic features, in WNT-medulloblastomas, the BBB is disrupted, leading to increased vascular permeability and enhanced chemotherapy penetration, contributing to the favorable prognosis of these tumors. Conversely, SHH-medulloblastomas and other subtypes retain an intact BBB, limiting drug delivery and making these tumors more resistant to systemic therapies. These differences underscore the importance of the BBB in determining treatment outcomes and highlight the potential for targeting tumor-specific BBB characteristics to improve therapeutic efficacy (Phoenix et al., 2016).

The immune response within the tumor microenvironment is another pivotal factor. Medulloblastomas evade immune surveillance by creating an immunosuppressive milieu. Tumor-associated macrophages (TAMs), which are abundant in this environment, exhibit dual roles by potentially promoting tumor progression while also representing promising targets for immunotherapy (Manfreda et al., 2023).

Additionally, medulloblastomas demonstrate significant metabolic adaptability to meet the demands of their rapid growth. This metabolic plasticity is characterized by the upregulation of glycolysis and glutamine metabolism, which provide the necessary energy and building blocks for tumor cell proliferation (Manfreda et al., 2023). These metabolic adaptations represent potential vulnerabilities that could be exploited for therapeutic purposes. The interplay of these factors within the tumor microenvironment underscores its importance in shaping medulloblastoma progression and treatment outcomes.

4. Risk stratification

Risk groups are often defined based on current survival rates:

- low risk (>90 % survival),
- average (standard) risk (75–90 %survival),
- high risk (50–75 % survival) and
- very high risk (< 50 % survival) disease (Ramaswamy et al., 2016).

Approximately 30 % of MB patients are diagnosed as high risk. With the advances in genomic signatures, the definition of high-risk features has and will continue to evolve. Expeditious validation of novel molecular markers are essential for effective clinical trial design and risk stratification.

High risk criteria are currently defined by the presence of both classical and newer features:

- Metastatic disease (i.e., M+),
- Large cell/anaplastic (LCA) histology,
- *MYC* or *MYCN* amplification or
- Molecular subgroup Group 3
- SHH- activated with *TP53* mutation

Isochromosome 17q remains a controversial cytogenetic marker and may be considered a high-risk marker in Group 3.

Staging.

CSF staging is completed using the modified Chang grading system.

Modified medulloblastoma staging system according to Chang (Table 3).

4.1 Liquid biopsy

Current research in assessing cerebrospinal fluid circulating cell free tumor DNA (cfDNA) as a biomarker is an emerging and promising tool for future development. Prospective clinical trial design incorporating liquid biopsies as a marker of minimal residual disease (MRD) could prove very effective with the potential to revolutionize diagnosis, response and surveillance monitoring. Liu et al., conducted a pivotal study describing the clinical utility of tumor-associated copy number variations as an MRD surrogate detected through low coverage whole genome sequencing (Liu et al., 2021). Notably, they demonstrated a superior sensitivity to CSF cytology

Table 3 Modified Chang staging.

M-stage	Degree of metastasis
MO	No evidence of gross subarachnoid or hematogenous metastasis
M1	Microscopic tumor cells found in the cerebrospinal fluid
M2	Gross nodular seeding demonstrated in the cerebellar/cerebral subarachnoid space or in the third or lateral ventricles
M3	Gross nodular seeding in the spinal subarachnoid space
M4	Extraneural Metastasis outside the cerebrospinal axis

with 62 % cytology-negative CSF samples (M0) harboring tumor cfDNA. Persistent MRD was prognostic and associated with a higher risk of recurrence, often preceding radiographic progression. In copy number neutral tumors, other recent studies have demonstrated the utility of MB-associated driver mutations, such as *TP53, PTCH* and *SUFU,* as surrogate markers (Liu et al., 2021; Escudero et al., 2020).

5. Therapeutic advances

5.1 Surgical therapy

Surgery remains the cornerstone of medulloblastoma treatment, with its primary goal being the safe removal of as much tumor as possible. Advanced surgical techniques, including intraoperative use of neuromonitoring (IONM) and neuronavigation, have significantly improved the safety and efficacy of medulloblastoma resections. This section outlines the objectives, techniques, challenges, and technological advances that shape surgical management while addressing potential complications and strategies to mitigate them. The extent of resection is attenuated when accounting for molecular subgroups (Thompson et al., 2016).

5.1.1 Goals of surgery

The principal objective of medulloblastoma surgery is to achieve maximal safe resection while preserving neurological function. Gross total resection (GTR), defined as no visible tumor on postoperative imaging, is associated with improved progression-free survival in specific subtypes, particularly Group 4 tumors without metastasis. However, the prognostic advantage of GTR over near-total resection (NTR), defined as $<1.5\ cm^2$ of residual tumor, remains a subject of debate. The European study HIT-SIOP-PNET 4 demonstrated residual tumor of $>1.5\ cm^2$ was associated with a poorer outcome which led to this then considered as a high-risk criteria in many contemporary trials (including within the Children's Oncology group and PNET V) (Lannering et al., 2012; Sabel et al. 2016, Bailey et al., 2024). Subtotal resection (STR), involving $> 1.5\ cm^2$ residual tumor, is generally associated with worse outcomes but may still be appropriate in cases where complete resection risks significant neurological damage.

Thompson et al. investigated the prognostic significance of the extent of resection (EOR) in medulloblastoma while accounting for molecular subgroups. A retrospective analysis of 787 patients from 35 international

institutions was performed. Surgical EOR was categorized as GTR, NTR or STR. Multivariable analyses of progression-free survival (PFS) and overall survival (OS) showed that, while increased EOR appeared beneficial in the overall cohort, this effect was largely diminished when molecular subgroups were considered. Notably, no significant survival advantage was found for GTR over NTR in any subgroup, while a PFS benefit of GTR over STR was observed in Group 4 patients, particularly those with metastatic disease (Thompson et al., 2016).

The findings challenge the conventional emphasis on maximal resection for all medulloblastoma patients, suggesting that aggressive removal of small tumor remnants may not improve outcomes, particularly when associated with a high risk of neurological morbidity. Given that molecular subgroup affiliation, metastatic status, and adjuvant therapy were stronger predictors of prognosis than EOR, a reassessment of surgical goals and risk stratification criteria should be taken into consideration. Specifically, the traditional classification of patients with residual tumors as high risk—leading to intensified craniospinal irradiation—may require revision. These results support a precision-medicine approach to medulloblastoma treatment, balancing surgical aggressiveness with molecular and clinical risk factors Table 4.

