An audit of central nervous system tumours as diagnosed at Universitas Academic Hospital in Bloemfontein, Free State from 2007 - 2017

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Declaration:

I, Martha Magdalena de Bruyn, declare that the coursework Master's Degree mini-dissertation that I herewith submit for the Master's Degree qualification MMed Neurosurgery at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education.

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Abstract:

Tumours of the central nervous system are a common and challenging entity seen by Neurosurgery Departments worldwide. It is the cause of significant morbidity and mortality worldwide. Since the advent of Neurosurgery there has been an immense interest in classifying these tumours to enable prognostication and optimize the management of these tumours. Various classification systems have been used with the latest being the 2016 WHO classification of tumours of the central nervous system. The discovery of the molecular and genetic basis of these tumours and the development of these characteristics to aid in the diagnosis and management of these tumours, have had a great impact on the classification of these tumours. In developed countries, tumour registries exist to optimize the diagnosis and management of these tumours and to identify fields of possible further research and development. There is a lack of such registries in most developing countries and the need exist to establish such registries. The aim of this study is to implement a central nervous system tumour registry at the Universitas Academic Hospital in Bloemfontein to assist with the diagnosis, management and further resource implementation to optimize our management of these tumours and to enable us to compare our data with the international and national data bases.

Keywords:

2016 WHO classification of tumours of the central nervous system

Supratentorial

Histology

Molecular

Genetic

Infratentorial

Biopsy

Debulking

Resection

Malignant/high grade/anaplastic

Low grade

List of abbreviations:

WHO – World Health Organization

CNS – central nervous system

NHLS – National Health Laboratory Services

IT – information technology

PNET – primitive neuro-ectodermal tumour

CBTRUS – central brain tumour registry

EBV – Epstein-Barr Virus

IDH – isocitrate dehydrogenase

UAH – Universitas Academic Hospital

FISH – fluorescence in situ hybridization

Shh – Sonic hedgehog

CT – computed tomography

MRI – magnetic resonance imaging

CSF – cerebrospinal fluid

NAA – N-acetyl aspartate

NOS – not otherwise specified

FLAIR – fluid-attenuated inversion recovery

STIR – Short-T1 inversion recovery

DWI – diffusion-weighted magnetic resonance

ADC – apparent diffusion coefficient

GFAP – glial fibrillary acidic protein

NSE – neuron-specific enolase

EMA – epithelial membrane antigen

PTEN – phosphatase and tensin homolog

TERT – telomerase reverse transcriptase

EGFR – epidermal growth factor receptor

PDGFR – platelet derived growth factor receptor

Rb – retinoblastoma

MGMT – O^6-methylguanine-DNA methyltransferase

VEGF – vascular endothelial growth factor

CEA – carcino-embryonic antigen

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Approval letter from the Ethics committee

Permission from NHLS to obtain and use data

Permission from the Department of Health

Protocol as approved by the HSREC

Data collection form

Turnitin proof

Introduction:

Tumours of the central nervous system (brain and spinal cord) cause significant morbidity and mortality worldwide (Armstrong et al, 2016). This has led to intensive research and classification systems to guide the management of these tumours since histological typing of tumours became possible. The first classification of brain tumours was published by the pathologist Rudolf Virchow in 1863. He was the first to attempt to correlate the microscopic and macroscopic appearance of CNS tumours. He coined the term “glioma” in 1860. Then Bailey and Cushing devised a classification in 1926 and proposed that brain tumours originated from primitive neuro-ectoderm. They classified 14 different tumours according to the cell that they arose from arrested at a certain developmental stage. The tumour cells were morphologically different from the normal cell. Thus astrocytomas arose from astrocytes and so forth. In 1949 Kernohan and his colleagues proposed that the histopathological difference was due to separate tumour types but rather secondary to different histological differentiation. They significantly reduced the number of brain tumour entities and included a grading system. In 1950 the Ringertz system was based on the hypothesis that different brain cells gave rise to different types of tumours. Ringertz thus proposed that an astrocytoma consisted of 3 grades: astrocytoma, astrocytoma with anaplastic features and glioblastoma. The first classification was edited by Zülch and published in 1979 as the WHO I classification. This classification used the terminology used by Bailey and Cushing and incorporated the grading system proposed by Kernohan. In 1981 the St. Anne-Mayo system was published. It served as a tumour grading system and tumours were graded on the absence or presence of the following 4 criteria: 1. nuclear atypia, 2. Mitoses, 3. Endothelial cell proliferation and 4. Necrosis. Thereafter immunohistochemistry developed and a new classification was published by Kleihues et al. The third edition included genetic profiles as an aid to define brain tumours and was published in 2000 under the guidance of Kleihues and Cavenee. This classification also included epidemiology, clinical signs and symptoms as well as imaging, prognosis and predictive factors. In 2006 a group of pathologists and geneticists convened in Germany and the 2007 WHO (World Health Organization) classification of tumours of the central nervous system was created (Louis et al, 2007). In 2014 a meeting was held in the Netherlands were neuropathologists, neuro-oncological clinical advisors and scientists convened to include the molecular parameters with the histology to define the different tumours. This enables both phenotypic and genotypic parameters for the classification of central nervous system tumours with potentially more homogenous and narrowly defined diagnostic entities that will enable more exact treatment and prognosis determination of patients living with central nervous system tumours (Louis et al, 2016; Louis, Perry et al, 2014).

With the new classification of 2016 a layered diagnosis was proposed. This layered effect includes an integrated diagnosis at the top that will correspond to the previous WHO 2007 classification. This will be followed by a histological classification that is based on the hematoxylin and eosin staining, immunohistochemistry and the electron microscopy. This will then be followed by the standard histological grade. This is determined by the natural

history of the tumour after surgical treatment and adjuvant chemotherapy and radiotherapy. The fourth and final layer will consist of the molecular information that was obtained with regards to the tumour. This allows the neuropathologist to obtain a layer 2 or 3 diagnosis should the molecular data not be obtainable. In certain tumours where the molecular information is yet unclear or not yet determined, this will be annotated with NOS (not otherwise specified). Unfortunately the molecular testing is not yet widely available in developing countries and utilizing the new classification system will render a large group of tumours as NOS (Mukherjee 2017, Louis, Perry et al 2014).

Layered diagnosis:

Layer 1: Integrated diagnosis – includes layer 2, 3 and 4

Layer 2: Histological diagnosis – histological classification

Layer 3: WHO grade

Layer 4: Molecular information (Banan et al 2017)

Several changes were made to the classification of tumours in the 2016 classification when compared to the previous 2007 classification and these changes will have to be taken into consideration with evaluation of the data provided.

Very little is known about the incidence and prevalence of central nervous system tumours in general in Africa and South Africa. The United States of America and most of the European countries keep extensive tumour registers with regard to brain tumours, the incidence, epidemiology and outcome.

In the United States of America a Central Brain Tumour Registry (CBTRUS) is kept. A fact sheet was published in 2016 that included all primary malignant and non-malignant tumours of the brain, central nervous system, pituitary and pineal glands as well as olfactory tumours of the nasal cavity. This included brain lymphoma and leukaemia. Their data is obtained from all newly diagnosed tumours as registered at the Centre of Disease Control and Prevention, the National Programme of Cancer Registries and their National Cancer Institute. They estimated an incidence rate of 22.36 cases per 100 000 for all primary malignant and non-malignant brain and other central nervous system tumours with a higher incidence in females (24.45 vs 20.1 per 100 000) and an estimated diagnosis of 79 270 new cases in 2017. According to their published data the worldwide incidence was 3.4 per 100 000 for primary malignant brain and other central nervous system in 2012 with the male and female incidence being 3.9 per 100 000 for males and 3.0 per 100 000 for females. The incidence in developed countries were also higher at 5.1 per 100 000 vs 3.0 per 100 000 in developing countries (CBTRUS factsheet, 2016).

The paediatric incidence in the age group of 0 – 14 years for primary malignant and non-malignant brain and other central nervous system tumours were 5,47 cases per 100 000. The rate was higher in males than in females (5.69 vs 5.24 per 100 000 respectively). For the age group 0 – 19 years of age an incidence of 5.67 cases per 100 000 was found with

a higher incidence in females than in males (5.71 vs 5.69 cases per 100 000). In the age group 15 – 39 years the incidence for primary malignant and non-malignant brain and central nervous system tumours was found to be 10.71 cases per 100 000 with a higher rate for malignant vs non-malignant tumours (7.47 vs 3.24 cases per 100 000).

The tumours are also defined by histopathological diagnosis and distribution in the brain. The histopathological distribution is as follows:

Table 1: Percentages of histopathological diagnosis (CBTRUS)

Percentage	Tumour type
36.2	Non-malignant meningioma
15.9	Non-malignant pituitary tumours
14.9	Glioblastoma
10.9	All other malignant glioma
8.2	Non-malignant nerve sheath tumours
6.7	Non-malignant tumours involving neuronal and non-neuronal glial tumours, pineal region tumours, embryonal tumours and other tumours of cranial and spinal nerves
5.7	Other malignant tumours from choroid plexus, neuronal and mixed neuronal glial tumours, pineal region tumours, embryonal tumours and nerve sheath tumours
1.1	Non-malignant glioma
0.5	Malignant meningioma

The distribution was further divided according to malignant and non-malignant tumours:

Table 2: Common locations of CNS tumours (CBTRUS)

%	Malignant tumours	%	Non-malignant tumours
23.6	Frontal lobe	53	Meninges
17.4	Temporal lobe	24.9	Pituitary and craniopharyngeal duct
10.6	Parietal lobe	9.6	Cranial nerves
4.8	Cerebellum	3.0	Spinal cord and cauda equina
4.5	Cerebrum	2.6	Other brain
3.0	Cauda equina and spinal cord	1.4	Cerebellum
2.8	Occipital lobe	1.2	Frontal lobe
1.8	Meninges	1.0	Ventricle
1.4	Ventricle	0.9	Temporal lobe
1.2	Cranial nerves	0.5	Parietal lobe
0.8	Pineal region	0.4	Brainstem
0.4	Pituitary and craniopharyngeal duct	0.4	Cerebrum
		0.3	Pineal region
		0.2	Occipital lobe

(Ostrom et al, 2016).

The aim of this study is to create and implement a central nervous system tumour registry at the Universitas Academic Hospital in Bloemfontein to assist with the diagnosis, management and allocation of resources, including possible molecular testing and a specialist neuropathologist's services, at our institution to facilitate the optimal management of these patients and their disease entities.

Methods:

A retrospective cohort analytical study was performed of all central nervous system (CNS) tumours that had either a biopsy, debulking or resection procedure at Universitas Academic Hospital in Bloemfontein from 01/01/2007 – 31/12/2017. All patients were included that had one of the abovementioned procedures regardless of age, race or sex.

The histological data was obtained from NHLS by submitting key words that should be contained in the diagnosis, ICD-10 codes and Snomed codes to their IT department. The data obtained were compiled in Microsoft Excel and presented to the Department of Biostatistics at the University of the Free State and certain statistics were compiled.

Results:

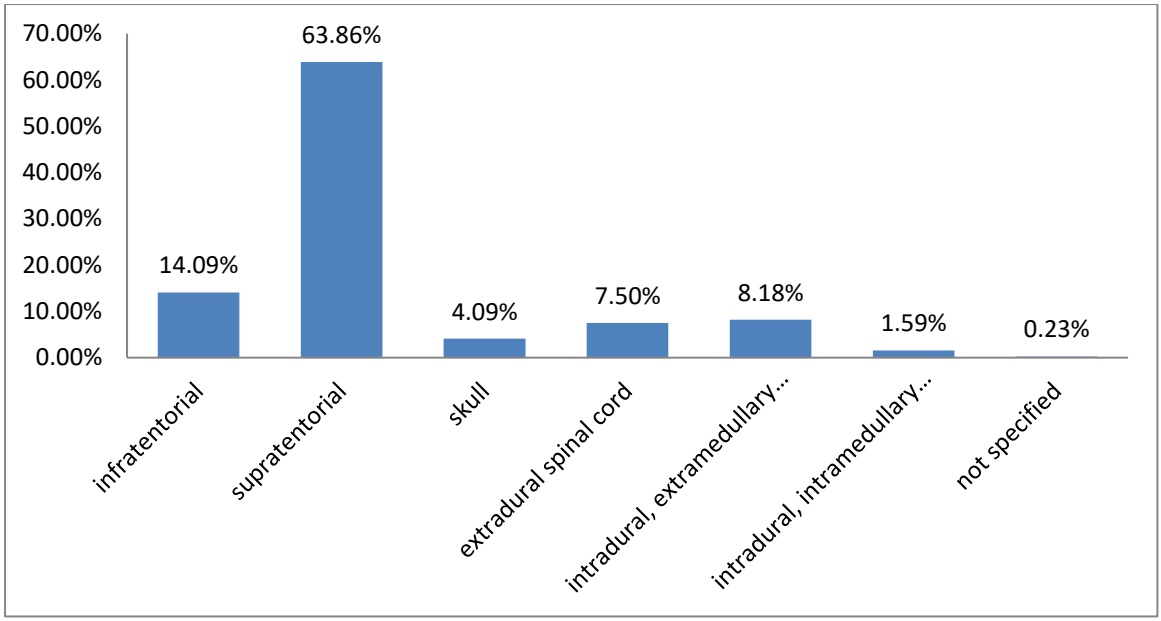
Histological data was obtained from the NHLS data base and 441 patients were identified for the period from 01/01/2007 – 31/12/2017 according to the data base. This equates to 44.1 central nervous system tumours being operated on per year. The patients had a mean age of 37 years with the youngest patient being 4 months old and the oldest patient being 80 years of age.

The surgical procedures performed to obtain a histological diagnosis consisted of 183 biopsies, 212 debulking procedures and 46 gross total resections.

The patient population consisted of 251 female vs 190 male patients with a male to female ratio of 1:1.3.

The tumours of the CNS could be found in different compartments in the CNS.

Fig. 1: Tumour location according to CNS compartments

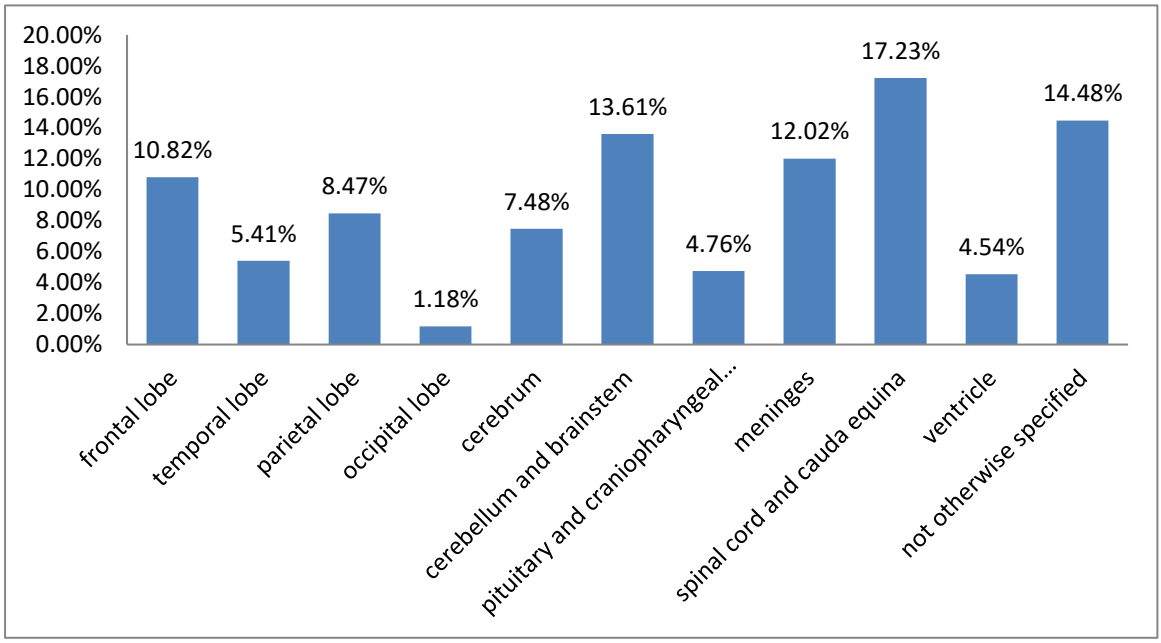


63.86% of the tumours surgically managed at Universitas Academic Hospital were located supratentorially (n = 281) and 14.09% infratentorially (n = 62). 17.25% (n = 76) of the tumours were located within the spinal canal with 7.50% (n = 33) of the tumours located in the extradural space, 8.18% (n = 36) located intradural, but extramedullary and 1.59% (n = 7) of tumours located intradural and intramedullary. Only 0.23% of the tumours diagnosed surgically at our institution had no location indicated on the histology report. 4.09% (n = 18) of the tumours were also documented to occur in the skull.

The tumours were also evaluated according to their location within the CNS.

A very varied distribution was noticed at our institution, once again as documented on the histology report. The highest percentage of tumours were located in the spinal cord and cauda equina as documented at 17.23%, followed by 13.61% of tumours in the cerebellum and brainstem. The meninges came in third place at a percentage of 12.02%. The most common location in the cerebrum was the frontal lobe at 10.82% followed in second place by the parietal lobe. A total of 14.48% of tumours did not have a specific location indicated on the histology report.

Fig. 2: Tumour location in the CNS



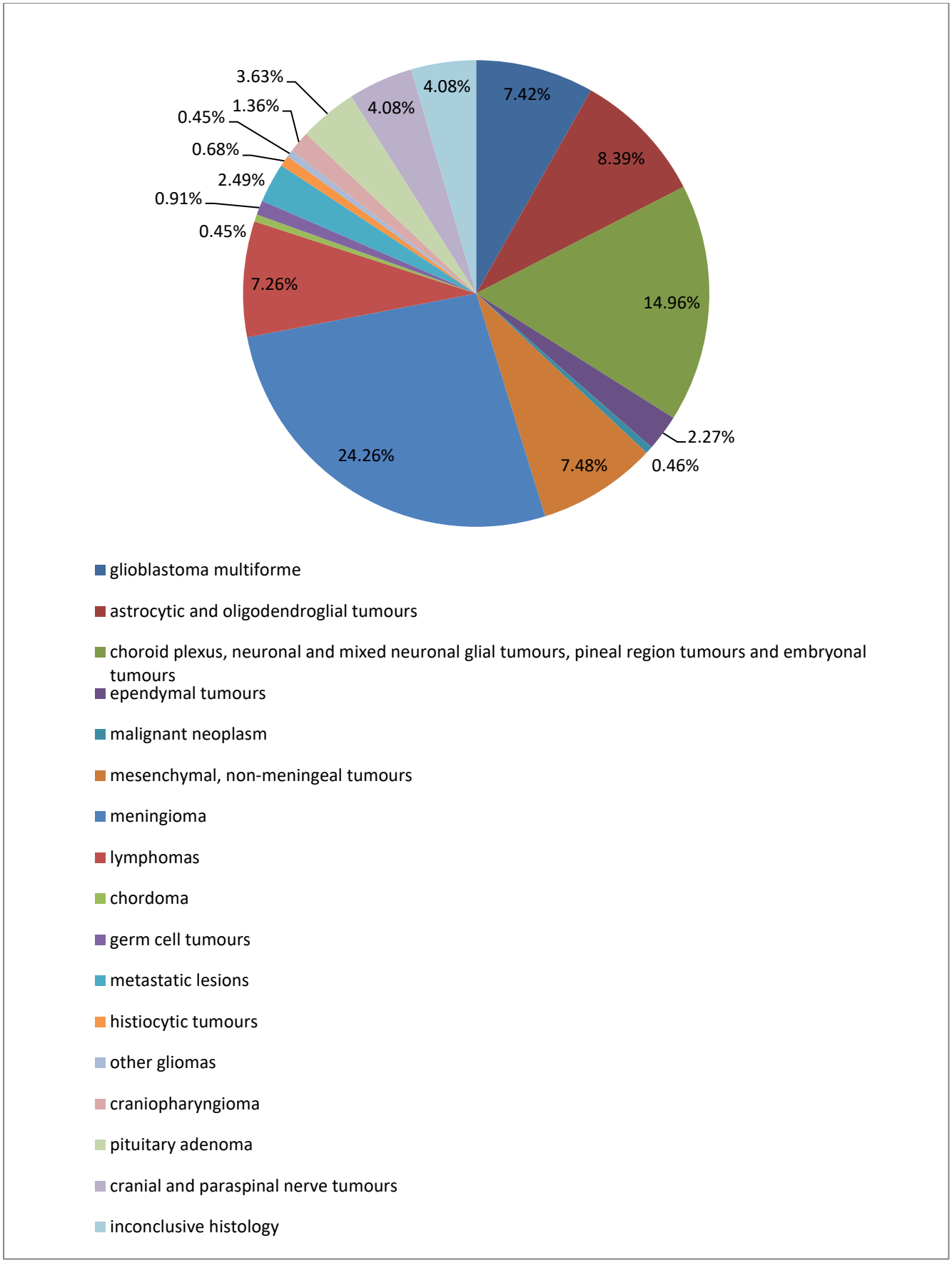
The tumours were then divided into histological subgroups as described in the CBTRUS report. The most common tumour diagnosed at our institution was meningiomas at 24.26% followed in second place by a combination of choroid plexus, neuronal and mixed neuronal glial tumours, tumours of the pineal region and embryonal tumours at 14.96%. The third most common tumour was astrocytic and oligodendroglial tumours at 8.39% and then mesenchymal, non-meningeal tumours at 7.48%. Glioblastoma multiforme was the fifth most common tumour at 7.42% and was closely followed by primary central nervous system lymphoma at 7.26%.

Cranial and paraspinal nerve tumours were the seventh most common tumour at 4.08% with pituitary tumours following at 3.63%. The rest of the histological subtypes all represented < 3% of the histological diagnosis obtained at our institution.

Of all the tumours sampled, 39.97% fell in the WHO I category, 6.12% were deemed WHO II and 0.68% fell in the WHO II/III category. 5.90% were WHO III tumours and 15.64% WHO IV. 39.22% of the tumours were not allocated to a WHO tumour group.

In 11.34% of the samples taken, normal brain or a specimen insufficient to obtain histological diagnosis was found.

Fig. 3: The histological subtypes at Universitas Academic Hospital



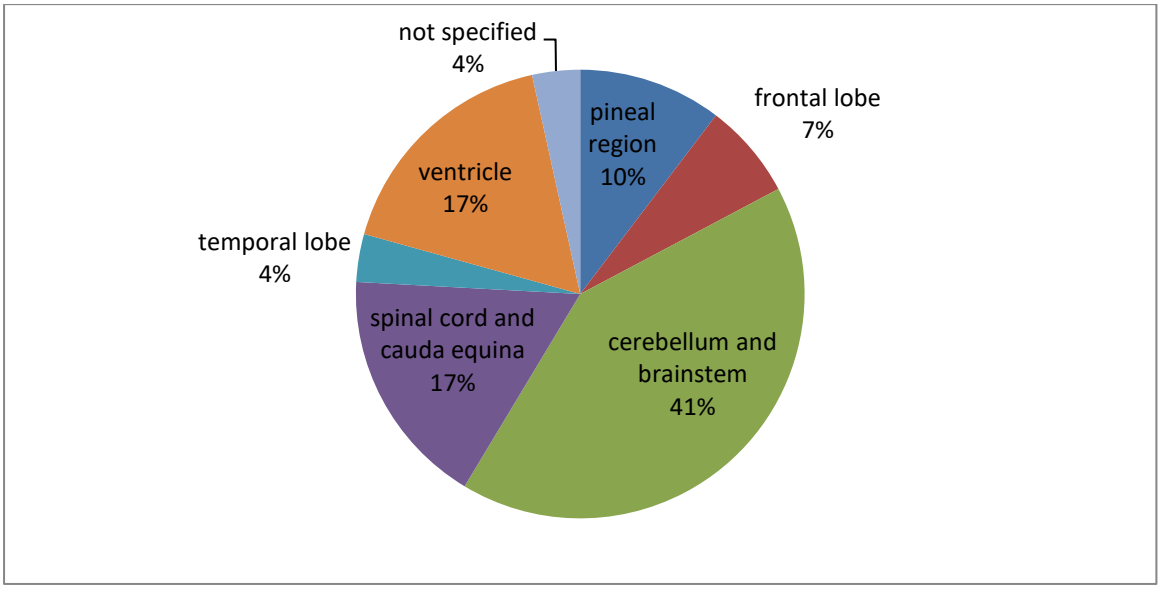
Of all the tumours sampled, 39.97% fell in the WHO I category, 6.12% were deemed WHO II and 0.68% fell in the WHO II/III category. 5.90% were WHO III tumours and 15.64% WHO IV. 39.22% of the tumours were not allocated to a WHO tumour group. In 11.34% of the samples taken, normal brain or a specimen insufficient to obtain histological diagnosis was found.

The tumours were divided into the different age groups in which they occurred. The first group being the age group 0 – 4 years, the second group 5 – 19 years of age, the third group 20 – 34 years of age and the fourth group age 35 years and above. This division of age groups was utilized to facilitate comparison with the CBTRUS fact sheet.

