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Chapter

An Overview of Brain Tumor

Manimekalai Pichaivel, Gayathri Anbumani, Panneerselvam Theivendren and Muruganantham Gopal

Abstract

Brain tumor is an abnormal growth of mass of cells in (or) around the brain. Brain tumors can be malignant (cancerous) or being non-cancerous. It is the most common malignant primary intracranial tumors of central nervous system. Brain tumor can affect brain function if they grow large enough to press on surrounding nerves, blood vessels and tissues. Only one third of tumors formed in the brain are formed as cancerous cells. Brain tumors release molecular information to the circulation. Liquid biopsies collect and analyse tumor component in the body fluid and there is an increasing interest in investigation of liquid biopsies as substitute from tumor markers. Tumor-derived biomarkers include nucleic acids, proteins and tumor-derived extracellular vesicles that accumulate in blood (or) cerebrospinal fluid. Circulating biomarkers like O-6-methylguanine DNA methyl transferase, epidermal growth factor, isocitrate dehydrogenase, circulating tumor cells, circulating cell free micro RNAs, circulating extracellular vesicles plays and important role in causing a cancer. Brain tumor can be treated by surgery, radiation therapy (or) targeted therapy. Radiation therapy is often given afterwards. As a consequence, the most recent review reviewed the present state of research with the hopes of discovering a new brain tumor inhibitor that may be used to treat advanced malignancies.

Keywords: brain tumor, bio-markers, circulating bio-marker, O-6-methylguanine DNA methyl transferase

1. Introduction

A brain tumor is one of the most malignant tumors in humans. It accounts for approximately 1.35% of all malignant neoplasm and 29.5% of cancer-related death [1]. Brain and CNS tumors include tumors of the brain, cranial nerves, spinal nerves, spinal cord, and the meninges. The tumor can be broadly classified as malignant and non-malignant (or benign) tumors. The world health organization (WHO) classification specifies a grading system ranging from grade, whereas, grade III/IV are malignant or high grade [2]. A brain tumor is a diverse group of neoplasm with different types of primary brain tumor (or) metastatic cancer. The most common malignant brain tumors are glioblastoma that originates from glial cells [3]. Metastatic brain tumors (MBTs) account for the majority of an intra-axial brain tumors in adult patients. It is estimated that up to one-third of patients diagnosed with a primary malignancy will develop central nervous system metastatic lesions during their disease course [4]. Pediatric central nervous system (CNS) tumors are the second most common childhood malignancy and the most

common solid tumor in children [5]. Early diagnosis and treatment of brain tumors are imperative to prevent permanent damage to the brain (or) death of the patient. At the level of medical data analysis, the features election and classification process are the ones intensively used to identify the patient data whether it is normal (or) abnormal [6]. Once the tumor is detected under the microscope. It is often too late for effective treatment prognosis in patients is correlated with the stage of disease at the time of detection and therefore, it is important to find markers that allow the early detection of the tumor. The treatment options for patients with brain metastases include corticosteroids, surgery, chemotherapy, whole-brain radiation therapy, and stereotactic radiosurgery [7]. A patient with a brain tumor suffers from a significant problem called neurocognitive dysfunction. To diagnose the neurocognitive dysfunction in the brain tumor needs new strategies for the early initiation of appropriate neurocognitive rehabilitation. Raman spectroscopy technique is used for the differentiation of brain tumors. This leads to accurate identification of two essential factors such as brain tumor boundary and the complete resection of the tumor which is important for removal of glioma tumor in brain surgery [8].

2. Pathophysiology

In the 19th century, Stephen Paget postulated the "seed and soil" hypothesis, which considers that metastatic growth depends on cancer cells (the seed) interactions with and affinity for specific distant organ tissues (the soil). Paget's assertion that a nutritional microenvironment is imperative for metastatic cells to grow in distant tissues is supported by conceptual frameworks of contemporary cancer research [9]. A more advanced understanding of the complex and multifactorial mechanisms of metastasis formation consists of three premises: first, the existence of tumor heterogeneity, including morphologically- and phenotypically-distinct profiles of cancer cells with different proliferative, angiogenic, invasive, and metastatic characteristics; second, a metastatic process that is selective for tumor cells that accomplish all the key steps of the metastatic cascade; and third, the metastatic potential of a tumor, which depends on multiple, reciprocal interactions between the primary tumor and the tumor microenvironment, as well as homeostatic mechanisms [10]. This reciprocal cross-talk determines tumor progression and the potential for metastatic growth. As in the periphery, a brain tumor's microenvironment plays a critical role in metastatic colonization of the brain; but the outgrowth of tumor cells to the brain depend on specific behaviors of the tumor cells and conditions in the brain tumor microenvironment. In the literature, at least three microenvironments have been considered involved in brain metastasis formation: the perivascular niche, the brain parenchyma, and the cerebrospinal fluid also termed the leptomeningeal niche [11]. As the brain tumor grows it creates pressure on and changes the function of surrounding cells and it leads to symptoms. Most cases of Brain Tumor travel by hematogenous spread and occur most often at the gray-white matter junction [4]. The markers involved in the brain tumor are as follows:

A. Circulating tumor cells

B. O-6 methylguanine-DNA mutations

C. Epidermal growth factor receptor

D. Isocitrate dehydrogenase

E. Circulating free DNA

F. Circulating proteins

G. Tumor protein39.

H. Tumor protein 53.

A. Circulating tumor cells

Circulating tumor cells (CTCs) are cells that are shed from primary or metastatic tumors in the body fluids, including blond, cerebrospinal fluid, and urine. CTCs determine the ability of epithelial tumor cells to metastasize [12]. These different types of potential biomarkers in the blood can be present in cell-free forms, attached to lipid or protein structures, or delivered by circulating extracellular vesicles or platelets [13]. CTCs are also used in the monitoring of glioblastoma patients. The level of CTCs detected after chemotherapy is significantly lower compared to their level before the treatment, which may provide invaluable insight in differentiating tumor progression from radiation necrosis [14, 15].

B. O-6 methylguanine-DNA methyltransferase mutations (MGMT)

The gene encoding O-6-methylguanine DNA methyltransferase (MGMT) is found on chromosome 10q26 [4]. By methylating DNA base pairs, alkylating chemotherapeutic drugs such as temozolomide impair DNA replication. Active MGMT reverses the effect of temozolomide, enabling normal DNA replication to occur within a tumor [16]. O-6-methyl transferase DNA methyltransferase contributes to DNA repair by reversing DNA alkylation and eliminating the guanine-alkyl group, therefore preventing apoptosis. MGMT has recently been established as a biomarker for tumor diagnosis [17]. Methylation promotes the gene code for MGMT in glioblastoma and is the genetic fingerprint with the greatest influence on clinical practice. The presence of O-6-methylguanine-DNA methyltransferase (MGMT) suggests that the current standard of treatment, adjuvant chemoradiotherapy with the alkylating drug temozolomide, is more effective [18–20].

C. Epidermal growth factor receptor

Most signaling pathways and physiological responses, including migration, proliferation, survival, and tumor development, are activated by the epidermal growth factor receptor (EGFR). EGF, TGF-, heparin-binding epidermal growth factor-like factor (HB-EGF), amphiregulin (AR), betacellulin (BTC), neuregulins (NRGs), also known as neuregulin; neu differentiation factors; glial growth factors; acetylcholine receptor inducing activity; and epiregulin are all members of the EGF superfamily (EPR) [21, 22].

D. Isocitrate dehydrogenase

Isocitrate dehydrogenase (IDH) is a protein enzyme that encodes genes on chromosome 2, the main function of IDH in the Krebs cycle is to catalyze oxidative decarboxylation [4]. IDH has been grouped into two classes (IDH 1 and IDH 2). Mutation of isocitrate dehydrogenase 1 (IDH-1) in glioblastoma was first noted by following an integrated genomic analysis of human

glioblastoma samples [16]. The IDH-1 protein protects the cytoplasm against oxidative damage. In 12% of glioblastoma samples, a heterozygous point mutation at R132 was discovered. Glioblastomas that were known to have developed from lower-grade tumors had a considerably greater prevalence of IDH-1 mutation (83%) [23]. Grade II/III astrocytomas, oligoastrocytomas, and oligodendrogliomas all have isocitrate dehydrogenase, which can be utilized to distinguish primary from secondary glioblastomas [24, 25].

