Medulloblastoma

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28.1 Introduction and Epidemiology

Medulloblastoma and other embryonal brain tumors such as atypical teratoid/rhabdoid tumors (AT/RT) represent the most frequent malignant central nervous system (CNS) tumors in children below 4 years and the second in children and adolescents up to 19 years [1]. These malignant neoplasias share common characteristics, such as undifferentiated cell morphology and an ability to disseminate throughout the CNS making those malignancies highly aggressive and particularly challenging to cure. The large majority of embryonal brain tumors are medulloblastomas; they account for around 10% of all pediatric brain tumors and are the most common malignant childhood posterior fossa tumor [2]. Predominantly occurring in children with a median age of 6 years and showing a male gender bias, medulloblastomas are prevalent across the entire age spectrum but rare in adults [2, 3]. In the United States, the incidence rate reported in children up to 9 years is 6 per million children compared to 0.6 per million adults [4]. Medulloblastoma etiology is largely unknown, and although potential risk factors such as epidemiological, environmental, and infectious factors have been studied, there is not yet any clear evidence [5]. Genetic predisposition is reported in up to 13% of medulloblastoma patients [6]. Several cancer predisposition syndromes, including Gorlin

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syndrome, Turcot syndrome, and the Li-Fraumeni syndrome, are associated with an increased risk of medulloblastoma [7, 8], and it was the study of these diseases that first suggested the molecular basis of medulloblastoma (MB) pathogenesis [9].

28.2 Pathology and Molecular Subgroups

The updated 2016 WHO classification of CNS tumors recently moved to an integrated diagnosis, including histology and genetics. All medulloblastomas are classified as WHO grade IV, which is the highest malignant tumor grade [10]. Long-established histological variants, which are the classic, the desmoplastic nodular (D/N), and the anaplastic/large cell (LCA) medulloblastomas as well as the medulloblastomas with extensive nodularity (MBEN), are still part of the present classification [10]. The main histological variant is classic medulloblastoma characterized by sheets of small cells with a high nuclear-to-cytoplasmic ratio, followed by D/N and LCA with variable frequencies across age groups [3].

Genome- and epigenome-wide tumor profiling studies have changed our understanding of medulloblastoma biology. Molecular insights and phenotype-genotype correlations have offered new perspectives in medulloblastoma characterization by redefining this tumor entity. It has been widely accepted and consensually defined that medulloblastoma consists of at least four entities: Wnt/Wingless (WNT), Sonic Hedgehog (SHH), Group 3, and Group 4 [11]. Each subgroup is characterized by specific genetic alterations, histological variants, patient demographics, and clinical outcomes [11, 12] (Table 28.1). Indeed, molecular subgroup affiliation has a direct correlation with survival and should be considered for patient risk assessment, adjustment of treatment, and development of specific subgroup therapies [13].

28.2.1 WNT Medulloblastoma

WNT represent the rarest subgroup and account for only 11% of all medulloblastoma tumors [3]. WNT medulloblastomas typically occur in older children and teenagers with a peak incidence around 10 years of age and a balanced sex ratio (1:1) [3]. WNT tumors are thought to arise from cells of the dorsal brain stem and are rarely metastatic at diagnosis [3, 11, 14]. The majority of WNT tumors have a deletion of one copy of chromosome 6 (monosomy 6), while further copy number alterations are rare [3, 12]. Hyperactivation of the WNT signaling pathway is often due to the presence of somatic mutations in the *CTNNB1* gene which leads to nuclear accumulation of a mutant beta-catenin 1 protein that is resistant to degradation [11]. In addition to the *CTNNB1* mutations, *TP53*, *SMARCA4*, and *DDX3X* mutations are also reported in WNT patients [15–18].

28.2.2 SHH Medulloblastoma

SHH medulloblastomas constitute ~33% of all medulloblastomas [3]. SHH medulloblastomas have a bimodal incidence, mostly occurring in infants under 3 years and teenagers and young adults older than 16 years of age; they do not show gender bias [3, 11]. SHH medulloblastomas frequently arise laterally, within the cerebellar hemispheres, and metastases are present at diagnosis in about 25% of cases [3, 14]. Histologically, D/N and MBEN variants are almost exclusively described in this subgroup. However, SHH tumors can also present with classic or LCA histological variants [15]. Mutations in the components of the Sonic Hedgehog signaling pathway, such as *PTCH1*, *SMO*, *and SUFU*, lead to "SHH pathogenesis" [19]. *PTCH1* mutations are described across all age groups, whereas mutations in *SUFU* are more often present in infants and adult tumors more frequently harbor mutations in *SMO*. *GLI2* and *MYCN* amplifications as well as *TP53* mutations are also often reported in SHH tumors [19].

28.2.3 Group 3 Medulloblastoma

Group 3 medulloblastomas account for 25% of all medulloblastomas and are typically diagnosed in

Table 28.1 Clinical and molecular features of the four medulloblastoma subgroups [3, 11, 15, 20]

Molecular subgroup:	WNT	SHH	Group 3	Group 4
Percentage				
Age group				
Gender ratio (♂:♀)	♂:♀	♂:♀	♂♂:♀	♂♂:♀
Histology	Classic, rarely LCA	Classic, desmoplastic nodular, LCA, MBEN	Classic, LCA	Classic, LCA
WHO grade	I II III IV	I II III IV	I II III IV	I II III IV
Cells of origin	Lower rhombic lip progenitor cells	Cerebellar granule neuron precursor cells of the external granule-cell layer	Unknown	Unknown
Typical anatomic location	Brainstem, fourth ventricle	Cerebellar hemispheres	Midline, fourth ventricle	Midline, fourth ventricle
Metastasis at diagnosis	Rarely (5–10%)	Uncommonly (15–20%)	Very frequently (40–45%)	Frequently (35–40%)
Pattern of recurrence	Rarely local or metastatic	Local	Metastatic	Metastatic
Prognosis	Very good	Infants good, others intermediate	Poor	Intermediate
Key genetic alterations	*CTNNB1*, *DDX3X*, *SMARCA4*, *TP53* mutation	*PTCH1*, *SMO*, *SUFU*, *TP53* mutation *GLI2*, *MYCN* amplification	*GFI1*, *GFI1B* activation, *MYC*, *PVT1*, *OTX-2* amplification, *SMARCA4* mutation	*KDM6A* mutation, *SNCAIP* duplication *CDK6*, *MYCN* amplification *GFI1*, *GFI1B* activation
Cytogenetics	Monosomy 6	3q gain 9q, 10q, 17p loss	i17q 1q, 7, 18 gain 10q, 11, 16q, 17p loss	i17q 7q, 18q gain 8p, 11p, X loss
Gene expression	WNT signaling	SHH signaling	Photoreceptor/ GABAergic signature	Neuronal/Glutamatergic signature

infants and children (peak incidence is between 3 and 5 years) with a male preponderance (2:1) [3]. Classic and LCA histological variants are only reported in this subgroup, which also presents with the highest prevalence of metastasis at diagnosis (up to 45%) [3, 20]. The tumor usually arises in the midline of the cerebellum. A GABAergic and photoreceptor pathway transcriptional signature characterizes this subgroup [11]. These tumors present multiple copy number and chromosomal structural alterations, for example, gain of isochromosome 17q (i17q), which correlates with worse outcome [20, 21]. Mutation in *SMARCA4,* enhancer activation of *GFI1* and *GFI1B* [22], and amplifications of *MYC*, *PVT1*, or *OTX-2* are other alterations in oncogenic drivers reported in Group 3 tumors [16, 20].

