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Medulloblastoma

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Abstract

Among the pediatric brain tumors, medulloblastoma (MB) is the most common solid variety and entirely occur in the posterior fossa with tendency to seed into CSF spaces. Despite innovations in technological developments and understanding of tumor biology, modern imaging facilities, advances in surgical practices, and newer chemotherapeutic and radiation techniques, this malignant type of tumor continues to be a formidable entity. Even though, the outcome in terms of survival rate is better than any time before, the overall result is still disappointing. With advances in management strategy, chances of survival with good quality of life have been amplified, where newer targeted therapies and rehabilitation plays an immense role. While the adverse effects of surgery and adjuvant therapies are still on play, researchers are trying ceaselessly to minimize those to give maximum wellbeing to these unfortunate children.

Keywords: medulloblastoma, surgery, radiotherapy, chemotherapy, molecular subgroup

1. Introduction

Medulloblastomas are a group of highly undifferentiated, rapidly growing, extremely malignant formidable solid tumor of childhood with worst estimated prognosis. Maximal safe resection, craniospinal irradiation (CSI) and chemotherapy remain the mainstays of first-line treatment of these aggressive embryonal tumors which are the most frequent primary malignant brain cancer in children.

The name “medulloblastoma” was first adapted by Harvey Cushing in 1930. Initially these tumors were termed as spongioblastoma indifferentiale, spongioblastoma multiforme, spongioblastoma cerebelli or simply spongioblastoma by different authors. Cushing presumed
this subset of tumors to be originating from one of the five pluripotent stem cells, the medullo-
blast, thought to populate the primitive neural tube [1–5]. It has meanwhile been established
that the concept of embryonal cell identified as medulloblast does not exist [6, 7]. Hence the
term medulloblastoma that Cushing erroneously coined, which is so strongly concreted to the
nomenclature, is actually a misnomer [7].

Medulloblastomas were considered as one of the most disappointing maladies in neurosurgery
until the 1960s as survival was still equally poor as was in the early periods of neurosurgery
when posterior fossa tumors were most daunting. Overall, improved diagnostic, surgical, and
radiation technologies, newer and more effective chemotherapy regimens have led to dramati-
cally improved patient outcomes with advanced research [8]. Multidisciplinary approach being
the keystone of success for this formidable disease, significant clinical challenge still remains
because of acute onset, rapid growth, rapid clinical course and early fatal termination leading to
great number of morbidity and mortality despite aggressive therapeutic strategies [2, 3, 9, 10].

Survival of medulloblastoma patients have become better over the last few decades nonethe-
less in patients with relapse, the outcome is still miserable. Long-term survival rates have
progressively improved from 22% by 1950s to 85% in 2015 with current approaches [11–14].
This significant development has resulted from combination of systemic chemotherapy and
improvement in supportive care measures in addition to the regular treatment with surgery
and radiotherapy [15–19]. Advances in genetic profiling with emergence of newer agents and
development of newer strategies targeting the key molecular alterations have improved the
outcomes further [20]. Efforts to improve survival results, dose reduction or elimination of
radiation or trial with less offensive chemotherapeutic agents are going on to standardize the
treatment of medulloblastoma.

2. Epidemiology

2.1. Incidence

Generally it is recognized that medulloblastoma is the most common malignant brain tumor
in children. However, recent data shows that as a group, high-grade gliomas are marginally
more prevalent. Approximately 350 new pediatric cases of medulloblastoma are diagnosed
in the United States every year and that represents about 30% of pediatric brain tumors and
7–10% of all brain tumors [2, 6, 8, 9, 21–23].

2.2. Age

There are characteristic bimodal peaks, having a higher incidence in children between 3 and
4 years of age and between 8 and 10 years of age. About 70% of childhood medulloblastomas
occur in this age range of the first decade. However, medulloblastoma has been reported in a
2-week-old infant and a 55-year-old adult [6, 9]. About 1–3% of cases are reported in adults,
mostly before the age of 40 years [8, 24, 25].
2.3. Sex

Curiously enough, Cushing found medulloblastomas to be three times more common in males than females and since then most published reports indicate a continuing male predominance. On an average the male to female ratio is 2:1 [2, 8, 9].

2.4. Location

The typical medulloblastoma develops in the midline of the posterior fossa [9, 25]. Some 70–80% of medulloblastomas have been found in the midcerebellum with or without extension into the lateral cerebellar hemispheres. Medulloblastomas typically arise from the medullary velum and fill the cavity of the fourth ventricle and has the propensity to spread throughout the brain and spine via the cerebrospinal fluid (CSF) and about one third of the cases infiltrate the dorsal brainstem [8, 26].

3. Etiology

The etiologies of medulloblastoma are still obscure for most patients. Though Parental pesticide use and parental occupational contact with hydrocarbons, exposure to N-nitroso compounds and metals have been associated with higher incidence in some studies [25]. For development of medulloblastoma, the most ventured postulation in the earlier literatures was cell misplacements during early embryonic development where genetic factors play vital role [9]. This has been proven true with time with the advancement of genetic studies. Association between several familial cancer syndromes in children with medulloblastomas like TP53 germline mutation syndromes, Gorlin syndrome, and Turcot syndrome also supports predisposition of hereditary factors [8].

Studies have identified Human Cytomegalovirus (HCMV) protein pp65 immunoreactivity in medulloblastomas, but the oncogenic role of HCMV is still debated. Yet HCMV is believed to play role as a significant oncomodulator and based on that researchers are on the quest to utilize the potential of HCMV as a novel immunotherapeutic agent [25, 27–29].

