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Epidemiological, descriptive and anatomopathological study of glioblastoma multiforme

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DEDICATION

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“Keep steadfast and push beyond your limits, you can do anything if you set your mind to it, the only person who can stop you is yourself.”

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Bibliographic part

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Practical part

LIST OF ABREVIATIONS

- **AKT:** Ak strain transforming / Protein kinase B.
- **APC:** Adenomatous polyposis coli.
- **ATRX:** alpha thalassemia/mental retardation syndrome X-linked.
- **CCNB1:** Cycline B1.
- **CDC20:** Cell division cycle protein 20.
- **CDK1:** Cyclin-dependent kinase 1.
- **CDKN2A/ CDKN2B:** Cyclin dependent kinase inhibitor 2A/2B.
- **CHU:** Centre Hospitalier Universitaire.
- **CMV:** Cytomegalovirus.
- **CNS:** Central nervous system.
- **CT:** Computed tomography.
- **DAB:** Di-Amino-Benzidine.
- **DNA:** Deoxyribonucleic acid.
- **ECD:** Ethyl-Cysteinate-Dimer.
- **EGFR:** Epidermal growth factor receptor.
- **Erk**: Extracellular signal-regulated kinase.
- **FDG:** Fluorodeoxyglucose.
- **FGF:** Fibroblast growth factors.
- **GBM:** Glioblastoma multiforme.
- **GFAP:** Glial fibrillary acid protein.
- **Gy:** Grays.
- **H2O2:** Hydrogen peroxide.
- **HGF/ SF:** Hepatocyte growth factor/Scatter factor.
- **HMPAO:** Hexamethyl-propylene-amine-oxime.
- **ICP:** Increased intracranial pressure.
- **IDH:** Isocitrate Dehydrogenase.
- **IL:** Interleukin.
- **IMT:**123 I-alpha-methylthyrosine.
- **JPA:** Juvenile Pilocytic Astrocytoma.
- **kD:** Kilodaltons.

- **KPS:** Karnofsky performance status scale.
- **MAPK:** Mitogen-activated protein kinase.
- **MGMT:** 06-Methylguanine-DNA methyltransferase..
- **MHC:** Major histocompatibility complex.
- **MIBI**: methoxy-iso-butyl-isonitril.
- **MMAC1:** Mutated in Multiple Advanced Cancers 1.
- **MRI:** Magnetic Resonance Imaging.
- **mTOR:** Mammalian/Mechanistic Target Of Rapamycin.
- **NADPH:** Nicotinamide adenine dinucleotide phosphate.
- **NF1:** Neurofibromin 1.
- **NF2:** Neurofibromin 2.
- **OSMR:** Oncoststin M Receptor.
- **P14ARF:** ADP-ribosylation factor.
- **p16INK 4a :** cyclin-dependent kinase inhibitor 2A.
- **P21waf1/Clip1:** cyclin-dependent kinase inhibitor 1.
- **P53:** Protein 53.
- **P53-MDM2:** Mouse double minute 2 homolog.
- **PAF:** Platelet-activating factor.
- **PAI:** Plasminogen Activator Inhibitor.
- **PBS:** Phosphate Buffered Saline.
- **PDGF-A:** Platelet derived growth factor sub-unit A.
- **PDGFRA:** Platelet derived growth factor receptor.
- **PET:** Positron emission tomography.
- **PGE2:** Prostaglandin E2.
- **PI3K:** Phosphatidylinositol 3 kinase.
- **PIP3:** Phosphatidylinositol triphosphate.
- **PKB:** Protein kinase B.
- **PTEN:** Phosphatase tensin homology.
- **RAF:** Oncogene protein raf.
- **RAS:** Oncogene-protein p21.
- **RB1:** Retinoblastoma 1.

- **ROS:** Reactive oxygen species.
- **RTK:** Receptor tyrosine kinase.
- **SAPK:** Stress-Activated Protein Kinase.
- **SEGA:** Sub-ependymal giant-cell astrocytoma.
- **Smad:** Suppressor of Mothers against Decapentaplegic.
- **SPECT:** Single-photon emission computerized tomography.
- **STAT3:** Signal transducer and activator of transcription 3.
- **TAK 1:** Transforming growth factor-β activated kinase 1.
- **TEP1:** Telolerase associated protein 1.
- **TERT:** Telomerase Reverse Transcriptase.
- **TGF :** Transforming growth factor.
- **TSG:** tumor suppressor gene.
- **UPA:** Urokinase Plasminogen Activator.
- **VEGF:** Vascular endothelial growth factor.
- **WHO:** World health organization.

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INTRODUCTION

INTRODUCTION

Gliomas refer to all forms of intra-axial tumors that originate from glial cells of the central nervous system (CNS). They are the most common type of CNS tumors, representing about 80% of all malignant brain tumors. Historically, they include types of cells that share similar histological characteristics, such as astrocytomas (high-grade astrocytomas are denominated glioblastomas), brain stem gliomas, ependymomas, oligodendrogliomas, optic pathway gliomas, and mixed gliomas.

The most common and yet most deleterious grade IV glioma subtype is glioblastoma multifome (GBM) **(Rajaratnam et al., 2020).** It forms from cells called astrocytes that support nerve cells. this tumor was first identified in 1863 by Rudolf Virchow as a tumor with glial cell origin using microscopic and macroscopic techniques which ultimately give rise to modern day classification of brain tumors (**Sameer et al., 2012).**

This tumor has an incidence rate of less than 10 per 100,000 people globally and the incidence is higher in men than in women. It is mostly common in adults with in the age range of 55 to 60 years. There is no knowledge about the carcinogenetic causes of brain neoplasms and the only confirmed risk so far is exposure to high dose ionizing radiation. To date, brain neoplasms are still highly incurable **(Farina et al., 2017).**

It is characterized as being heterogeneous with multifocal hemorrhage, necrosis, cystic and gelatinous areas, a pleomorphic cell population, a high mitotic activity and a vascular endothelial cell proliferation usually with a glomeruloid structure (**Habib Allah., 2008).**This type of brain tumor known as glioblastoma is one of the most difficult cancers to treat. Complete removal by surgery is impossible because of where and how this tumor infiltrates brain tissues **(Grisham et al., 2019).**

In our present study our objectives are to determine how it affects individuals, how it functions and why it is difficult to treat. In order to realize this, we carried out a descriptive epidemiological and anatomopathological study of GBM in Constantine region.

Bibliographic part

Chapter 01:
The nervous system

1. Definition

The nervous system is the body's command center, it is made up of the central nervous system (CNS) and the peripheral nervous system. The brain and spinal cord makes up the central nervous system, whereas the nerves that branch out from the brain and spinal cord form the peripheral nervous system [**(Cherry., 2022), (Thau et al., 2021)].**

2. Embryology

The nervous system develops from a section of the ectoderm called the neural plate, which begins to differentiate under the influence of the nearby notochord and paraxial mesoderm. During the third week of embryological development, the brain and spinal cord begin to form. The ectoderm starts thickening leading to the formation of the neural plate, the neural groove then forms from the inward folding of the neural plate. The neural groove is flanked by neural folds that migrate laterally. It develops into the neural tube, which gives rise to the CNS structures **(Figure.1) (Thau et al., 2021).**

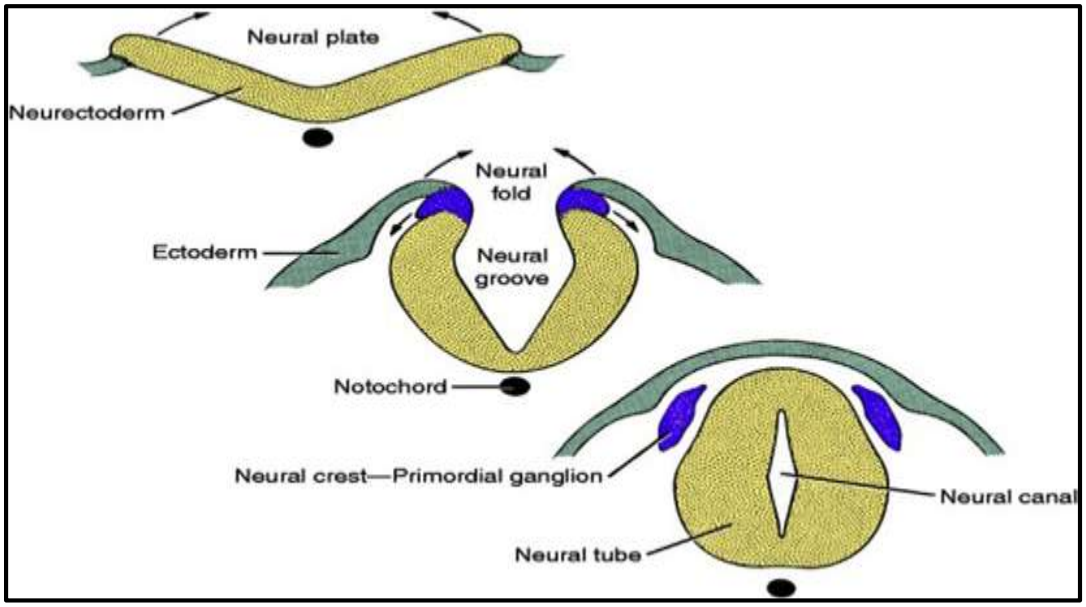

Figure.1: Transverse sections of the development of the neural tube (De Lahunta et al., 2016).

The neural tube separates to form the anterior and posterior end whereby the anterior end gives rise to the primary brain vesicles, prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain), whereas the posterior end gives rise to the spinal cord. The primary brain vesicles differentiate continuously to form secondary brain vesicles. The

telencephalon and diencephalon is formed from the separation of the forebrain whereas the metencephalon and the myelencephalon (spinal brain) is formed from the cleavage of the hindbrain. The midbrain does not cleave and remains the mesencephalon [**(Thau et al., 2021),** (**Stiles and Jernigan., 2010)].**

As development continues, the secondary brain vesicles develop and give rise to the adult brain structures:

- Telencephalon forms the cerebrum.
- Diencephalon forms the hypothalamus, thalamus, and retina.
- Mesencephalon forms the brain stem (midbrain).
- Metencephalon forms the brain stem (pons), cerebellum.
- Myelencephalon forms the brain stem (medulla oblongata).

Continuous hollow cavities called ventricles are formed from the central part of the neural tube. The cerebral cortex changes from a smooth to wrinkled, convoluted appearance due to the continued growth of the cerebral hemispheres during the sixth month of gestation, gyri are the elevated parts of the ridges whereas the grooves are called sulci. There are also areas called white matter consisting of myelinated axons and gray matter consisting of neuronal cell bodies, dendrites, glia, and unmyelinated neurons with in the brain. The caudal portion of the neural tube forms the spinal cord. The dorsal alar plate and ventral basal plate are formed from the aggregation of the gray matter during the sixth week of gestation. The alar plate gives rise to interneurons, the basal plate gives rise to motor neurons whereas the neural crest cells forms dorsal root ganglia which brings information from the periphery to the spinal cord **(Thau et al., 2021).**

3. Brain Anatomy

3.1. Weight

Brain size is sometimes measured by weight and sometimes by volume (by MRI scan or by Skull volume). The average brain weight of an adult male and female is approximately 1322g and 1219g respectively **(Mehrpour et al., 2010).**

3.2. Structure

The brain is a gelatinous mass enclosed in three connective tissue membranes called meninges which are arranged in successive layers. It is further surrounded by a protective outer capsule of bone called the skull. The brain is supported in the cerebrospinal fluid (CSF) in which it floats and serves as a shock absorber during fast head movements. The meninges contain major arteries and veins which supply the brain **(Strominger et al., 2012).**

3.3 Subdivisions

There are three major divisions of the brain which are the cerebrum, cerebellum and brain stem. These three are further subdivided into:

- The two cerebral hemispheres which remain in contact and communication with each other via the corpus collosum and each consist of an olfactory system, corpus striatum, cerebral cortex and white matter. Each hemisphere further splits to form a frontal, parietal, occipital and temporal lobe with each lobe performing different functions
- Thalamus, epithalamus, hypothalamus, and subthalamus.
- Midbrain which contains the tectum, and cerebral peduncles.
- Pons and cerebellum.
- Medulla oblongata [**(Kiernan and Barr., 2009), (Bui and Das., 2021)],** (**Figure 2, 3).**

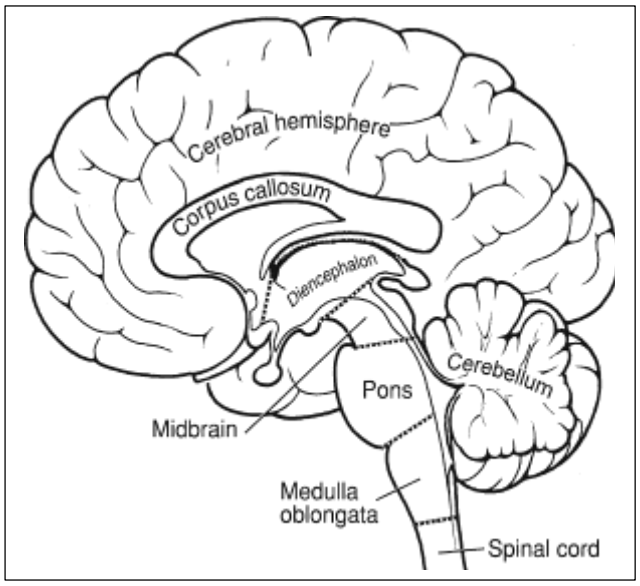

Figure.2: Major subdivisions of the central nervous system viewed in sagittal section (Strominger et al., 2012).

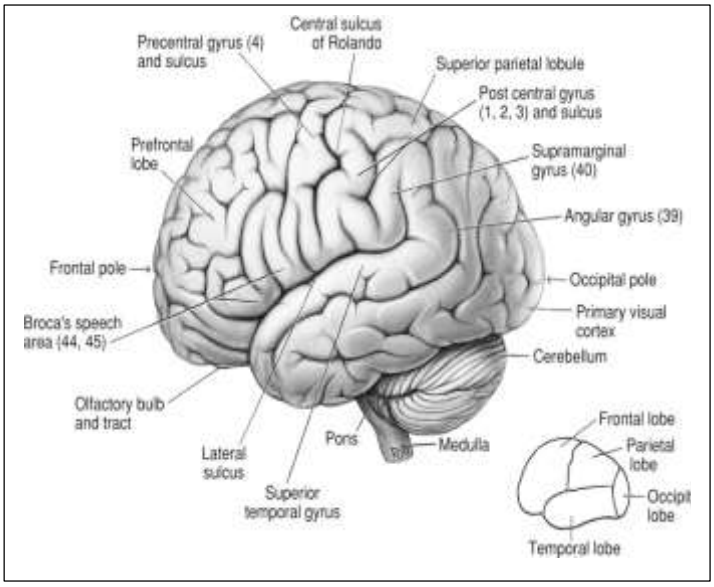

Figure.3: Lateral surface of the brain (Strominger et al., 2012).

3.4 Cells

The CNS consists of two principal types of cells, namely neurons or nerve cells and neuroglial cells. The neurons carry out conduction of nerve impulses and exchange of signals with other nerve cells **(Kiernan and Barr., 2009).** The neuroglial cells carry out a supportive function of forming myelin sheaths around axons thereby permitting fast conduction of signals and keep the concentrations of ions and neurotransmitters in the neuronal environment at normal level **(Jessen., 2004).** Astrocytes, oligodendrocytes, ependymal cells and microglia make up the neuroglial cells of the CNS while Schwann cells in nerves and satellite cells in ganglia make up the neuroglial cells of the peripheral nervous system **(Kiernan and Barr., 2009).** The regions of the brain richly consisting of neurons, synapses and glia are known as gray matter whereas white matter are the regions of the brain richly consisting of axons and glia **(Woolsey et al., 2017).**

3.5. Vasculature

3.5.1. Arterial system

Blood supply to the brain is primarily via the internal carotid artery and the vertebral artery which ascend through the neck and enter the skull. The internal carotid arteries form the anterior brain circulation, while the vertebral arteries (which combine to form the basilar artery) form the posterior circulation and they are interconnected via the circle of Willis, which is located in the subarachnoid cisterns at the base of the brain **(Figure.4) (Mastorakos and Mc Gavern., 2019).**

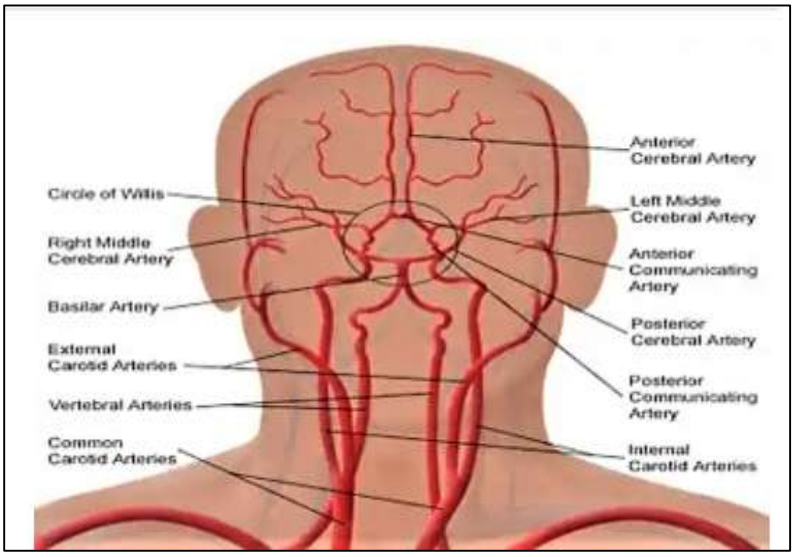

Figure.4: Arterial blood supply to the brain (Konan et al., 2021).

