THE PREVALENCE OF CENTRAL NERVOUS SYSTEM TUMOURS AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL, PAEDIATRIC ONCOLOGY UNIT BETWEEN 2006 AND 2015

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DECLARATION

I, Vongai Mashoko, declare that this research write-up is my own work. It is being submitted in partial fulfilment of Master of Science (Medicine)in the field of Paediatrics by Dissertation of the University of Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at this or any other university.

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(Signature)

On this day ……. of ……. 2021

DEDICATION

I dedicate this work to my husband Akim, my children Tinevimbo, Tinomuda and Kaitlyn for the love, support and encouragement throughout my studies and for being able to cope without me while I was away.

PRESENTATIONS ARISING FROM THIS STUDY

The findings from this study were presented by the author at the following meetings

1. The University of Witwatersrand Paediatrics Research day on 20 November 2020, Johannesburg as an oral presentation, virtual meeting.
2. First Pakistan Neuro-Oncology Symposium on 28 November 2020 as an oral presentation, virtual meeting.

ABSTRACT

Introduction: Tumours of the central nervous system are a diverse group of diseases that constitute the most common solid malignancy in children, accounting for more than 20% of all childhood cancers in high-income countries. According to the South African Children's Tumour Registry (SACTR), over a period of 25 years, central nervous system tumours were the third commonest tumours in children following leukaemia and lymphoma.

Objectives: To describe the epidemiology, spectrum and outcome of central nervous system tumours in children and adolescents aged zero to 19 years at a Paediatric Oncology Unit (POU) at an academic referral hospital in Johannesburg over 10 years, 2006-2015.

Methods: This was a health-facility based retrospective descriptive study. Children and adolescents aged zero to 19 years with primary central nervous system tumours seen at the POU during the study period were eligible for enrolment. Metastatic tumours to the central nervous system were excluded. Data was analysed using Stata version 14. The Kaplan- Meier survival estimates were used for 5-year survival rates. The outcome event was death. Patients without events were censored at their last follow-up visit. Univariate Cox proportional hazards models were used to identify possible risk factors for death. Multivariate regression was applied to the factors identified by univariate models.

Results: Central nervous system tumours were diagnosed in 169/1231 new patients during the 10-year period thus constituting 13.73% of all tumours. The mean age was 7.83 years (s.d 0.4). The commonest tumours were astrocytic (58/169; 34.3%), followed by embryonal tumours with medulloblastoma being the commonest (26/169; 15.3%), craniopharyngioma (25/169; 14.8%), ependymoma (11/169; 6.5%), primitive neuroectodermal tumours (9/169; 5.3%) and tumours of the pineal region (8/169; 4.7%) (with confirmed pineoblastoma cases being 5 of the 8). Other uncommon tumours were choroid plexus tumours (3), intracranial germ cell tumours (2), tumours of nerves and neuronal-glial tissue (3), malignant peripheral nerve sheath tumour (2) and anaplastic large cell lymphoma (1).

One hundred and thirty-seven records were available for survival analysis. The overall survival rates at 1 and 5 years were 69% and 51% respectively. Patients diagnosed with medulloblastoma were less likely to die (p-value = 0.008) whereas those with high-grade tumours were 2.44 times more likely to die (p-value = 0.013) compared to low-grade tumours.

Conclusions: The spectrum of paediatric central nervous system tumours are similar to what has been reported in other high-income and low- and middle-income countries. Overall survival rates were comparable to those reported by other low- and middle-income countries.

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LIST OF ABBREVIATIONS

ATRT	Atypical teratoid rhabdoid tumour
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CNS	Central nervous system
CSF	Cerebrospinal fluid
GCT	Germ cell tumour
HAZ	Height for age z-score
HGG	High-grade glioma
HIC	High-income countries
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee
LGG	Low-grade glioma
LMIC	Low- and middle-income countries
MPNST	Malignant peripheral nerve sheath tumour
MDT	Multidisciplinary team
OS	Overall survival
PI	Principal Investigator
PNET	Primitive neuroectodermal tumour

POU	Paediatric Oncology Unit
PSI	Pre-diagnosis symptom interval
SA	South Africa
SACTR	South African Children's Tumour Registry
SEGA	Sub-ependymal giant astrocytoma
VPS	Ventriculoperitoneal shunt
WAZ	Weight for age z-score
WHO	World Health Organization

1. INTRODUCTION

Childhood cancer is a relatively uncommon disease but has great impact on survival. In high-income countries (HIC), it is second to accidents as the leading cause of mortality in children (1). Tumours of the central nervous system (CNS) are a diverse group of diseases that constitute the most common solid malignancy in children, accounting for more than 20% of all childhood cancers in HIC. In the USA from 2011-2015, the average annual incidence of primary CNS tumours for children and adolescents under 19 years of age was 5.95 cases per 100 000 population (2). Lower incidences have been reported in other parts of the world e.g. Japan (3.61 per 100 000) (3) and Germany (2.6 per 100 000 children) (4). In Australia, CNS tumours contribute 23% of all childhood cancers (5). These epidemiological studies in paediatric CNS tumours are well documented in HIC but less so in low- and middle-income countries (LMIC). Paediatric CNS tumours, as a proportion of all childhood cancers has been reported to be as high as 30% in India (6), 6.1% in Zimbabwe (7), 5.4% in Sudan (8), 3.9% in Mozambique (9) and 1.4% in Malawi (10). The South African Children's Tumour Registry (SACTR) reported CNS tumours were the third commonest tumour over a period of 25 years, (11) following leukaemia and lymphomas. This pattern is in keeping with data from HIC (12). In Nigeria, CNS tumours were described as the fourth commonest tumours in children (13).

In LMIC, the incidence of CNS tumours may appear low and this may reflect underdiagnosis due to low diagnostic capacity and lack of adequate healthcare facilities (14).

CNS tumours are associated with significant morbidity and mortality both due to the malignancy and the therapy. Morbidity and mortality in children diagnosed with CNS tumours are higher than in any other paediatric cancers (15). There are many physical, neuro-psychological, and neuro-endocrine sequelae associated with CNS tumours. Central nervous system tumours require extensive resource allocation for diagnosis and treatment. In Nigeria, 1-year and 5-year survival rates at a large referral centre was reported as 56% and 47% respectively (16). Similarly, in Sudan, 2-year and 5-year survival

rate were 33% and 13% respectively (8). Other LMIC have also shown low survival rates in children diagnosed with CNS tumours (17).

Nutrition is an essential component in childhood cancer including paediatric CNS tumours. The prevalence of malnutrition in childhood cancer ranges from 6 to 50% depending on the type of malignancy (18). Malnutrition at diagnosis has been shown to be associated with poor outcome especially of associated with advanced disease at diagnosis (19). Children with diencephalic tumours are at higher risk of malnutrition (20).

1.1 CLASSIFICATION OF CENTRAL NERVOUS SYSTEM TUMOURS

Tumours of the CNS are a diverse group of diseases that range from indolent tumours to highly malignant, aggressive tumours. The recent World Health Organisation (WHO) classification of 2016 (Appendix 1) implements molecular parameters for the first time in addition to histology to define CNS tumours (21). However, most of the studies still use an earlier classification of the CNS tumours (22). Tumour location, histology and extent of the disease remain important factors that affect treatment, prognosis and outcome (23). More than 90% of the tumours occur in the brain and the remainder in the meninges, spinal cord and cranial nerves (24). In children and adolescents, the most common histological types are astrocytoma, medulloblastoma, germ cell tumours, brain stem gliomas and ependymomas (12). In our study, we used histological classification and anatomical location as molecular parameters were not available in our institution during the study period.

During the first two years of life, supratentorial tumours tend to predominate, while infratentorial tumours such as medulloblastoma, astrocytoma, brainstem gliomas and ependymoma are more common from 2 to 10 years of age. In late adolescence and young adulthood, supratentorial tumours

predominate again (12). Some studies have shown predominance of infratentorial tumours (8) (13) (24) (25) while some studies in South India and Uganda showed supratentorial tumours to be more common (6) (17).

In Nigeria, Ogun et al analysed 77 cases of intracranial tumours and found that the commonest were astrocytoma (25.9%), embryonal tumours and ependymomas were of equal proportion (19.5%), craniopharyngiomas (11.7%), and germ cell tumours (7.8%). Supratentorial tumours contributed 46.8% of intracranial tumours (13). A slightly different pattern was observed by Ndubuisi et al in south-east Nigeria where supratentorial tumours were more common (51.9%) than infratentorial tumours. The histopathological types observed were gliomas (37%), medulloblastoma (24.1%), craniopharyngioma (20.4%), meningiomas (3.7%) and others (14.8%) (26).

At a large paediatric cancer hospital in Egypt, Ezzat et al found that the commonest CNS tumours were astrocytic tumours (30%), embryonal tumours (23.2%), ependymoma (8.7%) and craniopharyngiomas (5.3%). Medulloblastomas were the majority of the embryonal tumours (24).

In South Africa, a health-based retrospective study at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and CHBAH showed that the commonest CNS tumours in children were astrocytomas (25.7%), medulloblastomas (21%) and brainstem gliomas (20%). The majority of the children (67%) had infratentorial tumours and younger children were more likely to have infratentorial tumours than older children. The study was a retrospective of patients seen between 1995 and 2005 [unpublished] done by the department of neurosurgery (27). One of the objectives of this study was to compare our findings with the findings from department of neurosurgery.

1.2 GLIOMAS

Gliomas are classified by the WHO as tumours of neuroepithelial tissue derived from glial cells such as astrocytes, oligodendrocytes and ependymal cells. Gliomas account for approximately 50% of all CNS tumours (12) . The most common are astrocytic and ependymal tumours.