4. Pathology

4.1. General

The World Health Organization (WHO) defines medulloblastoma as “a malignant, invasive embryonal tumor of the cerebellum with preferential manifestation in children, predominantly neuronal differentiation and an inherent tendency to metastasize via cerebrospinal (CSF) pathways” [30]. Although it is generally agreed that cerebellar medulloblastoma is an embryonic tumor, its origin is still a matter of speculation [9].
4.2. Macroscopic pathology

Macroscopically these midline globular, soft tumors are fairly well demarcated, and are apparently encapsulated. The marked vascularity gives them a dark, dirty brownish-red hue and occasionally they have extensive areas of necrosis. Consistency may vary from suckable to rubbery or to even firm sometimes. Calcifications are seen occasionally while hemorrhage in medulloblastoma is an extremely rare occurrence. Often marked edema of a wide zone of the neighboring tissue is also seen. They overlie the fourth ventricle as they develop in the midline in the roof of the fourth ventricle to occupy it, but most of the floors of the fourth ventricle in the great majority of cases are typically free. They usually block the aqueduct of Sylvius, with significant dilatation. These have a tendency to invade the meninges. Commonly they grow downward through the foramen magnum from the primary location between the tonsils of the cerebellum [1–3, 9]. CSF dissemination into the subarachnoid spaces often lead to local or widespread leptomeningeal metastases in the spinal axis or over the surface of the cerebral hemispheres or cerebellum and this also may cause characteristic pearly gray sheets of tumor in the meninges. Furthermore, widespread implantation of tumor can be found throughout the ventricles [9, 31].

4.3. Microscopic pathology

Generally medulloblastomas are categorized as small blue-cell tumors, based on presence of their deeply basophilic nuclei [25]. Histologically, these tumors comprise of densely packed rounded or pear-shaped or sometimes spindle-shaped cells having large ovoid nuclei containing plentiful network of chromatin with scanty cytoplasm and for the most part consisting of numerous embryonic glia fibrillae [1, 3, 8]. These are highly cellular tumors forming uniform sheets of cells, interposed with occasional thin-walled blood vessels. Low magnification reveals that the cells appear as a loose structureless mass, but the nuclei sometimes may form pseudo-rosettes or may show a palisade arrangement. Extensive areas of necrosis, numerous hemorrhagic foci and great vascularity often come across too [1, 3, 9]. Thin-walled blood vessels with delicate connective tissue confined to their walls can be demonstrated by special staining with Perdrau’s stain [9].

4.4. Electron microscopic examination

The electron microscopic picture is a mosaic of cells, processes, and fibers. The tumor cells are arranged in a tightly packed mass as also seen in light microscopy. Both the glial and neuronal cells can be recognized on electron microscopic analysis [9].

4.5. Immunohistochemistry

Immunohistochemistry can help in diagnosis of medulloblastoma and can provide information augmenting the plan for further management. Mitosis is seen in up to 80% of tumors, as assessed by positive staining with the Ki-67/MIB1 antibody. Medulloblastomas are frequently positive for vimentin and synaptophysin staining [32].

4.6. Genetic aspects

With the advent of genetic profiling and molecular analysis, evolving evidences point to the fact that the different precursor cell populations that form the cerebellum are vulnerable to
mutations in signal pathways that regulate their functions; these mutations modify normal
development pathways and may result in the development of distinct variants of medul-
loblastoma [33].

5. Classification

From the very beginning of history of this special type of tumor, these has been tried to be
classified in different ways. With the advent and development of molecular biology and incor-
poration of that with genetic profiling has taken the classification beyond the level of mere
histological classification. The molecular subgroupings are helpful in prediction of course
of the disease and outcome as well as choosing therapeutic options. Recently the treatment
plan is devised in accordance with the classification that integrates both histological and the
molecular subgroupings to have the best possible outcome on the basis of a personalized
treatment for individual patients.

5.1. Histological classification

Histopathological classification of medulloblastoma has evolved with time. Rubinstein and
Northfield [34] initially identified three variants of medulloblastoma: pigmented papillary
medulloblastoma, medullomyoblastoma, and desmoplastic medulloblastoma. With newer
technologies, newer histological types were being introduced. To alleviate the confusions,
the World Health Organization (WHO) in 1976 developed a common classification of brain
tumors in an effort to combine the various systems in use till then and the WHO publica-
tion “Histological Typing of Tumours of the Central Nervous System” in 1979 outlined and
illustrated the new classification system [30, 35, 36]. Since then modifications, additions and
characterization of classification of medulloblastoma has evolved a lot throughout the newer
classifications of medulloblastoma of the WHO editions of classifications gradually in 1993
[35], 2000 [37, 38] and 2007 [30]. The present histological classification that is in practice has
the following types:

1. **Classic medulloblastoma**: Most common histologic subtype (66%). Composed of sheets
   of densely packed, small to medium-sized, round to oval-shaped, blue cells (basophilic)
   with a high nuclear to cytoplasmic ratio and high mitotic and apoptotic activity. Reticulin
   staining shows a lack of nodular desmoplasia.

2. **Large cell/anaplastic medulloblastoma**: Large cell medulloblastomas have monomorphic
   cells with large, round, prominent nuclei, high mitotic activity, and frequent apoptosis,
   while the anaplastic medulloblastoma are characterized by hallmarks of anaplasia. Large
cell and anaplastic medulloblastomas have a significant degree of cytologic overlap and
   are differentiated only by the degree of anaplasia.

3. **Desmoplastic/nodular medulloblastoma**: Widespread desmoplasia, characterized by
   presence of nodular, reticulin-poor “pale islands” of neuroectodermal differentiation surrounded
   by densely packed, mitotically active cells having pleomorphic and hyperchromatic nuclei.
   Reticulin staining highlights internodular desmoplastia.
4. **Medulloblastoma with extensive nodularity (MBEN):** Similar to nodular type but has an expanded lobular architecture with more prominent reticulin-free zones that are more elongated and rich in neutrophil-like tissue. Reticulin staining highlights internodular desmoplasia. Advanced neurocytic differentiation in islands with strong nuclear NeuN expression is also seen.

Two other histologic types of medulloblastomas are also recognized but are not considered to be distinct variants. They are the Myogenic differentiation type and the Melanotic medulloblastoma. All the histopathological types have significant predictability of prognoses in accordance with the clinico-pathological characteristics of each tumor type as outlined in the WHO classification [6, 8, 30, 34].

5.2. Genetic classification and subgroups

Research in the molecular study has led to understanding of embryonal tumors of the CNS. This reflection has basically been driven by genomic studies characterizing prevalent genetic profiles and biological features. These have led to tumor reclassification, sub-typing and detection of novel entities [10, 39, 40]. Over the last two decades, individual molecular subgroups have been identified for medulloblastoma based on cytogenetic profiles. Each group is named for the cellular pathway activation or genomic alterations it exhibits and each subgroup is associated with distinct prognostic character and survival outcomes [8]. In 2010, in Boston, an international group of medulloblastoma authorities, came to a consensus to categorize medulloblastomas into four distinct subgroups: Wingless (Wnt), Sonic hedgehog (Shh), Group 3, and Group 4 based on their unique set of demographic and clinical features, genetics, gene expression, genome-wide transcriptomic and DNA methylomic profiles [41, 42]. Prediction of outcome and clinical behavior is more precise with the known molecular subgroups than the histopathology or clinical staging. [6, 43–45]. These molecular subgroups are distinct from the histologic subtypes, albeit there are certain areas of considerable overlap (Figure 1).

