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REVIEW

Advancing medulloblastoma therapy: strategies and survival insights

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Abstract
Medulloblastoma, the most common malignant brain tumor in children, presents unique challenges due to its molecular and histological heterogeneity. Advances in molecular profiling have refined risk stratification, enabling personalized treatment strategies and improved survival outcomes. This review synthesizes recent developments in the multimodal management of medulloblastoma, encompassing surgery, craniospinal radiation therapy, and chemotherapy, tailored to patient age and risk classification. Key highlights include subgroup-specific therapies, the role of molecular-targeted treatments, and the integration of genetic testing for germline mutations to guide clinical decision-making. Special emphasis is placed on minimizing treatment-related toxicity while preserving long-term quality of life. Additionally, this manuscript discusses the implications of novel therapeutic approaches for high-risk subgroups, including intensified regimens and systemic therapies for young children. Despite significant progress, challenges remain in addressing long-term complications such as neurocognitive impairments, endocrine dysfunction, and secondary malignancies. Future directions prioritize optimizing therapeutic efficacy while reducing morbidity, underscoring the importance of translating molecular discoveries into clinical practice.

Keywords Medulloblastoma therapy · Risk stratification · Molecular subgroups · Multimodal treatment · Long-term outcomes

Introduction

Medulloblastomas, the most common malignant brain tumors in children, originate exclusively in the cerebellum and exhibit significant molecular and histologic heterogeneity. These tumors are characterized histologically by high cellular density, densely packed, dark-staining round or oval nuclei with minimal cytoplasm, and abundant mitotic figures, with Homer Wright rosettes observed in up to 40% of cases [1–3]. Advances in molecular profiling have identified four distinct subgroups of medulloblastoma, each associated with unique histologic, genetic, and clinical characteristics. Histologic variants include classic, desmoplastic/nodular, large cell, and anaplastic subtypes [4]. The desmoplastic variant, frequently linked to PTCH1 mutations on chromosome 9, is defined by collagen-rich interstitial spaces and reticulin-free "pale islands," and is often associated with a favorable prognosis [3, 5]. In contrast, the large cell/anaplastic (LCA) subtype demonstrates aggressive clinical behavior, cerebrospinal fluid dissemination, and is commonly associated with group 3 tumors in children and group 4 tumors in adults, while SHH TP53-mutated medulloblastomas in children (SHH alpha subtype) also exhibit similar aggressive features with poor prognosis [6].

Immunohistochemically, medulloblastomas express neuronal markers such as synaptophysin, neuron-specific enolase, and nestin, reflecting their origin from cerebellar granule cells or multipotent progenitor cells [7–9]. Nuclear beta-catenin staining is characteristic of Wnt pathway-driven tumors, while p53 immunostaining identifies TP53 mutations. Approximately 5–6% of pediatric medulloblastomas involve germline mutations, with the highest prevalence among Sonic Hedgehog (SHH) pathway-driven tumors [10–12]. These genetic discoveries have deepened our understanding of medulloblastoma pathogenesis, encompassing both hereditary and sporadic cases.

Treatment for medulloblastoma typically involves a multimodal approach, including surgical resection, radiation therapy, and chemotherapy. This strategy achieves long-term

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survival in approximately 75% of patients. However, survival outcomes are highly variable across risk groups, and the intensive nature of treatment often results in delayed complications that profoundly affect survivors' quality of life. Current clinical trials are focused on refining therapeutic strategies to reduce treatment-related toxicity while maintaining high cure rates. These efforts aim to improve not only survival but also the long-term quality of life for both pediatric and adult patients.

This review discusses the management of medulloblastoma across age groups, emphasizing treatment-related challenges, long-term outcomes, and the importance of balancing efficacy with quality of life.

General principles

The initial management of medulloblastoma requires a comprehensive strategy addressing both symptomatic relief and tumor-specific treatment, beginning with critical diagnostic evaluations. Preoperative MRI scans of the brain and spine are essential, particularly for posterior fossa (PF) tumors showing diffusion restriction, to assess metastatic spread, as recommended by RAPNO guidelines [1, 13]**.** **P**ostoperative spine MRI may be confounded by artefacts mimicking metastases, potentially leading to treatment escalation. Lumbar cerebrospinal fluid (CSF) cytology, collected 14 days or more after surgery, is the standard for accurate staging, as earlier or alternative collections (e.g., ventricular CSF) are unreliable [2]. Radiomic studies further enhance management by aiding molecular subgrouping, offering prognostic and therapeutic insights [3, 4, 14, 15].

This dual approach mitigates elevated intracranial pressure through supportive interventions while initiating targeted oncologic therapies. Drawing on evidence from cooperative group studies, the standard of care emphasizes a multidisciplinary approach, typically involving maximal safe surgical resection, craniospinal axis radiation therapy (RT), and systemic chemotherapy. Treatment plans are tailored to specific risk stratifications, as detailed below, to optimize outcomes while minimizing treatment-related morbidity.

Management of intracranial pressure and edema

Patients with medulloblastoma often present with elevated intracranial pressure due to hydrocephalus, typically resulting from fourth ventricular obstruction caused by tumor growth. Surgical resection is the primary and urgent intervention to alleviate hydrocephalus and should proceed as soon as possible, rather than awaiting symptom resolution with steroids. For cases where hydrocephalus persists postoperatively, cerebrospinal fluid (CSF) shunting or endoscopic third ventriculostomy (ETV) are viable options, with ETV applicable either before or after tumor resection to restore CSF flow [16, 17]. Additionally, localized vasogenic edema from tumor-induced inflammation can exacerbate intracranial pressure. This edema is effectively managed with glucocorticoids, particularly dexamethasone, which offers potent anti-inflammatory effects and minimal mineralocorticoid activity, providing symptomatic relief (e.g., headaches, nausea, focal deficits like hemiparesis or aphasia) [18, 19]. Its high potency and equivalent efficacy via oral or intravenous routes make it versatile for acute and outpatient care.

In severe cases, dexamethasone treatment begins with a 10 mg intravenous loading dose, followed by a maintenance dose of 8–16 mg daily in divided doses. For mild symptoms, 2–4 mg daily suffices without a loading dose. Asymptomatic patients typically do not require treatment unless rapid deterioration is anticipated, especially in posterior fossa tumors [17, 19, 20]. Symptom improvement often occurs within 24–72 h, with headaches resolving quickly, though focal deficits may persist longer due to multifactorial causes. If standard dosing fails, a temporary escalation (doubling the dose for up to three days) can assess responsiveness; lack of improvement suggests alternative causes, prompting dose reduction to limit steroid exposure. Doses exceeding 16 mg daily are generally avoided due to limited efficacy and heightened side effects [21, 22].

Dexamethasone's rapid oral absorption (bioavailability within 30 min) supports its use in varied settings [23]. Once stable, tapering begins to minimize side effects like weight gain and muscle weakness—stable patients can reduce doses by 50% every four days, while progressive cases may need slower tapering or chronic use, potentially transitioning to less potent steroids like prednisone. Patients should monitor for recurring edema symptoms (e.g., headaches, focal deficits) during tapering and seek prompt intervention if needed [17, 24].

Maximal safe resection in medulloblastoma treatment

Maximal safe resection is a cornerstone in medulloblastoma management, playing critical roles in diagnosis, relieving intracranial pressure, and improving local tumor control. The primary surgical goal is to maximize tumor removal while preserving neurologic function and minimizing complications, such as persistent ataxia or cranial nerve deficits.

Advances in surgical techniques, including intraoperative imaging, have greatly increased the likelihood of achieving gross total resection (GTR) or near-total resection (NTR). However, complete resection is not always feasible due to the risk of severe neurologic impairment, and overly aggressive approaches should be avoided to limit morbidity. While no

randomized controlled trials have directly compared GTR to NTR for survival benefit, leaving this question unresolved, observational studies—particularly those predating routine craniospinal radiation and multi-agent chemotherapy—highlight the extent of resection as a key prognostic factor [25–30]. Emerging data suggest that prognostic significance may vary by molecular subgroup, indicating a nuanced relationship between resection extent and outcomes [31, 32]. Recent evidence also advises caution: Keeling et al. [33] suggest that subtotal resection (STR) as an isolated risk feature should not independently guide patient management, emphasizing the need for broader risk assessment [34]. Midline cerebellar tumor resection carries an additional risk of posterior fossa syndrome (PFS), or cerebellar mutism, occurring in about 25% of patients. This complication can profoundly impact long-term neurocognitive outcomes, including deficits in language production, attention, and intellectual ability, often persisting for months to years and contributing to reduced quality of life [35, 36]. These risks underscore the need to balance aggressive resection with preservation of neurologic function.

Radiation therapy

Radiation therapy (RT) is a key component of medulloblastoma treatment, aimed at eradicating residual disease in the posterior fossa, managing craniospinal metastases, and preventing recurrence. However, its use is constrained by potential toxicity to the brain and spinal cord, particularly in young children, where craniospinal irradiation is often delayed or avoided to minimize harm to the developing CNS.

Following surgery, standard management typically includes craniospinal axis irradiation with external beam RT, combined with a boost dose targeting the primary tumor site [24, 28, 35]. Radiation doses and delivery methods are adjusted based on patient age and risk stratification to optimize efficacy while minimizing toxicity. In many modern protocols in Europe and North America, radiation-sparing approaches extend beyond age three to four or five for select patients, such as those with SHH beta or gamma medulloblastoma subtypes, reflecting evolving strategies to reduce neurotoxicity [36].

Advances in RT techniques, such as proton therapy and intensity-modulated radiation therapy (IMRT), have improved treatment precision, reducing radiation exposure to adjacent tissues [36–40]. While whole-brain proton therapy offers limited safety advantages over photon-based methods, proton therapy and IMRT effectively spare critical structures (e.g., medial temporal lobes, inner ear, thyroid, and lungs) during primary site boosts and spinal irradiation, mitigating long-term adverse effects [36, 37, 39–45]. Hyperfractionated RT, which delivers smaller, more frequent doses, is also employed by some groups (e.g., PNET4 trial) to enhance tumor control while limiting toxicity, with evidence supporting its feasibility [46–54].

Table 1 provides a comparative overview of radiation therapy techniques, highlighting their respective advantages and limitations in the treatment of medulloblastoma.

For average-risk children, craniospinal RT typically involves 23.4 Gy to the craniospinal axis, followed by a 30.6 Gy boost to the primary tumor site, totaling 54 Gy. In high-risk cases, doses vary: the SJMB96 and SJMB03 trials used 36–39.6 Gy craniospinal, while ACNS0332 delivered 55.8 Gy to the posterior fossa (not just the tumor bed). Some protocols also recommend a 9 Gy boost to metastatic deposits [46]. Boosts target the tumor bed and margins, limiting exposure to unaffected brain tissue, with 50–70% of recurrences originating in the posterior fossa and isolated failures outside the tumor bed being rare [45, 55].

Table 2 summarizes craniospinal and boost radiation doses stratified by risk group in medulloblastoma, reflecting variations such as 36–39.6 Gy craniospinal in SJMB trials, 55.8 Gy to the posterior fossa in ACNS0332, and a 9 Gy boost for metastases, while maintaining a consistent baseline total dose of 54 Gy for standard cases.

