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A description of the profile of paediatric brain tumours in a tertiary neurosurgery service

Dissertation submitted in partial fulfilment of the requirements for the degree,

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I, Debbie de Beer (Student number: 04428188), declare that this dissertation is my own original work. It is being submitted for the degree MSc Human Physiology at the University of Pretoria. It has not previously been submitted by me for any degree at this or any other university.

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Date: 27/12/2023

Dedication

In loving memory of my father, my eternal hero, whose indomitable spirit guided me through every chapter of this journey. Though he is no longer physically present, his wisdom and love resonate in everything I do.

To my mother, the embodiment of strength and resilience, whose courage has been my guiding light. Your sacrifices and unyielding determination have shaped the person I am today. This dissertation stands as a testament to the values you instilled in me and the inspiration you continue to be.

In honour of both, who taught me that dreams are worth pursuing, challenges are meant to be conquered, and love is the greatest force in the universe. This work is dedicated to the enduring legacy of my parents.

Abstract

Background

Central nervous system (CNS) tumours are the most common form of solid tumours in children, leading to significant mortality and morbidity. In developing countries, survival rates for children with CNS tumours are lower than in developed nations. In South Africa, brain tumours account for 13% of paediatric cancers, yet local epidemiological data is scarce. No regional data exists for Steve Biko Academic Hospital in South Africa.

Aim and Objectives

This study aimed to describe the profile of paediatric brain tumours at Steve Biko Academic Hospital by examining patient demographics, histopathology, and imaging data.

Methods

This retrospective study reviewed medical records from the neurosurgery department at Steve Biko Academic Hospital. Data on patient demographics, tumour histopathology, and imaging from January 2019 to June 2023 were analysed to compile a comprehensive tumour profile.

Results

The study included 52 patients, with a male-to-female ratio of 1.74:1 and a mean age of 6.8 years. The highest tumour prevalence was in the 3–8-year age group. Infratentorial tumours were the most common. In descending order, the most prevalent tumour types were mixed glioma, medulloblastoma, astrocytoma, and ependymoma.

Discussion

The male predominance aligns with existing studies, potentially due to sex differences in brain development. The high incidence of infratentorial tumours may be linked to genetic susceptibility and rapid cell proliferation in this region. The common tumour types in this study all originate from highly prolific cells, contributing to an elevated risk of tumorigenesis.

Conclusion

The findings in this study, such as mean age, tumour location, and tumour prevalence, corroborate similar studies from Westernised countries. Understanding the epidemiology of paediatric brain tumours is vital for improving diagnosis, treatment, and healthcare policies. Regional data is essential for enhancing medical knowledge and improving patient outcomes.

Keywords: Paediatric brain tumours, malignancy, cancer, supratentorial, infratentorial, posterior fossa glioma, medulloblastoma.

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LIST OF ABBREVIATIONS

AT/RT	Atypical teratoid/rhabdoid tumour
CGNP	Cerebellar Granule Neuron Precursor
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT scan	Computerised Tomography scan
DIPG	Diffuse Intrinsic Pontine Glioma
DNA	Deoxyribonucleic Acid
DWI	Diffusion-Weighted Imaging
FBG	Focal Brainstem Glioma
GLI2	Glioma-Associated Oncogene Family Zinc Finger 2
GLOBOCAN	Global Cancer Observatory
Ha	Alternative hypothesis
Ho	Null hypothesis
ICP	Intracranial Pressure
IFN-γ	Interferon-gamma
MRI	Magnetic Resonance Imagining
NFIA	Nuclear factor I/A
PBT	Paediatric Brain Tumours
PDGFRα	Alpha-type platelet-derived growth factor receptor
PET scan	Positron Emission Tomography scan
PNET	Primitive Neuroectodermal Tumours
PWI	Perfusion-Weighted Imaging
SBAH	Steve Biko Academic Hospital

SD	Standard Deviation
SHH-MBs	Sonic Hedgehog-activated Medulloblastomas
TNF	Tumour Necrosis Factor
UP	University of Pretoria
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

Brain tumours are the second most common cancer in children, comprising 15–25% of all paediatric malignancies.[1] They are the most common solid tumours in this population, possessing the highest mortality rate of all cancers.[2, 3] The term "brain tumours" refers to a mixed group of neoplasms (abnormal and excessive growth of cells) originating from intracranial tissues and the meninges.[4] These tumours are classified as benign and malignant, with malignant tumours further classified according to aggressiveness. Each tumour type is characterised by its anatomy, treatment, prognosis, and associated risk factors. Even "benign" tumours can be lethal due to their location, ability to infiltrate locally to compress vital structures, and their propensity to transform into malignant tissue. This makes for a complex classification process and creates a challenge in describing the epidemiology of these brain tumours.[5]

The profile of paediatric brain tumours (PBTs) in developed countries is well documented, but such studies are scarce in developing countries, especially in sub-Saharan Africa. The annual incidence of childhood cancer was estimated to be between 33.4 and 47.2 million between 2003 and 2007.[6] Cancer is a significant non-communicable cause of death in children. It is estimated that about 148,000 children living in low-income countries have cancer, according to GLOBOCAN 2014.[7] A study published in Cancer Epidemiology in 2021 estimated a total of 360,114 childhood cancers occurring worldwide in 2015 with 28% of these in Africa.[8] Recent data suggests an estimated 13.7 million new cases of childhood cancer globally between 2020 and 2050, and 9.3 million of the affected children will be in lower-income countries.[9] Africa is the second largest continent, with a population of one billion, of whom the majority (874.8 million; 2011) live in sub-Saharan Africa,[7] yet the South African cancer registry reported the lowest overall incidence rates at 44.1 cases per million.[8] Overall survival rates for children in developing countries are far lower than in developed countries.[10] To address this disparity and improve childhood cancer survival rates in sub-Saharan Africa, the first step must be to collect accurate data on incidence and survival.[11] A cancer report from rural South Africa documented childhood cancer as comprising 2.9% of all cancers, and brain tumours represent roughly 13% of the total cancers diagnosed in children in South Africa.[7, 12, 13]

Paediatric brain tumours are unique in distribution, clinical presentation, pathologic types, management, and prognosis.[14-16] The incidence of PBTs differs by age, sex, geography, race, and ethnicity, with males having a higher prevalence.[5, 17] The epidemiology of paediatric brain tumours in other countries is well documented; however, few studies have been done on the South African population.

No studies have been conducted to establish such epidemiological data at the Steve Biko Academic Hospital in South Africa. There is a need to collect regional data for the Greater Tshwane areas, Mpumalanga, and the East Rand of Gauteng, all served by the hospital above. Studying the profile of paediatric brain tumours in a specific region is essential for advancing medical knowledge, improving patient outcomes, and enhancing the overall quality of healthcare services for affected children and their families.

Improved management of paediatric patients with brain tumours depends primarily on established protocols and the implementation of new strategies derived from appropriate research.[18] The information gained from the study will be valuable in providing recent statistics to the local cancer registry in managing subsequent patients, planning for treatment and further managerial follow-up of children with primary brain tumours.

This study aimed to describe the profile of brain tumours in the paediatric population at Steve Biko Academic Hospital by examining the demographic profile of this patient cohort, analysing the histopathological profile of these tumours, and investigating the imaging profile using radiographical data.

CHAPTER 2: LITERATURE REVIEW

2.1 Etiological factors contributing to the development of paediatric brain tumours

The origin of paediatric brain tumours involves genetic mutations, environmental factors, and disruption of intricate cellular processes.[19-21] Most brain tumours have abnormalities or mutations in genes involved in cell cycle control, causing uncontrolled cell growth.[22, 23] Genetic alterations or chromosomal rearrangements cause changes in the functions of a gene, resulting in either a loss of function or a gain of function mutation.[24] The two categories of genes playing a significant role in tumorigenesis and cancer induction include the tumour suppressor genes and the oncogenes.[25] Tumour suppressor genes are crucial in regulating the cell cycle and preventing cancer development. These genes, such as the TP53 gene, encode proteins that inhibit the progression of the cell cycle, promote DNA repair, and induce apoptosis (programmed cell death) in response to various cellular stresses, such as DNA damage or inappropriate cell division. Tumour suppressor genes thus act as guardians of genomic integrity, ensuring that cells with damaged DNA do not proliferate uncontrollably. Mutations leading to loss of function or inactivation of tumour suppressor genes can disrupt these regulatory mechanisms, allowing cells to evade normal growth controls, leading to uncontrolled cell growth and contributing to the initiation and progression of cancer. As for the oncogenes, overexpression and amplification are the most common alteration mechanisms. Oncogenes, when aberrantly activated, promote cellular transformation and malignant growth. Mutations in these genes can result in constitutive activation of the encoded proteins, leading to uncontrolled cellular proliferation and evasion of standard regulatory mechanisms. As shown in Figure 1, unchecked cell growth results from either a loss or a gain of function mutation. Consequently, paediatric brain tumours develop as a result of accumulated genetic alterations that permit cells to evade standard regulatory mechanisms and destruction by the immune system.[26-28]

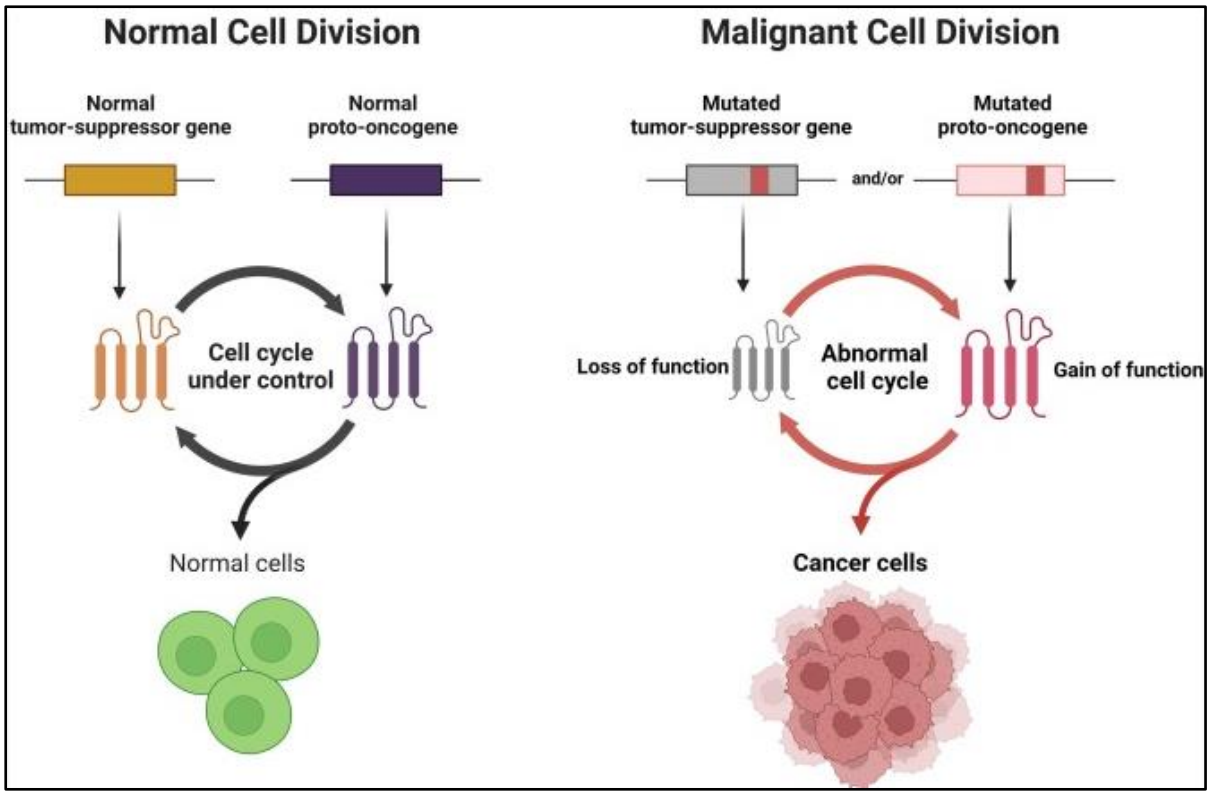

Figure 1: The effect of mutations in tumour-suppressor genes and proto-oncogenes on normal cell proliferation[29] *Mutations in tumour-suppressor genes lead to a loss of function, and mutations in proto-oncogenes lead to a gain of function. These alterations in function cause a disruption in cell cycle control, ultimately resulting in cancerous cells.*

Patients with certain genetic conditions (neurofibromatosis, von Hippel-Lindau disease, Li-Fraumeni syndrome, and retinoblastoma) exhibit an increased risk of developing CNS tumours due to specific underlying genetic mutations associated with these conditions.[30] In these genetic conditions, the mutations affect genes crucial for maintaining cellular homeostasis by regulating cell growth, differentiation, and apoptosis (programmed cell death). When these regulatory mechanisms are disrupted, it can lead to uncontrolled proliferation and the development of tumours, including those in the central nervous system. Neurofibromatosis (NF) type 1 results from mutations in the NF1 gene located on chromosome 17. The NF1 gene encodes for the neurofibromin protein that acts as a tumour suppressor. Mutations in this gene impair the protein's ability to effectively regulate cell growth and proliferation. Individuals with this mutation have an increased risk of developing CNS tumours,

particularly gliomas. Neurofibromatosis type 2 (NF2) is a dominantly inherited tumour predisposition syndrome caused by mutations in the NF2 gene on chromosome 22. The NF2 gene encodes for the protein Merlin (Schwannomin), a tumour suppressor. Mutations in this gene lead to the loss or dysfunction of Merlin and, subsequently, the formation of tumours in the nervous system. The tumours commonly associated with NF2 are schwannomas and meningiomas, as well as low-grade ependymomas and gliomas.[31] Schwannomatosis is the rarest form of neurofibromatosis and is characterised by the growth of multiple schwannomas. The genes thought to be implicated in this condition are SMARCB1 and LZTR1. These genes are involved in the regulation of gene expression and cell proliferation.[32] Von Hippel-Lindau disease arises from mutations in the VHL gene. The VHL gene is a tumour suppressor gene, and its mutation can lead to the formation of tumours in various organs, including the CNS.[33] Hemangioblastomas are prevalent CNS tumours in the VHL genotype. Li-Fraumeni syndrome is characterised by mutations in the TP53 tumour suppressor gene and entails an increased susceptibility to diverse cancers, including CNS tumours such as gliomas and medulloblastomas. Retinoblastoma arises from mutations in the RB1 gene, which is involved in cell cycle regulation. Individuals with hereditary retinoblastoma who inherit a mutated copy of RB1 have an increased risk of developing other cancers, including sarcomas and CNS tumours such as gliomas.

The risk of astrocytoma in childhood has been maternally genetically linked to age and a history of prior foetal deaths.[34] The most vital established environmental risk factor for CNS tumours is exposure to ionising radiation, especially early in life.[20-22] Children who received radiation for the treatment of tinea capitis, a fungal infection that affects the skin of the scalp and hair follicles, have been shown to have increased incidence of CNS tumours, especially meningiomas, gliomas, and nerve sheath tumours.[14, 23, 35]

Epidemiologic studies are essential in identifying which individual attributes and environmental exposures increase susceptibility to, and the probability of, adverse genetic mutations.

2.2 Types of paediatric brain tumours, prevalence, and age distribution

Primary paediatric brain tumours are abnormal growths that develop in children's brains. Brain tumours are often classified by the type of cells they originated from, their location, and other characteristics. The brain has two main cell types: neuronal and glial cells.[36] Neuronal cells are nerve cells or neurons. Glial cells surround and support neurons and are also called non-neuronal cells. Depending on the primary cell type of origin, PBTs can be classified into two major categories: glial and neuronal tumours. The following are common types of paediatric brain tumours that will be discussed in this study and their impact on the physiology of surrounding structures:

Gliomas:

According to the American Cancer Society, gliomas account for nearly half of paediatric brain tumours, and these tumours often present with benign and low-grade classifications.[37] Gliomas are tumours originating in glial cells and are classified further by the specific cell of origin. The most common subtypes of gliomas include astrocytomas, oligodendrogliomas, ependymomas, brainstem gliomas, and diffuse intrinsic pontine gliomas.