1.2.1 ASTROCYTOMA

Astrocytic tumours are classified by the WHO as low-grade (grade I and II) or high-grade (grade III and IV) (Appendix 2). Low-grade astrocytomas have a relatively favourable outcome especially if the tumour is completely resected(28). High-grade astrocytomas and brain stem gliomas are locally invasive and prognosis guarded(28). Studies from LMIC have shown the variable frequency of astrocytoma from 35% in Egypt (25), 30% in the Middle East (24), 25% in Nigeria (16) and 23% in Uganda (17).

1.2.2 EPENDYMOMA

Ependymomas constitute about 10% of intracranial tumours in children in HIC (12). In a study done in Nigeria, ependymomas were found in 19.4% of all the CNS tumours (13), Uganda 16.3% (17) and in Egypt 10% (25). According to the 2016 WHO classification ependymomas are divided into 5 subtypes. These are subependymoma (WHO grade I), myxopapillary ependymoma (WHO grade I), ependymoma (WHO grade II), ependymoma RELA fusion-positive (WHO grade II or III) and anaplastic ependymoma (WHO grade III). The clinical presentation depends on tumour location (29).

1.3 MEDULLOBLASTOMA

Medulloblastoma is the commonest malignant brain tumour in children and adolescents. Medulloblastomas constitute approximately 20% of all primary CNS tumours in children aged zero to 14 years (12). A study from south India, showed that medulloblastomas contributed to 34.6% of CNS tumours in children (6). Other studies from LMIC showed incidence ranging from 8.1% in Uganda to 25% in Nigeria (17) (25) (24) (26) (16). Medulloblastomas mainly arise in the cerebellum. Medulloblastomas are defined by molecular subtypes and histologic subtypes in the 2016 WHO classification (21).

Other embryonal tumours such as primitive neuroectodermal tumour (PNET) and atypical teratoid rhabdoid tumour (ATRT) have been re-defined according to the 2016 WHO classification (21).

1.4 GERM CELL TUMOURS

Primary intracranial germ cell tumours (GCT) constitute about 3-4% of all CNS tumours in children in the USA (2). Higher incidences have been reported in Asia (15%) (2). In Nigeria, Ogun et al reported a frequency of 7.8% of primary CNS GCT out of all CNS tumours in children at their institution (13). Intracranial GCT tumours are more common in males. They occur mainly in the pineal (45%) or suprasellar (30%) regions (30)(31). Intracranial GCT of suprasellar origin usually have a long latent history before presentation and may have subtle to overt hormonal deficiencies (32). The GCT arising from the pineal region tend to have a shorter history before presentation (32).

Tumours such as craniopharyngiomas have been reported ranging from 9.9% in Uganda to 20.4% in Nigeria (17) (25) (13) (26).

Studies of epidemiology, treatment modalities and outcomes of paediatric CNS tumours in LMIC are available but few. In South Africa, the SACTR has documented the prevalence of individual tumours, including CNS tumours (11). Our study was designed to evaluate CNS tumours in children and adolescents at a single POU in South Africa. There has been advancement in the treatment of CNS tumours with targeted molecular treatment playing an important role. It is important to document the spectrum of CNS tumours that are seen at a particular POU and then further studies may be done on individual tumours to improve care and targeted therapy.

2. STUDY OBJECTIVES

2.1 AIM

To describe the epidemiology, spectrum and outcome of CNS tumours seen in children and adolescents aged zero to 19 years at a paediatric oncology unit at CHBAH, a tertiary academic hospital in Johannesburg over 10 years, 2006-2015.

2.2 SPECIFIC OBJECTIVES

1. To determine the prevalence of CNS tumours at this unit
2. To document the demographic characteristics of the children and adolescents diagnosed with CNS tumours
3. To document the spectrum of the CNS tumours
4. To document treatment modalities used in the management of CNS tumours in children and adolescents at the unit
5. To determine the overall survival of the children and adolescents diagnosed with CNS tumours during this study period

3. METHODOLOGY

3.1 STUDY DESIGN

This was a health-facility based retrospective descriptive study. The period of study was January 2006 to December 2015 which enabled a large number of patients to be captured and also allowed an adequate follow-up time to document 5-year overall survival rate.

3.2 STUDY SETTING

Chris Hani Baragwanath Academic Hospital is a tertiary hospital in, Gauteng province situated in the south-western townships (Soweto), Johannesburg South Africa. It has a wide referral base including the local population of Soweto, other smaller hospitals in southern Gauteng, Mpumalanga, North West Province hospitals and neighbouring countries. It is one of the teaching hospitals for the Faculty of Health Sciences of the University of Witwatersrand, Johannesburg, South Africa.

The POU unit consists of two in-patient wards, one for children under seven years of age and another one for children and adolescents aged eight to 19 years. The unit has an outpatient where up to 650 patients are seen in a month [unpublished].

3.3 STUDY POPULATION

All children and adolescents diagnosed with CNS tumours and referred to the POU during the study period were eligible for enrolment.

3.3.1 INCLUSION CRITERIA

All children and adolescents aged zero to 19 years with CNS tumours seen at CHBAH POU between 1 January 2006 to 31 December 2015.

1.3.2 EXCLUSION CRITERIA

- Young adults older than 19 years were excluded from the study

- Patients who were initially seen and managed at other centres and referred to the unit as relapse
- Secondary metastatic tumour to the brain
- Patients with incomplete records that would make statistical analysis not possible

1.4 DATA COLLECTION

Health records for children and adolescents diagnosed and treated for CNS tumours seen at CHBAH from the first of January 2006 to 31 December 2015 were examined for the following using a data collection tool

1. Patient demographic details: age and sex and place of residence
2. Anthropometry: weight and height at diagnosis were recorded and body mass index (BMI) calculated. The WHO child growth standards were used to determine z-scores for weight for age and height for age. Underweight was defined as weight-for-age z-score less than -2z and stunting defined by a height-for-age z-score less than -2z.
3. Presenting symptoms, and duration of symptoms before diagnosis. This time interval was then used as prediagnosis symptom interval.
4. Comorbidity: HIV status
5. CNS tumour diagnosis, anatomic location and WHO grade. The basis of CNS tumour diagnosis was radiological and/or histological confirmation.
6. Treatment modalities such as surgical resection, cerebrospinal fluid (CSF) diversion methods, chemotherapy, radiation therapy and dose
7. The outcome of the child to determine overall survival rates. The date of death or date last seen was captured.

8. Presence of any morbidity in the child after treatment: motor disability, epilepsy, visual impairment, endocrine abnormalities, growth failure, mental and cognitive impairment.

3.5 DATA ANALYSIS

Data was entered and stored in Red Cap using a mobile tool. Data cleaning was performed before analysis. The data were analysed using STATA Version 14.

Means, medians and standard deviations were used for continuous variables and the Student t-test was used for significance level. A p-value of <0.05 was considered significant. Proportions and graphs were used for categorical data and Chi-square (from 2 by 2 tables) were used for confidence intervals.

The Kaplan- Meier survival estimates were used for 5-year overall survival rates. The outcome event was death. Patients without events were censored at their last follow-up visit. Univariate Cox proportional hazards models were used to identify possible risk factors for death. If univariate analysis indicated multiple significant factors contributing to survival, a multivariate regression analysis would be done.

4. ETHICAL CONSIDERATIONS

Permission to perform the study was granted by the local institutional review board at Chris Hani Baragwanath Academic Hospital to access the files in the POU. The study was approved by the Human Research Ethics Committee (HREC) of the University of Witwatersrand (protocol number M200546 MED20-04-091). Patient anonymity was safe guarded and data security maintained and protected by passwords only known to investigators.

5. RESULTS

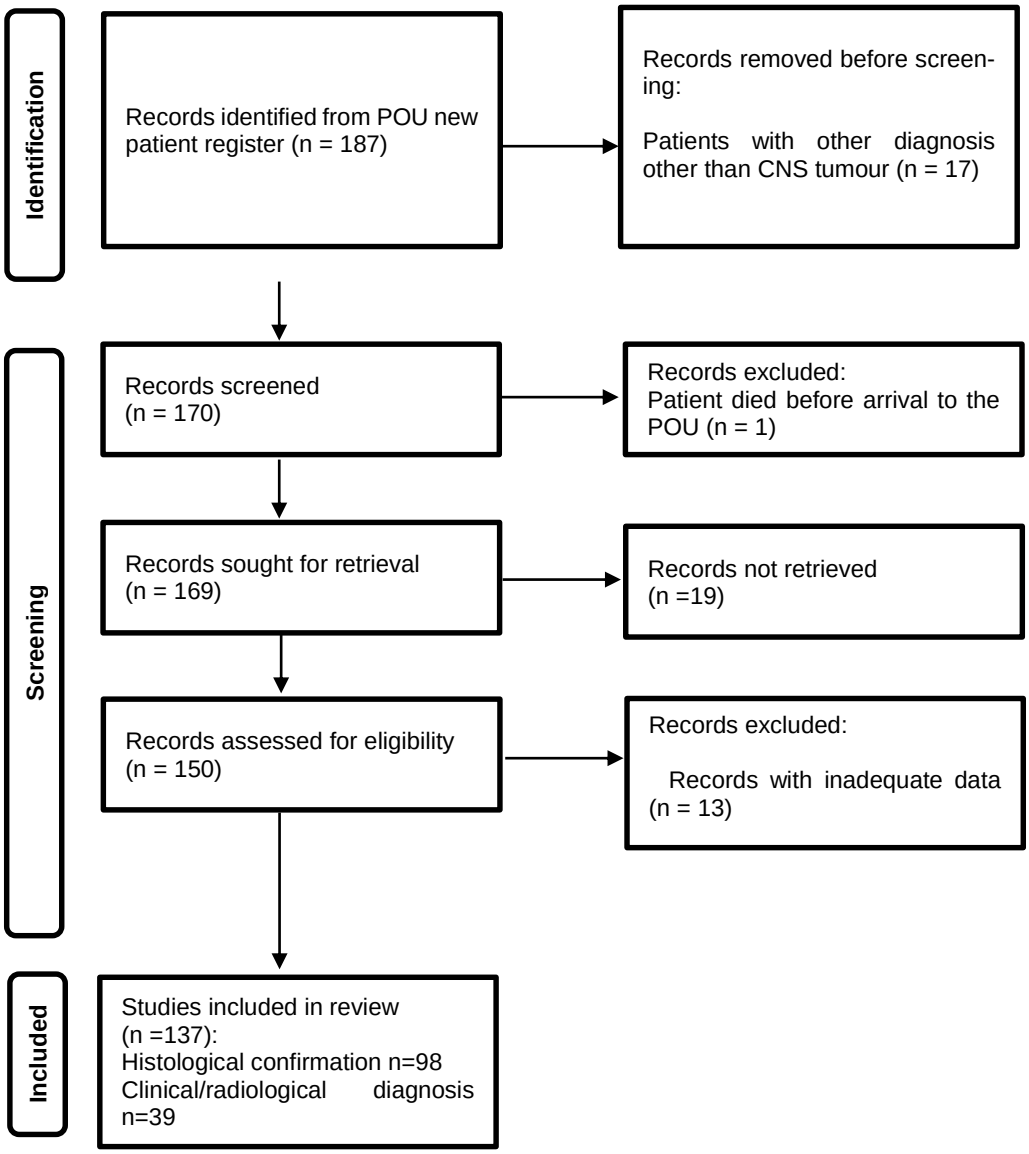
The results were presented under the following sections

