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Original Research Article

Advances in Pharmacological Strategies for Brain Tumors: Molecular Insights and Therapeutic Innovations

Journal of Pharmacology and Pharmacotherapeutics
17(3) 448–462, 2026
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DOI: 10.1177/0976500X251403645
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Abstract

Background: Cancer is a complex condition defined by the uncontrolled growth and proliferation of cells. Brain neoplasms, both primary and secondary, present a rising global health burden. Newer classification integrates key molecular markers; IDH mutation, 1p/19q co-deletion, and methylation promoter, enhancing diagnostic precision and guiding therapeutic targeted therapies.
Objectives: This review provides comprehensive molecular insights into the multistep pathophysiology of brain tumours, highlighting early genomic and epigenomic alterations that drive malignancy and metastasis.
Materials and Methods: Advancements in neuroimaging, such as magnetic resonance imaging (MRI) and computed tomography (CT) scans, have significantly improved the early detection and precise localization of brain tumors. Moreover, molecular and genetic profiling has revolutionized the classification and prognostication of these tumors, enabling more personalized therapeutic strategies.
Results: Treatment modalities for brain tumors include surgical resection, radiotherapy, and chemotherapy, often employed in combination to maximize efficacy. Innovations in surgical techniques and radiotherapy, such as stereotactic radiosurgery, have enhanced the precision of tumor removal and minimized damage to surrounding healthy tissue. Despite these advancements, the prognosis for many brain tumor patients remains challenging, with high-grade gliomas, like glioblastoma multiforme, having particularly poor outcomes.
Conclusion: Comprehensive literature collection was conducted using various scientific databases, including PubMed, ScienceDirect, and Google Scholar, focusing on the molecular mechanisms underlying tumorigenesis and therapeutic resistance, with the objective of identifying molecular therapeutic targets. Emerging diagnostic and therapeutic innovations, including liquid biopsy, MR-guided blood–brain barrier modulation, and nanotechnology-based drug delivery, are providing novel, targeted, and minimally invasive strategies for the effective management of central nervous system malignancies.

Keywords

Chemotherapy, radiotherapy, tumor, oncology, blood brain barrier

Received 09 October 2025; **revised** 03 November 2025; **accepted** 13 November 2025

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Introduction

Cancer in the broader context encompasses over 277 distinct forms of cancerous conditions. Researchers have delineated various phases of cancer development, signifying the involvement of numerous genetic mutations in the pathogenesis of cancer (abnormal cell growth). These genetic alterations instigate aberrant cell proliferation. Inherited genetic disorders play a crucial role in augmenting cellular growth. Utilizing advancements in bioinformatics and molecular methodologies provides further insights that could aid in early detection and appropriate treatment.[1]

The term "brain tumor" denotes a group of cancerous cells, each characterized by its unique biology, forecast, and remedy regimen. It is more precise to designate these tumors as "intracranial neoplasms," as certain ones originate from tissues other than the brain (e.g., meningiomas and lymphomas).[2] Gliomas stand as the predominant primary brain tumors in adults, believed to arise from glial cells and permeate the neighboring tissues.[3] The flow diagram (Figure 1) of normal and abnormal cell growth shows how normal cells follow regulated division and apoptosis, while abnormal cells escape control mechanisms, leading to uncontrolled proliferation and tumor formation.

Brain Tumor

Brain cancer, among the top 10 contributors to cancer-related fatalities, continues to pose a significant health risk and is predominantly untreatable. In the USA, the yearly occurrence of cerebral neoplasms stands at roughly 15–20 instances per 1 lakh individuals. The 5-year longevity percentage for individuals with cerebral neoplasms has maintained consistency at around 75% throughout the previous 10 years.[4]

