LONG TERM SURGICAL OUTCOME FOLLOWING MULTIMODALITY TREATMENT IN MEDULLOBLASTOMA

Dr. LOKESH VELLORE DASARATHAN

MCh - NEUROSURGERY

2021 - 2023

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

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A THESIS SUBMITTED BY

Dr. LOKESH VELLORE DASARATHAN

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

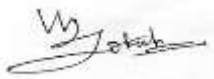
MCh - NEUROSURGERY

JULY - 2023

DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr. **Lokesh Vellore Dasarathan**, hereby certify that I had personally carried out the work depicted in the thesis titled, "**Long-term surgical outcome following multimodality treatment in medulloblastoma**". No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.



Dr. Lokesh Vellore Dasarathan

Department of Neurosurgery,

SCTIMST, Trivandrum

Date: 30/08/2023

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramed, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

CERTIFICATE BY THE RESEARCH GUIDE

Name of the Guide: **Dr GANESH DIVAKAR**

Department: **Neurosurgery**

This is to certify that **Dr Lokesh Vellore Dasarathan**, department of Neurosurgery of this institute has fulfilled the requirements prescribed for the **MCh Neurosurgery** degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum.

The thesis entitled, **"Long term surgical outcomes following multimodality treatment in medulloblastoma"** was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

*Clearance was obtained from the Institutional Ethics Committee of this **institute (IEC – 1800/Jan 2022)** for carrying out the study.

Signature

Date : 30/08/2023

Dr. Ganesh Divakar
Assistant Professor
Department of Neurosurgery
SCTIMST, Trivandrum

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

CERTIFICATE BY THE RESEARCH CO-GUIDE

Name of the Guide: **Dr. EASWER H V**

Department: **Neurosurgery**

This is to certify that **Dr Lokesh Vellore Dasarathan**, department of Neurosurgery of this institute has fulfilled the requirements prescribed for the **MCh Neurosurgery** degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum.

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*Clearance was obtained from the Institutional Ethics Committee of this **institute (IEC – 1800/Jan 2022)** for carrying out the study.

Signature

Date :31/08/2023

Dr. Easwer H V

Professor
Department of Neurosurgery
SCTIMST, Trivandrum

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

CERTIFICATE BY THE RESEARCH CO-GUIDE

Name of the Guide: **Dr. DEEPTI A N**

Department: **Pathology**

This is to certify that **Dr Lokesh Vellore Dasarathan**, department of Neurosurgery of this institute has fulfilled the requirements prescribed for the **MCh Neurosurgery** degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum.

The thesis entitled, "**Long-term surgical outcomes following multimodality treatment in Medulloblastoma**" was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

*Clearance was obtained from the Institutional Ethics Committee of this **institute (IEC – 1800/Jan 2022)** for carrying out the study.

Signature

Date : 30-08-2023

Dr. DEEPTI A N
Additional Professor
Department of Pathology
SCTIMST, Trivandrum

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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CERTIFICATE BY THE RESEARCH CO-GUIDE

Name of the Guide: **Dr RAJALAKSHMI P**
Department: **Pathology**

This is to certify that **Dr Lokesh Vellore Dasarathan**, department of Neurosurgery of this institute has fulfilled the requirements prescribed for the **MCh Neurosurgery** degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum.

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Date : 30.08.2023

Signature

Dr. RAJALAKSHMI P
Additional Professor
Department of Pathology
SCTIMST, Trivandrum

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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APPROVAL OF THE THESIS

The thesis entitled

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Submitted by
Dr LOKESH VELLORE DASARATHAN
for the degree of
MCh – NEUROSURGERY(AFTER MS)
of
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
is evaluated and approved by

Dr Ganesh Divakar
Assistant Professor,
Department of Neurosurgery,
SCTIMST, Trivandrum

(Name & Signature of the Guide)

Dr Ganesh Divakar

.....

(Name & Signature of thesis examiner)

ACKNOWLEDGEMENTS

I owe a deep sense of gratitude to Dr. Easwer H V, Ex.HOD and Professor of the Department of Neurosurgery and Dr. Krishna Kumar K, Professor and Head of the Department of Neurosurgery, for their invaluable advice, encouragement, and guidance, without which this work would not have been possible. Both of them continue to be a source of inspiration to me.

I owe a heartful gratitude to Dr Ganesh Divakar, Assistant Professor, Neurosurgery, as my guide and mentor. His critical remarks, suggestions, and above all, his trust in me, helped me in achieving a high standard of work.

The guidance of Dr. Rajalakshmi P, Additional Professor, and Dr Deepti A N, Additional Professor from the Department of Pathology has been invaluable and I am extremely grateful for their timely support, encouragement, suggestions, helping in data validation which involved tedious work of reviewing all previous slides and reporting as per current guidelines. It was an invaluable help during the entire work. Their remarks and suggestion helped me in achieving the current standard of work.

I owe a deep sense of respect to Dr Sowmya, Associate Professor, Department of Neurology for helping in formulating the Functional score of the patients on follow up.

I owe a deep sense of gratitude to Senior Medical Records Officer Dr. Shiva Prasad and MRD staff and the Department of Computer Engineering for helping with sample collection.

I am also deeply indebted to the nursing staff and the paramedical staff of the Department of Neurosurgery for the prompt help whenever needed, particularly the Nursing Officer Mrs. Dinimol, who with her kind and compassionate heart, helped in getting the follow-up data and survival data from the patients/bystanders via telephonic questionnaire. Their wholehearted support has made this study possible.

I owe a deep sense of gratitude to Dr. Thennarasu, HOD, and Professor, Dr. Binu, Associate Professor, Mr. Durai Guna, Ph.D scholar from the Department of Biostatistics, NIMHANS, Bengaluru for their kind acceptance, help and, contribution in Basic Data analysis and Survival analysis for the study.

I owe a deep sense of gratitude to all my patients and relatives without whom this work would not have been possible.

I am deeply indebted to my teachers, Dr. Mathew Abraham, Dr. George C Vilanilam, Dr. Jayanand B Sudhir, Dr. Prakash Nair, Dr. Tobin George and Dr. Gowtham M, for their constant encouragement and support.

I also owe a deep sense of gratitude to the institute for providing the opportunity to conduct the study. I am very grateful to my seniors Dr. Sanjay HM, Dr. Arun Gowda, Dr. Ajit, Dr. Anand Binu, to the PDFs Dr. Darshan and Dr. Sreenath, to my batchmates Dr. Akhilesh, Dr. Sam Scaria, Dr. Bhushan, Dr. Suraj and to my beloved juniors Dr. Pooja, Dr. Vamshi, Dr. Ram Kishan, Dr. Ashutosh, Dr. Ankush, Dr. Sagar, Dr. Niroop and Dr. Arwin Das for their constant encouragement and moral support.

Last, but not the least, I am indebted to my family and my wife Dr. Jayasree who were constantly supporting me, and holding my hand in all difficult times. I thank the Almighty, for being with us and blessing us in all walks of life.

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LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
	ICP	Intracranial pressure
	MB	Medulloblastoma
	MBEN	Medulloblastoma with extensive nodularity
	LC/A	Large cell/Anaplastic variety
	SHH	Sonic hedgehog
	WNT	Wingless
	WHO	World health organization
	MRI	Magnetic resonance imaging
	GTR	Gross total resection
	NTD	Near total decompression
	STD	Subtotal decompression
	OS	Over all survival
	DFS	Disease free survival
	SAR	Survival after recurrence
	CP angle	Cerebello-pontine angle
	RT	Radiotherapy
	CT	Chemotherapy
	DWI	Diffusion weighted imaging
	ADC	Apparent diffusion coefficient
	RCT	Randomized control trail
	EVD	External ventricular drain
	VP shunt	Ventriculo-peritoneal shunt
	CSF	Cerebro-spinal fluid
	CSI	Cranio-spinal irradiation
	OS	Over all survival
	DFS	Disease free survival
	SAR	Survival after recurrence
	HPR	Histopathology
	PedQL	Paediatric quality of life scale
	ADL	Activities of daily living
	EOM	Extra-ocular movements
	MLSO	Midline suboccipital craniotomy
	ETV	Endoscopic third ventriculostomy
	EDH	Extradural hemorrhage
	SDH	Subdural hemorrhage
	IHC	Immuno-histochemistry
	LCN	Lower cranial palsy

SYNOPSIS

Background:

Medulloblastoma is the most common childhood malignant tumour of the brain and accounts for 20% of CNS tumours in children. These tumours are grouped into four morphological types viz 1. classical type, 2. desmoplastic nodular, 3. with extensive nodularity; 4. anaplastic/large cell variety. Based on molecular profile, Medulloblastoma has been reclassified into four subtypes: They are Wingless(WNT), Sonic hedgehog(SHH), Group 3 and Group 4 types. Medulloblastomas are risk stratified based on various factors into standard/average risk and high risk, according to clinical risk factors, histological features, molecular markers, age at diagnosis, extent of tumour resection and presence or absence of metastases. The main form of treatment for this condition is surgical resection followed by various adjuvant therapies like chemotherapy and craniospinal radiotherapy. The main drawbacks of this treatment are significant side effects and long-term impairment due to adjuvant therapy and the morbidity related to surgery.

Methods:

This is retrospective observational study done in the Department of Neurosurgery, Sree Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum, Kerala, India. It includes patients of all age groups who were operated for posterior fossa lesions and subsequently diagnosed as Medulloblastoma in the Histopathological report. Clinical details were collected from the Electronic Medical Records, computer database and Medical records department. The follow up data were recorded from the OPD visits and via telephone call questionnaire. Relevant statistical analysis and Kaplan Meier survival analysis were done.

Results

The total number of patients included in the study was 249; the mean age of incidence in this study was 10.9 years (Median – 8 years, Mode – 5 years). The majority of population was between 3 to 12 years. The population below the age of 3 years in this study were 10%(25 patients). The male and female populations were near equally distributed in this study (54% vs 46%). The distribution of Morphological types in our study were as follows: Classic(78%), Desmoplastic/nodular(14%), Extensive nodularity(5%) and Large cell/Anaplastic(3%) type. In our study, the extent of resection was as follows: GTR in 64%, NTD in 29%, STD in 6.8%, and biopsy in 0.4%. Residual lesions were seen in 14%, and the relapse rate was 37%. The factors determining the residual lesion and/or the occurrence of relapse were the extent of resection (GTR-143,73% vs 15,29%)($p<0.0001$), planes with the brainstem(82,44% vs 30,68%)($p=0.004$), extension into the foramen of magendie or lushka(108, 61% vs 16, 38%) ($p=0.003$), and intraoperative evidence of metastasis as noted by nodular deposits over pia-arachnoid layers(sugar coating appearance)(147, 98% vs 23, 88%)($p=0.043$), which were noted to be significant. The molecular subtyping was done in our institute using Immunohistochemistry in 26 patients in whom the surgery was done after 2020. In these cases, WNT type was found in none, SHH and TP53 wild in 19%, non WNT and non SHH in 62%, and 19% of them were not assignable to any category. The post-operative complications, most commonly noticed were Nystagmus – Extraocular movement abnormality (42%), gait disturbances (34%), cerebellar ataxia (28%), cerebellar mutism (17%). In the current study, the 5 year

disease free survival rate was 58%, and the 10 year survival rate was 49%. The overall survival at 5 years was 81%, at 10 years 76%, and at follow up of 15 years was 68%. The Survival after recurrence was found to be 50% at the end of 5 year follow up.

Conclusion

Tumours arising from the fourth ventricle, having irregular borders, preoperative evidence of metastasis, and post operative residual lesion were all having higher odds for disease recurrence and lesser overall survival, which were statistically significant. The extent of resection did not seem to affect the DFS but patients who underwent total or near-total excision had better overall survival than those with residual lesions (statistically significant). The Desmoplastic/nodular and medulloblastoma with extensive nodularity had better survival rates than the classic and large cell/Anaplastic types. On molecular subtype analysis (in patients where this data was available), SHH-activated and TP53-wildtype group had better survival than non-WNT/non-SHH type and the group in which molecular sub-grouping was not assignable (though statistically not significant). Adjuvant therapy also had an influence on the long term sequelae and disability though statistically not significant.

INTRODUCTION

INTRODUCTION

Medulloblastoma is the most common malignant childhood tumour of the brain. It makes for 20% of the CNS tumours in children(Ostrom et al., 2018; Rios and De Jesus, 2022). Boys were more likely to be affected than girls (about 40 percent). The incidence is highest between the ages of 1 and 9, lower in infants, and lowest comes between the ages of 10 and 14. Patients with medulloblastomas exhibit a wide range of symptoms as a result of elevated intracranial pressure, nerve palsies, and cerebellar abnormalities viz headache, vomiting, ataxia, facial weakness, cranial nerve defects, gait disturbances(Khiantani et al., 2020; Long-term outcome of posterior fossa medulloblastoma in patients surviving more than 20 years following primary treatment in childhood | Scientific Reports, n.d.).

The main form of treatment for this condition is surgical resection, which is followed by various adjuvant therapies such as chemotherapy and Craniospinal Radiotherapy. The main drawbacks of this treatment is significant side effects and long-term impairment of this adjuvant therapy, morbidity related to the surgery. The majority of these patients present with hydrocephalus before surgery which usually resolves after tumour removal, but in some patients hydrocephalus persists, those patients need to undergo CSF diversion procedures like Ventriculoperitoneal shunt, Endoscopic third ventriculostomy. Before and after tumour surgery, MRI should be performed as a required diagnostic and follow-up imaging. Up to 40% of individuals might develop spinal metastases, which are most frequently found in the lumbosacral

and thoracic regions(Minn et al., 2001). A spine MRI must be performed before beginning any adjuvant therapy.

In spite of the aggressive management of these patients, only one-third has chance of good recovery, and long-term survivors suffer from significant treatment-related side effects (Enayet et al., 2021; Ribi et al., 2005). Numerous histological or biological factors that play different roles in the disease's prognosis have been discovered through retrospective investigations.

Based on Morphological criteria, Medulloblastoma has been grouped into 4 types viz: 1. classical type, 2. desmoplastic or nodular, 3. With extensive nodularity; 4. anaplastic type/Large cell variety(Louis et al., 2007). This was followed in WHO classification till 2016. The nodular/desmoplastic variety had a favourable prognosis according to clinical trials, however the giant cell/anaplastic variant had a noticeably inferior prognosis. Staging and subsequent risk stratification are crucial in the management of medulloblastoma

Medulloblastoma tumours are classified into average risk and high risk, according to a clinical risk stratification, based on histological features, age at diagnosis, extent of tumour resection and presence or absence of metastases(Hoff et al., 2009; McManamy et al., 2007). But these risk stratification schema is not predictable or sufficient for the accurate treatment prognostication(Entz-Werle et al., 2008).

With recent advances in modern genetics and analysis of the genetic profile of medulloblastoma tumours, lot of molecular and genetic data were accumulated in the last decade. The importance of DNA methylation, Whole genome sequencing is well noted in this studies(Alharbi et al., 2020). The genetics of Medulloblastoma differs

among various groups resulting in marked prognostic characteristics that can impact treatment decisions(Kohlruss et al., 2019).

Based on molecular profile, Medulloblastoma has been reclassified into four subtypes: They are Wingless(WNT), Sonic hedgehog(SHH), Group 3 and Group 4(Kool et al., 2012; Taylor et al., 2012) These have distinct origin, demographics, molecular alterations, and clinical outcomes (Menyhárt and Győrffy, 2020). With the incorporation of molecular information, currently this patients are typically separated into risk-stratified schemes according to their age, the severity of any remaining disease, the spread of the disease, their LC/A-MB, MYC, and WNT status(Ramaswamy et al., 2016).

In addition to infections and mechanical issues such as fluid leak and pseudomeningocele, direct neurosurgical manipulation can result in cerebellar mutism syndrome. The symptoms are severe cerebellar impairments, including dysmetria, hypotonia, paresis, and mood depression that can linger for several months, are linked to it. Most likely mechanism described was disruption of reticular substance pathways.

Long-term effects of medulloblastoma treatment include motor, sensory, endocrinological, cognitive, neuropsychological, and behavioural abnormalities and can significantly impact a patient's quality of life, academic performance, and ability to re-enter society and schoo(Khiantani et al., 2020).

Combining data from molecular group analysis and clinical risk factors enables us to better categorise the risk patients, so that therapy intensification can be done in high-risk children to increase survival and de-escalation of treatment in patients with low-risk disease to avoid substantial treatment-related problems(Menyhárt and

Győrffy, 2020). Medulloblastoma can recur, and more than half of these relapses include a disseminated disease component.().

As a tertiary care center, our institution has a long series of operated patients of medulloblastoma. In this study, We were planned to analyze the patients' demographic profiles, prevalence, distribution of pathological types, surgical outcomes, complications, and survival rates. This will give us the better picture of the disease status and its treatment outcomes in our part of the country which in turn can improve our patient care and give new insights into the current practice.

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AIMS AND OBJECTIVES

1. To analyze the demographic profile, clinical symptomatology profile, imaging characteristics, surgical approaches, histopathological subtypes, complications, need for CSF diversion procedures, adjuvant therapy, recurrence rates, metastasis, long term complications related to adjuvant therapy, and risk stratification in patients operated for medulloblastoma in our institution from 2005 to 2020.

2. To correlate the morphological and molecular subtypes of medulloblastoma with clinico-demographic profile, surgical outcome, complications, risk stratification, response to adjuvant therapy and survival outcomes.

3. To find the factors associated with survival after multimodality treatment in terms of overall survival, disease free survival and survival after recurrence.

REVIEW OF LITERATURE

Medulloblastoma belongs to the group of CNS embryonal tumours and it is the most common paediatric malignant brain tumour (Ostrom et al., 2018; Rios and De Jesus, 2022). Medulloblastoma occurs mainly in children with a median age of 9 years, peak incidence is noted in the age group between 3 and 7 years (Farwell et al., 1984; Roberts et al., 1991). There is a bimodal peak observed in adults which accounts for one-fourth of Medulloblastoma patients. It was first described in 1925 as a glioma arising from the cerebellum.

Medulloblastoma was originally described in the histogenetic classification developed by Baily and Cushing(Bailey, n.d.; Ferguson and Lesniak, 2005), in that CNS tumors were given a category based on the morphologic appearance similar to cell types noted in the developing brain(Ferguson and Lesniak, 2005).

The term was coined by Bailey in his description, he noticed there was a peculiar tumour in children that occurred primarily in the cerebellum. This primitive embryonic tumor was postulated to arise from an undifferentiated cell type termed the "medulloblast," which was thought to arise from the fourth ventricular ependymal lining. Bailey also observed that this tumor has the tendency to spread to leptomeninges which later proved valuable in terms of prognosis and treatment. Bailey and cushing also noted the poor prognosis of medulloblastomas, this has led to the introduction of radiotherapy in the medulloblastoma patients(Ferguson and Lesniak, 2005).

Even though the the cell type″medulloblast” has not been identified, the use of the the nomenclature has been there for decades. Current notion is that, medulloblastoma arises from the subependymal matrix zone actively replicating cells, located in the external granular layer of the posterior medullary velum(Trojanowski: In vivo and in vitro models of medulloblasto... - Google Scholar, n.d.).

Clinical presentation:

Medulloblastoma is a fast growing posterior fossa tumour. The presentation is quite early than the other posterior fossa tumours like ependymoma and astrocytoma(Vinchon and Leblond, 2021). Clinical symptoms depends on the tumour characteristics, location of tumour, duration of disease and status of CSF drainage.(Vinchon and Leblond, 2021)

These patients most commonly present with symptoms related to increased intracranial pressure due to hydrocephalus caused by the obstruction of CSF flow pathway. The average duration of symptoms usually noticed is 2 months. The presenting symptomatology is related to the age of the patient.

In nonverbal infants and children, they present with behavioral change. In younger children, they might have irritability, recurrent vomiting, and decreased social interactions. The older children and adults, complains of headache, especially in the early morning after awakening. Vomiting without nausea is noted more common in the morning, since sleeping in the recumbent position for long time increases ICP(intracranial pressure). Patients may also complain of double vision as the Abducent cranial nerve (CN 6) becomes stretched under the dura due to pressure

effects of hydrocephalus. Patients may also complain of visual blurring as a result of papilledema(Medulloblastoma Clinical Presentation: History, Physical, Causes, n.d.).

Cerebellar symptoms are noted in majority of patients. If the tumour is involving the cerebellar vermis, they present with gait ataxia. If the tumour is arising from the cerebellar hemisphere, they will have unilateral cerebellar symptoms like dysmetria. Adult patients with medulloblastoma most commonly diagnosed as histological type of desmoplastic medulloblastoma usually arises from the cerebellar hemisphere.

Neck stiffness is noticed in patients with tonsillar herniation below the foramen magnum due to meningeal irritation. Head tilt is noticed as a compensatory mechanism as a result of diplopia due to trochlear nerve compression by the tumour.

In patients with leptomeningeal dissemination, depending on the extent of spread of the disease, patients may have generalized weakness, hemiparesis, paraparesis, bowel and bladder incontinence, radiculopathy due to tumor compression of the spinal cord or nerve roots.

Clinical examination findings:

In young infants, increase in head circumference often will be the only presenting symptoms. They may also have bulging anterior fontanellae with splitting of cranial sutures. On fundus examination, papilledema can be present in as many as 90% of patients. Eye ball deviation can be present due to extraocular movements restriction because of cranial nerve palsy (CN IV or VI). Patients with CN 4 dysfunction have difficulty in going downstairs due to deficiency in medial rotation and depression(Eibl et al., 2021; Medulloblastoma Clinical Presentation: History,

Physical, Causes, n.d.; Vinchon and Leblond, 2021). While examining the EOM, nystagmus may be detected, which, although nonspecific can be, it can be related to the vermian lesion. On cerebellar examination, truncal ataxia and wide-based gait is more common than the unilateral dysmetria because Medulloblastoma is located most commonly in midline. Desmoplastic medulloblastoma is more commonly seen in adults and arises from the cerebellar hemisphere. This patients will have ipsilateral cerebellar signs in the arm or the leg in the form of dysdiadochokinesia, intentional tremor(Eibl et al., 2021).

Medulloblastoma association with other cancer syndromes:

Medulloblastomas can arise due to damaging germline mutations in a known cancer predisposition genes which leads to the association with several inherited cancer syndromes such as Gorlin syndrome (SUFU and PTCH1 mutations)(Waszak et al., 2018), Li-Fraumeni syndrome(TP53), familial adenomatous polyposis(APC), Rubinstein–Taybi (CREBBP mutations), and Nijmegen(NBN mutations). MBEN type is associated strongly with GS. Children with age <or=3 years have high chance of harbouring the germline mutations and their families should be investigated for any tumor predisposition genes(Brugières et al., 2012; Garrè et al., 2009). Recently, one new entity is identified, which is listed in WHO CNS5 classification, ELP1-medulloblastoma syndrome. ELP1 gene mutations can be present in 40% among pediatric patients with SHH medulloblastoma - TP53 wild-type(Huang et al., 2008; Waszak et al., 2020)

Imaging characteristics:

Medulloblastoma most commonly arise from the posterior medullary velum, inferior vermis projecting into the fourth ventricle. Around 75 to 90 % of tumours arise in the midline, 15% of cases extend into the CP angle from fourth ventricle, 3-8% arise from the CP angle region, 1015 % arise with in the cerebellar hemisphere(more frequent in adults). (Dangouloff-Ros et al., 2021; DeSouza et al., 2014). Superior medullary velum is displaced superiorly in medulloblastoma, whereas in pilocytic astrocytoma it is displaced anteriorly or inferiorly(Trasimeni, G., Lenzi, J., Di Biasi, C. et al. Midline medulloblastoma versus astrocytoma: the position of the superior medullary velum as a sign for diagnosis. Childs Nerv Syst 24, 1037–1041 (2008). https://doi.org/10.1007/s00381-008-0635-3, n.d.).

Tumour is well circumscribed in 80–100% of patients, nodular contours noted in 10% of cases. Cysts or necroses seen in 50–90%, calcifications in 10–40% of the tumours. Tumour bleeding in 5 to 15% of patients. Peritumoral edemas seen in 50–90% of medulloblastomas. Obstructive hydrocephalus seen in 50–95% of the patients due to compression of the fourth ventricle by the tumour.

In CT-scan, medulloblastomas are hyperdense compared to the cerebellum (62–97%) of the tumours. In MRI, T1-weighted show hypointense in 90% of tumours, hyperintense in 10% of the cases(usually seen in tumour bled). T2 weighted shows heterointense signal(hypo or iso relative to the cerebellar grey-matter. T2 hypersignal in up to 50% of the patients(Koeller and Rushing, 2003; Meyers et al., 1992). However, the signal is lower than those of the pilocytic astrocytomas. Medulloblastomas enhance in 85%–100% of the tumours, intense in 35–50%, subtle or heterogeneous also seen. Meningeal enhancement sometimes may mimick dural-tail sign. In MR spectroscopy, high level of taurine at 3.4 ppm, which is not noted in

other posterior fossa tumours(Vicente et al., 2013). Choline is elevated, more than ependymomas or pilocytic astrocytomas. N-acetyl-aspartate is low, Creatine is lower than the normal brain. Myo-inositol is higher than pilocytic astrocytomas, lower than in ependymomas. Medulloblastomas are highly cellular tumours shows a strong restriction of diffusion of water, shows hypersignal on DWI and a low ADC coefficient. ADC mapping predict infiltration into the brainstem. In 20% of tumours, no restriction of diffusion seen. The diffusion is more restricted in medulloblastomas than in ependymomas or pilocytic astrocytomas.

The ratio of ADC from tumour over the grey-matter noted to be between 0.70 and 0.88 for the solid component(Pediatric Cerebellar Tumors: Does ADC Analysis of Solid, Contrast-Enhancing Tumor Components Correlate Better with Tumor Grade than ADC Analysis of the Entire Tumor? - Orman - 2015 - Journal of Neuroimaging - Wiley Online Library, n.d.). High cerebral blood flow and relative CBF in medulloblastomas are higher than the pilocytic astrocytoma, but not different from ependymomas(Dangouloff-Ros et al., 2016)

In adults, tumour morphology is different probably due to different histological subtypes. Tumours are less delineated, more heterogeneous, and less contrast enhancement. They are more laterally located than in children, and centered in cerebellar hemispheres in 50% to 89% of patients(The Neuroradiological Spectra of Adult and Pediatric Medulloblastoma Differ | SpringerLink, n.d.). Spine screening is mandatory preferably before surgery whenever possible particularly when there is a strong suspicion of Medulloblastoma. The presence of metastasis in preop stage indicated poor prognosis.

Comparing imaging characteristics with different histopathological subtypes

Subtype	Classic	Desmoplastic/nodular/with extensive nodularity	Large cell/anaplastic
Frequency	80%	15%	5%
Localization	Midline 4th ventricle	Cerebellar hemispheres	Midline 4th ventricle
Morphology	Homogeneous, bleeding in 13%	Multinodular	Homogeneous, small
Contrast enhancement	++	+	++
Edema	40%	75%	40%
Diffusion restriction	++	+++	+
Spectroscopy	Choline and taurine ++	Choline and taurine +	
Initial dissemination	25%	Rare	66%

Source: V. Dangouloff-Ros, P. Varlet, R. Levy, K. Beccaria, S. Puget, C. Dufour, N. Boddaert, Imaging features of medulloblastoma: Conventional imaging, diffusion-weighted imaging, perfusion-weighted imaging, and spectroscopy: From general features to subtypes and characteristics.

Leptomeningeal dissemination is frequently noted at the time of diagnosis, reported in 11–43%. Spinal cord is the most common site, mainly along the posterior surface of the spinal cord, conus medullaris, MRI spine screening should be performed before surgery as the post op MRI shows false-positive because of inflammation, bleeding. MRI is more sensitive than CSF cytology to detect dissemination(Fouladi et al., 1999; Harrison et al., 1998). Intracranial dissemination is observed in the vermis, basal cisterns, subependymal part of lateral ventricles, third ventricular floor. Post surgery, a follow-up MRI is advised to determine the size of the residue.

Classification of Medulloblastoma:

Medulloblastoma term was introduced in 1925, it was included in the histogenetic classification scheme introduced by **Baily and Cushing** in 1926. In that, brain tumors were classified based on the morphologic characteristics and similarity to cell types in the the developing brain(Bailey, n.d.). The primitive embryonic tumor was believed to derive from an undifferentiated cell type called the medulloblast, it was thought to arise from the ependymal lining of the fourth ventricle. This diagnostic entity has been present over 95 years of revisions to brain tumor classification.

In 1969, Medulloblastoma was classified clinically by Chang based on the size and tumor invasiveness as determined intra-operatively and the status of the presence of metastases(Chang et al., 1969). The Chang system is is no longer use, but the components of it forms the current clinical risk stratification which is widely in use.

Risk classification	Characteristics
Standard-risk tumor	≥3 years of age without evidence of metastatic spread and having ≤1.5 cm^2 (maximum cross-sectional area) of residual disease after surgery
High-risk tumor	≥3 years of age with evidence of CSF spread (M1–M3) and/or those with less complete resection (≥1.5 cm^2) or <3 years of age at diagnosis

Adapted: Established prognostic variables accepted by the North American Children's Oncology Group (COG) and the SIOP (International Society of Pediatric Oncology) Group.

WHO 2007 Classification:

The World Health Organisation classification system in 2007, classified medulloblastomas based on histology alone. They were divided into three major groups:

In histology, the majority of medulloblastomas shows neuronal differentiation in the form of immunoreactivity to synaptophysin and few areas may display focal glial differentiation (Glial fibrillary acidic protein (GFAP) immunopositivity) Rarely, it may have myogenic differentiation (medullomyoblastoma) or melanotic differentiation

In WHO 2007 CNS classification, Medulloblastoma subtypes were organized as follows:

1	Classic subtype	Most common (66%) Densely packed sheets of small round blue cells, high nuclear to cytoplasmic ratio, high mitotic activity, occur in midline.
2	Desmoplastic/nodular/ medulloblastoma with extensive nodularity (MBEN)	Occur in 15%, favourable prognosis among all, arise laterally in cerebellar hemisphere, it contains small round blue cells, harbor reticulin free pale islands, immunopositive for synaptophysin
3	Large cell/ anaplastic medulloblastoma	a) Anaplastic occur in 15%, marked nuclear pleomorphism, nuclear molding, cell-cell wrapping b) Large cell variant (2-4%) displays large cells with prominent nucleoli, carries poor prognosis.

1. Anaplastic / Large cell variants were combined into single category. They are highly malignant and have considerable cytological overlap. The patterns may coexist. Hence, in the fourth edition of ICD-O, anaplastic medulloblastoma and large cell medulloblastoma has same code.
2. The medulloblastoma with extensive nodularity(MBEN) is closely related to the desmoplastic/nodular medulloblastoma. It was previously known as ‘cerebellar neuroblastoma’. It has markedly lobular architecture compared to

desmoplastic nodular variant. Both of these has a more favourable outcome than with classic medulloblastomas .

3. Medulloblastoma with myogenic differentiation was termed previously as medullomyoblastoma. As it is similar to other types, no longer considered a distinct entity.
4. Medulloblastoma with melanotic differentiation was termed previously as melanocytic medulloblastoma. The melanotic tumour cell clusters in the form of tubules or papillae can occur in any variant of medulloblastoma, they were not regarded as a distinct entity.

WHO 2016 classification:

In the 2016 update, first time, genomic data was incorporated into the classification system. A layered approach was used integrating morphologic and genomic data in accordance with the Haarlem guidelines, for CNS tumor classification and grading.

This schema separated the MB into two separate general designations viz, *MB, histologically defined* and the *MB, genetically defined*(KOMORI, 2017).

Histologically, Medulloblastoma can be separated into variants that includes classic, desmoplastic/nodular(DN), MB with extensive nodularity (MBEN) and large cell/anaplastic (LCA).

A second general category takes into account the molecular group of the tumor. *Medulloblastoma, genetically defined* is divided into

1. WNT-activated, 2. SHH-activated and *TP53*-mutant, 3. SHH-activated and *TP53*-wildtype, 4. non-WNT/non-SHH groups which is further subdivided to subclasses, group 3 and group 4
2. In cases where the material available is inadequate or testing not available which prevents further classification of the tumor tissue, Medulloblastoma, Not otherwise specified (NOS) is designated

Table: Medulloblastoma classification system in the *WHO Classification of Tumors of the Central Nervous System 2016*

Medulloblastoma, genetically defined
WNT-activated
SHH-activated, *TP53*-wild-type
SHH-activated, *TP53*-mutant
Non-WNT/non-SHH
Group 3
Group 4
Medulloblastoma, histologically defined
Medulloblastoma, classic
Desmoplastic/nodular medulloblastoma (DN)
Medulloblastoma with extensive nodularity (MBEN)
Large cell/Anaplastic medulloblastoma (LCA)
Medulloblastoma, NOS

CNS WHO 2021 classification:

As a result of extensive transcriptome and DNA profiling analysis, clinico-biological heterogeneity of these neoplasms is noted and current molecular classification incorporates this changes. In WHO CNS5, medulloblastomas were

classified according to a combination of both molecular and histopathological features. It maintains the original already established four principal molecular groups as in 2016 WHO classification(i.e., wingless-activated (WNT)-activated, sonic hedgehog (SHH)-activated, and non-WNT/non- SHH).

SHH tumors were divided on the basis of TP53 status into TP53- mutant and TP53-wildtype tumours as formulated in WHO 2016. Due to recent advances in DNA methylation profiling, it has led to the further subgrouping into 12 categories. Those are 4 subgroups in SHH category and 8 subgroups in non-WNT/ non-SHH (group 3 and group 4) category. Such further ramification of the molecular subgroups has been made for critical biological and clinical implications regarding the prognosis, therapeutic options, trials in the future and to identify the group of patients benefit from aggressive adjuvant therapy or de-escalation of therapy.

1. **Medulloblastomas, molecularly defined**

-Medulloblastoma, WNT-activated

-Medulloblastoma, SHH-activated and TP53-wildtype - 4 new subgroups recognized

-Medulloblastoma, SHH-activated and TP53-mutant

-Medulloblastoma, non-WNT/non-SHH - Includes group 3 and 4

- 8 new subgroups recognized

2. **Medulloblastomas, histologically defined**

- 4 morphological types viz 1. classic, 2. desmoplastic/nodular, 3. medulloblastoma with extensive nodularity and 4. large cell/ anaplastic have been

grouped into this single tumor type and described as a morphological patterns in the description.

In WHO 2021 recommendations, tumours has to be reported in a layered and integrated format containing the information of both the histopathological and molecular features. In situations, where there is absence of resources and impossibility to perform molecular analyses, pathologist can always given the option to report such tumors using the not otherwise specified (NOS) and not elsewhere classified (NEC) options(Louis et al., 2021; Mahajan et al., 2022)

Integrated diagnosis	Medulloblastoma; histological subtype; molecular sub-group; and histologic grade (grade IV)
Histologic diagnosis	Classic, Desmoplastic/Nodular (D/N), Medulloblastoma with Extensive Nodularity (MBEN), or Large-Cell/Anaplastic (LC/A)
WHO grading	Grade IV
Molecular sub-grouping	WNT-activated, SHH-activated (TP53 mutant or wild type), and non-WNT/non-SHH
Genetic alterations (wherever available)	MYC amplification, TP53 status, CTNNB1 mutation, SMO status, PTCH1 status, Isodicentric chromosome 17q, Monosomy 6

Source: Gupta T, Sarkar C, Rajshekhar V, Chatterjee S, Shirsat N, Muzumdar D, Pungavkar S, Chinnaswamy G, Jalali R. Indian Society of Neuro-Oncology consensus guidelines for the contemporary management of medulloblastoma. Neurol India 2017;65:315-32(Gupta et al., 2017)

Risk stratification:

Over the years, multiple risk stratification strategies has been in place incorporating the parameters which determine the prognosis, final outcomes and clinical decision making process.

