GLIOMA HISTOLOGY AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL, A FIVE YEAR RETROSPECTIVE STUDY.

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A research report submitted to University of Witwatersrand, Faculty of Health Sciences, as a requirement for the Degree of Master of Medicine in Neurosurgery.

Johannesburg 2024

DECLARATION

I Diapo Gerald Mohale declare that this research report is my own work, it is being submitted for the degree of Masters of Medicine in Neurosurgery at the University of Witwatersrand, Johannesburg.

This research has not been submitted before for any degree or examination at this or any other University.

Signature

17th day of June 2024

ACKNOWLEDGEMENTS

Dr Rambe Khohomela for brainstorming and ideas for the topic

Dr Christos Profyris and Morena Nthuse Mpanza for supervision and guidance on the study

Prof John Ouma for valuable advice and input

My wife Lungile Sibongile Mohale for her love and unmeasurable support

ABSTRACT

The epidemiology of gliomas has been described thoroughly by developed countries worldwide but information regarding gliomas is limited in developing countries including in our local setting in South Africa. This study will be describing glioma histology and the demographics of patients with gliomas for patients diagnosed at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) situated in Johannesburg South Africa.

The records of 44 patients ages between 12 and 70 years with histologically confirmed glioma from 2015 to 2919 was reviewed and our findings are as follows;

In our sector we see more Black population than White, Coloured and Asians combined.

Despite that literature commonly report gliomas to be more prevalent in males than females, we found females to be more prevalent than males (ratio 1,3:1) in our study group with males only showing prevalence over females with the advanced age group of 60 to 70 years.

Our mean age of glioma diagnosis is younger (43years) than the documented age group and we found the mean age to be even younger with patients confirmed HIV (38 years).

The study demonstrated that females were diagnosed at early average age of 40 year and males average age of 47 years.

In keeping with literature glioblastoma is the most common glioma in our study population. We also found gliomas to be more prevalent supratentorial in the temporal lobe than infratentorial and other lobes respectively in our study population.

Patients with higher grade gliomas presented with varied number of symptoms than lower grade.

With regard to biopsy procedures, most of our cases had undergone minimal invasive stereotactic biopsy and about seventy percent of the frozen biopsy cases were of patients who had minimal invasive stereotactic biopsy and only thirty percent had open biopsy.

The study found that glioma size increased with increase in glioma grade and patients who are HIV positive. There was no significant relationship found between patients' age groups and glioma size.

We found that immunochemistry is widely done , but molecular testing lacking behind with testing only started late 2017 and improving annually.

For patients with HIV it was found that grade III gliomas are the most prevalent.

Glioma grade increase with increase in age group and in patients wo are confirmed HIV positive.

A formal national registry for gliomas will help to determine disease demographics, distribution, frequencies and associations for early detection and patients management strategies.

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LIST OF ABBREVIATIONS

CMJAH:	Charlotte Maxeke Johannesburg Academic Hospital
CNS:	Central Nervous System
GBM:	Glioblastoma
PXA:	Pleomorphic Xanthochromic Astrocytoma
SEGA:	Subependymal Giant Cell Astrocytoma
HIV:	Human Immunodeficiency Virus
HAART:	Highly Active Anti -Retroviral Therapy
AIDS:	Acquired Immunodeficiency Syndrome
SA:	South Africa
USA:	United State of America
WHO:	World Health Organization
CTB:	Computed Tomography of the Brain
MRI:	Magnetic Resonance Imaging

DEFINITION OF TERMS

Compartment: In relation to the tentorium (supra of infratentorial)

Laterality: Left and Right hemispheres and Medially originating or positioned gliomas radiologically

Medial: Medial aspect of the brain(Corpus collosum. Basal Ganglia, Thalamus, Intraventricular ,Vermis)

Size: Glioma volume size using ellipsoid mass calculation formular (cm^3)

Diameter: The largest glioma diameter on any radiological plane in “cm”

CD4: White blood cells that play an important role in the immune system, the count give an indication of our immune status.

CNS: Central Nervous System

CHAPTER ONE

1.1 INTRODUCTION

1.1.1 BACKGROUND

Despite worldwide varying reports regarding intracranial lesions, specifically gliomas, there is limited information in South Africa regarding demographics and prevalence of gliomas. Patients with intracranial tumours in Africa typically have delayed diagnosis due to late presentation. On average patients present two years post initial symptoms. This negatively impact prognosis (1). Gliomas account for about 40% of all intracranial tumours. Primary brain tumours are among the ten most common causes of cancer related death and there is no screening test for them, but timely diagnosis and treatment improve the outcome (2).

This study will demonstrate prevalence and demographic aspects of patients with gliomas within a South African setting. It will also investigate the World Health Organisation (WHO) pathological grading of gliomas under investigation. It will also provide an inventory and determine an appropriate sample size & feasibility prospects to pilot future studies related to gliomas and to improve and expedite approach to patients suspected to have gliomas.

1.2 PROBLEM STATEMENT

The international society has described gliomas in their setting with regard to the most prevalent subtype, grade and anatomical prevalent positions in the brain relative to age group, gender and ethnicity. This study is to look at our population of patients treated at our institution at CMJAH to have an idea of how glioma is distributed in our setting compared to the rest of the world.

1.3 RESEARCH QUESTION AND OBJECTIVES

1.3.1 Specific Question

What are the demographic characteristics of patients with gliomas in Johannesburg?
What is the most prevalent glioma type and grade in Johannesburg?
Which compartment and brain lobe is commonly affected?

1.3.2 Specific Objectives

To determine the prevalence of gliomas in population age groups 12 and above.
To identify the most prevalent glioma.
To determine the most prevalent age group, age and gender.
To establish the most common anatomical location for brain gliomas.

1.4 STUDY SIGNIFICANCE

This data can be used to plan and strategize possible screening and to develop surveillance protocols also to expedite histology for patients outlined by the study to be the most prevalent group.

The study will also provide inventory baseline for any future studies related to gliomas in Johannesburg or South Africa and Africa.

CHAPTER TWO

2.1 LITERATURE REVIEW

2.1.1 Definition

Gliomas are tumours arising from glial cells and can occur anywhere in the central nervous system, but primarily occur in the brain. Glioma is a general term used to characterize any tumour that originates from glial brain cells. There are three main cell types of glial origin with the potential to produce tumours. These include astrocytes leading to astrocytomas (including glioblastomas), oligodendrocytes giving rise to oligodendrogliomas, and ependymal cells forming ependymomas. These potentially aggressive tumours tend to be invasive and destructive and are considered of the deadliest form of cancer affecting humans(3).

2.1.2 Epidemiology

Gliomas are the most common primary intracranial tumours, representing 80% of malignant brain tumours and comprise almost 41% of all CNS malignancies and 30 to 40% of all intracranial tumours(1,2,4). Gliomas develop in approximately 6.6 per 100 00 individuals each year and also occur at various ages depending on the subtype and with male to female ratio of 6:4(2,5). These tumours are most common in middle-aged adults with peak incidence between the ages of 45 and 65 years old causing significant morbidity and mortality(2,4,6). They are the third most common cause of cancer related death for individuals between the ages of 20 and 39(1,3).

Grade I astrocytoma occurs most often in children and teens and account for 2% of all brain tumours. Grade II astrocytomas occurs in adults between the ages of 20 and 60. Grade III astrocytomas most often occurs in adults between the ages of 30 to 60 and Grade IV

astrocytomas between the ages of 50 to 80(6,7). Certain gliomas like ependymomas and pilocytic astrocytomas are more common in children and young adults(2).

2.1.3 Etiology

The exact cause of gliomas is unknown, most gliomas are sporadic but there are factors that increase the risk of a brain tumor. Only about 1% to 5% of the gliomas can be classified as hereditary(5,6). The risk factors include age, exposure to radiation and family history of glioma. The risk of brain tumor increases as you age. It is rare for glioma to run in families, but having a family history of glioma can double the risk of developing glioma (5). People who have been exposed to ionizing radiation have an increased risk of brain tumor. Example of ionizing radiation include radiation therapy used to treat cancer and radiation exposure from atomic bombs. It is not clear if cell phone use increases the risk of brain cancer(5,8).

2.1.4 Anatomical Distribution

These tumors can occur anywhere in the central nervous system but primarily occur in the brain and arise in the glial tissue.(5,8) The symptoms associated with gliomas are similar among all types of glial tumors, however, can vary depending on the individual and the location of the tumor(3). Approximately 70% of gliomas in adults are supratentorial and 70% of the tumors in children are infratentorial. The anatomical location of the tumor determines the patients' symptoms (5,9,10).

2.1.5 Clinical Presentation

Symptoms in glioma patients can be caused by the tumor impact on the brain or occur as side effects of treatment. The ten most prevalent symptoms for the total disease trajectory from most prevalent to less prevalent are: seizures, cognitive deficit, drowsiness, dysphagia, headaches, confusion, aphasia, motor deficits, fatigue and dyspnoea (5,9,10). Rapid worsening of the clinical manifestations may indicate either malignant growth or impaired flow of cerebrospinal fluid. Occasionally initial presentation can be sudden (apoplectic form). Acute clinical manifestations that are a sign of life-threatening brain herniation due to intracranial hypertension include headache, vomiting and deterioration of consciousness leading to coma(2).

2.1.6 Gliomas and HIV

Glioblastoma occurs at an increased frequency and younger age in the HIV population than in the general population. The effect of HIV infection on reduced immune surveillance is thought to promote the development of these tumors(11). Direct effect of HIV on malignancy development has not been defined, there is an association between malignancy development and immune suppression, lower CD4 count in patients with AIDS defining malignancies. Improvement in antiretroviral therapies have been accompanied by increased frequency of non-Acquired Immune Deficiency Syndrome (AIDS) defining malignancies, such as glioblastoma multiforme. Human Immunodeficiency Virus (HIV) mainly targets microglia and macrophages within the central nervous system.

A number of studies have identified selective expression of viral proteins within astrocytoma which can serve as a mediator of HIV induced neuronal damage. Astrocytes have the potential to transform during HIV infection with activation of oncogenes or inactivation of tumor suppressors leading susceptibility to neoplasms (12). There are contrary studies regarding HIV and its association with glioma, like the observational studies done by L Jokonya, A Musara et al demonstrating reduced prevalence of HIV in glioma patients compared to the general population.

The immunosuppression from treatment with immunosuppression drugs has been strongly associated with increased frequency of intracranial gliomas in organ transplant recipients. A number of large epidemiological studies have found that patients with a history of allergic disease have a reduced risk for developing gliomas, suggesting that a heightened immune status may be associated with a more robust intracranial defence against certain neoplasms(12).

2.1.7 World Health Organization (WHO) Classification

For this study only the 2016 4th edition WHO classification will be applied as we will be looking at histology of biopsies done between 2015 and 2019. Classification of gliomas is complex and based partly on the microscopic appearance of the tumor (histological classification) and partly on the gene changes (mutations) that are implicated in tumor development (5). The latest fifth edition of the WHO classification of tumors of the CNS published in 2021 is the sixth version of

the international standard for the classification of brain and spinal cord tumors. The 2021 5th edition is building on the 2016 updated 4th edition and has introduced changes that advance the role of molecular diagnostics in CNS tumors classification (13). The previous edition 2016 4th edition WHO classification of tumors of the central nervous system (CNS) classified glial cells based on both histological appearance, as well as the advanced genetic categorizations into 4 grades ranging from I (benign) to IV(malignant)(3,14).

WHO four grades classification ranging from benign grade I to malignant grade IV:

- Grade I. e.g. Pilocytic astrocytoma
- Grade II. e.g. Diffused Astrocytoma
- Grade III. e.g. Anaplastic Astrocytoma
- Grade IV. e.g. Glioblastoma

The main molecular markers are the following:

Isocitrate dehydrogenase 1 and/or 2 (IDH-1/-2), which considered very early mutation in glioma pathogenesis typical of low-grade or anaplastic glioma. New-onset glioblastomas are typically IDH -1 wild type, a rare IDH -1 mutation in a glioblastoma implies that the tumor arose from a lower grade precursor.

Codeletions of chromosome segments 1p and 19q. In IDH-1 mutated tumors indicate that the tumor is of oligodendroglial origin. Astrocytoma is characterized by the lack of a 1p/19q codeletion and is strongly associated with IDH mutant and is mutually exclusive of ATRX and TP53.

ATRX and TP53 mutations are mutually exclusive of 1p/19q codeletion and as such may be used as confirmatory markers to distinguish astrocytomas from oligodendrogliomas.

Histone 3 mutation (H3 K27M) defines the new entity of diffuse midline glioma, which carries an unfavourable prognosis.

Methylation of the O6-methylguanine DNA methyltransferase (MGMT) promoter. This does not affect the WHO classification of the tumor, but is of high prognostic and predictive significance for patients with glioblastoma.

Alteration of C19MC (a cluster of microRNA encoding genes) and NOS (nitric oxide synthase gene) status for embryonal tumors with multi layered rosettes.

BRAF (proto-oncogene B-Raf protein) fusion gene can be found in more than 60% of pilocytic astrocytomas, but only rarely in diffuse astrocytomas.

A few rare glial cell tumors lack any differentiating mutations and are described primarily on histologic and phenotypic features. These tumor types include angiocentric glioma, astroblastomas, and choroid gliomas of the ventricle (2,3,14).

