CLINICOPATHOLOGICAL STRATIFICATION AND EARLY SURGICAL OUTCOME OF PAEDIATRIC MEDULLOBLASTOMA PATIENTS AT KENYATTA NATIONAL HOSPITAL.

BY

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I declare that this dissertation is my own original work and to the best of my knowledge, it has not been presented elsewhere for consideration of publication or award of another degree.

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DEDICATION

This is dedicated to children with medulloblastomas and their families.

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LIST OF ABBREVIATIONS AND ACRONYMS

Central Brain Tumour Registry of the United States……CBTRUS

Central Nervous System……. CNS

Computerized Tomography……. CT

Desmoplastic/Nodular……...D/N

International Classification of Diseases ……..... ICD

Kenyatta National Hospital……..… KNH

Large Cell/Anaplastic……. LCA

Magnetic Resonance Imaging……..... MRI

Medulloblastoma……. MB

National Hospital Insurance Fund…….. NHIF

Overall survival……. OS

Patched…….PTCH

Progression-free survival……PFS

Sonic Hedgehog……. SHH

Statistical Package for Social Sciences…….. SPSS

Wingless-related integration site……... WNT

World Health Organization…….. WHO

OPERATIONAL DEFINITIONS

1. **Neurosurgical Unit**: - Ward 3A, 3B, 3C, 3D, 4C, Neurosurgery Clinics, All consulting units within Kenyatta National Hospital (KNH).
2. **Risk stratification**: - The mode of separating patients into different groups based on age, metastatic and residual tumour post-surgical resection.
3. **Early surgical outcome**: - the period ranging from the day of surgery to the end of the six months.
4. **Overall survival**: - patients alive at the end of the stipulated study time.
5. **Progression-free survival**: - the period from surgery to study completion for which the tumour doesn't grow nor does the patient develops new symptoms.
6. The **extent of resection** (EOR) for medulloblastomas can be: -
    a. **Gross total resection** (GTR) with no residual tumor in post-operative contrast-enhanced MRI,
    b. **Near-total resection** (NTR) with < 1.5 cm^2 residual tumour on contrast MRI post-surgery
    c. **subtotal resection** (STR) with >1.5 cm^2 residual tumour on post-operative contrast MRI
    d. **Biopsy** of the tumour

ABSTRACT

Background: Brain tumors are the second most prevalent cancer in children, behind Leukaemia, and the most common solid tumour. Medulloblastomas (MBs) are the most prevalent malignant brain tumors in children (tumour grade IV according to WHO). These tumors are treated with surgery, radiation, and chemotherapy. Although long-term survival rates have significantly improved, the tumour is still incurable in around a third of patients, and long-term survivors experience cognitive deficiencies and other therapy-related adverse effects in large numbers. The effectiveness of treatment depends on the risk stratification of the patient based on the age at diagnosis, craniospinal metastasis, and the size of the residual tumour post-surgery. This guides adjuvant treatment and thus prognosis.

Recent research suggests, however, that these clinical characteristics are insufficient for determining disease risk. According to recent studies, categorizing MBs based on histology and molecular abnormalities may aid in better risk assessment of patients, rationalizing therapeutic approaches, enhancing cure rates, lowering long-term side effects, and generating novel therapeutic techniques. All these impact post-surgical outcomes.

This study seeks to evaluate risk stratification both clinically and based on histopathology of children presenting with Medulloblastoma and their impact on early outcome post-surgery at KNH. This will better inform therapeutic decisions and improve patient care.

Broad Objective: To describe clinicopathological stratification and early surgical outcome of children being surgically managed for Medulloblastomas at KNH.

Methodology: This was a combined prospective cohort and retrospective cohort study on childhood medulloblastoma patients who have undergone surgery at KNH from January 2019 to October 2022. Informed consent was obtained from the next of kin. At the patient interview,

data collected included patient demographics, radiological details, surgical intervention, postoperative management, and whether the patient underwent adjuvant therapy. The follow-up period was up to 6 months or an end point of death.

The main outcome measures included length of Intensive care unit (ICU) stay, length of hospital stay, the pattern of radiological presentation, histological types, duration of stay before initiation of adjuvant therapy, and reasons for the delay in initiation of adjuvant therapy.

Data management and results: Data was collected using predesigned data collection forms, then entered in SPSS 26.0.

Results: Twenty children with medulloblastomas were analyzed, fifteen patients in the retrospective arm and five in the prospective arm. The female-to-male ratio was 1: 1.22. On histopathology, 75% of the tumours were classic while 25% were desmoplastic in nature. A total of 13 patients underwent adjuvant therapy, constituting 65% of the patients analyzed. 80% of the patients were standard risk. At six months post-surgery, 75% of the patients were alive with 27% of that number exhibiting tumor recurrence. Duration of hospital stay, classic histological variant, and midline tumor location were the main risk factors associated with developing complications. The mortality rate at 6 months was 25% with overall survival of 75% and progression-free survival of 73.3%.

Conclusion: The study shows that there were more males than females presenting with medulloblastomas. The most common location of the tumour was the midline as per imaging. Sixty-five percent of patients underwent permanent CSF diversion, and the commonest histological variant was the classic medulloblastoma. The majority of patients are of standard risk disease at 80%. The study also shows that midline tumour location, telovelar approach, and classic histologic variant are the factors associated with increased complication occurrence.

CHAPTER ONE: INTRODUCTION:

Medulloblastoma is an embryonal tumour that develops from early progenitor cell populations in the early stages of development. Medulloblastomas are the most frequent malignant embryonal brain tumors in children, with 5-year survival rates of up to 70% (1,2).

A multimodality approach to treatment has been employed. This includes a maximal safe resection, chemotherapy, and radiotherapy. This treatment is based on clinical stratification into two major groups (3,4). These are high risk and average risk based on the following criteria:

i) Age at diagnosis,

ii) Extent of resection,

iii) Chang metastatic staging (Table 1).

This classification defines average risk patients as those above 3 years with no tumour metastasis and less than 1.5cm^2 of residual tumour on postoperative contrast-enhanced brain Magnetic Resonance Imaging (MRI) (5).

This has been helpful in guiding prognosis. However, Eberhart et al showed that this method cannot distinguish between high- and low-risk patients in the same clinical stage. Due to biological variations inside the tumour, patients with similar malignancies and clinical stages who receive identical treatments can have vastly divergent clinical outcomes (6).

Surgery alone will not cure MB; nonetheless, surgical tumor excision is an important part of existing multimodal therapy protocols for MB (7). The extent of resection (EOR) is either gross total resection (GTR) with no remaining tumor in post-operative contrast-enhanced MRI, near-total resection (NTR) with a residual tumor of less than 1.5 cm2, subtotal resection (STR) with a residual tumor of more than 1.5 cm2, or biopsy (8). The value of increasing the EOR has been a point of contention. As a result, patients with subtotal resections are considered high-risk patients in current treatment protocols, and they are assigned to more rigorous adjuvant

therapy procedures (9). Furthermore, overall survival (OS) is not dissimilar amongst children classified as non-metastatic (M0) vs those classified as suffering from micro-metastasis inside the brain, according to two distinct trials, the German trial HIT'91 and the Children Cancer Group 921 (CCG 921) (10,11). (M1). Moreover, brain stem invasion (stage III b), which was once thought to be a sign of poor prognosis, is now thought to have no bearing on prognosis (10).

In this study, we aim to evaluate these factors in relation to early surgical outcomes of patients undergoing MB surgery at the largest referral hospital in Kenya.

CHAPTER TWO: LITERATURE REVIEW

2.1: Epidemiology of Childhood Medulloblastoma:

Medulloblastoma is the most frequent malignant brain tumor in children, accounting for 10% to 25% of primary CNS tumors and around 40% of post fossa malignancies, with a peak frequency of 3 to 9 years (12). In children, the incidence is estimated to range from 2 to 7 per one million children per year (13-15). They have a bimodal distribution in children, with maxima at 3 to 4 years and 8 to 9 years (16), as well as a 1.5:1 male gender predilection. Some differences in incidence have also been shown across races and ethnicities (14).

MacDonald *et al*, showed that about 50% of the children are free of disease at 5 years with aggressive treatment and 80% to 90% achieve cure rates in non-disseminated disease (17).

In a cross-sectional study of 61 patients with childhood brain tumors at Kenyatta National Hospital, John *et al* (2017) found that 16.4% were Medulloblastomas. The frequency of juvenile medulloblastoma was 42.1 % in another prospective cohort study on clinicopathological characteristics and early surgical outcome of posterior fossa tumors at KNH by Njeru et al, (2021).

The pattern of risk stratification and histopathology of medulloblastomas in our setting is lacking, yet these factors are essential in dictating the adjuvant therapy needed and the eventual overall outcome for patients.

2.2. Pathology:

2.2.1. Gross:

The tumour (classified as grade IV by WHO) shows as a pinkish grey to purple mass on gross pathologic examination, most usually emerging from the medullary velum. Others are soft and friable, while others are hard, distinct masses. Central necrosis, cystic components, or occasionally gross haemorrhage can be seen. It fills the fourth ventricle and occasionally

invades the fourth ventricle's flooring, extending to the cisterna magna. The tumour spreads to the cerebellar surface and the spinal cord predominantly through the cerebrospinal fluid (CSF), giving it a white, "sugar-coated" look.

2.2.2. Microscopy and histological classification:

They have been categorized into one part in the WHO classification for 2021, which identifies them as morphologic variations of the Medulloblastoma tumour, which is characterized histologically. In the 2016 WHO classification, four histologic subtypes were identified. Classic, desmoplastic/nodular (DN), medulloblastoma with extensive nodularity (MBEN), and large cell/anaplastic (LC/A) (18). The differences morphologically have different outcomes and associations clinically as seen below (19-22).

These are:

1. *Classic medulloblastoma* is the most common type of MB, accounting for roughly 72% of all MBs (18). characterized by spherical nuclei, lack of increasing cell size (defined as less than 4 times the size of a red blood cell), and lack of regular mitotic activity or mitoses Rosettes from Homer Wright are very common. Intrinsic desmoplasia is uncommon in this type, and when it does occur, it is usually due to tumour involvement of the leptomeninges. In a retrospective study on the relations of overall survival (OS) and progression-free survival (PFS) to different clinicopathological parameters at 1year, Asmaa and Nehal demonstrated that the classic MBs have the best OS of 71.4% and PFS of 42.9% at 1 year. On the other hand, Large cell/Anaplastic MBs had the worst outcome at 1 year with an OS of 18.8% and PFS of 12.5%. Desmoplastic/nodular MBs showed an intermediate picture having an OS at 1 year of 70% and PFS at 1year of 30% (23).

2. *Desmoplastic/nodular (DN) variant;* described by nodules of neurocytic distinction with interstitial embryonal features describe. The term "desmoplasia" is used to describe the tendency of desmoplastic/nodular tumors to have pericellular collagen deposition, which may be detected by reticulin deposition but is absent from differentiation nodules. They are linked to moderate clinical risk and are all related to the SHH molecular group, which may be treated with targeted medicines in some individuals (24).

3. *medulloblastoma with extensive nodularity (MBEN);* This histologic variation is more common in infants (under 3 years) and is more central than more traditional DN tumors. In many cases, the nodules are irregular and fuse together. These have the best prognosis. Both DN medulloblastoma and MBEN share a favorable prognosis, and it has been proposed that the two be considered as one entity (25, 26).

4. *Large cell/Anaplastic histology (LC/A);* Large cell and anaplastic MBs are two separate histologic types that have been integrated in the most recent histologic classification scheme. In 1992, Giangaspero as al described the poor prognosis big cell MB subtype, while Eberhart et al devised a more thorough grading scheme for anaplasia in 2002. These have the worst prognosis, and treatment as high risk is a matter of debate (25).

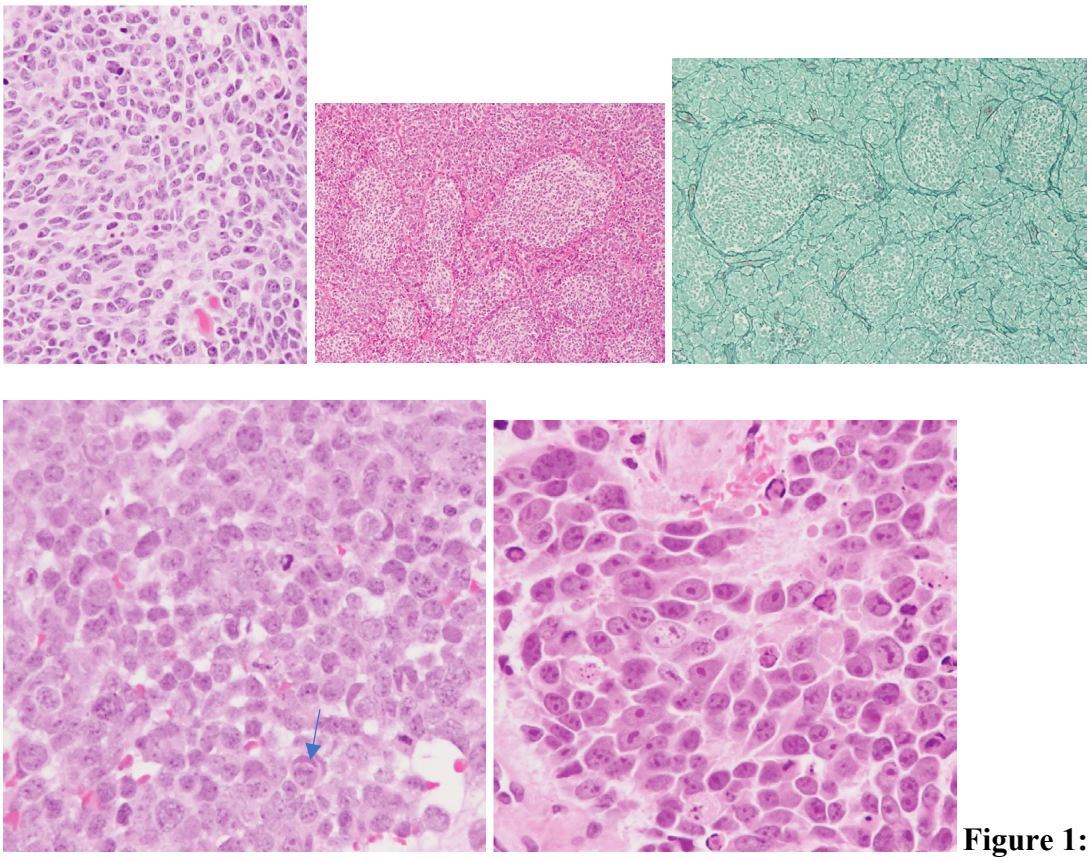


Figure 1:

Upper left: Appearance of classic or undifferentiated medulloblastoma, a highly cellular tumor with round blue or sheets of small oval cells.
Upper row middle and **Upper row right:** Hematoxylin and eosin staining (upper row middle) and reticulin staining (upper row right) of desmoplastic medulloblastoma.
Lower row left and **Lower row right:** Large cell/anaplastic medulloblastoma shows increased nuclear size with "cell-cell wrapping" (lower left blue arrow) and abundant mitoses (lower right).

Adopted from Youmans and Winn Neurological surgery, 8th Edition, page 3674.

Minimizing adjuvant therapy in patients with favorable histologic types can help to limit the treatment's long-term side effects, therefore identifying such patients is crucial for stratifying therapy. Consequently, identifying individuals with a higher risk of progression allows their care to be enhanced to improve their results (26-29).

2.2.3. molecular classification:

The categorization of medulloblastomas has changed in the WHO CNS tumor classification of 2021 to reflect new information of their clinical and molecular variability. Wingless-related integration site (WNT)-activated, sonic hedgehog (SHH)-activated, group 3, and group 4 were the first four molecular groups to be established (30).

The 2016 classification includes both the WNT and SHH, with SHH tumors being split based on TP53 status.

Non-WNT/non-SHH medulloblastomas were found in Groups 3 and 4, but thanks to large-scale methylation and transcriptome profiling, new subgroups have emerged beneath the four main molecular groups: four SHH subgroups and eight non-WNT/non-SHH medulloblastomas (31-35). These classifications have a wide range of outcomes, and current findings from clinical trials suggest that particular regimes of chemotherapy can help individuals with tumors (36,37).

Molecular classification as per WHO 2021 guidelines divides Medulloblastoma into four distinct groups:

1). Medulloblastoma, WNT-activated,

2). Medulloblastoma, SHH-activated, and *TP53*-wildtype

3). Medulloblastoma, SHH-activated, and *TP53*-mutant

4). Medulloblastoma, non-WNT/non-SHH (group 3 and 4 medulloblastomas)

1. The WNT subgroup is distinguished by the WNT pathway activation. This route is involved in a variety of developmental events, including brain progenitor cell proliferation and destiny (38, 39). The pathway comprises -catenin, a major transcriptional activator that binds with a complex in the cytoplasm that includes the AXIN-1, glycogen synthase kinase 3 (GSK3), and Adenomatous polyposis coli (APC) gene (38, 39). About 15% of sporadic MBs are caused by

mutations in this gene (40). Mutations in the APC gene also cause Turcot's syndrome, characterized by MB and intestinal tumors (41).

