CLINICAL PROFILE, DIAGNOSTIC MODALITIES, AND TREATMENT OUTCOMES OF PRIMARY PAEDIATRIC BRAIN TUMORS AT INKOSI ALBERT LUTHULI CENTRAL HOSPITAL IN DURBAN, SOUTH AFRICA

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2024

DECLARATION

I, Lucia Amolo, declare that:

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(ii) This dissertation has not been submitted for any degree or examination at any other university.

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ABSTRACT

INTRODUCTION: Primary paediatric brain tumours are associated with high mortality and morbidity in African countries with a five-year survival rate of 32% in sub-Saharan Africa vs 80% in Western countries. Data on the burden of these tumours in the African setting is sparse due to the lack of dedicated cancer registries.

METHODS: Approval was obtained from UKZN ethics and research committee (BREC/00005385/2023). A total of 337 patients with primary paediatric brain tumours admitted at Inkosi Albert Luthuli Central Hospital between 2003 and 2017 were included. Data on demographics, diagnostic and treatment modalities and outcome was analysed.

RESULTS: There was a male preponderance of 54.6% with a mean age of 6.8 years (range 1 month to 14 years). Most children were of the African race (89.9%). Infratentorial tumours were more common than supratentorial tumours (55.2% vs 43.6%) while 1.2% had extension into both compartments. The most prevalent tumours were brainstem gliomas [n=82; 24. 3%], pilocytic astrocytomas [n=45; 13.4%], medulloblastoma [n=41; 12.2%] and craniopharyngioma [n=36; 10.7%]. Treatment modalities were dependent on time of presentation tumour type and histology. Mean survival time was 4.54 years [95% CI: 3.764;5.312]. At 5 years, 44.5% were lost to follow-up, 31.3% died and 24.3% were alive. By bivariate analysis, factors associated with shorter survival included African race($p=0.009$), infratentorial tumours($p=0.044$), presence of hydrocephalus($p=0.002$) and lack of any treatment modality including no radiotherapy($p<0.0001$) or chemotherapy treatment ($p=0.036$), and surgical resection ($p=0.0001$).

CONCLUSION: There is need for a central brain tumour registry in KwaZulu-Natal. Collaboration between hospitals and engagement of stakeholders to avail resources is required.

Key words: brain tumours, supratentorial, infratentorial, treatment modalities, survival time

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1. LITERATURE REVIEW

1.1 EPIDEMIOLOGY

Primary paediatric brain tumours are associated with high mortality and morbidity in African countries with a five - year survival rate of 32% in sub-Saharan Africa vs 80% in Western countries [1, 2]. While the exact disease burden is unknown, it is thought to be much higher among African children than their Western counterparts. Stones et al noted that paediatric brain tumours in South Africa are among the most common childhood cancers (19.5%) second only to leukaemia (25%) [3]. This is supported by data from the South African Childhood Cancer Registry 2020 which reports CNS tumours are the third most common childhood cancers (14.3%) after leukaemia (21.1%) and lymphomas (15.5%) [4]. Prevalence of various CNS tumours noted by the registry include ependymomas and choroid plexus tumours (2.8%), astrocytomas (2.8%), embryonal tumours (3.9%), other gliomas (2.2%), unspecified tumours (0.5%) and other specified tumours (2.1%).

A study in Namibia showed that tumours of the central nervous system were the most common (18%) and reflected similar patterns among southern African countries [2]. A gap exists in documenting cases of brain tumours in the African continent and there is a need for a central registry to improve existing healthcare systems [5]. The National Cancer Registry was established by the Ministry of Health, South Africa under the National Health Act 2003(Act No. 61 of 2003) in 2011. Cancer was then classified as a reportable disease in recognition of the increasing burden of disease. Childhood cancers have been recently added as a national priority in the National Cancer Strategic Framework.

1.2 CLASSIFICATION

Paediatric brain tumours are traditionally classified based on histological findings and more recently by molecular biomarkers. The anatomical location can also be used to classify tumours into supratentorial versus infratentorial. Arnold-Day in Cape Town, South Africa

showed supratentorial tumours to be slightly more common (52%) than infratentorial tumours [6]. Further characterization is based on whether the tumour is benign or malignant. Benign tumours are slow-growing and remain confined to their location while malignant tumours spread rapidly to invade other tissues. Classification based on the age at diagnosis enables division into congenital brain tumours, those of infancy and childhood [7]. Congenital tumours are diagnosed within the first two months of birth, tumours of infancy within the first year of life, and tumours in children are diagnosed after one year of life.

The 2021 World Health Organization classification of paediatric brain tumours emphasizes the need to add molecular genetics to the traditional histopathological and radiological classification of paediatric brain tumours [8]. D'amati et al noted that this classification was useful for tumours that were not easily diagnosed as well as identifying associations between syndromes that predispose to cancer and newer tumour entities. It also allows for targeted therapy [8]. While molecular genetics is yet to be incorporated in the management of brain tumours in South Africa, in depth knowledge by clinicians can help in advocacy for its use in the foreseeable future.

Table 1 summarises the clinicopathological and molecular WHO paediatric brain tumour classification. Gliomas and glioneural tumour classification has advanced significantly with molecular genetics as shown. Low-grade gliomas are more frequent in the paediatric age group than high-grade gliomas [9]. Pilocytic astrocytomas are low-grade gliomas characterized by insidious growth and are benign [10]. They are the most prevalent paediatric brain tumours commonly seen in children between 5 and 8 years. Embryonal tumours are aggressive tumours in the paediatric population. Medulloblastomas, which fall under this classification, are one of the most common paediatric tumours seen in children below 10 years [7].

Table 1: 2021 WHO 5 Classification of Paediatric Brain Tumours

Paediatric low-grade gliomas and glioneuronal tumours		
Paediatric type diffuses low grade glioma	**Circumscribed astrocytic glioma**	**Glioneuronal and neuronal tumours**
Diffuse astrocytoma, MYB- or MYBL1 altered	Pilocytic astrocytoma	Ganglioglioma
Angiocentric glioma	High grade astrocytoma with piloid features	Gangliocytoma
Polymorphous low grade neuroepithelial tumour of the young		Desmoplastic infantile ganglioglioma/desmoplastic infantile astrocytoma
Diffuse low grade glioma, MAPK pathway altered	Subependymal giant cell astrocytoma	Dysembryoplastic neuroepithelial tumour
	Chordoid glioma	Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters
	Astroblastoma, MN1 altered	Papillary glioneuronal tumour
		Rosette forming glioneuronal tumour
		Myxoid glioneuronal tumour
		Multinodular and vacuolating neuronal tumour
		Dysplastic cerebellar gangliocytoma
		Central neurocytoma
		Extra ventricular neurocytoma
		Cerebellar liponeurocytoma
Paediatric type diffuse high-grade gliomas		
Diffuse midline glioma, H3 K27- altered		
Diffuse hemispheric glioma, H3 G34-mutant		
Diffuse paediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype		
Infant-type hemispheric glioma		
Ependymal tumours		
Supratentorial ependymomas	Posterior fossa ependymomas	
Supratentorial ependymoma, ZFTA fusion-positive	Posterior fossa ependymoma, group A	
Supratentorial ependymoma, YAP1 fusion-positive	Posterior fossa ependymoma, group B	
	Myxopapillary ependymoma	
Embryonal tumours		
Medulloblastoma		
Atypical teratoid/rhabdoid tumour		
Embryonal tumour with multilayered rosettes		
CNS neuroblastoma, FOXR2-activated		
CNS tumour with *BCOR* internal tandem duplication		
Mesenchymal tumours		

Significance in the molecular classification is seen with medulloblastomas which are now classified into 4 key molecular groups: wingless activated (WNT), sonic hedgehog (SHH)

activated, G3 and G4 [7, 8]. These groups can be further subdivided and have an influence on prognosis and treatment options with WNT having the best 5-year survival rate while G3 has the worst prognosis.

Mesenchymal tumours are those that originate from the meninges and less commonly, choroid plexus or CNS parenchyma. Ependymal tumours, which are relatively rare, arise from ependymal cells and are broadly classified as supratentorial or posterior fossa tumours [11]. The posterior fossa tumours are further classified by molecular genetics into group A and group B while supratentorial tumours are further subdivided into ZFTA fusion-positive YAP1 fusion-positive.

1.3 CLINICAL PRESENTATION

The clinical presentation of primary brain tumours varies in the paediatric population. It is dependent on several factors including age, tumour type and tumour location [7].

Age

Young children whose sutures have not fused can compensate for a growing mass with an increasing head size. These children are therefore likely to present with macrocephaly among other symptoms. Those whose sutures have fused often have signs of increased intracranial pressure as well as other neurological deficits at presentation. Signs of raised intracranial pressure include headaches which are usually worse in the morning, altered level of consciousness and Cushing's triad. This variability, particularly in the young can influence time of clinical presentation. Additionally, older children who can express themselves are more likely to present earlier than the younger child who has not yet attained this milestone.

Tumour location

The clinical presentation is also dependent on the site of the tumour. Paediatric brain tumours can be located either in the supratentorial or infratentorial region [7]. These tumours can

further be found in specific areas of these two regions. Ostrom et al, demonstrated the common location of primary paediatric brain tumours among US children 19 years and younger as shown in the diagram below [11].

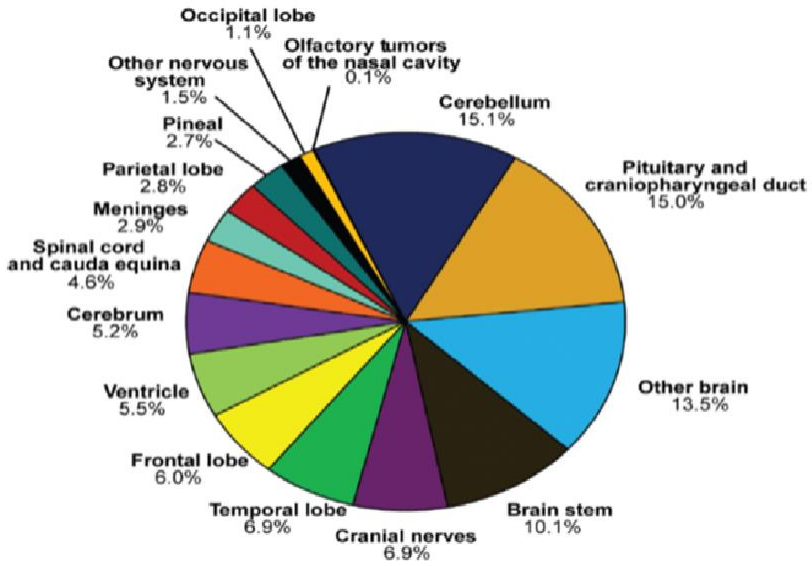

Figure 1: Distribution in Children and Adolescents (age 0-19 years) of Primary Brain and CNS tumours by site, CBTRUS Statistical Report, 2009-2013

Tumours located in the posterior fossa generally have an earlier presentation than supratentorial tumours due to the confined space as well as critical structures located here. Patients may present with cranial nerve deficits due to location of cranial nerves and their nuclei in the brainstem, motor deficits such as hemiparesis or paraparesis due to the descending corticospinal tract as well as sensory deficits such as pain and temperature abnormalities due to the ascending spinothalamic tract, joint position, vibration and proprioception abnormalities due to the posterior columns. The reticular activating system influences the sleep wake cycles and its neurons are in the brainstem. Altered level of consciousness may therefore be a presenting complaint. Among those with cerebellar lesions, symptoms depend on the specific location of the tumour in the cerebellum. For example, midline lesions involving the vermis and paramedian cerebellar hemispheres will present

with nystagmus and truncal ataxia while those involving the lateral hemispheres will present with appendicular ataxia. A pan-cerebellar tumour which would be much larger may have all the above symptoms.

For supratentorial tumours, clinical presentation is dependent on the lobe or region involved. Craniopharyngiomas are histologically benign but can cause serious pre- and post-operative symptoms based on their unique location in the suprasellar region. They lie near the optic pathway, pituitary, and hypothalamus and can lead to visual disturbances, endocrine dysfunction including diabetes insipidus, panhypopituitarism as well as headaches [12]. The frontal lobe has important anatomical and functional regions. Tumours in the Broca's area result in non-fluent aphasia while those involving the primary motor cortex will likely present with motor deficits such as hemiparesis and motor seizures. Tumours in the prefrontal lobe may result in behaviour abnormalities such as aggression, personality changes and dysexecutive functioning. Those with occipital lobe tumours may present with cortical visual impairment.

Tumour type and size

Histopathological and molecular genetic classification of tumour type may influence the clinical presentation. Table 1 demonstrates the newer classification that incorporates the newer classification. Rapidly growing or large tumours regardless of their location may present with a wide range of neurological deficits necessitating the need for neuroimaging to determine the exact origin of the tumour. Benign low-grade gliomas are typically slow growing and may present with subtle symptoms that may be missed initially while high-grade gliomas such as glioblastoma multiforme have a rapidly growing, progressive nature with most patients presenting acutely [9]. Medulloblastomas can spread locally or extracranially which may influence clinical presentation. They have a predilection for the cerebellar

parenchyma or fourth ventricle, so patients are more likely to present with cerebellar symptoms mentioned above [8].

1.4 RISK FACTORS

The incidence of brain tumour types varies by age, gender, and the extent of exposure to environmental agents. Progress has been made in identifying potential risk factors such as genetic predisposition, exposure to allergens, and ionizing radiations. These factors have been well documented and validated by many studies as risk factors for paediatric brain tumours [11, 13]. It is difficult to attribute a direct causal link of toxic environmental exposures to brain tumour occurrence due the overall low incidence.

Genetic factors

Genetic factors have a strong association with an increased risk of brain tumours. Mutations in *CCND2, PTCH1* and *GLI2* are associated with medulloblastoma [11]. Neurocutaneous disorders such as Neurofibromatosis 1 (NF1) and Tuberous Sclerosis Complex (TSC) associated with genetic mutations have shown predisposition to primary brain tumours. These conditions result from aberrant signals in the tumour regulatory pathways. Neurofibromatosis is caused by mutations in the *NF1* pathway which encodes neurofibromin, a tumour suppressor gene that regulates the *RAS/MAPK* pathway. *NF1* mutations are associated with optic pathway gliomas, astrocytomas and schwannomas [11]. A study following children with neurofibromatosis in Cape Town, South Africa over 5 years found that 14% of children presented with optic nerve gliomas [14].Tuberous sclerosis complex, an autosomal dominant disorder, is also associated with brain tumours and results from mutations in *TSC1* or *TSC2* gene which downregulate the *mTOR-PIK3CA* pathway. Mutations in these gene can result in subependymal giant cell astrocytomas which are low grade gliomas. Kija et al demonstrated that 23% of patients on follow-up at a Tuberous sclerosis complex clinic in Western Cape, South Africa had subependymal giant cell astrocytomas [15].

Infections

Viral infections such as HIV, CMV, and EBV have been strongly incriminated in the development of some childhood CNS tumours [16-18]. CMV infection has been associated with brain gliomas while EBV infection is associated with CNS lymphomas and gliomas [17, 19]. With an estimated 160,000 children under 14 living with HIV in South Africa, this incidence of co-infection may impact the clinical course of childhood brain tumours [20]. HIV infection predisposes children to opportunistic infections including space-occupying lesions such as tuberculomas, neurocysticercosis, and toxoplasmosis. This often cause diagnostic confusion in the assessment of brain tumours, especially in settings where access to ancillary tests is limited [21]. A lack of treatment response to a presumed brain infections often will prompt the clinician to think of an alternative diagnosis of brain tumours [21]. Additionally, some authors have postulated that HIV-infected patients have a higher predisposition to meningiomas than the general population [16]. Motebejane et al noted that intracranial meningiomas account for only 1.5% of all tumours in those under 20 years, but found a 2.9 fold increase in high grade meningiomas among HIV patients versus seronegative patients [16]. Although there has been a decline in HIV- associated primary central nervous system lymphomas with the advent of antiretroviral therapy, the risk remains higher than in the general population [22]. Besson et al noted a decline in incidence from 86 per 10000 persons in 1993-94 to 42.9 per 10 000 person-years in 1997-1998 [22].

Age

Certain brain tumours occur more commonly in the paediatric age group. Low-grade gliomas occur more frequently than high-grade gliomas in children [9]. Among the low-grade gliomas, astrocytomas are the most prevalent paediatric brain tumours in children between 5

and 9 years [23, 24]. Medulloblastomas, the most common childhood embryonal tumour, have a bimodal peak in incidence occurring between 3 to 4 years of age and between 7 and 10 years [24].

Gender

Gender differences in the distribution of paediatric tumours have long been investigated. Some studies have found no noticeable sex differences in paediatric tumours like pilocytic astrocytoma and medulloblastoma [11]. Non-malignant meningioma and high-grade gliomas are twice more common in females than in males while gliomas show a greater predilection in males[11]. This may be explained by genetic predispositions which are yet to be addressed.