E. Circulating free DNA

Cell-free DNA (cfDNA) as a double-stranded, DNA fragments released for the breakdown of cancer tissue by bloodstream that is approximately 150 to 200 base pairs in length, corresponding to nucleosome-associated DNA, can be released by cells under physiological and pathological conditions as well. It is suggested that cfDNA could be derived from apoptotic or necrotic cells, rapidly dividing cells, or CTCs [4]. Blood cfDNA is mostly derived from genomic DNA released during inflammation or cell death in people without cancer. Due to phagocyte clearance, the concentration of cfDNA in the blood is low in physiological settings. Circulating protein markers may be used to track the efficacy of therapy in patients with brain tumors. Current MR imaging techniques cannot effectively detect the unique biological tumor characteristics and complicated tissue changes produced by various cancer treatments [26, 27].

The incidence of detectable ctDNA varies significantly across patients with various tumor types. The concentration of cancer cell-generated ctDNA in plasma in glioblastoma is low when compared to other cancer types, which might be due to the existence of the blood–brain barrier. In glioblastoma, ctDNA analysis presents a number of difficulties. Aside from the common issues of short half-lives (1.5 h) of ctDNA fragments, distinguishing mutant from wild-type alleles, and developing mutation thresholds, the primary issue is the low amount of ctDNA in the samples [28].

F. Circulating proteins

Several tumor-derived circulating nucleic acids (e.g., ctDNA, cmtDNA, mRNA, non-coding RNAs including miRNAs, long non-coding RNAs) that can be detected from blood or other types of body fluids like urine, cerebrospinal fluid (CSF), saliva, pleural fluid, and ascites. In brain tumor patients, the secretion of the proteins may lead to an increase in the level of circulating proteins (CPs) in the blood and urine and/or CSF [4]. Angiogenesis-related protein markers were discovered in malignancies. The amount of vascular endothelial growth factor was shown to be substantially greater in brain tumor patients than in healthy persons, and even higher in patients with brain metastases [29]. There are two types of prognostic CP indicators: tumor-associated markers and related markers with endogenous systemic stress responses. Overall survival was adversely associated with the tumor-related plasma markers YKL-40, the extracellular domain of EGFR, and osteopontin [30, 31].

G. Tumor protein 39 (TP39)

Tumor protein 39A (TP39A) belongs to the Transmembrane protein 39 families (TMEM39), consisting of TMEM39A and TMEM39B. The two TMEM39 isoforms are produced via alternative splicing. The TMEM39A-

encoding gene may be a susceptibility causes the brain tumor [4]. Transmembrane proteins across the plasma membrane from one side to the other. The movement of materials across biological membranes is regulated by several transmembrane proteins. Multiple sclerosis susceptibility may be linked to the TMEM39A-encoding gene. TMEM39A has also been linked to systemic lupus erythematosus [32, 33].

H. Tumor protein 53 (TP53)

TP53 is a typical tumor suppressor gene located in 17p13.1. This encodes the nuclear protein p53. To regulate the expression of its target genes the p53 protein responds to diverse cellular stresses, thereby inducing cell cycle arrest, apoptosis, senescence, DNA repair, or metabolic changes. Several human malignancies, including Li-Fraumeni syndrome and numerous hereditary gliomas, are linked to mutated TP53 genes and overexpressed aberrant p53 protein, which has a longer half-life than wild type p53 [4]. If p53 mutations are important in the start of malignant transformation of glial cells, i.e., if they play the function of "mutator" mutations, families with hereditary mutations of one of the p53 alleles would be expected to develop CNS malignancies. Furthermore, the histological kind of glioma that was found should match the usual histology of gliomas with a p53 mutation [34].

The well-known tumor suppressor protein p53 is encoded by the TP53 gene. It is known as the genome's guardian, and it has a variety of tasks in preventing tumor development. Secondary brain cancers (90 percent) have considerably more TP53 point mutations than initial brain tumor (30%), and in rare cases, primary lesions had none at all [35, 36].

3. Epidemology

Population-based studies are generally considered more accurate and less biased than the more limited clinical (or) autopsy-based series [37]. The exact incidence of brain metastases is unknown. The epidemiological study is done by using the hospital records, tumor registers, and death certificates. Finally from this study, the incidence of brain metastases seems equal to the incidence of gliomas [38]. The survival rate by histology is summarized in **Figure 1.**

A. Meningiomas

Meningiomas are the most common brain tumors in adults accounts about 36% of all brain tumors in the central brain tumor registry of the united states (CBTRUS). In 2015 CBTRUS estimates that there will be approximately 24,000 new meningiomas diagnosed in the united states [37]. The incidence of meningioma steadily increases with age being twice as common in women as in men and 20% more common in blacks than in whites. A majority of meningiomas are benign (grade I), with 5–20% atypical (grade II) and 1–3% malignant in type (grade III) [38, 39].

Although benign meningiomas are a minor cause of death, skull-based tumors can cause considerable morbidity. Atypical and malignant meningiomas, on the other hand, are linked to high rates of recurrence and substantial morbidity and death [40, 41]. Meningioma is shown in **Figure 2**. Because telomerase activity is detected in all anaplastic/malignant (WHO grade III)

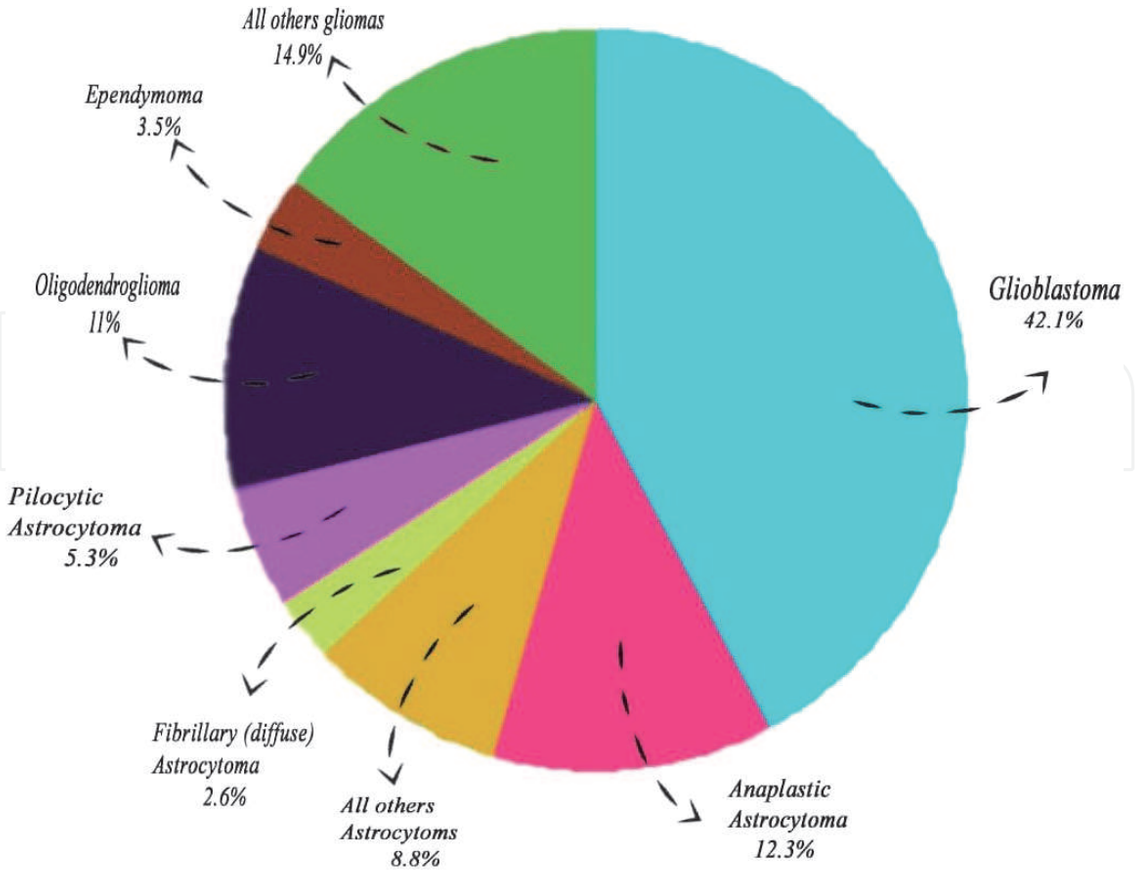

Figure 1.
CNS tumor epidemiology -the incidence of brain tssumor in different regions of brain.

