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Radical Surgical Excision of Paediatric Medulloblastoma as a Primary Goal with Augmented Radiotherapy and Chemotherapy: An Institutional Experience

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Abstract

The most common brain malignancy in children is medulloblastoma. It usually arises in the cerebellar vermis or in the posterior brainstem, often producing hydrocephalus. Medulloblastomas are WHO grade IV embryonal neuroepithelial tumors. There are four genetic "clusters" (categories): WNT-activated, SHH-activated (TP53-mutant and -wildtype), non-WNT/non-SHH, group 3 and non-WNT/non-SHH. These genetic clusters are further characterized by four histologic types: classic; desmoplastic/nodular; extensive nodularity; large cell/anaplastic. The standard of care consists of complete resection, followed by chemoradiotherapy. These tumors have tendency to metastasize along the neuraxis and rarely outside the same. Surgical debulking of as much tumor as possible (without causing neurological injury) to obtain tissue for classification and to improve outcome is considered standard. 30 - 40% of children require permanent ventriculo-peritoneal (VP) shunts following tumor resection. The risk of shunt-related seeding has been quoted as high as 10 - 20%, but this is probably overestimated. Following surgery, stratification of patients into risk groups guides subsequent therapy. Chemotherapy often used in children < 3 - 4 years of age with medulloblastoma. RT can be instituted once child grow more than 5 years. We share our experience of 15 years with an overview of the current knowledge of medulloblastoma through a molecular approach, and therapeutic prospects currently being developed in surgery, radiotherapy and targeted therapies to optimize the treatment of medulloblastoma with a multidisciplinary approach will also be discussed.

Keywords: *Medulloblastoma*; Neuroepithelial Tumor; Desmoplastic; Chemoradiotherapy; VP Shunt

Abbreviations

VP Shunt: Ventriculo-Peritoneal Shunt; XRT: X Ray Therapy; CT Scan: Computerized Tomography Scan; MRI: Magnetic Resonant Imaging; T1WI: T1 Weighted Image; T2WI: T2 Weighted Image; ICP: Intracranial Pressure; RT: Radiotherapy; CT: Chemotherapy; CSI: Craniospinal Irradiation

Introduction

The origin of Medulloblastoma is from medulla (Latin for marrow), blastos (Greek word for germ) and oma (Greek for tumor); means "tumor of primitive undeveloped cells located inside the cerebellum". It is the most common primary malignant brain tumor of children. This was first described by Percival Bailey and Harvey Cushing in 1930 [1]. As it was a soft, suckable tumor, it was described as "spongioblastoma cerebelli. Since it was considered to arise from the hypothetical multipotent cell i.e. medulloblast, it was termed as medulloblastoma in 1925 [1]. Presently it is considered to originate from Germinative neuroepithelial cells which are the part of external granular layer of cerebellum [2].

The standard of care consists of maximal resection surgery, followed by craniospinal irradiation and chemotherapy. Such treatment allows long-term survival rates of nearly 70%; however, there are wide disparities among patient outcomes, and in any case, major long-term morbidity is observed with conventional treatment.

Materials and Methods

It is a retrospective study extended over a period of 15 years i.e. from January 2005 to December 2019 with mean follow up of eight years. The clinical parameters which were used are demographics, symptoms and neurological deficit. Apart from contrast CT scan, contrast MRI brain with whole spine screening is done to assess the drop metastasis in spinal cord. Patients with the preoperative hydrocephalus underwent VP shunt before excision of primary tumor. Postoperative complications were documented. Patients who are less than three years are not subjected to the postoperative radiotherapy but are rather treated with chemotherapy. These patients had undergone radiotherapy if there was an evidence of recurrence in follow up period. Postoperative recurrence is noted in the patient in the follow up period.

Results and Discussion

Medulloblastoma constitutes about 20% of all pediatric brain tumors and is the most common pediatric primary brain malignancy [3]. Most of the medulloblastoma cases arise below 18 years of age and constitutes around 70% of overall adult and pediatric cases [4]. These are categorized into primitive neuroectodermal tumors (PNET) and are considered as high-grade embryonal tumors due to their cell origin and histological features. However, based on their molecular pathway which leads to tumorigenesis, these are subdivided into WNT-activated, SHH-activated, group 3, and group 4 [5].

The incidence of medulloblastoma is around 0.7 per 100,000 children per year. There is a male predominance especially in children older than 3 years with the relative risk for males is 1.5 times that of females [3,4]. However, male-to-female ratio of 1:1 is observed in children less than 3 years [4]. Females has relatively greater median survival i.e. 152 months while males show median survival of only 90 months. Thus, sex has prognostic value [4]. In our study, male to female ratio was 3:2.