0 – 4 year old group:

In the age group from 0 – 4 years 29 patients were documented with a male preponderance (20 male patients to 9 female patients) with a male to female ratio of 2.2:1. This age group comprised 6.58% of the all the tumours diagnosed surgically at our institution. In this age group 14 biopsies were performed, 13 debulking procedures and 3 gross total resections documented on the histology report. The location of the tumours in the CNS was as follows:

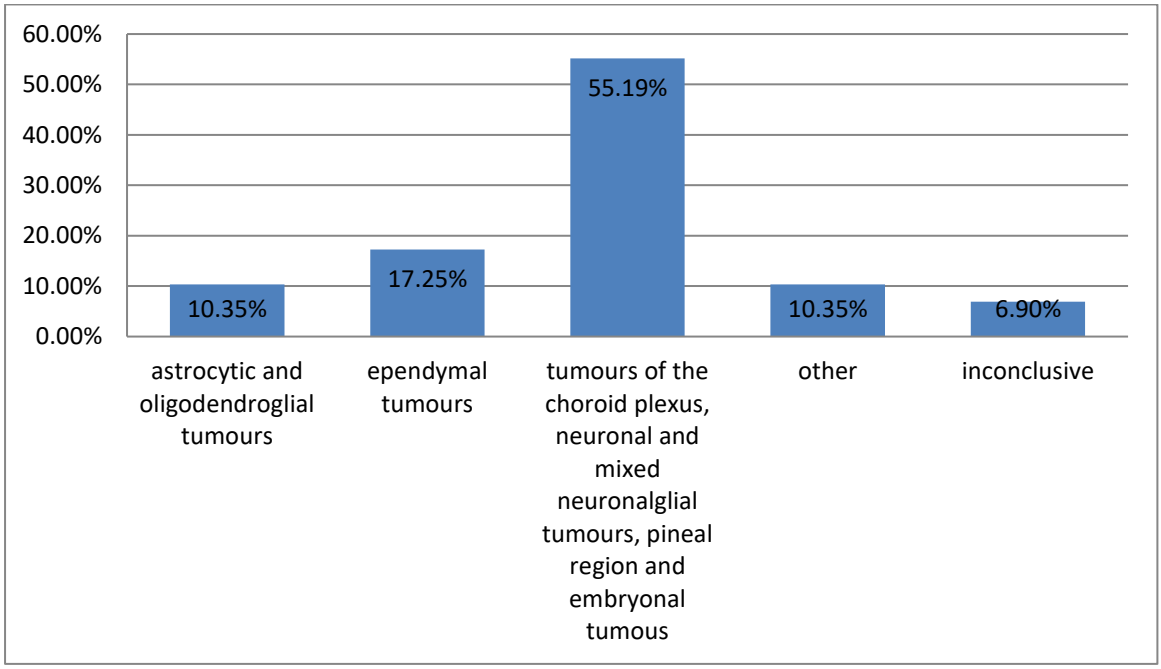
Fig. 4: Location in the CNS age group 0 – 4 years old



The highest affinity for tumours in this age group with regard to location was the cerebellum and brainstem at 41.38% followed in a distant second place by the ventricle and spinal cord and cauda equina at 17.24% respectively. 10.34% of the tumours in this age group occurred in the pineal region and 6.90% in the frontal lobe. Only 3.45% of the tumours were located in the temporal lobe with no tumours documented as located in the parietal or occipital lobes or the pituitary or craniopharyngeal duct. However, in 3.45% no specific location was documented on the histology report. This amalgamates to 41.38% of the tumours documented to be located infratentorially and 38% documented as a supratentorial location.

The histology for the age groups showed 16 WHO III/IV tumours with 6 WHO I/II tumours with 7 of which the WHO grade was not determined. The histology was as follows:

Fig. 5: Histological subtypes in the age group 0 – 4 years



In this age group 17 tumours were malignant (58.62%), 10 tumours were benign (34.48%) and in 2 of the tumours the histology was not determined due to inconclusive samples. The most common malignant tumour in this age group was a medulloblastoma at 20.69% followed by pineoblastoma at 13.79%.

In the astrocytic and oligodendroglial tumour group, no oligodendrogliomas were diagnosed. Two astrocytomas were diagnosed, namely one pilocytic astrocytoma (WHO I) and one anaplastic astrocytoma (WHO III).

Five ependymal tumours were diagnosed: three of which were ependymoma WHO II and two were classified as anaplastic ependymomas (WHO III).

In the largest group in this age group, the tumours of the choroid plexus, the neuronal and mixed neuronal-glial, pineal region and embryonal tumours, ten tumours were diagnosed. These tumours comprised of one tumour of the choroid plexus, a choroid plexus papilloma, and one desmoplastic infantile astrocytoma (WHO I), one pineal region tumour (a pineoblastoma WHO IV) and nine embryonal tumours: one atypical teratoid/rhabdoid tumour, one PNET (primitive neuro-ectodermal tumour) and six medulloblastomas. The medulloblastomas were classified according to the histological definition mainly, namely:

1. Classic medulloblastoma – 1 case
2. Desmoplastic medulloblastoma – 1 case
3. Desmoplastic/nodular medulloblastoma – 1 case

4. Medulloblastoma grade IV – 2 cases
5. Anaplastic/large cell medulloblastoma – 1 case

A nodular ganglioneuroblastoma was also diagnosed in the spinal cord of a two year old male. This is a tumour of intermediate malignancy. All the other embryonal tumours were classified as WHO IV.

The tumours that were classified under “other” included an astroblastoma classified under other gliomas in the 2016 WHO classification. This is a tumour that is currently not graded according to the WHO grading system and can be curable with a gross total resection if possible. It also included a dermoid and epidermoid cyst, one tumour simply documented to be a high grade tumour (no specific histological diagnosis available, tissue obtained from the spinal cord) and an osteoma classified under mesenchymal, non-meningeal tumours. These tumours comprised 10.35% of the total number of tumours diagnosed in this age group.

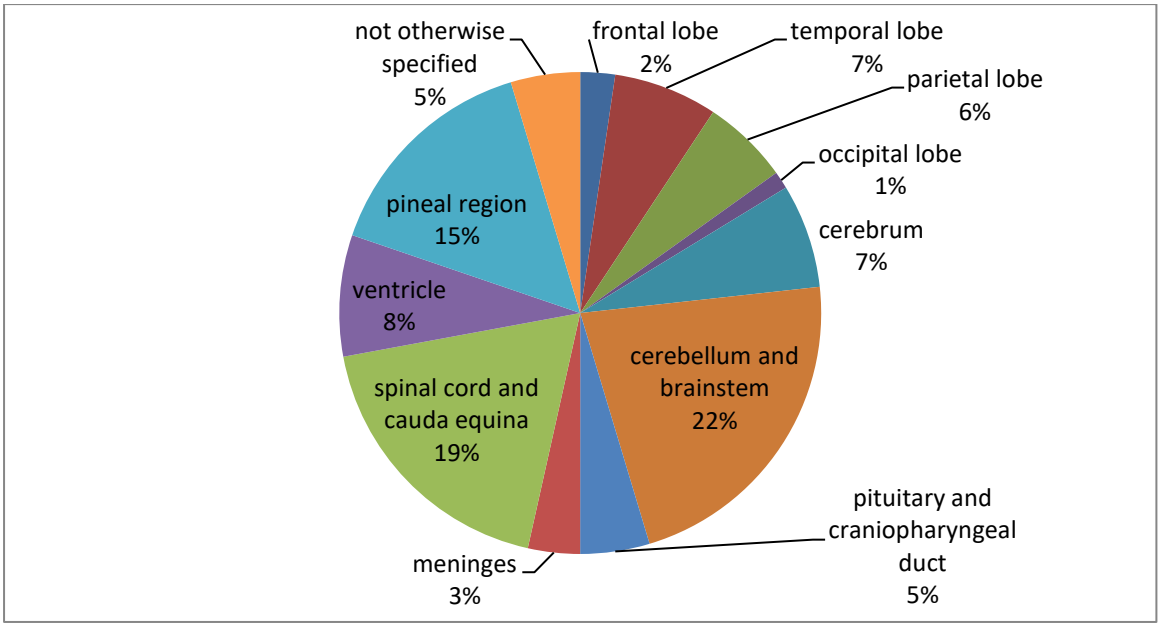
In this age group only two specimens yielded an inconclusive histological diagnosis which comprised 6.90% of the samples obtained. The one biopsy was from the posterior fossa of a 4 year old and the other from the spinal cord of a 2 year old.

<u>5 – 19 year old group:</u>

In the age group 5 – 19 years of age 87 patients were found with a male preponderance (55.17% to 44.83% female patients) and a ratio of male to female of 1.2:1. This group comprised 19.73% of the tumours diagnosed surgically at our institution. The surgical procedures performed in this age group consisted of 40 biopsies, 40 debulking procedures and 7 gross total resections as documented on the histology reports.

The most common location for tumours in this age group was the cerebellum and brainstem at 21.84%, followed by the spinal cord and cauda equina at 18.39%. The spinal cord and cauda equina is not traditionally a common location for tumours in this age group. In the CBTRUS data only 3% of tumours were located in the spinal cord and cauda equina. The pineal region was the third most common location at 14.94%. The temporal lobe was the most common location in the cerebrum at 6.90% followed by the parietal lobe at 5.75%. 4.60% of tumours occurred in the pituitary and craniopharyngeal duct and 8.05% were located in a ventricle. 4.60% of the tumours had no specific location specified. In total 54.04% of all the tumours in this age group were located in the supratentorial space, 21.84% in the infratentorial space and 18.34% in the spinal cord and cauda equina.

Fig. 6: Location of CNS tumours in the age group 5 – 19 years of age



The histological findings in this age group showed a wide variety. With 39.1% of the tumours allocated a WHO III/IV designation and 29.89%% a WHO I/II designation. The remaining 31.01% had no WHO status assigned. The most common malignant tumours in this age group were as follows:

1. Medulloblastoma (WHO IV) 14.94%
2. Pineoblastoma (WHO IV) 9.20%
3. Glioblastoma multiforme (WHO IV) 5.75%
4. Anaplastic astrocytoma (WHO III) 5.75%.

The most common low grade tumours in this age group were as follows:

1. Pilocytic astrocytoma (WHO I) 8.05%
2. Schwannoma 4.60%
3. Craniopharyngioma 4.60%
4. Subependymal giant cell astrocytoma (WHO I) 3.45%.

11.49% of the patients in this age group had inconclusive histology.

The largest group of tumours in this age group occurred in the choroid plexus tumours, neuronal and mixed neuronal glial tumours, pineal region tumours and embryonal tumours at 36.78%. In the choroid plexus tumour group, there was one atypical choroid plexus papilloma and in the neuronal mixed neuronal-glial tumour group, two central neurocytomas (WHO II), one malignant glioneural tumour and one papillary glioneural tumour.

The embryonal tumours consisted of thirteen medulloblastomas, two ganglioneuromas and one metastatic neuroblastoma. One of the medulloblastomas was a metastatic medulloblastoma in the spinal cord of a 7 year old male. The rest of the medulloblastomas were classified according to the histological definition as the following:

1. Classic medulloblastoma – 1 case
2. Desmoplastic medulloblastoma – 1 case
3. Nodular/desmoplastic medulloblastoma – 1 case
4. Medulloblastoma grade 4 – 9 cases

The pineal region tumours consisted of two pineal parenchymal lesions with intermediate differentiation and eight pineoblastomas.

The second largest group was formed by the astrocytic and oligodendroglial tumour group at 18.39% (excluding glioblastoma multiforme). Five anaplastic astrocytomas (WHO III) were diagnosed as well as one anaplastic oligodendroglioma (WHO III). There were also seven pilocytic astrocytomas (WHO I) and 3 subependymal giant cell astrocytomas (WHO I). Five glioblastoma multiforme (WHO IV) were diagnosed in this age group (5.75%).

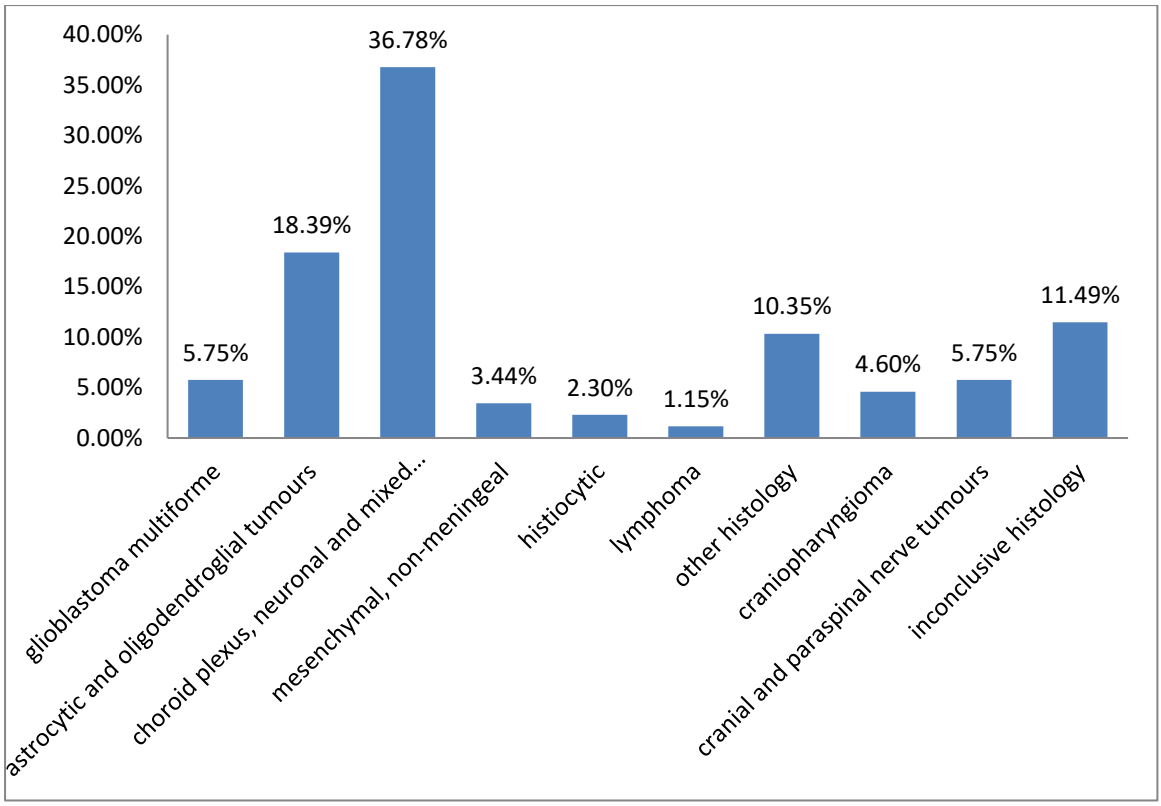
3.44% of all the tumours were consistent with tumours from the mesenchymal, non-meningeal subtype and consisted of 1 chondroblastic osteosarcoma, one metastatic rhabdomyosarcoma and one osteoma. 2.3% fell within the histiocytic group: one case of Langerhans histiocytosis and one of non-Langerhans cell histiocytosis. 5.75% of the tumours originated from the cranial and paraspinal nerves and consisted of 4 schwannomas and one malignant peripheral nerve sheath tumour. Only 4.6% of the tumours were craniopharyngiomas.

11.49% of the histology obtained in this age group was inconclusive. 40 biopsies were taken in this age group and the inconclusive histology was all presented in the biopsy group.

10.35% of the tumours fell into the “other histology” group and consisted of:

1. Aneurysmal bone cyst – 4 cases
2. Fibro-osseous lesion – 1 case
3. Fibrous dysplasia – 1 case
4. Germinoma (germ cell tumour) – 1 case
5. Lipomatous hamartoma – 1 case
6. Lymphoma – 1 case
7. Myxoid type glial cell mass – 1 case
8. Pachymeningitis – 1 case

Fig. 7: Histological subtypes in age group 5 – 19 years of age



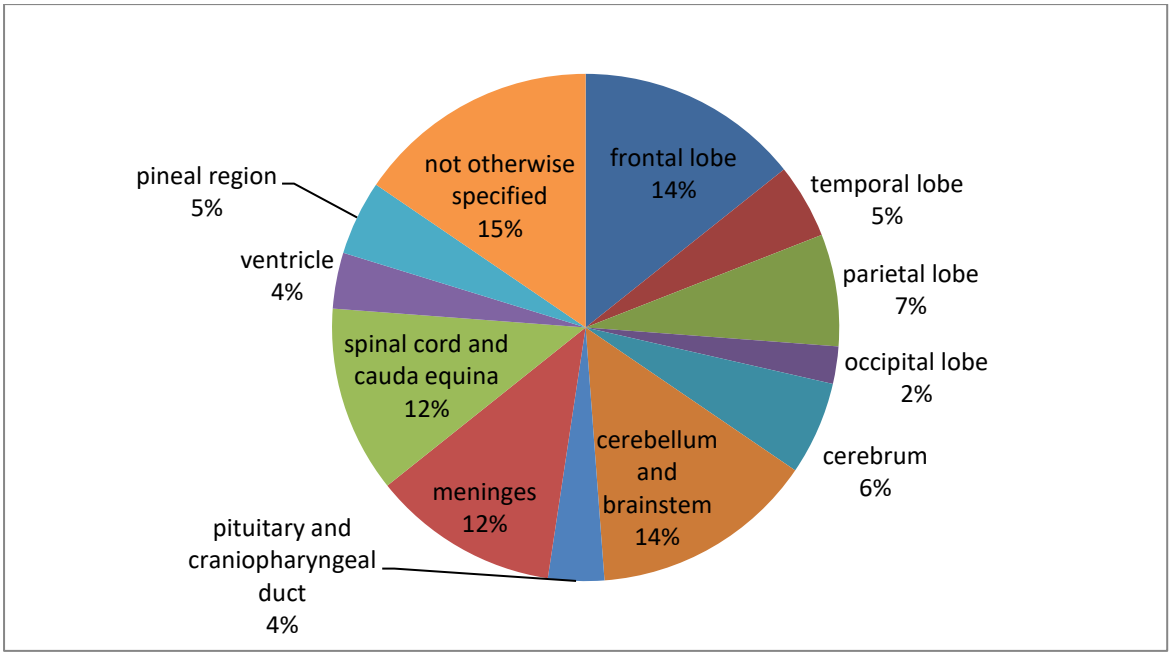
20 – 34 year old group:

The next age group consisted of all the patients between the ages of 20 and 34 years old. This group consisted of 84 patients of which 46 (54.76%) were female and 38 (45.23%) male patients. There was a slight female preponderance with a male to female ratio of 1:1.2. 40 of these patients had a biopsy, 38 a debulking procedure and 5 a gross total resection according to the histology reports.

The most common location for a central nervous system tumour in this group was in the frontal lobe and the cerebellum and brainstem each at 14.29%. These locations were then followed by the meninges and spinal cord and cauda equina both at 11.90%. This was followed by the parietal lobe at 7.14% and the temporal lobe and pineal region both at 4.76%. 3.57% of tumours in this age group were diagnosed at the pituitary and craniopharyngeal duct as well as 3.57% in the ventricles. 15% of the tumours had no specific location indicated on the histology report.

58.32% of these tumours were supratentorial and 14.29% infratentorial.

Fig. 8: Location of tumours in the age group 20 – 34 years of age



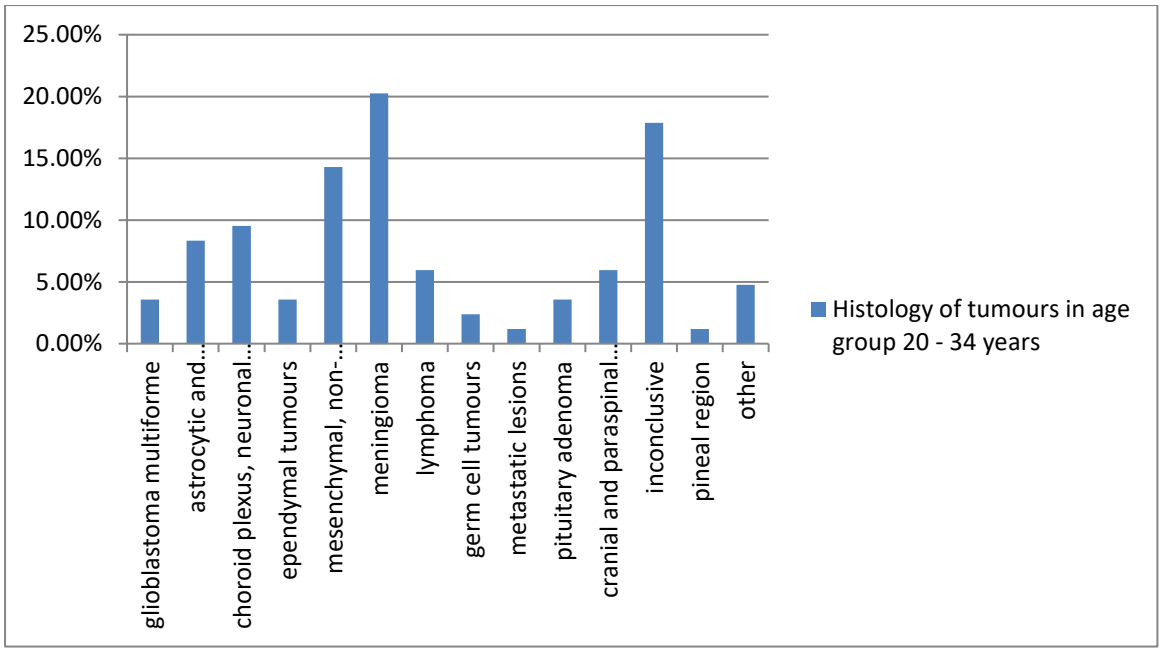
The histology in this age group also showed a great variety with 15.48% having a WHO III/IV destination and 38.10% having a WHO I/II destination and 46.42% not being allocated any WHO destination. The most common malignant tumours in this age group were glioblastoma multiforme, diffuse large B-cell lymphoma and embryonal tumours with multiple lines of differentiation all at 3.52%. The most common tumour in this age group was meningothelial meningioma (WHO) I at 11.90%.

The most common tumour group in this age group was meningiomas at 20.24%. It comprised of 17 meningiomas, most of which were WHO I grade. The meningiomas diagnosed were:

1. Meningothelial meningioma (WHO I) – 12 cases
2. Transitional meningioma (WHO I)– 1 case
3. Psammomatous meningioma (WHO I)– 1 case
4. Atypical meningioma (WHO II) – 3 cases.

The second most common tumour group in this age group were the mesenchymal, non-meningeal tumours at 14.28%. The tumours diagnosed in this group were one chondrosarcoma, one haemangioblastoma, one hemangiopericytoma (solitary fibrous tumour – no grade allocated), two osteomas and three osteosarcomas. One rhabdomyosarcoma was also diagnosed and three sarcomas.

Fig. 9: Histological subtypes in the age group 20 – 34 years of age



The third most common group were the tumours comprising of tumours of the choroid plexus, neuronal and mixed neuronal-glial tumours, pineal region tumours and embryonal tumours at 9.52%. In descending order, the tumours diagnosed were:

1. Embryonal tumour with multiple lines of differentiation (WHO IV) – 3 cases
2. Medulloblastoma (WHO IV) – 2 cases
3. Choroid plexus papilloma (WHO I) – 1 case
4. Extraventricular neurocytoma (WHO II) – 1 case
5. Pineoblastoma (WHO IV) – 1 case

Astrocytic and oligodendroglial tumours filled the fourth place in this age group with 7 tumours diagnosed in this group at a total of 8.33% of the tumours. Only one oligodendroglioma was diagnosed and it was sub-classified as a WHO II tumour, not otherwise specified. Six astrocytomas were diagnosed of which one was an anaplastic astrocytoma (WHO III); two were diffuse astrocytomas (WHO II), one pleomorphic xanthoastrocytoma (WHO II) and one subependymal giant cell astrocytoma (WHO I).

Central nervous system lymphoma comprised 5.95% of the tumours in this age group. The different types diagnosed were:

1. Diffuse large B-cell lymphoma – 3 cases
2. Lymphoma (not otherwise specified) – 1 case
3. Plasmablastic lymphoma – 1 case

Cranial and paraspinal nerve tumours also encompassed 5.95% of the tumours in this group with 4 schwannomas diagnosed as well as one malignant peripheral nerve sheath tumour.

Only 3 pituitary tumours were histologically confirmed in this age group comprising 3.57% of all the tumours surgically managed in this group. Two were pituitary adenomas and one was an atypical pituitary adenoma.

Glioblastoma multiforme was also confirmed in 3 patients. None of the molecular studies were performed and all are classified as not otherwise specified.

Three ependymomas were confirmed in this age group of which two were ependymoma WHO III (one anaplastic clear cell) and one ependymoma WHO II, not otherwise specified.

Two germinomas and one pineoblastoma as well as one metastatic ductal carcinoma (breast carcinoma) was diagnosed. One case of Erdheim-Chester disease was also diagnosed.

A very high percentage of the lesions biopsied had inconclusive histology at 17.87%.

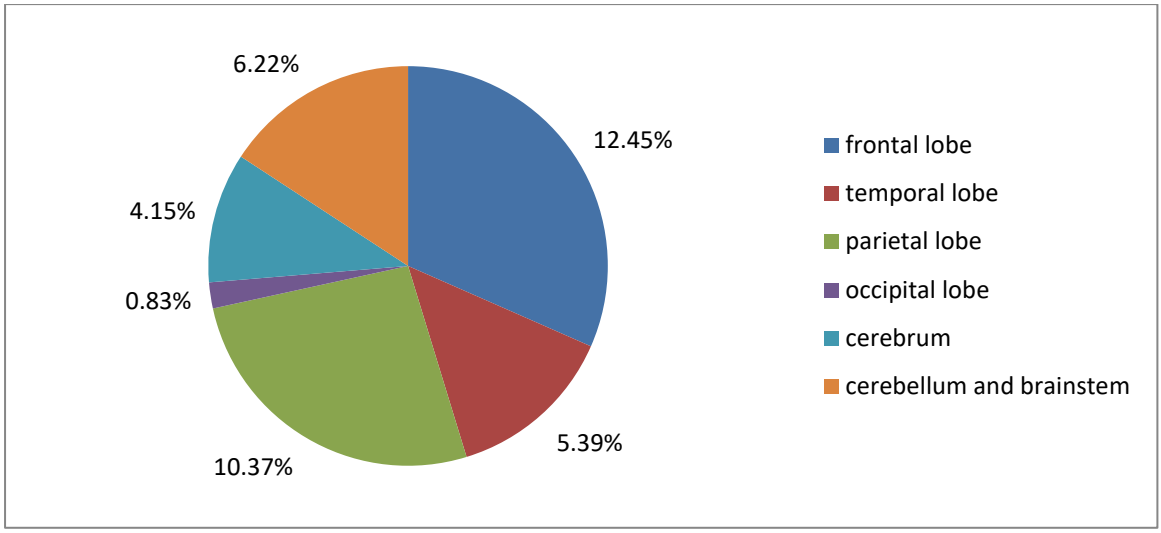
<u>35 year and older group:</u>

The next age group was the patients aged 35 years and older. This group consisted of 241 patients with the oldest being 80 years old. There were 157 (65.15%) female patients and 84 (34.85%) male patients with a male to female ratio of 1:1.87. 89 of the patients had a biopsy, 121 patients had a debulking procedure and 31 had a gross total resection according to the NHLS histology reports.

