# PAEDIATRIC BRAIN TUMOURS: THE UNIVERSITY OF CAPE TOWN EXPERIENCE FROM 1996-2017

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## DECLARATION

I, Christel Arnold-Day, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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## DEDICATION

To my husband, children, parents and family for their never ending support, encouragement, sacrifices and love.

## ACKNOWLEDGEMENTS

I would like to thank and acknowledge the assistance, guidance and support I received from my supervisor, Professor A Figaji, Head of Paediatric Neurosurgery at Red Cross Children's Hospital. You are an inspiration Prof!

I would also like to thank and acknowledge the following people for their substantial contributions to this MMED project, without their help and support this project would not have happened:

- Professor A Davidson from the Department of Paediatric Oncology at Red Cross Children's hospital for allowing me access and use of his database as well as for his advice and input.
- Dr J Riedemann from the Department of Radiation Oncology at Groote Schuur Hospital for allowing me access to his database on Paediatric Medulloblastomas.
- Prof Parkes and Dr Naicker from the Department of Radiation Oncology at Groote Schuur Hospital, thank you for your support, encouragement and advice.
- Prof Pillay, Head of the Department of Histopathology, for allowing me access to the Histopathology records and results.
- Dr U Rohlwink for her constant guidance on thesis preparation.
- My research assistants, Mr Samuel Lubega, Ms Dumsile Maduna, Mr Dada Temilola, Mr Javan Okendo and Ms Akiko Suzuki, without your dedication and hard work this project would never have seen its end. Thank you!

I would also like to thank the University of Cape Town as well as Groote Schuur and Red Cross Children's Hospitals for granting me permission to use patients' records to complete this research project.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ATRT | Atypical Teratoid Rhabdoid Tumours |
| BBB | Blood Brain Barrier |
| CNS | Central Nervous System |
| CT | Computed Tomography |
| DIPG | Diffuse Infiltrating Pontine Glioma |
| EC | Eastern Cape |
| GBM | Glioblastoma Multiforme |
| GSH | Groote Schuur Hospital |
| HIC | High-income Countries |
| ICP | Intracranial Pressure |
| JPA | Juvenile Pilocytic Astrocytoma |
| LGG | Low Grade Glioma |
| LMIC | Low- and Middle-Income Countries |
| LP | Lumbar Puncture |
| MRI | Magnetic Resonance Imaging |
| PET | Positron Emission Tomography |
| PNET | Primitive Neuroectodermal Tumour |
| PBT | Paediatric Brain Tumour |
| RCCH | Red Cross Children's Hospital |
| RSA | Republic of South Africa |
| SEGA | Subependymal Giant Cell Astrocytomas |
| USA | United States of America |
| WC | Western Cape |
| WHO | World Health Organization |

## DEFINITION OF TERMS

**Adjuvant treatment**: Therapy that is given in addition to the primary planned treatment, usually refers to surgery followed by chemo- and / or radiotherapy.

**Craniospinal radiation**: Whole brain and spinal cord radiation therapy, also referred to as craniospinal radiation, is often a radiotherapy technique used in more malignant CNS tumours (e.g. medulloblastomas) to help reduce the chances of tumour spread. It often results in more adverse effects than local radiation and is therefore avoided in children age 3 and under.

**Degree of resection:** Referring to the amount of tumour that a surgeon is able to remove at surgery.

**Diencephalic syndrome:** A syndrome that develops in patients where damage to the hypothalamus may lead to clinical manifestations such as weight loss, inability to regulate body temperature or heart rate.

**Dissemination:** Tumour spread beyond the primary site.

**Grade of tumour:** The description of a tumour based on how abnormal the tumour cells and the tumour tissue look under a microscope. It may be an indicator of the aggressiveness of the tumour, how fast it is likely to grow and it's tendency to spread and invade surrounding tissues.

**Hydrocephalus:** A pathological condition in which there is abnormal accumulation of cerebrospinal fluid (CSF) that may lead to enlargement of the ventricular system in the brain and may be caused by many disease processes.

**Immunohistochemical analysis:** A method for demonstrating the presence and location of proteins in tissue sections.

**Molecular-targeted therapy:** Therapy that targets very specific molecular biochemical pathways in cell cycles that causes tumour growth.

**Multicentred studies:** Research studies where multiple hospitals agree to treat children similarly, to pool research data. These are often run by co-operative groups.

**Neurofibromatosis type 1 (NF1):** A genetic disorder that is characterized by neurocutaneous abnormalities, including café-au-lait spots, skeletal dysplasias, and growth of benign and malignant nervous system tumours.

**Nystagmus:** Abnormal involuntary eye movements where the eyes move rapidly up and down (vertical nystagmus) or from side to side (horizontal nystagmus).

**Parinaud's syndrome:** A syndrome that is clustered by abnormalities of eye movement and pupil dysfunction. The clinical manifestation usually presents as an inability to look upward, and pupils which do not react well to light but react better to accommodation.

**Pineal region:** An area behind the upper part of the brainstem. Tumours in this area may result in Parinaud's syndrome, blockage with cerebrospinal fluid flow and signs of increased intracranial pressure.

**Posterior fossa:** A small space in the skull that contains the brainstem, cerebellum and fourth ventricle. It is a common location for brain tumours to develop, especially in the paediatric population. Tumours in this area of the brain often cause headaches, vomiting, imbalance, motor impairment and cranial nerve deficits.

**Suprasellar region:** An area behind the eyes, near the hormonal centre of the brain that includes the pituitary gland, thalamus and hypothalamus. Tumours here often present with visual disturbances as well as hormonal imbalances.

**Tuberous Sclerosis Complex (TSC):** A rare genetic disease that affects multiple systems and is caused by defects in the TSC genes that causes benign tumours to grow in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin. It usually affects the central nervous system and patients may present with a multitude of symptoms including seizures, developmental delay, behavioural problems, skin abnormalities, and kidney disease.

## ABSTRACT

### *INTRODUCTION*

Brain tumours are the second most common malignancy in children[1] [2], and despite some advancements being made over the last 2 decades, patient outcomes in general remain poor when compared with other childhood cancers. Optimal treatment of children with brain tumours is challenging and expertise and resources are not widely available in South Africa. This is important because the outcomes of children with brain tumours depend critically on the expertise and resources of a multidisciplinary team tasked with their treatment. Despite the importance of paediatric brain tumours though, little is known about childhood brain tumours in South Africa as limited data have been published and there have been no funded studies to support research in this area. In addition, we know very little about the resources available across the country to treat these children. In international centres of excellence the best outcomes are achieved by combining good epidemiological data, strong multidisciplinary teams, centralization or regionalization of services, available resources, and a research foundation. To start, we need to know more about the patients presenting to us with brain tumours.

### *PURPOSE*

The **overall aim** of this project was to collect epidemiological data for childhood brain tumours at a tertiary paediatric hospital in South Africa with a dedicated multidisciplinary team.

### *METHODS*

**Study design:** A retrospective review of records of patients diagnosed with a primary brain tumour and who presented to Red Cross Children's Hospital (RCCH) system from 1 January 1996 to 31 December 2017.

**Patient selection & data collection:** Patients were identified by combining databases and admission logs from paediatric neurosurgery, oncology, radiotherapy, histopathology and radiology. Data collected included: age at diagnosis, sex, province of referral, tumour site and diagnosis.

## *RESULTS*

A total of 554 paediatric patients with primary brain tumours were identified over the study period. Tumours were more common among males (55.4%) and were located in the supratentorial compartment in 52%. The median age at diagnosis was 5.92 years. The commonest tumours were astrocytomas (n=114 patients; 20.3%), followed by medulloblastomas (incl. PNETs) (n=107 patients; 19.1%), and craniopharyngiomas (n=55; 9.8%). As expected, most patients referred and seen at RCCH/GSH were from the expected drainage area in the Western Cape (73%), but a significant number of referrals (27%) were from outside the province referrals, especially in the last 10 years.

## *CONCLUSION*

Our findings were largely consistent with the published literature in terms of histological diagnosis, sex profile and age ranges for children diagnosed with brain tumours with some small differences possibly related to referral bias. More patients than expected were referred from outside of the province, which emphasizes the need for establishing an ongoing tumour database registry and co-ordinating patient care across institutions.

A follow-up study to assess patient management and outcomes is of critical importance to assess resource availability and patient outcomes.

# CHAPTER ONE

## *INTRODUCTION AND AIMS*

Brain tumours are the second most common malignancy in children[1, 2], and despite some progress being made over the last 2 decades, patient outcomes in general remain poor when compared with other childhood cancers. Optimal treatment of children with brain tumours is challenging and expertise and resources are not widely available in South Africa. This is important because the outcomes of children with brain tumours depend critically on the expertise and resources of a multidisciplinary team tasked with their treatment. Despite the importance of paediatric brain tumours (PBTs) though, little is known about childhood brain tumours in South Africa as limited data have been published, no data registry for childhood brain tumours exist in South Africa and there have been no funded studies to support research in this area. In addition, we know little about the resources available across the country to treat these children. In international centres of excellence the best outcomes are achieved by combining good epidemiological data, strong multidisciplinary teams, centralization or regionalization of services, available resources, and a research foundation. An important first step in that direction is to collect local epidemiological data.

The **overall aim** was to collect epidemiological data for PBTs at a tertiary paediatric hospital complex with a dedicated multidisciplinary team.

The **study objective** of this project was to collect data on children with brain tumours at a regional centre in South Africa (primarily based at Red Cross War Memorial Children's Hospital, affiliated to the University of Cape Town). The epidemiological data generated in this MMED will support a second study to assess treatment modalities and outcome data for these patients. The ultimate aim is to develop further capacity for infrastructure and research in paediatric brain tumour research and management.

## *INFRASTRUCTURE*

At Red Cross Children's Hospital (RCCH) there is a multidisciplinary team involved in the management of children with brain tumours, supported also by services at Groote Schuur Hospital (GSH). The team comprises specialists in paediatric imaging, anaesthesia, intensive care, neurosurgery, oncology, radiotherapy, endocrine, neuropathology, neuropsychological and neurorehabilitation services. There is a multidisciplinary clinic that follows these children for many years after diagnosis and management.

It is our responsibility to collect, audit, review and report our data regularly to assess trends in PBTs. We then also need to document the different treatment modalities used, and how this correlates to patient survival and functional outcomes. This is however outside the scope of this MMED project but is already planned as part of a follow-up study. The aim of this study was to focus on the presentation of patients to our unit.

## CHAPTER TWO

## *LITERATURE REVIEW AND INTRODUCTION TO PAEDIATRIC BRAIN TUMOURS*

A broad but summarised overview of paediatric brain tumours (PBTs) will be discussed under the following headings:

- Overall epidemiology
- Presentation
- Diagnosis
- Treatment modalities
- Most common paediatric brain tumours (summarised in table format)
    - Frequency
    - Diagnosis & Histology
    - Management
    - Prognosis

This will allow for simple reference and comparison to the study's findings, followed by discussion in chapter 5.

### *EPIDEMIOLOGY*

Brain tumours are by far the most common solid organ malignancy in children and the second most common cause of paediatric cancer overall. From data of children in the USA, leukaemias account for 30% of paediatric cancers and brain tumours 22.3%[(1)]. The most common solid organ malignancy in children after brain tumours is neuroblastoma at 7.3%. About 3750 new cases of childhood brain tumours are diagnosed in the USA annually and worldwide approximately 30,000 to 40,000 annually[(3)]. The average incidence of childhood brain tumours in the USA is 4.5/100,000 children, with a prevalence rate of 9.5/100,000[(1)].

Brain tumours occur with a comparatively similar incidence across different regions, with reports from developed countries estimates in children aged 0-15 years of 35.9 cases per million children in Sweden, 36.1 in Japan, 32.7 in Yorkshire, UK, 29.9 in a survey of 59 European cancer registries (with a regional rates up to 43.8), and 47.1 in the USA[4].