3.5.2. Venous system

The cerebral venous system is divided into a superficial and a deep system, whereby superficial surfaces of both cerebral hemispheres is drained by the superficial system which consists of sagittal sinuses and cortical veins whereas the deep system comprises the lateral sinus, straight sinus and sigmoid sinus and also draining deeper cortical veins. Both of these systems drain into the internal jugular veins **(Kiliç and Akakin., 2008).**

The figure below shows venous blood collected deep within the brain to the dural sinuses through superficial and deep cerebral vein. The red arrows in the diagram show the principal directions of venous blood flow in the major sinuses **(Figure.5).**

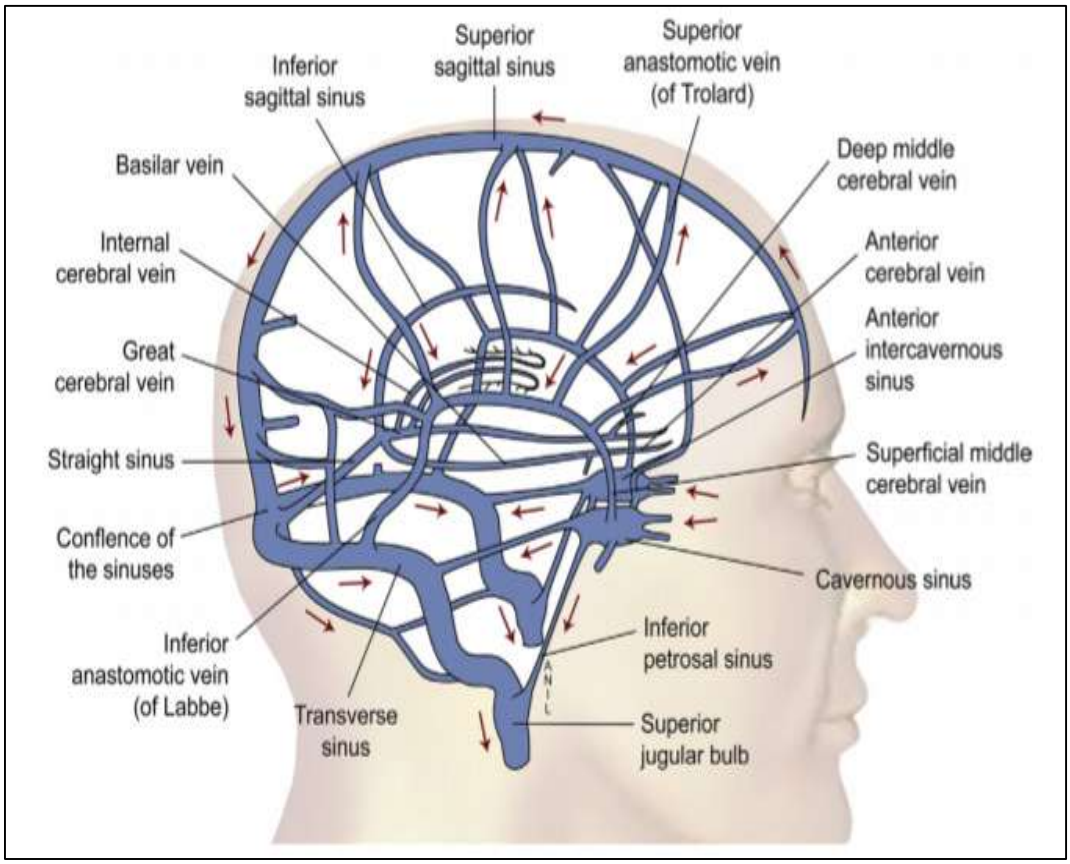

Figure.5: Anatomy of the cerebral venous system (Gupta., 2017).

Chapter 02:

GLIOBLASTOMA MULTIFORME

1. Definition

Glioblastoma multiforme (GBM) is a fast growing and aggressive brain tumor. It is the most frequent malignant tumor of the central nervous system and it is regarded as a grade IV glioma, according to the 2016 world health organization (WHO) classification of tumors; of the central nervous system. It accounts for 15 % to 20% of all intracranial tumors and represents approximately 50% of gliomas in adults **(Cheng et al., 2005).**

It can also affect the spinal cord to a lesser extent, representing only 1% to 5% of all glioblastomas and only 1.5% of all spinal cord tumors. Both spinal cord and cerebral GBM have an identical histomorphology **(Strik et al., 2000).**

It is divided into primary GBM and second secondary GBM depending on clinical characteristics. Primary GBM occur without any clinical and histological evidences of precursor lesion whereas secondary GBM develops slowly from preexisting low grade astrocytoma **(Farina et al., 2017).**

The diagnosis of GBM is based on histopathological examination and immunohistochemical examination which is necessary to provide additional information for diagnostic purposes **(Venugopal et al., 2015).**

Despite extensive treatment which comprises of surgical resection, radiotherapy and chemotherapy, GBM is still a lethal tumor with a poor prognosis and a median overall survival rate estimated at 15 months for newly diagnosed patients and 8 months for patients with tumor recurrence **(Chiara et al., 2016).**

2. Epidemiology

According to the worldwide incidences, GBM affects less than 10 per 100,000 people and has a poor prognosis with a short survival time of approximately 15 months after diagnosis. It represents 50% of all gliomas and is mostly affects people within the 50 to 60 age range. The incidence rate of GBM is higher in men than in women with a sex ratio of 1.6. Developed countries register more cases of gliomas than less developed countries. This is because there is less access to health care as well as differences in diagnostic practices in under developed countries compared to developed countries. Whites, Latinos and Asians are more susceptible to suffer from GBM as compared to blacks as pointed out in some research studies. Malignant

gliomas account for 2,5% of deaths as a result of cancers and represents the third leading cause of death as a result of cancer in people within the 15 to 34 age range **(Hanif et al., 2017).**

3. Classification

The world health organization (WHO) has developed a grading system to indicate a tumor's malignancy or benignity. In addition to the 2000 and 2007 WHO classifications, which regard histological features under a microscope as a basis for classification of tumors of the central nervous system, the most recent 2016, WHO classification also integrates molecular parameters into the classification of diffuse gliomas.

For tumors which cannot be classified precisely because of insufficient information for example tumors that do not show the diagnostic genetic alterations, the 2016 WHO classification categorizes such tumors as NOS (Not Otherwise Specified) **(Louis et al., 2016).**

3.1. Histological classification

WHO recognizes three main categories of glial tumors basing on the cell type from which the tumor proliferation is derived, and these tumors are; astrocytomas, oligodendromas (and oligoastrocytomas) and ependymomas**.** Astrocytic and oligodendroglial tumors are infiltrating gliomas which can be low or high grade as opposed to circumscribed gliomas, such as ependymomas **(Lamée., 2015).**

3.2. Classification based on genetic mutations

According to genetic mutations, GBM can be classified into primary and secondary GBM. Primary GBM or isocitrate dehydrogenase (IDH)-wild type does not originate from an identifiable lower-grade precursor lesion and there is absence of mutations in the IDH genes. It is also subdivided into giant cell GBM, gliosarcoma and epithelioid GBM variants. Secondary GBM or IDH-mutant originates from a low grade glioma and shows mutations in the IDH 1 or IDH 2 gene **(Louis et al., 2016).**

Primary GBM is characterized by epidermal growth factor receptor (EGFR) over expression, Telomerase Reverse Transcriptase (TERT) promoter mutations, homozygous deletion of Cyclin dependent kinase inhibitor 2A/2B (CDKN2A/CDKN2B), loss of chromosomes 10p and 10q, phosphatase tensin homology (PTEN) mutations/deletion, tumor protein 53 (TP53) mutations and phosphatidylinositol 3 kinase (PI3K) mutations [**(Tamimi and Juweid., 2017), (Louis et al., 2016)].**

Secondary GBM is characterized by IDH1 or IDH2 gene mutation, TP53 mutations, alpha thalassemia/mental retardation syndrome X-linked (ATRX) mutations and loss of the 10q chromosome arm **(Louis et al., 2016).**

3.3. Histological grading

Histological grading of tumors of the CNS according to WHO 2016, is based on the level of tumor malignancy (**Table 1)**.

- Grade I gliomas refer to lesions characterized by a low proliferative potential and have a high chance of cure by surgical resection alone.
- Grade II gliomas refer to lesions commonly infiltrative with a low degree of proliferation.
- Grade III gliomas are malignant lesions with nuclear atypia and a high mitotic activity.
- Grade IV gliomas are highly malignant tumors, with a high mitotic activity, necrosis-prone neoplasms and infiltrative **(Louis et al., 2016).**

Table 1: Characteristics and Statistics Related to Selected Gliomas (Davis., 2018).

	WHO Grade	Histology	Approximate percentage of all gliomas	Characteristics	Estimated 5-year survival(%)
Benign		Ependymoma: subependymoma, subependymal giant-cell astrocytoma (SEGA)	5.2	-Can be slow or fast growing. -Usually located in the ventricles but can extend to the spinal cord. -Common in children; occurrence peaks at age 5 then about age 34.	65
Low grade	I	Pilocytic astrocytoma, also known as Juvenile Pilocytic Astrocytoma (JPA)	5.1	-Slow growing, usually benign, often cystic. - Most common in the cerebrum, but can grow in optic nerve pathways, cerebellum, and brain stem. - Occurs most often in children and teens.	98
	II	Oligodendroglioma (5%) Astrocytoma (17.4%) Oligoastrocytoma (5.6%)	28.0	-Tend to be slow growing. -Rarely grow outside of brain. -Common among men.	50
High grade	III	Anaplastic astrocytoma Anaplastic oligodendroglioma Anaplastic oligoastrocytoma	6.7	-Grows faster and more aggressively than grade II. -Tend to invade neighboring tissue. -More common at ages 30 to 50. -More common in men than women.	30
	IV	Glioblastoma (GBM)	55.0	-Can develop directly (de novo) or evolve from low-grade tumor. -Highly invasive in brain -Most common in older adults than children and in men than women	< 5

4. Risk factors

The causes of GBM are not yet fully known however some risk factors have been noted. These risk factors are identical to those of other gliomas and they are subdivided into intrinsic and extrinsic risk factors **(Urbańska et al., 2014).**

4.1. Intrinsic risk factors

- **Genetic factors**

This is usually seen in patients with hereditary cancer syndromes and they include Li-Fraumeni syndrome, which is caused by mutations in the tumor suppressor gene TP53, neurofibromatosis types I and II which is caused by mutations in the neurofibromin 1 (NF1) and neurofibromin 2 (NF2) genes, or the Turcot syndrome which is caused by mutations in the deoxyribonucleic acid (DNA) repair gene, adenomatous polyposis coli (APC) **(Wirsching and Weller., 2017).**

- **Hormonal factors**

There is a high risk of GBM occurring in women during their post menopause compared to women in their reproductive years which suggests the likelihood that estrogens exerts a protective role during the premenopausal years **(Kabat et al., 2010).**

- **Sex**

According to the study carried out by Ostrom et al, there is a high likelihood of GBM occurrence in men than in women**,** relating to a sex ratio of 1.6 **(Kabat et al., 2010).**

- **Ethnic factors**

There is a high likelihood of GBM occurring in Whites, Asians, and Latinos than in Africans and African Americans. The reason for this occurrence is not yet fully known **(Hanif et al., 2017).**

- **Age**

The risk of GBM rises with age with most diagnosis in patients aged 60 years and above **(Aizer and Alexander., 2017).**

4.2. Extrinsic risk factors

▪ Ionizing radiation

It is the basic risk factor for brain tumors. Extensive prior therapeutic radiation has been reported to cause GBM or glioma **(Barnholtz-Sloan et al., 2018).**

▪ Occupational risk factors

Studies conducted among industrial workers with exposure to lead, workers in rubber industries, agricultural workers with frequent exposure to pesticides has shown inconclusive evidence for risk of occurrence of GBM with these occupational risk factors **(Chatel et al., 2005).**

▪ Electromagnetic fields

There is insufficient evidence to prove that electromagnetic fields are a risk factor for the occurrence of GBM **(Ohgaki and Kleihues., 2005).**

▪ Cellular phones

There is insufficient evidence to prove a link between the use of cellular phones and the risk of occurrence of GBM **(Frumkin et al., 2001).**

▪ Head injury

There is inconsistent and weak relationship between head injuries and risk of occurrence of gliomas **(Ohgaki and Kleihues., 2005).**

However, studies conducted by Hochberg et al on 160 GBM patients suggested that severe head trauma in adults is a significant risk factor for GBM **(Lan et al., 2021).**

Traumatic brain injury could lead to the migration of macrophages to the site of injury, followed by increased interleukin 6 (IL-6) production. Traumatic brain injury also induces enhanced IL-6 secretion by astrocytes and microglial cells. The increased IL-6 could thus activate signal transducer and activator of transcription-3 (STAT3), which increases cell proliferation at the site of injury, as well as inhibition of apoptosis. STAT3 suppresses T lymphocytes and inhibits major histocompatibility complex (MHC) class II molecules on cells of the immune system. The increased IL-6 also damages the blood-brain barrier (BBB). In addition, microglia secretes metalloproteinases in the tissues adjacent to the tumor, facilitating its migration and development. Prostaglandin E2 (PGE2) is also synthesized by microglia and suppress T lymphocytes, and also decrease the expression of MHC II molecules on antigen-presenting cells. Besides, reactive oxygen species (ROS) might lead to certain mutations in stem cells that migrate

to the site of injury. At the site of injury, the risk of these mutations, and cell proliferation increase, as well as the apoptosis inhibition, may jointly contribute to carcinogenesis (**Figure 6), (Lan et al., 2021).**

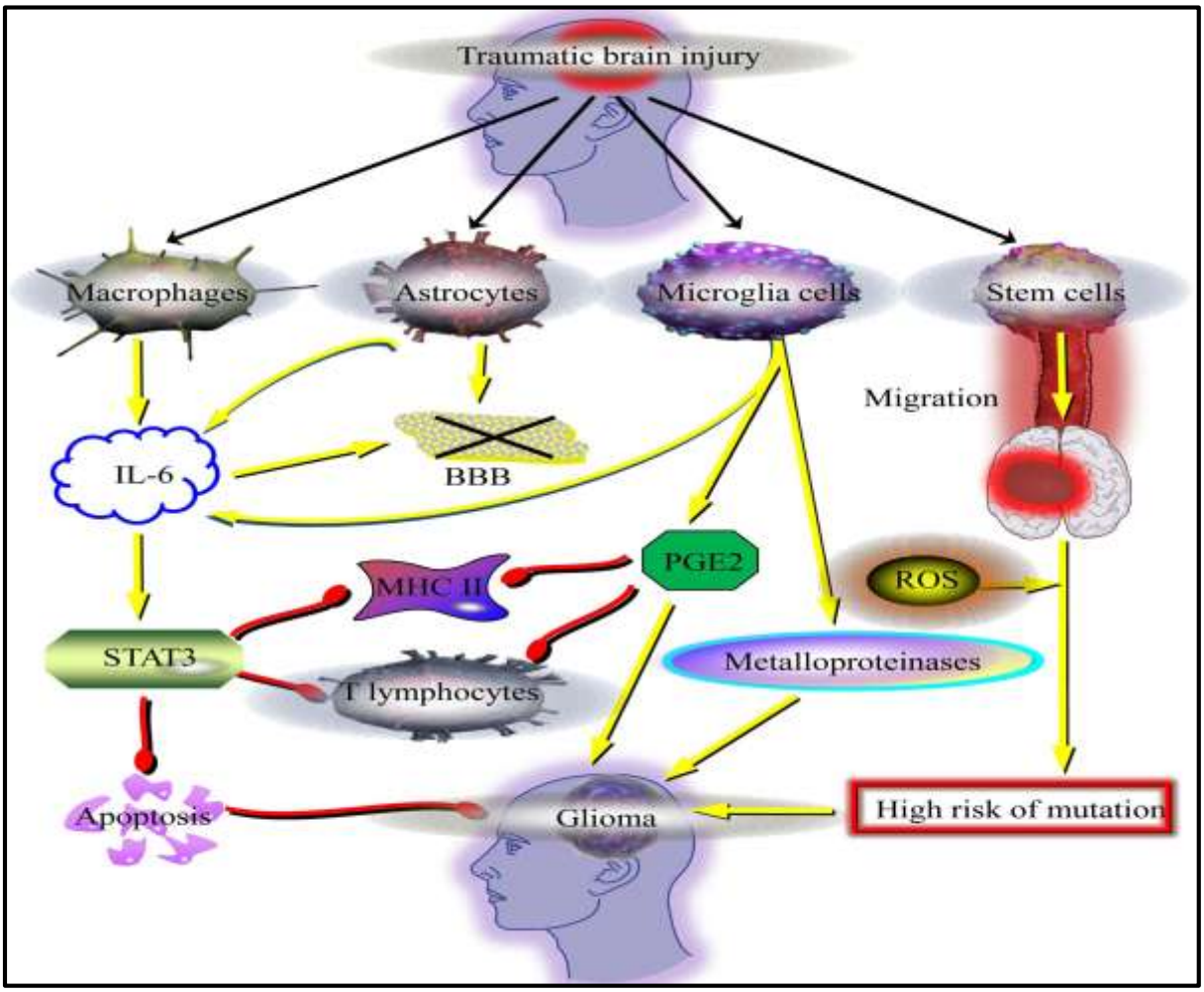

Figure.6: Schematic representation of various carcinogenic factors during traumatic brain injury (Lan et al, 2021).

- **Smoking**

There is inconclusive evidence to show the relationship between cigarette smoking and risk of occurrence of gliomas **(Zheng et al., 2001).**

- **Allergy and immunological conditions**

There is low risk of occurrence of gliomas in persons with a history of allergies and autoimmune diseases **(Brenner et al., 2002).**

▪ **Diet**

Epidemiological studies have shown an elevated risk of developing gliomas in adults from consuming foods containing high levels of nitrate, such as cured meat. Some studies have also shown that consuming cured meats and processed meats by mothers during their pregnancy can lead to an increased risk of astrocytic gliomas in their children. However these studies are still inconclusive **(Ohgaki and Kleihues., 2005).**

▪ **Viral infections**

Studies have shown that cytomegalovirus (CMV) gene products interact with glioblastoma core signaling pathways. Therefore, viral oncogenesis due to oncogenetic or oncomodulatory roles played by cytomegalovirus (CMV) in gliomagenesis has been postulated, though there is still rare experimental evidence to confirm the role of CMV in gliomagenesis **(Wirsching and Weller., 2017).**

5. Oncogenesis

The oncogenesis of GBM cannot be differentiated from general oncology models, it involves either amplification or overexpression of dominant oncogenes, or mutation, or deletion of tumor suppressor genes (**Rajaratnam et al., 2020).**

5.1. Oncogenes

These are genes that have the potential to cause cancer. In tumor cells these genes are often mutated or overexpressed at high levels. Among such genes is the EGFR gene, mutations in the epidermal growth factor receptor (EGFR) commonly occur in glioblastoma. Enhanced activation of EGFR can occur through a variety of different mechanisms, both ligand-dependent and ligand-independent. Numerous evidence has suggested that EGFR is overexpressed in most of primary glioblastomas and some of the secondary glioblastomas and is characteristic of more aggressive glioblastoma phenotypes **(Hongsheng et al., 2017).** Recent research has shown that EGF-stimulates EGFR activation leading to a dissociation of the EGFR VIII-Met complex with a concomitant loss of Met phosphorylation. The cytokine receptor Oncostatin M Receptor (OSMR) can form a coreceptor with EGFR VIII to activate Signal transducer and activator of transcription 3 (STAT3) which promotes GBM tumor growth **(Sun et al., 2018).** Further studies have shown that over expression or amplification of genes such as Cyclin-dependent kinase 1 (CDK1),

Cycline B1 (CCNB1) and Cell division cycle protein 20 (CDC20) are associated with poor survival in GBM **(Zhang et al., 2018).**

5.2. Tumor suppressor genes

Tumor suppressor genes, or antioncogenes, code for proteins that control the cell cycle, apoptosis, genome stability (repair) and interactions with the extracellular matrix or with other cells. The P53 gene located on chromosome 17p is currently the most important cancer gene. Its inactivation is a source of genomic instability, thus promoting the occurrence of additional genetic alterations facilitating tumor progression.