The tumours in this group were located in the CNS with a clear predilection for the frontal lobes at 12.45%. This was followed in second place with the parietal lobe at 10.37%. The brainstem and cerebellum contained 6.22% of the tumours and the temporal lobe 5.39%. 4.15% had no definitive location except for cerebrum and 0.83% of these tumours occurred in the occipital lobe.

Only 20% (n = 20) of the tumours in this age group occurred infratentorially and 69.17% (n = 168) occurred supratentorially. 7.47% of the spinal tumours were extradural, 9.96% intradural, extramedullary and 1.24% intradural, intramedullary. 2.9% of the tumours according to the histology reports originated from the skull and 1 tumour was located both infra- and supratentorially.

Fig. 10: Location of CNS tumours in the age group 35 years and older



The most common tumour in this age group was meningiomas (37.34%), followed by lymphoma (10.37%) and then glioblastoma multiforme (8.71%). Metastatic lesions were also quite common at 7.05%. The most common meningioma was the meningothelial type at 35.56% followed by transitional meningioma at 25.56%. One meningioma with a WHO III grade was diagnosed during this period. In this group 40.66% of the tumours were WHO I grade, 3.73% were WHO II grade, and 14.11% were WHO III/IV with 31.54% not receiving a WHO grade on the histology. 10.40% had inconclusive histology.

Meningiomas were the most common type of tumour diagnosed in the age group 35 years and older at 37.34%. The meningiomas diagnosed were as follows:

1. Angiomatous meningioma – 4 cases
2. Atypical meningioma (WHO II) – 1 case
3. Atypical transitional meningioma (WHO II) – 4 cases
4. Fibrous meningioma (WHO I) – 8 cases
5. Meningothelial meningioma (WHO I) – 40 cases
6. Microcystic meningioma (WHO I) – 6 cases
7. Papillary meningioma (WHO III) – 1 case
8. Psammomatous meningioma (WHO I) – 1 case
9. Secretory meningioma (WHO I) – 1 case
10. Transitional meningioma (WHO I) – 23 cases
11. 1 case suggestive of meningioma.

The location of the meningiomas surgically managed at our institution was as follows:

1. Parasagittal 4.44%
2. Convexity 17.78%

3. Tuberculum sellae 13.33%
4. Sphenoid ridge 14.44%
5. Olfactory groove 7.78%
6. Tentorium cerebelli 3.33%
7. Cerebellopontine angle 3.33%
8. Clivus 2.22%
9. Spinal cord 8.89%
10. Craniocervical junction 1.11%
11. Location not indicated 23.33%.

Lymphoma comprised 10.37% of central nervous system tumours diagnosed in this group. Both primary and metastatic (secondary) central nervous system lymphoma was diagnosed in this group. The different subtypes of lymphoma that was diagnosed in this group, was:

1. Primary CNS lymphoma:
    a. Diffuse large B-cell lymphoma – 15 cases
    b. EBV-associated diffuse large B-cell lymphoma – 2 cases
2. Metastatic/secondary CSN lymphoma:
    a. Plasmacell dyscrasia – 1 case
    b. Hodgkin's lymphoma – 2 cases
    c. Extra-nodal T-cell lymphoma – 2 cases
    d. Diffuse small cleaved B-cell lymphoma – 1 case
    e. Burkitt's lymphoma – 3 cases.

Glioblastoma multiforme was diagnosed in 21 of the patients in this group for a total of 8.71%. Two of the tumours had a genetic diagnosis with one being *IDH*-wildtype (44 year old female patient) and one being *IDH*-mutant (37 year old male patient). One giant cell glioblastoma (57 year old male patient) was also diagnosed, that under the 2016 WHO classification falls under the *IDH*-wildtype subtype. The 18 other glioblastomas diagnosed were all not otherwise specified.

Metastatic lesions were the fifth most common central nervous system tumour in this age group. Different metastatic carcinomas were identified, but unfortunately the presumed primary was not indicated on the histology report. The different metastatic lesions were as follows:

1. Adenocarcinoma – 6 cases
2. Adenosquamous carcinoma – 1 case
3. Carcinoma – 3 cases
4. Chondrosarcoma – 1 case
5. Large cell neuroendocrine carcinoma – 1 case
6. Prostate carcinoma – 1 case
7. Squamous cell carcinoma – 2 cases
8. Teratoma – 1 case

9. Undifferentiated carcinoma – 1 case
10. Prostate adenocarcinoma – 1 case

13 pituitary adenomas were histologically proven in this group. This comprised 5.39% of the tumours in this group. 2 craniopharyngiomas were also histologically proven (0.83%).

In the group of astrocytic and oligodendroglial tumours, both low grade and high grade tumours were diagnosed. Of the low grade tumours there was one pilocytic astrocytoma (WHO I) and one oligodendroglioma (WHO II). The high grade gliomas consisted of eight anaplastic astrocytomas (WHO III) and two anaplastic oligodendrogliomas (WHO III). No molecular diagnosis is available to confirm the diagnosis of the oligodendroglioma or to reclassify an anaplastic astrocytoma to an anaplastic oligodendroglioma. A total of 12 astrocytic and oligodendroglial tumours were diagnosed in this group with a percentage of 4.98% of the total of tumours diagnosed in this group.

The mesenchymal, non-meningeal tumours also comprised 4.15% of the tumours diagnosed in this group. The different tumours diagnosed were:

1. Anaplastic hemangiopericytoma (WHO III) – 1 case
2. Epithelioid leiomyosarcoma – 1 case
3. Haemangioblastoma – 4 cases
4. Hemangiopericytoma grade 3 – 1 case
5. Osteoma – 2 cases.

Tumours of the cranial and paraspinal nerves were diagnosed in 4.15%. Nine schwannomas were diagnosed, but no subtype indicated and one neurofibroma was diagnosed.

In the group “other” the following were noted:

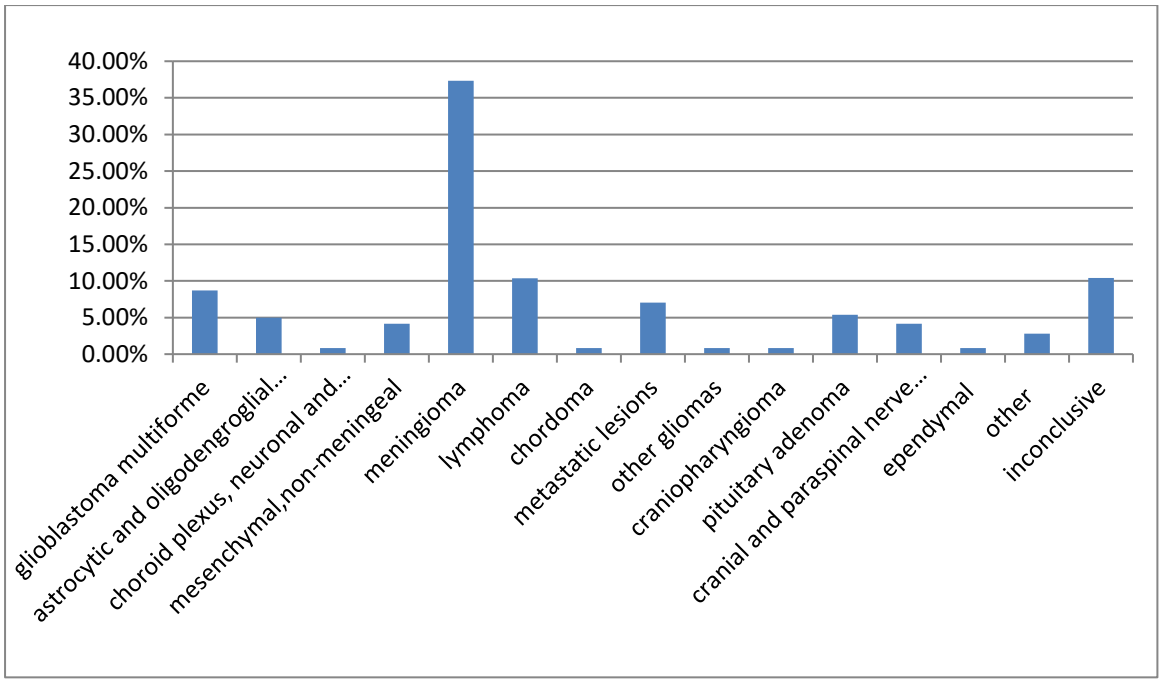
1. Paraganglioma – 5 cases
2. Epidermoid cyst – 2 cases
3. Chordoma – 2 cases
4. Calcified neoplasm – 1 case.

Ependymal tumours and other gliomas made up 0.83% each of the total amount of histological diagnosis in this group. The ependymal tumours consisted of 2 WHO grade II ependymomas and the other gliomas of 1 astroblastoma one unspecified high grade glioma WHO III/IV.

The grouping of choroid plexus tumours, pineal region tumours, neuronal and mixed neuronal-glial tumours and embryonal tumours there was one pineoblastoma and one choroid plexus papilloma diagnosed.

As mentioned 89 of the patients had biopsies only taken, of those 24 was inconclusive or normal brain/tissue. This equates to 10.40%. None of the patients had repeat biopsies or debulking procedures documented on the NHLS data base.

Fig. 11: Histological subtypes in the age group 35 years and older



Discussion:

At Universitas Academic Hospital in Bloemfontein, all central nervous system tumours that are diagnosed in the public health sector in the Free State Province, Lesotho and most of the CNS tumours diagnosed in the Northern Cape Province public health sector are managed. The Free State in the 2016 Census had 2 745 590 people, the Northern Cape Province 1 200 000 people and Lesotho 2 233 000 people in 2017.

Very little is known about the incidence and prevalence of central nervous system tumours in general in Africa and South Africa. The United States of America and most of the European countries keep extensive tumour registers with regard to brain tumours, the incidence, epidemiology and outcome.

The South African National Data is based in the National Tumour Registry by the National Health Laboratory Services. Their data base is only up to date until 2014 and only takes into account high grade lesions. This entails malignant tumours only of a WHO III and IV classification. No benign tumours are recorded in this registry.

In total 2851 malignant brain tumours were reported between the years 2007 to 2014. 1620 of these patients were male and 1231 were female. The age of the patients differed from less than 1 year to 106 years old. 17 of the patients had no age indicated on the pathology request form. The median age was 53 years.

The distribution of the malignant tumours was as follows:

Table 3: Distribution of malignant tumours as per SA Tumour Registry

%	Malignant tumours
57.2	No site specified
8.73	Cerebellum and brainstem
7.65	Frontal lobe
6.56	Parietal lobe
6.42	Temporal lobe
6.17	Cauda equina and spinal cord
2.49	Occipital lobe
2.30	Meninges
1.23	Ventricle not otherwise specified

It was very disappointing to note that 57.2% of the malignant tumours of the tumours of the South African Tumour Registry had no location allocated. This makes it impossible to compare the South African data with that of CBTRUS and our locally obtained data. Quite different to the CBTRUS data and the data obtained from our institution, cerebellar and brainstem tumours were the most common location second to the not specified location in the South African data, whereas in CBTRUS the most common location for malignant tumours were firstly in the frontal lobe at 23.6% and secondly in the temporal lobe at 17.4%. The malignant tumours diagnosed at Universitas Academic Hospital, occurred most commonly in the cerebellum and brainstem at 21.84% and secondly in the spinal cord and cauda equina at 19.54%.

The histopathological distribution was as follows:

Table 4: Histopathological distribution as per SA Tumour Registry

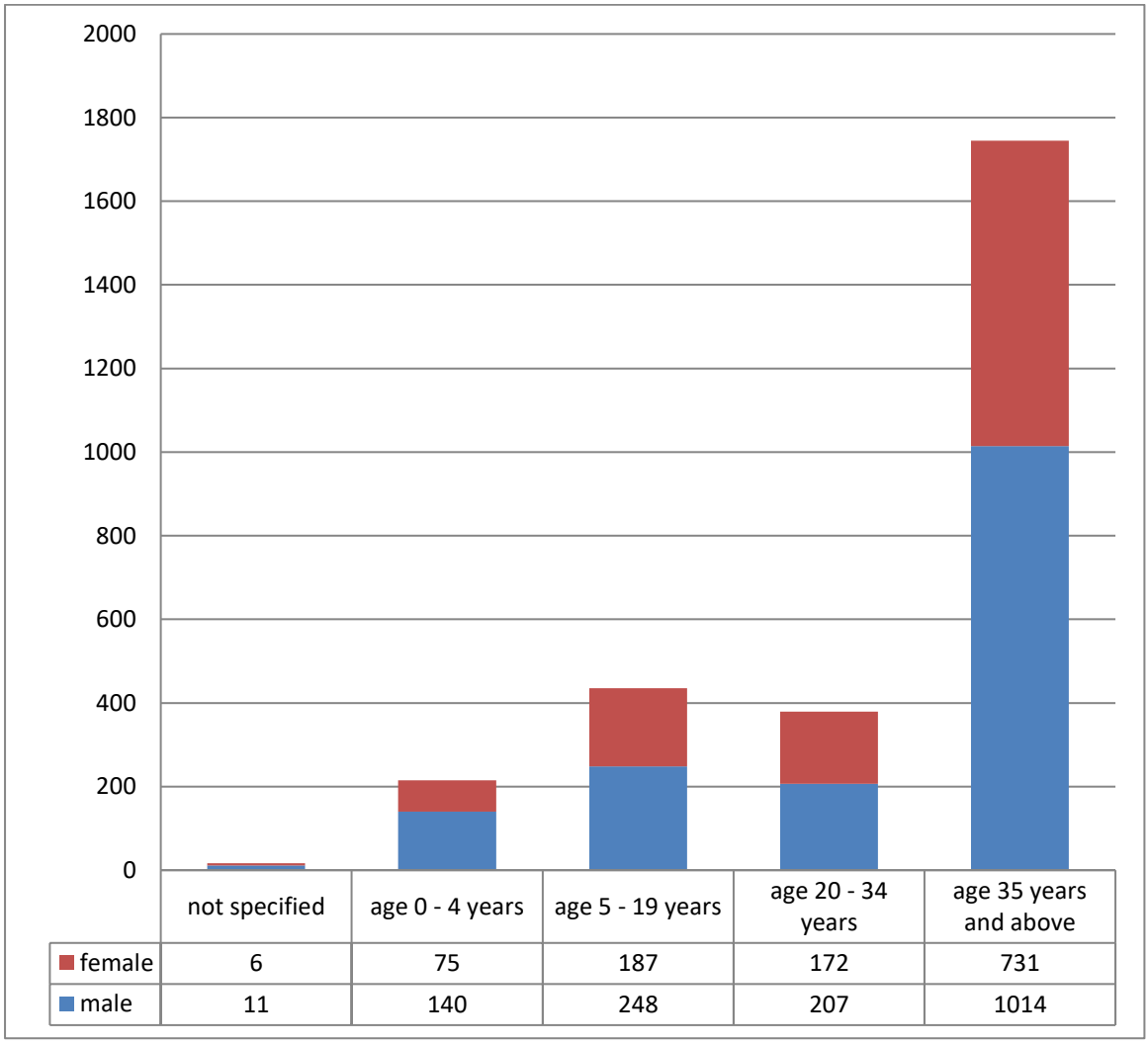
%	Tumour type
39.11	Glioblastoma
26.70	Astrocytic and oligodendroglial tumours
12.17	Malignant tumours of the choroid plexus, neuronal and mixed neuronal tumours, tumours of the pineal region, embryonal tumours and malignant nerve sheath tumours
7.65	Ependymal tumours
3.89	Malignant glioma
3.30	Mesenchymal, non-meningeal tumours
2.00	Malignant meningioma
1.72	Lymphomas
0.63	Malignant neoplasm – no definitive histological diagnosis
0.39	Chordoma
0.25	Germ cell tumours

The histological distribution was divided into 5 different age groups, namely:

1. Not specified
2. Age 0 – 4 years old
3. Age 5 – 19 years old
4. Age 20 – 34 years old
5. Age 35 years and above.

The group consisting of the patients were no age was specified, consisted of 6 female patients and 11 male patients with a male to female ratio of 1.83:1. The make-up of the different age population varies as well. In the age group 0 – 4 years old the male: female ratio in the National Data base was 1.87:1 and in the UAH group 2.2:1. The age group 5 – 19 years had a National male: female ratio of 1.33:1 vs the UAH group's 1.2:1. In the age group of 20 – 34 years old the male: female ratio was 1:1.2:1 in the National Data base vs 1:1.2 at UAH. In the last age group of patients 35 years old and older the male to female ratio in the National data was 1.39:1 vs the UAH group's 1:1.87.

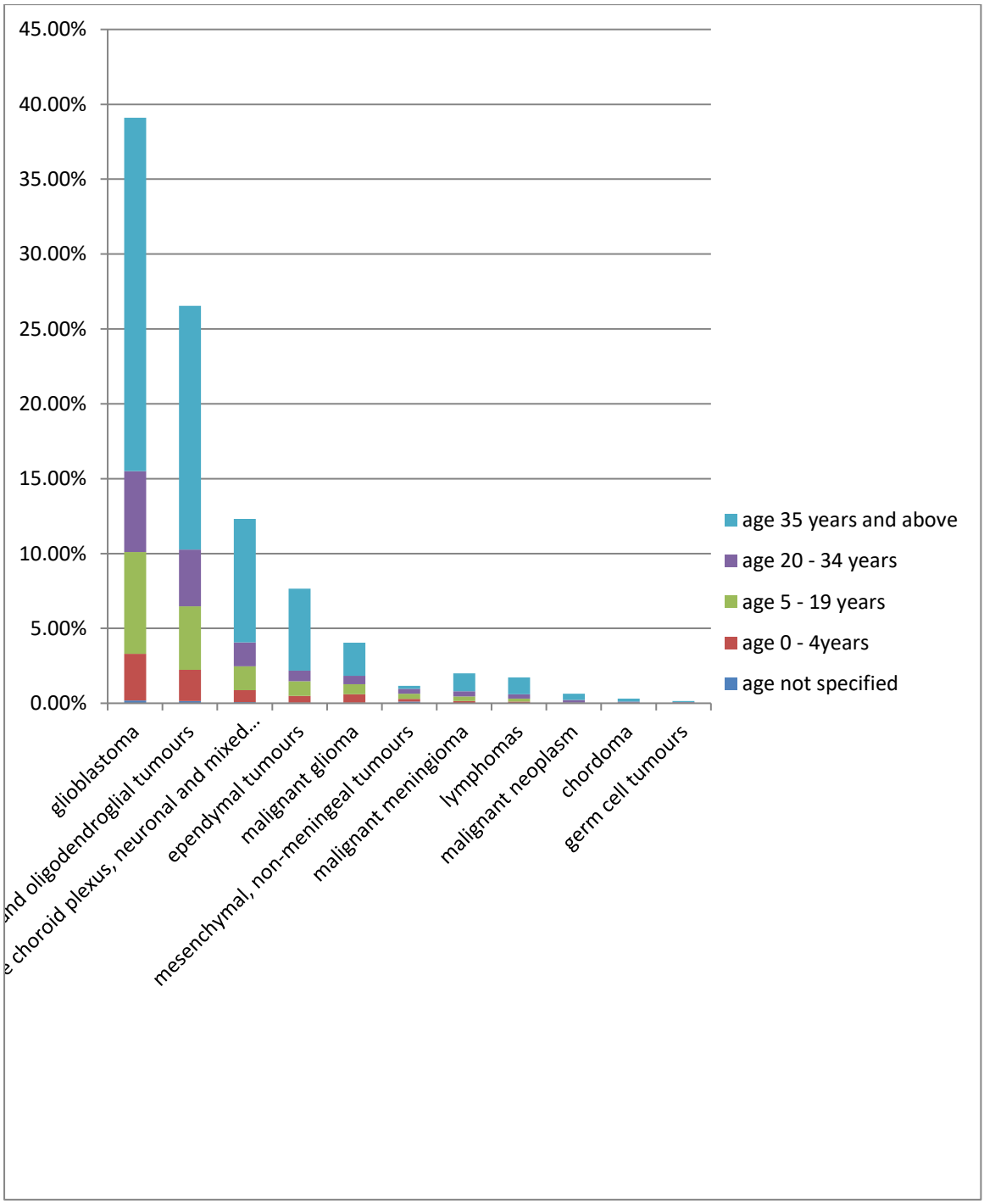
Fig. 12: Age distribution of malignant tumours



	not specified	age 0 - 4 years	age 5 - 19 years	age 20 - 34 years	age 35 years and above
female	6	75	187	172	731
male	11	140	248	207	1014

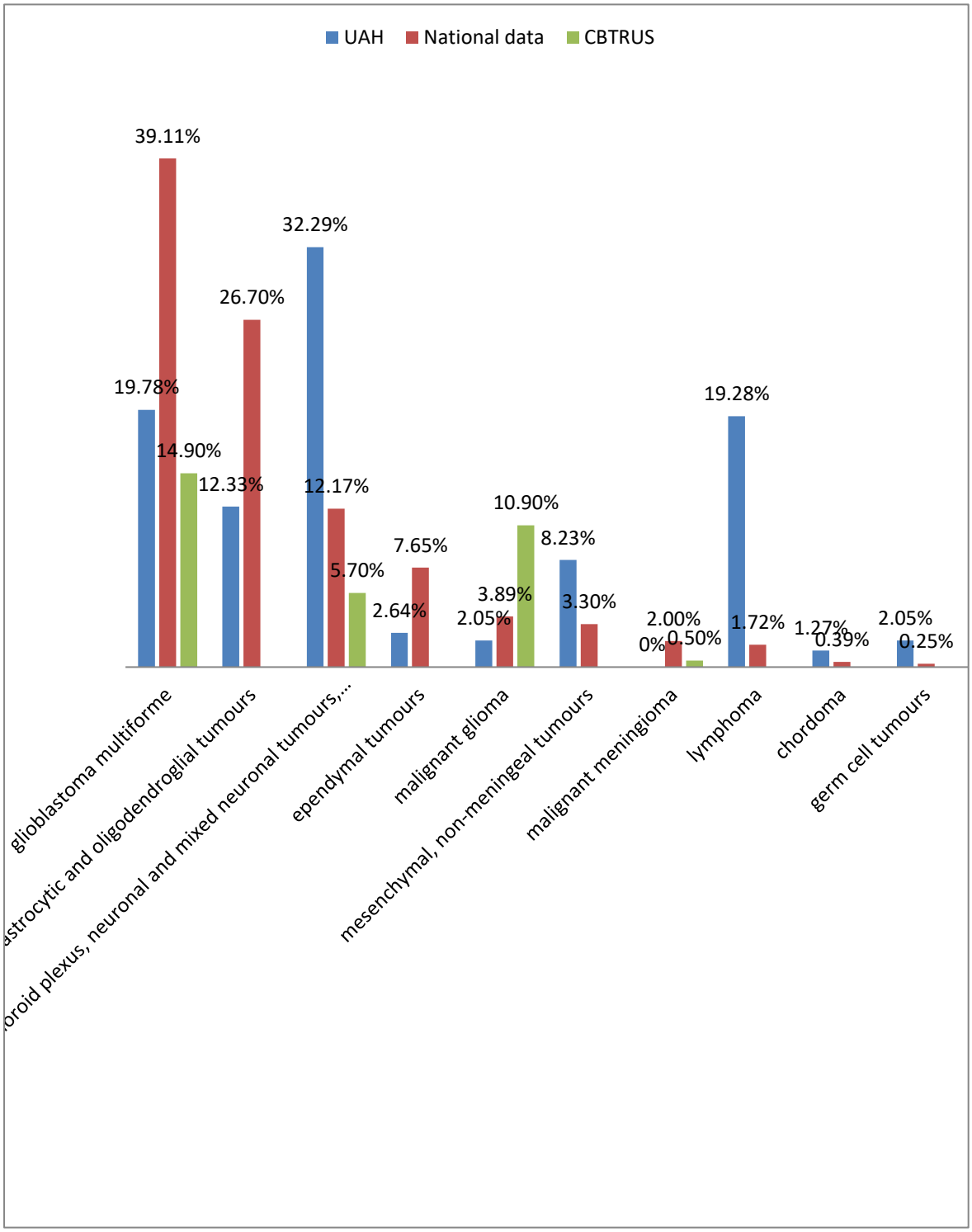
The histological subtypes were present in the age groups as follows:

Fig. 13: Histological subtypes according to the different age groups



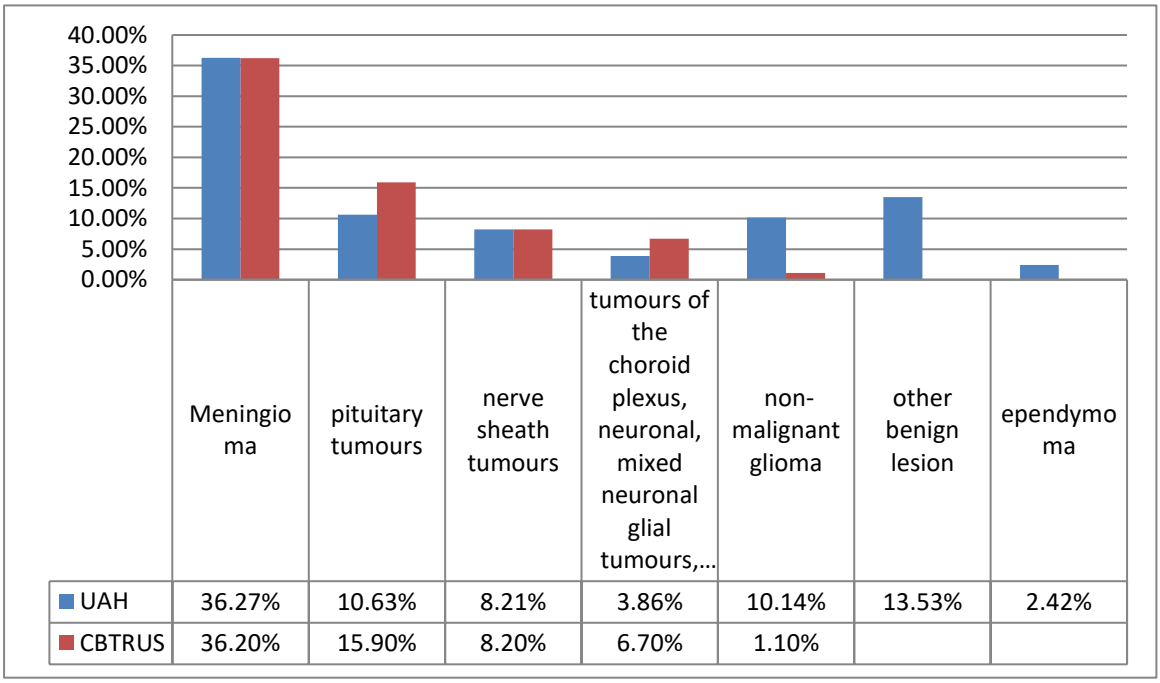
We compared the data obtained from Universitas Academic Hospital (UAH) with the South African data available on malignant tumours. At UAH a total of 146 malignant tumours were found in the data. This was compared to the South African (SA) National data.