Astrocytomas are tumours that develop from astrocytes. These neuroglia provide structural support to nerve cells by forming a scaffolding-like network in the CNS. Astrocytes are actively involved in maintaining the blood-brain barrier, a highly specialised and selectively permeable barrier system that separates the circulating blood from the brain and the CNS tissue, ensuring their structural and functional stability. The reuptake and recycling of neurotransmitters and maintenance of a stable chemical environment remain a pivotal function of these star-shaped cells.[38] Astrocytomas account for about 50% of all childhood brain tumours. However, they are most common in children between the ages of 5 and 8.[39] Depending on the rate of abnormal cell proliferation, these tumours exist as low-grade (slow-growing) and high-grade (fast-growing) tumours. Although high-grade astrocytomas are the most malignant of all brain tumours, most are present as low-grade tumours. This neoplasm affects the CNS through local compression and infiltration, leading to increased pressure within the cranium and potential damage to nearby structures. Clinical

features that present most commonly include headache, seizures, and focal neurological deficits.[40]

Oligodendrogliomas arise from oligodendrocytes and support and insulate nerve fibres by producing and maintaining the myelin sheath. Oligodendrogliomas are low-grade and usually develop in the frontal or temporal cerebral lobes, crucial areas that control higher functions such as reasoning and memory.[41] The growth of oligodendroglioma can interfere with normal neural function by compressing nearby structures or invading surrounding brain tissue. Common symptoms may include seizures, headaches, cognitive and memory difficulties, and changes in behaviour or personality.[40]

Ependymomas account for 10% of all brain tumours, making them the third most common intracranial paediatric malignancy.[37, 42,75] Ependymomas develop from ependymal cells called radial glial cells that line the ventricles of the brain and the spinal cord. The primary function of ependymal cells is to produce and circulate cerebrospinal fluid (CSF) via cilia on their surfaces. These tumours can obstruct the cerebrospinal fluid (CSF) flow within the ventricles, exerting this effect mainly in the brain's fourth ventricle. This leads to hydrocephalus. Increased pressure from hydrocephalus can cause headaches, nausea, vomiting, impaired vision, and other symptoms. Clinical features are determined by the patient's age and the tumour origin site. Non-specific clinical features are observed in young children, such as failure to thrive, lethargy, and irritability. Specific clinical features differ between infratentorial and supratentorial regions of origin. Posterior fossa tumours, situated infratentorially, manifest with heightened intracranial pressure (ICP), cervical discomfort, and/or ataxia. The fourth ventricle, centrally located within the posterior fossa, is susceptible to compression by tumours in this region, consequently elevating ICP and precipitating hydrocephalus. Adjacent structures, such as the cerebellum, are prone to compression-induced compromise, resulting in symptoms like ataxia. Conversely, supratentorial tumours exert their influence on cerebral structures, thereby affecting motor and sensory functions. Consequently, presentations of supratentorial tumours commonly include manifestations such as limb weakness, seizures, gastrointestinal and urinary dysfunction, paraesthesia, and pain.[43, 44] Intracranial ependymomas pose a significant risk of tumour recurrence due to the inherent challenges associated with achieving complete resection, owing to their intricate anatomical positioning and

infiltrative growth patterns. These patients exhibit a diminished five-year overall survival rate of approximately 50-70%.[45, 46]

Brainstem gliomas constitute 10-20% of PBTs. As the name implies, these tumours arise within the brainstem, a region responsible for regulating fundamental bodily functions.[47] The brainstem houses vital centres such as the cardiovascular centre, respiratory centre, and vasomotor centre. Brainstem gliomas can be broadly divided into focal brainstem gliomas (FBGs) and diffuse intrinsic pontine gliomas (DIPGs).[48] FBGs arise in the midbrain or medulla and are usually low-grade tumours. The growing tumour can compress adjacent structures like the spinal cord and nerves that innervate the muscles of the cervical region, leading to neck stiffness and discomfort. Another common clinical feature is contralateral hemiparesis, a neurological manifestation characterised by a diminished degree of motor strength or muscular power on one side of the body and on the opposing side of the tumour. This occurs due to compression or damage to the corticospinal tract that decussates at the level of the medulla oblongata. Isolated cranial nerve deficits are common. For example, damage to cranial nerves IX and X (Glossopharyngeal and Vagus) causes dysphagia (impaired or abnormal swallowing function). Interference with the nerve pathways of the respiratory centre can cause apnoea (a temporary cessation of breathing). Hydrocephalus is uncommon.[48-50] Long-term overall survival is near 100%, but chronic disability is common.[49]

Diffuse intrinsic pontine gliomas (DIPGs) represent 80% of all paediatric brainstem tumours and present as either high-grade, diffuse, or infiltrative tumours.[37, 48] Patients usually present around 7-years old, and the onset of symptoms develops rather quickly compared to FBGs. The triad of cranial neuropathy, long tract signs, and cerebellar findings present for less than a month and are highly specific to DIPGs.[51] Classic clinical features seen in over 50% of cases include facial asymmetry (caused by damage to the Facial nerve/Cranial nerve VII)[52] and diplopia (can be explained by damage to the Oculomotor nerve/Cranial nerve III, and the Abducens nerve/Cranial nerve VI).[52] Long tract signs, such as an upgoing Babinski reflex [51] and hyperreflexia, are common. The planter reflex is a neurological phenomenon characterised by an observable motor response upon the stimulation of the sole and is indicative of an abnormality in the corticospinal tract. In a typical planter reflex, upon stimulation of the

sole, the flexion (curling) of the toes downwards is observed and is considered a normal response beyond infancy. When the Babinski reflex is present, the opposite is observed: the extensor muscles of the big toe (extensor hallucis longus) are activated, causing the toes to extend upward. This is indicative of damage to the pyramidal tract.[53] Common cerebellar signs include ataxia and dysmetria.[48, 54, 55] Signs of increased ICP are seen in less than 10% of cases at diagnosis and are more common in the end stages of the disease.[55] Due to their location in the pons, this type of tumour tends to be inoperable, and the prognosis is poor, with less than 3% of patients surviving at 5 years.[54] Long-term survivors typically have neurological deficits and cognitive impairment.[56]

Neuronal tumours

Neuronal tumours arise from nerve cells or neurons. They are less common than glial tumours and often have a better prognosis as they tend to be benign or slow-growing.[26] The majority of neuronal tumours are embryonal tumours.[14, 17] Embryonal brain tumours develop from excess embryonic cells during gestation and remain within the infant's brain after birth.[15, 16] These embryonic cells are usually innocuous but can become malignant. Malignant embryonic cells metastasise to other parts of the brain and spinal cord via the CSF.[19, 20] The various types of neuronal tumours include medulloblastomas, gangliogliomas, pineoblastoma, and atypical teratoid/rhabdoid tumours.[21-23]

Medulloblastomas are embryonal tumours that originate from the developing cells of the cerebellum. This is the most common malignant brain tumour in children and accounts for 20-30% of all PBTs.[57, 58] The peak age of diagnosis is 6-8 years.[59] They are fast-growing, can invade nearby tissues, and spread to other parts of the CNS via the CSF. Medulloblastomas originate within the cerebellum, and subsequent metastasis along the spinal cord is not uncommon.[60] These tumours can disrupt the normal functioning of the cerebellum, leading to decreased motor coordination, ataxia, visual disturbances, and poor muscle control.[61, 62] The overall survival rate is approximately 75%.[63] Infants and children younger than three years have a poor prognosis with a 40-50% survival rate.[64]

Gangliogliomas contain abnormal ganglion cells (neurons) and glial cells and are usually classified as low-grade tumours.[65] Symptoms of gangliogliomas can vary depending on their location and size. Common signs may include seizures, headaches, neurological deficits such as weakness or difficulty with coordination, cognitive changes, and visual disturbances.

Pineoblastomas are rare, aggressive brain tumours that originate in the pineal gland, in the centre of the cerebrum, posterior to the 3rd ventricle. The pineal gland produces melatonin, a hormone that regulates sleep-wake cycles. These tumours are classified as embryonal tumours since they arise from immature cells. Pineoblastomas are highly malignant, tend to grow rapidly and invade surrounding brain tissue.

Atypical teratoid/rhabdoid tumour, or AT/RT, is a fast-growing, relatively rare, malignant tumour typically presenting in children under 3 years of age.[66] AT/RTs are characterised by the presence of abnormal cells that display features of both teratoid and rhabdoid tumours. Teratoid refers to the presence of cells that resemble multiple different cell types, while rhabdoid refers to the presence of cells with distinct features known as "rhabdoid cells", neoplastic cells with oval or round prominent nuclei with intracytoplasmic inclusions [67] Despite aggressive treatment, AT/RTs have a poor prognosis. The tumours tend to resist therapy and have a high recurrence rate. The overall survival rate for AT/RT is relatively low, nearly 30% 5-year survival, with a significant number of cases resulting in death.[68, 69]

Choroid plexus tumours:

Choroid plexus neoplasms are rare brain tumours that arise from the choroid plexus epithelium and are responsible for producing cerebrospinal fluid (CSF) in the ventricles. Their distribution corresponds to the choroid plexus in the different ventricles, with nearly 50% occurring in the lateral ventricles, 40% in the fourth ventricle, and 5% in the third ventricle.[70] These tumours can either restrict the circulation of CSF or cause an overproduction of CSF, resulting in hydrocephalus. Choroid plexus tumours account for 1% of all PBTs, constituting 15% of tumours in children under 1 year of age. [71]

Choroid plexus tumours are classified into three main types based on their histological characteristics:

Choroid Plexus Papilloma: This is the most common type and is generally considered a benign tumour with a WHO grade I classification. It tends to grow slowly and has a low tendency to spread to other parts of the brain or spinal cord. Histologically, they contain uniform cellularity with little to no atypical cells.[70]

Atypical Choroid Plexus Papilloma: This type is less common and has more aggressive characteristics than choroid plexus papilloma. They are generally classified as a grade II tumour, and due to their higher mitotic count, there is a greater potential for recurrence and invasion into nearby tissues.[70] Prognosis is excellent, however, with a 10-year survival rate exceeding 80%.[71, 72]

Choroid Plexus Carcinoma: This is the rarest and most aggressive form of choroid plexus tumour. It is considered a malignant tumour and has a higher likelihood of metastasising to other parts of the brain and spinal cord via the CSF pathways. The prognosis is poor, with a median survival rate of less than three years.[71]

Craniopharyngiomas:

Craniopharyngiomas are benign epithelial tumours that develop along the hypothalamo-hypophyseal tract near the pituitary gland, which controls hormone production. Craniopharyngiomas constitute 6-9% of PBTs and most commonly occur in the age groups 6-10 years, followed by the 11-15 year age group.[73, 74] Histologically, craniopharyngiomas exhibit a complex pattern of solid and cystic components. Nearly 90% of paediatric craniopharyngiomas demonstrate calcification, and approximately 90% of these tumours are predominantly cystic.[75, 76] The most common presenting symptom of craniopharyngiomas is visual impairment (present in 70-80% of cases)[73], often caused by optic chiasm compression. Endocrine dysfunction is also frequently observed, including deficiencies in growth hormone, thyroid-stimulating hormone, adrenocorticotropic hormone, and gonadotropins. In paediatric patients, this most commonly manifests as growth failure.[74] Survival rates for craniopharyngiomas are approximately 90%, but due to postoperative consequences such as hypothalamic obesity and panhypopituitarism (a rare medical condition characterised by the

profound deficiency of hormone secretion from the anterior pituitary gland), quality of life is impaired.[76]

Figure 2 shows the various brain areas in which tumours commonly arise.

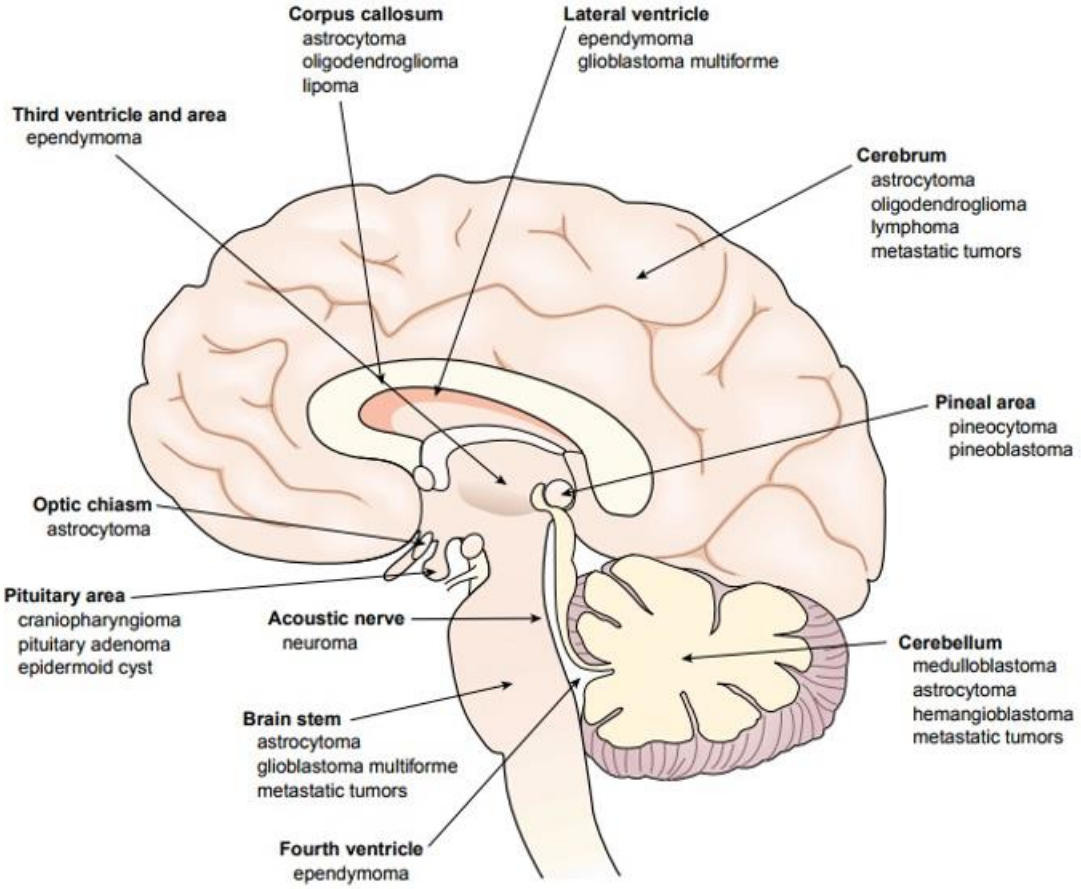

Figure 2: Common brain tumour areas[77] *Listed under the common tumour areas in the brain are the tumour types most frequently associated with that region.*

According to Cohen et al.(2001), 88% of all tumours fall into the following categories: astrocytoma, medulloblastoma, ependymoma, and craniopharyngioma.[37]

2.3 Anatomical classification of brain tumours

Paediatric brain tumours are classified anatomically into supratentorial and infratentorial regions to provide a comprehensive framework for understanding and managing these neoplastic conditions in children. This division is based on anatomical considerations and clinical implications, as well as the distinct characteristics

associated with tumours in these regions. Figure 3 illustrates the anatomical division of these regions.

Supratentorial tumours are localised within the cerebral hemispheres, which form the upper part of the brain and are situated above the tentorium cerebelli, the tough, crescent-shaped fold of dura mater that separates the cerebellum from the cerebral hemispheres. They predominantly affect the frontal, parietal, temporal, and occipital lobes. The significance of this classification lies in the fact that supratentorial tumours frequently manifest with specific clinical presentations related to their location, including seizures, hemiparesis (a neurological condition characterised by partial weakness or diminished muscular strength affecting one side of the body), cognitive impairment, and sensory deficits. Additionally, these tumours are more commonly associated with progressive focal neurological deficits and intracranial hypertension due to the limited space available for expansion within the rigid cranium.

Conversely, infratentorial tumours are below the tentorium cerebelli, primarily affecting the cerebellum and brainstem. The cerebellum plays a crucial role in coordinating voluntary movements and maintaining balance, while the brainstem acts as a conduit for vital functions such as breathing, heart rate regulation, and consciousness. The division of paediatric brain tumours into infratentorial locations is essential because tumours in this region often present with distinct clinical features, including gait disturbances, cranial nerve deficits, ataxia, and bulbar symptoms such as dysphagia and respiratory difficulties due to compression of the medulla oblongata. Moreover, these tumours can exert pressure on the fourth ventricle, leading to hydrocephalus, obstructive symptoms, and increased ICP.

The classification of paediatric brain tumours into supratentorial and infratentorial locations has substantial implications for diagnosis, treatment planning, and prognostication. It allows healthcare professionals to consider the specific anatomical and clinical characteristics associated with each location, facilitating more targeted and effective management strategies. This classification system is widely utilized in research studies, clinical trials, and treatment guidelines, enabling standardized reporting, comparison of outcomes, and the development of evidence-based approaches to improve patient care and outcomes in paediatric neuro-oncology.

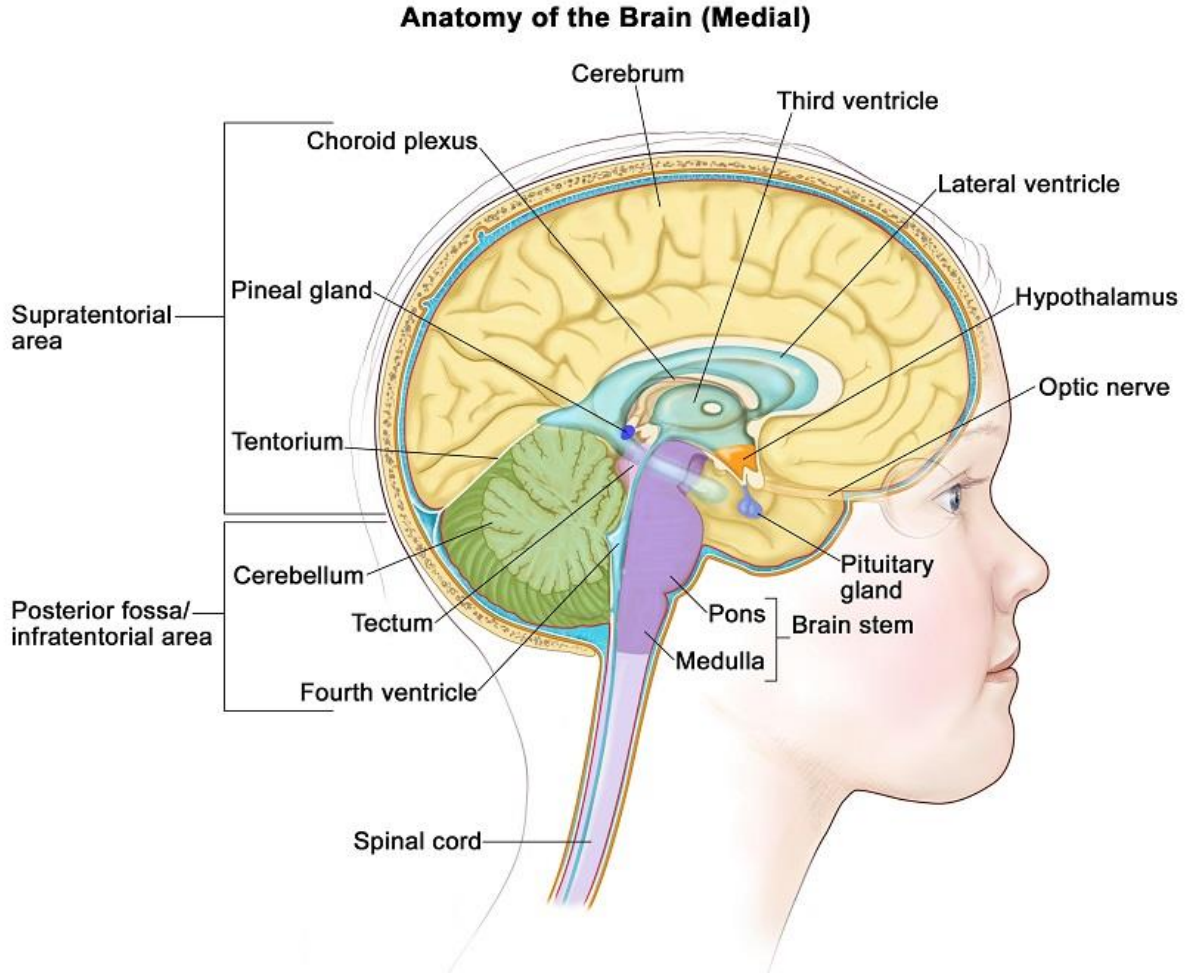

Figure 3: The supratentorial and infratentorial brain regions [78] *The supratentorial area includes all structures found above the tentorium and all structures below the tentorium are considered infratentorial.*

2.4 The diagnosis and classification of brain tumours

The diagnosis of PBTs is based on clinical presentation, as well as radiological and histopathological characteristics. Diagnosing and classifying paediatric brain tumours involves integrating various imaging techniques, histological analysis, and the World Health Organization (WHO) 2021 classification of central nervous system (CNS) tumours. This comprehensive method ensures accurate and precise identification of the tumour type and facilitates appropriate treatment planning.