Table 1 Summary of radiation therapy technique

Technique	Advantages	Limitations
Proton Therapy	High precision reduces radiation exposure to adjacent normal tissues Particularly beneficial for young children to minimize long-term side effects	Limited availability and higher cost compared to photon therapy Requires specialized facilities and expertise
Intensity-Modulated Radiation Therapy (IMRT)	Improved dose conformity allows for sparing of critical structures Effective for complex tumor shapes and high-risk cases	May increase integral dose to non-target tissues due to scatter radiation
Photon-Based Radiation Therapy	Widely available and cost-effective Suitable for average-risk patients with no complex anatomical challenges	Higher radiation exposure to surrounding normal tissues compared to proton therapy

Table 2 Radiation dose summary by risk group in medulloblastoma

Risk group	Craniospinal dose	Boost dose	Total dose
Average-risk	23.4 Gy	30.6 Gy	54 Gy
High-risk	36 Gy	18 Gy	54 Gy

Conventional RT uses distinct but adjacent fields for the brain and spine, requiring precise alignment at field junctions. Junction shifts, applied two to three times during craniospinal irradiation, reduce spinal cord overdose but may increase radiation to surrounding structures (e.g., thyroid gland, mandible), potentially causing late complications such as hypothyroidism and mandibular hypoplasia [56]. Higher RT doses improve tumor control [28, 57] but carry risks of significant neurocognitive impairment, particularly in young children, prompting delays in RT for those under three. Long-term effects include impaired skeletal growth, hypothyroidism, adrenal insufficiency, hypogonadism, and secondary malignancies, though advanced techniques and reduced doses lower these risks. Pediatric strategies often integrate adjuvant chemotherapy to complement reduced-dose RT in average-risk children or replace RT in infants, balancing tumor control with quality of life preservation.

Chemotherapy

Chemotherapy is a cornerstone in the multimodal treatment of pediatric medulloblastoma, tailored to specific clinical scenarios and regional protocols, particularly in Europe and North America:

- **Young children**: Post-surgery, chemotherapy is utilized to delay or potentially avoid craniospinal irradiation, safeguarding the developing brain and spinal cord from radiation-associated risks. Common regimens include cisplatin, vincristine, and cyclophosphamide, as seen in trials like SIOP PNET 4 and COG protocols.
- **Average-risk children**: Chemotherapy serves as an adjuvant therapy following surgery and radiation, reducing recurrence risk and minimizing craniospinal radiation exposure. Protocols such as COG ACNS0331 (cisplatin, etoposide, carboplatin) and HIT 2000 (cisplatin, lomustine, vincristine) are frequently used.
- **High-risk disease**: For high-risk patients, chemotherapy is employed alongside radiation therapy to maximize therapeutic efficacy. Multi-agent regimens, such as methotrexate-based protocols in SIOP or intensified cyclophosphamide/vincristine regimens in COG ACNS0332, are standard.

These strategies are detailed in Table 3, which outlines chemotherapy objectives, regimens, and variations across major protocols (e.g., COG, SIOP, HIT) in Europe and North America, emphasizing individualized approaches to optimize outcomes while minimizing long-term side effects.

Initial therapy

Children

The treatment of pediatric medulloblastoma has significantly advanced, with a combined-modality approach now considered the standard of care. Historically, surgical resection alone was insufficient, as no children survived without adjunctive therapy. The introduction of radiation therapy (RT) markedly improved outcomes, reducing local recurrence rates at the surgical site and along the craniospinal axis.

Management of medulloblastoma is typically conducted within multicenter clinical trials or institution-specific protocols. For additional information or to refer patients, resources like ClinicalTrials.gov, maintained by the United States National Library of Medicine, provide valuable data on ongoing studies.

Risk stratification

Modern medulloblastoma treatment is guided by two critical factors:

Table 3 Detailed Chemotherapy Strategies for Medulloblastoma by Risk Group and Protocol in Europe and North America

Patient group	Objective	Chemotherapy regimen (examples by protocol)	Region/protocol
Young children (< 3–5 yrs)	Delay or avoid craniospinal RT	Cisplatin, Vincristine, Cyclophosphamide	COG, SIOP PNET 4, HIT 2000
Average-risk children	Reduce recurrence and RT exposure	Cisplatin + Etoposide + Carboplatin; Cisplatin, Lomustine, Vincristine	COG ACNSO331, HIT 2000
High-risk children	Maximize therapeutic efficacy	Multi-agent (e.g., Methotrexate-based, Cyclophosphamide/Vincristine)	COG ACNSO332, SIOP PNET 5

Regimens vary by trial (e.g., SIOP, HIT, COG) and molecular subgroup; refer to specific protocols for detailed dosing and schedules

- Risk of recurrence, primarily determined by the extent of disease.
- Risk of treatment-related toxicity, particularly relevant for children under three to five years of age, who are more vulnerable to RT-induced neurologic impairments, with protocols now extending radiation-sparing strategies to older ages in select cases (e.g., SHH beta/gamma subtypes) [1].

Based on these considerations, patients are stratified into distinct treatment groups to enable personalized therapeutic strategies that optimize efficacy and minimize harm (see algorithm 1):

① **Infants and young children**: Typically under three years of age, this group is highly susceptible to severe neurologic toxicity from craniospinal RT. Sonic Hedgehog (SHH) pathway tumors account for approximately 40–50% of infant medulloblastomas, while Group 3 tumors constitute 40–50%, and Group 4 tumors are rare in this age group, based on series like SJYC07 (42/81 SHH) and SKK 2000 (19/45 desmoplastic/MBEN) [2, 57]. Metastatic medulloblastoma in infants shows striking survival differences: SHH patients have better outcomes, with five-year survival rates often exceeding 70%, whereas Group 3 patients exhibit poor prognosis, with survival rates below 30% despite intensive therapy [4, 58].

② **Children aged ≥3 years with average-risk disease**: Defined by total or near-total tumor resection, absence of disseminated disease on brain and spine MRI or lumbar CSF analysis, and histologic subtypes classified as classic or nodular desmoplastic.

③ **Children aged ≥3 years with high-risk disease**: High-risk medulloblastoma in children aged ≥3 years is defined by one or more of the following criteria: residual tumor ≥1.5 cm^2 after surgery, evidence of disseminated or metastatic disease, or large cell/anaplastic histology, though the prognostic significance of anaplasia is limited to SHH and Group 3 patients, not Group 4, as demonstrated in the SJMB03 trial [5].

In addition to clinical and histologic factors, medulloblastomas are now classified into four genetically distinct subgroups, each with unique molecular profiles, clinical behaviors, prognoses, and therapeutic targets (see Table 4). This evolving knowledge informs clinical trial designs, enabling more precise risk stratification and personalized therapeutic strategies. For example, SHH-II tumors show variable outcomes with chemotherapy-only regimens; in SJYC07, event-free survival (EFS) was 75%, and in ACNS1221, it was 66.7%, compared to 83% in HIT 2000 (with intraventricular methotrexate), highlighting the benefit of methotrexate inclusion [6, 7]. These tumors exhibit poorer outcomes when intraventricular chemotherapy is omitted [8, 9].

Infants and young children

For infants and young children, treatment typically involves multiagent chemotherapy, often combined with autologous

Table 4 Molecular landscape and clinical insights in medulloblastoma

Molecular subgroup	Relative frequency	Predominant age group	M:F Ratio	Predominant morphology	Key genetic alterations	Prognosis	Recommended treatment
Wnt-activated	10%	Childhood	1:2	Classic	CTNNB1 mutations	>90% 5-year OS	Reduced-dose RT + chemotherapy [59]
SHH-activated and TP53-mutant	10%	Childhood	3:1	Large cell/anaplastic	TP53 mutations	Poor prognosis	Intensive therapy, including SMO inhibitors [4]
SHH-activated and TP53-wildtype	20%	Infancy/adulthood	1:1	Desmoplastic/nodular	PTCH1 mutations	Variable	Age-dependent therapy; proton RT may benefit [60]
Non-WNT/non-SHH, group 3	25%	Infancy/adulthood	2:1	Classic	MYC amplification	Poorest	Standard RT + chemotherapy; high-dose for select cases [61]
Non-WNT/non-SHH, group 4	35%	All age groups	3:1	Classic	Unknown	Moderate to poor	Standard RT + chemotherapy [62]

A detailed overview of the molecular subgroups of medulloblastoma, offering insights into their prognosis and guiding tailored therapeutic approaches. **OS:** Overall Survival, **RT:** Radiotherapy, **HCT:** Hematopoietic Cell Transplantation, **SMO inhibitors:** Targeted therapy agents for SHH pathway tumors

Note: Treatment recommendations are based on current clinical trials and guidelines; proton RT for SHH TP53-wild-type is justified by reduced toxicity in infancy/adulthood, while Group 3 high-dose chemotherapy is reserved for metastatic or high-risk cases per recent evidence [59]

hematopoietic stem cell rescue, usually conducted within clinical trial protocols. The primary goal is to delay or avoid craniospinal RT, minimizing severe neurologic impairment while optimizing survival outcomes [60–62]. Craniospinal RT in this age group is associated with unacceptably high rates of long-term neurologic deficits.

Molecular subgroup classification plays an increasingly crucial role in guiding trial design and interpreting results in this population. However, cross-trial comparisons remain limited by small patient cohorts and variability in treatment protocols. Despite these challenges, three major molecular subgroups have been identified in infants:

① **Sonic Hedgehog (SHH)**

SHH pathway tumors constitute ~ 75% of infant medulloblastomas and are predominantly associated with desmoplastic/nodular and extensive nodularity histologic subtypes. The HIT-2000 trial demonstrated the efficacy of a regimen combining multiagent chemotherapy, intraventricular methotrexate, and risk-adapted local RT, achieving impressive five-year progression-free survival (PFS) and overall survival (OS) rates of 93% and 100%, respectively [63].

DNA methylation profiling has further stratified infantile SHH tumors into two subgroups with distinct therapeutic responses:

② **SHH-I tumors**: These tumors exhibit poorer outcomes when intraventricular chemotherapy is omitted. The HIT-2000 regimen is particularly effective in this subgroup [64–67].

③ **SHH-II tumors**: This subgroup demonstrates consistently excellent outcomes with chemotherapy-only regimens, regardless of intraventricular methotrexate inclusion [63–65].

④ **Group 3 and Group 4:** Group 3 and Group 4 tumors constitute approximately 25% of infant medulloblastomas and are associated with poorer outcomes compared to SHH tumors. Group 3 tumors, in particular, show a five-year survival rate of less than 50% with chemotherapy alone, and the addition of focal RT does not improve survival in this subgroup [63–68].

Future clinical trials aim to enhance outcomes by optimizing systemic chemotherapy and exploring pre-relapse reduced-dose craniospinal RT or novel therapeutic agents [69].

Average-risk disease in children ≥ 3 years of age

For children with medulloblastoma amenable to total or near-total resection, typically aged 3–5 years or older without high-risk features, the standard treatment includes surgery, craniospinal radiation therapy (RT) at 23.4 Gy to the craniospinal axis, followed by a tumor bed boost of 30.6 Gy, totaling 54 Gy [48]. This approach reflects modern protocols, such as COG ACNS0331, which enrolled 549 patients aged 3–21 years with average-risk medulloblastoma between 2004 and 2014 [48]. Two RT-related randomizations were conducted:

① Boost comparison: Involved field vs. posterior fossa RT.

② Dose reduction: Standard-dose (23.4 Gy) vs. reduced-dose (18 Gy) craniospinal RT for children aged 3–7 years.

All participants received weekly vincristine during RT, followed by alternating cycles of cisplatin, lomustine, and vincristine (cycle A) and cyclophosphamide with vincristine (cycle B) on an AABAABAAB schedule. However, subsequent trials, particularly SJMB, have discontinued weekly vincristine during craniospinal RT, while COG and SIOP protocols continue its use [69].