More than 90% of tumors don't have metastasis and have conventional histology, with just 9% of tumors having metastasis at the time of diagnosis. WNT-MBs are more widespread in children aged between 10 years to 12 years and less prevalent in infants, with almost equal numbers of boys and girls. Children under the age of 16 usually have a good prognosis, with a greater than 90% 5-year incident-free survival rate.

According to Clifford et al 2015, those at the time of diagnosis who were over 16 years old and those who got delayed radiotherapy had a greater rate of relapses, which indicated that radiation was a key component in treatment.

2. *SHH-activated MBs* account for approximately 30% of all MBs with a moderate prognosis (5-year OS of 70%). (42). The majority are nodular/desmoplastic; however, they can also have a classic or LCA histology, which is more common in youngsters. Infants with the nodular desmoplastic subtype have a higher chance of surviving (42). SHH pathway component mutations, specifically *Patched (PTCH) and Smoothened, Frizzled Class Receptor, are frequently seen in malignancies (SMO)*. SHH tumors affect persons of all ages and are the most prevalent tumour type in both adults and children aged below 3 years old, however, these mutations are more common in children between the age of 3-17, making them a relatively high-risk group with much worse outcomes (46). TP53-mutated SHH medulloblastoma patients have a poor prognosis, while young children have a better prognosis (43, 46).

SHH tumors return more frequently in the initial excision cavity and have the highest incidence of damaging germline alterations (14–20%) of all MBs (44, 45).

3. *Group 3 MBs* account for around 25% of all instances, peaking between the ages of 3 and 5, and are fatal of all MBs, with a 5-year survival rate of 58% in children and 45% in babies (47). The ratio of male to female is approximately 2:1. LCA histology is found in about 40% of LCA tumors, making this category the most common.

The poor prognosis is attributable to a confluence of variables, including early age associated with metastatic dissemination (up to 50%) and a high rate of LCA histology (45).

4. Despite being the most common subgroup (about 35 percent), Group 4 is the least characterized biologically. The most common anomaly is isochromosome 17q, which is followed by 11q deletion. The prognosis for patients with chromosome 11 deletion is excellent, with survival rates surpassing 90%. They have a moderate prognosis (5-year overall survival rate of 75–90%), are most common in adolescents and teenagers, and roughly 30-40% are metastatic upon diagnosis, making them high-risk cancer with a 5-year OS of 60%. Patients in Group 4 who have been irradiated are more likely to recur with metastatic disease and a tumour bed that is usually free of illness (45).

	Subgroup	WNT	SHH	Group 3	Group 4
Clinical Characteristics	% of Cases	10	30	25	35
	Age at Diagnosis				
	Gender Ratio (M:F)	1:1	1:1	2:1	3:1
	Anatomic Location				
	Histology	Classic, Rarely LCA	Desmoplastic, LCA, Classic, MBEN	Classic, LCA	Classic, LCA
	Metastasis at Diagnosis (%)	5-10	15-20	40-45	35-40
	Recurrence Pattern	Rare; Local or metastatic	Local	Metastatic	Metastatic
	Prognosis	Very good	Infants good, others intermediate	Poor	Intermediate
Molecular Characteristics	Proposed Cell of Origin	Progenitor cells in the lower rhombic lip	Granule precursors of the external granule layer	Neural stem cells	Unipolar brush cells
	Recurrent Gene Amplifications	-	*MYCN* *GLI1* or *GLI2*	*MYC* *MYCN* *OTX2*	*SNCAIP* *MYCN* *OTX2* *CDK6*
	Recurrent SNVs	*CTNNB1* *DDX3X* *SMARCA4* *TP53*	U1 snRNAs *PTCH1* *TERT* *SUFU* *SMO* *TP53*	*SMARCA4* *KBTBD4* *CTDNEP1* *KMT2D*	*KDM6A* *ZMYM3* *KTM2C* *KBTBD4*
	Cytogenetic Events Gain Loss	6	3q, 9p 9q, 10q, 17p	1q, 7, 18 8, 10q, 11, 16q i17q	7, 18q 8, 11p, X i17q
	Other Recurrent Genetic Events	-	Germline *ELP1* loss-of-function variants	*GFI1* and *GFI1B* enhancer hijacking	*PRDM6*, *GFI1*, and *GFI1B* enhancer hijacking

Age: Infant Child Adult

Figure 2: Molecular subgroups of medulloblastoma. Summary of key characteristics (both clinical and molecular) of medulloblastoma subgroups. (*Modified from Juraschka K, Taylor MD. Medulloblastoma in the age of molecular subgroups: a review. J Neurosurg Pediatr. 2019;24(4):353–363.*)

2.3. Clinical presentation of medulloblastomas

Medulloblastoma can present in children with variable signs and symptoms. Often the clinical presentation is that of raised intracranial pressure: headaches, vomiting, and lethargy. Whereas older children often complain of headache, nausea, or diplopia, younger children who cannot articulate their symptoms may present with irritability, weight loss, and failure to thrive, and initial workup may have been directed at gastrointestinal symptoms (48)

Fruehwald *et al* observed that the most common objective signs include papilledema (observed in 76%), truncal ataxia (62%), nystagmus (44%), and limb ataxia (35%) (49). The onset of symptoms is often abrupt, with a symptom duration of 4 weeks, and less than 12 weeks in 75% of patients (50).

Ramaswamy *et al* noted that children with medulloblastoma of different subgroups seem to present differently regarding the duration of symptoms. In comparing patients with SHH and Group 3 tumors (2 and 4 weeks, respectively; $P = .0001$), WNT and Group 4 tumour patients have longer intervals (8 weeks).

2.4. Diagnostic imaging.

MRI represents the "gold standard" in diagnostic imaging and staging for medulloblastoma. The tumour often appears as a midline enhancing mass lesion with distinct margins. Most exhibit midline location of the fourth ventricle though a subset has a more peripheral location in the cerebellar hemisphere or cerebellopontine angle (49).

On T1-weighted imaging, medulloblastomas are typically hypointense (90%) and hyperintense on T2-weighted imaging, albeit they can be heterogeneous on T2 (49, 51,52). However, desmoplastic/nodular and MBEN variants less consistently follow this pattern, with a minority (11% to 12%) of each appearing isointense on T1-weighted imaging and as many as 50% to 66% appearing isointense on T2-weighted imaging. LC/A tends to be smaller at presentation

with a higher rate of leptomeningeal dissemination (52). MBs show homogeneous or heterogeneous enhancement patterns with gadolinium, with about 80% to 100% enhancement. Medulloblastomas nearly uniformly demonstrate diffusion restriction within the tumour itself (diffusion-weighted imaging yields a high signal, whereas the apparent diffusion coefficient yields a low signal) (49,52). Intratumoral cysts may be present in approximately one-third of medulloblastomas. Rarely, calcifications or intratumoral haemorrhage are detected as seen by Koral *et al* (53).

Although leptomeningeal spread may be present in one-third of patients at diagnosis of medulloblastoma (detected by MRI, cytology, or myelography) (54) it may be evident on MRI at diagnosis in only 10% to 20% of patients. (55)

When medulloblastoma is the suspected diagnosis, a complete spinal MRI should be obtained preoperatively to assess for leptomeningeal dissemination, because postoperative changes may present difficulty in discriminating between true CSF dissemination and postsurgical artifact during the first 2 weeks following surgery (56,57). A postoperative MRI should be acquired within 48 hours of surgery to assess residual tumour for the purposes of staging and directing adjuvant therapy.

2.5. Staging and prognostic factors:

The traditional stratification model has been entirely clinical. This relates to the age at diagnosis with a cut-off of 3yrs, size of residual tumour post-surgery (cut-off 1.5cm^2), and the Chang Metastatic stage (16, 58,59).

Table 1: Chang staging system for Medulloblastomas (59,60)

Stage:	Description:
T stage	
T1	Tumor with a diameter of less than 3 cm, confined to the vermis' midline, the roof of the fourth ventricle, and, less frequently, the cerebellar hemisphere.
T2	Tumor with a diameter of more than 3 cm that has spread to one adjacent structure or is partly covering the fourth ventricle.
T3A	Tumor infiltrating two neighbouring structures or totally covering the fourth ventricle with expansion into the Sylvius aqueduct, Magendie foramen, or Luschka foramen, resulting in significant internal hydrocephalus.
T3B	Tumor growing from the fourth ventricle's floor or the brain stem and filling the ventricle
T4	Tumor spreading to the third ventricle or midbrain through the Sylvius aqueduct, or tumour spreading to the upper cervical chord
M stage	
M0	There were no signs of subarachnoid or hematogenous metastases.
M1	Cerebrospinal fluid contains microscopic tumour cells.
M2	In the cerebellum, cerebral subarachnoid space, or the third or lateral ventricles, gross nodule seedings can be seen.
M3	Seedings of gross nodules in the spinal subarachnoid space
M4	Extra-neuraxial metastasis

This traditional clinical stratification model defines high risk disease as patients below te age of 3 years, residual tumour post-surgery more than $1.5cm^2$ and metastatic tumour i.e, M1 to M4 stage. All the other patients are considered standard risk. Although these clinical characteristics remain important prognostically, more refined risk stratification criteria have been developed that incorporate important molecular features (31,61).

Histologic Classification and Prognosis

The histopathologic subtype is a strong predictor of outcome for medulloblastoma patients. In one study, Massimino et al found that DN and MBEN tumors had excellent 5-year PFS (82%), classic subtype tumors had intermediate PFS (78%), and LC/A tumors had poor PFS (44%). (22).

Molecular Subgroups and Medulloblastoma Prognosis

The differential in survival rates between molecular subgroups and several other important molecular characteristics that predict survival has resulted in proposed risk stratification schemes that are being integrated into contemporary clinical trials (31,45). Several studies are assessing craniospinal radiation dose reduction for WNT subgroup patients without high-risk clinical features (62). The next trials are likely to incorporate biologically informed risk stratification.

Schwalbe and associates proposed an alternative risk stratification in which the SHH, Group 3, and Group 4 subgroups are further divided based on methylation profiling, Figure 3 (31). The SHH subgroup is divided into SHH-Infant and SHH-Child. Group 3 and Group 4 are each split into high-risk and low-risk groups based on methylation profiling. Additional secondary molecular and clinical characteristics are then incorporated into the final proposed risk stratification (31).

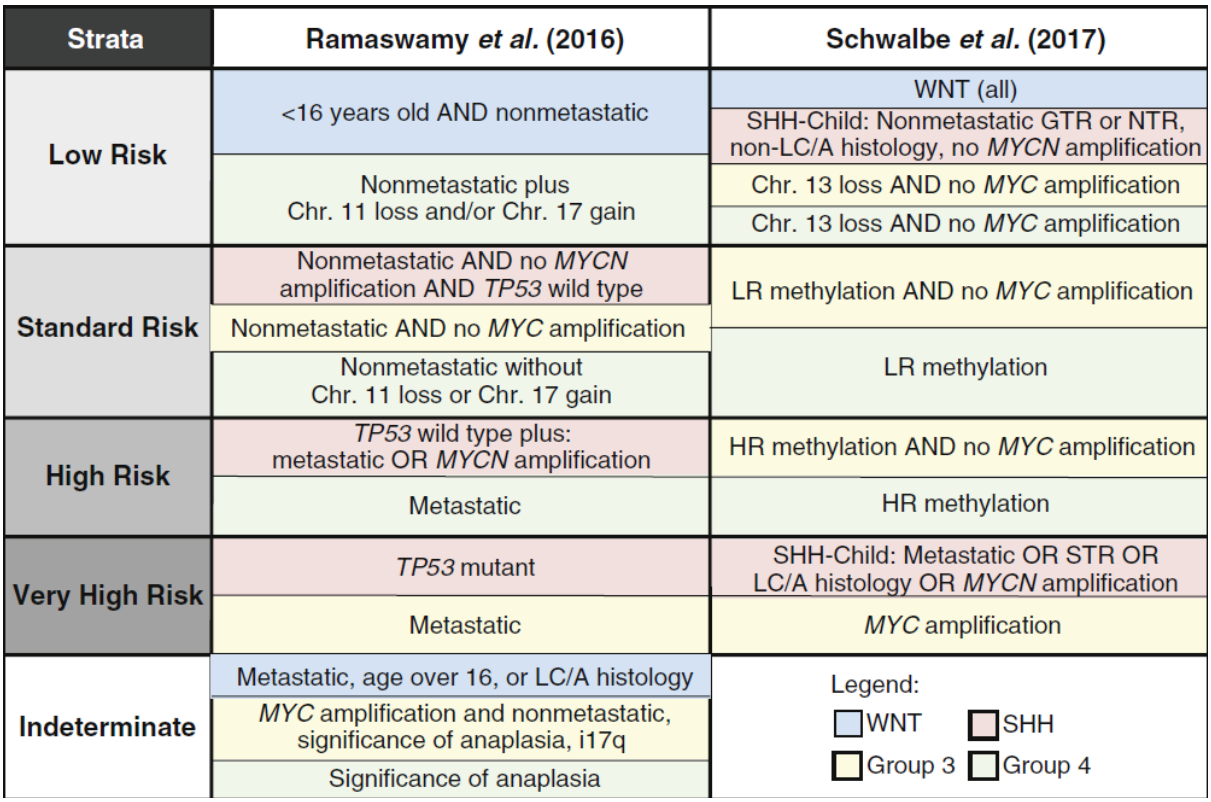


Figure 3: Proposed molecularly defined risk stratification schemes. Schwalbe and coworkers (31) used subgroup, methylation profiles, and clinical and other molecular factors to stratify patients into the following groups: Favorable, 91% 5-year PFS; Standard, 81% 5-year PFS; High, 42% 5-year PFS; Very high, 28% 5-year PFS. Ramaswamy and associates (61) combined subgroup, clinical, and molecular
SHH-Child is defined as SHH subgroup tumors in children 4.3 years of age or older. *Chr.,* Chromosome; *GTR,* grosstotal resection; *i17q,* isochromosome 17q; *LC/A,* large cell/anaplastic; (*NTR,* near-total resection; *STR,* subtotal resection.

2.6. Management of medulloblastoma

Current therapeutic procedures examine two main aspects when deciding on postoperative therapy: the danger of treatment toxicity and the chance of recurrence. Newborns and toddlers under the age of three are more vulnerable to treatment toxicity. In scenarios where there is a

metastatic disease or an inadequate resection of a tumour remnant (1.5cm²), the risk of recurrence is high. (63).

Following these criteria, three treatment cohorts can be formed that will separate children < 3 years, children >3 years but with high risk, and children >3 years with average risk (64).

2.6.1. Surgical intervention.

Surgical goals include maximal safe resection, relieving mass effect, obtaining tissue diagnosis, and treating symptomatic hydrocephalus.

The amount of degree of resection (EoR) may not meet the criteria, per an EoR retrospective systematic analysis and disease outcome, and hence deserves further examination (65). Thompson and colleagues discovered that molecular subgroups can affect prognosis: in Group 4 MB patients, gross total resection conferred a PFS benefit over subtotal excision (residual tumour =/>1.5cm2), particularly in the presence of illness dispersion, while the full scope of resection had no bearing on overall survival (OS) (66). This was not true for patients under 3 years.

In a retrospective study by Thompson and co-workers, they established that GTR and NTR (<1.5 cm^2 residual) had equivalent OS and PFS (66). In another study, Schwalbe and colleagues found that SHH patients under the age of 4.3 years receiving STR had worse PFS compared to those who underwent GTR (31).

Management of hydrocephalus:

This is a common finding present in 75% of medulloblastoma patients at diagnosis (49). Patients who come with an urgent condition may require the installation of an external ventricular drain (EVD) or if not presenting with markedly increased intracranial pressure, a high dose of dexamethasone (0.45 mg/Kg/ stat then per day) therapy to reduce peritumoral oedema and introduction of an EVD at the time of tumour resection is employed.

Although many patients need CSF diversion at the time of surgery, treatment with a ventriculoperitoneal shunt or endoscopic third ventriculostomy prior to tumor resection is not a recommendation because only 25% of patients require permanent CSF diversion (67,68). Risk factors for permanent CSF diversion include; metastatic disease, large tumors, and severe or long-standing hydrocephalus (69).

Definitive surgery: surgical technique.

Two approaches can be used:

1. The Telovelar approach which includes the first cervical vertebra (C1) laminectomy and utilizes the natural corridors of the posterior fossa anatomy,
2. or the Transvermian approach, in which the inferior vermis is transected on the way to the tumour.

Usually through a suboccipital craniotomy

- The patient is positioned in one of three positions: prone with the neck flexed, semi-seated with the neck flexed, or Concorde with the neck flexed. A 3 or 4-pin cranial fixation device, such as a Mayfield clamp, is used to hold the head in place.
- In infants, the head may be positioned on a horseshoe headrest, taking care to pad dependent areas and avoid pressure on the eyes.