Data from low- and middle-income countries though, are limited. Of the estimated 250 000 children in whom cancer is diagnosed every year world-wide, approximately 200 000 live in countries with limited resources. In Africa, approximately 50 000 new cases of childhood cancer are diagnosed every year. The reported frequencies at which different types of cancers occur differ between high-income countries (HICs) and low- and middle-income countries (LMICs). Indeed, income-based variations have been observed even within the same country[5]. In India, where there is also an absence of a comprehensive population-based registry, they report an incidence of PBTs that ranges from 0-2.11%[6].

If the incidence in South Africa is estimated from international figures, we would expect at least 500 new cases annually if adjusted for population size, and possibly more given the greater proportion of children in our population. The only published data in peer reviewed literature that we could find to date reflect findings from 20-30 years ago: Peacock et al[2] reported 145 children under the age of 14 years who presented between 1979 and 1985. Hesseling et al[8] reported 100 children with brain tumours nested within 492 children with all forms of cancer diagnosed between 1983 and 1993. Unpublished data from the Johannesburg area of 252 patients between 1995 and 2005 reported a much lower overall 5-year survival than described in the international literature[9]. Of those for whom there was follow-up, half died, 20% were alive, and 30% were presumed to be alive. However, there was a very high 50% loss to follow up that suggests actual mortality might be substantially higher.

Data from studies in LMIC are fraught with difficulties and tend to be skewed by late presentations (or non-presentation), suboptimal or inadequate management, and high rates of loss to follow-up, while incidence in HIC is

higher due to several factors, including the increasing numbers of incidentally diagnosed tumours from imaging obtained for other reasons. For several multifactorial reasons, intracranial tumours in children are less likely to be diagnosed in an African setting, presumably because of a failure to present or due to lack of diagnostic imaging. In a Nigerian study, intracranial tumours accounted for only 2.2% of all diagnosed childhood cancers in a series of 1325[10] and in a Ghanaian study, they accounted for a mere 5% in a series of 375 children[11]. A Namibian series reported a proportion closer to that seen in HICs (19%), but found a population incidence of only 9.3 per million, far lower than that reported in those countries[12].

Another challenge in determining and comparing data for this population of patients is that there is such heterogeneity in not only the terms “paediatric brain tumour”, but also in categorised age groups, diagnostic criteria, treatment modalities available, outcome measures as well as the major changes that has occurred in all the before mentioned terms over the past nearly 3 decades. The most significant of which must include the histopathological, immunohistochemical and molecular subtype advancements that have all undergone significant changes and advancements. The WHO classification on PBTs has been extensively revised from its first edition in 1979 to its latest and 4th revised edition in 2016, to keep up with the evolution and growth of knowledge in this field.

***Table 1*** below is adapted from a recently published paper in the journal of Child's Nervous System by Elhassan et al[3] from Sudan illustrating comparisons between various series published from African countries over the last 5 decades on epidemiological finding of childhood brain tumours.

***TABLE 1: Comparison of common paediatric brain tumours between various series from different African countries[3]***

| Country | Years of study | n | Mean age (years) | Age Ranges (years) | M:F | ST | IT | AST | MED | EPD | CPG |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Sudan** | 2000-2015 | 62 | 8.8 | 0-15 | 1.38 | 34 | 58 | 52 | 18 | 3 | 1.6 |
| **Nigeria** | 1960-1982 | 89 | NA | 0-15 | 2.0 | 53 | 47 | 51.1 | 17.6 | 5.9 | 11.9 |
| **South Africa** | 1979-1985 | 145 | NA | 0-14 | 1.16 | 47 | 53 | 24.8 | 26.2 | 10.3 | 8 |
| **Nigeria** | 1980-1990 | 75 | NA | 0-14 | 0.75 | NA | NA | 40 | 10 | NA | 16 |
| **Tunisia** | 1990-2004 | 492 | 8 (median) | 0-16 | 1.01 | 50.2 | 49.8 | 38 | 16.2 | 6.9 | 5.3 |
| **Morocco** | 2003-2007 | 542 | 9.3 | 0-19 | 1.08 | NA | NA | 31.6 | 28.9 | 10.3 | 6.6 |
| **Egypt** | 2005-2008 | 451 | NA | 0-14 | 1.06 | 46.6 | 49.7 | 35 | 18.8 | 10 | 11.3 |
| **Morocco** | 1991-2009 | 633 | 8.36 | 0-15 | 1.22 | 47 | 48 | 23.1 | 22.9 | 10.4 | 9 |
| **Uganda** | 2002-2012 | 172 | 6.5 | 0-19 | 1.4 | 62.2 | 37.8 | 32.8 | 8.1 | 16.3 | 9.9 |
| **Nigeria** | 1994-2006 | 40 | 9.75 | 1-15 | 1.2 | 40 | 60 | 25 | 25 | 2.5 | 12.5 |

n: number of patients / M:F Male:Female / ST: Supratentorial / IT: Infratentorial / AST: Astrocytoma / MED: Medulloblastoma / EPD: Epedymoma / CPG: Craniopharyngioma

Improvements in the therapeutic regimens and survival outcomes of children with leukaemia and other childhood cancers, have resulted in brain tumours being the leading cause of paediatric cancer-related deaths, as well as the tumour-type resulting in the greatest physical, neuro-cognitive and psychosocial morbidity[7]. Despite the clear importance then of this topic, it is surprising that there are such limited published epidemiological or outcome data for childhood brain tumours in South Africa, or for the resources available to treat affected children. Neither has there been any funded research on paediatric brain tumours in South Africa to our knowledge. Due to the lack of a national or even regional brain tumour data registry, we know little about the incidence and spectrum of paediatric brain tumours in South Africa, their presentation, means by which they are treated, the outcome of affected children, and how these patterns may have changed over time.

***PRESENTATION***

Awareness of PBTs in the public sphere in South Africa is low, particularly when contrasted with the successes of campaigns for childhood leukaemia. Because there is little co-ordination of health services for children with brain tumours, with wide variation existing between institutions in terms of expertise and resources, children are often treated inadequately. In desperation, and sometimes perhaps in ignorance of services available locally, parents may even resort to treatment outside the country and continent, occasionally even to extreme and unproven methods.

Primary and secondary level clinicians involved in the initial diagnosis are often poorly informed, and the diagnosis can be difficult. Most brain tumours often present in a non-specific manner, with vague symptoms associated with raised intracranial pressure (ICP) or developmental delay or regression. Delays in diagnosis are therefore common, as are inappropriate and potentially dangerous interventions such as lumbar punctures before imaging is obtained. Amongst clinicians involved in the definitive treatment of children with brain tumours, expertise and experience vary, as do resources available to achieve optimal outcomes. Currently, there are no local protocols or consensus

agreements on how best to manage childhood brain tumours on a national level.

Children with brain tumours may present in a variety of different ways and at different ages with the clinical presentation typifying the complexity of the pathology itself. PBTs may produce symptoms based on their location, size, and subsequent raised ICP caused by brain shift and/or hydrocephalus [7].
The tumour may cause direct neurological damage resulting in specific clinical localising signs and neurological deficits. Typically midline and infratentorial tumours often present with hydrocephalus as obstruction to CSF flow tends to occur earlier compared to tumours in other locations . Symptoms are often non-specific and may include headaches, vomiting, seizures, visual disturbances and lethargy. Although other causes of headaches in children are more common, a change in headache pattern, an acute onset, or association with vomiting are warning signs[7].

Posterior fossa tumours may often present not only with headaches and vomiting, but also with clinical features of cerebellar and / or cranial nerve and brainstem dysfunction, including imbalance, ataxia, cranial nerve palsies and bulbar dysfunction. Tumours in the suprasellar region often present with visual disturbances and/or endocrinopathies. Pineal region tumours usually present with hydrocephalus or Parinaud's syndrome which includes a clinical syndrome of abnormal eye movements, pupils which do not react well to light but react better to accommodation, and a downward gaze palsy[7].

Early diagnosis is often challenging, especially in infants and young children. For infants, a delay or regression in developmental milestones can be an early symptom of a brain tumour, particularly for those with sizable, midline low-grade tumours. Clinical signs may be subtle and often missed as visual changes are notoriously difficult to diagnose in infants and the presence of headaches difficult to establish at a young age. An abnormal increase in head circumference is often easier to pick up by serial measurements in head circumference and may indicate the presence of hydrocephalus. Hypothalamic / optic pathway tumours may present with features of diencephalic syndrome

often manifested by weight loss despite adequate diet or difficulty regulating body temperature. The euphoric elements of this syndrome are absent and infants are often excessively irritable. In school-age children, sizable midline or frontal lesions may result in a decline in school performance and associated behavioural dysfunction[7].

## *DIAGNOSIS*

### Imaging modalities

In most reports, more than half of brain tumours are infratentorial, a compartment that is notorious for hiding pathological changes on scans until the tumour is of obvious size or causing hydrocephalus. However, the diagnosis of PBTs has greatly improved over the past few decades and has been streamlined by the increased accessibility and quality of brain imaging.

Magnetic Resonance Imaging (MRI) has better sensitivity in the detection characterization of brain tumours. Other tests such as Positron Emission Tomography (PET) scans may be helpful, but are not widely used for diagnostic purposes. Very occasionally they are used for determining the aggressiveness of the tumour or distinguishing tumour from inflammation. Since brain tumours in childhood, especially the embryonal ones, may spread to other sites within the nervous system, most patients require an MRI of the entire craniospinal-axis for appropriate evaluation and staging prior to surgery or adjuvant therapy. Lumbar puncture (LP) may disclose leptomeningeal spread of the tumour not seen on MRI.

### Histopathological diagnosis

Tumours of the central nervous system (CNS) are challenging to treat for many reasons, even in the best circumstances, in part because there is great variety in the anatomical location and histological types. Multiple tumour histologies are seen in paediatrics tumours, both benign and malignant. Basic histologic subgroups include astrocytic and glial-derived tumours, neural and neuroglial tumours, ependymal tumours, ependymal tumours, embryonal or supratentorial primitive neuroectodermal tumours (PNETs), malignant rhabdoid tumours such

as ATRTs, choroid plexus tumours, pineal parenchymal tumours, germ cell tumours, meningeal tumours, pituitary tumours, and haematopoietic, skull or dermal-derived tumours. Astrocyte-derived tumours include pilocytic astrocytoma, pilomyxoid astrocytoma, pleomorphic xanthastrocytoma, subependymal giant cell astrocytoma, fibrillary astrocytoma, anaplastic astrocytoma and glioblastoma. Low-grade gliomas (LGGs), consisting of WHO I and II tumours, account for approximately 60% of hemispheric tumours in children[13], and they occur at an incidence of five per million children per year. The mean age of diagnosis is around 6-11 years[13].

While some tumours are benign and curable by complete, or sometimes even by near-complete resection (e.g. juvenile pilocytic astrocytomas (JPAs) or subependymal giant cell astrocytomas (SEGAs); others are highly malignant and likely incurable even with a gross total macroscopic resection (e.g. atypical teratoid rhabdoid tumours [ATRT], glioblastoma multiforme [GBM]). Additionally, brain tumours occur in different location in the cranium and therefore pose different risks to the neurological function of the child and suitability for treatment. The location of the tumour affects the surgical resectability of the lesion, which in most cases determines the likelihood of a cure. Even when tumours are treatable, a location in eloquent regions of the brain or brainstem may render the risks of surgery unacceptable for a reasonable quality of life, and the surgical procedure itself may be the cause of death. A benign JPA is theoretically curable but may occur deep within the hostile environment of the brainstem and so pose a mortal threat independent from its “benign” histological nature.