Table 4 Overview of extent of resection.

Extent of resection	Progression free survival (PFS)	Overall survival (OS)	Key observations
GTR (Gross Total Resection)	Reference standard (best PFS)	83 % in 3 y	No significant advantage over NTR in most subgroups.
NTR (Near Total Resection, < 1.5 cm^2 residual)	Similar to GTR (HR 1.05, p = 0.82)	Similar to GTR (HR 1.1 4, p = 0.55)	No significant difference from GTR; avoiding neurological morbidity is recommended.
STR (Subtotal Resection, ≥1. 5 cm^2 residual)	Worse than GTR (HR 1.45, p = 0.02)	No significant difference in OS across most subgroups	STR is associated with worse PFS in Group 4, especially in metastatic cases (HR 1.97, p = 0.01). Unclear survival disadvantage in other subgroups.

Preservation of function is paramount, particularly in tumors adherent to critical structures such as the brainstem or fourth ventricle floor. Aggressive resections aiming for GTR can lead to substantial morbidity without clear survival benefits in some subgroups. Therefore, the surgical approach must balance oncological goals with the potential for post-operative complications.

5.2 Surgical techniques

5.2.1 Preoperative preparation

A thorough preoperative evaluation is critical. This includes advanced imaging to delineate tumor boundaries and assess potential involvement of critical structures. Multidisciplinary discussions involving neurosurgeons, neuro-oncologists, and anesthesiologists optimize surgical planning. Patient-specific considerations, such as age and comorbidities, guide anesthesia and perioperative management.

5.2.2 Key surgical approaches to the posterior Fossa

Medulloblastomas typically require midline suboccipital craniotomies for access to the posterior fossa. Removal of the posterior arch of C1 is often required to allow a wider angle to the fourth ventricle approach. Neuronavigation can help the surgeon to reach the maximum safe resection. Tumors located in the cerebellar vermis or extending into the fourth ventricle necessitate careful dissection to minimize damage to cerebellar and brainstem structures. Ideally it is suggested to preserve cerebrospinal fluid (CSF) pathways to prevent postoperative hydrocephalus. A temporary intraventricular catheter is usually performed before the surgery, if patient has symptomatic hydrocephalus, or at the time of the surgery, for post-operative management of hydrocephalus and testing shunt-dependency. The height of the EVD usually is increased over the following post-operative days to check if patient will or not develop a shunt dependency. A duraplasty may be required to close the posterior fossa dura (Zhao et al., 2020).

Ultrasonic aspirators facilitate controlled tumor debulking. Techniques such as "piecemeal" resection reduce the risk of injury to adjacent structures while allowing maximal tumor removal. Intraoperative ultrasound can show the relationship of the tumor to the brainstem and identification of any residual lesions after gross total resection (Dixon et al., 2022; Giammalva et al., 2022). Fluorescein sodium can also be safely used to optimize the resection of medulloblastomas, but it is not clear if it reduces complications (Chen et al.,2022). IONM can potentially identify the

activity along the cerebello-dento-thalamo-cortical pathway, and may be a promising tool to minimize cerebellar mutism syndrome (CMS) (Giammalva et al., 2022).

Tumor adherence to the brainstem, fourth ventricle floor, or cranial nerves poses significant challenges. Dense fibrosis or prior treatment, such as radiation or chemotherapy, may further complicate dissection. Pediatric cases present additional complexities due to smaller anatomical structures and a higher risk of CMS.

5.2.3 Advances in surgical technology

Technological advancements have enhanced the safety and efficacy of medulloblastoma surgery. IONM allows real-time assessment of brainstem and cranial nerve function, potentially reducing the risk of injury. Neuronavigation system may assist surgical precision by integrating pre-operative imaging with intraoperative anatomy, while fluorescence-guided resection may highlight tumor boundaries for more complete removal. The advent of advanced imaging techniques, including intraoperative ultrasound and MRI, further enables surgeons to evaluate residual disease during the procedure, facilitating immediate additional resection if necessary.

5.3 Radiation therapy

Craniospinal irradiation (CSI) with a boost to the primary tumor site remains an imperative component in the curative treatment of MB. Studies that have attempted a complete omission of CSI altogether have resulted in unacceptable relapse rates emphasising the critical component of irradiation in curing MB. Advances in radiation has been driven by technical developments in planning and delivery and a deeper understanding of tumor biology (Grosshans, 2016).

Given the high radiosensitivity of developing tissues and the significant long-term impact of CSI, contemporary trials continue to review risk-adapted dosimetry and modalities that can improve conformity of dose delivery to limit the effect on healthy tissues, particularly in the younger and low-risk populations. A major advancement has been neuroaxis dose de-intensification. It is now an acceptable standard across most treating groups that average-risk MB patients receive to 23.4 Gy with tumor bed boost to 54 Gy, followed by adjunctive chemotherapy.

In addition to CSI dose reduction, there has been a transition from posterior fossa boost to tumor bed boost. The phase III Children's Oncology Group (COG) ACNS0331 trial randomized patients to receive

either posterior fossa boost or tumor bed boost with a 1.5 cm clinical target volume (CTV) margin to a cumulative dose of 54 Gy. The trial aimed to determine whether a more targeted boost could achieve similar outcomes with reduced radiation exposure to surrounding tissues. Involved field radiotherapy was deemed noninferior to posterior fossa radiotherapy in EFS with 5-year estimates 82.5 % (95 %CI, 77.2–87.8) and 80.5 % (95 %CI, 77.2–87.8), respectively (Michalski et al., 2021). In a post hoc subgroup analysis, the MB_{SHH} group were the only group to demonstrate a statistical difference in EFS with 5-year estimates 90.7 % (95 % CI, 80.1 to 100) in the involved field arm versus 74.9 % (95 % CI, 58.8 to 91.0) on the posterior fossa arm (Michalski et al., 2021; Leary et al., 2021). The shift towards tumor bed boosts has been supported by other studies highlighting this approach did not compromise on local control or survival outcomes in addition to sparing exposure of the cochlear.