- Demographic details of study participants
- The nutritional assessment of study participants
- Distribution and spectrum of central nervous system tumours
- Pre-diagnosis symptom interval
- The characteristics of the four commonest central nervous system tumours which are astrocytoma, medulloblastoma, craniopharyngioma and ependymoma
- Management of central nervous system tumours
- Outcome of the children with central nervous system tumours

5.1 DEMOGRAPHY

One hundred and eight-seven patients were identified using the POU clinic new patient register (Fig 1). CNS tumours were diagnosed in 169 patients out of 1231 children and adolescents with cancer seen during the 10 years at the unit. Accordingly, CNS tumours constituted 13.73% of all malignancies at CHBAH paediatric oncology unit. There were 88 (52.07%) males with a male: female ratio of 1: 0.92 with a mean age of 7.5 years ±4.64 and a median age of 6.7 years (IQR:3.94 - 11.66).

Figure 1. Patient flow chart



POU = paediatric oncology unit, CNS= central nervous system

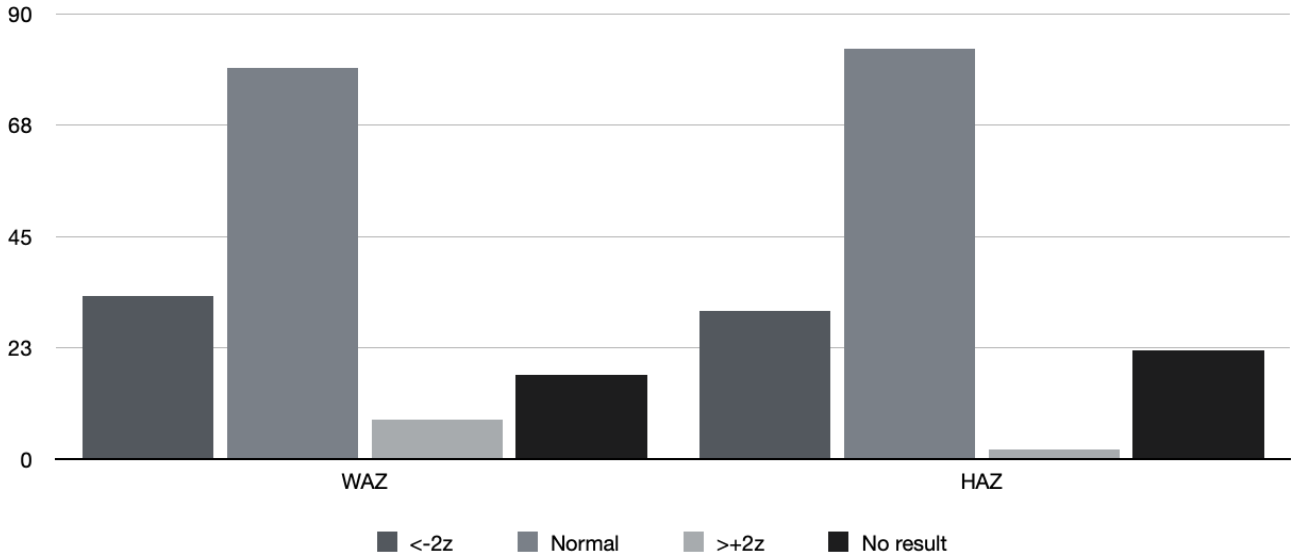
The final data analysis was done on 137 patients. Ninety-eight (71.53%) of the tumours were histologically confirmed while in the rest diagnosis was made clinically and radiologically. There were 73 males (male: female ratio = 1:0.88). The median age at diagnosis was 7.83 +/-0.40 years. A greater proportion (68.61%) of the patients were under 10 years of age. The majority were South Africans

(91.97%). Four (2.92%) were documented to be living with HIV while 109 (79.56%) were HIV-negative while the remaining 24 patients had no documentation of their HIV status.

5.2 NUTRITIONAL STATUS

Figure 2 below shows the nutritional status of the patients with CNS tumours. Underweight was observed in 24.09% of the patients and stunting in 21.90% of the patients .

Figure 2: Nutritional status at diagnosis of the patients with central nervous system tumours n=137



WAZ = weight for age z-score HAZ = height for age z-score

5.3 DISTRIBUTION OF PAEDIATRIC CENTRAL NERVOUS SYSTEM TUMOURS

The distribution of the CNS tumours in all the patients seen during the study period is shown in Table 1. The highest proportion was due to astrocytic tumours (34.31%) followed by embryonal tumours (15.38%), craniopharyngiomas (14.79%), ependymal tumours (6.51%), mesenchymal tumours (5.33%) and tumours of the pineal region (4.73%). Medulloblastoma was the predominant embryonal tumour (84.6% of the embryonal tumours). The other tumours were uncommon, representing less than 2% of the total and these were choroid plexus tumours (n=3), neuronal and mixed-neuronal-glial

tumours (n=3), intracranial germ cell tumours (n=2), malignant peripheral nerve sheath tumour (n=2) and lymphoma (n=1).

Table 1. Central nervous system tumour distribution n= 169

Clinical/histologic diagnosis	Frequency	Percentage	Males n (%)
Unspecified brain tumour	**21**	**12.43%**	**13 (61.90)**
Astrocytic tumours	**58**	**34.31%**	**22 (37.93)**
Brainstem glioma	19		
Pontine glioma	7		
Diffuse astrocytoma	7		
Thalamic	5		
Glioblastoma multiforme	4		
Pilocytic astrocytoma	3		
Oligodendroglioma	3		
Optic pathway glioma	4		
Anaplastic astrocytoma	2		
Fibrillary astrocytoma	2		
SEGA	2		
Embryonal tumours	**26**	**15.38%**	**13 (50.00)**
Medulloblastoma	22		
ATRT	2		
CNS neuroblastoma	2		
Tumours of the sella region	**25**	**14.79%**	**15 (60.00)**
Craniopharyngioma	25		
Ependymal tumours	**11**		**8 (72.73)**
Mesenchymal	**9**	**5.33%**	**7 (77.78)**
PNET	8		
Primary CNS sarcoma	1		
Tumours of the pineal region	**8**	**4.73%**	**2 (25.00)**
Pineoblastoma	5		
Not specified	3		
Choroid plexus tumours	**3**	**1.78%**	**2 (66.67)**
Choroid plexus papilloma	1		
Choroid plexus carcinoma	2		
Neuronal and mixed-neuronal glial tumours	**3**	**1.78%**	**1 (33.33)**
DIG	1		
Ganglioneuroma	2		
Germ cell tumours	**2**	**1.18%**	**2 (100.00)**
Germinoma	2		
Tumours of the cranial and paraspinal nerves (#MPNST)	**2**	**1.18%**	**2 (100.00)**
Lymphomas	**1**	**0.59%**	**1 (100.00)**

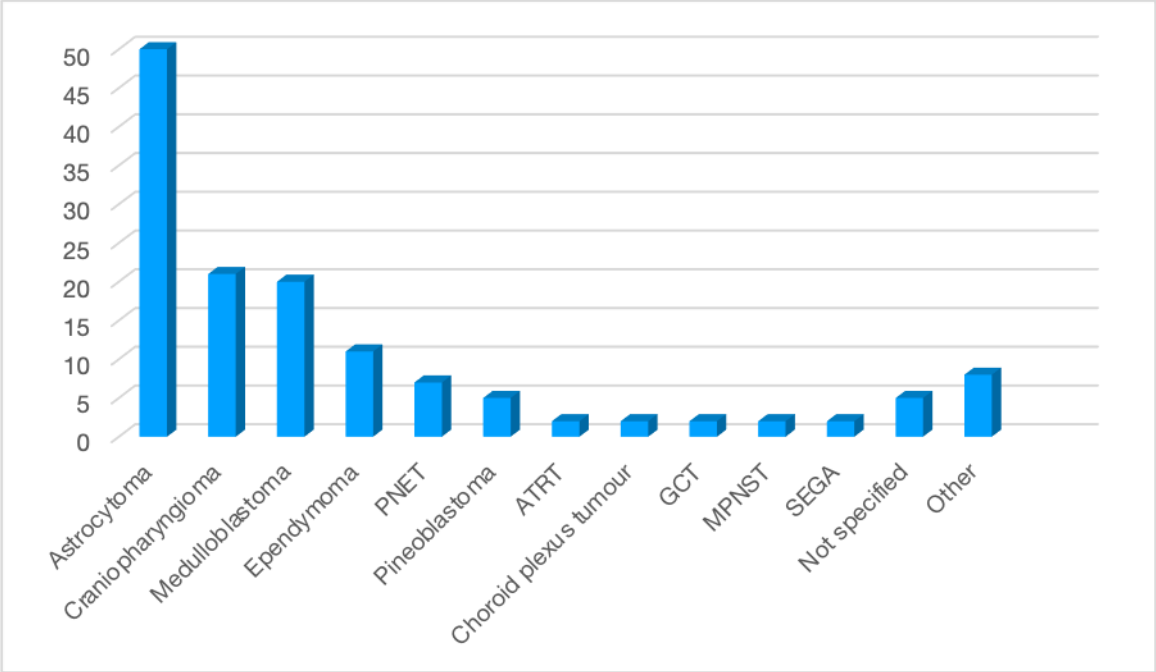
*SEGA= subependymal giant astrocytoma ¶DIG= Desmoplastic infantile ganglioglioma #MPNST = Malignant peripheral nerve sheath tumour ATRT = Atypical teratoid rhabdoid tumour CNS = central nervous system tumour PNET = primitive neuroectodermal tumour