28.2.4 Group 4 Medulloblastoma

The most common subgroup of medulloblastoma is Group 4, accounting for 35% of all medulloblastoma tumors [3]. Group 4 medulloblastomas develop across all age groups with a peak incidence around 9 years of age and are three times more frequent in males [3, 20]. The most common histological variant is classic medulloblastoma. Group 4 medulloblastomas usually arise in the cerebellar midline, and metastatic disease at diagnosis is seen in 35–40% of patients [3]. Although Group 4 tumors make up to one third of all medulloblastomas, the biology of this subgroup is not well understood; gene expression studies suggest a role for neuronal and glutaminergic pathways. The most common mutation involves *KDM6A*,

a gene located on the X chromosome and which encodes a histone demethylase (H3K27) [16]. Additionally, *CDK6* (cyclin-dependent kinase 6) and *MYCN* amplifications, as well as *SNCAIP* duplications, are commonly described [20]. Frequently identified cytogenetic alterations are isochromosome 17q, as well as loss of 11q and the X chromosome [20, 21].

28.3 Clinical Presentation

Children and teenagers with medulloblastoma often present with symptoms of obstructive non-communicating hydrocephalus due to the cerebellar tumor location in close proximity to the fourth brain ventricle and obstruction of the CSF flow causing an increase in intracranial pressure (ICP) [23]. In infants, open cranial sutures are protective against the increasing intracranial pressure and, to a certain degree, provide a compliant intracranial space. Thus, infants typically present with hydrocephalus causing progressive asymptomatic macrocephaly and bulging of fontanelles [24] and nonspecific symptoms such as lethargy, irritability, feeding difficulties, and developmental delay. The gradual closure of the cranial sutures in children and adolescents leads to a reduced tolerance to increased ICP and can typically cause headaches (especially in the early morning upon awakening) accompanied by vomiting and lethargy [25]. In severe cases, Cushing's triad consisting of increased blood pressure, bradycardia, and irregular breathing can occur and require emergent diagnostic and therapeutic action [26]. Papilledema can occur in medulloblastoma patients with hydrocephalus but is often a late sign.

Due to the localization of medulloblastomas in the posterior fossa, cerebellar symptoms, such as dysmetria, dysarthria, and ataxia, are common findings at presentation. Midline cerebellar masses are often associated with truncal ataxia, whereas patients with lateral tumors located in the cerebellar hemispheres more frequently present with limb ataxia showing abnormal findings in the finger-nose-finger, alternating movements and heel-to-shin testing. Diplopia can be observed due to sixth cranial nerve palsy, which can present as a result of a direct involvement of the cranial nerve or as a consequence of nerve damage due to increased ICP [27].

In the rare event of tumor bleeding, patients usually show an acute onset of symptoms. Cerebellar hemorrhages in the pediatric population are scarce and should always raise suspicion for an underlying neoplasm. The differential diagnosis for medulloblastoma in children includes other pediatric posterior fossa tumors such as pilocytic astrocytoma, ependymoma, and atypical teratoid/rhabdoid tumors. Evaluation with imaging and tissue collection during tumor resection for histopathology and molecular analyses are crucial for a definitive diagnosis.

The time from onset of symptoms to the diagnosis is, on average, 4 weeks [28]. Generally, rapid disease progression in patients correlates with a shorter time to diagnosis and a worse outcome [29]. Interestingly, the pre-diagnostic interval of patients with Group 4 and WNT tumors is distinctly longer compared to other medulloblastoma subgroups [28].

28.4 Imaging Characteristics

Medulloblastomas show specific neuroradiological features in CT and MR imaging. CT usually represents the initial imaging modality to diagnose patients with medulloblastoma. On non-contrast CT scans, medulloblastomas present as hyperdense posterior fossa tumors surrounded by peritumoral edema, which homogenously enhance following contrast administration. The majority of medulloblastomas arise from the vermis with close contact to the fourth brain ventricle, often causing an obstructive, high-pressure hydrocephalus with enlargement of the brain ventricles (in up to 95% of cases) [30].

MRI is the imaging modality of choice for staging (whole neuroaxis required), surgical planning, and follow-up examination as it provides good soft-tissue contrast and is superior to other modalities regarding the detection of meningeal dissemination. The standard MRI protocol for children with an undiag-

nosed posterior fossa tumor consists of T1- and T2-weighted, T1-weighted post-contrast, FLAIR (fluid-attenuated inversion recovery), and diffusion sequences. Medulloblastomas appear on T1-weighted images as iso- to hypointense masses with sharply defined margins. On T2-weighted and FLAIR sequences, medulloblastomas typically present hyperintense to the gray matter. Heterogeneous enhancement is usually detectable after contrast administration on T1-weighted images. Diffusion-weighted images show restricted diffusion caused by disturbed mobility of water molecules in the hypercellular medulloblastomas [31] (Fig. 28.1).

While large cysts and necrosis are typical characteristics of pilocytic astrocytomas, medulloblastomas can also present with smaller, often multiple, cysts [30]. Detection of calcification and extension of the tumor into the foraminae Luschkae and Magendii are more common in patients with ependymoma; however, when present, medulloblastoma should still be considered as a differential diagnosis [32].

28.4.1 Subgroup-Specific Features

Tumor location in the cerebellar peduncles and cerebellopontine angle, often extending into the fourth ventricle, is predictive for WNT medulloblastoma [33]. On MRI, WNT tumors present as well-defined masses with highly restricted diffusion; leptomeningeal metastases are commonly not detectable at diagnosis [34]. Medulloblastomas of the SHH subgroup are frequently located in the cerebellar hemispheres [33]. They often appear as well-circumscribed tumors, show extensive enhancement after contrast administration, and present with restriction on diffusion-weighted MRI images [34]. In contrast to the laterally located SHH medulloblastomas, Group 3 and Group 4 tumors typically arise in the midline often causing an obstructive hydrocephalus. Patients with tumors of these subgroups more often present with metastatic disease at the time of diagnosis. The typical appearance of Group 3 medulloblastomas on MRI is a high-contrast mass with ill-defined tumor margins. On the contrary, Group 4 tumors typically show minimal to no enhancement on MR imaging. Imaging features such as mineralization, edema, necrosis, cysts, and hemorrhage are not significantly overrepresented in any of the four molecular subgroups [33].