2.1.8 Diagnosis

Diagnosis requires extensive patient history as well as a complete physical and neurological examination. Magnetic resonance imaging (MRI) is the imaging modality of choice for initial evaluation of glioma(5). In our setting we start with clinical suspicion of intracranial pathology then start with CTB and when a lesion is identified then MRI is done to better describe the lesion for surgical planning or biopsy. There is no substitute for histological diagnosis because grade III tumors cannot be securely differentiated from grade II tumors on radiological grounds alone, nor can imaging studies conclusively show the presence or absence of an oligodendroglial component(2).

2.1.9 Prognosis

Advanced age of greater than 40 years is associated with worse clinical outcome, probably attributed to a higher prevalence of high grade lesion WHO grade III and IV in his age group compared to younger patients. A lower Karnofsky Performance Scale less or equal to 70, a duration of symptoms less than 3 months and non-Caucasian ethnicity were stated as an unfavourable prognostic factor in several trials as well. Some literature illustrate that direct involvement of cranial nerve V is associated with poor prognosis. Radiological poor

prognosticators are tumors arising from the brain stem and those tumors with lower apparent diffusion coefficient value which are associated with high grade gliomas (15).

The median life expectancy for patients with high grade gliomas like glioblastoma remains unchanged at 12 to 18 months, and only 5% of patients will be alive in 5 years after diagnosis (16).

2.1.10 Treatment

There are no means for early detection, prevention, or screening of gliomas, nor any specific tumor markers available(2). The treatment of gliomas often requires a combination of neurosurgical interventions, radiation therapy and chemotherapy(5,6). Grading a glioma is one of the most important classification when determining the overall severity of malignancy which requires a biopsy of the tumor and evaluation by a neuropathologist. Major factors influencing treatment decisions are patients' preferences, age, weight, anatomical location of the tumor, risk and benefits, prognosis with versus without treatment, quality of life, and grade of the glioma amongst others(3). Some gliomas are slow-growing and are likely to be curable, while others are fast growing, invasive, difficult to treat and are likely to recur(10).

The primary treatment of different types of glioma:

- Pilocytic Astrocytoma (WHO Grade I): Surgical resection
- Diffuse Astrocytoma (WHO Grade II): Surgical resection, or biopsy and wait see, or radiotherapy
- Anaplastic Astrocytoma, oligodendroglioma/oligoastrocytoma (WHO Grade II): Surgical resection or biopsy and chemotherapy or radiotherapy.
- Glioblastoma (WHO Grade IV): Surgical resection or biopsy and radiotherapy and chemotherapy (temozolamide)(2).

The modern clinical practice of neuro-oncology is dependent on accurate tumor classification. Classification is also the basis at which clinicians make critical therapeutic recommendations to their individual patients. Treatment of brain tumor is dictated by histological diagnosis(6)

A large multi-disciplinary team of medical specialists and health professionals is required for the therapeutic management of patients with gliomas. Therapeutic management depends on the type of glioma, its size and location and specific characteristics of the patient. Especially in patients where the tumor cannot be entirely removed because it is invading the brain in crucial areas or is not accessible, chemotherapy and radiation therapy will follow surgery(5).

CHAPTER THREE

3.1 METHODOLOGY

3.1.1. STUDY DESIGN

Retrospective descriptive study

3.1.2. SITE OF STUDY

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)

3.1.3. PERIOD OF STUDY

The study will look at data of patients diagnosed with gliomas who presented at the mentioned hospital from 2015 to 2019.

3.1.4. INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

All records of patients diagnosed with brain gliomas from ages of 12 years and above.

Exclusion Criteria:

Patients suspected to have brain tumours but not biopsied or without histological finding

Age less than 10 years.

CHAPTER FOUR

4.1 DATA COLLECTION

Patients' file numbers and documented histological specimen barcodes will be accessed from the neurosurgery theatre procedures registries for a period of five years according to the provisions of the Ethics Committee from Charlotte Maxeke Johannesburg Academic Hospital.

Histological findings will be accessed from national health laboratory services (NHLS) through an online service provided by NHLS for registered health care personnel.

A data link sheet was used to separate patient identifying details from the scientific data to be used for analysis.

Demographic data collection includes; age , sex, race accessed from NHLS records.

Radiological investigation will include: type of investigation (CT/MRI), Number of lesions, anatomical site, and radiological description and size of lesion. Each scan will be reviewed to ensure consistent reporting.

All data will then be recorded on an Excel spreadsheet.

4.2 DATA ANALYSIS

Microsoft Excel and was used for data cleaning then transferred to STATISTICA. Both STATISTICA and Microsoft Data Tool package were used for data management and all statistical analyses were carried out. Both Microsoft Excel and STATISTICAL were used for tables and graphs. Statistical significance was set at 95% with p value $< 0,05$ demonstrating significant study findings.

For the series of patients obtain mean for:

- Age at diagnosis (years)

For the series of patients obtain absolute numbers for:

- Ethnicity (Black, White, Coloured and Asians)
- Gender (male/female)

Tumor Location :

- Side (Supratentorial/ Infratentorial, left/right)
- Lobe (Frontal, Temporal, Parietal, Occipital)

Procedure biopsy (Open / Minimal invasive/ Excision)

Pathology reports with molecular diagnosis of glioma

Nominal Data

- Gender: Frequency table, Bar Charts, Pie charts & percentages
- Race: Frequency table, Bar Charts, Pie charts & percentages

Ordinal data

- Histological Grade: Frequency table, Bar Charts, Pie charts & percentages.

Interval or Ratio data

- Gender: Ratio of male to female for all cases,
- Age: Peak incidence
- Mean age: all cases, per race, gender, WHO grade.

Weighted mean: patients' age will be grouped and the weighted mean will be calculated per histological classification.

Stratified Analysis: patients will be divided into subgroups according to risk factor, then compared.

Continuous variables: like age (means and median) will be compared with histological finding.

Discrete variables: Correlation calculation, relationship between:

- Age groups and Histological findings.
- Gender and histological findings.
- Racial groups and histological findings.
- Radiological findings and histological findings.
- Radiological findings and age

CHAPTER FIVE

5.1 ETHICAL CONSIDERATIONS

Protocol will be submitted with an application form for ethics review and clearance and study will only commence after approval from the ethics committee.

To minimize risk of breach of confidentiality, patients' names will not be included in the data collection.

Patients will be identified using a designated number for the purpose of the study.

Transparency will be exercised regarding all procedures and results.

CHAPTER SIX

6.1 STUDY RESULTS

6.1.1 Study Demographics

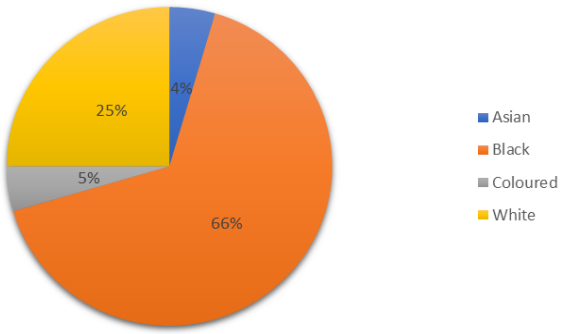
The study found that there was a significant disparity in race distribution of the 44 patients diagnosed with gliomas between 2015 and 2019, with black people diagnosed more than all ethnicities combined. Twenty nine (66%) of the gliomas were present in Blacks, Eleven(25%) in Whites , two(4.5%) in Asians and two(4.5%) in Coloureds. See table 6.1.1 and figure 1.

Table 6.1.1: Ethnicity Relative Prevalence

Ethnicity	n	Relative Prevalence (%)
Asian	2	4,55
Black	29	65,91
Coloured	2	4,55
White	11	25,00
Grand Total	44	100,00

n: count , %: percentage

Figure 1: Ethnicity Prevalence Chart



The ratio of Blacks to Whites is 3:1, ratio of Blacks to Coloureds and Asians is 15:1. A ratio of 6:1 for Whites to Coloureds and Asians respectively. This study findings reflect on the proportion of ethnicity our centre caters for.

6.1.2 Male to Female Relative Prevalence.

Table 6.1.2 Gender Relative Prevalence

Gender	n	Relative Prevalence(%)
Males	19	43%
Females	25	57%

n: count , %: percentage

In our study population nineteen(43%) were males and twenty five (57%) were female, with a male to female ratio of 1:1,3. More female were diagnosed with gliomas compared to males according to this study findings. See table 6.1.2. Odds ratio 0,76, 95% confidence interval 0,37 to 1,57 with significant level p=0,46.

6.1.3 Mean Age

Table 6.1.3 Mean Age Gender and Ethnicity

	Mean Age(yr)
Total study population	43,32
Gender	
Male	47
Female	40
Ethnicity	
Black	43
White	41
Asian	42
Coloured	45

Study population mean age is 43,32 years. Mean age at diagnosis for Black patients is 43years, Whites 41years, Coloureds 45 years and Asians 42 years with odds ratio of 1,02 and confidence interval of 0,56 to 1,86 and significance level p=0,938. Mean age at diagnosis for male and female is 47 years and 40 years respectively. Female are diagnosed at younger age compared to male and there is no significant differences in mean age at diagnosis per ethnicity with odds ratio 1,18, confidence interval of 0,65 to 2,13 and confidence level p=0,5965.

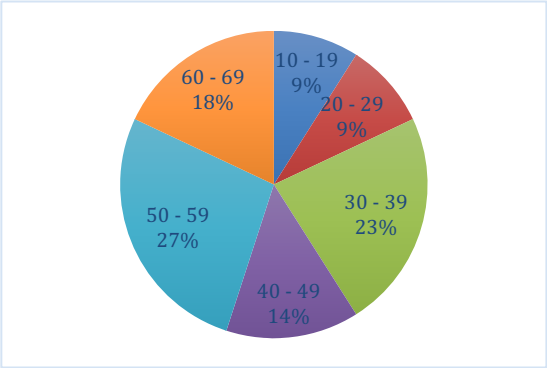
3.14 Age Range Relative Prevalence

Table 6.1.4. Age Range count

Age Range	n	%
10 - 19	4	9
20 - 29	4	9
30 - 39	10	23
40 - 49	6	14
50 - 59	12	27
60 - 69	8	18
Total	44	100

n: count, %: percentage

Figure 2: Age Range Prevalence Chart



The mean age at diagnosis for the patients under study is 43,32 years, with a minimum age of 12 years and maximum age of 68 years, age range of 56 years between the youngest and oldest patient and standard deviation of 15,25 years. 27% of the population group were between 50-59 years and 18 % between ages of 60 to 69 years of age, which together contribute 45% of glioma findings. Patients between ages of 30 and 49 years together add to 37% compared to the younger group ages 10 to 29 with a total relative prevalence of 18%. This finding shows prevalence of gliomas in elderly patients compared to younger age group. See Table 6.1.4 and figure 2.

6.1.5 Age Group Gender Ratio

Table 6.1.5: Age Group Gender Ratio

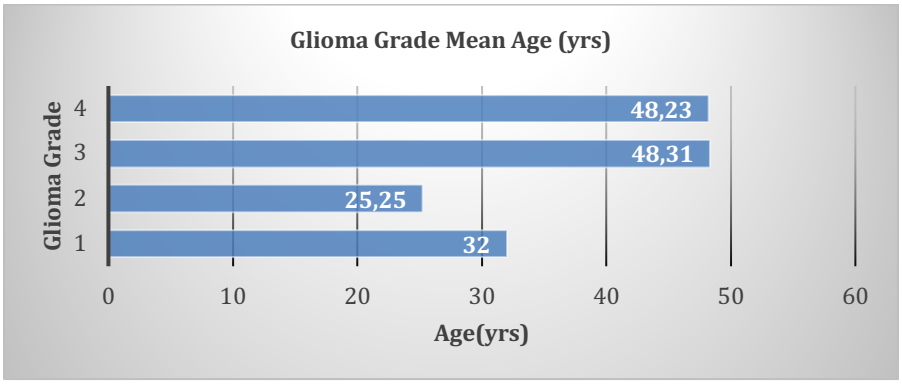
Age Group	M:F
10-19	**1:3**
20-29	**1:3**
30-39	**1:2,5**
40-49	**1:1**
50-59	**1:1**
60-69	**1,7:1**

M: male, F: female

The study demonstrated that from ages 10-39years group there are more females than male with male to female ratios of 1:2,8. Males were more prevalent for age group 60-69 with male to female ratios 1,7:1 . for ages 40-59 there were equal number of male and females with ratio of 1:1. See table 6.1.5.