Modified Chang Staging			
T stage		**M stage**	
T1	Tumor <3 cm in diameter	M0	No evidence of gross subarachnoid or hematogenous metastasis
T2	Tumor ≥3 cm in diameter	M1	Microscopic tumor cells found in CSF
T3a	Tumor >3 cm and with extension into aqueduct of Sylvius or foramen of Luschka	M2	Gross nodular seeding intracranially beyond the primary site (in cerebellar/cerebral subarachnoid space or in third or lateral ventricle)
T3b	Tumor >3 cm and with unequivocal extension into brainstem	M3	Gross nodular seeding in spinal subarachnoid space
T4	Tumor >3 cm with extension past aqueduct of Sylvius or down past foramen magnum	M4	Metastasis outside cerebrospinal axis
Risk Stratification			
Standard (Average) Risk (66%)		**High Risk (34%)**	
>3 years old		<3 years old	
<1.5 cm^2 residual disease after resection		Subtotal resection, >1.5 cm^2 residual tumor	
M0 by craniospinal MRI and CSF		M+, leptomeningeal seeding, and location outside of the posterior fossa	

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

Source: Sengupta et al, The evolution of medulloblastoma therapy to personalized medicine.

Langston modification of the Chang T staging system(Constine: Pediatric radiation oncology - Google Scholar, n.d.)

T1	Tumor <3 cm in diameter
T2	Tumor ≥3 cm in diameter
T3a	Tumor ≥3 cm in diameter with extension
T3b	Tumor ≥3 cm in diameter with unequivocal extension in to the brainstem
T4	Tumor ≥3 cm in diameter with extension up past the aqueduct of Sylvius and/or down past the foramen magnum (ie, beyond the posterior fossa)

Source: Constine LS, Tarbell NJ, Halperin EC. Pediatric radiation oncology. Lippincott Williams & Wilkins; 2016 Jul 5.

In **RCT by Zetlzer et al,** Medulloblastoma patients were designated into high risk and average risk based on the criteria of age (greater than or less than 3 years), residual tumor (greater than or less than 1.5 $cm^{2)}$, and the absence or presence of metastatic disease on MRI neuroimaging or LP CSF sampling(Packer and Finlay, 1988; Zeltzer et al., 1999).

Children with the age less than 3 years were predictive of poor outcome, probably due to the fact that they present more commonly with metastatic disease, less likely treated with conventional RT doses, more likely to undergone subtotal tumor resection(Deutsch, 1988; Duffner et al., 1993; Packer et al., 1999). Surgical extent of resection is better correlated with survival of patients without metastatic disease in a study by Albright et al(Albright et al., 1996)

Histological subtypes like classic, desmoplastic, and large cell/anaplastic histology also determines the prognosis in this group of patients. In one study involving 330 patients, medulloblastomas with extensive nodularity type was associated with better outcomes while the ones with large cell/anaplastic medulloblastomas were associated with worse clinical outcomes(Eberhart et al., 2002)

In a study by **Massimino et al**, they analysed 125 patients for histopathological diagnosis and found classic variant in 93 cases, nodular/desmoplastic type in 20 cases, anaplastic/large-cell type in 9 cases , and extensive nodularity (MBEN) noted in 3 cases. They found that risk stratification only by residual disease after resection, metastases, age are not sufficient, patients histology also determines the prognosis particularly the anaplastic/large-cell medulloblastoma is associated with poorer prognosis irrespective of the extent of resection and other parameters(Massimino et al., 2013).

In a study by **McManamy et al,** 273 children aged 3 to 16 years diagnosed as non-desmoplastic medulloblastomas (MBs) who entered into the SIOP/UKCCSG trial were included and histological morphometric analysis done. The multivariate survival analysis showed that significant prognostic indicators were histologic variant,

metastases at presentation, and subtotal surgical excision of tumor. The concept of Anaplastic variant among other subtypes of MBs, has clinical utility(McManamy et al., 2003, 2007)

Histological features of Medulloblastoma:

Medulloblastoma tumours are characterized by small round blue cells. The classic variant shows densely packed small blue cells with round to ovoid hyperchromatic nuclei displaying mitotic activity and apoptosis. Homer-Wright rosettes are present in some cases. In desmoplastic/nodular variant, it is characterized by nodules of neurocytic differentiation which are surrounded by more primitive internodular areas. The nodules show a desmoplasia surrounding the nodules which are detected by pericellular reticulin deposition Medulloblastoma with extensive nodularity (MBEN) variety contains high proportion of differentiated elements compared to primitive internodular elements. The nodules here often coalesce together and forms irregular patterns with linear streaming noted between the nodules. MBENs show reticulin deposition in the internodular regions similar to desmoplastic variant. The large cell/anaplastic variant (LCA) are a combination of two variants viz the anaplastic variant and the large cell variant. The anaplastic variant contains increased cell size, cytologic pleomorphism, with cell molding and wrapping, increased mitotic activity, and apoptotic bodies seen. The large cell variant contains large discohesive cells with prominent nucleoli.

The importance of immunohistochemistry in differentiating the atypical teratoid/rhabdoid tumors from the anaplastic medulloblastoma tumors were emphasized by **Ho et al** (Ho et al., 2002). In their study they revisited the previously

diagosed PNET/MB cases in which they found the hidden AT/RT cases by using Immunohistochemical markers like EMA, VIM, SMA and GFAP. AT/RT cases were showing reactive for minimum two of the above mentioned antibodies, but PNET/MB did not have any of the above features(Burger et al., 1998; Ho et al., 2000; Rorke et al., 1996). Immunohistochemistry for SMARCB1 (INI1) and SMARCA4 are most useful in the differential diagnosis between medulloblastoma and atypical teratoid/rhabdoid tumors. The nuclear expression for SMARCB1 (INI1) and SMARCA4 are retained in all medulloblastomas, whereas, atypical and teratoid tumors show loss of nuclear expression for either of these two proteins. Hence, immuno histochemistry plays a major role in differentiating medulloblastomas from other tumours and uniforming the group for prognosis, treatment.

This clinical risk stratification has been useful only as a broad guide for predicting prognosis of the patients; but it is not explaining the few situations like in particular, it does not identify the 20% to 30% of Average risk patients with resistant disease or the number of average risk patients who might be over-treated with current treatment protocols and having undesirable side effects of radiation therapy.

Currently, in wide variety of childhood and non-childhood, non-CNS malignancies, molecular profile evaluation and its correlation with disease prognosis is being done extensively.

Upcoming of Molecular classification in Medulloblastoma:

In 2010, there was conference held in Boston, Massachusetts in which four sub-groups of medulloblastoma has been defined based on the transcriptional profiling, which were WNT, SHH, Group 3 and Group 4(Taylor et al., 2012). In the

subsequent meeting of the 3rd annual meeting of the International **Medulloblastoma Working Group held in Perth, Australia, the diagnostic criteria for the four subgroups has been defined**(Gottardo et al., 2014)**.** These sub-groups has distinct biological entities and several ongoing efforts were underway to tailor therapy to this sub-groups. They suggested medulloblastoma classification combining the histopathologic and molecular characteristics as given below(Gottardo et al., 2014)

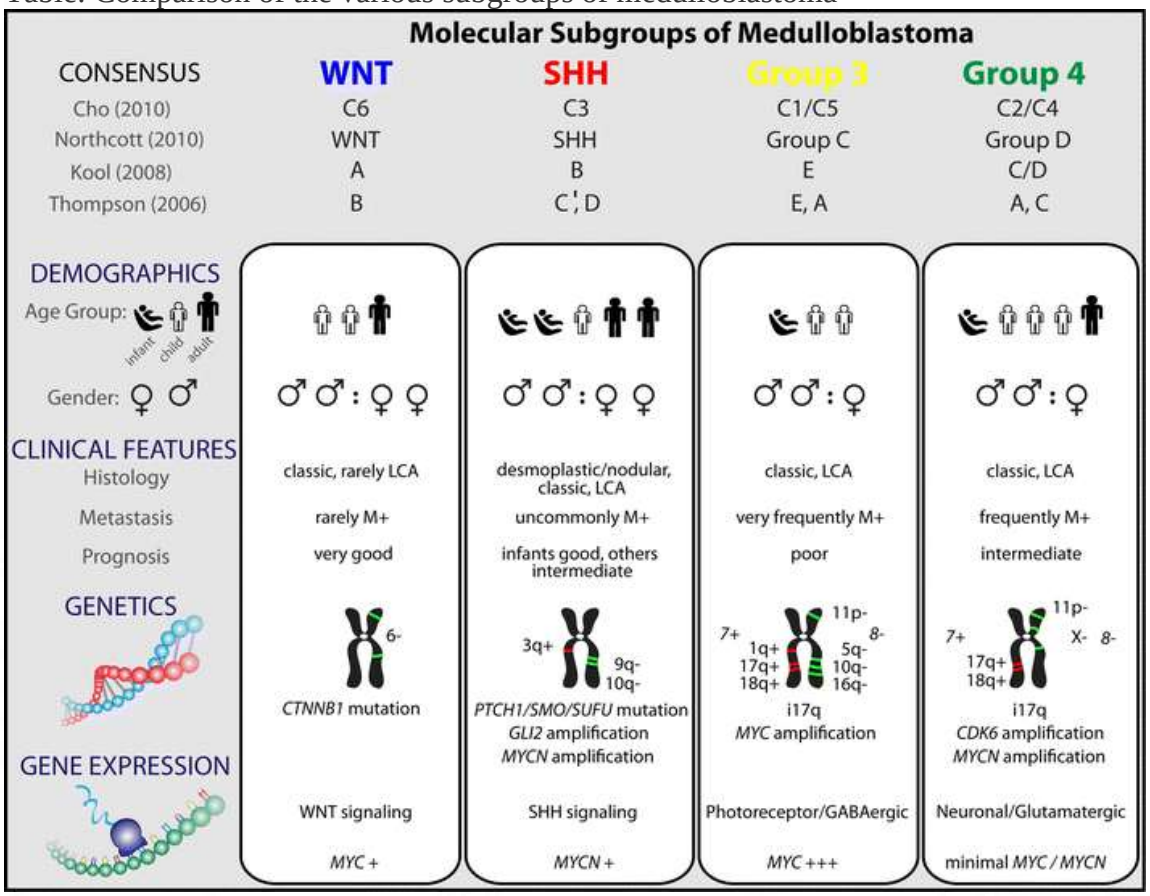
Molecular variant	Morphologic classification
WNT subgroup	Classic, LC/A
SHH subgroup	Desmoplastic (nodular), including MBEN, classic, and LC/A
Non-WNT/non-SHH subgroup	Classic, LC/A, differentiating, melanotic, medullomyoblastoma

LC/A large cell/anaplastic, *MBEN* medulloblastoma with extensive nodularity, *SHH* Sonic Hedgehog, ***WNT*** Wnt/Wingless

Source : Medulloblastoma Down Under 2013: a report from the third annual meeting of the International Medulloblastoma Working Group

Subsequently, based on further studies, the molecular classification is refined as follows, including Group 3 and Group 4 as separate categories.

Table: Comparison of the various subgroups of medulloblastoma



Source: Taylor, M.D., Northcott, P.A., Korshunov, A. *et al.* Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol* **123**, 465–472 (2012).

Currently, based on WHO CNS 2021 classification and further advances in the molecular subtyping using DNA methylation profiling, many further subgroups are identified.

A new categorization for groups 3 and 4 MLB was recently released after 1,501 patients in groups 3 and 4 MBL cohorts were examined(Cavalli et al., 2017). Recent high-resolution subclassification methods have assigned Groups 3 and 4 MBL a new classification as Types I−VIII. Groups 3 and 4 were combined with subtypes I, V, and VII. MYCC/MYCN amplification is a high-risk subtype III characteristic. KBTBD4 mutation is a feature of subtype VII. Each kind differs in

terms of survival, cytogenetics, and driving events(Ramaswamy et al., 2013; Sharma et al., 2019).

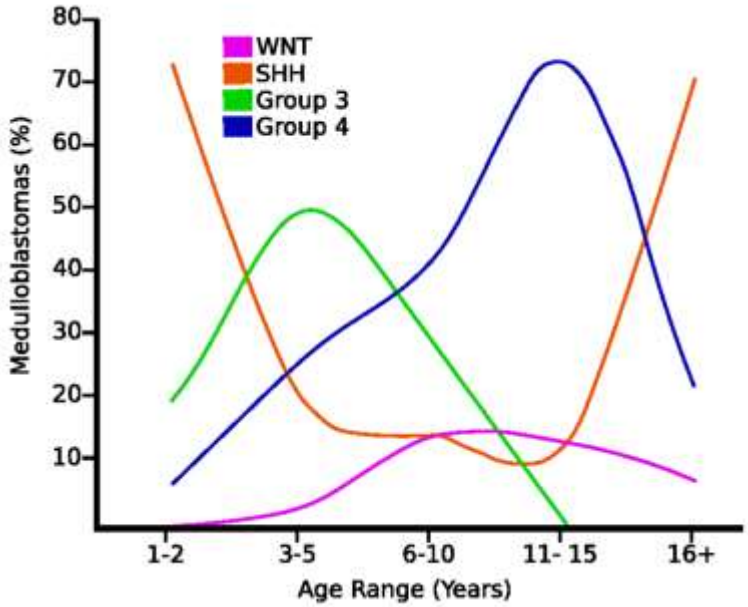
The intermediate subgroups 1 and 5 exhibit the molecular and cellular characteristics of both group 3 and group 4 MBs [56]. Most non-WNT/non-SHH MBs exhibit classic morphology, however subgroup 2 is more likely to have big cell/anaplastic tumours. In groupings 2-5, metastatic disease is present at presentation quite frequently. Tumors in subgroups 2 and 3 that have MYC/MYCN amplification are linked to a very poor prognosis(Northcott et al., 2017).

Table: Clinico-pathological, genetic characteristics of current medulloblastoma groups

Molecular groups	*WNT*	*SHH*		*G3*		*G4*
		TP53 wild type	*TP53 mutated*			
Age	Childood	Infancy/Adulthood	Childood	Childood		All age groups
Location	Central, frequently contiguous to brainstem		Hemispheric (rarely midline)	Midline (filling 4th ventricle)		Midline (filling 4th ventricle)
Histology	Mostly classic, rarely large cell anaplastic	Desmoplastic/Large cell/anaplastic	Nodular	Classic, Large cell anaplastic		Classic, Large cell anaplastic
Immunohisto chemestry	Nuclear beta-catenin Filamin A positive YAP1 positive GAB1 negative	P53 negative	Cytoplasmic beta catenin Filamin A positive YAP1 positive GAB1 positive p53 positive	Cytoplasmic beta catenin Filamin A negative YAP1 negative GAB1 negative		
Subgroups	α, β		α, β, γ, δ	II, III, IV (Group 3)	I, V, VII (Group 3/4)	VI, VIII (Group 4)
Genetics	CTNNB1, DDX3X, SMARCA4 and TP53 mutations	PTCH1, SMO, SUFU, TP53 mutation	TERT promoter mutations	MYC, OTX2, SMARCA4, NOTCH, TGF-β mutations		MYCN, KDM6A, CDKNA, mutation, SNCAIP duplications
Chromosomal abnormalities	Monosomy of chromosome 6	9q deletion, 10q loss	MYCN amplification, GLI2 amplification, 17p loss	MYC amplification, isodicentric 17q, 1q gain, 5q and 10q loss		MYC amplification, isodicentric 17q, 8, 10 and 11 loss, 4, 7 17, and 18 gain
Outcome of subgroups (5 years survival)	97% (α), 100% (β)	69.8% (α), 67.3% (β), 88% (γ), 88.5% (δ)		50% (II) 43% (III) 80% (IV)	77% (I) 59% (V) 85% (VII)	81% (VI) 81% (VIII)
Metastasis (%)	12%	20%(α), 33%(β), 9% (γ), 9% (δ)		57% (II) 56% (III) 58% (IV)	35% (I) 62% (V) 45% (VII)	45% (VI) 50% (VIII)

Source: Gianno F, Miele E, Antonelli M, Giangaspero F. Embryonal tumors in the WHO CNS5 classification: A Review. Indian J Pathol Microbiol. 2022 May;65(Supplement):S73-S82. doi: 10.4103/ijpm.ijpm_1049_21. PMID: 35562137.(Gianno et al., 2022)

Age distribution of molecular subtypes as mentioned below:



Source: Paediatric Medulloblastoma- update on molecular classification driving targeted therapies Ruth DeSouza, Benjamin R.T. Jones, Stephen P Lowis and Kathreena M Kurian.

Role of Immunohistochemistry in Molecular subtype analysis:

IHC can still be used to segregate between WNT, SHH, and non-WNT/ non-SHH medulloblastomas. WNT-activated group is identified by the beta-catenin immunoreactivity in nucleus.

The SHH-activated group is identified by the immunostaining for GAB1 and YAP1. For GAB1, expression is cytoplasmic and should be widespread and strong in intensity for it to be considered positive. For YAP1, expression is both cytoplasmic and nuclear. YAP1 nuclear expression should be widespread and strong in intensity for it to be considered positive. Additionally, p53 immunostain can be performed. A widespred and strong immunoreactivity for p53 in tumor cell nuclei is suggestive of SHH-activated and TP53-mutant subgroup. In WNT and SHH medulloblastoma groups, immunoreactivity for Filamin A is also noted in cytoplasm.

Non-WNT/non-SHH tumors show a beta-catenin expression in cytoplasm and are immunonegative for GAB1 and YAP1. It is not possible to differentiate between Group 3 and Group 4 by immunohistochemistry. The DNA methylation profiling is considered as the gold standard for determining the status of medulloblastoma group or subgroup(Gianno et al., 2022)

Table: Comparing various methods for MB classification:

Platform/Methodology	WNT	SHH	Non-WNT/non-SHH	
Immunohistochemistry				
Nuclear β-catenin	Positivity in ≥5% tumor cells	Negative	Negative	
GAB1 (cytoplasmic)	Negative	Positive*	Negative	
Nuclear YAP1	Positive	Positive*	Negative	
			Group 3	Group 4
Expression at RNA level using real time RT-PCR of 12 protein-coding genes	WIF1, DKK2, MYC, OTX2	HHIP, EYA1, MYCN	NPR3, IMPG2, EOMES, OTX2, MYC	EOMES, UNC5D, GRM8, OTX2, MYCN
Differential expression of 6 microRNAs using real-time RT-PCR (even with degraded RNA)	MiR-193a MiR-224 MiR-182	MiR-135b MiR-204 MiR-182	MiR-135b MiR-182	MiR-135b MiR-592
Expression at RNA level using nanoString assay	WIF1, DKK2, TNC, GAD1, EMX2	HHIP, EYA1, SFRP1, PDLIM3, ATOH1	NPR3, IMPG2, EOMES, GABRA5, EGFL11, MAB21L2, NRL	EOMES, UNC5D, KCNA1, KHDRBS2, OAS1
Genetic alterations: FISH	Monosomy 6	GLI2 amplification MYCN amplification	MYC amplification	Isodicentric Chr17q
Genetic alterations: Gene sequencing	CTNNB1 mutation	TP53 mutation PTCH1/SMO/SUFU		

RT-PCR = Reverse transcriptase polymerase chain reaction; FISH = Fluorescence in-situ hybridization; GAB1 = GRB2 associated binding protein 1; YAP1 = Yes associated protein 1; *Widespread, strong positivity (especially YAP1) in non-desmoplastic SHH = Stronger positivity (especially YAP1) in internodular regions in desmoplastic SHH. The genes indicated under each sub-group are overexpressed in the specified sub-group with the exception of underlined microRNAs which are under-expressed in the SHH sub-group tumors

Source: Gupta T, Sarkar C, Rajshekhar V, Chatterjee S, Shirsat N, Muzumdar D, Pungavkar S, Chinnaswamy G, Jalali R. Indian Society of Neuro-Oncology consensus guidelines for the contemporary management of medulloblastoma. Neurol India 2017;65:315-32 (Gupta et al., 2017)

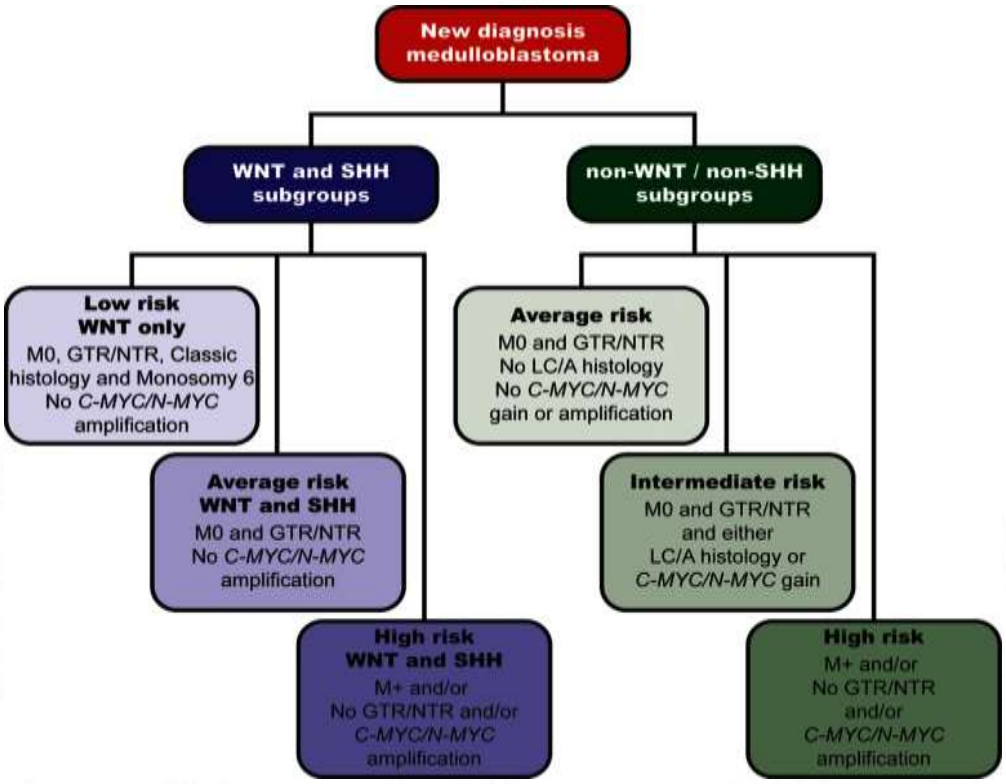
Method	**Description**	**Pros**	**Cons**
Immuno histoche mistry	*Description*: Classification based on pattern of expression of three proteins as detected by immunohistochemistry (YAP1, GAB1, and beta-catenin) *Classification*: Tumors separable into WNT, SHH, Non-WNT/non-SHH	-Easy implementation -Low capital expense -Technology available in most clinical labs -Protein is a relatively stable macromolecule -Works in samples with low tumor content. -Works well with ffpe	-Interpretation challenges in low-volume laboratories -Divergent differentiation yields indeterminant class -Cannot resolve g3 and g4 tumors -Cannot account for increasingly granular mb classification -Limited to mb classification

Method	Description	Pros	Cons
Transcription profiling	*Description*: Classification based on shared RNA expression signature as detected by transcription array, RNA sequencing, or nanostring ™ *Classification*: Tumors separated into WNT, SHH, G3, and G4	-Can separate tumors into all four canonical molecular groups -Works with ffpe or frozen material -Moderate to high capital expense	-Based on RNA, a relatively unstable macromolecule -Technology not available in many clinical laboratories -No supervised classification model currently available -Based on RNA, a relatively unstable macromolecule. -Limited to MB classification -More granular MB classification not currently available. -Requires relatively pure tumor
Methylation	*Description*: Classification based on methylation signature using unsupervised or supervised classification models. Typically utilize Illumina Human Infinium 450K/EPIC arrays. *Classification*: Tumors separated into WNT, SHH, G3, and G4. More granular class structure can be resolved	-Can separate all four canonical methylation classes -Scales well to other tumor types -Large reference series available for mb and other tumor types -Works with ffpe and frozen tissue -Utilizes dna, relatively stable macromolecule	-Not currently widely available -High capital expense -Not all clinical samples contain sufficient dna quantity for classification -Requires high proportion of pure tumor
DNA Sequencing	*Description*: Classification based on sequencing of class specific recurrent mutations. *Classification*: Reliable for WNT class in most instances, but cannot resolve all four canonical classes	Can be performed in most modern molecular laboratoriesMany commercial labs evaluate the genes recurrently mutated in mb. Works on ffpe or frozen material. Utilizes dna, relatively stable macromolecule	Many MB do not have contain defining mutations (ie. G3/G4). Some mutations cross class boundaries (ie. Subclonal SHH pathway mutations in WNT tumors)High capital expense

Source: Orr, B.A. (2020), Pathology, diagnostics, and classification of medulloblastoma. Brain Pathol, 30: 664-678. https://doi.org/10.1111/bpa.12837

Modified Risk stratification combining the Molecular subtype data:

(New risk criteria for medulloblastoma in recently opened St. Jude frontline medulloblastoma protocol (SJMB12))



Source: Gottardo NG, Hansford JR, McGlade JP, Alvaro F, Medulloblastoma Down Under 2013: a report from the third annual meeting of the International Medulloblastoma Working Group. Acta Neuropathol. 2014 Feb;127(2):189-201. doi: 10.1007/s00401-013-1213-7. (Gottardo et al., 2014)

Consensus risk-stratification in the molecular era for medulloblastoma

Risk category	WNT	SHH	Group 3	Group 4	Others
Low Risk (expected survival >90%)	<16 years				
Standard Risk (expected survival 75-90%)		TP53 wild type No MYC amplification Non-metastatic	All of the following No MYC amplification Non-metastatic	All of the following Non-metastatic Chr 11 loss	
High Risk (expected survival 50-75%)		One or both MYC amplification Metastatic		All of the following Non-metastatic No Chr 11 loss	
Very High Risk (expected survival <50%)		TP53 mutation (metastatic or non-metastatic)	Metastatic	Metastatic	
Unknown	Metastatic		Non-metastatic with MYC amplification; anaplasia; isochromosome 17q	Anaplasia	Melanotic medulloblastoma Medullomyoblastoma Indeterminate between groups 3/4

Source: Gupta T, Sarkar C, Rajshekhar V, Chatterjee S, Shirsat N, Muzumdar D, Pungavkar S, Chinnaswamy G, Jalali R. Indian Society of Neuro-Oncology consensus guidelines for the contemporary management of medulloblastoma. Neurol India 2017;65:315-32(Gupta et al., 2017)
(Cotter and Hawkins, 2022)

Treatment for Medulloblastoma:

Current treatment strategies for medulloblastoma are developed based on the risk stratification and age of the patient. In all groups of patients, the first line of treatment is surgery, i.e maximal reduction of tumour burden with low morbidity. Hydrocephalus if present can be addressed either before or after surgery based on the clinical symptoms, resources availability and situational emergency.

Corticosteroids can be administered prior to surgery, with Dexamethasone, can help in reduction of vasogenic tumor oedema before surgery. It is started at a loading dose of 0.5-1 mg/kg IV, followed by 0.25-0.5 mg/kg/day in divided doses every 6-8 hours, along with antacids. Cerebral decongestants (mannitol or frusemide) can be used for severe hydrocephalus. Elevation of the head-end by 30 degrees also helps in reducing ICP.

Prophylactic antiepileptic prophylaxis is not required. Despite MB is a tumor of the posterior fossa, some patients can develop a seizure probably because of hydrocephalus/dissemination. In those patients, anticonvulsant drugs can be started preoperatively also.

CSF DRAINAGE:

An emergent EVD(external ventricular drain) through Kochers point or Frazier burr hole can temporarily be placed. Alternatively, Endoscopic third ventriculostomy (ETV) also can be done. In most of the cases, tumour decompression relieves the obstruction-causing hydrocephalus and no further CSF diversion procedure is required. Shunting carries a risk of upward herniation and tumour seeding into the peritoneal cavity.

SURGICAL APPROACHES:

Various approaches for tumour resection depends on location of the tumour. For tumour in midline, suboccipital approach in prone position is ideal. In adults, tumours will be in CP angle or lateral aspect of cerebellum requiring requiring a retrosigmoidal approach in lateral position. The paramedian approach for cerebellar hemisphere tumors can be done in a prone or lateral position depending on convenience. Intraoperative neuro-monitoring is required for cerebellopontine angle tumours, not required for other locations. Tumors with in the fourth ventricle, not visible in the cisterna magna are done by one of the approaches viz, midline transvermian approach or the lateral telovelar approach(Gupta et al., 2017). Gross total resection can be achieved in 60–90% of adult medulloblastoma series. No role of fluorescence agents like 5-ALA in adult medulloblastoma surgery. Intraoperative MRI if available can be used to assess the extent of resection. Post op MRI within 48 hours is necessary to identify the residual lesion. A second look surgery can be considered if there is a residual lesion of more than 1.5 cm^2

Intraoperative CSF sampling can be done to assess CSF seeding. Ideally, it has to be done via lumbar puncture prior to or 2 weeks post surgery.

Complications of surgery can occur in 30% patients and it includes hematoma, CSF leak, infection/meningitis, pseudomeningocele, hydrocephalus, and cranial nerve palsy. Cerebellar mutism has been rarely described in adult patients after medulloblastoma surgery and usually resolves within 30 days.

A well-known side effect of posterior fossa surgery is cerebellar mutism syndrome, which Hirsch et al. originally identified in 1979. After surgery, mutism usually begins 1 to 4 days later and may be followed by personality changes, emotional instability, and a reduction in the initiation of voluntary movements. The disease

frequently comes with dysarthria, an ingestion disorder. Most frequently affecting children between the ages of 2 and 13 and typically lasting between 2 and 4 months. The root reason is not known. The dentate nucleus, a bilateral interruption of the dentothalamocortical circuit, and damage to the cerebellum's midline structures have all been proposed as potential causes of this condition(Hirsch et al., 1979; Janßen et al., 1998).

After cerebellar resection, there are 8 to 25 percent cases of posterior fossa syndrome(Doxey et al., 1999). It is not believed that the extent of surgical resection affects the development of this syndrome; nonetheless, in the majority of paediatric instances of posterior fossa syndrome, tumours involve the brainstem(Gajjar et al., 2008). This syndrome shouldn't be used as a reason to forgo or delay curative treatment.

Adjuvant therapy:

After surgery, the timing of adjuvant radiochemotherapy seems to be important in the process of disease control and recurrence. In a two RCT by kuhl et al and Bailey et al, it was showed that pre-radiation chemotherapy was associated with poor disease control than postoperative radiotherapy first followed by the concomitant chemotherapy (Bailey et al., 1995; Kühl et al., 1998)

Radiation therapy:

The cornerstone of therapy for the curative-intent management of medulloblastoma continues to be post-operative adjuvant radiation therapy (RT). To achieve effective disease control, therapy of the entire neuraxis, i.e. craniospinal irradiation (CSI), followed by boost irradiation of the tumour bed/posterior fossa, is advised. This is due to the tumor's strong potential to develop leptomeningeal spread.

General guidelines for RT

Following surgery, patient to be referred to an oncologist within 7–10 days so that additional adjuvant therapy can be planned and started right away. Adjuvant RT should ideally start as soon as is practical after surgery, ideally within 4 weeks, but most likely within 6 weeks (allowing 2-3 weeks for post-operative rest and neuraxial staging)(Gupta et al., 2017). The total treatment period for a fractionated course of radiotherapy should ideally not exceed 50 days, but in no case should it surpass 8 weeks. Interruptions to the course of the treatment during RT are undesirable and should be avoided wherever possible(del Charco et al., 1998). Ondansetron (0.2 mg/kg) should be administered orally 45–60 minutes before CSI as an anti-emetic prophylactic. During RT, complete blood counts should be checked at least once per week. Prophylactic growth factors should not be used during CSI unless absolutely essential. However, to maintain an absolute neutrophil count >1 109/L and avoid unneeded treatment interruptions, growth factors may need to be given. The same goes for platelet transfusions, which should only be used in cases of grade 3 or greater thrombocytopenia in order to keep the platelet count above 50 x109/L during CSI. Dexamethasone or prednisone usage is strongly advised to be avoided unless absolutely required.

Chemotherapy

Chemotherapy's role has significantly changed over the past 20 years, making it a crucial part of the multimodal approach to treating medulloblastoma(Evans et al., 1990; Packer et al., 2006; Thomas et al., 2000). There is now reliable, high-quality data that chemotherapy prolongs survival in patients with high-risk medulloblastomas and permits administration of reduced-dose CSI in conditions of standard risk without

impairing disease-related outcomes(Massimino et al., 2016; Packer et al., 2012; Packer and Finlay, 1996).

Chemotherapy in medulloblastoma is currently recommended in the following settings:

1. Adjuvant chemotherapy after RT
2. Adjuvant chemotherapy after surgery in infants(<3-years)
3. Pre-radiation chemotherapy in infants to defer RT (till 3-years)
4. High-dose chemotherapy with covering autologous stem-cell transplant rescue
5. Concurrent RT and chemotherapy
6. Palliative/Salvage therapy in relapsed/recurrent MB.