Brain tumours in children and adults differ significantly in their incidence, tumour type, and treatment. Overall survival rates for children with brain tumours are better than for

adults. Signs and symptoms of a brain tumour vary greatly and depend on the type, size, location, and growth rate of the brain tumour. Some signs and symptoms may not be easy to detect because of their similarities to symptoms of other conditions.[79] The symptoms that present most commonly are headache, nausea/vomiting, seizures, diplopia (double vision), and ataxia (staggering gait, lack of coordination, balance difficulties). Brain tumours in infants are often aggressive, and symptoms develop rapidly within a relatively short period. In children younger than 2 years, the most common initial signs and symptoms are seizures, vomiting, failure to thrive, and behavioural changes. Children are more likely to develop tumours in the lower parts of the brain, mainly the brain stem and cerebellum – which can cause abnormality in movement and coordination. The presence of a suspected tumour is confirmed with imaging. Imaging modalities are crucial in diagnosing paediatric brain tumours by providing structural information. Magnetic Resonance Imaging (MRI) is the primary imaging modality for paediatric brain tumour evaluation. It offers excellent soft tissue contrast and multiplanar imaging capabilities, providing detailed information about the tumour's location, size, and morphology. Moreover, advanced MRI techniques, such as diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI), help distinguish between different tumour types and evaluate their biological behaviour. Although MRI is the preferred imaging method, CT scans can be useful in certain situations, especially for assessing calcification, bony involvement, or emergency cases where MRI may not be immediately accessible. Tumour metabolism can be investigated using Positron Emission Tomography (PET) scans with a radiotracer like 18F-deoxyglucose, indicating sites of abnormal glucose metabolism and can characterise and localise tumours. Although imaging provides structural information about a tumour, it leaves important clinical questions such as tumour type, aggressiveness, and prognosis unanswered.[80, 81]

Once a brain tumour is suspected based on imaging findings, histological analysis is required to determine its cellular composition. Histopathological diagnosis is performed by examining a tumour tissue sample, identifying the anaplastic cells, and determining the tumour type according to the WHO Classification of Tumours of the Central Nervous System (WHO CNS5).[14] Tissue samples are obtained through biopsy or during surgical resection. The collected specimen is then processed, sectioned, and stained for microscopic examination. This process enables the identification and

classification of specific tumour types based on their histological appearance. Histopathological evaluation involves the assessment of cellular morphology, nuclear features, mitotic activity, and other characteristics. Cancer cells are characterised by abnormal cell growth and varying degrees of cellular atypia. Anaplastic cells often exhibit irregular shapes, sizes, and nuclear features, such as an increased nuclear-to-cytoplasmic ratio. Tissue architecture is another factor that is evaluated - tumour structure is analysed by observing the overall organisation of cells within the tissue. Disruption of normal tissue architecture and invasion into surrounding tissues indicate cancer. Mitotic activity refers to the rate of cell division, and increased mitotic activity is characteristic of rapidly dividing cancer cells.[82] Figure 4 shows the clear difference between healthy brain and cancer cells (glioma). The cell graphs illustrate the distinction between the self-organising clusters of cancer cells and healthy cells.[83] The tumour grade and stage are also determined and indicate the aggressiveness of growth and the level of metastases at that point in time. Most current classification systems use these two criteria, cell of origin and degree of anaplasia, as the primary basis for the classification of CNS tumours.[84]

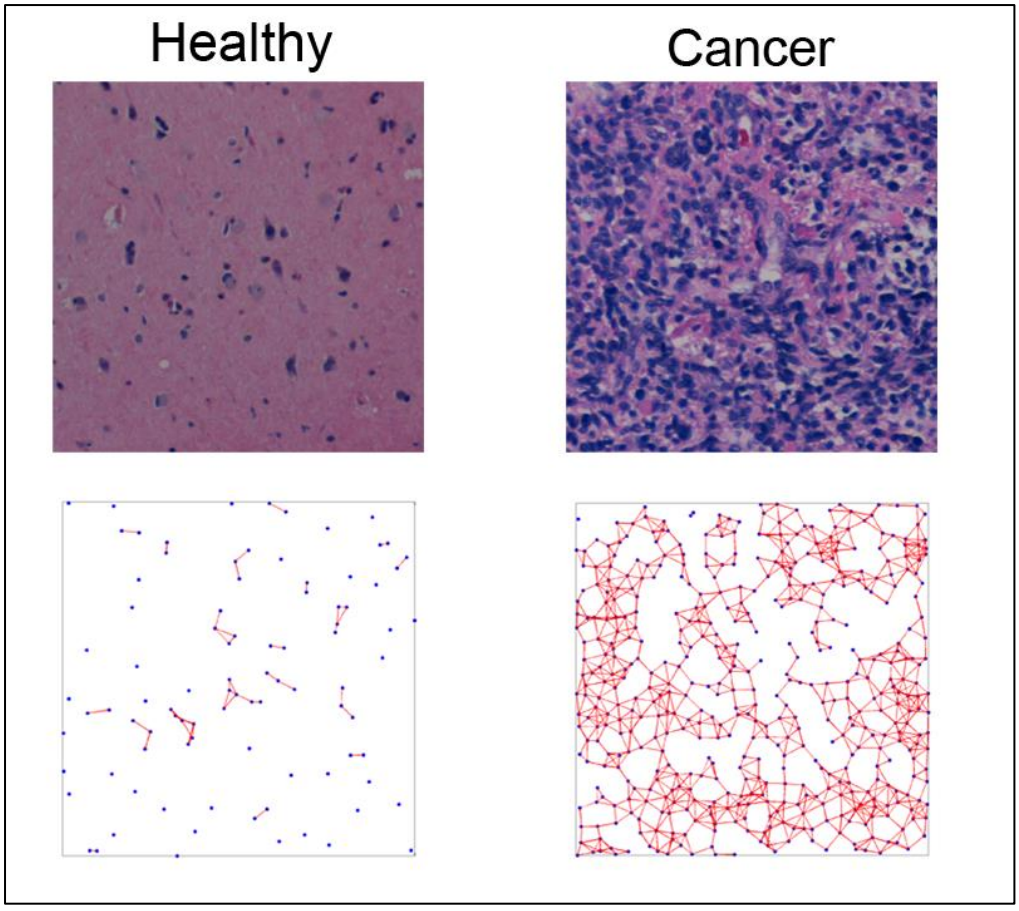

Figure 4: Example of healthy brain cells vs brain cancer cells (glioma) and their representations as cell-graphs.[85] *The nuclei can be observed clearly after the tissue sample is stained with haematoxylin and eosin. The cell graphs are generated by identifying nodes or cells and cell clusters and then representing the cells and the distance between them on a two-dimensional grid. The closer two cells are, the more likely they share a relationship. This probability quantifies the possibility for one of these nodes to be grown from the other; thus, the cell graphs aim to model the prevalence of the disease state in a tissue. As the tumour cells proliferate, the increased number of cells becomes an obvious distinguishing feature when comparing the tissue sample on the left vs the right.*

The WHO 2021 CNS classification system provides a standardised framework for classifying paediatric brain tumours based on their histological and molecular characteristics. This classification system categorises tumours into various entities, each with distinct diagnostic criteria and clinical implications. The classification considers cellular differentiation, genetic alterations, and prognostic factors. It allows

for better understanding and communication among healthcare professionals regarding tumour types, treatment strategies, and research endeavours. An overview of the WHO classification of CNS tumours is found in Table 1.

Integrating imaging modalities, histology, and the WHO 2021 CNS classification system is essential for accurately diagnosing paediatric brain tumours. This comprehensive approach enables clinicians to determine the tumour type, grade, and extent of spread, facilitating personalised treatment plans and prognostic assessments.

Table 1: An overview of the WHO classification of CNS tumours 2021[86]

Category	Gliomas, glioneuronal tumours and neuronal tumours						Choroid plexus tumours	Embryonal tumours		Pineal tumours	Mesenchymal/ Non-Meningothelial Tumours	Tumours of the sellar region
Family	Adult-type diffuse gliomas	Paediatric-type high-grade diffuse gliomas	Paediatric-type low-grade diffuse gliomas	Circumscribed astrocytic gliomas	Glioneuronal and neuronal tumours	Ependymal tumours		Medullo-blastoma	Other CNS Embryonal tumours		Uncertain differentiation	
Types	Astrocytoma, IDH-mutant	Diffuse midline glioma, H3 K27-altered	Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	High-grade astrocytoma with piloid features	Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC)	Supratentorial ependymoma, *ZFTA* fusion–positive	Choroid plexus papilloma	MB, WNT-activated	CNS neuroblastoma, *FOXR2*–activated	Desmoplastic myxoid tumor of the pineal region, *SMARCB1*-mutant	Intracranial mesenchymal tumor, *FET-CREB* fusion positive (provisional type)	Pituitary blastoma
	Oligodendro-glioma, IDH-mutant and 1p/19q-codeleted	Diffuse hemispheric glioma, H3 G34-mutant	Polymorphous low-grade neuroepithelial tumour of the young (PLNTY)	Pilocytic astrocytoma	Myxoid glioneuronal tumor	Supratentorial ependymoma, *YAP1* fusion–positive	Atypical choroid plexus papilloma	MB, SHH-activated, *TP53* -wildtype	CNS tumour with *BCOR* internal tandem duplication and the provisional type (CNS tumour *BCOR* ITD)	Pineocytoma	CIC-rearranged sarcoma	Adaman-tinomatous cranio-pharyngioma
	Glioblastoma, IDH-wildtype	Diffuse paediatric-type high-grade glioma, H3-wildtype/ IDH-wildtype	Diffuse low-grade glioma, MAPK pathway-altered	Pleomorphic xanthoastro-cytoma	Multinodular and vacuolating neuronal tumor (MVNT)	Posterior fossa group A (PFA) ependymoma	Choroid plexus carcinoma	MB, SHH-activated, *TP53* -mutant	Cribriform neuroepithelial tumour (CRINET)	Pineal parenchymal tumour of intermediate differentiation	Primary intracranial sarcoma, *DICER1*-mutant	Papillary cranio-pharyngioma
		Infant-type hemispheric glioma	Angiocentric glioma	Subependymal giant cell astrocytoma	Diffuse leptomeningeal glioneuronal tumor	Posterior fossa group B (PFB) ependymoma		MB, non-WNT/non-SHH	Atypical teratoid/ rhabdoid tumour (ATRT)	Pineoblastoma	Solitary fibrous tumour	Pituicytoma, granular cell tumour of the sellar region, and spindle cell oncocytoma
				Chordoid glioma	Ganglioglioma	Spinal ependymoma, *MYCN*-amplified		MB, histo-logically defined	Embryonal tumour with multi-layered rosettes (ETMR)	Papillary tumor of the pineal region	Ewing sarcoma	Pituitary adenomas
				Astroblastoma, *MN1*-altered	Desmoplastic infantile ganglioglioma/desmoplastic infantile astrocytoma	Myxopapillary ependymoma			CNS embryonal tumor			Pituitary neuro-endocrine tumour (PitNET)
					Dysembryoplastic neuroepithelial tumor	Subependymoma						
					Papillary glioneuronal tumor							
					Rosette-forming glioneuronal tumor							
					Gangliocytoma							
					Dysplastic cerebellar gangliocytoma							
					Central neurocytoma							
					Extraventricular neurocytoma							
					Cerebellar liponeurocytoma							

Note: for Mesenchymal/Non-meningothelial tumours, only the group of "Uncertain differentiation" is shown.

*Note: new tumour types are in grey cells

2.5 Pathophysiology of brain tumours and subsequent symptoms

Paediatric brain tumours are suspected based on their specific clinical features. Although certain symptoms are unique to specific tumours, in general, there are two major manifestations of PBTs. The first is increased ICP, and the second is due to the specific location of the tumour involving adjacent neural structures.[87] Increased ICP may be due to the tumour mass itself or secondary to hydrocephalus or cerebral oedema.

According to the Monro-Kellie hypothesis [88], the cranium is a rigid compartment, and the intracranial volume remains constant. The intracranial volume is made up of three main, non-compressible components:

1. Brain Tissue (cerebral parenchyma): This refers to the mass of the brain itself, including neurons, glial cells, blood vessels, and other supportive structures.

2. Blood: The total blood volume within the cranial cavity, including arterial and venous blood.

3. Cerebrospinal fluid (CSF)

Under normal physiological conditions, the sum of these three components must remain constant. Any increase in the volume of one component should be compensated for by a decrease in the volume of one or both of the remaining components to maintain intracranial volume equilibrium. The presence of an enlarging tumour disrupts this equilibrium by compressing adjacent neural structures, referred to as a space-occupying lesion. Compensatory adjustments may occur through compression of intracranial veins, a reduction of CSF volume by increased absorption or decreased production, a modest decrease in cerebral blood flow, and a reduction of intracellular and extracellular brain tissue mass. When these compensatory mechanisms fail, the intracranial volume exceeds the skull's capacity to accommodate it, resulting in increased ICP.

Brain tumour patients with increased ICP have the potential to deteriorate very rapidly.[79-81] The acute symptoms associated with increased ICP are headache, nausea and vomiting, altered states of consciousness, irritability, papilledema

(oedema of the optic nerve), hypertension, abnormal breathing, and seizures. In the long term, this may manifest as macrocephaly (an abnormal enlargement of the growing head), loss of appetite, delayed psychomotor development, and personality changes.[89]

Brain tumours manifest in different ways depending on the involvement of adjacent neural structures. The most common focal or localised symptoms are hemiparesis, seizures, and a change in mental state.[90] Depending on the specific brain region affected, additional focal or localised symptoms occur. In cerebral tumours, focal neurological deficits such as arm or leg weakness may be present. While posterior fossa tumours often present with ataxia and torticollis (a neurological disorder characterised by the involuntary contraction or spasm of the muscles in the neck region, resulting in an abnormal and often painful twisting or tilting of the head), also known as head tilt. Tumours in the sellar and parasellar region (hypothalamic-pituitary) region can indeed lead to endocrinopathies, as these tumours may disrupt the normal function of the hypothalamus and pituitary gland, impacting hormone regulation and causing hormonal imbalances. Tumours involving the cranial nerves are accompanied by symptoms affecting the special senses such as olfaction, vision, hearing, equilibrium, taste, etc.[89]

A tumour in the motor cortex often produces Jacksonian seizures (seizure-like movements localised on one side of the body). Tumours in the occipital lobe produce visual disturbances like contralateral homonymous hemianopsia (visual loss in half of the visual field on the opposite side of the tumour) and visual hallucinations. Cerebellar tumours cause ataxia, dizziness, muscle incoordination and motor function abnormalities, and nystagmus (involuntary, rapid, rhythmic eye movements), predominantly in the horizontal direction. Frontal lobe tumours often cause personality disorders, changes in emotional state and behaviour, and a shift in mental attitude. When a tumour irritates the vagal centres in the medulla, it typically leads to vomiting unrelated to food intake. Oedema of the optic nerve, known as papilledema, is present in 70% to 75% of patients and produces visual disturbances such as decreased visual acuity, diplopia, and visual field deficits.

2.6 Surgical and medical management of brain tumours

Treating PBTs requires a multimodal approach that prioritises the delicate balance between eradicating cancer cells and preserving healthy brain tissue to limit neurological deficits. Each treatment option is accompanied by a unique set of effects, both short-term and long-term, impacting physical health, cognitive abilities, and emotional well-being. The ultimate goal is to preserve the quality of life as best as possible. Treatment strategies for PBTs have evolved significantly, offering more tailored approaches and improved outcomes. The three major anti-cancer approaches that form the pillars of treatment in PBTs are surgery, radiotherapy, and chemotherapy.

Surgery is the primary treatment for the majority of PBTs , followed by chemotherapy and radiation, often a combination of both.[91] Tumour resection is performed via a craniotomy (temporary removal of a portion of the skull to access the brain tissue), where necrotic tissue is removed (if present), and the bulk of the tumour is removed to relieve ICP. Cytoreductive surgery (CRS) aims to reduce the amount of cancerous tissue or cells within the body, theoretically leaving behind fewer cells that can become resistant to radiation or chemotherapy. This means that even if the entire tumour is not resectable, surgery is still beneficial. Surgery has proven to be very effective in low-grade tumours. In some cases, total resection is impossible because it could damage critical structures. During the craniotomy, a biopsy is taken for histopathologic classification. Hydrocephalus is common in PBTs, especially if the tumour is in the posterior fossa. The placement of a CSF diversion device, such as a ventriculoperitoneal (VP) shunt, remains a key measure for alleviating hydrocephalus.[92]

In cases where total tumour resection is not possible, adjuvant therapy like chemotherapy is the next line of treatment. Chemotherapy is more effective in other organs than in the brain due to the blood-brain barrier that prevents adequate permeation of cytotoxic agents. Devices exist to make drug administration in this area more effective. One such tool is the Ommaya reservoir. The small reservoir is placed just beneath the scalp and is connected to a catheter that is surgically positioned within the ventricles or the subarachnoid space. This allows for drug administration directly into the CSF, which is more effective and efficient than systemic administration.[93]

Chemotherapy is a useful adjuvant approach for several common PBTs, such as medulloblastoma.

Radiotherapy has been the cornerstone of preventing recurrence after surgery and in treating tumours that could not be resected or only partially resected. Radiotherapy is particularly valuable in high-grade tumours and tumours with rapidly dividing cells. However, radiotherapy carries significant risks in the developing brains of paediatric patients. It can adversely impact neuronal development and have poor long-term cognitive outcomes. For these reasons, patients under three years of age do not receive radiotherapy.[92, 94]

Pharmacological treatment also forms part of the treatment plan to manage the debilitating symptoms of brain tumours. For example, corticosteroids are usually administered to reduce cerebral oedema, opioids are prescribed to manage pain, antiemetics are provided to control vomiting, anticonvulsants are administered to treat and prevent seizures, and skeletal muscle relaxants are provided to manage spasticity.