6.1.6 Glioma Grade Mean Age

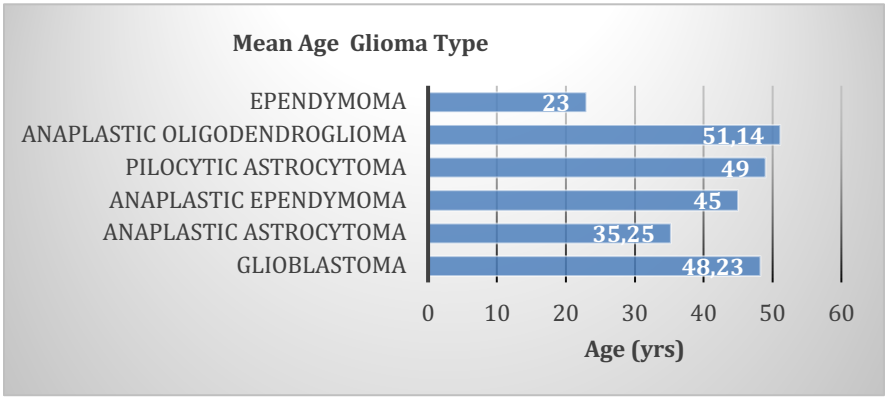
Figure 3: Grade Mean Age



Mean age at diagnosis for glioma grade 1 is 32 years, grade 2 is 25,25years, grade 3 is 48,31 years and grade 4 is 48,23 years which demonstrate an increase in age the higher the glioma grade. Grade I and Grade II have an average less than the study mean of 43 years while grade II and IV have mean age older than study population mean age.

6.1.7 Glioma Type Mean Age

Figure 4: Age Mean Age



Mean age of high grade gliomas like anaplastic oligodendroglioma (51,14 years) and glioblastoma (48,23 years) are among the highest mean age group at diagnosis. For low grade gliomas there is a varied mean age distribution shown by ependymoma's mean age of 23 years while pilocytic astrocytoma has a mean age of 49 years. Glioblastoma and all anaplastic subtypes have a mean age above study population mean age of 43 years except for anaplastic astrocytoma with mean age of 35,25 years. See figure 4 above.

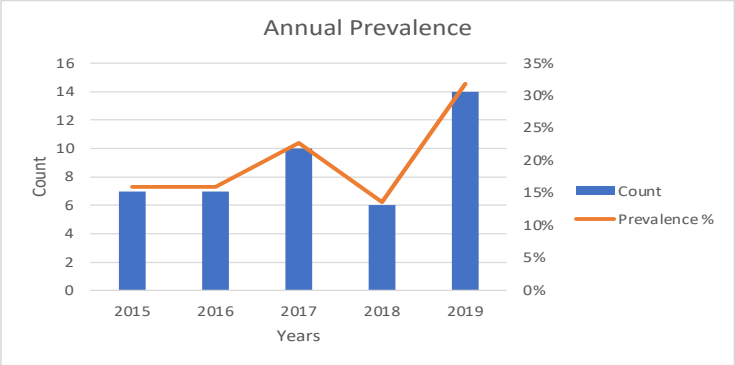
6.1.8 The Annual Glioma Frequency

Table 6.1.8: Annual Frequency

Year	n	%
2015	7	15,91
2016	7	15,91
2017	10	22,73
2018	6	13,64
2019	14	31,82
Grand Total	44	100

n: count , %: percentage

Figure 5: Annual Frequency



2015 and 2016 had a predictable frequency both with seven(15,91%) , followed by a peak increase in 2017 of ten patients (22,73%). There was a drop in frequency in 2018 followed by the highest peak in 2019. Demonstrated by the figure 5 annual prevalence graph. The average number of patients diagnosed per year is 8.8 with a variance of 10,7 and a standard deviation of 3,27 with confidence level of (p= 4,06).

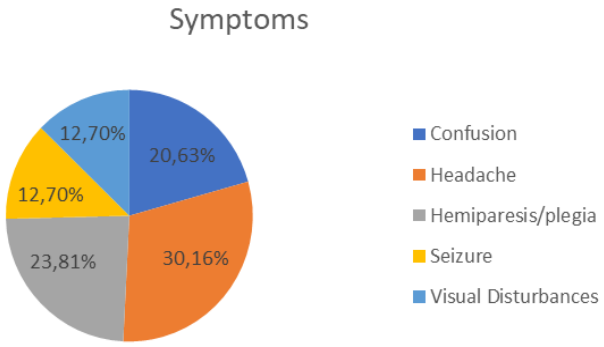
6.1.9 Frequency of Presenting symptoms

Table 6.1.9: Symptoms Frequency

Symptoms	n	%
Confusion	13	20,63
Headache	19	30,16
Hemiparesis/plegia	15	23,81
Seizures	8	12,7
Visual Disturbances	8	12,7

n: count , %: percentage

Figure 6: Symptoms Frequency Graph



Commonly noted symptom in the patients assessment details were compiled and headaches, limb weakness, confusion, seizures and visual disturbances were the most reported. “Confusion” was used for patients reported to be confused, or glascow comma scale”(GCS) less than 15/15 (no patient was reported to have presented to unconscious of those who were biopsied). “Hemiparesis/plegia” was used for any patient that reported weakness or assessed clinically to have weakness of any of the limbs or face. Visual disturbances was any reported visual changes and ophthalmologically confirmed visual defects.

As depicted by the table 6.1.9 and figure 6 the most prevalent symptom that patients presented with is headaches followed by hemiparesis hemiplegia weakness and confusion with prevalence of 30.16%, 23.81%, 20.63% respectively. Seizures and visual disturbances contribute to 12.7 % each. Headaches , limbs weakness and confusion are the most common symptoms.

6.1.10 Presenting Symptoms per Gender

Table 6.1.10: Symptoms & Gender

	H/A	CONF	SEIZURES	V.D	HEMI
M	15	5	1	5	8
F	19	7	8	4	11

H/A: headache, Conf: confusion, V.D: visual disturbances, Hemi: Hemiparesis/plegia

Females presented with the highest number of symptoms compared to males. In both genders headache was found to be the most common presenting symptoms and limbs weakness was the second most common symptom. See table 6.1.10.

6.1.11. Presenting Symptoms Glioma Lateralization

Table 6.1.11: Symptoms & lateralization

Glioma Hemisphere	Hemi	Conf	H/A	Seizure	V.D
Left	11	3	10	2	2
Medial	8	5	11	4	4
Right	13	4	11	3	1

H/A:headache, Conf: confusion, V.D: visual disturbances, Hemi: Hemiparesis/plegia

Table 6.1.11 above shows presenting symptoms in relation to site laterality of the glioma in the study. For laterality of the glioma site left, right and medial were used. Left and right referring to hemispheres, medial refers to anatomically medially positioned gliomas for supra and infratentorial. Medial gliomas anatomical site includes corpus collosum, basal ganglia, thalamus, intraventricular extension, brain stem and vermis. None of the gliomas were diagnosed midline H3K27 glioma in this study.

With regard to patients presenting with hemiparesis/plegia 34% were found in the left hemisphere , 26% in the medial region of the brain and 40% were on the right hemisphere. Twelve patient with gliomas presented with confusion, 25% of this patients were in the left hemisphere, 42% in the medial aspect and 33% in the right hemisphere. For the gliomas that presented with headaches 31% were in the left hemisphere, for both medial and right hemisphere

it was 34,5%. Nine patients presented with headaches and 22% were in the left hemisphere, 44% in the medial aspect with 33% having gliomas in the right hemisphere. Visual defects were more evident in gliomas positioned in the medial (57%) aspect of the brain a, left and right 29% and 14% respectively.

Interesting finding is that more right sided gliomas resulted with confusion compared to the left dominant side. Also the visual disturbances more for medial positioned gliomas could be as a result of interrupted visual pathway. Headache is evenly distributed among the glioma position. Medial positioned gliomas presented commonly with confusion and visual disturbances compared to gliomas in part of the brain. Only four (9%) of the patients presenting with gliomas in this study presented with hydrocephalus and three of them was gliomas positioned medially and only on had a large glioma.

6.1.12 Presenting Symptoms per Grade

Table6.1.12: Symptoms & Grade

Grade	Hemi	Conf	H/A	Seizures	V.D
1	4	0	4	2	0
2	3	0	5	1	3
3	5	3	12	2	1
4	7	8	11	4	4

H/A: headache, Conf: confusion, V.D: visual disturbances, Hemi: Hemiparesis/plegia

As depicted by table 6.1.12, patients with high grade glioma (grade 3 and 4) presented with majority of the symptoms ranging from (23)72% of all patients that presented with a headaches, confusion (11)100%, seizures (6)67%, visual disturbances (5)71% and hemiparesis/plegia(12)63%. With higher grade gliomas patients presented with multiple symptoms when compared to lower grade gliomas.

6.1.13 Glioma Location Frequency

Table 6.1.13: Location Frequency

Compartment	n	%
Supratentorial	39	89
Infratentorial	5	11

n: count, %: percentage

The main two compartments of the intracranial space are supratentorial and infratentorial compartment. Majority of the gliomas were found to be in the supratentorial compartment 39(89%) compared to infratentorial compartment 5(11%). Odds ratio of 9,75 and 95% confidence interval 3,21-29,60 and significance level (p=0,0001). This discrepancy is due to our study population age was mainly older children from 12 years and adults.

6.1.14 Supratentorial and Infratentorial per Glioma Grade

Figure 7: Supratentorial & Grade Chart

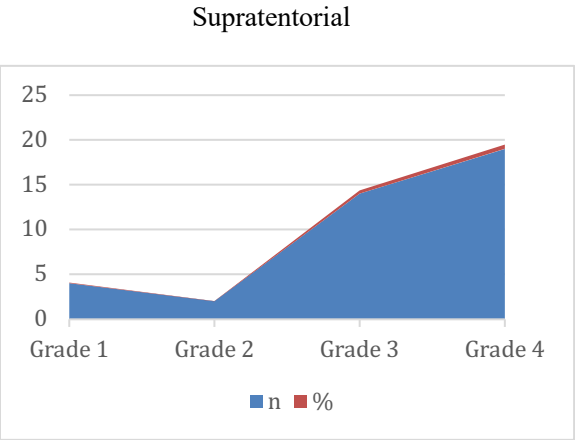
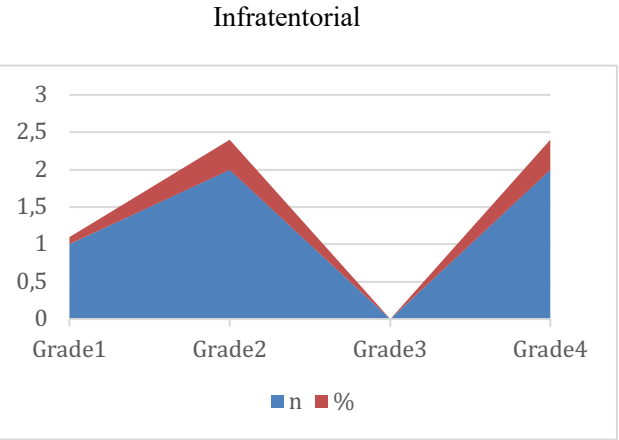


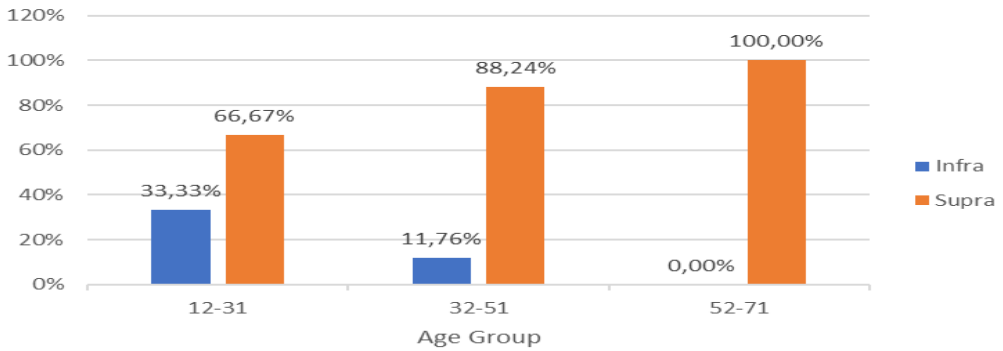
Figure 8: Infratentorial & Grade Chart



Of the 44 patients diagnosed with gliomas, 39(89%) of the gliomas were found in the supratentorial space. With high grade lesions displaying more prevalence than lower grades, grade 3 and 4 accounted for14(36%) and 19(49%) respectively. Only 5 glioma cases were found in the infratentorial with 1(10%) for grade 1 and 2(40%) for both grade 2 and 4 respectively. Zero Grade 3 gliomas was detected in the infratentorial space in this study population.

6.1.15 Supra-Infratentorial Age Group Distribution

Figure 9: Supratentorial Age Group Distribution Chart



Generally there were more supratentorial gliomas 88% found in this study than infratentorial of 12% however for age group 12-31 it is found that 33,33% were in the infratentorial space and 66,67% in the supratentorial space showing significance increase of infratentorial gliomas in the young group. For age group 32-51 infratentorial made up only 11,76% with 88,24% in supratentorial. 100% of patients over the age of 50 had supratentorial gliomas and no glioma was diagnosed in the infratentorial space for this study population. With increased age the chances of infratentorial glioma decreased.