***TREATMENT***

It is clear from published data that good outcomes depend on a dedicated multidisciplinary team, yet this cannot be achieved easily in the private sector, and its availability in the public sector is limited. Several factors affect outcome. A high level of suspicion increases the chance that children are imaged appropriately. Adequate imaging of PBTs requires a dedicated environment as magnetic resonance scans in young children are difficult, if not impossible,

without adequate and safe sedation or general anaesthesia. Once the tumour is identified on imaging, the most important treatment-related factor in the likelihood of affecting success is the extent of surgical resection where possible. This depends not only on the tumour, but considerably on the neurosurgeon's training, expertise and infrastructure supporting surgery. Few neurosurgeons in the country operate on childhood brain tumours frequently enough to achieve and maintain the required expertise. Moreover, the experience of the paediatric anaesthesiologist and the availability of dedicated paediatric intensivists are essential to secure optimal outcomes. Experienced neuropathologists are similarly important. Adjuvant treatment, and indeed further surgical decisions, depend on an accurate histopathological diagnosis. Because the definitive histological diagnosis of PBTs can be notoriously difficult, and because this has a substantial impact on decisions on how best to manage the child, specific experience in paediatric neuro-pathology is essential. For example, ATRTs are now increasingly recognized as small round blue cell tumours usually occurring in the posterior fossa, likely previously confused with medulloblastoma, but identified by the lack of expression of hSNF5, the protein encoded by the tumour suppressor gene SMARCB1. It has an extremely poor prognosis and the distinction from medulloblastoma is critical for management purposes. Existing data from African patients do not reflect this entity.

The treatment regimens are tailored to each patient and most often includes a combination of surgery, chemotherapy, and radiation therapy, as well as management for conditions that develop as consequence to the treatment administered, such as endocrinopathies requiring hormone replacements and long-term follow up.

**Surgery**

For most childhood brain tumours, surgery is a pivotal cornerstone in management, not only to confirm the histology of the tumour, but also to resect as much tumour as can be safely accomplished. The degree of resection, or more specifically the amount of tumour left after surgery (residual tumour), is closely related to patient prognosis. Adjuvant therapy is usually not decided on until there is histopathological confirmation, with few exceptions such as optic

pathway gliomas, germ cell tumours with markers, and radiologically-typical DIPGs.

Improvements in anaesthesia, surgical navigation, and intraoperative neurophysiology have improved surgical safety and in many cases have allowed more aggressive resections without compromising neurological function. However, the risk of neurologic injury and dysfunction after brain tumour surgery remains a significant problem. These relate to the specific area of brain involved, or may be general, including postoperative hydrocephalus, bleeding, or infection. A common surgical complication for infratentorial tumours is the "posterior fossa mutism syndrome", also known as the "cerebellum mutism syndrome". In this circumstance, after surgery for a posterior fossa tumour (primarily in those with medulloblastomas but also after surgery for any type of midline cerebellum tumour), the patient typically has a delayed recovery, with poor word output or complete mutism, often commencing after a couple of days. The cerebellar mutism syndrome is due to disruption of critical pathways from the dentate nuclei in the cerebellum through the upper brainstem and projecting to the thalamus and cerebral cortex[7]. This mutism is not an isolated finding and may be associated with restlessness or irritability, bulbar palsies, supranuclear cranial nerve palsies, hypotonia, and cerebellar symptoms. Often cerebellar mutism syndrome is transient and clinical improvement may occur over days to weeks, however patients may be left with residual speech and balance deficiencies.

**Radiotherapy**

Radiotherapy is essential in many forms of childhood brain tumours to treat residual tumour post-resection, prevent recurrence, and sometimes palliate, but may be limited by the age of the patient and potential injury to the developing brain, both for neurocognitive development and the risk of secondary malignancies.

Once again, decision-making, planning, mark-up, and delivery for PBTs require experience and infrastructure, without which, results are suboptimal. Many centres country-wide will not undertake paediatric radiotherapy due to lack of

experience and time constraints. Optimal sedation or anaesthesia is frequently required, and neuro-cognitive outcome is directly related to optimal techniques.

**Chemotherapy**

Chemotherapy has significantly changed outcome for leukaemias, but less so for brain tumours, partly because the blood brain barrier (BBB) restricts the delivery of certain chemotherapeutic agents.

Increasingly, children are receiving chemotherapy for brain tumours such as medulloblastomas, ependymomas, and midline astrocytomas. The decision-making, regimens, infrastructure and support in this all critical to the successful management of these patients. Ideally, all of these children should be followed-up in a multidisciplinary clinic, given the risk of recurrence and the potential for long term neurological, endocrine and neuropsychological complications; however, this is rarely available.

**Advances**

Recent new advances in treatment modalities and strategies have been promising for paediatric brain tumours but are not widely accessible. In surgery, recognition of subspecialist expertise, improved imaging and intraoperative visualization, and intraoperative neurophysiology have improved the safety of surgery and extent of resection achievable, even in critically eloquent areas. Radiotherapeutic advances in image fusion techniques, 3D conformal radiation therapy, intensity modulated radiotherapy, stereotactic radiosurgery, and proton beam therapy have also improved the safety and effectiveness of radiotherapy but again are not widely available. While most of the chemotherapy regimens use well-established agents, there have been improvements with drug delivery techniques such as the use of intra-Omayya reservoir interferon therapy for patients with craniopharyngiomas. While intensive approaches such as high dose therapy with autologous stem cell rescue have not yielded dramatic improvements in the outcomes of high risk brain tumours, there is a potential role for biological small molecules and monoclonal antibodies, as well as for anti-angiogenic and metronomic strategies[14].

Certainly one of the most exciting advancements in paediatric neuro-oncology research has been in the field of molecular biology. Classification of brain tumours has improved; this relies now not only on the histology of tumour cells but also increasingly on immunohistochemical markers, cytogenetic analysis and molecular subtyping. Recent work on medulloblastomas illustrates this principle: it is increasingly clear that the entity of medulloblastomas comprises at least 4 distinct subtypes that have epidemiological correlates, therapeutic implications and prognostic value. It is expected that identification of these subtypes will be required for entry into clinical trials and will eventually guide targeted therapeutic decisions in the future.

## *TABLE 2: Summary of some common specific paediatric brain tumour types[13]*

| *Tumour type* | *Epidemiology* | *Diagnosis (incl. histology)* | *Management strategies* | *Prognosis* | *Other* |
|---|---|---|---|---|---|
| ***Astrocytoma***<br>**4 types:**<br>**1. JPA (Grade I) most common (discussed here)**<br>2. Fibrillary (Grade II)<br>3. Anaplastic(Grade III)<br>4. GBM(Grade IV) | Most common age in children: 5-10yrs<br>M:F ±1:1 | Assoc with NF1<br>Location: Cerebellum 60%<br>Optic pathway 25-30% | Surgical resection is first option and if gross total resection is achievable may be curitive<br>± ChemoRx<br>± RadioRx | If GTR can be achieved tumour has good prognosis with at 5 and 10 year survival >95% | BRAF alterations in ±70%<br>Lacks IDH mutations and TP53 mutations |
| ***Medulloblastoma***<br>*Most common malignant tumour of childhood* | • WNT (least common ±10%)<br>○ Age median 10 yrs<br>○ M:F 1:1<br>○ Classic<br>• SHH (30%)<br>○ Age bimodal <3yrs and >16<br>○ M:F 1:1<br>○ Classic > Desmoplastic<br>• Group 3 (25%)<br>○ infants and children (rare in adults)<br>○ M > F (2:1)<br>○ Classic > Large cell anaplastic<br>• Group 4 (most common; 45%)<br>○ typically children, peak age 10 yrs (rare in infants)<br>○ M:F 3:1<br>○ Classic = Large cell anaplastic | 4 molecular subgroups currently recognised in the WHO classification:<br>1. WNT<br>2. SHH<br>3. Group 3<br>4. Group 4 | Multimodal strategy, including:<br>Surgery +/-<br>ChemoRx +/-<br>RadioRx | Prognosis is most strongly influenced by molecular subtype:<br>• WNT: very good<br>• SHH: infants good, others intermediate<br>• group 3: poor<br>• group 4: intermediate | Most common embryonal tumour<br>Associations with syndromes, including:<br>• Coffin-Siris syndrome<br>• Cowden syndrome<br>• Gardner syndrome<br>• Gorlin syndrome<br>• Li-Fraumeni syndrome<br>• Rubinstein-Taybi syndrome<br>• Turcot syndrome |

| | | | | | |
|---|---|---|---|---|---|
| ***Craniopharyngioma*** | Approx 4% of PBTs<br>Bimodal age distribution: 5-14 yrs and 45-65 yrs<br>M:F ± 1:1 | Two histologic subgroups:<br>• Adamantinomatous<br>• Papillary (mainly in adult group) | Surgery +/-<br>Radiotherapy +/-<br>Interferon therapy | Main predictor of outcome: hypothalamic involvement, tumour recurrence and endocrinologic dysfunction | Histologically benign but behaviour often more of a malignant course |
| ***Choroid plexus tumours*** | 2-4% of all PBTs<br>Main location: lateral ventricles (50-70%) | WHO 3 groups:<br>• Grade I choroid plexus papilloma (CPP)<br>• Grade II Atypical CPP (ACPP)<br>• Grade III choroid plexus carcinoma (CPC) | CPP: GTR of tumour is cornerstone of Rx<br>CPC: GTR +/- craniospinal RadioRx +/- chemoRx (adjuvant presurgical chemoRx may increase chance of GTR) | CPP: 90% 1-year-survival, and 77% 5-year-survival<br><br>CPC: 40% 5-year survival | Associations with Li-Fraumeni syndrome and Aicardi Syndrome |
| ***Ependymoma*** | Approx 8-12% of all PBTs<br>Median age 4-6 yrs<br>M>F<br>Location: 70% are infratentorial | Histology 3 groups WHO:<br>• Grade I myxopapillary or subependymoma<br>• Grade II cellular, papillary, clear cell or tanycytic<br>• Grade III anaplastic | Current standard of care is safe maximal surgical resection ± focal RadioRx post resection | Tumour location, grade, patient age and initial treatment all contribute to progression-free survival. Median time to recurrence is within 2 yrs of Dx in ±33% of patients | Most tumours are sporadic but associations with NF2 may be seen |
| ***Brainstem glioma*** | 10-20% of PBTs<br>Peak age 7-9 yrs<br>M:F ± 1:1 | Tumours broadly categorised as *diffuse infiltrating* or *focal* and further categorised on anatomical location, i.e. Midbrain, Pons, Medulla, cervico-medullary<br>DIPGs are the most commonly occurring brainstem tumour in children | DIPGs are not amenable to surgical resection and role of biopsy is to confirm diagnosis where there is doubt.<br>RadioRx remains the mainstay of Rx strategy ± palliative re-irradiation proposed at time of tumour progression. | DIPGs have the worst prognosis of the brainstem tumours with median survival of less than 1 year from time of Dx | Still on-going molecular biology discoveries showing promising future areas for potential targeted Rx. |
| ***Pineal***<br>*Includes*<br>*Pineal parenchymal tumours*<br>• ***Pineoblastomas (discussed here)***<br>• *Pineocytoma*<br><br>*Germ cell tumours*<br>*Astrocytomas*<br>*Pineal mets*<br>*Pineal cysts* | Young children (median age 5.5 yrs)<br>M:F ± 1:1 | WHO Grade IV tumours, highly aggressive | Treatment is usually multi-modal with a combination of surgery, chemoRx and radioRx. | Despite treatment, the prognosis has historically been poor, with a 5-year survival as low as 10%. More recently 5-year survival of 58-81% have been reported 8,12 with median overall survival times of 4-8 years. | Well established association with hereditary retinoblastoma. |

| | | | | | |
|---|---|---|---|---|---|
| ***ATRT*** | Present in young children: ±70% dx before age 1 yr; 90% dx before age 3yrs<br><br>M>F (±1.6:1) | Aggressive rare malignancy ±1-2% of PBTs<br><br>Location: 50-66% infratentorial with cerebellum the most common site<br><br>CSF dissemination present in ±20% | Depends on age of patient but needs multimodal approach combining maximal safe surgical resection, craniospinal RadioRx and intensive chemoRx | Clinically AT/RTs have much poorer prognosis than medulloblastomas, with little if any response to chemotherapy and death usually occurring within a year of diagnosis. | |

***OUTCOMES***

Treatment and long term outcomes depend on many factors, which attest to the complexity of treating these patients. Factors such as tumour type, location within the brain and surrounding structures, presence of metastatic disease as well as the patient's age and general health all contribute heavily towards developing the best, most feasible treatment strategy for each individual patient. Table 3 below summarises shows survival data for paediatric posterior fossa tumours with current best management strategies for some of the most common paediatric tumours. Because new treatments and technologies are continually being developed, several options may be available at different points in treatment.