Radiation

Ionizing radiation energy from medical scans like X-rays and Computed Tomography scans is a major risk factor for the development of paediatric cancers. The carcinogenic effect of exposure to this ionizing radiation was documented in a study done among Israel children that showed a 30-year cumulative risk of 0.8±0.2% [25]. Cranial irradiation even at small doses increases the overall risk of primary brain tumours including meningiomas and gliomas [13, 25]. The risk is even greater among the paediatric population due to increased sensitivity to radiation and a longer life span to express the risk [11, 26].

1.5 MANAGEMENT

Diagnosis of paediatric brain tumours begins with a detailed clinical evaluation including a thorough history and neurological examination to identify any neurological deficits and signs of raised intracranial pressure. Thereafter, neuroimaging, histopathological diagnosis and more recently molecular genetic testing is required. Haematological and biochemical investigations may provide useful information in patients with primary brain tumours but cannot be used as the sole diagnostic test. They aid in ruling out important differential

diagnosis such as a tuberculoma in a HIV patient who may be suspected of having a brain lymphoma.

Accurate histopathological diagnosis of brain tumours is important in determining appropriate treatment [27]. This remains the commonly used modality in South Africa to classify and manage brain tumours. Molecular genetic testing continues to gain traction in diagnosis and treatment of paediatric brain tumours as highlighted in the new WHO classification of paediatric brain tumours [8]. This new modality aids in correct classification of brain tumours thereby improving diagnostic accuracy and allows for precision medicine, a promising option in the management of these tumours [28].

Cerebral spinal fluid (CSF) analysis potentially offers a less invasive option for diagnosis of primary paediatric brain tumours. As noted by Lehner K et al, CSF is in direct contact with brain tumours and allows access to molecules that would otherwise be inaccessible due to the blood brain barrier [29]. The author conducted a systematic review of CSF fluid biomarkers in paediatric brain tumours and noted CSF studies have been increasingly analysed for proteomic, genomic and metabolomic biomarkers which is useful not only in diagnosis but monitoring treatment response and prognostication. This modality offers the option of reducing possible complications that may arise from surgical procedures to obtain tumour specimen for histopathological diagnosis.

Neuroimaging remains crucial for detecting brain tumours. Computerised Tomography (CT) scan is often used as the initial imaging modality in South Africa where other modalities may not be readily available. It is useful for detecting mass effect, haemorrhage or hydrocephalus that may be associated with the tumour as well as calcifications. Magnetic Resonance Imaging (MRI) offers superior resolution in the detection of brain tumours. progress has been made in moving from conventional MRI sequences to functional MRI that allow better visualisation of brain tumours[30]. The different MRI sequences can provide useful

information about the tumour: T1/T2 Weighted images delineate tumours from surrounding brain tissue; Contrast-Enhanced MRI highlight tumour vascularity and detects disruption of the Blood Brain Barrier; MR Spectroscopy is useful in detecting biochemical composition of brain tissue and helps distinguish tumours from other brain lesions; functional MRI is useful in mapping critical functional regions adjacent to the tumour; Positron emission tomography (PET) scans are useful in detecting metabolic aspects of brain tumours particularly in recurrent or metastatic cases; Diffusion Tensor Imaging is useful in mapping white matter tracts which can improve surgical approach techniques and minimise damage.

Neurophysiological tests such as Electroencephalography, Visual Evoked Potentials, Brainstem Auditory Evoked Potentials and can aid in detecting complications associated with brain tumours such as seizure activity, visual and hearing impairment.

Progress has also been made in management including advances in neurosurgical approaches, and an ever-expanding list of chemotherapeutic agents [31, 32]. In patients with unresectable low-grade gliomas, chemotherapeutic agents used include carboplatin and vincristine or thioguanine, procarbazine, lomustine, and vincristine[31]. Agents commonly used for medulloblastoma include cisplatin, carboplatin, lomustine, cyclophosphamide, and vincristine[33]. Evans et al noted an improved event free survival in medulloblastoma patients with advanced disease receiving chemotherapy alone (vincristine, 1-(2-chloroethyl)-3-cyclohexyl-nitrosourea) versus chemotherapy and radiotherapy[34]. While some of these resources are not widely available in some African countries, great strides have been made in management paediatric brain tumours.

A systematic analysis conducted to determine the surgical outcomes of paediatric brain tumours in sub-Saharan Africa noted difficulty in determining the overall state of affairs due to paucity of data on surgical outcomes, different surgical approaches to the same tumour and bias due to small sample size in the studies [35]. A small qualitative study conducted to

explore the factors influencing health-seeking behaviours for childhood cancers among the South African population demonstrated fear of stigma, lack of knowledge, inaccessibility of healthcare facilities, loss of schooling, and financial challenges as factors contributing to the late presentation[36]. Delayed presentation is associated with a higher risk of morbidity and mortality. Understanding the sociodemographic factors that influence health-seeking behaviour will assist in targeted health education. The age of the patient also influences management. Congenital brain tumours are often difficult to diagnose and manage. The definitive management is dependent on histopathological features, but most not amenable to biopsy due to the young age and location [37].

Diagnostic challenges have been encountered in the South African setting. Edwards LB noted that late presentation was a significant problem in South Africa attributed to various factors including lack of knowledge, fear of stigma and inaccessibility to health care[36]. This may make diagnosis difficult as patients may present in terminal stages or when they are too unstable to have a full diagnostic work up. Unavailability of equipment and personnel to interpret neuroimaging in many centres in KwaZulu Natal province remains a challenge as well as absence of advanced tests such as molecular genetics.

1.6 COMPLICATIONS

The survival rate and long-term quality of life of survivors of paediatric brains is dependent on many factors. Complications can arise from the tumour itself, its progression or treatment modalities. Sequalae of brain tumour treatment including radiotherapy and chemotherapy can be as devastating as the tumour itself and is not confined to the neurological system. Potential complications can be immediate or long term. Post-surgical complications include post-operative hydrocephalus, sepsis, haemorrhage, endocrinopathies, cognitive impairment, visual disturbances, motor deficits, epilepsy speech and sleep disturbances, motor deficits [38, 39]. Won et al demonstrated that 37.5% of paediatric patients with posterior fossa lesions

who underwent surgery developed post-operative hydrocephalus [38]. Medulloblastomas and astrocytomas were the commonest aetiology. Cognitive decline and intellectual disability were demonstrated in a study examining children treated for posterior fossa tumours with chemotherapy, radiotherapy, and surgery [39]. Contrary to this, Bloom et al reported that 82% of patients with medulloblastoma surviving 5 years had no long-term disabilities related to surgery or radiation [40]. For those with complications, these were attributable to the primary tumour.

1.7 PROGNOSIS

The prognosis of patients with paediatric brain tumours is dependent on several factors. These include patient factors such as age, comorbidities, heath status; disease specific variables such as tumour type, grade and location; treatment modalities such as complete versus partial tumour resection and response to therapy.

Prognostic markers for survival in a cohort of Polish children with primary brain tumours were the site of the tumour, histological classification grade of tumour, and time of presentation [41]. Outcomes measured in the study included relapse, progression or death none of which occurred after six years from initial diagnosis. The overall 10-year survival in this cohort was 58.2±4.7%. Survival was lowest for those with high grade gliomas (0% at 72 months); 48.1±9.6% for patients with medulloblastoma and primitive neuroectodermal tumours; 83.3±6.2% for low-grade astrocytoma while those with cerebellar tumours had a survival rate 69.0±7.1% at 10 years. Multivariate analysis for factors predicting poor outcome included grade III-IV tumour, incomplete surgical resection, and complications after surgical resection, while diagnosis of low-grade glioma was the only factor predicting good outcome. An understanding of these characteristics among South African children will aid in improving survival and quality of life. Patients with low-grade gliomas have a better outcome than those with high-grade gliomas [7]. Often, the high-grade gliomas involve midline structures such as

the brainstem and are therefore not amenable to surgical intervention. They also respond poorly to chemotherapy.

Neuronal plasticity in the setting of brain tumours is currently under exploration [42, 43]. The human brain has a unique capability of remodelling in response to various forms of injury as shown by Kośla et al who noted a reorganisation of the Broca's area post resection in a patient with low grade glioma from the left dominant frontal lobe to the right non dominant hemisphere [43]. The timely diagnosis and intervention could improve the quality of life of patients with paediatric brain tumours as it allows the tailoring of rehabilitative measures to maximize neuroplasticity.

2. STUDY JUSTIFICATION AND UTILITY

Primary paediatric brain tumours are a significant cause of morbidity and mortality worldwide. This has been under-reported in Africa due to a lack of dedicated cancer registries. No data is available on the burden of primary paediatric brain tumours in the KwaZulu-Natal (KZN) province.

Childhood cancers have been recently added as a national priority in the National Cancer Strategic Framework, South Africa. This is in recognition of the increasing burden that childhood cancers place on the South African Healthcare system. Results from this study will contribute to the database on childhood brain cancers in South Africa, particularly KZN province and sub-Saharan Africa

3. PROBLEM STATEMENT

The purpose of this retrospective study is to determine the clinical profile, diagnostic modalities, and treatment outcomes of primary paediatric brain tumours at a quaternary hospital in Durban, South Africa from 1st January 2003 to 31st December 2017.

4. STUDY QUESTION

- What are the common primary brain tumours among paediatric patients presenting to a South African Quaternary hospital?
- What is the epidemiology and outcome of primary paediatric brain tumours in the KZN province?

5. AIMS

To determine the clinical profile, diagnostic modalities, management, and outcome of primary paediatric brain tumours at a quaternary hospital in Durban.

5.1 Primary objective

- To describe the demographic profile of study participants
- To describe tumour types and their management
- To determine the five-year survival rate and neurological sequelae at the last hospital visit.

5.2 Secondary objectives

- To determine the association between demographic variables and the management of paediatric brain tumours.
- To determine factors related to morbidity and mortality of primary paediatric brain tumours.

MATERIALS AND METHODS

Ethical clearance was obtained for the study from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BREC/00005385/2023). Gatekeeper permission was obtained from the Department of Health and the Inkosi Albert Luthuli Central Hospital (IALCH) for data collection.

A hospital-based 15-year retrospective review of paediatric patients admitted with brain tumours at IALCH in Durban, South Africa between 1st January 2003 and 31st December 2017 was conducted.

Patients were identified from an admission electronic database. The sample size was calculated using Fisher's formula for the finite population with a minimum sample size of 160. Inclusion criteria consisted of all patients with a radiological or histological diagnosis of primary paediatric brain tumour aged 14 years or less. Exclusion criteria included confirmed or suspected metastatic brain tumours, infective or inflammatory space-occupying lesions and those with incomplete medical records.

Information collected did not have any identification details of the patient and strict confidentiality was maintained. Variables obtained included patient demographic data, clinical profile, radiology, laboratory and histological reports as well as treatment modalities. The treatment data obtained included chemotherapy administered, surgical procedures and radiotherapy offered. Data on complications during the hospital stay and at last hospital visit was obtained.

Data was entered into the Microsoft Excel database. At the end of the collection, data cleaning was done to eliminate errors that may have occurred during data entry. The data was initially summarized in the form of descriptive statistics including means, medians and

standard deviations for continuous variables, and counts with percentage frequencies for all categorical data. The mean differences of the continuous data between the two groups were compared using independent t-tests for significance or Wilcoxon rank test if the data from the two groups violated the normality test.

The associations between independent categorical variables were assessed using the Chi-square test or Fisher's exact test depending on the frequency distributions within the cross-tabulations. The risk factors associated with morbidity and mortality were assessed using binary logistic regression with stepwise regression. Proportions were presented as a percentage with a 95% confidence interval. Survival probability was analysed using Kaplan–Meier charts. Statistical analyses were conducted using SPSS software version 25.

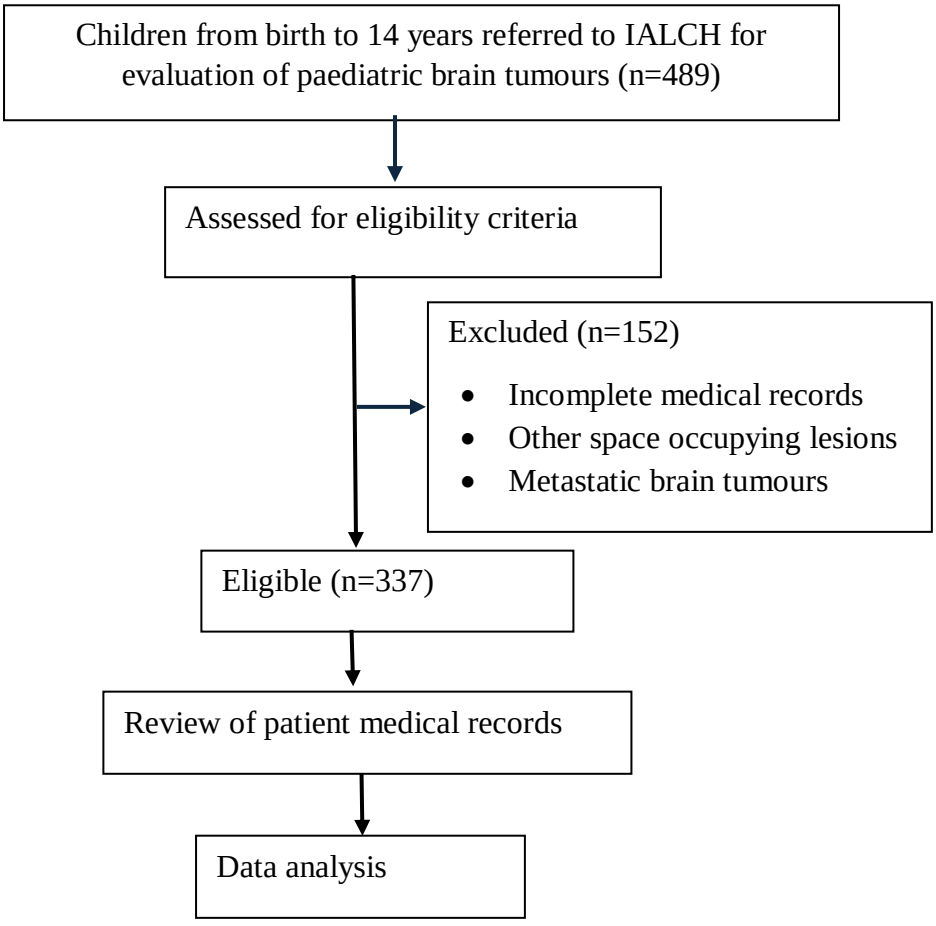

Figure 2:Flow diagram of patient recruitment and selection process

RESULTS

A total of 337 paediatric patients with brain tumours were included in the study with a male preponderance of 54.6%. The mean age of participants was 6.8 years (range 1 month to 14 years). There were 121 (35.9%) patients between 6 to 10 years and 26 (7.7%) were infants. Most patients (89.9%) were of African race, and majority were from KZN province 318 (94.4%). Two patients were from neighbouring countries of Lesotho and Mozambique and one (0.3%) was of unknown origin. Table 2 shows further sociodemographic characteristics of the participants.

Table 2: Sociodemographic characteristics of participants

VARIABLE		FREQUENCY	%
GENDER	Female	153	45.5
	Male	184	54.6
AGE BRACKET	0 - 1 years	26	7.7
	2 - 5 years	115	34.1
	6 - 10 years	121	35.9
	11- 14 years	75	22.3
RACE	African	303	89.9
	Asian	23	6.8
	Caucasian	8	2.4
	Coloured	3	0.9
PROVINCE	KwaZulu-Natal	318	94.4
	Eastern Cape	15	4.5
	Gauteng	1	0.3
	Lesotho	1	0.3
	Mozambique	1	0.3
	Unknown	1	0.3

Infratentorial tumours were more common (55.2%) than supratentorial tumours (43.6%). A small percentage of patients (1.2%) had both supratentorial and infratentorial tumour extension at presentation. The prevalence of supratentorial tumours in infants was higher than infratentorial tumours [n=15; 60%] vs [n=10; 40%] in our cohort. However, among those older than 1 year, the prevalence of infratentorial tumours was higher than supratentorial tumours [n=133; 43%] vs [n=175; 57%]. This was not statistically significant (p=0.118).

The presenting complaints at diagnosis are demonstrated in Table 3. The most frequent complaints at presentation were related to hydrocephalus and increased intracranial pressure (86%). These included headaches (46.6%), vomiting (29.1%), and altered level of consciousness (14.5%).

Table 3: Presenting complaints of participants

Clinical	Frequency	%
Headache	157	46.6
Motor deficits	104	30.9
Vomiting	98	29.1
Craniopathies	80	23.7
Seizures	78	23.1
Cerebellar signs	77	22.8
Impaired vision	69	20.5
Altered consciousness	49	14.5
Macrocephaly	33	9.8
Neuroregression	28	8.3
Gait disturbance	22	6.5
Dysphagia	16	4.7
Behavioural problems	14	4.2
Dysarthria	13	3.9
Bladder/bowel dysfunction	8	2.4

Co-morbidities were noted in 36 (10%) patients. Tuberculosis infection (3.5%) and HIV infection (2.1%) were the most common. One patient had a previous ovarian teratoma, and four (1.1%) had neurocutaneous syndromes, two of whom were classified as neurofibromatosis type 1.