28.5 Staging and Risk Stratification

Most studies completed over the last two decades have performed a risk assessment based on clinical criteria: age at diagnosis, metastatic status at diagnosis, extent of surgical resection, and (in some studies) histology. Brain and spine MRIs with and without gadolinium as well as CSF analysis are required to assess the metastatic disease at diagnosis. Extent of surgical resection is evaluated by postoperative MRI, and presence of more than 1.5 cm^2 of tumor is defined as local residual disease. Nowadays, based on their age and the presence or absence of residual disease (metastatic and/or local), patients are divided into two categories: high and average risk. High-risk patients are infants (under 3 years of age) or non-infants with a local residual disease >1.5 cm^2 and/or dissemination; all other patients are considered average risk.

Future tumor staging will integrate the four main subgroups of medulloblastoma as well as new biomarkers (specific key genetic aberrations and cytogenetic alterations) in order to refine risk stratification for children and teenagers up to 17 years of age [13]. Integration of these biological findings correlates with outcome and allows a more robust and detailed tumor risk stratification. New risk groups of patients have recently been proposed based on the prognosis: >90% survival for low risk, 75–90% survival for standard risk, 50–75% survival for high risk, and < 50% survival for very high risk [13]. Low-risk patients are WNT patients (below 16 years old) and Group 4 patients with localized disease and whole chromosome 11 loss. Standard-risk patients are all patients with localized disease and one of the following molecular tumor profiles: non-MYCN-amplified SHH tumors, non-MYC-amplified

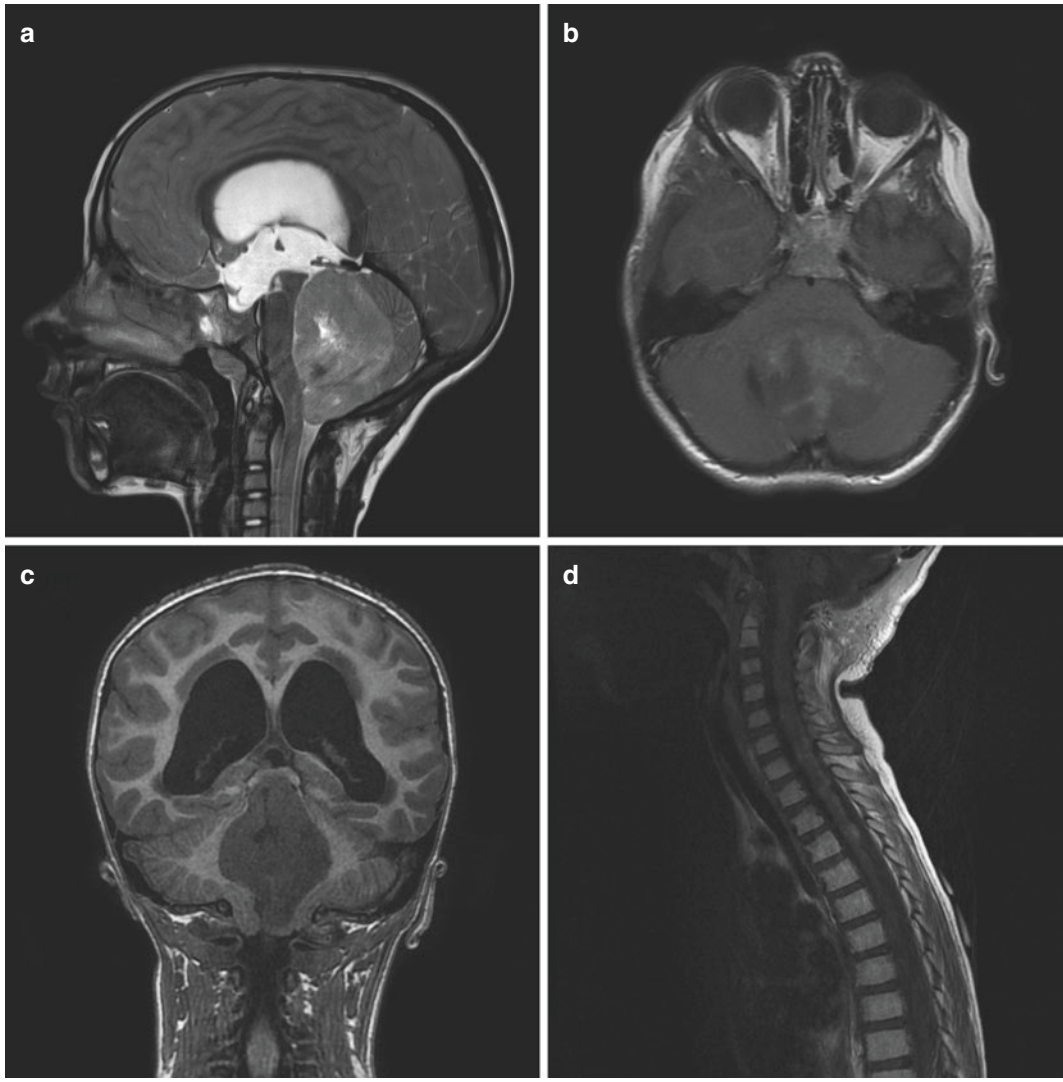

Fig. 28.1 MRI of a pediatric patient with medulloblastoma in close proximity to the fourth ventricle. (**a**) Sagittal T2-weighted image, the tumor is mildly hyperintense compared to the normal cerebellum tissue. (**b**) Post-contrast axial T1-weighted image, the tumor is partially enhancing. (**c**) Coronal T1-weighted image shows a hydrocephalic enlargement of the brain ventricles. (**d**) Sagittal T1-weighted post-gadolinium image shows leptomeningeal dissemination on the surface of the spinal cord

Group 3 tumors, and Group 4 medulloblastomas without chromosome 11 loss. High-risk patients are Group 4 and SHH patients with metastatic disease, as well as MYCN-amplified SHH patients with localized disease. Very high-risk patients are patients with *TP53* mutated-SHH tumors and children with disseminated Group 3 tumors [13] (Fig. 28.2).

28.6 Treatment

The current standard of care for pediatric medulloblastoma patients is a multimodal treatment consisting of maximal safe tumor resection, adjuvant chemotherapy, and for children over 3 years of age, radiotherapy to the whole craniospinal axis [15, 35].