5.2.1. **Wingless pathway tumors (Wnt pathway/Wnt-MB)**

The Wingless pathway (also termed as the β-catenin pathway) comprises of secreted glycoproteins which are secreted to act through signal transduction to regulate various parts of embryonic development. Uncontrolled activation of Wnt pathway signaling results in accumulation of β-catenin, encoded by the CTNNB1 gene, leading to aberrant up regulation of transcription and ensues oncogenesis [46]. Wnt pathway tumors are the least common of the four molecular subgroups that represents merely about 10% of sporadic medulloblastomas [47]. Genetic features of this subgroup are characterized by the aberrations like monosomy 6, CTNNB1 mutations, and nuclear β-catenin positivity by immunohistochemistry [47]. This subgroup of medulloblastomas is more common in children and in adults than in infants. The outcomes of these medulloblastomas are outstanding and 5-year overall survival rate is 95% in children and 100% in adults [6, 10, 42]. TP53 mutations are invariably present in both the Wnt and Shh subgroup medulloblastomas [6, 42, 48]. As Wnt-MB has uniformly good prognosis, treatment regimen can be de-escalated with reduced dose of craniospinal radiation, reduced-intensity of chemotherapy, or a combination of both in patients without metastatic disease [49].
5.2.2. Sonic hedgehog pathway tumors (Shh pathway/Shh-MB)

The Shh group of medulloblastomas is named after the Sonic Hedgehog signaling pathway, which is thought to drive this type of tumor initiation [42]. Medulloblastomas categorized by activation of Shh signaling are heterogeneous and are linked with a variety of genetic aberrations and outcomes, unlike the Wnt-MB [50]. As a whole, Shh subgroup tumors comprises nearly 30% of medulloblastomas overall [42, 48, 50].

Medulloblastomas of the Shh subgroup results from genetic predisposition of alteration of the sonic hedgehog pathway in the form of germline mutations in the patched-1 gene (PTCH1) or the suppressor of fused gene (SUFU). Loss of function PTCH1 and SUFU mutations lead to truncation of their associated protein products, leading to failure of their tumor suppressor effects and activation of Shh signaling with resultant tumorigenesis. Somatic mutations in PTCH1 and SUFU are also associated with sporadic medulloblastomas characterized by activation of the Shh pathway, along with PTCH2, MYC, SMO, GLI1 and GLI2 mutations [6, 42, 51, 52]. Deletion of chromosome 9q seems to be restricted to Shh medulloblastomas, which is fitting as the PTCH gene is located at chromosome 9q22 [42].

Clinical outcomes of individuals with Shh-MB can be divided into favorable and poor survival groups depending on TP53 mutation status which is particularly critical [48]. Patients with Shh/TP53 mutant variety medulloblastomas have extremely poor outcome than those with Shh/TP53 wild-type tumors as mutant TP53 has been associated with high rate of anaplasia and MYCN amplification, which are equally disastrous cellular events [48, 53]. Because of its clinical impact, TP53 mutation status has been incorporated into the 2016 WHO classification for CNS tumors and is part of routine assessment in all Shh-activated medulloblastomas [40].

![Figure 1. WHO 2016 classification of medulloblastoma subtypes, characterized by genetic and histological features.](http://dx.doi.org/10.5772/intechopen.76783)
Survival for Shh subgroup medulloblastomas is similar to Group 4 medulloblastomas and intermediate between that of Wnt and Group 3 medulloblastomas and varies significantly based on age and histologic subtype [10, 42, 48].

5.2.3. Non-Wnt/Shh tumors

The non-Wnt/Shh tumor subgroup encompasses Group 3 and Group 4, in which the underlying genetic predisposition of mutations have yet not been recognized [49]. These types are associated with a higher incidence of tumor dissemination and approximately 30% of patients have metastasis at the time of diagnosis [6]. Despite these similarities, features of Group 3 and Group 4 subgroup medulloblastomas vary regarding the demographic, clinical, transcriptional, and genetic differences between them and these advocate that they are actually distinct entities with molecular diversity [42, 54].

5.2.3.1. Group 3 MB

Nearly 30% of medulloblastomas are of the Group 3 subgroup and histologically mostly are of the “classic” variety of medulloblastomas [6, 55–57]. These tumors genetically are more likely to have high-level expression and amplification of MYC, MYCN and OTX2 with imbalance of chromosome 17 [42, 49, 51, 58]. Group 3 tumors show gain of chromosome 1q, and/or loss of chromosome 5q and chromosome 10q more than Group 4 tumors [42]. They occur more frequently in infants and children, and has the worst outcome among all molecular subgroups, with 10-year overall survival of 39% in infants and 50% in children [6, 42, 49, 51, 59].

5.2.3.2. Group 4 MB

About 35% of medulloblastomas overall are of Group 4 subgroup and the peak incidence for this subgroup is in late childhood and early adolescents [6, 42]. The prognosis of Group 4 tumors is similar to Shh subgroups tumors and is intermediate between those of Wnt and Group 3 subgroup tumors. Patients with metastatic disease or MYC amplifications in this Group have significantly poorer outcomes [49, 50]. Though isochromosome 17q is also seen in Group 3 tumors, it is more common in Group 4 tumors. Another prominent cytogenetic alteration among Group 4 tumors is loss of the X chromosome, which is found in 80% of females with Group 4 medulloblastoma [42].

Recently, the discovery of seven novel molecular subgroups has permitted to categorize patients further to envisage better disease subclassification and outcome predictions. These subgroup dependent grouping stratified patients into four clinical risk groups for 5-year progression-free survival: favorable risk (91% survival); standard risk (81% survival); high-risk (42% survival); and very high-risk (28% survival) [41]. Another study recommended total of 12 subgroups based on the integration of transcriptomic and methylation data. In that analysis medulloblastoma encompasses 12 subtypes; 2 Wnt, 4 Shh, 3 Group 3, and 3 Group 4 groups. These subtypes of each subgroup are clinically and biologically pertinent [54].