Among 464 evaluable patients (median follow-up: 9.3 years), five-year event-free survival (EFS) and overall survival (OS) rates were 81% and 85%, respectively [48]. Outcomes for involved field and posterior fossa RT boosts were comparable (five-year EFS: 82.5% vs. 80.5%; OS: 84.6% vs. 85.2%). No posterior fossa failures occurred outside the limited boost volume in the involved field group. Reducing the boost volume was hypothesized to lower toxicity, but ototoxicity and neurocognitive outcomes were similar between groups. Longer follow-up is needed to assess long-term benefits of reduced RT exposure.

In dose randomization, reduced-dose RT (18 Gy) yielded inferior outcomes compared to 23.4 Gy in children aged 3–7 years, with five-year EFS rates of 71.4% vs. 82.9% (HR 1.67; $p = 0.28$) and OS rates of 77.5% vs. 85.6% ($p = 0.049$) [48]. Post hoc analyses showed poorer survival primarily in Group 4 tumors, with no significant impact in the Wingless (Wnt) subgroup. Ongoing trials are testing reduced doses (15–18 Gy) for Wnt and low-risk Group 4 tumors with chromosome 11 loss. However, outside clinical trials, 23.4 Gy remains the standard for average-risk medulloblastomas due to inferior outcomes with reduced doses [48, 70, 71].

Adjuvant multidrug chemotherapy following RT is standard for average-risk disease. COG phase III trials [48, 72] show survival outcomes surpassing earlier RT-alone trials, even at higher doses [35, 50], and match or exceed intensive chemotherapy regimens [73, 74].

Toxicities observed in COG Trials

The combination of craniospinal RT and multiagent chemotherapy in average-risk medulloblastoma is associated with significant toxicities [48, 75–83]:

- **Hematologic toxicity**: Nearly all patients experienced grade 3 or 4 acute hematologic toxicity during treatment.

- **Ototoxicity**: Severe ototoxicity occurred in ~ 25% of patients. Secondary analyses indicated no correlation between cumulative cisplatin dose and survival, suggesting lower doses might reduce toxicity without compromising outcomes [76].
- **Neurologic sequelae**: Significant neurologic deficits were observed in ~ 25% of patients, with ~ 50% persisting after one year [75].
- **Secondary malignancies**: The 10-year secondary cancer rate was 4.2% [75].
- **Neurocognitive decline**: Progressive declines in IQ and processing speed were noted, particularly in younger children [50].
- **Endocrine abnormalities**: Endocrine dysfunction is prevalent, with growth hormone (GH) deficiency affecting up to 90% of survivors, requiring GH replacement to mitigate growth impairment and improve quality of life [76–78]. Other common issues include hypothyroidism (50%), adrenal insufficiency, and hypogonadism, with risks increasing with RT dose and younger age at treatment [79]. Recent data suggest proton RT reduces endocrine abnormalities (e.g., hypothyroidism) by minimizing thyroid exposure compared to photon RT, though central deficiencies persist [80].

High-risk disease in children aged ≥ 3 years

The optimal treatment for high-risk medulloblastoma, including metastatic, unresectable, or anaplastic/large cell histology, remains uncertain. Despite multimodal therapies combining radiotherapy (RT) and chemotherapy, these patients face elevated risks of recurrence and mortality.

Emerging evidence suggests that concurrent chemotherapy during craniospinal RT exacerbates toxicity without substantial survival benefits in most subgroups. Consequently, many centers and trials have shifted away from this approach, except in specific cases such as Group 3 tumors, as discussed below [69]. Post-RT multiagent chemotherapy remains the standard of care, with RT doses typically higher than those used in average-risk cases. Standard high-risk regimens include 36 Gy craniospinal RT with an 18 Gy primary site boost.

For example, the COG ACNS0332 trial evaluated 294 children aged 3–18 years with high-risk medulloblastoma (72% metastatic) [81]. Patients received craniospinal RT (36 Gy) with weekly vincristine, with or without daily carboplatin, followed by six cycles of maintenance chemotherapy (cisplatin, cyclophosphamide, vincristine). A secondary randomization to isotretinoin maintenance was terminated early due to futility. Among 261 evaluable patients (median follow-up 6.7 years), carboplatin addition did not significantly improve five-year event-free survival (EFS: 66.4% vs. 59.2%, $p = 0.11$) or overall survival (OS: 77.6% vs. 68.8%, $p = 0.28$). Carboplatin use increased hematologic toxicity during RT and initial chemotherapy cycles, though ototoxicity and neurocognitive outcomes were similar between groups.

Subgroup analysis revealed potential benefits of concurrent carboplatin for Group 3 tumors ($n = 79$), with improved five-year EFS (73.2% vs. 53.7%, $p = 0.047$) and a trend toward better OS (82.8% vs. 63.7%, $p = 0.06$) [81]. While further prospective validation is needed, these findings have led some clinicians to consider carboplatin during RT for Group 3 patients.

High-dose chemotherapy followed by autologous hematopoietic cell transplantation (HCT) has also been investigated for high-risk medulloblastoma. One prospective study reported a five-year EFS of 70% without treatment-related mortality following craniospinal RT (36–39.6 Gy), four cycles of high-dose chemotherapy, and autologous HCT [82]. Another study using a more intensive chemotherapy regimen but reduced craniospinal RT (23.4–30.6 Gy) achieved five-year EFS and OS rates of 70% and 74%, respectively, though treatment-related mortality was 10% [62, 83]. Larger trials are needed to determine whether the benefits of this approach justify the associated risks.

Hyperfractionated accelerated RT combined with multidrug chemotherapy is another investigational strategy. This approach has demonstrated feasibility in at least two prospective studies [79, 84–86], but its impact on long-term survival remains to be fully established.

To better illustrate the comprehensive treatment strategies for pediatric medulloblastoma across varying risk profiles, we present a summarized diagram (Fig. 1). This figure highlights the stratified management approach based on risk categories and patient age, emphasizing optimal safe excision followed by tailored adjuvant therapies. High-risk children (> 3 years) require intensified craniospinal irradiation (CSI) with adjuvant multi-agent chemotherapy, while average-risk children benefit from reduced-dose CSI combined with adjuvant therapy, focusing on de-escalation in low-risk molecular subgroups. For young children (< 3 years), systemic multi-agent chemotherapy plays a central role, with or without intraventricular chemotherapy based on tumor characteristics. Research priorities include exploring novel agents and consolidative high-dose chemotherapy for high-risk groups. This visual framework systematically presents the therapeutic roadmap, facilitating a clearer understanding of individualized strategies, recurrent disease management, and long-term complication surveillance in pediatric medulloblastoma care.

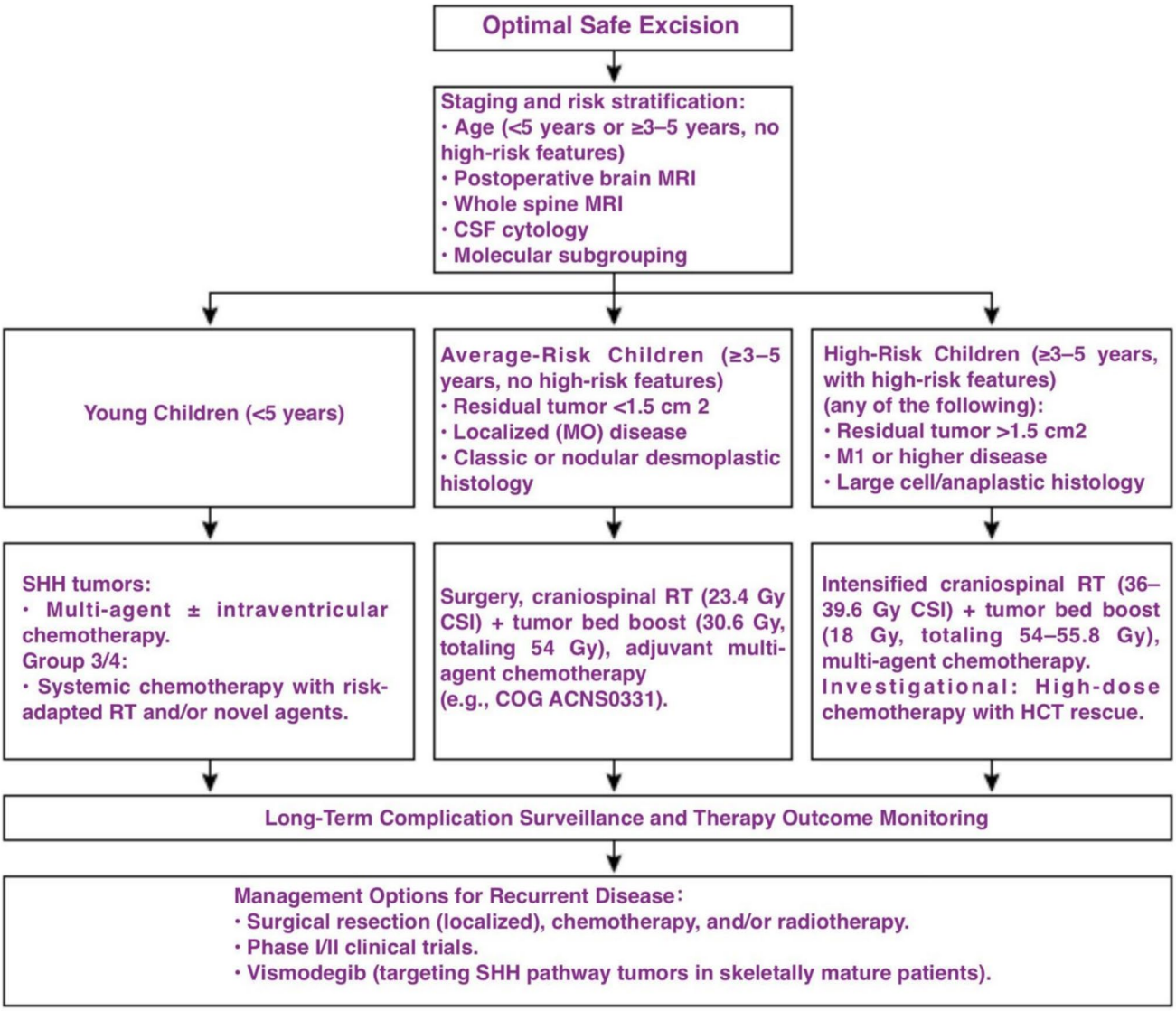

Fig. 1 This figure outlines the key treatment steps and strategies, offering readers a comprehensive framework for understanding the therapeutic landscape. CSI: Craniospinal Irradiation, Gy: Gray (a unit of radiation dose), SHH: Sonic Hedgehog, M0: Localized disease with no metastasis, PS boost: Posterior fossa boost, HCT: Hematopoietic Cell Transplant

Adults

Adults

Medulloblastoma in adults is rare, accounting for less than 1% of all brain tumors, with an annual incidence of approximately 0.5 per million, predominantly affecting individuals aged 20–40 years [1, 87–90]. Treatment strategies are largely extrapolated from pediatric data due to limited adult-specific randomized controlled trials (RCTs), particularly regarding chemotherapy's role. Adult medulloblastoma exhibits distinct molecular profiles, with Group 4 tumors and SHH TP53-mutated subtypes more common, often presenting with poorer outcomes compared to children [2].