CURRENT RISK STRATIFICATION OF MEDULLOBLASTOMA PATIENTS BASED ON CLINICAL CRITERIA*

Risk assessment	Clinical criteria
Standard risk	IF: ☑ non-metastatic **AND** ☑ < 1.5cm^2 of residual tumor
High risk	IF: ☑ metastatic **OR** ☑ > 1.5cm^2 of residual tumor

*For children > 3 years

Metastatic status defined by the Chang classification	
M0	No gross nodular or laminar subarachnoid or haematogenous metastasis
M1	Microscopic tumor cells found in CSF
M2	Gross nodular or laminar seeding in the cerebellum, cerebral subarachnoid space, or in the third or fourth ventricles
M3	Gross nodular or laminar seeding in the spinal subarachnoid space
M4	Extra-neuraxial metastasis

POTENTIAL FUTURE RISK STRATIFICATION OF MEDULLOBLASTOMA PATIENTS BASED ON MOLECULAR AND CLINICAL CRITERIA*

Risk assessment	WNT	SHH	Group 3	Group 4
Low risk (>90% survival)	IF: ☑ non-metastatic			IF: ☑ non-metastatic **AND** ☑ chromosome 11 loss
Standard risk (75-90% survival)		IF: ☑ non-metastatic **AND** ☑ TP53 WT **AND** ☑ No MYCN amplification	IF: ☑ non-metastatic **AND** ☑ No MYC amplification	IF: ☑ non-metastatic **AND** ☑ no chromosome 11 loss
High risk (50-75% survival)		IF: ☑ metastatic **AND** ☑ TP53 WT – **OR** – ☑ non-metastatic **AND** ☑ MYCN amplification		IF: ☑ metastatic
Very high risk (<50% survival)		IF: ☑ TP53 mutation	IF: ☑ metastatic **AND** ☑ MYC amplification	

Fig. 28.2 Current and potential future risk stratification for children with medulloblastoma: from the clinic to the molecular era [5, 13]

28.6.1 Surgery

Surgery is a key aspect of effective treatment for patients with medulloblastoma. The main objectives of surgical therapy are maximum safe tumor resection, hydrocephalus treatment, decompression of the brain stem, and other critical neighboring structures such as the cranial nerves and tissue collection for diagnosis and molecular tumor profiling.

The treatment of obstructive hydrocephalus often has priority, as most patients with medulloblastoma present with symptoms of increased ICP at the time of diagnosis. There are different therapeutic options for surgical treatment of hydrocephalus: The temporary implantation of an external ventricular drain (EVD), the placement of a permanent ventriculoperitoneal shunt (VP-shunt), an endoscopic third ventriculostomy (ETV), and early tumor resection with perioperative treatment with steroids. As only 30% of all medulloblastoma patients show hydrocephalus after tumor resection, a prediction tool—the Canadian Preoperative Prediction Rule for Hydrocephalus (CPPRH)—has been developed to identify the patients at high risk for persistent hydrocephalus. The CPPRH described by Cambrin et al. consists of the following criteria: Age < 2 years, presence of papilledema, degree of hydrocephalus, presence of cerebral metastases, and preoperative estimation of tumor pathology. The prediction tool supports the neurosurgeon with patient counseling, planning of the preresectional CSF diversion and evaluation of the required intensity of postoperative hydrocephalus surveillance [36]. Children classified as low risk for postresection hydrocephalus may be treated conservatively, with or without an intraoperative EVD. The implantation of an EVD during tumor resection as well as intensive postoperative monitoring is recommended for all high-risk patients; a preoperative ETV can also be evaluated [37]. Patients with SHH, Group 3, and Group 4 tumors require CSF diversion surgery more often than patients with a WNT medulloblastoma. The lack of metastases at the time of diagnosis and the older age of patients with WNT medulloblastoma are likely important factors in the decreased risk of hydrocephalus development in this MB subgroup [38].

The typical approach in order to resect a posterior fossa tumor has the child in prone position; the head is flexed allowing an easier approach to the craniocervical junction. A median suboccipital craniotomy is performed following a midline incision and the dissection of the soft tissue. A C1 laminectomy is required in order to create space for a Y-shaped dura opening. The transvermian and the telovelar approaches are the most common routes to access a tumor located in the fourth ventricle. Early visualization of the floor of the fourth ventricle is crucial to avoid damage to the underlying brain stem. The resection of tumor tissue infiltrating the floor of the fourth ventricle involving the brain stem should be avoided as brain stem damage can lead to severe neurological complications, including cranial nerve dysfunction and fatal cardiorespiratory failure. The tumor tissue is commonly removed using a cavitron ultrasonic surgical aspirator (CUSA). Before closure, the neurosurgeon ensures sufficient hemostasis of the resection cavity [24].

Neuro-navigation systems and intraoperative imaging are helpful and support the neurosurgeon in terms of orientation within the operative site and detection of residual tumor. This increases the likelihood of a safe total or near-total resection and reduces the risk of postoperative neurological morbidity and the necessity of early second-look surgery; however, these advantages come at a price of longer anesthesia and operating times [39].

When subgroup affiliation is taken into account, gross total resection, defined as no visible remaining tumor tissue on postoperative MR images, has no or minimal survival advantage in medulloblastoma patients compared to near-total resection with <1.5 cm^2 remaining tumor tissue on the postoperative scan. Patients with Group 4 medulloblastoma possibly benefit from gross total resection compared to subtotal resection (≥1.5 cm^2 tumor remaining) in terms of an increased progression-free survival; nonetheless, no difference was observed in overall survival. For this reason, neurosurgeons are advised to perform maximum safe tumor resection, considering

that aggressive surgery should be avoided at the risk of increased postoperative neurological deficiencies [40].

28.6.2 Postoperative Care

After posterior fossa surgery, patients require close surveillance, including repetitive neurological examinations at a specialized intensive care unit. Due to the limited space in the posterior fossa compared to the supratentorial region, complications such as a postoperative hemorrhage can quickly lead to a life-threatening situation. Therefore, unexpected neurological deficits or sudden deterioration of the patient's condition should always be evaluated for acute hydrocephalus, postoperative hemorrhage, and cerebellar edema using CT imaging. Delayed extubation can be considered in cases of extended operating time or manipulation of the cranial nerves during surgery; however, close monitoring of the patient must be ensured. An EVD provides the opportunity to closely observe the ICP curve and to drain CSF in case of increased ICP.

Complications after posterior fossa surgery are common but not yet fully understood. Posterior fossa syndrome (PFS)—also known as cerebellar mutism—presents in up to one third of children undergoing posterior fossa surgery. Patients typically develop symptoms within the first few days after surgery, presenting with irritability, mutism, behavioral changes, language deficits, and ataxia. The underlying pathophysiology remains unclear; however, there are some studies that describe an increased incidence of PFS following damage to the dentatothalamocortical pathways and/or the dentate nuclei. The duration of symptoms is variable; some pediatric medulloblastoma patients show only transient deficiencies, whereas others have to cope with persistent deficits [41].

More general symptoms such as headaches, vomiting, and neck pain are frequently present in children who have undergone posterior fossa surgery. The causes of postoperative headaches are multifactorial and can be due to pneumocephalus and intraventricular blood, among others. Vomiting can be explained by side effects of anesthesia, adjuvant chemo- and radiotherapy, as well as acute postoperative hydrocephalus. Neck pain is commonly provoked by intraoperative muscle damage and should be distinguished from neck pain due to meningeal irritation. Other possible complications following posterior fossa surgery are meningitis, CSF leakage, and wound infection [42]. Close monitoring and regular medical examinations allow for early diagnosis and treatment of postoperative complications.