- midline posterior fossa exposure is completed, exposing at minimum from the inion to C2.
- Dissection in the midline avascular plane and the cervical musculature are dissected from the occiput and from the bifid spinous process and C2 lamina in a subperiosteal fashion.
- Occipital craniotomy/craniectomy bone and the lamina of C1 are removed depending on the caudal extent of the tumor/cerebellar tonsils.
- The cerebellum's dura covering is opened in a Y shape, and the two hemispheres are withdrawn using either a split vermis or a telovelar technique.
- Visualize the 4th ventricle's floor to verify the excision does not extend into the brainstem.
- If possible place a cotton patty at the ventral aspect of the tumor, as a marker to avoid extending the tumor resection into the brainstem.
- Dissection of tumour margins with microsurgical technique to expose the interface between the tumor and the cerebellum. Samples of the tumor are taken for pathology review and diagnosis, followed by internal debulking with suction and with a cavitating ultrasonic surgical aspirator.
- After debulking, the margins of the tumor are much more easily dissected.
- At the completion of the surgical resection, the cotton patty placed at the beginning of the resection, protecting the underlying fourth ventricle, should again be identified.
- Inspection of the resection cavity for residual tumour before removal of the cotton patty.
- Intraoperative ultrasonography can be a useful adjunct to assess for residual tumors and redirect further resection if necessary.

- A hemispheric tumor requires a corticectomy through the overlying cerebellar cortex. Followed by tumor dissection, internal debulking, exposure of the brain-tumor interface, and inspection as above.
- Haemostasis: careful use of bipolar cautery, warm saline irrigation, and gentle tamponade with thrombin-soaked cotton balls.
- Valsalva manoeuvre to confirm haemostasis. Duroplasty is done in a watertight fashion.
- The bone is then replaced and the cervical paraspinal musculature re-approximated in the midline in a multilayered fashion.
- The EVD can be inserted at Frazier's point (6cm above the inion and 3cm off the midline) and can be weaned over a few days or a week (69,70)

Post-operative complications:

Preoperative impairments such as bulbar, dysmetria, ataxia, or cranial nerve palsies symptoms worsened, according to Kennedy and colleagues (71). Moreover, infection, aseptic meningitis, pseudo meningocele, and persistent hydrocephalus can complicate healing thus delaying the initiation of adjuvant therapies.

Cerebellar mutism has been observed in 10%–25% of cases following resection of a posterior fossa tumor (72,73). It arises within 4 days postoperatively and results in speech loss that progresses to mutism (74). Emotional lability, ataxia, and hypotonia are other manifestations. It ranges in severity, and typically resolves over weeks to months, with improvements first observed in oral intake prior to improvements in speech difficulties. Korah and co-workers demonstrated that severe symptoms and persistence of cerebellar mutism over 4 weeks are associated with the risk of prolonged or permanent neurological deficits, mainly ataxia and dysarthric speech (74).

The etiology still remains unclear but is thought to result from dividing the cerebellar vermis or from retraction on the medial cerebellar surfaces, with resultant oedema affecting the superior and middle cerebellar peduncles. Although brainstem invasion has been associated with risk for cerebellar mutism, Robertson and associates demonstrated that tumor size has not (75). Children who developed cerebellar mutism are at higher risk for long-term poor cognitive functions, psychological impairment, and difficulties with social adjustment; thus, it is essential to recognize these signs and symptoms early to support prompt rehabilitation of these patients (76).

2.6.2. Radiation Therapy (RT).

Patients get external beam radiotherapy to the craniospinal plane with a boost to the tumour spot following surgery, with varying radiation doses administered to diverse risk categories. Since local recurrences account for 50–70% of all recurrences, treatment is confined to the tumour bed instead of the whole posterior fossa, protecting important brain structures.

RT is commonly started 30 days following surgery because, according to Northcott and colleagues, delayed RT administration is linked to a worse survival rate (77). Also, a study conducted found that patients who started RT within 3 weeks of surgery had a worse 5-year survival rate, implying that enough healing time is equally important (78)

Low-risk patients get 23.4 Grays (Gy) of CSI to the whole brain and spine, as well as a posterior fossa boost, for a total dose of 54–55.8 Gy (79,80, 81).

In contrast, high-risk patients receive 36–39.6 Gy CSI plus a bump to the tumour area for a dosage of 54–55.8 Gy (81). Ris and colleagues discovered that high RT doses are connected to neurocognitive impairment in children, with younger children suffering the most (82).

Reduced dosage neuraxis photon RT, on the other hand, increases the likelihood of recurrence and decreases survival (83). In the phase III Children's Oncology Group ACNS0331 study, Michalski and colleagues found that a 5.4 Gy reduction in the CSI dose resulted in shorter survival in children aged 3 to 7 years old in comparison to standard-dose RT (84). Even in the present era of chemotherapy, deferring postoperative RT is associated with a worse overall survival rate and is therefore not recommended for patients over the age of three (85).

Yock and colleagues demonstrated that new techniques for hind fossa boost and spine RT, such as proton therapy and intensity-modulated RT, limit irradiation of normal tissues while preserving tolerable toxicity and survival rates equivalent to standard RT (86). Decreased normal tissue dose also reduces post-radiation ototoxicity, improving quality of life and preserving hearing (87,88).

2.6.3. Chemotherapy.

Chemotherapy has become a routine treatment for postsurgical RT because it increases survival and minimizes RT-related side effects. Risk-adapted RT and four rounds of cyclophosphamide-based, dose-intensive chemotherapy, followed by stem cell or bone marrow rescue, are the current therapeutic options (81).

Gajjar and colleagues found that the aforesaid regimen resulted in an 85 percent 5-year survival rate in the average-risk MB population and a 70% 5-year survival rate in the high-risk population (81). Large cell anaplastic tumors had the lowest 5-year event-free survival rate (57%) of all histological subtypes (81).

Infants and toddlers under the age of three are treated effectively with surgery and chemotherapy alone due to the obvious considerable risk of radiation-induced morbidity (89). In the Children’s Cancer Group (CCG-99703) protocol, high-dose chemotherapy (vincristine,

cyclophosphamide, etoposide, and cisplatin) is followed by autologous hematopoietic cell rescue, however, the HIT-SKK'92 protocol suggests systemic chemotherapy and intraventricular treatment (90).

2.7. Early surgical outcome.

In patients who have undergone surgery for medulloblastomas, that is posterior cranial fossa surgery, the outcome can be evaluated by assessing morbidity and mortality. Islam and co-workers documented the following parameters; duration of hospital stay, postoperative complications including cerebrospinal fluid leakage, pseudo-meningocele, seizures, meningitis, shunt blockage, and the final outcome in the modified Karnofsky performance scale (91), as influencing the outcome.

Other complications related to posterior fossa surgery include cerebellar mutism (72,73), and injury to the eloquent floor of the fourth ventricle which may interfere with the aerodigestive system prolonging ICU stay and dependence on tracheostomy and feeding tubes.

Kanna et al showed the mean duration of hospital stay in children after posterior fossa surgery in general varied between craniectomy and craniotomy. They reported an increased complication rate and duration of stay in patients who underwent a craniectomy (17.5 days) compared to a craniotomy (14 days). CSF leak, CSF infection, wound infection and hydrocephalus were the most common complications. (92). All these factors contribute to the outcome after medulloblastoma surgery.

2.8: Conceptual framework

Medulloblastomas can be stratified into:

1. Average risk and
2. High risk clinically.

The first logical step in the multimodal management of these tumors is maximum safe resection. The overall goal of management is to achieve an onco-functional balance. This means that we achieve maximum safe resection while maintaining an acceptable functional outcome and improving survival. However, the oncologic outcomes, age at tumour diagnosis, tumour size, histologic type, and postoperative residual tumour are interrelated as shown in the literature above and figure 4 below. In answering the research question, all these factors will have to be considered while factoring in the confounders.

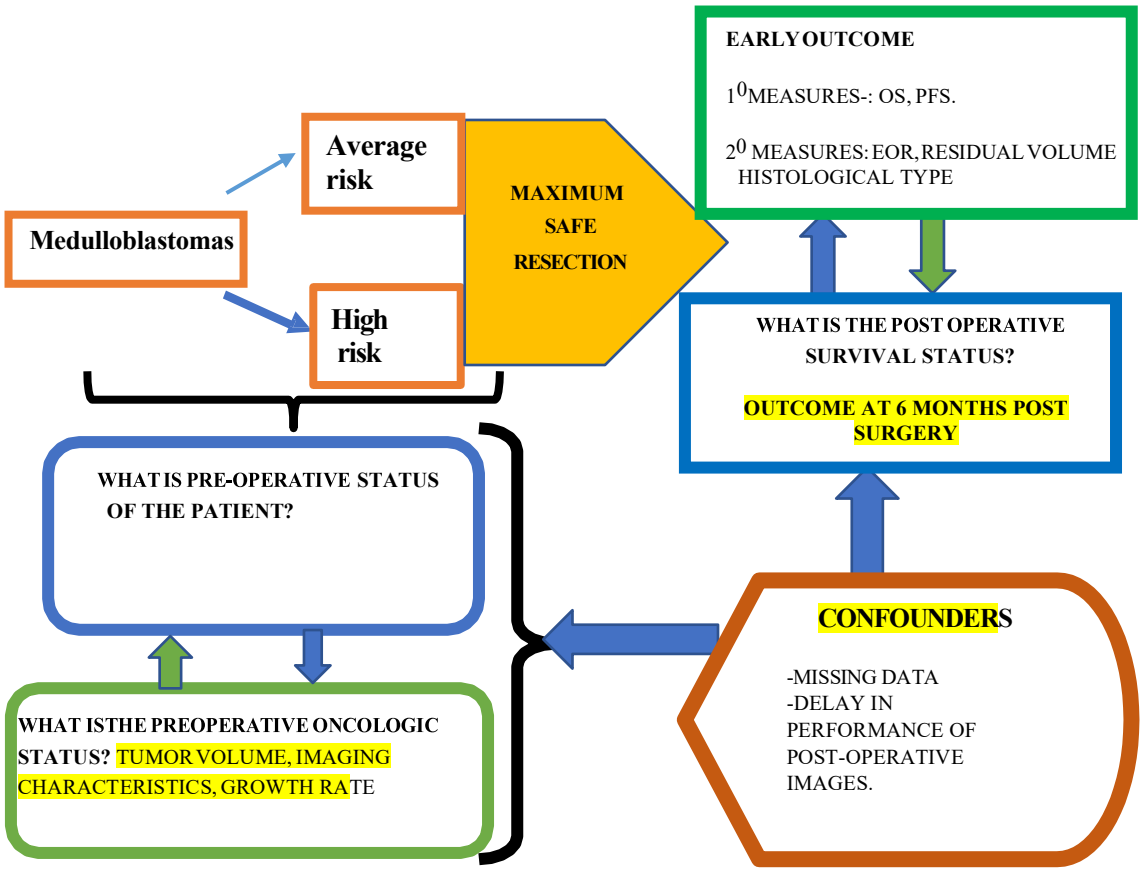


FIGURE 4: CONCEPTUAL FRAMEWORK

2.9. Study Justification.

Medulloblastoma accounts for a large disease burden among children and the complications arising from treatment are immense affecting neurocognitive, motor skills, and even social development among patients undergoing treatment. The patterns of histology have been shown to influence prognosis and even advice on adjuvant therapy. With increasing rates of disease recurrence in our setting and the paucity of data on the pattern of disease in our setting, this study will help kick start the inclusive knowledge of the disease in our setting and help in better patient care. It will also establish a basis for follow-up of these patients to ascertain survival and advice on treatment outcomes.

2.10. Study question.

What are the clinicopathological stratification and early surgical outcomes of paediatric patients presenting with medulloblastoma at the Kenyatta National Hospital?

2.11. Study Objectives

2.11.1. Broad Objective

To stratify paediatric patients undergoing medulloblastoma surgery at KNH both clinically and histologically in relation to early surgical outcomes.

2.11.2. Specific Objectives

1. To determine risk stratification of paediatric medulloblastoma patients at KNH
2. To determine the histological pattern of paediatric medulloblastoma patients at KNH.
3. To determine the surgical management pattern of paediatric medulloblastoma patients at KNH.

4. To determine the relationship between early surgical outcome and risk stratification, the histological pattern of disease, and surgical techniques of paediatric patients undergoing medulloblastoma treatment at KNH.

CHAPTER THREE: METHODOLOGY

3.1 Study design:

This was a combined retrospective cohort and a prospective cohort study of patients aged 0 to 12 years undergoing treatment for medulloblastoma at the KNH.

3.2 Study area:

The Kenyatta National Teaching and Referral Hospital, neurosurgical unit. The neurosurgical unit included the following neurosurgical wards, 4C, 3A, 3B, 3C, and 3D, the main critical care unit, the Neurosurgical outpatient clinic, and the Cancer Treatment Centre dealing with neurosurgical patients, the KNH records department, and the University of Nairobi neuropathology lab. The study duration for the retrospective arm was from 1st January 2019 to 28th March 2022, while the prospective arm was from 1st March 2022 to 31st October 2022.

3.3 Study Population:

The target population were all paediatric medulloblastoma patients between 0 to 12 years who had undergone surgery at the KNH and were still on follow-up within the neurosurgical unit.

3.3.1 Inclusion Criteria

1. All newly diagnosed medulloblastoma patients between 0 to 12 years who had undergone surgery at Kenyatta National Hospital and given informed consent to participate in the study.

3.3.2 Exclusion Criteria

1. Patients with recurrence of medulloblastoma post-surgery.
2. Patients who willingly opt-out of the study.

3.4. Sample size determination

The sample size was estimated using Cochran's formula below.

$$n = \frac{Z^2 x\ P(1-P)}{d^2}$$

Where:

n=is the sample size

Z=value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI).

P = expected true proportion (estimated at 10.0%, from a study conducted by John. et al (2017) at the KNH Hospital, Kenya; looking at Childhood brain tumors amongst paediatric patients, found 10.0% of them were medulloblastomas.)

d = desired precision (0.05)

$$n_0 = \frac{1.96^2 x\ 0.10(1-0.10)}{0.05^2} = 138$$

Records from the KNH brain registry indicated that there had been 23 paediatric medulloblastoma patients operated on since January of 2019. For finite populations of less than 10,000 people, the sample size was adjusted as follows;

$$nf = \frac{n_0}{1+\frac{n_0-1}{N}} = \frac{138}{1+\frac{138-1}{23}} = 20.$$

Hence, the study required 20 patients.

3.5 Sampling Procedure

Consecutive sampling technique was employed for the prospective arm and convenient sampling was for the retrospective study.

3.6. Data Collection.

3.6.1 Data collection procedure:

After the patient (a minor) or next of kin (parent or guardian) had consented to the study,

Relevant data was retrieved manually from the patients' medical records and from an interview of the patient or next of kin. Information regarding age, sex, and operative procedure were recorded. A unit number was issued to every patient for purposes of data collection.

For the *prospective arm*, a pre-operative craniospinal MRI was obtained, and a ventricular cerebrospinal sample at the time of surgery for cytology and post-operative histology of the tissue was recorded. A post-operative head CT scan was obtained within 48 hours after surgery and the size of the residual tumor was recorded. These patients were followed post-operatively in the critical care unit, the ward, and the clinic. A follow-up evaluation was done at 6 months after surgery to ascertain survival.

For the *retrospective arm*, these details were obtained from the patient's medical records, including the clinic, Cancer Treatment Centre, and in-patient care (ward) files. In addition, the patient was requested to avail of their images and reports of the same.

Other parameters including adjuvant therapy were recorded. Patients' overall survival at 6 months post-surgery was also recorded.

This was coded and entered in a preformed data collection sheet. The patients' names, physical addresses, or other identifying particulars were not included.

For the retrospective arm, this information was retrieved from medical records.

The validity and reliability of the procedure and data collection tool; the study collection tool is validated and was adopted from the study by Njeru *et al* on clinicopathological features and

early surgical outcome of posterior fossa tumors in children at KNH (93). The procedure was also adopted from the same study. In addition, a group of experts comprising my supervisors and senior consultants within the neurosurgery unit audited the tool and the procedure and approved it during the departmental meeting.

3.6.2. Quality Assurance

Permission was sought from the Ethics and Research Committee and the KNH research department to access the files. Retrieval of files was done using the ICD 10 coding system. Anonymity was ensured by assigning serial numbers to each patient.

The pre-operative and post-operative imaging were reported by a board-certified consultant radiologist.

-The histopathology and cytology were also done and reported by a board-certified consultant pathologist at the University of Nairobi histopathology laboratory.

-The data was retrieved by a qualified medical doctor (the principal researcher).

3.6.3 Data management and statistical analysis:

The collected data was entered, coded, and analysed using Statistical Package for Social Sciences version 26.0 (SPSS 26.0).

Subsequently, patients were categorized into 2 groups, standard and high risk based on both clinical and histopathological characteristics.

Demographic and clinical characteristics of the patients were analysed and presented as frequencies and percentages for categorical data, while those that were continuous were analysed and presented as means with standard deviation or as median with interquartile range. The risk stratification, the histological pattern, and surgical management of paediatric medulloblastoma were analysed and presented as frequencies and percentages. The

relationship between risk stratification, histological pattern, and surgical management with the early surgical outcome of paediatric patients undergoing surgery for medulloblastomas were analyzed with the use of Fisher's exact test. Statistical tests were considered significant where the p-value < 0.05. Kaplan Meier survival curves were used to assess overall survival at six months.