Medulloblastoma can be associated with many genetic syndromes. Gorlin syndrome patients are predisposed to develop basal cell carcinomas and medulloblastoma secondary to germline mutation in the PTCH1 or SUFU genes. Patients with SUFU mutations carrying the highest risk for medulloblastoma [6,7]. P53 mutations in Li-Fraumeni Syndrome, APC mutations in Turcot syndrome type 2, as well as BRCA2 and PALB2 are linked with the development of medulloblastoma [7-9].

Fourth ventricle is commonest location for the development of medulloblastoma. Due to this location, common symptoms of obstructive hydrocephalus and cerebellar signs including gait disturbance, and imbalance occur with due course [10,11]. Cranial nerve palsies can occur due to brainstem involvement [10]. 2 to 6 months is the average time from symptom onset till diagnosis [10,11]. In our study, most of the patient were presented at 7 to 10 years of age while only 10 Patients were presented before 2 years of age (Table 1).

Age group	No of patients N= 210	%
< 2 years	10	4.76%
2 to 7 years	30	14.28%
7 to 10 years	94	44.76%
10 to 12 years	76	36.19%

Table 1: *Age distribution of medulloblastoma.*

The most common symptom was headache and vomiting and least was the altered sensorium (Table 2).

Clinical Presentation	No of Patients 210	%
Headache	190	90.4%
Vomiting	180	85.7%
Ataxia	174	82.8%
Cranial nerve Involvement	23	10.9%
Altered sensorium	26	12.3%

Table 2: *Clinical presentation.*

Identification of signs and symptoms of increased intracranial pressure is important. Those presented with raised intracranial pressure can be subjected to either corticosteroids with or without external ventricular drainage or VP shunt. Leptomeningeal metastatic lesions can give rise to bowel or bladder incontinence or extremity weakness. Apart from corticosteroids, urgent decompressive surgery or emergency radiation is helpful to prevent development of permanent neurological deficit.

On non-contrast CT scan, these lesions are typically hyperdense (due to high cellularity) and on contrast scan most enhance and around 20% have calcifications. On MR T1WI, these lesions are hypo to isointense and T2WI heterogeneous due to tumor cysts, vessels,

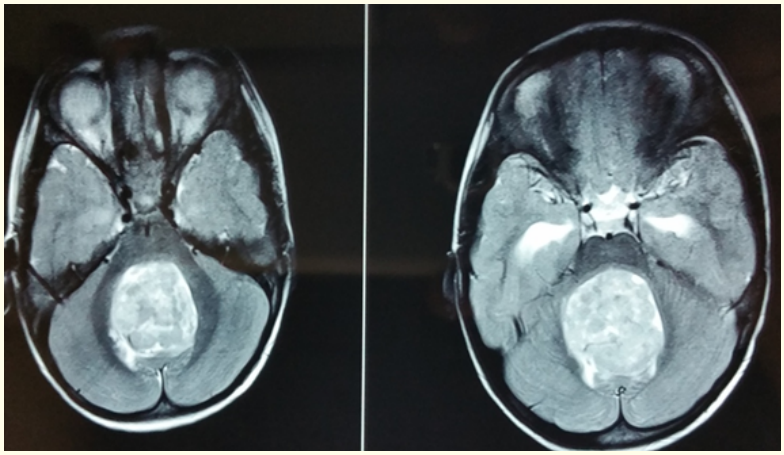

Figure 1: Heterogeneous lesion in the 4th ventricle on T2WI.

VP shunt performed preoperatively in cases with symptoms of raised ICP which are unresponsive to medical treatment. This can also facilitate the tumor excision in second stage. Permanent shunting is required in young patients with extensive preoperative ventricular dilatation, and large tumors [15]. Development a pseudomeningocele with lethargy in postoperative patient is an indication of development of hydrocephalus should be screened with proper imaging.

In telovelar approach i.e. through Cerebellomedullary fissure, there is no known functional neural tissue. Therefore, this approach is favored by many neurosurgeons. In larger tumors, there is thinning of vermis along with cerebellar peduncles. These might spread through foramen of Magendie. For partial restoration of normal anatomy, these lesions should be debulked [16]. In our series, around 76% patient required VP shunt due to presence of significant hydrocephalus and symptoms of raised ICP. Most of the patient i.e. 83%

patient underwent gross total resection while there was residual tumor observed in around 17% of patient on post-operative MRI scan due incomplete excision (Table 3).