5.3. Integrated classification

In 2016, for the first time, the molecular characteristics was incorporated into the WHO classification for the diagnosis of CNS tumors. This integration of histological features with genetic
information has considerably transformed the diagnostic work-up and reporting of tumors of the CNS. Nonetheless, this remains perplexing in embryonal tumors due to their de novo tumor heterogeneity that is being faced [10]. This integrated diagnosis is presented in a layered format; that includes the histological diagnosis, WHO grade, molecular genetic information and ultimately the integrated diagnosis. The value of this approach is clearly illustrated in embryonal tumors, in particular medulloblastoma, where the combination of molecular and histological data provides discrete diagnostic information [40]. In this new concept of a “layered diagnosis” brain tumors that are diagnosed purely morphologically are incorporated with molecular characteristics for an “integrated diagnosis” at the peak diagnostic level [60]. In the layered integrated classification, a patient would be labeled as having medulloblastoma of a definite histological subtype, the WHO grade and the molecular subgroup [61].

6. Staging

There is no well-established staging system for medulloblastoma for prediction from which treatment plan and outcome prediction can be made. In 1969, Chang et al. suggested an operative staging system for medulloblastomas adapting the TNM classification for other tumors [62]. According to the size and extent of primary tumor, T category was divided into four main groups with subdivisions of T3 (T1, T2, T3a, T3b or T4) and the M category had five groups (M0, M1, M2, M3 and M4) based on the degree of tumor spread in the CSF pathway or extra-CNS metastases [9]. Overall, M staging has remained more useful in prognostic evaluation, while the T staging is less valuable as a prognostic indicator [63]. Several studies have stratified the patients into “high-risk” and “average” or “standard-risk” groups depending on age of the patient, residual disease after surgery, pathologic variant, and M staging [8, 64]. This risk stratification is a good predictor of outcome. Standard-risk and high-risk categories have long term survival rates of approximately 85% and 70%, respectively [6].

7. Presentation

Because of its origin in the posterior fossa, the presenting symptoms of medulloblastoma are often vague complaints and understandably the diagnosis may be delayed. Presentation depends on various elements of the tumor subject to location, size, duration, compression on the surrounding structures. As these arise from the vicinity of cerebellum and brainstem, often the first feature to appear is instability of gait. Being a midline posterior fossa lesion, truncal ataxia appears first and appendicular ataxia gradually ensues as the tumor grows bigger to compress the cerebellar hemispheres, and other common cerebellar signs follow with time. When the tumor is big enough to compress the brainstem, long tract signs begin to appear and add more difficulty in movement of the patients. As the tumor grows further, especially downwards, the lower cranial nerves start to get involved and lower cranial nerve palsies manifest. If the tumor grows bigger to occupy and block the Aqueduct of Sylvius, hydrocephalus ensues. Hydrocephalus may also result from blockage of the fourth ventricular outlets, by compression, by the growing tumor, individually or in combination. Hydrocephalus in turn may lead to features of raised Intracranial Pressure (ICP) resulting in
headache, nausea, vomiting, irritability, lethargy, behavior alteration, personality change and impaired memory or attention, etc. Raised ICP occasionally gives rise to possibility of having seizure and 6th nerve palsy. Respiratory and cardiac manifestations may be evident, resulting from compromise of the respiratory and cardiac centers in the brainstem. Alteration of level of consciousness, starting from disorientation to deep coma, may result either from raised ICP or from compression on the brainstem. Papilledema or even visual impairment from raised ICP is not very uncommon, especially when presented in late stage.

Medulloblastoma is a very rapidly growing tumor and tends to follow a rapid progression in a very short period of time. The median time between onset of symptom until diagnosis (symptom interval) is 3.3 months (65 days) [65]. Rarely, patients may have symptoms for up to 6 months before diagnosis and younger patients have significantly longer interval to diagnosis while more aggressive subgroups of medulloblastoma have a shorter pre-diagnostic interval [66].

8. Diagnosis and differentials

The accurate diagnosis of pediatric tumors is essential to ensure balance between achieving a long-term cure and avoiding treatment related disability in survivors. The tentative diagnosis of medulloblastoma is relatively straight cut one from the age of the patient, history and neurological examination findings. Nonetheless, there are other maladies that are to be kept in mind. The two commonest differential diagnosis of a posterior fossa mass in children are pilocytic astrocytoma and ependymoma. Other lesions to be considered are atypical teratoid/rhabdoid tumors, exophytic brainstem glioma and choroid plexus papilloma as well as teratoma in infants and hemangioblastoma in patients with Von Hippel-Lindau syndrome. Metastasis is the first to be thought in adults as that is the most frequently encountered posterior fossa lesion [6, 10].

9. Investigation work ups

A variety of diagnostic studies are used to confirm the clinical diagnosis of medulloblastoma and to localize the tumor exactly. The first-line diagnostic test for medulloblastoma is brain imaging.

Up until introduction of CT scan in 1971, air studies (pneumoencephalography and ventriculography) were most reliable and almost accurate in the diagnosis of medulloblastoma in all age groups. Angiography also yielded useful results regardless of age. With advent of MRI, CT scan has become an adjunct to that. Skull x-ray studies, once useful for the detection of brain tumors, is now rarely of value. Nucleotide brain scans and bone scans, myelographic examination, CSF cytology were also helpful in diagnosing a moderate number of cases [6, 8, 9, 67, 68].

9.1. Computerized tomography (CT)

CT is often used as the first-line diagnostic imaging because of its readily availability, fastness in imaging and comparatively cheaper price [8]. This is a good tool for early diagnosis with state of hydrocephalus, serial evaluation of tumor, postoperative assessment of extent.
of tumor removal, detection of residual and recurrent tumor, and tumor deposits in the CSF pathways as well as convenient follow-up studies [4, 15, 42]. Medulloblastomas appear typically hyperdense and sharply demarcated lesion near the fourth ventricle in the plain CT scan with a surrounding hypodense zone of edema which show better delineation with contrast enhancement showing moderate to marked increase in density (Figure 2). Cystic components may also be seen. Leptomeningeal tumor deposits appear as areas of increased density in the subarachnoid space. Calcification may be seen in about 10–20% of medulloblastomas [5, 62].