Neuroimaging was performed on all children and included a Computerised Tomography (CT) scan of the brain [n=336; 99.7%] and MRI scan of the brain [n=324; 96.1%]. In our study, brain tumours were confirmed histologically in 215(63.8%) patients.

Radiological diagnosis was used as a diagnostic modality in 112 (36.2%) patients in whom the clinical presentation and progression of the mass lesions was compatible with brain

tumours and other infective causes were excluded. Figure 3a and 3b demonstrates the MRI images of one such patient. This was a 10-year-old who presented with a history of impaired vision and headaches. CSF shunting procedures were done. The patient died during initial admission before any therapy could be offered and was presumed to have a pineal region tumour.

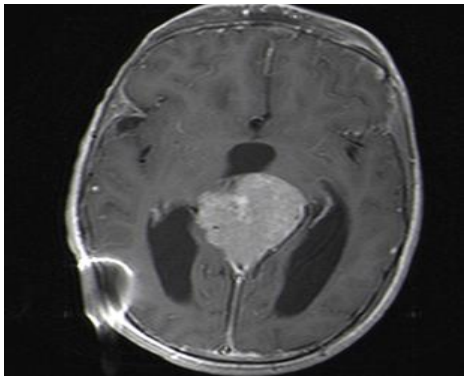

Figure 3a

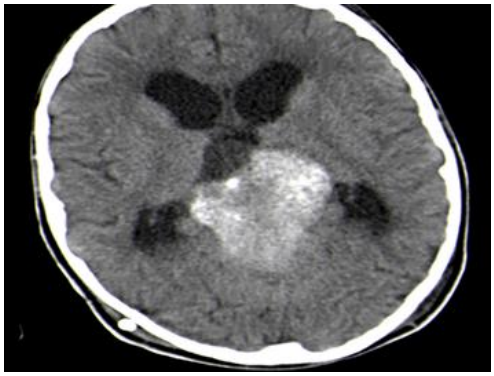

Figure 3b

Figure 3a is a T1W MRI axial view with contrast demonstrating a hyperintense mass in the pineal region. Figure 3b is a CT brain axial view of the same patient showing a hyperdense mass in the pineal region with associated hydrocephalus.

Two patients had a radiological diagnosis of subependymal giant cell astrocytoma (SEGA), none of whom had neurocutaneous manifestations. Figure 4 demonstrates the MRI images of one of the patients with SEGA. This was a four-year-old of African race presenting with a history of vomiting and headache.

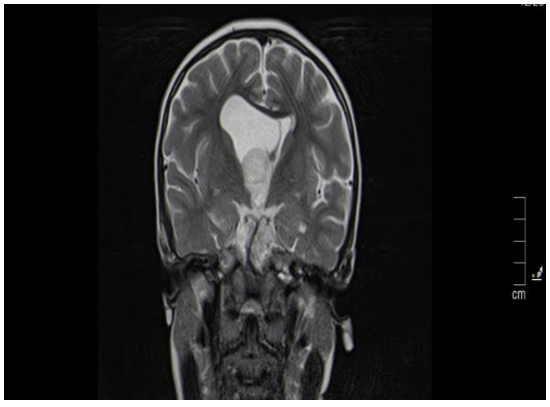

Figure 4a

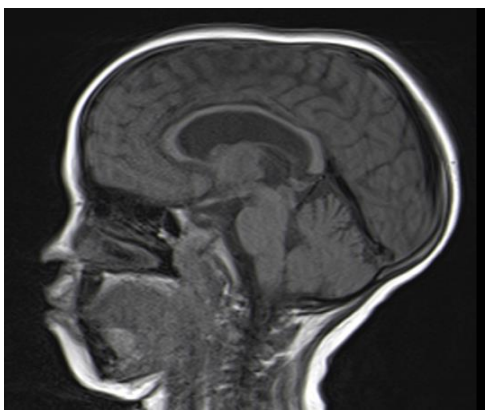

Figure 4b

Figure 4a (T2W MRI coronal view) and Figure 4b (T1W sagittal MRI) demonstrate a mass at the level of foramen of Monro with associated hydrocephalus. A radiological diagnosis of SEGA was made.

Among the 215 patients with a histological diagnosis, the most common brain tumour type confirmed were pilocytic astrocytomas [n=44; 20.4%], medulloblastomas [n=39; 18.1%], and craniopharyngiomas [n=22; 10.2%]. Further histological classification of tumours is shown in Figure 5.

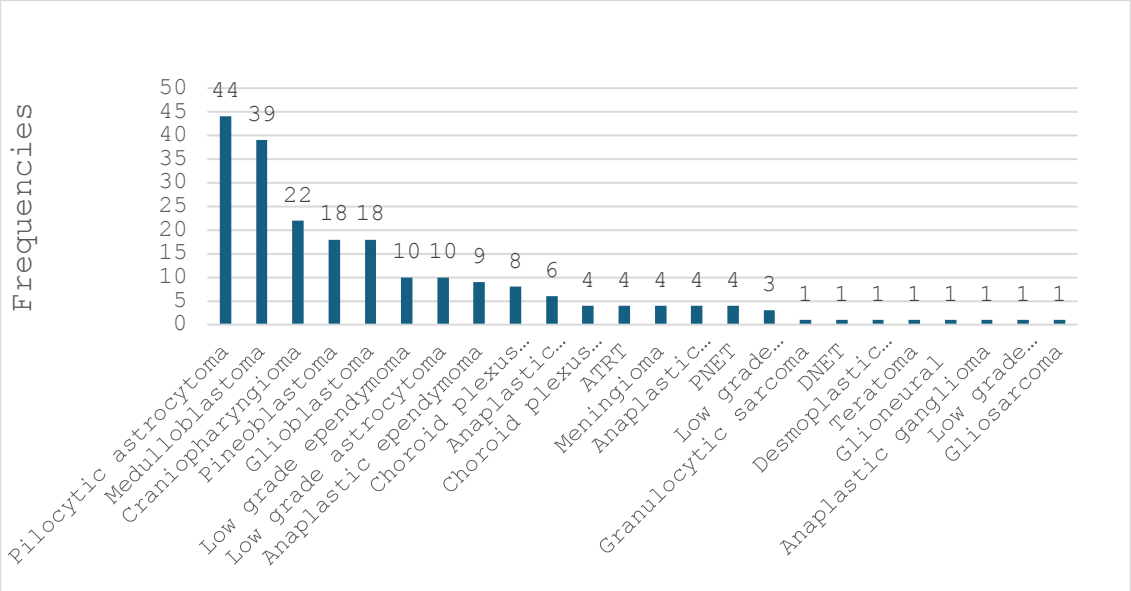

Figure 5: Frequency of tumours based on histology (n=215)

MRI images of youngest patient in our cohort with a cerebellar pilocytic astrocytoma, the commonest tumour diagnosed histologically in our settings is shown in figure 6. This patient was initially managed for pyloric stenosis until neuroimaging and later histology confirmed the diagnosis. Those patients who presented with clinical and radiological features compatible with primary brain tumours included brainstem gliomas [n=82; 24.3%], craniopharyngiomas [n=14; 4.2%], low-grade astrocytoma [n=3; 0.9%], unclassified pineal region tumours [n=14; 4.2%], medulloblastoma [n=2; 0.6%], ependymoma [n=1; 0.3%], choroid plexus papilloma [n=1; 0.3%], germinoma [n=1; 0.3%], low-grade glioma [n=3; 0.9%].

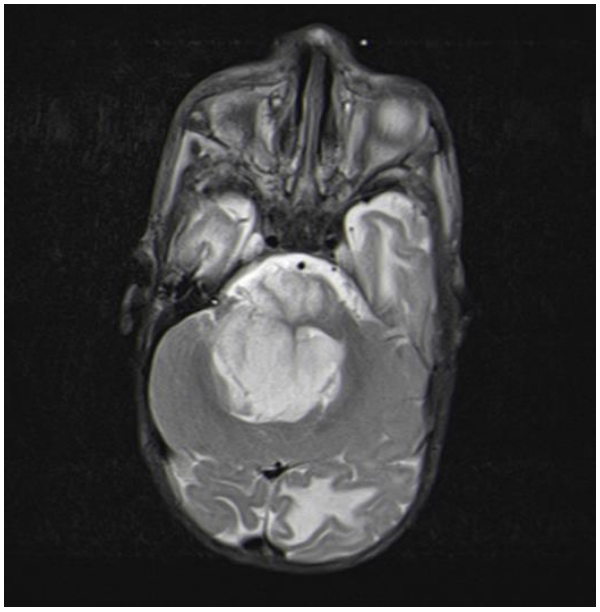

Figure 6a

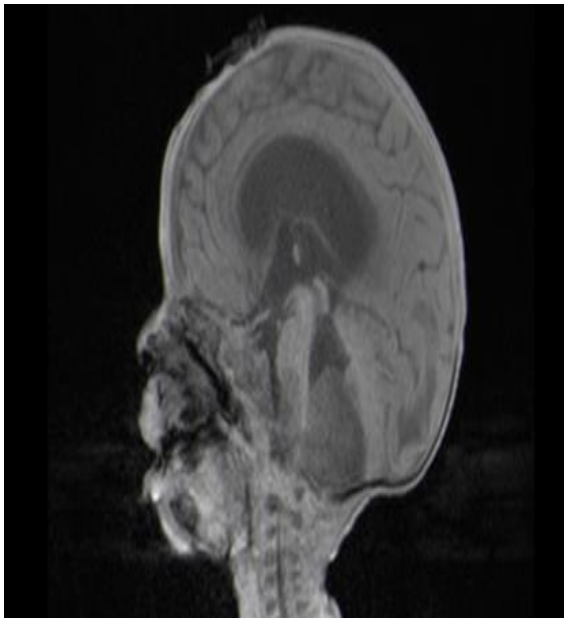

Figure 6b

Figure 6: MRI sequences of neonate with cerebellar pilocytic astrocytoma. 6a (T2W axial view) and 6b FLAIR sagittal view)

Overall, among all 337 patients, including those with no histology but clinical and radiological features compatible with brain tumours, the most prevalent tumours were brainstem gliomas [n=82; 24. 3%], pilocytic astrocytomas [n=45; 13.4%], medulloblastoma [n=41; 12.2%] and craniopharyngioma [n=36; 10.7%] as shown in Figure 7. Mixed neuroglial tumours were rarely encountered and included atypical teratoid rhabdoid tumours, choroid plexus carcinomas, primitive neuroectodermal tumours and germinomas that occurred in four patients each. Other tumours rarely encountered in paediatric patients were observed in our cohort and included granulocytic sarcoma, gliosarcoma, dysembroplastic neuroepithelial tumour, desmoplastic infantile ganglioglioma and teratoma occurring in one patient each. The youngest patients in our study were two patients presenting at one month of life with a histological diagnosis of ependymoma and atypical teratoid rhabdoid tumour.

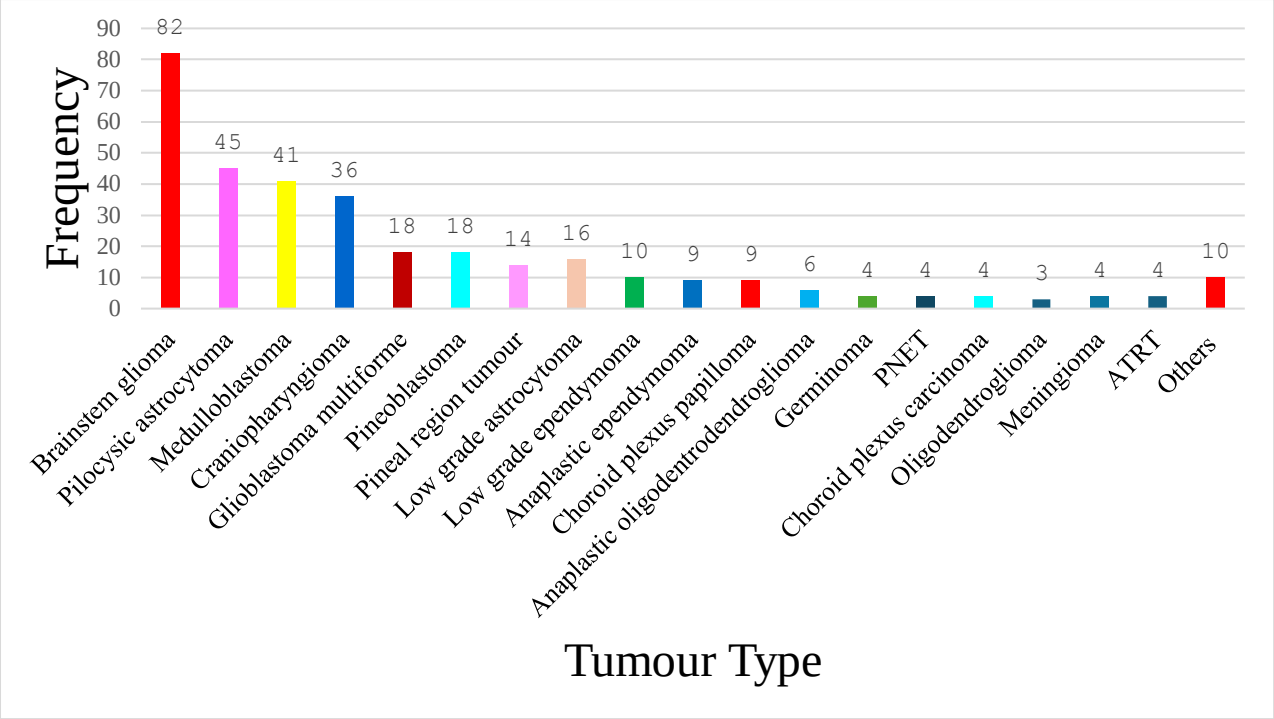

Figure 7: Frequency of tumours based on histology & radiology diagnosis (n=337)

Atypical Teratoid Rhabdoid Tumours (ATRT) which are embryonal tumours were encountered in only four patients. The youngest patient was a one-month-old with a history of rapidly expanding head circumference. He was subsequently found to have an ATRT tumour complicated by hydrocephalus (figure 8a,8b).

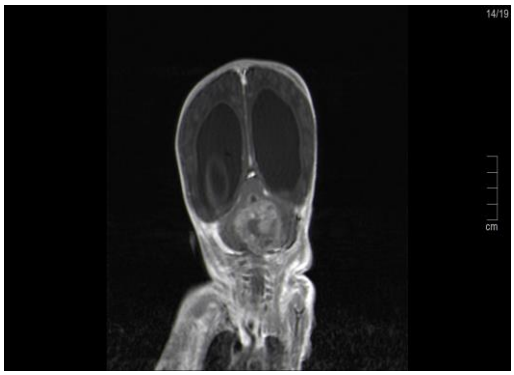

Figure 8a

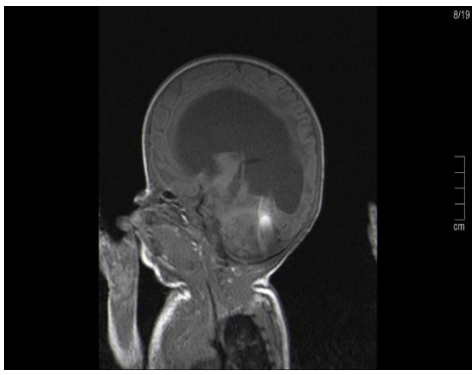

Figure 8b

Figure 8a, 8b: T1 weighted MRI coronal view (8a) and sagittal view (8b) demonstrate a heterogenous mass in the posterior fossa with associated hydrocephalus in a one-month-old presenting with progressive macrocephaly. Histology confirmed an ATRT tumour.

Some of the rare histologically confirmed paediatric brain tumours that were encountered in our study included granulocytic sarcomas, gliosarcomas, glioneural tumours, and anaplastic tumours as shown in figures 9a to g.

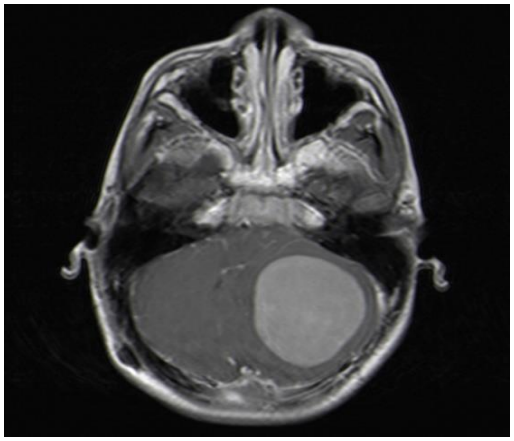

Figure 9a

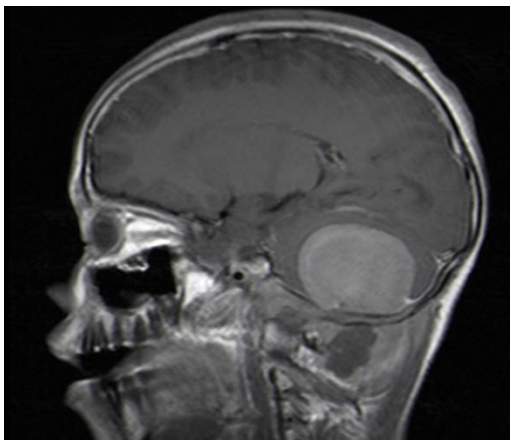

Figure 9b

Figure 9a, 9b: show T1W MRI axial (10a) and T1W MRI sagittal (10b) of a cerebellar granulocytic sarcoma. This was a 12-year-old boy who presented with a history of progressively worsening headaches and cerebellar signs. MRI of the brain revealed a large posterior fossa mass, and he underwent surgical resection with subsequent chemotherapy and radiotherapy. He later succumbed at 14 years old from shunt-related sepsis.