5.4 SPECTRUM OF CNS TUMOURS

The spectrum of the 137 clinical and histologically confirmed CNS tumours are shown in Figure 3. The commonest tumour type was astrocytoma (36.50%) followed by craniopharyngioma (15.32%), medulloblastoma (14.60%), ependymoma (8%), PNET (5.11%) and pineoblastoma (3.65%. The uncommon histological types were ATRT (n=2), intracranial germ cell tumours (n=2), subependymal giant astrocytoma (SEGA) (n=2), neuronal and mixed neuronal glial tumours (n=2) and malignant tumours of the peripheral nerve sheath (MPNST) (n=2).

The anatomic location of these tumours is shown in Figure 4. Half of the CNS tumours were supratentorial while 41% were located in the infratentorial region. Infratentorial tumours were predominant in the children aged 2 to 10 years while supratentorial tumours were the predominant tumours in children above 10 years of age (Table 2). Spinal cord tumours constituted eight per cent (n=11) of all the CNS tumours. The spinal cord tumours were astrocytomas (n=2), PNET (n=2) MPNST (n=2), ganglioneuromas (n=2), paraspinal neuroblastoma (n=1), rhabdomyoma (n=1) (patient had tuberous sclerosis) and an intramedullary pseudotumor (n=1).

Figure 3: Distribution of Paediatric central nervous system tumours by clinical/histological diagnosis n=137



PNET = primitive neuroectodermal tumour ATRT = Atypical teratoid rhabdoid tumour GCT = Germ cell tumour MPNST = malignant peripheral nerve sheath tumour SEGA = subependymal giant astrocytoma

Fig 4: Anatomic location of the paediatric CNS tumours, n=137

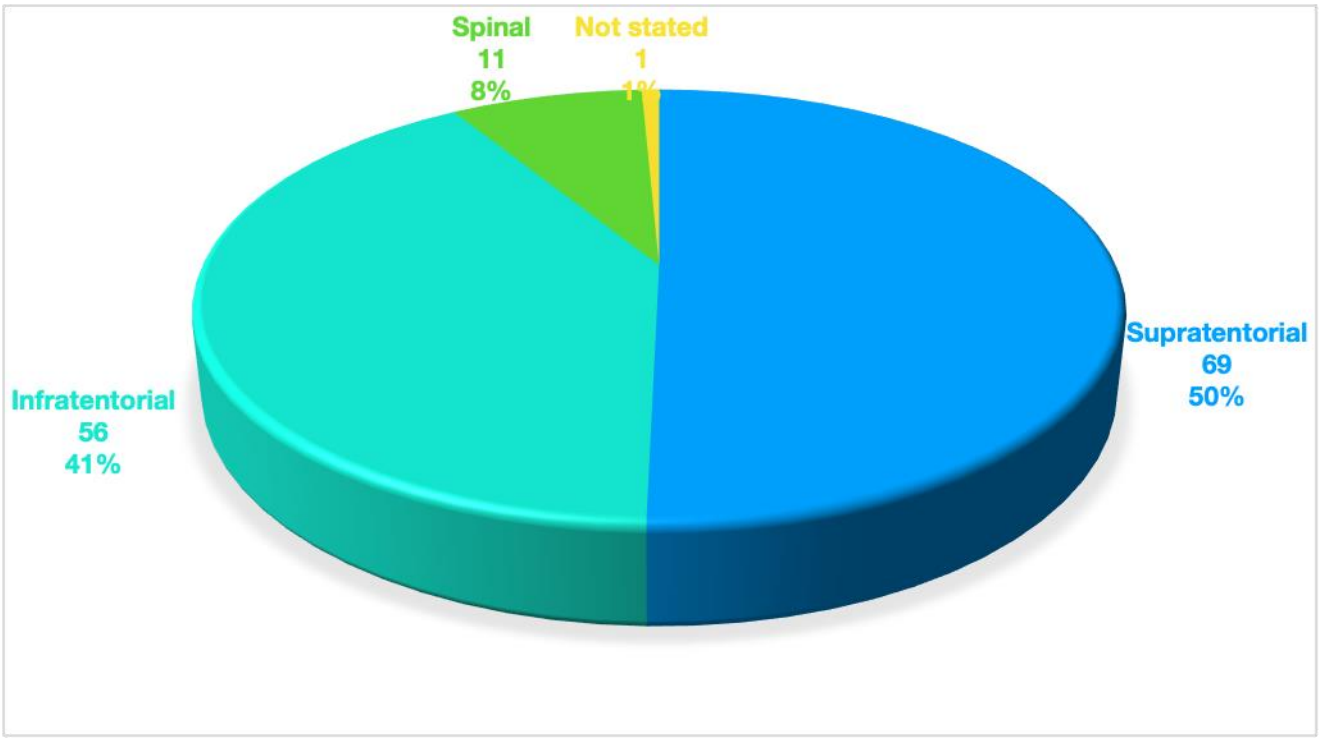


Table 2. Anatomic location of central nervous system tumours by age group

Age group (n=136+1)*	Infratentorial n=56	Supratentorial n=69	Spinal n=11
<2 years (n=11+1)*	4 (33.33%)	4 (33.33%)	3 (25%)
2-10 years (n=82)	42 (51.22%)	35 (42.68%)	5 (6.1%)
>10 years (n=43)	10 (23.26%)	30 (69.77%)	3 (6.98%)

*in one patient the anatomic location of the tumour was not indicated

5.5 PRE-DIAGNOSIS SYMPTOM INTERVAL

The mean time to presentation, pre-diagnosis symptom interval (PSI) was 108 +/-20 days for all CNS tumours. Time to presentation was shortest for pineoblastoma (median = 7 days) and longest for craniopharyngioma (median = 210 days).

Table 3. Pre-diagnosis symptom interval in paediatric patients with central nervous system tumours

Histology	Median duration of symptoms in days (Q1;Q3)
Pineoblastoma	7 (3;7)
Choroid plexus tumour	14 (14;14)
Astrocytoma (high-grade)	21 (10;60)
Atypical rhabdoid teratoid tumour	30 (30;30)
Medulloblastoma	30 (14;60)
Ependymoma	30 (14;30)
Astrocytoma (low-grade)	60 (30;210)
Germ cell tumour	165 (60;270)
Craniopharyngioma	210 (30;365)

Q1= first interquartile range Q3= third interquartile range

5.6 ASTROCYTOMA

Astrocytomas were the most common CNS tumours diagnosed among the study participants contributing 36.50% of all the CNS tumours. Thirty-four per cent were low-grade gliomas, and 20% were histologically proven to be high-grade gliomas and about 44% were presumed to be high-grade on clinical and radiological assessment. Brainstem gliomas were the most common (n=17, 34%) and pilocytic astrocytomas were only three (6%) (Table 4).

Table 4. Astrocytoma subtypes n=50

Astrocytoma subtype	Frequency n (%)
Brainstem glioma	17 (34)
Diffuse astrocytoma	7 (14)
Pontine glioma	6 (12)
Thalamic glioma	5 (10)
Glioblastoma multiforme	4 (8)
Oligodendroglioma	3 (6)
Optic pathway glioma	3 (6)
Pilocytic astrocytoma	3 (6)
Anaplastic astrocytoma	1 (2)
Fibrillary astrocytoma	1 (2)

The majority of the astrocytic tumours were infratentorial (52%) as shown in Table 5. The major presenting symptoms are as shown in the table. The overall median PSI for astrocytomas was 30 days. It was shorter for high-grade gliomas (median interval of symptoms = 21 days) compared to low-grade gliomas(median interval of symptoms =60 days). Astrocytic tumours were treated with the multimodal approach as shown in the table. Twenty out of 50 (40%) patients with astrocytic tumours died within 5 years of diagnosis. Those who died had clinical or histological diagnosis of brainstem glioma (n=11), pontine glioma (n=3), glioblastoma multiforme (n=2), oligodendroglioma (n=2), anaplastic astrocytoma (n=1) and fibrillary astrocytoma (n=1). The cause of death was attributed to disease progression in 19/20 (95%) of these patients and 1/20 (5%) had relapsed disease. The overall survival rates at 1 and 5 years were 59% and 45% respectively. Seventeen patients (34%) with astrocytoma were lost to follow up.