Brain tumours can significantly deteriorate a patient's quality of life, causing immense stress for the child and their caregivers due to the severe symptoms. The need for multidisciplinary neurorehabilitation is indeed a priority for these patients. This approach involves a team of healthcare professionals, each with their expertise, to address the various challenges faced by children with brain tumours. This could include neurosurgeons, physiotherapists, occupational therapists, speech therapists, and psychologists. Their collective goal is to improve the patient's physical, cognitive, and emotional well-being, thereby enhancing their quality of life and easing the stress experienced by both the child and their caregivers. It is a comprehensive strategy that addresses the patient's needs holistically, which is crucial given the complex nature of brain tumours.[95]

CHAPTER 3: METHODOLOGY

3.1 Aim

The aim of this study was to investigate the profile of primary brain tumours in children aged 0 – 18 years old (paediatric classification of the American Academy of Pediatrics) treated at Steve Biko Academic Hospital (SBAH) from January 2019 until June 2023.

3.2 Objectives

The objectives of this research study were:

- To establish the demographic profile of PBTs in SBAH by analysing age, gender, geographic area, and family socioeconomic status.
- To describe the histopathological profile of PBTs in SBAH by classification of tumour type and prevalence.
- To investigate the imaging -profile of PBTs in SBAH by analysing MRI and CT scan reports.

3.3 Study setting

All research was conducted at SBAH, a provincial hospital in Pretoria, Gauteng. SBAH is a purely tertiary training healthcare institution and serves as one of the main teaching hospitals of the University of Pretoria. It is also a referral hospital for other Gauteng and Mpumalanga provincial hospitals.

The target population of this study consisted of children between 0 and 18 years of age who had been diagnosed with a primary brain tumour and treated at SBAH from January 2019 to June 2023.

3.4 Study design

This medical record-based observational study retrospectively examined the epidemiological characteristics of PBTs by reviewing and analysing demographic, histopathological, and imaging data from patient records at SBAH.A flow diagram representing the research methodology and study design is shown in figure 5.

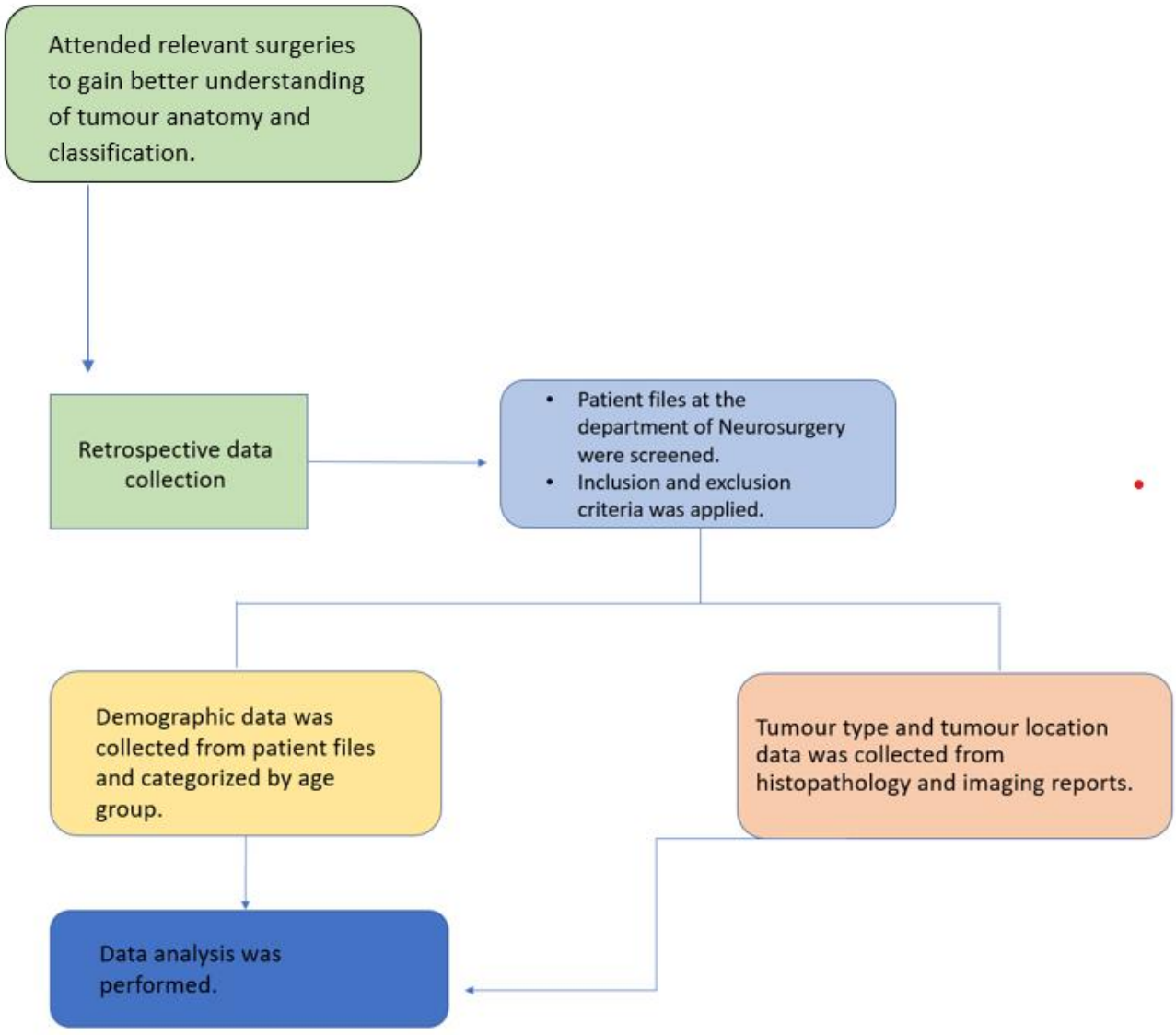

Figure 5: Flow diagram representing research methodology (made using Microsoft Word and PowerPoint)

3.5 Study population

Patient records were retrieved from SBAH neurosurgery department patient archives, and all relevant data was collected.

The study population consists of past paediatric patients with a history of primary brain tumours. Only patients that met the inclusion criteria were included in this study.

Inclusion criteria

- Male and female paediatric patients between the ages of 0 and 18 years
- Histologically proven primary brain tumours
- Admitted to SBAH between January 2019 and June 2023

Exclusion Criteria

- Patients with metastatic brain tumours
- Patients who have previously received radiation and surgery

Fifty-two patients with confirmed histopathological primary brain tumours who were treated at SBAH between January 2019 and June 2023 were included in this study. There were two patients with extracranial tumours who were excluded from this study. These patients had spinal tumours that fell outside the scope of this study.

3.6 Data collection

After approval was granted from the University of Pretoria Faculty of Health Sciences Research Ethics Committee (reference number 573/2022) (see Annexure B) and the National Health Research Database (approval number GP_202212_025) (see Annexure C), a patient list was obtained from the Department of Neurosurgery at SBAH. The data was then filtered to only include patients who met the abovementioned inclusion criteria. The subsequent file numbers were then obtained and requested from records. Once received from records, each patient file was screened for eligibility. Thereafter, the included files were further analysed to create patient demographic profiles. All relevant data was obtained from archived patient records. The data extracted from each file and recorded on the data collection sheet

included age, sex, geographic area, family medical history, patient medical history, parental educational level, and parental income level to produce a demographic profile for each anonymised patient. Each patient file had a coded entry to indicate the demographic details mentioned.

Magnetic resonance imaging (MRI) and computed tomography (CT) scans were used to collect imaging data of brain tumours in relation to localisation and prevalence in craniotomies and neuro endoscopies observed. The examination utilised the attached radiological report and imaging using XERO® Universal Viewer (Agfa Healthcare, Belgium) in collaboration with a neurosurgical registrar for analysis. Histological data was obtained from histopathology reports, and tumour type and tumour location were analysed and sorted into different age groups.

All data collection took place at the Department of Neurosurgery at SBAH, and a data collection sheet (annexure A) was used to collect data. Data was further categorised into age groups from the master data sheet. Once the data was extracted from a patient file, the file was returned to the archives.

3.7 Data analysis

The data was collected, anonymised, and separated categorically. STATA 17 (StataCorp. 2023. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC) data software program was used to run all statistical analyses. Descriptive statistics were applied to the patient's sex, age, tumour location and tumour type. The Shapiro-Wilks test was used to test for the normality of continuous variables. Continuous variables with normal distribution are represented as means ± standard deviations (SDs), and continuous variables with non-normal distribution are represented by medians and interquartile ranges. Normally distributed continuous variables were compared using the Student's t-test. The Wilcoxon rank-sum (Man-Whitney) test was utilized to compare the age medians between males and females and ascertain if there is a statistically significant difference in this cohort. For categorical variables such as age groups and sex, proportions and graphs were used. Spearman correlation analysis was performed to evaluate the monotonic relationships between selected parameters. The variables tested were sex and anatomic tumour location, age and anatomic tumour location, age and tumour type, sex and tumour

type, age and affected brain area, and sex and affected brain area. A p-value less than 0.05 was regarded as statistically significant.

3.8 Ethical considerations

Before the commencement and undertaking of this research project, the protocol was submitted for internal departmental approval and tendered to the MSc Committee of the Faculty of Health Sciences for approval and to the University of Pretoria Faculty of Health Sciences Research Ethics Committee for ethical clearance. A proposal was submitted to the NHRD for approval to access patient data. All relevant bodies granted approval.

To ensure the confidentiality of data, patient files were anonymised and numbered. Subject names and biographical information were captured on a master list, and each subject was given a subject code to ensure anonymity and protection of that subject's information. After data had been extracted, files were returned to the archives immediately. The principal investigator and supervisor had sole access to the master list. The master list was kept in the Department of Neurosurgery at SBAH, and it never left the hospital. Under no circumstances was any information linked to any patient, their identity, or personal results made available to any third party. Data will be stored at the University of Pretoria (UP) for 15 years.

CHAPTER 4: RESULTS

4.1 Introduction

The data underwent initial analysis, encompassing the entire study population, followed by subsequent analyses according to distinct age groups. The evaluated factors were age, sex, tumour type, affected brain area, and anatomical tumour location. This chapter includes the following sub-sections:

4.2 Description of study participants

A total of 90 patients between the ages of 0 and 18 years were admitted to the neurosurgery wards of SBAH between January 2019 and June 2023 with symptoms indicative of a PBT. A total of 52 Patients with confirmed histopathological primary brain tumours met the inclusion criteria for this study.

4.3 Subject's demographic characteristics

4.3.1 Overall sex distribution

Out of 52 patients, 33 patients were male (63.46%), and 19 patients were female (36.54%), shown in Figure 6 and Table 2. The male-to-female ratio was 1.74:1.

Table 2: Subjects' sex distribution

Sex	Frequency	Percentage
Female	19	36.54
Male	33	63.46
Total	52	100

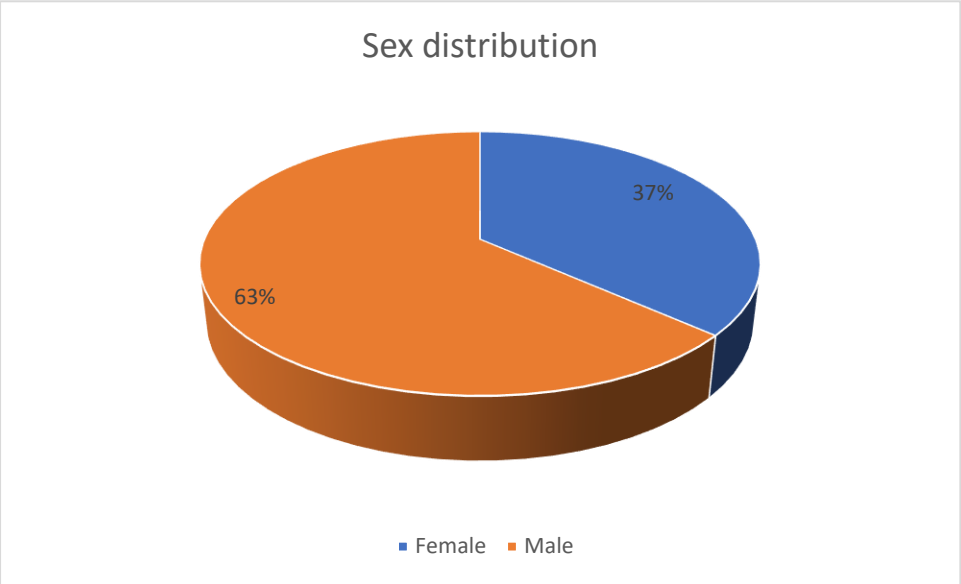

Figure 6: Overall sex distribution showing male predominance

4.3.2 Overall age distribution

The mean age of the study participants was 6.8 years (SD±4.9). Shown in Table 3, the youngest participant was 2 days old (0.005 years), and the oldest participant was 17 years old.

Table 3: Descriptive statistics of the age of participants

Variable	Observed	Mean	Standard deviation	Minimum	Maximum
Age	52	6.798558	4.925703	0.005	17

As depicted in Table 4 and Figure 7, in this study 4-year-olds had the highest prevalence for PBTs and represented 11.54% of the study population, followed by 2-year-olds and 7-year-olds, representing 9.62% of the study population each.

Table 4: Prevalence by age

Age in years	Frequency	Percentage
0.005	1	1.92
0.19	1	1.92
0.25	2	3.85
0.83	1	1.92
1	3	5.77
2	5	9.62
3	4	7.69
4	6	11.54
5	2	3.85
7	5	9.62
8	3	5.77
9	2	3.85
10	4	7.69
11	4	7.69
13	2	3.85
14	3	5.77
15	1	1.92
16	2	3.85

17	1	1.92
Total	**52**	**100**

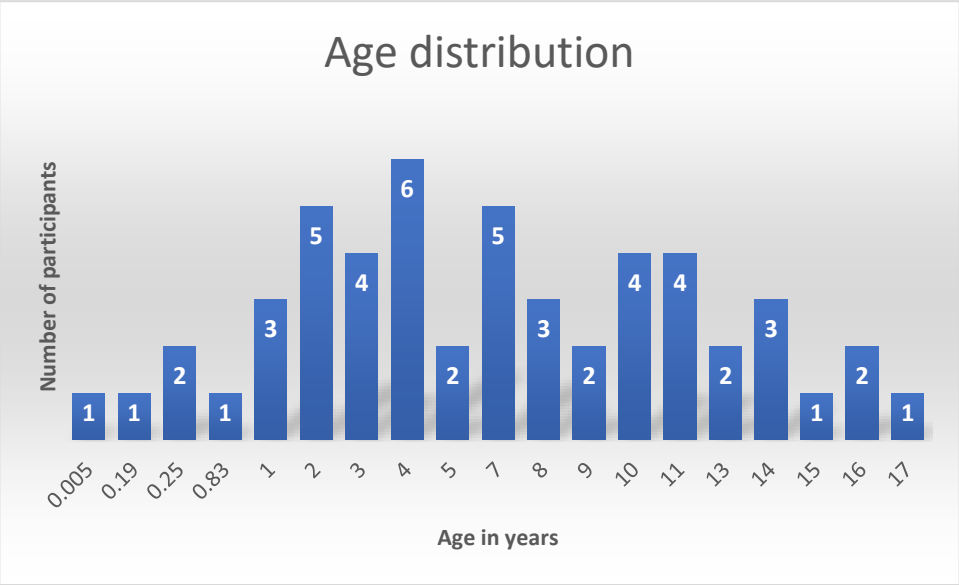

Figure 7: Visual representation of age distribution

Table 5 shows the results of mean age compared between the sexes.

Table 5: t-test results of sex vs age

Two-sample t-test with equal variances						
Group	Observed	Mean	Std. Err.	Std. Dev.	[95% Confidence Interval]	
Female	19	9.697368	1.166444	5.084412	7.24676	12.14798
Male	33	5.129545	0.7020558	4.033003	3.699505	6.559586
Combined	52	6.798558	0.6830721	4.925703	5.427233	8.169882
diff		4.567823	1.278729		1.999419	7.136227
t = 3.5722 *p value* = 0.0008						

As seen in Table 5, males appear to have an earlier disease onset than females in this cohort. The mean age for male participants in this study was 5.1 years with a SD of 4 years, while the mean age for female participants was 9.7 years with a SD of 5 years. A *p*-value of 0.0008 indicates a significant difference in mean age between the sexes in this population. To test whether this age difference between sexes is significant, a Wilcoxon rank-sum test was performed. The results are found in Table 6.

Table 6: Wilcoxon rank-sum test to test whether there is a significant age difference between sexes in this cohort

Two-sample Wilcoxon rank-sum (Mann-Whitney) test			
Sex	Observed	Rank sum	Expected
Female Male	19 33	662.5 715.5	503.5 874.5
Combined	52	1378	1378
Adjusted variance			**2754.83**
z = **3.029** Ho (Null Hypothesis): Asserting no significant age difference between females and males *p* = **0.0025** Ho rejected			

The Wilcoxon rank-sum test indicates sufficient evidence (p-value of 0.0025) to conclude a significant age disparity between females and males in this cohort based on the provided data.

4.3.3 Sex distribution by age group

Participants were divided into the following four age groups as per Table 7:

Table 7: Age groups

Age group	Number of participants
0-3 years	13
3-8 years	17
8-12 years	13
12-18 years	9

Participants were further divided by sex within the relative age groups. Table 8 shows the number of participants of each sex within their respective age groups.

Table 8: Sex distribution within the age groups

Age group	**Total number of participants**	**Number of male participants**	**Number of female participants**
0-3 years	13	10	3
3-8 years	17	15	2
8-12 years	13	6	7
12-18 years	9	2	7

Figures 8 to 11 depict the sex distribution per age group.