The ACNS0331 trial also attempted a further reduction of CSI in young children (aged 3–7years) with average-risk MB. They were randomly assigned to receive standard-dose CSI 24.4 Gy or low-dose CSI 18 Gy. Unfortunately, whilst low-dose CSI was associated with significantly better neurocognitive outcomes in this younger age group, it resulted in both inferior EFS and OS, thought to be driven by molecular subgroup (Michalski et al., 2021).

More recent trials have subsequently looked at dose reduction in favorable/low-risk groups. In an effort to mitigate irradiation-induced side-effects in older children, a pilot surgery and chemotherapy-only study (J1403) was trialed in a favorable MB_{WNT} subgroup (Cohen et al., 2023). The study terminated accrual after early relapse in the first two patients. Three recent prospective trials, SIOP-PNET5-MB, Children's Oncology Group trial ACNS1422 and SJMB12 looked at reducing the CSI dose for low-risk MB_{WNT} to 18 Gy, 18 Gy and 15 Gy, respectively (Gottardo & Gajjar, 2023). Preliminary results presented at ISPNO2024 by the St Jude's group demonstrated that these low-risk MB_{WNT} patients maintained a high 5-year EFS with only 4 of 72 patients having suffered a relapse. Further results from these studies are anxiously awaited.

High-risk patients currently continue to receive 36–39.6 Gy to the neuroaxis given in 1.8–2 Gy fractions, plus a boost up to 54 Gy to the primary site. Metastatic sites often also receive a boost from 45 Gy to 50.4 Gy, dependent on trial requirements or response to chemotherapy 9 (Bailey et al., 2024). The hyperfractionated-accelerated radiotherapy (HART) regimen represents a significant development in the treatment of

pediatric medulloblastoma for high-risk patients led by the SIOP group (Taylor et al., 2014). As previously described by Wheldon et al. and (Taylor et al., 2005) this approach involves delivering radiation in smaller, more frequent doses over a shortened period, aiming to enhance tumor control while minimizing damage to surrounding healthy tissue and could therefore offer potential radiobiological advantages in mitigating toxicity of high doses. Whilst the HIT-SIOP-PNET4 (2001–2008) clinical trial did not demonstrate a survival benefit in average risk MB, with EFS and OS at 10 years were 76 ± 2 % and 78 ± 2 % respectively between HART and conventional radiotherapy, a smaller study in the United Kingdom, which combined adjunctive Vincristine to HART hinted at a potential benefit in metastatic MB but was of statistical uncertainty. (Lannering et al., 2012; Taylor et al., 2014). The current open European high-risk MB study, SIOP HRMB, will continue to randomise HART to conventional radiotherapy to compare efficacy and safety (Seidel et al., 2021).

Possibly the most exciting advancement since the use of 3D conformal techniques with precision photon techniques, is the development and implementation of proton therapy. The particle charged therapy offers the most conformal delivery with significant reduction and sparing of surrounding normal health tissues outside the target volume. However, in consideration of cost and limited availability across the world, the overall benefit in the context of CSI remains a subject of contention. To date, whilst no survival benefit has yet been demonstrated, superior neurocognitive outcomes have been reported. Nevertheless, the potential to reduce other long-term effects particularly in anterior structures (heart, bowel, gonads) make proton therapy an attractive therapeutic option (Grosshans, 2016; Sienna et al., 2024; Seidel et al., 2021).

5.4 Chemotherapy

Adjuvant chemotherapy has repeatedly been demonstrated to provide a survival benefit in patients with MB with a substantial risk of relapse without chemotherapy (74 % versus 60 %). SIOP PNET 3. Multiple different combinations have been used after radiotherapy with no one regimen demonstrating superiority over the other. The COG A9961 study demonstrated no survival difference between a cyclophosphamide- and CCNU-based regimen (Packer et al., 2013).

Conversely to low-risk treatment reduction strategies, several studies have considered concurrent/concomitant chemoradiotherapy to intensify treatment regimens in high-risk settings. Recently concluded COG

ACNS0332 trial evaluated carboplatin as a radiosensitizer (Leary et al., 2021). Therapy intensification significantly improved EFS and OS (both by approximately 20 %) exclusively in MB_{Grp3} patients. Contemporary trials and modern national/standardized guidelines continue to aim to risk stratify patients molecularly.

5.5 Special group: Medulloblastoma in infants and young children (iMB)

Infants and very young children (age less than 3–5years) remain a major challenge for treatment with efforts to omit, replace or delay CSI having limited success to date. Historical trials that grouped infants to receive irradiation-sparing protocols were often associated with a high rate of recurrence only to for many patients to necessitate salvage treatment with CSI. Best survival data have been demonstrated by either using high-dose intensified chemotherapy regimens ("Head Start" III and 4 studies) or trials using intraventricular and high-dose intravenous methotrexate (HIT SKK'92 and HIT 2000 trials) with 5-year PFS for non-metastatic disease reported close to 90 % (Rutkowski et al., 2005; Mynarek et al., 2020; Bouffet & Lafay-Cousin, 2022).

Despite the favorable/excellent outcomes associated in children with desmoplastic nodular MB and MB with extensive nodularity (ND/MBEN) using dose-intensive chemotherapy regimens, attempts at therapy reduction in the single arm COG ACNS1221 trial (which eliminated both radiation and intraventricular methotrexate on a backbone of a modified German HIT SKK2000 regimen) resulted in an unexpected and unacceptable relapse rate that led to premature study closure (Lafay-Cousin et al., 2020). Similarly, the clinical and histologically risk-adapted trial SJYC study utilizing conventional dose chemotherapy failed to identify an acceptable benefit of conventional/risk reduction therapy across the iMB_{SHH} cohort with a 5year PFS of 51 % (Robinson et al., 2018).