At least 3 weeks should pass before adjuvant chemotherapy begins after finishing RT to enable myelo-recovery (preferably at 4-weeks, but definitely within 6-weeks). Before beginning adjuvant chemotherapy, neuraxial imaging should be performed to reassess the disease status.Adjuvant chemotherapy should be given in a total of 6–8 cycles, often spaced 3–6 weeks apart (depending upon the regimen used)(Gajjar et al., 2006; Rutkowski et al., 2005; Tait et al., 1990)

Recommended adjuvant chemotherapy regimens in medulloblastoma

Adjuvant chemotherapy regimens for childhood medulloblastoma (>3 years of age)		
Drugs	**Dosage**	**Days and route of administration**
Regimen I (Packer's regimen)		
Cisplatin	75 mg/m²	Day 1 only (intravenously)
Lomustine	75 mg/m²	Day 1 only (per orally)
Vincristine	1.5 mg/m²	Days 1, 8 and 15 (intravenously)
Regimen II		
Cisplatin	75 mg/m²	Day 1 only (intravenously)
Cyclophosphamide	1000 mg/m²	Days 1 and 2 (intravenously)
Vincristine	1.5 mg/m²	Days 1, 8 and 15 (intravenously)
Regimen III		
Cisplatin	75 mg/m²	Day 1 only (intravenously) in cycle 2, 4 and 6 only
Cyclophosphamide	1000 mg/m²	Days 1 and 2 (intravenously) in cycle 1, 3 and 5
		Days 2 and 3 (intravenously) in cycle 2, 4 and 6
Vincristine	1.5 mg/m²	Days 1 and 8 (intravenously) in all 6 cycles
Adjuvant chemotherapy regimen for infant medulloblastoma (<3 years of age)		
Carboplatin	600 mg/m²	Day 1 only (intravenously)
Cyclophosphamide	1000 mg/m²	Day 1 only (intravenously)
Etoposide	100 mg/m²	Days 1, 2 and 3 (intravenously)

Source: Gupta T, Sarkar C, Rajshekhar V, Chatterjee S, Shirsat N, Muzumdar D, Pungavkar S, Chinnaswamy G, Jalali R. Indian Society of Neuro-Oncology consensus guidelines for the contemporary management of medulloblastoma. Neurol India 2017;65:315-32(Gupta et al., 2017)

Older children Average risk:

Current treatment for average risk(AR-MB) is craniospinal irradiation to 23.4 Gy with posterior fossa or involved field (IF) boost to 54 Gy followed by chemotherapy regimen. The effectiveness of several chemotherapeutic drugs has also been studied. A randomised experiment contrasting chemotherapy using lomustine (CCNU), cisplatin, and vincristine with treatment using cyclophosphamide, cisplatin, and vincristine was conducted as part of the COG A9961 investigation. In terms of survival, there was no discernible difference between cyclophosphamide- and CCNU-based regimens.(Packer et al., 2006)

Further initiatives have now been made to reduce the radiation therapy dose and volume. The effectiveness of a smaller boost (radiation to the tumour bed) vs a regular volume boost (radiation to the entire PF) was compared in a phase III RCT. Additionally, young children (3–7 years old) were randomised to receive 23.4 Gy CSI as opposed to 18 Gy. When compared to posterior fossa radiation therapy (PFRT), involved field radiation therapy (IFRT) was considered to be non-inferior. Sadly, kids who received low-dose (LD) CSI had lower event-free survival (EFS) rates than kids who received standard-dose (SD) CSI (71.4% vs. 82.9%, p=0.028). In the WNT, SHH, and group 3, there was no discernible difference in the outcomes between LD and SD CSI. However, group 4 patients who received LD CSI had lower EFS than group 4 patients who received SD CSI.(Michalski et al., 2021)

Hyperfractionated (HF) vs. standard RT followed by maintenance chemotherapy were compared in the HIT-SIOP PNET 4 trial. HFRT did not increase survival in AR MBL(Lannering et al., 2012). For AR MBL, risk-adapted radiation with 23.4 Gy CSI was studied in the St Jude medulloblastoma (SJMB)-96 and -03 trials. The 5-year EFS for patients with AR MBL treated with risk-adapted radiation and brief, dose-intensive, alkylator-based chemotherapy was 82%-83% in the SJMB-96 and -03 studies.(Gajjar et al., 2021)

Table: Clinical trials of average risk medulloblastoma

Study	No. of patient	Cohort criteria	Study outcome	RT dose (Gy)	Chemotherapy	Survival
CCG 9892	65	3–10 yr, M0, R0	Non-RCT feasibility of reduced dose CSI (23.4 Gy) and adj. CT	CSI 23.4/PF 55.8	VCR during RT, CCNU/CDDP/VCR	5-yr PFS 79%
SIOP PNET3	179 (pre-RT CT 90, RT - 89)	3–16 yr, M0	RCT, pre-RT vs. RT alone	CSI 35/PF 55	None vs. VCR, VP, alternating CBP and CPM	5-yr EFS 67.0% (pre-RT CT 74.2% vs. RT alone 59.7%)
SJMB-96	86	3–21 yr M0, R0	Non-randomized trial, 5-yr EFS	CSI 23.4/ PF 36/ TB 55.8	CPM, CDDP, VCR+SCR (4 cycles)	5-yr EFS 83%
HIT-SIOP	169	4–21 yr, except	Randomized trial evaluating STRT vs. HFRT	Conv. RT CSI 23.4/ PF 54 HFRT CSI 36/PF 60	VCR during RT; adjuvant CDDP, CCNU, VCR 8 cycles	5-yr EFS 77% for STRT, 78% for conventional RT group 78%
PNET4	169	LC/A hpr				
COG A9961	A 193 B 186	3–21 yr, M0 or R0	Randomized trial evaluating adjuvant CPM vs. CCNU based chemo	CSI 23.4/PF 55.8	A: CCNU, CDDP, VCR B: CPM, CDDP, VCR	A: 5-yr EFS 81% B: 5-yr EFS 86%
SJMB-03	227	3–21 yr, M0, GTR or NTR (R0)	Non-randomized trial, evaluating dose-intensive chemotherapy	CSI 23.4/PF 55.8	VCR, CDDP, CPM with autologous SCR 4 cycles	5-yr PFS 83.2%
ACNS 0331	549	3–21 yr, M0, ≤1.5 cm^2	RCT, 1) evaluating PFRT vs. IFRT, 2) standard dose CSI (24 Gy) vs. low dose CSI	CSI 23.4 or 18/PF or IFRT 54	A: CDDP, CCNU, VCR B: CPM,VCR (AABAABAAB)	5-yr EFS 81.4 (82.5% for IFRT, 80.5% for PFRT; 82.9% for SDCSI

Study	No. of patient	Cohort criteria	Study outcome	RT dose (Gy)	Chemotherapy	Survival
			(18 Gy) for young children (3–7 yrs)			vs. 71.4% for LDCSI)

Source: Choi JY. Medulloblastoma: Current Perspectives and Recent Advances. Brain Tumor Res Treat. 2023 Jan;11(1):28-38. doi: 10.14791/btrt.2022.0046. PMID: 36762806; PMCID: PMC9911713.(Choi, 2023)

Older children high risk category:

Having one or more of the following features, such as metastatic disease (Chang stages M1–M4; M+), LC/A histology, MYC or MYCN amplification, or considerable residual disease (>1.5 cm2; R+), is now considered to be high risk (HR) MBL. A third of individuals have metastases, and their prognosis is not good. When compared to M0-M3 disease, M4 disease had a considerably poorer 5-year EFS in the POG 9031 research (70 percent vs. 22 percent). According to recent studies, the size of residual tumour has no bearing on the prognosis(Jakacki et al., 2012; Tarbell et al., 2013; Taylor et al., 2003).

The best course of action for HR MBL is still unknown. Currently, dose of 36–39.6 Gy to CSI and boost of up to 54 Gy to the primary site is followed. The SIOP/UKCCSG PNET-3 trial, which used pre-RT chemotherapy and radiation therapy to treat patients with M2-M3 MBL, did not result in satisfactory results, showing that HR MBL needed more intensive treatment.(Taylor et al., 2005)

The radiosensitizer carboplatin(35 mg/m2/dose 30) seems to be useful in a phase I/II research of M+ MBL (COG 99701).(Jakacki et al., 2012)

The SJMB-96, SJMB-03, HART, and PNET HR trials all used high-dose chemotherapy and autologous stem cell transplantation (HDC/ASCT).

Clinical trial results of high-risk medulloblastoma

Study	No. of patients	Cohort	Study outcome	Radiation dose (Gy)	Chemotherapy	Survival
POG 9031	224	3–21 yrs, T3b/T4 disease at time of surgery or M+ or R+	Randomized trial, pre-RT vs. post-RT CT; prognostic factor of response to pre-RT CT	M0–1 CSI 35.2/PF 53.2 M2–3 CSI 40/PF 54.4 Spinal or brain meta 44.8	Randomized CDDP, VP pre or post RT; maintenance with CPM/VCR	Pre-RT CT arm 5-yr EFS 66% (CR or PR 73% vs. not CR or PR 56% after pre-RT CT [*p*=0.1]) Post-RT CT arm 5-yr EFS 70%
SIOP PNET-3	68	3–16 yrs, M2-3	Non-randomized trial, outcome treated with PNET-3 pre-RT CT	CSI 35/PF 55	Pre-RT VCR, VP, alternating CBP/CPM alter (total 4 cycles)	5-yr EFS 34.7%
SJMB-96	48	R+ or M1–M3	Non-randomized trial, 5-yr EFS	CSI for M0–1 36/M2–3 39.6/TB 55.8/meta 50.4	TPT before RT; CDDP, CPM, VCR + SCR (4 cycles)	5-yr EFS 70%
HART	33	≥3 yrs, M+	Non-randomized trial, efficacy and toxicity of a HART regimen delivered after intensive sequential CT	CSI 39/TB 60 (HART regimen)	Pre-RT MTX, VP, CPM, CBP/2 cycles of thiotepa & SCR (not in CR before CSI) or 6 cycles of CCNU, VCR (CR before CSI)	5-yr PFS 72% (CR or PR 3-yr PFS 94%, not CR or PR 3-yr PFS 61% after pre-RT CT [*p*=0.04])
HIT 2000	123	4–21 yrs, M+	Non-randomized trial, outcome analysis by clinical risk factors, methylation/genetic subgroup status, and other biologic parameters	HF CSI 40/PF +20/spinal meta +10/supratentorial meta +28	Pre-RT CPM, VCR, MTX, CBP, VP, intraventricular MTX (2 cycles); maintenance with CDDP, CCNU, VCR (4 cycles)	5-yr EFS 62%
COG 99701	161	R+, M+ or supratentorial PNET	Phase I/II trial	CSI 36/PF +19.8	VCR, CBP during RT; maintenance with CPM, VCR +/- CDDP	5-yr EFS 77% for M1, 50% for M2, 67% for M3
COG ACNS 0332	294	R+, M+, LC/A histology	Randomized trial, 1) CBP concurrently with	CSI 36/PF 55.8	VCR/randomized CBP during RT; CDDP/CPM/VCR (6 cycles)	5-yr EFS 62.9% CBP 66.4% vs. No CBP 59.2% (*p*=0.11) Group 3: CBP 73.2%

Study	No. of patients	Cohort	Study outcome	Radiation dose (Gy)	Chemotherapy	Survival
			RT, 2) isotretinoin 12 cycles			vs. No CBP 3.7% (p=0.047)
PNET HR+5	51	5–20 yrs, R+, M+, *MYC/N* LC/A histology	Non-randomized trial, 3-yr PFS, molecular characteristics associated with PFS	CSI 36 (if R+ alone 23.4)/TB 54	Pre-RT CBP, VP (2 cycles); high dose thiotepa + SCR (2 cycles); maintenance with TMZ 6 cycles	3-yr PFS 78%, 5-yr PFS 76%
SJMB-03	103	3–21 yrs, M+, not GTR	Non-randomized trial, 5-yr PFS	CSI 36–39.6, boost 55.8–59.4	VCR, CDDP, CPM + SCR (4 cycles)	5-yr PFS 56.7%

Source: Choi JY. Medulloblastoma: Current Perspectives and Recent Advances. Brain Tumor Res Treat. 2023 Jan;11(1):28-38. doi: 10.14791/btrt.2022.0046. PMID: 36762806; PMCID: PMC9911713.(Choi, 2023)

Infant Medulloblastoma

Infant MB has a dismal survival rate due to limitations in the use of RT because of high susceptibility of the developing brain and the high dissemination rate at diagnosis. Several non-radiation therapies, such as intraventricular or high-dose methotrexate (HD MTX), HDC/ASCT, and main focal site RT, have been tried(Lafay-Cousin and Dufour, 2022)

In the COG P9934 study, focal RT for PF using 18 or 23.4 Gy was evaluated(Ashley et al., 2012). Induction chemotherapy (cisplatin, cyclophosphamide, vincristine, and etoposide), three cycles of HDC (carboplatin and thiotepa), and ASCT resulted in a 5-year PFS of 69.6% and a 5-year OS of 76.1 percent, according to the COG 99703 research(Lafay-Cousin et al., 2016). As part of the HeadStart III trial, patients received 3-5 cycles of adjuvant chemotherapy (cyclophosphamide, vincristine, etoposide, and HD MTX), as well as one cycle of HDC (thiotepa, etoposide, and carboplatin) and ASCT(Dhall et al., 2020).

Clinical trial results of infant medulloblastoma

Study	No.	Cohort	Study outcome	Radiation dose (Gy)	Chemotherapy	Survival
COG P9934	82	8 month–3 yr, M0	Non-randomized trial, Age- and response adjusted RT	PF 18/23.4	CPM, VCR, CDDP, VP	4 yr EFS 50%
COG 99703	53	<6 yr	Non-randomized trial, HDC/ASCT	None	CDDP, CPM, VCR, VP/CBP, TP & SCR	5 yr PFS 69.6%
SJYC07	81	<3 yr, M0	Non-randomized trial, risk-adapted treatment	Intermediate risk	Induction: HD MTX, VCR, CPM, CDDP, VBL (high risk), consolidation: CPM, CBP, VP	5 yr EFS 31.3%
HIT 2000	87	<4 yr, M0	Non-randomized trial, HIT-SKK chemotherapy	TB 54 for CMB/LC/A histology or DN/MBEN in incomplete remission	3 cycles of HIT-SKK chemotherapy with intraventricular MTX → 2 cycles of modified HIT-SKK chemotherapy	5-yr PFS 93% for DN or MBEN patients, 5-yr PFS 37% for CMB or LC/A histology
Head Start III	92	M0 & <4 yr, M2 or with post-op residual tumor & < 10 yr	Non-randomized trial, intensive induction followed by HDC/ASCT	>6 yr or not in CR	CDDP, CPM, VCR, VP, HD MTX 3–5 cycles → 1 cycle of thiotepa-VP-CBP	DN MBL 5-yr EFS 89%, classic 26%, LC/A 38%
ACNS0334	39	<36 months except ND M0	Randomized trial, addition of HD MTX	Physician discretion	CDDP, CPM, VCR, VP, randomized ±HD MTX → 3 cycles of CBP, thiotepa	5 yr EFS with HD MTX 68.2%, 5 yr EFS w/o HD MTX 45.8%

Source: Choi JY. Medulloblastoma: Current Perspectives and Recent Advances. Brain Tumor Res Treat. 2023 Jan;11(1):28-38. doi: 10.14791/btrt.2022.0046. PMID: 36762806; PMCID: PMC9911713.(Choi, 2023)

SURVIVAL OF EACH GROUP:

1. **Average risk older children:**

There have been reports of an above 80% survival. The 5 year survival outcome based on molecular subgroup was 93-98 percent for WNT, 75-83 percent for SHH, 63-67 percent for group 3, and 86-87 percent for group 4.(63,65) MB type Group 3 were

the worst, while the WNT subgroup's results were good. Five separate arms make up the current SIOP PNET 5 MBL trial: low-risk WNT-activated MBL, standard-risk non-WNT MBL, high-risk WNT-activated MBL, and biologically extremely high-risk SHH-activated MBL (TP53 mutant).

2. **High risk older children:**

The survival rate has increased by as much as 70%. Histologically, DN MB has best prognosis, the classic type has an intermediate prognosis, LC/A MBL has the worst prognosis (5-year EFS, 89 percent for DN, 61 percent for classic, and 40 percent for LC/A MBL in the HIT 2000 study)(Gajjar et al., 2021; Leary et al., 2021; von Bueren et al., 2016). According to the molecular subgroup, the 5-year EFS or PFS for clinical trials for HR MBL for WNT was 92% - 100%, for SHH it was 25% - 60%, for group 3 it was 40% - 60%, and for group 4 it was 66% - 68 %.

3. **Infant Medulloblastoma:**

In Infants, the SHH group outlived group 3 by a greater margin. Non-DN/MBEN revealed a poorer 5-year PFS of less than 60%, but DN/MBEN revealed more than 90% of 5-year PFS(Lafay-Cousin et al., 2016). DN/MBEN MBL demonstrated a greater rate of GTR than conventional MBL. In multivariate analysis, metastases and partial resection (GTR vs. non-GTR) were independent predictors of prognosis in young patients(Rutkowski et al., 2010). This suggests that the best course of action for treating MBL is to do a maximally safe resection.

New approaches and ongoing trials for MB:

The current HeadStart 4 trial examines treatment reduction from two cycles to a single cycle of HDC/ASCT in the children younger than 6 years old with SHH MBL, TP53 wild-type, regardless of metastases or amount of resection(Lafay-Cousin and Dufour, 2022)

Currently, it is accepted that the WNT subgroup aged under 16 years is regarded as a low-risk group because of its favorable prognosis. Therefore, efforts are being made to lower the intensity of treatment in this group.

SHH MBL in infants with DN histology often has good results, whereas SHH MBL with TP53 mutation and MYCN amplification has poor survival. New treatment approaches are therefore required. In a systemic analysis of phase I and II clinical studies, SMO inhibitors shown an objective response rate of 37% and 0% in recurrent SHH and non-SHH MBL, respectively (78).

Due to the lack of immunogenic antigens, tumour microenvironment, and a blood-brain barrier, immunotherapy is has limited use in MB.

Ongoing clinical trials in WNT medulloblastoma

	CSI	**Chemotherapy**	**NCT**
SIOP-PNET5	≥16 yrs: 23.4 Gy CSI+30.6 Gy to primary site (54 Gy) <16 yrs: 18 Gy CSI+36 Gy to primary site (54 Gy)	6 cycles of chemotherapy (CCNU+CDDP+VCR; CPM+VCR)	NCT02066220
ACNS 1422	18 Gy CSI+36 Gy to primary site (54 Gy)	7 cycles of chemotherapy (CCNU+CDDP+VCR; CPM+VCR)	NCT02724579
SJMB-12	15 Gy CSI+36.4 Gy to primary site (51.4 Gy)	4 cycles of chemotherapy (CDDP+CPM+VCR)	NCT01878617

Long term complications and Late effects:

Physical, neurocognitive, endocrine, and auditory late sequelae are common in MBL patients as well as secondary neoplasms associated with the treatment. The two most frequent endocrinologic consequences are growth hormone insufficiency and primary hypothyroidism. Neurocognitive effects on working memory, processing speed, and fine-motor skills are more likely to occur in children receiving CSI. Reduced-dose CSI, a lesser boost to the tumour bed, HFRT, and proton therapy have all been tried to lessen neurotoxicity. To assess IQ, processing speed, attention, memory, language preference, behavioral/social/emotional function, executive function, adaptive function, and quality of life, COG created a standard neuropsychological and behavioural battery. As a result, it's important to identify late impacts early and offer suitable remedies.

The current challenge in the treatment of medulloblastoma is to increase the current survival rates while reducing side effects. The risk stratification is evolving and various prospective trials are underway to segregate in to different groups for appropriate treatment.

MATERIALS AND METHODS

Methodology:

This is retrospective observational study done in the Department of Neurosurgery, Sree Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum, Kerala, India. It includes patients of all age groups who were operated for posterior fossa lesions and subsequently diagnosed as Medulloblastoma in the Histopathological report. Clinical details were collected from the Electronic Medical Records, computer database and Medical records department. The follow up data were recorded from the OPD visits and via telephone call questionnaire whoever was reachable by the available contact number.

Sample size: 249 patients operated for medulloblastoma.

Definition of cases:

All patients operated for intracranial space occupying lesions with histopathological report as medulloblastoma.

Study Population:

Study population included patients of all age groups who underwent surgery for intra cranial space occupying lesions and subsequently diagnosed as Medulloblastoma by histopathological report.

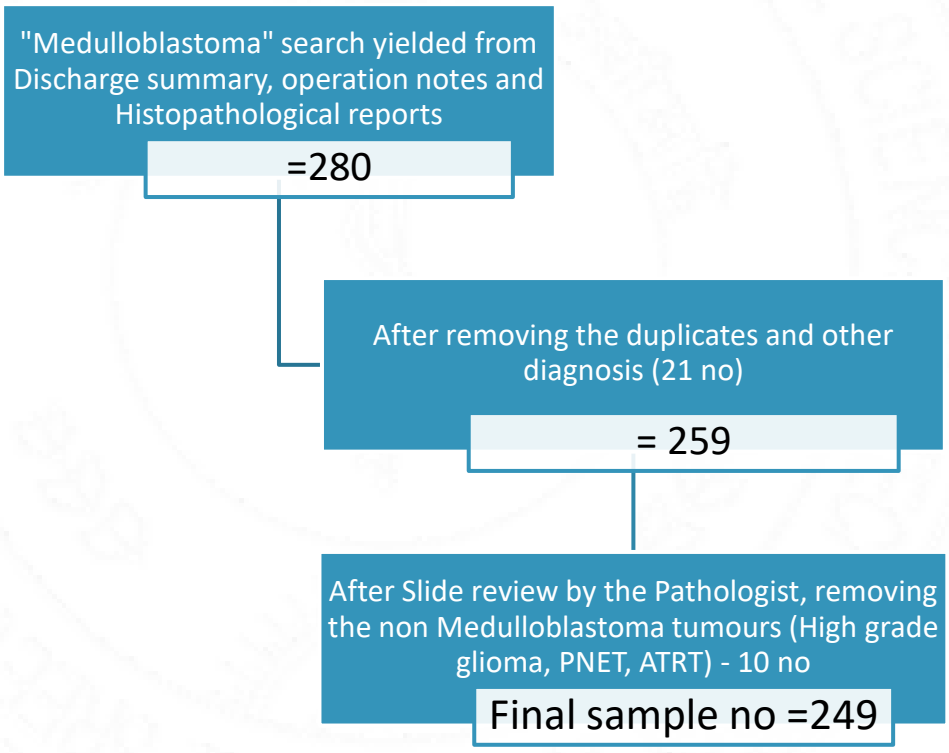
Inclusion criteria:

All patients operated in SCTIMST from 2005 to 2020 for Medulloblastoma as confirmed by histopathological report.

Exclusion criteria:

1. Inoperable cases especially those with extensive metastasis along the neuraxis.
2. Posterior fossa lesions where slide review altered the initial diagnosis of medulloblastoma
3. Patients in whom adequate imaging, histopathological or follow up data were not available.

SAMPLE COLLECTION PROTOCOL :



Data collection:

The demographic data, clinical presentation details were collected from the computer records and database. Surgical details about the CSF diversion procedures,

tumour surgery were collected from the operation records. Post op complications, adjuvant therapy, long term sequelae, Disease recurrence were collected from the OPD, Admission and Medical records. Patients contact number were collected from the records. Patients were contacted through the Institute Telephone and enquired about the disease status as per pre-planned questionnaire. Some missing details in data collection about the current health status, functional score, long term health issues were recorded as reported by the caregiver. Those patients who were reachable by phone but lost to follow up after surgery for OPD visits, not on regular follow up, not evaluated for any current health issues, unaddressed endocrine issues were advised to visit OPD for regular follow up, health educated about the importance of follow up. Care givers were advised to consult, concerned Specialist as per need according to the health issues.

Histopathological Slide review:

The Histopathological slides of proven Medulloblastoma patients were retrieved from the archives of Pathology Department in the time duration from 2005 to 2020. Two experienced Pathologists reviewed the slides independently and confirmed the diagnosis of Medulloblastoma. Any doubtful cases or features suggestive of other tumours were excluded from the study group.

Immuno histo-chemistry Analysis(IHC):

IHC testing for molecular subtyping was started only recently in the Department of Pathology and the molecular subtypes were available for only 26 cases included in this study.

Immunohistochemistry was performed using the standard protocol established in the Department of Pathology. For molecular subtyping, the following primary antibodies were used: Beta-catenin, YAP1, GAB1, Filamin A and p53.

Statistical analysis

- Data was entered using Microsoft Excel (Password protected computer)
- Statistical analysis was done using WHO Epi info / SPSS software
- Descriptive variables were analysed with Mean, Standard deviation and Proportions.
- Qualitative variables were compared using Fisher exact test and quantitative variables using ANOVA. Multiple logistic regression analysis was performed wherever needed.
- Kaplan Meier analysis was used for survival analysis.

Ethics Committee Approval:

This study was approved by the Institutional Ethics Committee of Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum(IEC No:1800, Year- 2022)

RESULTS

A. Demography

A total of 249 patients were taken for the analysis after the Inclusion criteria. The Mean age of incidence of Medulloblastoma was 10.9 years (Median – 8 years, Mode – 5 years). The majority of population was between 3 to 12 years. The minimum age in this study was 45 days infant, maximum age is 55 years.

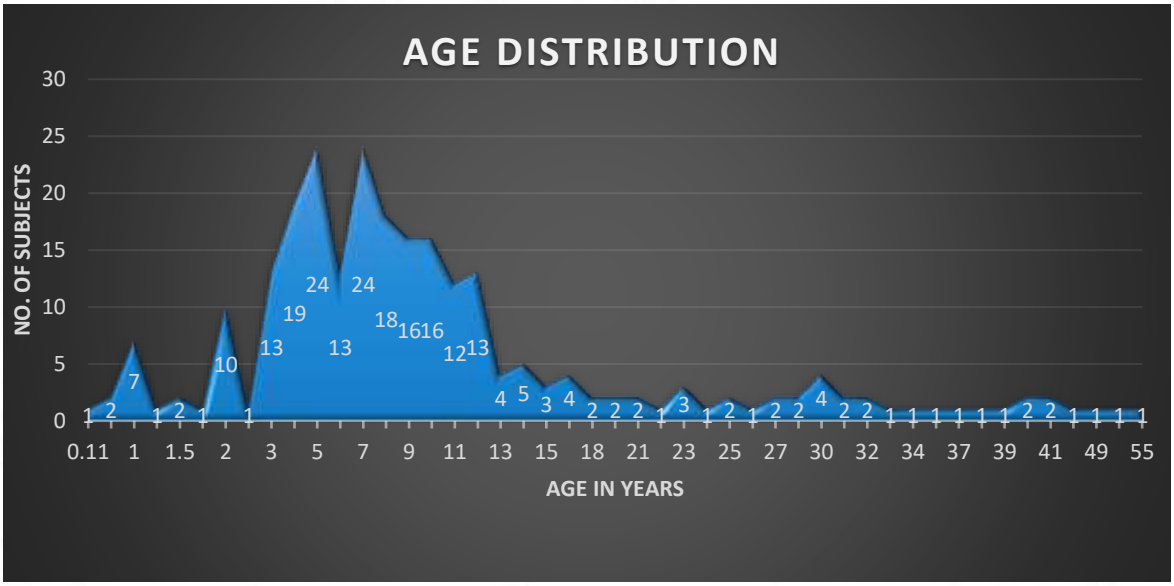


Figure 1: Distribution across different age groups

The Sex distribution was almost equally distributed with slight higher incidence in male population. The incidence of Medulloblastoma with extensive nodularity subtype was more prevalent in the males(9, 6.7%) than females(2, 1.7%) shown in **Table 1**

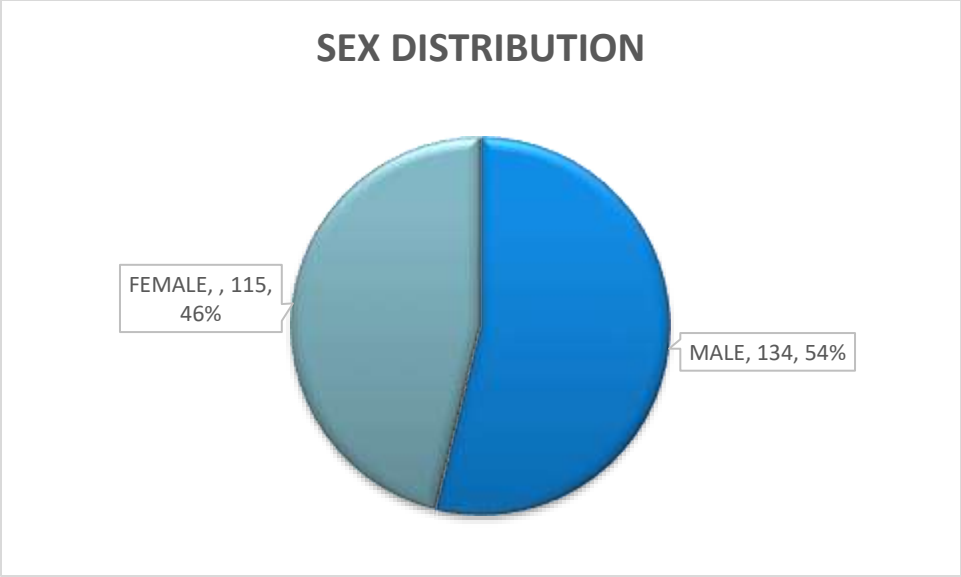


Figure 2 : Distribution of SEX

In our study, Morphological types were distributed as follows, Classic type was the majority consists of 194 (78%), followed by the Desmoplastic nodular (35, 14%), then followed by the Extensive nodularity type(11, 5%). Large cell/Anaplastic type was noted only in 8 patients(3%)

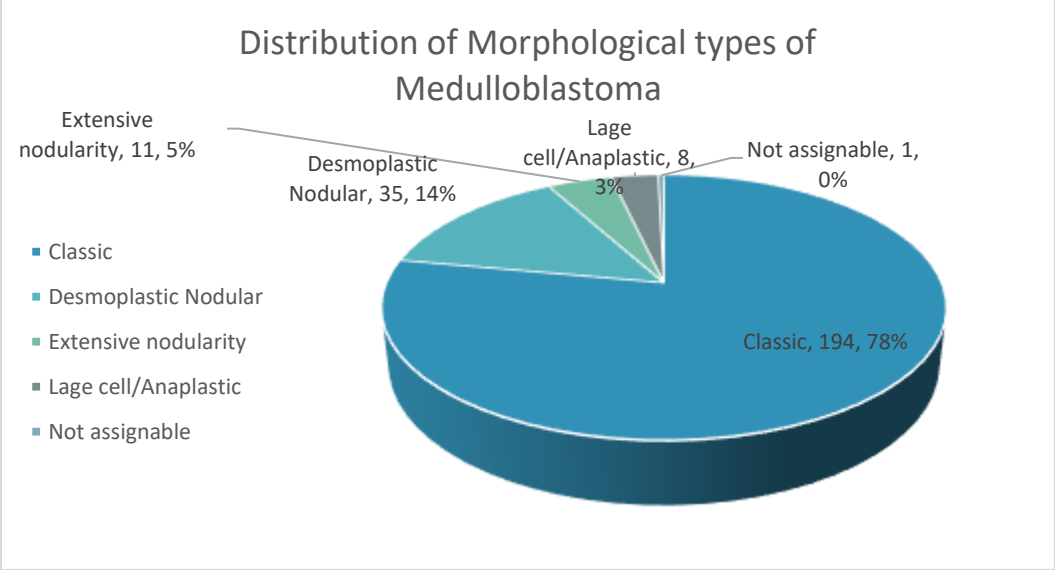


Fig 3 : Distribution of Morphological types of Medulloblastoma in Histopathology

Table 1 : Distribution of age and sex across the Morphological types of MB

Parameter	Classic (194, 77.9%)	Desmoplastic Nodular (35, 14.1%)	Extensive nodularity (11, 4.4%)	Large cell, Anaplastic (8, 3.2%)
Age	8 (5-11)	12 (7-28)	2 (1.7 - 9)	4.5 (3.2 – 13.2)
Sex – Male	103 (76.9%)	18 (13.4%)	9 (6.7%)	4 (3%) P=0.308
Sex - Female	91 (79.1%)	17 (14.8%)	2 (1.7%)	4 (3.5%)

B. Clinical Symptomatology:

The most common presenting symptom being the Increased ICP in the form of headache and vomiting, which was seen in 233 (93.6%) patients, followed by Gait disturbance (153, 61.4%), Cerebellar symptoms (50, 20.1%), Double vision (50, 20.1%). Seizures were noted in 14 (5.6%) patients. Other rare primary clinical presentations were developmental delay, milestone regression, facial deviation, motor power symptoms, cognitive disturbances, speech disturbances, lower cranial nerve palsy symptoms.

Table 2: Frequency of Clinical presentation of patients at the time of admission

Clinical symptoms	**Total no of patients (249)**	**In Percentage**
Increased ICP	233	93.6
Cerebellar symptoms	50	20.1
Eye – Diplopia	50	20.1
Eye – Nystagmus	14	5.6
Visual blurring :	23	9.2
Gait disturbances :	153	61.4
Facial deviation :	5	2.0
Lower cranial nerve symptoms:	5	2.0
Motor symptoms :	8	3.2
Speech :	7	2.8
Developmental delay	2	0.8
Cognition :	5	2.0
Milestones regression :	6	2.4
Seizures :	14	5.6
Hydrocephalic attack	6	2.4
Loss of appetite/weight : :	18	7.2
Spine related pain :	12	4.8

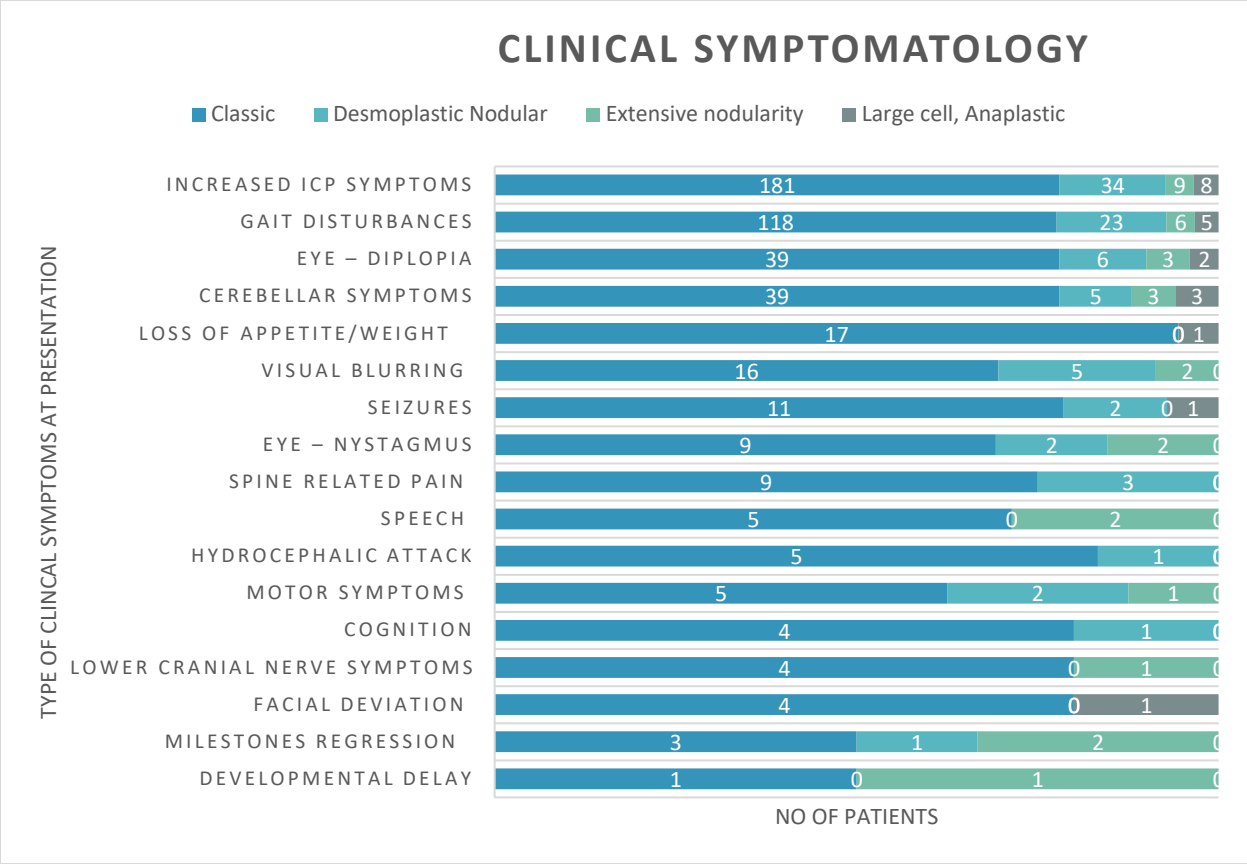


Figure 4: Distribution of Clinical symptoms across the Morphological types of MB

Table 3: Signs and clinical examination findings at admission

Signs/Deficits observed during Clinical Examination		No of patients	In Percentage
General condition at the time of admission	Stable	227	91.2%
	Unstable	22	8.8%
Motor deficit		6	2.4%
Sensory deficit		1	0.4%
Cerebellar signs		120	48.2%
LCN – Lower cranial palsy		7	2.8%
Facial palsy		15	6.0%
Extraocular movement palsy :		55	22.1%
Nystagmus		83	33.3%
Fundus - Papilledema		140	56.2%
Gait		132	53.0%
Neuropsychology changes		2	0.8%
Hearing loss :		5	2.0%

In this study (Table 3), 22 patients(8.8%) were presented in unstable state in the form of Bradycardia, decreased sensorium, sudden worsening which needed emergency CSF diversion in the form of shunt or external ventricular drainage(EVD). Papilledema noted in 140 (56.2%) patients, gait disturbances and cerebellar signs were seen in 132(53%) and 120 (48.2%) patients respectively. There was no correlation between the Morphological types and clinical presentation (as shown in Fig 4), the predominant clinical presentation in all morphological type is Increased ICP, Gait disturbances, diplopia and cerebellar symptoms.

Table 4: Details of outside Treatment

Outside surgery before admission	No of patients	Percentage
Shunt operation	23	9.2%
ETV operation	1	0.4%
Tumour surgery	13	5.2%

Table 5 :Comparing the Clinical symptomatology profile with Duration of symptoms

Clinical symptom	**Median (25^{th}-75^{th} percentile) in weeks**	**P value(MW test)**
Increased ICP	8 (4 - 12)	0.426
Cerebellar symptoms	8 (2 - 15)	0.509
Eye – Diplopia	8 (4 - 20)	0.468
Eye – Nystagmus	20 (7 - 40)	
Visual blurring/Papilledema	8 (4 - 12)	0.353
Gait disturbances	8 (4 – 15.25)	0.089
Facial deviation	20 (7 - 40)	-
Lower cranial nerve symptoms	22 (11.7 – 62.2)	-

Patients with increased ICP, cerebellar symptoms, diplopia and papilledema were presented early (8 weeks) than the patients with Facial nerve palsy, lower cranial palsy and Nystagmus (20 weeks).