9.2. Magnetic resonance imaging (MRI)

The relationship between the tumor and the surrounding brain structures can be vividly demonstrated in MRI with and without gadolinium. Screening MRI of the whole spinal axis is capable of displaying and evaluating tumor dissemination, when present and pre-operative whole spine MRI is preferred [20, 21].

Different sequences of MRI can provide different information to help in diagnosis and treatment planning. Medulloblastomas are hypointense to gray matter on T1-weighted imaging (T1WI) with heterogeneous gadolinium enhancement in 90% of cases, while they are generally iso to hyperintense to gray matter on T2-weighted imaging (T2WI). The heterogeneity in T1WI and T2WI results from cyst formation, calcification or necrosis. Diffusion-weighted imaging (DWI) shows restricted diffusion and in fluid-attenuated inversion recovery (FLAIR) imaging, medulloblastomas are generally hyperintense to surrounding brain (Figure 3). MR spectroscopy (MRS) shows elevated choline peaks and decreased creatine and N-acetyl acetate peaks, with occasional elevation in lactic acid and lipid peaks [62].

Figure 2. Plain axial CT scan (A) showing hyperdense and sharply demarcated lesion near the fourth ventricle with surrounding hypodense area of edema which with contrast enhancement (B) is well demarcated by increased density.
Figure 3. Medulloblastomas in T2-weighted imaging (T2WI), T1-weighted imaging (T1WI), with gadolinium enhancement (CONT), fluid-attenuated inversion recovery (FLAIR) (D) and diffusion-weighted imaging (DWI) in axial planes.
9.3. Molecular diagnosis

Molecular diagnosis is of immense importance and an integral part of the management protocol as it is invaluable in prediction of outcome and in formulation of dose of therapy, especially in cases of selection of agents for targeted therapy. As these state of the art assays are accessible merely in few laboratories of the first-world neuropathological institutions, it is often very difficult to come to an integrated diagnosis for most of the centers in the world. Nonetheless, molecular antibodies specifically targeting mutated proteins should be available in nearly all neuropathological laboratories.

10. Treatment

10.1. General

Treatment strategies for medulloblastomas have advanced slowly over the past 5 decades. Generally based on the histology and clinical factors, especially, disease dissemination at presentation and residual tumor after surgical resection, management of medulloblastoma has evolved to maximal safe surgical resection followed by radiation therapy and adjuvant chemotherapy [20, 22–24, 26, 69].

Adjuvant chemotherapy is recommended for all patients as this improves outcomes significantly. Following surgery, risks of recurrence and of neurocognitive effects of radiation therapy, doses of radiation and the type of chemotherapy protocol vary depending on extent of disease and age of the patient as well as institutional preferences [20, 29].

Though the medulloblastoma subgroups (Wnt, Shh, Groups 3 and 4) have distinct molecular and clinical profile, current adjuvant chemotherapy that are in practice are for the nontargeted ones. However, significant improvements, approximately 70% 5-year survival rate with these combined therapies are achieved at the high cost of the quality of life, resulting mostly from the effects of radiotherapy and nonspecific, antimitotic agents on the developing brains of young medulloblastoma patients [27–31]. A general approach carries significant risk of over or under-treatment [30, 34].

10.2. Surgery and surgical techniques

In March 1925, Cushing first succeeded in gross total removal of a medulloblastoma [1, 2]. Since then, the first-line treatment for medulloblastoma is surgery with the aim of maximal safe resection, along with treatment of any concomitant hydrocephalus [8]. But Cushing also cautioned that “the temptation will always be present for the surgeon to attempt an enucleation, a conservative attitude in this respect is the course of wisdom” [1, 8].

The basic principles of surgery for medulloblastoma have changed little in the modern era, but technological revolutions in surgical technique and supportive care have made surgery safer. Development of surgical skill and other facilities has dramatically reduced the perioperative
mortality from 25.2% during the period of Cushing to less than 1% in expert hands at the present time [70]. With recent technological advancements the goal of surgery is always a complete excision, but practically it can safely be accomplished only in about one fourth of cases [71].

Most surgeons prefer the prone position than to the sitting position to minimize the risk of air embolism, frontal pneumocephalus, and systemic hypotension. The straight vertical skin incision employed by almost all neurosurgeons today was described first by Naffziger in 1928 [70]. A wide craniectomy or craniotomy extending from the transverse sinuses to the foramen magnum is performed with or without removal of the posterior arch of C1. The dura is usually opened in a Y-shaped manner extending down to the level of C1 when the posterior arch is removed. The tumor may be readily evident as a red, semi circumscribed mass peeping into the vallecula when the tumor is large. The dorsal surface of the tumor is exposed and even though not truly encapsulated, medulloblastomas often have a clear interface between the tumor and surrounding brain where a dissection plane can be created. The tumor is excised in piece meal fashion either through the telovaler approach or by splitting the vermis (Figure 4). With the goal

Figure 4. Schematic diagram showing the exposure of medulloblastoma after splitting the vermis in the midline.
of maximal safe resection, gross total resection can often be accomplished. Superiorly, the tumor is often projected into the aqueduct, filling it and obstructing the CSF pathway. The part projecting into the aqueduct can be meticulously removed with gentle suction, reestablishing the CSF flow (Figure 5). The part of the tumor that is attached to the brain stem or peduncles, is carefully removed, keeping a thin mantle leaving behind to ensure not to injure any vital structure. To alleviate the post-operative morbidity or mortality, immediate postoperative care of the patient is of immense importance. This is a factor that can make enormous difference in outcome.

Whether preoperative shunting should be done to relieve hydrocephalus prior to tumor surgery remains controversial. A ventriculoperitoneal (VP) shunt permanently or an external ventricular drain (EVD) as a temporary measure can be employed to treat hydrocephalus, if present at the time of diagnosis [8, 26, 71]. An EVD can be placed in the operating room, just prior to posterior fossa craniotomy, if the hydrocephalus is not treated preoperatively. About 20% of patients require long-term treatment of hydrocephalus with a VP shunt insertion or an endoscopic third ventriculostomy (ETV), when the hydrocephalus persists even after tumor removal [8, 71]. There is high possibility that a preoperative shunt
may serve as a pathway of dissemination of the medulloblastoma, which has a tendency to spread by the CSF pathways. The use of millipore filters has been described to prevent dissemination [26, 70].