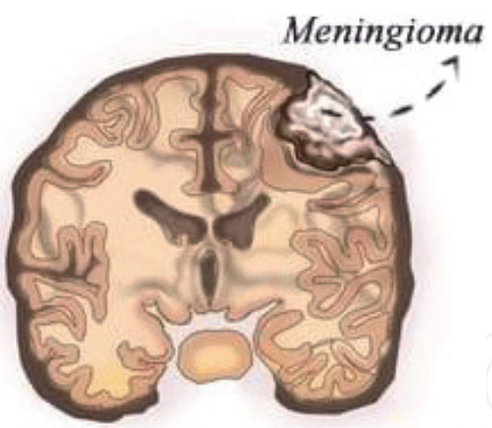

Figure 2.
Brain meningioma.

and the majority of atypical (WHO grade II) meningiomas, there is a link between telomerase activity and tumor grading in meningiomas [42, 43].

B. Glioma

Glioma is the second most common brain tumor in adults. In 2015 the CBTRUS estimates approximately 20,000 newly diagnosed gliomas in the united states. Approximately one-half of gliomas is glioblastoma, the commonest malignant primary brain tumor in adults. Glioma occurs almost in all four lobes in the brain: frontal (23.6%), temporal (17.4%), parietal (10.6%), occipital (2.8%), a small percentage in the brain stem, cerebellum and spinal cord [20].

Glioma is shown in **Figure 3.** Secondary glioblastomas are considered to develop as a result of progression from pre-existing astrocytomas, thus this finding is fascinating [44].

C. Pituitary tumor

The third most common brain tumor in adults is the pituitary tumor and it accounts for 15%. A majority of brain tumors are benign adenomas [45]. Even people who do not produce hormones might have symptoms as a result of the intracranial mass effect. Hormones that control normal pituitary function, as well as growth factors implicated in normal fetal pituitary development, appear to stimulate tumor growth [46, 47]. Pituitary tumor is shown in **Figure 4**.

D. Pediatric brain tumor

CNS tumors in children are the second most frequent malignancy in children and the most common solid tumor in children. According to CBTRUS, about 2000 children in the United States are diagnosed with a brain tumor before the age of 14. The most frequent solid tumor in babies and toddlers is a brain tumor. More than 8% of children and adolescent cancers are caused by genetic predisposition syndromes, and this percentage is anticipated to climb as research continues [3].

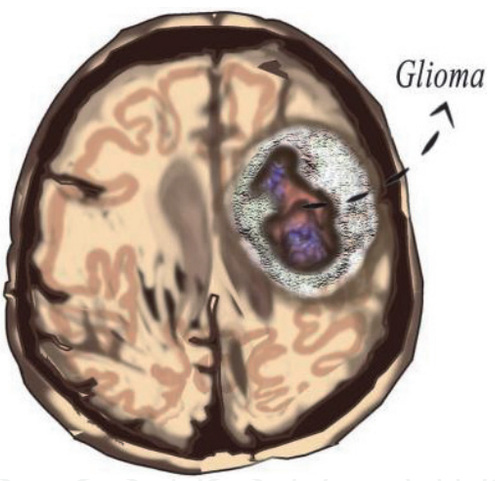

Figure 3.
Glioma.

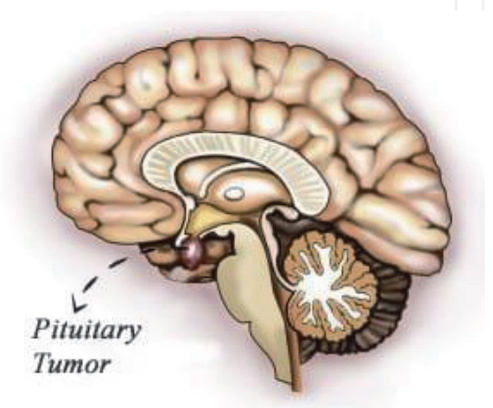

Figure 4.
Pituitary tumor.

Non–posterior fossa embryonal tumors, also known as CNS-primitive neuroectodermal tumors (PNETs), are a kind of uncommon juvenile brain tumor that accounts for less than 3% of all cases and has a dismal prognosis [46]. All CNS embryonal tumors are very malignant and are classified as WHO grade IV tumors by the World Health Organization. Many tumors classified as supratentorial embryonal tumors histologically cluster with other tumor types, such as high-grade gliomas and ependymomas, according to molecular studies; this has major therapeutic implications in terms of the amount of radiotherapy required for tumor control and the choice of adjuvant chemotherapy or biologic therapy [47, 48].

4. Signs and symptoms

A. Headache

Headache occurs commonly in all brain tumor patients. The headache is said to develop in the temporal and the spatial, relation to the neoplasm and resolves 7 days of surgical removal or treatment with corticosteroids [48].

Headache in pituitary brain tumor

The presence of headache has been shown to be more highly associated with family history than the tumor size [47].

Headache in pediatric brain tumor

Headache appears to be the most common presenting symptom (41% of patients in some studies). It tends to occur with other symptoms such as vomiting, unsteadiness, behavioral problems, and cranial nerve palsies, and most commonly nocturnally (or) in the early morning [49].

Mechanism of headache in brain tumor

The mechanism of headache in brain tumors may include the traction on vascular structure, cranial or central sensitization through neurogenic inflammation as well as the component of central sensitization through trigeminovascular afferents on the meninges and the cranial nerves [50].

B. Nausea and vomiting

Nausea and vomiting occur when the chemo trigger zone in the area postrema, located on the floor of the fourth ventricle is stimulated. Raised intracranial pressure leads to vomiting. It can also occur in the absence of elevated intracranial pressure in brain stem tumors involving the nucleus solitarius [51].

Mechanism of vomiting

Nausea and vomiting are highly conserved responses and the survival advantages in survival vertebrates. Vomiting is primitive, low-threshold, brain stem response that allows the human to purge the gastrointestinal tract of orally consumed noxious substances. Vomiting is multidimensional having a higher cognitive brain center, emotions, and interoceptive domains is more common disabling, and more difficult to control than vomiting [52].

C. Altered mental status

Mental and cognitive abnormalities may be specific, or nonspecific. Specific findings include aphasia, agnosia, abulia, alexia, or apraxia. In about 16–34%

of patients, the symptoms for brain tumor patients include irritability, change in personality, emotional liability, forgetfulness, lack of enthusiasm or spontaneity, and slowed response progressing apathy and lathery [53].

D. Papilledema

Papilledema is an indicator of increased intracranial pressure it is now rarely seen in patients at the time of presentation of the tumor. Like headache, papilledema is seen mostly seen in young adults and children, this is probably because older adults have tumor expansion due to tumor atrophy [53].

Mechanism of papilledema

The mechanism of papilledema is due to axoplasmic flow stasis. High intracranial pressure produces raise in cerebrospinal fluid pressure surrounding the optic nerve, which disturbs the normal gradient between intraocular pressure retro lamellar pressure leading to high pressure within the nerves and this leads to papilledema [54].

E. Seizures

Seizure is the most frequent symptom in patients with brain tumors. The incidence of brain tumors varies 30–100% depending on the tumor type and location with a slow-growing tumor that is being epileptogenic [53]. Brain tumor patients with epilepsy will have a high risk of seizure-related morbidities, mortality as well as experience a low quality of life [55].

Mechanism of seizure

The mechanism of seizure in brain tumor patients involves changes in aminoacid neurotransmission is the most important mechanism underlying tumor-related seizures and changes in extracellular ions also play an important role. Hypoxia, acidosis, metabolic, immunological, and inflammatory changes may also be involved in seizure occurrence [56].