Surgery and risk stratification

Maximal safe resection remains the cornerstone, followed by staging with postoperative brain MRI (within 48 h), spinal MRI with contrast, and lumbar CSF cytology (preoperative or 2–3 weeks postoperatively for specificity). Average-risk adults are defined by residual tumor < 1.5 cm^2, negative spine MRI/CSF, no metastases beyond the cerebellum, and classic/desmoplastic histology. High-risk adults have bulky residual disease (> 1.5 cm^2), leptomeningeal/distant metastases, or large cell/anaplastic histology, with molecular

markers like MYC amplification (Group 4) and TP53 mutations (SHH) indicating poorer prognosis [3, 4].

Average-risk adults

Standard treatment includes craniospinal RT (30–36 Gy) with a tumor bed boost to 54 Gy, followed by multi-agent chemotherapy (e.g., Packer protocol: cisplatin, cyclophosphamide/lomustine, vincristine), though RT alone may suffice for older or frail patients. Weekly vincristine during RT is generally avoided due to toxicity. The NCT01857453 trial (ongoing, reduced-dose RT) lacks adult efficacy data [5]. The EORTC trial (1634) was closed due to poor accrual [6]. Retrospective studies supporting these findings are summarized in Table 5 [91–98].

High-risk adults

High-risk adults receive intensified craniospinal RT (30–36 Gy) with a tumor bed boost, plus multi-agent chemotherapy, with pre-RT or concurrent chemotherapy for fit patients. A phase II trial (26 patients) reported 73% five-year OS with upfront cisplatin [7].

Recurrent disease

Recurrent cases require individualized management: re-resection, chemotherapy, re-irradiation, or high-dose chemotherapy with HCT for no residual disease, and vismodegib for SHH tumors [8]. Outcomes remain poor, emphasizing clinical trial enrollment.

A visual summary of these risk-stratified management strategies for adult medulloblastoma, encompassing excision, staging, treatment approaches, and surveillance, is presented in Fig. 2 to provide a comprehensive framework for clinical practice [9].

Post-therapy monitoring

Following treatment and restaging, patients undergo regular monitoring to identify treatment-related complications and detect disease recurrence. Our standard protocol involves:

- Every three months: Evaluations during the first 1–2 years.
- Semi-annual to annual visits: Over the next 5–10 years.
- Every 1–2 years: Long-term follow-up, or as clinically indicated.

Each visit includes a detailed history, physical examination, and brain MRI to assess for recurrence. Spine MRI is reserved for patients with a history of spinal involvement or when clinically warranted.

Routine screening spine MRIs offer limited utility in patients without prior disseminated disease. In an observational study of 89 medulloblastoma patients, 990 brain MRIs and 758 spine MRIs were performed over a median follow-up of 52 months [99]. Isolated spine recurrence was detected in only five spine MRIs, yielding a detection rate of 0.7% (7/1000).

Recurrent disease in medulloblastoma

Despite significant advancements in treatment, 20–30% of children with medulloblastoma experience relapse following initial therapy [100]. Recurrences are classified into three categories:

- Localized recurrence: ~ 33% of cases.
- Disseminated recurrence (brain or spine): ~ 33%.
- Combined local and disseminated recurrence: ~ 33% [35, 72, 101].

Table 5 Summary of retrospective studies on adult medulloblastoma treatment outcomes

Study (Refs.)	Patients (n)	Treatment	Follow-up	EFS/OS rates	Key findings
Kann et al.[91]	146	RT ± Chemo	Median 5 yrs	59%/67%(5-yr)	Chemo improves OS vs. RT alone
Padovani et al.[92]	253	RT ± Chemo	Median 6 yrs	62%/68%(5-yr)	Combined modality better than RT alone
Franceschi et al.[93]	112	RT + Chemo	Median 4 yrs	65%/71%(5-yr)	Chemo beneficial for average-risk
Brandes et al. [94]	38	Tailored RT/Chemo	Median 3 yrs	67%/70%(3-yr)	High/low-risk stratification effective
Kocakaya et al.[95]	Meta-analysis	RT ± Chemo	Variable	60%/65%(5-yr)	Chemo improves long-term survival
Beier et al.[96]	38	RT + Chemo (NOA-07)	3 yrs	67%/70%(3-yr)	High toxicity in older aduts
Friedrich et al.[97]	70	RT ± Chemo	44 months	68%/89%(4-yr)	Residual tumor predicts poor outcomes
Brandes et al. [98]	26	Chemo + RT	5 yrs	N/A/73%(5-yr)	Upfront chemo improves OS in high-risk

EFS = Event-Free Survival; OS = Overall Survival; RT = Radiotherapy; Chemo = Chemotherapy

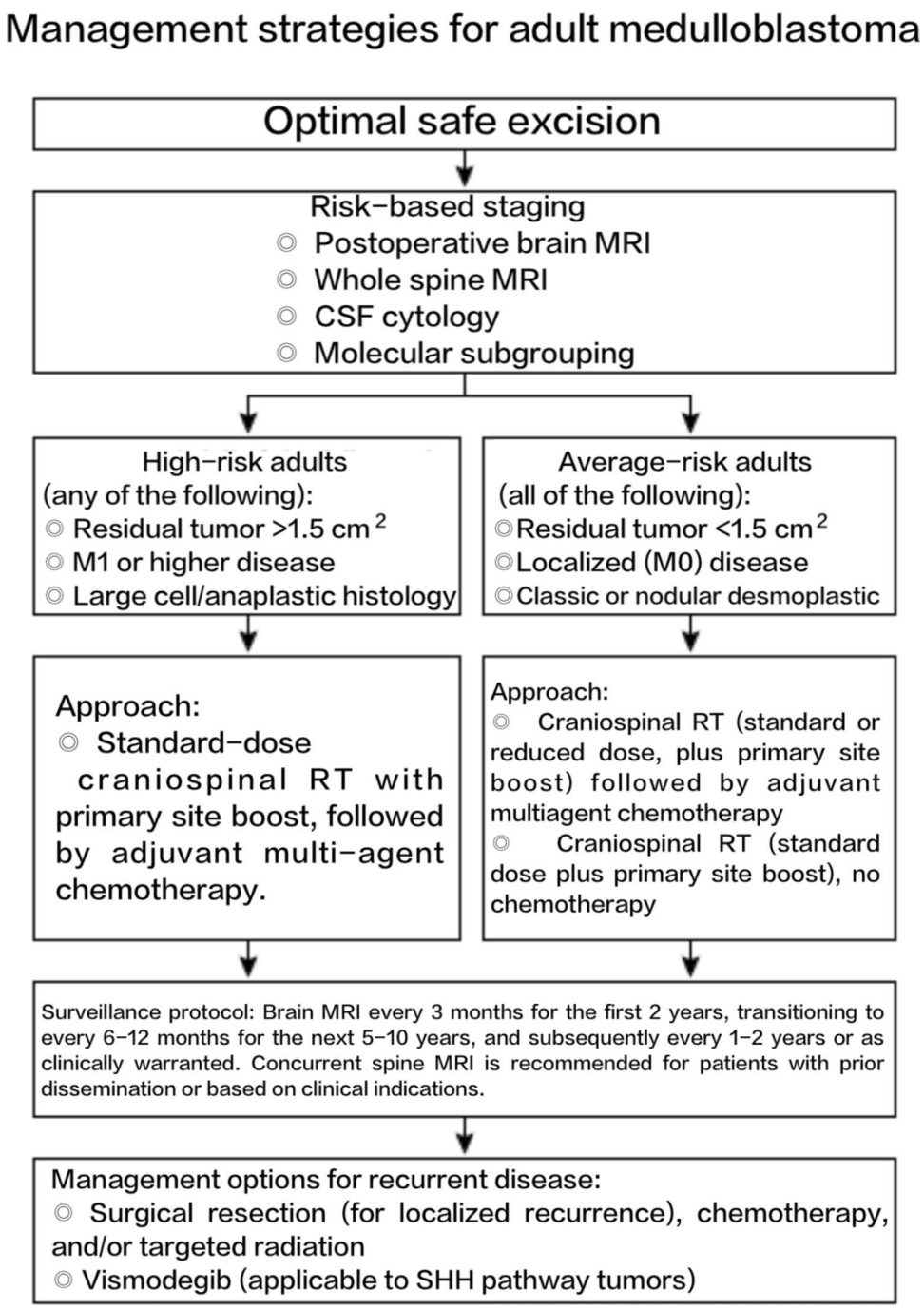

Fig. 2 Management Strategies for Adult Medulloblastoma. This figure illustrates a risk-stratified approach to adult medulloblastoma management, covering optimal safe excision, risk-based staging (postoperative brain MRI, whole spine MRI, CSF cytology, molecular subgrouping), treatment for average-risk (craniospinal RT ± chemotherapy) and high-risk adults (intensified RT + chemotherapy), long-term surveillance, and options for recurrent disease

In pediatric cases, most relapses occur within the first three years post-diagnosis, while adults are more likely to experience late relapses or extraneural metastases, particularly involving bone or bone marrow. Extraneural spread is rare in children treated with modern protocols [95, 102].

Prognosis and treatment

The prognosis for recurrent medulloblastoma remains poor, especially in patients with prior craniospinal radiation therapy (RT). High-dose chemotherapy with autologous hematopoietic cell transplantation (HCT) has

shown potential in selected patients, with studies reporting prolonged disease-free survival in 20–25% of those without prior RT exposure [97, 100, 103–105].

For patients who have received RT, HCT is generally ineffective. Alternative salvage regimens include:

- Chemotherapy combinations: Temozolomide, irinotecan, and bevacizumab [106].
- Multidrug oral regimens: Low-dose etoposide, cyclophosphamide, bevacizumab, thalidomide, fenofibrate, and celecoxib [107].

While these approaches may extend progression-free survival, long-term cures are rare. Enrollment in clinical trials exploring novel agents is strongly encouraged.

Special considerations for infants and young children

In infants and young children relapsing after surgery and chemotherapy without prior craniospinal RT, salvage RT can sometimes achieve prolonged disease-free survival. A multicenter retrospective study of 380 children with relapsed medulloblastoma after non-RT-based therapy reported promising outcomes [108]. Among 294 patients treated with craniospinal RT and systemic chemotherapy with curative intent, three- and five-year post-relapse survival rates were 52% and 43%, respectively.

Factors associated with improved outcomes

Multivariable analysis of 150 patients with molecular subgroup data identified the following factors associated with better survival [109]:

- Localized relapse.
- Sonic Hedgehog (SHH) subgroup.
- Treatment with craniospinal RT.
- Age ≥ 36 months at initial diagnosis.

The recurrence patterns of pediatric medulloblastoma and corresponding management strategies are presented visually in Table 6. To enhance clarity, the original tabular data has been converted into a graphical representation. This figure provides a concise overview of localized, disseminated, combined recurrence types, and the rare extraneural metastasis, along with their respective management strategies.

Emerging therapies

Targeting molecular pathways in medulloblastoma

Recent research has focused on targeting molecular pathways involved in medulloblastoma pathogenesis, particularly the Sonic Hedgehog (SHH) pathway [110]. Smoothened (SMO) inhibitors, such as vismodegib—FDA-approved for advanced basal cell carcinoma—have demonstrated variable efficacy in SHH-driven medulloblastomas [111, 112]. However, challenges remain, including understanding acquired resistance mechanisms and identifying molecular predictors of response within this genetically diverse subgroup [113, 114]. Clinical trial outcomes to date have been inconsistent.

Clinical trial data

① **Pediatric Brain Tumor Consortium Phase II Trials**:

- Participants: 31 adults and 12 pediatric patients with recurrent medulloblastoma treated with vismodegib (150–300 mg/day) [98].
- Findings:

None of the 31 patients with non-SHH pathway tumors responded.