Advances in molecular subtyping have managed to further characterise iMB with a predominance in two subgroups – SHH (iMB_{SHH}) and Group 3 iMB_{Grp3}. iMB_{Grp3} harbors second-generation subtypes II/III/IV. Group 4 is less common and WNT tumors largely absent in this population (Hicks et al., 2021).

iMB_{SHH} embodies two subgroups $iMB_{SHH\text{-}I}$ [SHH-β] and $iMB_{SHH\text{-}II}$ [SHH-γ], with the latter enriched with MBEN histology, demonstrating a significantly better survival outcome and supporting consideration for treatment de-escalation in a carefully selected group. Whilst both studies

ACNS1221 and SJY07 revealed inferior outcomes across all iMB_{SHH}, post-hoc molecular profiling revealed survival differences between the two subgroups. 2year PFS 30.0 % and 66.7 % (ACNS1221) 5-year PFS 27.8 % and 75.4 % (SJYC07) for iSHH-I and iSHH-II respectively. Of note, this difference in prognosis was not observed in either HIT or Head start studies implying that this may be overcome with increase dose intensity (Dhall et al., 2020). In addition, these studies support that a carefully selected molecular subgroup of iMB_{SHH} can be cured with conventional-dose chemotherapy.

Current clinical trials aim to prospectively stratify treatment to molecular subgroups. "Head Start" 4 is a randomized clinical trial that is stratified to molecular subgroups and response to induction chemotherapy to compare the efficacy of one versus three (tandem) cycles of myeloablative therapy. Children between 6–10years or those with confirmed residual tumor received radiation after consolidation. In the localised SHH group, 3-year EFS and OS was 96 % and 100 % respectively. The St Jude's SJiMB21 study will also aim to further risk stratify chemotherapy and/or aim to either omit or delay radiotherapy based on molecular subgroup (Table 5).

5.6 Targeted therapies

Whilst much understanding of the molecular and signalling pathways heterogeneity has been gained, attempts at targeting recurrent actionable mutations continue to be explored/investigated to improve outcomes.

SMO-inhibitors were the first small molecular inhibitors to be moved into upfront clinical trial setting based on their preclinical efficacy in the SHH pathway. Variable response to SMO inhibitors and early irreversible fusion of growth plates led to limitations of use to patients who are skeletally mature. It has been considered that targeting downstream mutations may be a new therapeutic strategy in investigating/overcoming resistance (Fig. 4).

Histone deacytlase (HDAC) inhibitors and PI3K/AKT inhibitors are other potential agents that continue to be explored. HDAC inhibitors have demonstrated some efficacy against MYC-driven MB cell lines whilst PI3K inhibitors have demonstrated in vitro and in vivo activity in medulloblastoma. PNOC016 was a target validation study using Fimepinostat, a pan-HDAC and PI3K inhibitor, in recurrent MB (and other malignant brain tumors). The study has now closed for accrual and data maturation.

Table 5 Summarizes the contemporary clinical trials in medulloblastoma.

Protocol	Yrs conducted	Risk group	n	Regimen	Radiation CSI/boost	Outcomes/ comment
SIOP/UKCC	1992-2000	SR	179			5-yr EFS 71.6% (total)
SG		(MO)	89(RT)	No chemotherapy vs	CSI alone vs	74.2% (chemo) vs.
PNET-3			90	Alternating VCR, VP16, CBP and VCR, VP16, CPM x 4 cycles	CSI 35 Gy/55 Gy	59.8% (RT alone) 5y-yr OS 70.7% (total) 76.7% (chemo) vs. 64.9% (RT alone)
		HR (M2/ M3)	68 M2 = 13, M3 = 55	Alternating VCR, VP16, CBP and VCR, VP16, CPM x 4 cycles	CSI 35 Gy/55 Gy	5-yr EFS 34.7% 5-yr OS 43.9%
COG-A9961	1996-2000	SR	313	Randomised CDDP, VCR, CCNU vs CDDP, VCR, CPM x 8 cycles	CSI 23.4 Gy/55.8 Gy Concurrent VCR	5-yr EFS:82% (CCNU) vs. 80% (CPM)
COG-A99701	1998-2004	HR	161	Randomised chemotherapy pre- or post-RT	CSI 36 Gy/55.8 Gy	5-yr EFS
			M1 = 18 M2 = 10 M3 = 49	CDDP, VCR then CPM, VCR x 6 cycles	Concurrent CBP; VCR	M1 = 77% M2 = 50% M3 = 67%
SJMB96	1996-2003	SR	86	HD CPM + CDDP + VCR with ASCR x 4 cycles	CSI 23.4 Gy CSl/55.8 Gy	5-yr EFS: 83% 5-yr OS: 85%

		HR	48 31	HD CPM + CDDP + VCR with ASCR x 4 cycles 6 weeks of pre-RT topotecan	CSl36-39.6 Gy/55.8-59.4 Gy	5-yr EFS: 70% 5-yr OS: 70%
SJMB03	2003-2013	SR	227	HD CDDP,VCR, CPM with ASCR x 4 cycles	CSI 23.4 Gy/55.8 Gy	5-yr EFS:82.3% 5-yr OS: 88.0%
		HR	103	HD CPM, CDDP, VCR with ASCR x 4 cycles	CSI 36-39.6 Gy/55.8-59.4	5-yr EFS: 56.7% 5-yr OS: 69.5%
COG-ACNS0331	2004-2016	All	464	Concurrent weekly VCR during irradiation, followed by maintenance chemotherapy containing CCNU + CDDP + VCR x 6 cycles and CPM + VCR x 3 cycles	(1) reduction in boost volume (54 Gy) from PF to limited tumor bed/ IFRT across all patients, and	5-yr EFS: 82.5% (IFRT) vs. 80.5% (PF)
					(2) reduction in CSI dosing from SDCSI 23.4 Gy to LDCSI 18 Gy for patients aged 3-7 years (n = 226)	CSI dosing: 71.4% (LDCSI) vs. 82.9% (SDCSI)
						5-yr OS: 84.6% (IFRT) vs. 85.2% (PF) CSI dosing: 77.5% (LDCSI) vs. 85.6% (SDCSI)

(continued)

Table 5 Summarizes the contemporary clinical trials in medulloblastoma. (*cont'd*)