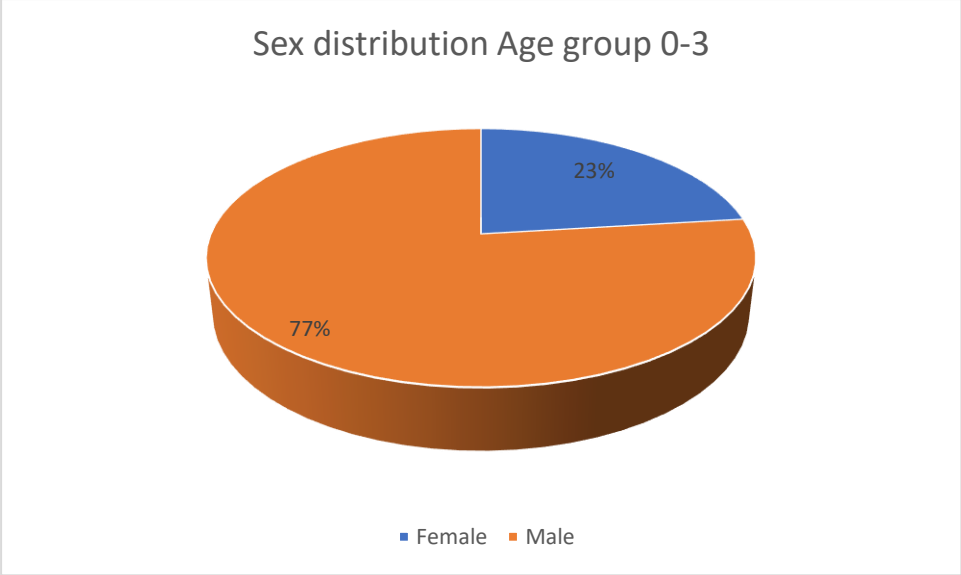

Figure 8: Sex distribution in age group 0-3 years

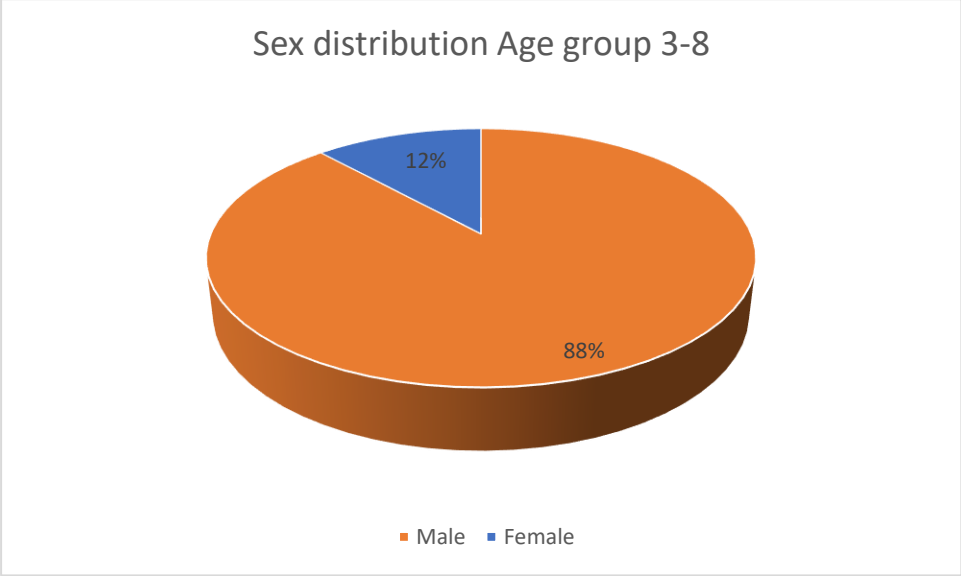

Figure 9: Sex distribution in age group 3-8 years

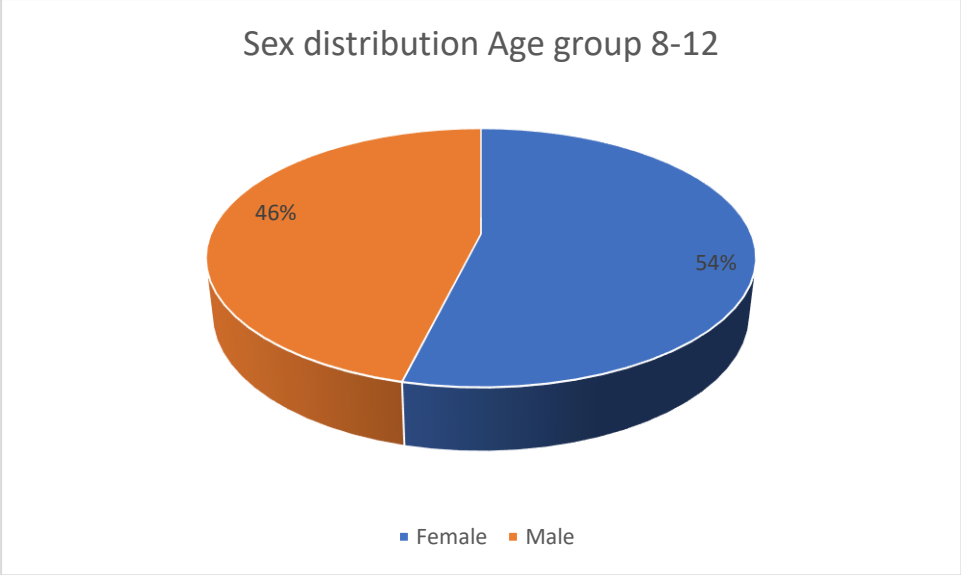

Figure 10: Sex distribution in age group 8-12 years

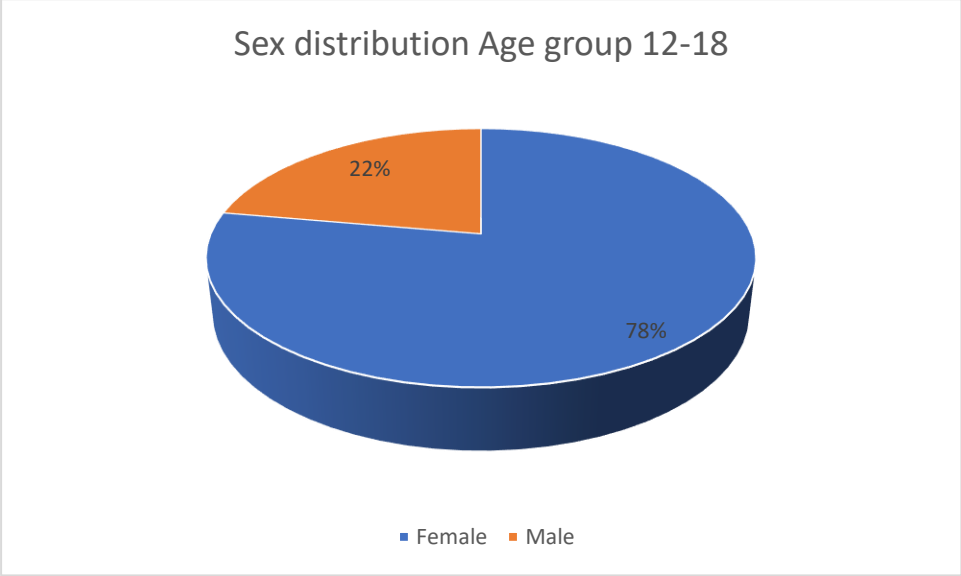

Figure 11: Sex distribution in age group 12-18 years

The two younger age groups, 0-3 years and 3-8 years showed a clear male predominance, with males constituting 77% of participants in age group 0-3 years and 88% of subjects in age group 3-8 years. Females represent 23% and 12% respectively in these age groups.

In both age groups, 8-12 and 12-18, predominance has shifted to the female demographic. In age group 8-12 years, females represent 54% of the study population and males 46%. In age group 12-18 females represent 78% of participants in this age group and males constitute 22%.

4.4 Anatomical location of primary tumours

The contents of the intracranial cavity are separated by the tentorium cerebelli into supratentorial and infratentorial regions. This data was collected from attached radiological reports and imaging scans form various imaging modalities (CT scan, MRI, PET scan) using XERO® Universal Viewer (Agfa Healthcare, Belgium).

4.4.1 Overall anatomic locations of primary brain tumours

Table 9 shows the number of infratentorial and supratentorial tumours. As seen in Figure 12, the majority of tumours were found in the infratentorial region 55.8% (n=29) and 44.2% (n=23) were found in the supratentorial region.

Table 9: Anatomical location of PBTs.

Tumour location	Frequency	Percentage
Infratentorial	29	55.77
Supratentorial	23	44.23

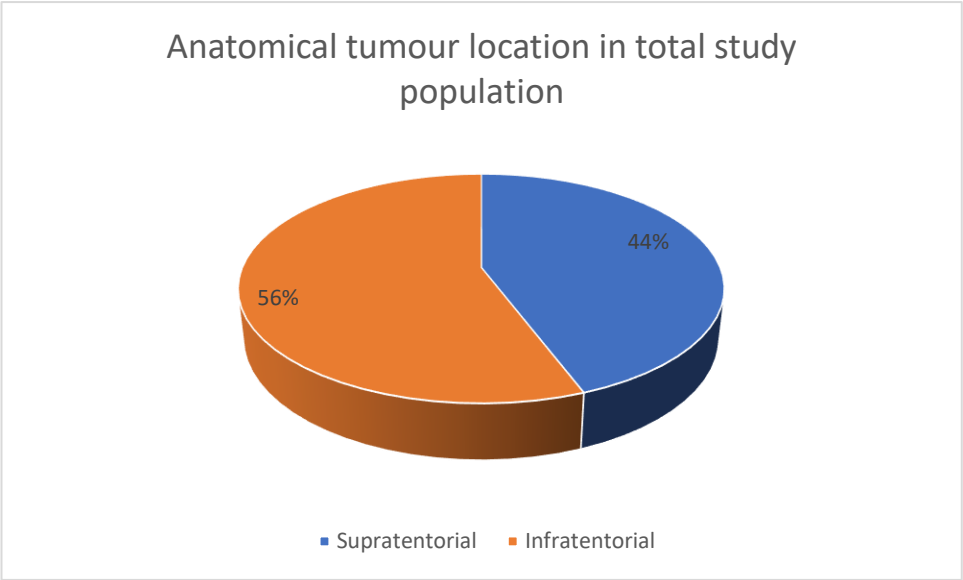

Figure 12: Visual representation of overall anatomical location of PBTs

4.4.2 Anatomical location distribution by age group

Figures 13 to 16 show the percentage of infratentorial vs supratentorial tumours in the four different age groups.

In the age group 0-3 years, 54% of tumours were supratentorial and 46% infratentorial.

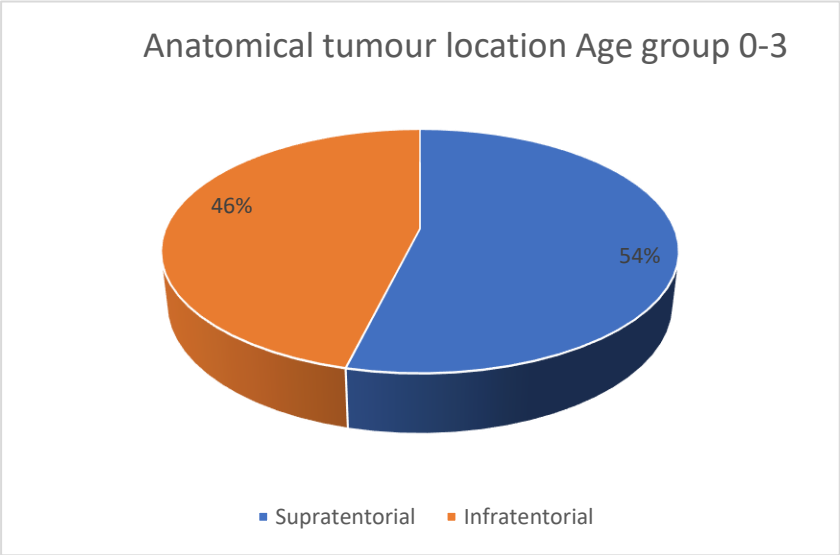

Figure 13: Distribution of anatomical location of PBTs in age group 0-3 years

As seen in Figure 14, in the age group 3-8 years, the majority of tumours (75%) were in the infratentorial region, and 25% of tumours were in the supratentorial region.

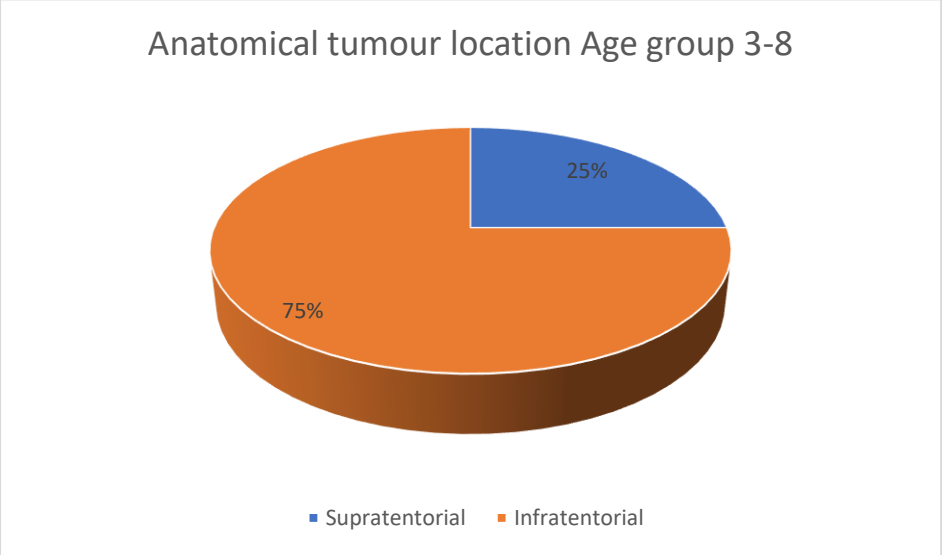

Figure 14: Distribution of anatomical location of PBTs in age group 3-8 years

In the age group 8-12 years old, 54% of tumours were infratentorial, and 46% were supratentorial.

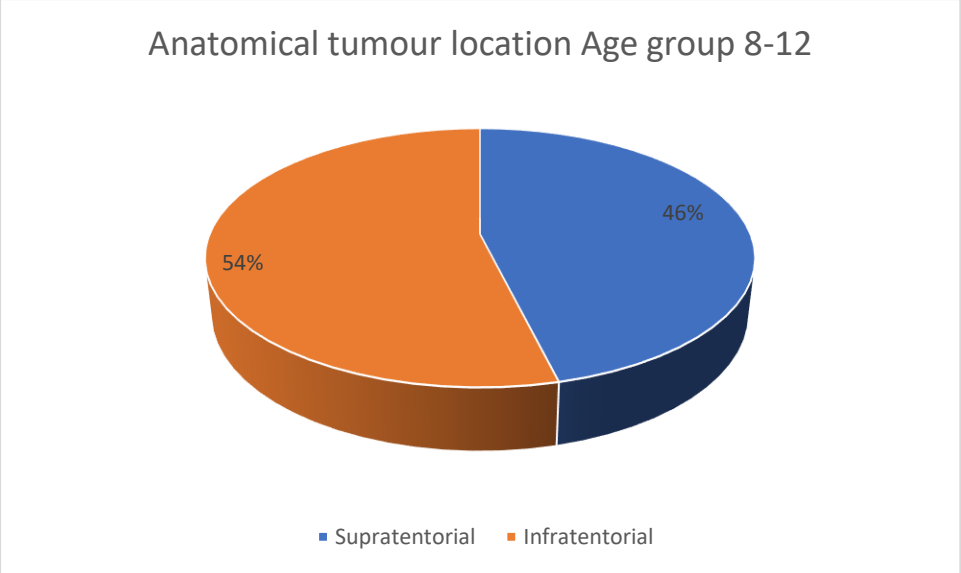

Figure 15: Distribution of anatomical location of PBTs in age group 8-12 years

In the age group 12-18, 44% of tumours were infratentorial, and 56% were supratentorial.

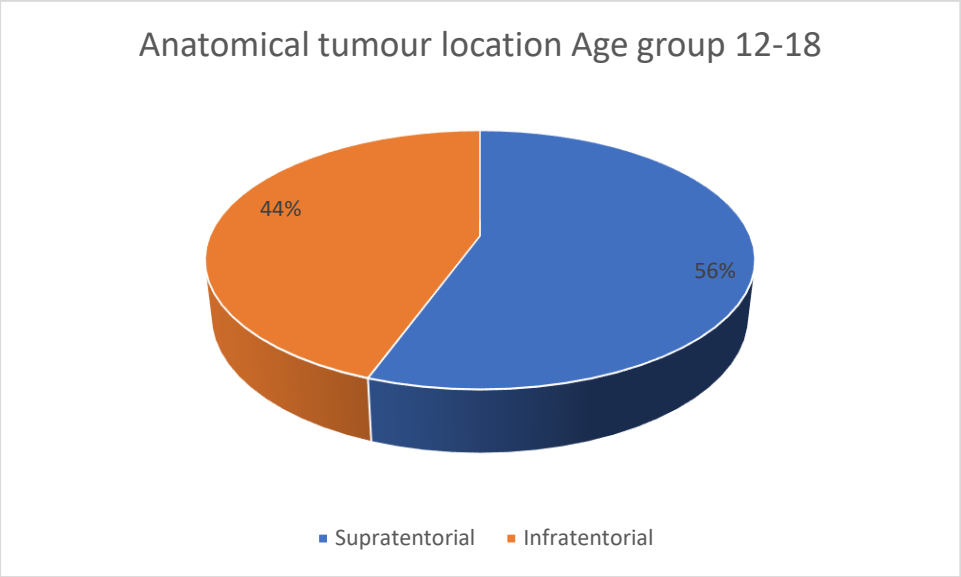

Figure 16: Distribution of anatomical location of PBTs in age group 12-18 years

4.5 Prevalence of different tumour types

4.5.1 Overall relative prevalence for different types of brain tumours

Table 10 shows the relative prevalence of tumour types in this study population. The most common tumour was medulloblastoma, with a relative prevalence of 17.31%. The second most common tumours were astrocytomas and ependymomas, each with a prevalence of 15.38%.