***TABLE 3: Survival data for paediatric posterior fossa tumours with current best management[13]***

| Tumour | Progression-Free Survival Rate | Overall Survival Rate |
|---|---|---|
| **Pilocytic astrocytoma** | >90% at 5 years | 85-95% at 10 years |
| **Medulloblastoma** | Average-risk MB:<br>85% at 5 years<br>High-risk MB:<br>70% at 5 years | High-risk MB <50% at 5 years |
| **Ependymoma** | 23-45% at 5 years | Children:<br>50-60% at 5 years<br>Infants:<br>42-55% at 5 years |
| **AT/RT** | Without RT:<br>20-30% at 2 years<br>With RT:<br>53% at 2 years | Without RT:<br>53% at 2 years<br>With RT:<br>70% at 2 years |
| **CPP** | 83% at 5 years | 100% at 5 years<br>85% at 10 years |
| **CPC** | | GTR: 52%<br>STR: 21% at 2 years |

## CHAPTER THREE

### *METHODOLOGY*

**Study objectives** To collect epidemiological data for childhood brain tumours at a tertiary paediatric hospital with a dedicated multidisciplinary team. A retrospective study was undertaken to collect data of all children with primary brain tumours presenting to RCCH and GSH.

**Study design** Retrospective study: The records of all patients diagnosed with a primary brain tumour and who presented to RCCH and GSH between 1 January 1996 and 31 December 2017 were examined. The patients were primarily based at RCCH, which has an upper age limit of 13 years; however, occasional patients referred to the multidisciplinary clinic were occasionally older (age range 0-17 years). All data were captured in an excel-based database, the excel spreadsheet developed is attached in the appendix section for reference.

**Patient selection & data collection** Until this study was undertaken, no single comprehensive database for children with paediatric brain tumours treated at RCCH and GSH existed. To assemble this database and ensure the most accurate and complete database was composed, multiple sources were used to develop a comprehensive, accurate list of patients.

This was done by creating 5 databases from multiple diverse sources:

***Histology database****:* This was created by capturing every histology result logged in the histology record books and result files from 1 January 1996 - 31 December 2017 for children that had neurosurgical specimens sent to the lab for diagnosis.

***Surgical database***: This was accessed from theatre logbooks capturing all patients who underwent a neurosurgical procedure.

***Neurosurgical ward admissions database (D1 database):*** All the admissions to the paediatric neurosurgical unit from 1 January 2000 - 31 December 2017 (the

electronic admission computer system was only introduced in 2000 and all admission records prior to 2000 were not obtainable) were scanned for diagnosis and folders were reviewed in cases where there were uncertainty of diagnosis. The admissions clerk captures all children on an electronic record platform (CliniCom) and admissions are typically done in the surgical speciality ward (including neurosurgery) under the patients name and diagnosis code (ICD -10). Nearly 8000 folders had to be screened to ensure that no patients were missed.

***Oncology database (G1):*** Oncology folders at RCCH were obtained from lists compiled of clinic visits as well as cross-referencing with clinician's databases; information was again cross-referenced for accuracy. Patients with brain tumours are occasionally referred directly to the oncology team without necessitating neurosurgical admission and therefore this database attempted to screen for those patients not seen by the neurosurgery team as primary treating doctors.

**Combined multidisciplinary *clinic at GSH (LE34):*** This is where paediatric patients are seen at a combined clnic involving all disciplines. This list was obtained from the oncology clinic clerks. Additionally a similar list for the adult neuro-oncology clinic was obtained and screened for children in the system who may have have been transferred to the adult neuro-oncology clinic.

***Other sources*** used to cross-reference information included Dr Riedemann's database (from the department of radiation-oncology at GSH) on his work done on children with medulloblastoma's; as well as the electronic radiology system (PACS) for checking information on patients from 2012 (when the electronic radiology system was introduced) until 2017.

These databases were combined, cross-referenced and collated into a final conglomerate master sheet database that was then analysed and used to report on the findings presented in this MMED. Every attempt was made to minimise on missing data by combining the various sources and databases described above.

Data collected included: age at diagnosis, sex, province of referral, tumour site and diagnosis (including histological diagnosis where biopsy or surgery was

performed). As part of a planned follow up study and paper, a detailed analysis will be done examining treatment modalities utilised and patient outcomes based on the list of patients identified in this MMED.

Demographic information included suburb/town and district of residence if the patients were from the Western Cape; or province if the patients where referred from outside the Western Cape or country of referral if the patients where international referrals.

The admission age for RCCH is usually limited to 0 to 13 years of age. Occasionally older patients are treated and appropriate overage consent forms were obtained from RCCH to treat these patients and they were not excluded from this study. Occasionally patients over that age are referred directly to the multidisciplinary clinic. Although the oldest patient in the study was 17 years old, patients over the age of 13 were not typical due to the admission criteria of the hospital. The focus of the study was primary brain tumours. Therefore, we excluded metastatic lesions where the primary tumour was outside the CNS were excluded, as well as primary spinal cord tumours (to be examined in a separate study).

Other important information that will reported in the follow up study includes details of the presentation, initial presentation, treatment delivered, results of treatments, complications, and outcome.

The attached excel datasheet (appendix 1) was used for the purpose of this study.

**Statistical analysis** The study was primarily descriptive. Graphs, charts and geographical maps were used to illustrate and describe the data obtained and to show various tumour types, ages of patients, gender as well as referral patterns from both provincial patterns within the Western Cape and outside of the Western Cape.

**Intervention** This is a retrospective observational study and no intervention was implemented.

### *CHALLENGES*

Retrospective data collection despite best efforts is always incomplete. Missing or incomplete data was found to be 1.1% of patients identified but does not include the "unknown" patients that were not identified throughout the various sources described above. Reasons for missing data are discussed in chapter 5.

Given that we continue to follow patients for many years after their diagnoses, missing data have been minimized and every attempt has been made to fill in the gaps. Where patients had died, we did not make any attempts to contact the family for information. While necessary, retrospective studies are known for these limitations.

### *ETHICAL CONSIDERATIONS*

Ethical approval was obtained from both the Human Ethics Board of the University of Cape Town (HREC REF: 229/2018) as well as the Departmental Research Committee (see appendix 2 and 3). All patient records were de-identified to maintain anonymity when analysing and publishing results. Patient management was in no way affected by the study.

### *CONFLICT OF INTEREST DECLARATION*

The investigator has no conflicts of interest to declare.

## CHAPTER FOUR

### *RESULTS*

Data from 554 patients identified and admitted to the combined paediatric neuro-oncology service between 1 January 1996 and 31 December 2017 were reviewed and are reported here according to:

- Geographic referral pattern
- Patient demographics: age and sex
- Anatomical location of tumour
- Pathology

### *Geographic referral pattern*

The paediatric neuro-oncology group at RCCH/GSH receives referrals at both provincial and national levels; occasionally this extends to other African countries.

***FIGURE 1: Geographic referral pattern of paediatric brain tumours***

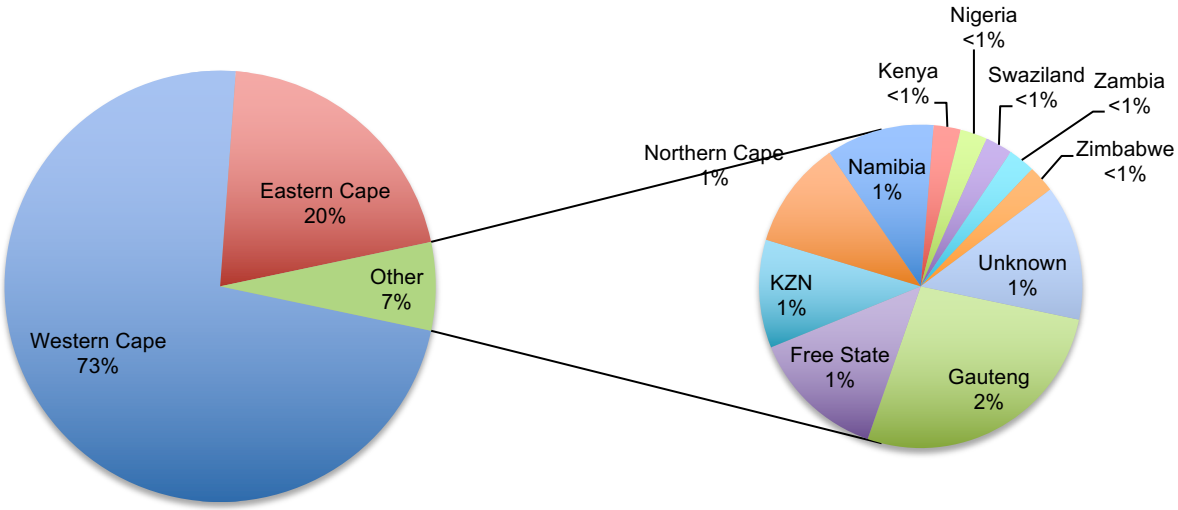
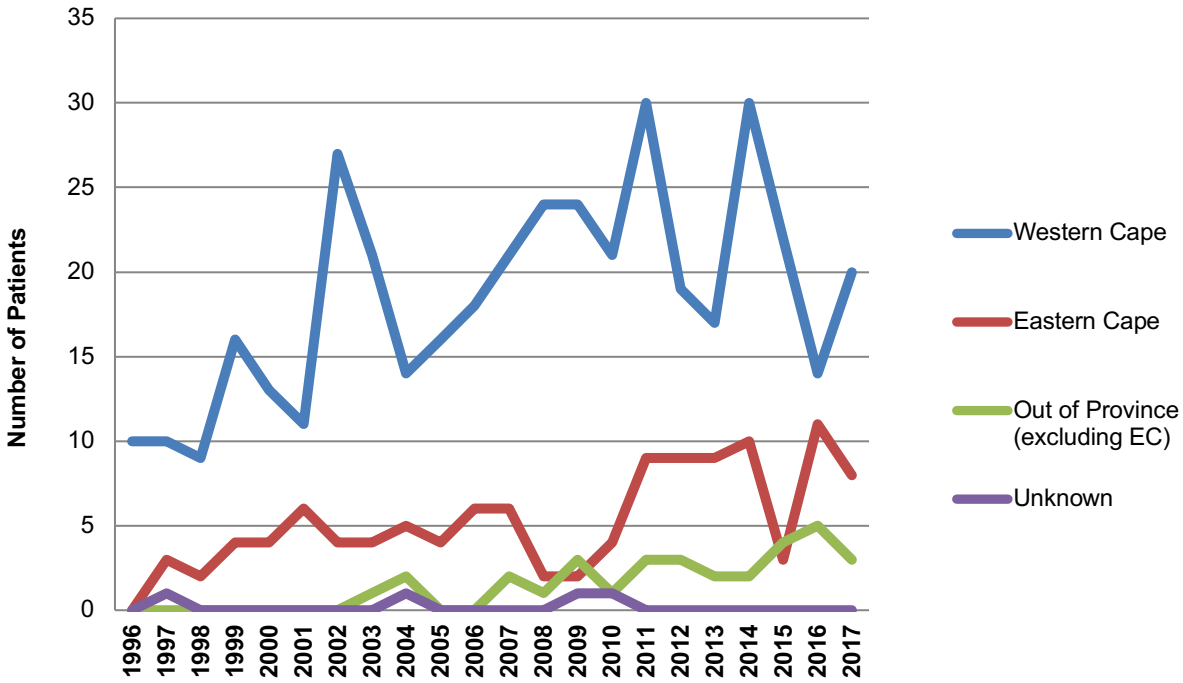


***Figure 1*** above depicts the overall referral pattern for all the patients referred from 1996-2017 to the paediatric neuro-oncology group at RCCH/GSH.