C. Imaging characteristics:

The average size of the lesion in this study was 4.28 cm (median – 4.2 cm, Mode – 5.0 cm, SD – 0.93 cm). The most common location of the tumour in posterior fossa was Vermis (148, 59.4% - Table 6), followed by the fourth ventricle(53, 21.3%) and cerebellar hemisphere(48, 19.3%). Epicentre of the tumour was corelated in relation to the floor of the fourth ventricle, most of the tumours were in mid(73, 46%) and lower part(61, 38.6%) of fourth ventricle. In T2 sequence, most of the tumours were hyperintense (118, 65.9%), desmoplastic type has more Isointense type of lesions(9, 27%), lesions with hypointense were very rare(2, 1.1%). In T1 sequence, most of the tumours were hypointense(141, 81.5%) and hyperintense was not seen. Most of the tumours show diffusion restriction(129, 97.7%) and predominant contrast enhancement pattern being heterogenous(126, 56.8%) followed by homogenous(62, 27.9%). Hydrocephalus was noted in 208(88.1%)

Table 6: Comparing Imaging characteristics with the Morphological types of MB

Parameter (Data available for analysis)		**Total no**	**In %**	**Classic (194, 77.9%)**	**DN (35, 14.1%)**	**MBEN (11, 4.4%)**	**LC/A (8, 3.2%)**	**P value**
Location/ Probable origin	Vermis	148	59.4	124(83.2%)	15(10.1%)	6 (4%)	3 (2%)	0.126
	Cerebellar hemisphere	48	19.3	26 (54.2%)	16 (33.3%)	4 (8.3%)	2 (4.2%)	
	Fourth ventricle	53	21.3	47 (87%)	4 (7.4%)	1 (1.9%)	2 (3.7%)	0.372
Tumour Epicentre in relation to the floor of fourth ventricle (158)	Upper	24	15.2	15 (62.5%)	7 (29.2%)	1 (4.2%)	1 (4.2%)	0.198
	Middle	73	46.2	55 (75.3%)	8 (11%)	6 (8.2%)	3 (4.1%)	
	Lower	61	38.6	52 (85.2%)	6 (9.8%)	3 (4.9%)	0 (0%)	
T2 (179)	Hyper	118	65.9	96 (81.4%)	12 (10.2%)	5 (4.2%)	4 (3.4%)	**0.028**
	Isointense	33	18.4	22 (66.7%)	9 (27.3%)	1 (3%)	1 (3%)	
	Hypointense	2	1.1	1 (50%)	0	0	1 (50%)	
	Hetero	26	14.5	18 (69.2%)	6 (23.1%)	2 (7.7%)	0	
T1 (173)	Hyperinten	0	0	0	0	0	0	
	Isointense	27	15.6	16 (59.3%)	6 (22.2%)	2 (7.4%)	3(11.1%)	0.382
	Hypointense	141	81.5	111(78.7%)	20 (14.2%)	6 (4.3%)	3 (2.1%)	
	Heterointen	5	2.9	4 (80%)	1 (20%)	0	0	

Parameter (Data available for analysis)		**Total no**	**In %**	**Classic (194, 77.9%)**	**DN (35, 14.1%)**	**MBEN (11, 4.4%)**	**LC/A (8, 3.2%)**	**P value**
DWI (132)	Present	129	97.7	99 (76.7%)	17 (13.2%)	9 (7%)	3 (2.3%)	**0.041**
	Absent	3	2.3	2 (66.7%)	0	0	1(33.3%)	
Contrast enhancement (222)	Absent	2	0.9	0	1 (50%)	1 (50%)	0	0.130
	Homogenous	62	27.9	49 (79%)	10 (16.1%)	2 (3.2%)	1 (1.6%)	
	Heterogenous	126	56.8	99 (78.6%)	16 (12.7%)	7 (5.6%)	3 (2.4%)	
	Patchy–mild	32	14.4	25 (78.1%)	5 (15.6%)	0	2 (6.3%)	
Tonsillar herniation(192)	Present	118	61.4	83 (70.3%)	23 (19.5%)	8 (6.8%)	3 (2.5%)	0.106
	Absent	74	38.5	63 (85.1%)	6 (8.1%)	2 (2.7%)	3 (4.1%)	
Planes with cerebellum(126)	Absent	75	59.5	53 (70.7%)	15 (20%)	3 (4%)	3 (4%)	0.295
	Present	51	40.5	40 (78.4%)	5 (9.8%)	5 (9.8%	1 (2%)	
Planes with 4th ventricle (138)	Absent	46	33.3	38 (82.6%)	2 (4.3%)	3 (6.5%)	3 (6.5%)	0.068
	Present	92	66.7	63 (68.5%)	20 (21.7%)	6 (6.5%)	2 (2.2%)	
Tumour borders (193)	Well defined	64	33.2	50 (78.1%)	10 (15.6%)	4 (6.3%)	0	0.628
	Lobulated	74	38.3	60 (81.1%)	8 (10.8%)	3 (4.1%)	2 (2.7%)	
	Irregular	55	28.5	41 (74.5%)	8 (14.5%)	3 (5.5%)	3 (5.5%)	
Hydrocephalus (236)	Present	208	88.1	161(77.4%)	29 (13.9%)	10(4.8%)	7 (3.4%)	0.994
	Absent	28	11.9	22 (78.6%)	4 (14.3%)	1 (3.6%)	1 (3.6%)	
Location inside posterior possa (195)	Intra-axial	13	6.67	6 (46.2%)	7 (53.8%)	0	0	<0.001
	Surfacing at 4th ventricle	155	79.5	133(85.8%)	10 (6.5%)	8 (5.2%)	3 (1.9%)	
	Surfacing at cerebellum	27	13.9	14 (51.9%)	9 (33.3%)	3(11.1%)	1 (3.7%)	
Foramen extension in Imaging(200)	No extension	109	54.5	78 (71.6%)	22 (20.2%)	6 (5.5%)	3 (2.8%)	0.145
	To Lushka	41	20.5	36 (87.8%)	4 (9.8%)	1 (2.4%)	0	
	To Magendie	17	8.5	14 (82.4%)	1 (5.9%)	2(11.8%)	0	
	Lushka and Magendie	24	12.0	18 (75%)	2 (8.3%)	1 (4.2%)	2 (8.3%)	
	CP angle cistern	9	4.5	8 (88.9%)	0	1(11.1%)	0	
Cystic areas (210)	Present	135	64.3	105 (77.8%)	18 (13.3%)	8 (5.9%)	3 (2.2%)	0.854
	Absent	75	35.7	59 (78.7%)	12 (16%)	3 (4%)	1 (1.3%)	
Volume of posterior fossa occupied (174)	<1/3	30	17.2	27 (90%)	2 (6.7%)	1 (3.3%)	0	0.168
	1/3-2/3	93	53.4	74 (79.6%)	14 (15.1%)	3 (3.2%)	2 (2.2%)	
	>2/3	51	29.3	33 (64.7%)	9 (17.6%)	6(11.8%)	2 (3.9%)	
Multiple lesions in MRI (194)	Present	14	7.2	12 (85.7%)	2 (14.3%)	0	0	0.852
	Absent	180	92.8	141(78.3%)	23 (12.8%)	10(5.6%)	5 (2.8%)	
Spinal lesions (75)	Nil	59	78.7	48 (81.4%)	7 (11.9%)	2 (3.4%)	2 (3.4%)	0.989
	Cervical	3	4.0	3 (100%)	0	0	0	
	Thoracic	0	0	0	0	0	0	
	Lumbar	2	2.7	2 (100%)	0	0	0	
	Sacral	7	9.3	7 (100%)	0	0	0	
	Multilevel	4	5.3	3 (75%)	1 (25%)	0	0	
Metastasis in MRI(83)	Present	18	21.7	17 (94.4%)	1 (5.6%)	0	0	*
	absent	65	78.3	52 (80%)	8 (12.3%)	2 (3.1%)	2 (3.1%)	
CT imaging (174)	Hyperdense	148	85.1	113(76.4%)	20 (13.5%)	8 (5.4%)	6 (4.1%)	*
	Hypodense	4	2.3	3 (75%)	1 (25%)	0	0	
	Mixed density	22	12.6	17 (77.3%)	3 (13.6%)	2 (9.1%)	0	
Calcifications in CT (178)		29	16.3%	27 (93.1%)	1 (3.4%)	0	1 (3.4%)	*

The predominant T2 hyperintensity was noted in Classic type (96, 81.4%), Isointense (9, 27.3%) and Heterointense(6, 23.1%) lesions were noted more in Desmoplastic nodular type. Multiple lesions along with the primary tumour was seen in 14 (7.2%) patients (Suprasellar region – 3, pituitary stalk – 1, other lesions were in Infratentorial region). Metastasis was noted in 18(21%) of 83 patients data available including the Spinal cord involvement(16 patients). In CT scan, 85% of the lesions were hyperdense and specks of calcifications noted in 29(16.3%) of patients.

Comparing the Imaging characteristics with the Clinical deficits (Table 7):

When corelating the Imaging characteristics with the clinical deficits, the location of the tumour did not have any correlation with the clinical signs except for the lesions in cerebellar hemisphere has more cerebellar signs(31 (64.6%) with P=0.011) and gait disturbances(37, 77.1% with P=0.013). The patients with tonsillar herniation in the MRI had more cerebellar signs(72, 61%, P=0.010) and gait disturbances (82, 69.5%, P=0.012). The other parameters like planes with cerebellum and tumour borders did not have statistically significant association. Tumour extending into foramen of lushka has more facial palsy noted (6, 14.6%) than magendie or both. EOM palsy and Gait disturbances were noted more with foraminal extensions than without extension although there was no statistical significant difference (P=0.304). As the volume of the tumour increased in proportion to cerebellum (Defined by the ratio of the amount of tumour volume occupied in comparison with the total cerebellar tissue volume), there was increase in cerebellar signs(P=0.026), EOM palsy(P=0.754) and Gait disturbances(P=0.011).

Table 7: Comparing the Imaging characteristics with the Clinical deficits

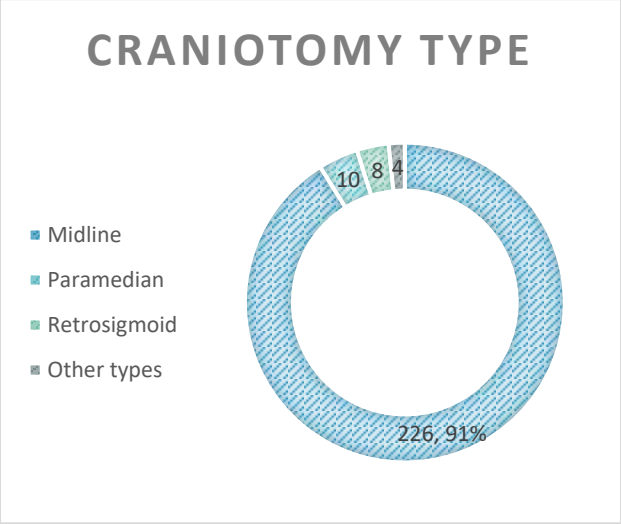
Imaging parameter		Total no	General condition		Motor	Cerebellar signs	Lower cranial palsy	Facial palsy	Extra ocular palsy	Gait
			STABLE	UNSTABLE						
Location/ probable origin	Vermis	148	138(92.6%)	11 (7.4%) P=0.312	4(2.7%)	72 (48.3%) P=0.896	4 (2.7%)	9(6%) P=0.995	33 (22.1%) P=0.861	89 (59.7%) P=0.536
	Cerebellar hemisphere	48	40 (83.3%)	8(16.7%) P=0.046	0.0%	31 (64.6%) P=0.011	3 (6.3%) P=0.133	3 (6.3%) P = 1.000	8 (16.7%) P=0.314	37 (77.1%) P=0.013
	Fourth ventricle	53	49 (90.7%)	5 (9.3%) P=1.000	2 (3.7%)	20 (37%) P=0.064	0 (0%) P=0.352	3 (5.6%) P=1.000	15 (27.8%) P=0.255	28 (51.9%) P=0.102
Tumour Epicentre in relation to the floor of fourth ventricle (158)	Upper	24	21 (87.5%)	3 (12.5%)	0.0%	14 58.3%	2 8.3%	2 8.3%	1 (4.2%)	17 (70.8%)
	Middle	73	65 (89.0%)	8 (11.0%)	2 (2.7%)	38 52.1%	2 2.7%	5 6.8%	14 (19.2%)	43 (58.9%)
	Lower	61	57 (93.4%)	4 (6.6%) P=0.592	3 (4.9%)	37 60.7% P=0.593	1 1.6%	4 6.6%	17 (27.9%) P=0.048	43 (70.5%) P=0.307
Tonsillar herniation (192)	Present	118	110 (93.2%)	8 (6.8%) P=0.201	3 (2.5%)	72 (61%)	4 (3.4%)	7 (5.9%)	24 (20.3%)	82 (69.5%)
	Absent	74	65 (87.8%)	9 (12.2%)	2 (2.7%)	31 (41.9%) P=0.010	1 (1.4%)	6 (8.1%) P=0.559	17 (23%) P=0.665	38 (51.4%) P=0.012
Planes with cerebellum(126)	Absent	75	66 (88%)	9 (12%)	1 (1.3%)	46 (61.3%)	2 (2.7%)	3 (4.0%)	7 (9.3%)	51 (68%)
	Present	51	47 (92.2%)	4 (7.8%) P=0.451	2 (3.9%)	28 (54.9%) P=0.472	3 (5.9%)	6 (11.8%) P=0.156	11 (21.6%) P=0.054	32 (62.7%) P=0.541

Imaging parameter		Total no	General condition		Motor	Cerebellar signs	Lower cranial palsy	Facial palsy	Extra ocular palsy	Gait
			STABLE	UNSTABLE						
Tumour borders (193)	Well defined	64	58 (90.6%)	6 (9.4%)	1 (1.6%)	27 (42.2%)	3 (4.7%)	4 (6.3%)	14 (21.9%)	35 (54.7%)
	Lobulated	74	69 (93.2%)	5 (6.8%)	1 (1.4%)	36 (48.6%)	2 (2.7%)	3 (4.1%)	11 (14.9%)	52 (70.3%)
	Irregular	55	47 (85.5%)	8 (14.5%) P=0.336	3 (5.5%)	32 (58.2%) P=0.218	1 (1.8%)	5 (9.1%)	14 (25.5%) P=0.307	33 (60%) P=0.157
Foramen extension in Imaging(200)	No extension	109	98 (89.9%)	11 (10.1%)	4 (3.7%)	50 (45.9%)	2 (1.8%)	5 (4.6%)	18 (16.5%)	61 (56%)
	To Lushka	41	38 (92.7%)	3 (7.3%)	2 (4.9%)	21 (51.2%)	1 (2.4%)	6 (14.6%)	10 (24.4%)	30 (73.2%)
	To Magendie	17	16 (94.1%)	1 (5.9%)	0.0%	12 (70.6%)	2 (11.8%)	0.0%	3 (17.6%)	10 (58.8%)
	Lushka and Magendie	24	24 (100%)	0.0%	0.0%	12 (50%)	0.0%	1 (4.2%)	7 (29.2%)	17 (70.8%)
	CP angle cistern	9	8 (88.9%)	1 (11.1%)	0.0%	6 (66.7%)	0.0%	0.0%	1 (11.1%)	5 (55.6%) P=0.304
Volume of posterior fossa occupied (174)	<1/3	30	29 (96.7%)	1 (3.3%)	2 (6.7%)	10 (33.3%)	0.0%	2 (6.7%)	6 (20%)	13 (43.3%)
	1/3-2/3	93	81 (87.1%)	12 (12.9%)	2 (2.2%)	57 (61.3%)	4 (4.3%)	6 (6.5%)	17 (18.3%)	58 (62.4%)
	>2/3	51	47 (92.2%)	4 (7.8%) P=0.264	1 (2%)	26 (51%) P=0.026	1 (2%)	3 (5.9%) P=0.987	12 (23.5%) P=0.754	39 (76.5%) P=0.011

D. SURGICAL CHARACTERISTICS:

Table 8: Effect of Surgical approaches, intraop tumour characteristics on the extent of tumour resection

Intraop surgical parameters		Total No	Gross total resection	Near total resection	Sub total resection	Biopsy	P value
Surgery type (248)	Midline	226	145, 64.4%	66, 29.3%	14, 6.2%	0.0%	
	Paramedian	10	7, 70.0%	1, 10.0%	2, 20.0%	0.0%	
	Retrosigmoid	8	6, 75.0%	2, 25.0%	0.0%	0.0%	
	Other types	4	0.0%	2, 50.0%	1, 25.0%	1, 25.0%	
Approach of surgery: (241)	Telovelar	104	62 (60.2%)	35 (34.0%)	6 (5.8%)	0	0.490
	vermian	43	29 (67.4%)	11 (25.6%)	3 (7.0%)	0	
	Others	68	46 (67.6%)	18 (26.5%)	4 (5.9%)	0	
	cortisectomy	24	18 (75.0%)	3 (12.5%)	3 (12.5%)	0	
	Supracerebellar	2	1 (50.0%)	1 (50.0%)	0.0%	0	
Plane with brainstem (230)	Good planes	118	97 (82.2%)	16 (13.6%)	5 (4.2%)	0.0%	**<0.0001**
	Poor planes	112	49 (43.8%)	53 (47.3%)	14 (8.0%)	1 (0.9%)	
Plane with Cerebellum (208)	Good planes	67	46 (68.7%)	18 (26.9%)	2 (3.0%)	1 (1.5%)	0.315
	Poor planes	141	89 (63.6%)	41 (29.3%)	10 (7.1%)	0.0%	
Infiltration into surroundings(202)	Present	130	57 (80.3%)	9 (12.7%)	5 (7.0%)	0.0%	**<0.0001**
	Absent	72	63 (48.5%)	56 (43.1%)	10 (7.7%)	1(0.8%)	
Consistency of the tumour(238)	Soft		97 (65.5%)	41 (27.7%)	10 (6.8%)	0.0%	**0.012**
	Firm	149	51 (62.2%)	27 (32.9%)	4 (4.9%)	0.0%	
	Hard	82	1 (14.3%)	3 (42.9%)	3 (42.9%)	0.0%	
Vascularity of the tumour (226)	Mild	8	4 (50.0%)	2 (25.0%)	2 (25.0%)	0.0%	0.212
	Moderate	136	90 (66.2%)	40 (29.4%)	6 (4.4%)	0.0%	
	High	82	52 (64.2%)	22 (27.2%)	7 (8.6%)	0.0%	
Intraop Extension to foramen (219)	No extension	124	83 (66.9%)	36 (29.0%)	5 (4.0%)	0.0%	0.160
	To Lushka	24	13 (56.5%)	7 (30.4%)	3 (13.0%)	0.0%	
	To Magendie	43	30 (69.8%)	10 (23.3%)	3 (7.0%)	0.0%	
	Lushka and Magendie	19	10 (52.6%)	7 (36.8%)	2 (10.5%)	0.0%	
	CP angle cistern	9	3 (33.3%)	4 (44.4%)	2 (22.2%)	0.0%	



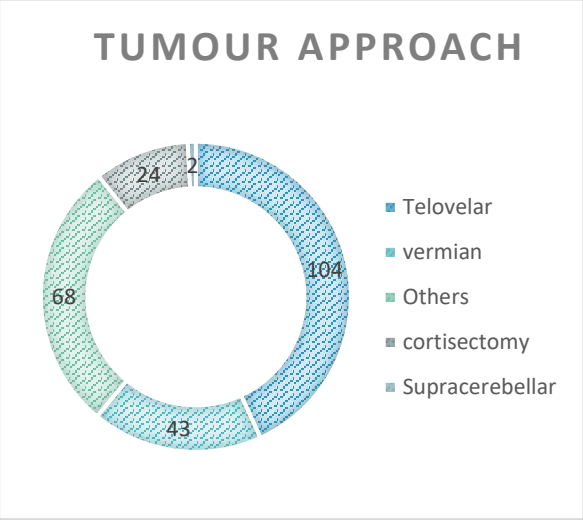


Fig 5a: Type of Craniotomy done for resection **Fig 5b : Types of approach for tumour resection**

In the above (Table 8), the various surgical parameters were compared with the Extent of tumour resection. The majority of the tumours were operated by the MLSO (Midline suboccipital – 226) craniotomy, followed by the paramedian(10), Retromastoid craniotomy(8) for lateral origin tumours in the posterior fossa. Other rare craniotomies were Krauss (Supracerebellar infratentorial) craniotomy- 1, Modified Poppen approach – 2, ETV and biopsy – 1).

Among the various approaches to reach the tumour after craniotomy, the most common were Telovelar tonsillar approach done in 104 patients, transvermian in 43, transcortical in 24, supracerebellar in 2 patients. In the rest of the tumours(68) the anatomy was distorted and the tumour was surfacing through the foramen/fissures from where the tumour decompression was commenced.

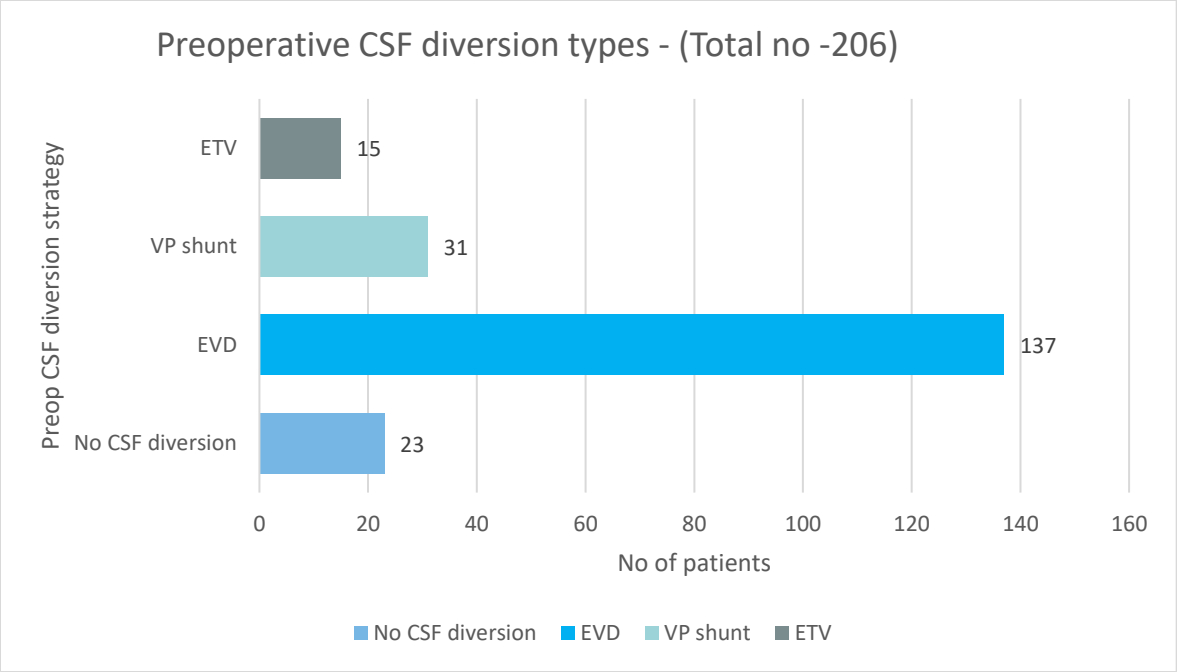


Figure 6: Types of CSF drainage strategies – preoperatively

The predominant CSF drainage strategy followed in this study was temporary EVD placement intraoperatively. The EVD was kept block post operatively, opened whenever there is clinical deterioration or continuous Increased ICP. The average days of EVD stay was 3 days. If the patient was EVD dependent (manifested in the form of deterioration in clinical status on blocking EVD and reversible on draining CSF), they subsequently undergo definitive CSF diversion procedure (VP shunt or ETV – Endoscopic third ventriculostomy)

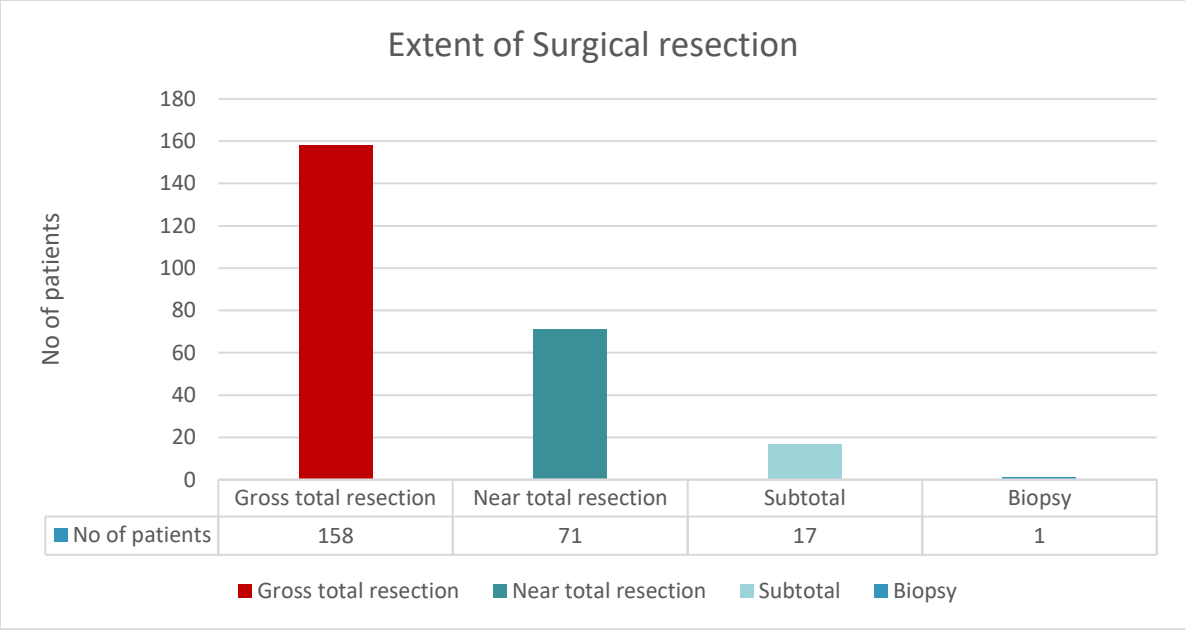


Figure 7: Extent of surgical excision

The patients who underwent gross total decompression had good planes with brainstem(97, 82%, P<0.0001) and had less infiltration into the surroundings(57, 80.3%, P<0.0001). Tumours with soft and firm consistency underwent more of Gross total/Near total decompression than patients with hard tumours who underwent less Gross total, more of subtotal decompression with P<0.0001(Table 8). The vascularity of the tumours, planes with cerebellum, extension into the foramen did not seem to affect the extent of resection.

Table 9: Comparing the different Morphological types with the Intraoperative Surgical parameters

Variable of Interest		No(%)	Classic (194,77.9%)	DN (35,4.1%)	MBEN (11,4.4%)	LC/A (8, 3.2%)	P
Perioperative shunt/EVD requirement shunt (206)	No CSF diversion	23 (11.16%)	18 (78.3%)	3 (13%)	2 (8.7%)	0	*0.958
	EVD	137 (66.50%)	107 (78.1%)	17(12.4%)	7 (5.1%)	5 (3.6%)	
	VP shunt	31 (15.04%)	25 (80.6%)	4 (12.9%)	1 (3.2%)	1 (3.2%)	
	ETV	15 (7.28%)	10 (6.3%)	4 (26.7%)	1 (6.7%)	0	
Surgery type (248)	Midline	226 (91.1%)	180 (79.6%)	26(11.5%)	11 (4.9%)	8 (3.5%)	0.062*
	Paramedian	10 (4.0%)	7 (70%)	3 (30%)	0	0	
	Retrosigmoid	8 (3.2%)	3 (37.5%)	**5 (62.5%)**	0	0	
	Other types	4 (1.6%)	3 (75%)	1 (25%)	0	0	

Variable of Interest		No(%)	Classic (194,77.9%)	DN (35,4.1%)	MBEN (11,4.4%)	LC/A (8, 3.2%)	P
Approach of surgery: (241)	Telovelar	104 (43.2%)	89 (85.6%)	7 (6.7%)	4 (3.8%)	3 (2.9%)	0.128*
	Transvermian	43(17.8%)	36 (83.7%)	4 (9.3%)	3 (7%)	0	
	Others(surfacing)	68(28.2%)	46 (67.6%)	15(22.1%)	4 (5.9%)	3 (4.4%)	
	cortisectomy	24(10.0%)	15 (62.5%)	8 (33.3%)	0	1 (4.2%)	
	Supracerebellar	2(0.8%)	2 (100%)	0	0	0	
Extent of resection(247)	Gross total	158(64.0%)	118 (74.7%)	27(17.1%)	8 (5.1%)	4 (2.5%)	0.938
	Near total resection	71(28.7%)	59 (83.1%)	7 (9.9%)	2 (2.8%)	3 (4.2%)	
	Subtotal	17(6.9%)	14 (82.4%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	
	Biopsy	1(0.4%)	1 (100%)	0	0	0	
Plane with brainstem (230)	Good planes	118(51.3%)	87 (73.7%)	24(20.3%)	5 (4.2%)	2 (1.7%)	**0.035***
	Poor planes	112(48.7%)	93 (83%)	8 (7.1%)	5 (4.5%)	5 (4.5%)	
Plane with Cerebellum(208)	Good planes	67(32.2%)	49 (73.1%)	14(20.9%)	4 (6%)	0	0.280*
	Poor planes	141(67.8%)	112 (79.4%)	17(12.1%)	7 (5%)	4 (2.8%)	
Infiltration into tissues (202)	Present	130(64.4%)	105 (80.8%)	16(12.3%)	5 (3.8%)	3 (2.3%)	0.774*
	Absent	72(35.6%)	56 (77.8%)	10(13.9%)	5 (6.9%)	1 (1.4%)	
Consistency of the tumour(238)	Soft	149(62.6)	124 (83.2%)	14 (9.4%)	5 (3.4%)	5 (3.4%)	***0.044**
	Firm	82(34.5)	58 (70.7%)	16(19.5%)	6 (7.3%)	2 (2.4%)	
	Hard	7(2.9)	3 (42.9%)	3 (42.9%)	0	1(12.5%)	
Hemorrhage in tumour	Present	10(4%)	6 (60%)	2 (20%)	2 (20%)	0	0.147*
	Absent	239(96%)	188 (78.7%)	33(13.8%)	9 (3.8%)	8 (3.3%)	
Necrosis present in tumour		20(8%)	18 (90%)	1 (5%)	1 (5%)		
Vascularity of the tumour (226)	Mild	8(3.5%)	5 (62.5%)	3 (37.5%)	0	0	0.635
	Moderate	136(60.17%)	107 (78.7%)	17(12.5%)	7 (5.1%)	5 (3.7%)	
	High	82(36.2%)	62 (75.6%)	12(14.6%)	4 (4.9%)	3 (3.7%)	
Intraop Extension to foramen (219)	No extension	124(56.6)	94 (75.8%)	22(17.7%)	6 (4.8%)	2 (1.6%)	0.171
	To Lushka	24(11.0)	22 (91.7%)	1 (4.2%)	1 (4.2%)	0	
	To Magendie	43(19.6)	35 (81.4%)	6 (14%)	1 (2.3%)	0	
	Lushka and Magendie	19(8.7)	13 (68.4%)	2 (10.5%)	2 (10.5%)	2 (10.5%)	
	CP angle cistern	9(4.1)	8 (88.9%)	0	1 (11.1%)	0	
Intraop Metastasis observed (249)		9 (3.6%)	9 (100%)	0	0	0	0.618*
CSF cytology (34)		8 (23.5%)	5 (62.5%)	2 (25%)	0	1 (12.5%)	

The Retrosigmoid approach was done predominantly in the Desmoplastic variety (5, 62.5%) due to its eccentric location in the cerebellar hemispheres. The majority of the tumours were removed by the Telovelar tonsillar approach (104, 43.2%), followed by the surfacing tumours through fissures and foramen(68, 28.2%), followed by Transvermian (43,17.8%). The good planes with brainstem were noted in 87(73.7%) in classic type, 24 (20.3%) in Desmoplastic type whereas poor planes were noted in 93(83%) of classic type, and only 8(7.1%) in Desmoplastic type with

significant P value 0.035. Other parameters like planes with cerebellum, infiltration in to tissues, hemorrhage, necrosis in tumour, vascularity of the tumour, foraminal extension did not have any statistically significant difference among the Morphological types. The consistency of the tumour was predominantly soft in classic type, but in Desmoplastic and Extensive nodular variety firm and hard consistency were seen dominant with significant P value 0.044. The intraoperative evidence of metastasis(nodular spread in the pia-arachnoid, sugar coating) was observed only in Classic type (9, 100%). **(Table 9)**

E. POST OPERATIVE OUTCOMES:

In this study, after surgery patients had undergone CT scan on the same day or next day, both plain and contrast scan as per institute protocol. In 229 patients, CT scan data was available.

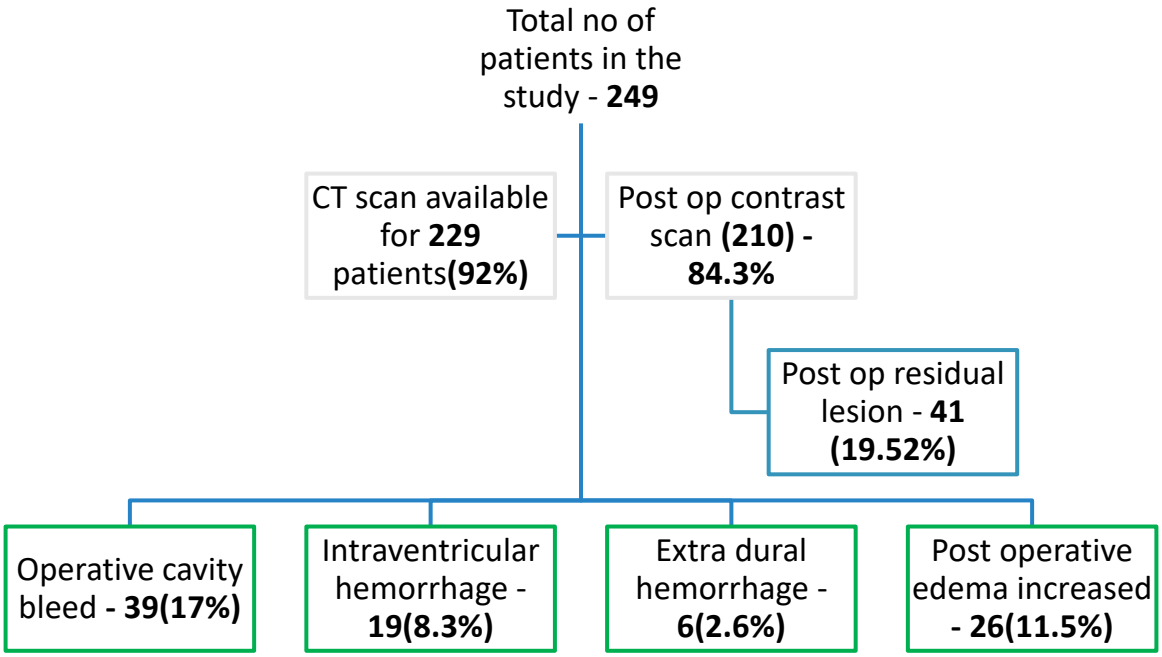


Figure 8 : Post operative CT scan results

Follow up MRI scan:

In this study, on follow up patients got the MRI scan with contrast and any significant residual tumour or relapse of tumour on MRI were detected and followed subsequently.