10.2.1. Complications of surgery

Clinical or subclinical venous air embolism, which is more common in sitting position, can happen in the prone position as well. With the goal of complete resection, major complications during tumor removal are usually caused by damage to the brain stem and injury to the lower cranial nerves. Aspiration pneumonia and respiratory failure often follows if the post-operative lower cranial nerve injuries are not handled meticulously. Though described frequently, cerebellar mutism, a commonly described complication of posterior fossa surgery, is less likely to occur now a days with microsurgical techniques. Meningitis, pseudomeningocele, postoperative tumor bed hematoma, epidural hematoma, subdural hematoma are among the other less often encountered complications.

10.3. Radiotherapy

Radiotherapy has been an adjunct of the treatment modality for medulloblastomas since the early twentieth century as these tumors are very responsive to radiotherapy. The survival rate has improved dramatically after the introduction of radiotherapy. Post-operative craniospinal irradiation (CSI) with or without boost to the posterior fossa are the customary protocol, as chosen by different centers [8, 72].

10.3.1. Treatment for average-risk patients ≥3 years of age

Post-operative radiotherapy dose for average risk medulloblastoma patients aged ≥3 years initially was set as 36 Gy CSI and 54 Gy boost for the posterior fossa (PF) because of high risk of local recurrence. Dose adjustment to 23.4–24 Gy CSI with the addition of adjuvant chemotherapy has been made with successful result [66, 73, 74]. Reduction in the posterior fossa radiation volume, in the form of 3-Dimensional conformal radiotherapy (3D CRT) has enabled to restrict the boost volume to the tumor bed plus a margin without compromising local control that minimizes morbidity associated with full PF irradiation by shielding normal vital structures [74–76]. Intensity-modulated radiotherapy (IMRT) or proton beam therapy similarly can reduce exposure to the heart and liver during CSI [72, 77–79].

10.3.2. Treatment for high-risk patients ≥3 years of age

The usual radiotherapy schedule for high-risk medulloblastoma patients of 3 years or more consists of standard dose regimen of 36 Gy CSI with a boost to both the posterior fossa and focal sites of metastasis of 55.8 Gy. Adjuvant chemotherapy, consisting of concurrent vincristine followed by maintenance chemotherapy with Lomustine, Vincristine, and Cisplatin has shown progression-free survival of 67% in M1, M2 and M3 stage [66, 80]. Outcomes for high-risk patients are equally poor even with inclusion of some neoadjuvant agents in addition to conventional chemotherapeutic agents [81–83].
10.3.3. **Treatment of infants and children <3 years of age**

As patients younger than 3 years are in risk of poor outcome of neurocognitive function following CSI, delay or omission of radiotherapy is recommended for this group of patients. M0 patients following gross total resection have commendable outcome with only chemotherapy after surgery [84].

10.3.4. **Radiation hazards**

The long-term sequelae of radiation therapy are well described, among which the most common ones are endocrinopathies, neurocognitive and neurosensory impairment following craniospinal irradiation depending on age of patient and radiation dose [85, 86]. Cancer survivors with a history of cranial irradiation have more tendency to have cerebrovascular disease and an increased risk of second malignancies in the radiation field [6]. Skin reactions, hair loss, growth problems, nausea and vomiting, chronic otitis media and/or otitis externa, myelosuppression are other commonly encountered side effects [71].

10.4. **Chemotherapy and combined radio-chemo therapy**

As medulloblastoma is a highly radiosensitive tumor, chemotherapy for this formidable tumor has been an adjunct in the treatment strategy for years. Various combinations of chemotherapeutic agents are used in conjunction with radiotherapy. The toxic effect of different chemotherapeutic agents have forced their use to be restricted in different circumstances. Now a days, the newer drugs are more soothing to the patients with better acceptability, tolerance and efficacy.

Penetrability of the blood-brain barrier of a drug is the most important feature for a chemotherapeutic agent to be a worthy regimen for brain tumors. Vincristine, Cisplatin, Cyclophosphamide, Lomustine, Etoposide, Methotrexate, Temozolomide, and Carboplatin are the commonly used effective chemotherapeutic agents for medulloblastomas [8, 87].

For average-risk medulloblastoma patients two common chemotherapy regimens are practiced. One is with a combination of Cisplatin, Lomustine, and Vincristine, while the second one comprises of a combination of Cisplatin, Cyclophosphamide, and Vincristine. These two regimens do not have significant difference in outcome regarding event-free survival (EFS) and overall survival (OS) [68]. Among conventional chemotherapeutics, Temozolomide-containing regimens have shown most promising activity. Two studies, one in monotherapy [88] and another in combination with Irinotecan [89], have shown the best results in a relatively large population, although follow up for disease-free survival is short. Its tolerable toxicity profile and synergies with other chemotherapeutics and targeted agents make it an attractive compound to serve as backbone for new strategies [20].

As children under the age of 3 years has worse long term cognitive effects, they are not commonly treated with the radiotherapy. To compensate this more intense chemotherapy is initiated instead [87]. In the last few decades, with the intention to avoid radiation and to have an equally better outcome in younger patients, protocols have been developed consisting of
intense systemic chemotherapy, followed by a consolidation cycle with myeloablative che-
motherapy along with autologous stem cell rescue (AuHCR) as an alternative management
in these patients under the age of 3 years [90]. The 5 year EFS and OS varies between patients
with localized disease, and patients with disseminated disease as well as between patients
with desmoplastic, classical and anaplastic MB [91].

10.4.1. Side effects of chemotherapy

Adverse effects of adjuvant chemotherapy have been significant and needs to be modified in
a good number of patients because of adverse reactions [92, 93]. The commonest side effect
of chemotherapy is hematologic toxicity in the form of leukothrombocytopenia. Other com-
mon adverse effects being anemia, somnolence, peripheral neuropathy, headaches, constipa-
tion, paresthesias, mucositis, nausea and vomiting, immune compromise and bone marrow
suppression, renal toxicities with electrolyte abnormalities, hepatotoxicity, infertility [8, 71].
Some drugs carry the risk of development of treatment-related cancers which is 4.2% at 10
years [94]. Vincristine and cisplatin is known to cause various types of neurotoxicity particu-
larly peripheral neuropathy and ototoxicity [95].