The deletion of the contiguous genes P16/CDKN2A, P15/CDKN2B (inhibitors of cyclin-dependent kinases) and P14/ARF (alternative reading frame) at 9p is frequent in glioblastomas. It is associated with the inactivation of the antioncogene RB1 (RB for retinoblastoma) at p13 and p14, CDK4 and CDK6 which are cyclic-dependent kinases are no longer inhibited by P16 and P15. They will cause the phosphorylation of the Rb protein (retinoblastoma protein), which then becomes inactive and can no longer block the cell cycle. The PTEN/MMAC1 gene (protein phosphatase and tensin homology and mutated in multiple advanced cancers) at 10q encodes an enzyme with phosphatase activity which plays a key role in intracellular signal transduction. The inactivation of PTEN/MMAC1 is at the origin of an inhibition of apoptosis, a deregulation of the cell cycle, as well as an increase in the invasive capacities of the cell. **(Figure 7).** [(**Habib Allah., 2008), (Ohgaki and Kleihues, 2007)].**

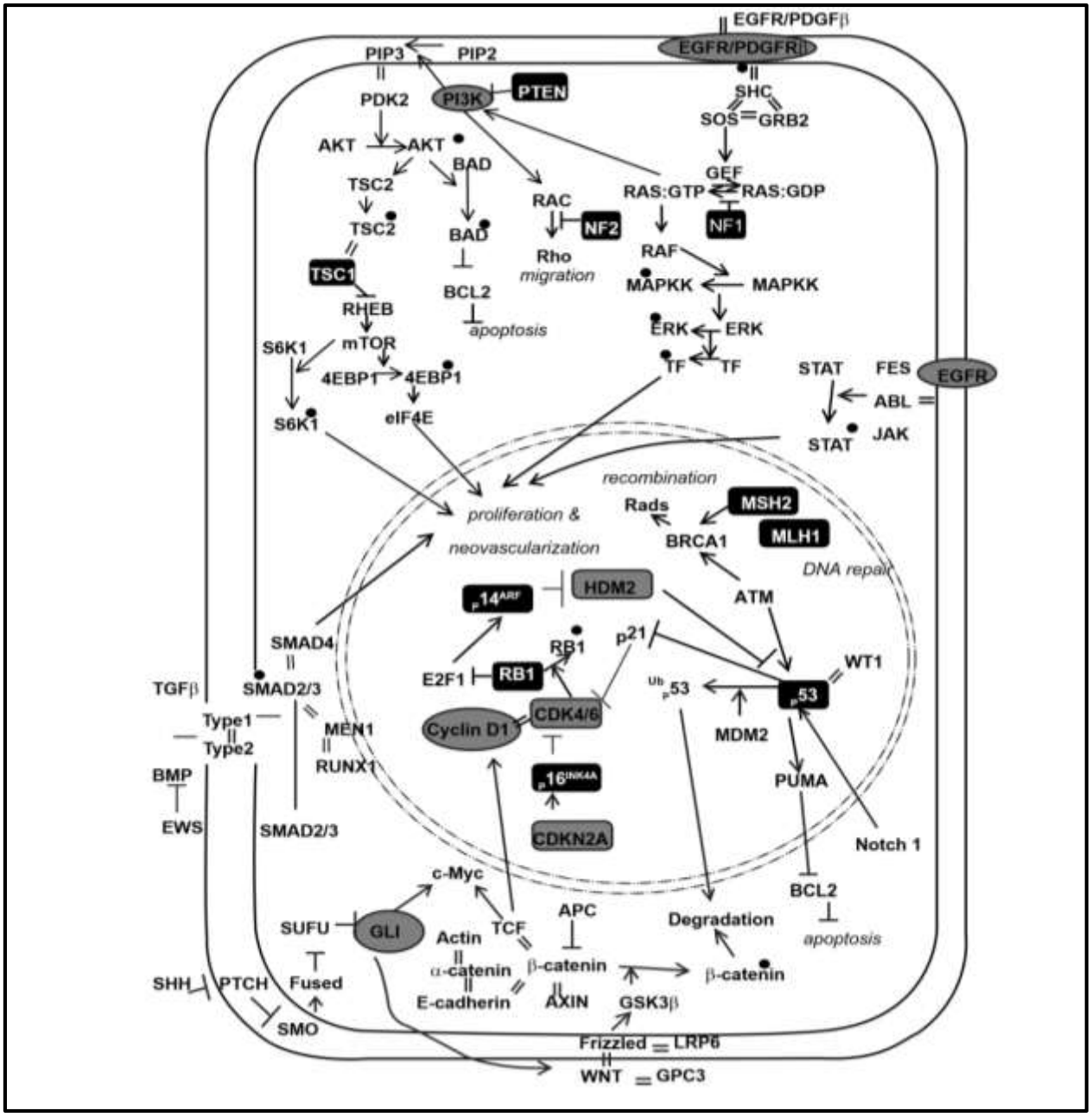

Figure.7: Signaling pathways implicated in GBM (oncogenes are in gray circles, tumor suppressor genes are in black boxes, black dots are phosphate groups, equal signs represent protein-protein interactions) (Okezie et al., 2009).

5.3. Signaling pathways

5.3.1. P53-MDM2-p14ARF pathway

The TP53 tumor suppressor gene encodes a protein that regulates genes involved in cell cycle arrest in the G1 and G2 phase, cell death and differentiation, DNA repair, and neovascularization **(Manzano et al., 2009**). There are various ways TP53 can be altered, such as indirect inactivation, mutation, deletion, or damage to the genes (**Oghaki et al., 2009)**.

The majority of malignant brain tumors, including GBM, demonstrate inactivating mutations in either the p53 and/or retinoblastoma (RB) pathways. These two pathways affect numerous cellular functions, but they are most intensely implicated in cell cycling regulation during times of cell repair or cell growth. They interact with each other via p21. P53 is a short-lived transcription factor which is upregulated in response to cellular stress such as radiation exposure, DNA strand breaks, and toxins. It facilitates DNA repair by halting the cell cycle for repair enzymes to work, or if the damage is too great, it induces cell death. It is a protein that sets a cell's apoptotic threshold in response to specific endogenous and exogenous stimuli. Following DNA damage, p53 is activated and induces transcription of genes such as p21Waf1/Cip1 which are stabilized by binding to p14ARF and degraded by MDM2 **(Okezie et al., 2009).**

5.3.2. Receptor Tyrosine kinase Mutations

Mutations and amplifications in the RTK (receptor tyrosine kinase) include EGFR, platelet derived growth factor receptor A (PDGFRA), basic fibroblast growth factor receptor 1, and insulin-like growth factor receptor. These proteins act in a cascade to drive and regulate cellular processes throughout the cell. Gliomas utilize two main signaling pathways: the RAS/ RAF/ MAPK pathway, which control cellular proliferation, differentiation and migration, in addition to P13K/AKT /mTOR pathway, which promotes cell proliferation and survival through the cell cycle and the inhibition of apoptosis. The tumor suppressor gene PTEN, which negatively regulates the pathway, regulates P13K**.** About 36% of gliomas lack PTEN, which upregulates the pathway and causes resistance to EGFR therapies [**(Ohgaki et al., 2007), (Mellinghoff et al., 2005), (Padfield et al., 2015)].**

5.3.3. TGF-β signaling

Transforming growth factor-β (TGF-β) can function as a tumor suppressor gene in GBM by inhibiting expression of CDKs or downregulating CDK activity by inducing CDK inhibitors p15, p27, and Cip/WAF1/p21. It can downregulate cell adhesion proteins, induce an epithelial to mesenchymal transition, and thereby, enhance cell migration and invasion. TGF-β can alter collagen synthesis, integrin expression, cell adhesion to reconstituted basement membrane, and invasiveness in gliomas. TGF-β1 and TβRII are expressed in GBM and not in normal brain or low-grade gliomas, where expression levels are indirectly correlated with survival. TGF-β induces expression of platelet derived growth factor sub-unit A (PDGF-A), which may serve as the primary mediator of TGF-β growth stimulatory effects. Instead of the standard Smad pathway that results in growth inhibition, TGF-β can deviate upstream of Smad to activate other mitogenic pathways implicated in GBM, including MAPK (Ras-Erk) and SAPK (Rho-JNK, TAK1-p38 Kinase). These pathways result in activation of different target genes leading to proliferation and transformation **(Okezie et al., 2009).**

5.3.4. Isocitrate dehydrogenase mutations

IDH1 and IDH2 genes are responsible for two important metabolic enzymes; isocitrate Dehydrogenase 1, which is present in peroxidase and cytosol, and isocitrate Dehydrogenase 2, which is present in the mitochondria. These enzymes are crucial in catalyzing the oxidative carboxylation of isocitrate to alpha – ketoglutarate, which forms nicotinamide adednine dinucleotide phosphate hydrogen (NADPH) in the citric acid cycle **(Xu et al., 2004).** When there are mutations in the IDH genes, reactions are catalyzed that generate an oncometabolite, 2-hydroxyglutarate (2- HG), which is a common feature in human brain cancer **(Dang et al., 2009).** These mutations have been found in secondary GBMs, in 73-85% of cases **(Yan et al., 2009).** Gliomas that contain the IDH mutation occur in the presence of other abnormalities, such as the TP53 mutation. These IDH-mutant tumors are connected to epigenetic changes like, DNA methylation disorders **(Figure 8)** [**(House et al., 2010), (Duncan et al., 2012)].**

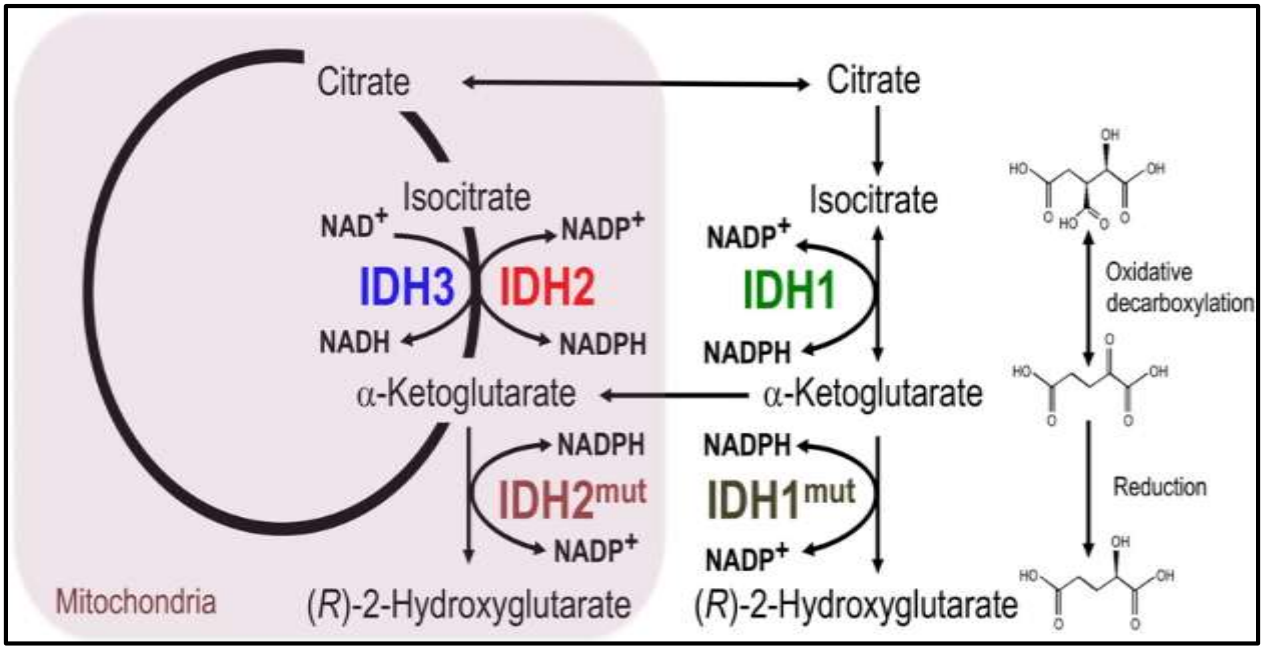

Figure .8: Subcellular localization and chemical reactions catalyzed by wild type IDH and tumor derived IDH mutant enzymes (Ghelfi et al., 2019).

5.3.5. RB1-p16INK4a pathway

RB1 controls the transition from G1 into S phase of the cell cycle by inhibiting the action of elongation factor E2F1. The cyclin-dependent kinase 4 (CDK4)/cyclin D1 complex phosphorylates the RB1 protein, thereby increasing release of the E2F1 transcription factor that activates genes involved in the G1 to S transition. p16INK4a binds to CDK4, inhibits the CDK4/cyclin D1 complex, and thus inhibits the G1 to S transition. Inactivating mutations in RB1 or the upstream factor p16INK4a (also called inhibitor of CDK4a), or activating mutations in the downstream factors CDK4 or cyclin D, cause dysregulated control of E2F1. This leads to the expression of S-phase-related genes and uncontrolled cell cycling. Additionally, it leads to expression of anti-apoptotic genes like Bcl-2, causing uncontrolled cell proliferation. The genetic locus INK4a/ARF on chromosome 9p21 produces both p14ARF and p16INK4a by alternative splicing. Since p16INK4a negatively regulates CDK4 and p14ARF (p19ARF in mice) inhibits MDM2, blocking rapid ubiquitin-mediated decay of p53, simultaneous inactivation of both genes by a homozygous deletion deregulates both the RB1 pathway and the p53 pathway. In other words, this single locus drives gliomagenesis (**Okezie et al., 2009).**

5.3.6. PTENAkt-1 pathway

Mutations of the tumor suppressor gene (TSG) phosphatase tensin homology (PTEN) on chromosome 10q23, also called MMAC1 and TEP1, occur frequently in familial developmental and cancer syndromes such as Cowden-Bannayan syndrome and Lhermitte Duclos disease. This type of mutation is almost exclusively seen in primary GBMs, but rarely in secondary GBMs. PTEN contains a central catalytic phosphatase core domain that negatively regulates PI3K by dephosphorylating phosphatidylinositol-3,4,5-triphosphate (PIP3) and phosphatidylinositol-3,4 diphosphate (PIP2). The N-terminus of PTEN is homologous to the cytoplasmic proteins tensin and auxilin, which interact with actin filaments at focal adhesions and clathrin-coated vesicles. In the case of mutant PTEN, the elevated lipid second messenger PIP3 is used by PI3K to hyperphosphorylate Akt (also known as protein kinase B [PKB]).This modulates the activity of proteins that play a critical role in cell survival, invasion, and proliferation. The catalytic activity toward phosphoinositide substrates is required for growth suppression, and PTEN-mediated growth inhibition is due to G1 cell cycle block rather than induction of apoptosis. The PTEN C2 domain binds phospholipid membranes and mutations in this domain reduce PTEN's membrane affinity and ability to suppress growth and motility of GBM cells (**Okezie et al., 2009).**

6. Invasion and Angiogenesis

Invasion and Angiogenesis are two main mechanisms that promote survival and progression of malignant brain tumors **(Bello et al., 2004).**

- **Invasion**

GBM has the ability to infiltrate brain tissue**.** This characteristic explains the cause of remote recurrences and why it is impossible to cure these tumors with surgical resections (**Habib Allah., 2008).**

- **Angiogenesis**

As evidenced by the presence of micro vascular proliferation, angiogenesis plays an essential role in GBM. Glioma cells require blood vessels for metabolic activities because these blood vessels supply the tumor with oxygen and nutrients, plays a vital role in waste removal and also in the creation of a vascular niche that may selectively support glioma stem cells **(Dunn et al., 2012).**

Glioma vasculature develops via several mechanisms namely;

- Angiogenesis which is the formation of new blood vessels from the existing vasculature.
- The recruitment of bone marrow-derived endothelial progenitor cells, a process known as vasculogenesis.
- The recruitment of tumor cells directly into the vascular wall.
- The differentiation of tumor stem cells directly into vascular endothelium **(Dunn et al., 2012).**

Under the influence of several factors including hypoxia, tumor cells secrete angiogenic substances such as VEGF (vascular endothelial growth factor) and FGF (fibroblast growth factor) which bind to specific receptors present on the surface of endothelial cells and induce their proliferation. In addition to these true angiogenic factors, there are also metalloproteases, urokinase-plasminogen system with its activators (UPA) and its inhibitors plasminogen activator inhibitor type 1 (PAI-1) and plasminogen activator inhibitor type 2 (PAI-2), cathepsins (B, D, L), which are also secreted by tumor cells and they degrade the extracellular matrix thereby facilitating the migration of endothelial cells via the integrins in addition to caderins and therefore allowing the formation of an intratumor vascularization (**Habib Allah., 2008).**

7. Metastases

Metastases mainly occur locally, by infiltration, along the myelinated fibers of the capsules, commissures, optic radiations, and from the corpus callosum to the contra-lateral hemispheres, allowing the formation of other tumor foci. In spite of the fast and highly invasive nature of GBM, it does not usually invade the subarachnoid spaces and therefore, metastasis via the cerebrospinal fluid is rare (**Habib Allah., 2008).**

8. Anatomopathology

This study shows the morphology of the macroscopic and microscopic abnormalities of GBM in biological tissues and normal or pathological cells**.**

- **Macroscopy**

The tumor is usually large in size at the time of diagnosis. The localization of the tumor is generally unilateral though it can be bilateral or symmetrical at the corpus callosum and at the brainstem. The visible tumor surface may vary in colour. The tumor consists of a peripheral zone

which appears macroscopically as a soft, gray edge, an intermediate zone which appears as a gray band of tumor tissue, and a yellowish central zone or the necrotic area which represents about 80% of the tumor mass. GBM is also characterized by the presence of red foci which represents recent hemorrhagic foci and brown foci which represents old hemorrhagic foci, cystic portions which contain a turbid liquid which can be obtained by liquefaction of the necrotic tissue. Most hemispheric GBMs usually infiltrate the cerebral parenchyma and they are rarely in contact with the leptomeninges and the dura mater. (**Habib Allah., 2008).**

- **Microscopy**

Generally, GBM is characterized by poorly differentiated astrocytic cells, sometimes pleomorphic cells, with nuclear atypia and high mitotic activity. It is also characterized by the presence of necrosis and microvascular vascularization which are vital criteria for diagnosis. (**Habib Allah., 2008).**

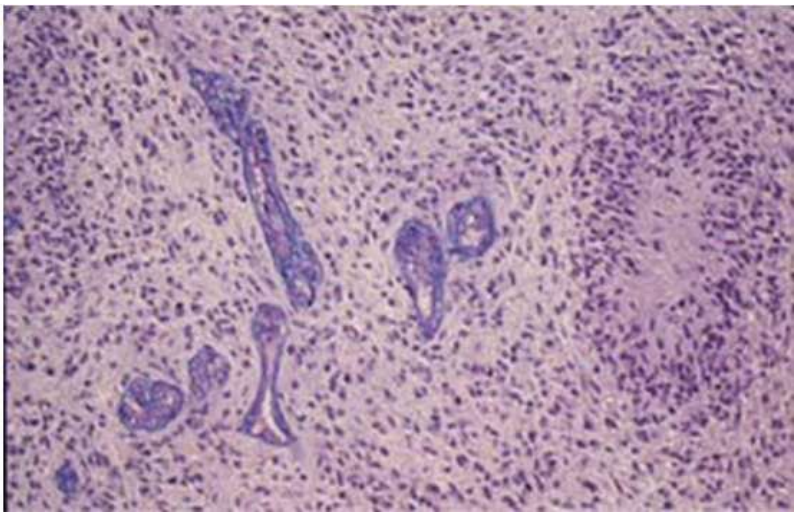

Figure.9: Glioblastoma: high density of +/-differentiated and sometimes very polymorphic glial cells, numerous mitoses, numerous vessels with endothelial proliferation, focal necrosis surrounded by a palisade-like arrangement of tumor cells (X50) (Habib Allah., 2008).