Table 10: Residual and relapse disease status on follow up MRI scan

Parameter (Data available)		No of patients	In %
Residual lesion (176)		26	14.8%
Relapse on follow up (181)	Present	67	37%
	No relapse	114	63%
On Follow up with Serial MRI - tumour status (115)	No tumour	91	79.1
	Decrease in size	4	3.5
	Stable size	8	7.0
	Progressive size	12	10.4
Relapse site number (53)	Single	23	43.4%
	Multiple	30	56.6%
Relapse disease location in Neuraxis (52)	Supra-tentorial	10	19.2%
	Infratentorial	10	19.2%
	Spinal mets	6	11.5%
	Leptomeningeal spread	26	50.0%
Relapse Site (56)	Same site as previous	18	32.1%
	Different site	38	67.9%
Different site location (23)	Vermis	3	13.0%
	Fourth ventricle	9	39.1%
	Cerebellum	7	30.4%
	Brain stem	4	17.4%
Disseminated disease		38	15.3%
Reason for Expiry (31)	Tumour related	21	8.4%
	Other causes	10	4%

The residual disease observed in this study was 26 (14.8%), the relapse on follow up was noted in 67 patients(37%). Details of the disease relapse were summarized in the above table.

From the data available from 56 patients, the average duration after surgery in years for relapse is **2.2 years** (Median - 1.65 years, Mode-2 years, SD – 2.09 years, Minimum – 1 year, Maximum – 11 years).

The Average duration after adjuvant therapy in years were 1.58 years (Median – 1 year, Mode-1 year, SD – 1.654 years, Minimum – 0 years, Maximum – 6 years). In this study, 21 (8.4%) patients expired on follow up due to tumour related causes, 10 (4%) patients expired due to non-tumour related problems (Infection, RTA, Pneumonia)

Table 11: Comparing Post op Residual lesion detected in MRI and Relapse of tumour on follow up with surgical parameters

Surgical parameters		Residue			Relapse		
		Absent	Present	P value	Absent	Present	P-value
Craniotomy type	Midline	183 (92.9%)	43(84.3%)	*	105 (92.1%)	62(92.5%)	*
	Paramedian	8(4.1%)	2(3.9%)		5 (4.4%)	3 (4.5%)	
	Retrosigmoid	6(3%)	2(3.9%)		4 (3.5%)	1(1.5%)	
	Other types	0	4(7.8%)		0 0.0%	1 (1.5%)	
Approach of surgery	Telovelar	83(43.2%)	21(42.9%)	0.736	45(40.2%)	28(42.4%)	0.994
	Vermian	33(17.2%)	10(20.4%)		21 18.8%	11(16.7%)	
	Others	55(28.6%)	13(26.5%)		33 29.5%	20(30.3%)	
	Cortisectomy	20(10.4%)	4(8.2%)		12(10.7%)	7(10.6%)	
	Supracerebellar	1(0.5%)	1(2%)		1(0.9%)	0(0.0%)	
Extent of resection:	Gross total	143 (73.0%)	15(29.4%)	**<0.0001**	74(65.5%)	46(68.7%)	0.258
	Near total	52(27%)	18(35.3%)		33(29.2%)	14(20.9%)	
	Sub-Total	0	17(6.9%)		6(5.3%)	7(10.4%)	
	Biopsy	0	1(0.4%)		0	0	
Plane with brainstem	Good planes	104(55.9%)	14(31.8%)	**0.004**	55(51.4%)	33(55.0%)	0.655
	Poor planes	82(44.1.%)	30(68.2%)		52(48.6%)	27(45.0%)	
Plane with Cerebellum	Good planes	59(34.9%)	8(20.5%)	0.083			
	Poor planes	110 (65.1%)	31(79.5%)				
Tumour infiltration	Present	98(62.0%)	32(72.7%)	0.190	35(36.8%)	21(40.4%)	0.672
	Absent	60(38.0%)	12(27.3%)		60(63.2%)	31(59.6%)	
Tumour Consistency	Soft	122 (64.2%)	27(56.3%)	0.248	70(63.1%)	37(58.7%)	0.693
	Firm	64 (33.7%)	18 (37.5%)		39(35.1%)	24(38.1%)	
	Hard	4 (2.1%)	3 (6.3%)		2(1.8%)	2(3.2%)	

Surgical parameters		Residue			Relapse		
		Absent	Present		Absent	Present	
Vascularity of the tumour	Mild	6(3.3%)	2(4.7%)	0.403	4(3.7%)	2(3.3%)	0.910
	Moderate	114(62.3%)	22(51.2%)		68(63.6%)	40(66.7%)	
	High	63(34.4%)	19(44.2%)		35(32.7%)	18(30.0%)	
Extension into the foramen noted Intraop	No extension	108(61.0%)	16(38.1%)	**0.003**	53(50.5%)	32(57.1%)	0.750
	To Lushka	19(10.7%)	5(11.9%)		12(11.4%)	8(14.3%)	
	To Magendie	32(18.1%)	11(26.2%)		26(24.8%)	9(16.1%)	
	To Magendie and Lushka	15(8.5%)	4(9.5%)		9(8.6%)	5(8.9%)	
	CP angle cistern	3(1.7%)	6(14.3%)		5(4.8%)	2(3.6%)	
Intraop evidence of Metastasis deposits :	Present	3 (2%)	3 (11.5%)	0.043*	3 (2.6%)	2 (3%)	
	Absent	147 (98%)	23 (88.5%)		111(97.4%)	65 (97%)	
Hemorrhage	Present	6 (4%)	1 (3.8%)		4 (3.5%)	4 (6%)	0.335
	Absent	144 (96%)	25 (96.2%)		110(96.5%)	63 (94%)	

*Numbers not enough to consider the P value as significant

The surgical parameters which determines the presence of post op residual disease were extent of resection(<0.0001), planes with brainstem(0.004) and tumours extension into foramens(0.003). Other parameters like type of craniotomy, surgical approach, planes with brainstem, tumour infiltration status, tumour consistency, vascularity, presence of hemorrhagic areas were not significant for the residual disease as per the study. But, the occurrence of relapse of the tumour on follow up, either during/after the completion of adjuvant chemotherapy or radiotherapy were not determined by any of the surgical parameters as mentioned above **(Table 11)**

Morbidity related to Redo-surgery, CSF diversion procedures:

Table 12: Morbidity of Readmission, Redo surgery for tumour and CSF diversion procedures

Parameter		No of patients	In %
Total no of patients Readmission		55	22.1%
One time admission		43	17.3
Two times admission		10	4.0
Three times admission		1	0.4
Four times admission		1	0.4
Purpose for admission	Conservative	12	21.8%
	Surgery	43	78.2%
No of times Shunt	Not required	165	66.3%
	One time	71	28.5%
	Two times	11	4.4%
	Three times	2	0.8%
No of CSF diversion procedures (ETV and Shunt)	Not needed	155	62.2%
	One time	75	30.1%
	Two times	16	6.4%
	Three times	3	1.2%
CSF Diversion Failure Times (ETV and shunt)	One time	16	6.4%
	Two times	3	1.2%
ETV status (24)	Success	19	79.2%
	Failure	5	20.8%

Parameter		No of patients	In %
CSF diversion requirement Shunt requirement/ETV:	Shunt	81	32.5%
	ETV	18	7.2%
Redo-sx post op (immediate)		16	6.4%
Redo surgery here, operated outside first for tumour		11	4.4%
Redo surgery number(overall):	One time	32	12.9%
	Two times	7	2.8%
	Three times	1	0.4%
No of Redo surgery for tumour:		25	10%
No of Redo surgery for other problems		17	6.8%

In the above **Table 12**, the number of readmission in this study was 55 (22.1%), for various reasons like CSF diversion procedures(Shunt and ETV), Relapse of tumour and Redo surgery, wound complications and for MRI under sedation. In that, 43 patients admitted for surgical intervention(Shunt, Tumour surgery, shunt removal), 12 patients admitted for conservative management. The relapse on follow up was seen in 67/181 (37%) patients, of them 25 patients underwent Redo surgery for tumour, 17 patients underwent redo surgery for other conditions either in immediate post op or on follow up like **posterior fossa decompression, Hematoma**

evacuation, EDH evacuation, Wound debridement for MRSA infection, SDH evacuation, D4-D8 metastasis, Bone flap removal, shunt internalization, Supratentorial metastasis decompression -Right frontal dural, Basifrontal metastasis, dural metastasis, IDEM metastasis. ETV success rate was 79.2%(19 of 24). Success was determined by the successful CSF diversion by the ETV alone not requiring any other shunt at later date.

Table 13: Comparing Different morphological types with the Residual and Relapse disease status and outcomes (Redo surgery, palliative care, Expiry)

Variable of interest (Data available)		**Classic (194, 77.9%)**	**Desmoplastic Nodular (35, 14.1%)**	**Extensive nodularity (11, 4.4%)**	**Large cell, Anaplastic (8, 3.2%)**
Redo surgery for tumour (249)	25 (10%)	23 (92%)	2 (8%)	0	0
Residual lesion(176)	26 (14.8%)	23 (88.5%)	1 (3.8%)	1 (3.8%)	1 (3.8%)
On Follow up with Serial MRI - tumour status (115)	No tumour (91)	71 (78.9%)	13 (86.7%)	5 (71.4%)	1 (50.0%)
	Decrease in size (4)	3 (3.3%)	0.0%	1 (14.3%)	0.0%
	Stable size (8)	5 (5.6%)	2 (13.3%)	1 (14.3%)	0.0%
	Progressive size (12)	11 (12.2%)	0.0%	0.0%	1 (50.0%)
Relapse site number (53)	Single(23)	21 (46.7%)	1 (20%)	0	(4.3%)
	Multiple(30)	24 (53.3%)	4 (13.3%)	1 (3.3%)	1 (3.3%)
Relapse disease location in Neuraxis (52)	Supra-tentorial(10, 19.2%)	10 (22.2%)	0.0%	0.0%	0.0%
	Infratentorial (10, 19.2%)	10 (22.2%)	0.0%	0.0%	0.0%
	Spinal mets (6, 11.5%)	4 (8.9%)	0.0%	1 (100.0%)	1 (50.0%)
	Leptomeningeal spread (26,50%)	21 (46.7%)	4 (100.0%)	0.0%	1 (50.0%)
Relapse Site (56)	Same site as previous (18)	14 (77.8%)	1 (5.6%)	2 (11.1%)	1 (5.6%)
	Different site (38)	34 (89.5%)	3 (7.9%)	0	1 (2.6%)
Different site location (23)	Vermis, (3)	1 (5.6%)	1 (33.3%)	1 (50.0%)	0
	Fourth ventricle,(9)	8 (44.4%)	0.0%	1 (50.0%)	0
	Cerebellum, (7)	7 (38.9%)	0.0%	0.0%	0
	Brain stem,(4)	2 (11.1%)	2 (66.7%	0.0%	0
Disseminated disease (38, 15.3%)		30 (78.9%)	4 (10.5%)	1 (2.6%)	3 (7.9%)
Reason for Expiry (31)	Tumour related (21, 8.4%)	18 (9.3%)	1 (2.9%)	1 (9.1%)	0
	Other causes (10, 4%)	7 (3.6%)	2 (5.7%)	0	1 (12.5%)
Palliative care		39 (83%)	3 (6.4%)	2 (4.3%)	3 (6.4%)

The redo-surgery was done in 25(10%) of patients predominantly in Classic type(23, 92%). The predominant relapse of the disease was noted as Leptomeningeal spread(26, 50%). Relapse at single site was noted in 23 patients, multiple sites were noted in 30 patients (predominantly in classical type – 24(53.3%). The tumour related death was seen predominantly in classic type(18, 9.3%)

Table 14: Correlating Preop CSF CYTOLOGY with Post op Disease dissemination or Relapse of the tumour on follow up

Parameter		**CSF cytology positive**	**CSF cytology negative**
Disseminated disease		3 (42.8%)	4 (57.14%)
Relapse disease location in Neuraxis	Supra-tentorial	1 (25%)	4(57.1%)
	Infratentorial	0	2(28.6%)
	Spinal mets	0	1(14.3%)
	Leptomeningeal spread	3 (75%)	0
Relapse Site	Same site as previous	0	5(62.5%)
	Different site	4(100%)	3(37.5%)
Different site location-	Vermis	1(50.0%)	0.0%
	Fourth ventricle	0.0%	1(50.0%)
	Cerebellum	0.0%	1(50.0%)
	Brain stem	1(50.0%)	0.0%

Preop CSF cytology was done in 34 patients(**Table 14**), as the sensitivity was low, it was not performed regularly in all patients. Because of the small numbers available for analysis, meaningful statistical testing was not possible.

F. RISK STRATIFICATION:

In our study, as per guidelines patients were stratified into two risk groups – Average risk and High risk based on prognostic factors(**Table 15**) like Age < 3, Post operative scan residue > 1.5cm, Preoperative metastasis stage, High risk histopathology (Large cell/Anaplastic type).

Table 15: Prognostic Risk factors compared with the Relapse of the disease

Prognostic risk factor		No Relapse	Relapse	P value
AGE RISK CATEGORY	Less than 3 years	6(35.3%)	11(64.7%)	**0.013**
	More than 3 years	108(65.9%)	56(34.1%)	
Post op residue >1.5 (1- present,0-absent)	>1.5 cm	12(36.4%)	21(63.6%)	**0.000**
	<1.5 cm	102(68.9%)	46(31.1%)	
Pre op metastasis present	Present	17(42.5%)	23(57.5%)	**0.002**
	Absent	97(68.8%	44(31.2%)	
High risk HPR	Present	3(60.0%)	2(40.0%)	*
	Absent	111(63.1%)	65(36.9%)	
RISK stratification	High	30(43.5%)	39(56.5%)	**<0.001**
	Average	84(75.0%)	28(25.0%)	

In this study, all prognostic factors mentioned above shows statistically significant correlation($P<0.05$) with the relapse of the disease except for the High risk HPR histology (due to less number of patients diagnosed as Large cell/Anaplastic histology).

Table 16: Prognostic Risk factors compared among the Morphological types

Prognostic risk factor		Relapse	Classic (194, 7.9%)	DN (35,4.1%)	MBEN (11,4.4%)	LC/A (8, 3.2%)
AGE RISK CATEGORY	Less than 3 years	11(64.7%)	15 (60.0%)	3 (12.0%)	6 (24.0%)	1 (4.0%)
	More than 3years	56(34.1%)	179 (79.9%)	32 (14.3%)	5 (2.2%)	7 (3.1%)
Post op residue	>1.5 cm	21(63.6%)	46 (90.2%)	2 (3.9%)	2 (3.9%)	1 (2.0%)
	<1.5 cm	46(31.1%)	148 (74.7%)	33 (16.7%)	9 (4.5%)	7 (3.5%)
Pre op metastasis	Present	23(57.5%)	46 (85.2%)	5 (9.3%)	1 (1.9%)	2 (3.7%)
	Absent	44(31.2%)	148 (75.9%)	30 (15.4%)	10 (5.1%)	6 (3.1%)
RISK stratification	High	39(56.5%)	77 (76.2%)	9 (8.9%)	6 (5.9%)	8 (7.9%)
	Average	28(25.0%)	117 (79.1%)	26(17.6%)	5 (3.4%)	0.0%

Among the Morphological types, the average risk was predominant in classic type and Desmoplastic type, whereas High risk group was seen more in Extensive nodularity and large-cell/Anaplastic type **(Table 16)**.

G. Molecular subtype classification of Medulloblastoma by Immunohistochemistry:

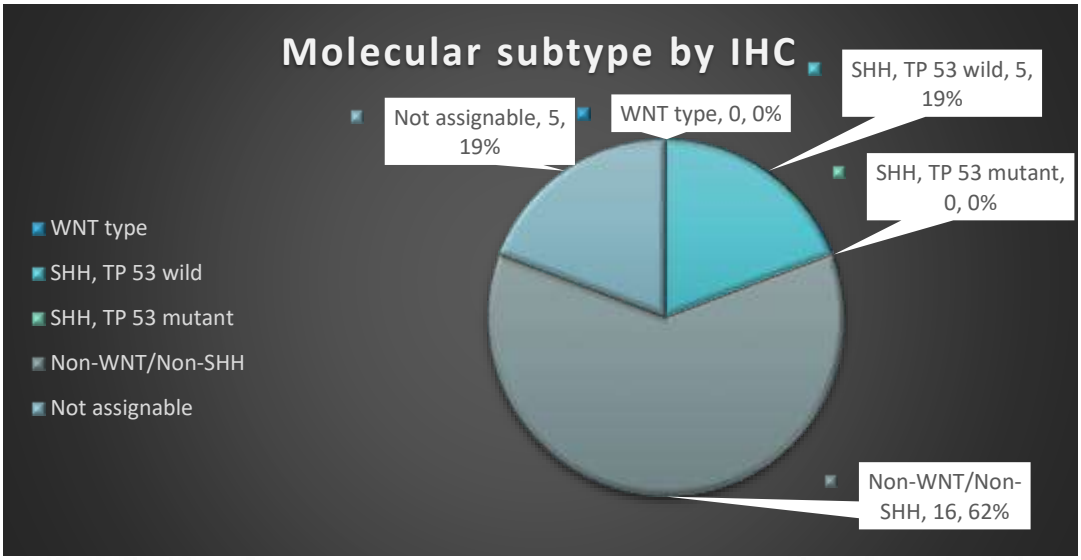


Fig 9: Molecular classification of Medulloblastoma by Immunohistochemistry(IHC)

In this study, molecular subtyping was available only for 26 patients (**Figure 9**). In WHO 2016 classification of CNS tumours, Molecular subtyping was introduced first time in the classification of the Medulloblastoma as separate category. Hence, the molecular subtyping of the tumour tissue by Immunohistochemistry was started since 2020 in our institute after procurement of reagents. In this study group, some molecular types were not yet identified like WNT-activated and SHH-activated and TP53 mutant type. Some tumours could not be assigned to any of the Molecular types by IHC. Those samples required transcriptome/methylation profiling to assign a molecular category which could not be done due to resource constraints and non-availability at our Centre.

Other Histopathological characteristics:

Table 17: Histopathological characteristics

Parameter		No	In %
CSF cytology (34)	Positive	8	23.5%
	Negative	26	76.5%
MIB-1 labelling index range	Minimum	Mean – 39%,SD – 18.3%	
	Maximum	Mean – 47%,SD – 20%	
Infiltration to surrounding structures noted in the Histology		111	44.6%
Infiltration into cerebellum		35	14.1%
Infiltration into choroid plexus		24	9.6%
Infiltration into Leptomeninges		84	33.7%

The tumour cell proliferation was assessed using MIB-1 and the MIB-1 labelling index was calculated. The mean MIB-1 labelling index range was 39-47%. Tumour was showing infiltration into surrounding structures in 111(44.6%). CSF analysis was done in 34 patients and it was positive only in 8(23.5%) patients. **(Table 17)**

Table 18: Comparing Histopathological characteristics among the morphological subtypes

Parameter	No	In %	Classic (194, 7.9%)	DN (35,4.1%)	MBEN (11,4.4%)	LC/A (8, 3.2%)
Infiltration to surrounding structures noted in the Histology	111	44.6%	94 (48.5%)	11(31.4%)	4 (36.4%)	2 (25%)
No infiltration	138	55.4%	100(51.5%)	24(68.6%)	7 (63.6%)	6 (75%)
Infiltration into cerebellum	35	14.1%	30 (15.5%)	2 (5.7%)	2 (18.2%)	1 (12.5%)
Infiltration into choroid plexus	24	9.6%	21 (10.8%)	1 (2.9%)	2 (18.2%)	0
Infiltration into Leptomeningeal infiltration	84	33.7%	71 (36.6%)	8 (22.9%)	4 (36.4%)	1 (12.5%)

On analysing the histopathological characteristics in the different morphological types, infiltration into surrounding strutures were seen more in the classic type(94, 48.5%) than others. Leptomeningeal infiltration(71, 36.6%) was noted predominantly than cerebellar or choroid plexus infiltration in all morphological types(**Table 18**).

H. SURGERY RELATED COMPLICATIONS:

Table 19: Comparing Post operative surgical complications among the Morphological types

Post op complication	No	In %	Classic(194, 7.9%)	DN (35,4.1%)	MBEN (11,4.4%)	LC/A (8, 3.2%)	P value
Tracheostomy	14	5.6%	8(57.1%)	4 (28.6%)	0	2 (14.3%)	0.051*
Cerebellar Mutism	44	17.7%	33 (75%)	8 (18.2%)	1 (2.3%)	2 (4.5%)	0.778
Posterior fossa syndrome	8	3.2%	5(62.5%)	2 (25%)	1 (12.5%)	0	0.649*
EOM abnormality	104	41.8%	84(80.8%)	13(12.5%)	3 (2.9%)	3 (2.9%)	0.575*
Lower cranial nerve palsy	32	12.9%	25 (78.1%)	5 (15.6%)	1 (3.1%)	1 (3.1%)	0.986*
Facial palsy	41	16.5%	**35 (85.4%)**	2 (4.9%)	2 (4.9%)	1 (2.4%)	0.076*
Cerebellar signs	31	12.4%	27 (87.1%)	2 (6.5%)	2 (6.5%)	0	
Ataxia	71	28.5%	56 (78.9%)	6 (8.5%)	4 (5.6%)	4 (5.6%)	*
Motor deficits – Not affected	216	86.7%	171 (79.2%)	27(12.5%)	11 (5.1%)	6 (2.8%)	0.359
paresis	27	10.8%	19 (70.4%)	7 (25.9%)	0	1 (3.7%)	
Plegia	6	2.4%	4 (66.7%)	1 (16.7%)	0	1 (16.7%)	
Gait disturbances	84	33.7%	61 (72.6%)	13(15.5%)	6 (7.1%)	3 (3.6%)	
Cognitive disturbances	12	4.8%	9 (75%)	3 (25%)	0	0	
Behavioural / Psychiatric issues	5	2%	2 (40%)	3 (60%)	0	0	
Seizures	26	10.4%	18 (69.3%)	5 (19.2%)	0	3 (11.5%)	
CSF leak	13	5.2%	7 (53.8%)	2 (15.4%)	2 (15.4%)	2 (15.4%)	
Meningitis	31	12.4%	21 (67.7%)	5 (16.1%)	2 (6.5%)	3 (9.7%)	
Fever	28	11.2%	23 (82.1%)	2 (7.1%)	1 (3.6%)	2 (7.1%)	
Wound infection	12	4.8%	7 (58.3%)	2 (16.7%)	1 (8.3%)	2 (16.7%)	
Pseudomeningocele:	42	16.9%	30 (71.4%)	4 (9.5%)	5 (11.9%)	3 (7.1%)	**0.040**
DVT/CVT	4	1.6%	3 (75%)	0	0	1 (25%)	
Readmission	55	22.1%	44 (80%)	5 (9.1%)	3 (5.5%)	3 (5.5%)	0.585

In this study**(Table 19)**, most of the complications were distributed evenly across the morphological types except few like Pseudomeninigocele which was comparatively higher in MBEN type (5 out of 11, P=0,040). The Most common complication observed in this study was EOM abnormality(104, 41.8%) in the form of severe nystagmus or diplopia due to nerve palsy (CN6). It was followed by gait disturbanes(84, 33.7%) and ataxia(71, 28.5%). Cerebellar mutism was noted in 44 patients(17.7%) with 75% of patients in classic type, 18% in Desmoplastic type. Posterior fossa syndrome was assigned when there was symptom cluster not fitting into mutism

and not explainable by post op scan. Post op seizures noted in (26, 10.4%), meningitis in 31(12.4%), CSF leak in 13(5.2%). Post operative venous thrombosis in the form of DVT was observed in 4 patients(1.6%).

Effect of Intraop surgical parameters on the Post operative complications:

The extent of resection and the approach to the tumour did not have any statistically significant association with the post op cerebellar mutism and other complications. However, the Transvermian approach has slightly higher incidence of cerebellar mutism (10/43, 23.2%) than with the Telovelo-tonsillar approach(19/104, 18%) but it was not statistically significant. The Telovelar approach and transvermian has more incidence of EOM abnormality than other approaches(P=0.018), facial palsy was seen more with the Telovelar approach (1 out of 5 patients) than others. Patients with poor planes with brainstem has higher incidence of cerebellar mutism(P=0.055), EOM abnormality(P=0.002), Lower cranial nerve palsy(0.023), motor plegia symptoms(P=0.402), lower incidence of facial palsy(P=0.015), equal incidence of Motor paresis symptoms. Patients with poor planes with cerebellum has higher incidence of all complications but has no statistical significant. Intraoperative infiltration into surrounding tissues has higher incidence of EOM abnormality(P<0.0001), LCN palsy(P=0.004), Facial palsy(0.012). Intraoperative extension to foramen of Lushka and magendie has higher incidence of cerebellar mutism(P=0.010), EOM abnormality(P<0.0001) and LCN palsy(0.045) when compared to tumours without extension.**(Table 20)**

Table 20: Correlating the post op complications with the various surgical parameters									
Variable of interest		**Cerebellar mutism**		**PFS**	**EOM abnormality**	**LCN palsy**	**Facial palsy**	**Motor deficits**	
		Present	**Absent**					**Paresis**	**Plegia**
Extent of resection (247)	Gross total resection	30 (68.2%)	128 (63.1%)	5 (62.5%)	60 (57.7%) P=0.152	20 (62.5%) P=0.632	23 (56.1%) P=0.204	15 (55.6%)	3 (50.0%)
	Near total resection	13 (29.5%)	58 (28.6%)	3 (37.5%)	37 (35.6%)	11 (34.4%)	17 (41.5%)	9 (33.3%)	2 (33.3%)
	Subtotal	1 (2.3%)	16 (7.9%)	0.0%	7 (6.7%)	1 (3.1%)	1 (2.4%)	3 (11.1%)	0.0%
	Biopsy	0.0%	1 (0.5%) P=0.605	0.0%	0.0%	0.0%	0.0%	0.0%	1 (16.7%)
Approach of surgery: (241)	Telovelar (104)	19 (43.2%)	85 (43.1%)	5 (62.5%)	50 (49.0%) **P=0.018**	11 (36.7%) P=0.470	20 (50.0%) P=0.881	12 (48.0%)	2 (40.0%)
	Vermian (43)	10 (22.7%)	33 (16.8%)	2 (25.0%)	22 (21.6%)	9 (30.0%)	8 (20.0%)	5 (20.0%)	3 (60.0%)
	Others (68)	11 (25.0%)	57 (28.9%)	1 (12.5%)	26 (25.5%)	7 (23.3%)	9 (22.5%)	6 (24.0%)	0.0%
	Cortisectomy (24)	4 (9.1%)	20 (10.2%)	0.0%	4 (3.9%)	3 (10.0%)	3 (7.5%)	2 (8.0%)	0.0%
	Supracerebellar(2)	0.0%	2 (1.0%)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Plane with brainstem (230)	Good planes	15 (37.5%)	103 (54.2%)	3(37.5%)	40 (39.6%)	10 (32.3%)	27(65.9%) **P=0.015**	13 (50%)	1 (20%) P=0.402
	Poor planes	25 (62.5%)	87 (45.8%) P=0.055	5 (62.5%)	61(60.4%) **P=0.002**	21(67.7%) **P=0.023**	14 (34.1%)	13 (50%)	4 (80%)
Plane with Cerebellum (208)	Good planes	13 (34.2%)	54(31.8%) P=0.771	0	31 (32.6%) P=0.905	9 (32.1%)	12(33.3%) P=0.874	5 (20.8%)	2 (40.0%)
	Poor planes	25 (65.8%)		7 (100%)	64 (67.4%)	19 (67.9%)	24 (66.7%)	19 (79.2%)	3 (60.0%)
Intraop Infiltration into tissues(202)	Present	28 (75.7%)	102 (61.8%)	6 (85.7%)	70 (77.8%) **P<0.001**	27(87.1%) **P=0.004**	29(82.9%) **P=0.012**	19 (79.2%)	5 (100%) **P=0.057**
	Absent	9 (24.3%)	63 (38.2%) P=0.112	1 (14.3%)	20 (22.2%)	4 (12.9%)	6 (17.1%)	5 (20.8%)	0
Intraop Extension to foramen (219)	No extension	15 (37.5%)	109 (60.9%) **P=0.010**	4 (50.0%)	40 (43.5%) P<0.0001	13 (44.8%) **P=0.045**	17 (48.6%)	12 (52.2%)	2 (66.7%)
	To Lushka	7 (17.5%)	17 (9.5%)	0.0%	7 (7.6%)	3 (10.3%)	4 (11.4%)	2 (8.7%)	0.0%
	To Magendie	14 (35.0%)	29 (16.2%)	3 (37.5%)	28 (30.4%)	6 (20.7%)	11 (31.4%)	6 (26.1%)	1 (33.3%)
	Both foramen	4 (10.0%)	15 (8.4%)	1 (12.5%)	14 (15.2%)	7 (24.1%)	2 (5.7%)	2 (8.7%)	0.0%
	CP angle cistern	0.0%	9 (5.0%)	0.0%	3 (3.3%)	0.0%	1 (2.9%)	1 (4.3%)	0.0%
Infiltration noted in HPR		19(43.2%)	25 (56.8%)	4 (50%)	45 (43.3%)	16 (50%)	14(34.1%)	12 (44.4%)	2 (33.3%)

I. ADJUVANT THERAPY:

Table 21: Adjuvant therapy related statistics

Variable		No of patients	In %	Missing data
Adjuvant Chemotherapy status (194)	Not taken	19	9.8%	55(22.1%)
	Taken Incomplete	9	4.6%	
	Complete	166	85.6%	
Adjuvant Radiotherapy status(205)	Not taken	14	6.9%	44(17.7%)
	Taken Incomplete	2	1%	
	Complete	189	92.2%	
Timing of starting Adjuvant therapy after surgery (149)	Less than 3 months	136	91.3%	100(40.2%)
	3 to 6 months	10	6.7%	
	6-12 months	2	1.3%	
	More than 12 months	1	0.7%	

In our study**(Table 21)**, most of the patients underwent Post op Chemotherapy and Radiotherapy with the compliance rate of 85.6% and 92.2% respectively. Majority of the patients started taking adjuvant therapy less than 3 months(91.3%)

Table 22: Comparing Adjuvant therapy with Tumour relapse, Disseminated disease, Need for Recurrence surgery

The incidence of relapse, redo surgery and disseminated disease was compared with the status of adjuvant radiotherapy and chemotherapy. As the numbers were less in the group of adjuvant therapy not taken, incompletely taken, the meaningful correlation could not be made and P value cannot be determined. However, with the adjuvant therapy, the incidence of relapse and redo-surgery was lesser. On the contrary, the disseminated disease incidence was more probably because of skewed numbers.

Table 22: Comparing Adjuvant therapy with Tumour relapse, Disseminated disease, Need for Recurrence surgery

Variable		Relapse			Redo-surgery for tumour			Disseminated disease		
		Present	Absent	P Value	Done	Not done	P value	Present	Absent	P value
Adjuvant Chemotherapy status	Not taken	5(55.6%)	4(44.4%)	*	1(5.3%)	18(94.7%)	0.883	2(100%)	0(0%)	*
	Taken Incomplete	3(42.9%)	4(57.1%)		1(11.1%)	8(88.9%)		1(50%)	1(50%)	
	Complete	51(35.4%)	93(64.6%)		21(12.7%)	145(87.3%)		27(79.4%)	7(20.6%)	
Adjuvant Radiotherapy status(205)	Not taken	5(83.33%)	1(16.67%)	*	2(14.28%)	12(85.71%)	*	1(50%)	1(50%)	*
	Taken Incomplete	1(100%)	0(0%)		0(0%)	2(100%)		1(100%)	0 (0%)	
	Complete	55(34.2%)	106(65.8%)		20(10.6%)	169(89.4%)		32(82.1%)	7(17.9%)	
Timing of starting Adjuvant therapy after surgery (149)	Less than 3 months	34(30.1%)	79(69.9%)	*	14(10.3%)	122(89.7%)	*	19(73.1%)	7(26.9%)	*
	3 to 6 months	3(37.5%)	5(62.5%)		1(10.0%)	9(90.0%)		2(100.0%)	0.0%	
	6-12 months	2(100.0%)	0(0%)		1(50.0%)	1(50.0%)		1(50.0%)	1(50.0%)	
	More than 12 months	0(0%)	1(100%)		0.0%	1(100.0%)		0		

J. FUNCTIONAL OUTCOMES:

Table 23: Functional outcomes scoring in different domains

Variable		No	In %	Missing data no
Physical activity (129)	Normal	66	51.2%	120(48.2%)
	Need Mild assistance	40	31.0%	
	Need Significant assistance	18	14.0%	
	Bed ridden	5	3.9%	
Activities of daily living (126)	Independent	77	61.1%	123 (49.4%)
	Partial	37	29.4%	
	Completely dependent	12	9.5%	
Schooling status(107)	Normal school	85	79.4%	167(67.1%)
	Special school	6	5.6%	
	Not attending any school	16	14.91%	
Peformance in School (91)	Good	2	2.2%	158(63.5%)
	Average	36	39.6%	
	Below average	36	39.6%	
	Poor	17	18.7%	
Behavioural issues	Present	12	4.8%	
Social interaction(89)	Good	76	85.4%	160(64.3%)
	Moderate	11	12.4%	
	Poor	2	2.2%	

The Functional assessment was done in various domains like Physical activity, Activities of daily living, schooling performance, social interaction and behavioural issues. The physical activity and ADL was adapted from the PedsQL questionnaire. It was designed to get the score from the caretaker or from the patient if they are capable of answering it. The results were collected over the telephonic questionare and the score was calculated. In this study, the physical activity data was calculated for 129 patients and the Normal activity score was found in 66(51.2%). The activities of daily living was able to do independently in 77(66%) of patients. Most of the patients had average or below average performance in the school. The social interaction score was good in 76(85.4%) patients but the behavioural issues were prevalent in 12(4.8%) of patients**(Table 23)**.

Table 24: Comparing the Effect of the adjuvant therapy, extent of resection on the Functional outcomes of the patient – Physical activity status and ADL

Variable		Physical activity status				Activities of Daily Living – ADL status		
		Normal	**Mild Assistance**	**Significant assistance**	**Bed ridden**	**Independent**	**Partial depend**	**Completely Dependent**
Adjuvant Chemo therapy status	Not taken	6(37.5%)	1 (6.3%)	5 (31.3%)	4(25.0%)	5 (31.3%)	6 (37.5%)	5 (31.3%)
	Incomplete	0.0%	3 (50.0%)	3 (50.0%)	0.0%	1 (16.7%)	3 (50.0%)	2 (33.3%)
	Complete	57(55.3%)	35 (34.0%)	10 (9.7%)	1 (1.0%)	69 (67.6%)	28 (27.5%)	5 (4.9%)
Adjuvant Radio therapy status(205)	Not taken	3 (30.0%)	1 (10.0%)	3 (30.0%)	3 (30.0%)	3 (30.0%)	3 (30.0%)	4 (40.0%)
	Taken Incomplete	1 (50.0%)	0.0%	0.0%	1 (50.0%)	1 (50.0%)	0.0%	1 (50.0%)
	Complete	60 (52.6%)	38 (33.3%)	15 (13.2%)	1 (0.9%)	72 (63.7%)	34 (30.1%)	7 (6.2%)
Extent of resection:	Gross total	45(51.1%)	29 (33.0%)	10 (11.4%)	4 (4.5%)	53 (61.6%)	22 (25.6%)	11 (12.8%) **P=0.383**
	Near total	14(45.2%)	9 (29.0%)	7 (22.6%)	1 (3.2%)	17 (56.7%)	12 (40.0%)	1 (3.3%)
	Sub-Total	6(66.7%)	2 (22.2%)	1 (11.1%)	0.0%	6 (66.7%)	3 (33.3%)	0.0%
	Biopsy	**0**	**0**	**0**		**0**	**0**	

As the side effects of adjuvant therapy, radiotherapy and extent of resection has significant effect on the functional status of the patient, those parameters were analysed and compared in this study**(Table 24)**. In the adjuvant therapy completed group, 57(55.3%) in chemotherapy and 60(52.6%) in radiotherapy and 45(51.1%) in Gross total decpmpression had normal physical activity status. However, in view of small numbers in other categories, statistically significant results were not obtained.