Table 5. Characteristics of patients with astrocytoma N=50

Characteristic	Frequency n (%)

Median age (years)	6.9 (Q1=4.6; Q3=11.7)
Sex	
Male	19 (38%)
Female	31 (62%)
Presenting signs and symptoms	
Hemiparesis	22 (44%)
Gait disturbances	16 (32%)
Visual disturbances	15 (30%)
Seizures	8 (16%)
Headache	8 (16%)
Vomiting	7 (14%)
Location	
Infratentorial	26 (52%)
Supratentorial	22 (44%)
Spinal	2 (4%)
WHO histology grade	
I	7 (14%)
II	10 (20%)
III	4 (8%)
IV	28 (56%)
Not indicated	1 (2%)
Median time to presentation (days)	30 (Q1=14; Q3=61.5)
Treatment	
Radiation only	18 (36%)
CSF diversion	10 (20%)
Surgical resection only	7 (14%)
Surgery and radiation	5 (10%)
Surgery, chemotherapy and radiation	2 (4%)
Surgery and chemotherapy	1 (2%)
Chemotherapy and radiation	1 (2%)
None	16 (32%)
Survival	
1-year survival	59% +/-7.62
5-year survival	45% +/-9.53

Q1= first interquartile range Q3 = third interquartile range CSF = cerebrospinal fluid WHO = World health Organisation

5.7 MEDULLOBLASTOMA

The characteristics of patients with medulloblastoma are shown in Table 6. Medulloblastoma contributed 15.38% of the paediatric CNS tumours. Twenty out of 22 files were available for analysis. The median age at diagnosis was 9.14 years (Q1=6.21; Q3=12.62). They were predominantly males with a male to female ratio of 1.2:1. The median PSI was 30 days and the main presenting symptoms were headache and vomiting. Fourteen out of 20 (70%) of the patients with medulloblastoma were stratified as high-risk while in 4 patients it was not indicated and 2 were standard risk. The majority (85%) received all the 3 multimodal treatment methods that are surgical resection, chemotherapy and radiation. The radiation field was craniospinal. Ten out of 14 (71.43%) patients with high-risk medulloblastoma received 36Gy craniospinal irradiation with a boost to the posterior fossa to 54Gy. The rest of the patients received 23.4Gy to the craniospinal axis with a boost to the posterior fossa to 54Gy. The survival rates at 1 and 5 years were 84.6% and 67.7% respectively. All 3 patients who died after one year had spinal metastasis, one at diagnosis and 2 as metastatic relapse.

Table 6. Characteristics of patients with medulloblastoma n=20

Characteristic	Frequency n (%)
Median age (years)	9.14 (Q1=6.21; Q3=12.62)
Sex	
Male	11 (55%)
Female	9 (45%)
Presenting signs and symptoms	
Headache	12 (60%)
Vomiting	8 (40%)
Gait disturbances	9 (45%)
Visual disturbances	6 (30%)
Seizures	3 (15%)
Limb weakness	3 (15%)
Median time to presentation (days)	30 (Q1=14; Q3=60)
Risk stratification	
High-risk	14 (70%)
Average risk	2 (70%)
Not indicated	4 (20%)
Treatment	
Surgical resection, chemotherapy and radiation	17 (85%)
CSF diversion	7 (35%)
Surgical resection only	2 (10%)
Surgical resection, chemotherapy	1 (85%)
Survival	
1-year survival	84.6%
5-year survival	67.7%

Q1 = first interquartile range Q3 = third interquartile range CSF = cerebrospinal fluid

5.8 CRANIOPHARYNGIOMA

The characteristics of the patients diagnosed with craniopharyngiomas are shown in Table 7. There were 21 out of 137 (15.33%) cases of craniopharyngiomas. The median age at diagnosis was 6.9 years. They were predominantly males (61.90%). The median PSI was 210 days (Q1=30; Q3=365). At least 76.19% had an endocrinopathy at diagnosis and in the remainder, it was not indicated in the records. Nine out of the 21 (42.86%) cases were of the adamantinomatous histology. In the remaining 12 (57.14%) patients the histological type was not indicated. All the patients were all treated with multimodal approaches in different combinations with surgical resection, radiation therapy and Omaya reservoir insertion for intralesional interferon administration as shown in Table 7. One patient had intralesional Yttrium. The survival rate at 1 and 5 years were 77.8% and 69.6% respectively. Of the patients with craniopharyngioma who were still being followed up in the clinic five years after diagnosis, eight out of nine had morbidity, mainly endocrine deficiencies, visual impairment and epilepsy.

Table 7. Characteristics of patients with craniopharyngioma n=21

Characteristic		Frequency n (%)
Median age (years)		6.9 (Q1=5.30; Q3=13.36)
Sex	**Male**	13 (61.9%)
	Female	8 (38.1%)
Presenting signs and symptoms		
	Visual disturbances	14 (66.67%)
	Stunted	8 (38.10%)
	Headache	7 (33.33%)
	Vomiting	7 (33.33%)
	Underweight	7 (33.33%)
	Wasted	7 (33.33%)
	Seizures	5 (23.81%)
Median time to presentation (days)		210 (Q1=30; Q3=365)
Endocrinopathies at presentation		
	One axis affected	3 (14.29%)
	More than one axis affected	13 (61.90%)
	Not indicated	5 (23.81%)
Histology	**Adamantinomatous**	9 (42.86%)
	Not indicated	12 (57.14%)
Treatment	**Omaya reservoir**	9 (42.86%)
	CSF diversion	5 (23.81%)
	Radiation, surgery and interferon	4 (19.05%)
	Radiation and surgery	4 (19.05%)
	Radiation and interferon	3 (14.29%)
	Radiation only	2 (9.52%)
	Surgical resection only	2 (9.52%)
	Interferon and surgery	1 (4.76%)
Survival	**1-year survival**	77.8%
	5-year survival	69.6%

Q1 = first interquartile range Q3 = third interquartile range CSF = cerebrospinal fluid

5.9 EPENDYMOMA

The characteristics of the patients with ependymoma are shown in Table 8 below. There were 11 patients diagnosed with ependymoma during the study period and all the files were available for review. The median age at diagnosis was 5.35 years and they were predominantly males (72.73%). The median PSI was 30 days (Q1=14; Q3=30). Six patients had supratentorial ependymal tumours and five were infratentorial. There were no patients with spinal ependymal tumours during the study period. They were all histologically classified as WHO grade II (six out of 11) or anaplastic ependymoma WHO grade III (five out of 11). Ten out of the 11 patients had surgical resection and one patient had biopsy only. Seven patients had adjuvant radiotherapy and the doses ranged from 46.8 to 59.4Gy (focal radiation in four, craniospinal radiation in one patient who had drop metastases of the spine and in two patients the field and dosages were not indicated. Three patients were lost to follow up. The survival rate at 1 and 5 years were 70% and 43% respectively.

Table 8. Characteristics of patients with ependymomas n=11

Characteristic	Frequency n (%)

Median age (years)	5.35 (Q1=2.56; Q3=9.31)
Gender Male	8 (72.73%)
Female	3 (27.27%)
Presenting signs and symptoms	
Hemiparesis	5 (45.45%)
Headache	4 (36.37%)
Visual disturbances	4 (36.37%)
Seizures	4 (36.37%)
Vomiting	3 (27.27%
Median time to presentation (days)	30 (Q1=14; Q3=30)
Location	
Supratentorial	6 (54.55%)
Infratentorial	5 (45.45%)
Spinal	0
Histological grading	
Grade I	0
Grade II	6
Anaplastic ependymoma, grade III	5
Treatment	
CSF diversion	3
Surgical resection only	2
Resection and radiation	6
Surgery and systemic chemotherapy	1
Surgery, chemotherapy and radiation	1
Biopsy only	1
Survival	
1-year survival	70%
5-year survival	43%

Q1 = first interquartile range Q3 = third interquartile range CSF = cerebrospinal fluid

5.10 MANAGEMENT OF PAEDIATRIC CNS TUMOURS

The overall management of the patients with CNS tumours seen during the study period was as shown in Table 11. Cerebrospinal fluid diversion methods for hydrocephalus were done in 27.94% of the patients. More than half of the patients received radiation therapy (54.07%), 55.89% had surgical resection while 50 (37.88%) required chemotherapy.

Table 9. Management of patients with paediatric central nervous system tumours

Management	Frequency	Percentage
CSF diversion		
VP shunt	33	24.26
External ventricular drainage	5	3.68
None/not indicated	99	72.26
Surgery		
Biopsy only	22	16.18
Subtotal resection/debulking	73	53.68
Gross total resection	3	2.21
None	38	27.94
Radiation therapy		
Yes	73	54.07
No	53	39.26
Not indicated	9	6.67
Chemotherapy		
Yes	50	37.88
No	82	62.12
Not indicated	5	3.65

CSF = cerebrospinal fluid VP shunt = ventriculoperitoneal shunt

5.11 OUTCOME

The outcome event was death. Patients without outcome were censored on the date last seen. The following factors were assessed to find out if there was an association with mortality

- Age group
- Sex
- Histological diagnosis
- WHO grade of tumour
- Treatment modality