5. Diagnosis

Diagnostic tests to detect these changes using biomarkers show significant potential for early detection [57]. Development of neurologic deficits and new-onset seizures are commonly followed by neurologic workup that includes magnetic resonance imaging (MRI). Computer tomography (CT) with contrast enhancement is less sensitive in detecting the typical features of glioblastoma [58].

A. WCFS-IBMDNT

Many recent studies have attempted to define the characteristics of brain tumors to diagnose the illnesses. However, with a large dataset, the correlations across brain tumor characteristics limit the illness diagnosis performance. Furthermore, when using standard approaches for categorization, misclassification outcomes might arise. The WCFS-IBMDNL approach employs the IBMDNN classifier after selecting a subset of characteristics for efficient brain tumor diagnosis with low time complexity. The most significant diagnostic approach used to diagnose brain tumors is Weighted Co-relation Feature Selection Based Iterative Bayesian Multivariate Deep Neural Learning (WCFS-IBMDNT). The WCFS-IBMDNT approach was

created to enhance brain tumor diagnosis by requiring the least amount of time [59]. The major importance of WCFS-IBMDNT are as follows:

1. The WCFS-IBMDNT technique was designed to enhance the prediction of brain tumors based on classification. Weighed correlation-based feature selection is the traditional method and performs WC-FS for highlighting the characterization of brain tumors by the subset of medicinal hights [59]

2. First it is proposed to enhance the performance of brain tumor prediction via a classification technique. The proposed WCFS-IBMDNL technique is designed with the implementation of WC-FS and IBMDNN classifier [59].

3. The feature selection procedure for providing effective brain tumor detection diagnostic is carried out using WC-FS. The Pearson correlation coefficient is used in WCFS-IBMDNL, which is a first. The Pearson correlation coefficient is used to determine the relationship between two medical variables to choose a group of medical parameters that are most important to the categorization of brain tumors [59].

4. The IBMDNN classifier is used in the proposed WCFSIBMDNL method to improve brain tumor diagnostic classification performance. BMLR is also utilized in the IBMDNN classifier to analyze medical characteristics to categorize patients as normal or abnormal. The least absolute error is calculated after the categorization. Finally, to reduce the error rate, the IRLS technique is utilized. This contributes to a higher illness detection rate while lowering the FAR [59].

B. Magnetic resonance imaging (MRI)

MRI is the most important technique for the diagnosis of brain tumors. MRI is used in the biomedical to detect and visualize finer details in the internal structure of the body. This technique is used to detect the differences in the tissues. MRI is fundamentally better than CT scanning [60]. This study proposes the computer-assisted computed organization feature extraction with abnormal MRI images of brain tumors to develop the accuracy of classification results according to the original feature classification. The initial input database images are fed for pre-processing and the images are transferred as 3×3 blocks. Then for each image of 3×3 blocks, 22 number of texture feature was extracted. Then the extracted feature was used to classify the brain tumor as normal as unusual [61].

The most prevalent metabolites of the brain, such as N-acetyl aspartate (NAA), choline (Cho), creatine (Cr), lipid, and lactate, may be quantified using MR spectroscopy (MRS) [57]. Choline is considered to correspond with cell turnover, therefore variations in Cho might be linked to the stage of radio-necrosis. Cho rises in the first few months following radiation therapy, according to two studies, but it declines as radionecrosis develops, according to Rock et al. Rapid Cho, on the other hand, is a common characteristic of tumor recurrence due to high cell turnover [62].

C. CT Scanning (computer tomography)

Computer tomography has a high accuracy than magnetic resonance imaging MRI. CT uses ionizing radiation for the diagnosis of brain tumors. This is used

for the diagnosis of primary glaucoma and lymphoma of the Central Nervous System (CNS) was performed [59]. A CT scan may reveal hypodensity in the white matter, as well as a mass effect on surrounding structures. In vascular metastases, localized bleeding may be observed [63].

D. Fused MRI and CT Analysis

Tumor identification is done using a combination of computed tomography CT and MRI scans. Multiple modalities such as CT and MRI are utilized to create the merged pictures (MRI). CT pictures, which are utilized to determine the difference in tissue density, and MRI images, which give a good contrast between distinct bodily tissues, play a vital role in medical image processing [64]. CT pictures show differences in tissue density based on the tissues' capacity to respond to X-rays, whereas MRI images show the contrast between soft tissues. When compared to the source pictures, the fused image retains the complementary and redundant information from both source images, including tumor size and position, allowing for better tumor detection [65].

E. Positron emission tomography [PET]

The brain's major energy source is aerobic glucose metabolism. The most commonly used PET radiotracer, F18-FDG, is actively transported across the BBB and accumulates in areas where aerobic glucose metabolism is enhanced. FDG accumulation is proportional to glucose metabolism in the cell, and higher accumulation correlates to higher cellular metabolism. The brain's typical strong metabolic activity causes high uptake in the normal brain parenchyma, resulting in poor tumor-to-brain contrast. Another possible stumbling block is the nonspecific nature of FDG absorption, which may be seen in inflammatory and infectious processes [66].

PET radiolabelled amino acids increase proportionately to cellular proliferation due to enhanced transport. Tumors increase transporter activity, metabolic enzyme activity, and demand, resulting in increased radiotracer accumulation proportionate to protein synthesis and food demand [67].

F. Single-photon emission computed tomography [SPECT]

SPECT is a low-cost imaging technique that is readily available and may be used in conjunction with CT and MRI to evaluate tumors and RN. In the post-treatment context, a variety of SPECT radiotracers are available for brain tumor imaging. Thallium201 is very accurate for post-treatment evaluation of tumor burden because it concentrates on living tumors; nevertheless, Thallium201 has nonspecific absorption in non-neoplastic processes such as granulomatous or fungal etiologies [66].

Thallium201 absorption is unaffected by the BBB and is primarily determined by the pace of cell growth, making it highly selective for brain tumors. Thallium201-SPECT had a sensitivity of 71.7 percent and a specificity of 80.9 percent for supratentorial brain tumors, according to a retrospective analysis of 90 patients. Because tumor growth rates are substantially greater than normal brain parenchyma, thalllium201 accumulates in brain malignancies without considerable absorption in the normal brain parenchyma, producing good tumor-to-background contrast [68, 69].

6. Types of brain tumor

The brain plays an important role in the body by controlling voluntary and involuntary processes. It is highly necessary to maintain a healthy brain to live longer. But some factors like environmental and genetic factors tumors in the brain can be developed [70]. These tumor causes the damage in healthy tissues and increases the pressure in the brain. Thus, some tissues may get pushed against the skull.

The tumors are classified according to the place they occur and the type of cell as follows:

1. The type and grade
2. Primary or secondary tumor
3. Malignant or benign tumor
4. Tumor location [71].

According to WHO (World Health Organization) brain tumors are classified as:

1. Astrocytoma
2. Glioblastoma
3. Oligodendroglioma [71].

1. Astrocytoma

Astrocytoma tumors arise from the supportive glial cells of the brain. About 7% of the primary brain tumor are astrocytoma. A star-shaped tumor that begins in the brain is called astrocytoma. In adults, the astrocytoma most often arises in the cerebrum, wherein in children it occurs in the brain stem [63].