Fig. 14: Comparison of UAH vs SA vs CBTRUS data (malignant tumours)



As there is no data base for benign tumours in South Africa, the benign tumours diagnosed at Universitas Academic Hospital were only compared with those obtained from the CBTRUS data base.

Fig. 15: Comparison of benign histology between UAH and CBTRUS



	Meningioma	pituitary tumours	nerve sheath tumours	tumours of the choroid plexus, neuronal, mixed neuronal glial tumours,...	non-malignant glioma	other benign lesion	ependymoma
UAH	36.27%	10.63%	8.21%	3.86%	10.14%	13.53%	2.42%
CBTRUS	36.20%	15.90%	8.20%	6.70%	1.10%		

Since the data obtained at Universitas Academic Hospital for this period varies from that contained in CBTRUS and the absence of a benign tumour registry for South Africa, the tumours need to be evaluated individually to be comparative and to determine the short comings and possible pit falls at Universitas Academic Hospital.

According to the WHO classification of tumours of the central nervous system as published in 2007, the following main groups of tumours were classified:

A. Tumours of neuro-epithelial tissue
B. Tumours of the cranial and paraspinal nerves
C. Tumours of the meninges
D. Lymphomas and haematopoietic neoplasms
E. Germ cell tumours
F. Tumours of the sellar region
G. Metastatic tumours.

The 2016 WHO classification of tumours of the central nervous system differs from the 2007 version with regards to the main division of the tumours as well as the sub-classification of tumours in the classification. The main groups of tumours in the 2016 classification are as follows:

A. Diffuse astrocytic and oligodendroglial tumours
B. Other astrocytic tumours
C. Ependymal tumours
D. Other gliomas
E. Choroid plexus tumours
F. Neuronal and mixed neuronal-glial tumours

G. Tumours of the pineal region
H. Embryonal tumours
I. Tumours of the cranial and paraspinal nerves
J. Meningiomas
K. Mesenchymal ,non-meningeal tumours
L. Melanocytic tumours
M. Lymphomas
N. Histiocytic tumours
O. Germ cell tumours
P. Tumours of the sellar region
Q. Metastatic tumours.

The main differences between the 2007 and the 2016 WHO classification of central nervous system tumours were due to the discovery of genetic and epigenetic markers in the last couple of decades. This has started a molecular era in neuropathology. The main reasons these discoveries are challenging the previous classification systems is due to the fact that histogenetic diagnosis can overlap in numerous types of tumours as these variations can co-exist in different tumours, for example astrocytic and oligodendroglial variations in astrocytomas or oligodendrogliomas. The prognosis also closely correlates with a molecular diagnosis and less so with the WHO grading. The third and most important reason, according to the researcher, is that with making a pathological diagnosis there can be great inter-observer differences that can be completely excluded by making a molecular diagnosis. For this reason, molecular testing overs a greater objectivity and reproducibility than pathological diagnosis. Neuropathology is a very specialized field with currently no specified training in neuropathology being offered in Southern Africa and currently in South Africa only Dr D Zaharie at Tygerberg Hospital has had training in neuropathology (Folkerth et al, 2016). This makes the likelihood of great inter-observer differences tremendous. By obtaining a molecular diagnosis this could be excluded.

The major points of revision in the 2016 WHO classification consisted of:

1. Oligodendrogliomas: this nomenclature is intended to include the 1pq19 co-deletion which implicates a classic histology of oligodendroglioma. Once the tumour becomes anaplastic, the classic histology will become unclear and the genetic testing for the 1p19q co-deletion will become mandatory to confirm the diagnosis.
2. Diffuse astrocytomas: in adult patients the second stratifier will be the presence or absence of *IDH*-mutations (*IDH* = isocitrate dehydrogenase). If no 1p19q co-deletion is detected in an *IDH 1 or 2* mutation glioma, the classification is that of an astrocytoma. In patients under the age of 10 years, *IDH* mutations and co-deletions are highly unlikely and these tumours will fall into the category of diffuse or anaplastic astrocytoma, IDH-wildtype.
3. Glioblastomas: *IDH*-mutations should be determined in this group of histological tumours. If an *IDH*-mutation is present, it can be considered as a secondary

glioblastoma multiforme (arising from a previous lesion) and *IDH*-wildtype glioblastomas are considered to be *de novo* of primary glioblastoma multiforme. A new variant has also been identified, namely epithelioid glioblastoma. It lacks the *INI1* or *BRG1* mutation, but generally has a *BRAF V600E* mutation.

4. Paediatric diffuse astrocytomas and oligodendrogliomas: these tumours are grouped in the 2016 WHO classification with their adult counterparts despite having a clear cut difference in behaviour and prognosis.
5. Diffuse midline glioma, *H3K27M*-mutant: diffuse midline gliomas have an infiltrative, high grade nature with predominantly astrocytic differentiation. These tumours are mostly found in a midline location, for example the thalamus, brain stem or spinal cord. The *K27M* mutation is present in either the *H3F3A* or *HIST1H3B/C*.
6. Ependymomas: the proposed molecular classification is based on DNA methylation profiling that is available in a restricted amount of institutions. Therefor few changes have been made to the classification of ependymomas. The genetic alteration in the subtype, ependymoma *RELA* fusion-positive is however determined with fluorescence in situ hybridization (FISH). This is more readily available. This variant accounts for most of the supratentorial ependymomas diagnosed.
7. Neuronal and mixed neuronal-glial tumours: 2 new entities have been added, namely diffuse leptomeningeal glioneural tumour and multinodular and vacuolating neuronal tumour.
8. Embryonal tumours: a couple of changes occurred in this category, namely the addition of genetically defined medulloblastomas, the addition of an embryonal tumour with multi-layered rosettes and the elimination of primitive neuro-ectodermal tumours. For medulloblastomas the *sonic hedgehog (SHH)* and *WNT* and non-*WNT*/non-*SHH* was adopted. The SHH tumours were divided into those with and those without a *TP53* mutation (Komori, 2017).

The histological data obtained is mostly applicable to the 2007 WHO classification as the new classification was only published in 2016. Only 2 tumours had a molecular layer attached to the histological classification in this current series. The WHO grading system was mentioned as allocated according to the grading system. The WHO grading system consists of a grade I – IV. The grading system is defined by the mitotic activity of the cells, the morphology of the cells, the amount of invasion of the surrounding tissue as well as the presence of angiogenesis and necrosis.

The WHO grading system is defined as follows:

Table 5: Definition of the WHO grades

Grade I (low-grade/benign)	Slow growing cells Cells appear almost normal under microscope Least malignant/aggressive Usually associated with long-term survival
Grade II (low-grade)	Relatively slow-growing cells Slightly abnormal appearance under light microscope Can invade healthy tissue Can recur as higher grade tumour
Grade III (high-grade)	Actively reproducing abnormal cells Cells abnormal under light microscope Invades nearby normal tissue Tends to recur and become a higher grade tumour
Grade IV (high-grade)	Rapidly reproducing abnormal cells Very abnormal appearance under light microscope Angiogenesis to maintain rapid growth Central necrosis present

The tumours will be discussed individually based on either the cell of origin, location or histologic behaviour.

1. Low grade gliomas:

Low grade gliomas are neuro-epithelial tumours. Low grade gliomas originate from the glial cells of the central nervous system, namely the astrocytes, oligodendrocytes or neuronal-glial cells. As glial cells are the most prominent cell in the brain with up to 72% of the cerebral cortex consisting of glial cells, these are the most common primary central nervous system tumour diagnosed yearly. Up to 15% of these glial tumours diagnosed are low grade gliomas.

Low grade gliomas consist of a heterogeneous group of tumours that may be astrocytic, oligodendrocytic or mixed cell in histology. These tumours are WHO I or WHO II in classification indicating slow growth and probable good long-term survival. (Forst et al, 2014).

Low grade gliomas include the following tumours (combined 2007 and 2016 WHO classification):

Table 6: Low grade gliomas

WHO I	WHO II
Pilocytic astrocytoma*	Pleomorphic xanthoastrocytoma*
Subependymal giant cell astrocytoma*	Diffuse astrocytoma, *IDH*-mutant
Ganglioglioma*	Diffuse astrocytoma, *IDH*-wildtype
Angiocentric glioma	Diffuse astrocytoma, NOS*

Desmoplastic infantile astrocytoma/ganglioglioma*	Oligodendroglioma, *IDH*-mutant and 1p19q co-deletion
Papillary glioneural tumour*	Oligodendroglioma, NOS*
Rosette forming glioneural tumour	Chordoid glioma of the 3rd ventricle
Subependymoma	Ependymoma ● Papillary ● Clear cell ● Tancytic
Myxopapillary ependymoma*	Ependymoma, *RELA* fusion positive

The low grade gliomas indicated with an asterisk are the tumours histologically diagnosed at Universitas Academic Hospital and will be further discussed in relation to available international data.

In the paediatric population, low grade gliomas include: cerebellar astrocytomas, optic pathway and hypothalamic gliomas as well as brainstem gliomas and hemispheric low grade gliomas.

WHO I low grade gliomas are primarily a disease of children. WHO I tumours are generally well circumscribed and is considered curable with complete surgical resection and are often considered an entity separate from the WHO II – IV gliomas. Grade II low grade gliomas all progress to high grade gliomas (WHO III/IV) and will eventually become secondary glioblastoma multiforme (Claus et al, 2015).

Low grade gliomas have a bimodal age distribution with the first peak observed at the age group 6 – 12 years and the second peak between 30 – 50 years (Winn et al, 2017).

The low grade gliomas indicated with an asterisk are the tumours histologically diagnosed at Universitas Academic Hospital and will be further discussed in relation to available international data.

1.a) Pilocytic astrocytoma:

Pilocytic astrocytomas (WHO I) represents approximately 17% of all central nervous system tumours in children aged 0 – 14 years (Kimberley et al, 2015). They represent about 5 – 6% of all gliomas and are the most common glioma subtype in children and is most commonly found infratentorially in the cerebellum. In both adults and children these tumours might also occur in the optic nerves, optic chiasm, thalamus or basal ganglia and the cerebral hemispheres. These tumours have a predilection for midline structures as noted by the most common location in which these tumours occur. Histologically these tumours are characterized by the presence of eosinophilic Rosenthal fibres and hyalinization of the blood vessels occurs commonly. The histological features can however be quite heterogeneous with some areas in the same tumour mimicking diffuse astrocytomas and oligodendrogliomas. Spread to the subarachnoid space and periventricular space is possible and dissemination along the craniospinal axis has been documented. These tumours are normally treated with surgical resection and adjuvant chemotherapy and radiotherapy for residual tumours. An excellent long term prognosis is then achieved with a >96% 10-year survival rate (Frost et al, 2014; Kimberley et al, 2015).

At Universitas Academic Hospital 9 pilocytic astrocytomas were diagnosed from 2007 – 2017. 1 of these tumours occurred in the age group 0 – 4 years, 7 in the age group 5 – 19 years of age and 1 in the age group older than 35 years. In the age group 0 – 4 years, one male patient had a pilocytic astrocytoma in the cerebellum. In the age group 5 – 19 years, 7 patients had pilocytic astrocytomas: 5 male and 2 female patients. Their age varied between 7 – 15 years. 4 of the tumours were supratentorial and 3 infratentorial. In the paediatric population approximately 66% of these tumours are located infratentorially in the international literature. Pilocytic astrocytomas at Universitas hospital compromised 7.76% of all the central nervous system tumours in the group 0 – 19 years of age. Corrected for the age group 0 – 14 years the incidence of pilocytic astrocytomas diagnosed at Universitas Academic Hospital was 8.42% that is significantly lower than that reported by Kimberley et al in 2015. At our institution there was also an equal distribution between infratentorial and supratentorial occurrence.

South Africa is a developing country and the regions serviced by Universitas Academic Hospital are mainly rural and deep rural areas. An almost equal distribution was found at Universitas Academic Hospital between supra- and infratentorial pilocytic astrocytomas, whereas internationally pilocytic astrocytomas are mostly found infratentorially in this age group. Infratentorial pilocytic astrocytomas present with cerebellar signs, neck stiffness and decreased level of consciousness, headache, nausea and vomiting as well as failure to thrive and malnourishment. Clinically they often present with hydrocephalus, papilledema, ataxia, dysmetria, head tilt and cranial nerve VI palsy (Chourmouzi et al, 2014). These are all symptoms that can be confused with meningitis. It is possible that these patients present late to district level hospital and are then diagnosed with meningitis, often having a lumbar puncture and demising prior to referral for further imaging and investigation. There is a significant lack of ability to perform computed tomography (CT) scan and no possibility to perform magnetic resonance imaging (MRI) in the rural areas. This could explain the large discrepancy between international data and the data obtained at Universitas Academic Hospital. It is also possible that at the time of referral of these patients to Universitas Academic Hospital their general medical condition did not permit any surgical intervention due to delayed presentation and referral.

1.b) Subependymal giant cell astrocytoma:

Subependymal giant cell astrocytomas are also benign and indolent tumours that generally arise from the wall of the lateral ventricle near the foramen of Munro and often cause obstructive hydrocephalus. On MRI imaging these tumours often appear as an intraventricular mass with some calcifications with a heterogeneous MRI signal and vivid contrast enhancement. Histologically these tumours appear mainly astrocytic in nature with a gemistocytic appearance. Large polygonal cells are present with dominant eosinophilic cytoplasm. As the ependymal lining over these tumours remain intact, CSF seeping is highly unlikely. These tumours are generally associated with tuberous sclerosis that is an autosomal dominant neurocutaneous syndrome. Tuberous sclerosis is characterized by cognitive impairment, cutaneous angiofibromas, cardiac rhabdomyomas and angiomyolipomas. These tumours normally present in the first 20 years of life and

can cause seizures or signs of raised intracranial pressure. It is managed by surgical excision and lately the FDA has approved the use of everolimus as treatment as it decreases tumour size and improves the frequency of seizures (Forst et al, 2014). This tumour is seen as exclusive to tuberous sclerosis that occurs in 1:6000 births. Subependymal giant cell astrocytomas occur in approximately 20% of patients with tuberous sclerosis. It is a rare tumour.

At Universitas Academic Hospital, 4 subependymal giant cell astrocytomas were confirmed on histological diagnosis with all of the patients having a subtotal resection of the tumour. This places the incidence of subependymal giant cell astrocytomas at 0.91% which is comparative with international data.

1.c) Pleomorphic xanthoastrocytoma:

Pleomorphic xanthoastrocytoma is a WHO II tumour that is most commonly found in children under the age of 18 years. It only comprises 1% of all astrocytic tumours and it generally adheres to the meninges. These tumours are normally located quite superficially and supratentorially and generally present with seizures. It has a predilection for the temporal lobe and may have a cystic component and tends to enhance vividly with contrast on MRI imaging. A dural tail that enhances might be present and this tumour needs to be distinguished from meningiomas for this reason. Calcifications are however quite rare in these tumours. There is quite often deformation of the skull as these tumours are very slow growing. These tumours are managed with surgical resection in view of their location and have very good long term survival rates. Local recurrence or malignant transformation can occur in up to 20% of patients. With malignant transformation or dedifferentiation (mitoses of more than five per 10 high-power fields) the tumour is known as an anaplastic pleomorphic xanthoastrocytoma and is then classified as a WHO III grade tumour with a decreased long term survival rate. Up to 20% of cases will dedifferentiate into a WHO III grade tumour or a glioblastoma multiforme or recur locally after resection. The patients normally have a >90% five year survival rate and a 5-year disease free survival of 5 years. (Winn et al, 2017).

Only 1 pleomorphic xanthoastrocytoma (WHO II) was diagnosed histologically at Universitas Academic Hospital in the period reviewed with an incidence then of 0.22% which is comparative with international data. This tumour was diagnosed in a 23 year old female patient in her parietal lobe which is the third most common location for this tumour to occur in. These tumours normally have a predilection for the temporal lobe and then secondly for the frontal lobe.

1.d) Diffuse astrocytoma:

The diffuse astrocytomas in the 2016 WHO classification encompass the previous 2007 WHO classification of fibrillary astrocytomas. Gemistocytic astrocytomas are still a separate entity from the diffuse astrocytoma *IDH*-mutant and the protoplasmic subtype

does not exist anymore (Louis et al, 2016). The new 2016 WHO classification denotes diffuse astrocytomas to be *IDH*-wildtype, *IDH*-mutant or not otherwise specified (NOS) all of which are WHO grade II tumours. As previously mentioned, the period of collection of the data was prior to the annotation of a molecular diagnosis and currently we still have very limited access to molecular identification. These tumours are also known as infiltrative astrocytomas as are evident on their radiological presentation.

Diffuse astrocytoma can be divided into two different molecular groups according to their *IDH*-status. The *IDH* could be mutant or wild-type. In the case of an *IDH*-mutant subtype, the 1p19q status should be determined as all *IDH*-mutant with a concomitant 1p19q co-deletion is denoted as an oligodendroglioma regardless of an astrocytic histology. It is quite possible that the *IDH*-wildtype diffuse astrocytoma diagnosis might disappear in the future as further genetic assessment of these tumours are performed as the general consensus is that these tumours all encompass collections of other tumours with an astrocytic histological differentiation. (Louis et al, 2016). As mentioned previously none of the astrocytomas evaluated in this study had *IDH* or 1p19q status evaluation and were all denoted as not otherwise specified if the histology showed a fibrillary astrocytoma.

At our institution a total of 2 diffuse astrocytomas were diagnosed histologically. The first was in a 23 year old male that presented with a lesion in his cerebellum and a debulking procedure was performed and the second in a 29 year old female that presented with a lesion in her frontal lobe that was debulked. In international data, diffuse astrocytomas comprise approximately 25% of all gliomas. In our institution this rate was 6.25%. This could possibly be attributed to several factors:

1. Radiological diagnosis made on CT scan and MRI imaging: Diffuse astrocytomas have a distinct radiological appearance. These tumours appear isodense or hypodense on CT scan with no enhancement with contrast. On MRI T1W imaging the tumours appear isointense to hypointense to white matter with expansion of the adjacent cortex. While on T2W imaging it appears as hyperintense mass-like lesions following the white matter distribution. This is due to oedema, demyelination and other degenerative changes. On the DWI/ADC there is facilitated diffusion present with lower ADC levels suggesting a higher tumour grade. There is no enhancement with contrast and if enhancement does occur it is normally indicative of a higher grade tumour. On MRI spectroscopy an elevated choline peak, low NAA peak and elevated choline: creatine ratio will be found (Winn et al, 2017). This is typical for diffuse astrocytomas and these patients may have a radiological diagnosis of a diffuse astrocytoma. This may lead to a decision to perform serial imaging and to perform a maximal resection once signs of dedifferentiation occur.
2. Late presentation only once dedifferentiation has occurred: Diffuse astrocytomas generally present with seizures, headache or in rare instances with mass effect resulting in signs of increased intracranial pressure, hydrocephalus or focal neurological deficit (Winn et al, 2017). Seizures and headaches might be treated at a lower level of care for a long period of time prior to referring the patient for imaging

to determine the cause of the seizures or chronic headaches. This can lead to late presentation only once focal neurological deficit occurs or once dedifferentiation has occurred with a resultant higher grade tumour. As the long term survival for patients with diffuse astrocytomas vary from 6 – 8 years, it is possible that these patients may demise prior to referral for imaging and work up for their presenting complaints or symptoms.

3. Inconclusive histology obtained from a biopsy of a lesion: As these lesions are not well-circumscribed and follow the white matter tracts, complete excision or surgical debulking may lead to significant neurological deficits even when using a technique such as an awake-craniotomy with extensive neuro-monitoring. For this reason a stereotactic biopsy is generally performed using frameless or a frame with neuro-navigation. As the tumour on T2W imaging is hyperintense indicative of oedema/demyelination or degenerative changes, it is possible to obtain a specimen not containing any abnormal cells with no diagnosis possible. An inadequate specimen size might also be obtained that contains only a partial representation of the cellular make-up of the tumour with a resultant incorrect histological diagnosis. A debulking procedure or subtotal resection with the aid of an awake-craniotomy would be a better option to obtain a histological diagnosis, but it is still not a guarantee to ensure minimal or no neurological deficit
4. Non-referral due to a lack of suspicion of an intracranial lesion as the cause of the symptoms of the patient.

1.e) Oligodendroglioma:

Oligodendrogliomas in the 2016 WHO classification can be subdivided into oligodendroglioma with *IDH*-mutant 1p19q co-deletion and oligodendroglioma not otherwise specified (NOS). The diagnosis of an oligodendroglioma not otherwise specified required histopathological diagnosis of a typical oligodendroglioma. The oligodendrogliomas that occur in the paediatric population seldom have *IDH*-mutations or 1p19q co-deletions and should then be annotated as an oligodendroglioma not otherwise specified. In the paediatric population great care should be taken to differentiate between oligodendrogliomas, pilocytic astrocytomas, dysembryoplastic neuro-epithelial tumours and clear cell ependymomas as they might appear quite similar histologically. (Louis et al, 2016). Oligodendroglioma can be either WHO II or WHO III grade tumours with the grade III tumours denoted as anaplastic. Anaplastic oligodendrogliomas tend to have histology that is not congruent with an oligodendroglioma secondary to the aplasia and high mitotic count and diagnosis is confirmed with the 1p19q co-deletion being present. Oligodendrogliomas account for 10 - 15% of all gliomas and 4% of all primary intracranial tumours. Oligodendrogliomas are the 3rd most common glioma. These tumours occur more to the surface of the cortex and may contain areas of calcification as these are one of the most common tumours to show calcifications, haemorrhage or cystic degeneration and is hypointense to grey matter on T1W imaging and hyperintense to grey matter on T2W imaging. Oligodendroglioma WHO II grade have a better overall survival than diffuse astrocytomas with a median survival of 10 – 12 years after diagnosis. Due to the cortical

location of the tumours, patients generally present with seizures, chronic headaches and depending on location can present with focal deficit such as a hemiparesis. These tumours occur most commonly in the 4th and 5th decades (Winn et al, 2017).

At Universitas Academic Hospital 2 oligodendroglioma WHO II tumours were diagnosed during the period 2007 – 2017. Both the patients were male and both had mass lesions in the frontal lobes. The one patient was 28 years old and the other 56 years old. The 56 year old male had a debulking procedure and with the 28 year old patient the type of surgery (biopsy vs debulking vs resection) was not indicated on the histology report.

With the new classification of oligodendrogliomas on the WHO 2016 classification it is quite possible that a multitude of oligodendrogliomas were misclassified as astrocytomas due to the astrocytic histology that some oligodendrogliomas possess.

In the neuronal and mixed neuronal-glial tumour group of the WHO 2016 classification, we find ganglioglioma, desmoplastic infantile astrocytoma and ganglioglioma, papillary glioneural tumours and rosette-forming glioneural tumours.

1.f) Ganglioglioma:

Gangliogliomas are a benign WHO I tumour that is very rare. It comprises of < 1% of central nervous system tumours and mostly occurs in children and young adults with a peak incidence in the 2nd decade of life. It has a strong predilection for the temporal lobe (85%) and is the tumour mostly associated with temporal lobe epilepsy. These tumours can however occur anywhere in the central nervous system. 5% of these tumours can exhibit aggressive behaviour and is categorized as anaplastic with a WHO III grading. This occurs very rarely and can originate de novo or due to malignant transformation of a pre-existing lesion. These tumours are comprised of variable proportions of dysplastic neuronal elements and neoplastic glial elements. Surgical resection can be curative and is the most effective treatment. Gangliogliomas have a 10-year survival rate of 84 – 93% for WHO I tumours (Song et al, 2014). No gangliogliomas have been diagnosed histologically at Universitas Academic Hospital. As gangliogliomas exhibit two cell types in the histology, namely ganglion cells (or large, mature neuronal elements) and some neoplastic neuroglial element that is mainly astrocytic, but may be oligodendroglial in nature or may even contain some elements that are compatible with a pilocytic astrocytoma, it is possible that due to the high rate of biopsies taken, a ganglioglioma might have been missed (Winn et al, 2017).