Protocol	Yrs conducted	Risk group	n	Regimen	Radiation CSI/boost	Outcomes/ comment
HIT2000	2001-2007	HR	123	Induction: CPM, VCR, MTX, CBP, VP16, and intraventricular MTX), followed by hyperfractionated CSI Maintenance: CDDP + CCNU + VCR x 4 cycles	CSI 40 Gy/20 Gy PF + 8-12 Gy tumor site	5-yr EFS: 62% 5-yr OS: 73%
COG	2007-2018	HR	261	Randomized (1) CBP given concurrently with RT vs (2) isotretinoin given during and following maintenance; Maintenance: CDDP + CPM + VCR x 6 cycles	CSI 36 Gy/ 55.8 Gy PF boost with concurrent weekly VCR	5-yr EFS: 66.4% (CBP) vs.59.2% (No CBP)
ACNS0332						5-year OS: 77.6% (CBP) vs.68.8% (no CBP) isotretinoin randomization: 68.6% (isotretinoin) vs. 67.8% (no isotretinoin) (discontinued at interim futility analysis) Group 3: 5-yr EFS 73.2% (CBP) vs. 53.7% (no CBP) 5-yr OS 82.8% (CBP) vs. 63.7% (No CBP)

PNET4	LC/A	169	CDDP, CCNU, VCR x 8 cycles	Randomised STRT 23gy/ 54 Gy vs. HFRT 36GY/ 60 Gy Concurrent VCR	5yr-EFS 79% 5-yr EFS STRT 77% vs HFRT 81%
SIOP PNET5	LR		CCNU+CDDP+VCR; CPM +VCR x 6 cycles	<16 yrs + WNT: 18 Gy CSl+36 Gy to primary site (54 Gy)	
	HR			≥16 yrs: 23.4 Gy CSl +30.6 Gy to primary site (54 Gy)	
PNET HR+5	HR	51	Pre-CSI: VP16, CBP x 2 cycles Post-CSI HD Thiotepa x 2 cycles Maintenance: TMZ x 6 cycles	CSI 36 Gy/54 Gy	5-yr EFS: 76% 5-yr OS: 76%
COG	LR		CCNU+CDDP+VCR; CPM +VCR x 7 cycles	CSI 18 Gy/54 Gy	Results pending
ACNS1442	WNT			(36 Gy)	Still recruiting
SJMB12	WNT				
	W1	72	CDDP+CPM+VCR) x 4 cycles	CSl15Gy/51.4 Gy	5-yr EFS: 90.4%
	(MO)			(36.4 Gy)	5-yr OS: 98.6%
	SHH	107			

(continued)

Table 5 Summarizes the contemporary clinical trials in medulloblastoma. (*cont'd*)

Protocol	Yrs conducted	Risk group	n	Regimen	Radiation CSI/boost	Outcomes/ comment
		S1	62	CDDP+CPM+VCR) x 4 cycles Maintenance Vismodegib if skeletally mature	CSl23.4 Gy/54 Gy	5-yr EFS 91.7% (TP53WT) 5-yr EFS 28.6% (TP53mutant)
		S2	45 NonWNT/ Non-SHH		CSl36Gy/54 Gy	5-yr EFS 84.2% 5-yr EFS 25.0% Results pending
Infant and young MB						
COG-ACNS0334		iMB	39	Non-DN MB received the 99703 backbone Randomization of added HD MTX to induction	At oncologist's discretion	5-yr EFS with HD MTX: 68.2% vs 45.8% without HD MTX Benefit primarily driven by Grp 3 patients SHH EFS 100% EFS irrespective of MTX
COG-		iMB	25	Modified HIT SKK chemotherapy without IV MTX		Failure to maintain 2-yr
ACNS1221						PFS ≥ 90%,

CCG99703	iMB	92	Induction: VCR, CPM, CDDP; V16 x 3 Consolidation: Thiotepa and CBP x 3 with ASCR		5-yr EFS 70% SHH 86% vs Grp 3 49%
SJYC07	All	81			5-yr EFS 31.3% (total)
(<5years)	LR	23	Induction: HDMTX, VCR, CPM, CDDP x 4 cycles Consolidation: CPM, VP16, CBP x 2 cycles		5-yr EFS 55.3
	IR	32	Induction: HDMTX, VCR, CPM, CDDP x 4 cycles Consolidation: PO CTX/TOPO alternating with PO VP16	Focal RT 54 Gy tumor bed	5-yr EFS 24.6%
	HR	26	Induction: HDMTX, VCR, CPM, CDDP, VBL x 4 cycles Consolidation: CPM/TOPO x 2 cycles	Or CSI 23.4-39.6 Gy (>3 yrs)	5-yr EFS 16.7%
	All		Maintenance: PO CPM/TOPO/ erlotinib x alternating 6 cycles		(5-yr EFS SHH-I 27.8%; SHH-II 75.4%; Grp 3 8.3%)
PBTC-026 (<4years)		31	Induction 3 cycles x CDDP, CPM, VCR, VP16 with Vorinostat and isotretinoin Maintenance: Vorinostat and isotretinoin 3 cycles CBP-Thiotepa	Focal RT For MO MB at physician discretion for other patients	2-yr PFS: 68.2%

(continued)

Table 5 Summarizes the contemporary clinical trials in medulloblastoma. (*cont'd*)

Protocol	Yrs conducted	Risk group	n	Regimen	Radiation CSI/boost	Outcomes/ comment
Headstart Ill (<10years)			92	Induction 3-5 cycles x CDDP, CPM, VCR, VP16, HD MTX Consolidation 1 cycle Thiotepa-VP16-CBP	For children > 6 years or children not in CR	5-yr EFS: 89% (ON MB) 5-yr EFS: 26% (Classic) 5-yr EFS: 38% (LCA)
Headstart		LR	39 (SHH)	Induction: VCR, CDDP, CPM, V16, HD MTX x3	For children 6-1Oyears or not in CR	3-yr EFS: 96.4%
IV			28	(5 cycles if not in CR)		(Localised); 36.4%
(<10years)			localised	Consolidation: Thiotepa, CBP, V16 + ASCR x 1		(Disseminated); 3 yr 0S: 100% (Localised); 90% (Disseminated)