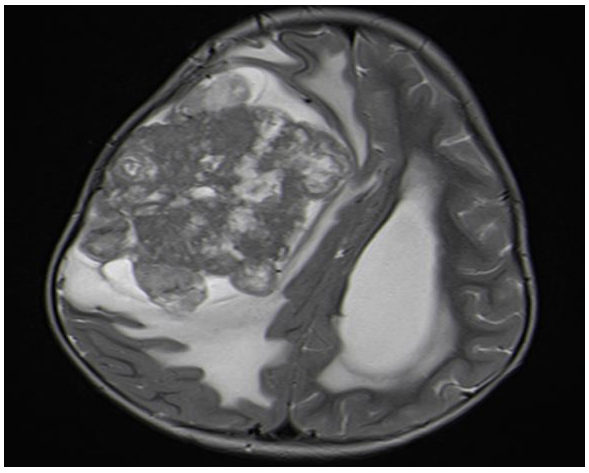

Figure 9c

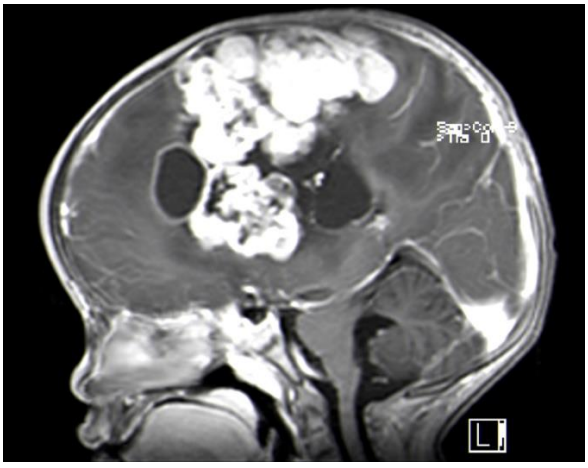

Figure 9d

Figure 9c-d: MRI brain of a 2-year-old male presenting with left hemiparesis and seizures. His T2 weighted (9c) and T1W MRI with contrast (9d) revealed a large heterogeneous mass

in the right hemisphere. He underwent debulking surgery followed by whole-brain radiotherapy. His histology confirmed a WHO grade 4 gliosarcoma and he was discharged for palliative care and presumed to have passed on.

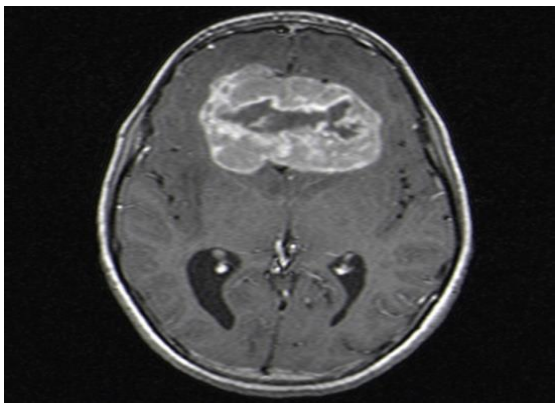

Figure 9e

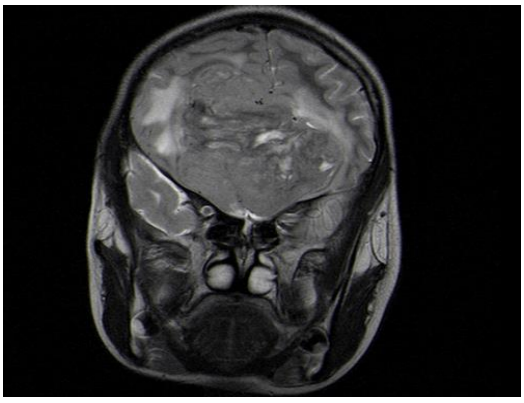

Figure 9f

MRI T1W axial (9e) with contrast and T2W coronal (9f) of a 12-year-old boy who presented with a 6-month history of progressive worsening headaches. His MRI brain revealed a large heterogenous midline mass in the frontal lobe with surrounding vasogenic oedema and compression of frontal horns of the lateral ventricles. His tumour was determined to be irresectable, but he underwent debulking surgery. Histology revealed features in keeping with a high-grade glioneural tumour. He was discharged for palliative care and presumed to have passed on.

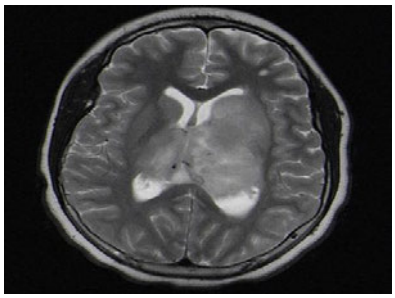

Figure 9g

Figure 9g: A 13-year-old girl referred with history of right-sided hemiparesis and confusion. T2W MRI axial view revealed a hyperintense mass involving the midbrain, thalamus, and basal ganglia on the left. She underwent a stereotactic biopsy with histology confirming a

WHO grade 3 anaplastic ganglioglioma. She was scheduled for radiotherapy and chemotherapy but did not return for her follow-up visits and was lost to follow-up.

The most frequent neurological deficits present in the patients at the last hospital visit are demonstrated in Figure 10. These include motor deficits such as paraparesis and hemiparesis, visual impairment, endocrine abnormalities, and seizures.

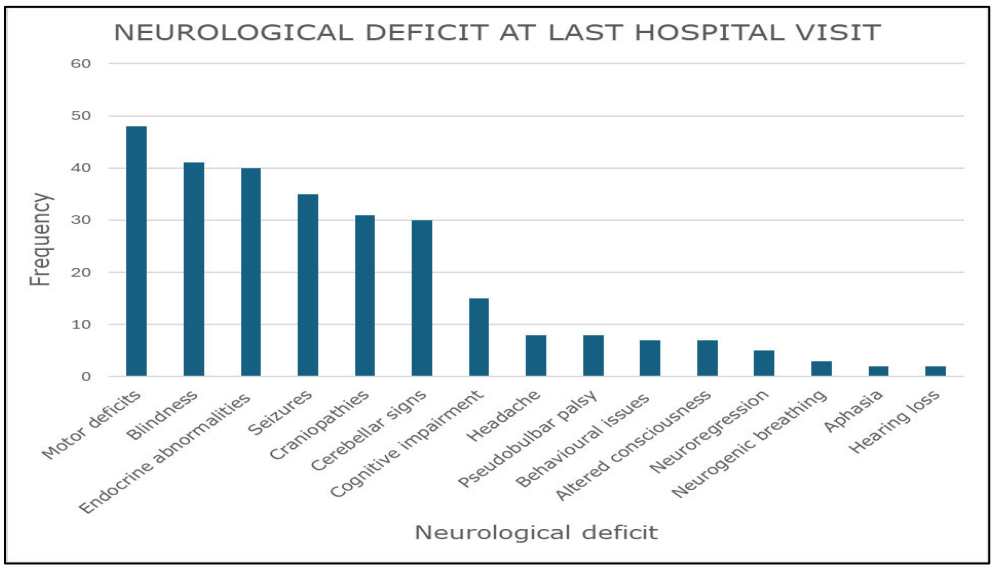

Figure 10: Neurological deficits at last hospital visit

At initial discharge, 77.2% of patients were alive while 22.8% had died. At 5 years of follow-up, 150 (44.5%) of patients were lost to follow up and their outcome was unknown. Of the remaining, 84 (24.3%) were alive while 103 (31.2%) had died from tumour-related complications. 77 of the deaths were at the initial discharge and 26 during the 5 years. Most deaths were related to disease progression followed by sepsis, postoperative complications, tumour recurrence, status epilepticus, and bleeds.

The mean survival time of patients was 4.54 years [95% CI: 3.764 - 5.312]. Males had a higher mean survival time of 4.8 years [95% CI: 3.704 - 5.822] than females 4.3 years [95% CI: 3.151;5.451, p=0.242]. Mean survival time among African cases was lowest at 4.07 years

[95% CI; 3.28 – 4.85, p=0.009], Coloured were 8.67 years [3.50 – 13.83], Asians 8.74 years [95% CI; 4.14 – 13.33] and Caucasians 6.33 years [3.47 – 9.20].

Among those who were followed up for 5 years in our cohort, 85 (45.5%) had infra-tentorial tumours while 101 (54.0%) had supra-tentorial tumours and the rest had extensive tumour infiltration at presentation [n=1; 0.5%]. During the five-year follow-up, 150 (44.5%) patients were lost to follow up, 84 (24.3%) were alive and 103 (31.2%) had died with 77 having died at initial discharge and 26 during the 5-year period. The mean survival time for supra-tentorial tumours was 5.25 years [95% CI; 4.07 – 6.43] while that of infratentorial tumours was 3.75 years [95% CI; 2.15 – 3.23].

Figure 11 demonstrates the treatment modalities instituted based on the tumour type. A total of 195 patients had surgical resection. Surgical procedures done among the cohort included surgical resection of tumours198 (58.5%), biopsy only 19 (5.6%), CSF shunting procedures 277 (82.2%), and Ommaya reservoir placement 19 (5.6%) the latter occurring only in patients with diagnosis of craniopharyngioma.

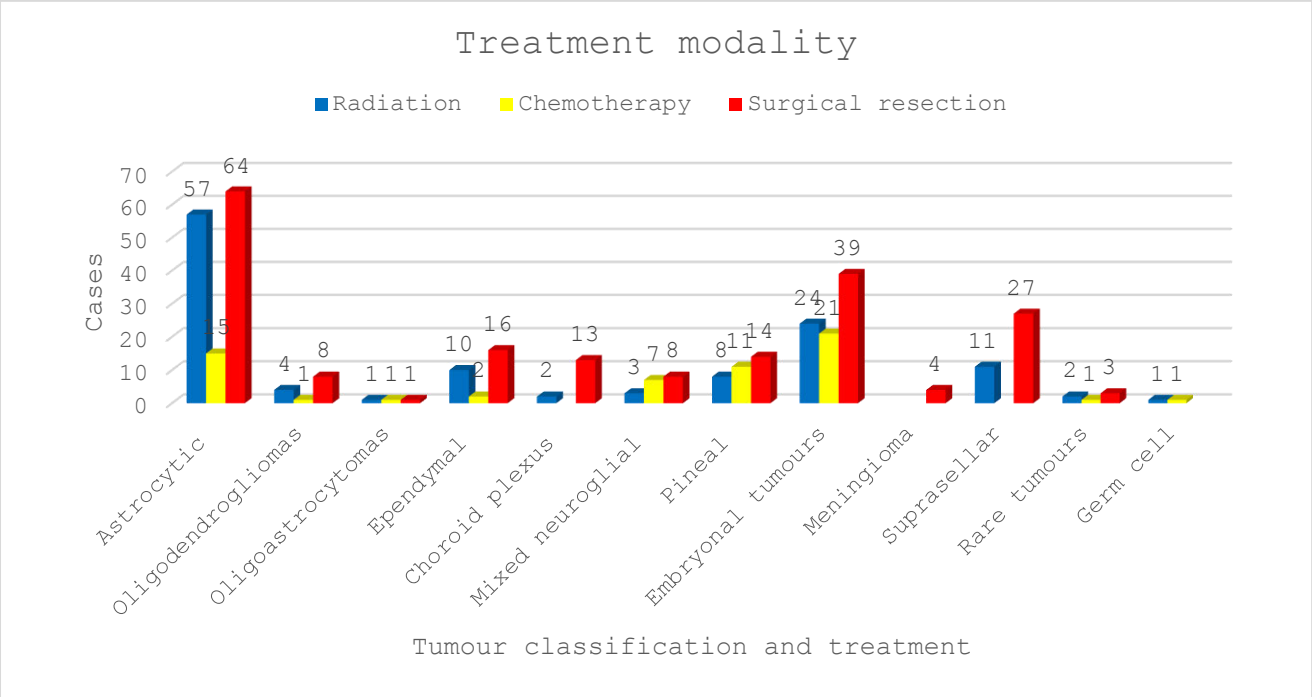

Figure 11: Treatment modalities

Out of those who had surgical resection of tumour; 118 (60.5%) had resection only, 8 (4.1%) had chemotherapy and surgical resection, 35 (17.9 %) had radiotherapy and surgery while 34 (17.5%) had all 3 treatment modalities. Among the 19 patients who had a biopsy with no surgical resection, four were dead within five years and the tumour types included PNET, pineoblastoma, anaplastic oligodendroglioma, and ependymoma. The majority of those who were alive at 5 years with biopsy only had astrocytic tumours ranging from WHO grade 1 to grade 4. Surgical complications occurred in 172 (52%) patients. The main surgical complications included sepsis, VP shunt complications such as blocked shunt, and endocrine abnormalities as demonstrated in Table 4.

Table 4: Surgical complications

Complication	**Frequency (n=337)**	**%**
VP shunt related disorders	30	8.9
Post operation endocrine anomalies	24	7.2
Meningitis	19	5.6
Intracerebral bleed	10	3
Post op low GCS	10	3
Sepsis	10	3
Subdural Hygroma	10	3
Seizures	8	2.4
Ventriculitis	6	1.8
Cerebellar mutism	5	1.5
Cognitive decline	5	1.5
Visual decline	5	1.5
Pneumocephalus	4	1.2
Pseudo meningocele	4	1.2
Cardiac arrest intraoperative	3	0.9
Malignant brain swelling	3	0.9
Brain herniation	2	0.6
Intraoperative hypotension	2	0.6
Air embolus	1	0.3

Among the 123 patients who received radiotherapy, 42 (34.1%) received radiotherapy only, 12 (9.8%) had additional chemotherapy, 35 (28.5%) had surgical resection and chemotherapy while 34 (27.6%) had all 3 modalities including radiotherapy, chemotherapy and surgical

resection. Acute and long-term radiation related complications were noted in 19 (15.4%) of the patients. Acute complications included vomiting [n=3; 15.8%], radiation burns [n=2; 10.5%] and reduced appetite [n=1; 5.3%] while long term complications included cognitive decline [n=5; 26%], panhypopituitarism [n=4; 21%], post radiation changes on MRI [n=2; 0.6%] and visual deterioration [n=1; 5.3%].

Of the 60 (17.8%) patients who received chemotherapy, 6 (10%) had chemotherapy only, 8 (13.3%) received both chemotherapy and underwent surgical resection, 12 (20%) had chemotherapy and radiotherapy and 34 (56.7%) had all 3 treatment modalities. Combined drug regimens were used based on the tumour type. Medulloblastomas were the most common tumours treated with chemotherapy. Out of the 41 patients with medulloblastoma, 21 (51%) received chemotherapy with the regimen frequently used consisting of cisplatin, etoposide, and ifosfomide. Complications occurred in 33.3% of these patients including neutropenia in 18.3% followed by intracerebral haemorrhage and vomiting in two (3.3%) each. Less frequent complications included tachycardia, hyperpigmentation, renal disease, and deep venous thrombosis in one patient each.

Table 5 demonstrates bivariate analysis for factors associated with survival time. The factors associated with shorter survival time included African race, presence of hydrocephalus, and lack of any intervention including radiotherapy, chemotherapy, and surgery.

Multivariate binary logistic regression was used to further explore factors associated with reduced survival time as shown in Table 6. During analysis, adjusted odds ratios were reported to deal with confounders. The odds of survival were reduced by 85% in patients with hydrocephalus at presentation [OR 0.15; 95% CI 0.056-0.489; p=0.002]. Those who received radiotherapy with or without any other treatment modality were 5.5 times more likely to

survive [OR=5.5; 95% CI 2.218-13.619; P<0.0001]. Complete surgical resection increased chances of survival by 6.6 [OR 6.6; 95 CI 2.890-14.970; P<0.0001].