1.g) Desmoplastic infantile astrocytoma:

Only one desmoplastic infantile astrocytoma has been diagnosed histologically at Universitas Academic Hospital. It was diagnosed in a 4 year old female that presented with a tumour in her frontal lobe. She had a debulking procedure of the tumour. Desmoplastic infantile astrocytomas are rare supratentorial tumours that normally occur in the first 24 months of life. Cases have also been reported in children older than 2 years. These tumours are dural based, large and normally cystic in nature with an ominous

radiological picture. These tumours are classified as WHO I astrocytomas. Desmoplastic infantile astrocytomas are managed with gross surgical resection that might be curative. With residual tumour adjuvant chemotherapy and radiation therapy and follow up surgery might be needed (Samkari et al, 2017). As this is a rare tumour our data is consistent with that of international literature, except for the age of the patient that is double that of the usual presenting age. This was probably due to delayed detection of any neurological sequelae of the tumour and delayed referral. These tumours are very slow growing and compensation for the mass effect of the tumour might occur with delayed neurological presentation.

1.h) Papillary glioneural tumour:

Papillary glioneural tumours are a new identity that was first recognized in the 2007 WHO classification. It is a grade I tumour that is well circumscribed and consists of a complex solid-cystic structure. These tumours mostly occurs supratentorially. According the Winn et al these tumours are mostly diagnosed in young patients with a median age of 23 years. Papillary glioneural tumours are most frequent in the cerebral hemispheres, but may also occur intraventricular. These tumours have both astrocytic and neural elements on histology with characteristics histological features of a hyalinised vascular pseudopapillary architecture with cuboidal cells that appear pseudostratified and some focal collections of neurocytes and ganglion cells. Only one papillary glioneural tumour has been diagnosed at Universitas Academic Hospital in the period reviewed which would comply with the rare occurrence of these tumours as up to 2015 only 67 cases were reported in the literature (Carangelo et al, 2015).

1.i) Ependymoma:

Ependymomas are the next large group of tumours that will be reviewed. As the current discussion is on low grade gliomas, only the WHO II ependymomas will be reviewed here. The WHO III ependymomas will be evaluated under high grade gliomas.

In our review of the histological diagnosis of central nervous system tumours diagnosed at our institution, no subependymomas were identified. Subependymomas are WHO I tumours that have an indolent course and is non-invasive. These tumours occur generally in middle aged and older patients and are normally an incidental finding as it seldom causes symptoms and mass effect due to its size.

WHO I/II ependymomas according to the 2016 WHO classification can be divided into different subsets namely myxopapillary ependymoma, papillary, clear cell and tanycytic ependymoma and the new ependymoma *RELA*-fusion positive. The *RELA*-fusion ependymoma is the first genetically defined subtype to be accepted. It expresses *L1CAM* specifically and this is still under evaluation to determine possible immune-histochemical management of these tumours. These tumours accounts for the majority of supratentorial ependymomas in children (Louis et al, 2016). As previously mentioned, this molecular layer of the diagnosis is currently not available at our institution.

Myxopapillary ependymoma is a variant of spinal ependymomas that occurs almost exclusively in the conus medullaris and filum terminale with a possible origin from the ependymal glia of the filum terminale or conus medullaris. They are classified as WHO I tumours. The incidence reported is 0.05 – 0.08/100 000 persons per year. These tumours are mostly intradural and extramedullary, but may be extradural. It is a slow growing tumour and the patients report leg or back pain and up to 25% present with radiculopathy and sphincter dysfunction. These tumours might disseminate through the spinal canal. Histologically these tumours appear as papillary elements that are arranged around a fibrovascular core that forms perivascular pseudorosettes. There is often myxoid material between blood vessels and the tumour cells. Management is usually gross total resection with adjuvant radiation if metastasis or residual tumour is present.

Papillary, clear cell and tanycytic ependymomas are all WHO II grade tumours. Approximately 60% of ependymomas are located in the posterior fossa and usually arise from the floor of the fourth ventricle. The rest occur supratentorially and approximately 50% of these will be intraparenchymal. These tumours are typically heterogeneous in appearance on imaging and contain calcifications, cystic areas, areas of necrosis and haemorrhage.

Approximately 10% of paediatric brain tumours are ependymomas of which 90% will be intracranially (60% infratentorial, 30% supratentorial and 10% in the spinal cord and cauda equina). 5% of these patients will already have leptomeningeal dissemination at the time of diagnosis. The mean age at diagnosis is at 4 – 6 years of age. These tumours have a 5 year survival rate estimated at 50 – 64% and the survival is determined by the age at presentation, extent of resection and the histological grade. The histological grade has recently become a contentious subject with a general movement towards molecular markers to subdivide ependymomas. Anaplastic ependymomas have a far worse prognosis (Winn et al, 2017).

Histologically ependymoma WHO II tumours have very well differentiated cells with characteristics ependymal rosettes. These rosettes are not common, but are pathognomonic for ependymomas. Ependymomas also contain perivascular pseudorosettes that occur far more commonly. These tumours commonly contain areas of dystrophic calcification, haemorrhage and myxoid degeneration and rarely metaplasia of bone or cartilage. Radiologically these tumours characteristically spread through the foramina of Luschka and Magendie, which is radiologically distinct from medulloblastomas that are less plastic.

At our institution 10 of these tumours were histologically diagnosed. Of the 10, 4 had a WHO III designation and 6 were WHO II. Only one myxopapillary ependymoma was diagnosed in a 43 year old female that presented with a conus medullaris tumour. All of the paediatric patients between age 2 – 4 years that were diagnosed with ependymomas, had infratentorial tumours and the adult patients all had supratentorial tumours. 5 paediatric patients had a diagnosis of ependymoma with an incidence of 5.26% in the

age group 0 – 14 years. This is almost half of the expected incidence as ependymomas are supposed to comprise 10% of all paediatric central nervous system tumours.

Due to the infratentorial location of these tumours mostly in the paediatric population and the propensity to originate from the 4th ventricle, these tumours commonly present with hydrocephalus and signs of raised intracranial pressure and ataxia. Some of these symptoms can be confused for meningitis and these children can present with headache, neck stiffness and a decreased level of consciousness once decompensation occurs. They could then be incorrectly diagnosed with meningitis which is quite common in our population and have a lumbar puncture performed with dire consequences. Ependymomas also tend to infiltrate through the foramina of Luschka and Magendie and is often not completely resectable at late presentation. Many of our patients are extremely late referrals from the primary and secondary health care tiers which often result in a patient that is not suitable medically for surgery or have a very poor outcome expected.

The abovementioned factors can explain why a lower rate of ependymomas is diagnosed at our institution compared to international data. Often children with posterior fossa tumours are in such a poor neurological state and medical condition that the hydrocephalus is addressed, but they never sufficiently improve to allow surgical intervention of the tumour that is the primary pathology and a radiological diagnosis is often made in these patients with referral to oncology without any histological diagnosis.

2. <u>Other gliomas:</u>

This group of tumours in the 2016 WHO classification contains the choroid glioma of the third ventricle, an angiocentric glioma and an astroblastoma. Of these only astroblastoma have been diagnosed at our institution. As choroid gliomas of the third ventricle and angiocentric gliomas are very rare, this is compatible with international data. Only 50 cases of choroid gliomas of the third ventricle was found and the literature and 27 cases of angiocentric gliomas.

Astroblastomas are a very rare type of neuroglial tumour that accounts for approximately 0.45 – 2.8% of all neuroglial tumours. It shares histological features with both astrocytomas and ependymomas and therefor controversy still exists whether it should be deemed a separate entity. It normally has a bimodal age distribution with one peak at age 5 – 10 years and a separate peak between 21 – 30 years of age. It has a very distinct female preponderance with a male to female ratio of 1:11. It usually occur supratentorially, quite superficially, with the frontal lobe and occipital lobe being mostly affected although infiltration into the corpus callous, optic nerve and cerebellum and brainstem have been reported. The main treatment modality is that of gross total resection with adjuvant treatment proposed for tumours with high grade features. Subtotal resection is associated with a worse outcome, but even tumours with gross total resection should be followed up closely after surgical intervention due to the unpredictable nature of these tumours. The two astroblastomas diagnosed at our institution was in a three year old male in the frontal lobe and in a 47 year old female in the temporal lobe. The diagnosis in the 47 year old

female can possible be explained by late presentation due to the naturally indolent course of these tumours. As the clinical presentation of the patient is not known, it is impossible to deduce the possible latent course of this rare tumour in this specific patient.

Radiologically these tumours have a typical appearance with a supratentorial and superficial location on MRI. It is usually large with a well demarcated border and quite lobular. It has solid and cystic areas with a “bubbly” appearance in the solid component secondary to the vascular architecture. There is also inhomogeneous contrast enhancement with minimal surrounding vasogenic oedema. It is hyperintense to the white matter on FLAIR and T2W imaging, and hypointense to isointense on T1W imaging.

The great debate regarding its cell of origin is still ongoing. Histologically it is defined by the presence of perivascular pseudorosettes and very prominent perivascular hyalinization. The pseudorosettes provide a very typical “cartwheel” look. Characteristic epithelioid cells with cytoplasmic processes with blunt-ended foot processes are present that are adjacent to the basal lamina of the blood vessels. The perivascular hyalinization differs between tumours with higher grade tumours showing expansive acellular areas without tumour architecture being present. There should also be a lack of fibrillary background to diagnose these tumours. These tumours are divided into low grade/well-differentiated and high grade/anaplastic groups histologically. The low grade group contains uniform perivascular arrangement of the pseudorosettes with low to moderate numbers of mitotic figures, minimal cellular atypia with minimal vascular endothelial proliferation and mostly sclerosis of the blood vessel walls. The high grade tumours show the following:

- Focal or multifocal areas of high cellularity
- High mitotic figures
- Vascular endothelial proliferation
- Necrosis with pseudopalisading of cells.

Immunohistochemically various stains have been reported through the literature to be of value. GFAP is usually positive which is considered by some as support that it is a tumour from the astrocyte cell line. Positive stains have also been reported with vimentin, S-100 protein, NSE, EMA, cytokeratin and CAM 5.2. These reports are quite variable in the current literature.

These tumours are difficult to diagnose and a combination of histological and radiological information is required to make the diagnosis. The astroblastic features can be found in other tumours as well and the main differential diagnosis is that of an ependymoma and angiocentric glioma. The differentiation between ependymomas and astroblastomas occur with the shorter and broader end-foot plates and the hyalinised or sclerosed blood vessels. The pseudorosettes in ependymomas also occur in the tight vascular architecture associated with ependymomas and are not a rarefied space as is found in astroblastomas.

The molecular genetics is a new field and some information is currently available. These tumours show gains on both chromosome 19 and 20 that is significantly different from that of ependymomas and astrocytic tumours. This indicates that astroblastomas are a different entity to ependymoma and not just a variant. It was also noted that these tumours show losses on 9q, 10 and the X-chromosome. It was also identified that astroblastomas have an absence of *IDH* and *TP53* mutations that are known to be present in low grade glioma development (Hammas et al, 2018) .

3. <u>High grade gliomas:</u>

High grade gliomas have a WHO III or IV grading and are characterized by the ability to invade the adjacent structures. This makes a gross total resection fairly unlikely. These tumours have a poor prognosis and low 5 year survival grade.

High grade gliomas include the following tumours:

1. *Anaplastic astrocytoma, IDH-mutant (WHO III)*
2. *Anaplastic astrocytoma, IDH-wildtype (WHO III)*
3. *Anaplastic astrocytoma, NOS (WHO III)**
4. *Anaplastic oligodendroglioma, IDH-mutant and 1p19q co-deletion (WHO III)**
5. *Glioblastoma, IDH-mutant (WHO IV)**
6. *Glioblastoma, IDH-wildtype (WHO IV)**
7. *Glioblastoma, NOS (WHO IV)**
8. *Diffuse midline glioma, H3K27M mutant (WHO IV)*
9. *Anaplastic pleomorphic xanthoastrocytoma (WHO III)*
10. *Anaplastic ganglioglioma (WHO III)*
11. *Anaplastic ependymoma (WHO III)**
12. *Anaplastic ependymoma, RELA fusion-positive (WHO III).*

- Indicates high grade gliomas diagnosed at Universitas Academic Hospital. As most of the other high grade gliomas depend on a molecular diagnosis, it has been impossible so far to diagnose these tumours at our institution. Anaplastic pleomorphic xanthoastrocytomas are very rare and an absence of diagnosing this tumour at our institution can be expected.

Anaplastic astrocytomas (WHO III) and glioblastoma multiforme (WHO IV) is the most common primary brain tumour in adults and account for approximately 2% of all malignancies in adults. On CBTRUS glioblastoma had an incidence of 14.9% and all other malignant gliomas an incidence of 10.9%. Hussain et al documented an incidence of 37% glioblastomas multiforme all of which were supratentorial. Their mean age for diagnosis of glioblastoma was 46.48 years vs the 64 years in international data. Malignant central nervous system tumours are the leading cause of death from solid tumours in children and the third leading cause of death in adolescents and young adults aged 15 – 34 years. Anaplastic astrocytomas generally develop around the age of 40 years. The average age of diagnosis of a glioblastoma is 53 years of age with a peak incidence between 65 – 74 years of age (Winn et al, 2017).

These tumours mostly occur in the cerebral hemispheres and can originate from low grade gliomas or start de novo as previously noted with *IDH*-wildtype vs *IDH*-mutant.

Anaplastic astrocytomas tend to dedifferentiate to glioblastomas. These tumours often recur locally even after gross total resection due to the microsatellites of tumour cells that scatter through the normal brain parenchyma. High grade gliomas tend to spread into eloquent areas of brain which makes gross total resection impossible without causing grave morbidity to the patient.

On review of imaging for these tumours, MRI is the modality of choice. CT can be utilized though to delineate acute haemorrhage and calcifications in the tumours. High grade gliomas generally present on T1W imaging as hypodense areas that are irregular with various degrees of contrast enhancement and oedema. A large irregular ring enhancing area surrounding areas of presumed necrosis is quite common. It is however imperative to keep in consideration that anaplastic astrocytomas and glioblastomas might present without any contrast enhancement initially. With glioblastoma a typical “bear-claw” pattern of oedema can be seen on T2W FLAIR imaging (Winn et al, 2017).

Giant cell glioblastomas are a variant of glioblastoma *IDH*-wildtype and was previously named a monstro-cellular tumour due to the macro size of the tumour cells. Genetically it contains a very high frequency of *TP53* mutations in 70 – 90% of cases and less commonly *PTEN*-mutations at 33% and *TERT*-mutations in 25% of cases. It represents approximately 5% of all glioblastomas and tends to occur in younger individuals. It usually occurs in the cerebral hemispheres, but extradural and spinal leptomeningeal cases have been reported (Winn et al, 2017).

The molecular biology of glioblastoma multiforme has evolved over the last couple of decades. It has been determined that malignant transformation of gliomas is the result of the sequential accumulation of several distinct genetic mutations and some deregulation of certain growth factor signalling pathways due to failure of the cell cycle control mechanisms or a combination of both. Glioblastomas have always been categorized in two groups, namely primary and secondary glioblastomas. Morphologically these subtypes are the same and react similarly to conventional treatment. The difference between primary and secondary glioblastomas is on a molecular and genetic level which causes a different response between the two to targeted molecular therapies.

Primary glioblastomas occur typically in patients older than 50 years and between 40 – 50% contain *EGFR* amplification and mutations to form a mutant form named *EGFR (viii).* This mutant form of *EGFR (viii)* is present in 20 – 50% of these *EGFR*-gene amplified glioblastomas. *EGFR (viii)* lacks the extracellular ligand binding domain and is currently an important therapeutic target for kinase inhibitors, peptide vaccines and immunotoxins. This *EGFR* amplification correlates well with a very poor survival or prognosis. There is often loss of heterozygosity of chromosome 10q. These tumours also have deletion of the phosphatase and tensin homologue on chromosome 10 and deletion of chromosome p16 (Lieberman, 2017).

Secondary glioblastoma however occur in younger patients and originate from dedifferentiation of an anaplastic astrocytoma (WHO III) or a diffuse astrocytoma (WHO

II) to a glioblastoma. These secondary glioblastomas are reported to occur much less frequently than primary glioblastoma. It is characterized by *TP53*-suppressor gene mutations, over expression of platelet derived growth factor receptor (PDGFR), abnormalities in the p16 and retinoblastoma (Rb) pathways and also loss of heterozygosity of chromosome 10q. *IDH*-mutations are present in approximately 80% of secondary glioblastomas and only about 5% of primary glioblastoma. The *IDH*-mutation might be associated with a better prognostic group in the realm of glioblastoma (Lieberman, 2017).

Mutations in tumour suppressor genes that control the cell cycle have also been observed. Most commonly were mutations in TP53 that were more common in secondary glioblastoma and *PTEN* that was more common in primary glioblastoma. *PTEN* negatively regulates the phosphatidylinositol-3-kinase (PI3K) pathway and is inactivated in 40 – 50% of primary glioblastoma. This inactivation is very rarely seen in lower grade astrocytic tumours. This compromised function may add to gliomagenesis by disrupting the regulation of proliferation, stem cell self-renewal, angiogenesis and migration as well as migration, invasion and the regulation of other tumour suppressor pathways (Winn et al, 2017).

O6-methylguanine-DNA methyltransferase (MGMT) is important for the functioning of the O06-methylating agents such as temazolomide as it is involved in the DNA repair of these agents. This MGMT promoter methylation is important in the prognostication of patients with glioblastoma as these patients have a better median survival of 22 months vs 12 months in the absence of MGMT promoter methylation. The MGMT promoter methylation is present in approximately 50% of glioblastoma, but more so in secondary glioblastoma (Lieberman, 2017). Approximately 75% of glioblastomas have the telomerase reverse transcriptase gene (*hTERT*). By itself this mutation does not appear to have any prognostic implication for glioblastomas, but with the MGMT promoter methylation it has. It seems as if the MGMT promoter methylation relies on a concomitant mutation in *hTERT* to signify a favourable prognosis with an improved response to temazolomide (Lieberman, 2017).

These mutations have opened up a window to create more specific gene-directed therapies to manage glioblastoma. It creates the opportunity to create cell-based and check-point inhibitors to better manage patients with glioblastoma to obtain a, hopefully, longer 5-year survival figure as it is currently at < 10%.

One giant cell glioblastoma was identified at our institution in a 56 year old male in the parietal lobe after a biopsy of the lesion was performed. 29 glioblastoma multiforme were diagnosed in total with the incidence then of the giant cell glioblastoma at 3.45% which is congruent with international literature reviewed.

Only two glioblastoma multiforme had genetic studies performed and one showed *IDH*-mutant in a 37 year old male patient and one showed *IDH*-wildtype in a 44 year old female. The rest of the glioblastomas were classified as NOS. Glioblastoma incidence at our institution was 8.38% if the age group 0 – 14 years old was excluded for all central

nervous system tumours diagnosed. Glioblastoma comprised of 19.78% of all the malignant tumours diagnosed at Universitas Academic Hospital.

Anaplastic astrocytomas (WHO III) are also diffusely infiltrating and malignant primary central nervous system tumours. It occurs at a median age of 41 years. According to the 2016 WHO classification these tumours have been subdivided into three groups, namely anaplastic astrocytoma *IDH*-mutant, anaplastic astrocytoma *IDH*-wildtype and anaplastic astrocytoma NOS (Louis et al, 2016). The histological definition encompasses characteristics of nuclear atypia, increased cellularity and significant mitoses with proliferative activity, the presence of glial markers like GFAP, the absence of neuronal markers and no endothelial proliferation or necrosis (typical of glioblastoma multiforme). Approximately 25% are thought to originate de novo with the remaining 75% resultant of dedifferentiation of a previously low grade tumour. The median overall survival is estimated at 3 years with a 5 year survival rate of approximately 28%. Only 46% of these tumours will initially present with seizures and the other presenting symptoms depend on the location of the tumour.

There are a couple of risk factors associated with the formation of anaplastic astrocytomas including early ionizing radiation, neurofibromatosis (both types), Li-Fraumeni syndrome and tuberous sclerosis.

On imaging these tumours are best seen on MRI imaging and are optimally visualized with gadolinium administration. It is an ill-defined tumour that is hypointense on T1W imaging and hyperintense on T2W imaging with significant surrounding vasogenic oedema best seen on the FLAIR sequence. There is usually nodular enhancement of the tumour on imaging, but up to 33% will show no enhancement with contrast. If the tumour enhances with contrast it usually implies a higher grade tumour even if a biopsy indicates a low grade glioma.

The histology of these tumours normally contains areas of low and high grade tumour though to be indicative of the usual progression from a low grade to a high grade tumour. Therefor sampling errors may occur with biopsy of these tumours. There is also a great variation between pathologists on the grading of astrocytic tumours into low grade and high grade and the grading is poorly reproducible. Thus the molecular classification is reproducible and is now more commonly used to diagnose these tumours and to guide the clinical decision process.

With regard to the molecular markers, mutations in *TP53* and *ATRX* is common in >70% of anaplastic astrocytomas, whereas the anaplastic oligodendrogliomas are identified by the 1p19q co-deletion mutation. This differentiates between the two tumours in a consistent and definitive manner. The *ATRX* gene mutation is mutually exclusive from the qp19q co-deletion mutation and *TERT* promoter mutations. *IDH*-mutations are a critical part of the pathogenesis of anaplastic astrocytomas and can involve both *IDH1/2.* These mutations are currently under investigation in clinical trials to determine whether targeting

the mutation will therapeutically be beneficial. If an *IDH*-mutation is present in an anaplastic astrocytoma it is a positive predictor of a better outcome (Grimm et al, 2016).

On review of the anaplastic astrocytomas diagnosed at Universitas Academic Hospital, 15 anaplastic astrocytomas were diagnosed. Of the 15, nine were diagnosed with a stereotactic brain biopsy. This places the incidence of anaplastic astrocytomas at our institution at 3.40%. It is quite possible that due to the high rate of biopsy only taken, that these tumours might represent glioblastomas. With stereotactic biopsy it is possible to biopsy a part of the tumour that is of lower grade than the actual tumour itself. Neuro-navigation is of the utmost importance when taking a biopsy and then surgical planning as well to ensure that the radiologically highest grade of the tumour is the part where a biopsy is taken. This normally implicates the area of highest contrast uptake. Neuro-navigation systems generally have an accuracy of up to 1.8mm (Winn et al, 2017). The accuracy depends on the quality of the imaging, the positioning of the patient and the registration of the neuro-navigation system. Intra-operative brain shifts also occur that can only be determined by real-time imaging like intra-operative MRI and ultrasound.

Most of the high grade gliomas present with significant surrounding oedema that is invariable managed with intravenous dexamethasone. In our setting the imaging is often acquired prior to, or shortly after, dexamethasone has been administered for the oedema. This renders our imaging during stereotactic biopsy inaccurate due to the deformation of tissue and brain shift that would have occurred secondary to the resolution of the surrounding oedema. Even with careful planning it is quite possible that the 9 patients that had a biopsy diagnosis of an anaplastic astrocytoma might have had a higher grade glioma.

Anaplastic oligodendroglioma is a rare tumour and comprises of < 2% of all primary brain tumours and has an incidence of < 4 per 1 million people per year. These tumours have a bimodal distribution and have a peak incidence at 6 – 12 years of age and another at 35 – 44 years of age. Anaplastic oligodendroglioma are rare in paediatric patients and < 7.5% of all anaplastic oligodendrogliomas is diagnosed in childhood. These tumours are supratentorially in > 90% of cases. Quite a high number of oligodendrogliomas are anaplastic at 23%. These tumours can appear *de novo* or from dedifferentiation of a WHO II oligodendroglioma. Leptomeningeal invasion, drop metastasis and spreading outside the central nervous system are quite common, but might be secondary to the longer survival rate of patients with these tumours (Winn et al, 2017).

Histologically these tumours have both oligodendroglial and astrocytic features with increased atypia and mitoses. The molecular marker associated with the diagnosis of an oligodendroglioma is the 1p19q co-deletion which is pathognomonic. This co-deletion is associated with an improved response to treatment with an improved survival rate.

At our institution two anaplastic oligodendrogliomas have been diagnosed. The first was in a 74 year old female that presented with a supratentorial lesion and a biopsy of the lesion was performed and an anaplastic oligodendroglioma diagnosed. The second

patient was a 14 year old male patient that presented with a frontal lobe lesion and a debulking procedure was done and an anaplastic oligodendroglioma diagnosed. 0.45% of the central nervous system tumours diagnosed at Universitas Academic Hospital were anaplastic oligodendrogliomas.

Anaplastic ependymomas have a WHO III grading in the 2016 WHO classification system. Two anaplastic ependymomas were diagnosed at Universitas Academic Hospital during the period 2007 – 2017. The first patient was a 26 year old male with a supratentorial anaplastic ependymoma and the second a 2 year old female patient with an infratentorial anaplastic ependymoma.

Histologically these tumours are characterized by pleomorphism, multi-nucleation, giant cells, mitotic figures, vascular changes and areas of necrosis.

Worldwide there is still no consensus whether the anaplastic variant has a poorer outcome and prognosis than the WHO II variant. What is known is that the anaplastic *RELA* fusion-positive variant is associated with supratentorial ependymomas in paediatric patients and that the *RELA*-fusion positive variant does have a poorer prognosis and long term survival rate.