ASCR:Autologous stem cell rescue; CBP Carboplatin; CCNU: Lomustine; CDDP: cisplatin; CPM: cyclophosphamide; CR: complete remission; CSI: craniospinal irradiation; DN nodular desmoplastic; EFS: event-free survival; HOC: High-dose chemotherapy; HD: high-dose; HR: high-risk; IFRT: Involved field RT; IV MTX: intraventricular methotrexate; Gy: Gray; LCA: Large cell anaplastic; LDCSI: Low-dose CSI; LR: Low-risk; MB: medulloblastoma; MO: non-metastatic; MTX: methotrexate; PF: posterior fossa; RT: radiotherapy; SDCSI: Standard-dose CSI; SHH-I: Sonic hedgehog Type I; SHH-II: Sonic hedgehog Type II; SR: standard-risk; TMZ: Temozolomide; VCR: vincristine;VP16: Etoposide;

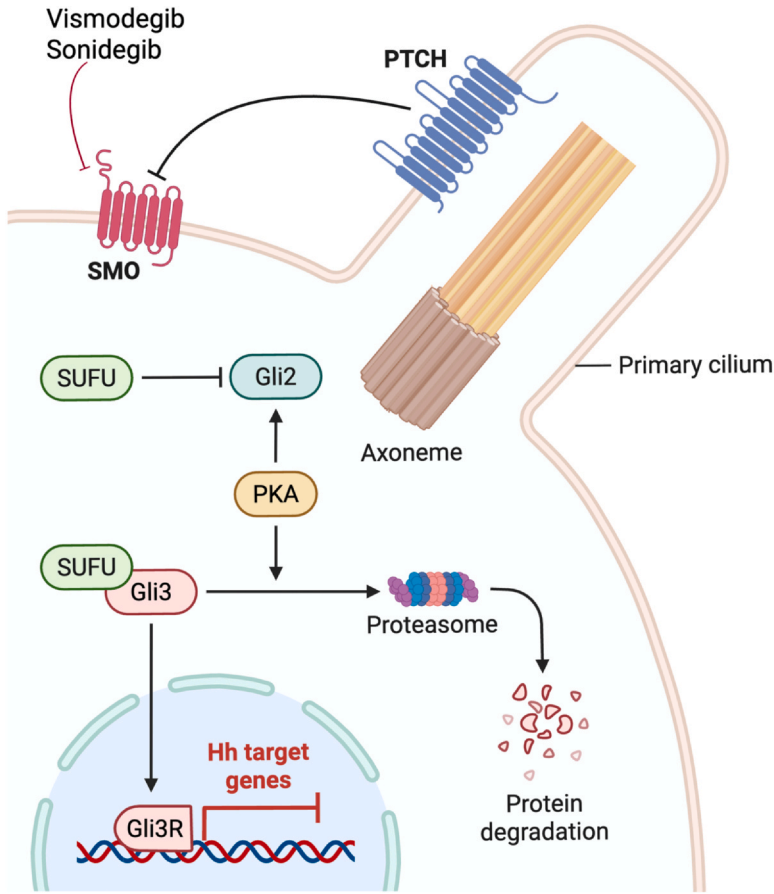

Fig. 4 SHH pathway and SMO inhibitor - Created in BioRender. Govender (2025) https://BioRender.com/9iy89m3.

Another area if growing interest is immunotherapeutic options. Studies reviewing chimeric antigen receptor T (CAR-T) cell therapy, oncolytic viruses and immune checkpoint inhibitors are being evaluated.

Given the heterogeneity of medulloblastoma, combination therapy with/without a chemotherapy backbone is likely still required. PNOC027 is a novel pilot trial in determining the benefits of a precision medicine approach in recurrent medulloblastoma using genomic and real time drug testing to determine an individual treatment plan (Cooney et al., 2023).

6. Relapsed medulloblastoma (rMB)

Relapses occur in approximately 30 % of patients with medulloblastoma. Tragically, after multimodal therapy with upfront CSI, it is almost invariably fatal accounting for a significant proportion of cancer-related childhood deaths (Cooney et al., 2023; O'Halloran et al., 2024).

Substantial advances have gone into understanding rMB biology, prognostic factors and patterns of relapse in the context of molecular subgrouping. Median time to relapse can vary but is notably related to molecular subgroup with Group 3 patients having a rapid progression course in comparison to the more indolent course seen in Group 4 subtype. Time to relapse is also associated with time to death. Most patients relapse at distant/metastatic sites with some variability across subgroups. Relapses in the MB_{SHH} are more frequent in the posterior fossa when compared to $MB_{Gp3/Grp4}$ (Lannering et al., 2012).

There are currently no standard treatments for rMB. There have been significant international efforts to characterize biology at relapse. Whilst surgery at the time of relapse can be limited, particularly in metastatic disease, biopsy at the time of relapse can distinguish molecular drivers and help exclude secondary malignancies, and resection of isolated nodular relapses can be associated with a prolonged survival outcome. Individual strategies regarding chemotherapy and re-irradiation are necessary and can slow down tumor progression. Notably, durable remissions in young children who receive deferred CSI at relapse can be achieved with reported post relapse 5-year survival rates approximately 40 %. High-dose chemotherapy (HDC) with autologous stem cell rescue (ASCR) may be offered as part of salvage therapy (especially in patients with localized disease and prior favorable response to prior chemotherapy). Whilst outcomes vary, studies have demonstrated that this can lead to prolonged PFS in a subset of patients when complete or near complete response is achieved prior to ASCR (O'Halloran et al., 2024).

There are now several early phase trials exploring potential drug targets in rMB. Ongoing research in combining novel therapeutics with HDC continues to be explored. A detailed review of the recent open trials is beyond the scope of this chapter.

7. Survivorship

Although survival rates have dramatically improved with the use of multi-modal therapies, the long-term negative impact is considerable. Survivors

of medulloblastoma are amongst those with the most severe clinical and wide-ranging disabilities. Known risk factors include but are not limited to age at diagnosis and CSI, radiotherapy and cumulative alkylator therapy.

An in-depth review of the late sequelae in medulloblastoma survivors is beyond the scope of this review but we have chosen to expand on a few specific treatment related effects.

7.1 Acute complications

Cerebellar mutism syndrome, also known as Posterior Fossa Syndrome, is a unique and common complication of posterior fossa surgery in children. It manifests as transient speech loss, emotional lability, and ataxia, with variable recovery times (Jabarkheel et al., 2020). The risk of CMS may be less common in SHH subgroup (Fabozzi et al., 2022).

Hydrocephalus is also frequently encountered, both pre- and post-operatively, due to obstruction of the fourth ventricle. Management may involve temporary CSF diversion via external ventricular drainage (EVD), permanent ventriculoperitoneal shunt placement or endoscopic third ventriculostomy.