28.6.3 Adjuvant Radiotherapy

The long-term survival of patients with medulloblastoma increased significantly after the introduction of craniospinal irradiation described by Paterson and Farr in 1953 [43]. Based on current knowledge, early adjuvant radiotherapy is recommended, as delayed radiation is associated with worse outcome [44]. Treatment of residual tumor cells at the primary site and the prevention of leptomeningeal dissemination are the main goals of adjuvant craniospinal irradiation. Radiation protocols have been adjusted over time in order to improve overall survival and reduce long-term side effects.

With the implementation of the most recent, risk-adapted regimens, the total radiation dose has been decreased for average-risk patients over 3 years of age, with no survival disadvantage given that adjuvant chemotherapy is administered [45]. Children older than 3 years of age with average-risk disease commonly receive 23.4 Gy of craniospinal irradiation (CSI) and a boost to the tumor bed with up to 54 Gy, whereas a dose of 36 Gy CSI and a boost of 54 Gy to the primary site are considered standard protocols for high-risk patients with extensive disease (> 3 years old). New protocols, such as the ACNS1422 study from the Children's Oncology Group (COG) and the PNET 5 study from the International Society of Pediatric Oncology (SIOP), will treat low-risk patients with WNT medulloblastoma with even more reduced CSI doses (NCT02066220, NCT02066220).

Irradiation treatment is avoided in children under 3 years of age as it is associated with severe

sequelae. Common side effects of radiotherapy to the developing brain include neurocognitive deficits, sensorineural hearing loss, and endocrinopathies due to dysfunction of the pituitary and thyroid glands [46, 47]. Studies investigating a further reduction of the overall radiation dose and boost volumes in order to reduce radiation toxicity and improve long-term survival are ongoing [48].

28.6.4 Adjuvant Chemotherapy

Adjuvant chemotherapy has proven to be a survival benefit in average risk as well as high-risk patients and is therefore part of the current standard treatment protocols of all medulloblastoma patients.

Several trials have shown that children with average-risk disease benefit from an adjuvant multimodal therapy consisting of craniospinal radiation as described above and postradiation chemotherapy, including combinations of cisplatin, vincristine, cyclophosphamide, and/or lomustine. The efficacy of combination chemotherapy allowed a reduction of total radiation dose from 36 to 23.4 Gy, maintaining an overall survival of children with average-risk disease above 85% [49, 50]. The St. Jude's clinical trial SJMB96 showed similar results based on craniospinal radiation and cyclophosphamide-based high-dose chemotherapy cycles with tandem autologous stem cell rescue [51].

A more intense radiotherapy with 36 Gy to the neuroaxis and a boost to the primary site with up to 54 Gy is still the cornerstone of treatment of patients with high-risk disease. The drugs shown to be of benefit to patients with high-risk disease are the same used to treat average-risk disease. The POG 9031 study compared in a randomized fashion the efficacy of chemotherapy pre- and postirradiation and found no significant difference between the two regimens, with 5-year overall survival around 75% [52]. Other studies have shown that neoadjuvant chemotherapy and delayed irradiation may in fact be associated with a survival disadvantage [53] and thus the standard practice remains of using chemotherapy after craniospinal irradiation. The clinical trial SJMB96 showed similar survival results in high-risk patients given a combination treatment consisting of radiotherapy followed by an early high-dose four-cycle cyclophosphamide-based chemotherapy [51]. There is evidence that carboplatin can have a radiosensitizing effect with a survival advantage in high-risk patients [54].

The postsurgical treatment of infants under 3 years of age is especially challenging and consists of chemotherapy-based approaches, as radiation treatment should be avoided due to its devastating effects on the developing brain. It has been shown that a prolonged remission in medulloblastoma patients <3 years of age can be achieved by postoperative chemotherapy, especially in children with desmoplastic histology (which belongs exclusively to the SHH subgroup) and without initial metastases [55]. The Head Start clinical trials use a brief high-dose myeloablative chemotherapy followed by autologous stem cell rescue [56]. The CCG99703 study of the Children's Cancer Group is comparable and includes a high-dose myeloablative chemotherapy consisting of three induction cycles of cisplatin, cyclophosphamide, etoposide, and vincristine followed by three consolidation cycles of carboplatin and thiotepa with consecutive autologous stem cell rescue [57].

28.6.5 Molecular Therapeutic Targets

Based on epidemiological, genetic, and transcriptional differences and the identification of key signaling pathways, four molecular medulloblastoma subgroups were described in 2010 [11]. The WNT and SHH pathways have been studied extensively using molecular analyses of primary tumor samples and specific animal models in order to identify new molecular targets and agents for selective therapies. The smoothened (SMO) inhibitor vismodegib showed promising results in the treatment of patients with SHH medulloblastoma [58], and its effect is currently being further investigated in the St. Jude's clinical trial SJMB012 (NCT01878617). Key molecules of other overexpressed signaling pathways such as the AKT and TGF-β represent promising

molecular targets and new therapeutic opportunities for patients with SHH medulloblastoma [59].

Efforts are underway to de-escalate the treatment of patients with WNT medulloblastoma as this subgroup has a good prognosis with low risk for recurrence and metastasis. Therefore, even though molecular targets of the WNT signaling pathway have been identified, there is currently no strong indication to further investigate these therapeutic options [60]. Furthermore, the clinical trial NCT02212574 is currently ongoing and is evaluating the feasibility of a treatment consisting of only surgery and chemotherapy.

Compared to the well-studied drivers of the WNT and SHH medulloblastomas, there are a lack of key targetable molecules for Group 3 and Group 4 medulloblastomas due to a shortage of spontaneous mouse models hindering their identification. BET bromodomain inhibitors [61] and inhibitors of the PI3K/AKT signaling pathway [62], as well as the combination treatment consisting of gemcitabine and pemetrexed, showed promising preclinical results in the treatment of MYC-driven mouse models [63] and possibly represent a therapeutic potential for patients with Group 3 medulloblastoma. Due to the development of drug resistance with monotherapy, combined targeted therapies may be administered with conventional chemotherapy to favor improved outcomes and decreased resistance.

Patient stratification based on the biology and the molecular characteristics of the tumor will open the door for subgroup-specific treatment in the future. The goal of specific treatment is an improvement of overall survival and quality of life in long-term survivors.