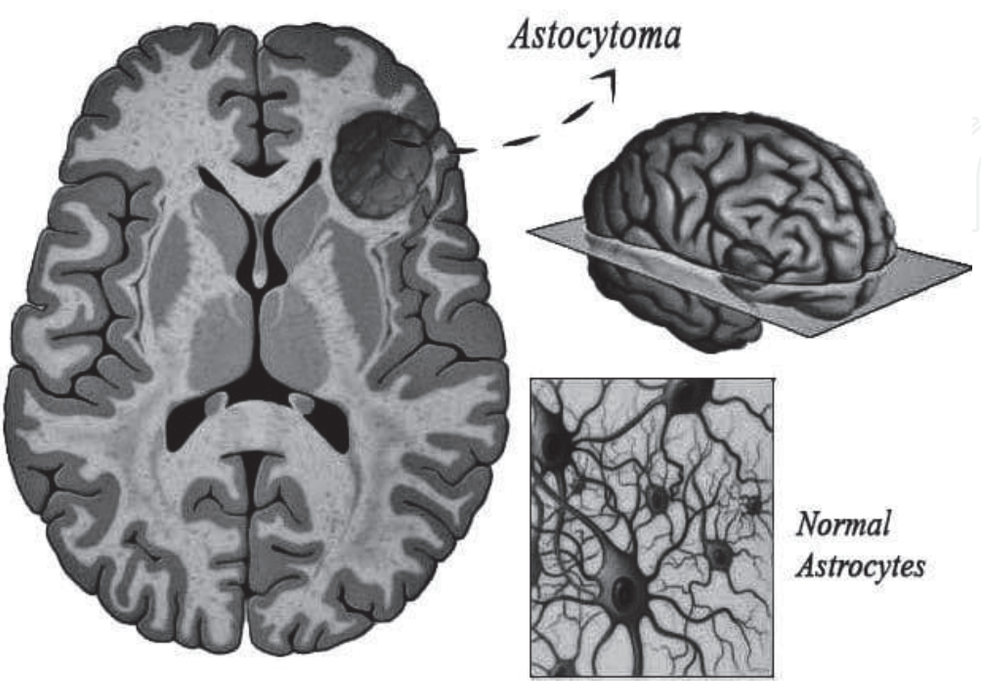

Figure 5.
Astrocytoma.

Astrocytoma is shown in **Figure 5.** The basal ganglia and thalamus are the two most likely locations where the long-term prognosis is poorer than for hemisphere injuries [72]. Post-operative radiation is a treatment option for low-grade gliomas. However, one disadvantage of radiation is that it causes neurocognitive damage and does not result in considerable improvement. As a result, radiation is often reserved for individuals with tumors that are at high risk of malignant transformation [73].

2. Glioblastoma

Glioblastomas (GBMs) is the most common and primary aggressive brain tumor. Glioblastoma is shown the **Figure 6**. Glioblastoma accounts for 45.6% of primary malignant brain tumors. Typical molecular changes in glioblastoma include mutation in gene-regulating receptor tyrosine kinase (RTK) / phosphoinositide 3-kinase (PI3K), p53, and retinoblastoma protein (RB) signaling [71]. Secondary glioblastoma is a kind of glioblastoma that develops in younger people when a previous malignancy, such as grade II astrocytoma or anaplastic astrocytoma, somatically mutates into a glioblastoma [74].

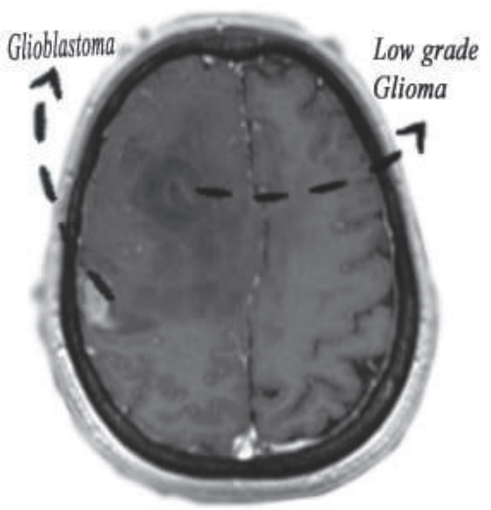

Figure 6.
Glioblastoma.

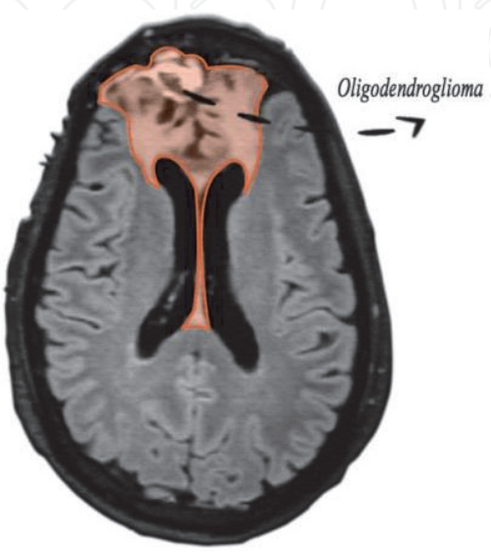

Figure 7.
Oligodendroglioma.

3. Oligodendroglioma

Oligodendroglioma is a rare form of brain tumor. The brain is made up of many supporting cells that are called glial cells. Any tumor of these glial cells is called glioma. A tumor that arises from the glial cells (oligodendrocyte cells) is called oligodendroglioma [72]. Oligodendrogliomas vary from other glial tumors in their molecular genetic makeup. On chromosome 1p and chromosome 19q, LOH is seen often in oligodendrogliomas of all grades [75]. Oligodendroglioma is shown in **Figure 7.**

7. Pediatric brain tumor

The pediatric brain tumor is the second most childhood malignant brain tumor and the most common solid tumor in children. The genetic syndromes that cause brain tumors are due to NF-1, tuberous sclerosis, Li-Fraumeni syndrome, and other less common inherited conditions, such as Gorlin syndrome or Turcot syndrome [76].

1. low-grade glioma

Low-grade gliomas (LGGs) is the most common pediatric central nervous system (CNS) tumor and it comprises for 30–40% of all CNS tumor. LGGs are infiltrative and incurable primary brain tumors with a typical slow evolution. Treatment of this low-grade glioma includes chemotherapy, radiation therapy, and targeted therapy [77].

2. High-grade glioma

High grade comprises up to 12% of pediatric CNS tumors and it includes anaplastic astrocytoma (WHO grade III) and glioblastoma (WHO grade IV). The symptoms depend on tumor location. The treatment method includes chemotherapy regimens that have been studied in the patients with high-grade gliomas, including temozolomide, lomustine, and thalidomide but have unfortunately not resulted in significant improvement in survival rates [78].

3. Medulloblastoma

Medulloblastoma is the most common CNS embryonal tumor. It represents about 10% of all pediatric brain tumors [**79**]. Medulloblastoma is the most common malignant brain tumor in children accounting for approximately 25% of pediatric brain tumors, with many reports indicating an increase in medulloblastoma in recent years [80].

4. Ependymoma

Ependymomas are tumors of the central nervous system that derive from the ependymal cells that line the ventricles of the brain and the central canal of the spinal cord [81]. Ependymoma can occur throughout the neuroaxis-supratentorial, posterior fossa, and spinal cord; however, 90% of pediatric ependymomas occur intracranially with 2/3 in the posterior fossa and 1/3 supratentorially [82].

8. Molecular genetics of brain tumor

The molecular genetics of brain tumors is due to the mutation in enzymatic activity. The mutation rate that commonly occurs in various gene to cause brain tumor are:

1. Astrocytoma a grade II, III type of brain tumor is due to IDH mutation, P53 mutation, ATRX mutation.

2. Glioblastoma a grade IV type is due to amplification of EGFR, PDGFRA amplification mutation of EGFRvIII, deletion of PTEN homozygous, CDKN2A homozygous deletion, BRAF V600E mutation, (epithelioid GBM) TP53 mutation.

3. Oligodendroglioma a grade II, III is due to IDH mutation, 1p/19q codeletion, CIC/FUBP1 mutation, TERTp mutation [83].

A. Mutation IDH1/2

IDH catalyzes the oxidative decarboxylation of isocitrate to generate (-KG) and CO2, however, mutant IDH1/2 preferentially binds -KG rather than isocitrate outside of the citric acid cycle, resulting in the formation and accumulation of the oncometabolite 2-hydroxyglutarate (2HG) [84].

HIF1 (Hypoxia Inducible Factor) levels and alterations in the HIF1 downstream pathway are modulated by -KG–dependent prolyl hydroxylases, resulting in an increase in reactive oxygen species levels and potentially contributing to the risk of cancer [85].

B. TP53 mutation

TP53 is a tumor suppressor gene that encodes the nuclear protein p53 and is found on the 17p13.1 chromosome [86]. Several human malignancies, including Li-Fraumeni syndrome and numerous hereditary gliomas, are linked to mutated TP53 genes and over-expressed aberrant p53 protein, which has a longer half-life than wild type p53 [87].