Table 25: Comparing the Effect of the adjuvant therapy, extent of resection on the Functional outcomes of the patient – School performance, Social Interaction, Behavioral problems

Variable		SCHOOL PERFORMANCE				SOCIAL INTERACTION			BEHAVIOURAL ISSUES	
		GOOD	AVG	BELOW AVG	POOR	GOOD	MODE RATE	POOR	ABSENT	PRESENT
Adjuvant Chemo therapy status	Not taken	0.0%	2 (40.0%)	2 (40.0%)	1 (20.0%)	9 (81.8%)	1 (9.1%)	1 (9.1%)	2 (66.7%)	1 (33.3%)
	Incomplete	0.0%	0.0%	2 (40.0%)	3 (60.0%)	5 (83.3%)	0.0%	1 (16.7%)	0.0%	1 (100.0%)
	Complete	2 (2.5%)	34 (43.0%)	30 (38.0%)	13 (16.5%)	60 (85.7%)	10 (14.3%)	0.0%	4 (28.6%)	10 (71.4%)
Adjuvant Radio therapy status (205)	Not taken	0.0%	1 (50.0%)	0.0%	1 (50.0%)	5 (71.4%)	1 (14.3%)	1 (14.3%)	1 (50.0%)	1 (50.0%)1
	Incomplete	**0**	**0**	**0**	**0**	1(100%)	0.0%	0.0%	**1 (100%)**	**0**
	Complete	2 (2.3%)	34 (38.6%)	36 (40.9%)	16 (18.2%)	69 (86.3%)	10 (12.5%)	1 (1.3%)	4 (26.7%)	11 (73.3%)
Extent of resection	Gross total	1 (1.7%)	21 (36.2%)	24 (41.4%)	12 (20.7%)	49 (83.1%)	9 (15.3%)	1 (1.7%)	6 (46.2%)	7 (53.8%)
	Near total	1 (4.0%)	13 (52.0%)	7 (28.0%)	4 (16.0%)	18 (85.7%)	2 (9.5%)	1 (4.8%)	0.0%	4 (100.0%)
	Sub-Total	0.0%	1 (14.3%)	5 (71.4%)	1 (14.3%)	8 (100.0%)	0.0%	0.0%	0.0%	1 (100.0%)
	Biopsy	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	

On comparing the adjuvant therapy status with the school performance, social interaction and behavioural issues, those who completed the adjuvant therapy(RT and CT) has average and below average schooling performance in 43% and 38% respectively. Around 16%-18% had poor schooling performance. Only in 2-3% of children were having good performance in schooling as per the age appropriate level. The subtotal excision patients had below average academic performance in 71%. The social interaction score was good in majority of the categories**(Table 25)**.

K. LONG TERM SEQUELAE IN THE SURVIVED PATIENTS:

Effect of Adjuvant therapy, Extent of resection on the Long term sequelae of the survived patients:

The patients who survive longer after surgery and adjuvant therapy tend to develop long term deficits in the form of hearing impairment, visual impairment, hormone deficiency – hypopituitarism, puberty and menstrual related problems, cognitive impairment in the long run. . In our study, the hearing impairment was noted in 38/126 (28%) of patients and visual impairment was noted in 23/124(17.4%) of patients. In relation to the adjuvant therapy, comparison was not feasible because of the skewed distribution of the adjuvant therapy data. However, Growth hormone deficieny and Hypothyroidism occurred significantly in the adjuvant therapy group(P=0.01). The steroid deficiency was noted very rare. Menstrual related issues in the form of Delayed puberty, irregular periods were noted in 21/126 (15.7%). Cognitive impairment was noted in 21/124 (15.9%) of patients. The extent of resection did not have any statistically significant effect on the Long term sequelae**(Table 26)**.

LONG TERM SEQUELAE:

Table 26 : Effect of Adjuvant therapy, Extent of resection on the Long term sequelae of the survived patients

Variable		**Hearing impairment (126)**	**Visual Impairment (124)**	**Development delay (123)**	**Hypo thyroid (127)**	**GH deficiency (127)**	**Steroid deficieny (123)**	**Menstrual issues (126)**	**Speech disturbances (123)**	**Cognitive impairment (124)**
No of patients affected		38 (28.1%)	23 (17.4%)	6 (4.6%)	47 (34.8%)	41 (30.4%)	1 (0.8%)	21 (15.7%)	13 (9.9%)	21 (15.9%)
Adjuvant Chemo therapy status	Not taken	0(0.0%)	2(12.5%)	0.0%	1(6.3%)	1(6.3%)	0.0%	0.0%	0.0%	1(6.3%)
	Incomplete	0.0%	1(20.0%)	0.0%	1(20.0%)	0.0%	1(20.0%)	0.0%	1(20.0%	0.0%
	Complete	37(35.2%)	20(19.4%)	5(4.9%)	47(44.4%)	39(36.8%) **(P – 0.01)**	0.0%	20(19.0%)	12(11.8%)	19(18.4%)
Adjuvant Radio therapy status	Not taken	0.0%	0.0%	0.0%	0.0%	1(9.1%)	0.0%	0.0%	0.0%	1(10.0%)
	Incomplete	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	Complete	38(32.2%)	23(20.0%)	6(5.2%)	50(38.8%)	40(34.2%)	1(0.9%)	21(17.9%)	13(11.4%)	20(17.4%)
Extent of resection:	Gross total	28(30.8%) P=0.305	13(14.9%) P=0.446	4(4.6%)	32(35.5%)	28(30.8%) (P=1.000)	0.0%	13(14.6%) (P=0.404)	11(12.6%)	14(15.9%) (P=0.935)
	Near total	6(18.2%)	9(26.5%)	2(5.8%)	14(41.2%)	10(30.3%)	1(3.0%)	5(14.7%)	2(6.1%)	6(18.2%)
	Sub-Total	4(44.4%)	1(11.1%	0.0%	5(55.6%)	3(33.3%)	0.0%	3(33.3%	0.0%	1(11.1%)
	Biopsy	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Approach of surgery: (241)	Telovelar	22(36.7%)	14(23.7%)	3(5.1%)	28(45.9%)	24(38.7%)	0.0%	12(20.0%)	7(11.9%)	6(10.0%)
	vermian	4(26.7%)	2(15.4%)	0.0%	4(26.7%)	2(14.3%)	0.0%	3(20.0%)	1(7.7%)	2(15.4%)
	Others	10(23.8%)	5(11.6%)	3(7.0%)	14(33.4%)	14(33.3%)	0.0	3(7.1%)	4(9.5%)	10(23.8%)
	cortisectomy	2(15.4%)	2(16.7%)	0.0%	4(33.3%)	0.0%	1(8.3%)	2(16.7%)	1(8.3%)	2(16.7%)
	Supracerebellar	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1(50.0%)

L. SURVIVAL ANALYSIS DATA:

Table 27: Unadjusted COX regression analysis - Overall Survival

Variable		Sig. (P Value)	Exp(B) Hazard Ratio	95.0% CI for Exp(B)	
				Lower	Upper
AGE </= 3(1- present,0-absent)		.188	.043	.000	4.652
Post op residue >/=1.5 cm (Present, Absent)		.581	1.231	.588	2.578
Pre op metastasis status (Present, absent)		.319	1.419	.713	2.823
RISK stratification (High / Average)		.812	1.081	.569	2.055
Extent of resection	GTR	**Ref**			
	NTR	1.000	1.000	.501	1.995
	STD	1.000	1.000	.313	3.197
	Biopsy	1.000	1.000	.000	*
Plane with BS(Good/Poor)		.212	.671	.358	1.257
CSF cytology (Positive/Negative)		.158	5.639	.511	62.222
Infiltration into tissues in HPR		.600	1.176	.642	2.156
CEREBELLAR MUTISM		.691	.848	.376	1.911
Morphological type	Classic	.260	.551	.196	1.552
	Desmoplastic	.274	.330	.045	2.408
	Extensive Nodularity	.603	1.699	.230	12.523
	Large cell/Anaplastic	.974	.000	.000	*
Molecular subtype(SHH and P53 wild, non SHH and WNT)		.953	30007.804*	.000	*
		.949	74473.599*	.000	
Chemotherapy status	Nil	Ref			
	Incomplete	.077	.259	.058	1.157
	Complete	.000	.108	.053	.218
Radiotherapy status	Nil	.897	32069.455*	.000	*
	Incomplete	.876	*	.000	*
	Complete	.925	2020.541*	.000	*
Adjuvant therapy starting time	Less than 3 mon	**Ref**			
	3 to 6 months	.195	2.225	.663	7.467
	6 to 12 months	.986	.000	0.000	
	>12 months	.989	.000	0.000	

* Results not significant

In this study**(Table 27)**, COX unadjusted analysis was done to look for the significant risk factors affecting the overall survival. The Hazards ratio was calculated and the factors like CSF cytology, Preop metastasis, post op residue was having higher odds of reduced survival.

Disease free survival:

Table 28: COX analysis unadjusted - for Disease free survival

Variable		Sig. (P Value)	Exp(B) Hazard Ratio	95.0% CI for Exp(B)	
				Lower	Upper
Location Of Tumour	Vermis	.531	.856	.526	1.393
	Cerebellar Hemisphere	.078	.495	.226	1.083
	Fourth Ventricle	.006	2.055	1.235	3.417
Epicentre	Upper	.416			
	Middle	.211	.562	.228	1.385
	Lower	.241	.582	.236	1.438
Borders - Well/Lob/Irreg	Well Defined	.042			
	Lobulated	.883	1.060	.487	2.311
	Irregular	.025	2.256	1.107	4.599
Tumour Plane In Posterior Fossa	Ref	.960			
	Intraaxial	.680	.772	.226	2.640
	Surfacing At Fourth Ventricle	.830	.939	.530	1.664
	Surfacing At Cerebellum	.849	1.090	.448	2.654
Size Of Tumour In Relation To Posterior Fossa	Less Than 1/3rd	.858			
	1/3RD TO 2/3RD	.731	.860	.363	2.037
	>2/3RD	.921	1.050	.397	2.777
Infiltration noted during surgery		.339	.764	.439	1.327
Infiltration noted in HPR		.999	1.000	.618	1.617
Chemotherapy status	Nil	.068			
	Incomplete	.775	.815	.200	3.321
	Complete	.038	.402	.170	.952
Radiotherapy status	Nil	.853	1.228	.140	10.773
	Incomplete	.354	3.957	.215	72.717
	Complete	.006	.057	.007	.446
Pre op metastasis status (Present, absent)		.002	2.212	1.350	3.624
Post op residue >/=1.5 cm (Present, Absent)		.017	1.868	1.121	3.112
Morphological type	Classic	.386	.706	.322	1.551
	Desmoplastic	.980	.985	.307	3.159
	Extensive Nodularity	.255	2.276	.553	9.372
	Large cell/Anaplastic	.975	.000	.000	*
Molecular subtype(SHH and P53 wild, non SHH and WNT)		.673			Ref
		.966	85689.851*	.000	*
		.963	*	.000	*

***Results not significant**

In DFS, tumours located in the fourth ventricle, lobulated or irregular tumour margins in MRI, preop metastasis, post op residue, classic type has higher odds of developing recurrence(HR>1).**(Table 28)**

Survival after recurrence:

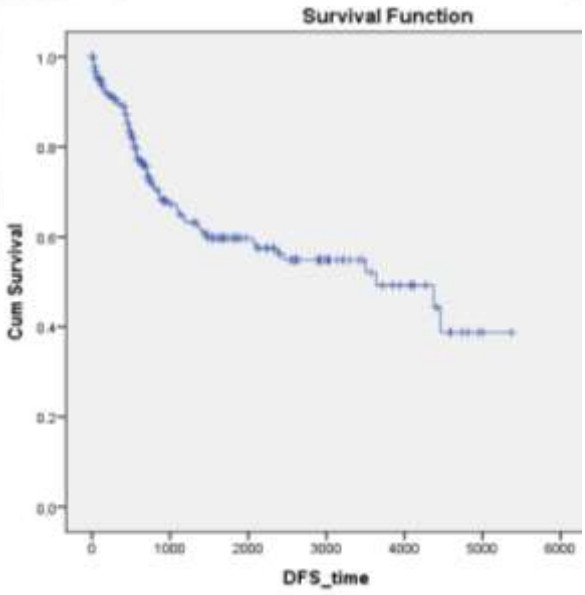
Table 29: COX analysis unadjusted - done for Survival after recurrence

Variable		Sig. (P Value)	Exp(B) Hazard Ratio	95.0% CI for Exp(B)	
				Lower	Upper
Morphological type	Classic	.304			
	Desmoplastic	.242	.030	.000	10.753
	Extensive Nodularity	.311	.030	.000	26.564
	Large cell/Anaplastic	*			
Molecular subtype		.807	8163.866*	.000	*
Chemotherapy status	Nil	.003			
	Incomplete	.069	.126	.013	1.179
	Complete	.001	.132	.041	.424
Radiotherapy status	Ref	.020			
	Nil	.943	48129.755*	.000	*
	Incomplete	.934	*	.000	*
	Complete	.950	13454.027*	.000	*

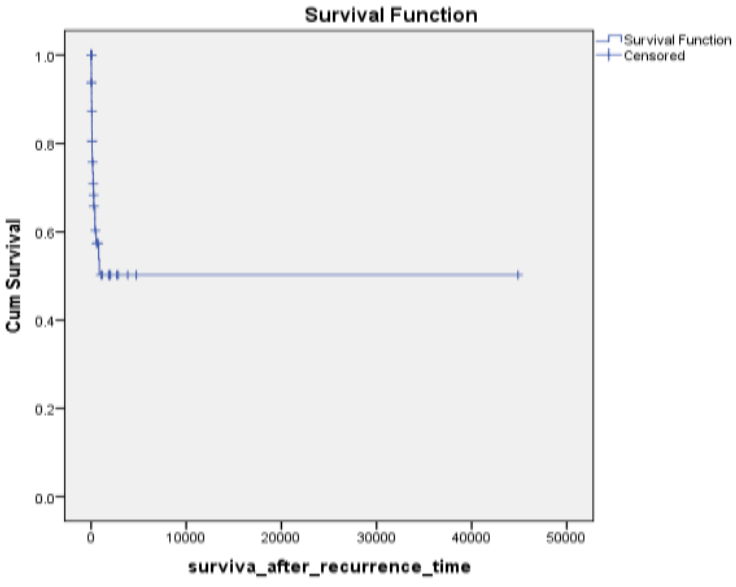
*Result not significant

On calculating the Survival after recurrence, no significant association was found in between morphological, molecular subtype, status of adjuvant therapy**(Table 29)**.

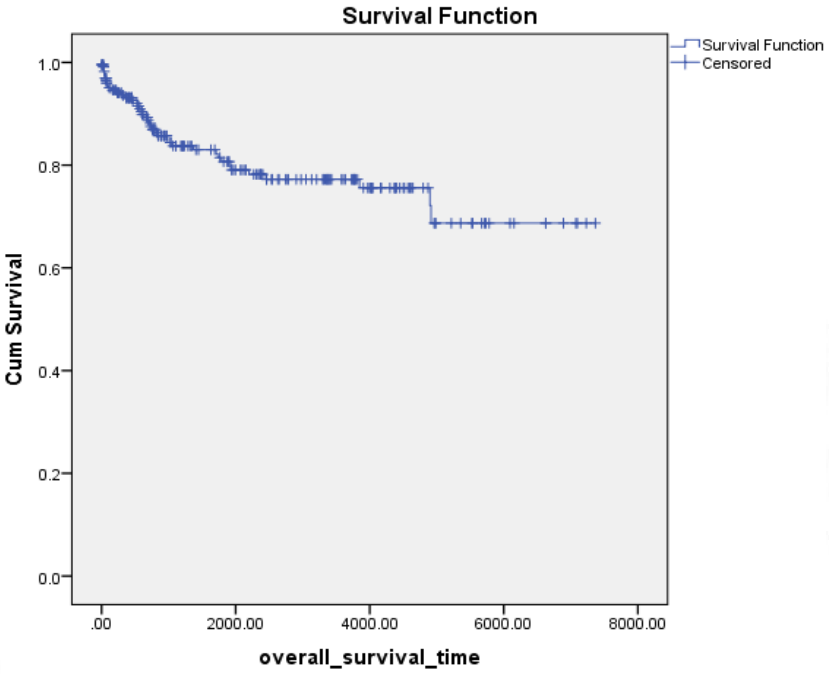
TOTAL SURVIVAL STATUS IN THE CURRENT STUDY:



10a. Disease free survival



10b. Survival after recurrence



variable	Mean (+/- 2SD) in days	Median (+/- 2SD)
OS	5661(5193 - 6129)	
DFS	3101(2704 - 3498)	3634(1817 - 5450)
SAR	22657(15421 - 29893)	

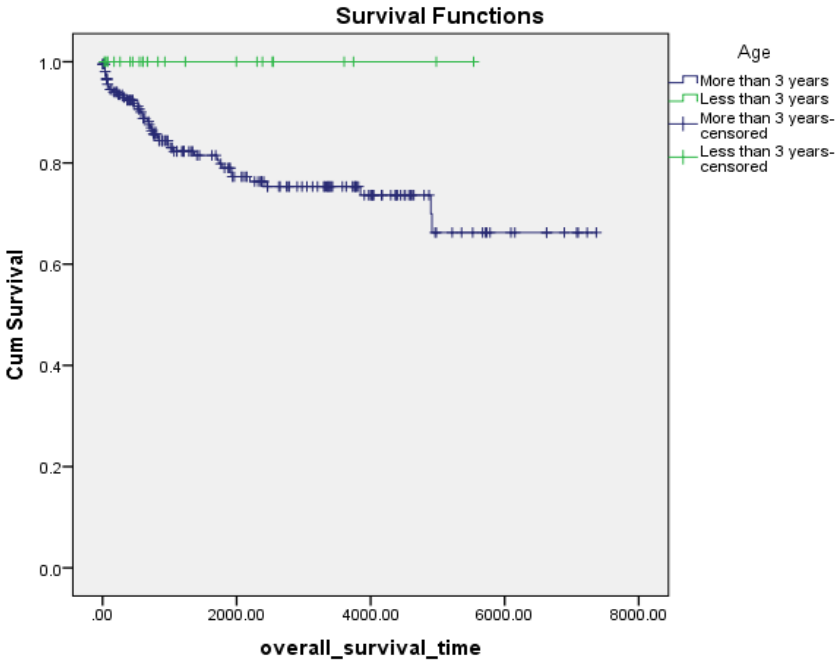
10c. Overall survival rate in this study

In this study, three survival outcomes were measured viz Overall survival(From the time of treatment till the last survival), Disease free survival (Time of surgery till the recurrence of tumour) and Survvial after recurrence (From the time of recurrence till the last survival).

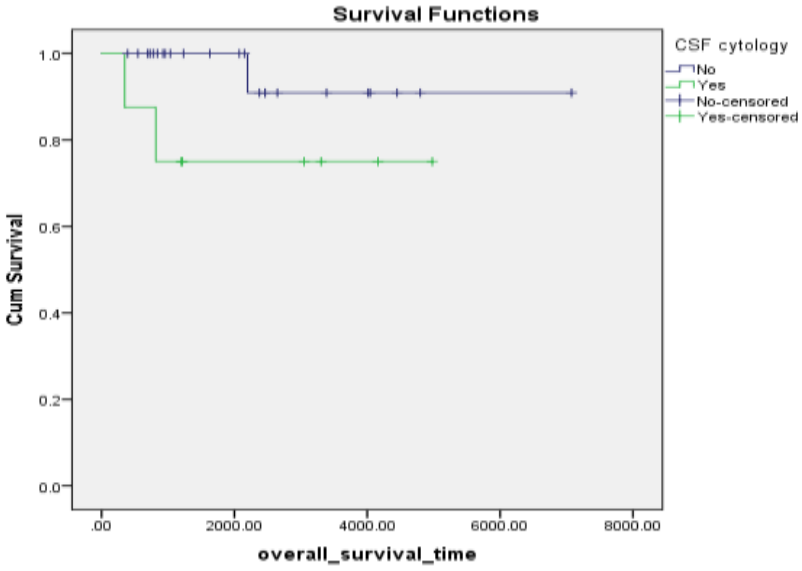
In DFS, the 5 year survival rate in this study was 58%, 10 year survival rate was 49%. The overall survival at 5 years was 81%, at 10 years 76%, and at follow up of 15 years is 68%. The Survival after recurrence was found to be 50% at the end of 5 year follow up, beyond that there is not adequate numbers to compute the survival analysis.

Figures 11(a - m) : Overall Survival analysis with respective to various prognostic factors

a. Age wise category (less than 3 years, more than 3 years)

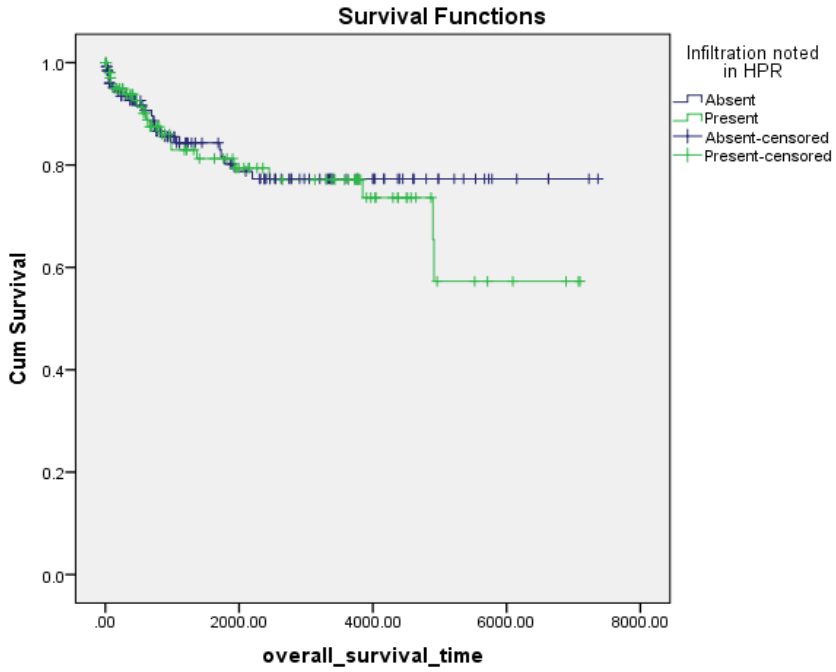


b. CSF Cytology



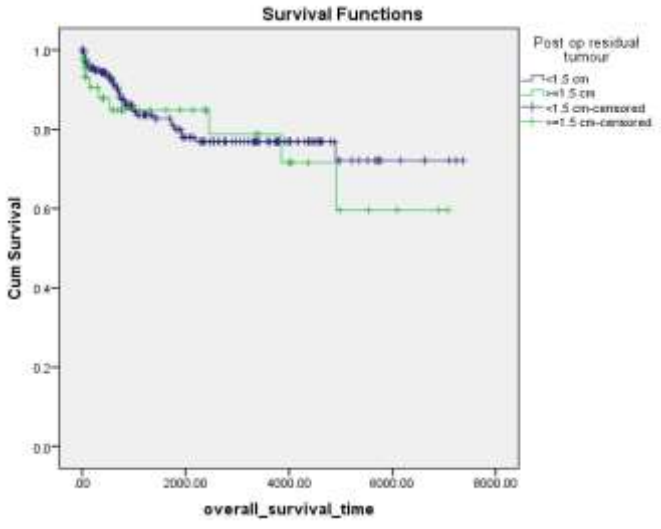
Log Rank (Mantel-Cox)	
Chi-Square	2.542
Sig.(P-Value)	0.111

c. Infiltration of the tumour into tissues noted in Histopathology



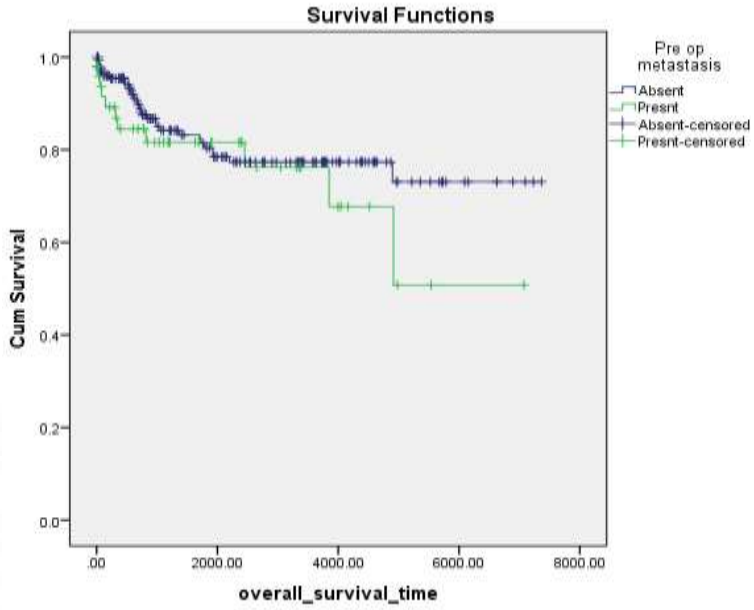
Log Rank (Mantel-Cox)	
Chi-Square	0.276
Sig.(P-Value)	0.599

d. Post operative Residual tumour status (Size <1.5cm, >/= 1.5cm)



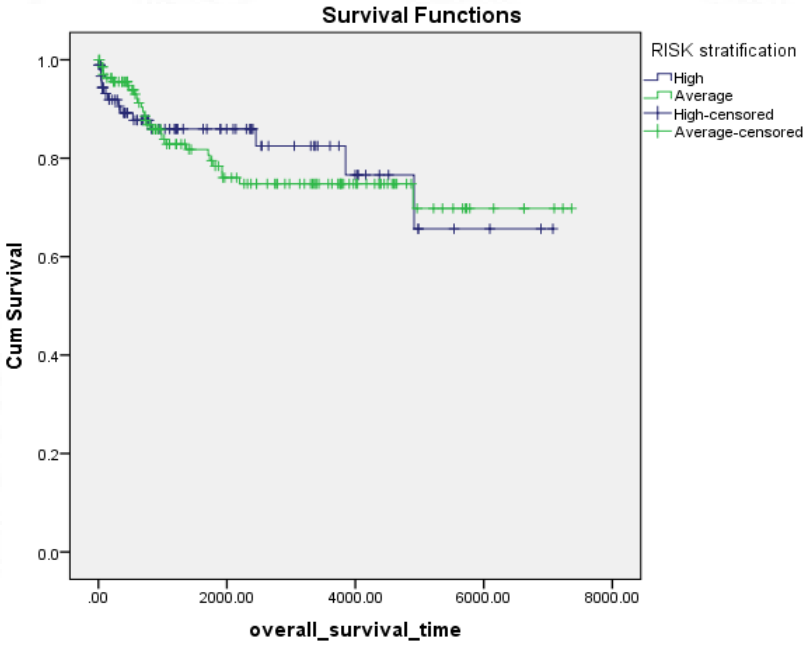
Log Rank (Mantel-Cox)	
Chi-Square	0.305
Sig.(P-Value)	0.580

e. Pre op Metastasis status: (Present vs Absent)



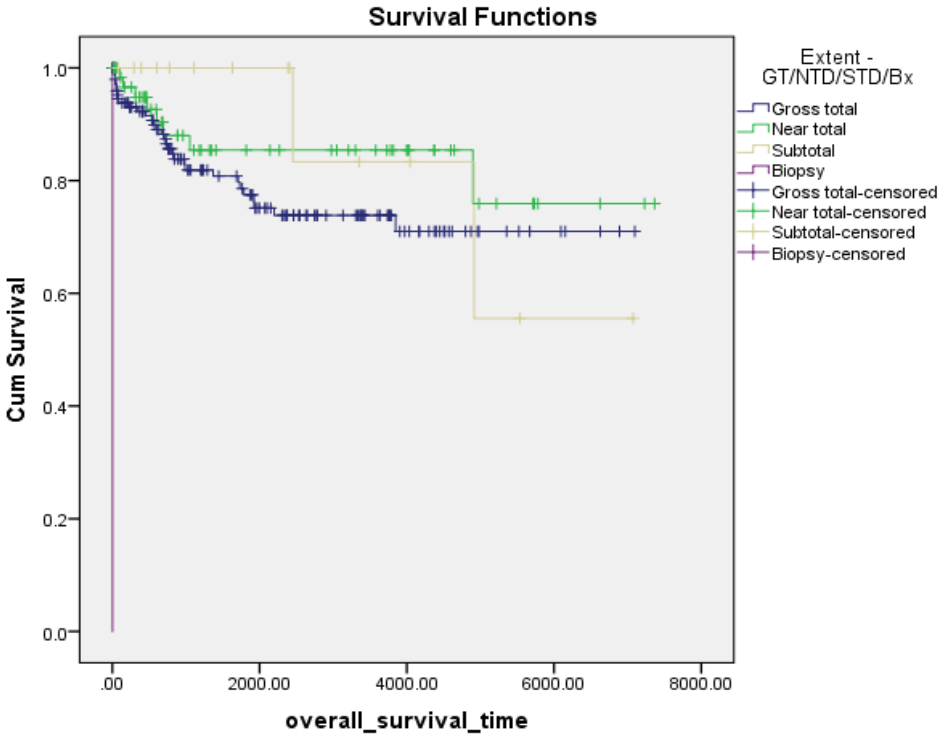
Log Rank (Mantel-Cox)	
Chi-Square	1.003
Sig.(P-Value)	0.317

f. Risk stratification (Average risk vs High risk)



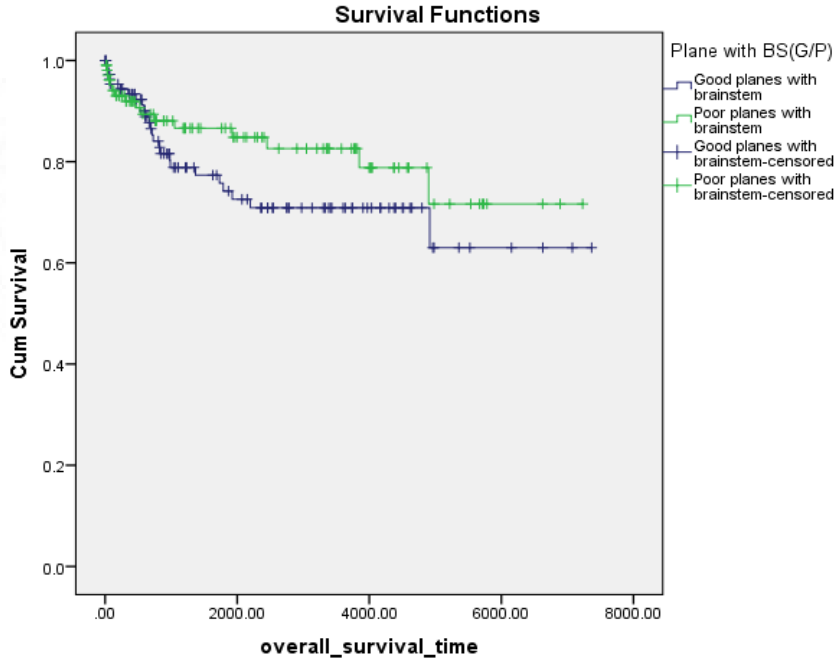
Log Rank (Mantel-Cox)	
Chi-Square	0.057
Sig.(P-Value)	0.812

g. Extent of Surgical resection: (Gross total/Near total/Sub-total/Biospy)



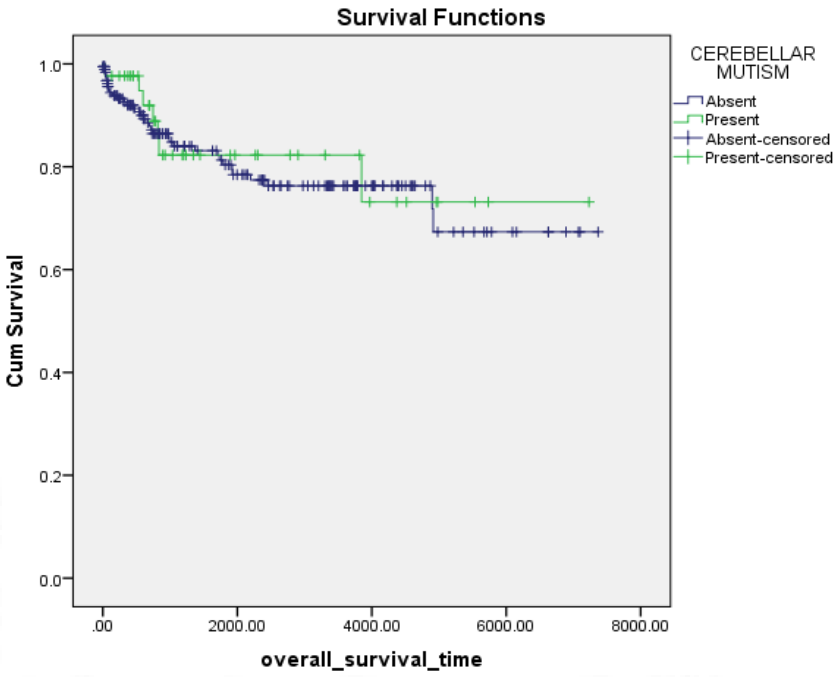
Log Rank (Mantel-Cox)	
Chi-Square	233.047
Sig.(P-Value)	<0.0001

h. Tumour plane with the Brain stem(Good planes/Poor planes):