Cranial nerve deficits, particularly involving the abducens (VI), facial (VII), and lower cranial nerves (IX–XII), may result from direct tumor compression or surgical manipulation, leading to facial weakness, dysphagia, or aspiration.

Wound-related complications such as cerebrospinal fluid leaks, pseudomeningocele, and surgical site infections can also occur, especially when watertight dural closure is not achieved.

Additionally, patients may experience other neurological deficits, including ataxia, dysmetria, and hemiparesis, due to cerebellar or brainstem injury. While not always immediate, some patients may develop secondary endocrine dysfunctions or cerebellar deficits requiring long-term management. Careful preoperative planning, intraoperative neuromonitoring, and meticulous microsurgical techniques are essential to minimize these risks and optimize outcomes (Table 6).

7.2 Late-effects

Survivors of MB are at a significant high risk of cumulative late-effects. Whilst a detailed review of all these late-effects are beyond the scope of this chapter, a summary of a few pertinent sequelae are mentioned below.

Table 6 Strategies for minimizing and managing acute complications.

Hydrocephalus	**Temporary or permanent CSF diversion techniques, such as external ventricular drains or ventriculoperitoneal shunts, are employed as needed.**
Posterior fossa syndrome	Avoid aggressive dissection near the midline structures of the vermis and use intraoperative neurophysiological monitoring to identify early risks.
Cranial nerve deficits	Prompt rehabilitation and close monitoring help mitigate long-term impacts.

7.2.1 Neurocognitive effects

Global cognitive dysfunction is a frequent sequela of treatment with impairment in working memory, processing speed, attention and executive function. Age at CSI plays a critical role in neurocognitive sequelae. A recent study performed by the Childhood Cancer Survivor Study (CCSS) group demonstrated that in comparison to siblings, MB survivors were less likely to earn a bachelor's degree or work more than 30 h a week or be socially independent. Neurocognitive decline can be seen years after treatment has completed and it is important to serially review neurocognitive testing (King et al., 2017).

Emerging evidence suggests proton therapy may offer significant neurocognitive advantages across multiple endpoints including intelligence quotient, verbal comprehension and perceptual reasoning indices, visual motor integration, and verbal memory (Lassaletta et al., 2023). Most large neuro-oncology clinical trial designs now include formal testing to continue to collect prospective data. Current efforts to limit neurocognitive decline through pharmacological interventions continue to be investigated.

7.2.2 Second malignant neoplasms (SMNs)

In 2019 the CCSS published the cohort study comparing survivors with siblings across three decades (1970'2,80's,90's). At 15 years from diagnosis, there was no increase in cumulative incidence amongst the three decades. However, survivors of multimodal regimens, had a 9.5 % increase in SMNs. In the A9961 study cohort, the estimated ten-year cumulative incidence rate of secondary tumors of 4.2 % (CI 2–6.5 %) with a median time for SMN diagnosis at 5.6years post diagnosis (range, 3.1–16.8 y) (Packer et al., 2013). Other large studies, including SEER and COG, had

similar cumulative incidence rates of approximately 4–5 % at 15years. Tumors of the CNS and thyroid have repeatedly been demonstrated as the highest proportion of secondary malignancy. Whilst modern conformal techniques and proton therapy purport a potential advantage of reducing secondary malignancy, further longitudinal data are required. In a recent study comparing photons and protons, there was no significant difference in SMN incidence rates based on RT group with 5-year and 10-year rates 1.0 % and 6.9 %, respectively (P = .74) (Paulino et al., 2021). Diffuse midline gliomas, myelodysplastic syndrome and non-CNS solid tumors have all been reported as SMN in survivors of MB (Paulino et al., 2021; Millard & De Braganca, 2016, Salloum et al., 2019).

As survival of these patients continue to improve, consideration of increased surveillance for secondary malignancies, specifically radiation-induced SMN, must be made particularly in the context of germline predispositions.

7.2.3 Endocrinopathies

Endocrinopathies in survivors of medulloblastoma is common with a previously presented Canadian study demonstrating a 5-year cumulative incidence of 71 % (ASCO 2009, Bahl). The incidence and time to onset can be influenced by dose and age at the time of radiation therapy. The recently published results from SJMB03 were consistent with historical data. Injury to the pituitary-hypothalamic axis are associated with growth hormone deficiency, central hypothyroidism, adrenal insufficiency and hypogonadotrophic hypoganidism (Merchant et al., 2023, Merchant et al., 2023). Growth hormone deficiency has the highest cumulative incidence. Low dose gonadal exposure is still associated with a significant impact on gonadal function with females and peripubertal children seen to be the most at risk.

Further specifics on endocrinopathies are beyond the scope of this review. Early identification of hormonal dysfunction can result in early management and reduction in resultant associated sequelae. Notably, the effect the CSF shunt has been shown to have an effect on incidence of some of radiation related endocrinopathies.

7.2.4 Ototoxicity

Many survivors of MB, suffer profound sensorineural hearing loss (SNHL) secondary to chemoradiation effects. Multivariate analyses have confirmed cumulative doses of cisplatin > 200 mg/m2, young age and cochlear