As expected, most patients referred and seen at RCCH/GSH were from the expected drainage area in the Western Cape (73%); 26% were out of province referrals. This is discussed in further detail in chapter 5.

***Figure 2*** illustrates how the referral pattern over the time period of the study. In the last 10 years, the median percentage of cases referred from outside of the province was 28.6% compared with 20.7% of cases managed prior to that. Most of these out of province referrals (excluding the Eastern Cape) were from the private sector.

***FIGURE 2: Geographic referral pattern per year of diagnosis***




The maps below illustrate the geographical referral patterns, 1) in South Africa, and 2) within the six districts of the Western Cape.

***MAP 1: Map of South Africa showing number of referrals per province***


*Map taken from Google images and modified with data as inserted above

***MAP 2: Map of Western Cape showing number of referrals per district***


*Map taken from Google images and modified with data as inserted above

***Demographics***

***TABLE 4: Summary of age, sex, referral site, and anatomical location***

| Variable | Number (n) / Percentage (%) |
|---|---|
| **Age (years)** | |
| **0-3** | 147 / 26.5 |
| **4-9** | 259 / 46.8 |
| **10-13** | 113 / 20.4 |
| **>13** | 35 / 6.3 |
| **Sex** | |
| **Male** | 307 / 55.4 |
| **Female** | 243 / 43.8 |
| **Unknown** | 4 / 0.7 |
| **Referral** | |
| **Western Cape** | 404 / 72.9 |
| **Out of Province (incl. international)** | 145 / 26.1 |
| **Unknown** | 5 / 0.9 |
| **Tumour location** | |
| **Supratentorial** | 288 / 52.0 |
| **Infratentorial** | 259 / 46.8 |
| **Unknown** | 7 / 1.3 |

***Gender***

***Figure 3*** summarises the gender distribution of the population. We found in this study that the overall male-to-female ratio was 1.26:1, consistent with the international published experience.

The male predominance held true over most histological tumour types with the exceptions being (M:F) JPAs (0.92:1), DIPGs (0.89:1), choroid plexus tumours (0.89:1) and optic pathway gliomas (0.83:1) as shown in ***Figure 4***. It is likely

that tumours captured as optic pathway gliomas were treated as such without histological diagnosis.

***FIGURE 3: Tumour distribution by gender***

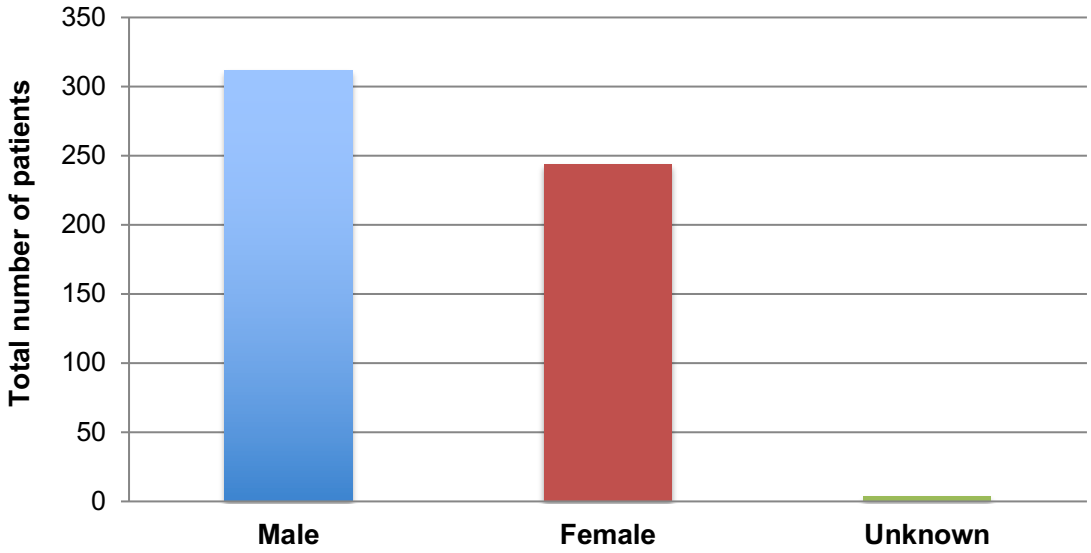
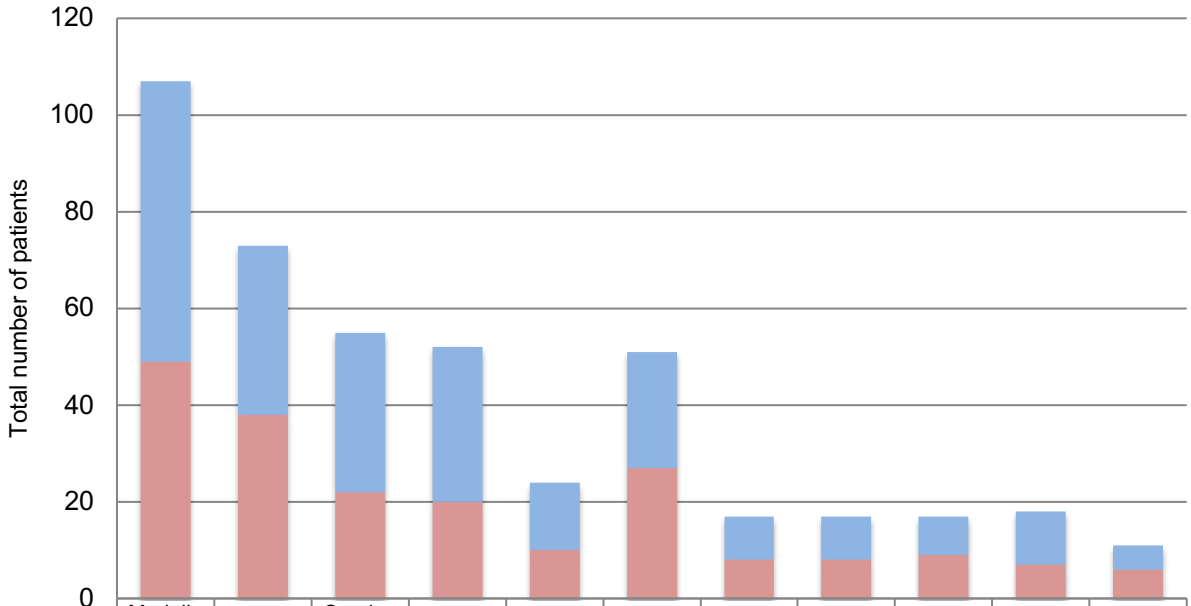



***FIGURE 4: Sex distribution by histological tumour types***



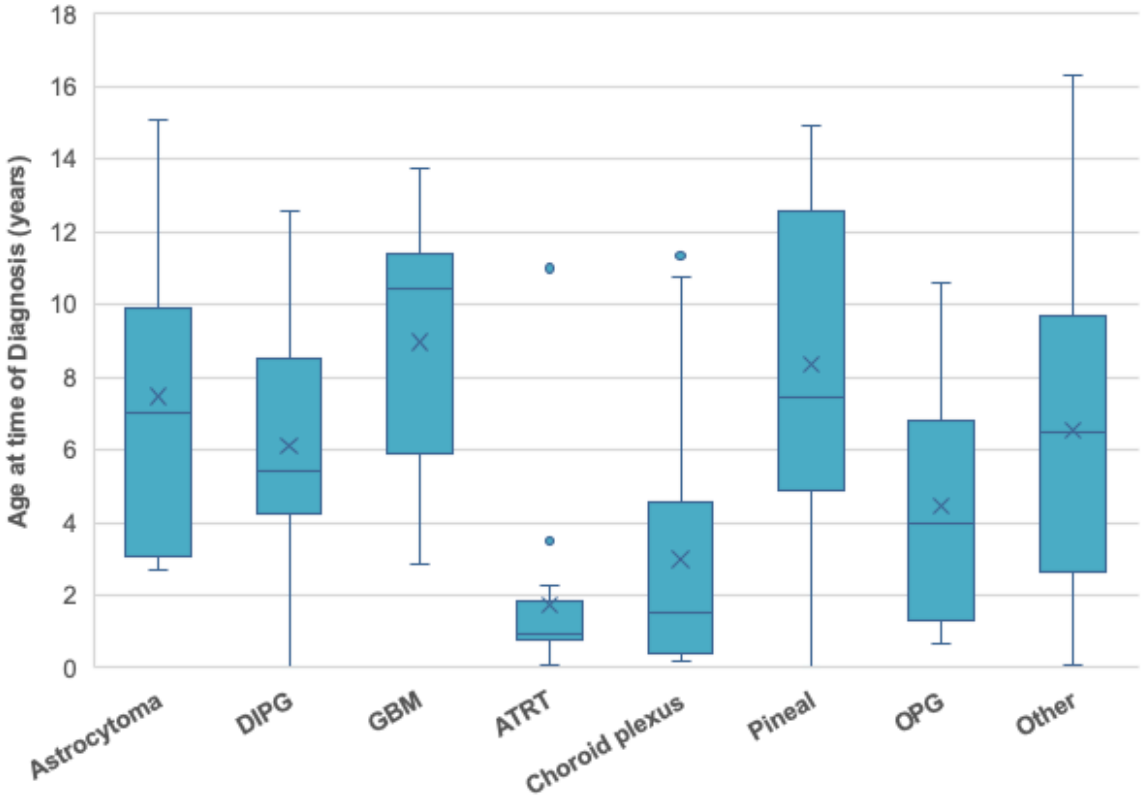

| | Medulloblastomas | JPA | Craniopharyngiomas | Ependymomas | Astrocytomas | DIPG | GBM | ATRT | Choroid plexus | Pineal | OPG |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Male | 58 | 35 | 33 | 32 | 14 | 24 | 9 | 9 | 8 | 11 | 5 |
| Female | 49 | 38 | 22 | 20 | 10 | 27 | 8 | 8 | 9 | 7 | 6 |

***Age***

***Figure 5*** demonstrates some of the most common histological tumour types plotted against age of diagnosis.

Unsurprisingly, the median ages of diagnosis for ATRT and choroid plexus tumours were younger, 0.92 years and 1.5 years respectively.

***FIGURE 5: Box plots of histological tumour types against age of diagnosis***




*DIPG Diffuse Intrinsic Pontine Glioma / GBM Glioblastoma Multiforme / ATRT Atypical Teratoid Rhabdoid Tumour / OPG Optic Pathway Glioma

***Anatomical location***

***Figure 6*** illustrates the tumour distribution by anatomical location: supratentorial tumours comprised 52%, infratentorial 47% and unknown location in 1%. This was somewhat different to most reports, where infratentorial tumours are more common in children compared to their adult

counterparts. Some literature and textbook sources quote a ratio as high as 60:40 for infratentorial vs supratentorial tumours. This is discussed in chapter 5.