3.7 Ethical Considerations

Permission was sought from the Ethics and Research Committee, and the KNH research department.

- Serial numbers were assigned to the patients for purposes of confidentiality and all the data was kept under lock and key in the records department, KNH.
- All the data obtained was only accessible to the researchers and will be destroyed upon completion of the study, after 3 years.

3.8 Study Limitations

The ideal would be to cover a much longer follow-up period (e.g. 5 years), but due to budgetary and time constraints, the study was limited to six months outcome. However, we are confident that the results will achieve the objectives of the study and will provide useful, actionable information to guide improved management of this condition in our setup. It will also serve as a baseline study for future inquiry on the subject. The study is limited to Kenyatta National Hospital hence the results may not be generalizable to the population of similar patients in other settings. Additionally, missing data from the patient's records for the retrospective arm of the study. This included but was not limited to clinical presentation and the Lansky performance score which would have provided the characteristics of the patients before surgery.

These patients were left out of the study.

CHAPTER FOUR: RESULTS

In this study, 23 patients were seen. Three patients were left out for not meeting the inclusion criteria, thus 20 patients were analyzed. Fifteen patients were from the retrospective arm while five were in the prospective group. All the patients were analysed together since the parameters being analyzed were similar.

PATIENT'S DEMOGRAPHICS

A. PATIENT DETAILS

Age

The mean age of the patients at diagnosis was 6.8 (SD 3.3) years, whereas the median age was 6.0 (IQR 3.5 – 10.0) years. The youngest patient was 2.0 years while the oldest was 12.0 years.

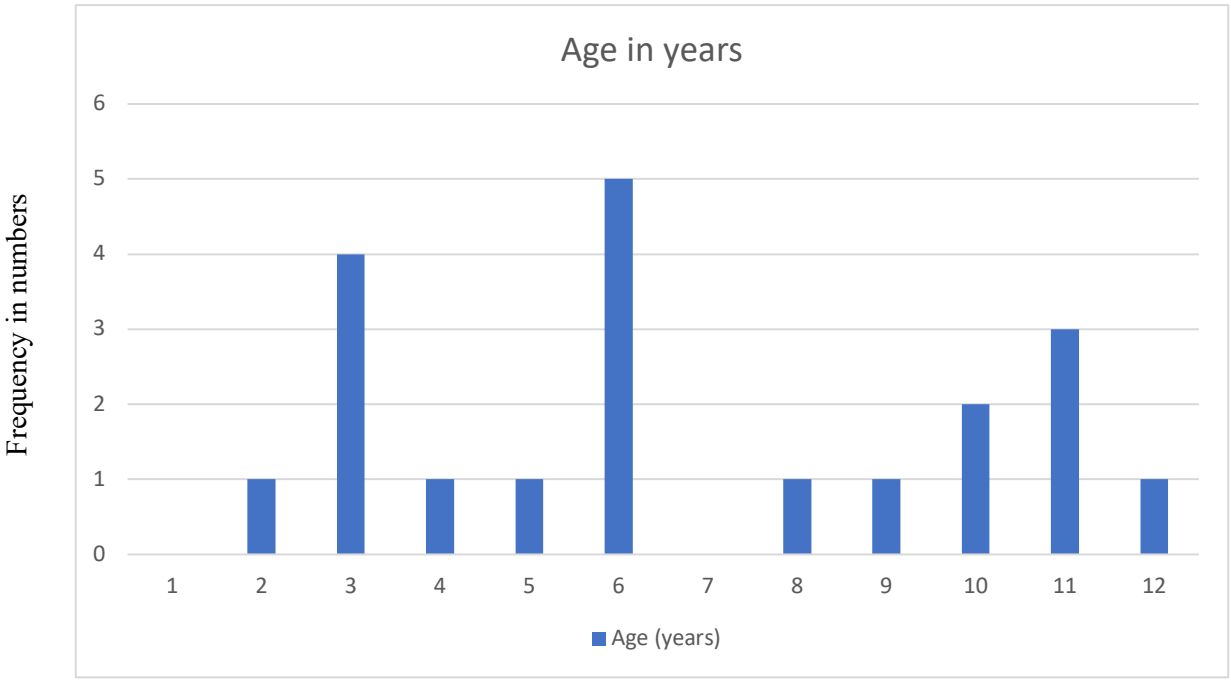


Figure 5: Bar graph showing age distribution

Sex

There was a slight male preponderance of 11 (55%) to 9 (45%) females. This is shown in the figure below.

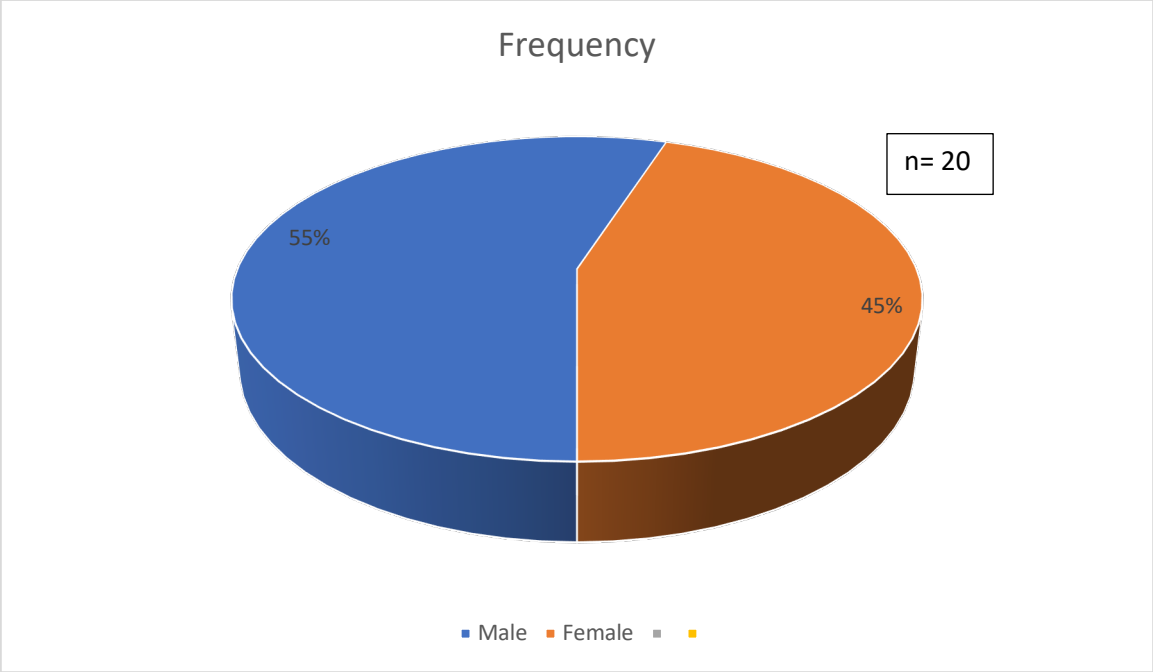


Figure 6: Pie chart showing sex distribution among patients

Residence.

25% of the patients came from Nairobi County while the remaining 75% were from the neighbouring counties. The furthest county was Taita-Taveta.

Economic background: Parent's/guardian's occupation

Most patients came from low-income families as shown in the figure below displaying their respective occupation. Most of the patients came from small-scale business-owning families at 65%.

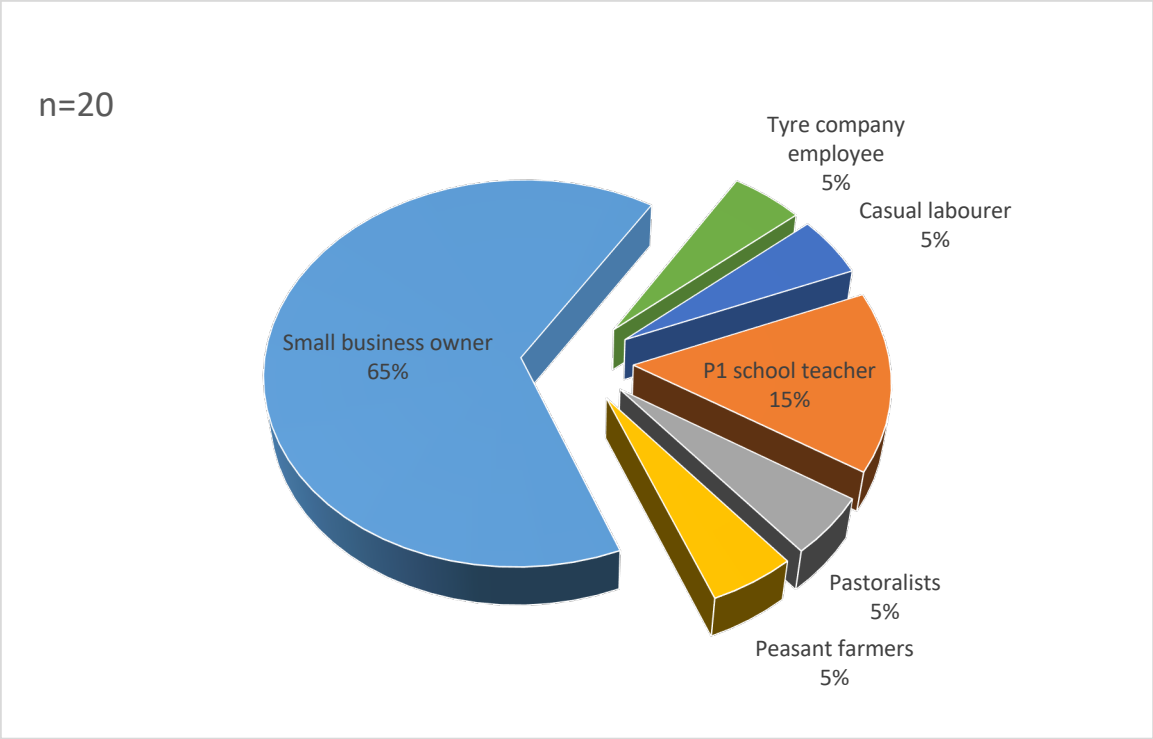


Figure 7: Pie chart showing Parent's/guardian's occupation

B. IMAGING

All 20 patients underwent head CT scans preoperatively. The size of the tumour on the scan was more than 3cm in diameter. The location of the tumour on the head CT scan was majorly midline (70%) filling the fourth ventricle. 30% of the tumors were hemispherical. Additionally, 17 (85%) patients underwent a craniospinal MRI before and after surgery, 2 (10%) patients only before surgery, and 1 (5%) patient only post-operatively.

The two patients who only had pre-operative craniospinal MRI died within three days of surgery.

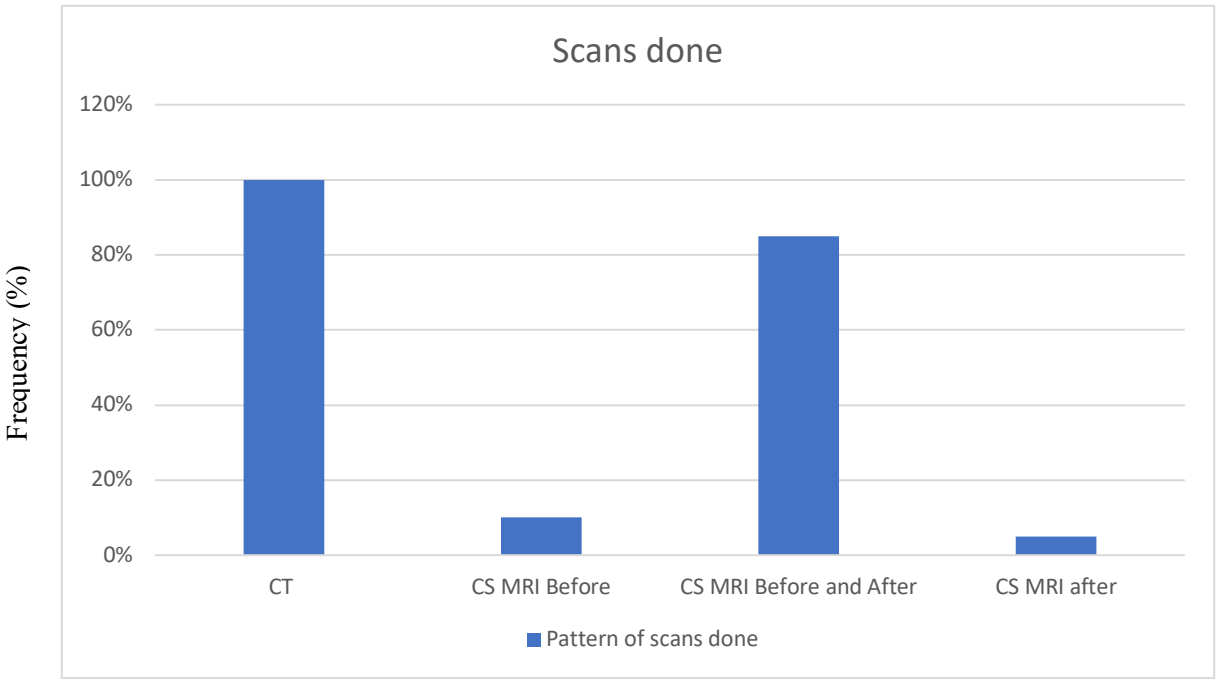


Figure 8: Bar graph showing scans done

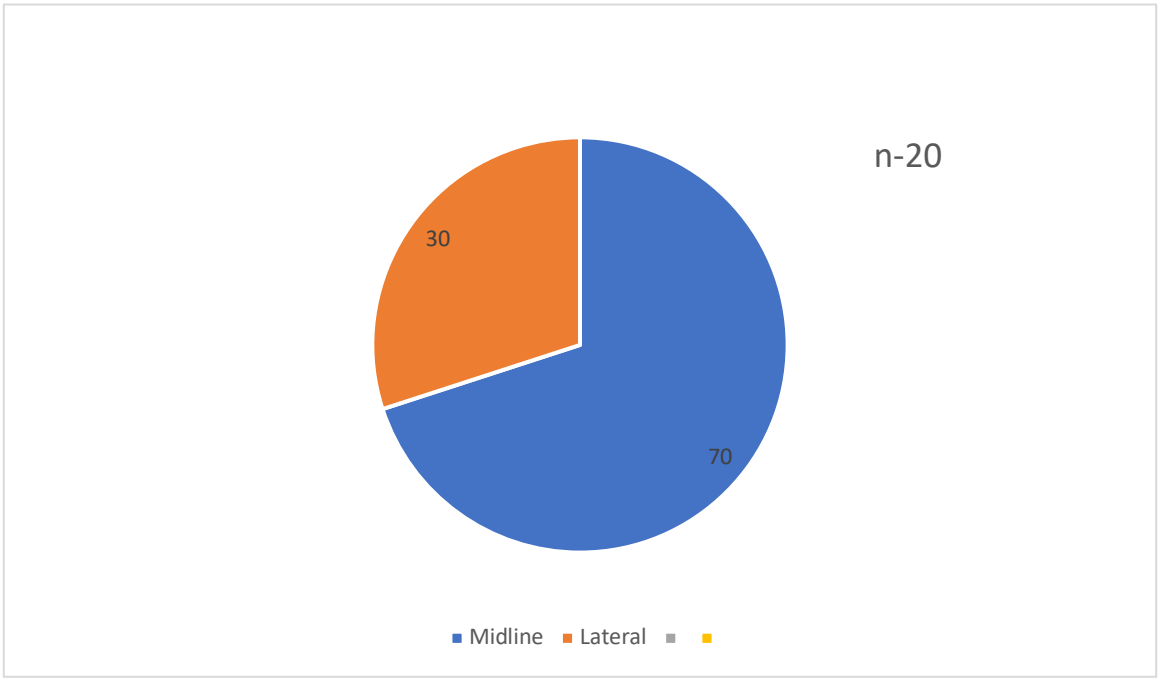


Figure 9: Pie chart showing pattern of tumour location on CT scan

1. Risk stratification of Paediatric medulloblastoma patients at KNH

Of the 20 patients observed, 16 (80%) had a standard-risk disease while 4 (20%) patients had high-risk disease. All the patients with high-risk disease had a classic histological type. The mean age for the high-risk disease was 3.5 years with a M:F of 3:1.