6.1.16. Glioma Laterality

Table 6.1.16: Glioma Laterality

Side	n	%
Left	13	29,55
Medial	15	34.09
Right	16	36,36

n: count , %: percentage

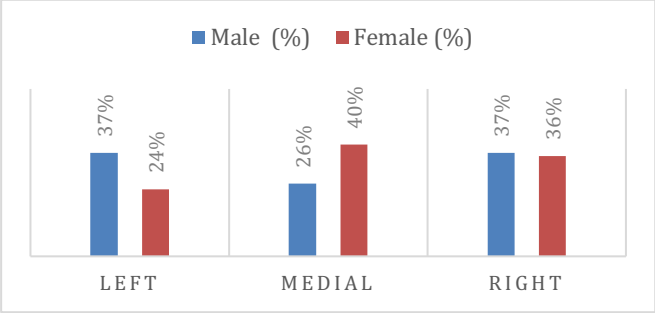
For laterality of the glioma site; left, right and medial were used. Left and right referring to hemispheres, medial refers to anatomically medially positioned gliomas for supra and infratentorial. Medial gliomas anatomical site includes corpus collosum, basal ganglia, thalamus, intraventricular extension, brain stem and vermis. There were no midline brainstem gliomas identified on this study, this could be as a result of most midline gliomas are radiologically diagnosed and biopsy is deferred. In this study majority of the gliomas were found on the right side of the brain 16(36,36%) compared to medial and left sided gliomas 15(34,09%) and 13(29,55%) respectively. See table 6.1.16. Odd ration of 0,8125, 95% confidence interval 0,35-1,89 and significance level (p=0,63).

6.1.17 Gender and Laterality

Table 6.1.17: Gender Laterality

Laterality	Male n(%)	Female n(%)
Left	7(37)	6(24)
Medial	5(26)	10(40)
Right	7(37)	9(36)
Total	19(100)	25(100)

Figure 10: Gender Laterality Chart



n: count, %: percentage

Males have displayed equal glioma distribution between the left and right hemisphere with 7(37%) in each hemisphere, and females were more medial and right dominant with 10(40%) and 9(36%) respectively. This study findings have an odds ratio of 0,9074, confidence Interval range of 0,2084 - 3,9516 and study significance (p=0,8970).

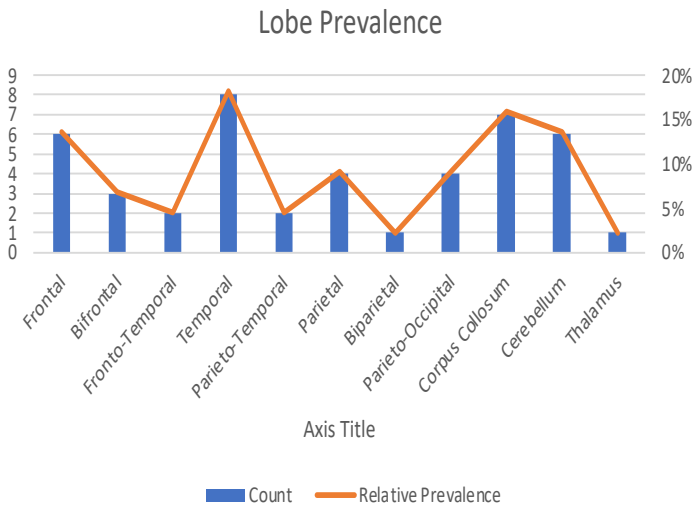
6.1.18 Lobe Frequency

Table 6.1.18: Lobe Frequency

Lobes	n	%
Frontal	6	13,64
Bifrontal	3	6,82
Fronto-Temporal	2	4,55
Temporal	8	18,18
Parieto-Temporal	2	4,55
Parietal	5	11,36
Biparietal	1	2,27
Parieto-Occipital	4	9,09
Corpus Collosum	7	15,91
Cerebellum	5	11,36
Thalamus	1	2,27
Total	**44**	**100**

n: count, %: percentage

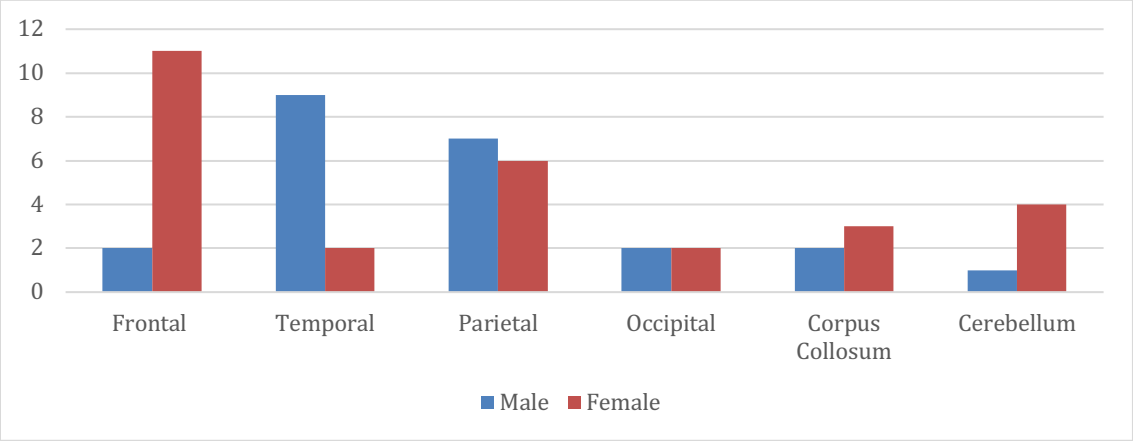
Figure 11:



Gliomas are found to frequently affect the temporal lobe, corpus collosum and frontal lobes collectively contributing to over 50% of glioma distribution found in this study. Corpus collosum and thalamic gliomas grouped under medial gliomas account for over 18%, while the rest of the gliomas affecting more than one lobe (fronto-temporal, parieto-temporal & parieto-occipital) accounting for 18% . Posterior fossa cerebella gliomas accounts for 5 out of total 44 intracranial gliomas, contributing 11,36% of gliomas in this study. The study found the temporal lobe to be the most common and the occipital lobe the least prevalent lobe for gliomas to occur.

6.1.19 Gender and Lobe Distribution

Figure 12: Gender Lobe Distribution Chart

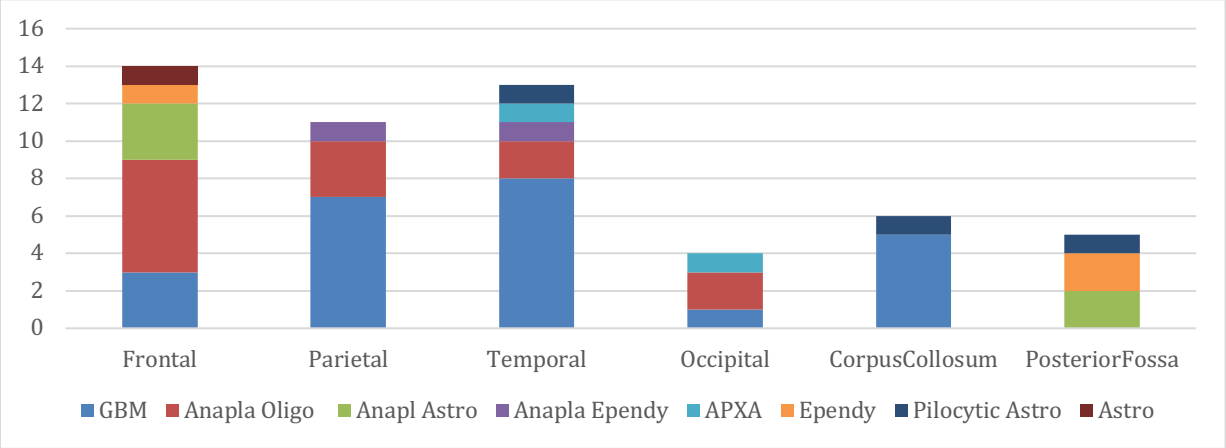


As displayed by figure 12, there is a relatively higher prevalence of gliomas in the frontal lobe and the cerebellum for females compared to males and male patients' gliomas are more prevalent in the temporal and parietal lobe.

Of the gliomas in the frontal lobe 84% are found in females while only 16 % are found in males. Of the total temporal lobe gliomas an opposite prevalence to the frontal lobe was noted with males at 81% and females at 19%. Parietal lobe and occipital lobe was relatively equally distributed between males and females with males at 53%, females at 46% and 50% for males and 50% for females respectively. In the corpus collosum male to female distribution was 40% to 60% respectively. For posterior fossa(cerebellum) 80% were found in females with 20% in males. Statistically it is found that there was a mean count of 3,83 with 10,97 variance for males and for females a mean of 4,67 with 11,8 variance per lobe and statistical significance (p=0,356).

6.1.20 Glioma Type Lobe Distribution

Figure 13: Glioma Type Lobe Distribution Chart



GBM: Glioblastoma, Anapla Astro: Aplastic Astrocytoma, Apla Ependy: Anaplastic Ependymoma, Ependy: Ependymoma, Astro: Astrocytoma

Glioblastoma is the most common glioma and is distributed throughout all lobes except in the posterior fossa, it dominates the temporal, parietal, corpus collosum and frontal lobe followed by anaplastic oligodendroglioma which is not represented in the posterior fossa and corpus collosum. In the frontal lobe anaplastic oligodendroglioma was more prevalent with 46% followed by both anaplastic ependymoma and glioblastoma at 23% each and the lowest with 8% each was ependymoma and pilocytic astrocytoma. Glioblastoma was found to be more prevalent in the parietal, temporal and corpus collosum with incidence of 64%, 61% and 83% respectively. For the parietal and temporal lobe, oligodendroglioma is 27% and 15% respectively. Glioblastoma dominates parietal and temporal compared to anaplastic oligodendroglioma which was found in the frontal lobe than any other lobe, with an odd ratio of 0,61, confidence interval 0,31 – 1,20 and statistical significance p=0,1530. Two types of gliomas dominated corpus

collosum namely glioblastoma and pilocytic astrocytoma at 83% and 17% respectively. The three gliomas found in the posterior fossa are anaplastic astrocytoma, ependymomas and pilocytic astrocytoma with incidence of 40%,40% and 10% respectively.

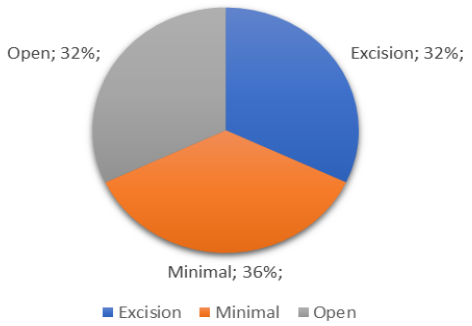
6.1.21. Biopsy Procedures Type Frequency

Table 6.1.21: Biopsy Type Frequency

Biopsy Procedure	Biopsy n (%)	Frozen n (%)
Excision	14(32)	0(0)
Minimal Invasive	16(36)	9(56)
Open	14(32)	4(29)
Total	44(100)	11(25)

n: count, %: percentage

Figure 14: Biopsy Type Frequency Chart



There are two main types of surgical intervention when a glioma is suspected radiologically, biopsy and resection. Types of biopsies that can be performed is open and minimal invasive stereotactic. For the purpose of our study we grouped procedures as excision/ gross total resection, minimal invasive (stereotactic) and open biopsy.

Excision: gross total resection, tumour debulk surgery

Minimal Invasive: stereotactic minimal invasive biopsy

Open: craniotomy and biopsy.

Majority of the cases were biopsied using minimally invasive procedure with a count of 16 (36%), excision and open procedures were both 14(32%) each. Eleven (25%) of these biopsy procedures had a frozen section assessment done intraoperatively. Nine (56%) and four (29%) of the eleven frozen section biopsies were minimal invasive stereotactic and open biopsy procedures respectively. Eight (50%) of the minimally invasive biopsy patient had glioblastoma(grade IV) and five(31%) were anaplastic Astrocytoma and anaplastic

oligodendroglioma(grade III). 56% of minimal invasive procedures were for medially positioned gliomas. Frozen section matched 100% with the final histology report in this study population.

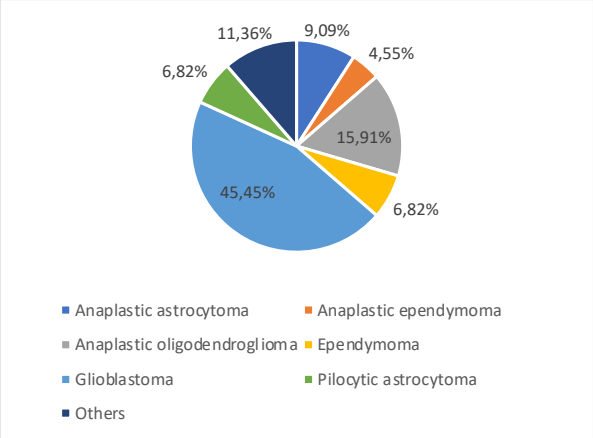
6.1.22 Glioma type

Table 6.1.22: Glioma Type

Glioma Type	n	Relative Prevalence%
Anaplastic astrocytoma	4	9,09
Anaplastic ependymoma	2	4,55
Anaplastic oligodendroglioma	7	15,91
Ependymoma	3	6,82
Glioblastoma	21	45,45
Pilocytic astrocytoma	3	6,82
Others	5	11,36
Total	44	100%

n: count, %: percentage

Figure 15: Glioma Type Chart



In this study group glioblastoma is found to be the most prevalent glioma with a count of 20 out 44 with relative prevalence of 45%, followed by anaplastic oligodendroglioma with a count of 7 and relative prevalence of 15,91%. Glioma type named “others” represents anaplastic pleomorphic xanthochromic astrocytoma(APXA), central neurocytoma , subependymal giant cell astrocytoma (SEGA) and diffused astrocytoma which account for 5(11%). Anaplastic astrocytoma has a relative prevalence of 9,09% and both ependymoma and pilocytic astrocytoma with 6,82% respectively. The mean of the relative prevalence per glioma type per lobe is 4, with minimum of 1 and maximum relative prevalence of 20 with standard deviation of 5,63 and confidence level of 3,78.