***FIGURE 6: Tumour distribution by anatomical location***

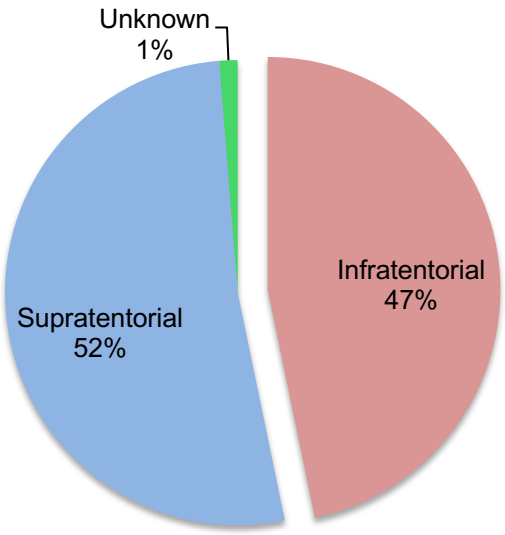
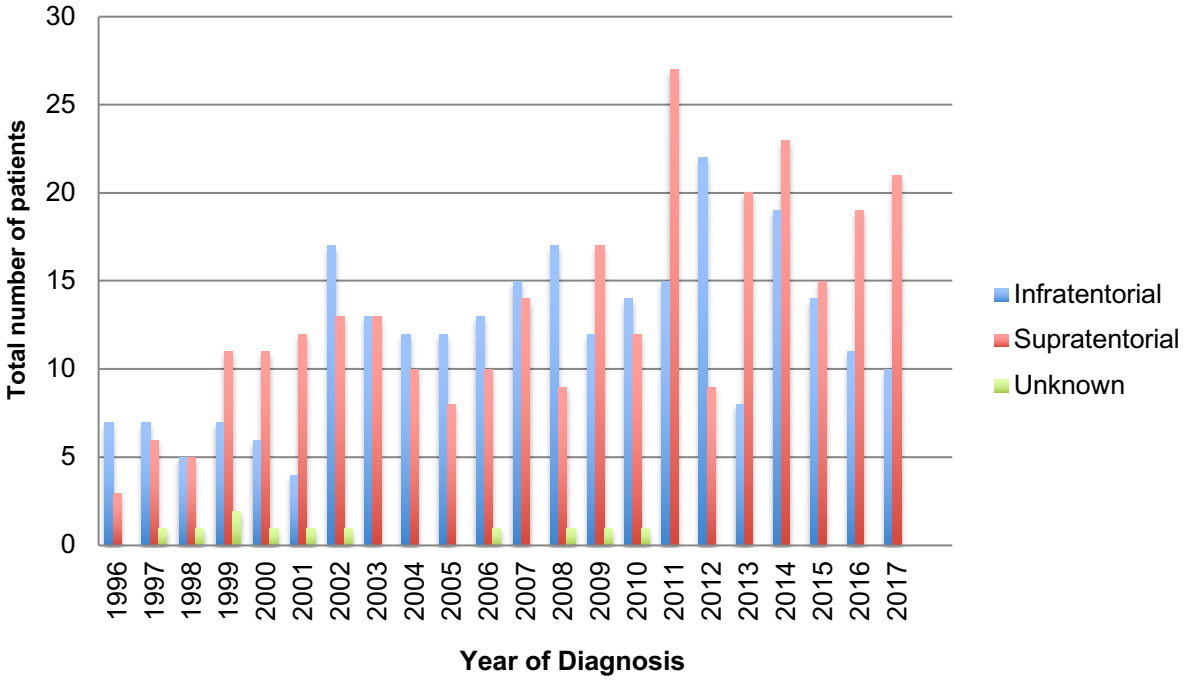


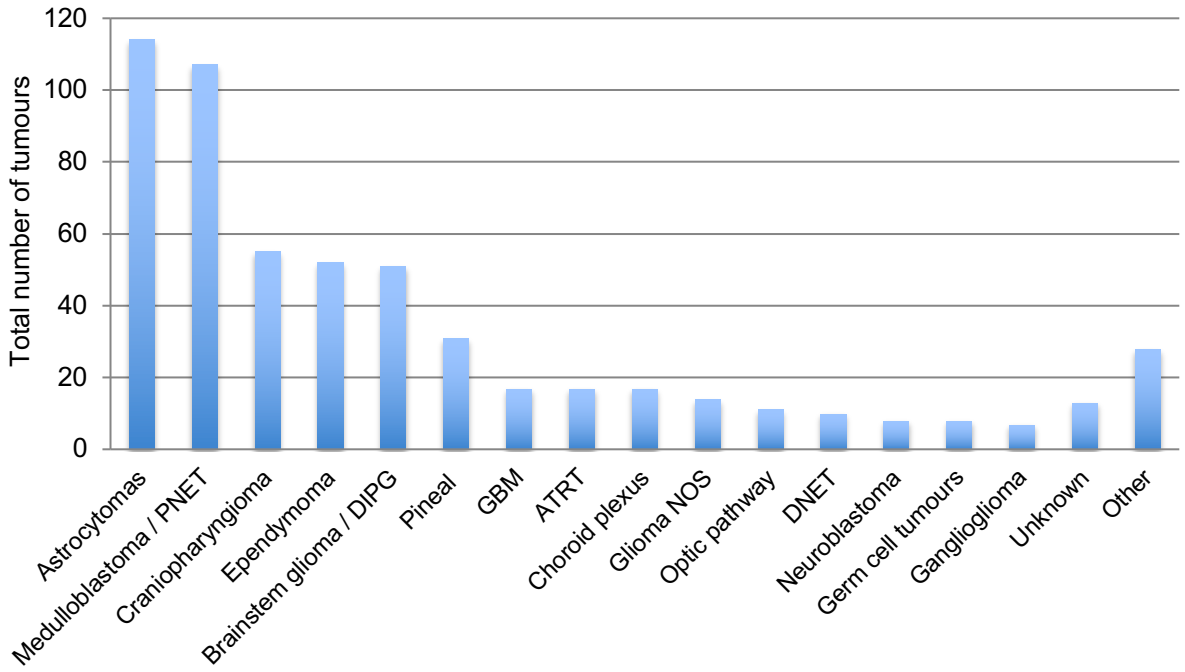

***FIGURE 7: Anatomical location of tumours per year of diagnosis***



***Pathology***

***Figure 8*** summarizes the most common tumour types diagnosed by histology or imaging characteristics over the study time period. The commonest tumours were astrocytomas (n=114 patients; 20.3%), followed by medulloblastomas (incl. PNETs) (n=107 patients; 19.1%), and craniopharyngiomas (n=55; 9.8%).

***FIGURE 8: Frequency of paediatric brain tumours at UCT, 1996-2017***




*PNET: Primitive neuroectodermal tumour; JPA: Juvenile Pilocytic Astrocytoma; DIPG: Diffuse infiltrating pontine glioma; GBM: Glioblastoma Multiforme; DNET: Dysembryoplastic neuroepithelial tumour; SEGA: Subependymal Giant Cell Astrocytoma; PXA: Pleomorphic Xanthoastrocytoma

***Table 5*** shows the median age of diagnosis, male-to-female ratio, and frequency of the most common tumours diagnosed. In keeping with most international literature there is a slight male-to-female (M:F) predominance. As expected, ATRT presented in younger patients.

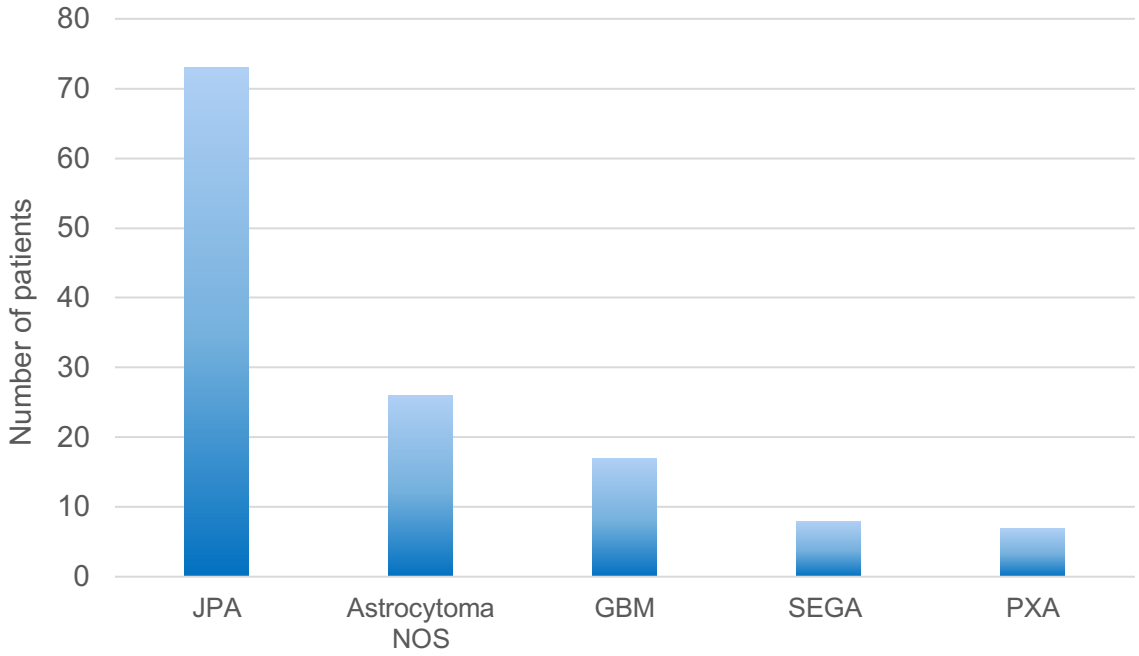
***TABLE 5: The most common paediatric brain tumours by diagnosis, gender and median age at presentation.***

| | All Tumours | Astrocyt | Medullos (incl. PNET) | Cranio | Epend | BSG / DIPG | ATRT |
|---|---|---|---|---|---|---|---|
| **Median age of Dx (years)** | 5.92 | 6.25 | 5.5 | 7.25 | 4.71 | 5.42 | 0.92 |
| **M:F** | 1.26 : 1 | 1.29:1 | 1.18 : 1 | 1.5 : 1 | 1.6 : 1 | *0.89* : 1 | 1.13 : 1 |
| **Total number** | 554 | 114 | 107 | 55 | 52 | 52 | 17 |

*Astrocy: Astrocytomas / Medullos/PNET: Medulloblastomas, incl PNET / Cranio: Craniopharyngioma / ATRT: Atypical Teratoid Rhabdoid Tumour / Dx: diagnosis / mo: months

## *Astrocytomas by specific sub-type*

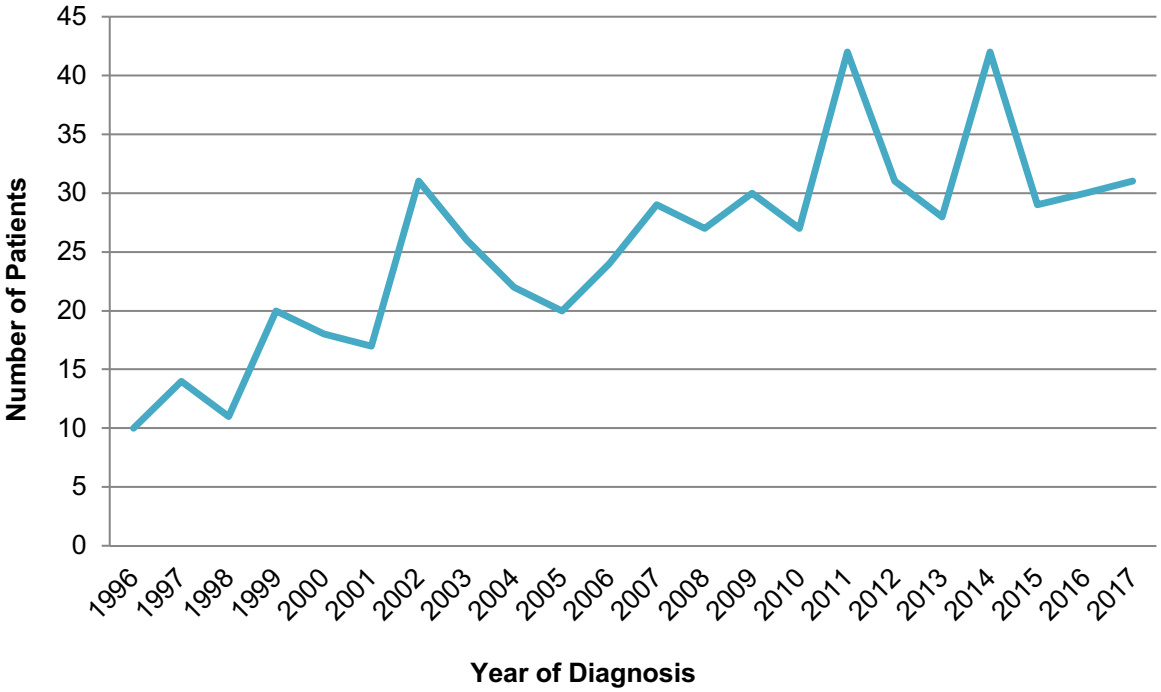
***FIGURE 9: Breakdown of astrocytoma diagnosis by specific sub-type***




*JPA: Juvenile Pilocytic Astrocytoma / NOS: not otherwise specified / GBM: Glioblastoma multiforme / SEGA: subependymal giant cell astrocytoma / PXA: pleomorphic xanthoastrocytoma

**Figure 10** shows the number of cases diagnosed for each year.

***FIGURE 10: Number of patients with paediatric brain tumours per year***



## CHAPTER FIVE

## *DISCUSSION*

The epidemiology of paediatric brain tumours has been widely studied in the developed countries with high quality national registries existing in high income countries (HICs), but little comparison can be easily made with developing countries as much less data have been published.