Table 10: Relative prevalence of PBT types

Tumour type	Frequency	Percentage
Astrocytoma	8	15.38
Atypical choroid plexus papilloma	2	3.85
Brainstem Glioma	3	5.77

Craniopharyngioma	5	9.62
Diffuse Pontine Glioma	4	7.69
Embryonal	1	1.92
Ependymoma	8	15.38
Ganglioglioma	1	1.92
Glioblastoma	3	5.77
Glioma	1	1.92
Medulloblastoma	9	17.31
Meningothelial Meningioma	1	1.92
Midline Glioma		1.92
Oligodendroglioma	1	1.92
Optic nerve Glioma	1	1.92
Parameningeal Rhabdomyosarcoma	1	1.92
Tectal plate Glioma	2	3.85
Total	52	100

In Table 10, all the subcategories of gliomas were presented separately to show the prevalence of each. When the gliomas are grouped, they become the most common tumour type in this study population (26.9%), followed by medulloblastoma, ependymoma and astrocytoma. The rarest tumour types were embryonal tumours, meningothelial meningioma, and parameningeal rhabdomyosarcoma. Figure 17 shows the prevalence of tumour types, indicated by number of cases, with gliomas as one group.

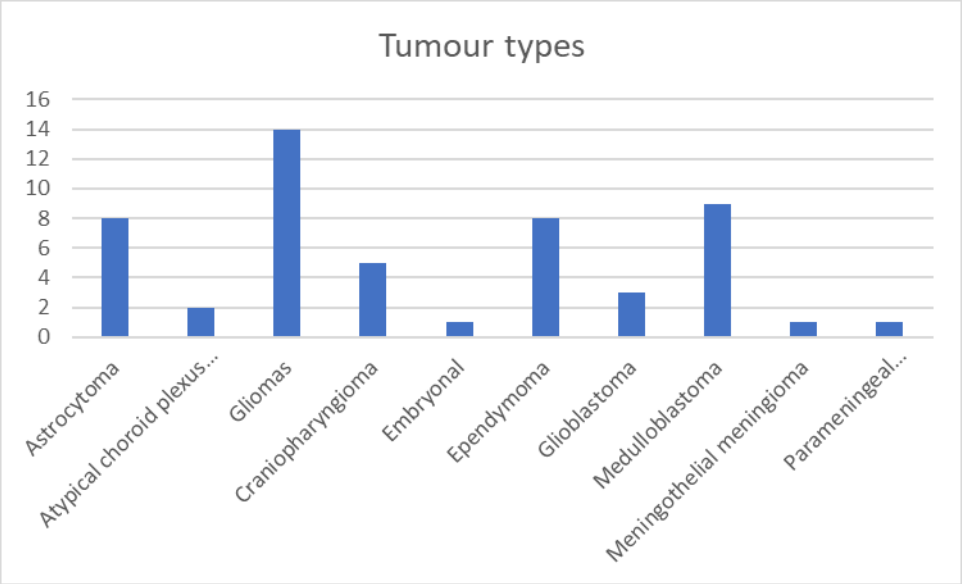

Figure 17: Prevalence of tumour types with gliomas as one group

Within the glioma tumour type classification, diffuse pontine gliomas were the most prevalent in this study population, constituting 28.6%. The second most common glioma was brainstem gliomas, with a prevalence of 21.4%, followed by tectal plate gliomas in third place with a prevalence of 14.2%. The frequencies, indicated by number of cases, of the glioma subgroups can be seen in Figure 18.

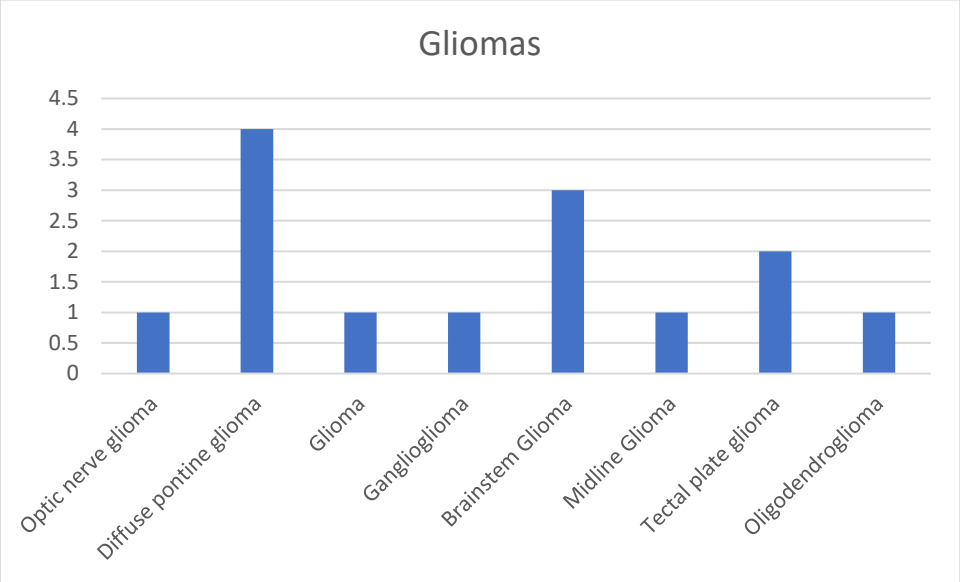

Figure 18: Tumour-type frequencies within the glioma classification

4.5.2 Prevalence of different tumour types by sex

When separated according to sex, the most prevalent tumour type in the male demographic is gliomas, with a prevalence of 30.3%. The most prevalent glioma in males was diffuse pontine glioma, followed by brainstem glioma. Second to gliomas, the most common tumour types are astrocytoma, ependymoma, and medulloblastoma, all with a prevalence of 18.2%.

In the female demographic, the most common tumour types are craniopharyngiomas and gliomas, with a prevalence of 21%. The most prevalent glioma subtype was tectal plate gliomas. The second most common tumour types following craniopharyngiomas and gliomas were glioblastomas and medulloblastomas, with a prevalence of 15.8%. Table 11 below shows the tumour types divided by sex.

Table 11: Tumour type by sex

	Sex					
Tumour type	**Female**	**%**	**Male**	**%**	**Total**	**%**
Astrocytoma	2	10.5%	6	18.2%	8	15.4%

Atypical choroid plexus papilloma	0	0	2	6.1%	2	3.9%
Brainstem Glioma	0	0	3	9.1%	3	5.8%
Craniopharyngioma	4	21%	1	3%	5	9.6%
Diffuse Pontine Glioma	0	0	4	12%	4	7.7%
Embryonal	1	5.3%	0	0	1	2%
Ependymoma	2	10.5%	6	18.2%	8	15.4%
Ganglioglioma	0	0	1	3%	1	2%
Glioblastoma	3	15.8%	0	0	3	5.8%
Glioma	0	0	1	3%	1	2%
Medulloblastoma	3	15.8%	6	18.2%	9	17.3%
Meningothelial Meningioma	0	0	1	3%	1	2%
Midline Glioma	1	5.3%	0	0	1	2%
Oligodendroglioma	1	5.3%	0	0	1	2%
Optic nerve Glioma	0	0	1	3%	1	2%
Parameningeal Rhabdomyosarcoma	0	0	1	3%	1	2%
Tectal plate Glioma	2	10.5%	0	0	2	3.9%
Total	**19**	**100%**	**33**	**100%**	**52**	

4.5.3 Prevalence of different tumour types by age group

Tumour types were further categorised into the four age groups. As seen in Figure 19, the most prevalent tumour type in the age group 0-3 is medulloblastoma, with a prevalence of 38.5%. The rarest tumours in this age group are choroid plexus papilloma and embryonal tumours, with a prevalence of 7.7%.

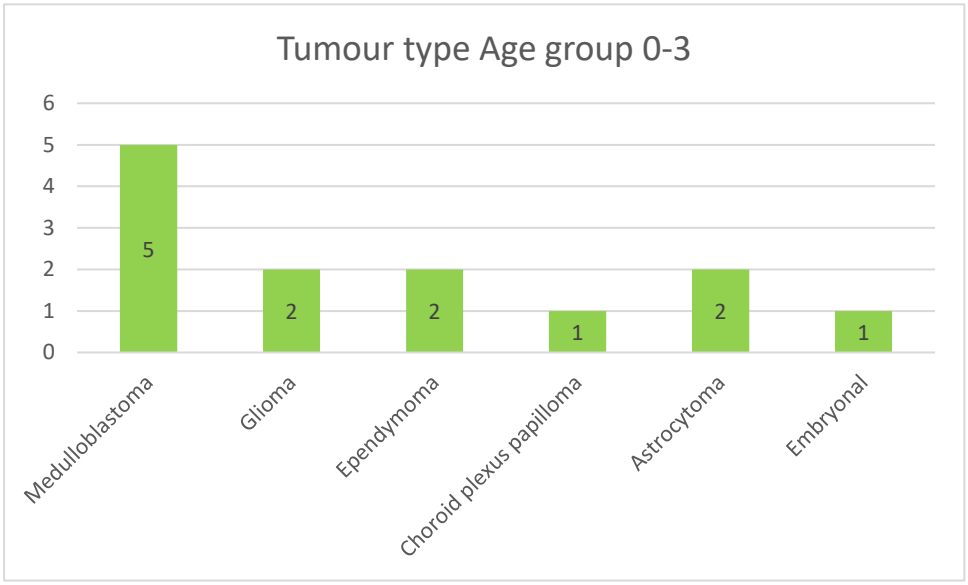

Figure 19: Tumour types in age group 0-3 years

In the 3-8-year-old age group, the most common tumour type is gliomas, with a total prevalence of 47%. The most prevalent glioma is brainstem gliomas (23.5%), followed by DIPG (17.6%) and ganglioglioma (5.9%). Ependymomas are the second most common tumour in this age group, with a prevalence of 23.5%. Figure 20 depicts the number of cases per tumour type in this age group.

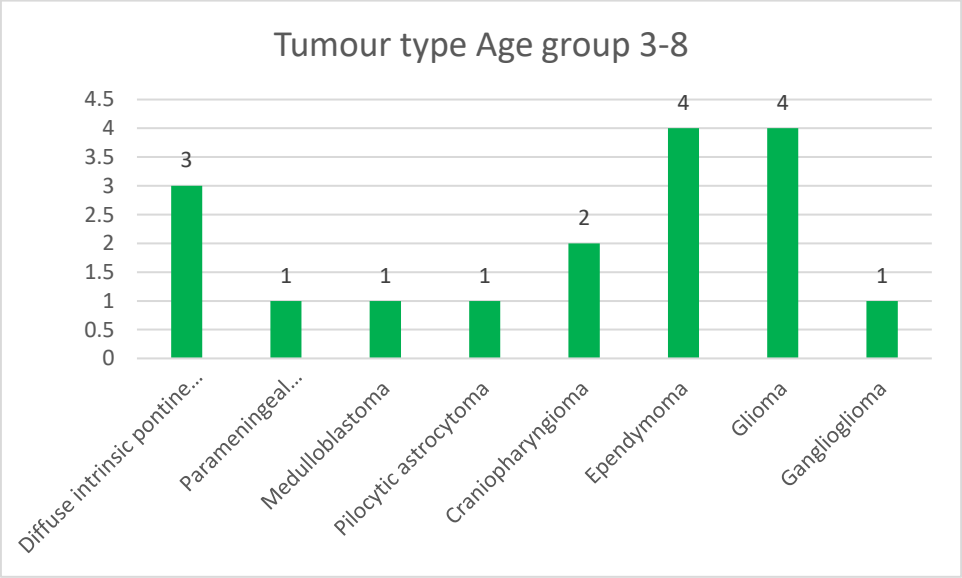

Figure 20: Tumour types in age group 3-8 years

In the 8-12-year-old age group, the most common tumour type is astrocytoma, with a prevalence of 30.8%, followed by medulloblastoma, with a prevalence of 23.1%. Figure 21 shows the number of cases per tumour type in this age group.

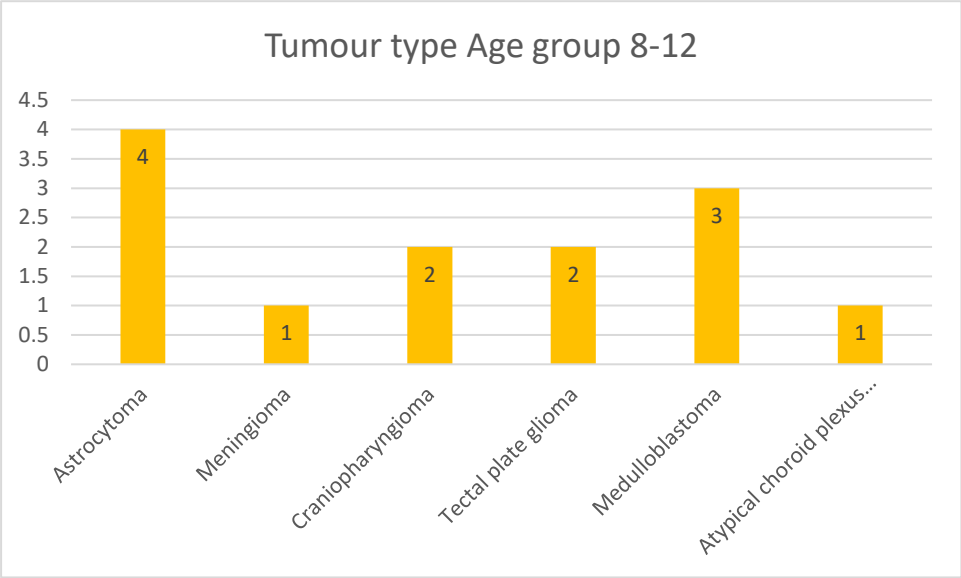

Figure 21: Tumour types in age group 8-12 years

The most prevalent tumour type in the age group 12-18 years old is glioblastoma, with a prevalence of 33.3%, followed by ependymomas, with a prevalence of 22.2%. Figure 22 indicates the number of cases per tumour type in this age group.

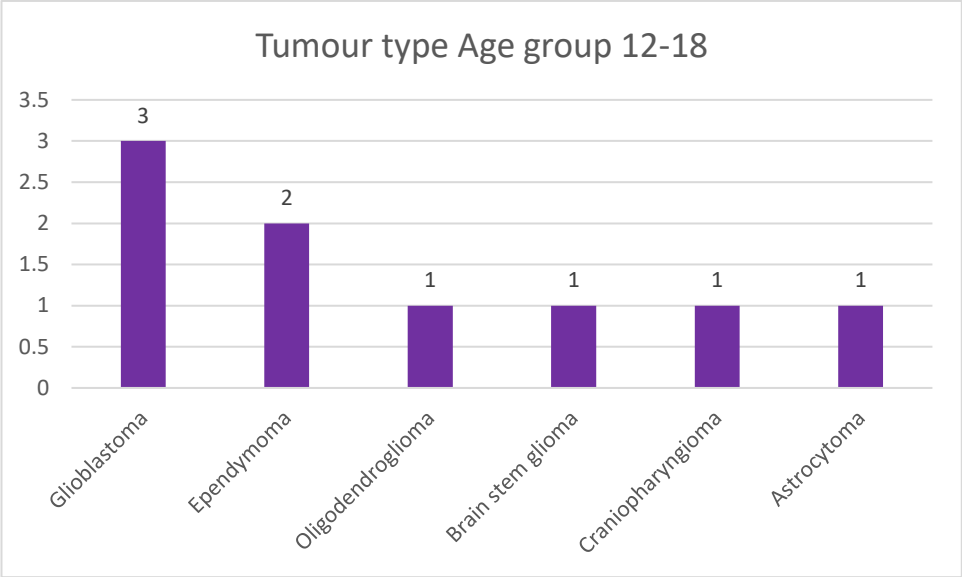

Figure 22: Tumour types in age group 12-18 years

4.6 Brain areas affected by primary paediatric brain tumours

4.6.1 Overall brain areas affected by primary paediatric brain tumours

Table 12 depicts the various brain areas affected by tumours in the study population. The most affected area was the posterior fossa, with 36.5% of tumours originating in this region. The second most common areas for tumours to occur were the brainstem (11.5%) and the suprasellar region (11.5%). Figure 23 provides a visual representation of brain areas affected per number of cases.

Table 12: Brain areas affected by PBTs

Brain area	Frequency	Percentage
Brainstem	6	11.54
Intra-axial	1	1.92
Intra-ventricular	5	9.62
Occipital	1	1.92
Orbital intracranial	1	1.92
Parietal	4	7.69

Parieto-occipital	4	7.69
Parieto-temporal	1	1.92
Posterior fossa	19	36.54
Pre-frontal cortical	1	1.92
Suprasellar	6	11.54
Tectum	2	3.85
Temporal	1	1.92
Total	52	100

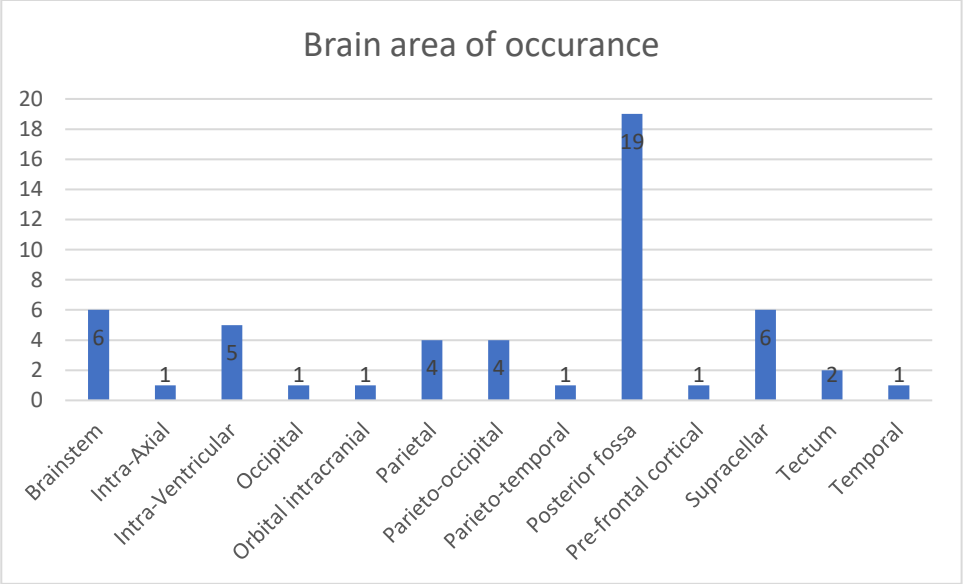

Figure 23: Visual representation of brain areas affected by PBTs

4.6.2 Brain areas affected per sex

When further divided into sex groups, different areas appear to be more prevalent in a specific sex. In the female group, the most affected brain area was the posterior fossa, with 21% of female tumours originating in this area. The second most commonly affected region was the parieto-occipital area, where 15.8% of tumours were found.