Brain tumors are commonly identified following the onset of symptoms such as headaches, nausea, alterations in personality, seizures, or focal neurological deficits. Timely and precise detection of a brain tumor is crucial for effective disease control. Histological categorization of central nervous system (CNS) tumors is based on the microscopic characteristics of tumor cells, including their origin, structure, differentiation, and growth pattern, classifying them into major types such as gliomas, meningiomas, ependymomas, medulloblastomas, and neuronal or mixed cell tumors (Figure 2). Varieties of cerebral neoplasms comprise glial cell tumors, meningeal tumors, and hypophyseal tumors, among additional types. Glial cell tumors may be classified into astrocytomas, oligodendrogliomas, ependymal neoplasms, and mixed glial tumors. Magnetic resonance imaging (MRI) and computed tomography (CT), the predominant and favored evaluative techniques for identifying potential initial cerebral neoplasms, can pinpoint the location of cerebral neoplasms and assess for fluid retention, blood loss, and cerebrospinal fluid (CSF) accumulation.[5]

Epidemiology

As per the estimations provided by the American Cancer Society in 1999, around 16,800 new instances of brain tumors have been reported. This surpasses the incidence of Hodgkin's disease by more than twofold and accounts for over half of the reported cases of melanoma within the same period. Such statistics underscore the significant burden imposed by intracranial tumors on public health during that timeframe. The initial phase of a brain tumor involves multiple stages, including genetic mutation in neural or glial cells, abnormal cell proliferation, angiogenesis for nutrient supply, disruption of the blood–brain barrier (BBB), and formation of a localized mass that exerts pressure on

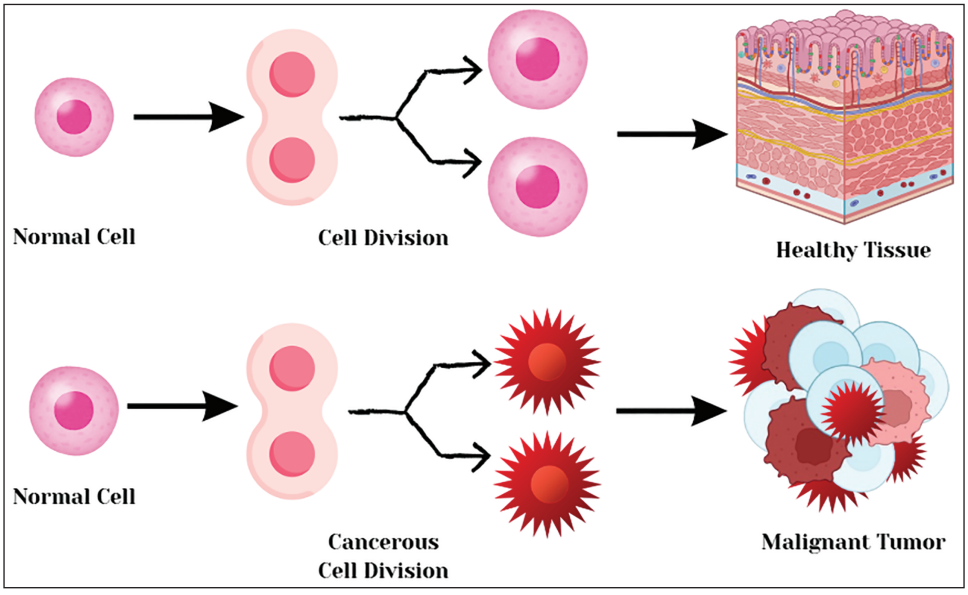


Figure 1. Flow Diagram of Normal and Abnormal Cell Growth.