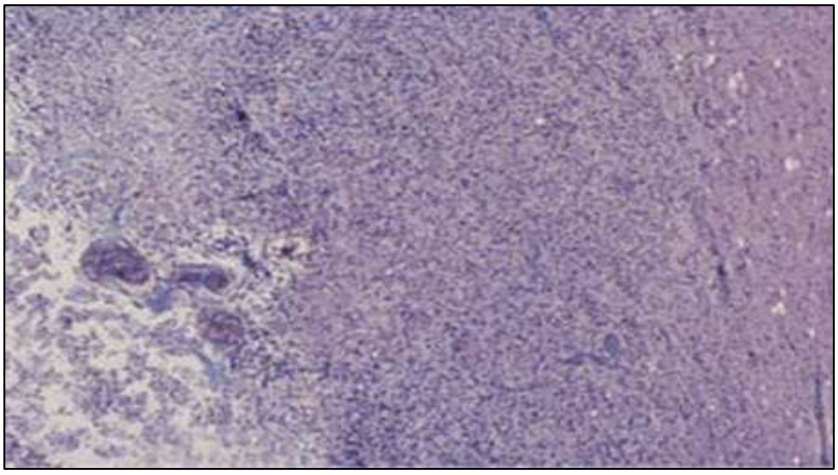

Figure.10: Glioblastoma: High cellularity, presence of large abnormal vessels and a large focus of necrosis. Edema of the surrounding nervous tissue (X16) (Habib Allah., 2008).

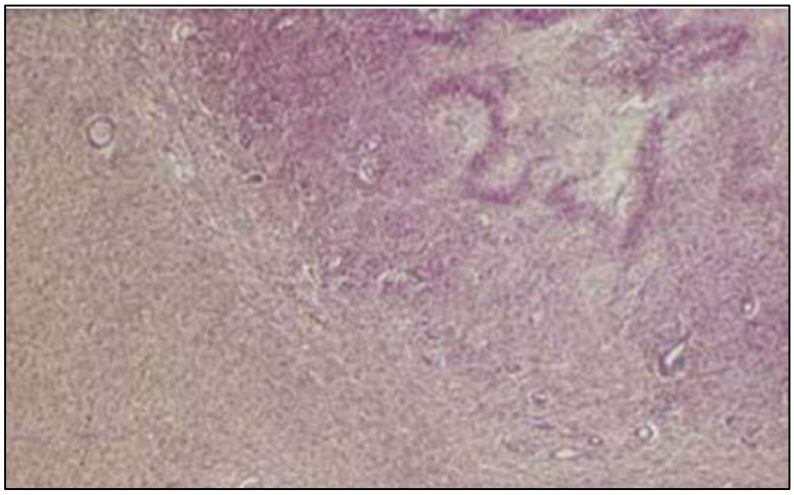

Figure. 11: Glioblastoma: Vast highly cellular focus containing necrosis bordered by palisades (X10) (Habib Allah., 2008).

- **Immunohistochemistry**

GBMs are characterized by a variable expression of GFAP (Glial fibrillary acid protein). There is a disappearance of its expression in undifferentiated cells and the intensity of its expression varies from one tumor cell to another. Apart from GFAP, other markers such as EGFR (Epidermal growth factor receptor), PDGFR (Platelet derived growth factor receptor), HGF/SF (Hepatocyte growth factor/Scatter factor) can also be highlighted but they are still under research. The proliferation index also varies from one region to another. The anti-Ki67 antibody marks the

nucleus of cells in cycle but is more rarely expressed in gemistocytes. More and more often, immunohistochemical techniques are performed with the aim of highlighting antigens of diagnostic or prognostic interest (**Habib Allah., 2008).**

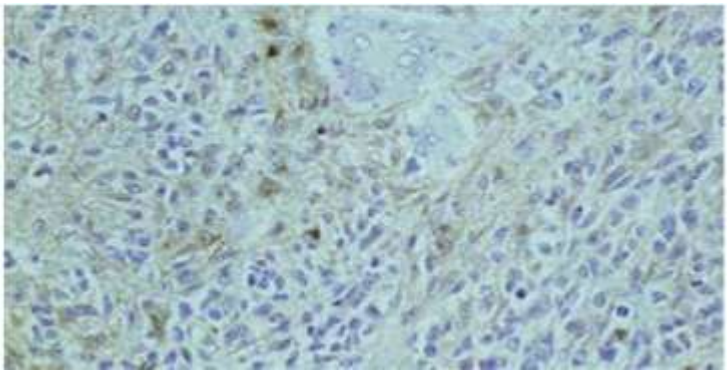

Figure. 12: Glioblastoma: Some cells positive for GFAP, but most tumors elements and endothelium are negative (X100) (Habib Allah., 2008).

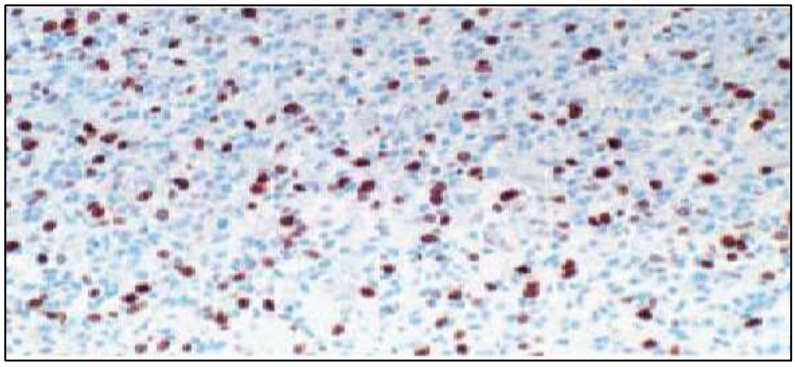

Figure.13: Glioblastoma: Numerous labeled nuclei indicating strong proliferation index (Ki67) (X25) (Habib Allah., 2008).

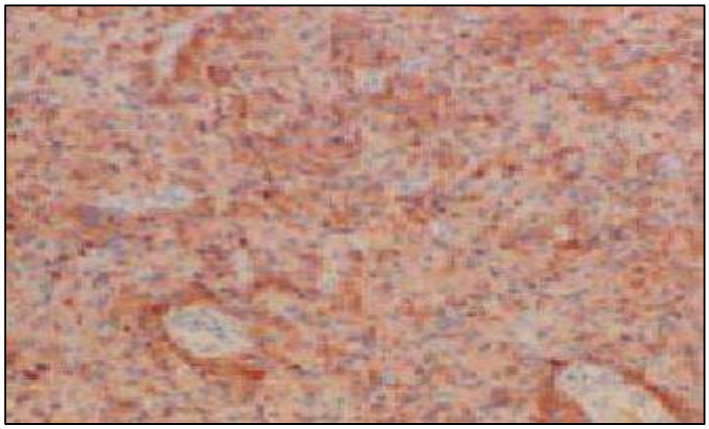

Figure. 14: **Glioblastoma: Diffuse membrane positivity to anti-EGFR (X25) (Habib Allah., 2008).**

However, the variants of primary GBM including gliosarcorma, giant cell glioblastoma, epithelioid glioblastoma also have specific anatomopathologic features which are discussed below;

8.1. Gliosarcorma

- **Macroscopy**

It is characterized by a gross appearance of a firm, well circumscribed mass and high connective tissue content **(Burger et al., 2016).**

- **Microscopy**

It is a tumor with mixture of gliomatous and sarcomatous tissues which gives it a biphasic tissue pattern. The glial component consists of astrocytes and anaplastic features linking it to a glioblastoma whereas the sarcomatous portion shows features of malignant transformation such as nuclear atypia, mitotic activity, and necrosis. The sarcomatous portion also show a pattern of a spindle cell sarcoma, with densely packed long bundles of spindle cells surrounded individually by reticulin fibres. It may also show more pleomorphism, additional lines of mesenchymal differentiation like the formation of cartilage, bone, osteoid-chondroid tissue, smooth and striated muscle plus lipomatous features **(Figure .15) (Burger et al., 2016).**

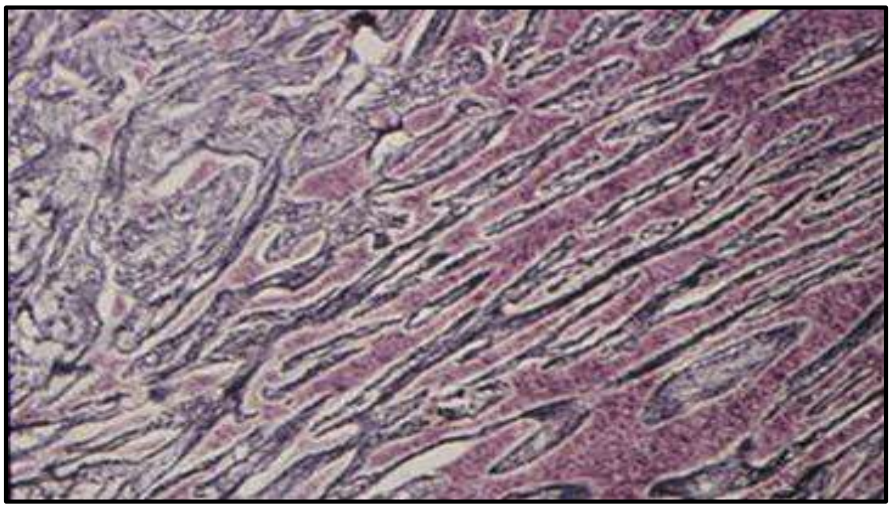

Figure .15: Gliosarcoma: Mixed tumor composed of islets of glioblastoma separated from each other by numerous sarcomatous trabeculae, rich in reticulin fibers (X40) (Habib Allah., 2008).

- **Immunohistochemistry**

The glial portion is positive for GFAP and is separated from the sarcomatous portion which contain reticulin fibers. The sarcomatous portion is negative for GFAP. This helps to differentiate gliosarcoma from classic GBM and thus confirms the diagnosis of gliosarcoma (**Habib Allah., 2008).**

8.2. Giant cell glioblastoma

- **Macroscopy**

It is characterized by a gross appearance of a firm, well circumscribed mass, and a high connective tissue content **(Ohgaki et al., 2016).**

- **Microscopy**

It is characterized by the presence of numerous multinucleated giant cells, small fusiform syncytial cells, and a reticulin network. The giant cells are usually angulated and contain prominent nucleoli. Giant cell GBM is also characterized by atypical mitoses, palisading, large ischaemic necroses, and a perivascular accumulation of tumor cells with the formation of a pseudorosette-like pattern **(Figure.16) (Ohgaki et al., 2016).**

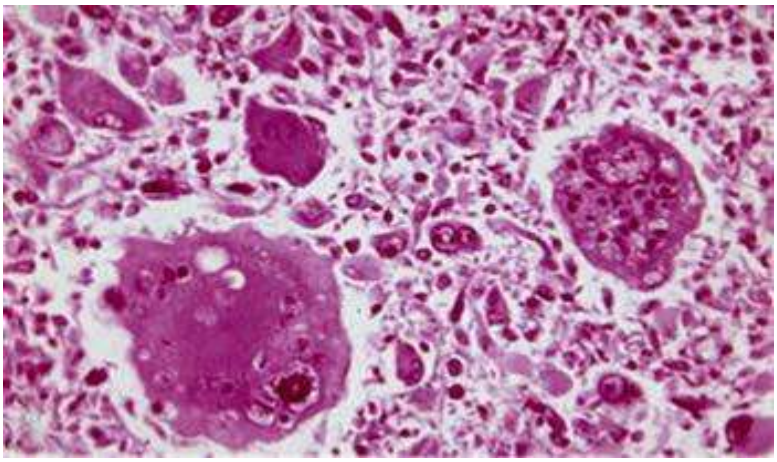

Figure. 16: Giant cell glioblastoma; significant cellular monstrosities: giant size, multiple and polymorphic nuclei sometimes containing a very large nucleolus (X100) (Habib Allah., 2008).

- **Immunohistochemistry**

It is inconsistently positive for GFAP and shows immunopositivity with S-100 protein, Vincristine, p53 and EGFR (**Habib Allah., 2008).**

8.3 Epithelioid glioblastoma

- **Macroscopy**

They are typically unifocal lesions. They may also be characterized by the presence of necrosis, presence of haemorrhage and cysts which form rarely **(Ellison et al., 2016).**

- **Microscopy**

They are characterised by a relatively uniform population of epithelioid cells showing focal discohesion, scant intervening neuropil, a distinct cell membrane, eosinophilic cytoplasm, a paucity of cytoplasmic processes, and a laterally positioned nucleus. They are also characterised by the presence of zonal necrosis **(Ellison et al., 2016).**

- **Immunohistochemistry**

Epithelioid glioblastoma usually show immunoreactivity for GFAP, vimentin and S100 protein **(Ellison et al., 2016)**

9. Physiopathology

9.1. Increase in intra cranial pressure.

The main intracranial structures namely, cerebral tissue, intravascular blood, cerebrospinal fluid are enclosed with in an inextensible cranial box. Due to development of the tumor and the vasogenic edema that surrounds it, there is consequent increase in cerebral volume, which must be compensated by a reduction in the volume of the cerebrospinal fluid or blood compartments because the brain is incompressible. However, this compensation capacity is temporary and limited and once exceeded, the intra cranial pressure increases rapidly leading to deterioration of cerebral circulation and cerebral functions (**Habib Allah., 2008).**

9.2. Changes in the blood-brain barrier.

These modifications are mostly limited to the circumference of the tumor, but can exceed it sometimes. These modifications result in an increase in the permeability to water, electrolytes and large hydrophilic molecules, leading to vasogenic cerebral edema, which can persist or even increase after excision of the tumor. This increase in capillary permeability plays a role in the

diffusion of factors such as VEGF, PAF (platelet aggregating factor), arachidonic acid derivatives, and free radicals secreted by the tumor cells**.** (**Habib Allah., 2008).**

10. Diagnosis

When a patient shows symptoms such as seizures, cognitive impairment, nausea, vomiting, motor weakness and headaches as a result of increased Intra cranial pressure (ICP), GBM is suspected, and usually an MRI (Magnetic resonance imaging) scan is used as a tool for primary diagnosis before conducting a biopsy or a surgical attempt to remove the lesion **(Batash et al., 2017).**

Histopathological examination of tumors is carried out using histological, cytological and histochemical methods for definitive diagnosis. The tumor samples are obtained by neurosurgical tumor resection or by fine needle aspiration biopsy **(Urbańska et al., 2014).**

Morphological diagnosis is carried out according to the criteria defined by the WHO. Staging of the tumors in the CNS is based on the assessment of their morphology, grade of malignancy (grade I–IV), proliferative index, response to treatment and survival time. **(Urbańska et al., 2014).**

Immunohistochemistry is carried out to determine the presence of glial fibrillary acidic protein (GFAP) in the glioma cells as verification of primary diagnosis. GFAP is a major intermediate filament protein of mature astrocytes. This protein weighs 50 kD and it is the most specific marker of astrocytes, both in normal and pathological conditions. This protein is considered to play a role in maturation of astrocytes. The loss of GFAP expression in glioma cells plays a role in the increasing malignancy of tumors of astrocytic origin. Glioma cells that show negative results for GFAP proliferate faster compared to glioma cells that show positive results for GFAP **(Urbańska et al., 2014).**

10.1. Imaging

There are three types of imaging namely; magnetic resonance imaging (MRI), computed tomography (CT) and metabolic imaging. (**Habib Allah., 2008).**

10.1.1. Magnetic resonance imaging

Magnetic resonance imaging (MRI) scans are commonly used to visualize tumors. They use the gold standard imaging technique which allows the complexity and the heterogeneity of

the tumor lesion to be visualized due to their soft tissue contrast. The T1-weighted MRI scans are used to visualize hypo-intense lesions while the photon density weighted; and the T2-weighted MRI scans are used to visualize hyper-intense lesions. Imaging of the tumor is enhanced by the use of gadolinium which enables visualization of central areas of necrosis **(Figure.17) (Hanif et al., 2017).**

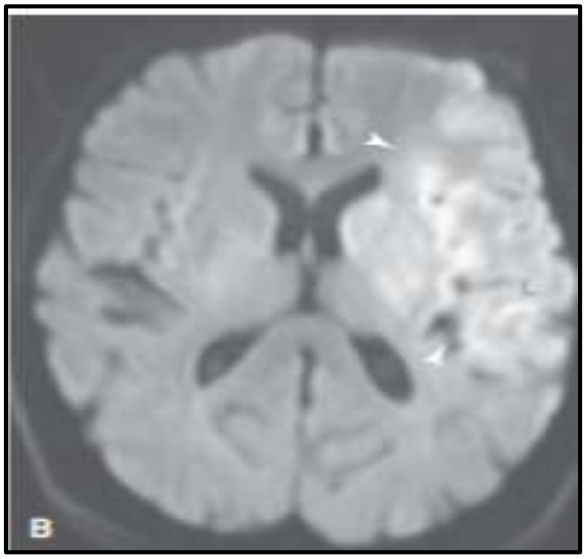

Figure.17: Diffusion-weighted magnetic resonance imaging (MRI) demonstrating hyperintensity in the distribution of the left middle cerebral artery (arrowheads) confirms the presence of a subacute left cerebral infarct. (Perry and Brat., 2010).

10.1.2. Computed tomography scan

Computed tomography (CT) scans are usually carried out when a patient cannot undergo an MRI scan due to some reasons, such as, if a patient has a pacemaker. Lesions viewed on a CT scan usually appear as hypointense areas in comparison to adjacent brain tissue and usually show a midline shift as a result of moderate to severe edema **(Figure.18) (Hanif et al., 2017).**

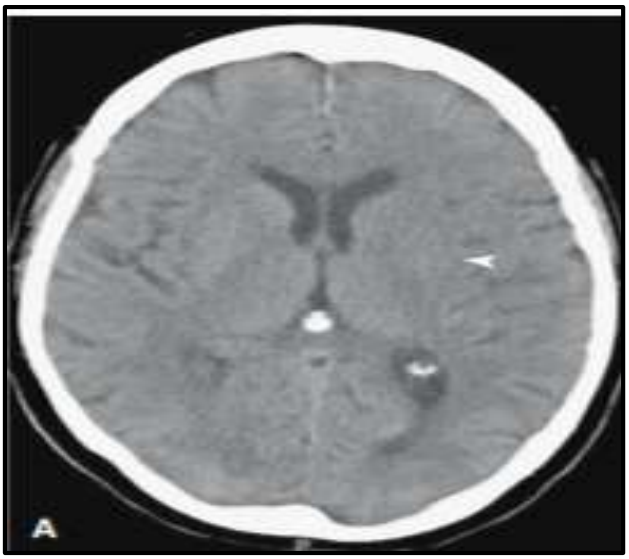

Figure. 18: Computed tomography (CT) scan demonstrates subtle left hemisphere cytotoxic edema manifested by loss of definition of the lateral margin of the basal ganglia (arrowhead) and relative effacement of the left cerebral sulci (Perry and Brat., 2010).