28.7 Recurrence and Metastatic Disease

Medulloblastoma recurrences tend to occur with a specific location, incidence, and timeline across the different subgroups. At the time of relapse, tumors can arise locally in the posterior fossa or as metastases, most commonly through leptomeningeal dissemination. A significant proportion of SHH tumors recur locally at the primary site of the disease, whereas the majority of Group 3 and Group 4 medulloblastomas relapse with metastatic disease. WNT tumors rarely recur [64]. SHH and Group 3 tumors tend to recur early, with a shorter survival when compared to Group 4 tumors [64]. Metastatic disease at presentation is a prognostic factor that correlates with poor outcome. Previously irradiated Group 3 and Group 4 tumors are typically metastatic at time of relapse and often incurable [64]. Interestingly, metastasis and primary tumors share the same subgroup affiliation, and medulloblastoma subgroup affiliation stays stable at the time of recurrence [64, 65]. However, even if subgroup affiliation is conserved (over time and between locations), recent genetic comparison between treatment-naïve primary tumors and recurrent tumors found significant clonal divergence and selection of genetic events through treatment [66]. At the time of relapse, *MYCN* amplifications and *TP53* mutations may emerge and become therapeutic targets [67]. This significant biological and temporal heterogeneity across subgroups and between primary and relapse tumors has important potential therapeutic and diagnostic implications. At the time of relapse for all tumors, a biopsy should be performed, especially if targeted therapies are an option [13].

28.8 Prognosis and Quality of Life

Overall 5-year survival for medulloblastoma patients has reached 60–80% using a combination of maximal safe resection, craniospinal radiation (in children older than 3 years), and chemotherapy [13]. Outcome greatly correlates with tumor subgroup affiliation and is significantly different across the medulloblastoma subgroups [3]. Patients younger than 16 years of age presenting with WNT tumors have an excellent prognosis, over 90% event-free survival at 5 years with current standard of treatment [15]. SHH patient outcomes can be highly correlated with patient age and/or *TP53* status. Infants generally have a good prognosis, and children with *TP53* mutated tumors a dismal prognosis compared to *TP53* wild-type tumors [68]. Group 3 patients pres-

ent with a globally poor outcome using current treatment modalities [35]. Dissemination, *MYC* amplification, and i17q are factors that must be taken into consideration because they confer a less favorable prognosis for Group 3 patients [21]. Group 4 tumor patients have an intermediate prognosis [35], and loss of chromosome 11 is a favorable biomarker [21].

Although current standard therapies cure a large number of medulloblastoma patients, the majority of survivors suffer with long-term side effects including neurological, otological, endocrine, and psychosocial impairments, as well as higher risk of developing secondary malignancies [69]. Important neurological morbidity related to the treatment modalities impacts these patients in their daily life [70, 71]. Radiation therapy, especially in the youngest children, impacts the quality of life of these patients, and radiation avoidance in infants as well as proton therapy advances may improve the global neurological outcome of medulloblastoma patients [72–74]. Long-term quality of life studies and potential interventions to decrease treatment burden are under investigation [75, 76]. By implementing recent biological findings, future studies will evaluate the possibility of adjusting conventional and specific therapies, in order to treat newly diagnosed medulloblastomas and prevent relapse with the goal of maintaining the best outcome while decreasing toxicities and long-term side effects.

28.9 Future Perspective and Challenges

There has been much improvement in the treatment of patients with medulloblastoma since the first description by Bailey and Cushing in 1926; however, recurrent and metastatic medulloblastomas remain a challenge. Extensive molecular analyses resulted in the identification of the four medulloblastoma subgroups and opened the door for biology-based risk stratification of patients. Recently, a further breakdown into 12 medulloblastoma subtypes has been suggested [77]. The detection of subgroup- and subtype-specific therapeutic targets opens the door for specific treatments resulting in improved survival and reduced treatment-related toxicity. Scientists as well as clinicians are focused on the development of more efficient treatment protocols, which can be implemented in new clinical trials. Assessment of treatment toxicity and resulting long-term sequelae as well as functional outcomes will be essential in future trials and improve the quality of life for long-term survivors [78].

Development of new treatment regimens for the often still fatal recurrent disease, based on preclinical research on therapy-naïve primary tumors, has proven unsuccessful as therapeutic targets discovered at disease presentation may no longer play a major role at the time of relapse. Therefore, the indication for re-biopsy at the time of recurrence should be evaluated if a targeted treatment is considered as a therapeutic option [13].

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References

1. Ostrom QT, Gittleman H, Xu J, Kromer C, Wolinsky Y, Kruchko C et al (2016) CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2009-2013. Neuro-Oncology 18(suppl_5):v1–v75
2. Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C et al (2015) CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. Neuro-Oncology 17(Suppl 4):iv1–iv62
3. Kool M, Korshunov A, Remke M, Jones DT, Schlanstein M, Northcott PA et al (2012) Molecular subgroups of medulloblastoma: an international meta-analysis of transcriptome, genetic aberrations, and clinical data of WNT, SHH, Group 3, and Group 4 medulloblastomas. Acta Neuropathol 123(4):473–484
4. Smoll NR, Drummond KJ (2012) The incidence of medulloblastomas and primitive neurectodermal tumours in adults and children. J Clin Neurosci 19(11):1541–1544
5. Massimino M, Biassoni V, Gandola L, Garre ML, Gatta G, Giangaspero F et al (2016) Childhood medulloblastoma. Crit Rev Oncol Hematol 105:35–51