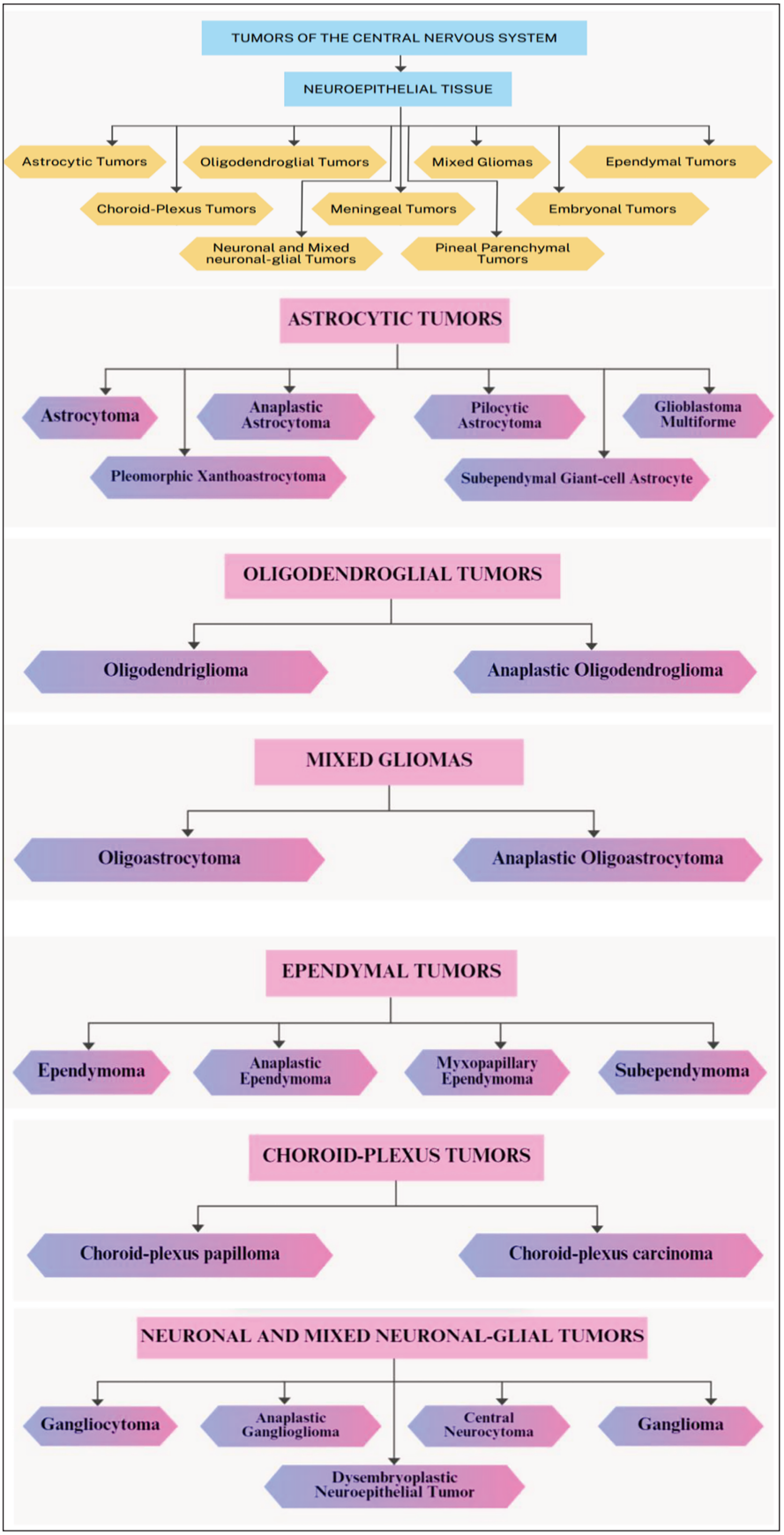


Figure 2. Histological Categorization of Central Nervous System Tumor.