10.1.3. Metabolic imaging

There are two types of metabolic imaging namely;

- Single photon emission computed tomography (SPECT).
- Positron emission tomography (PET).

Metabolic imaging is used as a complement to the conventional radiological diagnosis. It is used in the analysis of tumor metabolism without modifying it. It is also used in therapeutic and prognostic follow-up such as in distinguishing between tumor progression and radionecrosis, determining the effectiveness of chemotherapy and limiting active tumor areas. (**Habib Allah., 2008).**

10.1.3.1. Single photon emission computed tomography (SPECT)

This type of metabolic imaging uses radioactive makers such as:

- Intraparenchymal flow markers: hexamethyl-propylene-amine-oxime (HMPAO) and ethyl-cysteinate-dimer (ECD).
- Markers of metabolic activity: thallium-201 and 99Tc-methoxy-iso-butyl-isonitril (MIBI).
- The uptake of amino acids by 123I-alpha-methylthyrosine (IMT).

Isotopic imaging by MIBI, whose uptake is based on metabolic activity, is currently used in the diagnosis difference between radionecrosis and progressive recovery post-radiotherapy. A good correlation between MIBI retention and tumor activity has been observed in several studies. (**Chatel et al., 2005).**

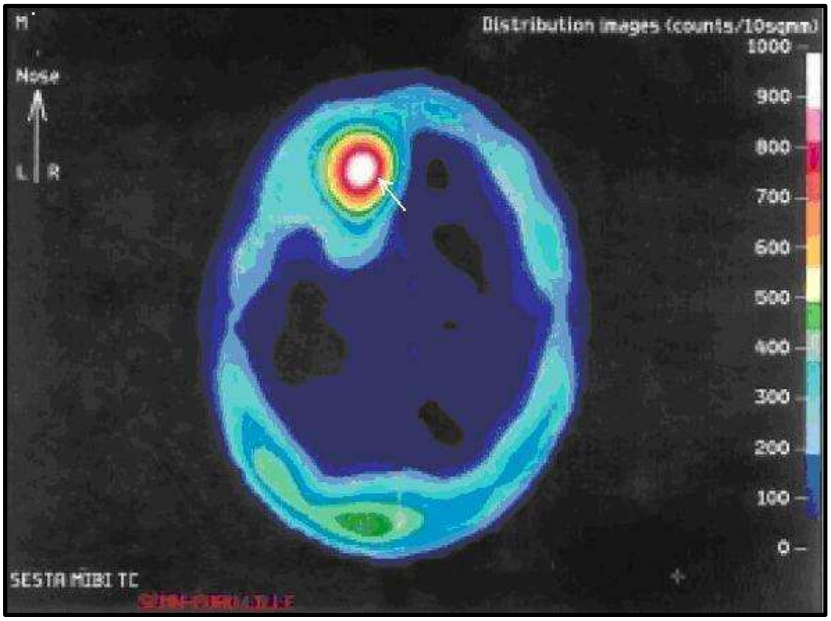

Figure. 19: Axial tomoscintigraphic slice showing abnormal uptake of 99m Tc Sestamibi next to the left frontal region (arrow) in favor of tumor recurrence. (**Habib Allah., 2008).**

10.1.3.2. Positron emission tomography (PET)

This type of metabolic imaging is based on glucose consumption which is measured using 18F-FDG (18 Ffluoro-deoxyglucose) as a marker for imaging. It can also be measured depending on amino acid uptake using either 11c-methionine or 18F-Thymidine or 18F-Thyrosine as markers for imaging. PET is used in stereotactic biopsy procedure and in differentiating between tumor recurrence and radionecrosis (**Habib Allah., 2008).**

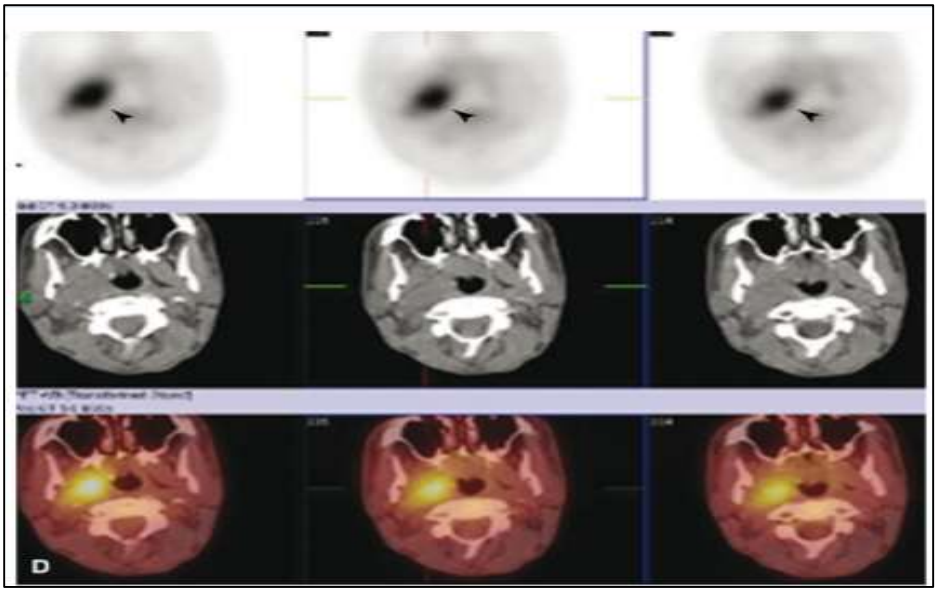

Figure. 20. Positron emission tomography (PET) scan fused with the corresponding CT slices reveals hypermetabolism within the right skull base mass (arrowheads) (Perry and Brat., 2010).

11. Treatment

11.1. Surgery

Complete resection is the optimal goal of glioma surgery, but it is highly impossible and the chances of recurrence is high since GBM is infiltrative. Therefore, bulk reduction of the tumor and consequent decompression of the brain with alleviation of the symptoms of cranial hypertension is the most likely goal in most patients since curative surgery is not possible. Tissue samples for histopathological examination can also be obtained by cytoreductive surgery. This histopathological examination is done prior to radiation therapy or chemotherapy. Gross tumor resection results in immediate decompression of the brain. Due to the consequent reduction in neoplastic cells in the surgical cavity, the chances of response to radiotherapy and/or chemotherapy is increased. However, patients with supratentional gliomas usually undergo limited surgical resection because of the fear of risks of neurological deterioration. In these patients, surgical resection depends on extensiveness of the tumor and the associated neurological deficits **(Brandes et al., 2008).**

11.2. Radiotherapy

Radiation therapy usually follows surgery. It is sometimes associated with chemotherapy. The radiation dose mostly ranges from 54 to 60 grays (Gy) and is delivered in 27 to 33 fractions basing on the tumor size and the proximity of the organs at risk. The objective of this treatment is to treat the tumor while minimizing the irradiation of healthy tissue **(Bondiau et al., 2010).**

11.2.1. External radiotherapy

Conventional external radiotherapy uses photons from linear accelerators. Using a scanner, the target volume (the tumor macroscopic volume) plus a safety margin of up to 25mm is determined by imaging. A dose of 60Gy is then applied in a period of 6 to 7 weeks (**Habib Allah., 2008).**

11.2.2. Hyperfractionated radiotherapy

Hyperfractionated radiotherapy consists of administering a reduced dose per day over several sessions so as to finally reach a total dose of high irradiation. The delay between two sessions is to allow tissue repair from radiation-induced damage **(Simon et al., 2005).**

11.2.3. Radiotherapy under stereotactic conditions (radiosurgery)

It is an external radiotherapy technique that delivers a single dose of between 15 and 25 Gy in the target tumor volume and also offers a significant protection to surrounding healthy tissue **(Simon et al., 2005).**

11.2.4. Brachytherapy

This technique involves implanting a radioactive material within the target tumor volume to deliver a dose of 50 to 60 Gy **(Bondiau et al., 2010).**

11.3. Chemotherapy

It is usually administered at different moments relative to other treatments. It can be administered to GBM patients prior to surgery and/or radiation therapy as neoadjuvant therapy, at the time of surgery and/or radiation as concurrent therapy, after surgery and/or radiation as adjuvant therapy, or at tumor recurrence **(Figure. 21) (Parney and Chang., 2003).**

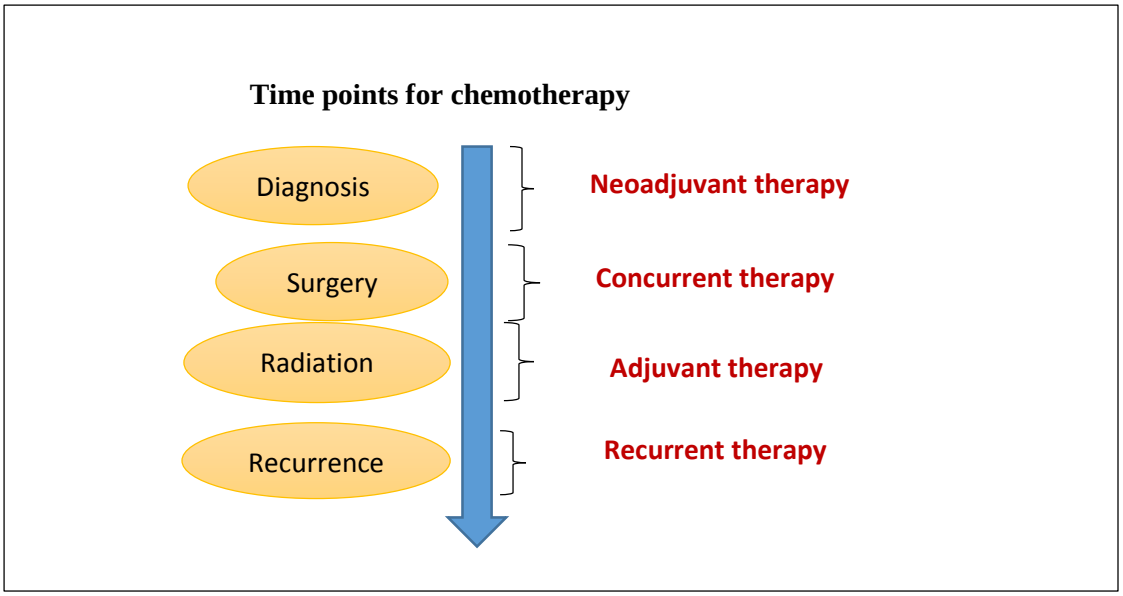

Figure .21: Time points for chemotherapy for glioblastoma patients (Parney and Chang, 2003).

Chemotherapeutic agents are divided into cytotoxic and cytostatic agents. Cytotoxic agents cause tumor cell death by several mechanisms such as DNA alkylation, DNA cross-linkage, DNA strand breaks, and mitotic spindle disruption. Cytostatic agents do not kill tumor cells directly but alter tumor biology by inhibiting tumor growth, tumor spread, or both **(Figure.22), (Parney and Chang., 2003).**

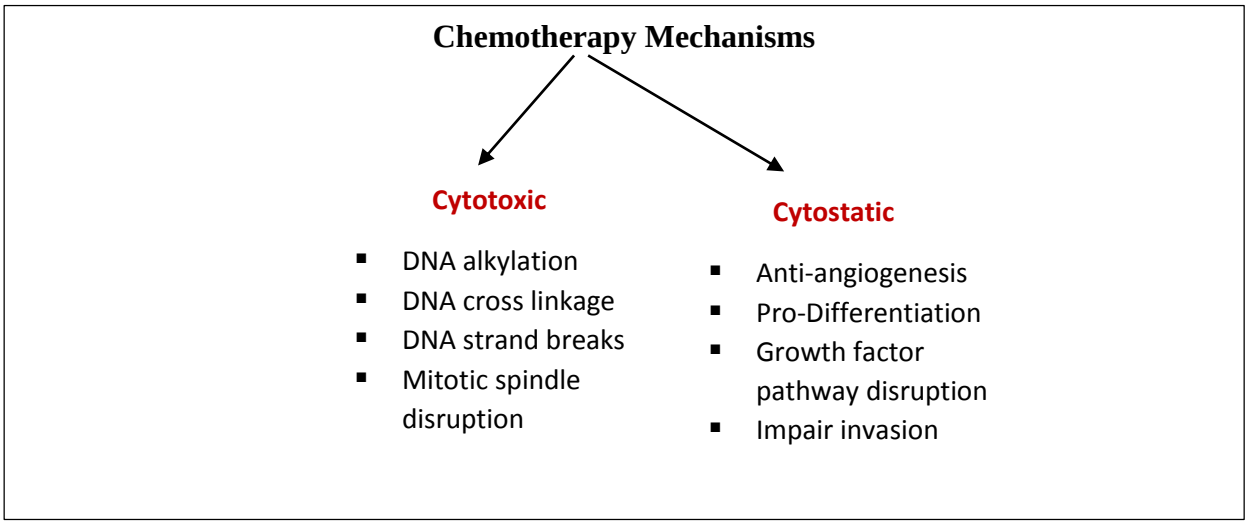

Figure. 22: Glioblastoma chemotherapy Mechanisms (Parney and Chang., 2003).

PRACTICAL PART

1. Patients and methods

In order to study the epidemiological consequences of glioblastoma multiforme, we carried out an epidemiological retrospective study on 70 patients, who were diagnosed with intracranial GBM, over a period of three years, from 2019 to 2021, at anatomopathology department in Centre Hospitalier Universitaire Ben Badis-Constantine (CHUC).

We exploited different parameters which we obtained from the medical files at anatomopathology department and from the medical staff at the Neurosurgery department.

These parameters include;

- Age
- Sex
- Origin
- Patient history
- Symptomology
- Tumor location

The software application used to analyze the data was Microsoft Excel 2013.

2. Anatomopathological study

In our study, we considered a female patient aged 70 years who showed the following symptoms;

- Right vestibular cochlear syndrome.
- Statokinetic cerebellar syndrome.

Note: The patient was conscience.

2.1. MRI Imaging.

The cerebral imaging was carried out on the patient using magnetic resonance imaging (MRI) and it revealed an intraparenchymal multifocal fronto-parietal and right cerebellar tumoral process.

2.2. Obtention of tissue samples

The tissue sample was obtained from the unconscious patient by wide excision. After which it was taken to anatomopathology laboratory for examination and study. The tissue sample then underwent a series of preparations.

2.3. Macroscopic Observation

Generalities

Macroscopic examination is essential to determine the choice of sample to be examined. The macroscopic management of tumor resection specimens aims to obtain information concerning the morphological, topographical and prognostic aspects useful for the diagnosis and treatment of GBM lesions. It conditions the subsequent microscopic study.

2.4. Fixation

The purpose of the fixation is to oppose the premature dehydration of the cells and tissue putrefaction. The tissue sample was arranged in a cassette and labelled by a number. After which the sample was put in a formalin solution diluted to 10%, to preserve the tissue.

Figure.23: Fixing jar.

2.5. Dehydration

The tissue sample was then gradually dehydrated by successive passages in more and more concentrated alcoholic solutions until all the water from the tissues were subtracted and the tissue sample was totally impregnated with absolute alcohol. The alcohol was then replaced by an organic solvent in which can be dissolved both alcohol and paraffin (paraffin is not soluble in alcohol).

Figure.24: Circulation apparatus.

2.6. Embedding

The tissue sample was then immersed in paraffin heated to a temperature exceeding its melting point, since it is solid at room temperature.

Figure.25: Complete embedding module.

Cooling

Once the sample was well impregnated, it was left to cool in a mold filled with paraffin which solidified after some time thereby forming paraffin blocks.

Figure. 26: Paraffin blocks.

2.7. Sectioning

Paraffin – embedded samples were then cut by cross section, using a macrotome, into thin slices of 5 microns. The cut samples were then attached onto slides and placed onto a hot plate in order to ensure uniform spreading of the sample.

Figure. 27: Making sections.

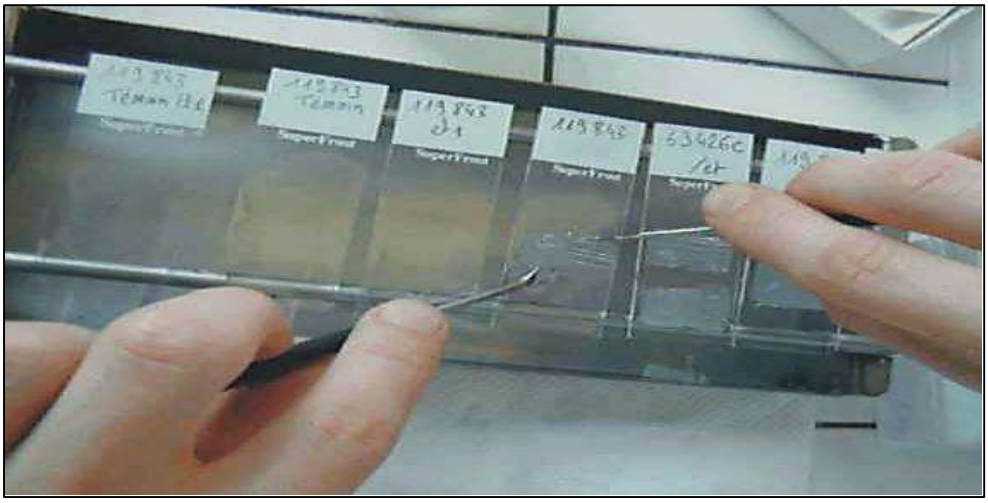

Figure. 28: Spreading on slide.

2.8. Staining of sections with Hematein-Eosin (HE)

- It was then rinsed with running water then with distilled water;
- It was then stained in 1% eosin solution for 2 min (staining the cytoplasm pink);
- The tissue sample was then rinsed quickly with running water and dehydrated in 100° alcohol;
- The tissue sample was then pass quickly in alcohols (Methanol – Ethanol) for clarification.

Figure. 29: Automatic coloring.

Figure.30: Manual coloring.

2.9. Mounting the slides

Mounting the slides consists of protecting them definitively with a glass strip glued using a transparent synthetic product (EUKIT) which polymerizes in air.

Figure. 31: Mounting the slides.

3.0. Microscopic observation

The observation of the stained slides was carried out using an optical microscope.

Figure. 32: Analysis of slides under an optical microscope.