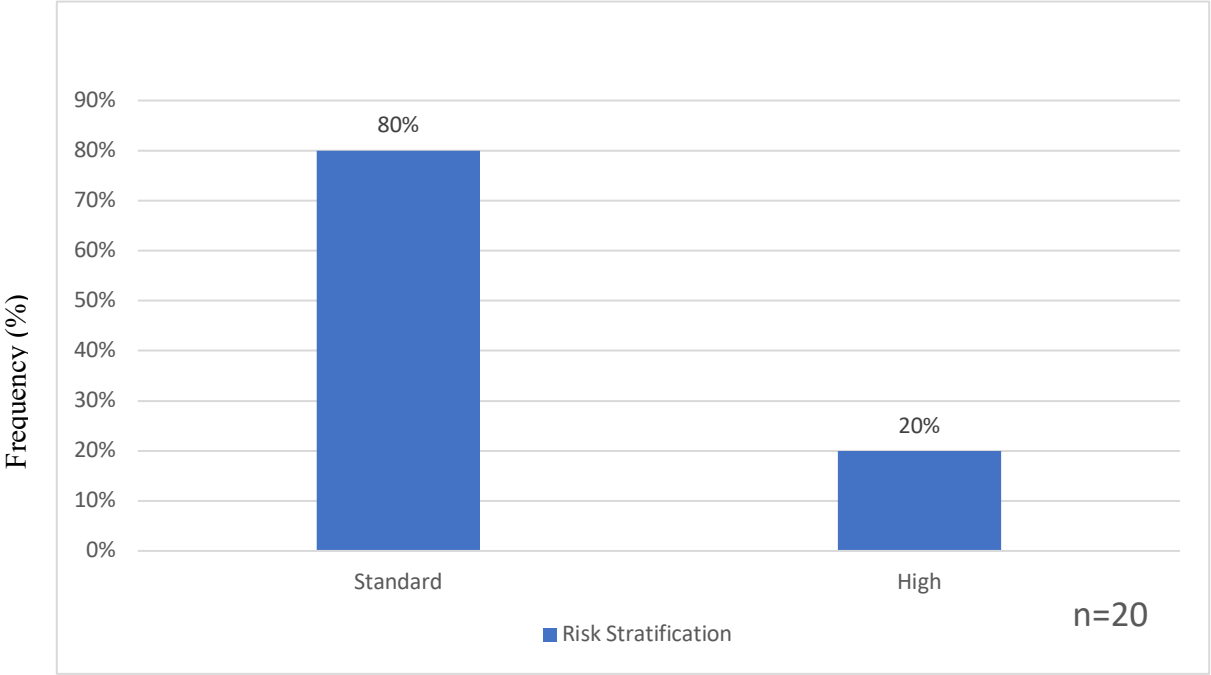


Figure 10: Bar graph showing risk stratification

2. Histological pattern of paediatric medulloblastoma patients at KNH

Classic medulloblastomas represented most of the histological subtype, i.e., 15 (75%). The remaining 5 (25%) were desmoplastic type. The mean age for the classic MB was 6.4 years while for desmoplastic MB was 7.8 years.

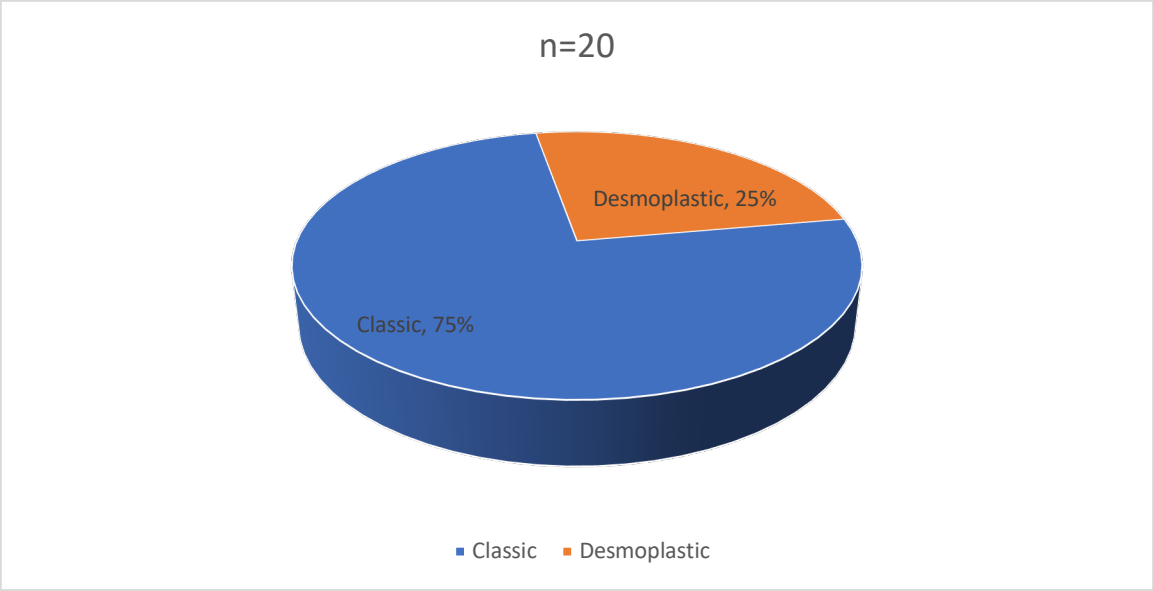


Figure 11: Pie chart showing the histological pattern of Medulloblastomas.

3. Surgical management pattern of paediatric medulloblastoma patients at KNH

CSF cytology:

Sixteen patients underwent CSF cytology with 7 (35%), being done pre-operatively, 4 (20%) post-operatively, and 5 (25%) having undergone both before and after surgery. One (5%) patient had a CSF positive for metastasis.

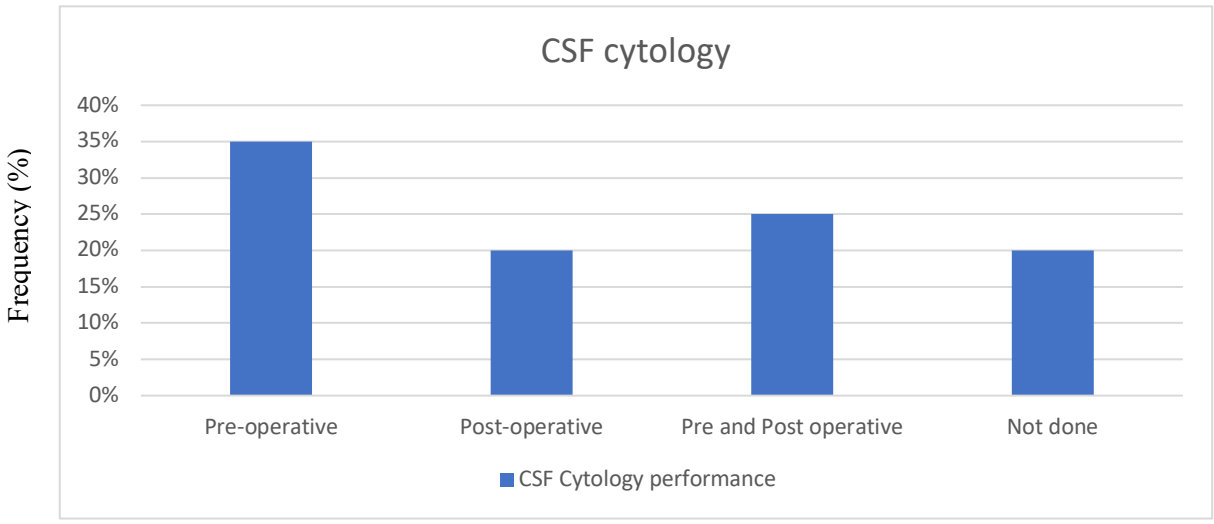


Figure 12: Bar graph showing pattern of CSF cytology performance

CSF diversion

The most common type of CSF diversion done was emergency VPS insertion 13 (65%), followed by EVD 4 (20%). However, 3 (15%) of the patients did not undergo CSF diversion.

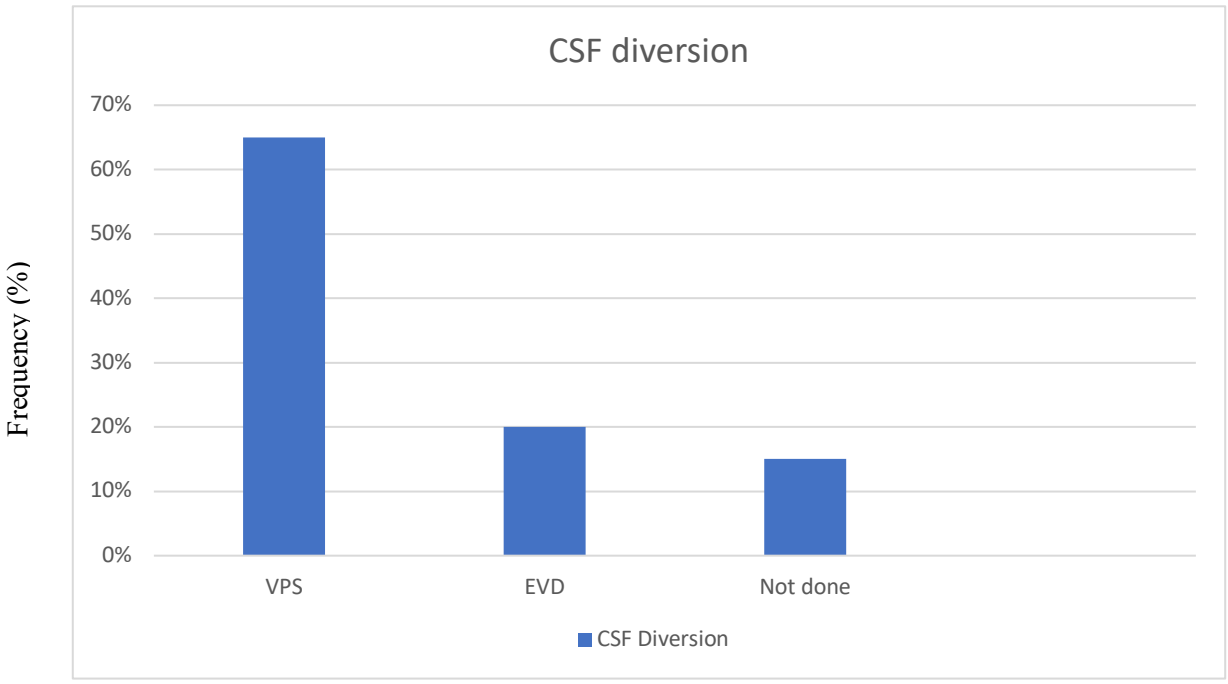


Figure 13: Bar graph showing the type and frequency of CSF diversion

Duration of delay from diversion to definitive surgery

The mean duration of a delay from CSF diversion to definitive surgery was 16.1 day in eleven observations. Range 4-30, median 14.

Bony exposure and complications occurrence

The main method of bony exposure was Craniotomy and C1 laminectomy for 11 (55%) patients while the remaining 9 (45%) patients only had craniotomies done. No craniectomies were done.

Surgical approaches

The majority of the patients, 11 (55%), underwent a telovelar approach, followed by transfoleal 5 (25%) patients, and finally, 4 (20%) patients had a transvermian approach.

Table 2: surgical approaches to medulloblastoma

Surgical approach	Frequency n=20	percent
Telovelar	11	55.0
Transvermian	4	20.0
Transfoleal	5	25.0

Extubation timing

Ten (50%) of patients were extubated immediately after at the end of the surgery, 9 (45%) had delayed extubation later in the ICU and one patient succumbed intraoperatively.

The mean duration of intubation among delayed extubation patients was 3.2 (SD 7.3) days, and the median duration was 0.0 (IQR 0.0 – 2.5) days.

One patient underwent a tracheostomy after 28 days of intubation.

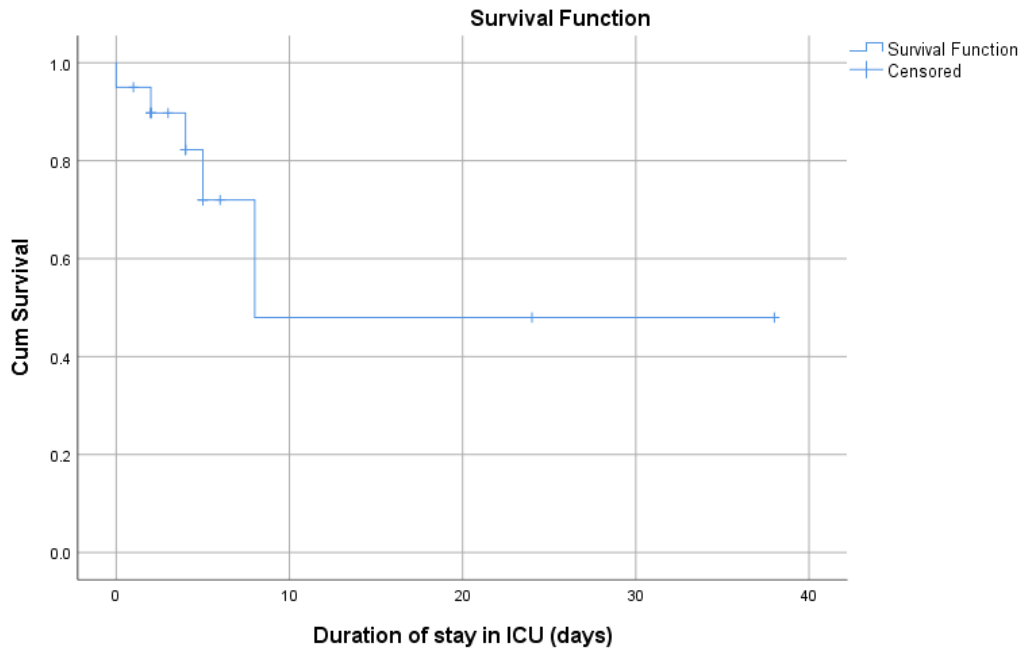
Length of ICU stay among delayed extubation patients.

Nine patients had delayed extubation with a mean stay of 10.4 days in ICU, median of 5. Days (Range 3-38 days). The length of ICU stay among delayed extubation was associated with increased rate of complications. These complications included respiratory failure, Aspiration pneumonia, pleural effusion, and seizures.

The overall duration of ICU stay

The mean duration of stay in ICU was 6.3 (SD 8.9) days, and the median duration was 4.0 (IQR 2.0 – 5.0) days.

Figure 14: Kaplan Meier survival estimate of duration of ICU stay by complications/ by mortality



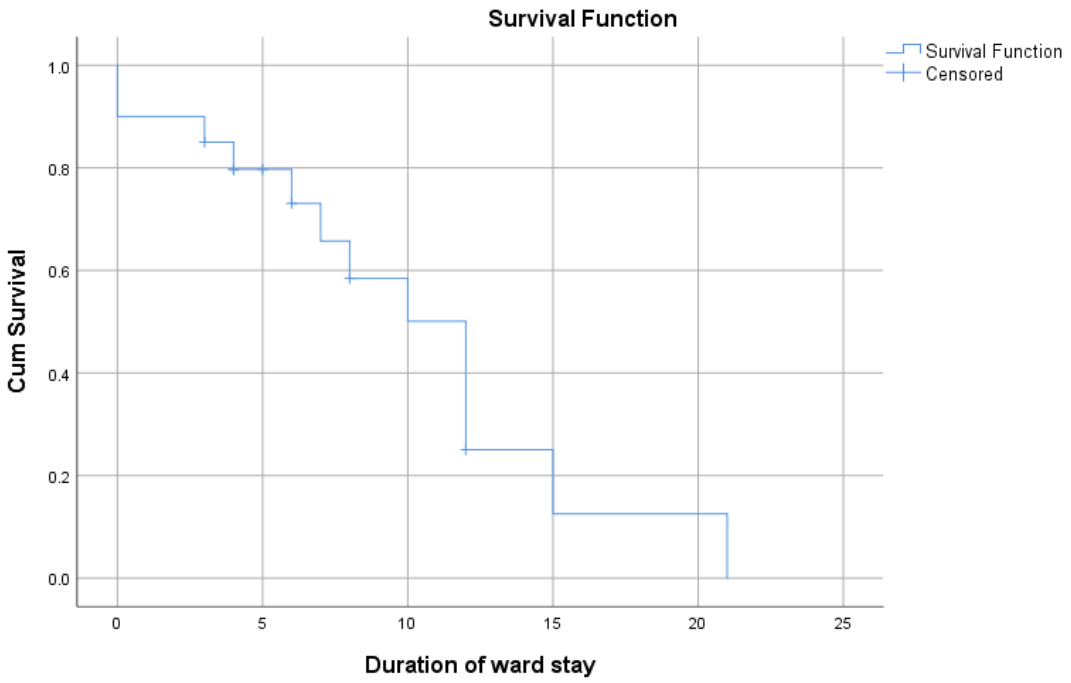
The mean for this was 21.1 days.

The overall duration of ward stay

Among the 18 participants observed, the mean duration of ward stay was 7.6 (SD 5.3) days, and the median duration was 6.5 (IQR 4.0 – 12.0) days.

The increasing duration of hospital stay was associated with increased complications.

Figure 15: Kaplan Meier survival function of duration of hospital stay by complications



The mean duration was 10.2 days.

The extent of tumour resection

17 patients had a gross total resection, i.e residual tumour less than 1.5cm^2. The remaining three had a subtotal tumour resection with residual tumour >1.5cm^2. Two of the three patients had a subtotal resection due to brainstem invasion while one had hemodynamic instability and he succumbed intraoperatively.

C. ADJUVANT THERAPY

Only thirteen of the twenty patients underwent adjuvant therapy. Twelve patients (60%) had both radiotherapy and chemotherapy while one patient had only radiotherapy. The mean duration of a delay in receiving adjuvant therapy was 43.6 days (Range 7-115 days). The factors affecting adjuvant therapy acquisition included delay in the performance of a craniospinal MRI, delay in acquisition of the radiotherapy mask, and finally, patients who were too sick at the time to withstand adjuvant therapy.