In males, the most affected brain area was also the posterior fossa, with 45.5% of tumours in the male group originating in this area. The second most prevalent area of

origin was the brainstem, 18.2% of tumours in the male demographic were found in this area. Table 13 shows the affected brain areas per sex.

Table 13: Affected brain regions per sex

	Sex				
Brain area	**Female**		**Male**		**Total**
Brainstem	0	-	6	18%	6
Intra-axial	0	-	1	3%	1
Intra-ventricular	2	10.5%	3	9.1%	5
Occipital	1	5.3%	0	-	1
Orbital intracranial	0	-	1	3%	1
Parietal	2	10.5%	2	6.1%	4
Parieto-occipital	3	15.8%	1	3%	4
Parieto-temporal	0	-	1	3%	1
Posterior fossa	4	21%	15	45.5%	19
Pre-frontal cortical	0	-	1	3%	1
Suprasellar	4	21%	2	6.1%	6
Tectum	2	10.5%	0	-	2
Temporal	1	5.3%	0	-	1
Total	**19**		**33**		**52**

4.6.3 Brain areas affected per age group

Brain areas were affected differently in the various age groups, but across all four age groups, the posterior fossa was the most commonly affected region in each group.

In the age group 0-3 years, the area affected most prevalently is the posterior fossa, with 46% of tumours originating here. The number of tumours per affected region is shown in Figure 24.

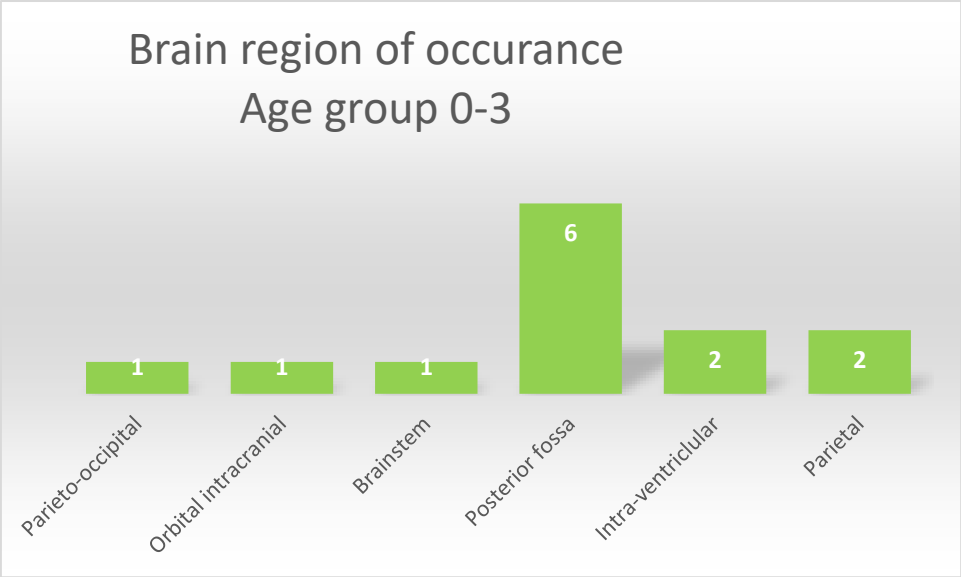

Figure 24: Brain areas affected in age group 0-3 years

The posterior fossa was also the most common brain area affected in the age group 3-8 years, with 41.2% of tumours originating in this area. The second most common area is the brainstem (23.5%). The number of tumours per affected region is shown in Figure 25.

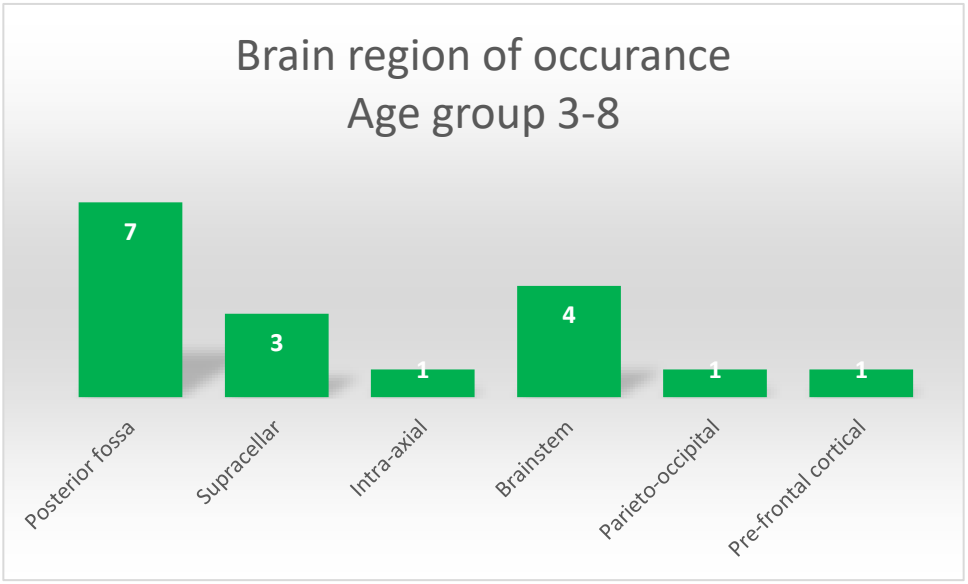

Figure 25: Brain areas affected in age group 3-8 years

In the age group 8-12 years, again, the posterior fossa is most affected, with 38.5% of tumours originating here. The number of tumours per affected region is shown in Figure 26.

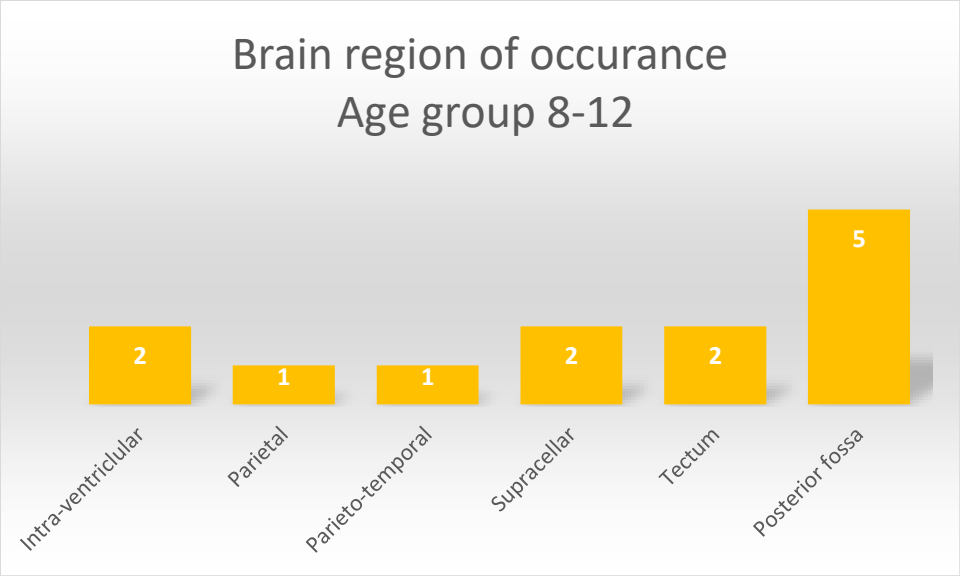

Figure 26: Brain areas affected in age group 8-12 years

In the age group 12-18 years, there are two areas most commonly affected. The majority of PBTs in this age group originated in the posterior fossa (22.2%) and in the parieto-occipital area (22.2%). The number of tumours per affected region is shown in Figure 27.

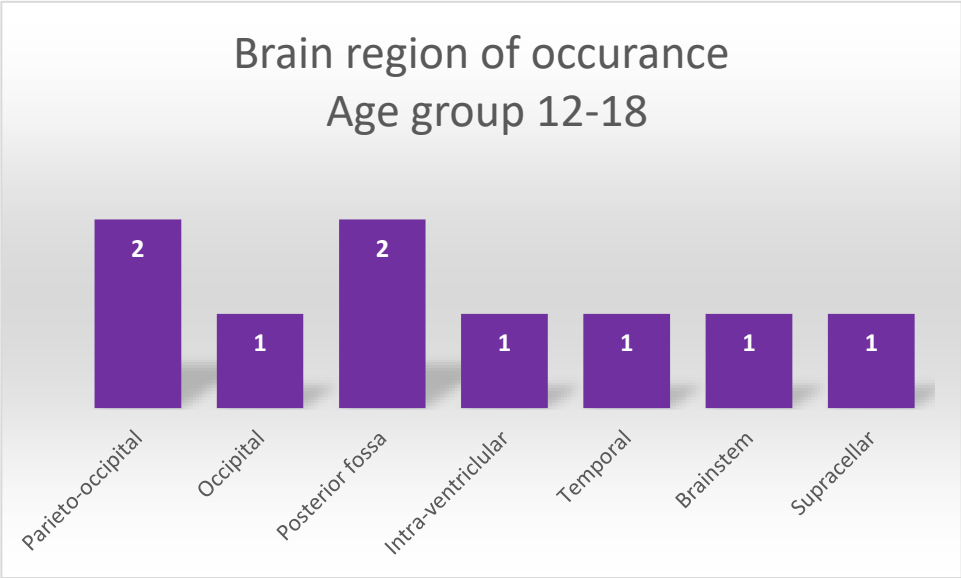

Figure 27: Brain areas affected in age group 12-18 years

4.7 Correlation analyses

4.7.1 T-test Age and Anatomical tumour location

A T-test was done with variables “age” and “anatomical tumour location” to determine if there is a significant difference in the mean age between the supratentorial group and the infratentorial group of the study population, as depicted in Table 14.

Table 14: T-test with variables “age” and “anatomical tumour location”

Two-sample t-test with equal variances						
Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
Infratentorial	29	6.394483	0.7950785	4.281629	4.765838	8.023127
Supratentorial	23	7.308043	1.187367	5.694411	4.845596	9.770491
Combined	52	6.798558	0.6830721	4.925703	5.427233	8.169882
Diff		-0.9135607	1.382994		-3.691385	1.864264
t = -0.6606 Ho: No difference in mean age of supratentorial vs infratentorial groups *p* = 0.5119						

The infratentorial group had 29 observations with a mean age of 6.39 years and a SD of 4.28, while the supratentorial group had 23 observations with a mean age of 7.3 years and a SD of 5.69. The null hypothesis tested was that there was no difference between the mean ages of the supratentorial and infratentorial groups. There was no statistically significant difference (p = 0.5119) in the mean ages between the infratentorial and supratentorial groups.

4.7.2 Spearman correlation between age and tumour location

The correlation between the variables "Age" and "Anatomic tumour location" was tested in this cohort.

Number of observations = 52

Spearman's rho = 0.0569

Test of Ho: Age and Anatomic tumour location are independent

p = 0.6886

Based on this analysis, there is insufficient evidence to suggest a significant relationship between "Age" and "Anatomic tumour location."

4.7.3 Spearman correlation between sex and anatomic tumour location

The correlation between sex and anatomic tumour location was tested.

Number of observations = 52

Spearman's rho = -0.2892

Test of Ho: Sex and Anatomic tumour location are independent

p = 0.0376

There is evidence to suggest (p = 0.0376) that "sex" and "anatomic tumour location" are not independent variables in this study population, and there is a significant association between them.

4.7.4 Spearman correlation between age and tumour type

The correlation between age and tumour type was tested to determine if there is a significant relationship between these two variables in this cohort.

Number of observations = 52

Spearman's rho = -0.0351

Test of Ho: Age and Tumour type are independent

p= 0.8048

This means that there is not enough evidence to conclude that there is a significant relationship between "Age" and "Tumour type" in this cohort.

4.7.5 Spearman correlation between sex and tumour type

The relationship between sex and tumour type was evaluated.

Number of observations = 52

Spearman's rho = -0.1889

Test of Ho: Sex and Tumour type are independent

p = 0.1798

There is not enough evidence (p = 0.1798) to conclude that there is a significant association between "Sex" and "Tumour type" in this cohort.

4.7.6 Spearman correlation between age and affected brain area

In this analysis, the correlation between age and affected brain area was tested.

Number of observations = 52

Spearman's rho = 0.2031

Test of Ho: Age and Brain area affected are independent

p= 0.1488

There is not enough evidence (p = 0.1488) to conclude that there is a significant relationship between age and affected brain area in this cohort.

4.7.7 Spearman correlation between sex and affected brain area

The relationship between sex and the affected brain area was tested.

Number of observations = 52

Spearman's rho = -0.2598

Test of Ho: Sex and Brain area affected are independent

p= 0.0629

There is no significant relationship between “sex” and “affected brain area” in this cohort.

CHAPTER 5: DISCUSSION

The epidemiology of primary paediatric brain tumours has been studied extensively in developed countries. Different epidemiological details have been analysed, creating a clear profile of these paediatric brain tumours and the children affected by them. Such studies are few and lacking in developing countries, especially sub-Saharan Africa. Although a hospital-based study cannot provide the exact incidence rate, the information is useful in describing the patterns of PBTs in this region.

The study investigated the characteristics of PBTs at SBAH. This analysis focused on three key areas: demographics, histopathological profile, and imaging characteristics.

Fifty-two patients between the ages of 0 and 18 years with histopathologically confirmed primary brain tumours admitted to SBAH between January 2019 and June 2023 were included in this study.

Out of 52 patients, 33 patients were male (63.46%), and 19 patients were female (36.54%). The male-to-female ratio was 1.74:1. This finding is in keeping with other studies that found a higher prevalence of PBTs in males.[96-101] The exact cause that gives rise to this preponderance in males is still unknown, and further research on this topic is necessary, but current hypotheses being explored by researchers point to multiple contributing factors. Hormonal differences between males and females have been suggested as a potential factor; for instance, oestrogen has protective effects on the nervous system, and the absence/lower levels of this hormone in males could contribute to an increased susceptibility to tumours.[102] The brain is particularly vulnerable to changes in the oxidative environment. Oestrogen protects against the oxidative activity of reactive oxygen species that may lead to mutations in DNA.[102] However, these hormonal effects would only be observed at puberty. In this study, it would have been observed in the last two age groups, where one would expect to see a clear male prevalence and a decrease in female prevalence compared to the previous two age groups. The opposite effect was observed, however. From ages 8 to 18, females showed a higher prevalence than males. Could it be possible that the very neuro-protective properties of oestrogen aids in the development of cancer? Oestrogen is able to interfere with cellular pathways that lead to apoptosis. It directly effects the transcription of genes that code for proteins that suppress apoptosis.[102] This could lead to the proliferation of damaged cells and contribute to tumorigenesis. Other possible contributing factors include immune system differences between males and females. Various studies suggest that female immune systems may be more responsive to certain pathogens than male ones. This difference can influence susceptibility to some diseases and potentially impact tumour development.[103, 104] Different immune responses and sensitivities between sexes have been implicated in sexual dimorphism in glioblastoma multiforme, where females have been found to have a more active adaptive immune system.[105, 106] A study by Shireman et. al. 2022 found that males have a higher frequency of natural killer cells and females have a higher frequency of CD4+ T cells, accompanied by enhanced antigen processing and presentation, and chemokine response.[107] In a recent study, it was found that male CD8+ T cells infiltrating glioblastoma tumours express more inhibitory receptors, leading to a higher rate of T cell exhaustion compared to females. T cell exhaustion results in impaired control of disease, and leads to divergent disease outcomes in males and females. Moreover, female CD8+ T cells produced more IFN- γ (interferon-

gamma) and TNF (tumour necrosis factor) in response to stimuli.[108] This suggests that females exhibit stronger immune responses than males. There is evidence to support the assertion that genetic factors could influence the development of brain tumours, or more importantly, perhaps, that specific genetic mutations might interact with sex-specific factors, contributing to the sex disparity.[109] One such example is the significant difference in incidence of glioblastoma between males and females, both in adults and children. Males are 60% more likely to develop glioblastoma, and the standard treatment for glioblastoma is much more effective in females.[110, 111] The molecular basis for this difference in treatment response is attributed to the difference in gene expression between the sexes. In males, survival was significantly determined by the expression of genes that regulate cell division, whereas survival in females was determined by the expression of integrins – genes involved in tumour metastasis.[110, 112] In a study by Yang et al.(2019), it was found that the downregulation of cell cycle pathways correlated with a better survival rate in males than in females and that downregulation of the Integrin signaling pathway correlated with better survival in female patients.[113] In a separate investigation by Khan et al. (2021), it was found that elevated expression of the genes ECEL-1 and LILRB5 correlated with a better prognosis in males, while lower expression of these genes was linked to a better prognosis in females.[114] Mutations in the gene *IDH1* have been associated with better survival outcomes, but this is only true in males.[110] A study done by Stiller et al. (1995) found that the sex ratio of PBTs is male-biased for all tumours except astrocytomas.[115, 116] A 10-year study done by Williams et al. (2021) found that globally, all cancers exhibited a male predominance.[117] The underlying mechanisms remain to be elucidated.

The mean age of the study participants was 6.8 years, with a standard deviation of 4.9 years. The youngest participant was 2 days old (0.005 years), and the oldest participant was 17 years old. 4-year-old children had the highest prevalence for PBTs, representing 11.54% of the study population, followed by 2-year-old children and 7-year-old children, representing 9.62% of the study population each. The most affected age group was 3-8-year-old children, who comprised 32.69% of the study population. Authors from Pakistan and the United States of America have reported similar results in this age group.[96, 98, 99, 118] The mean age for male participants in this study was 5.1 years with a SD of 4 years, while the mean age for female participants was 9.7 years

with a SD of 5 years. Males appear to have an earlier onset of disease compared to females. Biological differences between the sexes are apparent even from the early gestational phases.[119] Male and female foetuses respond differently to the same intrauterine environment, suggesting a fundamental biological variation, most likely at the cellular and molecular level. The growth of male foetuses is greater than female fetuses,[120, 121] with cell division occurring more rapidly in males than in females.[122, 123] These differences in the rate of brain development and maturation between males and females could influence the vulnerability to tumour development at different ages.