Results and Discussion

1. Results and Discussion

1.1. Year

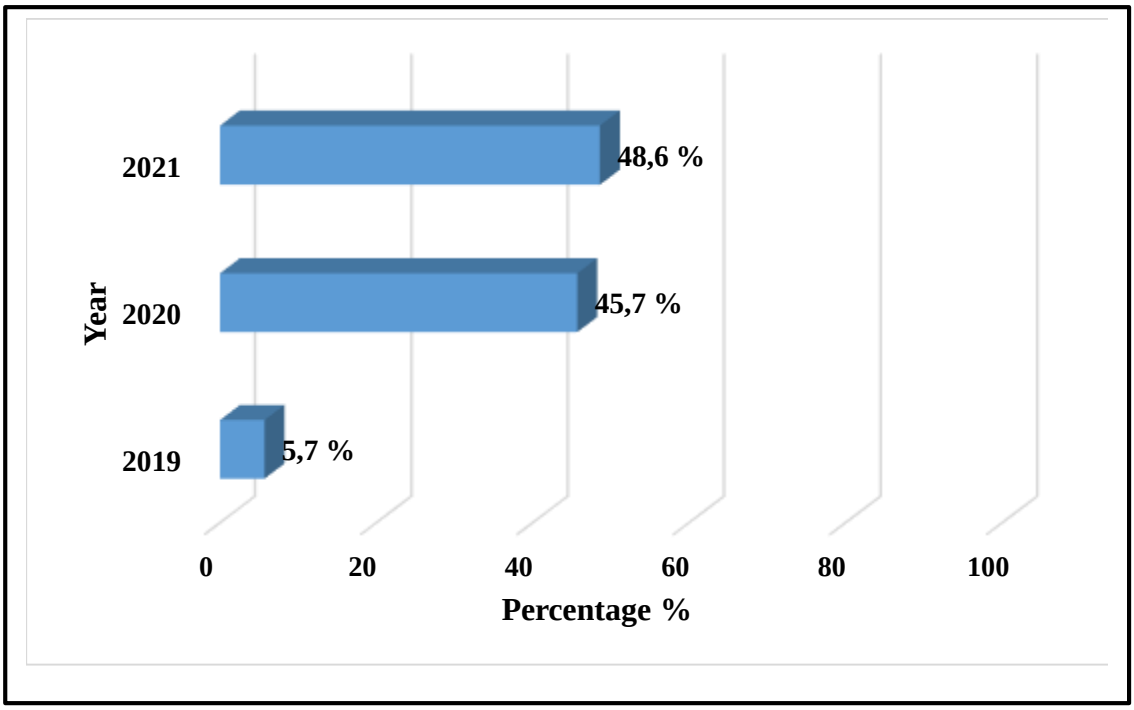

Figure. 33: Reparation of GBM patients according to year.

The year with the highest percentage of GBM patients was 2021 with 48, 6% followed by 2020 with 45,7% and 2019 with 5,7%.

There were very low cases of GBM recorded in 2019 compared to 2020 and 2021. This was due to the outbreak of Coronavirus diseases (COVID-19), which made the hospital to reduce or limit activities in most departments including the neurosurgery department in order to attend to the vast number of corona patients. This therefore resulted into the screening of less patients for brain tumors.

1.2. Geographical origin

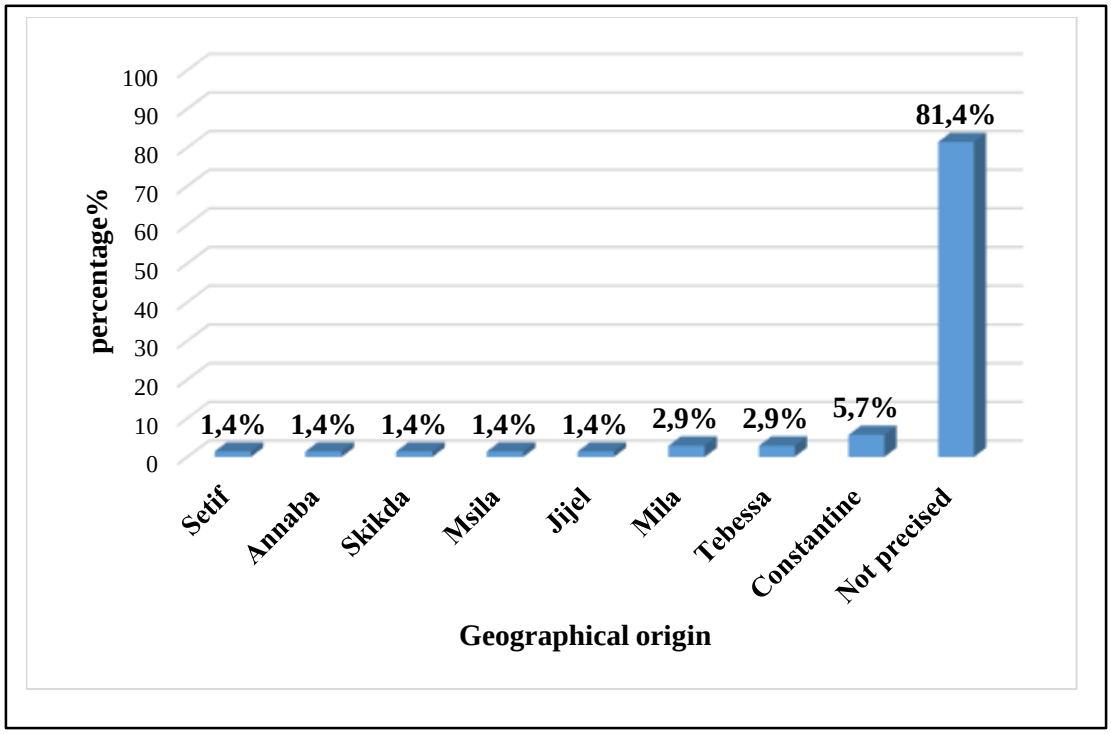

Figure. 34: Repartition of GBM patients according to geographical origin.

The geographical origin of the patients in our study was only precised in 13 patients (18,6%). The geographical origin of the other 57 patients (81,4%) weren't precised in the medical records. 2,9% of the patients were from Mila, 2,9% were from Tebessa and 5,7% were from Constantine.

1.3. Age

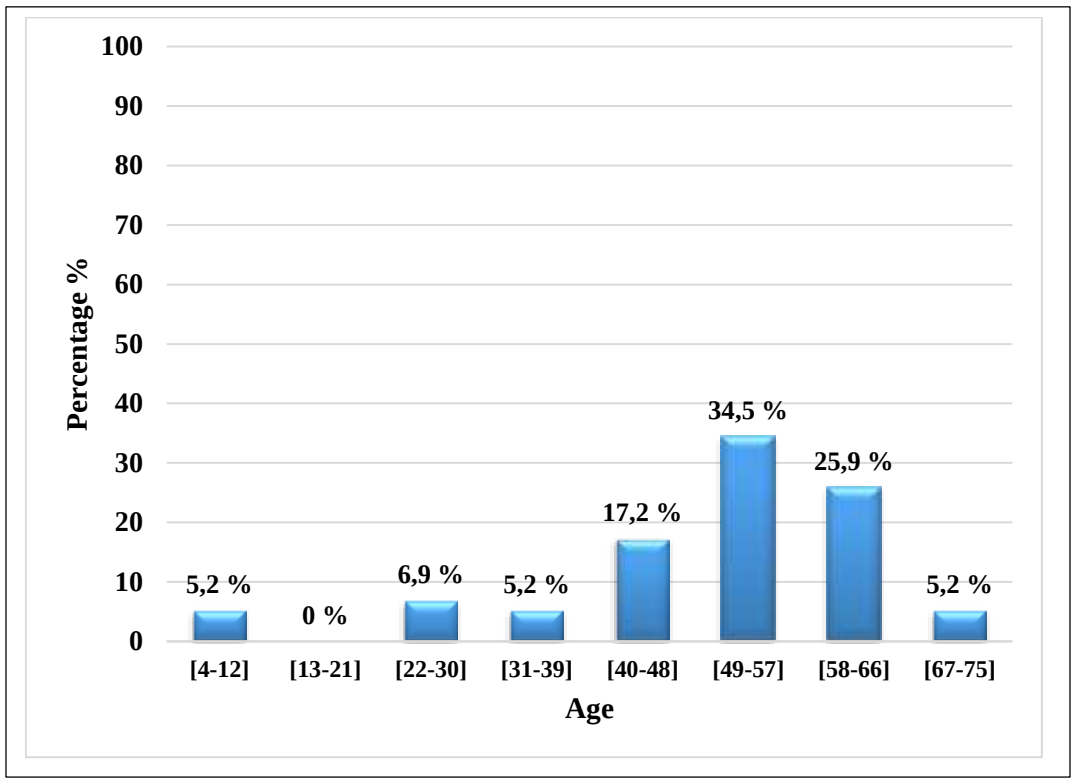

Figure. 35: Repartition of GBM patients according to age.

The age range of patients in our study ran from 4 to 70 years, with an average age of 50 years. Furthermore, we noted that the age range most affected by GBM was 49 to 57 years, representing 34,5%, and 58 to 66 years, representing 25,9 % of the patients. However, this observation was noted for 58 patients out of the 70 patients since the age of 12 patients weren't indicated in the medical record. We also observed a minimum occurrence of GBM in children, adolescents and young adults.

In conclusion, according to our study we can say that age is a critical factor in GBM occurrence. This means the older you are, the more likely you are to suffer from GBM.

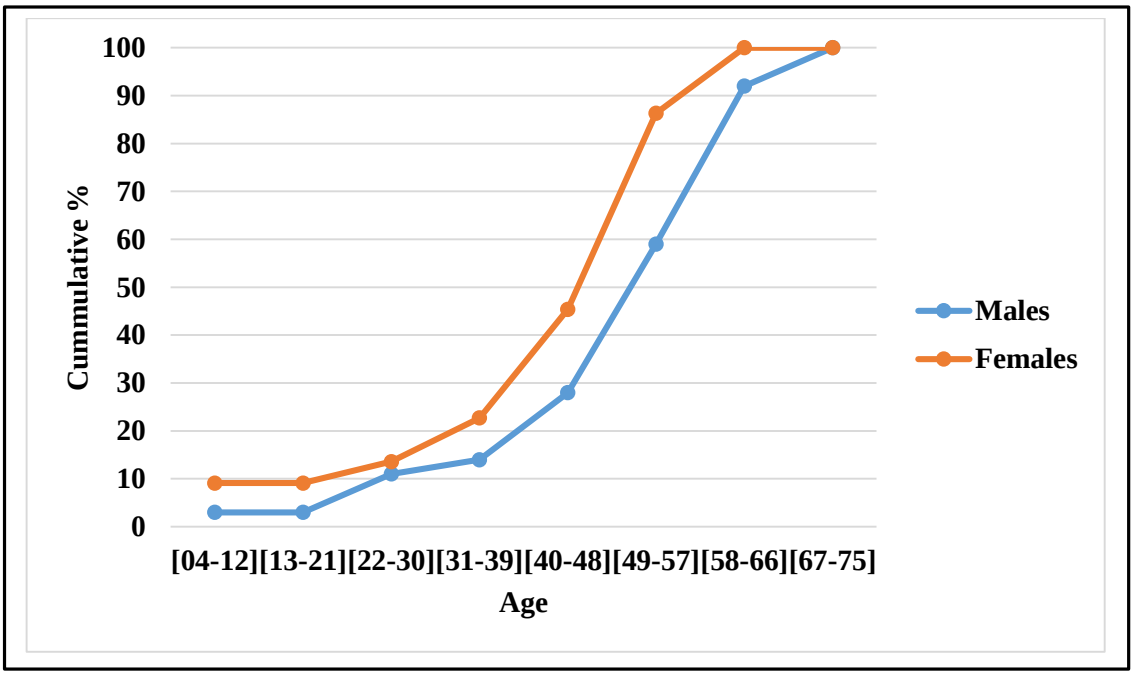

Figure. 36: Cumulative distribution of patient's age according to sex.

Figure 36 shows that the lowest incidence of GBM occurred within the age range of 04-12 years corresponding to 9,1 % and 3 % in both females and males respectively. The incidence then increased exponentially by 63,6% and 64% to the age range of 49 to 57 years and 58-66 years in females and males respectively. The incidence then increased gradually to reach a peak by 13,7% and 8% at the age range of 58 to 66 years and 67 to 75 years in females and males respectively. The incidence then remained constant within the age range of 67 to 75 years in females.

Our results share a number of similarities with different studies such as **(Louis, 2016)** findings, which suggests that GBM affects the elderly with peak incidence occurring in patients aged 55 to 85 years. Their study also suggests that the occurrence of GBM is not common in patients less than 40 years.

The reasons for this result are not yet wholly understood, however, (Ladomersky, 2019) in their study stated that, the incidence and mortality rate of GBM increases with age. This is because the effectiveness of the immune system is decreased with advanced aging. They also stated that aging negatively affects the process of apoptosis thereby leading to tumor development and growth.

1.4. Sex

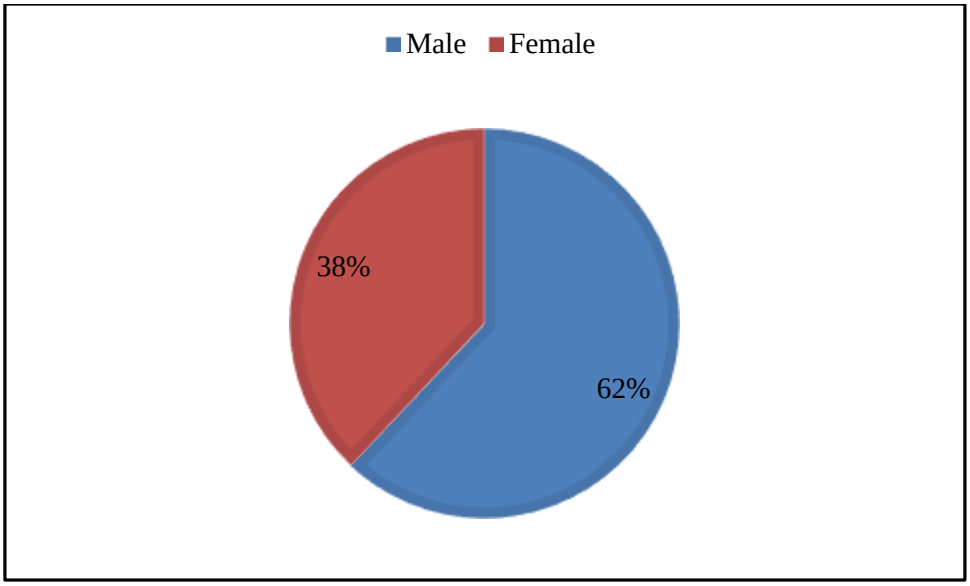

Figure. 37: Repartition of GBM patients according to sex.

Our study reveals that the male-to-female ratio for GBM is 1,63, which indicates that the occurrence of GBM was more predominant in males accounting for 36 cases (62%) compared to the occurrence in females which accounted for 22 cases (38%).

Our study corroborates with the CBTRUS (Statistical Report for Primary Brain and Central Nervous System Tumors) Diagnosed in the United States in 2007-2011 which states that the male-to-female sex ratio for GBM is 1,6 **(Ostrom et al., 2014).**

The reasons for this result are not yet completely known, however, a study of **(Carrano, 2021)** suggested that estrogen hormone provides a protective role against GBM in females, whereas testosterone hormone in males plays an important role in GBM tumorigenesis thereby explaining the male predominance of the disease.

1.5. Medical history

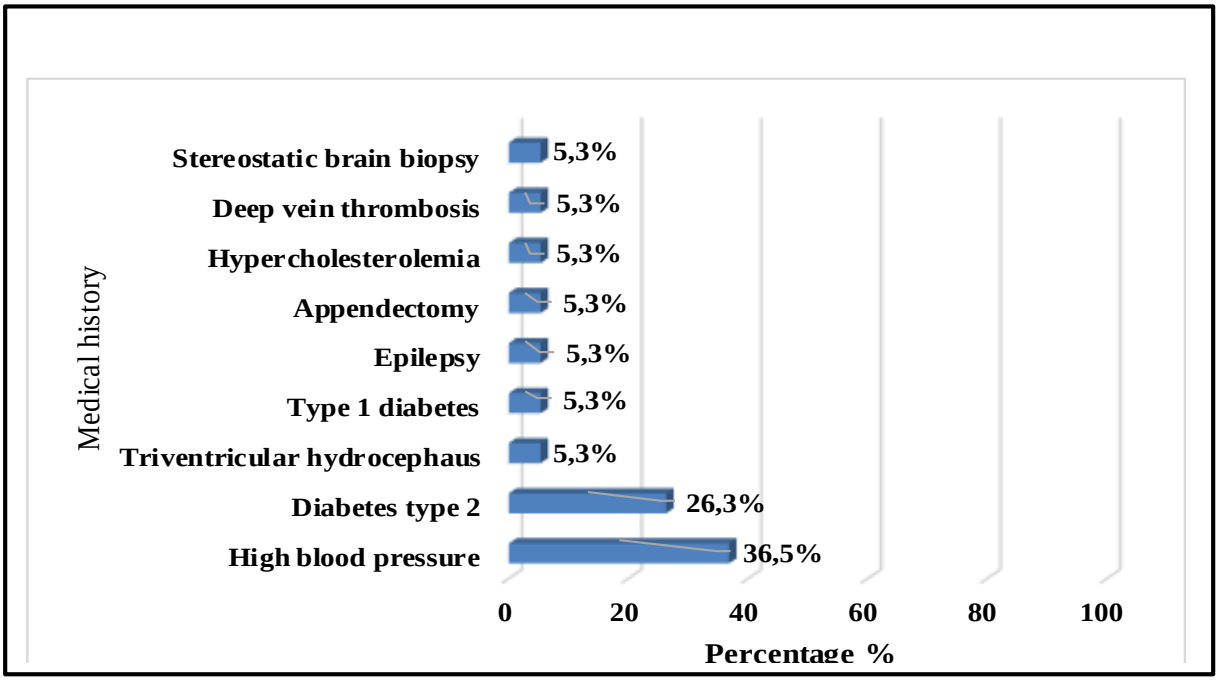

Figure. 38: Repartition of GBM patients according to Medical history.

According to the data collected on the medical history of the patients, we discovered that majority of the patients diagnosed with GBM had a medical history of high blood pressure and diabetes type 2 representing 36,5% and 26.3% respectively. It is not yet fully known if there is a relationship between high blood pressure or diabetes type 2 and GBM occurrence.