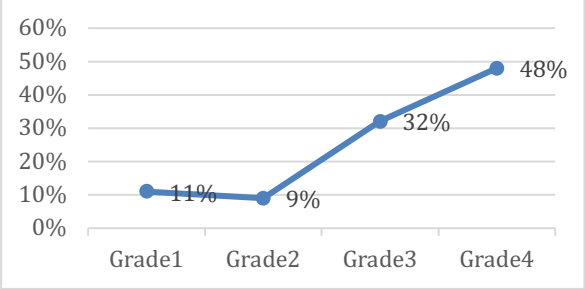
6.1.23 Glioma Grade

Table 6.1.23: Glioma Grade

Grade	n	%
Grade I	5	11
Grade II	4	9
Grade III	14	32
Grade IV	21	48

n: count , %: percentage

Figure 16: Glioma Grade Graph



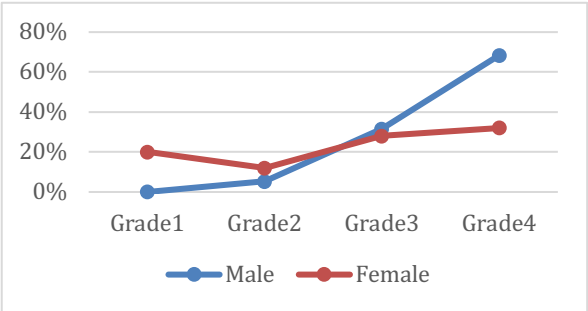
The study demonstrated increase in prevalence with increase in grade. Grade I with prevalence of 11% (n=5), grade 2 at 9%(n=4), and grade III and IV at 32%(n=14) and 48% (n=21) respectively. High grade gliomas grade III and grade IV together has a relative prevalence of 70%. Mean grade prevalence of 25% and a standard deviation of 18 with minimum prevalence of 9% of grade II gliomas and maximum range of 48% of grade IV glioma resulting in prevalence range of 39%.

6.1.24 Gender Grade Relative Prevalence

Table 6.1.24: Gender Grade

Grade	Male n(%)	Female n(%)
1	0(0)	5(20)
2	1(5,26)	3(12)
3	6(31,58)	7(28)
4	13(68,42)	8(32)

Figure 17: Gender Grade Graph



Total	**19(43)**	**25(57)**

n: count, %: percentage

Despite that the total number of female 25(57%) being more than males 19(43%), male patients were diagnosed more frequently with higher grade (4) glioma 13(68%) of total number of gliomas in males compared to females (8)32% of total females diagnosed with glioma. Females had wide spread distribution in all grades with a mean of 5,75 , standard deviation of 2,22 and 4,92 sample variation and range of 5 with confidence level of 3,53. Males had no grade I gliomas and only had one(5,26%)glioma for grade II, six(31,58%) grade III with 13(68%) for grade IV. Males have minimum of zero(0) and maximum of thirteen (68%) resulting in a mean of 5, wide standard deviation 5,94 and sample variation of 35,33 and standard error of 2,97 with confidence level of 9,46. Statistical significance (p= 0,372)

6.1.25 Grade Ethnicity Relative Prevalence

Table 6.1.25: Grade Ethnicity Prevalence

Grade	Blacks n (%)	Whites n (%)
I	4(14)	1(9)
II	2(7)	1(9)
III	9(31)	2(18)
IV	14(48)	7(64)
Total	29(100)	11(100)

n: count, %: percentage

Not demonstrated on this table is Asians and Coloureds grade prevalence, and the study found that the two Asians on this study had grade II and III while the two Coloureds both had grade III gliomas. Blacks and Whites in this study were found to have high prevalence of high grade gliomas. Black for grade III and IV with nine(31%) and fourteen(48%) and coloured two(18%) and seven (64%) respectively. Relatively White patients presented with more grade IV gliomas compared to Black patients, and Black patients presented relatively more with grade IV gliomas (31%) than White patients (18%). Statistically with an odds ratio of 1.0862 , with 95% confidence interval of 0,1906 to 6,190 and significance level (p= 0,9258).

6.1.26 Glioma Size

Tumour size and diameter was assessed using radiological images and MRI was preferred to CT scan when both were available. For diameter the maximum diameter axis of any plane was used. 33 patients had an MRI done and 11 patients had no MRI records, of the 11 without MRI 8 had no CT scan on the record. As a result an adjusted mean was calculated for diameter in cm and mass volume size in cm^3.

Table 6.1.26: Glioma Diameter & Size

Diameter	**cm**
Mean	6,25
Maximum	12,3
Minimum	2,2
Range	10.2
Standard Deviation	2.24
Confidence Interval	5,49-7,01
Confidence level	0,76
Volume Size	**cm3**
Mean	60,02
Maximum	247,5
Minimum	4,8
Range	242,7
Standard Deviation	53,35
Confidence Interval	41,12-79,1
Confidence level	18,9

The mean diameter size for gliomas findings is 6,25cm, with maximum diameter 12,3cm and minimum 2,2cm and a range of 10,1cm with standard deviation of 2,24 and confidence level of 0,76 (confidence interval of 5,49 -7,01). Glioma size was calculated using volume ellipsoid equation [(A x B x C)/2] in cm3 using MRI images, were A,B and C are largest diameter of axial, sagittal and coronal planes respectively. The mean volume glioma size is 60,02 cm3, with minimum and maximum glioma size of 4,8 cm3 and 247,5 cm3 respectively and a range of

242,7cm3, with standard deviation of 53,35 and confidence level 18,9 (confidence interval 41,12 – 79,1).

6.1.27. Demographics Average Diameter and Size

Table 6.1.27: Demographic Average Diameter & Size

	Av. Diameter (cm)	Av. Size(cm3)
Total Sample	6,25	60,02
Ethnicity		
Black	6,77	68,82
White	5,39	34,69
Asian	7,80	116,4
Coloured	5,25	27,75
Gender		
Male	6,16	60,31
Female	6,07	57,57
Age Group		
20-29	7,50	100,8
30-39	5,60	39,69
40-49	6,33	46,00
50-59	9,22	96,60
60-69	5,60	66,68

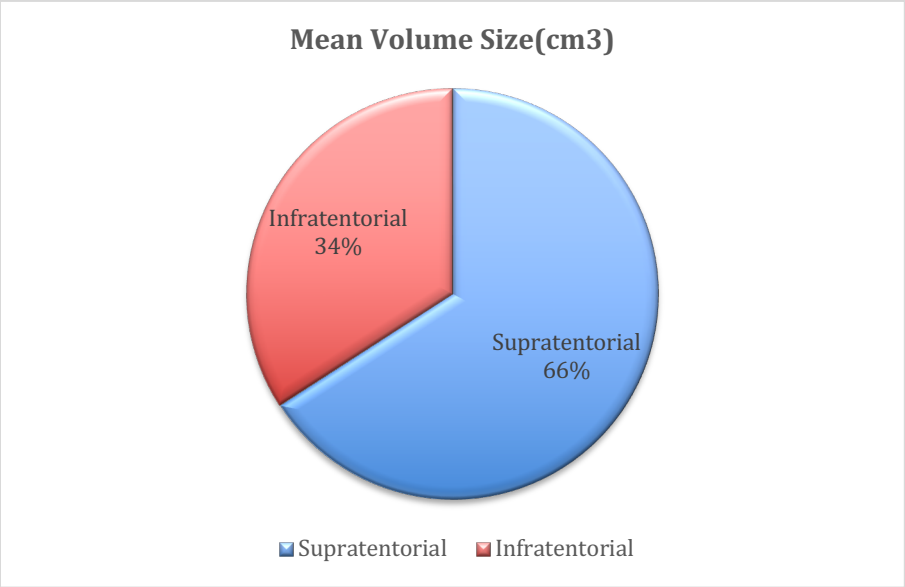
Av.: Average

Despite that the largest average glioma was found in Asian population, the largest glioma size was found in a HIV positive black 24 year old female diagnosed with anaplastic ependymoma in the supratentorial right parietal lobe with a maximum diameter 11cm and tumour volume size of 247,50cm^3 which excision biopsy was performed. The smallest glioma was found in a 14 years old HIV negative white female diagnosed with ependymoma in the right frontal lobe with maximum diameter of 2,2cm and volume size of 4 cm^3 and had a minimal invasive biopsy performed. As demonstrated on the table Coloured patients had the smallest tumour size with an

average of 27,75 cm^3, followed by whites, then blacks with 34,69cm^3 and 68,82cm^3 respectively and then Asians with 116,4cm^3. This data may be affected by small number of Asians and coloureds in proportion to the Black and White group in this study. There was minimal difference between male and females with average diameter of 6,16cm and 6,07cm and average size 60,31cm^3 and 57,57cm^3 respectively. This finding resulted in statistical odds ratio of 1,0526 and confidence interval 0,3208 to 3,4541 with significance value (p=0,9326). Due to insufficient data age group 10-19 average diameter and size were not included, however as alluded the largest was a patient age 24years old with tumour size 247,50 and diameter of 11cm and the smallest tumour was from a 14 year old glioma maximum diameter 2,2 cm and an average size 4,8cm^3. There was no particular trend noticed with regard to age group with average size and diameter. The largest glioma size was found in age group 20-29 years with average of 100,8cm^3 and smallest was 30-39 years with 39,69cm^3. The oldest age group (61-70) has the second smallest average diameter of 5,60cm and third most common average size of 66,68cm^3.

6.1.28 Compartment Glioma Size

Figure 18: Compartment Size Chart



On average infratentorial gliomas are smaller than supratentorial gliomas average diameter (5,78cm and size volume 28,68cm^3) and (average diameter 6,12cm size volume 55,34cm^3) respectively. Infratentorial gliomas account for 34%and supratentorial glioma 66%of the total mean average glioma size of our sample population. Statistically odds ratio 0,2381, 95% confidence interval 0,767 to 0,739 and significance level (p =0,0130).

6.1.29 Laterality and Glioma Size

Table 6.1.29: Laterality & Glioma Size

	Av. Diameter (cm)	Av. Size(cm3)
Left	6,5	73,94
Medial	5,48	52,27
Right	6,3	67,86

Av.: Average

The left side gliomas have been found to be larger than the medial and right positioned gliomas, with average diameter of 6,5cm and average size of 73,94 cm^3 which is more that the study's total average glioma size of 60,02cm^3 . Medial positioned gliomas were found to be generally smaller of the sides with average diameter of 5,48cm and size of 52,27cm^3. Medial positioned gliomas include gliomas found on the corpus collosum, thalamus , basal ganglia and intraventricular. Majority of medial positioned gliomas were found on corpus collosum and commonly the genu of the corpus collosum. This findings have a left and right odds ratio of 1,0721 with confidence interval of 0,3432 to 3,3490 and significance level (p=0,9047).

6.1.30 Glioma Type Average Diameter and Size

Table 6.1.30: Glioma Type Diameter & Size

Glioma Type	Av. Diameter (cm)	Av. Size (cm3)
Glioblastoma	6,82	65,79
Ana Oligo	8,53	112,54
Ana Astro	4,88	33,67

Ependy	5,5	57,35
Pilo Astro	3,1	11,08
Others	5,46	48,05

Av.: Average. Ana Olig: Anaplastic Oligodendroglioma. Ana Astro:Anaplastic Astrocytoma. Ependy: Ependymoma. Pilo Astro: Pilocytic Astrocytoma. Others: Diffused Astrocytoma, Pleomorphic Xanthochromic Astrocytoma, Subependymal giant cell astrocytoma

The study findings with regard to glioma type and size is in keeping with the grade findings, a grade III anaplastic oligodendroglioma is the largest with average diameter of 8,53cm and size average size 112,54cm^3, second to it is glioblastoma with average diameter of 6,82cm and average size of 65,79cm^3 . For low grade gliomas, ependymoma is the largest with average diameter of 5,5cm and average size of 57,35 cm^3 and pilocytic astrocytoma is the smallest tumour with average diameter of 3,1cm and average size 11,08cm^3. This findings support the study findings that the higher the glioma grade the larger the glioma size which is also demonstrated by glioma grade size table.

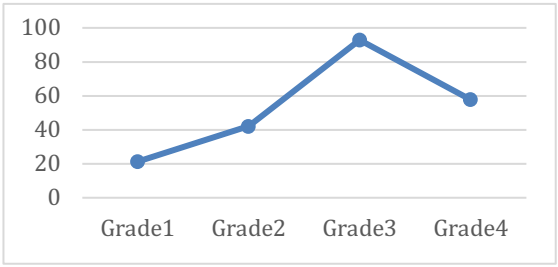
6.1.31 Glioma Grade and Average Diameter and Size

Table 6.1.31: Grade Diameter & Size Graph

Grade	Av. Diameter (cm)	Av. Size (cm3)
I	3,9	21,32
II	5,9	42,13
III	11,72	92,88
IV	6,27	57,72

Av.: Average

Figure 19: Grade Diameter & Size



The study found that the average diameter and size increased with increase in glioma grade, however with high grade gliomas (grade III&IV) grade III gliomas was found to be larger than

grade IV. This could possibly be attributed to diseases progression and patient survival for patients with grade III gliomas compared to grade 4 gliomas given the time for lesions to increase in size. Grade III glioma average diameter of 11,72 cm is almost twice the average diameter of grade IV glioma 6,27cm with statistical significance (p=0,020).