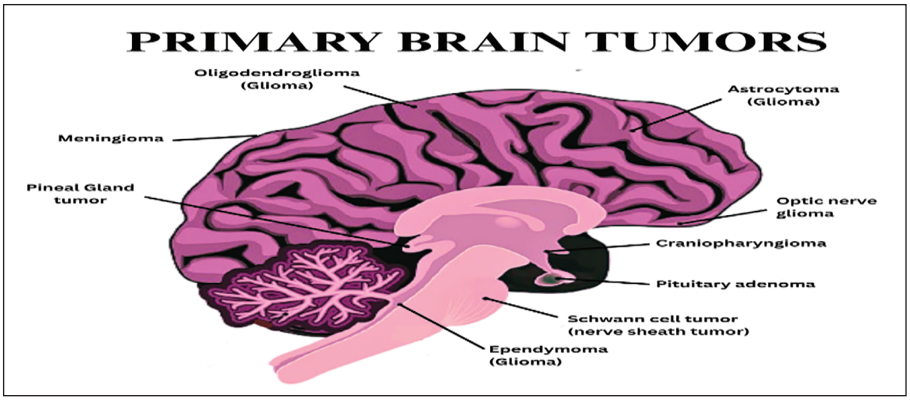


Figure 3. Different Parts of Initial Phase of Brain Tumor.

surrounding brain tissues, leading to early neurological alterations (Figure 3). Intracranial tumors, also known as brain tumors, originate within the brain or its surrounding structures. These neoplasms encompass a diverse array of pathological entities, ranging from benign to malignant, and can arise from various cell types and locations within the CNS. The prevalence of intracranial neoplasms is influenced by multifaceted factors, including genetic predisposition, environmental exposures, and advancing age.[6] In 1999, approximately 13,100 individuals succumbed to primary cancers originating in the CNS. One estimate posits that over 100,000 patients annually experience mortality due to symptomatic metastatic lesions within the cranial cavity.[7] Between the years 1950 and 1989, Mayo Clinic reported an age- and sex-adjusted annual new case rate of 19.1 per 1 lakh individuals for initial tumors of the brain and the spinal column, that is, the CNS.[8] The frequency of these occurrences closely mirrors the information documented by the Central Brain Tumor Registry of the USA, indicating a yearly incidence frequency of 11.47 per 1 lakh individuals.[9]

Ionizing radiation stands out as the sole unequivocal risk factor linked to the progression of glial and meningeal malignancies. Exposure to cranial irradiation, even at decreased levels, can increase the risk of meningiomas tenfold, while the risk of glial tumors rises by a factor of three to seven, usually with a dormancy period of 10 to over 20 years post-exposure.[10,11] While various environmental exposures and behaviors, such as cellular telephone usage, closeness to power lines, hair coloring procedures, cranial injuries, and consumption of *N*-nitrosourea substances or other dietary elements, have been suggested as potential risk factors for brain tumors, none have been definitively confirmed. The existing data on these factors are inconsistent and lack convincing evidence to establish a clear association with increased risk.[12–15]

Pathophysiology of Brain Tumor

Years or even decades prior to the manifestation of a CNS metastasis, cells originating from organs like the lung, breast, or colon go through a sequence of genomic or epigenomic modifications,[16] enabling uncontrolled proliferation and the onset of cancer. A cell, on its path to becoming cancerous, experiences two categories of genetic changes. In the initial scenario, "gatekeeper" genes regulating cellular proliferation are activated, while in the subsequent scenario, "caretaker" genes accountable for maintaining genetic uniformity are silenced. Consequently, neoplasmic cells relinquish manage over cellular replication and experience genetic instability, resulting in the accumulation of further mutations. Genetic alterations comprise single-nucleotide variations, genomic deletions, excessive expression, and chromosomal rearrangements. Epigenetic changes involve the attachment of methyl groups to the promoter regions of tumor-suppressor genes, leading to their deactivation and a consequent inability to prevent tumor growth.[17]