C. ATRX is an X-linked gene of α- Thalassemia and mental retardation syndrome

ATRX is a 280-kDa nuclear protein that has been implicated in a variety of biological activities including DNA recombination, repair, and transcription control. It is found on chromosome 21.1 and encodes a 280-kDa nuclear protein [88]. When ATRX and DAXX connect, the resulting complex acts as a histone chaperone, allowing histone variation H3.3 to be deposited into heterochromatic repeats such as pericentric, telomeric, and ribosomal DNA repeat regions [89].

D. EGFR amplification and EGFRvIII truncation mutation

EGFR, also known as Erb1 or HER1, is an ErbB family receptor tyrosine kinase that is found on chromosome 7q12. EGFR over-expression is linked to EGFR amplification. The EGFRvIII mutation is a frame deletion of 801 bytes from exons 2 to 7 of the EGFR gene, which is linked to EGFR amplification, antibody response, and poor prognosis [90, 91].

E. BRAF mutation

Pilocytic astrocytoma is defined by BRAF V600E mutations and BRAF fusions with KIAA1549 or FAM131B. A tandem duplication at 7q34 was verified, and a novel fusion gene was discovered in pilocytic astrocytoma, which was previously uncharacterized by a fusion between the KIAA1549 and BRAF genes [92].

9. Treatment method of brain tumor

A. Immunotherapy

When it comes to treating brain tumors, immunotherapy is a potential treatment option. Chemotherapy, radiation treatment, and surgery have all been used to treat it in the past. An immune-based cancer therapy uses the body's immune system to destroy cancer cells [93]. If the cells are no longer required or pose a hazard, apoptosis, or programmed cell death, will occur to halt cell growth [94]. Cancer progresses and develops through eight processes, which are as follows:

1. Stained proliferation
2. Evasion of growth suppressor
3. Cell death resistance
4. Replicative immortality
5. Angiogenesis
6. Metastasis
7. Reprogrammed metabolism
8. Evasion of immune destruction [95].

The evasion of immune destruction has been studied for decades. Because EphA2 is abundantly expressed in glioblastoma but only at low levels in normal brain tissue, CAR T cell treatment targeting the glioblastoma antigen EphA2 is an appealing strategy to enhance outcomes [93].

Since brain tumor immunotherapy has been extensively studied [94–96], we will focus in this work on the most recent and late-stage clinical trial treatments, as well as the engineering problems these immunotherapies confront in the brain tumor environment [96].

i. Vaccines

Traditional vaccinations against viral illnesses (for example, influenza) employ attenuated or live viruses in combination with a danger signal (as an adjuvant) to activate DCs. DCS then takes up the viral antigen, digests it, moves to lymph nodes through lymphatic channels, and activates T-cells via the presentation of various peptide antigens/antigenic epitopes on MHC molecules [93].

a. Peptide vaccines

Immunization using peptide vaccine when released at the tumor site, peptide vaccinations stimulate T-cell responses by releasing antigen-specific peptides. APCs take up peptides, which are often associated with carrier proteins and adjuvants, and display them on the cell surface by way of MHC [97]. The treatment method by peptide vaccine is explained in **Figure 8**.

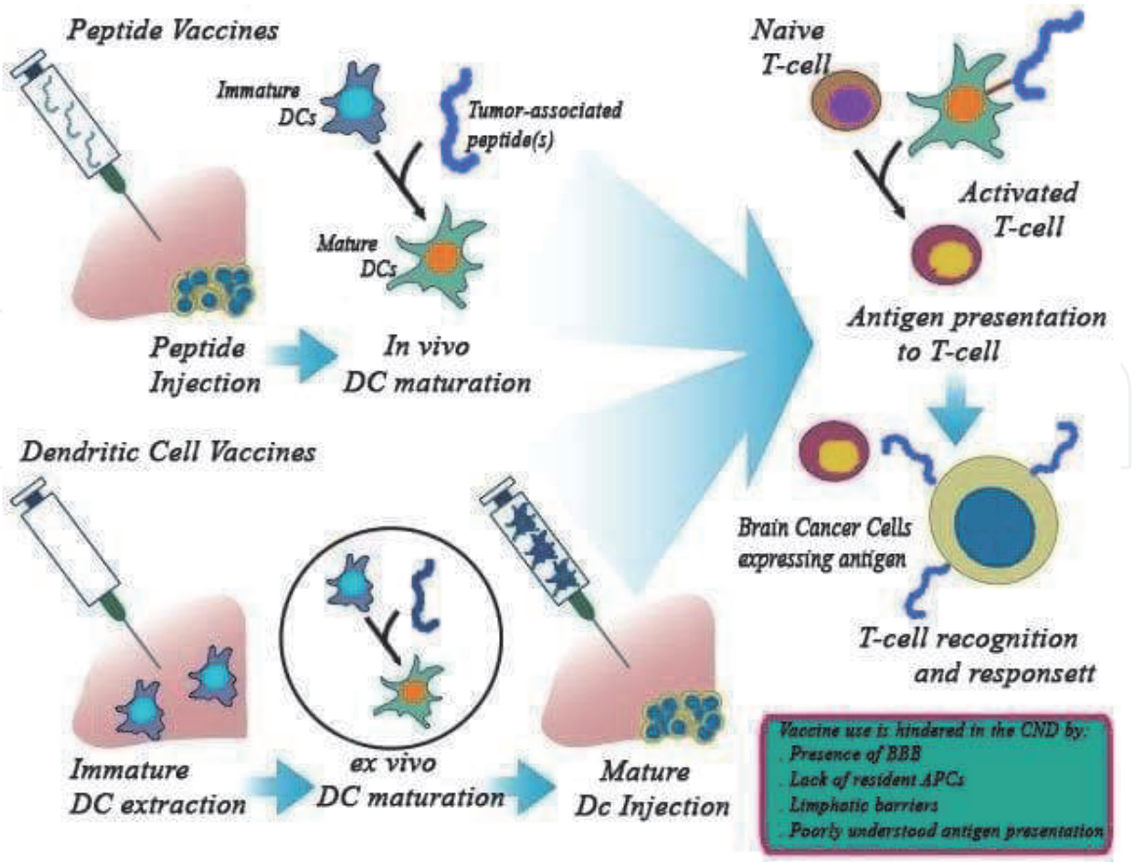

Figure 8.
Dendritic vaccine therapy and treatment method by peptide vaccine.

APCs take up peptides, which are often associated with carrier proteins and adjuvants, and display them on the cell surface by way of MHC. Molecules of human leukocyte antigens (HLA) MHC I (HLA) [98].

b. Dendric cell vaccines

If you are looking for an alternative to peptide vaccines in situ, you may also use direct activation of DCs ex vivo to create a cancer vaccine. Autologous dendritic cells derived from peripheral blood monocytes primed with tumor-related antigens have been utilized in cancer immunotherapy instead of injecting a peptide that is given to an APC [99]. If there are inflammatory signals, immature CD4+ T cells can deliver antigen to T-cells that recognize it in an MHC-restricted way as a result of immature DC maturation. T-cells activated with CD8 + antigens and MHC I complexes may now identify tumor cells and seek to lyse them [100]. Dendritic vaccine therapy is explained in **Figure 8.**

ii. Adaptive cell therapy (ACT)

T-cells, x-cells, and other tumor infiltrating lymphocytes (TILs) can be activated directly via Adoptive Cell Therapy (ACT) instead of DC activation [101].

Adaptive cell therapy is shown in **Figure 9**. It is most usual to utilize cytokine-induced killer (CIK) and CAR T-cells in the ACT process.