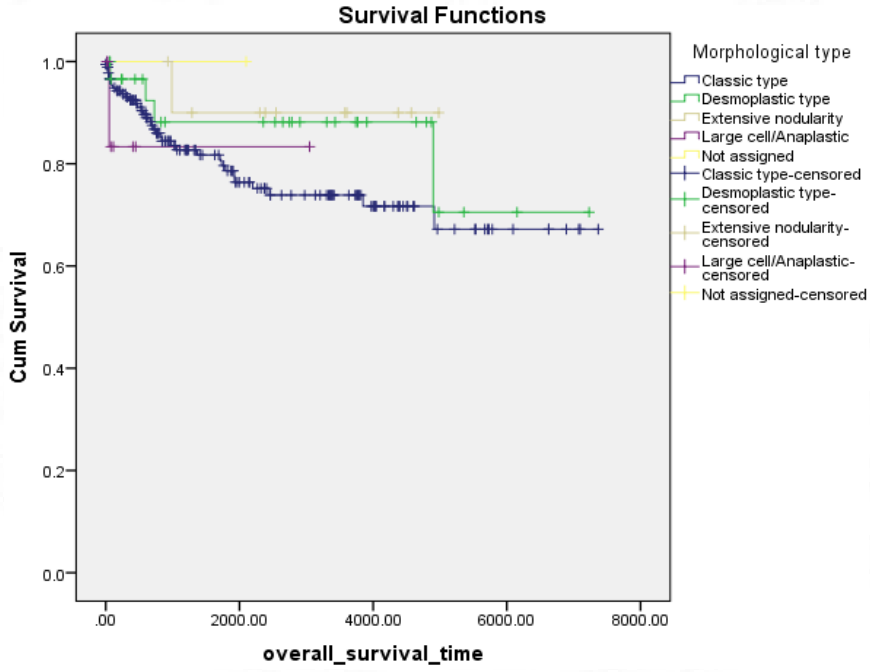
Log Rank (Mantel-Cox)	
Chi-Square	1.575
Sig.(P-Value)	0.209

i. Survival status in relation to Cerebellar mutism



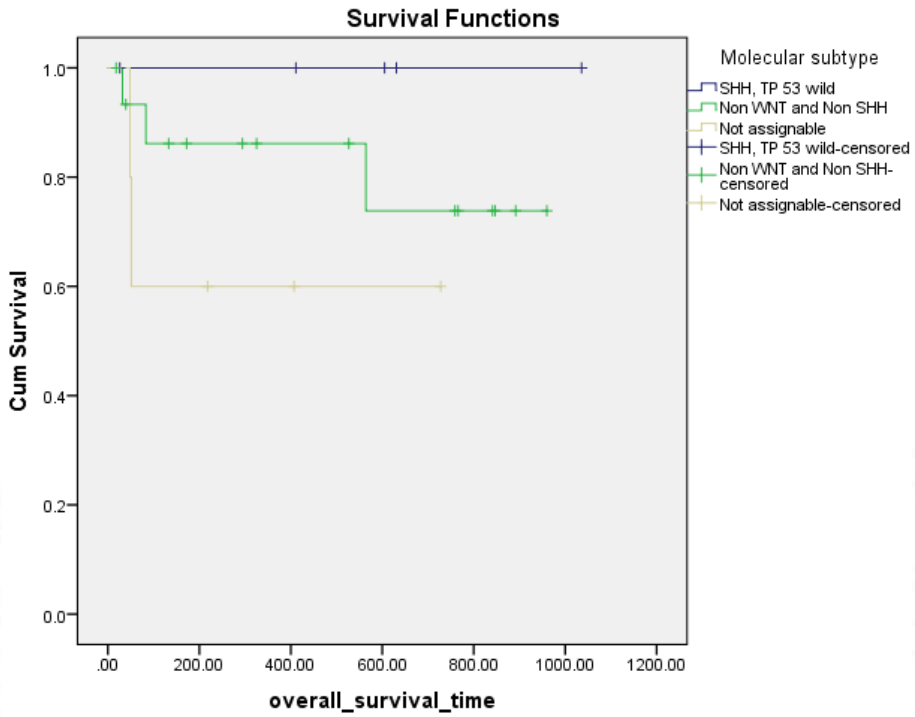
Log Rank (Mantel-Cox)	
Chi-Square	0.158
Sig.(P-Value)	0.691

j. Survival among various Morphological types



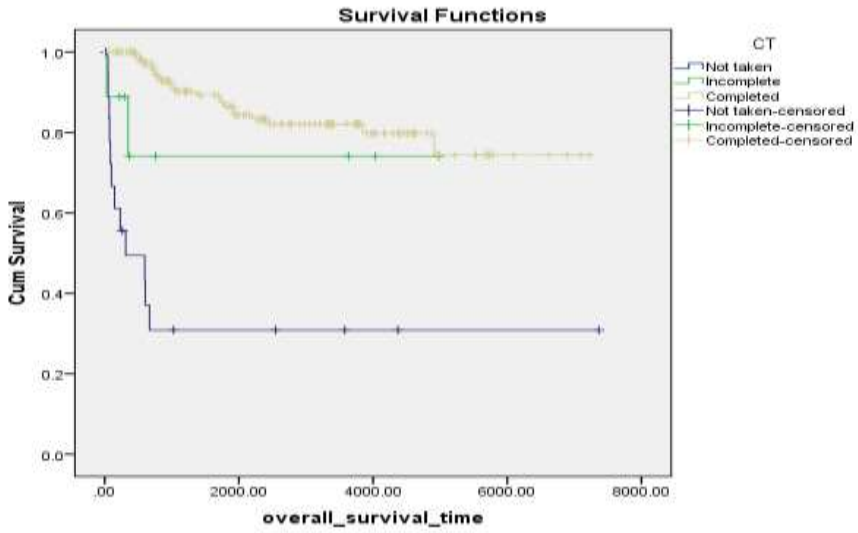
Log Rank (Mantel-Cox)	
Chi-Square	3.135
Sig.(P-Value)	0.536

k. Survival among various Molecular subtypes



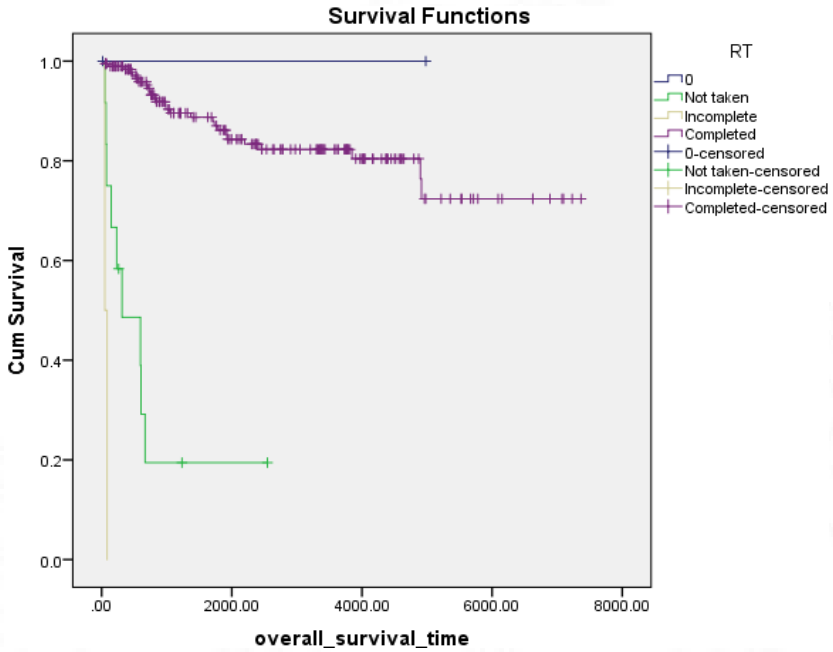
Log Rank (Mantel-Cox)	
Chi-Square	2.547
Sig.(P-Value)	0.280

l. Comparing the Overall Survival status based on the adjuvant chemotherapy status



Log Rank (Mantel-Cox)	
Chi-Square	55.664
Sig.(P-Value)	<0.0001

m. Comparing the Overall Survival status based on the adjuvant radiotherapy status



Log Rank (Mantel-Cox)	
Chi-Square	170.834
Sig.(P-Value)	<0.0001

On further analysing the factors affecting the Overall survival**(Figures 11a-m)**, significant contributing factors were identified after COX unadjusted regression analysis. The effect of each factor on the overall survival survival analysis were calculated. Among them, Age less than 3 years had better survival than more than 3 years. This was in discordance with the literature where the children less than 3 years has poor survival. This can be explained by the fact that the cohort of children less than 3 years did not have any event till the follow up data available for the analysis. Hence, this cannot be taken as significant. However, the presence of factors like CSF cytology positivity for malignant cells, presence of preop metastasis, post operative residual tumour > 1.5cm, infiltration noted in histopathology had lesser survival rate than the corresponding groups(Not statistically significant).

In the Risk stratification, 5 year and 10 year survival was better in high risk compared to average risk but at the long run, average risk has better overall survival(not statistically significant,P=0.812).

On comparing the extent of resection, near total excision has better overall survival than the gross total with statistically significant P value(<0.001).

At the same time, poor planes with the brainstem had better survival than good planes(P=0.209) in contrary to the literarture.

Cerebellar mutism did not seem to be influencing the overall survival.

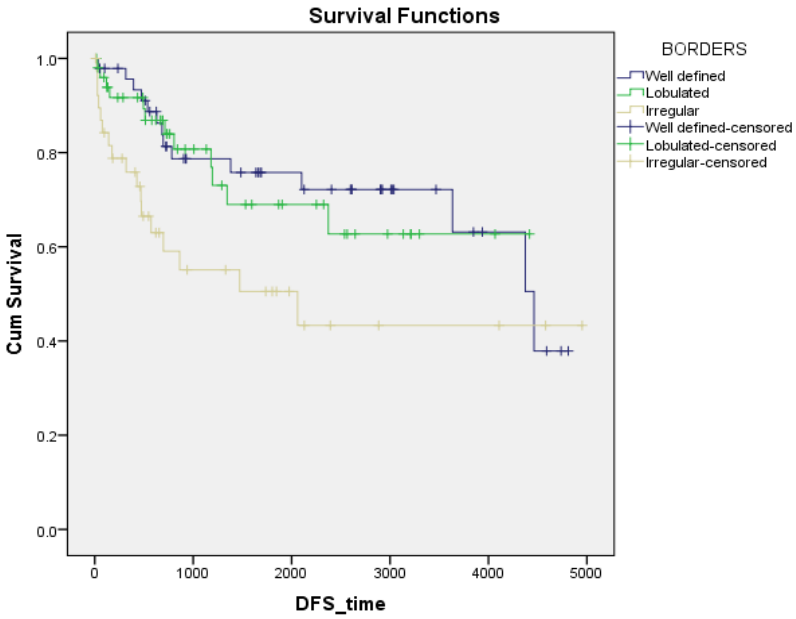
Among the morphological types, Desmoplastic and MBEN had better outcomes than classic and Large cell variety (P=0.536) with no statistical significance.

In the Molecular group done in few cases, SHH, TP 53 had better survival than non WNT, non-SHH type; tumours not assignable to any group by IHC has the worst prognosis overall(P=0.280).

Among the adjuvant therapy groups, those completed the chemotherapy or radiotherapy had better overall survival than the incomplete ones or not taken group(P<0.0001).

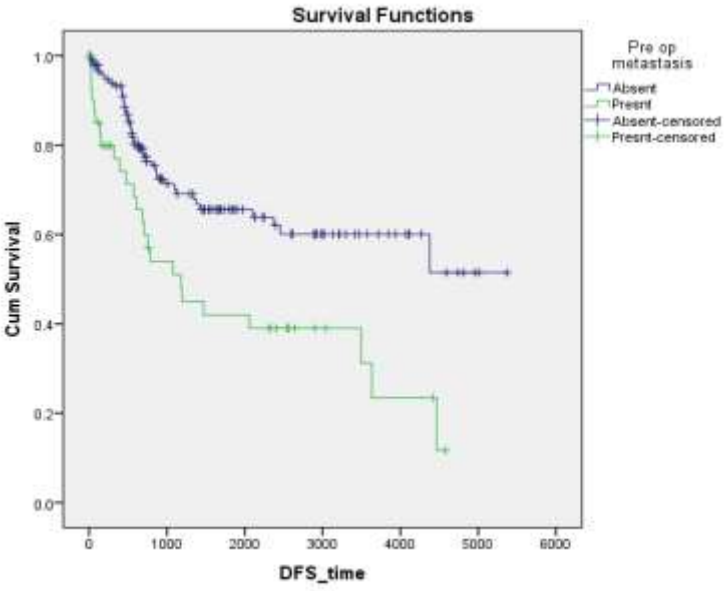
Figure 12(a-)Factors influencing the Disease Free Survival:

a. **Disease Free Survival – Based on Tumour Morphology in MRI**



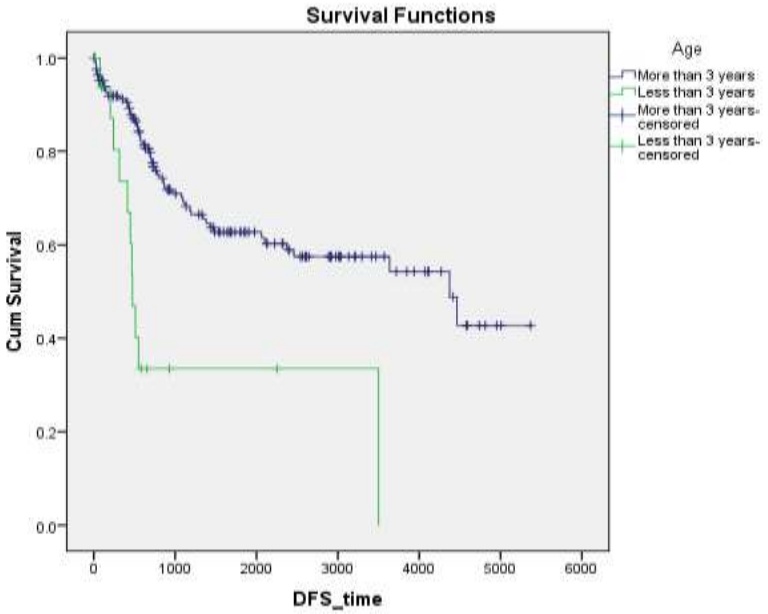
Log Rank (Mantel-Cox)	
Chi-Square	6.654
Sig.(P-Value)	0.036

b. **DFS in Pre-operative metastasis:**



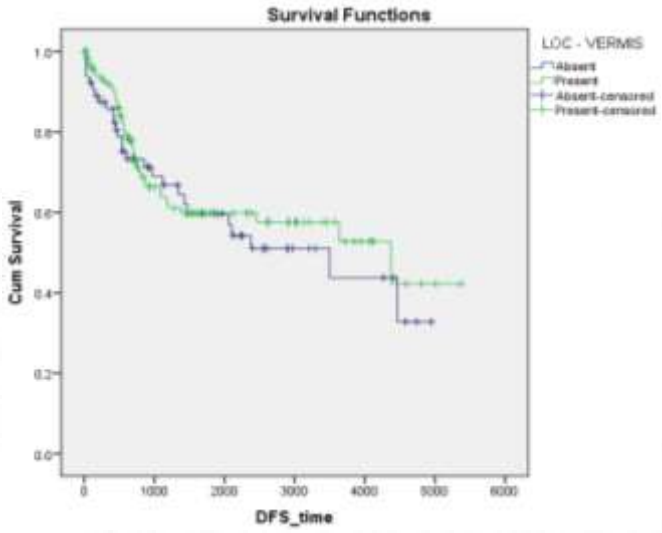
Log Rank (Mantel-Cox)	
Chi-Square	10.468
Sig.(P-Value)	0.001

c. DFS based on Age Group risk(Age>3 years, Age<3 years)

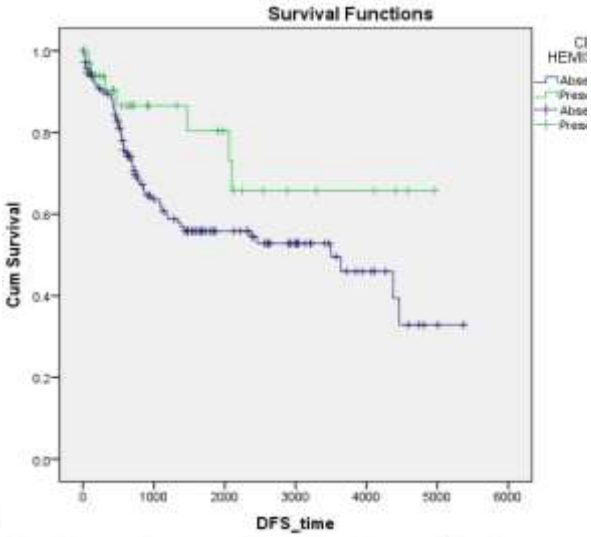


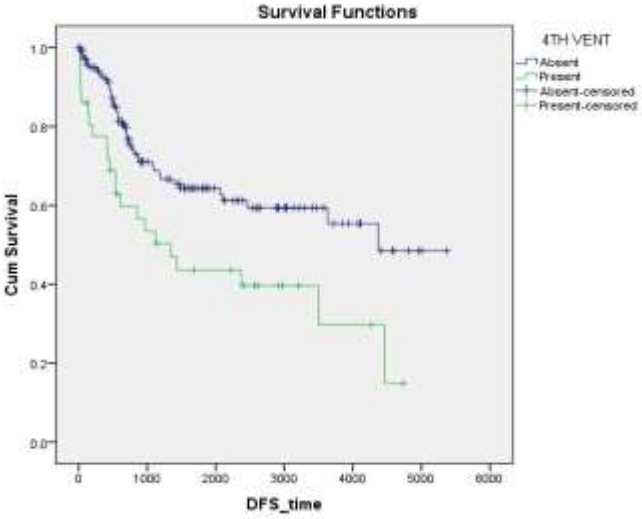
Log Rank (Mantel-Cox)	
Chi-Square	16.785
Sig.(P-Value)	<0.0001

d. Epicentre of the lesion origin in the posterior fossa – determining the DFS



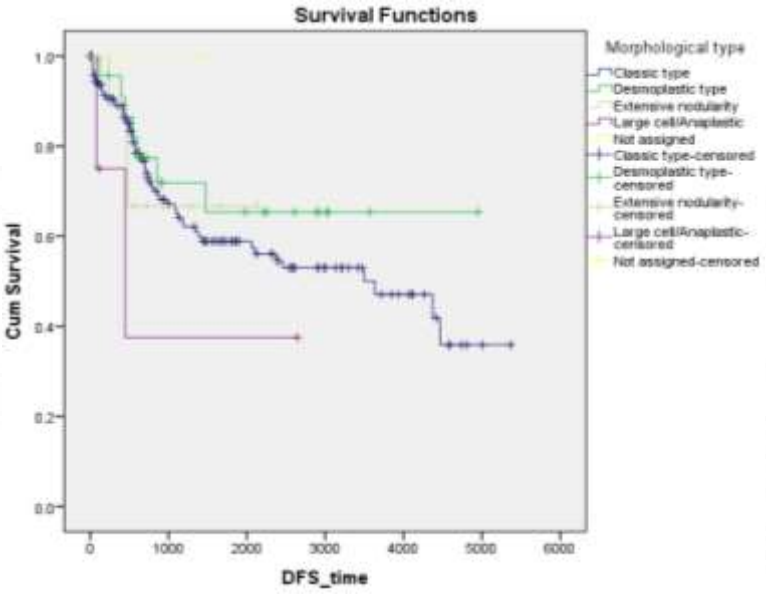
Log Rank (Mantel-Cox)	Vermis	Cerebellar Hemisphere	Forurth Ventricular Floor
Chi-Square	0.394	3.229	8.040
Sig.(P-Value)	0.530	0.072	0.005



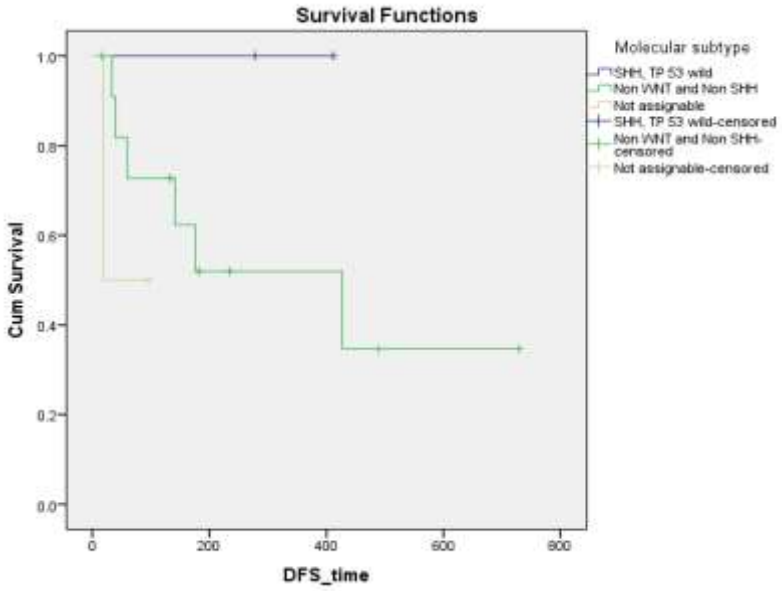


e. DFS in different Morphological Type:

Log Rank (Mantel-Cox)	
Chi-Square	2.829
Sig.(P-Value)	0.587

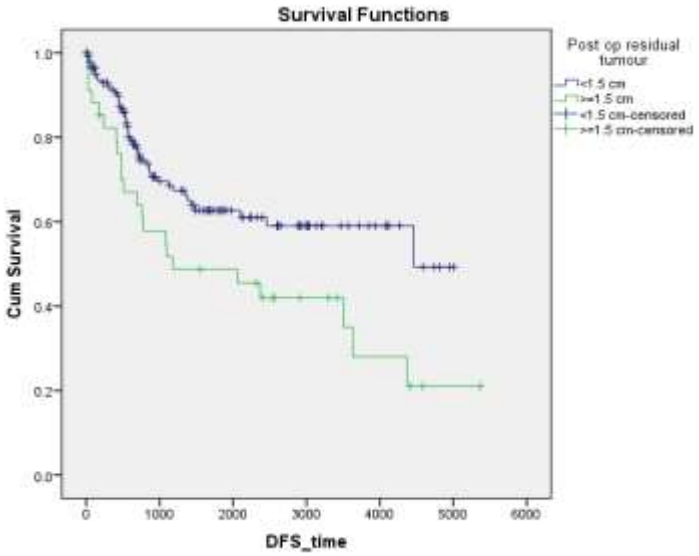


f. DFS Analysis in different Molecular Subtypes:



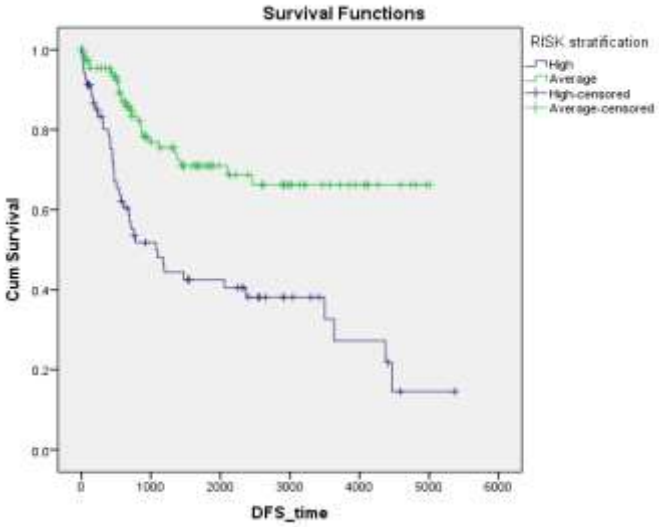
Log Rank (Mantel-Cox)	
Chi-Square	2,310
Sig.(P-Value)	0.315

g. Post op residual tumour(<1.5cm, >/= 1.5cm)



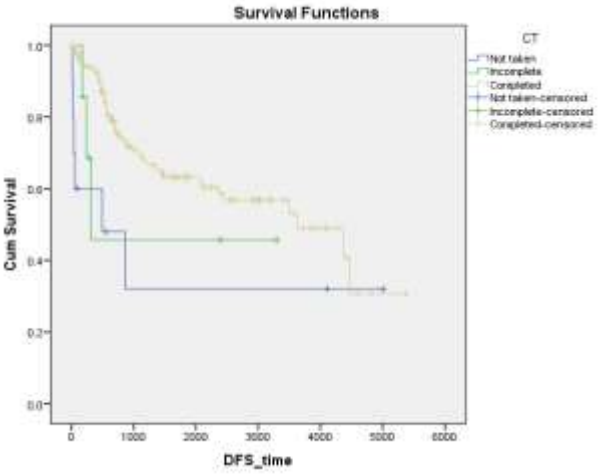
Log Rank (Mantel-Cox)	
Chi-Square	5.935
Sig.(P-Value)	0.015

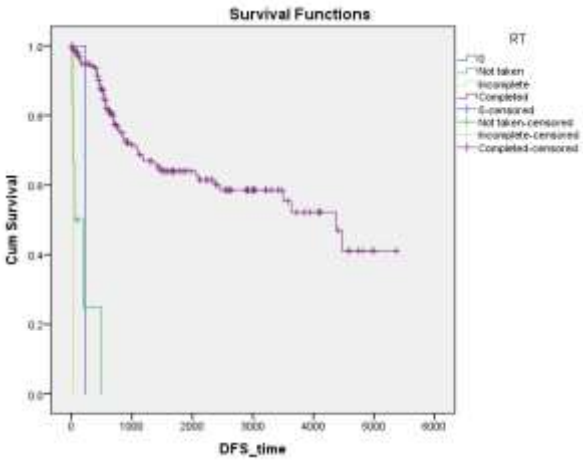
h. Risk stratification (Average and High):



Log Rank (Mantel-Cox)	
Chi-Square	20.640
Sig.(P-Value)	<0.0001

i. DFS in adjuvant therapy status





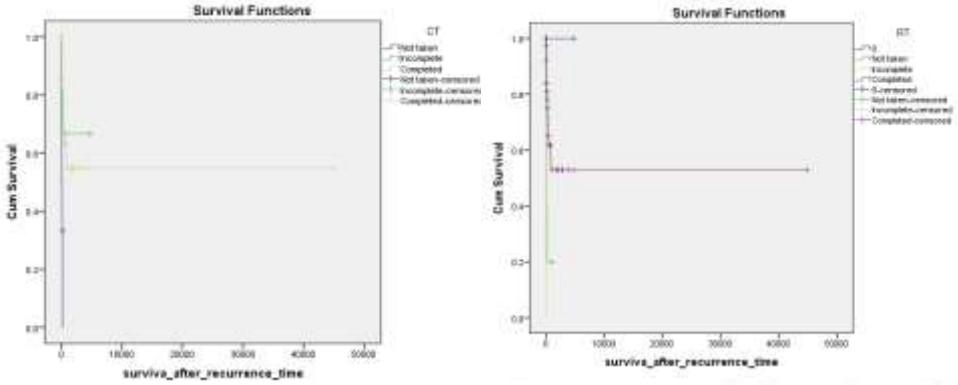
Log Rank (Mantel-Cox)	CT	RT
Chi-Square	5.716	3
Sig.(P-Value)	0.057	0.072

In Disease free survival analysis**(Figure 12a-i),** on comparing the preoperative morphology of the tumour in MRI, tumours with the well defined borders had lesser chance of recurrence than the lobulated and irregular border ones with significant P value of 0.036. The patients with pre op metastasis(P=0.001), age less than 3

years(P<0.0001), post op residual tumour > 1.5cm(P=0.015), High risk stratification (P<0.0001), those not completed adjuvant chemotherapy/radiotherapy (P=0.057) had poor disease free survival. Based on the epicentre of tumour origin or attachment, tumour arising from the fourth ventricle has high chance of recurrence(P=0.005) than other locations like vermis and cerebellar hemisphere. Among the Morphological subtypes, desmoplastic and MBEN had more chance of recurrence free survival than the classic and Large cell variety. In Molecular subtyping done in few numbers, non-WNT and non-SHH along with the not assigned category has higher rate of recurrence than SHH TP 53 wild type(P=0.315) eventhough not significant statistically

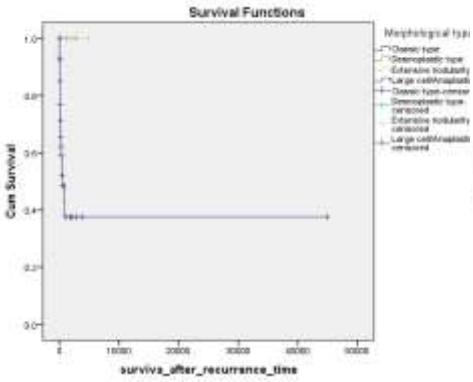
Figure 13(a-c): Survival after Recurrence(SAR):

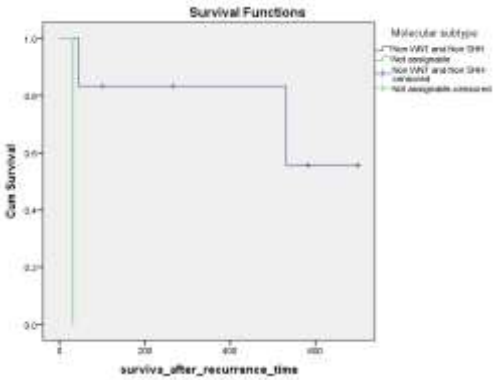
a. Status of Adjuvant chemotherapy with the SAR



Log Rank (Mantel-Cox)	CT	RT
Chi-Square	16.177	15.611
Sig.(P-Value)	<0.0001	0.001

b. Morphological subtype and Molecular subtype:

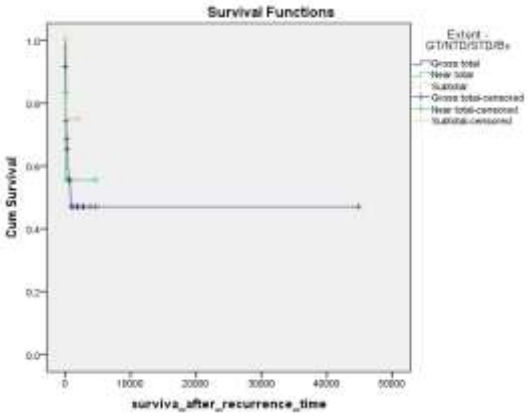


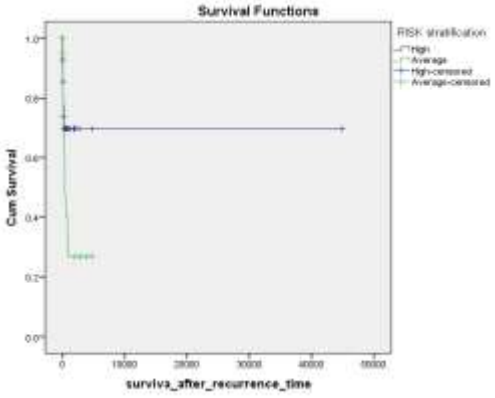


Log Rank (Mantel-Cox)	Morpho-logical	Mole-cular
Chi-Square	6.081	6
Sig.(P-Value)	0.108	0.014

c. Extent of resection and risk stratification

Log Rank (Mantel-Cox)	Extent of resection	Risk group
Chi-Square	0.841	3.986
Sig.(P-Value)	0.657	0.046





For Survival after recurrence**(Figure 13a-c)**, as the numbers were small in number and skewed significantly, significant results were not obtained in terms of adjuvant therapy, Morphological or molecular subtypes, risk stratification.

In the extent of resection group, gross total has poor survival after recurrence than subtotal or neartotal group (P-0.657) which was contrary to the available literature and also suggests the hypothesis that the recurrence and survival are determined by the tumour biology than the extent of surgery and adjuvant therapy status.

DISCUSSION

This proposed Retrospective observational study was aimed to assess the full spectrum of natural history of Medulloblastoma treatment starting from the Basic demography, Clinical presentation, neurological deficits, Imaging characteristics, surgical aspects, CSF diversion strategies, immediate post operative complications, Histopathological analysis, Adjuvant therapy related complications, Post op residual disease, relapse of the disease, functional outcomes, long term sequelae and survival analysis. In this study, we have collected data in the span of 17 years(2004 - 2021) from the medical records. Histopathological slides were reviewed, doubtful cases were filtered. Images were gathered from the Hospital PACS and discussed with radiologist. Post op follow up data and adjuvant therapy details were collected from the follow up OPD records. Telephonic and Whatsapp communication was made to the patients bystanders wherever feasible and data about the current health status were collected. Previously, there were multiple studies reported their single centre experience on the outcomes of medulloblastoma like Bleil et al in 2019 with 69 patients (Bleil et al., 2019), Enayet et al in 2021 with 405 patients (Enayet et al., 2021)

The mean age of incidence in this study was 10.9 years (Median – 8 years, Mode – 5 years). The majority of population was between 3 to 12 years. In a study by Bleil et al, the mean age reported was 7.3 years(Bleil et al., 2019).

In literature, 12% of the population were below the age of 3 years, in our study it was 10%(25 patients). The male and female populations were near equally distributed in this study (54% vs 46%). In Enayet et al, male and female ratio were 63.5% and 36.5% respectively. The most common clinical presentation noted was increased ICP (Headache, vomiting) in 94% followed by gait disturbances(61%),

cerebellar symptoms(20%) and diplopia(25%) due to nerve palsy or nystagmus. The rare clinical presentations noted were facial palsy(2%), motor deficits(3%), lower cranial palsy(2%), seizures(5.6%), spine related complaints(4.8%), systemic symptoms(7%), hydrocephalic attack(2.4%), cognitive disturbances(2%) which were sparcely reported in the literature (Seizures 2%, cranial nerve palsy 2%, ataxia – 40%)(Enayet et al., 2021)

On clinical examination, cerebellar signs were noted in 48%, papilledema noted in 56%, gait unsteadiness in 53%. Around 8.8% were presented in unstable clinical condition requiring urgent intervention in the form of CSF diversion, tumour decompression, ICU admission. Patients with increased ICP, cerebellar symptoms, visual blurring were presented early in clinical course than patients presenting with the cranial nerve palsies(even though no statistical significant P value found). This information was not available in the literature to compare.

On preop imaging, most common location of tumour was noted in vermis (59%), followed by fourth ventricle(21%) and cerebellar hemisphere(19%). Hydrocephalus noted in 88% of patients. In a study by (Park et al., 1983), tumour arising from vermis was found in 93%, with brainstem infiltration noted in 32%. The incidence of metastasis was 21.7% in our study as compared to 40% as mentioned in the literature(Massimino et al., 2016)

Most of the lesions were showing diffusion restriction (P=0.041) with the predominant contrast enhancement being heterogenous pattern. In classic type, the planes with fourth ventricle were absent in more proportion than other morphological types. Similarly, planes with the cerebellum were absent more in desmoplastic types

(75%) than others. In cerebellar hemisphere, Desmoplastic variety was noted in more proportion than other types. But the subtype specific radiological findings as reported by (Yeom et al., 2013) that focal cysts in classic and desmoplastic types, leptomeningeal enhancement in LC or anaplastic medulloblastoma, ring enhancement with tumor necrosis in LC or anaplastic subtype were not observed in our study.

On comparing the imaging features with the clinical deficits, lesions in cerebellar hemisphere has higher probability of having cerebellar signs(P=0.011) and gait disturbances(P=0.013). Patients with the Tonsillar herniation noted in MRI has higher probability of having cerebellar signs (P=0.010) and gait disturbances(0.012). This correlation was not done before.

In this study, midline suboccipital craniotomy(91%) followed by the Telovelar tonsillar approach(43%) was the most commonly performed. The factors determining the extent of resection were tumour planes with the brainstem, infiltration into the structures, consistency of the tumour($P<0.05$).

The number of patients who underwent initial CSF diversion procedure before tumor surgery was 88.5%(including EVD, shunt and ETV). In (Enayet et al., 2021), the preop diversion percentage was 85%(VP shunt and ETV). In our study, the pre-op CSF diversion (88.5%%) was done mainly through the External ventricular drainage(137, 66.5 %), followed by VP shunt in (31,15.4%) and ETV in 15(7%).

The Gross total resection was done in 81%, Near total in 7%, and subtotal in 12% of patients in the literature(Enayet et al., 2021). In our study, the extent of

resection was as follows, GTR was 64%, NTD was 29%, STD was 6.8%, Biopsy in 0.4%. Gross total excision was 64% as compared to 81% in the literature. But, the subtotal decompression was 6.8% as compared to 12% in the literature. This has led us to compare the effect of GTD, NTD and STD, which revealed NTD has better overall survival than GTD in our study($P<0.001$).

Tumour characteristics observed during the surgery did not have any significant correlation with the morphological tumour types except for the consistency (Classic tumours were predominantly soft, whereas desmoplastic and MBEN had majority of firm consistency, $P=0.04$).

In literature, the morbidity of surgery and other related factors were not available sufficiently, like operative cavity bleed(17%), IVH (8%), EDH (2.6%) and increase in tumour related edema(11.5%)

The residual lesion was 14%, relapse rate in this study was 37%. Relapse seems to occur in either same site or different site. The details regarding the disseminated disease (15%), other sites of relapse, leptomeningeal spread were recorded sparsely in the literature which has been analysed in this study.

On analysing the factors determining the residual lesion or occurrence of relapse, extent of resection($P<0.0001$), planes with the brainstem($P=0.004$), extension into the foramen($P=0.003$), intaop evidence of metastasis($P=0.043$) were noted to be significant which is in agreement with the available literature.

The morbidity of readmission and redosurgery was less known for this condition. The readmission rate in our study was 22%, in that 22% admitted for

conservative management, 78% admitted for additional surgical procedures. The CSF diversion failure times were 8.8% in this study. Overall 39% require permanent CSF diversion procedures in that 32% underwent Ventriculo-peritoneal shunt, 7% underwent Endoscopic third ventriculostomy.

On analysing the residual disease and relapse in the different morphological types, there no significant correlation observed probably due to less numbers in each category. The CSF cytology positive rate depicted in literature was around 30%(Terterov et al., 2010) which was not affecting the survival time. In the initial days of the study, CSF cytology analysis was done, later that practice was stopped as it did not had much role or help in the decision making in the patient management and also requires tedious process in storage and analysis. The CSF positivity rate in our study was 23.5%. On comparing the CSF cytology results with the tumour relapse factors, leptomeningeal disease has more CSF positivity(Fouladi et al., 1999)

The redo-surgery required in immediate post op was 6.4% which included hematoma evacuation, decompression, bone flap removal. The redosurgery was required later in 40 patients(16%), in that 10% done for tumour related, 6.8% done for other problems.