Occasionally, brain metastasis originating from an unidentified primary tumor results in the demise of patients, even when the primary tumor remains undetectable, occasionally until post-mortem examination.[18] Analysis of gene transcription in secondary tumors originating from glandular carcinoma has revealed a distinct gene transcription pattern, consisting of eight genes that are upregulated and nine genes that are downregulated, capable of differentiating initial tumors from invasive ones. Presence of this signature within the initial tumor has been linked to a worsened prognosis, indicating that the potential for metastasis in human tumors emerges at an early stage within the primary tumor itself. Primary CNS lymphoma (PCNSL) is a rare form of non-Hodgkin's B-cell lymphoma, primarily of the diffuse large B-cell type (>90%), confined to the CNS, including the brain, eyes, CSF, or spinal cord, without systemic involvement. It represents about 4%–6% of extranodal lymphomas and roughly 4% of newly diagnosed CNS tumors, with an incidence of ~0.47 per 100,000 person-years. Compared to systemic diffuse large B-cell lymphoma (DLBCL), PCNSL shows a more invasive growth pattern, frequent ocular involvement, and a poorer prognosis. The heterogeneity of brain metastases reflects their distinct molecular evolution from the primary tumor, driving therapeutic resistance. Before colonizing the brain, tumor cells develop specialized adaptations—such as modulating the BBB, evading immune surveillance, and reprogramming metabolic and astrocytic functions thrive within the unique cerebral microenvironment.[19,20]

Angiogenesis

For a tumor to expand beyond 1–2 mm, it must establish its own vascular network to supply blood. While the process of hijacking host blood vessels does happen. It typically is not adequate to sustain tumor growth across most organs.[21] Vascular endothelial growth factor (VEGF) is among several factors that trigger blood vessel formation, with certain members of the VEGF family also facilitating lymphangiogenesis. The resultant newly formed blood and lymph vessels might exhibit heightened vulnerability to infiltration by tumor cells compared to their normal vessels.[22] Mammary tumor clusters are encircled by endothelial cells and move through the bloodstream as tumor emboli inside blood vessels. Subsequently, the neoplasm can proliferate within the lung vasculature without leaking into the lung parenchyma.[23]

Invasion

In order for the majority of tumors to metastasize, they typically need to infiltrate the host tissue of origin. This process comprises three primary stages.[24]

1. The neoplastic cell adheres to the matrix of the extracellular space of the affected organ.
2. It breaks down the matrix utilizing various substances, notably proteolytic enzymes like metalloproteinases. These enzymes are generated by stromal cells surrounding the tumor, in addition to cancer cells themselves.[25] Inflammatory cells drawn to cancerous tissues further enhance the metastatic potential of cancer cells.[26]
3. Subsequently, the tumor cell traverses the extracellular matrix to access either blood or lymphatic vessels. Tumor cells exhibiting a heightened propensity for metastasis display a stronger alignment with blood vessels and are less prone to fragmentation compared to non-metastatic tumor cells.[27]

Under hypoxic conditions, there is an elevation in the levels of hypoxia-inducible factor, which subsequently triggers the upregulation of genes such as VEGF and mesenchymal-epithelial transition factor (C-MET). These genes play crucial roles in promoting cell motility and invasion.[28] Another gene is activated by low oxygen levels, CXCR4, functions as a receptor for cytokines. It not only enhances cell movement but also aids tumor cells in homing to particular distant organs.[29]

Intravasation

Intravasation plays a pivotal role in the progression of metastatic neoplasms. Neoplastic circulatory channels exhibit notable distinctions from the normal vasculature of the affected organ, primarily characterized by the less complete nature of tumor-induced endothelial cells. This facilitates the easier entry of cancer cells into the vessel lumen.[30] This results in the shedding of more than 1,000,000 cells per gram of neoplastic tissue into the blood each day.[31]

Cancer cells have the ability to infiltrate venules, capillaries, or lymphatic channels by producing enzymes like heparinase, which breaks down the vessel's basement membrane. Once inside either capillaries or lymphatic vessels, the cancer cells enter venous circulation through major routes such as the portal vein, vena cava, or Batson's vertebral veins. Alternatively, a neoplasm may directly breach a large vein, facilitating the entry of a sizable tumor embolus into the circulation.