6.1.32 Molecular markers and Immunohistochemistry

Within the five year study period only seven (16%) of the biopsies out of 44 underwent molecular testing. Molecular testing was only introduced in our centre late 2017. Molecular testing was done in two specimens in 2017, three in 2018 and two specimen in 2019. Of the seven only one IDH molecular testing was done and it turned out to be anaplastic astrocytoma WHO grade III IDH wild type. The rest(6) of the molecular testing was done testing for 1p19q code deletion. Two of the six molecular testing were negative for 1p19q code deletion. One of the negative 1p19q code deletion was histologically a glioblastoma and the other one was anaplastic oligodendroglioma. Four of the positive 1p19q code deletion confirmed anaplastic oligodendrogliomas. Thirty three (75%) of specimen were diagnosed gliomas on microscopy and immunochemistry and eleven(25%) of gliomas specimen were diagnosed only on microscopy. The two anaplastic ependymoma and ependymomas had epithelial membrane antigen (EMA) positive and glial fibrillary acid protein (GFAP)was reported to be positive in twenty six (79%) of the thirty three gliomas that had immunochemistry reported. Ki 67 proliferative index was reported in twenty nine (88%) of thirty three patients. Twelve patient diagnosed with glioblastomas had their Ki-67 recorded. The lowest index of <1% for some of the grade I gliomas like pilocytic astrocytoma. Maximum index of 50% for was seen for grade IV glioblastoma and minimum 5%. See table 6.1.32 for glioblastoma Ki-67 proliferative index.

Table 6.1.32: Glioblastoma Ki-67 Proliferative Index

Mean	27,08%
Standard Error	4,06
Median	30%
Mode	30%
Standard Deviation	14,05

Sample Variance	197,5
Kurtosis	-0,378
Skewness	0,252
Range	45%
Minimum	5%
Maximum	50%
Count	12
Confidence Level(95,0%)	8,93

6.1.32 HIV and Glioma

Eighteen(41%) patients of the study population were tested for HIV according to data recorded on laboratory system , five patients tested negative and twelve(27%) were confirmed HIV positive. The rest of the patients(59%) had a noted history of HIV negative as per patients notes. It was found that all twelve patients confirmed HIV positive were already on treatment at the time of glioma diagnosis. As a result anti-retrovirals the patients' immune status was not severely compromised with average CD4 count of 518 cells/ml with a minimum of 247 cells/ml and maximum of 1004 cells/ml and a range of 759cells/ml. Nine patients had a viral load of less than detectable levels and less than 20 copies/ml, one patient had no viral load data on the system and 2 had viral load of 120 copies/ml and 150 copies/ml respectively.

Ten(83%) had viral load lower than detectable and two(17%) had viral load 120 and 150 copies. Eight (67%) were female and four (33%) were males. Eleven(91%) are black patients and only one(9%) white patient.

Table 6.1.32 HIV Demographic Prevalence

	n(%)
Relative HIV Prevalence	12(27)
On ARV's	12(100)
Ethnicity	
Black	11(91)
White	1(9)
Gender	

Male	4(33)
Females	8(67)
Mean Age	
Total	38,25
Females	38.11
Male	38,66
Av. CD4	518,17cells/ml

n: count, %: percentage

Of the twelve patients confirmed HIV positive eleven were (91%) were Blacks and one (9%) was white, with more female count of eight(67%) than males with count of four(33%). Male to female ratio of 1:2 versus 1:1,3 of the total study population. Of the twelve patients only one was white. Mean age for HIV patients is 38.25 years and mean age for male and females is 38,66 years and 38,11 years respectively which is younger than the study population mean age of 43,32 year. Odds ratio 3,24, 95% confidence interval 1,50 to 7,02 and significance level p=0.0029.

6.1.33 Anatomical Site

Table: 6.1.33: Anatomical Site

Site	n	(%)
Laterality		
Left	1	(8)
Medial	7	(58)
Right	4	(14)
Compartment		
Supratentorial	10	(83)
Infratentorial	2	(17)

n: count, %: percentage

Opposite to the general study findings for HIV patients gliomas are found to be more prevalent in medial seven(58%) aspect(corpus collosum, thalamus and ventricle) than peripheral with right

side four(14%)more than left one(8%). Odds ratio of 0,2500, 95% confidence interval 0,0220 to 2,8366 with significance level of p=0,2633. Supratentorial gliomas remain dominant in the supratentorial 10(83%) compared to infratentorial 2(17%) in this study population with an odds ratio of 0,6410, confidence interval 0,1080 to 3.8048 and significance level (p=0,6248)

6.1.34 Lobe Prevalence in HIV

Table 6.1.34: Lobe & HIV

Lobe	n	(%)
Frontal	2	(17)
Parietal	3	(25)
Temporal	2	(17)
Occipital	0	(0)
Corpus Collosum	3	(25)
Cerebellum	2	(17)

n: count, %: percentage

The lobe distribution in HIV patients is more evenly distributed compared to the general findings in this study. With parietal and corpus collosum both 3(25%) most prevalent than frontal, temporal and cerebellum at 2(17%) respectively. Statistically with a mean of 2,4, standard deviation of 0,55 and confidence level of 0,68.

6.1.35 Glioma Size and HIV status

Table 6.1.35: Size & HIV

	HIV (+)	HIV(-)	Total Study Group
Av. Diameter(cm)	6,88	4,44	6,25
Av. Size(cm3)	87,12	33,40	64,06

Av.: Average, HIV: Human immunodeficiency virus

This tables compares patients with confirmed HIV positive (+) on laboratory service with patients confirmed negative and those presumed negative (-)on laboratory services and patients hospital notes. The mean diameter and mean size of patients with HIV is larger at 6,88cm and 87,12cm3 respectively compared to HIV negative and unconfirmed and total study group with 4,44cm and 33,40cm3 , 6,25cm and 64,06cm3 respectively. With odds ratio 0,6638, confidence Interval of 0,1823 to 2,4167 with study significance (p=0,5342).

6.1.36 Glioma Type Prevalence in HIV

Table 6.1.36: Glioma Type & HIV

Gliomas	n	(%)
GBM	4	(33)
Anaplastic Astro	2	(17)
Pilocytic Astrocytoma	2	(17)
Anaplastic Oligodendroglioma	2	(17)
Ependymoma	1	(8)
Anaplastic ependymoma	1	(8)

n: count, %: percentage

Glioblastoma demonstrate dominance also in the HIV group as in the total study population with count of four and relative prevalence of 33% compared to anaplastic astrocytoma, pilocytic astrocytoma and anaplastic oligodendroglioma with a count of two and relative prevalence of 17% respectively. Ependymoma and anaplastic ependymoma are less prevalent with count of one and prevalence of 8% respectively. Statistical mean of 2, standard deviation of 1,09 and 95% confidence level of 1,149.

6.1.37 Grade Prevalence in HIV

Table 6.1.37: Grade & HIV

Grade	n	(%)
I	2	(17)
II	1	(8)
III	5	(42)
IV	4	(33)

n: count, %: percentage

In keeping with this study's findings grade III gliomas are the most prevalent, followed by grade IV gliomas with count of 5(42%) and 4 (33%) respectively, together contributing to 75% of HIV gliomas in this study. Grade I and II has a count of 2(17%) and 1(8%) respectively. Statistical mean of 3 per grade, standard error 0,91,standard deviation of 1,83 with 95% confidence level of 2,905.

CHAPTER SEVEN

7.1 DISCUSSION

7.1.1 Demographics

Brain tumour epidemiology is currently unknown in many countries, including South Africa. The reason for this is that in many countries, including South Africa, there is no compulsory national registry for brain tumours. Even in countries where a registry exists, it is commonly limited to recording only malignant tumours. While the Unites States, France, and Spain do have these registries, they do not include clinical, tumour, surgical, or outcome measures. The association of brain tumour type and age is well recognised in the literature.(17) In South Africa over 80% of the population identifies as Black , Coloured 8.8% White 8,4% and Asian 2,5%, and this demographic proportions with differences in socioeconomic differences is reflected by the proportion of patients presenting in our public health sectors and also in this study(19)

There is a wide racial difference demonstrated in our study findings with black patient accounting more than twice the number of other races combined. Studies have shown that this differences varies according to country or regions also influenced by racial distribution were the study was conducted. There are numerous potential underlying explanations for the racial effect of differences in the findings that some studies have uncovered. It is hypothesized that these differences may be attributable to underlying genetic differences or to the social determinants of

health. Another rational for this finding may include socioeconomic status and lack of access to healthcare, and endemic public health challenge affecting non white communities across according to a study done in the United State.(18)

A study in the United State by Cao J et al (2023) demonstrated that Black patient were diagnosed with gliomas much more than White patients, with a relative prevalence of 66% for Blacks compared to 25% for Whites, in the same study it was found that low grade gliomas showed White prevalence at 84,9% and Blacks 6,5%.(20) Regions with the highest reported rates of primary malignant brain tumours (e.g Northern Europe, US white population and Israel: rates of 11-20 per 100 000 population) generally have better access to medical imaging than with the lowest rates (e,g Indians and Phillipines with rates 2-4 per 100 000 people). Some of the variation suggest ethnic differences in inherited susceptibility and /or cultural or geographic differences in risk factors. (21)

7.1.2 Gender Prevalence

Gender differences in brain tumours are also seen and overall a male predominance is reported in most studies, however in thus study we found more females than males with a ratio of 1,3:1. Besides the increased incidence in females, several studies also report that males have a poorer response to treatment which translates into a decreased overall survival. (17) In other epidemiological studies like study by Cao J et all (2023) male patients comprised majority of patients diagnosed with gliomas with 56% of the total study group while female patients accounted for 43%. (20) Another study by Li K et al (2018) also displayed males to be more affected than females with a ratio male to female of 1,3 :1 which is an inverse of this study findings.(22)

Some studies have reported that men have higher incidences rates of glioma, embryonal tumors, germ cell tumors, and primary central nervous system (CNS) lymphoma, whereas women have higher incidence rates of meningioma and pituitary tumors. The 1.3-fold increased risk of glioma in males versus females is among the most consistent findings in brain tumor epidemiology. Because of the consistency of this finding, even in pediatric populations, a comprehensive understanding of glioma etiology must account for this observation. However, this important

epidemiologic observation remains unexplained. (21) Also a study by Miller K et al (2021) reported that like all gliomas, glioblastoma is more common in males than females.(23) In general, malignant brain tumors are more common in men, while meningiomas and other non-malignant tumors are more common in women. (24)

7.1.3 Age Prevalence

In this study the mean age for the study group is 43 years, males 47years and females 40 years. Mean age for high grade gliomas (grade III and IV) was 48 years and for anaplastic astrocytoma, anaplastic oligodendroglioma and glioblastoma were 35, 51 and 48 years respectively. The mean age for lower grade gliomas was younger with grade I and II was 32 and 25 years respectively. With regard to age groups we found that ages 10-29 years had prevalence of 18%, 20-39 years 30% and 50-70 years was 45% with no patient over the age of 70 in our study. The study by Cao et al 2023 found that age group with most gliomas was 40-59 year (32%)followed by 20-39 years(31%) and the groups with the least was age 80year and above (18%) and 00-19 with (15,4%) of the study population. (20) Some studies like descriptive study by L K et al(2018) demonstrated that glioblastoma incidence increased continually with age, reaching a peak at 75-79 years and decreased thereafter. The increase was more moderate with low grade gliomas like astrocytoma, also younger patients 20-39 years made about 40% of patient diagnosed with oligodendroglioma and mixed oligoastrocytoma. (22)

According to demographic variation study on frequency of gliomas by Persaud-Sharma D et al (2019) which found that mean age at diagnosis of gliomas was older in white patients (55,9 years) as compared to the non-whites (48,5 years). The significant findings between age and glioma status echo similar results among many other types of cancer, where greater age allows an increased number of genetic mutations that may ultimately lead to cancer.(18) In this study findings black patients had the oldest mean age 43 years compared to non black patients (whites and Asians 41 and 42 years respectively) except for coloureds with mean age of 45 years.