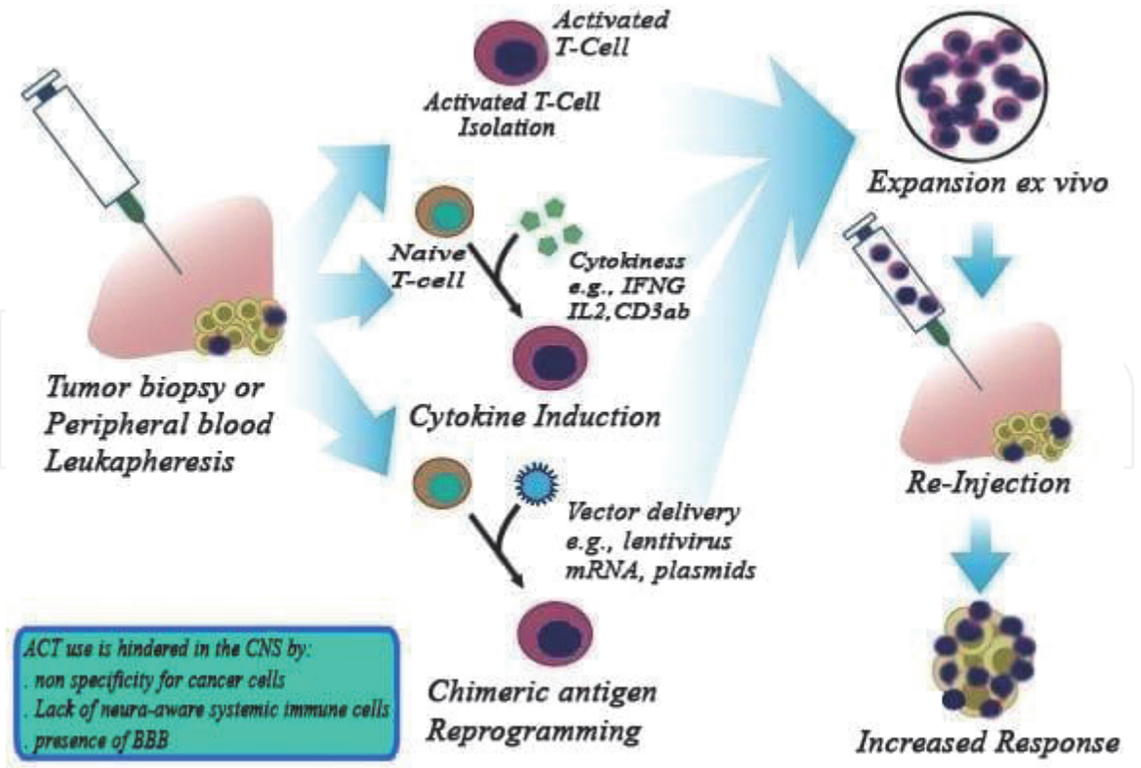

Figure 9.
Adaptive cell therapy.

IFN, IL2, and CD3 monoclonal antibodies are used to induce peripheral blood lymphocytes into CIK cells in vitro. Cells that have been modified to express a single or many costimulatory tumor antigens are called CAR T-cells [102].

iii. Monoclonal antibodies

Using monoclonal antibodies is a passive method of immunotherapy that does not need the body's immune system. **Figure 10** shows the monoclonal antibodies treatment method [93]. Antibodies that target abnormally expressed surface receptors in malignancies or receptors implicated in carcinogenesis are generally selected. However, Nimotuzumab, another monoclonal antibody widely used in brain tumors, is an anti-EGFR inhibitor that has only slightly improved overall survival when administered in children with high-grade gliomas [103].

To some extent, monoclonal antibody treatment in the brain has suboptimal survival benefits because monoclonal antibodies are unable to penetrate the BBB without causing considerable barrier disruption and because patient-specific antigen mutations affect antibody binding efficiency [104].

iv. Virotherapy

Non-pathogenic viruses are used in oncolytic virotherapy to selectively infiltrate or express proteins in brain tumor cells that can directly destroy cancer cells or else activate an immune response. Many virotherapy techniques have been investigated, but their broad use in the brain remains a problem [105]. The virotherapy method for brain tumor treatment is shown in **Figure 11**.

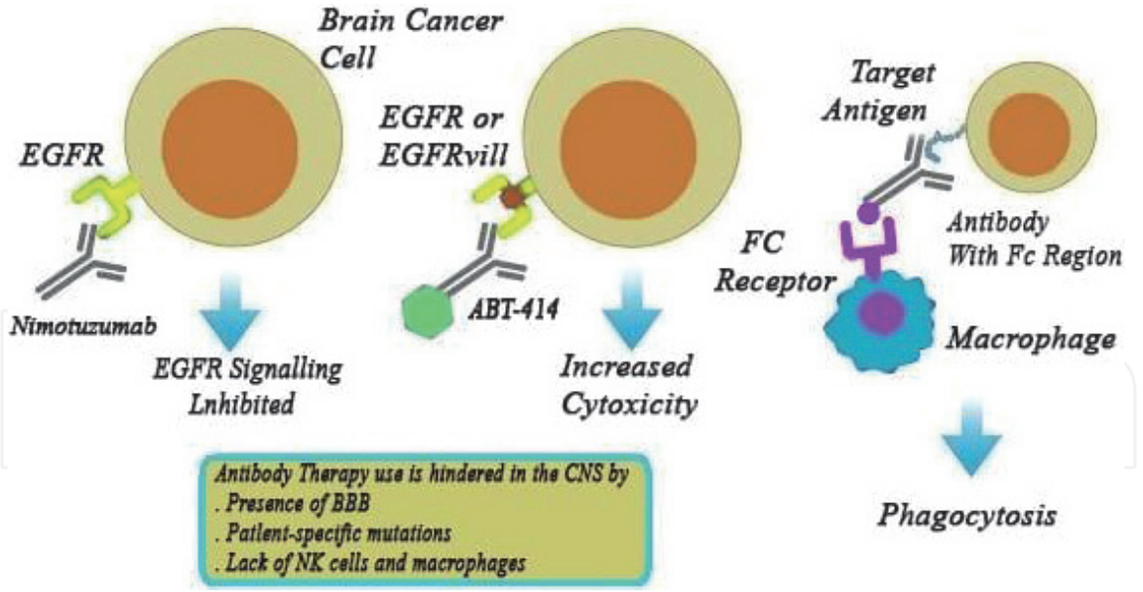

Figure 10.
Monoclonal antibodies treatment method.

Furthermore, the targeting of non-neuronal lineage cells may make a method like PVSRIPO appealing; nevertheless, other component cells in the CNS may be misidentified for cancer cells, resulting in negative side effects. The BBB can also limit viral migration to the tumor site, which is important in virotherapy for brain cancers [106].

B. Radiation therapy

Patients with primary brain tumors benefit from radiation therapy because it helps them maintain local control or prolong their progression-free life. In the treatment of primary brain tumors, radiation therapy (RT) plays a crucial role, with the majority of patients experiencing local control or prolonged progression-free survival. On the other hand, RT can have a negative

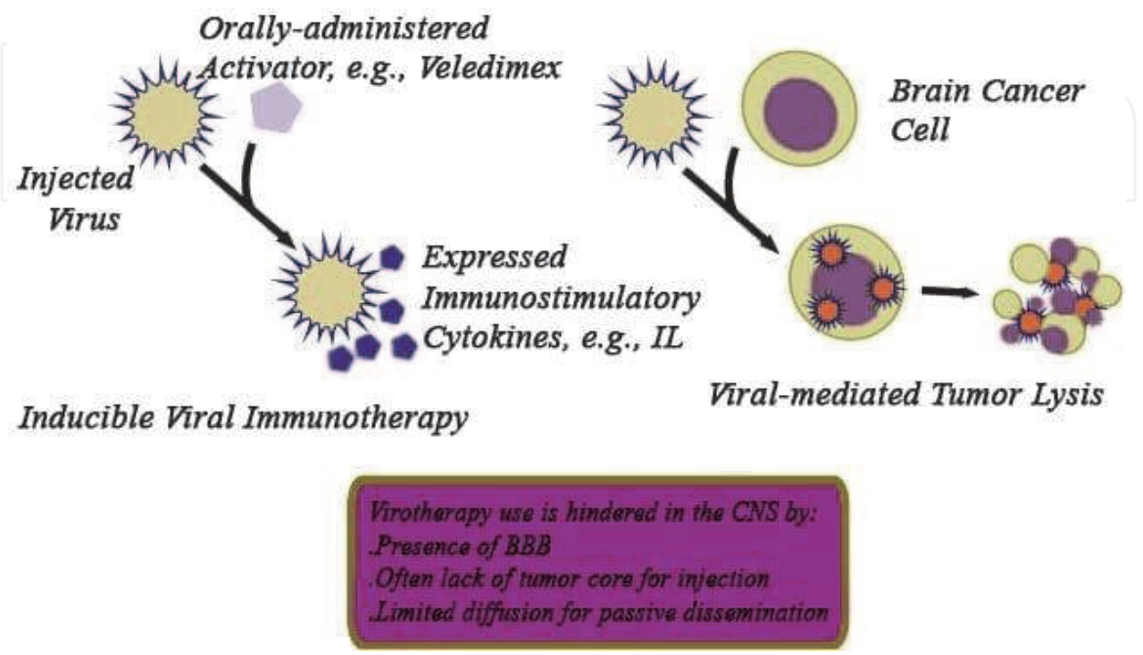

Figure 11.
Virotherapy method for brain tumor treatment.

influence on cognitive performance, which can have a detrimental effect on the quality of life. When one or more cognitive processes, such as attention, memory, language, and executive function are impaired [107, 108].