Among 12 SHH pathway tumor patients, four achieved a protocol-defined response (complete or partial response lasting ≥8 weeks).

Predictors of Response: Mutations in PTCH1 and/or loss of heterozygosity were associated with positive responses.

Resistance Markers: Nonresponders predominantly exhibited downstream alterations (e.g., SUFU, GLI2 mutations)

Table 6 Pediatric medulloblastoma: clinical guide to recurrence and treatment

Recurrence type	Frequency	Common sites	Management strategy
Local recurrence	30–40%	Tumor bed (posterior fossa)	Repeat surgery + focal RT or intensified chemotherapy
Disseminated (brain/spine)	30–50%	Leptomeningeal spread	Craniospinal RT + multi-agent systemic chemotherapy
Combined recurrence	~20%	Brain and spine	Personalized therapy (e.g., molecular-targeted therapy, high-dose chemotherapy + HCT)
Extraneural metastasis	Rare (< 5%)	Bones, bone marrow	Systemic chemotherapy; consider clinical trial enrollment

The original tabular data has been adapted for better visual presentation

or diffuse p53 staining, indicative of TP53-mutant SHH tumors.

② **Phase I/II Trial: Temozolomide With or Without Vismodegib**:

Participants: 24 adult patients with recurrent or refractory medulloblastoma, focusing on those with Sonic Hedgehog pathway activation [114].

Findings: The combination of temozolomide and vismodegib was safe but did not improve progression-free survival outcomes [115].

Genetic predisposition and prognosis

Advancements in Multimodality Therapy and Prognosis in Medulloblastoma.

With significant progress in multimodality therapy, approximately 75% of children diagnosed with medulloblastoma now survive into adulthood. However, certain clinical and histologic factors are associated with worse outcomes, including younger age (< 3 years), disseminated or metastatic disease at diagnosis, residual tumor > 1.5 cm^2 after resection, large cell/anaplastic histology, and MYC amplification.

Genetic factors also play a critical role in prognosis. Germline mutations associated with cancer predisposition are identified in 5–6% of all medulloblastoma patients, with up to 20% of those in the SHH subgroup harboring these mutations (Table 2) [12]. Testing for germline mutations is recommended in high-risk subgroups or in cases with a family history suggesting increased cancer risk. Identifying these mutations is essential for genetic counseling and surveillance for associated malignancies.

Patients with germline mutations generally have poorer outcomes, with five-year progression-free survival (PFS) rates of 52% (95% CI 40–69) and overall survival (OS) rates of 65% (95% CI 52–81) [12].

Prognosis by subgroup

Children aged ≥ 3 years

Prognostic stratification has been significantly refined through molecular subgrouping, as demonstrated in the SJMB03 trial, which investigated risk-adapted therapy in 330 children aged 3–21 years [69].

- SHH Tumors: Two prognostic groups were identified:
- Low-risk SHH: Defined by the absence of metastatic disease, TP53 mutations, large cell/anaplastic histology, MYC amplification, GLI2 mutations, and chromosome 17p loss. These patients showed excellent outcomes, with a five-year PFS of 100%.
- High-risk SHH: Characterized by poor outcomes, with a PFS of < 50%. Germline mutations in SUFU, PTCH1, TP53, PALB2, and BRCA2 are common, with TP53 mutations particularly linked to poor prognosis [12].
- Wnt Tumors: All 53 children with Wnt pathway tumors remained progression-free at five years. However, four late deaths occurred due to second malignancies or pulmonary fibrosis [69]. Current trials are exploring the potential of reduced therapy for this subgroup. Germline APC mutations are more frequent in patients lacking CTNNB1 somatic mutations [12].
- Group 3 and Group 4 Tumors: These subgroups exhibit overlapping biology and are classified into three risk categories based on molecular and methylation analyses. Poor prognostic factors include MYC amplification and metastatic disease at diagnosis, with a five-year PFS of ~ 50% for patients with either risk factor. Germline mutations in PALB2 and BRCA2 are more frequently observed in these groups [12].

Infants and children aged < 3 years

For children under three years of age, the prognosis has improved with modern protocols, with five-year survival rates varying by risk and molecular subtype. In non-metastatic cases, such as those in the HIT 2000 trial, 45 patients (median age 2.5 years) achieved a five-year event-free survival (EFS) of 57% ± 8% and overall survival (OS) of 80% ± 6% at a median follow-up of 4.5 years [63]. Survival is significantly lower (15–30%) in those with disseminated disease at diagnosis, reflecting challenges in reducing or omitting radiation therapy in this vulnerable population. Germline mutations in SUFU and PTCH1 are most prevalent in infants, with a median diagnosis age of two years [12].

Adults

Adults diagnosed with medulloblastoma generally have worse outcomes than children, with long-term survival rates ranging from 50–80% [116–121]. Modern multimodality treatments may improve these survival figures [120]. Poor prognostic factors in adults include older age (> 30 years), incomplete resection, and disseminated disease.

Late recurrences (> 5 years) and extracranial metastases are rare but have been documented [120]. Group 4 tumors in adults are particularly challenging due to a high prevalence of high-risk features and large cell/anaplastic histology [122]. Germline mutations in PALB2 and BRCA2 are also more commonly observed in adults [12].

Complications of treatment

Medulloblastoma survivors, particularly those diagnosed in childhood or adolescence, often experience delayed and early treatment-related complications that significantly affect their quality of life (QoL) and longevity [123, 124]. Craniospinal radiation therapy (RT) and chemotherapy are primary contributors to these late effects, with multimodal treatment exacerbating many adverse outcomes [35, 125]. Survivorship guidelines for childhood central nervous system (CNS) tumors, published by the Children's Oncology Group (COG), provide comprehensive recommendations for monitoring and managing these complications [126]. This section focuses on the most impactful long-term complications, prioritizing cognitive decline and rehabilitation, vascular complications, secondary tumors, endocrine issues, hearing loss, early aging, and socio-economic outcomes for survivors.

Posterior fossa syndrome (PFS)

PFS, or cerebellar cognitive affective syndrome, is an early complication occurring in ~ 25% of medulloblastoma patients, typically within 1–2 days post-surgery [127]. It results from injury to the inferior cerebellar vermis and outflow pathways, disrupting cerebellum-mediodorsal thalamus communication. PFS manifests as difficulties in language production, emotional instability, impaired attention, and, in severe cases, motor initiation challenges, with additional symptoms like cranial nerve palsies and bowel/bladder incontinence [128–131]. Symptoms may improve over weeks to months but can persist for years in severe cases. In a COG study of 450 children, 24% experienced PFS, with 92% moderately to severely affected [132]. Long-term neurocognitive deficits, including declines in intellectual ability, processing speed, and attention, often worsen over time, necessitating early rehabilitation [133].

Cognitive decline and rehabilitation measures

Neurocognitive deficits are frequent and severe after medulloblastoma treatment, particularly in young children, with adult survivors half as likely as siblings to attain a college degree [134]. Risk factors include younger age at treatment, high-risk disease, and higher RT doses [124, 135]. Deficits include processing speed, attention, and working memory impairments, with late-onset toxicities more pronounced in younger patients [136–142]. Repeated anesthesia exposure may exacerbate risks [141]. Limited evidence suggests proton RT mitigates decline compared to photon RT [38, 39, 135]. Rehabilitation strategies—neuropsychological evaluations, cognitive therapy, and educational support—are critical to improve QoL, especially during school transitions [143].

Vascular complications (stroke)

Survivors face an elevated risk of cerebrovascular complications, including occlusive disease, intracranial hemorrhage, and cavernous malformations, heightened in children and worsened by concurrent chemotherapy [144]. Stroke risk increases with RT dose and age at treatment, with long-term studies reporting a 5–10% incidence by adulthood [145]. Preventive measures include regular cardiovascular monitoring, lipid management, and lifestyle interventions to mitigate vascular aging, significantly impacting survivor independence and QoL.

Secondary neoplasms

Medulloblastoma survivors are at increased risk for secondary malignancies, including brain and thyroid cancers, meningiomas, and hematologic malignancies [49, 145]. A COG phase III study reported a 10-year secondary cancer incidence of 4.2%, with 15 cases at a median of 5.8 years [75]. A long-term study of nearly 1,000 survivors found a 9.5% cumulative incidence, with meningiomas accounting for one-quarter of cases [124]. Annual physical exams, dermatologic evaluations, and brain MRIs are recommended for early detection, critical for maintaining QoL and longevity.

Endocrine abnormalities

Endocrine dysfunction is common, involving growth hormone (GH) deficiency (94% of survivors), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), or gonadal hormone deficiencies, plus primary hypothyroidism or early puberty [146–155]. A study of 88 children found GH deficiency requiring replacement to mitigate growth impairment and improve QoL [154]. Proton RT reduces thyroid exposure and primary hypothyroidism but not central deficiencies [151, 156]. Annual endocrine evaluations are essential for managing these complications and optimizing survivor health.

Hearing loss

Ototoxicity affects 40–60% of long-term survivors, often requiring hearing aids [38, 124, 134]. Proton RT and IMRT may reduce this risk, but longer follow-up is needed [38, 42, 141]. Baseline audiograms before cisplatin/RT, followed by biennial monitoring, are critical. Sodium thiosulfate, FDA-approved in 2022, reduces cisplatin-induced hearing loss

Table 7 Key long-term complications in medulloblastoma survivors: incidence, impact, and management strategies

Complication	Incidence	Management strategies
Posterior fossa syndrome	~25%	Supportive care, intensive rehabilitation
Persistent hydrocephalus	15–30%	CSF shunting or ETV (endoscopic third ventriculostomy)
Neurological deficits	Varies	Physical therapy, multidisciplinary follow-up

by ~ 40%, though its role in medulloblastoma requires further evaluation [142–145]. Hearing loss impacts communication, education, and QoL, necessitating early intervention.

Early aging

Medulloblastoma survivors, especially those treated in childhood, experience accelerated aging, manifesting as premature cardiovascular, musculoskeletal, and cognitive decline [156]. Craniospinal RT and chemotherapy contribute to cellular senescence, increasing risks of frailty, osteoporosis, and chronic fatigue by adulthood [157]. Preventive strategies—exercise, nutrition, and regular health screening—are vital to mitigate early aging and maintain QoL.

Socio-economic insertion of long-term survivors

Long-term survivors often face challenges in socio-economic independence, including employment, driving capacity, and social integration, due to neurocognitive, physical, and endocrine deficits [158]. Studies show survivors are less likely to achieve full-time employment or live independently compared to peers, with QoL impacted by treatment-related disabilities [159]. Rehabilitation programs, vocational training, and policy support are essential to enhance independence, job opportunities, and driving safety, improving overall well-being.

A visual summary of these key long-term complications, including their incidence, clinical impact, and management strategies, is presented in Table 7 to facilitate understanding and guide clinical practice [160].

This Table 7 summarizes the incidence, clinical impact, and management approaches for cognitive decline, vascular complications, secondary neoplasms, endocrine abnormalities, hearing loss, early aging, and socio-economic outcomes, emphasizing rehabilitation and QoL preservation.

Conclusion

Advancements in molecular classification have revolutionized medulloblastoma risk stratification and treatment, enabling precision therapy and guiding clinical trial designs. Genetic testing for germline mutations is recommended for cancer risk assessment, and clinical trial participation is encouraged to access advanced therapies.