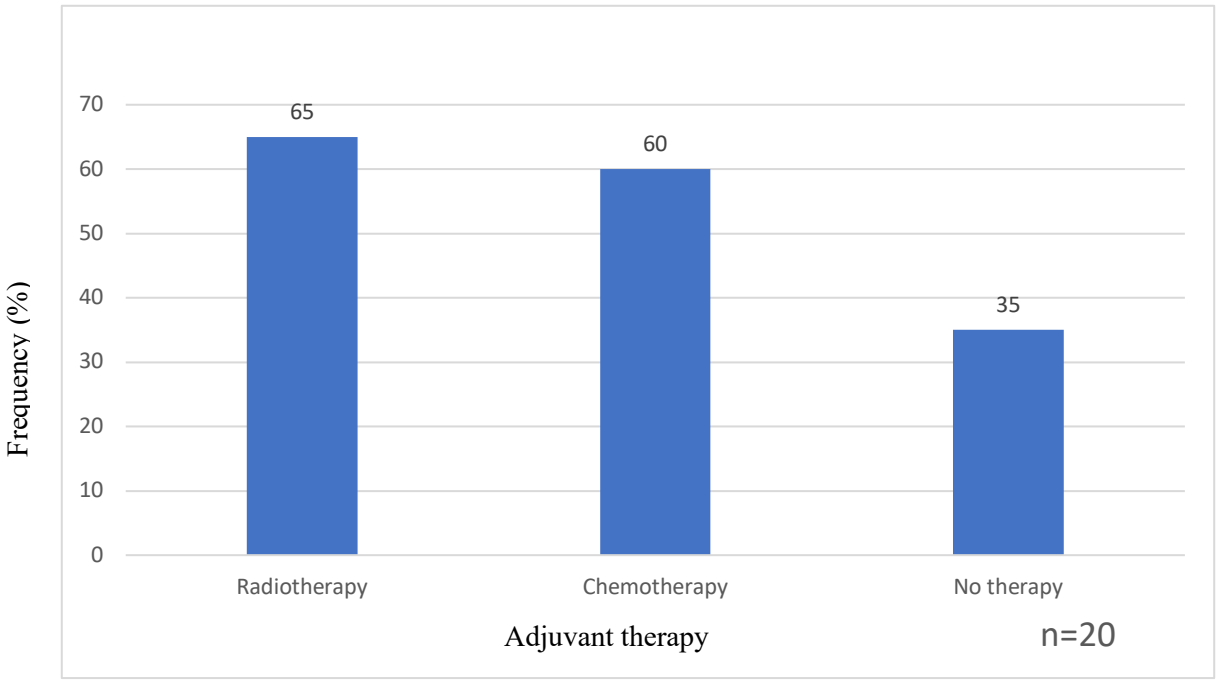


Figure 16: Bar graph showing adjuvant therapy administered

Overall survival at 6 months

Fifteen patients were alive at the end of 6 months of follow-up, representing an overall survival of 75%. The mortality rate was 25%, all of which didn't get adjuvant therapy. Four of the patients surviving at the end of 6 months had a recurrence of the disease. Two out of the four patients didn't undergo adjuvant therapy.

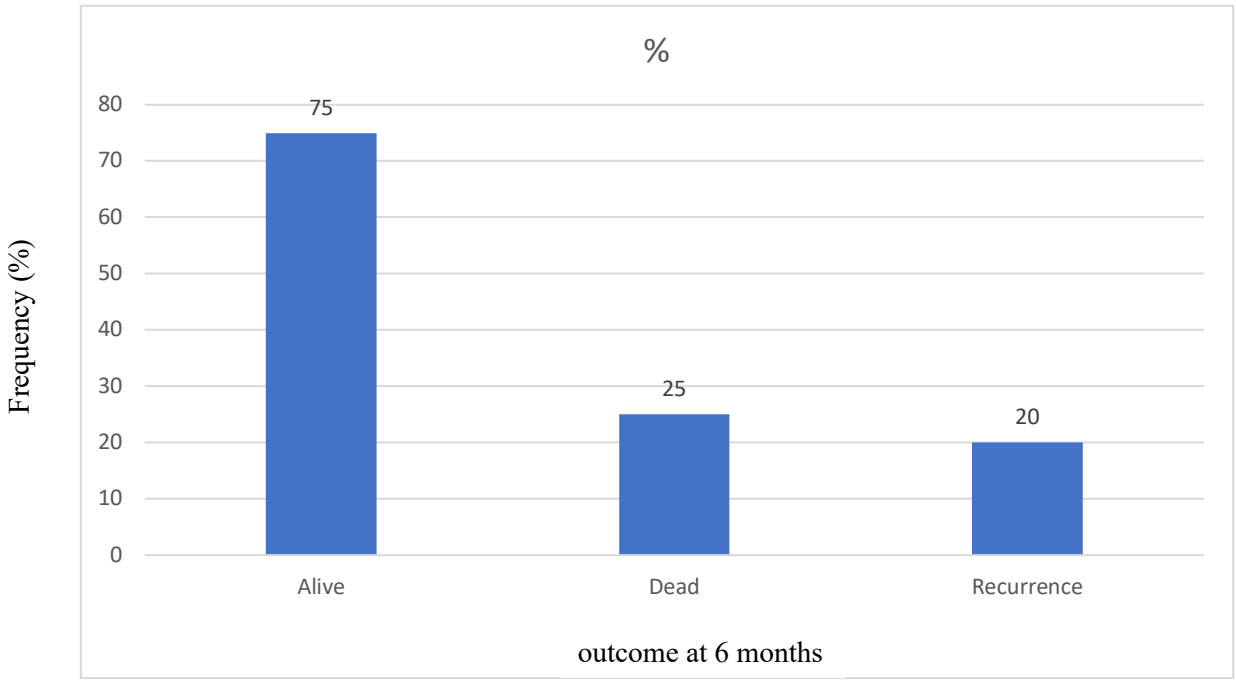
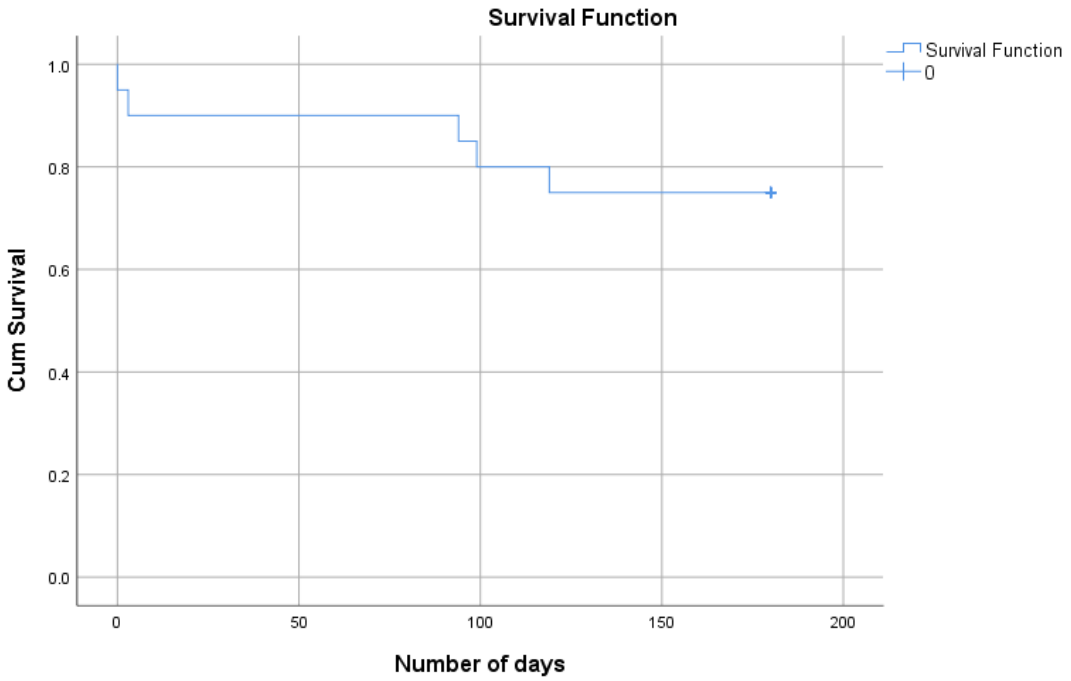


Figure 17: Bar graph showing overall survival at 6 months and recurrence post-surgery

Figure 18: Kaplan Meier survival function for the 6-month follow-up post-surgery.



The mean survival time was 150 days.

4. The relationship between risk stratification, histological pattern, and surgical management with the early surgical outcome

I). Table 7 shows the results of the association between the type of tumour in relation to the duration of stay in ICU, intubation, and ward stay. None of the associations were found to be statistically significant.

Table 3: Tumour type on length of ICU stay, intubation and ward stay

	Type of tumour		
Duration of stay in ICU (days)	**Classic**	**Desmoplastic**	**p-value**
0	1 (6.7)	0 (0.0)	1.000
1 - 7	12 (80.0)	4 (80.0)	
> 7	2 (13.3)	5 (20.0)	
Duration of intubation (days)			
0	7 (46.7)	4 (80.0)	0.156
1 - 7	7 (46.7)	0 (0.0)	
> 7	1 (6.7)	1 (20.0)	
Duration of ward stay (days)			
0	2 (13.3)	0 (0.0)	0.248
1 - 7	5 (33.3)	4 (80.0)	
> 7	8 (53.3)	1 (20.0)	

II). Table 8 show the results of the association between risk stratification in relation to the duration of stay in the ICU, intubation, and ward stay. Duration of ward stay was found to be statistically significantly associated with risk stratification, and the difference can be observed where 100% of the patients in the standard risk had 1 or more ward days as compared to high where 50% had no ward days and the other 50% had 1 or more ward days. This can also be attributed to the fact that 50% of the high-risk patients died before reaching the ward.

Table 4: Risk stratification of the length of ICU stay, intubation and ward stay

	Risk stratification		
Duration of stay in ICU (days)	**Standard**	**High**	**p-value**
0	0 (0.0)	1 (25.0)	0.278
1 - 7	13 (81.3)	3 (75.0)	
> 7	3 (18.3)	0 (0.0)	
Duration of intubation (days)			

0	9 (56.3)	2 (50.0)	1.000
1 - 7	5 (31.3)	2 (50.0)	
> 7	2 (12.5)	0 (0.0)	
Duration of ward stay (days)			
0	0 (0.0)	2 (50.0)	**0.032**
1 - 7	8 (50.0)	1 (25.0)	
> 7	8 (50.0)	1 (25.0)	

III). Table 9 shows the results of the association between the surgical approach in relation to the duration of stay in ICU, intubation, and ward stay. Duration of ward stay was found to be statistically significantly associated with the surgical approach, and the difference can be observed in the distribution of proportions for the 3 approaches in regards to the duration of ward stay i.e. for the 0 days of ward stay, the highest proportion was from Transvermian which was not comparable to the other 2 approaches, and this observation was the same for the 1 – 7 days, where 100% of the patients in the Transfoleal had the highest in comparison to the proportions of the other 2 approaches. This observation was the case for the greater than 7 days of which the proportions were not comparable.

Table 5: Type of approach on length of ICU stay, intubation and ward stay

	Surgical approach			
Duration of stay in ICU (days)	**Telovelar**	**Transvermian**	**Transfoleal**	**p-value**
0	1 (9.1)	0 (0.0)	0 (0.0)	0.273
1 - 7	9 (81.8)	2 (50.0)	5 (100.0)	
> 7	1 (9.1)	2 (50.0)	0 (0.0)	
Duration of intubation (days)				
0	5 (45.5)	1 (25.0)	5 (100.0)	0.141
1 - 7	5 (45.5)	2 (50.0)	0 (0.0)	
> 7	1 (9.1)	1 (25.0)	0 (0.0)	
Duration of ward stay (days)				
0	1 (9.1)	1 (25.0)	0 (0.0)	**0.014**
1 - 7	4 (36.4)	0 (0.0)	5 (100.0)	
> 7	6 (54.5)	3 (75.0)	0 (0.0)	

D. COMPLICATIONS

Rates of complication

The patients who developed complications were 13 out of 20. Some patients had more than one complication. There were complications in 65% 0f the patients compared to 35% without complications.

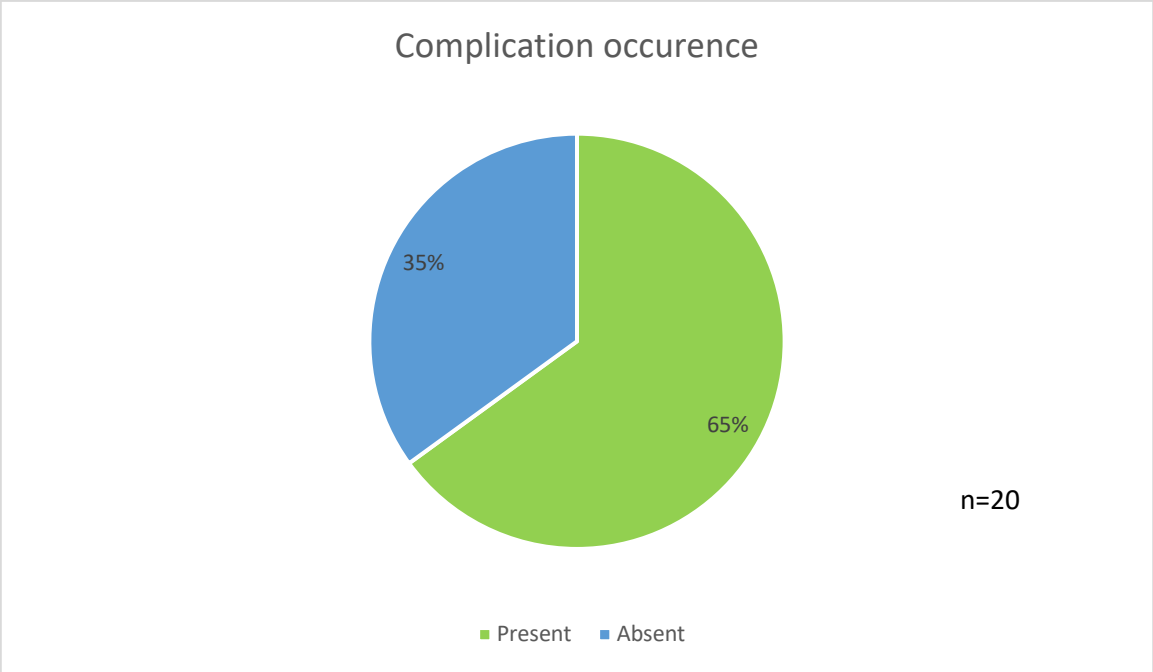


Figure 19: Pie chart showing the occurrence of complications.

Types of complications

Among the 13 children presenting with complications, 6 (30%) developed cerebellar mutism, 3 (15%) had respiratory failure, 2 (10%) hydrocephalus, ventilated associated pneumoniae and pleural effusion, 1 child developed hemiparesis, and another had a seizure. Some patients had more than one complication.

Table 6: Types of complications

	Complications	
	Yes	**No**
Cerebellar mutism	6 (30.0)	14 (70.0)
Hydrocephalus	2 (10.0)	18 (90.0)
Respiratory failure	3 (15.0)	17 (85.0)
Pneumonia	2 (10.0)	18 (90.0)
Hemodynamic instability	1 (5.0)	19 (95.0)
Hemiparesis	1 (5.0)	19 (95.0)
Pleural effusion	2 (10.0)	18 (90.0)
Seizures	1 (5.0)	19 (95.0)

Factors associated with complication occurrence

Factors associated with complications occurrence included the histological type of the tumour with classic medulloblastomas having more complications (p-value<0.031). Also, midline location of the tumour (p-value <0.007) and the surgical approach with telovelar approach presenting with majority of the complications (p-value<0.032).

Factors not

Table 7: Complication occurrence

	Complication occurrence		
Tumor	**Yes**	**No**	
Classic	12 (92.3)	3 (42.9)	**0.031**
Desmoplastic	1 (7.7)	4 (57.1)	
Tumor location			
Midline	12 (92.3)	2 (28.6)	**0.007**
Lateral	1 (7.7)	5 (71.4)	
Risk stratification			
Standard	9 (69.2)	7 (100.0)	0.249
High	4 (30.8)	0 (0.0)	
Surgical approach			
Telovelar	8 (61.5)	3 (42.9)	**0.032**
Transvermian	4 (30.8)	0 (0.0)	
Transfoleal	1 (7.7)	4 (57.1)	

CHAPTER SIX: DISCUSSION

Medulloblastoma is an embryonal tumour and the most common malignant brain tumour in children. It accounts for 10% to 25 % of primary CNS tumours.

6.1: Pattern of patient demographics

In this study, 20 patients on management for medulloblastomas were followed up at KNH, of this, 11 (55%) were male while 9 (45%) were female, with a female to male of ratio of 1:1.2. This is similar to what is seen in CBTRUS and Packer *et al* (12, 16). This study demonstrated a peak incidence of 3 years to 9 years, which is also compared with studies on childhood medulloblastomas (12).