Primary brain tumors, both benign and malignant, are commonly treated with radiation therapy (RT). Post-treatment neurocognitive deterioration has been documented with RT in verbal and visuospatial memory most commonly (i.e., difficulty encoding, retaining, and retrieving visual information) [109, 110].

C. Surgery

The majority of therapy is surgical resection. Patients with persistent hydrocephalus despite tumor excision require a third ventriculostomy or CSF diversion to cure the condition. A cardiac examination should be performed on neonates suspected of having tuberous sclerosis before an intraventricular tumor is surgically removed [111].

D. Chemotherapy

The discovery of chromosomal markers that indicate greater chemosensitivity in patients with low-grade astrocytoma and other histopathologies has sparked renewed interest in using chemotherapy in the treatment of low-grade astrocytoma patients with other histopathologies. Temozolomide is the most widely used chemotherapy regimen in adult low-grade astrocytoma patients, followed by procarbazine, CCNU, and vincristine (PCV) if temozolomide fails [112].

The Southwest Oncology Group conducted an early randomized trial to see if treating low-grade astrocytoma patients with single-agent CCNU after radiation was beneficial. In this research, adding CCNU to the therapy schedule had no further benefits. Furthermore, individuals in the CCNU arm experienced a high rate of hematologic adverse effects after chemotherapy [113].

The effectiveness of temozolomide, an oral alkylating drug, in treating patients with low-grade astrocytoma is now a staple of adjuvant treatment, although it is also being investigated in several trials [114]. Response rates range from 31 to 61 percent when minor replies are considered. Despite the short duration of follow-up, the median time to advancement ranged from 31 months to >36 months. It was concluded by Brada and co-workers (2003, in a phase 2 study) that the drug temozolomide has single-agent action against low-grade astrocytoma and may also assist control seizures in this patient group and that it is safe and effective in this patient population [115].

10. Recent research in brain tumor

In 2020, A new improved WOA is used to propose a comprehensive method for brain tumor detection based on optimal feature extraction and feature selection. On a set of benchmark cases, IWOA's experimental results are compared to those of other common optimizers, and the results are verified [116].

Z.U. Rehman, M.S. Zia, G.R. Bojja, and F. Jinchao explained Two recent and useful trends for brain tumor localization: (1) using the texton-map to create the image in texture form (2) extracting the features from the superpixels The three contributions were used in this paper. First, superpixel segmentation is performed on texton-map images, which reduces the computational cost of image

segmentation in small regions, improves spatial smoothness of superpixels, and improves low-level feature accuracy. Second, we covered the concept of data balancing, which aids in the development of vision-based classifiers. Third, we created a quick comparison of four different classifiers and examined their performance in terms of model training accuracy. Initially, our image denoising method is shown to effectively remove false-positive regions [117].

Ratan et al. developed watershed segmentation and used edge detection, contrast, and greyscale on 2D and 3D images to detect brain tumors. Somasundaram and Kalaiselvi used ten data sets with normal and abnormal subjects to detect brain tumors. Muscles, scalp, skull, and fats the unwanted brain areas are removed first in their proposed framework, followed by fuzzy segmentation. Finally, for tumor region detection, and intensity-based extended maxima transform is used. [18] proposes a systematic model that starts with a diagnosis of the brain tumor and then extracts the brain tumor region. A classifier called Naive Bayes is used to diagnose the tumor from brain MR images. After a diagnosis, the brain tumor region is extracted using K-mean clustering and boundary detection techniques. It had an accuracy rate of over 80%. To detect the brain tumor region, researchers propose a segmentation method based on color and edge detection. Edge detection is done with the Prewitt, Canny, Sobel, and Laplacian of Gaussian operators, while color-based segmentation is done with the K-mean clustering technique [118].

Alexander Winkler-Schwartz and his colleagues have created a comprehensive research framework for studying oncological neurosurgery's technical performance and resection extent. This platform works by incorporating a low-cost alginate-based artificial brain tumor into an ex-vivo calf brain in a controlled operative environment. To our knowledge, this is the first time an artificial tumor has been created using the biomechanical properties of human specimens obtained through resection. Given that its components are relatively inexpensive and combined in small quantities, the overall cost of the artificial tumor is well under 2 cents/mL. To put this into perspective, 1 kg of alginate and 5800 mL of calcium sulphate, respectively, can yield 40,000 and 5800 mL of final tumor. Gadobutrol (Bayer AG) or its analogues, arguably the most expensive compound in the mix, can often be obtained for a low price from clinical units' expired stockpiles. Even if one were to pay the full cost for an average 30-mL vial, this would yield 27,000 mL of tumor. A 10e100-mL pipette and a laboratory-grade scale are required, but they are both one-time purchases. The recordings from the surgical microscope and ceiling-mounted camera, as well as the movements generated by the instrument-mounted fiducial markers, can be used to evaluate operative "performance" [119].

Medical imaging is still the gold standard for detecting, diagnosing, and examining gliomas and other diseases. Magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), functional MRI, computed tomography, and positron emission tomography is the most commonly used imaging techniques in clinical practice [120].

11. Discussion

The brain is responsible to control all activities of the human body. It is well-known that a disease occurred in the brain may affect human life negatively. A brain tumor is one of the critical diseases that originate from the abnormal growth of cells in the brain. Automatic brain tumor classification plays an important role in the early stage of tumor detection and this system allows patients to be diagnosed in time and chance of survival. Also, this system may help radiologists in decision-making and treatment plans. In this paper, we proposed a new scheme to classify

three types of brain tumors, namely, Meningioma, Glioma, and Pituitary tumors from MRI images. First, pre-processed is applied to images [70].

Recent laboratory advances in primary brain tumors have shown that specific molecular signatures can predict the biological behavior of tumors. Current brain tumor classification systems based on histology and morphology may soon be supplemented by a system based on molecular markers of tumor differentiation and progression [74].

12. Conclusion

The quantitative, domain-specific data acquired through these studies will improve our understanding of brain toxicity and cognitive decline associated with radiation dosage to non-targeted tissue and can provide the basis for evidence-based cognition-sparing brain radiotherapy. Interestingly, this study introduces an association between certain WM diffusion changes and radiation-induced memory decline, which may indicate that there are other ROIs not studied in this paper that should be investigated as potentially vulnerable areas contributing to post-RT cognitive decline. Further research is needed to investigate the dynamic trajectories of tissue response to radiation to better understand how MRI changes can be used to predict important neurocognitive trajectories post-treatment [60].

Treatments and better outcomes for primary brain tumors have long lagged behind those of other tumors. However, a new era in neuro-oncology has emerged, with major advances in both cancer and CNS immunology, and progress in genomics [55].

Abbrevations

ATRX	Alpha- Thalassemia X- linked mental Retardation
BBB	Blood Brain Barrier
CAR T cells	Chimeric Antigen Receptor
CDKN2A	Cyclin-Dependent Kinase inhibitor 2A
CD4+	Cluster of Differentiation 4
CD3	Cluster of differentiation 3
IFN	Interferon
IL-2	Interleukin-2
MIB-1	Monoclonal antibody-1
qRT- PCR	Quantitative Real-Time Polymerase Chain Reaction
NK	Natural Killer
MHC	Major histocompatibility complex

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