Maximal safe resection remains essential for diagnosis, intracranial pressure relief, and tumor control, with postoperative treatments tailored to factors like age, disease status, and molecular subgroup. Standard therapies for average-risk patients include craniospinal radiation therapy (RT) and chemotherapy, while high-risk patients require intensified regimens.

For young children, chemotherapy with stem cell rescue is preferred to minimize neurologic toxicity, while older children and adults generally undergo craniospinal RT and chemotherapy, adjusted for age and risk. High-risk cases may require pre-RT chemotherapy or modifications to reduce toxicity.

Despite improved survival rates, long-term complications such as neurocognitive deficits, hearing loss, and secondary malignancies remain significant challenges. Ongoing research focuses on refining treatment strategies to balance survival outcomes with quality of life.

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Declarations

Competing interests The authors declare that they have no competing interests.

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human participants or animals. As such, ethics approval and consent to participate were not required for this work. The article adheres to ethical publishing standards in medical research.

Consent for publication All authors have reviewed the manuscript and provided their consent for its publication in.

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References

1. Eberhart CG, Kepner JL, Goldthwaite PT, et al. Histopathologic grading of medulloblastomas: a Pediatric Oncology Group study. Cancer. 2002;94:552.
2. Kleihues P, Burger PC, Scheithauer BW. Histological typing of tumors of the central nervous system. Berlin: Springer; 1993.
3. Katsetos CD, Liu HM, Zacks SI. Immunohistochemical and ultrastructural observations on Homer Wright (neuroblastic) rosettes and the "pale islands" of human cerebellar medulloblastomas. Hum Pathol. 1988;19:1219.
4. Giangaspero F, Eberhart CG, Haapasalo H, et al. Medulloblastoma. In: WHO Classification of Tumours of the Central Nervous System, 4th ed, Louis DN, Ohgaki H, Wiestler OD, Cavenee WK editors, IARC, Lyon 2007. p. 132.
5. Sure U, Berghorn WJ, Bertalanffy H, et al. Staging, scoring and grading of medulloblastoma. A postoperative prognosis predicting system based on the cases of a single institute. Acta Neurochir. 1995;132:59.
6. Leonard JR, Cai DX, Rivet DJ, et al. Large cell/anaplastic medulloblastomas and medullomyoblastomas: clinicopathological and genetic features. J Neurosurg. 2001;95:82.
7. McLendon RE, Friedman HS, Fuchs HE, et al. Diagnostic markers in paediatric medulloblastoma: a Paediatric Oncology Group Study. Histopathology. 1999;34:154.
8. Kozmik Z, Sure U, Rüedi D, et al. Deregulated expression of PAX5 in medulloblastoma. Proc Natl Acad Sci U S A. 1995;92:5709.
9. Yokota N, Aruga J, Takai S, et al. Predominant expression of human zic in cerebellar granule cell lineage and medulloblastoma. Cancer Res. 1996;56:377.
10. Evans G, Burnell L, Campbell R, et al. Congenital anomalies and genetic syndromes in 173 cases of medulloblastoma. Med Pediatr Oncol. 1993;21:433.
11. Evans DG, Farndon PA, Burnell LD, et al. The incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma. Br J Cancer. 1991;64:959.
12. Waszak SM, Northcott PA, Buchhalter I, et al. Spectrum and prevalence of genetic predisposition in medulloblastoma: a retrospective genetic study and prospective validation in a clinical trial cohort. Lancet Oncol. 2018;19:785.
13. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, DeGroot J, Wick W, Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Chang SM, Yung WK, Vogelbaum MA, van den Bent MJ, Carlson MD, Giannini C, Henderson F, Mehta MP, Prados MD. Response assessment in neuro-oncology clinical trials. J Clin Oncol. 2017;35(21):2430–40. https://doi.org/10.1200/JCO.2017.73.6229.
14. Iv M, Zhou M, Shpanskaya K, Perreault S, Wang Z, Tranvinh E, Lanzman B, Vajapeyam S, Vitanza NA, Fisher PG, Cho YJ, Laughlin S, Ramaswamy V, Taylor MD, Cheshier SH, Grant GA, Young Poussaint T, Gevaert O, Yeom KW. MR imaging-based radiomic signatures of distinct molecular subgroups of medulloblastoma. Am J Neuroradiol. 2019;40(1):154–61. https://doi.org/10.3174/ajnr.A5899.
15. Zhang M, Wong SW, Wright JN, Wagner MW, Toescu S, Han M, Tam LT, Zhou Q, Ahmadian SS, Shpanskaya K, Lummus S, Lai H, Eghbal A, Radmanesh A, Nemelka J, et al. MRI radiogenomics of pediatric medulloblastoma: a multicenter study. Radiology. 2022;304(2):406–16. https://doi.org/10.1148/radiol.212137.
16. Galicich JH, French L, Melby J. Use of dexamethasone in treatment of cerebral edema associated with brain tumors. J Lancet. 1961;81:46.
17. Chang SM, Messersmith H, Ahluwalia M, et al. Anticonvulsant prophylaxis and steroid use in adults with metastatic brain tumors: summary of SNO and ASCO endorsement of the Congress of Neurological Surgeons guidelines. Neuro Oncol. 2019;21:424.
18. Roth P, Pace A, Le Rhun E, et al. Neurological and vascular complications of primary and secondary brain tumours: EANO-ESMO Clinical Practice Guidelines for prophylaxis, diagnosis, treatment and follow-up. Ann Oncol. 2021;32:171.
19. Vecht CJ, Hovestadt A, Verbiest HB, et al. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day. Neurology. 1994;44:675.
20. Ryken TC, McDermott M, Robinson PD, et al. The role of steroids in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2010;96:103.
21. Use of glucocorticoids in neuro-oncology. In: Neurological complications of cancer. New York: Marcel Dekker; 1995. p. 199.
22. Lim-Fat MJ, Bi WL, Lo J, et al. Letter: when less is more: dexamethasone dosing for brain tumors. Neurosurgery. 2019;85:E607.
23. Kehlet H, Binder C, Blichert-Toft M. Glucocorticoid maintenance therapy following adrenalectomy: assessment of dosage and preparation. Clin Endocrinol. 1976;5:37.
24. Kaal EC, Vecht CJ. The management of brain edema in brain tumors. Curr Opin Oncol. 2004;16:593.
25. Raimondi AJ, Tomita T. Medulloblastoma in childhood. Acta Neurochir (Wien). 1979;50:127.
26. Park TS, Hoffman HJ, Hendrick EB, et al. Medulloblastoma: Clinical presentation and management. Experience at the hospital for sick children, Toronto, 1950–1980. J Neurosurg. 1983;58:543.
27. Berry MP, Jenkin RD, Keen CW, et al. Radiation treatment for medulloblastoma. A 21-year review. J Neurosurg. 1981;55:43.
28. Hughes EN, Shillito J, Sallan SE, et al. Medulloblastoma at the joint center for radiation therapy between 1968 and 1984. The influence of radiation dose on the patterns of failure and survival. Cancer. 1988;61:1992.
29. del Charco JO, Bolek TW, McCollough WM, et al. Medulloblastoma: Time-dose relationship based on a 30-year review. Int J Radiat Oncol Biol Phys. 1998;42:147.

30. Zeltzer PM, Boyett JM, Finlay JL, Albright AL, Rorke LB, Milstein JM, Allen JC, Stevens KR, Stanley P, Li H, Wisoff JH, Geyer JR, McGuire-Cullen P, Stehbens JA, Shurin SB, Packer RJ. Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: a Children's Cancer Group Study. J Clin Oncol. 1999;17(7):2127–36. https://doi.org/10.1200/JCO.1999.17.7.2127.
31. Thompson EM, Hielscher T, Bouffet E, et al. Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: a retrospective integrated clinical and molecular analysis. Lancet Oncol. 2016;17:484.
32. Thompson EM, Bramall A, Herndon JE 2nd, et al. The clinical importance of medulloblastoma extent of resection: a systematic review. J Neurooncol. 2018;139:523.
33. Keeling RM, Kumar R, Han X, Gerber NU, Hansford JR, Gottardo NG, Hanssen R, Wood P, Gottardo NG. Extent of resection and molecular subgrouping as predictors of survival in pediatric medulloblastoma: a single-institution cohort study. Neuro-Oncol Adv. 2024;6(1):vdae015. https://doi.org/10.1093/noajnl/vdae015.
34. Tarbell NJ, Loeffler JS, Silver B, et al. The change in patterns of relapse in medulloblastoma. Cancer. 1991;68:1600.
35. Taylor RE, Bailey CC, Robinson K, et al. Results of a randomized study of preradiation chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: The International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study. J Clin Oncol. 2003;21:1581.
36. St Clair WH, Adams JA, Bues M, et al. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. Int J Radiat Oncol Biol Phys. 2004;58:727.
37. Yuh GE, Loredo LN, Yonemoto LT, et al. Reducing toxicity from craniospinal irradiation: using proton beams to treat medulloblastoma in young children. Cancer J. 2004;10:386.
38. Huang E, Teh BS, Strother DR, et al. Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. Int J Radiat Oncol Biol Phys. 2002;52:599.
39. Moeller BJ, Chintagumpala M, Philip JJ, et al. Low early ototoxicity rates for pediatric medulloblastoma patients treated with proton radiotherapy. Radiat Oncol. 2011;6:58.
40. Brown AP, Barney CL, Grosshans DR, et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. Int J Radiat Oncol Biol Phys. 2013;86:277.
41. Eaton BR, Esiashvili N, Kim S, et al. Clinical outcomes among children with standard-risk medulloblastoma treated with proton and photon radiation therapy: a comparison of disease control and overall survival. Int J Radiat Oncol Biol Phys. 2016;94:133.
42. Yock TI, Yeap BY, Ebb DH, et al. Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study. Lancet Oncol. 2016;17:287.
43. Kahalley LS, Ris MD, Grosshans DR, et al. Comparing intelligence quotient change after treatment with proton versus photon radiation therapy for pediatric brain tumors. J Clin Oncol. 2016;34:1043.
44. Kahalley LS, Peterson R, Ris MD, et al. Superior intellectual outcomes after proton radiotherapy compared with photon radiotherapy for pediatric medulloblastoma. J Clin Oncol. 2020;38:454.
45. Baliga S, Gallotto S, Bajaj B, et al. Decade-long disease, secondary malignancy, and brainstem injury outcomes in pediatric and young adult medulloblastoma patients treated with proton radiotherapy. Neuro Oncol. 2022;24:1010.
46. Fukunaga-Johnson N, Lee JH, Sandler HM, et al. Patterns of failure following treatment for medulloblastoma: Is it necessary to treat the entire posterior fossa? Int J Radiat Oncol Biol Phys. 1998;42:143.
47. Wolden SL, Dunkel IJ, Souweidane MM, et al. Patterns of failure using a conformal radiation therapy tumor bed boost for medulloblastoma. J Clin Oncol. 2003;21:3079.
48. Michalski JM, Janss AJ, Vezina LG, et al. Children's oncology group phase III trial of reduced-dose and reduced-volume radiotherapy with chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol. 2021;39:2685.
49. Narayana A, Jeswani S, Paulino AC. The cranial-spinal junction in medulloblastoma: does it matter? Int J Radiat Oncol Biol Phys. 1999;44:81.
50. Thomas PR, Deutsch M, Kepner JL, et al. Low-stage medulloblastoma: Final analysis of trial comparing standard-dose with reduced-dose neuraxis irradiation. J Clin Oncol. 2000;18:3004.
51. Goldwein JW, Radcliffe J, Johnson J, et al. Updated results of a pilot study of low dose craniospinal irradiation plus chemotherapy for children under five with cerebellar primitive neuroectodermal tumors (medulloblastoma). Int J Radiat Oncol Biol Phys. 1996;34:899.
52. Ris MD, Packer R, Goldwein J, et al. Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. J Clin Oncol. 2001;19:3470.
53. Gandola L, Massimino M, Biassoni V, Pecori E, Schiavello E, Spreafico F, Poggi G, Morosi C, Sardi I, Balestrini A, Terenziani M, Ferrari A, Casanova M, Meazza C, Podda M, Belfontali T, Conte G, Arrigoni F, Cereda C, Giussani C, Solero C, Antonelli M, Fossati P, Potepan P, Piva L, Luksch R. Hyperfractionated radiotherapy for medulloblastoma: Long-term follow-up of the Milan experience. Pediatric Blood Cancer. 2020;67(11):e28629. https://doi.org/10.1002/pbc.28629.
54. Taylor RE, Bailey CC, Robinson K, et al. Outcomes after intensity-modulated radiation therapy for pediatric medulloblastoma: a single-institution experience. Int J Radiat Oncol Biol Phys. 2017;97(2):324–31. https://doi.org/10.1016/j.ijrobp.2016.10.027.
55. Douglas JG, Barker JL, Ellenbogen RG, Geyer JR. Concurrent chemotherapy and reduced-dose cranial spinal irradiation followed by conformal posterior fossa tumor bed boost for average-risk medulloblastoma: efficacy and patterns of failure. Int J Radiat Oncol Biol Phys. 2004;58:1161.
56. Duffner PK, Horowitz ME, Krischer JP, et al. Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. N Engl J Med. 1993;328:1725.
57. Kretschmar CS, Tarbell NJ, Kupsky W, et al. Pre-irradiation chemotherapy for infants and children with medulloblastoma: a preliminary report. J Neurosurg. 1989;71:820.
58. Walter AW, Mulhern RK, Gajjar A, et al. Survival and neurodevelopmental outcome of young children with medulloblastoma at St Jude Children's Research Hospital. J Clin Oncol. 1999;17:3720.
59. Rutkowski S, Bode U, Deinlein F, et al. Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. N Engl J Med. 2005;352:978.
60. Grill J, Sainte-Rose C, Jouvet A, et al. Treatment of medulloblastoma with postoperative chemotherapy alone: an SFOP prospective trial in young children. Lancet Oncol. 2005;6:573.
61. Mason WP, Grovas A, Halpern S, et al. Intensive chemotherapy and bone marrow rescue for young children with newly diagnosed malignant brain tumors. J Clin Oncol. 1998;16:210.
62. Geyer JR, Sposto R, Jennings M, et al. Multiagent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: a report from the Children's Cancer Group. J Clin Oncol. 2005;23:7621.
63. Mynarek M, von Hoff K, Pietsch T, et al. Nonmetastatic medulloblastoma of early childhood: results from the prospective clinical