4. <u>Meningiomas:</u>

The incidence of meningiomas varies in the literature available, but is generally considered to be between 19 – 30% of all primary intracranial tumours. In CBTRUS the incidence is at 36.2% for WHO I – II meningiomas and at 0.5% for malignant (WHO III) meningiomas. Hussain et al found meningiomas to comprise 8.42% of all central nervous system tumours in their registry over a 4 year period.

Meningiomas originate from the arachnoid cap cells that are the cells of the arachnoid villi that are in close contact with the venous endothelium. These cells are at the densest at the trilaminar meninges. Cap cells are at their highest concentration at the superior sagittal sinus, cavernous sinus, tuberculum sellae, lamina cribrosa, the foramen magnum and the torcular herophili.

Meningiomas are found most commonly in the following locations:

1. Parasagittal (20.8%)
2. Convexity (15.2%)
3. Tuberculum sellae (12.8%)
4. Sphenoidal ridge (11.9%)
5. Olfactory groove (9.8%)
6. Falx cerebri (8%)
7. Lateral ventricle (4.2%)
8. Tentorium cerebelli (3.6%)
9. Middle fossa (3%)

Meningiomas are extra-axial tumours that are usually encapsulated, globular and slow growing and attached to the dura. Meningiomas have a typical radiological appearance with hyperostosis of the skull on plain X-ray and calcifications in up to 10% of tumours. On CT scan these tumours appear isodense to slightly hyperdense compared to the brain with homogenous enhancement with contrast. On MRI the tumour will be isointense on T1W and isointense to hyperintense on T2W imaging with vivid enhancement with contrast. Oedema might be present surrounding the tumour and this can be due to venous stasis or occlusion, compressive ischaemia, aggressive growth, parasitasion of pial vessels, secretory subtype or the production of vascular endothelial growth factor (VEGF) (Winn et al, 2017).

According to the 2016 WHO classification multiple subtypes of meningiomas occur ranging from a WHO I to a WHO III grading (Louis et al, 2016). The subtypes are as follows:

Table 6: Meningioma subtypes

WHO grade I	WHO grade II	WHO grade III
Meningothelial*	Chordoid	Rhabdoid
Fibrous*	Atypical*	Anaplastic (malignant)
Transitional*	Clear cell	Papillary*
Psammomatous*		
Angiomatous*		
Microcystic*		
Secretory*		
Lymphocyte-rich		
Metaplastic		

*indicates the subtypes of meningiomas diagnosed histologically at Universitas Academic Hospital for the period 2007 – 2017.

Meningothelial meningiomas (WHO I) are the most common subtype of meningioma diagnosed according to the literature. Histologically it consists of syncytial and epithelial cells with both indistinct cell borders and classic whorls. These tumours might contain a few psammoma bodies. Complete resection is curative for these tumours, but complete resection depends on the size of the tumour, location and proximity to adjacent structures to ensure maximal safe resection. No adjuvant treatment is required and if a piece of residual tumour was left, it can be monitored with serial imaging and repeat complete resection or a further debulking procedure attempted at a later stage.

At our institution 52 of the 107 meningiomas diagnosed were meningothelial meningiomas. This equates to 48.60% of all the meningiomas diagnosed at our institution. All the meningiomas diagnosed at our institution were in the age groups older than 19 years.

Fibrous meningiomas (WHO I) are firm tumours that consist of spindle cells with indistinct cell boundaries. These tumours normally have a sheet-like architecture and often do not contain whorls or lobules. Fibrous meningiomas might resemble schwannomas or solitary fibrous tumours, but stain focally positive for EMA and often contain thick bundles of

collagen. Only 8 fibrous meningiomas were diagnosed at our institution for a percentage of 7.48% of all the meningiomas diagnosed here.

Transitional meningiomas (WHO I) contain both meningothelial and fibrous features with generally prominent whorls, psammoma bodies as well as clusters of syncytial cells. Transitional meningiomas are a mix between meningothelial and fibrous meningiomas. At our institution 24 transitional meningiomas were diagnosed. These tumours comprised 22.43% of all meningiomas diagnosed at Universitas Academic Hospital.

Psammomatous meningiomas (WHO I) are normally find in the spinal region and contains numerous psammoma bodies. Two psammomatous meningiomas were diagnosed at our institution. The first was in a 29 year old female in the posterior fossa and the second in a 63 year old female in the parasagittal area. None were diagnosed in the spinal region. The meningiomas that were diagnosed in the spinal region were transitional meningiomas. Psammomatous meningiomas comprised 1.87% of the meningiomas diagnosed at our institution.

Angiomatous meningiomas (WHO I) comprise 2% of all meningiomas in the international literature. With this subtype, the vascular component should exceed 50% of the total volume of the tumour. Histologically meningothelial cells are wrapped around small blood vessels in the presence of large blood vessels. The average Ki67 index is approximately 2%. These tumours do not recur if a complete resection was achieved. Radiologically it needs to be distinguished from a haemangioblastoma. Histologically angiomatous meningiomas can be distinguished from haemangioblastomas as the latter stain positive with inhibin and NSE. Four angiomatous meningiomas were diagnosed at Universitas Academic Hospital. This comprised 3.74% of all meningiomas histologically diagnosed.

The *microcystic meningiomas* (WHO I) rarely have extensive microcystic formation and consist of cells that have elongated processes with a loss of the myxoid background. Overall the tumour resembles micro-cysts histologically. It has focal “classic” features with variable pleomorphism of the cells without any cords or trabeculae and an absence of inflammatory infiltrate. On electron microscopy extracellular micro-cysts are seen (Kresak et al, 2019). 5.61% (n = 6) microcystic meningiomas were diagnosed at Universitas Academic Hospital.

Only one *secretory meningioma* was histologically confirmed in the period 2007 – 2017. Secretory meningiomas (WHO I) secrete an eosinophilic substance and may also secrete CEA (carcino-embryonic antigen - a tumour marker that might be elevated by smoking, infections, inflammatory bowel disease, pancreatitis and liver cirrhosis. It is mainly used to monitor the response to treatment of gastro-intestinal, breast and lung malignancies. It is also associated with certain types of thyroid and ovarian cancers). These tumours may also contain cytological atypia. Despite the cytological atypia that may occur, it is still graded as a WHO I grade tumour (Kresak et al, 2019).

There was also one biopsy that was reported as “suggestive of a meningioma”. As this histology was obtained with a biopsy, it is possible that the sample size was too small to

facilitate a definitive histological diagnosis and that only some of the stains and histological evaluation could be performed without defining the subtype of meningioma or confirmation of the diagnosis of a meningioma.

Eight *atypical meningiomas* were diagnosed during this period at our institution with one just defined as an atypical meningioma and four defined as atypical transitional meningiomas. Atypical meningiomas are WHO II grade tumours that comprise a total of 5 – 15% of all meningiomas confirmed histologically. The diagnostic criteria consist of:

1. 4 – 19 mitotic figures per high powered field OR
2. Brain invasion OR
3. Three of the following histological features;
    a. Increased cellularity
    b. Small cells with a high nucleus to cytoplasm ratio
    c. Large and prominent nucleoli
    d. Random or sheet-like growth with loss of the lobular architecture
    e. Foci of “spontaneous” or geographic necrosis.

It is important to take into account that neither invasion of the bone, dura or soft tissue or pleomorphic or atypical nuclei affects the grade of these tumours. The Ki67 is normally greater than 4%, but less than 20%. These tumours have an association with previous radiation and up to 29% will recur in comparison to grade I meningiomas where recurrence is only about 9%. The 10 year survival is 79% with 26% of these tumours that will progress to a malignant subtype. Up to 85% of atypical meningiomas will stain positive for progesterone receptors.

Atypical meningiomas can be confused with a hemangiopericytoma, malignant meningioma, meningioma with atypical features that are insufficient to fulfil the criteria as stated above and necrosis due to previous radiation therapy (Kresak et al, 2019).

The atypical transitional meningiomas had both meningothelial and fibroblastic features, but fulfilled the criteria as stated above to be classified as atypical. These atypical meningiomas comprised 7.48% of the total of meningiomas diagnosed histologically at our institution which is on par with the international average.

Only one WHO grade III meningioma was diagnosed at our institution for the period reviewed. It was diagnosed by a debulking procedure in a 71 year old female patient that presented with a lesion in the tentorium cerebelli, but on the superior aspect of the tentorium. It was classified as a *papillary meningioma* WHO III. These WHO grade III meningiomas are aggressive tumours that have a recurrence rate of up to 50% and have the ability to metastasize. Papillary meningiomas are mostly diagnosed supratentorially, but have been found in the posterior fossa as well as in the spinal cord.

Malignant meningiomas are still not well defined, but are considered when some of the following are present:

1. In the presence of distal metastasis. This normally involves the liver, lung, pleura and lymphatic system.
2. With frank parenchymal infiltration of the underlying brain parenchyma
3. If it appears histologically similar to a sarcoma, carcinoma or melanoma
4. In the presence of a mitotic index of > 20 per high power field.

Histologically these tumours have papillary features that are most commonly found near the edges of the tumour and can be focal, but should comprise at least 50% of the tumour to justify a diagnosis of papillary meningioma WHO III. On cross section through the papillae an ependymoma-like histology with perivascular pseudorosettes. The histological picture might be heterogeneous with areas that might be typical for a classic meningioma or there might be absence of any typical meningothelial features like whorls, psammomatous bodies and nuclear pseudo-inclusions. It often contains features compatible with an atypical meningioma, for example hypercellularity, brain invasion, increased mitosis and prominent nucleoli. These tumours can stain positive for EMA (epithelial membrane antigen) (varied), NSE (neuron specific enolase), progesterone receptors and vimentin. It stains negative for GFAP (glial fibrillary acidic protein) and keratins. Different hormone-based receptors have been identified in meningiomas, namely progesterone, oestrogen, dopamine and growth hormone mainly. These receptors have been utilized as specific treatment targets with varying success. The presence of progesterone receptors have been deemed a good prognostic factor, where as if the oestrogen receptors are more dominant, it is usually associated with a higher grade tumour with a more aggressive growth pattern (Winn et al, 2017).

Radiologically these tumours show irregular borders with heterogeneous enhancement and peritumoural oedema on MRI imaging. The management of these tumours is gross total resection combined with radiotherapy post-operatively and radiosurgery for residual tumour. These tumours need to be differentiated from choroid plexus papilloma, ependymoma, glioma and metastatic carcinoma.

The prognosis of these tumours is determined by the complete surgical resection (most favourable prognostic indicator), a low Ki67 index and the presence of progesterone receptors in the tumour (Kresak et al, 2019).

5. <u>Embryonal tumours:</u>

The 2016 WHO classification includes medulloblastomas (histological and molecular diagnosis), embryonal tumours with multi-layered rosettes, medulloepithelioma, CNS neuroblastoma, CNS ganglioneuroblastoma, atypical teratoid/rhabdoid tumour and CNS embryonal tumour with rhabdoid features.

Medulloblastomas comprise of up to 10% of all paediatric brain tumours. It occurs almost exclusively in the infratentorial space in paediatric patients and may spread along the leptomeninges. According to CBTRUS 9.2% of brain tumours in the age group 0 – 14 years comprise of medulloblastomas. Up to 30% of medulloblastomas occur in the adult population mostly in the age group younger than 40 years. There is a bimodal peak in the

paediatric population at the age of 3 – 4 years and again at 8 – 10 years of age. It has a slight male preponderance.

Medulloblastomas are defined as a WHO grade IV embryonal tumour that are multipotent, but predominantly undifferentiated or with neuronal differentiation (Pfister et al, 2010).

Radiologically medulloblastomas need to be differentiated from ependymomas, atypical teratoid/rhabdoid tumours and pilocytic astrocytomas. Further down the differential are exophytic brainstem gliomas, choroid plexus papillomas and teratomas in infants. Up to 75% of medulloblastomas originate from the vermis and then invade the fourth ventricle. In adults it originates most commonly from the cerebellar hemisphere. Medulloblastomas do not typically extend into the basal cisterns like ependymomas through the foramina of Luschka and Magendie. On CT imaging these tumours are hyperdense and extend from the vermis with compression of the fourth ventricle with resultant obstructive hydrocephalus. There is clear enhancement with contrast with calcifications present in up to 10% of these tumours. On MRI imaging these tumours are hypointense to grey matter on T1W imaging with heterogeneous contrast enhancement present in 90% of these tumours. On T2W imaging these tumours are typically iso- to hyperintense to grey matter and appear heterogeneous secondary to cyst formation, necrosis and calcifications. On MRI spectroscopy there is elevated choline peaks and decreased creatine and N-acetyl acetate peaks. Some tumours show elevation of the lactic acid and lipid peaks (Millard et al, 2016).

Medulloblastomas in the 2007 WHO classification were classified as:

1. Classic medulloblastoma
2. Desmoplastic/nodular medulloblastoma
3. Medulloblastoma with extensive nodularity (MBEN)
4. Anaplastic medulloblastoma
5. Large cell medulloblastoma (Louis et al, 2007).

The classic variant occurs most frequently and has small to medium, round hyperchromatic nuclei with minimal cytoplasm. Homer-Wright nuclei are sometimes intermingled with these cells and can be associated with high mitotic activity and an increase in nuclear pleomorphism. The desmoplastic variant has widespread desmoplasia and also contains nodular, reticulin-poor islands of neurocytic differentiation that are surrounded by densely packed mitotically active cells. The MBEN variant has a much expanded lobular appearance with prominent reticulin free zones. These reticulin free zones are elongated and rich in a neutropil-like tissue. The desmoplastic/nodular and MBEN types are associated with an overall improved prognosis compared to the classic type. The large cell and anaplastic variants in general have a dismal prognosis. These two types consist of large, round vesicular nuclei with very prominent nucleoli, hence the large cell variant name. The large cell and anaplastic variants contain atypical mitotic forms and abundant apoptotic bodies with marked nuclear pleomorphism and a high degree of anaplasia (Millard et al, 2016).

In the 2016 WHO classification the molecular subtypes are included, namely:

1. Medulloblastoma, *Wnt* activated
2. Medulloblastoma, *Shh*-activated and *TP53*-mutant
3. Medulloblastoma, *Shh*-activated and *TP53*-wildtype
4. Medulloblastoma, non *Wnt/*non-*Shh*
    a. Medulloblastoma, group 3
    b. Medulloblastoma, group 4
5. Medulloblastoma, NOS (Louis et al, 2016).

The *Wnt* subgroup indicates the wingless subgroup. In a meta-analysis performed 97% of the *Wnt* pathway tumours histologically were classic medulloblastomas and 89% of the desmoplastic/nodular medulloblastomas were *Shh* (Sonic hedgehog) molecular subgroup. The group 3 and group 4 medulloblastomas had neither *Wnt* nor *Shh* genetic mutations. No specific molecular basis has been found for group 3 and group 4 medulloblastomas. The medulloblastoma NOS indicates a lack of molecular testing according to the molecular subtypes. In these cases the histological subtype can however still be used. The molecular subgroup identification lends itself to a more accurate predictor of outcome and the tumour's clinical behaviour than the histological subgroup. Medulloblastomas also retain the molecular subgroup affiliation even during recurrence and metastasis different to other tumours that often have a change in molecular subclass with recurrence or metastasis (Millard et al, 2016).

The *Wnt* pathway tumours secrete glycoproteins that act through signal transduction to develop different aspects of embryonal development. During unregulated activation of the *Wnt*-pathway, there is accumulation of β-catenin with aberrant upregulation of the transcription with resultant oncogenesis. This pathway only represents about 10% of the sporadic medulloblastomas. These tumours are more common in children and adults and less so in infants with no predilection for a specific gender. Less than 10% of these tumours present with metastatic disease and these tumours have an excellent 5 year survival rate at > 95% for children and 100% in adults. *TP53* mutations are commonly found in these tumours, but this does not impact the outcome as in the *Shh* subgroup. There is an increased risk of *Wnt* activated medulloblastomas in patients with familial adenomatous polyposis as the loss of the functional adenomatous polyposis coli (APC) gene is part of the process to degrade β-catenin and thus the loss of the APC gene leads to accumulation of β-catenin in the nucleus and cytoplasm. This risk is increased compared to the risk in the general population (Millard et al, 2016).

The *Shh*-pathway tumours comprise approximately 30% of all medulloblastomas and are found commonly in patients < 3 years old and those above the age of 16 years. There is also no predilection for either gender with this subgroup. These tumours are more likely to metastasize than the *Wnt*-subgroup, but less so than the group 3 and group 4 tumours who often present with metastasis. The prognosis differs between the age group that these tumours occur in as well as the underlying histological diagnosis. In infants with a desmoplastic/nodular tumour the overall 10 year survival is at 84% compared to the 51%

in children and 34% in adults who do not have a desmoplastic/nodular histology. However, if an associated *TP53* mutation is present, the outcome is significantly worse. This mutation is mostly present in the age group 5 – 18 years of age, which is the most infrequent age group for these tumours to occur in.

The group 3 and group 4 subtypes has had no genetic driver mutation identified yet and has a clear male predominance. Approximately 30% of the patients with these subgroups present with distant metastasis at the time of diagnosis. Group 3 and group 4 subtypes have very distinctly different clinical courses and genomic features. The group 3 subtype comprise of approximately 30% of all medulloblastomas and are likely to have a high-level expression and amplification of *MYC.* This tumour occurs more frequently in infants and children and has the least favourable outcome of all the medulloblastomas with a 10 year survival of 39% in infants and 50% 10 year survival in children. Group 4 medulloblastomas represent approximately 35% of all medulloblastomas and is the most common subtype. The group 4 medulloblastomas have a similar prognosis than that of the *Shh*-subgroup with a peak incidence in late childhood and early adolescence. The outcome in this subgroup is significantly worse with distant metastasis present or with *MYCN* amplification (Millard et al, 2016).

At our institution none of the medulloblastomas had molecular testing performed so far and the diagnosis was classified according to the 2007 WHO classification. A total of 21 medulloblastomas were diagnosed at our institution with 6 in the age group 0 – 4 years, 13 in the age group 5 – 19 years old and 2 in the age group 20 – 34 years of age. It comprised 16.38% of all CNS tumours diagnosed in the age group 0 – 19 years that can be subdivided into 20.69% of all CNS tumours in the age group 0 – 4 years and 14.94% in the subgroup 5 – 19 years of age. 13 of these tumours had no histological subtype specified and two were classified as classic medulloblastomas, 2 as desmoplastic medulloblastomas, 2 as desmoplastic/nodular medulloblastomas and only one as anaplastic/large cell subtype. One metastatic medulloblastoma was confirmed in a 7 year old male in the spinal cord. The tumour burden ascribed to medulloblastomas in our population group was much higher than in the international data with 20.64% in the paediatric group at our institution versus approximately 10% in the world literature. This might be due to the location of the tumour in the midline of the posterior fossa with a high probability of a gross total resection and the goal to improve the survival of the child with maximum resection of the lesion leading to a more aggressive surgical approach in these patients. With histological confirmation of the tumour type it is also possible to provide adjuvant radiation (if the child is older than 3 years) and chemotherapy with a higher overall 5 year survival rate. Due to the short prelude to diagnosis which is estimated to a weeks to a couple of months, the general medical and nutritional condition of these patients on presentation often allow surgical intervention with tumour resection/debulking. All the medulloblastomas diagnosed histologically at our institution had either a debulking procedure or a gross total resection performed, except for the metastatic spine lesion that only received a biopsy probably due to fear of further neurological impairment with complete surgical resection.

There were also 3 diagnoses of *embryonal tumours with multiple lines of differentiation* that we will discuss under the heading of medulloblastomas, as all three occurred in the age group 20 – 34 years of age. All three the patients were males with 2 of the tumours occurring supratentorially and one was located infratentorially. It is difficult to assess the full histological classification of these tumours as the full histological report was not available on the data provided by NHLS and there was no specialist neuropathologist that evaluated these tumours. In the absence of a specialist neuropathologist and molecular testing, these tumours might fall into any category of the embryonal tumours according to the 2016 WHO classification.

Atypical teratoid/rhabdoid tumours (AT/RT) are embryonal tumours also classified as WHO IV. These tumours are very rare and comprise about 1.3% of CNS tumours in the paediatric population and 6.7% of CNS tumours in patients under the age of 2 years. These tumours have a predilection for the posterior fossa with 38 – 65% of these tumours occurring infratentorially and 27 – 62% supratentorially. Between 4 – 8% will occur in multiple sites in the CNS at the time of diagnosis. The 1 year survival rate is at 71% and the 5 year survival rate at 28%. With the dismal prognosis associated with AT/RT the reported mean survival rate is between 6 – 15 months. The survival is improved with gross total resection of the tumour, but these tumours are usually large and situated in difficult accessible areas which makes gross total resection in most cases impossible (Meyers et al, 2006).

Radiologically these tumour appear heterogeneous due to the different cell types present in these tumours and the areas of necrosis, haemorrhage with or without calcification that can be seen. These tumours appear isointense to hyperintense to the grey matter on T2W imaging and on the FLAIR, especially in the solid portions. It enhances non-homogenously with contrast on the T1W series with contrast and shows restricted diffusion on the DWI and ADC. On spectroscopy there is an elevated peak of choline and decrease in the NAA peak. These features are quite similar to those ascribed to the tumour group previously known as primitive neuro-ectodermal tumours. Up to 15% of these patients will have leptomeningeal spread at the time of diagnosis and up to 34% will develop leptomeningeal spread in the first year after diagnosis. The leptomeningeal spread is determined by performing a cranial-axial MRI and obtaining CSF for cytology (Winn et al, 2017).

Histologically these tumours consist of rhabdoid cells with eccentric round nuclei with prominent nucleoli and fibrillary or eosinophilic cytoplasm. It usually contains multiple mitotic figures with associated necrosis, haemorrhage and ill-defined margins with infiltration of the adjacent brain. It also contains varying amounts of small round blue cells, malignant mesenchymal spindle-shaped cells as well as cells with epithelial differentiation. There are no germ cell and tissue differentiation present that is associated with teratomas. In up to 70% of these tumours there might be features associated with PNET's leading to the often misdiagnosis of the tumours as PNET's (Meyers et al, 2006). Molecularly these tumours showed an almost uniform genetic alteration with most alterations occurring in the *SMARCB1 (INI1/hSNF5)* locus on chromosome 22q11. This

results in the loss of the SMARCB1 protein expression. These alterations might be homozygous deletions, copy-number neutral loss of heterozygosity and heterozygous deletions. These genetic alterations can be proven in up to 75% of AT/RT with FISH and genomic sequencing and in a 100% with high-resolution methods. Other AT/RT may have an inactivation of the ATPase subunit of the *SMARCA4 (BRG1)* gene located on chromosome 19p13:2 (Pfister et al, 2010). According to the 2016 WHO classification, AT/RT are now defined by the alterations in either *INI1* or rarely *BRG1* and without these alterations the diagnosis of a tumour with rhabdoid features without these alterations will be classified as a CNS embryonal tumour with rhabdoid features (Louis et al, 2016). Only one AT/RT was confirmed histologically at Universitas Academic Hospital in the time frame evaluated. The tumour occurred in the spinal cord of a 5 month old infant intradural and intramedullary and only a biopsy was performed. This equates to 3.45% of all the central nervous system tumours that were diagnosed in the age group 0 – 4 years. This relates to 12.5% of all CNS tumours diagnosed in the age group 2 years and younger this might be due to the small amount of tumours histologically confirmed in this age group. Only eight central nervous system tumours were histologically confirmed in this age group which might indicate the reluctance to perform large and extensive surgeries in this population, the lack of comfort of the surgeon performing these surgeries in patients so young, non-referral from the primary health care and late presentation with patients not in a suitable general medical and nutritional state to enable such extensive surgical procedures in patients so young.

As most of the tumours were diagnosed prior to the publication of the 2016 WHO classification, some of the tumours were still classified as CNS primitive neuro-ectodermal tumours or PNETs. These are also embryonal tumours with a WHO IV grading and have a very poor prognosis with most patients showing a very poor response to standard therapies. This is significantly more so in early childhood when craniospinal radiotherapy is avoided. These tumours were divided into CNS neuroblastoma, CNS ganglioneuroblastoma, medulloepithelioma and ependymoblastoma. At our institution one central PNET (no other histological diagnosis provided), one ganglioneuroblastoma, one metastatic neuroblastoma and two ganglioneuromas were diagnosed. No molecular diagnosis was available in any of these tumours. The two ganglioneuromas diagnosed at out institution is categorized in this group due to a similar origin from neural crest cells as the neuroblastoma and ganglioneuroblastoma, with the ganglioneuroma being the most differentiated of the spectrum and neuroblastomas the least differentiated (Perrino, 2019). The ganglioneuromas diagnosed were in the spine of an 18 year old female and, as indicated on the histology report, a skull lesion in a 10 year old male. The CNS PNETs have different degrees of differentiation along different cell line types, for example neuronal, astrocytic, muscular or melanocytic. CNS neuroblastomas have neuronal differentiation and ganglioneuroblastomas have ganglion cells present. CNS neuroblastomas have undifferentiated and poorly differentiated neuro-epithelial cells with varying frequencies of Homer-Wright rosettes. Ganglioneuroblastomas, on the other hand, consist of both primitive-appearing and terminally differentiated cells.

Molecularly no consistent genomic or molecular abnormality could be attributed specifically to these tumours and the only definitive finding up to date was that these tumours differ significantly from medulloblastomas with regards to molecular abnormalities (Pfister et al, 2010).