6. Zhang J, Walsh MF, Wu G, Edmonson MN, Gruber TA, Easton J et al (2015) Germline mutations in predisposition genes in pediatric cancer. N Engl J Med 373(24):2336–2346
7. Evans G, Burnell L, Campbell R, Gattamaneni HR, Birch J (1993) Congenital anomalies and genetic syndromes in 173 cases of medulloblastoma. Med Pediatr Oncol 21(6):433–434
8. Villani A, Malkin D, Tabori U (2012) Syndromes predisposing to pediatric central nervous system tumors: lessons learned and new promises. Curr Neurol Neurosci Rep 12(2):153–164
9. Taylor MD, Mainprize TG, Rutka JT (2000) Molecular insight into medulloblastoma and central nervous system primitive neuroectodermal tumor biology from hereditary syndromes: a review. Neurosurgery 47(4):888–901
10. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK et al (2016) The 2016 World Health Organization Classification of tumors of the central nervous system: a summary. Acta Neuropathol 131(6):803–820
11. Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC et al (2012) Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol 123(4):465–472
12. Northcott PA, Korshunov A, Witt H, Hielscher T, Eberhart CG, Mack S et al (2011) Medulloblastoma comprises four distinct molecular variants. J Clin Oncol 29(11):1408–1414
13. Ramaswamy V, Remke M, Bouffet E, Bailey S, Clifford SC, Doz F et al (2016) Risk stratification of childhood medulloblastoma in the molecular era: the current consensus. Acta Neuropathol 131(6):821–831
14. Gibson P, Tong Y, Robinson G, Thompson MC, Currle DS, Eden C et al (2010) Subtypes of medulloblastoma have distinct developmental origins. Nature 468(7327):1095–1099
15. Gajjar AJ, Robinson GW (2014) Medulloblastoma-translating discoveries from the bench to the bedside. Nat Rev Clin Oncol 11(12):714–722
16. Jones DT, Jager N, Kool M, Zichner T, Hutter B, Sultan M et al (2012) Dissecting the genomic complexity underlying medulloblastoma. Nature 488(7409):100–105
17. Lindsey JC, Hill RM, Megahed H, Lusher ME, Schwalbe EC, Cole M et al (2011) TP53 mutations in favorable-risk Wnt/Wingless-subtype medulloblastomas. J Clin Oncol 29(12):e344–e346. author reply e7-8
18. Robinson G, Parker M, Kranenburg TA, Lu C, Chen X, Ding L et al (2012) Novel mutations target distinct subgroups of medulloblastoma. Nature 488(7409):43–48
19. Kool M, Jones DT, Jager N, Northcott PA, Pugh TJ, Hovestadt V et al (2014) Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. Cancer Cell 25(3):393–405
20. Northcott PA, Jones DT, Kool M, Robinson GW, Gilbertson RJ, Cho YJ et al (2012) Medulloblastomics: the end of the beginning. Nat Rev Cancer 12(12):818–834
21. Shih DJ, Northcott PA, Remke M, Korshunov A, Ramaswamy V, Kool M et al (2014) Cytogenetic prognostication within medulloblastoma subgroups. J Clin Oncol 32(9):886–896
22. Northcott PA, Lee C, Zichner T, Stutz AM, Erkek S, Kawauchi D et al (2014) Enhancer hijacking activates GFI1 family oncogenes in medulloblastoma. Nature 511(7510):428–434
23. Kumar V, Phipps K, Harkness W, Hayward RD (1996) Ventriculo-peritoneal shunt requirement in children with posterior fossa tumours: an 11-year audit. Br J Neurosurg 10(5):467–470
24. Sutton LN, Phillips PC, Molloy PT (1996) Surgical management of medulloblastoma. J Neurooncol 29(1):9–21
25. Lee M, Wisoff JH, Abbott R, Freed D, Epstein FJ (1994) Management of hydrocephalus in children with medulloblastoma: prognostic factors for shunting. Pediatr Neurosurg 20(4):240–247
26. Stevens RD, Shoykhet M, Cadena R (2015) Emergency neurological life support: intracranial hypertension and herniation. Neurocrit Care 23(Suppl 2):S76–S82
27. Millard NE, De Braganca KC (2016) Medulloblastoma. J Child Neurol 31(12):1341–1353
28. Ramaswamy V, Remke M, Shih D, Wang X, Northcott PA, Faria CC et al (2014) Duration of the prediagnostic interval in medulloblastoma is subgroup dependent. Pediatr Blood Cancer 61(7):1190–1194
29. Gerber NU, von Hoff K, von Bueren AO, Treulieb W, Deinlein F, Benesch M et al (2012) A long duration of the prediagnostic symptomatic interval is not associated with an unfavourable prognosis in childhood medulloblastoma. Eur J Cancer 48(13):2028–2036
30. Eran A, Ozturk A, Aygun N, Izbudak I (2010) Medulloblastoma: atypical CT and MRI findings in children. Pediatr Radiol 40(7):1254–1262
31. Fruehwald-Pallamar J, Puchner SB, Rossi A, Garre ML, Cama A, Koelblinger C et al (2011) Magnetic resonance imaging spectrum of medulloblastoma. Neuroradiology 53(6):387–396
32. Tortori-Donati P, Fondelli MP, Rossi A, Cama A, Caputo L, Andreussi L et al (1996) Medulloblastoma in children: CT and MRI findings. Neuroradiology 38(4):352–359
33. Perreault S, Ramaswamy V, Achrol AS, Chao K, Liu TT, Shih D et al (2014) MRI surrogates for molecular subgroups of medulloblastoma. Am J Neuroradiol 35(7):1263–1269
34. Raybaud C, Ramaswamy V, Taylor MD, Laughlin S (2015) Posterior fossa tumors in children: developmental anatomy and diagnostic imaging. Childs Nerv Syst 31(10):1661–1676
35. Ramaswamy V, Remke M, Adamski J, Bartels U, Tabori U, Wang X et al (2016) Medulloblastoma subgroup-specific outcomes in irradiated children: who are the true high-risk patients? Neuro-Oncology 18(2):291–297