The mean age of the patients at diagnosis was 6.8 (SD 3.3) years. This is also similar to studies that show a mean range of 6.5 years to 7.9 (94). All the patients were noted to be from low socio-economic backgrounds.

6.2: Imaging pattern

In this study, all patients underwent a preoperative head CT scan. The most common tumour location was midline (70%). Donati et al reported 80% midline occurrence (49, 95). These midline tumors were larger than 3 cm and filled the fourth ventricle. Additionally, 85% of the patients underwent a craniospinal MRI (CS MRI) before and after surgery to assess for leptomeningeal dissemination. None of these patients had any disease spread outside the posterior cranial fossa. Two (10%) patients had the CS MRI only before surgery. These two paints died within 72 hours of surgery and therefore never underwent the post-operative CS MRI. One patient had a CS MRI done after surgery.

Of the 14 patients with midline tumors, 11 (55%) had radiological evidence of hydrocephalus and needed permanent CSF diversion compared to only 2 (10%) of the hemispherically placed tumours that required permanent diversion. In total, 13 (65%) of the patients had hydrocephalus at diagnosis. This is congruent with Fruewhwald et al who found 75% in his series.

The duration of waiting for a post-CSF diversion MRI is on average 16.1 days due to the fact that paediatric MRIs are done once a week within our facility and patients have to wait for their scheduled time.

6.3: Risk stratification

Standard-risk disease represented 80% of the population while the remaining 20% were high-risk disease patients. Among the high-risk disease patients, three had a residual tumour post-operative of $>1.5cm^2$ while one had a positive metastatic workup on cytology.

6.4: Histological pattern of medulloblastomas

The most common histologic variant was the classic medulloblastoma, with 15 (75%) patients compared to 5 (25%) patients who had the desmoplastic variant. The classic variant is the most common variant in literature constituting 72% of all MBs (18). In this study, the OS for pts with the classic variant was 73.3% at 6 months and PFS at six months was 86%. Asmaa et al demonstrated an OS of 71.4% and PFS of 42.9% at 1 year. For desmoplastic variant, this study showed an OS of 80% and a PFS of 60% at six months, the sample size was small though at only five patients and drawing conclusions from the above may not be a better representative picture of the population. An intermediate picture of OS at 1year of 70% and PFS at 1 year of 30% has been reported in desmoplastic medulloblastomas (23).

6.5: Surgical management pattern

In addition to definitive surgery, 85% of patients had CSF diversion. 60% had emergency CSF diversion prior to definitive surgery. In KNH, this is frequently done since most patients present with signs of acutely increased intracranial pressure and require CSF diversion before definitive surgical planning due to logistical constraints. One (5%) patient developed post-operative hydrocephalus and had also to undergo VPS. Twenty percent of the patients underwent EVD insertion intraoperatively, of which were weaned off the EVD by the fifth postoperative day. In studies done, VPS or ETV prior to tumour resection is not recommended because only 25% of patients need permanent CSF diversion (67,68).

Risk factors in these patients that may have contributed to permanent CSF diversion include large tumors and long-standing hydrocephalus.

All patients were admitted to ICU post operatively. The overall mean duration of ICU stay was 6.3 days and a median of 4.0 (IQR 2.0-5.0) days. This duration was affected by whether the patient had immediate post-operative extubation or delayed extubation. Ten (52.6%) of patients were extubated immediately, the average duration of ICU stay was 3.2 days with a median of 2 (Range 1-6) day stay. Nine (47.7%) patients had delayed extubation, with an average ICU stay of 10.4 days and a median of 5 (Range of 3-38) days. Additionally, longer duration of ICU stay was associated with occurrence of complications and increased mortality.

The mean duration of hospital stay was 14.5 days. prolonged hospital stay correlated with complication occurrence. This study mirrors the findings by Kanna et al who reported duration of hospital stay as 14 days for patients undergoing posterior fossa craniotomy (92).

6.6: Early surgical outcomes and complications following surgery of medulloblastomas.

This study evaluated various outcome measures for children with PCF tumours. These were the duration of hospital stays, duration of stay in the intensive care unit, the occurrence of

complications, and overall outcome at six months. Complications were reported in 13 (65%) patients out of the 20 undergoing treatment. Thirty percent of the patients had cerebellar mutism, compared to 10%-25% in studies (72,73), 10 % had hydrocephalus which compares to the reported 25% in literature (67,68), 10% had a weak respiratory effort with associated ventilator-associated pneumonia. A further 10% developed immediate post-operative seizures which were managed. Three patients had more than one complication.

Factors noted to be associated with complication occurrence in this study included, delayed extubation, classic medulloblastomas variant (p-value<0.031), midline tumour location (p-value<0.007), telovelar approach (p-value<0.032).

Risk stratification was not seen to be associated with complications.

The mortality rate in this study, at 6 months of follow-up was 25% with overall survival of 75% and progression-free survival of 73.3%. Mortality was associated with not having received adjuvant therapy.

6.7: Adjuvant therapy and factors affecting timely intervention.

A total of 13 (65%) of the patients in this study underwent adjuvant therapy. Twelve patients had radio-chemotherapy while one patient only had radiotherapy. Seven (35%) of the patients didn't get adjuvant therapy. Of the 7 patients, 2 died within three days of surgery, 2 were too sick to undergo treatment, and 2 lacked funds for CS MRI, radiotherapy mask, and recurrent travel expenses. There was also a notable delay in receiving adjuvant therapy for the patients who underwent adjuvant therapy. Only 3 patients received their adjuvant therapy on time. The mean delay was 43.6 days. Forty percent of the remaining 10 patients reported a delay in performing CS MRI, 40% delay in acquiring the radiotherapy mask, 10% had a protracted

recovery time before adjuvant therapy (115 days) and 10% complained of being informed about adjuvant therapy late (90 days after surgery).

6.8: Conclusion

The study shows that there were more males than females presenting with medulloblastomas, and the peak incidence is between 3 to 9 years.

The most common location of the tumour was the midline as per imaging. A delay in MRI imaging performance by a mean of 16.1 days results in a delay in definitive surgery.

Sixty-five percent of patients underwent permanent CSF diversion, and the commonest histological variant was the classic medulloblastoma. Most patients undergoing ventriculoperitoneal shunting present with advanced signs of hydrocephalus as seen in this study.

The high rate of permanent CSF diversion is also due to the fact that patients have to undergo an emergency reduction in intracranial pressure as they await elective surgery scheduling.

Sixty-five percent of the patients had complications with 30% having cerebellar mutism. The rates of complications were associated with the length of hospital stay, classic variant, and midline tumour location.

There was a mean delay in adjuvant therapy acquisition of 43.6 days and reasons for delay included delay in performance of the CS MRI, delay in acquisition of the radiotherapy mask, prolonged recovery post-surgery, and recurrent travel expenses.

The mortality rate at the 6-month follow-up was 25%, OS was 75%, and progression-free survival was 73.3%.

The twenty percent mortality rate was associated with not having undergone adjuvant therapy post-surgery mostly due to the factors established above.

6.9: Recommendation

1. A prolonged follow-up of these children for a longer period beyond six months to assess survival and recurrence, especially of the patients who missed adjuvant therapy.
2. To establish at least two days a week for children's MRI imaging to reduce the duration between CSF diversion and definitive surgical intervention.
3. Patients under NHIF coverage can have their imaging pre-authorization forms filled at first contact with the patient to reduce post-operative imaging delays and financial strain on patients who are forced to pay out of their pockets.
4. Patients without NHIF coverage can also be advised to apply for the same to help cover treatment costs, this can be included to cover the craniotomy drill which is paid for by cash.
5. Kenyatta National Hospital can also reduce the cost of surgery for these patients in lieu of the morbidity that may follow post-surgery.
6. The neurosurgical unit sets up protocols regarding medulloblastoma tumour management, especially for patients presenting with hydrocephalus to undergo emergency definitive surgery to reduce the rate of permanent CSF diversion.
7. The surgical team is to work in liaison with the cancer treatment team (CTC) from the time the patient first presents to the unit (KNH) and advise the patient on the possible treatment plan including radiotherapy mask purchase and follow-up CS MRI. This will reduce delays in adjuvant therapy and help parents/guardians plan ahead financially.
8. A follow-up study especially on molecular patterns of these disease as outlined in WHO 2021 brain tumour classification will help in the acquisition and application of targeted therapy.

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APPENDICES:

Appendix 1: Ethical Approval Letter

UNIVERSITY OF NAIROBI
FACULTY OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/340

14th September, 2022

Dr. Wilfred Mwangale Munialo
Reg. No. H58/87149/2016
Dept. of Surgery
Faculty of Health Sciences
University of Nairobi

Dear Dr. Munialo,

RESEARCH PROPOSAL: CLINICOPATHOLOGICAL STRATIFICATION AND EARLY SURGICAL OUTCOME OF PAEDIATRIC MEDULLOBLASTOMA PATIENTS AT KENYATTA NATIONAL HOSPITAL (P416/05/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P416/05/2022.** The approval period is 14th September 2022 – 13th September 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Protect to discover

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

c.c. The Dean, Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Assistant Director, Health Information Dept., KNH
The Chairperson, KNH- UoN ERC
The Chair, Dept. of Surgery, UoN
Supervisors: Dr. Peter Kithikii Kitunguu, Dept. of Surgery, UoN
Dr. Kiboi Julius Githinji, Dept. of Surgery, UoN
Dr. John Boore, Dept. of Surgery, Division of Neurosurgery, KNH

Appendix 2: Consent form

This informed consent is for parents/guardians of paediatric neurosurgical patients undergoing medulloblastoma treatment at the Kenyatta National Hospital. We are requesting this patient to participate in this research project whose title is: CLINICOPATHOLOGICAL STRATIFICATION AND EARLY SURGICAL OUTCOME OF PAEDIATRIC MEDULLOBLASTOMA PATIENTS AT KENYATTA NATIONAL HOSPITAL.

PRINCIPLE INVESTIGATOR

DR WILFRED MWANGALE MUNIALO

NEUROSURGERY RESIDENT,

UNIVERSITY OF NAIROBI

CONTACT: 0725394943

EMAIL: drmunialo@gmail.com

Introduction

The purpose of this consent form is to give you the information you will need to help you decide whether or not to be a participant in the research. Feel free to ask any questions about the purpose of the research, what happens if you participate in the study, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide to be in the study or not. This process is called 'informed consent. Once you understand and agree to be in the study, I will request you to sign your name on this form. Your decision to participate is entirely voluntary. You may withdraw from the study at any time without necessarily giving a reason for your withdrawal. Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities. We will give you a copy of this form for your records. May I Continue? YES……. NO…….

This study has approval by The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee protocol No…….

WHAT IS THIS STUDY ABOUT?

This Research will assess the clinical and histological stratification of medulloblastoma patients in relation to the early surgical outcome. Medulloblastomas are among the commonest brain tumors. There will be approximately 34 participants in this study. These participants will be children aged 0 to 12 years with a medulloblastoma and who meet our inclusion criteria. We are asking for your consent to consider participating in this study.

WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS RESEARCH STUDY?

If you agree to participate in the study. The following will happen.

1. We will take you to a doctor's consultation room and one of our researchers will assign you a unique participant number that we shall use to track your record. The researcher will then ask you about your family demographics and your illness. He/she will then study your file and scans and record the findings on the data collection form.
2. If you are still admitted in the ward after surgery, then I will review you within the ward. We will also follow you till discharge.
3. Another interview will be conducted at the end of six months after surgery to ascertain the survival of the patient.
4. You shall then be reviewed routinely in the Neurosurgery clinic after the sixth month review.
5. The interview shall last about 20 minutes.

ARE THERE ANY RISKS, HARMS DISCOMFORTS ASSOCIATED WITH THIS STUDY?

Medical research has the potential to introduce psychological, social, emotional and physical risks. Effort should always be put in place to minimize the risks. One potential risk of being in the study is loss of privacy. We will keep everything you tell us as confidential as possible. We will use a code number to identify you in a password-protected computer database and will keep all of our paper records in a locked file cabinet. However, no system of protecting your confidentiality can be absolutely secure, so it is still possible that someone could find out you were in this study and could find out information about you. Also, answering questions in the interview may be uncomfortable for you. If there are any questions you do not want to answer, you can skip them. You have the right to refuse the interview or any questions asked during the interview. No additional surgical risk beyond what would be experienced outside of the study shall be introduced. If before surgery it is deemed that surgery is contraindicated, we shall act in your best interest and cancel the surgery. No new surgical technique shall be introduced beyond

that which is routinely done for all our glioma patients. However, in the event that we have a surgical adjunct that the surgical team deems to be beneficial to you we shall inform you accordingly.

ARE THERE ANY BENEFITS BEING IN THIS STUDY?

Should the study reveal need for further care we shall refer you appropriately. Also, the information you provide will help us better understand how our surgery impacts patients with medulloblastomas. This information is a contribution to science and helps improve patient outcomes.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

Being in this study will not cost you anything beyond what you would have spent were you not part of the study. You will need to pay for your consultation, Lab works, drugs, imaging studies and histology besides the surgical fee.

WILL YOU GET REFUND FOR ANY MONEY SPENT AS PART OF THIS STUDY?

We shall endeavor to ensure that you do not spend anything beyond what you would have spent were you not a part of the study.

WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about participating in this study, please call or send a text message to the study staff at the number provided at the bottom of this page. For more information about your rights as a research participant you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke.The study staff will pay you back for your charges to these numbers if the call is for study-related communication.

WHAT ARE YOUR OTHER CHOICES?

Your decision to participate in research is voluntary. You are free to decline participation in the study and you can withdraw from the study at any time without injustice or loss of any benefits.

CONSENT FORM (STATEMENT OF CONSENT)

Participant's statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw any time. I freely agree to participate in this research study.

I understand that all efforts will be made to keep information regarding my personal identity confidential.

By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I agree to participate in this research study:	Yes	No
I agree to have (define specimen) preserved for later study:	Yes	No
I agree to provide contact information for follow-up:	Yes	No

Participant's Full name:……..

Participants Signature? Right Thumb print……..

Date:…… …….

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Researcher 's Name:…….

Signature……..

Date:…….

For more information contact DR WILFRED MUNIALO on 0725394943 or email @ drmunialo@gmail.com from 8:00am to 5:00 PM Monday to Friday

Witness

Name…… Signature /Thumb stamp: ……

Contact information…….. Date: .....

Appendix 3: consent form Swahili version.

RC/FORM/IC01

FOMU YA TAARIFA NA RIDHAA YA MAZI/MLEZI

Form hii ya makubaliano ni kwa WAZAZi/walezi wa wale Watoto wanaougua saratani ya medulloblastoma wanaotibiwa hospitalini kuu Kenyatta. Namualika mtoto wako kuwa mmoja wa wale watakaofanyiwa uchunguzi huo katika huu kwa hiari yako**. Mada ya utafiti ni:**

UTABIBU WA KITABIBU NA KITAMBI NA MATOKEO YA MAPEMA YA UPASUAJI WA WAGONJWA WA MEDULLOBLASTOMA WA WATOTO KATIKA HOSPITALI YA TAIFA YA KENYATTA.

MTAFITI MKUU

DR WILFRED MWANDALE MUNIALO

MKAZI WA UPASUAJI WA UBONGO KATIKA CHUO KIKUU CHA NAIROBI

MAWASILIANO: 0725394943

BARUA PEPE: drmunialo@gmail.com

UTANGULIZI

Daktari Wilfred Munialo ni Mkazi mkuu wa Upasuaji wa Ubongo katika UON. Madhumuni ya fomu hii ya idhini ni kukupa taarifa utakayohitaji ili kukusaidia kuamua kama kuwa mshiriki au la katika utafiti. Jisikie huru kuuliza maswali yoyote kuhusu madhumuni ya utafiti, nini kitatokea ukishiriki katika utafiti, hatari na manufaa yanayoweza kutokea, haki zako kama mtu wa kujitolea, na jambo lingine lolote kuhusu utafiti au fomu hii ambalo haliko wazi. Wakati tumejibu maswali yako yote kwa kuridhika kwako, unaweza kuamua kuwa katika utafiti au la.Utaratibu huu unaitwa 'kibali cha taarifa'. Ukishaelewa na kukubali kuwa katika utafiti, nitakuomba utie sahihi jina lako kwenye fomu hii. Uamuzi wako wa kushiriki ni wa hiari kabisa. Unaweza kujiondoa kwenye utafiti wakati wowote bila kutoa sababu ya kujiondoa kwako. Kukataa kushiriki katika utafiti hakutaathiri huduma unazostahiki katika kituo hiki cha afya au vituo vingine. Tutakupa nakala ya fomu hii kwa rekodi zako.

Naweza kuendelea? NDIYO ……. HAPANA …….

Utafiti huu umeidhinishwa na Itifaki ya Kamati ya Maadili na Utafiti ya Hospitali ya Kitaifa ya Kenyatta-Chuo Kikuu cha Nairobi No……..

UTAFITI HUU UNAHUSU NINI?