Like glioblastoma, incidence rates for other diffuse gliomas generally increase with age, with the exceptions of oligodendroglioma and anaplastic oligodendroglioma, for which rates peak in

patients aged 40 to 64 years. Because of the rarity of glioblastoma in younger age groups, other diffuse gliomas account for a larger proportion of glioma cases in patients aged 20 to 39 years compared with those aged ≥65 years. Glioblastoma incidence increase with age with the highest rate occurring among patients aged 75 to 84 years. (23) The median age at diagnosis for all brain and CNS tumors is 59 years, incidence rates of gliomas vary by histology, with pilocytic astrocytomas occurring more in children and adolescents, low-grade oligodendrogliomas peaking at ages 30 to 40, and glioblastoma in those in their 60s and 70s.(24) which is in keeping with trend of our study findings despite that our average mean age is lower at 43 years and for glioblastoma 48 years. This finding of lower mean age and no patients diagnosed after age of 70 years could be related to lower life expectancy in South Africa of 65years (19)

Although our study population is small (n=44) it is concerning that our glioma population showed relative (mean =43, median =42 years) which is younger than Algerian glioma population (mean= 48, median = 49 years), French (median = 58 years) and the American (mean= 51.9), Tunisian (median = 48) and older than the Chinese (median = 41).(25)

6.1.4 Annual Frequency

A study done in the United Stated looking at trends and patterns of incidence of diffuse gliomas in adults showed a gradual increase in incident of gliomas between 1973 and 2014. It displayed an overall glioma increase by 2,4% per year from 1973 to 1985 then decreased to 0,5% per year from 1985 to 2014. This was attributed to the steady increase in the use of CT scan in the United State in this periods.(22) Our study findings with regard to annual frequency showed consistency for the first two years (15,91% yearly), then a spike to 22% for 2017, dropped to 13% in 2018 then another spike in 2019 to 31% with a total average frequency of 20% per year. This trend is attributed possibly to the invent of molecular testing which was instituted in 2017 in our centre also addition and improvement of district and regional hospital radiology facilities in Gauteng. Due to lack of data (national registry) there are is no information about South African glioma annual frequency in literature to compare with our study findings(17).

6.1.5 Presenting Symptoms in Glioma(Gender and Grade)

The most common presentations in brain gliomas are headaches, nausea, vomiting, seizures, and in more advanced cases weakness or altered mental status. Headaches are the most common initial presenting symptom of patients with glioma. The pathophysiology of headaches is theorized to be the result of tumor growth that places a mass effect on surrounding tissue. The mass effect, in turn, leads to pressure in the microvasculature and leads to edema. (26)

Depending on the location of the tumor in the brain, the mass effect leads to signs of a brain tumor. For example, frontal lobe tumors can present with behavioural changes while dominant temporal lobe tumors can present with receptive speech problems. Other symptoms related to mass effects include nausea, vomiting, and change in vision. Seizures are the second most common symptom of presentation. seizures is attributed to tumor irritation to the cerebral cortex that leads to focal or generalized seizures. Other presenting symptoms of gliomas are tingling sensations, weakness, difficulty ambulation, and in rare cases, patients can present in a comatose state due to haemorrhage within the tumor which leads to an acute herniation syndrome. (27). Gliomas are commonly characterized by neurocognitive deficits that strongly impact patients' and caregivers quality of life.(28)

In a study were 2074 unique papers were identified the ten most prevalent symptoms were: seizures (37%), cognitive deficits (36%), drowsiness (35%), dysphagia (30%), headache (27%), confusion(27%), aphasia (24%), motor deficits (21%), fatigue (20%) and dyspnea (20%). Seizures show a high prevalence in all grades. Cognitive disorders are more prevalent in grade III and IV tumors, but their prevalence in grade II tumors is still considerable.(29) A study done in Denmark found that focal deficits was the most common symptom, reported in 64% of all glioma patients, while seizures (31%), cognitive change (43%), and headache (35%) were less frequently reported (30) In our study headaches were the most common (30,16%) followed by weakness at (23,81%) , confusion (20,63%) and both seizures and visual disturbances at (12 %). Seizure were not as common in our study as it is reported in most literatures. We also found that the possibility of low frequency in other symptoms could be as a result of patient confusion and poor collateral, for example a confused patient will be a poor historian and challenging to assess.

7.1.6 Glioma location (Compartment, Side and Lobe)

In the study we found that most gliomas were single lesion,(n= 33) out of (n=44) 75% with had MRI records, of the (n=33) (n= 31) 94% were single lesion and (n=2) 6% were multiple lesions glioblastoma. We found gliomas to be more prevalent in the supratentorial then infratentorial space which could be affected by our study population age group(adults) Most patients had a single lesion, and this was more likely to be located in the infratentorial region. Patients with multiple lesions had them distributed equally between supratentorial and infratentorial regions. In a study that reviewed African literature found that most patients had solitary lesions located in the infratentorial region. The precise locations of these lesions were not always reported, though their data suggests the majority were located in the cerebellum, followed by the brainstem. We hypothesize that the higher incidence of infratentorial LGGs could be due to the large proportion of reported paediatric patients. (31)

Li K et al (2018) found that gliomas were more prevalent in the temporal lobe than nongliomatous brain tumours, however they could not exclude possibility of reoperation in the cases they studied.(22) Diffuse gliomas other than glioblastoma are largely diagnosed as WHO grade 3 and 4 tumors found in the frontal lobe . Diffuse or anaplastic astrocytomas have an anatomic subsite distribution similar to that of glioblastoma(frontal lobe), whereas oligodendrogliomas are slightly more commonly diagnosed in the supratentorial region also frontal lobe.(23) In keeping with the study by Li K et al, we found that most of the lesion were in the temporal lobe and also involve temporal with frontal, parietal and rarely with occipital lobe. Second common lobe is frontal lobe

Although gliomas occur almost exclusively in the four lobes of the brain: frontal (23.6%), temporal(17.4%),parietal(10.6%),and occipital (2.8%), a small percentage can appear in the brain stem, cerebellum, and spinal cord (24) Our results demonstrate considerable differences in distributions of gliomas, with the densest occurrence in the frontal lobe and a higher frequency in the right hemisphere than in the left hemisphere. The occurrence of bilateral gliomas was toward the frontal lobes, because most gliomas involving both hemispheres are bifrontal. Also, the more frequent involvement of the right hemisphere has been reported in a previous study. In more detailed analyses, the tumors were distributed toward frontal subcortical areas. (32) Although we

found gliomas more prevalent in the temporal lobe we also found increased prevalence in the right hemisphere (36%) than the left (30%) with majority of the gliomas in the medial aspect (corppus collosum, basal ganglia, thalamus, vermis and intraventricular) (34%) no brain stem lesion was diagnosed on this study.

The cortical areas consist of gray material, whereas the subcortical areas contain more glial cells. The nonuniform anatomic distribution of gliomas with frontal and temporal predominance may reflect the involvement of developmental, neurochemical, or functional factors in the pathogenesis of gliomas. The distribution of gliomas by anatomic site differs between adults and children. Pilocytic astrocytomas in children occur typically in the cerebellum and brainstem, whereas in adults diffuse supratentorial astrocytomas predominate (33) We found that glioblastoma was more prevalent in the temporal, parietal and corpus collosum, and anaplastic oligodendroglioma in the frontal lobe.

A study conducted in Algeria found that gliomas mainly occur in the frontal, temporal, parietal, and occipital lobes combined (60.8%). Only a very small proportion of gliomas occurred outside the brain. (25, 34) Over 60% of gliomas in our study were found in the temporal lobe, frontal lobe, parietal and corpus collosum. Our study also displayed more gliomas on the right side than the left. We also looked at glioma location in relation to gender and we found that males had gliomas equally in the left and right hemisphere and female had more left than right hemisphere and females had more medial gliomas than males. We also found that female gliomas dominated frontal lobe and cerebellum, and male temporal and parietal lobe.

7.1.6 Biopsy Procedures Type

There are two main types of surgical intervention when a glioma is suspected radiologically, biopsy and resection. Types of biopsies that can be performed is open and minimal invasive stereotactic. For the purpose of our study we grouped procedures and excision/ gross total resection, minimal invasive and open biopsy. Study by Cao J et al found that most cases (30,8%)were diagnosed with procedure gross total resection (GTR) and the rest either radiologically diagnosed and sent for radio oncology stereotactic radiation(23,8%) (20)

Minimally invasive biopsy provide both histological and molecular diagnosis, and may be more suitable for multimorbid or frail patients with very high surgical risk factors for midline tumors or patients with gliomas in highly eloquent areas of the brain bearing a high functional risk in case of extensive tumor reduction. (35) 36% of our cases were done minimal invasive stereotactic guided, this was done mostly in who were ill and deep lesions like medially position gliomas, mean age of minimally invasive biopsy is 41 years, 50% of minimally invasive biopsy were glioblastoma and 56% of minimal invasive procedures were for medially positioned gliomas.

A literature review study done in Africa showed that only 3.1% of low grade glioma (LGG) patients in Africa underwent awake surgery, despite one fifth of patients with solitary lesions having their tumour in the supratentorial region, therefore being amenable to awake surgery. Given the lack of availability of surgical equipment and intraoperative adjuncts in Africa, increasing service provision of awake craniotomy may be a possible solution to improving patient outcomes. (31) In our study we did not find patient who had an awake surgery.

Intraoperative frozen section (FS) diagnostics is an important diagnostic tool in neurosurgery, but agreement with final histopathology diagnoses may vary. Agreement between frozen biopsy diagnoses and formal fixed paraffin embedded section diagnoses was seen in 504/558 (90.3%), while there was lack of agreement in 54/558 (9.7%). In 20 cases, agreement was not classifiable. Agreement was lower in low-grade gliomas (82.5%) than in high-grade gliomas (93.2%).(36) We found that 25% of the patients biopsied and a frozen section procedure, 56% of minimally invasive and 29% of the open biopsy procedure. The frozen biopsy and the final results from a formalin embed section were the same 100% on this study population.

6.1.7 Glioma Histological Type & Grade

WHO CNS5 has taken a new approach to classify the Gliomas, Glioneuronal Tumors, and Neuronal Tumors, and dividing them into 6 different families: Adult-type diffuse gliomas (the majority of primary brain tumors in neuro-oncology practice of adults, eg, glioblastoma, IDH-wildtype); Pediatric-type diffuse low grade gliomas(expected to have good prognoses); Pediatric-type diffuse high-grade gliomas (expected to behave aggressively); Circumscribed astrocytic

gliomas (“circumscribed” referring to their more solid growth pattern, as opposed to the inherently “diffuse” tumors in groups 1, 2,and 3); Glioneuronal and neuronal tumors (a diverse group of tumors, featuring neuronal differentiation); and Ependymomas (now classified by site as well as histological and molecular features). Choroid Plexus Tumors, with their marked epithelial characteristics, are separated from the category of Gliomas, Glioneuronal Tumors, and Neuronal Tumors.(37)

The most common glioma types in adults include glioblastoma(grade IV), astrocytic tumors (grade I–III), oligodendroglial tumors (grade II–III), and ependymomas (grade I- III). A study by Birthe KR in 2017 in Denmark demonstrated that the most common gliomas are high grade glioma grade IV followed by grade III then grade II with grade I being the least prevalent.(30) Our finding are consistent with this findings above with the most common was grade IV followed by grade III then grade II followed by grade I. Glioblastoma with a relative prevalence of 45% followed by anaplastic oligodendroglioma 17% then the rest.

For the purpose of this study the WHO 2016 revised fourth edition classification was used for histological diagnosis, immunochemistry , molecular assessment and grading as we looked at data prior 2021. In some studies like Cao J et al (2023) found that for glioma histological subtype, the largest group was astrocytoma with 39,3% followed by oligodendroglioma 24,7% and then mixed glioma of 14,2%.(20)

6.1.8 Glioma Size

Both, clinical and neuroimaging variables, have been repeatedly recommended as prognostic factors. Resonance Imaging (MRI) measurements of two-dimensional (2D) diameters of the tumor through the imaging plane were recommended initially by Macdonald et al, however, the efficacy of the 2D protocol remains currently under debate, particularly, in morphologically irregular tumors. (38, 39)

The 3D ellipsoid method, calculating the glioma volume and using three orthogonal diameters, was implemented for different gliomas, including gliomas. The use of T2 Flair hyperintensity volume was advocated for more accurate mass volume , however most studies use T1 post gadolinium using the Orthogonal ellipsoid method: as the product of the longest

perpendicular diameters in axial (a), sagittal (b), and coronal (c) sections divided by two (a × b × c/2).(40) We used a 3 D ellipsoid method to calculate glioma mass volume in cm^3 and the largest diameter was recorded in cm and our average glioma diameter was found to be 6,25cm and mass volume 60,02cm^3. The minimum diameter 2,20cm and maximum diameter 12,43cm and for mass volume the minimum and maximum were 4,80cm and 247,5cm^3 respectively.

According to studies by Agrawal A & Ulutin C the diameter of gliomas at the time of diagnosis is usually approximately 4 cm, although data collected by Simpson *et al*. (1993) showed that in 38% of 645 patients, the glioma diameter at the diagnosis was < 5 cm, in 56% of cases was within 5–10 cm, while in 6% of patients the tumor was > 10 cm. The tumor involving the corpus callosum and growing bilaterally into occipital and temporal lobes results in a butterfly pattern on MR imaging ("butterfly glioma"). (41, 42)

We looked at diameter and mass volume in relation to ethnicity, age groups, gender, anatomical site, glioma grade and glioma type. Generally we found that diameter sizes correlated with gliomas mass volume. Asians followed by black patients recorded largest gliomas with whites and coloured with smallest gliomas. Minimal differences between male and female gliomas diameter and volume with male slightly larger gliomas mean diameter 6,16cm and mean mass volume 60,31cm^3 than females mean diameter 6,07cm and mean mass volume 57,57 cm^3 mass volume. The age group with smallest glioma was 30-39 years with mean diameter 5,60 cm and mean mass volume size of 39,69 cm^3 , age group 20-29 and 50-59 years have the largest tumours with mean diameter and mass volume (7,50cm and 100,8cm^3) and (9,22cm and 96,60cm^3) respectively.