Table 5: Factors associated with survival time among patients (bivariate analysis)

Variable	Outcome		Total	Mean Survival Time-years	95% CI	P value
	Alive (n =84)	Died (n =103)				
Gender						
Female	38 (20.3)	53 (28.3)	91 (48.7)	4.30	[3.15;5.45]	0.242
Male	46 (24.6)	50 (26.7)	96 (51.3)	4.76	[3.70;5.82]	
Race						
African	67 (35.8)	98 (52.4)	165 (88.2)	4.07	[3.28;4.85]	0.009
Coloured	3 (1.6)	0	3 (1.6)	8.67	[3.50;13.83]	
Asian	9 (4.8)	4 (2.1)	13 (7.0)	8.74	[4.14;13.33]	
Caucasian	5 (2.6)	1 (0.5)	6 (3.2)	6.33	[3.47; 9.20]	
Tumour location						
Infra tentorial	34 (18.2)	51 (27.3)	85 (45.5)	3.75	[2.79;4.70]	0.044
Supra tentorial	50 (26.7)	51 (27.3)	101 (54.0)	5.25	[4.07;6.43]	
Hydrocephalus						
Yes	67 (35.8)	98 (52.4)	165 (88.2)	4.10	[3.32;4.87]	0.002
No	17 (9.1)	5 (2.7)	22 (11.8)	7.86	[4.98;10.73]	
Radiotherapy						
Yes	38 (20.3)	18 (9.6)	56 (29.9)	7.27	[5.81;8.72]	<0.001
No	46 (24.6)	85 (45.5)	131 (70.1)	3.37	[2.52;4.22]	
Chemotherapy						
Yes	19 (10.1)	13 (7.0)	32(17.1)	6.18	[4.53;7.83]	0.036
No	65 (34.8)	90 (48.1)	155 (82.9)	4.20	[3.33;5.07]	
Tumour resection						
Yes	73 (39.0)	57 (30.5)	130 (69.5)	5.54	[4.64;6.44]	0.0001
No	10	47	57 (30.5)	2.25	[0.91;3.60]	

Table 6: Factors associated with reduced survival using multivariable binary logistic regression

Factor	Adjusted Odds Ratio	95% Confidence Interval	P value
Gender			
Male	1.29	[0.678;2.458]	0.438
Female	Reference		
Hydrocephalus			
Present	0.15	[0.056;0.485]	0.002
Absent	Reference		
Tumour Location			
Supratentorial	1.44	[0.806;2.582]	0.218
Infratentorial	Reference		
Radiotherapy ± other interventions			
Received	5.50	[2.218;13.619]	<0.0001
Not received	Reference		
Chemotherapy ± other interventions			
Received	2.70	[0.801;9.112]	0.109
Not received	Reference		
Complete surgical resection			
Yes	6.57	[2.890;14.970]	<0.001
No	Reference		
Presence of comorbidities			
Yes	0.74	[0.503;1.078]	0.233
No	Reference		

Figures 12 to 16 demonstrate Kaplan Meier survival analysis based on gender, tumour location, radiotherapy treatment, chemotherapy treatment, and surgical resection.

KAPLAN MEIER SURVIVAL ANALYSIS

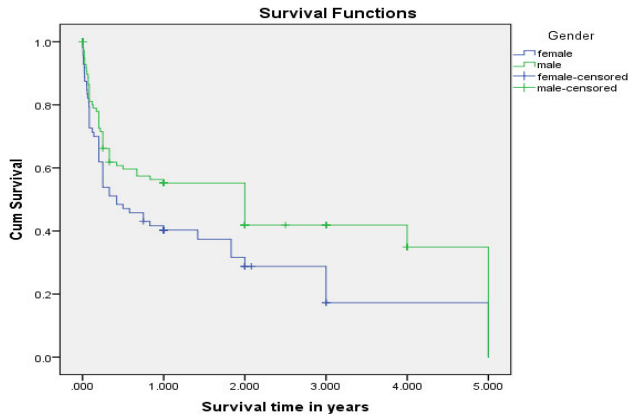

Figure 12: Gender

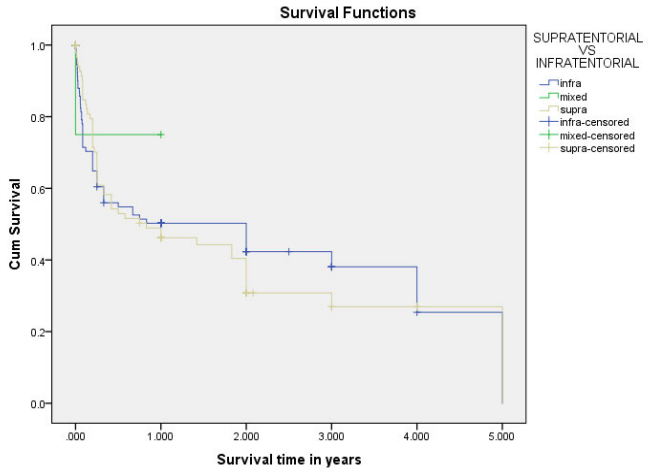

Figure 13: Tumour location

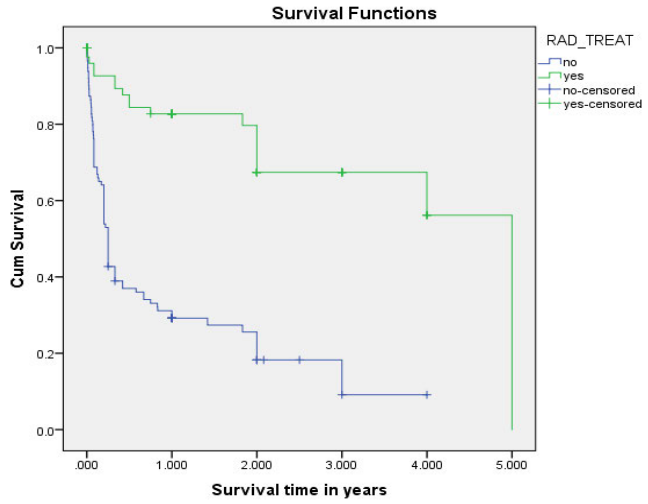

Figure 14: Radiotherapy

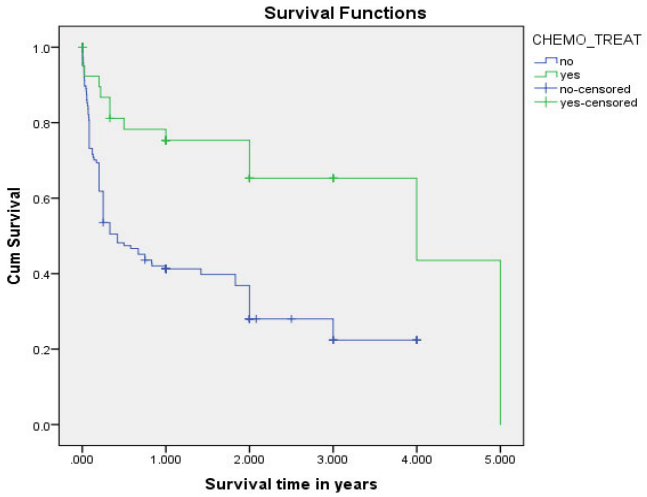

Figure 15: Chemotherapy

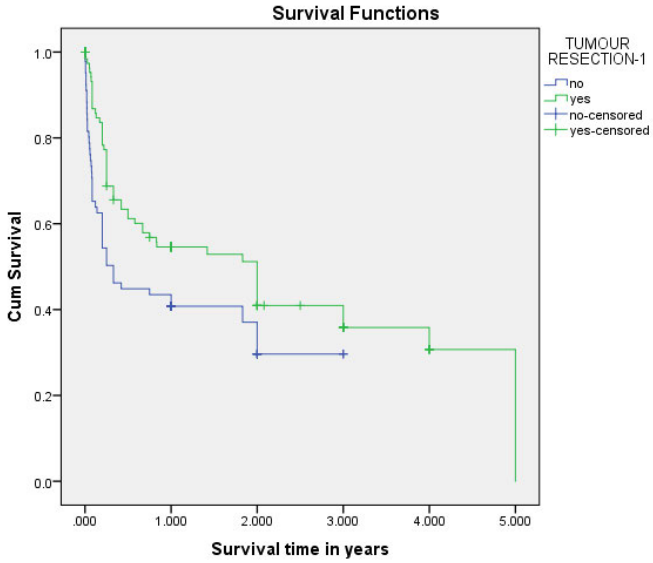

Figure 16: Tumour resection

DISCUSSION

Inkosi Albert Luthuli Central Hospital (IALCH) was commissioned in 2002 and since then all patients with paediatric brain tumours have been referred to the hospital for specialized care under a multidisciplinary team. Referrals are received from all 12 districts in KZN. The provincial health services have a referral system with district, regional, and tertiary hospital facilities. Data on the distribution of paediatric brain tumours in the KZN region and sociodemographic factors influencing early access to healthcare is currently unknown. This has partly been due to the paucity of brain tumour registries and underdeveloped electronic health records systems in the province and South Africa.

Paediatric brain tumours have been well studied in Western countries but data on their incidence, demographic pattern, and management in the African setting has been scarce and irregular [5]. In our study, most of the children seen were of the African race which was in keeping with the demographics in KZN province where more than 80% of the population is of African race [44]. Majority of the African population in KZN are of lower socioeconomic status than their Asian, Caucasian, and Coloured counterparts which could explain the larger number of African patients seeking care at IALCH, a quaternary public facility. Other races likely have access to private healthcare facilities with medical aid hence the fewer numbers seen and more deaths seen among African patients.

Histopathological confirmation and neuroimaging were used to diagnose brain tumours among patients presenting to the hospital. Despite the trend towards molecular genetics, none of our patients had access to this diagnostic modality. This is due to the limited resources available in Africa for this advanced modality although great strides continue to be made in this direction.

The patients diagnosed with neuroimaging only were included as a subset for analysis. While histological diagnosis remains the gold standard, some tumours have a characteristic radiological appearance on MRI or CT scan of the brain that can aid in making a presumptive diagnosis [45, 46]. These include brainstem gliomas, pilocytic astrocytomas, and craniopharyngiomas. Brainstem gliomas were the most common tumour identified by neuroimaging only in our study. This is in keeping with diagnosis of most brainstem gliomas worldwide [46]. A brain biopsy is typical not done due to site of the tumour in the critical region of the brainstem making neuroimaging the main diagnostic modality. It is therefore difficult to assess the true incidence of brainstem gliomas [47]. Neuroimaging is useful for patients with large extensive tumours presenting with a wide array of neurological symptoms. In our study, a small percentage (1.2%) of patients had extensive tumours on neuroimaging at presentation implying aggressive fast-growing tumours or late presentation.

MRI brain was done in most patients and a subgroup had Magnetic Resonance Spectroscopy (MRS) as an additional modality. MRS was done mostly in those whom the diagnosis of brain tumour was uncertain. There is a high incidence of opportunistic infections in South Africa and patients may present with space-occupying lesions that are difficult to distinguish from brain tumours [21]. MRS can aid in distinguishing this by the presence of a choline peak highly suggestive of malignancy. However, lactate peak cannot be reliably used as it is present in other brain lesions such as those with mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes (MELAS) as well as in neonates with hypoxic ischemic encephalopathy.

In our study, brainstem gliomas [n=82, 24. 3%], pilocytic astrocytomas [n=45; 13.4%], medulloblastoma [n=41; 12.2%] and craniopharyngioma [n=36; 10.7%] were the most frequent brain tumours encountered. This was a similar pattern to Cape Town, South Africa which found astrocytomas [n=114; 20.3%], medulloblastomas [n=107 patients; 19.1%],

craniopharyngiomas [n=55; 9.8%] as the most common tumours [6]. With these similarities, findings in KZN may accurately depict the national burden of paediatric brain tumours. This can help with advocacy on increasing resources for the care of childhood cancers. The main difference was that brainstem gliomas were more frequently found in KZN province (24.3% vs 9.3%). Brainstem gliomas encompass any tumour from the midbrain, pons, or medulla. They are often diagnosed based on clinical features and neuroimaging with MRI brain being the modality of choice [48]. All the patients in our study had a radiological diagnosis with none having a confirmatory histological report. Brainstem gliomas can be classified radiologically into Diffuse Intrinsic Pontine Gliomas (DIPG) and non-DIPG tumours such as focal intrinsic or exophytic brainstem gliomas and tectal gliomas [47]. All except two of our participants had DIPG which carries a poor prognosis with a mean survival of less than 1 year [47]. The five-year survival was known for only about one-third of the individuals with DIPG with the majority discharged for palliative care and lost to follow-up. No attempt was made by the authors to contact these patients to find out outcome. Among those whose outcome was known, all except one died with the longest survival being 9 months. Molecular genetics can help in prognostication of patients with brainstem gliomas who traditionally carry a poor prognosis[47]. Hoffman et al noted that long term survivors of DIPG were more likely to harbour a *HIST1H3B* mutation.

The standard treatment for those with DIPG is radiotherapy while those with focal brainstem gliomas can undergo surgical resection with or without chemotherapy and/or radiotherapy [47]. Radiotherapy was offered to 37.5% of patients with brainstem gliomas. Three patients received a combination of chemotherapy and radiotherapy while one received chemotherapy alone. Chemotherapy options given in our cohort included temozolomide, cisplatin/carboplatin, vincristine, etoposide, and ifosfamide. A significant number of those with brainstem glioma did not receive any treatment as they were too unstable or had

advanced disease and were referred for palliative care. Due to the location and infiltrative nature, DIPGs often not amenable to surgical resection hence carry a poor prognosis[31]. Given that brainstem gliomas were the most common tumour in our cohort, counselling on prognosis should be incorporated early in as part of the advanced care plan. Some predictors of long-term survival of patients with DIPG that have been identified include age < 3 or > 10 years, longer symptom latency, lack of CN palsy, and systemic therapy at diagnosis [47]. These can be applied locally to predict those who are likely to have good outcomes.

Pilocytic astrocytomas were the second most frequent tumours observed in our cohort. These WHO grade 1 glial astrocytic tumour have a range of imaging appearances, but most cases have a characteristic cystic component with a mural nodule making them easily identifiable [45]. All 45 patients had histologically confirmed cases. Like other regions worldwide, we found that the most common location for pilocytic astrocytomas was the cerebellum [10]. These tumours carry a good prognosis. Among our patients, more than half were alive at 5-year follow-up. This was slightly lower than other regions of the world where 10 year survival is more than 90%[10]. Possible reasons were a third were lost to follow up and their outcome was unknown as well as late presentation. For these tumours, the mainstay of treatment is surgical resection aiming for complete resection of the tumour. The majority (95%) of our patients underwent surgical resection. Additional radiotherapy and chemotherapy were necessary due to the recurrence of tumour or incomplete surgical resection [49].

The occurrence of embryonal tumours was slightly higher in our cohort (14.2%) than that quoted in other studies. The US cancer registry noted embryonal tumours occurred at a frequency of 9.2% over five years from 2015 to 2019 [11]. Like US findings, medulloblastomas were the most frequent embryonal tumours encountered in our setting. Standard therapy for medulloblastoma consists of surgical resection of the tumour followed

by radiotherapy and more recently adjuvant chemotherapy. In our study, all patients with medulloblastoma had surgical resection of the tumour. Out of these, almost half had additional radiotherapy, while the rest had either radiotherapy or chemotherapy in addition to surgery. Advanced disease was the cause of death in six of our patients, three died from post-op complications and one from status epilepticus. The molecular classification of medulloblastoma into the four main subgroups (WNT, SHH, G3, G4) has a bearing on prognosis and treatment options[8]. This should in future be incorporated into use in South Africa which would confer additional useful information.

Atypical Teratoid Rhabdoid Tumours (ATRT) are relatively rare in paediatric patients and if present have a predilection for those less than 6 months [50]. However, in our study, only one of the four patients with this tumour presented before 6 months of life. The frequency of these tumours in our study was 1.1% like other studies [51]. Ostrom et al, however, noted a much higher frequency of ATRT (14%) among USA paediatric patients [11].

The paucity of data on paediatric brain tumours in the African continent has made it difficult to report on outcomes following various interventions including surgery, radiotherapy, and chemotherapy [5]. The main independent adverse prognostic factors associated with reduced survival time by bivariate analysis in our cohort were African race, infratentorial tumours, presence of hydrocephalus at diagnosis, and lack of any form of intervention including surgical resection, radiotherapy, and chemotherapy. Additionally, during multivariate binary logistical regression, survival time was increased by those who did not have hydrocephalus, those who received radiotherapy and those who had complete surgical resection of the tumour as indicated in Table 6.

Worse outcomes among the African race could be attributed to strong cultural beliefs with many patients seeking alternative therapy from traditional healers contributing to late

presentation to hospital[36]. Fear of stigma in patients with cancer is another contributing factor as demonstrated by Edwards LB et al [36]. There is a high burden of CNS infections such as Tuberculosis and HIV with resultant opportunistic infections presenting as space-occupying lesions. A lack of response to treatment often triggers clinicians to think of alternative diagnoses as noted by Zafar et al [21].