Utafiti huu utatathmini **matokeo ya utambuzi baada ya upasuaji kwenye uvimbe wa ubongo uitwao Medulloblastoma.** Uvimbe huu ni moja ya uvimbe wa kawaida wa ubongo. Kutakuwa na takriban washiriki 34 katika utafiti huu. Washiriki hawa watakuwa Watoto walio na medulloblastoma na wanaofikia vigezo vyetu vya kujumuishwa. Tunaomba idhini yako ili kuzingatia kushiriki katika utafiti huu.

NINI KITAENDELEA UKIAMUA KUWA KATIKA UTAFITI HUU?

Ikiwa unakubali kushiriki katika utafiti. Yafuatayo yatatokea.

1. Tutakupeleka kwenye chumba cha mashauriano cha daktari na mmoja wa watafiti wetu atakupa nambari ya kipekee ya mshiriki ambayo tutatumia kufuatilia rekodi yako. Kisha mtafiti atakuuliza kuhusu idadi ya watu wa familia yako na ugonjwa wako. Kisha atasoma faili yako na kuchanganua na kurekodi matokeo kwenye fomu ya kukusanya data.
2. Ikiwa bado umelazwa katika wodi baada ya upasuaji, basi nitakupitia ndani ya wodi. Pia tutakufuata hadi utakapotoka
3. Mahojiano mengine yatafanywa mwishoni mwa miezi sita baada ya upasuaji ili kujua maisha ya mgonjwa.
4. Kisha utapitiwa mara kwa mara katika kliniki ya Neurosurgery baada ya ukaguzi wa mwezi wa sita.
5. Mahojiano yatadumu kama dakika 20.

JE, KUNA HATARI, MADHARA YOYOTE YANAYOHUSISHWA NA UTAFITI HUU?

Utafiti wa kimatibabu una uwezo wa kuanzisha hatari za kisaikolojia, kijamii, kihisia na kimwili. Jitihada zimewekwa kila wakati ili kupunguza hatari. Hatari moja inayoweza kutokea ya kuwa katika utafiti ni kupoteza faragha. Tutaweka kila kitu unachotuambia kama siri iwezekanavyo. Tutatumia nambari ya msimbo kukutambua katika hifadhidata ya kompyuta iliyolindwa na nenosiri na tutaweka rekodi zetu zote za karatasi kwenye kabati ya faili iliyofungwa. Hata hivyo, hakuna mfumo wa kulinda usiri wako unaoweza kuwa salama kabisa, kwa hivyo bado kuna uwezekano kwamba mtu anaweza kujua ulikuwa kwenye utafiti huu na kupata taarifa kukuhusu.

Pia, kujibu maswali katika mahojiano kunaweza kuwa na wasiwasi kwako. Ikiwa kuna maswali yoyote ambayo hutaki kujibu, unaweza kuyaruka. Una haki ya kukataa mahojiano au maswali yoyote yaliyoulizwa wakati wa mahojiano.

Hakuna hatari ya ziada ya upasuaji zaidi ya ile ambayo ingepatikana nje ya utafiti . Iwapo kabla ya upasuaji itaamuliwa kuwa upasuaji hauhitajiki, tutatenda kwa manufaa yako na kughairi upasuaji. Hakuna mbinu mpya ya upasuaji itakayoanzishwa zaidi ya ile ambayo hufanywa mara kwa mara kwa wagonjwa wetu wote wa glioma. Hata hivyo, katika tukio ambalo tuna kiambatanisho cha upasuaji ambacho timu ya upasuaji itaona kuwa ya manufaa kwako tutakujulisha ipasavyo

JE, KUNA FAIDA YOYOTE KUWA KATIKA UTAFITI HUU?

Iwapo utahitaji utunzaji zaidi, tutakuelekeza ipasavyo. Pia, maelezo utakayotoa yatatusaidia kuelewa vyema jinsi upasuaji wetu unavyoathiri wagonjwa wenye Glioma. Habari hii ni mchango kwa sayansi na husaidia kuboresha matokeo ya mgonjwa.

JE, KUWA KATIKA UTAFITI HUU KUTAGHARIMU CHOCHOTE?

Kuwa katika utafiti huu hakutakugharimu chochote zaidi ya kile ambacho ungetumia kama hukuwa sehemu ya utafiti. Utahitaji kulipia ushauri wako, kazi za Maabara, dawa, masomo ya picha na histolojia kando na ada ya upasuaji.

JE, UTAREJESHWA KWA PESA ZOZOTE ULIZOTUMIA SEHEMU YA UTAFITI HUU?

Tutajitahidi kuhakikisha kuwa hutumii chochote zaidi ya kile ambacho ungetumia kama hukushiriki katika utafiti.

VIPI IKIWA UNA MASWALI BAADAYE?

Ikiwa una maswali zaidi au wasiwasi kuhusu kushiriki katika utafiti huu, tafadhali piga simu au tuma ujumbe mfupi wa maandishi kwa wafanyikazi wa utafiti kupitia nambari iliyotolewa chini ya ukurasa huu.

Kwa maelezo zaidi kuhusu haki zako kama mshiriki wa utafiti unaweza kuwasiliana na Katibu/Mwenyekiti, Hospitali ya Kitaifa ya Kenyatta-Kamati ya Maadili na Utafiti ya Chuo Kikuu cha Nairobi Nambari 2726300 Ext. 44102 barua pepe uonknh_erc@uonbi.ac.ke.

Wafanyikazi wa utafiti watakurudishia malipo yako kwa nambari hizi ikiwa simu ni ya mawasiliano yanayohusiana na masomo.

UCHAGUZI WAKO MWINGINE NI GANI?

Uamuzi wako wa kushiriki katika utafiti ni wa hiari. Uko huru kukataa kushiriki katika utafiti na unaweza kujiondoa kwenye utafiti wakati wowote bila dhuluma au hasara ya manufaa yoyote.

KNH-UoN/ERC/FORM/IC0

FOMU YA RIDHAA (TAARIFA YA RIDHAA)

Kauli ya Mshiriki

Nimesoma fomu hii ya idhini au nimesomewa maelezo. Nimepata nafasi ya kujadili utafiti huu na mshauri wa utafiti. Nimejibiwa maswali yangu kwa lugha ninayoielewa. Hatari na faida zimeelezewa kwangu. Ninaelewa kuwa ushiriki wangu katika utafiti huu ni wa hiari na kwamba ninaweza kuchagua kujiondoa wakati wowote. Ninakubali kwa uhuru kushiriki katika utafitihuu.

Ninaelewa kuwa juhudi zote zitafanywa ili kuweka taarifa kuhusu utambulisho wangu wa kibinafsi kuwa siri.

Kwa kutia saini fomu hii ya idhini, sijaacha haki zozote za kisheria nilizo nazo kama mshiriki katika utafiti wa utafiti.

Ninakubali kushiriki katika utafiti huu: Ndiyo…☐…… Hapana…☐……

Ninakubali sampuli kuhifadhiwa kwa ajili ya utafiti wa baadaye: Ndiyo☐ Hapana…☐

Ninakubali kutoa maelezo ya mawasiliano kwa ufuatiliaji: Ndiyo ☐ Hapana ☐

Jina lililochapishwa la mshiriki:……

Sahihi ya mshiriki / Muhuri wa kidole gumba……Tarehe……

Kauli ya mtafiti

Mimi, niliyetia sahihi chini, nimeeleza kikamilifu maelezo muhimu ya utafiti huu kwa mshiriki aliyetajwa hapo juu na ninaamini kuwa mshiriki ameelewa na ametoa ridhaa yake kwa hiari na kwa uhuru.

Jina la Mtafiti:……..Sahihi……..…Tarehe……

Jukumu katika utafiti:……

Kwa maelezo zaidi wasiliana na DR WILFRED MUNIALO kwa 0725394943 au barua pepe drmunialo@gmail.com kutoka 8:00 AM asubuhi hadi 5:00 PM Jumatatu hadi Ijumaa.

Shahidi

Jina……..…..Sahihi / Muhuri wa kidole gumba:……

Maelezo ya mawasiliano…….. Tarehe……

Appendix 4: Assent form in English.

STUDY TITLE: CLINICOPATHOLOGICAL STRATIFICATION AND EARLY SURGICAL OUTCOME OF PAEDIATRIC MEDULLOBLASTOMA PATIENTS AT KENYATTA NATIONAL HOSPITAL.

INVESTIGATORS

Principal Investigator:

Dr. Munialo Mwangale Wilfred

Supervisors:

1. Dr. Peter Kithikii Kitunguu,
2. Dr. Kiboi Julius Githinji,
3. Dr. John Boore,

1. **Why are you here?**

The doctor wants to tell you about a study concerning medulloblastomas in children undergoing treatment at Kenyatta National Hospital. Medulloblastoma is a common childhood brain tumour. The wants to see if you would like to be in the study. This form tells you about the study; if there is anything you do not understand, please ask your parent/guardian or doctor.

2. **Why are they doing the study?**

The investigators want to assess the outcomes of treatment of this illness in relation to the clinical presentation, histological type of the tumour, and the treatment techniques at the Kenyatta National Hospital.

3. **What will happen to you?**

The interview will take about 30 minutes.

The following information will be filled in the questionnaire.

- Your age and gender.
- Your ethnicity, religion, and the occupation of your parent/guardian.
- The doctor will then look at the imaging done and record the details.
- The doctor will also record details from both your inpatient and outpatient files.
- The doctor will then ask you if you underwent further treatment after undergoing surgery.

4. **Will the study hurt?**

No. You might feel a bit tired during the interview period.

5. **Will you get better if you are in the study?**

During the study, you will receive the usual treatment for your condition.

6. What if you have any questions?

You can ask anytime, now or later. You can talk to the doctors, parent, or guardian.

7. Who will know what I did in the study?

Any information you give to the study staff will be kept private. Your name will not appear in study papers.

No one except the study staff and your parent/guardian will know that it was you who was in the study.

8. Do you have to be in the study?

No. No one will be angry at you if you do not want to be in the study.

I will also ask your parent/guardian if they would like you to be in the study.

Even if your parent/guardian wants you to be in the study, you can still say no. even if you say yes now, you can change your mind later.

The doctor will still treat you for the brain tumour even if you say no to the study.

Assent

I want to take part in this study. I know I can change my mind at any time.

A) Verbal assent. (Print name of child)…… verbal assent given.
B) Written assent.
   Sign……. Age……. Date……
   I confirm that I have explained the study to the participant to the extent compatible with the participant's understanding and that the participant has agreed to be in the study.

   Name…… Sign…….. Date…….

Appendix 5: Assent form in Swahili: Fomu ya Makubaliano

KICHWA CHA UTAFITI: UTABIBU WA KITABIBU NA KITAMBI NA MATOKEO YA MAPEMA YA UPASUAJI WA WAGONJWA WA MEDULLOBLASTOMA WA WATOTO KATIKA HOSPITALI YA TAIFA YA KENYATTA.

Watafiti

Mtafiti mkuu

Dkt. Munialo Mwangale Wilfred

Wasimamizi

1. Dkt. Peter Kithikii Kitunguu,
2. Dkt. Kiboi Julius Githinji,
3. Dkt. John Boore,

1. **Mbona uko hapa?**

Daktari anataka kukueleza kuhusu utafiti wa watoto wanaougua saratani ya Medulloblastoma hospitali kuu ya Kenyatta. Daktari anataka kujua kama ungependa kuhusika kwa huu utafiti. Fomu hii ina maelezo kuhusu utafiti huu. Ikiwa kuna jambo usilolielewa, tafadhali uliza kutoka kwa mzazi/mlezi au madaktari.

2. **Mbona utafiti huu?**

Wachunguzi wanataka kutathmini matokeo ya matibabu ya ugonjwa huu kuhusiana na wasilisho la kliniki, aina ya kihistoria ya uvimbe huo, na mbinu za matibabu katika Hospitali ya Kitaifa ya Kenyatta.

3. **Mwelekeo**

Mahojiano yatachukua mda wa karibu dakika thelathini.

Ujumbe ufuatao utajazwa kwenye dodoso:

- Umri na jinsia
- Kabila lako, dini, na kazi ya mzazi/mlezi wako.
- Kisha daktari ataangalia picha iliyofanywa na kurekodi maelezo.
- Daktari pia atarekodi maelezo kutoka kwa faili zako za kulazwa na za kliniki
- Kisha daktari atakuuliza ikiwa ulipitia matibabu zaidi baada ya kufanyiwa upasuaji.

4. **Iko hatari yeyote?**

Hakuna hatari yeyote utakayoipata. Unaweza kupata uchovu wakati wa mahojiano.

5. **Iko matibabu kwa utafiti?**

Utapata matibabu ya kawaida wakati wa utafiti.

6. **Maswali?**

Unaweza kuuliza maswali wakati wowote. Utapata majibu kutoka kwa madaktari au mzazi/mlezi.

7. **Nani atajua kuhusika kwangu?**

Ujumbe kuhusu majibu yako yatahifadhiwa vyema. Ujumbe kuhusu ushiriki wako katika utafiti huu utaweza kupatikana na wewe, mzazi/mlezi na wanaoandaa utafiti na wala si yeyote mwingine. Jina lako halitatumika kwenye utafiti.

8. **Kuhusika ni kwa lazima?**

Hapana. Hakuna yeyote atakayekulaumu usiposhiriki kwa utafiti. Mzazi/mlezi wako ataulizwa ruhusa ya kushiriki pia; si lazima ushiriki hata ikiwa mzazi/mlezi wako amekubali. Unayo haki ya kujitoa katika utafiti wakati wowote unapoamua na kukataa kwako hakutatumiwa kukunyima tiba.
Makubaliano

Nimeamua kushiriki kwa utafiti huu, naelewa ninaweza kujitoa wakati wowote.

A) Makubaliano ya matamshi (jina la mtoto)……
B) Makubaliano kwa maandishi

Sahihi……. Umri…… Tarehe…….

Nimethibitisha ya kwamba nimemweleza mshiriki kuhusu utafiti huu kulingana na kuelewa kwake na amekubali kushiriki.

Jina…….. Sahihi…….. Tarehe……

Appendix 6: Validated Data collection sheet

CLINICOPATHOLOGICAL STRATIFICATION AND EARLY SURGICAL OUTCOME OF PAEDIATRIC MEDULLOBLASTOMA PATIENTS AT KENYATTA NATIONAL HOSPITAL.

Demographics:

Study number

Age in years at diagnosis: 1. 0-</=3 2. >3-12

Sex: 1. M 2. F

Residence (County):

Ethnicity: Religion:

Parent/guardian Occupation:

Imaging:

Imaging: size of lesion on the head CT scan: 1: <3cm 2. >3cm

Tumor Location: 1. Midline 2. Lateral

Craniospinal MRI done: 1. Before surgery

2. After surgery

3. Not done If not, reason

Surgical intervention:

CSF cytology: 1. Pre-operative

2. Post-operative

3. Not done

Metastasis at diagnosis: 1. M0 2. M+

CSF diversion: 1. Before surgery 2. After surgery 3. None

Type of CSF diversion 1. VPS 2. ETV 3. EVD

Duration of stay in days from shunting to definitive surgery: Reason:

Date of surgery / /

Opening of the skull: 1. Craniotomy 2. Craniectomy

Surgical approach: 1. Telovelar 2. Transvermian

Post-surgical follow-up:

Duration of ICU stay in days:

Duration of intubation in days: Tracheostomy:

Residual tumour size post operation 1. <1.5cm^2 2. =/>1.5cm^2

Reason for incomplete tumour resection: 1. Brainstem invasion

2. Haemodynamic instability

3. Other

Histopathology:

1. Classic Medulloblastoma

2. Desmoplastic Medulloblastoma

3. Large cell/Anaplastic Medulloblastoma

4. Medulloblastoma with extensive nodularity

Adjuvant therapy:

1. Next of kin informed ☐
2. Chemotherapy ☐
3. Radiotherapy ☐
4. None ☐

Risk stratification:

1. Standard risk: ☐
2. High risk: ☐

Overall survival at 6 months after surgery:

1. Alive: ☐
2. Recurrence: ☐
3. Dead: ☐

Appendix 7: Similarity Index

CLINICOPATHOLOGICAL STRATIFICATION AND EARLY SURGICAL OUTCOME OF PAEDIATRIC MEDULLOBLASTOMA PATIENTS AT KENYATTA NATIONAL HOSPITAL.

ORIGINALITY REPORT

13%	9%	11%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	link.springer.com Internet Source	3%
2	Erepository.uonbi.ac.ke Internet Source	1%
3	D. Kombogiorgas. "Medulloblastoma☆", Elsevier BV, 2017 Publication	1%
4	Otília Menyhárt, Balázs Győrffy. "Molecular stratifications, biomarker candidates and new therapeutic options in current medulloblastoma treatment approaches", Cancer and Metastasis Reviews, 2020 Publication	1%
5	"Oncology of CNS Tumors", Springer Science and Business Media LLC, 2019 Publication	1%
6	Abd Elrhman Enayet, Mohamed Nabil, Mohamed Reda Rady, Yasser Yousef, Eman Badawy, Mohamed A. El Beltagy. "Surgical	1%