6. Neuronal and mixed neuronal-glial tumours:

The 2016 WHO classification of neuronal and mixed neuronal-glial tumours contains only one significant change from that of the 2007 WHO classification, namely that of the addition of the *diffuse leptomeningeal glioneuronal tumour*. The rest have remained unchanged. This diverse group of tumours consist of:

1. *Dysembryoplastic neuro-epithelial tumour*
2. *Gangliocytoma*
3. *Ganglioglioma*
4. *Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)*
5. *Desmoplastic infantile astrocytoma/ganglioglioma**
6. *Papillary glioneural tumour**
7. *Rosette-forming glioneuronal tumour*
8. *Diffuse leptomeningeal glioneuronal tumour*
9. *Central neurocytoma**
10. *Extraventricular neurocytoma**
11. *Cerebellar liponeurocytoma*
12. *Paraganglioma*.*

*indicates neuronal and mixed neuronal-glial tumours diagnosed at Universitas Academic Hospital

These tumours are very diverse with regards to the morphology and genetics, but have several factors in common, namely the preponderance to occur in children and young adults, a predilection for the temporal lobes and their close association with epilepsy. These tumours comprise of a neuronal component, but often contain a glial component, and some such as the central and extraventricular neurocytomas might even show gangliogliomatous differentiation.

Tan et al suggested that this tumour group be evaluated in two different subgroups according to the growth pattern of solid versus patterned. The solid growth pattern group consists of gangliogliomas, dysplastic cerebellar gangliocytoma, desmoplastic infantile astrocytomas/gangliogliomas, central or extraventricular neurocytoma, cerebellar liponeurocytoma and diffuse leptomeningeal glioneural tumour. The patterned group consists of the dysembryoplastic neuro-epithelial tumour, papillary glioneural tumour and the rosette-forming glioneural tumour.

The subependymal giant cell astrocytoma, pleomorphic xanthoastrocytoma and hypothalamic hamartomas and pineocytomas might mimic these tumours and needs to be carefully distinguished from these tumours radiologically and histologically. Molecular studies might be very helpful in these instances as gangliogliomas are usually of the *IDH*-wildtype and can contain the *BRAFV600E*+ mutation. The central and extraventricular neurocytomas are also *IDH*-wildtype and does not possess the 1p19q co-deletion.

Gangliogliomas are indolent tumours with biphasic morphology and contains a variable amount of dysplastic ganglion cells as well as neoplastic glial cells. Its usual presentation is in young adults in the temporal lobe and secondly in the frontal lobe with a longstanding history of epilepsy. These tumours are often cystic-solid tumours that are well-defined. The most important aspect is to differentiate these tumours from pilocytic astrocytomas histologically as the dysmorphic ganglion cells normally occur in a glial background typical for a pilocytic astrocytoma with common occurrence of Rosenthal fibres and/or eosinophilic granular bodies. Perivascular lymphocytes are also commonly found and it is imperative to closely observe for ganglion cells in what might seem like a typical pilocytic astrocytoma. The grading of these tumours is based on the astrocytic (glial) component and can elevate a ganglioglioma from a WHO I to an anaplastic WHO III or even a glioblastoma multiforme. Therefor it is important to determine the neoplastic nature of the ganglion cells and not just comment on potentially trapped neurons in the infiltrating glioma. If an *IDH*-mutation is found it supports the diagnosis of an infiltrating glioma with trapped neurons. Testing for CD34 is also supportive of the diagnosis of a ganglioglioma as this stem cell epitope is usually not present in neurons in adult brain, but can be seen in up to 80% of gangliogliomas (Tan et al, 2018).

At our institution a ganglioglioma has not been diagnosed up to now. This can possible be ascribed to the difficulty in confirming this tumour histologically, the lack of genetic/molecular testing at our institution up to now and the lack of an experienced neuropathologist at our institution. It is possible that the neoplastic ganglion cells have been missed in some of the infiltrating gliomas diagnosed at our institution or in the case of a biopsy, that a specimen was submitted that did not contain neoplastic ganglion cells to facilitate the diagnosis, i.e. an insufficient specimen (inadequate size).

Desmoplastic infantile astrocytoma and desmoplastic infantile ganglioglioma are two related neoplasms that are classified as one entity in the 2016 WHO classification. These tumours present as superficial cortical mass lesions in infancy and normally have a dural attachment with a dense desmoplastic reaction. If a neuronal population is present it is deemed a desmoplastic infantile ganglioglioma and in the absence of a neuronal population it is known as a desmoplastic infantile astrocytoma. Most of these tumours will present in the first year of life, but several cases have been reported in the literature in the age group between 5 and 25 years of age. The desmoplastic infantile astrocytoma diagnosed histologically at our institution occurred in the frontal lobe of a 4 year old female.

The neuronal component is usually comprised of ganglion cells and the desmoplastic area is normally found in a low-grade glial component. This stains positive with GFAP IHC. The non-desmoplastic area may however contain poorly differentiated or primitive neuro-epithelial cells which might lead to the diagnosis of a WHO grade IV embryonal tumour instead of a WHO I desmoplastic infantile astrocytoma/ganglioglioma or even the diagnosis of a pilocytic astrocytoma. This is especially prevalent were small biopsy specimens have been taken. This is very important to take into consideration as these tumours might subsequently be significantly over treated in view of the higher WHO

grading when it is clear that the presence of poorly differentiated or primitive neuro-epithelial cells in desmoplastic infantile astrocytoma/ganglioglioma does not impact on the prognosis of these patients in general (Tan et al, 2018).

Paragangliomas are low grade neuro-endocrine tumours arising in the paraganglionic tissue. These tumours are classified as WHO grade I tumours and the terminology is derived from the usual site of occurrence which in the central nervous system is the spine (spinal paraganglioma) and the temporal bone (jugulotympanic paraganglioma). In the spine paragangliomas comprise approximately 3.5% of all tumours of the cauda equina or filum terminale whereas jugulotympanic paragangliomas are the second most common tumour of the temporal bone. These tumours usually present in the fourth to sixth decade and the spinal paragangliomas have a slight male predilection and the jugulotympanic paraganglioma a definitive female predilection. Intracranially these tumours are rarely found in the sellar or suprasellar region as well as in the posterior fossa.

Spinal paragangliomas, on MRI, enhance discreetly with contrast and have a typical "sausage" shape with scalloping of the vertebral bodies on CT. The jugulotympanic paragangliomas have a "salt and pepper" pattern on T2W imaging and on CT a "moth-eaten" appearance of the temporal bone.

Histologically these tumours have an organoid pattern with "Zellballen" consisting of nests of chief cells that are surrounded by bipolar sustentacular cells and a delicate capillary network entwining the "Zellballen" (Abdelzaher, 2014).

At our institution 6 paragangliomas were diagnosed of which two were in the spinal cord (no specific location in the cord indicated) and it was present in a 29 year old male and a 63 year old female. The other 4 paragangliomas were documented to originate from the skull, with two documented to originate from the temporal bone and one just from the skull (no specific location allocated) and another one from the posterior fossa in a 44 year old female. Except for the paraganglioma that occurred in the posterior fossa of one of the patients and the age of the one spinal paraganglioma (29 year old) the rest of the findings at our institution was congruent with international data.

Central and extraventricular neurocytomas consist of a compact population of round, uniform neurocytic cells that form honeycombed sheets on a cross-section. The neurocytic cells contain spherical nuclei with a chromatin that is finely granular with small nucleoli and minimal cytoplasm. The cytoplasmic processes are usually very delicate. This can mimic an oligodendroglioma. Areas with large fibrillary stroma might be present that can mimic pineocytomatous rosettes and gangliogliomatous differentiation has been detected with the then label of "ganglioneurocytoma". With extraventricular neurocytomas atypical features such as increased mitotic activity, microvascular proliferation with or without necrosis can be present which supports the higher incidence of recurrence compared to central neurocytomas. These tumours are *IDH*-wildtype and an *IDH*-mutation and 1p19q co-deletion will exclude the diagnosis of a central or extraventricular neurocytoma. If the location of the tumour is not known to the pathologist, the histological

features might be confused with that of a pineocytoma (Mukherjee et al, 2016). None of the central neurocytomas and extraventricular neurocytomas diagnosed at our institution was confirmed on a molecular level, but the location of the tumours was specified on the histology report which might have facilitated a definitive histological diagnosis. The incidence and age groups involved at our institution was congruent with international data.

Papillary glioneural tumours usually occur supratentorially and may displace the ventricular system. It is a WHO grade I tumour with a papillary architecture and both astrocytic and neuronal or neurocytic cell populations are found in these tumours. Approximately 68 cases have been reported in the literature since it became an entity in the 2007 WHO classification and the tumour has been described in a wide age range of 4 – 75 years of age.

On MRI these tumours are usually well circumscribed and may extend to the cortex or the adjacent white matter or may be located deep with displacement of the ventricular system. Cystic changes frequently occur. Due to the papillary structure these tumours are quite friable and may present with large bleed enabling an incorrect diagnosis of a possible cavernoma. On T1W imaging the solid components can be isointense to hypointense with contrast enhancement that may be diffuse, patchy or ring-enhancing. On T2W imaging the solid components can be isointense to hyperintense to grey matter. These tumours can also present as mural nodules within cystic masses (can be confused radiologically with pilocytic astrocytomas or haemangiopericytomas (solitary fibrous tumours)). Calcifications might be present in these tumours and superficial siderosis might be seen secondary to previous haemorrhage. These tumours often have very little surrounding oedema even though the size might be up to 9cm in diameter.

Histologically these tumours have a glial component consisting of astrocytic cells with a pseudopapillary formation and obvious hyalinised vasculature. These blood vessels are surrounded by a single layer of cuboidal cells with no atypia and minimal cytoplasm. These cells all stain positive for GFAP and S-100 antibodies. The interpapillary spaces have small neuronal cells with perinuclear halos that resemble oligodendrocytes. These often stain positive for anti-oli and synaptophysin. Most of these tumours also contain Rosenthal fibres (Carangelo et al, 2015).

Only one papillary glioneural tumour has been diagnosed at our institution in a 14 year old female in temporal lobe. As there are not many cases documented internationally, this will be congruent with international data.

7. <u>Lymphomas:</u>

Primary central nervous system lymphoma (PCNSL) is rare and attributes approximately 2% of all primary intracranial tumours. It is an aggressive form an extranodal non-Hodgkin's lymphoma that affects the brain, spinal cord, eyes and leptomeninges. There is no systemic involvement. The 2016 WHO classification subdivides PCNSL into the following:

1. *Diffuse large B-cell lymphoma of the CNS**
2. *Immunodeficiency-associated CNS lymphoma*
    a. *AIDS-related diffuse large B-cell lymphoma*
    b. *EBV-positive diffuse large B-cell lymphoma**
    c. *Lymphomatoid granulomatosis*
3. *Intravascular large B-cell lymphoma*
4. *Low-grade large B-cell lymphoma of the CNS*
5. *T-cell and NK/T-cell lymphomas of the CNS**
6. *Anaplastic large cell lymphoma, ALK-positive*
7. *Anaplastic large cell lymphoma, ALK-negative*
8. *MALT lymphoma of the dura.*

Diffuse large B-cell lymphomas (DLBCL) constitute about 90% of all PCNSL and the T-cell, Burkitt's and lymphoblastic with the low-grade lymphomas constituting the rest. Radiologically these tumours normally present as single mass lesions in immunocompetent patients and multiple lesions in the immune-incompetent. The most common locations are supratentorial and periventricular. MRI is the modality of choice to diagnose these lesions. PCNLS enhance uniformly with gadolinium and has well-defined borders. Significant perilesional oedema is common. These lesions appear hypointense on T2W imaging and show restricted diffusion on DWI secondary to the high cellularity and the compacted cells with a high nuclear to cytoplasmic ratio. On MRI spectroscopy these lesions also show a significantly increased lipid peak with higher choline: creatine ratios and choline: NAA ratios. This can help to differentiate these lesions from tumours such as a glioblastoma multiforme. DLBCL can concurrently occur in the CSF and the eye at 15 – 20% and 5 – 20% respectively. These tumours require early and aggressive treatment and stereotactic biopsy as soon as possible is indicated (Löw et al, 2018).

Of all the PCNSL diagnosed at our institution, 17 of the 25 PCNSL diagnosed were DLBCL which relates to 70.8% which is significantly lower than in the international literature. This lower number might be attributed to a pure radiological diagnosis of PCNSL being made with possible CSF confirmation and referral of these patients to oncology without a biopsy being taken. 9 of the 17 patients presented with lesions in the spinal cord that was biopsied. PCNSL comprised 5.67% of all the CNS tumours diagnosed at our institution. The higher number might be attributed to the high level of HIV infection in our population of approximately 20% in the Free State and the higher incidence of this devastating disease in this population group. Unfortunately no indication was given on the histology reports to indicate the HIV status of the involved patients which would clarify this statement.

8. <u>Mesenchymal, non-meningeal tumours:</u>

This subset of tumours contains a wide variety of primary brain tumours that may contain different cell line differentiation and may mimic meningiomas. The most significant change in the 2016 WHO classification is that of the hemangiopericytoma. It has now been concluded that the solitary fibrous tumour and the hemangiopericytoma are on the

histological spectrum of the same tumour entity. For that reason a new term has been allocated, namely that of solitary fibrous tumour/hemangiopericytoma. This term has been created to avoid confusion as the solitary fibrous tumour that occurs in the dura has been deemed a benign tumour of WHO I grading versus the hemangiopericytoma which tend to recur and show malignant behaviour including distant metastasis. Both these entities show fusions of the *NAB2* and *STAT6* genes. These tumours are still graded as grade 1, 2 and 3. Grade 1 tumours show hypocellularity and collagenisation with low mitotic activity. The grade 2 and 3 tumours are more cellular and the distinction is made by the mitotic count in the tumour: <5 per high power field are deemed grade 2 and >5 per high power field are deemed as grade 3 tumours. Staining for *STAT6* is recommended to prove the fusion of the two genes. If this stain is negative, it is recommended that a diagnosis of fibrous meningioma, synovial sarcoma and other entities should be considered (Sahm et al, 2018).

At our institution 7.48% of the tumours diagnosed were classified under this group of primary brain tumours. As single entities these tumours are described in the international literature as comprising 1 – 2% of all brain tumours. The higher diagnostic rate at our institution raises a couple of questions with regards to the accuracy of the histological diagnosis and the decision to perform surgical intervention in other tumour subgroups. With the lower incidence of low grade gliomas, pituitary adenomas and craniopharyngiomas at our institution it may imply the ratio of diagnosis of these tumours in the context of the tumours operated on in our institution is skewed. If a clear record was available with regard to tumours not surgically managed due to the radiological picture, patient clinical condition or the location of the tumour with a possible radiological diagnosis, the context of the high rate of diagnosis of these rare tumours might be better explained.

9. <u>Pineal region tumours:</u>

The pineal gland and its surrounding tissues consist of a wide variety of cell types and thus a heterogeneous pool of tumours may occur in this region, from tumours specific for the pineal gland, gliomas, metastasis, and germ cell tumours. We will specifically evaluate the pineal gland specific tumours in this section. 15 pineal region tumours have been histologically confirmed at Universitas Academic Hospital.

The 2016 WHO classification divides pineal region tumours into the following:

1. Pineocytoma
2. Pineal parenchymal tumour of intermediate differentiation
3. Pineoblastoma
4. Papillary tumour of the pineal region (very rare neuro-epithelial tumour).

These tumours are rare and present mostly in childhood with it comprising 3 – 8% of all paediatric intracranial tumours and < 1% of adult intracranial tumours. Of these tumours 10% will be truly benign and > 80% will be malignant.

Pineocytomas are WHO grade I tumours that comprise of 14 – 60% of all pineal parenchymal neoplasms and usually occurs in young adults with a median age of 36 years. The 5 year survival rate is between 86 – 100%. Histologically these tumours consist of small round cells with an ill-defined cytoplasm and cells that are arranged in pineocytomatous rosettes. No mitotic features are present in these tumours. It has a hypointense to isointense appearance on T1W imaging and an isointense to hyperintense appearance on T2W imaging and enhances vividly with contrast. These tumours can sometimes be difficult to distinguish from the normal pineal parenchyma. Pineocytomas are managed with gross total resection and adjuvant radiotherapy if residual tumour is present. Only one pineocytoma was histologically confirmed at our institution in a 54 year old male. Pineocytomas at our institution comprised 6.67% of all the pineal parenchymal tumours diagnosed which is significantly lower than in the literature.

The *pineal parenchymal tumour of intermediate differentiation* is classified as a WHO II or WHO III tumour. It is generally 20% of all pineal parenchymal tumours diagnosed. Young adults are usually affected and the mean age at diagnosis is at 32 years. It usually has a slight female predilection. Histologically it consists of diffuse sheets or lobules of cells that might appear quite similar to that of the pineocytoma and pineoblastoma. It has mild to moderate nuclear atypia with some mitotic activity. It appears quite similar to pineocytoma on imaging, but is less likely than pineoblastomas to disseminate through the CSF. These tumours have a 5 year survival rate of 39 – 79%. Only one pineal parenchymal tumour of intermediate differentiation has been histologically confirmed at our institution. These tumours thus comprised of 6.67% of all pineal parenchymal tumours diagnosed at our institution (Winn et al, 2017).

Pineoblastomas are WHO grade IV tumours that often disseminate through the CSF. It infiltrates the surrounding tissue even though it may seem well circumscribed. Pineoblastomas usually occur in patients younger than 20 years of age and has a 5 year survival rate of approximately 58%. Most deaths are caused by metastasis or CSF seeding. Poor prognostic factors include >7 mitotic figures per high power field, presence of necrosis and absent neurofilament staining. Radiologically these tumours appear hypointense on T1W and hyperintense on T2W imaging with areas of restricted diffusion and heterogeneous contrast enhancement. Areas of haemorrhage may be present. Histologically these tumours consist of sheets of densely packed cells with unequivocal anaplastic features, namely high nucleus to cytoplasm ratio, large hyperchromatic nuclei, necrosis, frequent mitotic features, Homer-Wright or Flexner-Wintersteiner rosettes and may even contain areas representing pineocytomas and pineal parenchymal tumour of intermediate differentiation (Pernick, 2019). 13 pineoblastomas were histologically confirmed at our institution and constituted 86.7% of all pineal parenchymal tumours diagnosed at our institution. This is congruent with international literature.

Pineal gland tumours are located in an area that requires surgical expertise to perform a gross total resection as is required in the management of all the pineal tumours. The surgical approaches are not approaches that are utilized often and the risk associated with these surgical interventions can be incredibly high. For these reasons all the pineal

region tumours diagnosed at our institution, the histology was obtained from either a stereotactic or endoscopic biopsy. None of these tumours at our institution had an attempt at resection due to lack of experience in the surgical approaches required to successfully resect these tumours. In view of the high percentage of insufficient biopsies documented at our institution, it is probable that the incidence of pineal region tumours at our institution where biopsy was attempted was higher than the successful biopsies taken. If a pineocytoma was suspected in view of radiological presentation (significant increase in calcifications surrounding the pineal area) it is possible that these patients received no surgical attempt to confirm the diagnosis, but that the tumour was followed up radiologically only. The pineal parenchymal tumours often lead to obstructive hydrocephalus due to the location of the tumours with obstruction of the aqueduct of Sylvius and it is possible that these patients demise prior to referral from the hydrocephalus or that their neurological state at presentation is poor enough to warrant no further surgical intervention except for the management of the hydrocephalus.

10. Germ cell tumours:

Germ cell tumours according to the 2016 WHO classification can be divided into the following:

1. Germinoma
2. Embryonal carcinoma
3. Yolk sac tumour
4. Choriocarcinoma
5. Teratoma
    a. Mature
    b. Immature.
6. Teratoma with malignant transformation
7. Mixed germ cell tumour.

Germ cell tumours account for 0.3 – 3.4% of the brain tumours in the Western world with a much higher incidence in the Asian population. Germinoma is the most common of these tumours at 50% followed by teratomas at 15%. Germ cell tumours are however the most common tumour to occur in the pineal region.

Germinomas are mainly located in the pineal region at 65% and the rest at the suprasellar region. It comprises 3 – 5% of all paediatric intracranial tumours and < 1% of intracranial tumours in adults. Microscopically these tumours consist of 2 main cell types containing islands and trabeculae of large round or polyhedral cells. These cells have a well-defined cytoplasmic membrane and contain clear or eosinophilic cytoplasm. Variable amounts of mitosis are present, but these tumours have a good 5 year survival rate of up to 90%. On MRI these tumours show a solid mass in the pineal gland or suprasellar with isointense to hyperintense to grey matter on both T1W and T2W imaging. Up to 50% of these tumours have cystic components. Pathognomonic for these tumours is simultaneous occurrence in the pineal gland and suprasellar area. Typical for these tumours is a

positive placental alkaline phosphatase (PLAP) and up to 50% will have positive β-HCG test. These tumours respond very well to radiation therapy (Winn et al, 2017). Only 3 germinomas were histologically confirmed at our institution. All 3 occurred in the pineal region and were diagnosed with a biopsy only. Very few germinomas at our institution are surgically diagnosed as the combination of the classic imaging combined with a positive β-HCG or PLAP often results in a non-histological diagnosis of a germinoma and the patients are then referred to oncology for radiotherapy with very good effect. The only indication to obtain a biopsy at our institution is with atypical radiological presentation and negative blood investigations.

The other germ cell tumours are rare and none of them were diagnosed at our institution. This might be due to non-presentation or a decision to refer the patient to oncology based on the radiological diagnosis of a germ cell tumour without confirming the diagnosis histologically.

11. Tumours of the sellar region:

The WHO 2016 classification classifies sellar tumours as follows:

- Craniopharyngioma
    - Adamantinomatous craniopharyngioma
    - Papillary craniopharyngioma
- Granular cell tumour of the sellar region
- Pituicytoma
- Spindle cell oncocytoma.

The researcher will include the discussion on pituitary adenomas in this section as these tumours also occur in the sellar region. The 4th WHO classification of pituitary adenomas was published in 2017 and pituitary adenomas were classified as follows:

- Somatotroph adenoma
- Lactotroph adenoma
- Thyrotroph adenoma
- Corticotroph adenoma
- Gonadotroph adenoma
- Null cell adenoma
- Plurihormonal and double adenoma.

The 4th WHO classification of pituitary adenomas is based on the adenohypophyseal cell lineage as determined by immunohistochemical markers including pituitary hormones and pituitary-specific transcription factors (Khani et al, 2018).

The tumours of the sellar region that has been diagnosed at our institution include craniopharyngiomas and pituitary adenomas. None of the other sellar region tumours have been diagnosed at out institution.

Pituitary adenomas are the third most common intracranial tumour, following meningiomas and gliomas, according to the literature. In the CBTRUS statistics it comprised 15.9% of all histological diagnosis and was second only to non-malignant meningiomas. At our institution, pituitary adenomas only comprised 3.68% of all intracranial tumours diagnosed histologically. 15 – 30% of pituitary adenomas are non-functioning and present through persistent headaches, blurred vision (loss of visual fields, blindness) and sometimes seizures. These tumours occur in the sella turcica and most is found in the anterior part of the hypophysis. Up to 50% of these tumours will be micro-adenomas (<10mm) and the rest will be macro-adenomas (≥10mm). Hormonally these tumours can secrete different hormones including prolactin, growth hormone, ACTH and the thyrotrophic hormones. Thus these tumours may present with acromegaly, Cushing's disease and hyperthyroidism. The most common functional pituitary adenoma is one that secretes prolactin (Andino-Rios et al, 2018). Female patients present earlier with these tumours as it can cause galactorrhoea and amenorrhoea which leads to early medical consultation and investigation. These tumours are imaged with MRI as micro-adenomas can be identified on a post contrast MRI. CT brain will only be of help if a very large adenoma is present (Winn et al, 2017).

There are a couple of reasons for the low histological confirmation of pituitary adenomas at our institution, namely most of the patients present vey late with invasion of the sphenoid sinuses, encasement of the internal carotid and often the middle cerebral arteries which reduces the possibility of gross total resection and increases the risk of debulking by surgical intervention, complete blindness and poor medical grade secondary to the hormonal effects of these tumours. Once medically stabilized and the risks involved with resection of these tumours is discussed with the patient and their family, they often refuse surgical intervention and opt for hormonal treatment only. As most of the pituitary adenomas are prolactinomas, these patients also tend to opt for treatment with either bromocriptine or cabergoline.

None of the pituitary adenomas confirmed histologically at our institution could be allocated according to the 4th WHO classification of pituitary adenomas as the cell line involved was not specified. Without access to the clinical notes, it was also impossible to discern between non-functional and functional pituitary adenomas that were operated on.

Craniopharyngiomas are a rare embryonic malformation with a low histological grade (WHO I). These tumours have a very high survival rate with a 20 year survival figure of up to 87 – 95% in developed countries. Craniopharyngiomas have a bimodal distribution with most of the tumours occurring in childhood and adolescence between the ages of 5 – 14 years and the second peak in adults between the ages of 50 – 74 years. The main histological subtype seen in children is the adamantinomatous subtypes and in adults mostly papillary craniopharyngiomas. Craniopharyngiomas represent approximately 1-2 – 4% of all paediatric brain tumours and are quite rare in adult patients.

Adamantinomatous craniopharyngiomas present as a cystic tumour of the sellar region with calcifications on CT brain and highly variable presentation on MRI due to the varied

protein concentration that is found in the cystic fluid. Calcifications are present in up to 90% of craniopharyngiomas. The histology of these tumours shows squamous epithelium that is present in cords or nodules or irregular trabeculae. These densely packed cells can be loosely bound to aggregates of squamous cells that are known as the stellate reticulum. Cystic cavities are also present that contain squamous debris. These cavities are lined with flattened epithelium. There is often piloid gliosis with numerous Rosenthal fibres present on the infiltrative surface of the tumour and this can possibly be confused with the histology of a pilocytic astrocytoma,

Papillary craniopharyngioma often present as a solid sellar and suprasellar mass that should be distinguished from a pituitary adenoma. These tumours very seldom contain calcifications and are more common in the adult population. Histologically it is a monomorphic mass that consists of well-differentiated squamous epithelium with no surface maturation. It also contains picket fence-like palisades and wet keratin.