1.6. Tumor localization

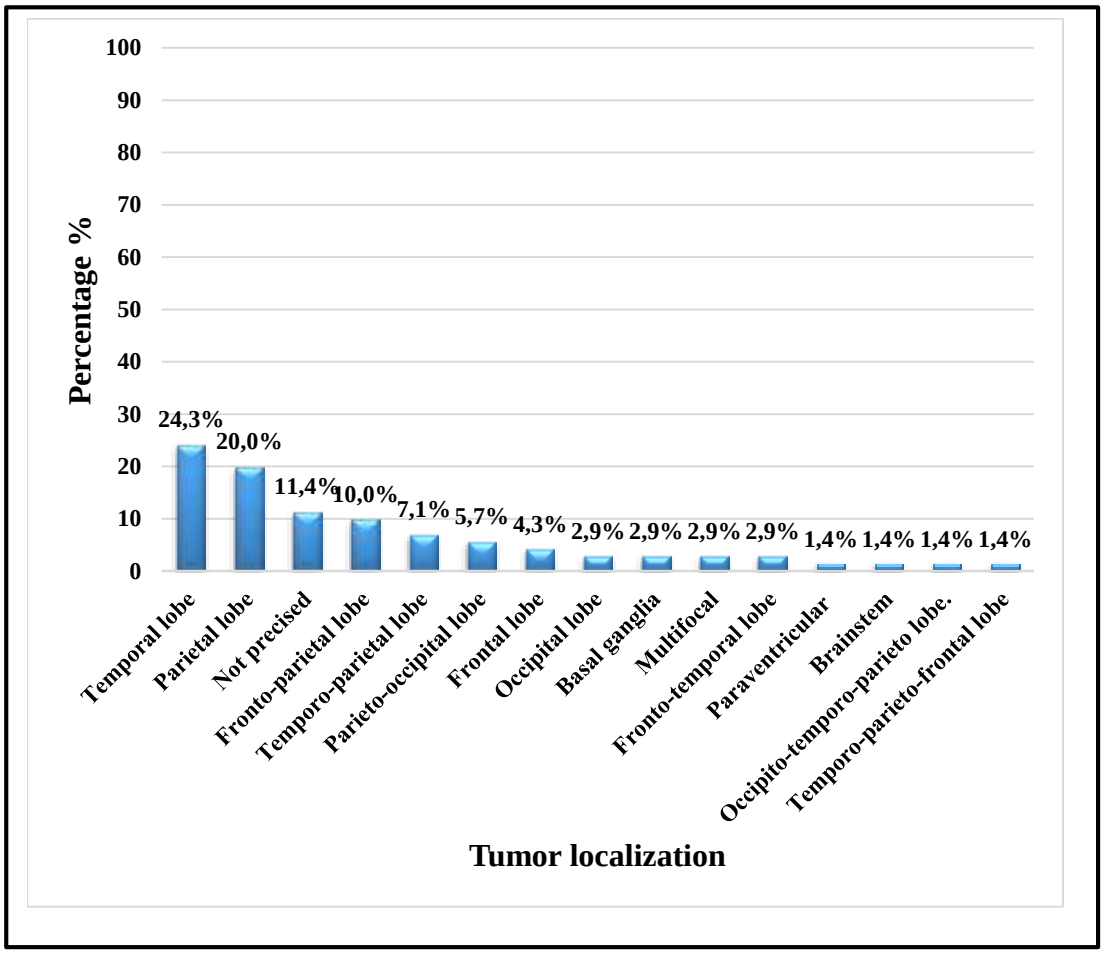

Figure. 39: Repartition of GBM patients according to tumor localization.

Based on the data collected on GBM localization, it's predominantly located either in the temporal lobe or in the parietal lobe accounting for 24,3% and 20% of patients respectively. Our results have some similarities with the study below.

GBM is commonly localized in the subcortical white matter and deeper grey matter of the cerebral hemispheres. According to study conducted at the University Hospital of Zurich that considered 987 GBM patients, the most frequently affected sites were the temporal lobe (in 31% of patients), the parietal lobe (in 24%), the frontal lobe (in 23%), and the occipital lobe (in 16%) **(Louis et al., 2016).** .

1.7. Symptoms

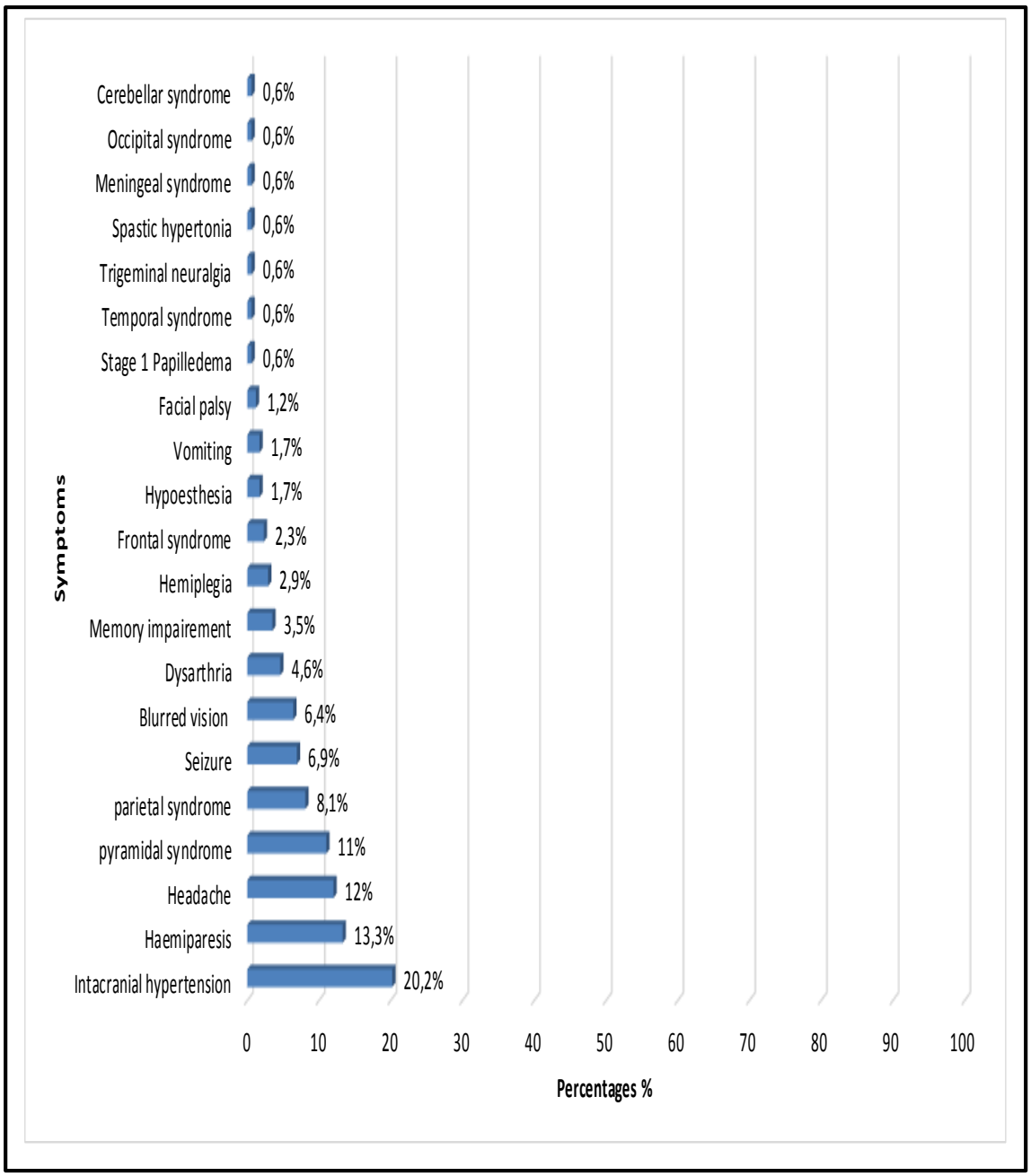

Figure. 40: Repartition of GBM patients according to symptoms.

This data revealed that intracranial hypertension was the most common symptom accounting for 20,2%, followed by hemiparesis and headaches accounting for 13,3% and 12% respectively.

To a larger extent, GBM symptoms depend on the tumor location, as the tumor grows, it can press on surrounding tissue, affecting the function controlled by that part of the brain. The

symptoms primarily manifest as focal neurological deficits such as hemiparesis and aphasia, and tumor-associated oedema with increase in intracranial pressure. Other symptoms include seizure, behavioural and neurocognitive changes, nausea and vomiting, and severe pulsating headaches **(Louis et al., 2016).**

1.8. Tumor grade.

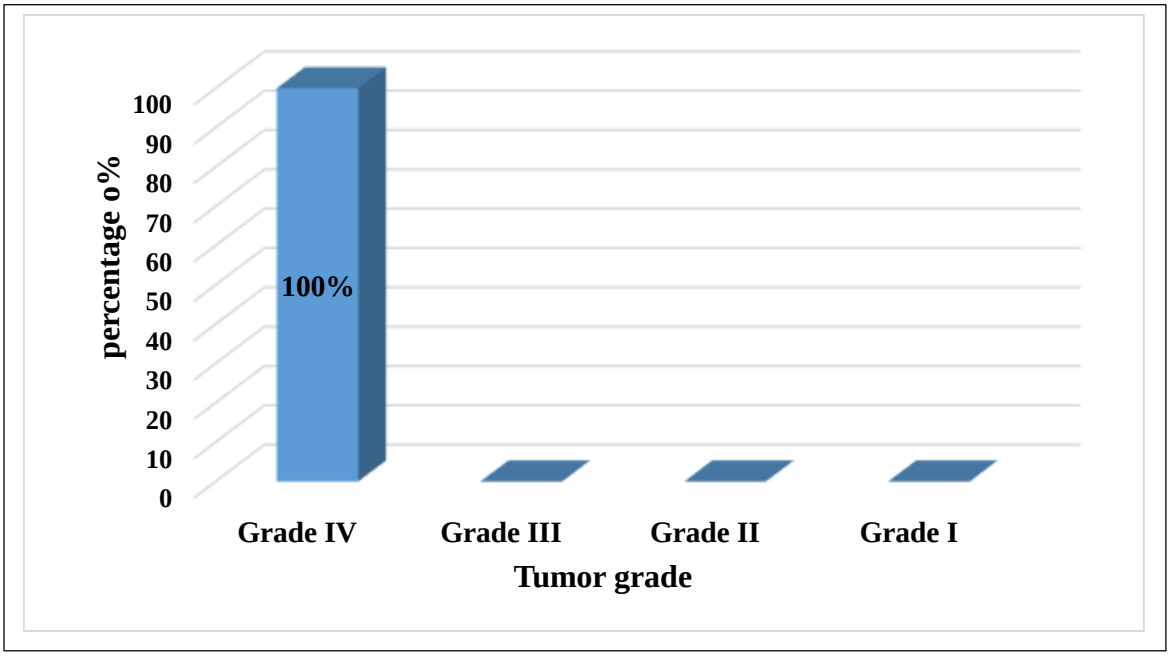

Figure. 41: Repartition of patients according to tumor grade.

Our study revealed that all the patients (100%) had grade IV tumors. This indicates that their tumors were highly malignant, with a high mitotic activity, necrosis-prone neoplasms and infiltrative. This is also an indicator of a poor prognosis.

1.9. Characteristics of the tumors observed in MRI.

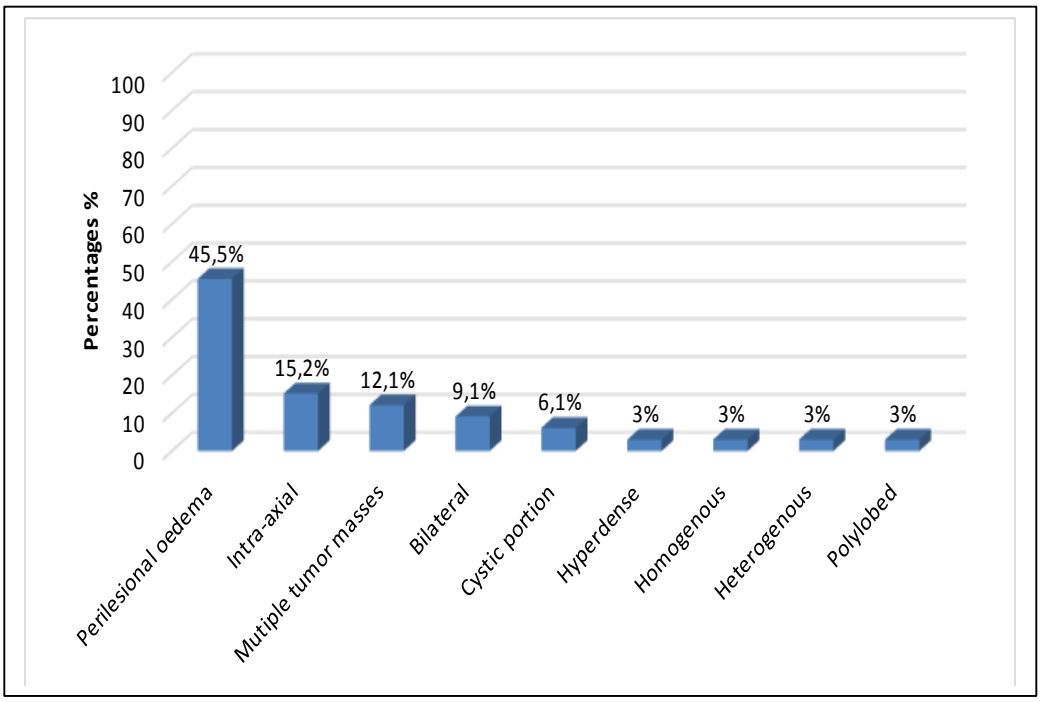

Figure. 42: Representation of the characteristics of the tumors observed in MRI.

The MRI revealed that most GBM patients had perilesional oedema accounting for 45,5%. Therefore, our data suggests that GBM is often associated with perilesional oedema.

2. Surgical treatment

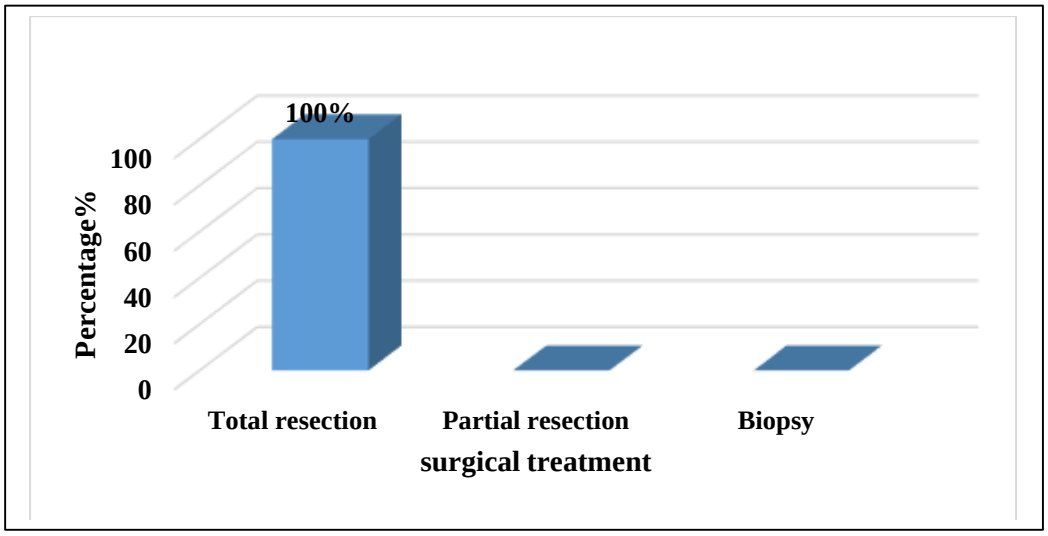

Figure.43: Repartition of patients basing on surgical treatment.

Patients who undergo total resection have a better prognosis than patients who undergo partial resection, and patients who undergo partial resection have a better prognosis than patients who undergo biopsy. **(Brandes et al., 2008).**

Our study revealed that 100% of the patients under went total resection. There for, it is safe to say that total resection at present is the most effective way of extracting the tumor and usually associated with good prognosis.

2.1. The characteristics tumors based on macroscopic observation

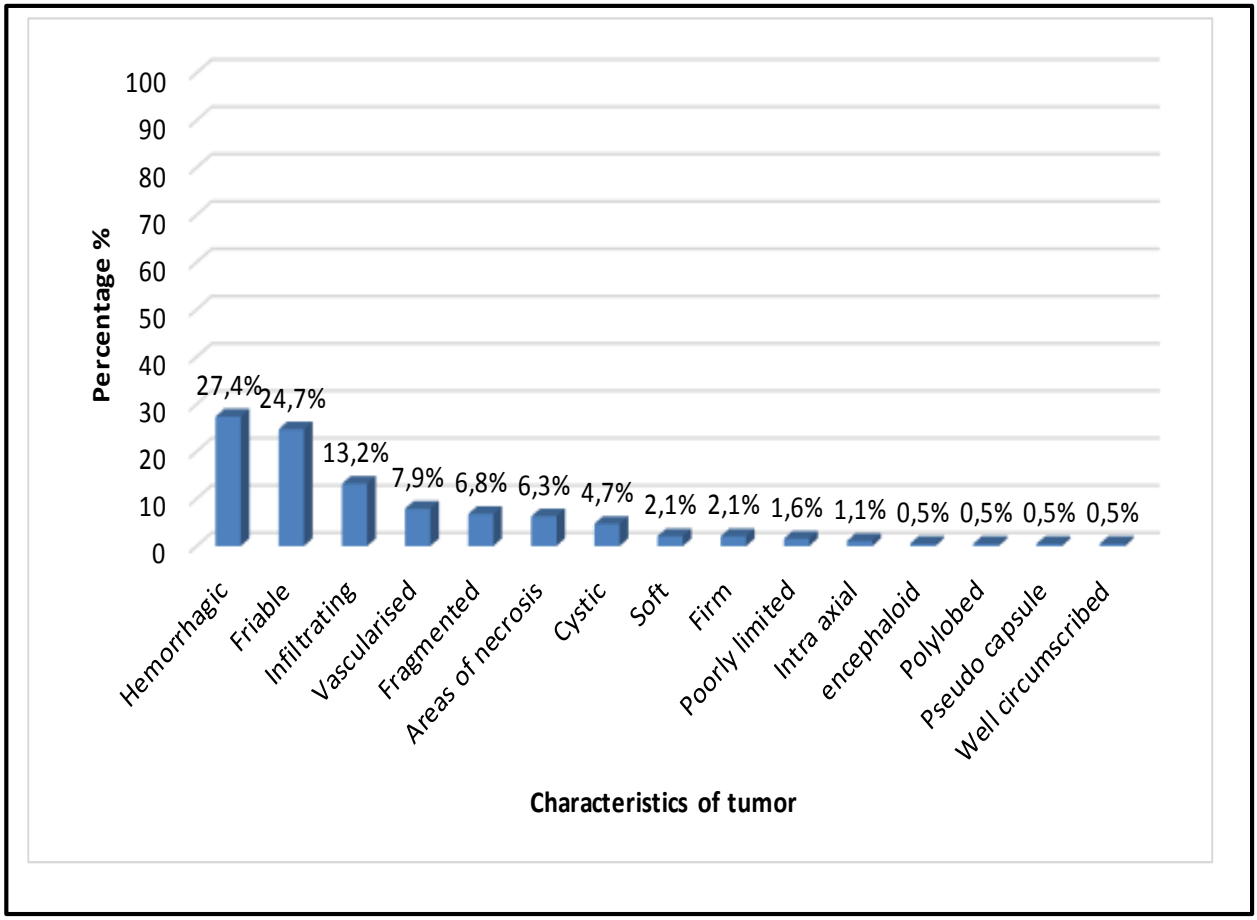

Figure. 44.A: Representation of the characteristics of the tumors based on macroscopic observation.

According to our study based on the characteristics of GBM, we found that it is highly hemorrhagic, friable and infiltrating accounting for 27,4%, 24,7% and 13,2% respectively.