trial HIT-2000 and An Extended Validation Cohort. J Clin Oncol. 2020;38:2028.
64. Robinson GW, Rudneva VA, Buchhalter I, et al. Risk-adapted therapy for young children with medulloblastoma (SJYC07): therapeutic and molecular outcomes from a multicentre, phase 2 trial. Lancet Oncol. 2018;19:768.
65. Lafay-Cousin L, Bouffet E, Strother D, et al. Phase II study of nonmetastatic desmoplastic medulloblastoma in children younger than 4 years of age: a report of the Children's Oncology Group (ACNS1221). J Clin Oncol. 2020;38:223.
66. Robinson GW, Gajjar A. Genomics paves the way for better infant medulloblastoma therapy. J Clin Oncol. 2020;38:2010.
67. Dhall G, O'Neil SH, Ji L, et al. Excellent outcome of young children with nodular desmoplastic medulloblastoma treated on "Head Start" III: a multi-institutional, prospective clinical trial. Neuro Oncol. 2020;22:1862.
68. Yeo KK, Margol AS, Kennedy RJ, et al. Prognostic significance of molecular subgroups of medulloblastoma in young children receiving irradiation-sparing regimens. J Neurooncol. 2019;145:375.
69. Gajjar A, Robinson GW, Smith KS, et al. Outcomes by clinical and molecular features in children with medulloblastoma treated with risk-adapted therapy: results of an international phase III trial (SJMB03). J Clin Oncol. 2021;39:822.
70. Kann BH, Park HS, Lester-Coll NH, et al. Postoperative radiotherapy patterns of care and survival implications for medulloblastoma in young children. JAMA Oncol. 2016;2:1574.
71. Gupta T, Pervez S, Dasgupta A, et al. Omission of upfront craniospinal irradiation in patients with low-risk WNT-pathway medulloblastoma is associated with unacceptably high risk of neuraxial failure. Clin Cancer Res. 2022;28:4180.
72. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol. 2006;24:4202.
73. Kortmann RD, Kühl J, Timmermann B, et al. Postoperative neoadjuvant chemotherapy before radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the treatment of medulloblastoma in childhood: results of the German prospective randomized trial HIT '91. Int J Radiat Oncol Biol Phys. 2000;46:269.
74. Kühl J, Müller HL, Berthold F, et al. Preradiation chemotherapy of children and young adults with malignant brain tumors: results of the German pilot trial HIT'88/'89. Klin Padiatr. 1998;210:227.
75. Packer RJ, Zhou T, Holmes E, et al. Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. Neuro Oncol. 2013;15:97.
76. Nageswara Rao AA, Wallace DJ, Billups C, et al. Cumulative cisplatin dose is not associated with event-free or overall survival in children with newly diagnosed average-risk medulloblastoma treated with cisplatin based adjuvant chemotherapy: report from the Children's Oncology Group. Pediatr Blood Cancer. 2014;61:102.
77. Robertson PL, Murasko KM, Packer RJ, et al. Prospective study of the cerebellar mutism syndrome after posterior fossa surgery in two large cohorts of medulloblastoma. Ann Neurol. 2002;52:S115.
78. Jakacki RI, Burger PC, Zhou T, et al. Outcome of children with metastatic medulloblastoma treated with carboplatin during craniospinal radiotherapy: a Children's Oncology Group Phase I/II study. J Clin Oncol. 2012;30:2648.
79. von Bueren AO, Kortmann RD, von Hoff K, et al. Treatment of children and adolescents with metastatic medulloblastoma and prognostic relevance of clinical and biologic parameters. J Clin Oncol. 2016;34:4151.
80. Esbenshade AJ, Kocak M, Hershon L, et al. A Phase II feasibility study of oral etoposide given concurrently with radiotherapy followed by dose intensive adjuvant chemotherapy for children with newly diagnosed high-risk medulloblastoma (protocol POG 9631): A report from the Children's Oncology Group. Pediatr Blood Cancer. 2017;64:e26373.
81. Leary SES, Packer RJ, Li Y, et al. Efficacy of carboplatin and isotretinoin in children with high-risk medulloblastoma: a randomized clinical trial from the Children's Oncology Group. JAMA Oncol. 2021;7:1313.
82. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): Long-term results from a prospective, multicentre trial. Lancet Oncol. 2006;7:813.
83. Sung KW, Lim DH, Son MH, et al. Reduced-dose craniospinal radiotherapy followed by tandem high-dose chemotherapy and autologous stem cell transplantation in patients with high-risk medulloblastoma. Neuro Oncol. 2013;15:352.
84. Gandola L, Massimino M, Cefalo G, et al. Hyperfractionated accelerated radiotherapy in the Milan strategy for metastatic medulloblastoma. J Clin Oncol. 2009;27:566.
85. National Comprehensive Cancer Network (NCCN) guidelines. https://www.nccn.org/professionals/physician_gls/default.aspx#cns. Accessed 28 Aug 2020.
86. Franceschi E, Hofer S, Brandes AA, et al. EANO-EURACAN clinical practice guideline for diagnosis, treatment, and follow-up of post-pubertal and adult patients with medulloblastoma. Lancet Oncol. 2019;20: e715.
87. U.S. National Library of Medicine. https://www.clinicaltrials.gov/ct2/show/NCT01857453?term=NCT01857453&draw=2&rank=1. Accessed 27 Jul 2020.
88. Kann BH, Lester-Coll NH, Park HS, et al. Adjuvant chemotherapy and overall survival in adult medulloblastoma. Neuro Oncol. 2017;19:259.
89. Padovani L, Sunyach MP, Perol D, et al. Common strategy for adult and pediatric medulloblastoma: a multicenter series of 253 adults. Int J Radiat Oncol Biol Phys. 2007;68:433.
90. Franceschi E, Bartolotti M, Paccapelo A, et al. Adjuvant chemotherapy in adult medulloblastoma: is it an option for average-risk patients? J Neurooncol. 2016;128:235.
91. Brandes AA, Franceschi E, Tosoni A, et al. Efficacy of tailored treatment for high- and low-risk medulloblastoma in adults: a large prospective phase II trial (abstract #2003). J Clin Oncol. 2010;28:182s.
92. Kocakaya S, Beier CP, Beier D. Chemotherapy increases long-term survival in patients with adult medulloblastoma—a literature-based meta-analysis. Neuro Oncol. 2016;18:408.
93. Beier D, Proescholdt M, Reinert C, et al. Multicenter pilot study of radiochemotherapy as first-line treatment for adults with medulloblastoma (NOA-07). Neuro Oncol. 2018;20:400.
94. Dirven L, Luerding R, Beier D, et al. Neurocognitive functioning and health-related quality of life in adult medulloblastoma patients: long-term outcomes of the NOA-07 study. J Neurooncol. 2020;148:117.
95. Friedrich C, von Bueren AO, von Hoff K, et al. Treatment of adult nonmetastatic medulloblastoma patients according to the paediatric HIT 2000 protocol: a prospective observational multicentre study. Eur J Cancer. 2013;49:893.
96. Brandes AA, Franceschi E, Tosoni A, et al. Long-term results of a prospective study on the treatment of medulloblastoma in adults. Cancer. 2007;110:2035.
97. Dunkel IJ, Gardner SL, Garvin JH Jr, et al. High-dose carboplatin, thiotepa, and etoposide with autologous stem cell rescue for patients with previously irradiated recurrent medulloblastoma. Neuro Oncol. 2010;12:297.