Hydrocephalus occurs due to obstruction to CSF flow by the tumour. It was frequently encountered at the time of diagnosis occurring in 86% of our patients. This is much higher than in other studies where it occurred in about 50% of cases at diagnosis [52]. Higher occurrence implies late presentation, and this may further contribute to worse outcomes as shown in our cohort during multivariate binary logistic regression for factors associated with reduced survival. Some complications of hydrocephalus include macrocephaly, cognitive decline, and blurred vision, all of which were encountered among our patients.

Our study demonstrated that those patients who had complete surgical resection were more likely to survive. Similar to worldwide trends, patients who have complete surgical resection of tumours are more likely to have longer survival times [53].

Infratentorial tumours are those located in the posterior fossa which lies below the tentorium cerebelli while supratentorial tumours are found above the tentorium cerebelli. While most paediatric brain tumours are infratentorial, infants have been shown to have supratentorial tumours more commonly than infratentorial tumours [54, 55]. The reverse is true for children older than one year who are more likely to have supratentorial tumours. Our study findings were similar to these international trends.

Infratentorial tumours often have devastating consequences due to their critical location in a relatively confined space and the important structures that lie within them. They commonly include medulloblastomas, pilocytic astrocytomas, and brainstem gliomas [54]. In our study,

slightly more than half the patients [n=184; 54%] had posterior fossa tumours. Patients with these tumours are at high risk of complications such as compression of the brainstem, brain herniation, and death. Patients with infratentorial tumours had a lower survival rate than those with supratentorial tumours at 3.75 years [95% CI; [2.79 - 4.70] vs 5.25 years [95% CI; 4.07-6.43]]. This is in keeping with outcomes noted in other studies [54].

STUDY STRENGTHS

This is the first study that aims at collecting data on the burden of paediatric brain tumours in Durban, South Africa. Findings will contribute toward the South African Paediatric Cancer Tumour registry.

LIMITATIONS

A total of 150 (44.5%) patients in the study were lost to follow up so five-year survival could not be determined. Some medical records were incomplete. Lack of molecular genetics that could aid in further characterization of tumour types. As the study was conducted in KZN, some findings may not be generalized to the entire country.

CONCLUSION AND FUTURE DIRECTION

There is an urgent need for a central tumour brain registry in KZN, South Africa. Public health interventions for early tumour detection in KZN include targeted education to the population at risk to ensure early presentation which will improve long-term outcomes. Better internetworking between hospitals in the province to ensure a continuum of care for patients with paediatric brain tumours. This will reduce the large number of patients lost to follow-up.

Engagement of stakeholders to increase resources in the management of paediatric brain tumours is needed. This includes the incorporation of newer molecular classifications of tumours for better management and prognostication, increasing availability of neuroimaging

modalities in referral hospitals and training of more personnel involved in the care of patients with paediatric brain tumours.

AUTHORS CONTRIBUTION

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REFERENCES

1. Gatta, G., et al., *Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study.* Lancet Oncol, 2014. **15**(1): p. 35-47.
2. Wessels, G. and P.B. Hesseling, *Incidence and frequency rates of childhood cancer in Namibia.* S Afr Med J, 1997. **87**(7): p. 885-9.
3. Stones, D.K., et al., *Childhood cancer survival rates in two South African units.* S Afr Med J, 2014. **104**(7): p. 501-4.
4. Registry, N.C., *Childhood Cancer Registry* in *National Cancer Registry*, D.o.t.N.H.L. Services, Editor. Annual Report 2020.
5. Mbi Feh, M.K., et al., *The need for a central brain tumor registry in Africa: A review of central nervous system tumors in Africa from 1960 to 2017.* Neurooncol Pract, 2021. **8**(3): p. 337-344.
6. Arnold-Day, C., *Paediatric brain tumours: The University of Cape Town experience from 1996 - 2017.* Unpublished data(Master's thesis), 2019.
7. Subramanian, S. and T. Ahmad, *Childhood Brain Tumors*, in *StatPearls*. 2024, StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.: Treasure Island (FL).
8. d'Amati, A., et al., *Pediatric CNS tumors and 2021 WHO classification: what do oncologists need from pathologists?* Front Mol Neurosci, 2024. **17**: p. 1268038.
9. Qaddoumi, I., I. Sultan, and A. Gajjar, *Outcome and prognostic features in pediatric gliomas: a review of 6212 cases from the Surveillance, Epidemiology, and End Results database.* Cancer, 2009. **115**(24): p. 5761-70.
10. Bornhorst, M., D. Frappaz, and R.J. Packer, *Pilocytic astrocytomas.* Handb Clin Neurol, 2016. **134**: p. 329-44.
11. Ostrom, Q.T., et al., *Risk factors for childhood and adult primary brain tumors.* Neuro Oncol, 2019. **21**(11): p. 1357-1375.
12. Capatina, C., et al., *Craniopharyngioma - Clinical and therapeutic outcome data in a mixed cohort of adult and paediatric cases.* Acta Endocrinology (Buchar), 2018. **14**(4): p. 549-555.
13. Braganza, M.Z., et al., *Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review.* Neuro Oncol, 2012. **14**(11): p. 1316-24.
14. Ramanjam, V., et al., *Clinical phenotype of South African children with neurofibromatosis 1.* J Child Neurol, 2006. **21**(1): p. 63-70.

15. Kija, E., et al., *P115 – 2579: Clinical presentation of Tuberous Sclerosis Complex in Cape Town, South Africa.* European Journal of Paediatric Neurology, 2015. **19**: p. S126-S127.
16. Motebejane, M.S., I. Kaminsky, and I.S. Choi, *Intracranial Meningioma in Patients Age <35 Years: Evolution of the Disease in the Era of Human Immunodeficiency Virus Infection.* World Neurosurgery, 2018. **109**: p. e292-e297.
17. Idowu, O.E. and M.A. Idowu, *Environmental causes of childhood brain tumours.* Afr Health Sci, 2008. **8**(1): p. 1-4.
18. Khurshid, A., et al., *Meningioma in four patients with human immunodeficiency virus infection.* Mayo Clin Proc, 1999. **74**(3): p. 253-7.
19. Zhang N., Z.Y., Jiang L. et al, *Epstein-Barr Virus and Neurological Diseases.* Frontiers in Molecular Bioscience, 2022. **8**.
20. UNAIDS. *HIV and AIDS estimates*. 2023; Available from: https://www.unaids.org/en/regionscountries/countries/southafrica.
21. Zafar, S., et al., *Primary central nervous system lymphoma presenting as multiple space-occupying lesions in advanced human immunodeficiency virus infection.* SA J Radiol, 2017. **21**(2): p. 1234.
22. Besson, C., et al., *Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy.* Blood, 2001. **98**(8): p. 2339-44.
23. Sievert, A.J. and M.J. Fisher, *Pediatric low-grade gliomas.* J Child Neurol, 2009. **24**(11): p. 1397-408.
24. Wells, E.M. and R.J. Packer, *Pediatric brain tumors.* Continuum (Minneap Minn), 2015. **21**(2 Neuro-oncology): p. 373-96.
25. Ron, E., et al., *Tumors of the brain and nervous system after radiotherapy in childhood.* N Engl J Med, 1988. **319**(16): p. 1033-9.
26. Wang, W.H., et al., *Risks of leukemia, intracranial tumours and lymphomas in childhood and early adulthood after pediatric radiation exposure from computed tomography.* Cmaj, 2023. **195**(16): p. E575-e583.
27. Newton, H.B. and S. Shroff, *Chapter 1 - Overview of Brain Tumor Epidemiology and Histopathology*, in *Handbook of Brain Tumor Chemotherapy, Molecular Therapeutics, and Immunotherapy (Second Edition)*, H.B. Newton, Editor. 2018, Academic Press. p. 3-20.
28. Park, S.H., et al., *Molecular Testing of Brain Tumor.* J Pathol Transl Med, 2017. **51**(3): p. 205-223.

29. Lehner, K.R., et al., *Cerebrospinal Fluid biomarkers in pediatric brain tumors: A systematic review.* Neoplasia, 2023. **35**: p. 100852.
30. Nikam, R.M., et al., *Advanced Neuroimaging Approaches to Pediatric Brain Tumors.* Cancers (Basel), 2022. **14**(14).
31. Pollack, I.F., S. Agnihotri, and A. Broniscer, *Childhood brain tumors: current management, biological insights, and future directions.* J Neurosurg Pediatr, 2019. **23**(3): p. 261-273.
32. Cargnelutti, E., et al., *What do we know about pre- and postoperative plasticity in patients with glioma? A review of neuroimaging and intraoperative mapping studies.* Neuroimage Clin, 2020. **28**: p. 102435.
33. Malik, J.R., et al., *Chemotherapy in pediatric brain tumor and the challenge of the blood–brain barrier.* Cancer Medicine, 2023. **12**(23): p. 21075-21096.
34. Evans, A.E., et al., *The treatment of medulloblastoma. Results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine, and prednisone.* J Neurosurg, 1990. **72**(4): p. 572-82.
35. Herdell, V., et al., *Surgical outcomes of pediatric brain tumors in Sub-Saharan Africa: A systematic review.* Brain Spine, 2022. **2**: p. 100912.
36. Edwards LB, G.L., *A descriptive qualitative study of childhood cancer challenges in South Africa: Thematic analysis of 68 photovoice contributions.* South African Journal of Oncology, 2017. **1**(a14).
37. Sugimoto, M., et al., *Congenital Brain Tumor within the First 2 Months of Life.* Pediatr Neonatol, 2015. **56**(6): p. 369-75.
38. Won, S.Y., et al., *Management of hydrocephalus after resection of posterior fossa lesions in pediatric and adult patients-predictors for development of hydrocephalus.* Neurosurg Rev, 2020. **43**(4): p. 1143-1150.
39. Duffner, P.K., *Risk factors for cognitive decline in children treated for brain tumors.* Eur J Paediatr Neurol, 2010. **14**(2): p. 106-15.
40. Bloom, H.J., E.N. Wallace, and J.M. Henk, *The treatment and prognosis of medulloblastoma in children. A study of 82 verified cases.* Am J Roentgenol Radium Ther Nucl Med, 1969. **105**(1): p. 43-62.
41. Pogorzala, M., J. Styczynski, and M. Wysocki, *Survival and prognostic factors in children with brain tumors: long-term follow-up single center study in Poland.* Anticancer Res, 2014. **34**(1): p. 323-6.

42. Bonnetblanc, F., M. Desmurget, and H. Duffau, *[Low grade gliomas and cerebral plasticity: fundamental and clinical implications]*. Med Sci (Paris), 2006. **22**(4): p. 389-94.
43. Kośla, K., et al., *Reorganization of Language Areas in Patient with a Frontal Lobe Low Grade Glioma - fMRI Case Study*. Pol J Radiol, 2015. **80**: p. 290-5.
44. SA, s., *Statistics South Africa*, Statistics, Editor. 2019.
45. Chourmouzi, D., et al., *Manifestations of pilocytic astrocytoma: a pictorial review.* Insights Imaging, 2014. **5**(3): p. 387-402.
46. Kaushik, R., M. Mital, and K. Gupta, *Imaging features of brainstem glioma in a 6-year-old child.* Sudan J Paediatr, 2021. **21**(1): p. 98-101.
47. Hoffman, L.M., et al., *Clinical, Radiologic, Pathologic, and Molecular Characteristics of Long-Term Survivors of Diffuse Intrinsic Pontine Glioma (DIPG): A Collaborative Report From the International and European Society for Pediatric Oncology DIPG Registries.* J Clin Oncol, 2018. **36**(19): p. 1963-1972.
48. Board, P.D.Q.P.T.E., *Childhood Brain Stem Glioma Treatment (PDQ®): Health Professional Version*, in *PDQ Cancer Information Summaries*. 2002, National Cancer Institute (US): Bethesda (MD).
49. Kayama, T., T. Tominaga, and T. Yoshimoto, *Management of pilocytic astrocytoma.* Neurosurg Rev, 1996. **19**(4): p. 217-20.
50. Biswas, A., et al., *Atypical teratoid/rhabdoid tumors: challenges and search for solutions.* Cancer Manag Res, 2016. **8**: p. 115-125.
51. Arora, R.S., et al., *Age-incidence patterns of primary CNS tumors in children, adolescents, and adults in England.* Neuro Oncol, 2009. **11**(4): p. 403-13.
52. Pilotto, C., et al., *Risk Factors of Persistent Hydrocephalus in Children with Brain Tumor: A Retrospective Analysis.* Pediatr Neurosurg, 2021. **56**(3): p. 205-212.
53. Królikowska, A., et al., *Quality of Life after Surgical Treatment of Brain Tumors.* J Clin Med, 2022. **11**(13).
54. Emara, M., A.-E. Mamdouh, and M.M. Elmaghrabi, *Surgical outcome of posterior fossa tumours: a Benha experience.* Egyptian Journal of Neurosurgery, 2020. **35**(1): p. 18.
55. Ghodsi, S.M., et al., *Brain tumors in infants.* J Pediatr Neurosci, 2015. **10**(4): p. 335-40.

APPENDICES

APPENDIX 1: FINAL STUDY PROTOCOL APPROVED BY BREC

CLINICAL PROFILE, DIAGNOSTIC MODALITIES, AND TREATMENT OUTCOMES OF PRIMARY PAEDIATRIC BRAIN TUMORS AT A QUATERNARY HOSPITAL IN DURBAN, SOUTH AFRICA

By Lucia Amolo

Submitted in partial fulfilment of the academic requirements for the degree of MMed Science in Paediatric Neurology in the Department of Paediatrics, School of Clinical medicine College of Health Sciences, University of KwaZulu Natal, Durban

2024

As the candidate's supervisor I have approved this thesis for submission.

Supervisor_____ Date_____ Signature_____

Supervisor_____ Date_____ Signature_____

DECLARATION

I declare that this thesis is my work and has not been submitted in any form for any other degree or diploma at any university or other institution of tertiary education.

Information derived from the published or unpublished work of others has been acknowledged in the text and a list of references is given.

Name: Lucia Amolo Date: 07/11/2022

EXECUTIVE SUMMARY

The purpose of this study is to describe the clinical profile, diagnostic modalities, and treatment outcomes of primary brain tumours among paediatric patients presenting to Inkosi Albert Luthuli Hospital over a 15-year period from January 2003 to December 2017.

The Department of Neurosurgery has BREC class approval to maintain a database of admissions and procedures performed in this unit for research purposes. The study intends to use this database.

(BREC reference number: BCA 219/15).

ABSTRACT

Primary paediatric brain tumours are associated with high mortality and morbidity in African countries (1-3). Data on the burden of these tumours in the African setting is sparse due to the lack of dedicated cancer registries (2). Primary paediatric brain tumours are among the most common childhood cancers in South Africa (19.5%) second only to leukaemia (25%) (1).

A hospital-based descriptive retrospective study aimed at determining the clinical profile, diagnostic modalities, and treatment outcomes of paediatric patients with primary brain tumours from birth to 14 years of age presenting to Inkosi Albert Luthuli Hospital will be conducted. Medical records over a 15-year period of patients with a confirmed diagnosis of primary brain tumour will be reviewed. Relevant data will be retrieved and entered on a standard pre-coded case record form for analysis. The study will be conducted after approval by UKZN ethics and research committee.

The primary outcome will be the classification of tumours based on anatomical location, diagnostic modalities, histopathological diagnosis and management strategies. The secondary outcome will be to describe the association between sociodemographic variables and management outcomes of paediatric brain tumours as well as the short- and long-term survival rate.

The findings will aid better understanding the burden of disease as it pertains to primary paediatric brain tumours in the Province of KwaZulu-Natal as the data is lacking. The findings will also contribute towards creating a registry for paediatric brain tumours in the province, with the aim of contributing to the national brain tumour registry and fostering research collaborative efforts both locally and internationally, to improve monitoring and outcomes.

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LITERATURE REVIEW

HISTORY

KwaZulu-Natal is the second most populous province in South Africa with an estimated population of 11.3 million people (4). It has one of the highest population of children with about 28.8% of the current population under 15 years (4). All paediatric patients in KwaZulu-Natal region requiring specialized care are referred to Inkosi Albert Luthuli Central Hospital (IALCH), the sole quaternary state of the art hospital in KwaZulu-Natal province. Only a small percentage of the population in KwaZulu-Natal have access to medical aid with more than 90 % relying on public services. Therefore, majority of paediatric patients with brain tumours are managed in public hospitals.