Information and research in general has increased exponentially over the last 4 decades and despite this there is little information on the incidence and epidemiology of childhood brain tumours in South Africa, with inconsistent and slow transitioning into the digital era, gathering information on patients still remain a colossal and laborious task that yields unsatisfying results. Accurate electronic record keeping would be an important step towards developing and maintaining a national tumour data registry by allowing for the consolidation of information and contributing not only to better understanding of disease burden but also the available resources at each centre to treat specific conditions and diseases.

The reported incidence of childhood brain tumours is 2-5 / 100 000 / year[(2)], and based on this figure approximately between 340-850 children with brain tumours should present annually in South Africa, based on updated population estimates from Statistics South Africa 2017 for children under the age of 14. RCCH and GSH paediatric neuro-oncology units are not the only centres in the Western Cape, let alone in South Africa to treat paediatric brain tumours, neither does it account for the public versus private sector division. Furthermore, provincial population statistics are in constant flux. Therefore no reasonable attempt could be made at accurately calculating the incidence or prevalence of paediatric brain tumours in South Africa or even in the Western Cape. The South African Children Tumour Registry (SACTR) was started in 1987 to document the cancer burden of the national paediatric population. Data is collected by all the registered Peadiatric Oncology Units of South Africa on all maligancies of resident children in the Republic of South Africa under the

age of 18 years. This registry does not however include all types of paediatric brain tumours, only those that get referred to oncology units for treatment. This again stresses the importance of a paediatric brain tumour registry that can account for both provincial and national data to be collected.

**Geography**

The unit receives referrals at both a provincial as well as national level, public and private, and occasionally extending beyond the borders of the country.

As expected, most patients were from the Western Cape (73%), but still a significant percentage of referrals where from outside our drainage area both out of province and international referrals making up the remainder of the patients seen (26%). Over time, the proportion of patients referred from outside the province increased. In 1999, for example, 80% of the patients were from Western Cape (WC) and 20% were referred from outside the province. In 2016, by contrast, 46% were referred from outside the province. Most of the patients referred from outside of the Western Cape were from the private sector and the Eastern Cape.

Possible reasons for increased referrals from outside of the province include the development of specialized services locally, increased awareness of the need for specialized services, and a changing medicolegal environment.

**Demographic data**

***Sex distribution*** Consistent with most of the international literature, a slight male predominance was recorded in this study (M:F 1.26:1). This was similar to the results of Rickert and Paulus, in their meta-analysis of 10,582 childhood brain tumours, in which there was a M:F ratio of 1.29:1[15].

***Age*** It is unsurprising that ATRT and choroid plexus tumours were seen in younger children (median ages of 11 months and 18 months respectively),

whereas craniopharyngiomas were diagnosed in older children (median age of 87 months) (***Table 2, Chapter 2)***.

It is clear though from both literature and this study that different tumour types affect different age groups and even within certain tumour subgroups, e.g. medulloblastomas the various molecular subtypes also present at different age ranges. We are unable, at this stage to compare this with our own dataset as molecular subtyping of medulloblastomas are is not routinely done in SA and has only recently been examined locally in a research capacity.

**Anatomical Location**

This study found supratentorial tumours comprised 52% and infratentorial 47% (1% unknown). Infratentorial tumours are usually more common in the paediatric population compared to their adult counterparts: some sources quote a ratio as high as 60:40 for infratentorial vs supratentorial tumours. Another study in Africa, conducted by El-Gaidi in Egypt, reported supratentorial tumours comprising 48% and infratentorial tumours 52%[16]. A treatment-skewed bias may have influenced the distribution in the current study. It is possible that non-specialist centres may be more comfortable managing standard cerebellar tumours, compared to more complex supratentorial tumours. In keeping with this, suprasellar tumours (especially craniopharyngiomas) were more likely to be referred from out of province in this series. It is also possible that patients with diffuse pontine gliomas who did not receive surgery (and therefore may not be captured in in the surgical database) and who did not receive radiotherapy may represent missing data of "unknown" patients.

One of the difficulties in comparing tumour distribution by anatomical location is that definitions of anatomical locations for tumour types vary. Although some studies share the same basic categories of supratentorial vs infratentorial, many other studies use more complicated systems such as intrinsic vs extrinsic, primary vs secondary or categorising by histopathological subtyping alone.

## Pathology

Astrocytomas were the most common tumour (n=114 patients, 20.3%), followed by medulloblastomas (incl. PNETs) (n=107 patients, 19%), and craniopharyngiomas (n=55, 9.8%). Rickert and Paulus, in their meta-analysis of 10,582 childhood brain tumours accumulated from 16 international surveys showed some similarities: astrocytomas (37.6%), medulloblastomas (17.7%), ependymomas (9.9%), craniopharyngiomas (7.3%) and germ cell tumours (4.4%). Local differences might be explained by treatment options offered at our centre leading to a treatment-skewed bias of patients referred from the private sector or out of province. Not all tumours are equally managed in non-specialist centres and there is likely a bias in patients who are referred.

***TABLE 6: Comparison of common paediatric brain tumours between various series from different African countries[3]***

| *Study Ref* | *Country* | *Years of study* | *n* | *Mean age (years)* | *Age Ranges (years)* | *M:F* | *ST* | *IT* | *AST* | *MED* | *EPD* | *CPG* | *SCT Included* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Current study*** | *South Africa* | *1996-2017* | *554* | *6.3* | *0-17* | *1.26* | *288* | *259* | *114* | *107* | *52* | *55* | *N* |
| **(3)** | Sudan | 2000-2015 | 62 | 8.8 | 0-15 | 1.38 | 34 | 58 | 52 | 18 | 3 | 1.6 | **Y** |
| **(17)** | Nigeria | 1960-1982 | 89 | NA | 0-15 | 2.0 | 53 | 47 | 51.1 | 17.6 | 5.9 | 11.9 | N |
| **(2)** | South Africa | 1979-1985 | 145 | NA | 0-14 | 1.16 | 47 | 53 | 24.8 | 26.2 | 10.3 | 8 | N |
| **(18)** | Nigeria | 1980-1990 | 75 | NA | 0-14 | 0.75 | NA | NA | 40 | 10 | NA | 16 | N |
| **(19)** | Tunisia | 1990-2004 | 492 | 8 (median) | 0-16 | 1.01 | 50.2 | 49.8 | 38 | 16.2 | 6.9 | 5.3 | **Y** |
| **(20)** | Morocco | 2003-2007 | 542 | 9.3 | 0-19 | 1.08 | NA | NA | 31.6 | 28.9 | 10.3 | 6.6 | N |
| **(16)** | Egypt | 2005-2008 | 451 | NA | 0-14 | 1.06 | 46.6 | 49.7 | 35 | 18.8 | 10 | 11.3 | N |
| **(21)** | Morocco | 1991-2009 | 633 | 8.36 | 0-15 | 1.22 | 47 | 48 | 23.1 | 22.9 | 10.4 | 9 | **Y** |
| **(22)** | Uganda | 2002-2012 | 172 | 6.5 | 0-19 | 1.4 | 62.2 | 37.8 | 32.8 | 8.1 | 16.3 | 9.9 | N |
| **(23)** | Nigeria | 1994-2006 | 40 | 9.75 | 1-15 | 1.2 | 40 | 60 | 25 | 25 | 2.5 | 12.5 | N |

n: number of patients / M:F Male:Female / ST: Supratentorial / IT: Infratentorial / AST: Astrocytoma / MED: Medulloblastoma / EPD: Epedymoma / CPG: Craniopharyngioma / SCT: Spinal Cord Tumours

**Challenges faced, limitations of the study and possible solutions**

Several challenges were faced in conducting this study. First, there is a lack of a standardised method for categorising, classifying and even describing the epidemiological data published on paediatric brain tumours, which creates inconsistency in how findings of different studies are reported and has made it difficult to compare and contrast findings. Attempting to draw comparisons for example of tumour type by anatomic location requires a standardised way of defining certain anatomic locations, e.g. infratentorial vs supratentorial locations.

Second, the absence of a nationalised, or even institutional, paediatric brain tumour databank or registry has also highlighted the importance of this information not only to quantify the disease burden in the population but also to improve on referral to specialized, multi-disciplinary treatment centres, enabling better resource allocation for the specialized treatment of these patients and to minimise on patients lost to follow up by creating better documentation of patient treatment and progress. This has been recently addressed at our institution.

Third, creating a complete dataset from retrospective collection is fraught with general limitations, as well as limitations specific to our hospitals. Some records were incomplete because of the hospital policy to destroy records that had been inactive over a certain period. For research, this has major implications for a study over a twenty year period. For clinical purposes, this is also a limitation because some patients are transferred to adult services but their original data are lost; thereby leading to discontinuity of care. Missing data from folders is also a limitation of paper-based records and highlights the need for transition to electronic data capture. This has occurred in both our radiology as well as histopathological services, but records prior to the transition (in 2012) were also subject to similar hospital policies. Therefore, radiology reports had to be relied on.

Fourth, this study focussed on epidemiological data only, as a snapshot of the patients presenting to our service, and no attempt was made to analyse provision of services and clinical outcome. This will be the focus of a separate study. Limitations of follow up are expected to be a challenge also for these objectives, especially for non-local patients.

# CHAPTER SIX

## *CONCLUSION*

The findings in this were broadly consistent with published literature in terms of histological diagnosis, sex profile and age ranges for patients diagnosed with PBTs, with some differences thought to be possibly related to a referral bias. It documents the progressive increase in both the total number of cases diagnosed over the 22 year study period as well as in the number of patients seen from out of province referrals. The reported data and the limitations of the study emphasizes the importance of establishing an on-going tumour database registry for complete data capture of referred patients, their treatment, and their outcomes.

Despite the challenges typical of retrospective hospital-based studies with missing or incomplete data, the study provides a valuable foundation on which to build a high quality prospective paediatric brain tumour registry. Not only will this stimulate ongoing research in this field, it will aid in establishing treatment modalities employed, identifying limits of the service, and determining success and failures in achieving desired clinical outcomes.

## *RECOMMENDATIONS*

Continuation of high quality data registry and establishing an on-going prospective paediatric brain tumour registry for RCCH and GSH.

Standardised classification to describe childhood brain tumours, especially by anatomical location.

Cost analysis to assess feasibility of transitioning to electronic record keeping as is already done at some of the major tertiary hospitals in SA (Albert Lethuli Hospital in KZN and Tygerberg Hospital in the Western Cape).

## *WAY FORWARD*

The need for a follow up study to assess patient management and outcomes is of critical importance to assess effect of treatment modalities available and utilized and comparing outcomes and long-term survival for these group of patients. The second phase of data collection is already being planned and will commence as soon as appropriate ethical clearance has been obtained.

Many factors, the most detrimental being the destruction of patient records, led to the study prioritising breath of data (i.e. making sure that as few patients as possible were missed) rather than depth of information. Therefore the second part of the study will be to focus on depth of information including data points as planned in the original study protocol, including presenting symptoms, investigations including specific imaging modalities used, treatment plans and complications, outcomes and follow up data.