11. Recurrence

The majority of treatment failures develop within the first 2–3 years, and then the failure rate tends
to decrease. Tumor recurrence occurs most frequently in the posterior fossa and that may or may
not be associated with subarachnoid dissemination in the craniospinal axis [8, 9]. Inadequate
post-operative dose of the radiotherapy and large volume of residual tumor are the major causes
of recurrence. Commonly the outcomes in patients with relapsed disease are grave, with five-
year survival rate of only about 25% and which has not improved much, even with development
in treatment strategies [96–98]. Repeat surgical resection, re-irradiation, stereotactic radiosur-
gery, high-dose chemotherapy with AuHCR, low-dose oral Etoposide, the use of biologically
targeted agents, singly or in combination, have been tried and success in control was more for
localized recurrence than for disseminated recurrence [97–107]. At recurrence medulloblastomas
often change towards a more anaplastic pathological variant. Interestingly Shh tumors tend to
recur locally while Groups 3 and 4 recur almost entirely with metastases [10, 20, 44].

12. Metastasis

Medulloblastomas exhibit a strong propensity to metastasize through CSF pathways and
tend to form tumors of variable size along ventricular surfaces, in subarachnoid space, or
along nerve roots or may grow en plaque on surface of brain or spinal cord or may deposit
in the ventricles [25]. Dissemination through the CSF route may be augmented by ventricular
or spinal punctures or by manipulations of the lesion during operation. VP shunting has
frequently been reported to cause extraneural metastases to the peritoneum. Invasion of the
meninges is not very uncommon [2, 9]. Extra CNS metastases have been reported to be in the
bone marrow, lymph nodes, and viscera. Though very rare, metastasis to skin, liver, lung, mediastinum and retroperitoneal structures has also been reported [8, 9].

13. Surveillance

Surveillance is important as relapses encountered on surveillance imaging can be better dealt with and show improved survival as paralleled to those identified by reemergence of the clinical symptoms [108]. Though consensus about the schedule is debated, generally clinical and radiographic follow-up is recommended at three-month intervals during the first year after completion of scheduled therapy, at three to four-month intervals in the second year, every 6 months during the third year, and annually thereafter [109–112] (Figure 6). It is generally

![Figure 6. Preoperative contrast enhanced MRI in sagittal (A), axial (C) and coronal (E) planes and 1 year post-operative contrast enhanced MRI following radiotherapy in sagittal (B), axial (D) and coronal (F) planes of a 9 years old boy.](http://dx.doi.org/10.5772/intechopen.76783)
agreed that surveillance imaging of the brain should be complemented with full spinal MRI as it often might prove to be crucial and beneficial for the patient [110]. It is also recommended that, endocrine screening and neuropsychological testing be performed in those who were treated with craniospinal irradiation [6].

14. Medulloblastoma in adults

Medulloblastoma is much less common in adults, accounting for less than 1% - 3% of primary CNS tumors [24, 113, 114]. The annual incidence of medulloblastoma is 1–1.5 cases per million in the general adult population and 80% occur before the end of the fourth decade [24, 113–115]. Treatment protocols are limited for adults and they are treated by heterogeneous ways using various chemo-radiotherapy regimens with surgery with post-operative CSI being the mainstay of treatment [115]. As late relapse is common among adult medulloblastoma patients, long-term follow-up is warranted. Spinal seeding at presentation is a poor prognostic factor for recurrence [114, 115]. Adult medulloblastomas are clinically similar to that in the pediatric population, but lateral location and desmoplastic type is more frequent in adults as opposed to the pediatric age group. Adult medulloblastomas are thus, more amenable to complete resection and better outcome is expected because of their locations and histopathological variants respectively [24, 113–116]. Relapse following complete treatment is relatively late in adults as compared to children and they have a relatively prolonged time from relapse to death [116]. As most treatment recommendations for adults are extrapolated from the experience in pediatric patients, a protocol from the time of diagnosis includes: increasing the intensity to identify metastasis; increasing the radiotherapy dose to the primary site; adding chemotherapy following radiotherapy in medically fit patients; and following-up the patients with PET or bone scan every 6 months for at least 3 years [117, 118].

15. Outcome

Though the outcomes need to be judged cautiously because of the marked heterogeneity between studies, overall outcome of medulloblastoma patients has improved tremendously over the last decades. Still, outcome in a good number of patients with metastatic disease, adverse molecular or cytogenetic features, infants and relapsed or refractory patients remains depressing.

Many factors play role in outcome of medulloblastoma patients and outcomes have been variable in different series. The outcome has gradually improved from survival from onset to death of 8–9 months in 1930s to 54% 3-year survival in 1950s, about 75% 5-year survival in 1980s [71]. Till the last decade the five-year EFS and OS has raised to 81 ± 2.1 and 86 ± 9%, respectively [68]. Among the factors that play role in poor outcome, the noteworthy are younger age, larger residual tumor volume after surgery, inadequate dose of radiotherapy, presence of metastatic disease at diagnosis, presence of hydrocephalus, anaplastic or large cell histology, insufficient chemotherapy, MYC amplification or expression, 17p loss or 1q gain, and tumors of
Group 3 or Shh subgroup with TP53 mutations. On the contrary, patients having monosomy 6, mutation of CTNNB1, and trkC expression demonstrate a favorable outcome [6, 9, 33, 41, 49, 59]. Generally, OS for children with medulloblastoma are reported as 50–60%, whereas for average-risk and high-risk patients OS is 70–80% and 30–40% respectively [8, 119].

16. Newer therapies/future

The future of medulloblastoma treatment lies on the basis of its genetic coding and molecular subgroupings. A few drugs have been tested preliminarily and that made the researchers as well as the patients optimistic. Endeavor is going on to determine whether the intensity of treatment can be reduced safely, keeping the optimum efficacy, to mitigate the treatment-related long term developmental and cognitive morbidity without affecting survival rates, thus improving the quality of life for medulloblastoma survivors [6, 10]. The molecular biology of the subgroups have emerged to be the key elements of success in future and, with the early success and the potential utility of molecular biomarkers in prognostication and prediction, researchers are in search of more personalized and tailored therapies for the patients [8, 42, 49].