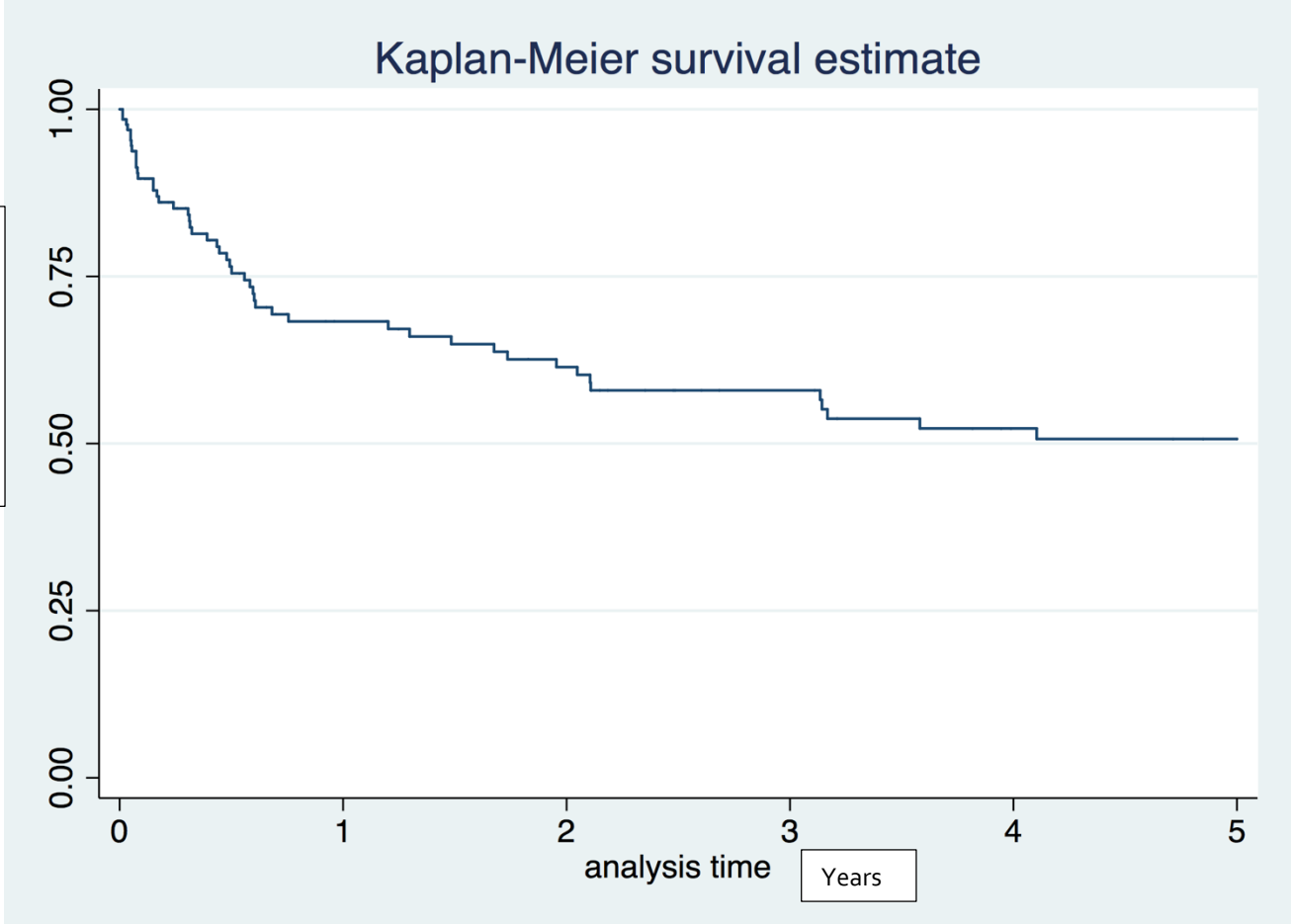
5.11.1 Overall Survival rates

The overall survival rates of all the patients analysed are shown in Table 10. The overall survival at 1 and 5 years was 69% and 51% respectively. Fig 5 shows the Kaplan Meyer survival estimates. The overall survival rates by histological type are indicated in the respective sections.

Table 10. Overall survival rates in paediatric central nervous system tumours n=137

Time	Survival (%)	95% CI (%)	Standard error (%)
1-year	69.36	60.16-76.84	4.25
2-year	62.48	52.62-70.86	4.67
3-year	58.66	48.48-67.50	4.88
4-year	52.72	40.27-60.87	5.21
5-year	51.07	40.27-60.87	5.31

Figure 5. The Kaplan-Meier survival curve for overall survival for children and adolescents diagnosed with CNS tumours at CHBAH, n=137



5.11.2 OTHER CNS TUMOURS

The rest of the CNS tumours were described in a few patients as shown in Figure 3. There were five patients with pineoblastoma. All five had resection of their tumour and three patients received chemotherapy and radiation. At 5 years, three had died and two were lost to follow-up.

Primitive neuroectodermal tumours (PNET) were diagnosed in seven patients. Five of the patients died within 5 years of diagnosis and two were lost to follow up. Both patients with ATRT died within a year of diagnosis. There were two patients with intracranial germinomas, and both are

long term survivors. Two patients with MPNST were lost to follow-up. Four patients had posterior fossa tumours whose histological types were not specified. Three of these patients died within 5 years of diagnosis.

5.11.3 FACTORS ASSOCIATED WITH MORTALITY

The factors which were found to have reduced likelihood of dying in this study were the histological diagnoses of medulloblastoma and craniopharyngioma (p-value= 0.008 and 0.007 respectively). Patients treated with all three modalities surgery, radiotherapy and chemotherapy had reduced likelihood of dying and this was statistically significant (p-value = 0.028). High-grade tumours (WHO grade III and IV) were 2.44 times more likely to die than low-grade tumours and this was statistically significant p=0.013 (Table 11). The other factors such as age, sex and nutrition were not found to be statistically significant. On multivariate analysis, high-grade tumours remained statistically significantly associated with mortality. Patients with medulloblastoma were less likely to be associated with mortality.

Table 11. Factors associated with mortality, univariate analysis

Factor	Hazard ratio	s.e	p-value	95% confidence interval
Gender				
Male	0.72	0.21	0.253	0.41-1.26
Nutrition				
WAZ <-2	1.08	0.39	0.833	0.53-2.18
HAZ <-2	0.63	0.28	0.309	0.26-1.53
Histology type				
Astrocytoma	0.27	0.20	0.078	0.06-1.16
Craniopharyngioma	0.11	0.09	0.008	0.02-0.56*
Medulloblastoma	0.11	0.09	0.007	0.02-0.55*
Ependymoma	0.25	0.21	0.098	0.047-1.294
PNET	0.40	0.34	0.278	0.08-2.09
Pineoblastoma	0.45	0.41	0.383	0.74-2.72
WHO				
Low grade (I and II)	0	0	0	0
High grade (III and IV)	2.44	0.88	0.013	1.21-4.93*
Treatment modality				
Radiotherapy only	0	0	0	0
Surgery only	1.89	1.02	0.237	0.66-5.45
Chemotherapy only	0.64	0.68	0.677	0.08-5.21
Chemotherapy and radiotherapy	0.36	0.38	0.342	0.04-2.95
Surgery and radiation therapy	0.15	0.16	0.077	0.02-1.23
Surgery and chemotherapy	0.33	0.35	0.295	0.04-2.66
Surgery, chemotherapy and radiotherapy	0.22	0.15	0.028	0.06-0.85*

*Statistically significant

PNET = primitive neuroectodermal tumour WHO = World Health Organisation WAZ = weight for age z-score HAZ = height for age z-score

Table 12. Factors associated with mortality, multivariate analysis

Factor	Hazard ratio	s.e	p-value	95% confidence interval
Gender **Male**	0.75	0.28	0.443	0.362-1.560
Age at diagnosis **0-3 years** **3-5 years** **5-10years** **>10years**	 0 1.7 1.73 2.53	 0 1.24 1.26 1.85	 0 0.456 0.447 0.203	 0 0.415-7.069 0.419-7.210 0.605-10.572
Histology type **Astrocytoma** **Craniopharyngioma** **Medulloblastoma** **Ependymoma** **PNET** **Pineoblastoma**	 0.29 0.33 0.073 0.48 1.06 0.33	 0.24 0.37 0.07 0.48 1.12 0.34	 0.143 0.322 0.005 0.463 0.953 0.275	 0.054-1.524 0.037-2.951 0.012-0.462* 0.069-3.381 0.134-8.457 0.741-2.717
WHO grade **Low grade (I and II)** **High grade (III and IV)**	 0 4.18	 0 2.45	 0 0.015	 0 1.325-13.159*
Treatment modality **Surgery, radiotherapy and chemotherapy**	0.085	0.12	0.022	0.010-0.720*

*Statistically significant

WHO = World Health Organisation PNET = primitive neuroectodermal tumour WAZ = weight for age z-score HAZ = height for age z-score

5.11.4 MORBIDITY

Thirty-five patients were documented to be alive 5 years after the diagnosis of CNS tumour. Of these, 26 (74.3%) had some morbidity. Predominantly, the patients had motor deficits followed by a seizure disorder. These are summarised in Table 13 below.

Table 13. Morbidity in survivors of paediatric central nervous system tumours n=35

Morbidity	Frequency n (%)
Motor deficits	13 (37.14)
Seizure disorder	11 (31.43)
Endocrinopathy	8 ((22.86)
Visual impairment	7 (20.00)
Mental and cognitive impairment	7 (20.00)
Short stature	3 (8.57)
Obesity	1 (2.86)
Migraine	1 (2.86)
Other	2 (5.71)

6. DISCUSSION

6.1 EPIDEMIOLOGY

Paediatric CNS tumours are a heterogenous group of tumours that has been found to be the most frequent solid tumours in children and adolescents (2)(5)(33). They constitute about 20 to 25% of all paediatric tumours as described in studies from HIC (2)(5)(34). In our study, CNS tumours were diagnosed in 13.7% of the children with cancer seen over the same period. The prevalence of CNS tumours found at CHBAH over this study period parallels that of the South African paediatric national tumour registry (11). This is lower than the reported rate from HIC (2)(5)(33), but is much higher than those reported from other institutions in LMIC such as India (5.6%), Nigeria (2.5%), Malawi (1.4%) and Kenya (1%) (10)(13)(35)(36). The discrepancy between HIC and LMIC could be partly explained by inconsistent reporting in LMIC, missed cases as some children may die before being diagnosed and inadequate access to proper diagnosis. The lack of coordination between neurosurgeons and paediatric oncologists may also contribute to inaccurate data reporting. Some patients may be seen in the neurosurgical department and not included in the statistics.

There was a slight male preponderance, which is similar to findings from other studies both in HIC and LMIC (8)(16)(17)(25)(36)(13)(27)(37). The male predominance has been partly explained by the disproportionate incidence of medulloblastoma and ependymoma in males. The disproportionate higher frequency of males with medulloblastoma and ependymoma were also demonstrated in our study.