The haemorrhage, is as a result of large vessels being invaded by the tumor leading to the weakening and break down of their walls **(Seidu et al., 2018).**

2.2. Colour of tumor.

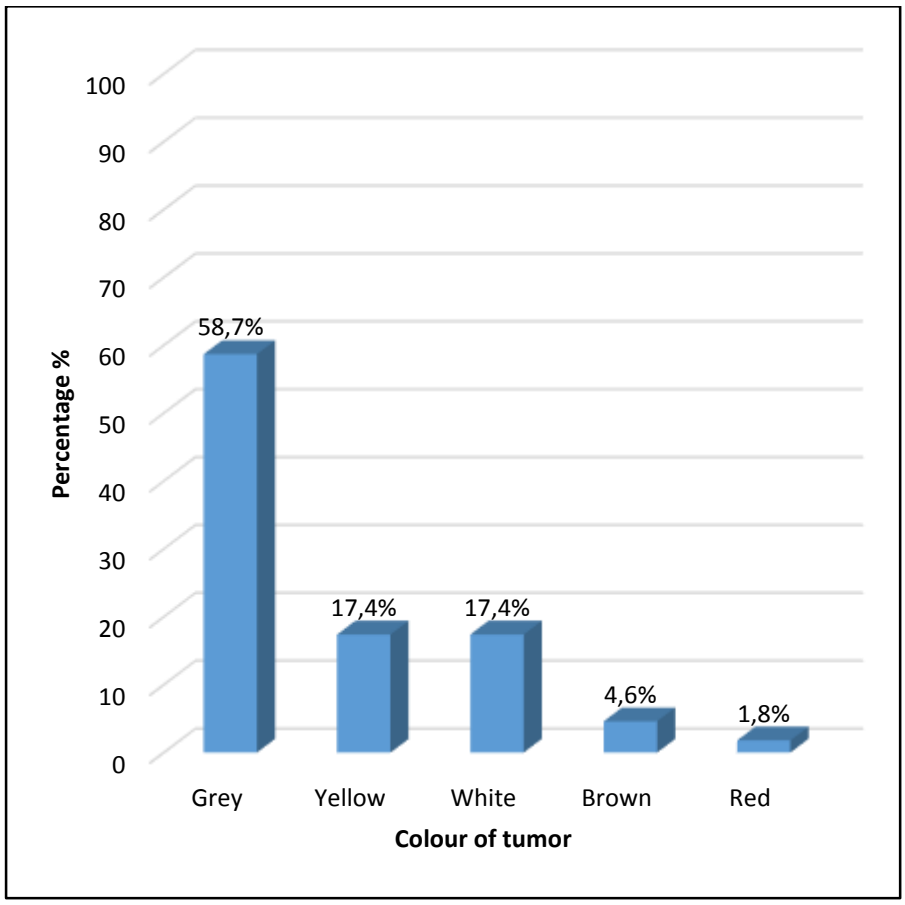

Figure.44.B : Macroscopic observation of the tumors based on colour.

According to the data collected on macroscopic observation, GBM appeared to be greyish and yellowsh in colour representing 58,7% and 17,4% respectively.

The visible tumor surface may vary in colour. The tumor consists of a peripheral zone which appears macroscopically as a soft, gray edge, an intermediate zone which appears as a gray band of tumor tissue, and a yellowish central zone or the necrotic area which represents about 80% of the tumor mass. GBM is also characterized by the presence of red foci which represents recent hemorrhagic foci and brown foci which represents old hemorrhagic foci**. (Habib Allah., 2008).**

2.3. The characteristics of the tumors based on microscopic observation

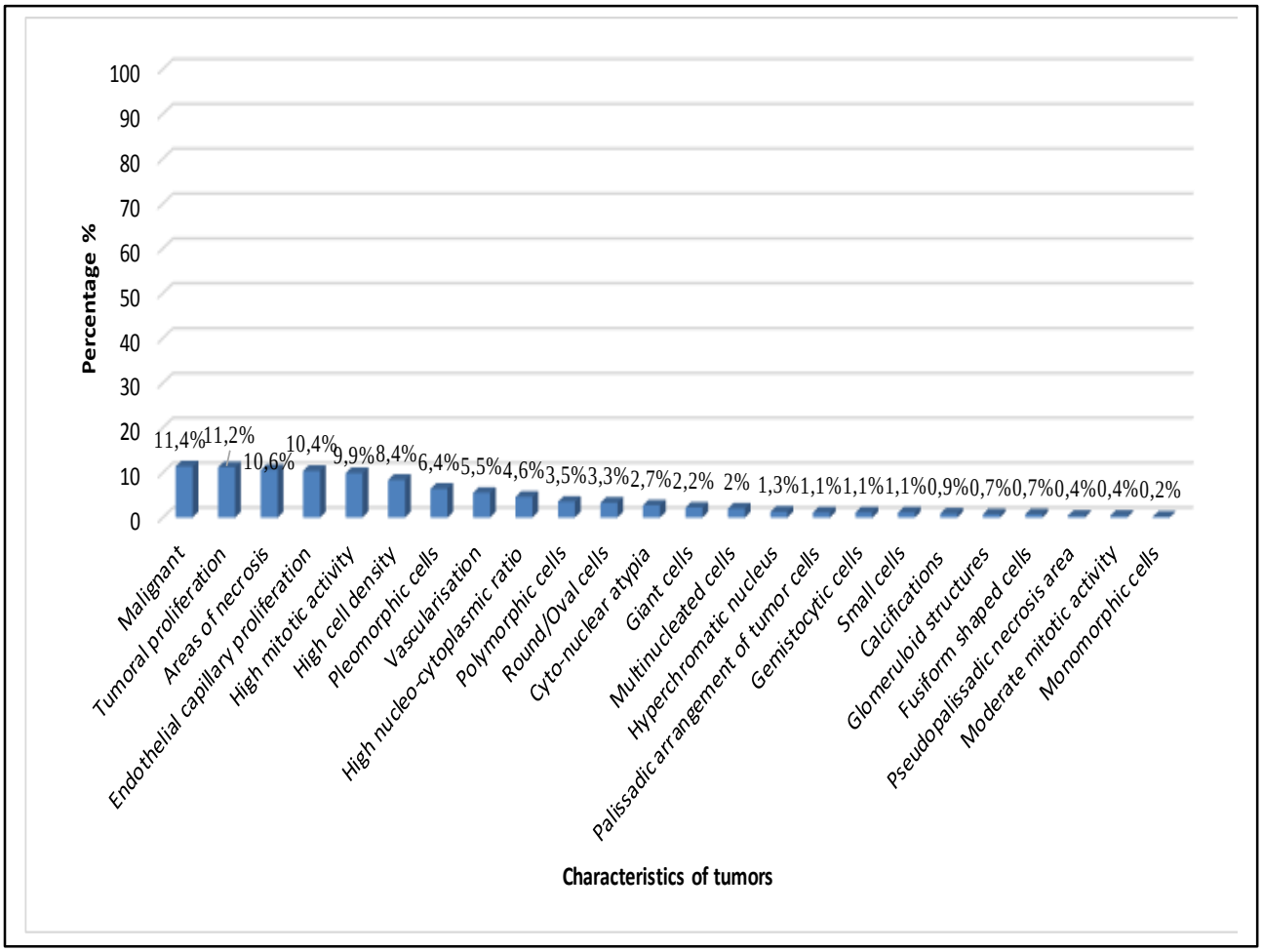

Figure. 45: Representation of the characteristics of the tumors based on microscopic observation.

The microscopic observation based on tumor characteristics revealed that its, malignant, proliferative, necrotic, with high capillary proliferation and high mitotic activity accounting for 11,4%, 11,2%, 10,6% , 10,4% and 9,9% respectively. This result therefore confirms in relation to Louis et al, that GBM is a highly malignant tumor.

2.4. Anatomopathology results

In our study, the macroscopic aspect of the lesion revealed, a fragmented sample, friable and beige in appearance, with necrotic and hemorrhagic areas.

The microscopic observation of the slides under the optical microscope showed, a cerebellar parenchyma which was the site of tumor proliferation of nervous origin, having infiltrating glial nature, high cell density, and was made up of a polymorphic cell proliferation, round, polygonal and spindal- shaped cells. The cells showed cytonuclear atypia and had a high mitotic activity. The microscopic observation equally revealed tissue vascularization which was ensured by blood vessels having a proliferative endothelium.

The presence of numerous foci of palisade necrosis was also noted.

Below are the microscopic images of the patient's tissue sample.

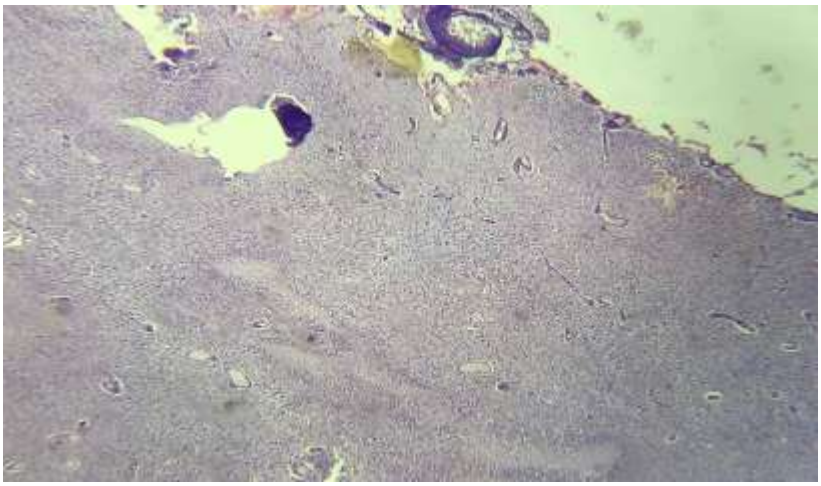

Figure. 46: Microscopic observation (X4)

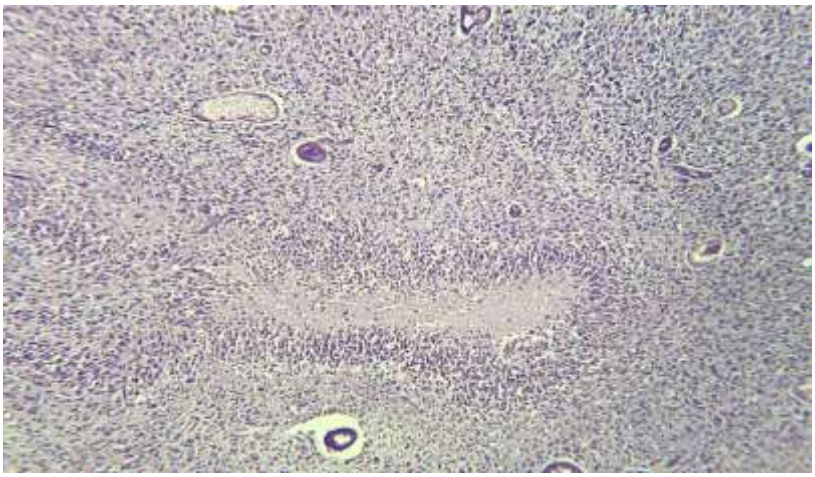

Figure. 47: Microscopic observation (X10)

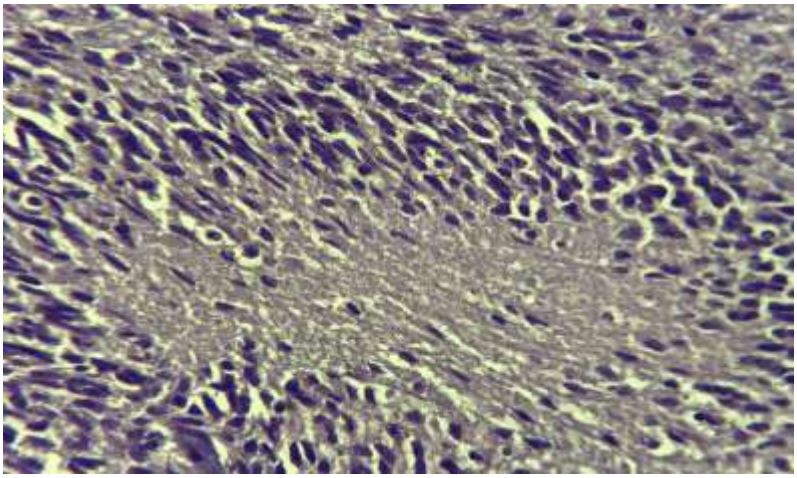

Figure. 48: Microscopic observation revealed a palisade-like necrosis (X40).

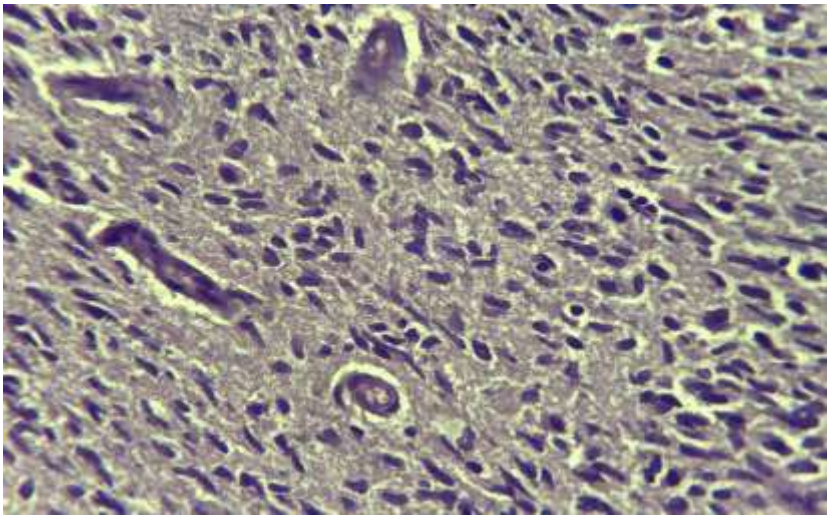

Figure. 49: Microscopic observation revealed endothelial proliferation (X40).

The histopathological findings revealed a high grade glial tumor corresponding to grade IV glioblastoma, according to the 2016, WHO classification.

CONCLUSION

CONCLUSION

This thesis has given an account of the epidemiological and anatomopathological aspect of glioblastoma multiforme.

The major findings of this study indicate that glioblastoma multiforme is a malignant tumor, and it is common among the elderly.

Despite the major advancements in the medical sector, glioblastoma remains a major public health problem due to its severity and the difficulties of treatment it poses. The cause of most cases of glioblastoma is not known. Some risk factors include genetic disorders, such as neurofibromatosis and Li–Fraumeni syndrome, and Ionizing radiation.

Despite the knowledge acquired through basic research, the clinical results remain modest and the overall prognosis poor. In our work, the particularities are related to the lack of therapeutic means, follow-up, and prognostic evaluation.

This study was limited by insufficient information for some patients in the medical records.

Our perspective is to encourage proper keeping of detailed medical records so as to enable adequate epidemiological studies and also promote multidisciplinary collaboration between neurosurgeons, radiologists, pathologists, biologists, oncologists, anesthesiologists for a good care of patients.

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ABSTRACTS

Abstract

The study of cases of Glioblastoma multiforme collected at the anatomopathology department at CHUC, allowed us to define the epidemiological and anatomopathological particularities of glioblastoma in the Constantine region.

The study population is composed of 70 patients, whose age varied between 4 and 70 years, with an average age of 50 years. 34,5% of the patients are located in the 49 to 57 age group and 62% are male, with a sex ratio of 1,63.

In our series, we noted that most patients experience this tumor in the temporal lobe and in the parietal lobe accounting for 24,3% and 20% of patients respectively.

Intracranial hypertension was the most common symptom representing 20,2%, followed by hemiparesis and headaches representing 13,3% and 12% of the symptoms respectively.

In our study we also noted that glioblastoma is characterised by a high degree of malignancy, tumoral proliferation, necrosis, perilesional oedema and endothelial capillary proliferation.

All the patients following diagnosis were treated by complete surgical resection coupled with radiotherapy and chemotherapy.

However, despite these treatment methods GBM is still associated with worst survival rates among all human cancers.

Key words: *Central nervous system, Glioblastoma Multiforme, Anatomopathology, oncogenesis, Diagnosis, Treatment.*

Résumé

L'étude des cas de glioblastome multiforme, colligés au service d'anatomopathologie du CHUC, a permis de définir les particularités épidémiologiques et anatomopathologiques du glioblastome dans la région de Constantine.

La population étudiée est composée de 70 patients, dont l'âge varie entre 4 et 70 ans, avec un âge moyen de 50 ans. 34,5% des patients se situent dans la tranche d'âge 49 à 57 ans, dont 62% sont des hommes avec un sexe ratio de 1,63.

Dans notre série, nous avons noté que la plupart des patients présentent cette tumeur au lobe temporal et au lobe pariétal représentant respectivement 24,3 % et 20 % des patients.

L'hypertension intracrânienne était le symptôme le plus fréquent avec 20,2 %, suivie de l'hémiparésie et des céphalées représentant respectivement 13,3 % et 12 % des symptômes.

Dans notre étude, nous avons également noté que le glioblastome est caractérisé par un degré élevé de malignité, de prolifération tumorale, de nécrose, d'œdème périlésionnel et de prolifération capillaire endothéliale.

Tous les patients après diagnostic ont été traités par exérèse chirurgicale complète couplée à une radiothérapie et une chimiothérapie.

Cependant, malgré ces méthodes de traitement, le GBM est toujours associé aux pires taux de survie parmi tous les cancers humains.

Mots clés : Système nerveux central, Glioblastome Multiforme, Anatomopathologie, Oncogenèse, Diagnostic, Traitement.

ملخص

سمحت لنا دراسة حالات الورم الأرومي الدبقي الذي تم جمعه في قسم علم الأمراض التشريحي في مستشفى CHUCبتحديد الخصائص الوبائية والتشريحية المرضية للورم الأرومي الدبقي في منطقة قسنطينة.

يتكون مجتمع الدراسة من 70 مريضًا ، تراوحت أعمارهم بين 4 و 70 عامًا ، بمتوسط عمر 50 عامًا. يقع 34.5٪ من المرضى في الفئة العمرية 49-57 و 62٪ من الذكور ، بنسبة جنس تبلغ 1.63.

في سلسلتنا ، لاحظنا أن معظم المرضى يعانون من هذا الورم في الفص الصدغي والفص الجداري وهو ما يمثل 24.3٪ و 20٪ من المرضى على التوالي.

كان ارتفاع ضغط الدم داخل الجمجمة هو أكثر الأعراض شيوعاً بنسبة 20.2٪ ، يليه الشلل النصفي والصداع بنسبة 13.3٪ و 12٪ من الأعراض على التوالي.

لاحظنا في دراستنا أيضًا أن الورم الأرومي الدبقي يتميز بدرجة عالية من الأورام الخبيثة ، والتكاثر الورمي ، والنخر ، والوذمة حول الجلد ، وتكاثر الشعيرات الدموية البطانية.

تم علاج جميع المرضى بعد التشخيص عن طريق الاستئصال الجراحي الكامل إلى جانب العلاج الإشعاعي والعلاج الكيميائي.

ومع ذلك ، على الرغم من طرق العلاج هذه ، لا يزال GBM مرتبطًا بأسوأ معدلات البقاء على قيد الحياة بين جميع أنواع السرطان البشرية.

الكلمات المفتاحية: الجهاز العصبي المركزي ، الورم الأرومي الدبقي متعدد الأشكال ، علم الأمراض التشريحي ، تكوين الأورام ، التشخيص ، العلاج.

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Etude épidémiologique, descriptive et anatomopathologique du glioblastome multiforme

Mémoire pour l'obtention du diplôme de Master en Immunologie moléculaire et cellulaire

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Mots-clefs : *Système nerveux central, Glioblastome Multiforme, Anatomopathologie, Oncogenèse, Diagnostic, Traitement.*

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