With regard to glioma site on average large gliomas were found in the supratentorial than infratentorial region and medial positioned gliomas were smaller compared to large gliomas on the left hemisphere. With regard to glioma type the largest was anaplastic oligodendroglioma followed by glioblastoma with mean volume 112,54cm^3 and 65,79cm^3 respectively, the smallest was pilocytic astrocytic astrocytoma with 11,08cm^3. This correlates of glioma according to grades with grade III largest followed by grade IV and the smallest grade I gliomas.

6.1.9 Molecular & Immunohistochemistry

In 2016 the classification system for the diagnosis of gliomas was revised to include biochemical changes in addition to cell type location and grade. Among many changes are the addition of isocitrate dehydrogenase (IDH) mutation status, 1 p/19q deletion status, ATP dependent helicase(ATRX) among others.(18) Technological advancements and research in the field of surgical neuro-oncology have focused on techniques, equipment and perioperative treatment modalities that aim to facilitate and optimize maximal resection of tumours. Study by Ooi S et al in 2022 found that many of these were not available or were not regularly practiced in Africa (31) The study found that in our setting molecular testing was done from late 2017 only on selected cases on referral bases to a private institution, prior that there were no specimen considered for molecular testing.

In our study on seven(16%) patients' specimen had molecular testing done and of the seven patients only one had IDH molecular testing done and six of had 1p19q code deletion testing with two of the six were negative for 1p19q code deletion and one of the negative was histologically a glioblastoma and the other one found to be an anaplastic oligodendroglioma. Only one IDH was done this study group which came back as anaplastic astrocytoma IDH wild type. The combined loss of genetic material from the chromosomes 1p19q code deletion is a positive prognostic marker, seen most frequently in oligodendroglial tumors. 1p/19q codeletion is present in 23% to 46% of anaplastic oligodendroglial tumors and in 10% to 15% of anaplastic astrocytomas. While loss of 1p or 19q alone has been seen, co-deletion of both is more prognostically significant nearly all 1p/19q co-deleted tumors also harbour IDH1/2 mutation.(24) In an African study by Ooi S et al (2022) the majority of LGGs were sent to histopathology (71.7%, 95% CI = 69.2–74.2%), of which astrocytic tumours were the most common type (81.1%, 95% CI = 78.5–83.7%) and none of the studies reported using molecular pathology.(28)

Mutation in gliomas place tumours onto a spectrum of tumour aggression, where IDH-mutant, 1p/19q co-deleted oligodendrogliomas follow the most benign clinical course, while IDH-wildtype astrocytomas are the most aggressive. In addition to playing a role in prognosis, the

identification of mutations in LGGs has contributed to the development of novel therapeutic approaches . For example, adjunctive chemotherapy is now being guided and refined by patients' specific molecular parameters. It is of paramount importance for African countries to employ molecular testing for purposes of prognostication and directed management plan.(43)

In a study by Goyal R et al in 2015 they found that the best combination of immune markers useful in differentiating metastatic carcinoma from high-grade gliomas in central nervous system (CNS) are glial fibrillary acidic protein (GFAP)and cytokeratin (CK) (CAM5.2). In the present study, glial tumors were widely reactive for GFAP except few oligodendrogliomas and mixed glial tumors and metastatic tumors were negative for GFAP. GFAP is currently used as a routine antigenic marker for normal developing and mature astroglial cells and for pathologically altered astrocytes. This protein is typically absent in primitive or neoplastic neuroepithelial cells, ganglion cells, oligodendrocytes, vascular endothelium, meningeal cells, fibroblasts, and other mesenchymal elements. The value of immunoperoxidase stain for GFAP is relevant in documenting astrocytic differentiation in the tumor growing outside the CNS parenchyma. GFAP found to be highly specific and sensitive marker for glial tumours when compared with other special stains and markers.(44, 45)

We found in our study that Ki 67 proliferative index was reported in twenty-nine (88%) of thirty-three patients were immunochemistry was recorded, with the lowest index of <1% for some of the grade I gliomas like pilocytic astrocytoma. The minimum was index of 5% maximum index of 50% for grade IV glioblastoma and minimum 5%. A study looking at role of Ki-67on the outcome of glioblastoma patients, found that prognostic role of Ki-67 is less clear. Some groups showed that a high Ki-67 was associated with improved overall survival, whereas other groups reported that high levels of Ki-67 were associated with poor overall survival. This study found no association of Ki-67 proliferative index with overall survival of glioblastomas. Like our study it is clear that Ki-67 index increase with increase with glioma grade. (46, 47)

6.1.10 HIV and Glioma

Although gliomas are the most common primary CNS tumors, they are rare in patients living with HIV/AIDS and are difficult to diagnose because it often shows unusual aspects of tumor localization, growth behavior, and also presents at a younger age in the HIV-infected population. It is reported that the incidence of glial central nervous system tumors is 0.05%, while other focal masses account for up to 6%. The impact of the infection on immune surveillance is thought to promote the development of gliomas mostly glioblastomas. (48)

We found 27% of the study population to have a confirmed HIV test and over 91% of HIV group were black patients, mostly female more than male with a ratio of 2:1 respectively and an average young age of 38 years which is much lower compared to documented average age for adult glioma in literature. Both males and female had mean age of 38 respectively, which is younger than this study population mean age of 43years and for male and female which is 47 and 40 years respectively. A 2011 study by Laurent F and colleagues also found that HIV positive patients develop high-grade gliomas at an earlier age and have an increased incidence compared to that in the general population. In 2009 a study that reviewed glioblastoma described 21 cases in HIV-infected patients; most of those patients were young (mean 38years) and had a mean CD4 count of 400 cells/mm.(49) The study did not find any evidence to suggest that these patients should be treated differently from other patients with glioma, and the current recommendations include surgery followed by radiotherapy and chemotherapy (temozolomide). Even with patients with gliomas it was found that disease prognosis was dictated by tumor progression.(17, 49) We also found that the average age of glioma patients with HIV at the time of diagnosis was young also 38 years with mean CD4 of 518 cells/mm^3 with viral load either lower than detectable or less than 20 copies. The HIV patients in this study were already on treatment at the time of diagnosis. The South African " HIV test and treat" initiative could be responsible for suppressed viral load and CD4 count levels reported by this study.

A South African study by Kelly A and colleagues in 2020 showed an increase in glioma grade with HIV patients compared to general population. They noted that opportunistic infections and aggressive behaviour of brain tumours was more common in HIV infected individuals compared to HIV non-infected individuals. Patients with brain tumours, whether HIV positive or not, show

characteristic histological tumour types that are age specific. (17) In our study group we also found that there was increase in glioma grade in patients with HIV. 33% of the HIV patients were glioblastoma, although collectively the grade III gliomas were more prevalent with total of 42% which includes: anaplastic astrocytoma, anaplastic ependymoma and anaplastic oligodendroglioma. Both grade III and IV contributed to over 70% of glioma patients with HIV. While being HIV positive does have a detrimental influence, the primary histology of the lesion and the extent of resection were found to be the major determinants of patient out-come. (49)

With the advent of HIV, some cases have been reported of HIV and brain glioma comorbidity, leading to the assumption that HIV infection increases the incidence of gliomas, (especially the higher grades) as it does for other tumors.(50) However, observational studies have shown an ever-decreasing rate of comorbidities of HIV and brain gliomas. This has led to speculations that HIV or its treatment may have a protective effect from brain gliomas. In a 20-year study done in Mexico and Brazil, they showed an ever-decreasing incidence of gliomas in HIV patients. This led the researchers to hypothesize that gliomas are becoming exceedingly rare in HIV/AIDS patients. With regard to HIV and glioma the glioma cells have not been found to have the virus which could possibly explain this findings.(50)(51) however in this study we found that HIV seemed to have influence or other parameter like glioma size and grade prevalence and we found 27% of our study population to be HIV positive.

According to Chaudry NS and colleagues “while HIV patients may still have gliomas, it is unlikely that the HIV itself would be responsible”.(52)

Literature documenting radiological findings of gliomas in HIV patients is very limited. Using literature search there was no literature dedicated to describing or comparing radiological differences in gliomas of HIV patients. For patients with glioma and HIV we looked at prevalence of anatomical site (compartment, lateralization and lobe) and glioma size. Glioma diameter in cm and volume mass size (ellipsoid formular)in cm^3 were measured. HIV positive patients gliomas were bigger in comparison with HIV negative patients with mean diameter 6,88cm compared to 4,44cm respectively and the total study population mean of 6,25 cm. Glioma volume size for HIV positive compared to HIV negative patient had mean of 87,12cm^3 and 33,40cm^3 respectively compared to total study population with 64,06cm^3 . This findings

clearly demonstrate increased glioma size for patients with HIV compared to those who are negative at the time of diagnosis.

Although duration of HAART for our study group could not be determined because some patients were initiated at prereferral hospitals it is most had viral load lower than detectable and an average CD4 count above 500cell/ml which demonstrated compliance. Yet despite compliances there is still differences the study alluded between HIV positive and HIV negative patients. However the clinical outcome was not compared. The effect of HAART on the immune system and glioma disease progression is not completely understood. Treatment trends for HIV-associated glioblastoma are similar to non-HIV glioblastoma, with temozolomide being well tolerated in this specific patient population (53, 54).

7.2 Limitations

Histology barcode not documented in the theatre procedure book.

Unavailable barcode and wrong patient details captured on theatre book.

Duplication of information or patient registration.

Small sample size to for study significance.

Some patients only had CT scan done without MRI for correct glioma size measurements.

No Radiological images on the picture archiving and communication system.

Inconclusive biopsy specimen, biopsy specimen too small to process.

Data from 2015 was prior to the new revised 2016 4th edition WHO grading.

Molecular testing was partially available from late 2017.

Incomplete and incomprehensible patients notes.

CHAPTER EIGHT

8.1 CONCLUSION

Malignant and nonmalignant brain and other CNS tumors exhibit wide heterogeneity in occurrence by age, sex, and race/ethnicity, and they cause substantial morbidity and mortality in South Africa. The following have been consistently associated with improved glioma prognosis: age, Karnofsky performance scale score , radiological feature (like anatomical position and size), biopsy histology findings(microscopy, immunochemistry and molecular findings), have also been identified which can help in counselling patients and reasonable management plan. (21) In keeping with literature glioblastoma is the most common glioma and temporal lobe is the common site for this lesions followed by frontal lobe. Contrary to most literatures the study findings was that we see more females in our institution than male presenting with gliomas. Opposite to most literature we found differences in gliomas of HIV positive compared to HIV negative patients for example; glioma prevalence in younger group, medial positioned lesions, higher grade and larger glioma size in HIV patients.

8.2 RECOMMENDATIONS

In South Africa like most African countries expansion of resources for central cancer registries to collect and report data in a way that is timely, specific, and broadly consistent across the country and continent is necessary to advance biologic understanding of brain and other CNS tumors. In addition, ongoing research with bigger sample size is needed to elucidate the causes of sex, age, racial/ethnic and HIV status differences in occurrence, especially for rarer subtypes and understudied populations in African countries like South Africa. Thorough documentation of findings and accurate record keeping requires to be more structured and improved. Also further research at a large scale is recommended that will look specifically at gliomas and HIV to determine effect of one on the other. Ethnic disparities in treatment access and receipt should also be further explored for equal health service distribution. It is important to equip pathology facilities across the country and continent to enable molecular testing of gliomas to help

determine molecular characteristics which is important for diagnosis and prognosis that has implication on current and future management strategies. We hope and believe that the implementation of national health insurance(NHI) will assist to address the above and improve South African health system in general.

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Appendix A

Data Collection Sheet

	Unique Number	Age	Gender	Ethnicity	Glioma type	Glioma grade	Anatomical compartment	Lobe	Glioma Size	Presenting Symptoms	HIV Status	HAART
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Appendix B

Ethics Clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr DG Mohale

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M230615

NAME: Dr DG Mohale **DEGREE:** MMed
(Principal and Co-Investigators)

DEPARTMENT: School of Clinical Medicine
Departmernt of Surgery
Division of Neurosurgery
Medical School
University

PROJECT TITLE: *Glioma histology at Charlotte Maxeke Johannesburg Academic Hospital, a 5 year retrospective study*

DATE CONSIDERED: 2023/06/30

DECISION: Approved unconditionally

CONDITIONS:

NOTE: If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>

SUPERVISOR: Dr C Profyris and Dr MN Mpanza

APPROVED BY:
Professor P Ruff, Chairperson, HREC (Medical)

DATE OF APPROVAL: 2023/10/26 **EXPIRY DATE:** 2028/10/25

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **June** and therefore reports and re-certification will be due in the month of **June** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator Date 30/10/2023

Appendix C

Plagiarism Report

Mmed 1-2.docx

ORIGINALITY REPORT

7%	7%	8%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.researchgate.net Internet Source	1%
2	www.ncbi.nlm.nih.gov Internet Source	1%
3	Adrian Kelly, Patrick Lekgwara, Siyazi Mda. "The epidemiology and outcome of patients admitted for elective brain tumour surgery at a single neurosurgical centre in South Africa", Interdisciplinary Neurosurgery, 2020 Publication	1%
4	rarediseases.org Internet Source	1%
5	www.mdpi.com Internet Source	1%
6	academic.oup.com Internet Source	1%
7	www.perlego.com Internet Source	1%
8	coek.info Internet Source	