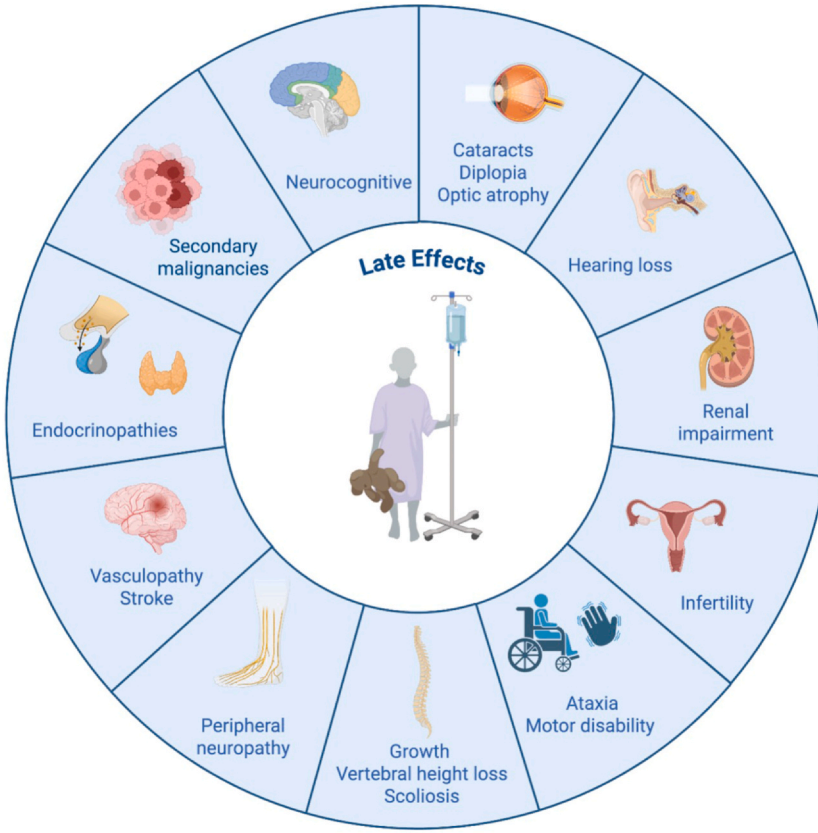

Fig. 5 Spectrum of late effects – Created in BioRender. Govender (2025) https://BioRender.com/vw333wk.

exposure are risk factors to hearing loss. Given the significant association associated with intellectual and academic decline, poor socialisation and impaired quality of life, multiple therapies have been investigated to reduce the risk of long-term ototoxicty without impacting survival rates. A recent study by Paulino et al. comparing protons and photons demonstrated that whilst cochlear doses were reduced, there was no improvement in Grade 3 and 4 ototoxicity (Paulino et al., 2021). Advances in otoprotective agents are currently being evaluated in prospective trials.

7.2.5 Cerebrovascular disease

Survivors of medulloblastoma are at an increased risk of cerebrovascular disease including stroke and vasculopathies. Whilst all brain tumor

survivors are at increased risk of stroke, the risk of stroke increases in a radiation dose dependent manner. Increased time from diagnosis and age also increases the risk. Data from CCSS suggested a 10-fold increase in incidence between the ages of 10 and 30 years (1.3 % and 14.2 % respectively) (Salloum et al., 2019) (Fig. 5).

8. Future directions and challenges

Preclinical models have also played a crucial role in advancing knowledge about medulloblastoma. Animal models, particularly mouse models of MB_{SHH} and MB_{WNT} tumors, and patient-derived xenografts have provided valuable insights into tumorigenesis and the complex signalling pathways driving tumor growth and progression (Roussel & Stripay, 2020; Kawauchi et al., 2012). These models have been instrumental in testing novel therapeutic approaches, offering a bridge between laboratory discoveries and clinical applications.

Advances in proteomics and metabolomics have expanded the understanding of medulloblastoma at the molecular level. Proteomic studies have identified biomarkers that aid in diagnosis and monitoring treatment responses, while metabolomic analyses have highlighted specific metabolic adaptations and vulnerabilities in tumor cells (Hovestadt et al., 2020). These findings hold potential for the development of new therapies targeting metabolic pathways critical for tumor survival and growth. Collectively, these research advancements have laid a strong foundation for translating basic scientific knowledge into improved clinical outcomes for medulloblastoma patients.

Immunotherapy represents another frontier, with trials evaluating immune checkpoint inhibitors and vaccine-based approaches to leverage the immune system against tumor cells (Sengupta, Pomeranz Krummel & Pomeroy, 2017; Conney et al., 2023). Additionally, studies are investigating the use of angiogenesis inhibitors like bevacizumab to enhance chemotherapy efficacy by disrupting tumor vasculature (Levy et al., 2021).

Artificial intelligence (AI) and machine learning are poised to further revolutionize the diagnosis and management of medulloblastoma. AI algorithms can analyze large datasets from genomic, transcriptomic, and radiomic studies to identify novel biomarkers, predict treatment responses, and optimize surgical planning. For instance, AI-driven radiological tools can enhance tumor segmentation and detect subtle patterns indicative of

disease progression. In therapy, AI could aid in selecting the most effective treatment combinations and predicting outcomes based on individual patient profiles (Huang et al., 2022; Wang et al., 2024). Machine learning also has been used to determine prognosis using automated image segmentation (Wang et al., 2024). Integrating AI into clinical workflows demands robust validation, regulatory approval, and clinician training to ensure its effective use.

Despite these promising advancements, significant challenges remain in translating research findings into clinical practice. The variability in clinical trial designs and the limited availability of pediatric patient populations further hinder the validation of new treatments.

Access to advanced molecular diagnostics and cutting-edge therapies remains unequal across healthcare systems, particularly in low-resource settings. Additionally, the high costs associated with targeted therapies and immunotherapies pose financial challenges for widespread implementation. Ethical considerations, such as ensuring equitable access and addressing the potential long-term effects of novel treatments, also require attention. Addressing these challenges will require collaboration among researchers, clinicians, policymakers, and patient advocacy groups to bridge the gap between innovation and real-world application.

9. Conclusion

The story of medulloblastoma is one of remarkable progress and ongoing evolution. From the identification of molecular subgroups to the development of cutting-edge therapies, each advancement has brought us closer to a more comprehensive understanding and effective treatment of this disease.

Despite these strides, significant challenges remain. Translating research into clinical practice is fraught with obstacles, including the heterogeneity of the disease, the high costs of novel therapies, and disparities in access to care. Moreover, the long-term impacts of treatment, such as cognitive deficits and secondary malignancies, highlight the importance of ongoing survivorship care and rehabilitation.

The future of medulloblastoma management lies in addressing these challenges through collaborative, multidisciplinary efforts. Continued investment in research is essential to uncover the mechanisms underlying tumorigenesis and resistance, develop more effective therapies, and refine

existing modalities. Equally important is the need to ensure equitable access to these advancements, reducing disparities in outcomes across different populations and healthcare settings. As we move forward, the integration of biology, technology, and clinical expertise will remain central to improving the lives of patients and their families.

This chapter serves as both a reflection on the strides made and a call to action for continued innovation and collaboration in the fight against medulloblastoma.

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