98. Robinson GW, Orr BA, Wu G, et al. Vismodegib exerts targeted efficacy against recurrent sonic hedgehog-subgroup medulloblastoma: results from phase II pediatric brain tumor consortium studies PBTC-025B and PBTC-032. J Clin Oncol. 2015;33:2646.
99. Perreault S, Lober RM, Carret AS, et al. Surveillance imaging in children with malignant CNS tumors: low yield of spine MRI. J Neurooncol. 2014;116:617.
100. Kadota RP, Mahoney DH, Doyle J, et al. Dose intensive melphalan and cyclophosphamide with autologous hematopoietic stem cells for recurrent medulloblastoma or germinoma. Pediatr Blood Cancer. 2008;51:675.
101. Sethi RV, Giantsoudi D, Raiford M, et al. Patterns of failure after proton therapy in medulloblastoma; linear energy transfer distributions and relative biological effectiveness associations for relapses. Int J Radiat Oncol Biol Phys. 2014;88:655.
102. Chan AW, Tarbell NJ, Black PM, et al. Adult medulloblastoma: prognostic factors and patterns of relapse. Neurosurgery. 2000;47:623.
103. Graham ML, Herndon JE 2nd, Casey JR, et al. High-dose chemotherapy with autologous stem-cell rescue in patients with recurrent and high-risk pediatric brain tumors. J Clin Oncol. 1997;15:1814.
104. Ridola V, Grill J, Doz F, et al. High-dose chemotherapy with autologous stem cell rescue followed by posterior fossa irradiation for local medulloblastoma recurrence or progression after conventional chemotherapy. Cancer. 2007;110:156.
105. Gururangan S, Krauser J, Watral MA, et al. Efficacy of high-dose chemotherapy or standard salvage therapy in patients with recurrent medulloblastoma. Neuro Oncol. 2008;10:745.
106. Levy AS, Krailo M, Chi S, et al. Temozolomide with irinotecan versus temozolomide, irinotecan plus bevacizumab for recurrent medulloblastoma of childhood: Report of a COG randomized Phase II screening trial. Pediatr Blood Cancer. 2021;68: e29031.
107. Peyrl A, Chocholous M, Sabel M, et al. Sustained survival benefit in recurrent medulloblastoma by a metronomic antiangiogenic regimen: a nonrandomized controlled trial. JAMA Oncol. 2023;9:1688.
108. Müller K, Mynarek M, Zwiener I, et al. Postponed is not canceled: role of craniospinal radiation therapy in the management of recurrent infant medulloblastoma—an experience from the HIT-REZ 1997 & 2005 studies. Int J Radiat Oncol Biol Phys. 2014;88:1019.
109. Erker C, Mynarek M, Bailey S, et al. Outcomes of infants and young children with relapsed medulloblastoma after initial craniospinal irradiation-sparing approaches: an international cohort study. J Clin Oncol. 2023;41:1921.
110. Gajjar AJ, Robinson GW. Medulloblastoma-translating discoveries from the bench to the bedside. Nat Rev Clin Oncol. 2014;11:714.
111. Rudin CM, Hann CL, Laterra J, et al. Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. N Engl J Med. 2009;361:1173.
112. Gajjar A, Stewart CF, Ellison DW, et al. Phase I study of vismodegib in children with recurrent or refractory medulloblastoma: a pediatric brain tumor consortium study. Clin Cancer Res. 2013;19:6305.
113. Metcalfe C, de Sauvage FJ. Hedgehog fights back: mechanisms of acquired resistance against Smoothened antagonists. Cancer Res. 2011;71:5057.
114. Ransohoff KJ, Sarin KY, Tang JY. Smoothened inhibitors in sonic hedgehog subgroup medulloblastoma. J Clin Oncol. 2015;33:2692.
115. Frappaz D, Barritault M, Montané L, et al. MEVITEM-a phase I/II trial of vismodegib + temozolomide vs temozolomide in patients with recurrent/refractory medulloblastoma with Sonic Hedgehog pathway activation. Neuro Oncol. 2021;23:1949.
116. Majd NK, Mastall M, Lin H, et al. Clinical characterization of adult medulloblastoma and the effect of first-line therapies on outcome; The MD Anderson Cancer Center experience. Neurooncol Adv. 2021;3:vdab079.
117. Buglione M, Ghirardelli P, Triggiani L, et al. Radiotherapy for adult medulloblastoma: long term result from a single institution. A review of prognostic factors and why we do need a multi-institutional cooperative program. Rep Pract Oncol Radiother. 2015;20:284.
118. Quinones MC, Bélanger K, Lemieux Blanchard É, et al. Adult medulloblastoma demographic, tumor and treatment impact since 2006: a canadian university experience. Curr Oncol. 2021;28:3104.
119. Liu IC, Holtzman AL, Rotondo RL, et al. Proton therapy for adult medulloblastoma: acute toxicity and disease control outcomes. J Neurooncol. 2021;153:467.
120. Saraf A, Yock TI, Niemierko A, et al. Long-term outcomes and late toxicity of adult medulloblastoma treated with combined modality therapy: A contemporary single-institution experience. Neuro Oncol. 2022;24:2180.
121. Neth BJ, Raghunathan A, Kizilbash SH, et al. Management and long-term outcomes of adults with medulloblastoma: a single-center experience. Neurology. 2023;101: e1256.
122. Zhao F, Ohgaki H, Xu L, et al. Molecular subgroups of adult medulloblastoma: a long-term single-institution study. Neuro Oncol. 2016;18:982.
123. Ning MS, Perkins SM, Dewees T, Shinohara ET. Evidence of high mortality in long term survivors of childhood medulloblastoma. J Neurooncol. 2015;122:321.
124. Salloum R, Chen Y, Yasui Y, et al. Late morbidity and mortality among medulloblastoma survivors diagnosed across three decades: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2019;37:731.
125. Bull KS, Spoudeas HA, Yadegarfar G, et al. Reduction of health status 7 years after addition of chemotherapy to craniospinal irradiation for medulloblastoma: a follow-up study in PNET 3 trial survivors on behalf of the CCLG (formerly UKCCSG). J Clin Oncol. 2007;25:4239.
126. Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group long-term follow-up guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. J Clin Oncol. 2004;22:4979.
127. Albazron FM, Bruss J, Jones RM, et al. Pediatric postoperative cerebellar cognitive affective syndrome follows outflow pathway lesions. Neurology. 2019;93: e1561.
128. Wisoff JH, Epstein FJ. Pseudobulbar palsy after posterior fossa operation in children. Neurosurgery. 1984;15:707.
129. Rekate HL, Grubb RL, Aram DM, et al. Muteness of cerebellar origin. Arch Neurol. 1985;42:697.
130. Janssen G, Messing-Jünger AM, Engelbrecht V, et al. Cerebellar mutism syndrome. Klin Padiatr. 1998;210:243.
131. Siffert J, Poussaint TY, Goumnerova LC, et al. Neurological dysfunction associated with postoperative cerebellar mutism. J Neurooncol. 2000;48:75.
132. Robertson PL, Muraszko KM, Holmes EJ, et al. Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: a prospective study by the Children's Oncology Group. J Neurosurg. 2006;105:444.
133. Schreiber JE, Palmer SL, Conklin HM, et al. Posterior fossa syndrome and long-term neuropsychological outcomes among children treated for medulloblastoma on a multi-institutional, prospective study. Neuro Oncol. 2017;19:1673.

134. King AA, Seidel K, Di C, et al. Long-term neurologic health and psychosocial function of adult survivors of childhood medulloblastoma/PNET: a report from the Childhood Cancer Survivor Study. Neuro Oncol. 2016;2016:242.
135. Moxon-Emre I, Bouffet E, Taylor MD, et al. Impact of craniospinal dose, boost volume, and neurologic complications on intellectual outcome in patients with medulloblastoma. J Clin Oncol. 2014;32:1760.
136. Fouladi M, Gilger E, Kocak M, et al. Intellectual and functional outcome of children 3 years old or younger who have CNS malignancies. J Clin Oncol. 2005;23:7152.
137. Mulhern RK, Palmer SL, Merchant TE, et al. Neurocognitive consequences of risk-adapted therapy for childhood medulloblastoma. J Clin Oncol. 2005;23:5511.
138. Mulhern RK, Kepner JL, Thomas PR, et al. Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study. J Clin Oncol. 1998;16:1723.
139. Jenkin D, Danjoux C, Greenberg M. Subsequent quality of life for children irradiated for a brain tumor before age four years. Med Pediatr Oncol. 1998;31:506.
140. Palmer SL, Armstrong C, Onar-Thomas A, et al. Processing speed, attention, and working memory after treatment for medulloblastoma: an international, prospective, and longitudinal study. J Clin Oncol. 2013;31:3494.
141. Jacola LM, Anghelescu DL, Hall L, et al. Anesthesia Exposure during Therapy Predicts Neurocognitive Outcomes in Survivors of Childhood Medulloblastoma. J Pediatr. 2020;223:141.
142. Gross JP, Powell S, Zelko F, et al. Improved neuropsychological outcomes following proton therapy relative to X-ray therapy for pediatric brain tumor patients. Neuro Oncol. 2019;21:934.
143. Vieira WA, Weltman E, Chen MJ, et al. Ototoxicity evaluation in medulloblastoma patients treated with involved field boost using intensity-modulated radiation therapy (IMRT): A retrospective review. Radiat Oncol. 2014;9:158.
144. FDA approves sodium thiosulfate to reduce the risk of ototoxicity associated with cisplatin in pediatric patients with localized, non-metastatic solid tumors. US Food and Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-sodium-thiosulfate-reduce-risk-ototoxicity-associated-cisplatin-pediatric-patients. Accessed 21 Sep 2022.
145. Freyer DR, Chen L, Krailo MD, et al. Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): A multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2017;18:63.
146. Orgel E, Villaluna D, Krailo MD, et al. Sodium thiosulfate for prevention of cisplatin-induced hearing loss: updated survival from ACCL0431. Lancet Oncol. 2022;23:570.
147. Brock PR, Maibach R, Childs M, et al. Sodium thiosulfate for protection from cisplatin-induced hearing loss. N Engl J Med. 2018;378:2376.
148. Anderson NE, Sheffield S, Hope JK. Superficial siderosis of the central nervous system: a late complication of cerebellar tumors. Neurology. 1999;52:163.
149. Paulino AC, Suzawa HS, Dreyer ZE, et al. Scoliosis in children treated with photon craniospinal irradiation for medulloblastoma. Int J Radiat Oncol Biol Phys. 2021;109:712.
150. Xu W, Janss A, Packer RJ, et al. Endocrine outcome in children with medulloblastoma treated with 18 Gy of craniospinal radiation therapy. Neuro Oncol. 2004;6:113.
151. Eaton BR, Esiashvili N, Kim S, et al. Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma. Neuro Oncol. 2016;18:881.
152. Jussila MP, Remes T, Anttonen J, et al. Late vertebral side effects in long-term survivors of irradiated childhood brain tumor. PLoS ONE. 2018;13: e0209193.
153. van Atteveld JE, Pluijm SMF, Ness KK, et al. Prediction of low and very low bone mineral density among adult survivors of childhood cancer. J Clin Oncol. 2019;37:2217.
154. Laughton SJ, Merchant TE, Sklar CA, et al. Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. J Clin Oncol. 2008;26:1112.
155. Vatner RE, Niemierko A, Misra M, et al. Endocrine deficiency as a function of radiation dose to the hypothalamus and pituitary in pediatric and young adult patients with brain tumors. J Clin Oncol. 2018;36:2854.
156. Aldrich KD, Horne VE, Bielamowicz K, et al. Comparison of hypothyroidism, growth hormone deficiency, and adrenal insufficiency following proton and photon radiotherapy in children with medulloblastoma. J Neurooncol. 2021;155:93.
157. Pfitzer C, Chen CM, Wessel T, et al. Dynamics of fertility impairment in childhood brain tumour survivors. J Cancer Res Clin Oncol. 2014;140:1759.
158. Vern-Gross TZ, Bradley JA, Rotondo RL, Indelicato DJ. Fertility in childhood cancer survivors following cranial irradiation for primary central nervous system and skull base tumors. Radiother Oncol. 2015;117:195.
159. Balachandar S, Dunkel IJ, Khakoo Y, et al. Ovarian function in survivors of childhood medulloblastoma: Impact of reduced dose craniospinal irradiation and high-dose chemotherapy with autologous stem cell rescue. Pediatr Blood Cancer. 2015;62:317.
160. Duffner PK, Krischer JP, Horowitz ME, et al. Second malignancies in young children with primary brain tumors following treatment with prolonged postoperative chemotherapy and delayed irradiation: A Pediatric Oncology Group study. Ann Neurol. 1998;44:313.

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