ETV success rate was 79% in this study. In a study by (Salah et al., 2022) the reported ETV success rate was 100%, in a study by (Grand et al., 2016) the success rate of ETV was 72.8% in 250 patients.

In this study, participants were risk stratified into average risk and high risk, as per available criteria in the literature. The high risk group has statistically significant($P<0.05$) risk of developing the tumour relapse in terms of all available risk

factors like age < 3 years, preop metastasis, post op residual disease, high risk histology($P<0.05$)(Gilbertson et al., 2001).(Gajjar et al., 2006; Tarbell et al., 2013)

The molecular subtyping was done in our institute using Immunohistochemistry in 26 patients. In that WNT type was found in none, SHH and TP53 wild was 19%, Non WNT and Non SHH were 62%, 19% of them were not assignable to any category (Need further transcriptome analysis)(Cotter and Hawkins, 2022; Gianno et al., 2022; KOMORI, 2017; Louis et al., 2021).

The distribution of Morphological types in our study were as follows: Classic(78%), Desmoplastic/nodular(14%), Extensive nodularity(5%) and Large cell/Anaplastic(3%) type. In (Enayet et al., 2021; Tarbell et al., 2013) the classic type was 44%, Desmoplastic type was 12%, MBEN was 5.4%, Anaplastic type was 31% reported in the literature. In this study, the classic variety was predominant and the proportion of large cell/Anaplastic variety was less than what is reported in the literature. In (Park et al., 1983), the classic type was seen in 82%, desmoplastic was seen in 15% of the patients.

Among the post operative complications, most commonly noticed was Nystagmus – Extraocular movement abnormality(42%), gait disturbances(34%), cerebellar ataxia(28%), cerebellar mutism(17%). The cerebellar mutism reported in literature ranges from 0 to 30%, 9% in (Enayet et al., 2021), 25% in (Robertson et al., 2006), 16% in (Wibroe et al., 2018). Post op meningitis was noted in 12%, wound infection noted in 4.8%, Fever for other causes has been found to be (11%).

The rate of Pseudomeningocele was 17%, CSF leak occurred in 5.2%, Post op DVT in 1.6% of patients. The overall readmission rate was 22% in our study either due to infection, meningitis, shunt, redo tumour sugery(Enayet et al., 2021).

On comparing the post operative complications with the intraop surgical parameters, poor planes with the brainstem and infiltration into surrounding structures has higher occurrence of EOM abnormality(P=0.002), lower cranial palsy and facial palsy(P=0.023),

In this study, the intraop tumour extension into the foramen is associated with the higher incidence of cerebella mutism and lower cranial palsies($P<0.05$). This correlation was not available in the literature.

Regarding the adjuvant therapy, patients were given appropriate radiotherapy dose and chemotherapy regimen based on evidence from time to time guidelines at another centre(Regional cancer centre, Trivandrum). In this study, majority had radiation first followed by chemotherapy. Around 85% of patients completed chemotherapy and 92% completed radiotherapy. Around 15% of patients either did not take chemotherapy or partially completed; 8% of patients either did not taken radiotherapy or taken incompletely.

On comparing adjuvant therapy status with the disease relapse, redo-surgery for tumour, and disseminated disease, there was no significant correlation observed, probably because of low numbers in the non-compliant group (as majority was following advice unless in some unforeseen circumstances)

On follow up, functional outcomes were documented and current functional status was enquired via the telephonic questionnaire to the caregiver or from the patient based on PedsQl score. It was analysed in the four domains physical activity, Activities of daily living, Scholastic Performance, behavioural issues and social interactions. The physical activity was normal/Need mild assistance in 82%, need significant assistance/bed ridden in 18% of patients. Scholastic performance was good only in 2%, rest had average(40%), below average(40%) and poor(19%) performance(Odame et al., 2006).

The functional outcomes of the patient were largely affected by the adjuvant therapy and to a a small extent by the extent of resection. In this study, we did not find any statistical correlation between adjuvant therapy and functional scores(Packer et al., 2003).

On long term follow up, patients had developed complications like hearing impairment(28%), visual impairment(17%), developmental delay(4.6%), Hypothyroidism(35%), Growth hormone deficiency(30%), menstrual related issues in (15%), speech disturnbances(10%), cognitive impairment in 16% of patients(Nandagopal et al., 2008).

Survival status in this study:

Most of the publications on the survival of medulloblastoma patients were based on the results of clinical trials, which may have specific inclusion criteria and end point. Therefore, those studies may not represent the actual survival data of the general population and the natural history of the treated medulloblastoma patients.

In this study, COX regression analysis done for overall survival, progression free survival and survival after recurrence. Hazards ratio calculated for various related variables. For overall survival, preop metastasis, high risk group, post op residue>1.5cm has lesser overall survival but not statistically significant P value.

On COX multivariant regression unadjusted analysis for disease free survival, Tumour location in the fourth ventricle(HR – 2.05, P=0.006), irregular morphology(HR – 2.256, P=0.025), preop metastasis(HR-2.2, P=0.002), post op residual tumour>1.5cm(HR-1.8,P=0.017) are all having higher odds for disease recurrence which is statistically significant. In (Liu et al., 2022) it was showed that the absence of metastasis in preop stage, extent of resection, morphological type(Desmoplastic), molecular subtype and adjuvant therapy seems to affect the survival parameters. On the other hand, patients who underwent adjuvant therapy has lesser chances of disease recurrence. For Survival after recurrence, no significant factors found to be statistically significant probably because of less numbers in this group which skew the distribution.

For OS,DFS and SAR – Kaplan Meier analysis was done with respect to each risk factor. The overall survival reported in the literature was 44.5%(Bleil et al., 2019) PFS was 36.4%. In (Massimino et al., 2013, 2016), the 5 year OS was 81%, PFS was 76%. In the current study, the 5 year DFS survival rate in this study was 58%, 10 year survival rate was 49%. The overall survival at 5 years was 81%, at 10 years 76%, and at follow up of 15 years was 68%. The Survival after recurrence was found to be 50% at the end of 5 year follow up.

In OS analysis, age group less than 3 years had better survival advantage which was in contrary to the literature where children less than 3 years group falls under high risk category and hence has poor survival. This can be explained by the fact that those children did not have any events till the follow up data was available.

The risk stratification schema did not seem to affect the OS as mentioned in the literature(Tarbell et al., 2013), this points out that the tumour biology plays a significant role in survival than any other prognostic factors(Gilbertson et al., 2001). This needs further trails comparing the survival and recurrence among the molecular types.

The presence of factors like CSF cytology positivity for malignant cells, presence of preop metastasis, post operative residual tumour > 1.5cm, infiltration noted in histopathology had lesser survival rate than the corresponding groups(though not statistically significant). On comparing the extent of resection, near total excision has better overall survival than the gross total with statistically significant P value(<0.001). At the same time, poor planes with the brainstem had better survival than good planes(P=0.209) in contrary to the literature. This can be explained by the fact that the tumours with the poor planes seldom undergoes gross total in view of difficulty in resection hence most of them undergone Near total resection (as depicted in table 8, P<0.0001). This reiterates the fact that the aggressive surgical approach to achieve Gross total was not essential to achieve the better survival outcomes as reported in the study(Haque et al., 2020). This finding has been showed in Thompson et al, they found that among the 787 patients operated, there was no overall survival benefit observed between gross total and near total excision group after accounting for the molecular subgroup analysis(Thompson et al., 2016). The multimodality treatment plays a vital

role in improving the survival among the patients not only the extent of resection. The occurrence of Cerebellar mutism did not seem to be influence the overall survival. Among the morphological types, Desmoplastic and MBEN had better outcomes than classic and Large cell/anaplastic variety (P=0.536) with no statistical significance. In the Molecular subtyping done in few cases, SHH-activated, TP53-wildtype had better survival than non-WNT/non-SHH type; tumours not assignable to any molecular group by IHC had the worst prognosis overall(P=0.280). In Susral et al, non-WNT and non-SHH had poor survival than other groups(Sursal et al., 2022).

In DFS, one interesting findings noted in this study was that the tumours with the irregular borders and fourth ventricular location had higher chances of recurrence and lesser disease free survival (P<0.05). This corelation was not reported elsewhere in the literature eventhough the theoretical idea exists.

The disease-free survival was less in patients with pre-op metastasis (P=0.001), age less than 3 years (P<0.0001), post-op residual tumour > 1.5 cm (P=0.015), high risk stratification (P<0.0001), and those who have not finished adjuvant chemotherapy/radiotherapy (P=0.057).Desmoplastic/nodular and MBEN morphological subtypes had a higher likelihood of surviving without recurrence than the classic and large cell/anaplastic subtypes. This findings has been already reported in children less than 3 years by(Ryzhova et al., 2013). Although not statistically significant, non-WNT/non-SHH subtype as well as the category not assignable to any types did have a greater risk of recurrence than SHH-activated and TP53-wildtype in the molecular subtyping of the tumours (P=0.315)(Liu et al., 2022).

The Adjuvant therapy, morphological subtypes, molecular subtypes, or risk stratification did not yield significant results for survival following recurrence probably due to the small sample size and substantially skewed data. In this study, the gross total resection group has worse survival after recurrence than the subtotal or near-total group (P-0.657) which was contrary to the traditional belief. This supports the idea that the tumour biology has major role in disease recurrence and survival, rather than the extent of surgery and adjuvant therapy status. This suggests the need for further comparison analysis with large number of molecular subtype data about the Medulloblastoma.

CONCLUSION

1. In our study, tumours arising from the fourth ventricle(HR – 2.05, P=0.006), irregular borders (HR – 2.256, P=0.025), evidence of metastatic disease prior to surgery (HR-2.2, P=0.002), and postoperative residual tumour > 1.5cm(HR-1.8,P=0.017) were all having higher odds for disease recurrence and lesser survival rates, which were statistically significant.
2. The overall survival at 5 years was 81%, at 10 years was 76%, and at follow up of 15 years was 68%. The 5 year disease free survival rate in this study was 58%, 10 year DFS rate was 49%. The survival after recurrence was found to be 50% at the end of 5 year follow up.
3. Though the extent of resection did not seem to affect the DFS, those patients undergoing complete or near-total excision had better overall survival than those with partial or sub-total resection; this was statistically significant.
4. Adjuvant therapy had an influence on the long term sequelae though statistically not significant.
5. The Desmoplastic/nodular and medulloblastoma with extensive nodularity had better survival rates than the classic and large cell/Anaplastic types.
6. On molecular subtype analysis in a minor subgroup of patients where this data was available, SHH-activated and TP53-wildtype group had better survival than non-WNT/non-SHH type and the group in which molecular subtyping was not assignable (though statistically not significant). This suggests further molecular subtype studies in large numbers to determine the significance.

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ANNEXURES

List of publications from Thesis: Not yet published

Curriculum Vitae

CV of the Investigators – Principle Investigator

<table>
<tr><td colspan="2"></td><td></td></tr>
<tr><td>Last Name VELLORE DASARATHAN</td><td>First Name LOKESH</td><td>Middle Name</td></tr>
<tr><td colspan="2">Date of Birth (dd/mm/yy) 05/07/1992</td><td>Sex - MALE</td></tr>
<tr><td colspan="3">Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator)
PRINCIPAL INVESTIGATOR, SCTIMST</td></tr>
<tr><td colspan="2">Professional Mailing Address (Include Institution name) :
vdmlokesh@sctimst.ac.in</td><td>Study Site Address (Include Institution name)</td></tr>
<tr><td colspan="2">DEPARTMENT OF NEUROSURGERY,
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
THIRUVANANTHAPURAM
KERALA 695011</td><td>DEPARTMENT OF NEUROSURGERY,
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
THIRUVANANTHAPURAM
KERALA 695011</td></tr>
<tr><td colspan="2">Telephone (Office):</td><td>Mobile Number: 9597193749</td></tr>
<tr><td colspan="2">Telephone (Residence):</td><td>Email: vdmlokesh@sctimst.ac.in, vdmlokesh@gmail.com</td></tr>
<tr><td colspan="3">Academic Qualifications (Most recent qualification first)</td></tr>
<tr><td>Degree/Certificate</td><td>Year</td><td>Institution, Country</td></tr>
<tr><td>MS GENERAL SURGERY</td><td>2017 - 2020</td><td>CHRISTIAN MEDICAL COLLEGE, VELLORE
TAMILNADU, INDIA</td></tr>
<tr><td>MBBS</td><td>2009 - 2015</td><td>GOVERNMENT CHENGALPATTU MEDICAL COLLEGE, CHENGALPATTU,
TAMILNADU, INDIA</td></tr>
<tr><td colspan="3">Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration
TRAVANCORE COCHIN MEDICAL COUNCIL
REGISTRATION NUMBER: 79088
YEAR OF REGISTRATION: 2021</td></tr>
<tr><td colspan="3">Current and previous positions (most recent position first)</td></tr>
</table>

Month and Year	Title	Institution/Company, Country
JANUARY, 2021	SENIOR RESIDENT, NEUROSURGERY	SCTIMST, INDIA
SEP 2020 – DEC 2020	SENIOR RESIDENT, DEPARTMENT OF GENERAL SURGERY	SRM INSTITUTE OF MEDICAL SCIENCES AND RESEARCH, KATTANKALATHUR, CHENGALPATTU DIST, TAMILNADU
DEC 2015 – MAY 2016,	NON PG JUNIOR RESIDENT IN DEPT OF SURGERY, ORTHOPAEDICS AND PAEDIATRICS,	MELMARUVATHUR ADHIPARASAKTHI INSTITUTE OF MEDICAL SCIENCES, MELMARUVATTUR

Brief summary of relevant research experience:

PUBLICATIONS

1. An overview of GIST in stomach – Dr M.G.R University Surgical e-Journal.
2. Landouzy sepsis – presenting as surgical emergency, A rare case report and review of literature – BMJ case reports.

CONFERENCE PRESENTATIONS:

1. IASGCON 2019, AIIMS, NEW DELHI, presented special mention poster on the topic. "Molecular approach and Microsatellite instability in Gastric cancers"
2. TRAVANCORE NEUROCON 2021, Poster presentation on "**Acute paraplegia with severe dorsal kyphotic deformity in a young adult with dorsal spine aneurysmal bone cyst"**
3. Association of spine surgeons of India – ASSI 2022, INSTRUCTIONAL COURSE IN SPINE, BHUBHANESHWAR Nov 2022 – Oral Paper presentation on "**A retrospective observational study on rare intramedullary spinal lesions – Clinical and demographic profile, surgical outcome and prognosis"**
4. SKULLBASECON 2023 – Interim meet – Presented e-poster on "**Pterional Approach For Anterior Skull Base Midline Meningiomas Against "The More The Merrier" Approach-An Institutional Experience**

MS DISSERTATION

Pathologic downstaging of adenocarcinoma stomach following neoadjuvant chemotherapy and the role of microsatellite instability (MSI) in predicting response.

Current project/s at hand:

- Long term surgical outcome following multimodality treatment in medulloblastoma

Signature: 	Date: 11/10/2021 Place: Trivandrum

CV of the Guide:

Last Name DIVAKAR	First Name GANESH	Middle Name
Date of Birth (dd/mm/yy) - 04/03/1970		Sex Male
Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator) CO-INVESTIGATOR		
Professional Mailing Address (Include Institution name)		Study Site Address (Include Institution name)
Assistant Professor, Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695011, Kerala, India.		Assistant Professor, Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695011, Kerala, India.
Telephone (Office): 0471 2524646		Mobile Number: 9447095720
Telephone (Residence): nil		Email : gd@sctimst.ac.in

Academic Qualifications (Most recent qualification first)		
Degree/Certificate	Year	Institution, Country
Fellowship in spine surgery	2017	AIMS, Kochi, India
MCH - NEUROSURGERY	2008	SCTIMST, Trivandrum, Kerala, India
MS – General surgery	2005	Govt. MCH, Kottayam, Kerala, India
MBBS	2001	Govt. MCH, Trivandrum,Kerala, India

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration – TCMC 29932, year: 2001		
Current and previous positions (most recent position first)		
Month and Year	Title	Institution/Company, Country
Aug 2018 to present	Assistant Professor, Neurosurgery	SCTIMST, Trivandrum

April 2009 to Nov 2016	Consultant spine and Neurosurgeon	SIMS, Kollam, India

Brief summary of relevant research experience:

I have a special interest in spine surgery and does complex spinal instrumentation cases along with cranial neurosurgery. With active interest in spine surgery, I completed a 1 year fellowship in advanced spine surgery at Amrita institute of medical sciences, Kochi in 2017. In 2018, I joined as Assistant professor in SCTIMST, and is actively involved in teaching of senior residents, research, clinical and surgical work in the field of cranial and spinal Neurosurgery with multiple ongoing intramural and extramural funded projects.

Current project/s at hand:

Extramural funded projects:

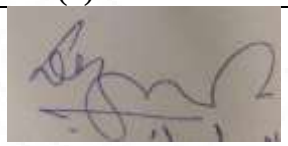
1. OMI/6/2020 – ECD-I: A prospective study on cerebrospinal fluid (CSF) diversion catheter-related infections in a tertiary referral neurosurgical care centre(co-PI) – funded by ICMR(INR 12 lakhs)

Intramural funded projects:

1. TRC/8220/PSN: Spinal fixation system for thoracolumbar stabilization(co-PI)(INR 1 crore 42 lakhs)
2. RC06 P04: High strength titanium castings for orthopaedic applications(co-PI) (INR 66 lakhs)
3. TDF project: Design of novel polyaxial pedicle screws(co-PI)

Recent publications to indexed journals/chapters in books:

1. Divakar G Head injury in Babu RD,editor, Surgical handicraft, 2nd ed. New Delhi, Jaypee Publishers, 2020
2. Spinal angiolipoma-a rare but reversible cause of paraplega in a child. (Review article: corresponding author) Jaiswal PA, Divakar G, Krishnakumar K, Karthikeyan A, Sawakare Y MhatreI R, Abraham M. Childe Nerv Syst 2020 Jan, 36(6) 1121-1125 doi:10.1007/s00381-020-04542-5. Epub 2020 Feb 12
3. Split Cold Malformation Type 2 with Double Dorsal Lipoma: A Sequela or a Chance, Jamaludin MA, Nair P, Divakar G, Gohil JA, Abraham M. Paediat. Neurosci, 2020 Apr-Jun: 15(2):135-139. Doi: 10.4103/jpnJPN_131_19. Epub 2020 Jun 27

Signature: 	Date: 11/10/2021 Place: Trivandrum

CV of the Co-Guide 1:

Last Name HV	First Name EASWER	Middle Name
Date of Birth (dd/mm/yy) - 29/05/1971		Sex Male
Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator) CO-INVESTIGATOR		
Professional Mailing Address (Include Institution name)		Study Site Address (Include Institution name)
Professor and Head, Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695011, Kerala, India.		Professor and Head, Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695011, Kerala, India.
Telephone (Office): 91 471 2443152, Fax: +91 471 2550728		Mobile Number: 9847010577
Telephone (Residence): nil		Email : easwer@sctimst.ac.in

Academic Qualifications (Most recent qualification first)		
Degree/Certificate	Year	Institution, Country
PDF (Post Doctoral Fellowship): Vascular Neurosurgery	2003-04	Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum,Kerala, India
MCH - NEUROSURGERY	1998-2002	Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India
MBBS	1989-1996	Medical College Trivandrum/ University of Kerala, Trivandrum, Kerala, India

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration – TCMC 24156 / 1996		
Current and previous positions (most recent position first)		
Month and Year	Title	Institution/Company, Country

July 2021	Head of the Department,Neurosurgery	SCTIMST, Trivandrum
Aug 2015 – Jun 2021	Professor, Neurosurgery	SCTIMST, Trivandrum
2013 - 2015	Additional Professor	SCTIMST, Trivandrum
2009 - 2014	Associate Professor	SCTIMST, Trivandrum

Brief summary of relevant research experience:

1.Bharathan Bhavya C. R. Anand, U. K. Madhusoodanan, P. Rajalakshmi, K. Krishnakumar, H. V. Easwer, A. N. Deepti & Srinivas Gopala .*Cellular and Molecular Neurobiology* volume 40, pages53–63(2020)

2. Sanish Sathyan, Linda V. Koshy, Lekshmi Srinivas, H. V. Easwer, S. Premkumar, Suresh Nair, R. N. Bhattacharya, Jacob P. Alapatt & Moinak Banerjee . Pathogenesis of intracranial aneurysm is mediated by proinflammatory cytokine TNFA and IFNG and through stochastic regulation of IL10 and TGFB1 by comorbid factors. *Journal of Neuroinflammation* volume 12, Article number: 135 (2015).

3. Padmakrishnan CJ1 & Easwer H V 2 & Vinod Vijayakurup1 & Girish R Menon2,3 & Suresh Nair2 & Srinivas Gopala1.High LC3/Beclin Expression Correlates with Poor Survival in Glioma:
a Definitive Role for Autophagy as Evidenced by In Vitro Autophagic Flux

4. George C Vilanilam, HV Easwer, Girish R Menon, Vikram Karmarkar. “Magister neurochirurgiae”: A 3-year 'crash course' or a 5-year 'punctilious pedagogy'? Year : 2017 Volume : 65 Issue : 2

5. Bharathan Bhavya, H.V. Easwer, G.C. Vilanilam, C.R. Anand, K. Sreelakshmi, Madhusoodanan Urulangodi, P. Rajalakshmi, Issac Neena, C.J. Padmakrishnan, Girish R. Menon, K. Krishnakumar, A.N. Deepti, Srinivas Gopala.MutT Homolog1 has multifaceted role in glioma and is under the apparent orchestration by Hypoxia Inducible factor1 alpha. Life Sciences, Volume 264, 1 January 2021, Pages 118673

6. Vilanilam GC, Easwer H V, Vimala S, Radhakrishnan A, Devi B I, Nair SN. Women and Neuroscience Publishing: Is the Gender Gap closing in?. Neurol India 2016;64:583-5

7. Appavoo Arulvelan, Sethuraman Manikandan, Hari Venkat Easwer, Kesavapisharady Krishnakumar Cerebral vascular effects of loading dose of dexmedetomidine: A Transcranial Color Doppler study.

8. Vilanilam GC, Kumar K K, Aggrawal V, Sudhir B J, Nair P, Easwer H V, Abraham M, Nair SN.
Simulated neurosurgical reality: Could it fall short of the real thing?. Neurol India 2016;64:1108-10.

9. Suresh Nair, C. V. Gopalakrishnan, Girish Menon, H. V. Easwer, and Mathew Abraham Interhemispheric transcallosal transforaminal approach and its variants to colloid cyst of third ventricle: Technical issues based on a single institutional experience of 297 cases.

10. Easwer HV, Chatterjee N, Thomas A, et al. Usefulness of flat detector CT (FD-CT) with biplane fluoroscopy for complication avoidance during radiofrequency thermal rhizotomy for trigeminal neuralgia. *J Neurointerv Surg* 2015; 8:830–833.

11. Arulvelan A, Manikandan S, Easwer HV, Krishnakumar K. Effect of Loading Dose of

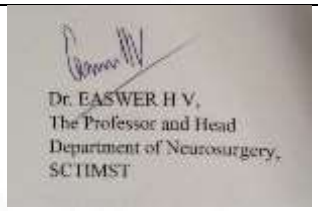
Dexmedetomidine on Dynamic Cerebral Blood Flow Autoregulation in Patients with Intracranial Glial Neoplasms. J Neurosurg Anesthesiol 2015 Jan 16. [Epub ahead of print]
12. Gopalakrishna KN, Dash PK, Chatterjee N, Easwer HV, Ganesamoorthi A. Dexmedetomidine
as an Anesthetic Adjuvant in Patients Undergoing Transsphenoidal Resection of Pituitary Tumor. J Neurosurg Anesthesiol 2014 Dec 9. [Epub ahead of print]
13. Sathyan S, Koshy LV, Balan S, Easwer HV, Premkumar S, Nair S, Bhattacharya RN, Alapatt
JP, Banerjee M. Association of Versican (VCAN) gene polymorphisms rs251124 and rs2287926 (G428D), with intracranial aneurysm. Meta Gene. 2014; 2:651-60.
14. Patil AS, Menon G, Easwer HV, Nair S. Extraventricular neurocytoma, a comprehensive review. Acta Neurochir (Wien) 2014; 156: 349-54.
15. Pradeep Kumar SS, Easwer HV, Maya Nandkumar A. Multiple drug resistant bacterial biofilms on implanted catheters - a reservoir of infection. J Assoc Physicians India 2013; 61: 702-7.
16. Sathyan S, Koshy L, Sarada Lekshmi KR, Easwer HV, Premkumar S, Alapatt JP, Nair S, Bhattacharya RN, Banerjee M.Lack of association of lysyl oxidase (LOX) gene polymorphisms with intracranial aneurysm in a south Indian population. Mol Biol Rep 2013; 40: 5869-74.
17. Thomas AJ, Gross BA, Jacob A, Easwer HV. Essential hypertension as a result of neurochemical changes at the rostral ventrolateral medulla. J Clin Neurosci 2013; 20:1682-7.
18. Ajith Cherian, Neeraj N Baheti, HV Easwar, Divya S Nair, Thomas Iype. Recurrent meningitis
due to epidermoid. Journal of Pediatric Neurosciences 2012; 7: 47-8.
19. CV Gopalakrishnan, Adesh Shrivastava, HV Easwer, Suresh Nair. Primary Ewing's sarcoma of the spine presenting as acute paraplegia. Journal of Clinical Neurosciences 2012; 7: 64-6.
20. R Neelima, HV Easwer, TR Kapilamoorthy, Divyata Hingwala, VV Radhakrishnan. Embryonal
tumor with multilayered rosettes: Two case reports with a review of the literature. Neurology India 2012; 60: 96-9.
21. Linda Koshy, Easwer HV, Prem Kumar, Jacob Alappat, Marthanda Pillai, Suresh Nair, RN Bhattacharya, Moinak Banerjee. Risk factors for aneurismal subarachnoid hemorrhage in an Indian population. Cerebrovascular Disorders 2010; 29: 268-74.
22. Bahuleyan B, Menon G, Nair S, Rao BR, Easwer HV, Krishna K. Non-surgical management
of cystic prolactinomas. J Clin Neurosci 2009; 16: 1421-4.
23. Menon G, Nair S, Sudhir BJ, Easwer HV, Rao BRM. Menigiomas of the lateral ventricle: a report of 15 cases. British Journal of Neurosurgery 2009; 23:297-303.
24. Menon G, Easwer HV, Radhakrishnan VV, Nair S. Symptomatic granular cell tumour of the pituitary. Br J Neurosurg 2008; 22: 126-30.
25. Koshy L, Easwer HV, Neetha NV, Natarajan C, Bhattacharya RN, Banerjee M. Role of endothelial nitric oxide synthase gene polymorphisms in predicting aneurysmal subarachnoid hemorrhage in South Indian patients. Disease Markers 2008; 24: 333-9.
26. Easwer HV, Bhattacharya RN, Nair S, Rao BRM, Menon G, Abraham M, Krishna Kumar K.

Pre-coronal, para-median minicraniotomy: a minimal access approach for microsurgical, transcallosal, transforaminal removal of colloid cysts of the third ventricle. Minimally Invasive Neurosurgery 2008; 51:253-7.
27. Rajesh BJ, Rao BRM, Menon G, Abraham M, Easwer HV, Nair S. Telovelar approach: technical issues for large fourth ventricle tumors. Childs Nerv Syst 2007; 23: 555-8.
28. Easwer HV, Rajeev A, Varma HK, Vijayan S, Bhattacharya RN. Cosmetic and radiological outcome following the use of synthetic hydroxyapatite porous-dense bilayer burr-hole buttons. Acta Neurochirurgica 2007; 149: 481-86.
29. S Nair, G Menon, BRM Rao, BJ Rajesh, A Mathew, HV Easwer. Incidental intracranial aneurysms. Annals of Indian Academy of Neurology 2007; 10: 12-20.
30. Linda V Koshy, HV Easwer, RN Bhattacharya, Moinak Banerjee. Lack of association of endoglin insertion polymorphism in intracranial aneurysms in South Indian population. Indian Journal of Human Genetics 2006; 12: 111-5.
31. Menon G, Easwer HV, Nair S, Radhakrishnan VV. Symptomatic granular cell tumor of pituitary. British J Neurosurgery 2008; 22: 126-30.
32. Bhattacharya RN, Rao BRM, Easwer HV et al. Changing trends in the management of Pineal
region tumors. Progress in Clinical Neurosciences 2004.

Current project/s at hand:

Development of Cerebral Dialysis Catheter

Development of Cerums Boue substitutes

Signature: 	Date: 11/10/2021 Place: Trivandrum

CV of the Co-Guide 2:

Last Name AN	First Name Deepti	Middle Name
Date of Birth (dd/mm/yy): 17/07/1974		Sex: Female
Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator): Principal Investigator		
Professional Mailing Address:		Study Site Address

(Include Institution name)	(Include Institution name)
Department of Pathology SCTIMST, Trivandrum	Department of Pathology SCTIMST, Trivandrum
Telephone (Office): 0471-2524594	Mobile Number: 9481036933
Telephone (Residence): -	Email: akkihebbal@sctimst.ac.in

Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
PhD	2014	Université catholique de Louvain, Belgium
Postdoctoral fellowship in Neuropathology	2005-2006	National Institute of Mental Health and Neurosciences, Bangalore, India
MD (Pathology)	2004	Christian Medical College, Vellore, Tamil Nadu, India
MBBS	1998	Karnataka University, Dharwad, Karnataka, India

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration

Tamil Nadu Medical Council Registration Number: 67785 Year: 2008

Current and previous positions (Most recent position first)

Month and Year	Title	Institution/Company, Country
December 2015 to date	Associate Professor (Pathology)	SCTIMST, Trivandrum
June 2006 to June 2008	Lecturer, Department of General Pathology	Christian Medical College, Vellore
June 2004 to June 2005	Demonstrator (Non-PG), Department of General Pathology	Christian Medical College, Vellore

A brief summary of relevant research experience: Experience in Neuropathology, immunohistochemistry, molecular techniques (PCR, including RT-PCR; FISH), in silico analysis (gene expression profiling, microarray-based)

Current project/s at hand: -

Signature: 	Date: 27-09-2018 Place: Thiruvananthapuram

Curriculum vitae of the Investigators

P	RAJALAKSHMI	
Last Name	**First Name**	
Date of Birth (dd/mm/yy): 19/03/1984		**Sex:** F
Study Site Affiliation: Assistant Professor, Department of Pathology, SCTIMST		
Professional Mailing Address (Include Institution name)		**Study Site Address (Include Institution name)**
Department of Pathology SCTIMST Trivandrum- 695011		Department of Pathology SCTIMST Trivandrum- 695011
Telephone (Office): 0471 2524494		**Mobile Number:** 9620643510
Telephone (Residence):		**Email:** rajalakshmi.p.19@gmail.com

Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
PDF- Neuropathology	2015	NIMHANS, Bangalore, India
MD- Pathology	2011	Mysore medical College and Research Institute, Mysore, India
MBBS	2005	JIPMER, Puducherry, India

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration

Registration no: 80327 Year of registration: 2007
Tamil Nadu Medical Council

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
Aug 2016 till date	Assistant Professor	SCTIMST, Trivandrum, India
Jan 2016 to June 2016	Senior Resident	NIMHANS, Bangalore, India
Aug 2015 to Dec 2015	Junior Consultant	Bangalore Hospital, Bangalore, India
Aug 2014 to June 2015	PDF- Neuropathology	NIMHANS, Bangalore, India
March 2013 to June 2014	Senior Resident	JIPMER, Puducherry, India
July 2011 to March 2013	Assistant Professor	Sri Manakula Vinayagar Medical College and Hospital, Puducherry, India

Brief summary of relevant research experience: Nil

Current project/s at hand: Nil

Signature: 	Date: 31.01.2019 Place: Trivandrum

Appendices

APPENDIX A – ETHICS COMMITTEE APPROVAL

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1800/JANUARY/2022 25.03.2022

Dr. Lokesh VD
Senior Resident
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

Dear Dr. Lokesh,

The Institutional Ethics Committee held on 29th January, 2022, reviewed and discussed your application to conduct the study titled "**LONG TERM SURGICAL OUTCOMES FOLLOWING MULTIMODALITY TREATMENT IN MEDULLOBLASTOMA**" (IEC/1800).

The following members of the Ethics Sub-committee were present at the meeting held on 29th January, 2022.

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
2.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
3.	Dr. Harikrishna Varma P. R	Ph.D (Materials Sciences)	Male	Medical Technology	Yes
4.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
5.	Dr. Ashalatha R	MBBS, MD,DM	Female	Clinician	Yes
6.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
7.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

Page 1 of 2

The following documents were reviewed:

Original submission

1. Project Proposal
2. IEC Application Form
3. Declaration form
4. Principal Investigator's Certification
5. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 25.11.2021
6. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 11.10.2021 from Dr. Easwer, Professor and Head, Department of Neurosurgery, SCTIMST
7. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 11.10.2021 from Dr. Ganesh Divakar, Assistant Professor and Head, Department of Neurosurgery, SCTIMST
8. Proforma
9. Subject Information and Informed Consent in English and Malayalalam
10. Informed consent in English and Malayalam
11. CV of PI and Co-PI s
12. Checklist Form
13. SRC Recommendation

Revised submission

1. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 19.03.2022
2. Project Proposal
3. IEC Application Form
4. Declaration form
5. Principal Investigator's Certification
6. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 25.11.2021
7. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 11.10.2021 from Dr. Easwer, Professor and Head, Department of Neurosurgery, SCTIMST
8. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 11.10.2021 from Dr. Ganesh Divakar, Assistant Professor and Head, Department of Neurosurgery, SCTIMST
9. Proforma
10. Subject Information and Informed Consent in English and Malayalalam
11. Informed consent in English and Malayalam
12. CV of PI and Co-PI s
13. Checklist Form
14. Telephone Recruitment Script

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Dr. G. Srinivas
Member Secretary, IEC

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

APPENDIX B – SUPPLEMENTARY TABLES - Nil

APPENDIX C - PUBLICATIONS – Not yet published

APPENDIX D – PLAGIARISM CHECK REPORT

PLAGIARISM SCAN REPORT

Date	August 31, 2023
Exclude URL:	NO

Unique Content	91%
Plagiarized Content	9%
Paraphrased Plagiarism	0

Word Count	22,004
Records Found	10

CONTENT CHECKED FOR PLAGIARISM:

Medulloblastoma belongs to the group of CNS embryonal tumours and it is the most common paediatric malignant brain tumour (Ostrom et al., 2018; Rios and De Jesus, 2022). Medulloblastoma occurs mainly in children with a median age of 9 years, peak incidence is noted in the age group between 3 and 7 years (Farwell et al., 1984; Roberts et al., 1991). There is a bimodal peak observed in adults which accounts for one-fourth of Medulloblastoma patients. It was first described in 1925 as a glioma arising from the cerebellum.

Medulloblastoma was originally described in the histogenetic classification developed by Baily and Cushing(Bailey, n.d.; Ferguson and Lesniak, 2005), in that CNS tumors were given a category based on the morphologic appearance similar to cell types noted in the developing brain(Ferguson and Lesniak, 2005).

The term was coined by Bailey in his description, he noticed there was a peculiar tumour in children that occurred primarily in the cerebellum. This primitive embryonic tumor was postulated to arise from an undifferentiated cell type termed the "medulloblast," which was thought to arise from the fourth ventricular ependymal lining. Bailey also observed that this tumor has the tendency to spread to leptomeninges which later proved valuable in terms of prognosis and treatment. Bailey and cushing also noted the poor prognosis of medulloblastomas, this has led to the introduction of radiotherapy in the medulloblastoma patients(Ferguson and Lesniak, 2005). Even though the the cell type"medulloblast" has not been identified, the use of the the nomenclature has been there for decades. Current notion is that, medulloblastoma arises from the subependymal matrix zone actively replicating cells, located in the external granular layer of the