Craniopharyngiomas are managed with gross total resection if the optic pathways and the hypothalamic structures are not involved, conventional external radiation, proton beam therapy, stereotactic radiotherapy, radiosurgery, and intra-cystic interferon-α (Muller, 2014).

At our institution the 6 patients that had histological confirmation of the craniopharyngioma, 4 were below the age of 14 and the other two were respectively 36 and 51 years old. The 4 paediatric patients all had a biopsy of the lesion taken and the 2 adult patients had debulking procedures. It is possible that more paediatric patients had surgical intervention for a craniopharyngioma, as we often insert an ommayo shunt for instillation of intra-cystic interferon-α. The cystic fluid was then sent for cytological assessment and not for histological interpretation. Most of the paediatric patients that present with craniopharyngiomas have a very large cystic component with an unresectable small solid component. There is often involvement of the hypothalamic structures and the optic structures and we have had very good results with intra-cystic interferon-α. Due to the low number of sellar and suprasellar tumours that are surgically managed at our institution as seen by the statistics for the pituitary adenomas, it is quite possible that a number of adult craniopharyngiomas are currently managed as pituitary adenomas with serial imaging and best medical management.

12. <u>Tumours of the cranial and paraspinal nerves:</u>

These tumours can be classified as follows according to the 2016 WHO classification:

- Schwannoma
    - Cellular schwannoma
    - Plexiform schwannoma
- Melanotic schwannoma
- Neurofibroma
    - Atypical neurofibroma
    - Plexiform neurofibroma

- Perineuroma
- Hybrid nerve sheath tumours
- Malignant peripheral nerve sheath tumours (MPNST)
    - Epithelioid MPNST
    - MPNST with Perineural differentiation.

Schwannomas are benign nerve sheath tumours that arise from the differentiated Schwann cells. It can occur in all ages with a more common occurrence in patients between the ages of 20 – 50 years. Up to 90% of schwannomas occur sporadic and 3% are associated with neurofibromatosis type 2. Radiologically these tumours present as well circumscribed masses that displace adjacent structures. No direct invasion of adjacent structures occurs. Cystic and fatty degeneration is often seen especially in larger tumours with heterogeneity on imaging. Histologically these tumours are biphasic with two components, namely compact hypercellular areas known as Antoni A areas and myxoid hypocellular areas known as Antoni B areas. There is nuclear palisading around the fibrillary processes known as Verocay bodies. Antoni B areas are often absent in small tumours. Mitotic figures are very rare. These tumours are managed by complete surgical excision and due to the fact that adjacent structures are not infiltrated, recurrence very seldom occurs (Abdellatif, 2018).

17 schwannomas were confirmed histologically at our institution with none being allocated a WHO sub-classification. On the histology reports provided there was no indication of the patient's neurofibromatosis status or the nerve the schwannoma was associated with.

Malignant peripheral nerve sheath tumours are also known as malignant schwannomas. It has a 50% association with neurofibromatosis with the rest arising de novo. It usually occurs in adults with a high rate of local recurrence and distant metastasis. It comprises 3 – 10% of all soft tissue sarcomas. Microscopically these tumours have monomorphic serpentine cells with large gaping vascular spaces and palisading. There is also plump perivascular tumour cells and geographic necrosis that can resemble glioblastoma multiforme. These tumours contain frequent mitotic figures with bizarre cells and up to 15% can contain metaplastic cartilage, bone and muscle (Shanker, 2012). The correct histological diagnosis is made in approximately 17 – 41% of new cases as these tumours are often classified as a different type of sarcoma. The histological diagnosis is difficult due to the lack of specific immunohistochemistry for these tumours or a unique chromosomal abnormality, the lack of a uniform histological pattern for these tumours and the lack if distinct clinical criteria. Therefor it is important to combine the clinical, radiological and histological presentation to support the diagnosis. Radiologically these tumours appear hyperintense on STIR and T2W imaging and hypointense on T1W imaging with homogenous contrast enhancement. The most sensitive MRI sequence for diagnosis is the STIR sequence. The heterogeneous appearance on T2W and T1W imaging is due to the high water content of the myxoid matrix and the central areas of hypointensity can be due to areas of fibrosis. The 5 year overall survival rate is 44 – 50% and depends greatly on a gross total resection of the tumour (Kragha, 2015) .

Shortcomings and limitations of the study:

Several shortcomings and limitations were identified during the compilation of the research topic and assembling of the mini dissertation.

The first limitations identified were the lack of confirmation of the histological data received from NHLS. The data was obtained from NHLS by providing them with key words/phrases and Snomed and ICD10 codes. Consent was not obtained from the Free State Department of Health to gain access to the clinical notes and theatre logbooks to confirm whether the histology obtained represented all the cases that had surgical intervention for a central nervous system tumour. In retrospect, the theatre logbooks should also have been accessed to ensure that all the histology obtained for CNS tumours were represented in this study.

Secondly, in review of the data it was obvious that sampling errors occurred with 11.34% of the stereotactic biopsy performed resulting in inconclusive histology. This might have been due to inadequate sample size, incorrect location of the biopsy, malfunctioning of the neuronavigation, free hand biopsy prior to our institution receiving a neuronavigation system. From the data obtained, none of these patients had a repeat biopsy attempted which skewed our data. 41.5% of all the tumours surgically managed at our institution had a biopsy performed which could also lead to an erroneous histological diagnosis as is described throughout with a large amount of the tumours diagnosed having similar, overlapping histological features. This could have led to underdiagnosis of high grade lesions if only a small specimen of the low grade component was sampled in the biopsy.

The radiological imaging of most of these tumours was unavailable as our institution started making use of a new radiological server from 2015. All imaging obtained prior to 2015 is not available anymore. The radiological features could have been compared with the histological features to determine whether the diagnosis, especially in the event of a biopsy, was representative or not. In the same setting, no consent was obtained to access the patients' clinical notes to compare the histological features with the clinical presentation and to access the initial differential diagnosis to compare it with the histological diagnosis obtained in the end. In retrospect this would have assisted with the confirmation of the histological diagnosis based on the clinical information and differential diagnosis initially postulated.

Only 441 patients had histological data according to NHLS. This represents a small amount of the patients seen at Neurosurgery at Universitas Academic Hospital. The other patients are either still awaiting surgical intervention, or are not suitable candidates for surgical intervention or have refused surgical intervention. It would have been helpful to have access to these numbers with their possible radiological diagnosis in placing the data obtained in perspective with international data. Due to a lack of ICU beds and theatre time, some of our patients have a fairly long waiting time prior to surgical intervention and some are lost to follow up. A register with the name, age, sex and possible diagnosis of these patients would have been helpful, especially with some of the tumours that are

grossly underdiagnosed at our institution such as pituitary adenomas. There was also a complete lack of outcome for these patients with the absence of consent to access the clinical records.

Lastly the biggest limitation of this study is the lack of a specialist neuropathologist at our institution. As documented by Folkerth et al, there is only one specialized neuropathologist in sub-Saharan Africa and that is Dr D Zaharie at Tygerberg Hospital. This is due to the fact that there is no sub-speciality training available in South Africa for anyone to become neuropathologist. The other reason is the low volume of neurology specimen in comparison to that of general surgery, which would not be sufficient to support a dedicated neuropathologist at most institutions. It has been noted that in only up to 50% of specimens the histological diagnosis between a neuropathologist and a general pathologist will be congruent. As it was noted, most of the histological diagnosis is not clear cut for a specific tumour and careful evaluation is required to distinguish between different tumour types, especially in the same tumour group. This also could have led to skewed results and it is possible that it may have contributed to the large amount of inconclusive histology results obtained. With the recent advent of molecular and genetic testing of tumours the diagnosis and confirmation of the diagnosis of some of the tumours have been simplified which allows for less interobserver discrepancies. It is our hope that we will soon have access to this at our institution, also to facilitate the targeted treatment of CNS tumours.

Conclusion:

Central nervous system tumours are a great contributor to morbidity and mortality worldwide. With the advent of molecular and genetic testing of these tumours, more targeted treatment has become available for some of the tumours.

CNS tumours diagnosed in the Free State vary from those reported in the CBTRUS fact sheet and from the SA National tumour registry. The main categories were the difference was very apparent was in the pituitary adenoma subgroup and the low grade gliomas.

By compiling a National Brain Tumour Registry that included all benign and malignant histology obtained from both the NHLS and private laboratories, we would be able to determine the needs to facilitate the proper diagnosis of these tumours by motivating for molecular and genetic testing that would aid in the diagnosis of these tumours and the possible targeted treatment of these tumours. This would enable the neurosurgical community to motivate for a specialist neuropathologist to review all samples, motive young pathologists to super-specialize in neuropathology and enlighten shortcomings in the current management of CNS tumours in South Africa as a whole.

By documenting the presenting symptoms and signs and the outcomes of the management of these tumours, we would be able to compile a fact sheet that could be distributed to the referring hospitals and clinics to enable possible early detection of these

lesions with speedy referral and management to attempt to minimize the high rate of morbidity and mortality associated with tumours of the central nervous system.

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Appendices:

health
Department of Health
FREE STATE PROVINCE

18 June 2018

Dr M De Bruyn
Dept. of Neurosurgery
UFS

Dear Dr M De Bruyn

Subject: An audit of central nervous system tumours that have been hospital, detailed or operated and universities Academic Hospital, Free State.

- Please ensure that you read the study document. Permission is hereby granted for the above mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State Department of Health and co-ordinator of the study.
- Assurance that your data collection exercise neither interferes with the day to day running of Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to Free State Department of Health.
- Any amendments, extensions or other modifications to the protocol or investigation must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to [illegible] before you commence with the study.**
- No financial liability will be placed on the Free State Department of Health.
- Please discuss your study with the [illegible] before commencement for logistical arrangements.
- Department of Health to be fully indemnified from any harm that participants and staff members in the study.
- Researchers will be required to enter into a formal agreement with the Free State Department of Health regarding the intellectual property relationship (Document will follow).
- You are encouraged to present your study findings here in the Free State Provincial Health research day.
- Patient records will only be granted permission if correct procedures are followed see [illegible]

Trust you find the above in order.
Kind Regards

Dr D Moeaki
HEAD: HEALTH
Date: _____

NATIONAL HEALTH LABORATORY SERVICE

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21 February 2019

Applicant: Dr Martha de Bruyn
Institution: University of the Free State
Department: Neurosurgery
Email: [illegible]
Cell: 082 319 6925

Re: Approval to access National Health Laboratory Service (NHLS) Data

Your application to undertake a research project "**An audit of central nervous system tumours as diagnosed at Universitas Academic Hospital in Bloemfontein, Free State**" using data from the NHLS database has been reviewed. This letter serves to advise that the application has been approved and the required data will be made available to you ***without patient names*** to conduct the proposed study as outlined in the submitted application.

Please note that final approval is granted on your compliance with the NHLS conditions of service and that the study can only be undertaken provided that the following conditions have been met.

- Processes are discussed with Prof Jacqueline Goedhals Head of Department of Anatomical Pathology Universitas and relevant NHLS departments (i.e. Information Management Unit and Operations Office) and are agreed upon.
- Confidentiality is maintained at participant and institutional level and there is no disclosure of personal information or confidential information as described by the NHLS policy.
- A final report of the research study and any published paper resulting from this study are submitted and addressed to the NHLS Academic Affairs and Research office and the NHLS has been acknowledged appropriately.
- NHLS Data cannot be used to track patients as no pre-approval/consent is obtained from Patients.

Please note that this letter constitutes approval by the NHLS Academic Affairs and Research Office. Any data related queries may be directed to NHLS Corporate Data Warehouse, contact number: 011 386 6074 email: carina.sabat@nhls.ac.za

[signature]

Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

11-Sep-2018

Dear **Dr Martha De Bruyn**

Ethics Clearance: **An audit of central nervous system tumours that have been biopsied, debulked or resected at Universitas Academic Hospital, Free State.**

Principal Investigator: **Dr Martha De Bruyn**

Department: **Neurosurgery Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is **UFS-HSD2018/0435/2509**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
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An audit of central nervous system tumours as diagnosed at Universitas Academic Hospital in Bloemfontein, Free State from 2007 - 2017

ORIGINALITY REPORT

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5	Nathan E. Millard, Kevin C. De Braganca. "Medulloblastoma", Journal of Child Neurology, 2016 Publication	<1%
6	Takashi KOMORI. "The 2016 WHO Classification of Tumours of the Central Nervous System: The Major Points of Revision", Neurologia medico-chirurgica, 2017 Publication	<1%

				Data capture sheet: CNS tumour audit				
				01/01/2007 - 31/12/2017				
Number	**Pat*ient number***	**Age**	**Sex**	**Location of tumour**	**biopsy**	**Debulking**	**Resection**	**Histology**

An audit of central nervous system tumours as diagnosed at Universitas Academic Hospital in Bloemfontein, Free State

16/05/2018 (Version 2)

Principal investigator:

Dr MM de Bruyn

University of the Free State

Bloemfontein

082 319 6929

Supervisor:

Dr A van Aswegen

University of the Free State

Bloemfontein

051 405 3009

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7. Appendix C – Letter to The CEO Universitas Academic Hospital
8. Appendix D – Letter to The HOD Neurosurgery
9. Appendix E – Communication from NHLS regarding National CNS tumour information

Summary:

The study will be performed by collecting all the information that was obtained from performing a biopsy (obtaining a small piece of the growth), a debulking (removing only a part of the growth to make the growth smaller) and/or resection (removing the whole growth) of growths of the central nervous system (brain and spinal cord) at the Universitas Academic Hospital from 01/01/2007 – 31/12/2017.

The patients to be included in this study will be all the patients that had a biopsy, debulking or a resection of a growth that was found in the central nervous system regardless of their age, sex or race.

This study is done to determine what types of growths are found in the brain and spinal cord of patients at Universitas Academic Hospital. This information can be used to improve the care of patients and to see if the information gathered here is the same as in the rest of the world.

Introduction:

Tumours of the central nervous system (brain and spinal cord) cause significant morbidity and mortality worldwide (Armstrong et al, 2016). This has led to intensive research and classification systems to guide the management of these tumours since histological typing of tumours became possible. The 1st classification of brain tumours was published the pathologist Rudolf Virchow in 1863. He was the first to attempt to correlate the microscopic and macroscopic appearance of CNS tumours. He coined the term "glioma" in 1860. Then Bailey and Cushing devised a classification in 1926 and proposed that brain tumours originated from primitive neuro-ectoderm. They classified 14 different tumours according to the cell that they arose from arrested at a certain developmental stage. The tumour cells were morphologically different from the normal cell. Thus astrocytomas arose from astrocytes and so forth. In 1949 Kernohan and his colleagues proposed that the histolopathological difference was due to separate tumour types but rather secondary to different histological differentiation. They significantly reduced the number of brain tumour entities and included a grading system. In 1950 the Ringertz system was based on the hypothesis that different brain cells gave rise to different types of tumours. Ringertz thus proposed that an astrocytoma consisted of 3 grades: astrocytoma, astrocytoma with anaplastic features and glioblastoma. The first classification was edited by Zülch and published in 1979 as the WHO I classification. This classification used the terminology used by Bailey and Cushing and incorporated the grading system proposed by Kernohan. In 1981 the St. Anne-Mayo system was published. It served as a tumour grading system and tumours were graded on the absence or presence of the following 4 criteria: 1. nuclear atypia, 2. Mitoses, 3. Endothelial cell proliferation and 4. Necrosis. Thereafter immunohistochemistry developed and a new classification was published by Kleihues et al. The third edition included genetic profiles as an aid to define brain tumours and was published in 2000 under the guidance of Kleihues and Cavenee. This classification also included epidemiology, clinical signs and symptoms as well as imaging, prognosis and predictive factors. In 2006 a group of pathologists and geneticists convened in Germany and the 2007 WHO (World Health Organization) classification of tumours of the central nervous system was created (Louis et al, 2007). In 2014 a meeting was held in the Netherlands were neuropathologists, neuro-oncological clinical advisors and scientists convened to include the molecular parameters with the histology to define the different tumours. This enables both phenotypic and genotypic parameters for the classification of central nervous system tumours with potentially more homogenous and narrowly defined diagnostic entities that will enable more exact treatment and prognosis determination of patients living with central nervous system tumours (Louis et al, 2016; Louis, Perry et al, 2014).

With the new classification of 2016 a layered diagnosis was proposed. This layered effect includes an integrated diagnosis at the top that will correspond to the previous WHO 2007 classification. This will be followed by a histological classification that is based on the hematoxylin and eosin staining, immunohistochemistry and the electron microscopy. This will then be followed by the standard histological grade. This is determined by the natural history of the tumour after surgical treatment and adjuvant chemotherapy and radiotherapy. The fourth and final layer will consist of the molecular information that was obtained with regards to the tumour. This allows the neuropathologist to obtain a layer 2 or 3 diagnosis should the molecular data not be obtainable. In certain tumours where the molecular information is yet unclear or not yet determined, this will be annotated with NOS (not otherwise specified). Unfortunately the molecular testing is not yet widely available in developing countries and utilizing the new classification system will render a large group of tumours as NOS (Mukherjee 2017, Louis, Perry et al 2014).

Layered diagnosis:

Layer 1: Integrated diagnosis – includes layer 2, 3 and 4

Layer 2: Histological diagnosis – histological classification

Layer 3: WHO grade

Layer 4: Molecular information (Banan et al 2017)

Several changes were made to the classification of tumours in the 2016 classification when compared to the previous 2007 classification and these changes will have to be taken into consideration with evaluation of the data provided.

Very little is known about the incidence and prevalence of central nervous system tumours in general in Africa and South Africa. The United States of America and most of the European countries keep extensive tumour registers with regard to brain tumours, the incidence, epidemiology and outcome.

In the United States of America a Central Brain Tumour Registry (CBTRUS) is kept. A fact sheet was published in 2016 that included all primary malignant and non-malignant tumours of the brain, central nervous system, pituitary and pineal glands as well as olfactory tumours of the nasal cavity. This included brain lymphoma and leukaemia. Their data is obtained from all newly diagnosed tumours as registered at the Centre of Disease Control and Prevention, the National Programme of Cancer Registries and their National Cancer Institute. They estimated an incidence rate of 22.36 cases per 100 000 for all primary malignant and non-malignant brain and other central nervous system tumours with a higher incidence in females (24.45 vs 20.1 per 100 000) and an estimated diagnosis of 79 270 new cases in 2017. According to their published data the worldwide incidence was 3.4 per 100 000 for primary malignant brain and other central nervous system in 2012 with the male to female incidence being 3.9 per 100 000 for males and 3.0 per 100 000 for females. The incidence in developed countries were also higher at 5.1 per 100 000 vs 3.0 per 100 000 in developing countries (CBTRUS factsheet, 2016).

The paediatric incidence in the age group of 0 – 14 years for primary malignant and non-malignant brain and other central nervous system tumours were 5,47 cases per 100 000. The rate was higher in males than in females (5.69 vs 5.24 per 100 000 respectively).for the age group 0 – 19 years of age an incidence of 5.67 cases per 100 000 was found with a higher incidence in females than in males (5.71 vs 5.69 cases per 100 000). In the age group 15 – 39 years the incidence for primary malignant and non-malignant brain and central nervous system tumours was found to be 10.71 cases per 100 000 with a higher rate for malignant vs non-malignant tumours (7.47 vs 3.24 cases per 100 000).

The tumours are also defined by histopathological diagnosis and distribution in the brain. The histopathological distribution is as follows:

Percentage	Tumour type
36.2	Non-malignant meningioma
15.9	Non-malignant pituitary tumours
14.9	Glioblastoma

10.9	All other malignant glioma
8.2	Non-malignant nerve sheath tumours
6.7	Non-malignant tumours involving neuronal and non-neuronal glial tumours, pineal region tumours, embryonal tumours and other tumours of cranial and spinal nerves
5.7	Other malignant tumours from choroid plexus, neuronal and mixed neuronal glial tumours, pineal region tumours, embryonal tumours and nerve sheath tumours
1.1	Non-malignant glioma
0.5	Malignant meningioma

The distribution was further divided into distribution according to malignant and non-malignant tumours:

%	Malignant tumours	%	Non-malignant tumours
23.6	Frontal lobe	53	Meninges
17.4	Temporal lobe	24.9	Pituitary and craniopharyngeal duct
10.6	Parietal lobe	9.6	Cranial nerves
4.8	Cerebellum	3.0	Spinal cord and cauda equina
4.5	Cerebrum	2.6	Other brain
3.0	Cauda equina and spinal cord	1.4	Cerebellum
2.8	Occipital lobe	1.2	Frontal lobe
1.8	Meninges	1.0	Ventricle
1.4	Ventricle	0.9	Temporal lobe
1.2	Cranial nerves	0.5	Parietal lobe
0.8	Pineal region	0.4	Brainstem
0.4	Pituitary and craniopharyngeal duct	0.4	Cerebrum
		0.3	Pineal region
		0.2	Occipital lobe

(Ostrom et al, 2016).

The South African National Data will be obtained and inserted later as they require approval of the protocol prior to releasing any data (please see appendix E).

1. Aim:

The aim of this study is to create an audit of central nervous system tumours for Universitas Academic hospital.

2. Methods:

2.1 Study design:

A retrospective audit will be performed on all tumour biopsies, resections and debulking procedures performed at Universitas Academic Hospital from 01.01.2007 until 31.12.2017. The patient's age, gender and the location of the tumour will be included. This information will be obtained from the patient's histological diagnosis as available. This information will be obtained from histology results from the Department of Anatomical Pathology (National Health Services

Laboratory) at Universitas Academic Hospital.

2.2 Study participants:

The study will comprise of all patients that presented to the Department of Neurosurgery at Universitas Academic Hospital from 01/01/2007 until 31/12/2017 with a central nervous system tumour that had a procedure to diagnose the tumour histologically. All patients, regardless of age, gender or race that had a tumour biopsy, resection or debulking procedure during this period will be included. No patient will be excluded and those with no clear histological diagnosis will also be included and it will be stated as such. Approximately 500 patients will be included into the study.

2.3 Measurement:

2.3.1 Measurement instrument:

A data collection form will be used to document the patient's age, gender, type of procedure, location of the tumour and their laboratory number. As some of the patients will have more than one laboratory number the UM-number will be utilized to ensure no double entries of a patient into the system. The reason for the multiple laboratory numbers is that some patients will have had a biopsy prior to resection of the tumour to delineate the grade of tumour and to motivate for Gliolan should a glioblastoma multiforme be present to enable maximum resection. Neither the laboratory number nor the UM number will be utilized on the final Excel spread sheet to ensure anonymity. Therefor only the anonymous data will be sent to the Department of Biostatistics. The laboratory number will only be utilized while collecting the data to ensure that no double entries will be made. The laboratory number will otherwise not be utilized to protect the patient's anonymity. This form will be completed with the histological diagnosis and clinical information sent to the Department of Anatomical Pathology at Universitas Academic Hospital.

2.3.2 Collection of data:

The relevant histological results will be obtained from the Department of Anatomical Pathology for the period 01.01.2007 until 31.12.2017. The data collected will be stored in the Department of Neurosurgery in a secured environment. The only personnel with access to the records will be Dr A van Aswegen (supervisor), Dr J Basson (Head of Department of Neurosurgery) and Dr MM de Bruyn (researcher). As the data will be obtained from laboratory records, the time spend to obtain the data will only impact on the researcher and not on other health care workers or patients.

2.3.3 Pilot study:

A pilot study will be performed on 2 patients.

2.3.4 Measurement errors:

There is a possibility that the histology results can be incomplete or not available. Incorrect histological data can also be obtained due to sampling errors. It will be impossible to compare the histological data with radiological diagnosis due to the unavailability of imaging predating 2015. No bias or measurement errors are otherwise expected.

2.5 Analysis:

Descriptive statistics namely means and standard deviations or medians and percentiles will be calculated for continuous data. Frequencies and percentages will be calculated for categorical data. The analysis will be done by the Department of Biostatistics.

2.6 Implementation of findings:

The findings obtained will be utilized to create a data form for everyday use in order for tumours to be neatly classified and accessible on a data base for future use. The data can also be used to expedite the diagnosis and appropriate treatment for the various tumours that are more prevalent in the patient population serviced by the Department of Neurosurgery of the University of the Free State.

The data obtained can also be used to motivate the use of more genetic-based histological diagnosis to ensure a more definitive treatment of the tumour according to the WHO classification of 2016. The findings can be utilized to motivate for more funding to be made available to ensure the more detailed histological diagnosis of tumours and to motivate to obtain the appropriate chemotherapy and genetic treatment for the tumours as indicated by the histological diagnosis obtained.

The information obtained regarding biopsy vs resection vs debulking procedure can be utilized to determine whether the procedure performed was the most appropriate for the tumour and the patient involved. This is important in view of the possible outcome in certain tumours with regards to gross total resection, complete resection and the overall prognosis of the patient as determined by histological type of tumour.

2.7 Time schedule:

The following time schedule is proposed for the study:

	Date
Literature review	October 2017 – February 2018
Seeking ethical approval	March – April 2018
Data collection	May - July 2018
Data analysis	August - September 2018
Writing up	October - November 2018

2.8 Budget:

Approximately R1500 will be budgeted to be contributed by the researcher.

Photocopies	R500
Data usage	R1000
Total	R1500

3. Ethical aspects:

As this is a retrospective audit of surgeries already performed at the Universitas Academic Hospital no potential ethical issues is expected. The research will all be performed on histological diagnosis already available at the NHLS attached to the Universitas Academic Hospital.

Consent to utilize these records will be obtained from the NHLS Anatomical Pathology at Universitas Hospital and the Chief Executive Officer of Universitas Academic hospital.

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