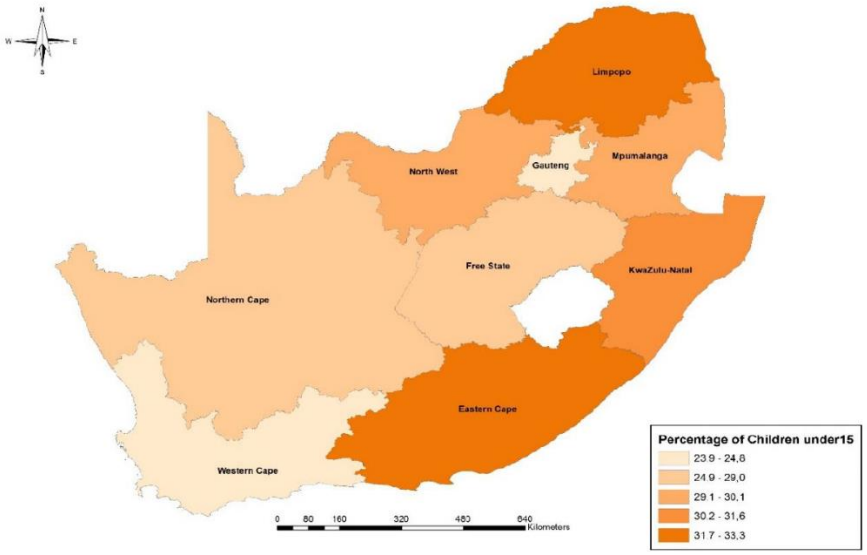

Figure 1: *Source statistics South Africa,* Population of children under 15 years of age

IALCH was commissioned in 2000 and opened its doors in 2002. Since its inception, all paediatric brain tumours are referred for specialized care under a multidisciplinary team consisting of paediatric neurosurgeons, oncologists, paediatric neurologists and radiologists.

Referrals are received from all 12 district KwaZulu-Natal municipalities. Each municipality has district, regional and tertiary hospital facilities. Information on the distribution of paediatric brain tumours in the KwaZulu Natal region and sociodemographic factors influencing early access to healthcare is currently unknown.

BACKGROUND

Primary paediatric brain tumours are a significant contributor of morbidity and mortality worldwide (1, 3, 5). While the exact disease burden is unknown, it is thought to be much higher among African children than their Western counterparts (2, 5-7). Stones et al noted that paediatric brain tumours in South Africa are among the most common childhood cancers (19.5%) second only to leukaemia (25%) (1). This is supported by data from the South African Children's Cancer Study Group Tumour Registry, 2016 which reports brain cancers as the second most common of the childhood cancers. Additionally, a study in Namibia showed that tumours of the central nervous system were the most common (18%) implying similar patterns among southern African countries (3). A gap exists in documenting cases of brain tumours in the African continent and there is need for a central registry to improve existing healthcare systems (2). In 2011, the National Cancer Registry was established by the Ministry of Health, South Africa under the National Health Act 2003(Act No. 61 of 2003). This made cancer a reportable disease in recognition of the increasing burden of disease. Childhood cancers have been recently added as a national priority in the National Cancer Strategic Framework.

CLASSIFICATION

Paediatric brain tumours are traditionally classified based on histological findings and more recently by molecular biomarkers. The anatomical location also can be used to classify tumours into supratentorial versus infratentorial. Unpublished data by Arnold-Day in Cape

Town, South Africa showed supratentorial tumours to be only slightly more common (52%) than infratentorial tumours (8). Further characterization is based on whether the tumour is benign or malignant (9). Benign tumours are slow growing and remain confined to their location while malignant tumours spread rapidly to invade other tissues. Tumours can also be classified according to the tissue involved (9). Classification based on the age at diagnosis enables division into congenital brain tumours, those of infancy and of childhood (10). Congenital tumours are diagnosed within the first two months of birth, tumours of the infancy within the first year of life and tumours of children diagnosed after one year of life.

WHO classifies paediatric gliomas into low grade gliomas (such as pilocytic astrocytoma) and high-grade gliomas (such as glioblastoma multiforme) (9). This classification is important as the former has a higher survival rate than the latter (11). Low grade gliomas are more frequent in the paediatric age group than high grade gliomas (11). Astrocytomas are low grade gliomas characterized by insidious growth and are benign. They are the most prevalent of paediatric brain tumours commonly seen in children between 5 and 8 years. Medulloblastomas are one of the most common of paediatric tumours seen in children below 10 years (10).

CLINICAL PRESENTATION

Clinical presentation of primary brain tumours can be varied in the paediatric population. The site of paediatric tumour determines clinical presentation. Young children whose sutures have not fused can compensate for growing mass with an increasing head size while those whose sutures have fused often have signs of raised intracranial pressure along with other neurological deficits at presentation. This variability, particularly in the very young, can contribute towards a delay in diagnosis.

South Africa has a high burden of tuberculosis and Human Immunodeficiency Virus (HIV) infection. This predisposes children to opportunistic infections including space-occupying lesions such as tuberculomas, neurocysticercosis, and toxoplasmosis which may confuse clinicians when assessing for brain tumours especially in settings where access to ancillary tests is limited (12). A lack of treatment response to an infection may often prompt the clinician to an alternative diagnosis of brain tumours (12).

Histological classification of tumour type may influence the clinical presentation. Low grade gliomas are typically slow growing while high grade gliomas have a rapidly growing, progressive nature with most patients presenting acutely (11). The location of the tumour is an additional factor that determines clinical presentation. Craniopharyngiomas, despite being histologically benign, can produce a wide array of serious pre- and post-operative symptoms based on its unique location in the suprasellar region. They lie near the optic pathway, pituitary and hypothalamus contributing to varied and often devastating clinical presentation including visual disturbances, endocrine dysfunction along with neurological deficits.

RISK FACTORS

Brain tumours represent diverse group of neoplastic conditions with strong variation of incidence by age, gender and exposure to environmental agents. The overall low incidence of presents challenges in directly linking paediatric brain tumours to many environmental exposures with certainty. Despite this, progress has been made in identifying some potential risk factors such as heritable genetics, exposure to allergens and ionizing radiations. These factors have been well documented and validated by many studies as risk factors for paediatric brain tumours (13,14).

Viral infections from HIV, CMV and EBV have been strongly incriminated in the development of some childhood CNS tumours (13 - 15). With an estimated 500,000 children living with HIV in South Africa, this high incidence of co-infection impacts the clinical course of childhood brain tumours. Some authors have postulated that HIV infected patients have a higher predisposition to meningiomas than the general population (15). Unpublished data from KwaZulu-Natal showed that intracranial meningiomas in HIV positive patients occurred at a younger age and had a higher histological grade (16). Although there has been a decline in HIV- associated primary central nervous system lymphomas with the advent of antiretroviral therapy, the risk remains higher than in the general population (17).

Genetic factors have a strong association with increased risk of brain tumours. Genome sequencing has identified over 30 specific inherited variants linked to increased risks of adult brain tumours (14). Studies among paediatric population are underway. Genetic neurocutaneous disorders such as tuberous sclerosis complex (TSC), neurofibromatosis 1 and 2 (NF1 and NF2) predispose to low-grade gliomas. For NF1, gliomas commonly arise in the optic pathway including the optic nerve and optic chiasm. A study following up children with neurofibromatosis in Cape Town, South Africa over a 5-year period found that 14% of children presented with optic nerve gliomas (18). TSC predisposes to subependymal giant cell astrocytomas. Kija et al demonstrated 23% of patients on follow up at a Tuberous sclerosis complex clinic in Western Cape, South Africa had subependymal giant cell astrocytomas (19).

Age is a significant predictor of childhood cancers. Low grade gliomas occur more frequently than high grade gliomas in children (11). Among the low-grade gliomas, astrocytomas are most prevalent paediatric brain tumours in children between 5 and 9 years (20,21). Medulloblastomas, the most common childhood embryonal tumour, have a bimodal peak in

incidence. They are seen in children between 3 and 4 years of age and then again between 7 and 10 years (21).

Gender difference in distribution of paediatric tumours has long been investigated. Some studies have found no noticeable sex differences in paediatric tumours like pilocytic astrocytoma and medulloblastoma (14). Non-malignant meningioma and high-grade gliomas are twice more common in female than in males while gliomas show greater predilection to males (14). This may be explained by genetic predispositions which are yet to be addressed.

Ionising radiation energy from medical scans like x-rays and Computed Tomography which are used as hallmark in diagnosis of many diseases are a major risk factor for development of paediatric cancers. The carcinogenic effect of exposure to this ionizing radiation is well documented (13,14). Cranial irradiation even at small doses increases the overall risk of primary brain tumours. The risk is even greater among the paediatric population due to increased sensitivity to radiation and longer life span to express the risk (14).

MANAGEMENT

In developed countries, significant progress has been made in the diagnosis and treatment of primary paediatric brain tumours over the last century (5). These include neuroimaging advances such as use of functional and intraoperative Magnetic Resonance Imaging, neurophysiology techniques such as free running electromyography during surgery, advances in neurosurgical approaches and an ever-expanding list of chemotherapeutic agents (5, 7). While some of these resources are lacking in African countries, great strides have been made in managing paediatric brain tumours.

A systematic analysis conducted to determine the surgical outcomes of paediatric brain tumours in sub-Saharan Africa reported difficulty in identifying the general tendency towards outcome (22). This was attributed to various factors including an overall paucity of data on

surgical outcome paediatric brain tumours, considerable bias in studies conducted due to small sample size and different surgical approaches to the same tumour. A small qualitative study conducted to explore the factors influencing health seeking behaviours for childhood cancers among the South African population demonstrated included fear of stigma, lack of knowledge, inaccessibility of healthcare facilities, loss of schooling and financial challenges as factors contributing to late presentation (23). Delayed presentation is associated with higher risk of morbidity and mortality. Understanding of the sociodemographic factors that influence health seeking behaviour will assist in targeted health education. Age of the patient also influences management. Congenital brain tumours are often difficult to diagnose and manage. The management is dependent among other things on histopathological features, yet many are not amenable to biopsy due to the young age (24).

PROGNOSIS

The survival rate and long-term quality of life of survivors of paediatric brain is dependent on many factors. Sequalae of brain tumour therapy can be as devastating as the tumour itself and is not confined to the neurological system. Potential complications include post-operative hydrocephalus, endocrinopathies, cognitive impairment, visual disturbances, speech and sleep disturbances, motor deficits as well as epilepsy.

Won et al demonstrated that 37.5% of paediatric patients with posterior fossa lesions who underwent surgery developed post-operative hydrocephalus (25). Medulloblastomas and astrocytomas were the commonest aetiology. Cognitive decline and intellectual disability were demonstrated in a study examining children treated for posterior fossa tumours with chemotherapy, radiotherapy and surgery (26). Contrary to this, Bloom et al reported 82% of patients with medulloblastoma surviving 5 years had no long-term disabilities related to surgery or radiation (27). For those with complications, these were attributable to the primary

tumour. Prognostic markers for survival in a cohort of Polish children with primary brain tumours were site of tumour, histological classification and grade of tumour and time of presentation (6). An understanding of these characteristics among South African children will aid in improving survival and quality of life. Patients with low grade gliomas have a better outcome than those with high grade gliomas (10). Often, the latter involve midline structures such as the brainstem and are therefore not amenable to surgical intervention. They also have a poor response to chemotherapy. Secondary brain tumours from cranial irradiation have been shown to occur (28). These include cavernomas and meningiomas. Radiation induced vasculopathies, including Moya disease, predispose to ischemic strokes which can increase morbidity.

Neuronal plasticity in the setting of brain tumours is currently under exploration (29,30). The human brain has a unique capability of remodelling in response to various forms of injury including tumours (30). The role of neuroplasticity was supported by a study which demonstrated tumours in the left inferior frontal gyrus resulted in transfer of the Broca's area to the healthy hemisphere (29). The timely diagnosis and intervention could improve the quality of life of patients with paediatric brain tumours as it allows tailoring of rehabilitative measures to maximize on neuroplasticity.

STUDY JUSTIFICATION AND UTILITY

Primary paediatric brain tumours are a significant cause of morbidity and mortality worldwide. This has been under-reported in the African setting due to a lack of dedicated cancer registries. No data is available on the burden of primary paediatric brain tumours in KwaZulu-Natal.

Childhood cancers have been recently added as a national priority in the National Cancer Strategic Framework, South Africa. This is in recognition of the increasing burden that childhood cancers place on the South African Healthcare system. Results from this study will contribute to database on childhood brain cancers in South Africa, and particularly KwaZulu-Natal province.

RESEARCH PROBLEM

About a quarter of all paediatric cancers involve the central nervous system. Brain tumours are the leading cause of cancer related deaths globally (31).

KwaZulu-Natal is the second most populous province in South Africa with approximately 30% of the population being under 15 years of age. Most patients with primary paediatric brain tumours are seen in Inkosi Albert Central Hospital, the only quaternary hospital in the province. The exact burden of primary brain tumours among South African paediatric population in the KwaZulu-Natal area remains unknown. This is due partly to the lack of dedicated paediatric cancer registries.

Risk factors for primary paediatric brain cancers in the South African context are unexplored. Understanding the sociodemographic factors of paediatric population with brain cancers can aid in the identification of risk factors and assist in targeted health education and early health-seeking behaviour. With a high prevalence of Human Immunodeficiency Virus infection among the South African paediatric population, this is one modifiable risk factor that may predispose to primary brain lymphomas.

In developed countries, significant progress has been made in the diagnosis and treatment of primary paediatric brain tumours over the last century due to access to advanced diagnostic tools and wider treatment options. African countries have limited access to these resources which play a role in long- and short-term outcomes of primary paediatric brain tumours.

Research question

What are the common primary brain tumours among paediatric patients presenting to a South African Quaternary hospital?

What is the epidemiology and outcome of primary paediatric brain tumours in the KwaZulu-Natal province?

AIMS

To determine the clinical profile, diagnostic modalities, management, and outcome of primary paediatric brain tumours at a quaternary hospital in Durban.

Primary objective

To describe tumour types and their management

To describe the demographic profile of study participants

To determine five-year survival rate and neurological sequelae at the last hospital visit.

Secondary objectives

To determine the association between demographic variables and management of paediatric brain tumours.

To determine factors related to morbidity and mortality of primary paediatric brain tumours.

METHODS

Study design

A hospital-based retrospective review of patient records.

Study period

The study will review patient records over 15 years from 1st January 2003 to 31st December 2017.

Setting

Paediatric neurology, neurosurgical, and paediatric oncology wards at Inkosi Albert Luthuli Central Hospital.

Participant selection

Paediatric patients with primary brain tumours referred for management who meet the inclusion criteria will be recruited. Patients will be identified from a patient admission electronic database of paediatric patients in the paediatric neurosurgical and medical wards.

Inclusion criteria

All paediatric patients' children from birth to 14 years of age admitted with a confirmed diagnosis of primary brain tumours.

Exclusion criteria

Children with confirmed or suspected metastatic brain tumours.

Children with infective or inflammatory space-occupying lesions in the brain.

Children above 14 years with primary brain tumours

Children with incomplete medical records.

Sample size

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

n = Sample size

Z = the critical value for 95% confidence level which in this case is 1.96

E = the allowable error which is 0.05

P = the proportion of paediatric patients with brain tumours among those with cancers in South Africa which in this case is 0.195 (2).

1-p = proportion of paediatrics patients with cancers (brain tumours excluded).

$$n = \frac{1.96^2 * 0.195(1-0.195)}{0.05^2}$$

$$= \frac{3.8416 * 0.195 * 0.805}{0.0025}$$

$$= \frac{0.603035}{0.0025}$$

= 241 Patients

It is approximated that 160 patients with paediatric brain tumours have been seen in the facility over the last 15 years. For finite population we adjust the sample using finite correction factor.

$$n_f = \frac{n}{1+\frac{n-1}{N}}$$

$$n_f = \frac{241}{1+\frac{241-1}{160}}$$

$$n_f = \frac{241}{1+\frac{240}{160}}$$

$$n_f = \frac{241}{2.5}$$

n_f = 96 patients

The minimum sample size for the study is 96.

RECRUITMENT

Study subjects will be identified using the hospital admission and clinic attendance register. All patients referred for evaluation and management of suspected primary brain tumours will be enrolled into the study consecutively.

Electronic medical records will then be reviewed, and relevant data retrieved.

Clinical variables to be obtained include:

Patient's demographic data (age, gender, residence)

Patient's clinical diagnosis, presenting complaints, and findings on examination.

Radiology reports, laboratory, and histological findings

Surgical reports: tumour size, location, resection margin, operative and post-operative complications

Other treatment modalities: Chemotherapy, central nervous system irradiation

Complications during hospital stay including mortalities and morbidities.

Five-year survival rate and neurological sequelae at last hospital visit.

DATA MANAGEMENT

Storage: Data will be entered into the Microsoft Excel database.

Cleaning: At the end of collection, data cleaning will be done to eliminate errors that may have occurred during data entry

Analysis: The data will initially be summarized in the form of descriptive statistics including means, medians, and standard deviations for continuous variables, and counts with percentage frequencies for all categorical data. The mean differences of the continuous data between two groups will be compared using independent t-tests for significance or Wilcoxon rank test if the data from the two groups violate the normality test. The associations between

independent categorical variables will be assessed using the Chi-square test or Fisher's exact test depending on the frequency distributions within the cross-tabulations. The risk factors associated with morbidity and mortality will be assessed using binary logistic regression with stepwise regression. Proportions will be presented as a percentage with a 95% confidence interval. Statistical analyses will be conducted using SPSS software version 25.

ETHICAL CONSIDERATIONS

Ethical clearance will be sought from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal. The Department of Neurosurgery has BREC class approval to maintain a database of admissions and procedures performed in this unit for research purposes (BREC reference number: BCA 219/15). The study intends to use this database.