The median age at diagnosis was 7.8 years, was similar to other studies in both HIC and LMIC, (17)(24)(13)(38), including a study done earlier at our hospital for the period 1996 to 2005 (27). In Morocco, where the study population was the same age group as in our study, the mean age was slightly older (9.3 years) (37). Approximately 13% of the children were under three years of age which is a different pattern from Uganda where 29% were less than 2 years of age (17). The differences in median age may be due to the difference in the age limit in different studies at different

institutions with some including children in the whole second decade while some studies only including children up to 14 or 15 years of age.

The HIV seroprevalence in our study was low, 2.92%. There were no other studies identified which reported on the prevalence of children living with HIV who were also diagnosed with CNS tumours. Primary CNS lymphoma has been shown to be an AIDS-defining malignancy in the CNS (39) of which none were present in our study.

6.2 PRE-DIAGNOSIS SYMPTOM INTERVAL

The median duration of symptoms before presentation was 108 days +/-20 days which is delayed compared to the findings by other studies from HIC where they have shown PSI ranging 30 to 60 days (38)(40)(40)(41). There was no delay in diagnosis of the patients once they arrived at the hospital. However, the median duration of symptoms prior to presentation, diagnosis and referral was long. The PSI was shortest in patients with pineoblastoma and longest for craniopharyngioma. Tumour biological factors such as high-grade or presenting complaints such as ataxia, loss of consciousness have been associated with a shorter PSI (42). Other studies have also shown a long PSI to be correlated to tumour histology and age (41). This is similar to our findings where low-grade gliomas had a long PSI compared to high-grade gliomas and other high-grade tumours. Craniopharyngiomas are WHO grade I tumours which may have long periods of other endocrine defects such as growth failure but more likely to present with mainly visual symptoms due to anatomic location of the tumours (43)(44). Accordingly, these tumours tend to have a long PSI. Intracranial GCT have also been shown to have long PSI (32)(42) especially if arising from the suprasellar region and this was similar to our findings (median duration 165 days).

6.3 ANATOMIC LOCATION OF CENTRAL NERVOUS SYSTEM TUMOURS

In our study, supratentorial tumours constituted 50% of all CNS tumours while infratentorial tumours were seen in 41% of the patients. Some studies have shown that infratentorial tumours are commoner in children than supratentorial (8)(25)(27). However, some studies have reported a higher proportion of supratentorial tumours, as observed in our study(17)(41). It has been shown that in the first two years of life, supratentorial tumours predominate whereas infratentorial tumours predominated the rest of the first decade after two years of age. In adolescents, supratentorial tumours start to predominate again (12). This same pattern was demonstrated in our study where infratentorial tumours were predominant (54.5%) in children between two and 10 years of age and supratentorial tumours were predominant in children above 10 years of age (75%). There was an equal proportion of infratentorial and supratentorial CNS tumours in children below two years of age. It could be due to the small numbers of these children in our study.

Primary spinal cord tumours were observed in 8% which is twice that reported by Ezzat at al in a LMIC(24) but almost half of what was described in India by Shirazi et al (36).

6.4 SPECTRUM OF CNS TUMOURS

Astrocytic tumours were the commonest, consistent with studies in both HIC and LMIC, (8)(16)(17)(24)(25)(13)(27). However, pilocytic astrocytomas were less frequently observed in our study compared to findings from other studies(16)(24)(25)(38)(45)(34). This may be due low referral to our unit from the neurosurgical department and primary care level centres.

The order in frequency of other histological types vary between countries and institutions but the other common tumours were medulloblastoma, ependymoma, craniopharyngioma and PNET (8)(17)(24)(13)(27). Embryonal tumours (with medulloblastoma being the predominant type) are the second commonest tumours in many studies both in HIC and LMIC similar to our study

(24)(25)(13)(38). Craniopharyngiomas were the third commonest and contributed about 15% of all CNS tumours in our study which is slightly higher than other reported rates (24)(13). This may be due to high referral in this tumour with multiple comorbidities which need multidisciplinary management.

Ependymomas have also been found to be fairly common by studies from both HIC and LMIC as was found in our study, being the fourth commonest CNS tumour (24)(25)(13)(38)(45).

Less common tumours found in this study were choroid plexus tumours, intracranial germ cell tumours, atypical teratoid rhabdoid tumours and neuronal glial tumours as shown by other studies (24)(25)(38)(41). Intracranial germ cell tumours are reported to be rare, with geographical variation being more common in Japan and Asian countries (3)(31)(46).

There was histological confirmation in 71.5% of the cases. This is comparable to the studies from Japan (75.7%), France (86%), the Middle East (80.2%) but higher than Sudan (60%) (3)(8)(24)(45). Histological confirmation of CNS tumours may be a challenge in LMIC where the experts (neurosurgeons and pathologists), infrastructure and diagnostic capabilities may be limited.

Astrocytoma

As described above, astrocytic tumours constituted the majority of CNS tumours in our study in keeping with findings from other studies (8)(16)(24)(25). The low-grade gliomas were 34% of all the astrocytic tumours seen during this period. There were only three patients with confirmed pilocytic astrocytoma which is very low compared to what is expected and what has been shown by other studies(16)(24)(25)(34)(47). The low frequency of pilocytic astrocytomas may be due to a low referral to the paediatric oncology unit at the hospital or missed diagnosis from the referring institutions. The low-grade gliomas were more likely to have a long PSI. None of the tumours had molecular subtyping due to the unavailability of diagnostic capacity.

Most of the patients were treated with multimodal therapy consisting of debulking surgical resection, chemotherapy and radiotherapy as indicated. Patients with low-grade tumours were more likely to survive than those with high-grade tumours as will be discussed below.

Medulloblastoma

Medulloblastomas are the commonest embryonal tumours in childhood (13)(25)(38) with a male predominance (12)(48). This is similar to our findings with a male to female ratio of 1.2:1. Medulloblastoma is stratified into standard or high-risk using the modified Chang criteria (49) which is based on the age of the patient at diagnosis, the extent of resection, histological subtype, extent of the nervous system and extraneural spread. The majority were treated with the multimodal treatment approach of debulking surgery, chemotherapy and radiation therapy.

Craniopharyngioma

Craniopharyngioma was the second commonest CNS tumour (15.3%) in our study which is slightly higher than what was found by others in LMIC (24)(25)(50). The craniopharyngiomas were mainly the adamantinomatous histological subtype in nine of the 15. In the remaining six patients, the histology results were not documented. However, almost all paediatric cases are adamantinomatous(50) and the papillary type is found in adults. The majority (76%) of patients with craniopharyngioma had an endocrinopathy at diagnosis and it has been shown that at least 40-87% have at least one hormonal deficit at the time of diagnosis (43).

Ependymoma

Ependymoma has been described as the third commonest paediatric CNS . In our study, we found it to be the fourth commonest brain tumour. There is little variation to findings from other studies (13)(25)(37)(38). In our study, ependymal tumours had a male predominance, consistent with what has been documented in the literature (12)(51). Ependymomas were almost equally distributed between infratentorial and supratentorial regions. In literature it is reported that about two-thirds of

ependymomas occur in the infratentorial region (12). This pattern was not shown in our study and could be due to small numbers of patients with ependymal tumours. There were almost equal numbers of WHO histological grade II and the grade III anaplastic ependymoma. The distinction between histological grade II and III is subjective with poor correlation to prognosis (51).

6.5 MANAGEMENT

The majority of the children received multimodal treatment consisting of surgical resection, radiotherapy and/or chemotherapy. Gross total resection (GTR) was achieved in three (2.2%) and subtotal resection (STR) in 53.7% of children with brain tumours. This is low compared to other studies from Nigeria, where GTR was done in 51.9% and STR in 48.1% (52) and Sudan GTR and STR were done in 21% and 54% of the patients, respectively (8). In Uganda, some patients were re-operated to complete tumour debulking (17). However, these studies were done in the neurosurgical department and likely to capture all those operated and more accurately record extent of tumour resection. Seventy-three of 126 patients (57.94%) who needed adjuvant radiotherapy received the radiotherapy. This is similar to studies from other LMIC, Sudan 38% (8), Nigeria 27.5% (52) and Uganda (17).

Sixteen (32%) of children with astrocytoma received no treatment at all and most of these died due to disease progression before treatment could be commenced.

6.6 OUTCOME

6.6.1 Survival rates

The 1-year 5-year overall survival rates for the study participants were 69% and 51% respectively. This is higher than the findings from the previous decade (5-year survival rate 37.5%) which was done at CHBAH and CMJAH(27). The OS is lower than what has been reported by studies from HIC where survival rates in childhood CNS tumours are above 70% (45)(53). Other LMIC have shown variable survival rates: Uganda, 5-year survival rate of 60% (17), Nigeria 1-year survival rate 55.6% (52) and at another institution in Nigeria survival at 1 and 5 years was 56% and 47% respectively(16).

Overall survival rates were very low in Sudan, 2-year and 5-year survival rates of 33% and 13% respectively (8).

Generally, worldwide the trend has been an increase in survival in children with CNS tumours(53). The lower survival rates in LMIC may be due to inadequate healthcare infrastructure and personnel as well as late diagnosis. As shown in this study, there was a long overall PSI. High treatment abandonment has been shown in a number of studies from LMIC and is also illustrated in this study by a high lost to follow up rate (8). This contributes to lower survival rates in LMIC. Lack of and delayed adjuvant radiotherapy may also contribute to low survival rates in these settings.

The 1 and 5-year OS rates for medulloblastoma were 83% and 69% respectively which is comparable to findings by Rutokwski et al who showed an 8 year overall survival rate of 76% in 5 HIC (France, Germany, Italy, United Kingdom and the United States) treated with national study protocols (54).

The deaths after the first year of diagnosis were attributed to spinal drop metastasis which occurred at relapse. Four out of 14 patients who met the definition of high-risk was treated with standard-risk dose of craniospinal radiation 23.4Gy and a boost to 54Gy instead of CSI dose of 36Gy. Information regarding the timing of radiation was not collected in this study but adjuvant radiotherapy must be done within 3 to 4 weeks after surgery to optimise outcome (51). There was no molecular subtyping in these tumours. Some molecular features are associated with poor prognosis e.g. group 3 tumours (47).