36. Riva-Cambrin J, Detsky AS, Lamberti-Pasculli M, Sargent MA, Armstrong D, Moineddin R et al (2009) Predicting postresection hydrocephalus in pediatric patients with posterior fossa tumors. J Neurosurg Pediatr 3(5):378–385
37. Lin CT, Riva-Cambrin JK (2015) Management of posterior fossa tumors and hydrocephalus in children: a review. Childs Nerv Syst 31(10):1781–1789
38. Schneider C, Ramaswamy V, Kulkarni AV, Rutka JT, Remke M, Tabori U et al (2015) Clinical implications of medulloblastoma subgroups: incidence of CSF diversion surgery. J Neurosurg Pediatr 15(3):236–242
39. Choudhri AF, Klimo P Jr, Auschwitz TS, Whitehead MT, Boop FA (2014) 3T intraoperative MRI for management of pediatric CNS neoplasms. Am J Neuroradiol 35(12):2382–2387
40. Thompson EM, Hielscher T, Bouffet E, Remke M, Luu B, Gururangan S et al (2016) Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: a retrospective integrated clinical and molecular analysis. Lancet Oncol 17(4):484–495
41. Tamburrini G, Frassanito P, Chieffo D, Massimi L, Caldarelli M, Di Rocco C (2015) Cerebellar mutism. Childs Nerv Syst 31(10):1841–1851
42. Dubey A, Sung WS, Shaya M, Patwardhan R, Willis B, Smith D et al (2009) Complications of posterior cranial fossa surgery—an institutional experience of 500 patients. Surg Neurol 72(4):369–375
43. Paterson E, Farr RF (1953) Cerebellar medulloblastoma: treatment by irradiation of the whole central nervous system. Acta Radiol 39(4):323–336
44. Rieken S, Mohr A, Habermehl D, Welzel T, Lindel K, Witt O et al (2011) Outcome and prognostic factors of radiation therapy for medulloblastoma. Int J Radiat Oncol Biol Phys 81(3):e7–e13
45. von Hoff K, Rutkowski S (2012) Medulloblastoma. Curr Treat Options Neurol 14(4):416–426
46. Uday S, Murray RD, Picton S, Chumas P, Raju M, Chandwani M et al (2015) Endocrine sequelae beyond 10 years in survivors of medulloblastoma. Clin Endocrinol 83(5):663–670
47. Frange P, Alapetite C, Gaboriaud G, Bours D, Zucker JM, Zerah M et al (2009) From childhood to adulthood: long-term outcome of medulloblastoma patients. The Institut Curie experience (1980-2000). J Neurooncol 95(2):271–279
48. Moxon-Emre I, Bouffet E, Taylor MD, Laperriere N, Scantlebury N, Law N et al (2014) Impact of craniospinal dose, boost volume, and neurologic complications on intellectual outcome in patients with medulloblastoma. J Clin Oncol 32(17):1760–1768
49. Packer RJ, Gajjar A, Vezina G, Rorke-Adams L, Burger PC, Robertson PL et al (2006) Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 24(25):4202–4208
50. Lannering B, Rutkowski S, Doz F, Pizer B, Gustafsson G, Navajas A et al (2012) Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: results from the randomized multicenter HIT-SIOP PNET 4 trial. J Clin Oncol 30(26):3187–3193
51. Gajjar A, Chintagumpala M, Ashley D, Kellie S, Kun LE, Merchant TE et al (2006) 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 7(10):813–820
52. Tarbell NJ, Friedman H, Polkinghorn WR, Yock T, Zhou T, Chen Z et al (2013) High-risk medulloblastoma: a pediatric oncology group randomized trial of chemotherapy before or after radiation therapy (POG 9031). J Clin Oncol 31(23):2936–2941
53. Kortmann RD, Kuhl J, Timmermann B, Mittler U, Urban C, Budach V et al (2000) 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 46(2):269–279
54. Jakacki RI, Burger PC, Zhou T, Holmes EJ, Kocak M, Onar A et al (2012) Outcome of children with metastatic medulloblastoma treated with carboplatin during craniospinal radiotherapy: a Children's Oncology Group Phase I/II study. J Clin Oncol 30(21):2648–2653
55. Rutkowski S, Bode U, Deinlein F, Ottensmeier H, Warmuth-Metz M, Soerensen N et al (2005) Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. N Engl J Med 352(10):978–986
56. Dhall G, Grodman H, Ji L, Sands S, Gardner S, Dunkel IJ et al (2008) Outcome of children less than three years old at diagnosis with non-metastatic medulloblastoma treated with chemotherapy on the "Head Start" I and II protocols. Pediatr Blood Cancer 50(6):1169–1175
57. Cohen BH, Geyer JR, Miller DC, Curran JG, Zhou T, Holmes E et al (2015) Pilot study of intensive chemotherapy with peripheral hematopoietic cell support for children less than 3 years of age with malignant brain tumors, the CCG-99703 phase I/II study. A report from the Children's Oncology Group. Pediatr Neurol 53(1):31–46
58. Rudin CM, Hann CL, Laterra J, Yauch RL, Callahan CA, Fu L et al (2009) Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. N Engl J Med 361(12):1173–1178
59. de Bont JM, Packer RJ, Michiels EM, den Boer ML, Pieters R (2008) Biological background of pediatric medulloblastoma and ependymoma: a review from a translational research perspective. Neuro-Oncology 10(6):1040–1060
60. Northcott PA, Dubuc AM, Pfister S, Taylor MD (2012) Molecular subgroups of medulloblastoma. Expert Rev Neurother 12(7):871–884
61. Bandopadhayay P, Bergthold G, Nguyen B, Schubert S, Gholamin S, Tang Y et al (2014) BET bromodo-

main inhibition of MYC-amplified medulloblastoma. Clin Cancer Res 20(4):912–925
62. Pei Y, Moore CE, Wang J, Tewari AK, Eroshkin A, Cho YJ et al (2012) An animal model of MYC-driven medulloblastoma. Cancer Cell 21(2):155–167
63. Morfouace M, Shelat A, Jacus M, Freeman BB 3rd, Turner D, Robinson S et al (2014) Pemetrexed and gemcitabine as combination therapy for the treatment of Group3 medulloblastoma. Cancer Cell 25(4):516–529
64. Ramaswamy V, Remke M, Bouffet E, Faria CC, Perreault S, Cho YJ et al (2013) Recurrence patterns across medulloblastoma subgroups: an integrated clinical and molecular analysis. Lancet Oncol 14(12):1200–1207
65. Wang X, Dubuc AM, Ramaswamy V, Mack S, Gendoo DM, Remke M et al (2015) Medulloblastoma subgroups remain stable across primary and metastatic compartments. Acta Neuropathol 129(3):449–457
66. Morrissy AS, Garzia L, Shih DJ, Zuyderduyn S, Huang X, Skowron P et al (2016) Divergent clonal selection dominates medulloblastoma at recurrence. Nature 529(7586):351–357
67. Hill RM, Kuijper S, Lindsey JC, Petrie K, Schwalbe EC, Barker K et al (2015) Combined MYC and P53 defects emerge at medulloblastoma relapse and define rapidly progressive, therapeutically targetable disease. Cancer Cell 27(1):72–84
68. Zhukova N, Ramaswamy V, Remke M, Pfaff E, Shih DJ, Martin DC et al (2013) Subgroup-specific prognostic implications of TP53 mutation in medulloblastoma. J Clin Oncol 31(23):2927–2935
69. Packer RJ, Zhou T, Holmes E, Vezina G, Gajjar A (2013) Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. Neuro-Oncology 15(1):97–103
70. Fay-McClymont TB, Ploetz DM, Mabbott D, Walsh K, Smith A, Chi SN et al (2017) Long-term neuropsychological follow-up of young children with medulloblastoma treated with sequential high-dose chemotherapy and irradiation sparing approach. J Neurooncol 133(1):119–128
71. King AA, Seidel K, Di C, Leisenring WM, Perkins SM, Krull KR et al (2017) Long-term neurologic health and psychosocial function of adult survivors of childhood medulloblastoma/PNET: a report from the Childhood Cancer Survivor Study. Neuro-Oncology 19(5):689–698
72. Lafay-Cousin L, Bouffet E, Hawkins C, Amid A, Huang A, Mabbott DJ (2009) Impact of radiation avoidance on survival and neurocognitive outcome in infant medulloblastoma. Curr Oncol 16(6):21–28
73. Lafay-Cousin L, Smith A, Chi SN, Wells E, Madden J, Margol A et al (2016) Clinical, pathological, and molecular characterization of infant medulloblastomas treated with sequential high-dose chemotherapy. Pediatr Blood Cancer 63(9):1527–1534
74. Yock TI, Yeap BY, Ebb DH, Weyman E, Eaton BR, Sherry NA et al (2016) Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study. Lancet Oncol 17(3):287–298
75. Kulkarni AV, Piscione J, Shams I, Bouffet E (2013) Long-term quality of life in children treated for posterior fossa brain tumors. J Neurosurg Pediatr 12(3):235–240
76. Piscione PJ, Bouffet E, Mabbott DJ, Shams I, Kulkarni AV (2014) Physical functioning in pediatric survivors of childhood posterior fossa brain tumors. Neuro-Oncology 16(1):147–155
77. Cavalli FMG, Remke M, Rampasek L, Peacock J, Shih DJH, Luu B et al (2017) Intertumoral heterogeneity within medulloblastoma subgroups. Cancer Cell 31(6):737–754. e6
78. Kuzan-Fischer CM, Guerreiro Stucklin AS, Taylor MD (2017) Advances in genomics explain medulloblastoma behavior at the bedside. Neurosurgery 64(CN_suppl_1):21–26