Gatekeeper permission will be sought from the department of health and the institution (IALCH) before any data is collected.

Information collected from the study will not have any identification details of the patient and strict confidentiality will be maintained.

This being a retrospective study, there will be no health risks to the patient.

CONTROL OF ERRORS AND BIASES

Data collected will be assessed and keyed into a pre-programmed computer. The data entered will be crosschecked to ensure validity of the entries.

STUDY ASSUMPTIONS

The information stored on medical records is accurate.

Misinterpretation of collected data will be minimal.

Errors during analysis and presentation of the results will be minimal.

STUDY LIMITATIONS

Some information pertinent to the study may not be captured on the stored medical records resulting in non-response bias.

As the study is carried out in the KwaZulu-Natal province, findings may not be generalized to the whole country.

BUDGETARY ESTIMATES

The principal investigator will not incur any costs because data collection will be in electronic version.

TIMELINES

	Jan. 2023	March 2023	July 2023	Sept. 2023	Dec. 2024
Submission to ethics					
Data collection					
Data Analysis					
Manuscript					
Submission for publication					

CONTRIBUTORS AND AUTHORSHIP

Name	Department	Contribution	Author
Dr. Lucia Amolo	Paediatric Neurology	Principal Investigator	Author

Dr. Lawrence Mubaiwa	Paediatric Neurology	Supervisor	Co-author
Dr. Enicker Basil	Neurosurgery	Supervisor	Co-author
Mr. John Supra	Statistician	Statistician	Statistician

REFERENCES

1. Stones DK, De Bruin GP, Esterhuizen TM, et al. Childhood cancer survival rates in two South African units. South African Medical Journal 2014; 104(7): 501-504
2. Mbi Feh MK, Lyon KA, Brahmaroutu AV et al. The need for a central brain tumour registry in Africa: A review of central nervous system tumours in Africa from 1960 to 2017. Neuro-oncology Practice 2021; 8(3): 337-344
3. Wessels G, Hesseling PB. Incidence and frequency rates of childhood cancer in Namibia. South African Medical Journal 1997; 87(7): 885-9
4. stats SA 2019. Statistics South Africa. Republic of South Africa. https://www.statssa.gov.za/publications/P0302/P03022019.pdf
5. Pollack IF, Agnihotri S, Broniscer A. Childhood brain tumours: Current management, biological insights, and future directions. Journal of Neurosurgery: Paediatrics 2019;23(3):261-273
6. Pogorzala M, Styczynski J, Wysocki M. Survival and prognostic factors in children with brain tumours: long-term follow-up single centre study in Poland. Anticancer Research 2014 Jan; 34(1): 323-326
7. Cargnelutti E, Ius T, Skrap M, et al. What do we know about pre- and postoperative plasticity in patients with glioma? A review of neuroimaging and intraoperative mapping studies. Neuroimage: Clinical 2020; 28:1024-1035.

8. Arnold-Day C. Paediatric brain tumours: The University of Cape town experience from 1996-2017. Faculty of Health Sciences, Division of Paediatric Surgery. Unpublished data (Masters thesis). https://srvubudsp002.uct.ac.za/handle/11427/32084
9. Louis DN, Perry A, Wesseling P, Brat DJ, et al. The 2021 WHO Classification of Tumours of the Central Nervous System: A summary. Neuro-Oncology 2021. Aug 2; 23(8):1231-1251.
10. Subramanian S, Ahmad T. Childhood Brain Tumours. [Updated 2022 Aug 8]. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2022 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535415/
11. Qaddoumi I, Sultan I, Gajjar A. Outcome and prognostic features in paediatric gliomas: a review of 6212 cases from the Surveillance, Epidemiology and End Results database. Cancer 2009 Dec; 115(24):5761-5770.
12. Zafar S, Javed M, Rockwood N, Kazmi F. Primary central nervous system lymphoma presenting as multiple space-occupying lesions in advanced human immunodeficiency virus infection. *South African Journal of Radiology* 2017*;* 21(2).
13. Idowu OE, Idowu MA. Environmental causes of childhood brain tumours. African Health Sciences 2008 Mar; 8(1):1-4
14. Ostrom QT, Adel Fahmideh M, Cote DJ, et al. Risk factors for childhood and adult primary brain tumours. *Neuro-Oncology* 2019; 21(11): 1357-75.
15. *Khurshid* A, Jeffrey T, Rachlin J, et al. Meningioma in Four Patients with Human Immunodeficiency Virus Infection. Mayo Clinic Proceedings 1999; Mar; 74(3):253-257.
16. Motebejane SM, Mogwale S. Intracranial Meningioma in the Era of HIV and Antiretroviral Therapies, in KwaZulu-Natal, South Africa. An Observational Case-Control Study. Neurosurgery 2017;64 (1): 97-104

17. Besson C, Goubar A, Gabarre J, et al. Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy. Blood 2001 Oct 15; 98(8): 2339-44
18. Ramanjam V, Adnams C, Ndondo A, et al. Clinical phenotype of South African children with neurofibromatosis 1. J Child Neurol. 2006 Jan; 21(1):63-70
19. Kija E, Schlegel B, Samia P, *Wessels M, et al.* Clinical presentation of Tuberous Sclerosis Complex in Cape Town, South Africa. *European Journal of Paediatric Neurology* 2015; 19: S126-S127.
20. Sievert AJ, Fisher MJ. Paediatric low-grade gliomas. Journal of Child Neurology 2009 Nov; 24(11):1397-408
21. Wells EM, Packer RJ. Paediatric brain tumours. *Continuum (Minneapolis) Neuro-oncology* 2015; 21:373-96.
22. Herdell V, Lassarén P, Boop FA, et al. Surgical outcomes of paediatric brain tumours in Sub-Saharan Africa: A systematic review. Brain Spine 2022 Jul 3; 2:100912
23. Edwards LB, Greeff LE. A descriptive qualitative study of childhood cancer challenges in South Africa: Thematic analysis of 68 photo voice contributions. South African Journal of Oncology 2017; 1(0), a14.
24. Sugimoto M, Kurishima C, Masutani S, et al. Congenital Brain Tumour within the First 2 Months of Life. Paediatrics and Neonatology 2015 Dec; 56(6):369-75
25. Won SY, Dubinski D, Behmanesh B, et al. Management of hydrocephalus after resection of posterior fossa lesions in paediatric and adult patients-predictors for development of hydrocephalus. Neurosurgery Review 2020 Aug; 43(4):1143-1150
26. Duffner PK. Risk factors for cognitive decline in children treated for brain tumours. European Journal of Paediatric Neurology 2010 Mar; 14(2):106-15

27. Bloom HJ, Wallace EN, Henk JM. The treatment and prognosis of medulloblastoma in children. A study of 82 verified cases. The American Journal of Roentgenology Radium Therapy and Nuclear Medicine 1969 Jan; 105(1):43-62.
28. Fujii M, Ichikawa M, Iwatate K, et al. Secondary brain tumours after cranial radiation therapy: A single-institution study. Reports of Practical Oncology and Radiotherapy 2020 Mar-Apr; 25(2):245-249
29. Kośla K, Bryszewski B, Jaskólski D, et al. Reorganization of Language Areas in Patient with a Frontal Lobe Low Grade Glioma - fMRI Case Study. Polish Journal of Radiology 2015 Jun 4; 80:290-5
30. Bonnetblanc F, Desmurget M, Duffau H. Low grade gliomas and cerebral plasticity: fundamental and clinical implications. Medecine Sciences (Paris) 2006 Apr; 22(4):389-94
31. Arora RS, Alston RD, Eden TO, et al. Age-incidence patterns of primary CNS tumours in children, adolescents, and adults in England. Neuro Oncology 2009 Aug; 11(4):403-13

APPENDIX 2: GUIDELINES FOR PUBLICATION

SOUTH AFRICAN JOURNAL OF CHILD HEALTH (SAJCH)

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AUTHORSHIP

All named authors must give consent to publication. Authorship should be based only on substantial contribution to: (i) conception, design, analysis, and interpretation of data; (ii) drafting the article or revising it critically for important intellectual content; (iii) final approval of the version to be published. All three of these conditions must be met (Uniform requirements for manuscripts submitted to biomedical journals; www.icmje.org/index.html).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with the product or subject that may constitute conflict of interest.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. Informed consent for this purpose requires that the patient be shown the manuscript to be published. (www.icmje.org)

ETHNIC CLASSIFICATION

Work that is based on or contains reference to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Short items are more likely to appeal to our readers and therefore to be accepted for publication. Original articles of 3 000 words or less, with up to 6 tables or illustrations, should normally report observations or research of relevance to clinical medicine. References should preferably be limited to no more than 15. Short reports or scientific letters, which include case reports, side effects of drugs and brief or negative research findings should be 1000 words or less, with 1 table or illustration and no more than 6 references. Editorials, Opinions, Issues in Medicine, etc. should be about 800 words and are welcome, but unless invited, will be subjected to the SAMJ peer review process. Review articles are rarely accepted unless invited. Letters to the editor, if intended for the correspondence column, should be marked 'for publication' and signed by all authors. Letters should be no longer than 400 words with only one illustration or table. Obituaries should not exceed 400 words and may be accompanied by a photograph.

MANUSCRIPT PREPARATION

Research articles should have a structured abstract not exceeding 250 words (50 for short reports) comprising: Objectives, Design, Setting, Subjects, Outcome measures, Results and Conclusions. Refer to articles in recent issues for guidance on the presentation of headings and subheadings. Abbreviations should be spelt out when first used in the text and thereafter used consistently. Scientific measurements should be expressed in SI units except blood pressure should be given in mmHg and haemoglobin values in g/dl. If in doubt, refer to 'uniform requirements' above.

ILLUSTRATIONS

Figures consist of all material that cannot be set in type, such as photographs and line drawings. If any tables or illustrations submitted have been published elsewhere, the author should obtain written consent to republication from the copyright holder and the author(s).

All illustrations, figures etc. must be of high resolution/quality, preferably jpeg or equivalent but not PowerPoint, and preferably attached as supplementary files.

REFERENCES

References should be inserted in the text as superior numbers and should be listed at the end of the article in numerical and not in alphabetical order. Authors are responsible for verification of references from the original sources. References should be set out in the Vancouver style and approved abbreviations of journal titles used; consult the List of Journals in Index Medicus for these details. Names and initials of all authors should be given unless there are more than six, in which case the first three names should be given followed by et al. First and last page numbers should be given.

Journal references should appear thus: Price NC. Importance of asking about glaucoma. BMJ 1983; 286: 349-350.

Book references should be set out as follows: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975: 96-101. Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974: 457-472.

Manuscripts accepted but not yet published can be included as references followed by (in press). Unpublished observations and personal communications may be cited in the text, but not in the reference list.

GALLEY PROOFS

Galley proofs will be forwarded to the author before publication and if not returned within 2 weeks will be regarded as approved. Please note that alterations to typeset articles are costly and will be charged to the authors.

CHANGES OF ADDRESS

Please notify the Editorial Department of any address changes so that proofs and invoices may be mailed without delay.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

- The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).
- The submission file is in Microsoft Word, RTF, or WordPerfect document file format.
- When available, the URLs to access references online are provided, including those for open access versions of the reference. The URLs are ready to click (e.g., http://pkp.sfu.ca).
- The text is single-spaced; uses a 12-point font; employs italics, rather than underlining (except with URL addresses).
- Figures consist of all material that cannot be set in type, such as photographs and line drawings. If any tables or illustrations submitted have been published elsewhere, the author should obtain written consent to republication from the copyright holder and the author(s).
- All illustrations, figures etc. must be of high resolution/quality, preferably jpeg or equivalent but not PowerPoint, and preferably attached as supplementary files.
- The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines, which is found in About the Journal.

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APPENDIX 3: ETHICAL APPROVALS

05 May 2023

Dr Lucia Apiyo Amolo (222118355) School of Clinical Medicine Medical School

Dear Dr Amolo,

Protocol reference number: BREC/00005385/2023

Project title: Clinical profile, diagnostic modalities, and treatment outcomes of primary paediatric brain tumours at a quaternary hospital in Durban, South Africa

Degree: MMedSc

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 05 May 2023. Please ensure that any outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from 05 May 2023. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on RIG on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 13 June 2023.

Yours sincerely,

[redacted]

Prof D Wassenaar

Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee Chair: Professor D R Wassenaar

UKZN Research Ethics Office Westville Campus, Govan Mbeki Building Postal Address: Private Bag X54001, Durban 4000

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Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

KWAZULU-NATAL PROVINCE

HEALTH

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Reference: BREC 0000 3RS/2023

Enquiries: Medical Management

4 April 2023

Dr L A Amolo (222118355)

School of Clinical Medicine Medical School

Dear Dr Amolo

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: Clinical Profile, Diagnostic Modalities, and treatment outcomes of Primary Paediatric Brain Tumours at a Quaternary Hospital in Durban, South Africa.

Kindly take note of the following information before you continue:

Please ensure that you adhere to all the policies, procedures. protocols and guidelines of the Department of Health with regards to this research.

This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.

Kindly ensure that this office is informed before you commence your research.

The hospital will not provide any resources for this research.

You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

Dr A Harrichandparsad

Acting Medical Manager

GROWING KWAZULU-NATAL TOGETHER

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:
Health Research & Knowledge Management

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Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:

NHRD Ref: KZ_202304_007

Dear Dr L Amolo
(UKZN)

Approval of research

1. The research proposal titled **'CLINICAL PROFILE, DIAGNOSTIC MODALITIES AND TREATMENT OUTCOMES OF PRIMARY PAEDIATRIC BRAIN TUMORS AT A QUATERNARY HOSPITAL IN DURBAN, SOUTH AFRICA'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central hospital.

2. You are requested to take note of the following:
   a. ***Kindly liaise with the facility manager BEFORE your research begins.***
      This is to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.
   b. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Dr. G Khumalo on 033-395 3189.

Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Provincial Health Research Committee
Date: 19/04/2023.

APPENDIX 4: DATA COLLECTION TOOL

Study identification number……. Date of collection……

SOCIODEMOGRAPHIC CHARACTERISTICS OF PATIENT

Tick where appropriate

1. Age (specify exact years and months) ……
2. Sex of patient

	Male
	female
	Other (specify)

3. Residence of patient…….
4. Referral hospital…….

CLINICAL COURSE:

1. Primary diagnosis of patient…….
2. Presenting complaints:

	Altered consciousness
	Seizures (specify in space below)
	Focal signs (specify in space below)
	Other (specify in space below)

3. Duration of symptoms before presentation in weeks/months ……..……
4. Pre-existing co-morbidities? ……
5. Previous malignancies?

	Yes(specify)
	No

6. HIV status of patient (tick appropriate)

	Positive
	CD4 count …… ARV regimen ……
	Negative

7. Examination findings (Tick appropriate and describe in space provided)

	Mental status examination
	Signs of raised intracranial pressure
	Cranial nerves
	Motor
	Sensory
	Cerebellar
	Gait
	Other (specify)

8. Location of tumour

	Supratentorial (specify exact hemisphere, lobe, structure)
	Infratentorial (Specify involved structure, exact location

9. Neuroimaging done?

	Yes
	No

If no, skip to 11.

10. Type of neuroimaging done (describe findings in space provided)

YES	Cranial ultrasound							
NO	Findings:							
YES	CT brain							
NO	Findings:							
YES	MRI brain (tick all done)	T1	T2	FLAIR	DWI/ADC	MRA	MRV	OTHER
NO	Findings:							
	Other (specify)							
	Findings							

11. EEG done?

	Yes
	No
	Unknown

If no, skip to 13.

12. EEG findings

……

13. Treatment modalities instituted (tick all relevant)

	Neurosurgery
	Chemotherapy
	Radiotherapy
	Palliative
	None
	Other (specify)

14. If more than one modality instituted, please indicate the order of treatment by number (1,2,3)

	Chemotherapy
	Neurosurgery
	Radiotherapy
	Other (specify)

If neurosurgery done:

15. Type of surgery

	Total resection
	Partial resection of tumour
	Biopsy only
	Other (specify)

16. Please indicate any perioperative complications documented.

Neurology	
Endocrine	
Anaesthetic	
Surgical	
Respiratory	
Other	

17. Histological sample obtained.

	Yes
	No
	Unknown

18. If yes, Histology findings

……

If chemotherapy instituted:

19. Please indicate treatment regimen

……

20. Please indicate any complications documented from chemotherapy during hospital stay.

……

If radiotherapy instituted:

21. Please indicate any complications documented during hospital stay.

……

22. Duration of hospital stay?.....

23. What, if any, complications were documented during hospital

stay?.....

24. What was the treatment outcome of the patient during hospital stay?

	Deceased
	Discharged
	Not documented

25. Patient's clinical status at 5 years

	Deceased
	Alive
	Not documented

26. If deceased, what was the cause of death? (Tick all relevant)

	Tumour complications (provide details in space provided)
	Treatment complications (provide details in space provided)
	Other (provide details in space provided)

27. If alive, please indicate any neurological

deficits…….