Procedure	No of Patients N 210	%
Gross total resection	174	82.9%
Partial Excision	36	17.1%
VP Shunt	160	76.2%
Radiotherapy	200	95.2%
Chemotherapy	38	18.1%

Table 3: *Management of medulloblastoma.*

Cerebellar mutism syndrome, also referred to as posterior fossa syndrome can occur following excision of larger tumors [17]. This can be presented as emotional lability, hypotonia, speech apraxia and ataxia. As much as 30% of patients can develop cerebellar mutism after undergoing medulloblastoma surgery. Multiple theories are proposed but none have been proven. One theory proposed inferior vermis splitting can leads to development of mutism but avoiding splitting does not improve the rate of mutism [17,18]. The dentatothalamic pathway may be associated along with other factors. Speech improve in some patients which may be partial along with abnormal tone and imbalance [17,19]. Other associated complications can be pseudomeningocele, CSF leak and infection. Most common complication following surgery was ataxia which was recovered partially in 50% of the patients. There was a neurological deficit along with cranial nerve palsy observed in the patients with the large sized tumor invading the brain stem. Around 14 patients died in our series due to complications like aspiration pneumonia or sepsis. Two patients died due to meningitis (Table 4).

Post-operative Hemorrhage	3	1.4%
Neurological deficit	9	4.2%
Ataxia	16	7.6%
Mutism	12	5.7%
Cranial Nerve Involvement	4	1.9%
Death	14	6.6%

Table 4: *Complications.*

Medulloblastoma is considered as small round blue cell tumor of the neuronal lineage. It is a high-grade embryonal neoplasm with high mitotic activity, apoptotic cells along with foci of necrosis. Synaptophysin positivity is observed in most tumors which proves neuronal differentiation. Medulloblastoma is divided into following histological subtypes as classic, large cell, nodular/desmoplastic, anaplastic and extensive nodularity. Medulloblastoma with classic histology show cells with dense basophilic nuclei which present in diffuse sheets and scanty cytoplasm. Homer Wright (neuroblastic) rosettes can be observed (Figure 2A). There is increased cytoplasm along with conspicuous nucleoli within large nuclei in large cell medulloblastoma. Atypical mitotic figures along with marked nuclear pleomorphism is observed in anaplastic medulloblastoma (Figure 2B). Dense intercellular reticulin network with nodules of neurocytic differentiation is characteristic of Nodular or desmoplastic medulloblastoma. Nodules with thin internodular zones is feature of Medulloblastomas with extensive nodularity and lacks primitive elements [20,21].

Medulloblastoma classified according to molecular differences and signaling pathways leading to tumor development as WNT-activated, SHH-activated, group 3, and group 4 [22]. Medulloblastomas can be categorized in to molecular subgroups according to immunohistochemistry as WNT-activated tumors which are β-catenin positive with classic histology; SHH-activated are positive for GAB1 with nodular/desmoplastic histology; Group 3 and Group 4 tumors are negative for GAB1 and nuclear β-catenin and commonly have either classic or large cell/anaplastic histologic features [22]. The relation of the histologic variants and the genetic subgroups is shown in figure 3.

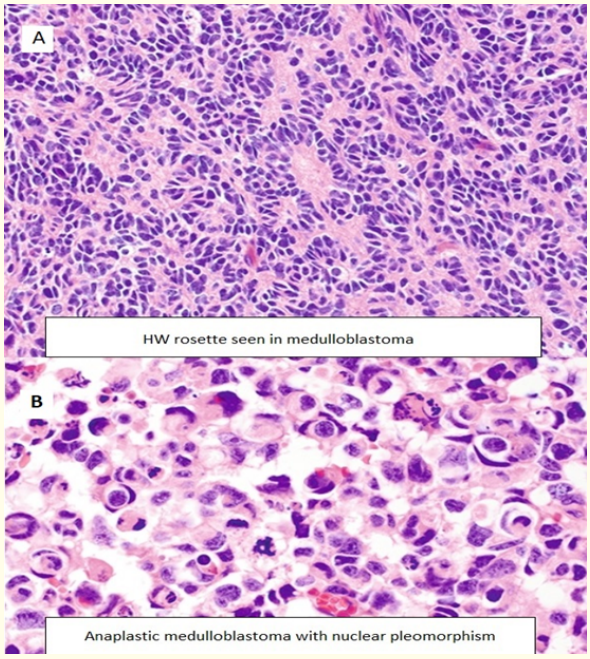

Figure 2: *Histopathology suggestive of Homer Wright (neuroblastic) rosettes (2A) and nuclear polymorphism observed in anaplastic medulloblastoma (2B).*

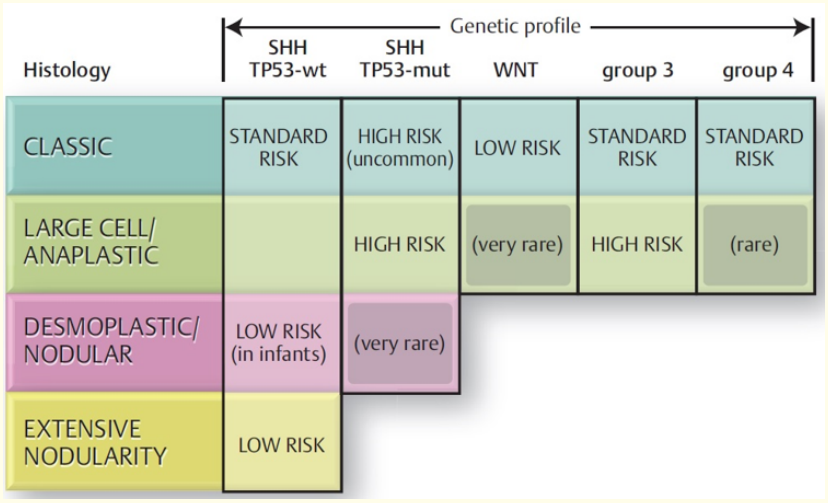

Figure 3: *Graphic distribution of the histologic variants among the genetic subgroups.*