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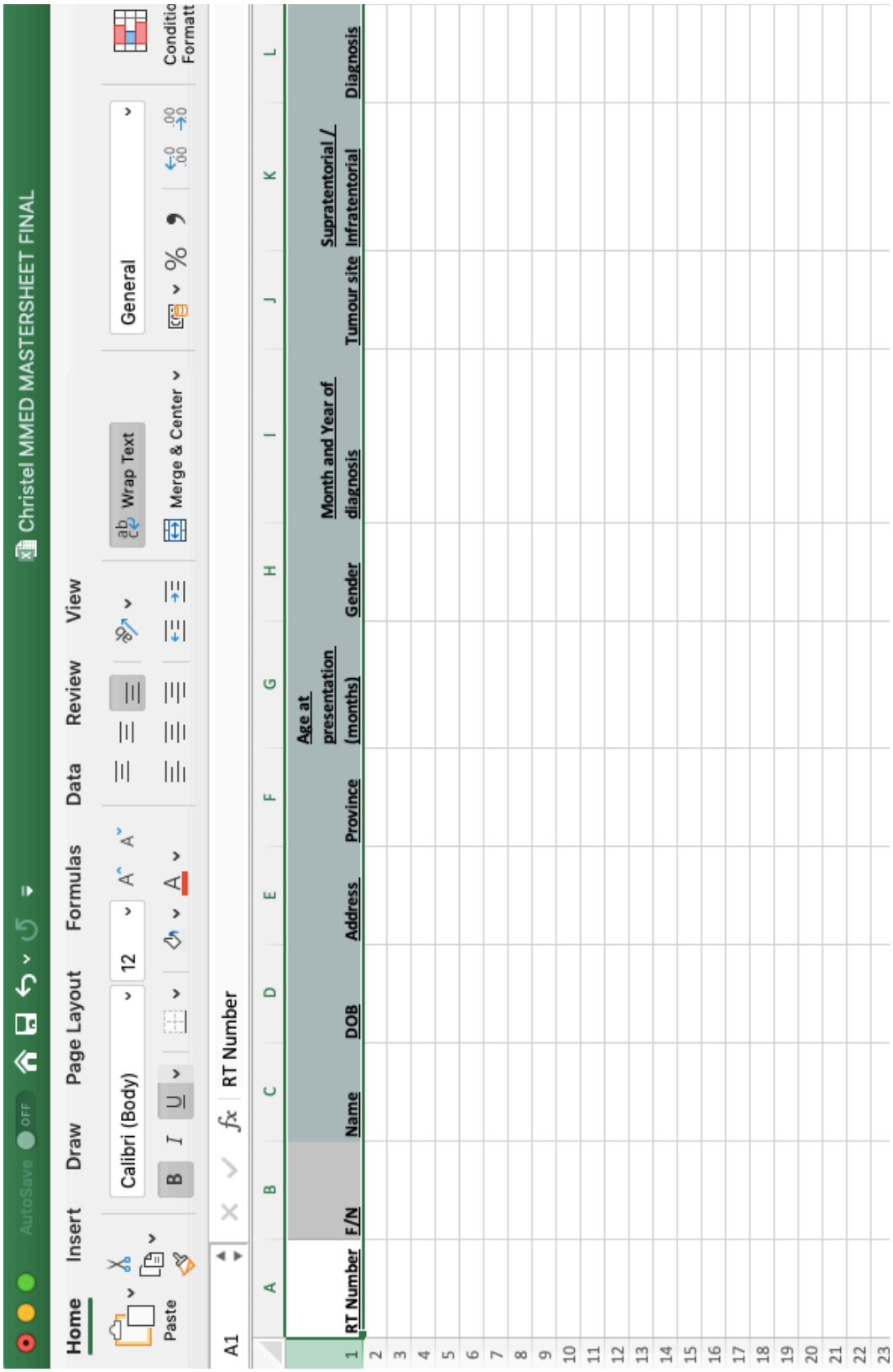
## APPENDICES

## APPENDIX 1: Excel spreadsheet for data collection



## APPENDIX 2: Departmental Research Committee Approval

UNIVERSITY OF CAPE TOWN

**Department of Surgery**

**Departmental Research Committee**
**Dr Timothy Pennel**
D24 Office, Groote Schuur Hospital,
Observatory 7925, South Africa
**Tel** (021) 404 3430
**Email:** tim.pennel@uct.ac.za

14 April 2017

Dr C Arnold-Day

Department of Surgery
Groote Schuur Hospital
University of Cape Town

Dear Dr Arnold-Day

RE: PROJECT 2016/085

PROJECT TITLE: **Paediatric brain tumours: the red cross children's hospital experience from 1996-2016**

The above proposal has been reviewed by the Department of Surgery Research Committee. I am pleased to inform you that the committee approved the scientific merit of the study, and endorse the protocol for submission to the relevant ethics committee.

Please use the above project number in all future correspondence.

Yours sincerely

Signature removed

DR TIMOTHY PENNEL
CHAIRMAN: RESEARCH COMMITTEE

## APPENDIX 3: Human Research Ethics Committee Approval

**UNIVERSITY OF CAPE TOWN**
**Faculty of Health Sciences**
**Human Research Ethics Committee**

**Room E53-46 Old Main Building**
**Groote Schuur Hospital**
**Observatory 7925**
**Telephone** [021] 406 6492
**Email:** sumayah.ariefdien@uct.ac.za
**Website:** www.health.uct.ac.za/fhs/research/humanethics/forms

30 April 2018

**HREC REF: 229/2018**

**Prof A Figaji**
Division of Neurosurgery
H-53
OMB

Dear Prof Figaji

**PROJECT TITLE: PAEDIATRIC BRAIN TUMOURS: THE RED CROSS CHILDREN'S HOSPITAL EXPERIENCE FROM 1996-2016 (MMed-candidate-Dr C Arnold-Day)**

Thank you for your response letter dated 16 April 2018, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**Approval is granted for one year until the 30 May 2019.**

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Stancard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

***We acknowledge that the student: Dr C Arnold-Day will also be involved in this study.***

**Please quote the HREC REF in all your correspondence.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.
Yours sincerely

Signature removed to avoid exposure online

**PROFESSOR M BLOCKMAN**
**CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE**

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

# APPENDIX 4: Groote Schuur Hospital Institutional Approval


**GROOTE SCHUUR HOSPITAL**
**Enquiries**: Dr Bernadette Eick
**E-mail** : Bernadette.Eick@westerncape.gov.za

Professor A. Figaji
**Division of Neurosurgery**

E-mail: christelday@gmail.com / Anthony.Figaji@uct.ac.za

Dear Professor Figaji

**RESEARCH PROJECT: Paediatric Brain Tumours: The Red Cross Children's Hospital Experience from 1996-2016 (MMed. Dr Christel Arnold-Day)**

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 May 2019,** subject to the approval of **Professor Fieggen and Dr Z. Mohamed, for combining of databases.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must be maintained at all times.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
**l) Kindly submit a copy of the publication or report to this office on completion of the research.**

I would like to wish you every success with the project.

Yours sincerely

**DR BERNADETTE EICK**
**CHIEF OPERATIONAL OFFICER**
**Date:** 16 May 2018
Signanture removed
C.C. Mr L. Naidoo
Professor G. Fieggen
Dr Z. Mohamed

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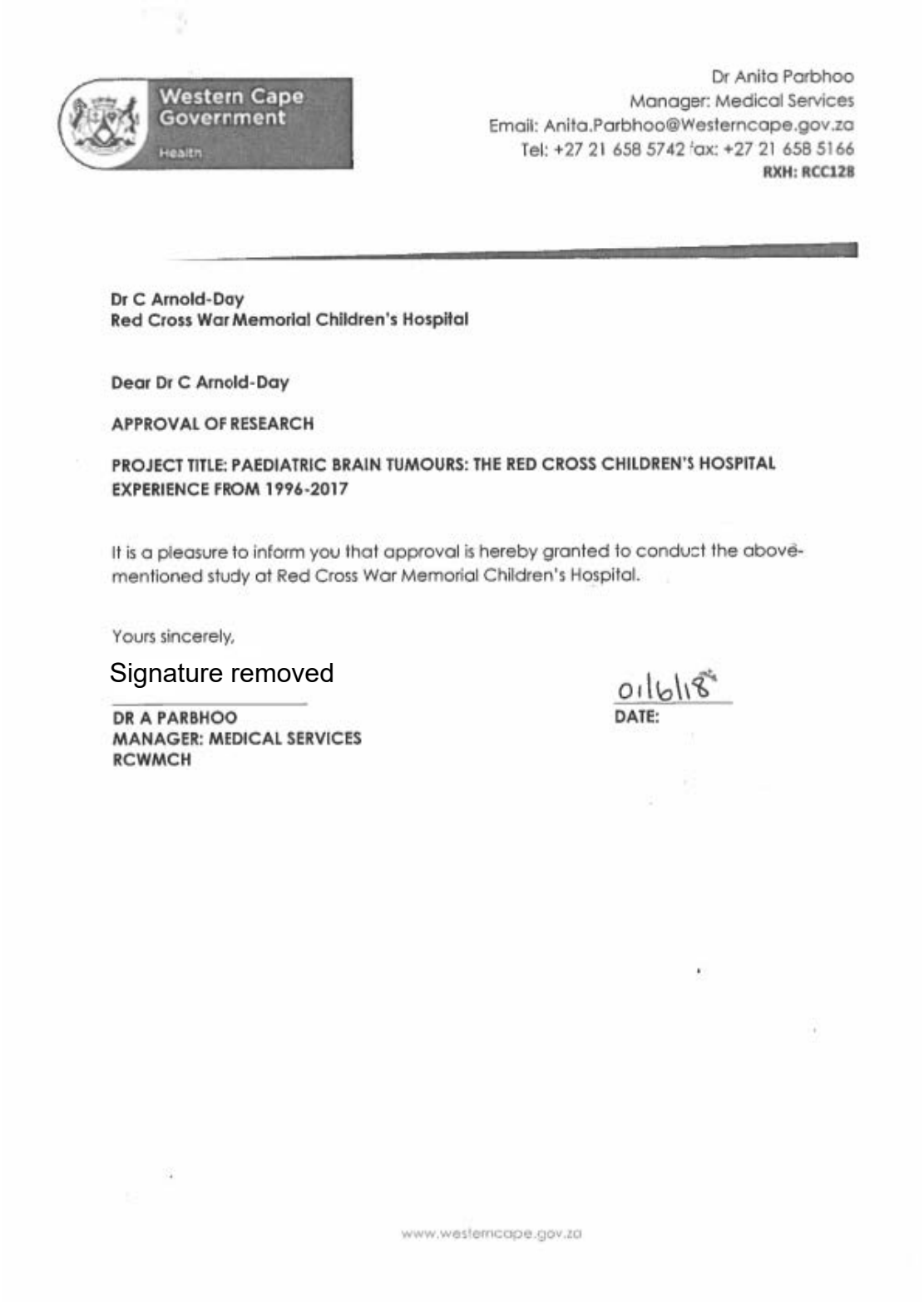
## APPENDIX 5: Red Cross War Memorial Children's Hospital Institutional Approval



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Dr C Arnold-Day
Red Cross War Memorial Children's Hospital

Dear Dr C Arnold-Day

APPROVAL OF RESEARCH

PROJECT TITLE: PAEDIATRIC BRAIN TUMOURS: THE RED CROSS CHILDREN'S HOSPITAL EXPERIENCE FROM 1996-2017

It is a pleasure to inform you that approval is hereby granted to conduct the above-mentioned study at Red Cross War Memorial Children's Hospital.

Yours sincerely,

Signature removed

DR A PARBHOO
MANAGER: MEDICAL SERVICES
RCWMCH

01/6/18
DATE:

www.westerncape.gov.za