The 1-year survival rate for patients with ependymoma was 70% and 43% at 5 years. The rapid decline in survival at 5 years is mainly due to relapse. Ependymoma usually does not have leptomeningeal metastasis at diagnosis but when they relapse. One of the most important determinants of prognosis is the extent of surgical resection (55)(56) and early adjuvant radiotherapy within four weeks of surgery (56) and this is especially true for posterior fossa ependymoma. The aim of surgical resection is at maximal safe gross total resection. However, in our study, many patients had significant residual tumour as determined by post-operative imaging. There was also delay in getting radiation

therapy. The survival in ependymal tumours is lower than what has been described in the USA where 5-year and 10-year survival rates are 83.4% and 79.1% respectively (2). There was no molecular subtyping in these patients, and it has been shown that 1q gain and RELA fusion are associated with poor prognosis whereas YAP1 fusion is associated with an excellent prognosis (51).

Craniopharyngiomas are benign tumours with high survival rate as illustrated in our study and in literature. Nonetheless, they have a high level of impaired function due to tumour and treatment-related factors resulting in visual impairment and endocrine effects (42).

6.6.2 Factors associated with mortality

The factors which were found to have reduced likelihood of dying by univariate regression in this study were the histological diagnoses of medulloblastoma and craniopharyngioma (p-value= 0.008 and 0.007 respectively) and multimodality treatment (p-value=0.028). surgical resection and radio-therapy as combined treatment was also less likely to be associated with dying although it was not statistically significant (p-value = 0.077). However, medulloblastoma and multimodality treatment persisted as factors less likely associated with dying on multivariate analysis (p-value = 0.022). Me-dulloblastoma has been shown to have high survival rates in the USA with up to 76% 8-year overall survival rate (54) which is comparable to our findings although our analysis was limited to 5-year survival. It was beyond the scope of this study to determine the extent of resection as defined by modified Chang criteria (49) as the information was not documented in most of the patient records. Molecular subtyping was not being offered at our unit at the time, hence we were not able to define the molecular subtypes.

High-grade tumours (WHO grade III and IV) were 2.44 times more likely to die than low-grade tumours and this was statistically significant p=0.013. High-grade tumours are more aggressive and also may be inoperable due to anatomic location. The HGG are associated with high mortality with a 2-year survival less than 10% (12). The treatment plan is usually palliative in most cases. Patients with BMI below -2z and those aged 3-5 years were 1.7 times more likely to die although this was not

statistically significant. Craniopharyngiomas are low-grade tumours, WHO grade I with high overall survival rates but have significant morbidity and impact on quality of life (50).

6.7 MORBIDITY

Paediatric CNS tumours are associated with high morbidity due to the disease and its effects and the treatment toxicity. In our study, about 26 out of 35 (74%) were alive with morbidity. These included endocrine abnormalities, motor disturbances, seizure disorder, mental and cognitive impairment, visual disorders, blindness and obesity. Although these were not further explored, they cause a significant impact on the quality of life among the survivors. A study in Nigeria showed that about 55.6% were at least independent at I year (52). Significant morbidity has also been shown among patients with craniopharyngioma (44)(50).

7. STUDY LIMITATIONS

Our study was retrospective and there was some data missing for some variables making analysis limited. Some files could not be found, resulting in exclusion of these patients which might have introduced bias. Some tumours were not graded histologically, which makes analysis inaccurate. There may be under-reporting as some patients may not have been referred from the neurosurgeons, who are usually the first to see patients with paediatric CNS tumours. There was a high loss to follow up rate, affecting outcome analysis.

8. CONCLUSIONS

Our study shows that the spectrum and characteristics of paediatric CNS tumours at the paediatric oncology unit at CHBAH are generally similar to those reported in the literature, with only minor differences. There was a male predominance in primary paediatric CNS tumours. Overall survival rates at 1 and 5 years are less than survival rates in HIC but comparable and higher than other LMIC. Morbidity from paediatric CNS tumours at CHBAH paediatric oncology unit is very high and there is a high loss to follow-up rate. Recently, there have been developments in the diagnostic capacity of our laboratory with molecular subtyping of medulloblastoma. This will assist in risk stratification of medulloblastoma, with prognostic and treatment implications.

Documentation of patient records is good, as the records were very informative. However, not all the files are easily accessible.

9. RECOMMENDATIONS

Based on our findings, follow-up of patients' needs to be intensified in order to reduce the number of loss to follow-up and document outcomes more accurately. There should be campaigns to increase awareness in community about signs and symptoms of CNS tumours to enable early presentation. There should be regular education and in-service training of healthcare workers to improve early referral, improved access to radiation, strengthen multidisciplinary teams in the management of these patients such as occupational therapy, physiotherapy, speech, child psychologist, social worker and palliative care specialists to ensure the best outcome possible. In an effort to improve the care of the children with CNS tumours at our hospital, we have started having regular multidisciplinary team meetings consisting of paediatric oncologists, neurosurgeons, radiologists, social workers, occupational therapists and physiotherapists.

There is need for a follow-up prospective study to document the findings, with attempts to accurately describe histological types and molecular subtypes where possible so as to further risk stratify and manage appropriately. We recommend that a national prospective study be performed in order to have a broader perspective. Record keeping needs to be upgraded to electronic with back-up, to facilitate research.

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11. APPENDICES

11.1 APPENDIX 1: WHO CLASSIFICATION OF TUMOURS OF THE CNS 2016

WHO classification of tumours of the central nervous system

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Melanotic schwannoma	9560/1
Neurofibroma	9540/0
Atypical neurofibroma	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Hybrid nerve sheath tumours	
Malignant peripheral nerve sheath tumour	9540/3
Epithelioid MPNST	9540/3
MPNST with perineurial differentiation	9540/3
Meningiomas	
Meningioma	9530/0
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0
Angiomatous meningioma	9534/0
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma**	
Grade 1	8815/0
Grade 2	8815/1
Grade 3	8815/3
Haemangioblastoma	9161/1
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma / PNET	9364/3
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Desmoid-type fibromatosis	8821/1
Myofibroblastoma	8825/0
Inflammatory myofibroblastic tumour	8825/1
Benign fibrous histiocytoma	8830/0
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma	8802/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteochondroma	9210/0
Osteosarcoma	9180/3
Melanocytic tumours	
Meningeal melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Meningeal melanoma	8720/3
Meningeal melanomatosis	8728/3
Lymphomas	
Diffuse large B-cell lymphoma of the CNS	9680/3
Immunodeficiency-associated CNS lymphomas	
AIDS-related diffuse large B-cell lymphoma	
EBV-positive diffuse large B-cell lymphoma, NOS	
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Low-grade B-cell lymphomas of the CNS	
T-cell and NK/T-cell lymphomas of the CNS	
Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9702/3
MALT lymphoma of the dura	9699/3
Histiocytic tumours	
Langerhans cell histiocytosis	9751/3
Erdheim–Chester disease	9750/1
Rosai–Dorfman disease	
Juvenile xanthogranuloma	
Histiocytic sarcoma	9755/3
Germ cell tumours	
Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumour	9085/3
Tumours of the sellar region	
Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1
Granular cell tumour of the sellar region	9582/0
Pituicytoma	9432/1
Spindle cell oncocytoma	8290/0
Metastatic tumours	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [742A]. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.
*These new codes were approved by the IARC/WHO Committee for ICD-O.
Italics: Provisional tumour entities. **Grading according to the 2013 *WHO Classification of Tumours of Soft Tissue and Bone.*

11.2 APPENDIX 2: GRADING OF SELECTED CNS TUMOURS ACCORDING TO THE 2016

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3K27M-mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q co-deleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, RELA fusion-positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Choroid glioma of the third ventricle	II
Choroid plexus tumours	
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III
Neuronal and mixed neuronal-glial tumours	
Dyseembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum	I
Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Central neurocytoma	II
Extra ventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Tumours of the pineal region	
Pineocytoma	I
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III

Embryonal tumours	
Medulloblastoma (all subtypes)	IV
Embryonal tumour with multi-layered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour , NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV
Tumours of the cranial and paraspinal nerves	
Schwannoma	I
Neurofibroma	I
Perineuroma	I
Malignant peripheral nerve sheath tumour (MPNST)	II, III or IV
Meningiomas	
Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I
Tumours of the sellar region	
Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

11.3 APPENDIX 3: DATA COLLECTION TOOL

Study number	
1. Date of birth (age)	
2. Date of presentation (age at presentation)	
3. Sex	
4. Residence	
5. HIV status	1. uninfected 2. infected 3. unknown
6. Anthropometry	Weight (kg) WAZ Height (cm) HAZ BMI z-score
7. Date of diagnosis (age at diagnosis)	
8. Histological diagnosis	
9. Clinical stage	
10. WHO grade	
11. Presenting complaint	Headache

	Vomiting Paraparesis Hemiparesis Convulsions
12. Duration of symptoms 13. Imaging modality	 CT scan MRI
14. CSF studies	1. negative 2. positive 3. not done 4 N/A
15. Chemotherapy protocol	1. 2. N/A
16. Surgical intervention	1. Biopsy only 2. Resection/debulking 3. Total resection 4. None

17. CSF diversion	1. VP shunt 2. ETV 3. EDV 4. None 5. not indicated
18. Post op imaging	1. CTS 2. MRI 3. None 4. N/A
19. If imaging done, residual tumour	1.Yes 2.No 3.N/A
20. Radiation	1. Yes 2. No 3. N/A
21. If yes,	1. Field 2. Dosage
22. Date of completion of treatment	
23. Date last seen	
	1. Alive

24. Outcome at 5 years	2. Deceased 3. Lost to follow up
25. Cause of death	1. Refusal of treatment 2. Disease progression 3. Chemotherapy related

11.4 APPENDIX 4: HUMAN RESEARCH ETHICS COMMITTEE APPROVAL