In 2016, integrated medulloblastoma classification, including both histologic and molecular features into the diagnosis is advised in the revised fourth edition of the WHO Classification of Tumors of the Central Nervous System [23]. These guidelines highlight five commonly identified molecularly and histologically integrated subgroups with related prognoses (Figure 4, derived from Louis., *et al*. and Ramaswamy., *et al.*) [23,24].

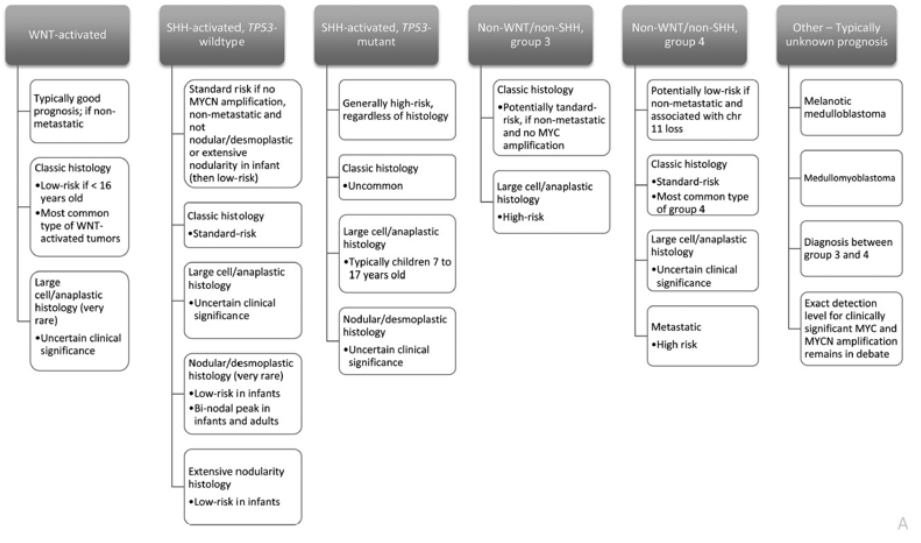

Figure 4: *Five commonly identified histologically and molecularly integrated subgroups with associated prognoses (derived from Louis et al and Ramaswamy., et al).*

Adjuvant radiotherapy for the treatment for medulloblastoma often recommended usually within 3 to 4 weeks after surgery. It involves craniospinal irradiation (CSI).

Conventionally patients with standard-risk disease have received CSI with 23.4 Gy with a boost to 54 to 59.4 Gy to the posterior fossa. Historically, the posterior fossa was radiated with at least a 1-cm margin with inferior border set at C2. However, it has been found that focal radiation of surgical bed rather than whole posterior fossa radiation is found to be comparable with less risk of radiation exposure to other vital structures [25,26]. In this study around 95% patients received the RT (Table 3). The major sequelae of CSI is neurologic, neuroendocrine, and skeletal insult leading to stunted growth and cognitive impairment.

Chemotherapy consists of vincristine, platinum agents i.e. cisplatin or carboplatin and alkylating agents i.e. lomustine or cyclophosphamide [26-30]. The promise for multimodal therapy is focus of a number of multicenter clinical trials [31,32]. Children with high-risk medulloblastoma showed improved overall survival with CT and RT [28,29,33,34]. Postoperative chemotherapy can be helpful in delaying the radiation in patients less than 3 years as per pediatric oncology group [35-37]. Around 18% patient received chemotherapy following surgery in this study (Table 3).

Poor prognosticators of medulloblastoma are younger age (especially if < 3 yrs), disseminated (metastatic) disease, inability to perform gross-total removal (especially if residual > 1.5 cm^2 with localized disease) and poor Karnofsky performance scale score.

Conclusion

Medulloblastoma is the most frequent pediatric malignant CNS tumor and commonly present with signs of raised ICP. CT, MRI have important role in diagnosis and treatment. Surgery and Adjuvant therapy form the main line of management. RT/CT result in long term toxicity and increased morbidity hence modalities like Molecular subtyping and TARGET therapy for Signaling pathways is the way for future for management of these tumors.

Conflict of Interest

Nil.

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