Of the different pathways of tumor origin and progression, the sonic hedgehog (Shh) pathway is a front-runner in research in this perspective. Smoothened (SMO), is an intriguing protein in developmental processes involving the hedgehog signaling pathway [120]. Assuming the role of SMO in the Shh pathway in tumorogenesis, molecules that target SMO are under intensive research and preliminary success have been achieved in some clinical trials [42, 121]. Of these, smoothened inhibitor Vismodegib showed promising result in studies with varying outcomes, having both short-term and long-lasting response, especially in standard-risk Shh medulloblastoma patients [122–125]. Trial with another SMO inhibitor Sonidegib, in cases of patients with relapsed disease also reveals promise for future [123]. Blocking GLI1 with Arsenic trioxide [126], combining SMO inhibitors with PI3K inhibitors [124], or inhibition of PIN1 by either Juglone or the flavonoids Epigallocatechin gallate and Quercetin [127], have attained certain levels of success as these aberrations are frequently encountered in this subset of patients [20]. Quercetin has been found to be a probable worthy radio-sensitizer [127]. Saridegib and Erismodegib are other potent SMO inhibitors under trial that seem to have potential in regression of tumor and inhibition of tumor progression [128].

For Non-WNT/Non-SHH medulloblastomas comprising molecular subgroups 3 and 4, Gemcitabine, a nucleoside analog, and Pemetrexed, a folate antimetabolite are currently being investigated in combination to evaluate their role in prognosis [20, 49]. Combination of these two drugs have been found to be active, particularly against Group 3 medulloblastomas [129]. These were tried separately previously in medulloblastoma patients but only combination of Gemcitabine with Oxaliplatin was found to have promising results with a disease control rate (DCR) of 50% [130]. On the other hand, the combination of Vorinostat and Retinoic acid was found to have a 5-month disease stabilization in patients with Group 4 medulloblastomas [131].

Temozolomide-containing regimens are well tolerable and have good antitumor activity against relapsed/refractory medulloblastomas [20]. Evaluation of temozolomide and
Irinotecan in a study with short follow-up has shown to have good prospect with a DCR of 73% [89]. Trials with multiagent oral antiangiogenic regimen like Bevacizumab, Cilengitide, Lenalidomide and Thalidomide either in monotherapy or in combination with Vincristine, Irinotecan, Temozolomide or Temsirolimus in patients with medulloblastoma yielded only short-lasting disease stabilizations with a tolerable toxicity profile [132–137].

Tyrosine kinase inhibitors (TKIs) like imatinib, sorafenib, lapatinib, nilotinib, dasatinib, ponatinib and bafetinib have shown to block the migration and invasion properties of MB cells which may prove to be effective alternative agents in the treatment of medulloblastomas [128]. In order to reduce treatment related side effects, newer radiotherapy techniques are being evaluated. IMRT and helical tomotherapy have been evaluated, but results were not very pleasing [24].

Immunotherapy is another novel therapeutic approach that is being evaluated for the treatment of medulloblastoma. The target antigens that have been identified are cancer testis antigens (CTAs), MAGE and GAGE proteins. MAGE-4, MAGE-A and GAGE expression have been found in 50, 62 and 84% of medulloblastomas respectively [138, 139]. MAGE antigens, are a promising targets for immunotherapy in patients with medulloblastoma as it has paved the way of immunotherapy already by targeting successfully in some other tumors [140, 141]. Vaccinations against EGFRvIII in combination with GM-CSF, is another potential immunotherapeutic approach, which have already been tested in other brain tumors [142].

In the post-surgery treatment process, delivery of anticancer drugs across the BBB remains a challenge. A number of methods have been tried to facilitate effective drug delivery across the BBB to the brain. Of those, a very promising technique is Nanoparticles (NP) encapsulating magnetic materials such as iron oxide. Upon entering the systemic circulation, through NPs a drug can be directed remotely to the disease site. The addition of receptor-specific ligands to magnetic NPs for active targeting can significantly increase their efficacy [128].

17. Rehabilitation

Quality of life and psychosocial outcomes following treatment of medulloblastoma are progressively recognized as crucial issues in decision-making regarding therapy. Long-term outcome was less emphasized than survival previously as survival was nominal in the earlier period of history of medulloblastoma, though the thought of prolongation of life and making it worth living was always there with the encouragement to persist in efforts [2]. Over the past decades, survival has improved significantly, and expectantly will continue to improve with the development of molecularly targeted agents and other modalities of treatment. With time, thoughts regarding quality of life is becoming increasingly vital both in decision-making concerning therapy and in the design of future treatment protocols where quality of life is the prime target next to survival [6]. Treatment-related endocrinologic, cognitive, and psychological sequelae, especially in Infants and very young children with medulloblastoma remain a difficult therapeutic challenge which can be tackled prudently with rehabilitation programs. For that it is an obvious need to develop active rehabilitative programs and special
educational assistance for the children who survive the multi-modality therapy [71]. Optimum therapy has led to long-term survival in patients of medulloblastoma and it is expected to be increased with time with the anticipated need of more intense and dedicated rehabilitation regime for this group of patients. Thus the long-term survivors of medulloblastoma badly require multifaceted medical rehabilitation care involving team of subspecialists including oncologist, neurologist, endocrinologist, psychologist, psychiatrist and physiotherapist to overcome the challenges that they have to face in the longer run [8, 64].

18. Conclusion

Medulloblastomas have been neurosurgeons’ nightmare for years. MB, a highly aggressive tumor of the cerebellum, treated with a combination of surgery, craniospinal irradiation and chemotherapy, still remains a challenge. Enriched knowledge of histological and molecular subgroups with their aberrant signaling pathways has provided novel therapeutic targets for MB to regress their growth and has enhanced both the prognostic and therapeutic implications. Efforts to modify and refine the MB treatment strategy are ongoing as toxicity and off-target effects of various newer drugs are yet not under total control. Regardless of marked advancements in overall survival for medulloblastoma patients over the past decades, substantial successes remain to be achieved, especially concerning improvement in survival, mitigating treatment-related morbidities as well as improving quality of life for survivors. These have led to modifications of therapies and research, with the emphasis on novel, less toxic and more targeted agents for the best possible survival with least long-term adverse consequences for a worthwhile post-therapy quality of life. The combination of molecular pharmacology, neurogenetics, cell biology, and biophysics will ultimately drive the utmost hope of a cure for medulloblastoma. With the advancement of modern research, medulloblastoma, once a dreaded and hopeless entity, is looming to be a potentially curable disease.

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