When considering anatomical tumour location, infratentorial tumours were more prevalent than supratentorial tumours. These findings complement most published data on the subject.[96-98, 124] The anatomical differences between the infratentorial and supratentorial regions, as well as the developmental aspects of the CNS during childhood, may contribute to the prevalence of infratentorial tumours. The infratentorial region primarily houses the cerebellum and brainstem, both of which are critical for motor coordination, balance, and vital physiological functions. The intricate nature of these structures and the rapid growth and maturation of the cerebellum and brainstem during early childhood could render the infratentorial region more susceptible to genetic mutations and tumorigenesis.[109, 125]

The most affected brain area in the overall study population was the posterior fossa, with 36.5% of tumours originating in this area, followed by the brainstem and the suprasellar region. Research has shown that most paediatric neoplasms occur in the posterior fossa.[126] In the cortical region, the most affected areas were the parietal and parieto-occipital areas. Considering the heightened prevalence of infratentorial tumours, it is not surprising that the posterior fossa is the most affected brain area. The posterior fossa accommodates vital structures such as the cerebellum, brainstem, and associated vasculature. In addition to the complex nature of these structures and the enhanced rate of cellular division that contributes to the areas' susceptibility to tumorigenesis[109], supplementary factors that should be considered are anatomical constraints and cerebrospinal fluid dynamics. Anatomically, the posterior fossa is compact, and the intricate interplay between neural structures, blood vessels, and CSF pathways necessitates precise spatial organisation. Any aberrations in this delicate balance may result in tumorigenesis, given the limited space available for

accommodating structural anomalies. The fourth ventricle is located in the centre of the posterior fossa. Alterations in CSF flow dynamics, such as obstructed pathways or impaired absorption, can lead to increased intracranial pressure and subsequently create an environment conducive to tumour initiation. Elevated ICP can compress blood vessels, leading to decreased blood flow and oxygen delivery to the surrounding brain tissue and, eventually, hypoxia.[127] Chronic hypoxia and ischaemia can induce cellular stress and initiate specific molecular pathways as compensation.[128] Hypoxic conditions can activate Hypoxia-inducible factors (HIFs), a transcription factor that regulates gene expression of intracellular proteins and receptors.[129] HIF activation is a common event in cancer, and HIFs have been found to promote key steps in tumorigenesis, including angiogenesis, metabolism, proliferation, metastasis, and differentiation.[128, 130-132]

In the overall study population, mixed gliomas had the highest frequency of occurrence, constituting 26.9% of all tumours. However, regarding individual tumour types, medulloblastoma had the highest frequency of occurrence, followed by astrocytoma and ependymoma. This is comparable to other studies of this nature.[96, 98, 133] In the general population, gliomas account for nearly half of PBTs.[37] Two main cell types make up the CNS, namely neurons and glial cells. Glial cells outnumber neurons, and the two cell types occupy a similar amount of space in nervous tissue.[134] Glial cells occupy half the brain volume, and most malignant brain tumours are derived from glial cells.[115] Glial cells originate from progenitor cells, which differentiate to form neural tissue under the control of progenitor/stem cell-intrinsic and local microenvironmental (extrinsic) cues. Molecular differences among progenitor/stem cells in different regions of the CNS render these cells uniquely susceptible to various cancer-inducing mutations, and accumulation of these mutations results in glial cell tumours.[135] Furthermore, gliomas produce oncometabolites in the tumour microenvironment that correspondingly stimulate their progression.[136] One such an oncometabolite is succinate, a mitochondrial metabolite of the tricarboxylic acid cycle. Elevated plasma concentrations of succinate may induce metabolic reprogramming of the tumour microenvironment to promote the growth of cancer cells. Therapy-resistant tumour cells incorporate oncometabolites that activate proliferation, causing repopulation of the tumour mass. Additionally, succinate can promote a state of pseudohypoxia, where despite normal oxygen levels, gene expression is regulated by

HIF-1. This leads to the expression of genes involved in glycolysis, angiogenesis, and metastases, as previously discussed.[136] These factors are a key obstacle in treating this tumour type. Medulloblastoma is the most common malignant brain tumour in children and accounts for 20-30% of all PBTs.[57, 58] They are embryonal tumours that originate from the developing cells of the cerebellum. These undifferentiated cells are more susceptible to genetic errors. The cerebellum undergoes significant development during early childhood, increasing the risk of abnormalities in cell growth and differentiation. Medulloblastoma is fundamentally characterised by dysregulation of core developmental pathways,[137] with frequent mutations of genes involved in normal developmental processes. Mutations leading to abnormal activation of pathways that regulate cell proliferation, such as *Sonic Hedgehog* and *Wingless* pathways, are common.[138] Sonic hedgehog-activated medulloblastomas (SHH-MBs) represent 25-30% of all medulloblastomas.[138, 139] SHH-MBs arise from cerebellar granule neuron precursors (CGNPs) of the brainstem.[140] During early postnatal development, Purkinje neurons express SHH and promote the rapid expansion of CGNPs. Continuous SHH signaling leads to overproliferation.[141-143] In paediatric tumour pathogenesis, the most frequently mutated genes that lead to a disruption in these pathways include PTCH1, TP53, Glioma-Associated Oncogene Family Zinc Finger 2 (GLI2), and MYCN.[144] PTCHI and TP53 are crucial tumour suppressor genes, and when muted, their inhibitory function is lost. This results in the upregulation of proliferation pathways. Furthermore, when these tumour suppressor genes are muted, the damaged cells evade apoptosis. Because of TP53s crucial role in DNA repair, genome maintenance, and cell death, TP53 alterations in medulloblastomas are often associated with a poorer prognosis.[145] In children older than 5 years, malignancies with TP53 mutations account for two-thirds of mortality occurrences.[146] GLI2 and MYCN are important transcription factors that directly regulate the expression of genes involved in the SHH signalling pathway.[138] Mutations in these genes that result in amplification lead to excessive expression of target genes involved in various cellular processes, including cell proliferation, survival, and differentiation. GLI2 is the main transcription effector of SHH-signalling in granule cell precursors [147], and genomic amplification of this gene has been associated with more aggressive disease. [148, 149]

Astrocytomas have a much higher prevalence than the other glioma sub-types and account for over 75% of all gliomas.[150] In a 10-year study conducted by Williams et al.

(2021), it was found that astrocytic tumours had incidence rates 2 – 4-fold higher than those observed for other tumour types.[117] This could be attributed to the fact that astrocytes are more numerous than other glial cells[134], which are present in both infratentorial and supratentorial regions. These factors increase the probability of mutations occurring during cell proliferation, leading to tumorigenesis. Mutations can lead to the initiation of transcription factors that would not be present or active under normal circumstances. The induction of transcription factors plays a pivotal role in initiating tumorigenesis. Nuclear factor I/A (NFIA) is highly expressed in all grades of astrocytoma and regulates tumorigenesis via direct transcriptional repression of p21, also known as cyclin-dependent kinase inhibitor 1.[151] P21 inhibits the activity of cyclin-dependent kinases, enzymes that promote cell cycle progression, and thus acts as a tumour suppressor by inducing cell cycle arrest.[152] Cell cycle arrest is crucial to allow the cell sufficient time to repair damage or undergo apoptosis if necessary. When p21 is effectively suppressed, the proliferation of damaged cells persists unabated.

In the 0-3-year-old age group, 77% of participants were male, and 33% were female. Anatomically, 54% of the tumours were located in the supratentorial region and 46% in the infratentorial region. The posterior fossa was the most commonly affected brain area in this age group, followed by the brainstem. Histologically, the most prevalent tumour type in this age group was medulloblastoma, with a relative frequency of 38.5%, followed by gliomas, ependymomas, and astrocytomas. This coincides with studies that have found the risk of medulloblastoma, gliomas, and ependymal tumours to be higher in younger children.[117, 153, 154] The prevalence of medulloblastoma culminates in children below the age of 10 years, with about 50% of patients diagnosed before the age of 5.[14, 155] Roughly 40% of patients have progressed to metastatic disease upon diagnosis.[156]

In the age group 3-8, 88% of participants were male and 12% were female. This group had the highest male-to-female ratio out of all the age groups. Anatomically, 75% of tumours were found in the infratentorial region, and 25% were supratentorial tumours. Like in the previous age group, the most common brain area of origin was the posterior fossa, followed by the brainstem. Histologically, in this age group, the most common tumour type was mixed gliomas, with a total prevalence of 47%. The most prevalent glioma was brainstem gliomas (23.5%), followed by DIPG (17.6%) and ganglioglioma

(5.9%). Ependymomas were the second most common tumour in this age group, with a prevalence of 23.5%. Studies have shown that younger children exhibit a higher risk of developing gliomas and ependymomas.[117, 153, 154] Interestingly, astrocytomas and medulloblastomas had the lowest relative prevalence in this age group. This is not in keeping with global incidence rates, where the incidence of both medulloblastoma and astrocytoma are the highest in the age group 5-9 years.[117]

The age group 8-12 had a 46% male to 54% female sex split. Anatomically, infratentorial tumours constituted 54% of the tumour locations in this group, while supratentorial tumours were found in 46% of participants. The brain area of origin with the highest prevalence was again the posterior fossa. Histologically, the most common tumour type in this age group was astrocytoma, with a prevalence of 30.8%, followed by medulloblastoma at 23.1%. This is in keeping with studies by Mehrazin et al. (2007).[89] Various studies have found that older children have a higher risk of developing astrocytomas compared to younger age groups.[117, 153, 154] Globally, in children aged 0-14, astrocytoma and medulloblastoma have the highest incidence rates.[157] Meningioma and atypical choroid plexus tumours were the least prevalent in this group.

In the age group 12-18 years, only 22% of participants were males and 78% were females. The two most common brain areas of origin were the posterior fossa and the parietal-occipital area. Anatomically, 44% of tumours were located in the infratentorial region and 56% in the supratentorial region. This is the first age group that exhibited a significantly higher tumour prevalence in the supratentorial region. A study conducted by Arora et al. (2009) found that tumours located in the infratentorial region decreased in proportion with increasing age, and supratentorial-located tumours increased in proportion.[158] In a study executed by Mahvash et al. 2011 on glioblastoma in children, it was found that the location of glioblastoma shows a strong correlation with age: infratentorial tumours were exclusively found in children under the age of 11 years, while supratentorial tumours were exclusively found in those aged 11 years or older.[159] The findings in this study corroborate the correlation between age and tumour location. All three of the glioblastoma cases in this age group were above 11 years of age, and the three tumours were all located supratentorially. Histologically, glioblastoma was the most prevalent tumour type, with a prevalence of 33.3%,

followed by ependymomas with a prevalence of 22.2%. Glioblastoma stands as the prevailing and most aggressive primary brain tumour found in adults.[160] However, its occurrence in children is rare, comprising roughly 7-9% of CNS tumours in the paediatric population.[159, 161-163] Glioblastomas are high-grade gliomas (WHO grade IV), and regarding their pathogenesis, malignant transformation results from the sequential accumulation of genetic alterations and abnormal regulation of growth factor signalling pathways.[164] In paediatric glioblastoma, driver mutations (molecular changes that are required for tumorigenesis and progression) are highly prevalent.[165] Alpha-type platelet-derived growth factor receptor (PDGFRα) is amplified and overexpressed in paediatric high-grade gliomas.[166, 167] PDGFRα acts as a mitogen – a substance that promotes cell division and proliferation – in the early phases of stem cell differentiation to expand the pool of immature neurons.[168] Amplification of PDGFRα promotes aggressive glioma growth.[169, 170] Other common aberrations include mutations involving histone H3.3, chromatin remodelling genes (changes in the chromatin architecture is a major factor in tumour pathogenesis), and ACVR1 genes (which are involved in signalling pathways related to cell growth, proliferation, and differentiation).[171-173] H3.3 histones are nuclear proteins that are important in regulating transcription and replication.[174] Paediatric glioblastoma often exhibits mutational inactivation of the p53 tumour suppressor gene.[175] In children with high-grade glioma (such as glioblastoma), H3.3 mutations overlap with TP53 mutations in approximately 64% of cases.[167] These alterations primarily lead to dysregulation of two major cellular systems- the growth factor-mediated signalling pathways and the cell cycle- both of which are key contributing factors to the increased cellular proliferation, inhibition of apoptosis, invasion, and angiogenesis.[176] Mitotic activity in glioblastomas is abundant, and vascular endothelial proliferation is prominent. These characteristics are suggestive of a rapid growth rate.[177] Glioblastoma has a poor prognosis and is a leading cause of cancer-related deaths in children, with a 2-year survival rate of 12%.[178]

To summarise the key findings in this retrospective study of primary PBTs:

- This study showed male preponderance with an overall male-to-female ratio of 1.74:1
- The mean age of study participants was 6.8 years

- The mean age of the male group was 5.1 years, while the mean age for the female group was 9.7 years
- The age group with the highest prevalence for PBTs was 3-8 year olds
- Infratentorial tumours were more prevalent than supratentorial tumours
- The posterior fossa was the most common area of origin
- In descending order of frequency, the most common tumour types were mixed glioma, medulloblastoma, astrocytoma, and ependymoma
- In the age group 0-3 years, the most common tumour type was medulloblastoma
- In the age group 3-8 years, mixed gliomas were the most prevalent tumour type
- In the age group 8-12 years, the most common tumour type was astrocytoma
- In the age group 12-18 years, the tumour type with the highest prevalence was glioblastoma

CHAPTER 6: CONCLUSION

Paediatric brain tumours are the leading cause of cancer death among children. When this debilitating disease does not lead to death, it often leads to a severely reduced quality of life. CNS tumours encompass over 100 histological subtypes and varying incidence rates based on age and geography. The extensive histological heterogeneity in these tumours complicates aetiological studies, thereby limiting the identification of environmental risk factors beyond ionising radiation. Although progress has been made in the treatment of childhood cancers, significant mortality and morbidity are still associated with malignant brain tumours. Improved management of paediatric patients with brain tumours depends largely on established protocols and the implementation of new strategies derived from appropriate research.

The purpose of this study was to describe in detail the profile of brain tumours in the paediatric population of the Greater Tshwane region by examining the demographic profile of patients and tumours, analysing the histopathological profile, and investigating the anatomical profile by analysing imaging data. In this region, it was found that the mean age of brain tumour diagnosis in the paediatric population is 6.8 years, and the age group that exhibited the highest prevalence was 3–8-year-old children. Males showed a greater prevalence, and the male-to-female ratio was 1.74:1. The most common tumour types were mixed glioma, medulloblastoma, astrocytoma, and ependymoma. Infratentorial tumours were more prevalent than supratentorial tumours, and the posterior fossa was the most common brain area of tumour origin. The findings from this study, such as mean age, tumour location, and tumour prevalence, are in accordance with other similar epidemiological studies done on PBTs in Westernised countries. The information gained from the study will be valuable in managing subsequent patients, planning for treatment, and further follow-up of paediatric patients with primary brain tumours. Understanding the prevalence and distribution of specific tumour types within a particular population enables clinicians to better anticipate and prepare for future cases, and gaining insight into the genetic and molecular profiles of these tumours can lead to more personalised treatment approaches.

Limitations

The present research constitutes a study conducted within a single institution, and therefore, its findings should be interpreted with care. It is imperative to conduct studies on a broader population level to accurately assess the extent of cancer impact stemming from brain malignancies in the South African paediatric population.

This study relied on existing data. Due to missing or incomplete information on key variables, several participants had to be excluded. This had a limiting effect on the study population and, thus, the statistical significance. The small sample size could compromise the generalisability of the results, as it may not accurately represent the broader population under study. Furthermore, small samples may have more variability in their characteristics, making it difficult to identify true patterns and trends.

Future research

- To establish an accurate national frequency of tumour prevalence, similar studies should be conducted at other referral hospitals throughout the country.
- Population-based studies are required to determine the precise cancer burden of our childhood population.
- Insights into the age, gender, and other demographic factors associated with various tumour types can guide the development of a screening program. Recognising common presenting symptoms and signs for various PBTs can lead to earlier and more accurate diagnoses.

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Annexure A

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
1	Patient data number	Patient number	File number	Patient name	Date of birth	Date of first visit	Date of discharge	Age (at time of first presenting symptom)	Gender	Nationality	Geographic location (patient residence)	Existing medical conditions/ Previous procedures	Presenting symptoms	Date of first symptom onset	Date of Imaging diagnosis	Imaging findings (MRI/CT Scan)	Histopathology findings	Tumour diagnosis	Tumour location
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Annexure B

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

Faculty of Health Sciences **Research Ethics Committee**

27 October 2022

Approval Certificate
New Application

Dear Miss D de Beer

Ethics Reference No.: 573/2022
Title: A description of the profile of paediatric brain tumours in a tertiary neurosurgery service

The **New Application** as supported by documents received between 2022-09-27 and 2022-10-25 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on 2022-10-25 as resolved by its quorate meeting.

Please note the following about your ethics approval:

- Ethics Approval is valid for 1 year and needs to be renewed annually by 2023-10-27.
  Please remember to use your protocol number (573/2022) on any documents or correspondence with the Research Ethics Committee regarding your research.
  Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

Approved on condition that all references to race and ethnicity to be removed as comparisons with populations elsewhere will not be valid in a single racial category study.

We wish you the best with your research.

Yours sincerely

On behalf of the FHS REC, Dr R Sommers
MBChB, MMed (Int), MPharmMed, PhD
Deputy Chairperson *of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria*

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health)

Research Ethics Committee
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Fakulteit Gesondheidswetenskappe
Lefapha la Disaense tša Maphelo

Annexure C

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

STEVE BIKO ACADEMIC HOSPITAL

Enquiries: Dr JS Mangwane Tel No: +2712 3452018

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For attention: Debbie De Beer

NHRD Ref Number: GP_202212_025

Re: REQUEST FOR PERMISION TO CONDUCT RESEARCH AT STEVE BIKO ACADEMIC HOSPITAL

TITLE: A description of the profile of paediatric brain tumours in a tertiary neurosurgery service

Permission is hereby granted for the above-mentioned research to be conducted at Steve Biko Academic Hospital. This is done in accordance to the "Promotion of access to information act No 2 of
2000".

Please note that in addition to receiving approval from Hospital Research Committee, the researcher is expected to seek permission from all relevant department. Furthermore, collection of data and consent for participation remain the responsibility of the researcher.

The hospital will not incur extra cost as a result of the research being conducted within the hospital.

You are also required to submit your final report or summary of your findings and recommendations to the office of the CEO.

STATUS OF APPLICATION: Approvec

Date: 2023-01-04

Dr. J S. Mangwane
Manager: Medical
Service