Circulation

Various mechanisms collaborate to eliminate tumor cells once they enter the bloodstream. Among these mechanisms, the immunological system, particularly cytotoxic lymphocytes, actively target and destroy neoplastic cells circulating in the plasma.[32] Mechanical damage induced by shear forces during circulation likely contributes to the destruction of a significant portion of tumor cells. According to a study, merely 1.5% of cancer cells injected intravenously managed to survive beyond 24 h.[33] Tumor cells have the capability to associate with platelets and leukocytes, creating complexes that shield the cells from mechanical harm and immune system assaults. These complexes also facilitate the tumor's entrapment within larger capillary beds, offering protection in those locations. P-selectin, an adhesion molecule, is notably instrumental in the formation of such complexes in certain tumor types.[34]

Arrest (in First Capillary Bed)

As tumor cells typically exceed the size of capillary vessels, they tend to halt within the initial capillary bed they encounter upon entering the systemic circulation.[35] Thus, it is logical to anticipate that cancers originating from organs aside from the lungs would initially metastasize to the lungs, liver, or vertebral bodies, contingent on whether their venous outflow leads to the portal vein, vena cava, or Batson's plexus.[36] Nevertheless, certain neoplasmic cells traverse the initial capillary network to enter the arterial circulation and subsequently spread into the capillary networks of different organs. The arrest process is not solely determined by the size of tumor cells; rather, it is also influenced by the neoplasmic cells' recognition of molecules present on the endothelium surface. These endothelial addressins, exclusive to particular organs like the brain, play a crucial role in this recognition process.[37]

Pathway to Arterial Blood Flow

Pulmonary carcinoma frequently leads to brain metastasis, primarily due to the direct access of lung tumors to

pulmonary veins, which subsequently connect to the arterial blood flow through the left heart. Unlike cancers originating from different organs, which typically enter the venous circulation before reaching the right cardiac chamber and then travel via the pulmonary artery to access the lung capillary network, lung cancer cells have a more direct route to the brain. Brain metastases typically manifest in the advanced stages of cancer progression, often when the neoplasm has already metastasized widely to different organs. When the main cancer site has been successfully treated, brain metastases can arise from secondary proliferation, like when a lung proliferation stemming from breast carcinoma spreads to the brain.

In order to access the arterial blood flow and spread to the brain, the neoplasm must undertake one of the following actions:

1. Tumors originating or growing within the lung have the potential to invade the pulmonary venous circulation, subsequently entering the left cardiac chamber, and then spreading through the systemic blood flow.
2. Traverse through the pulmonary capillary network to reach the left cardiac chamber
3. Passing through a patent foramen ovale, a neoplasm that infiltrates the veins of the affected organ can cause embolization in the cerebrum, resulting in an infarct.[38]

Several months after the initial embolus, tumor cells within the capillary bed extravasate and proliferate, leading to the recurrence of symptoms identical to those caused by the original embolus.[39]

Arrest

Upon entering the arterial circulation, the dissemination of tumor cells is anticipated to correlate with the blood flow to specific organs. Considering that the cerebrum typically obtains 15% of blood flow from the heart under relaxing conditions, it is reasonable to anticipate that this fraction of circulating neoplastic cells would also reach the brain. Experimental studies have shown that circulating tumor cells often become trapped in the brain in line with blood flow patterns, a phenomenon that is backed by specific clinical findings. For example, brain metastases frequently appear at the junction of gray and white matter and in the brain's watershed areas, corresponding to locations where cerebral emboli are likely to settle.[40]

Brain metastases from lung cancer are prevalent, potentially due to the pulmonary capillary bed acting as a barrier, preventing tumors from other body parts from entering the arterial circulation. Certain forms of pulmonary carcinoma, such as small-cell carcinoma of the lung, have a higher propensity to spread to the brain compared to non-small cell lung cancer, while adenocarcinomas exhibit a greater tendency to metastasize to the brain than squamous carcinomas.[41]

Dormancy

Tumors that extend beyond the CNS vasculature into the brain, the spinal cord, and the leptomeninges may not always exhibit growth. If the soil is not conducive, tumor cells might perish or remain inactive for extended periods, ranging from months to even years. Substantial evidence supports the occurrence of solitary brain metastases emerging in patients long after the apparent elimination of the primary cancer, a phenomenon notably prevalent in melanoma and breast cancer, though observed in other malignancies too. Despite surgical removal of the primary tumor and successful chemotherapy targeting micro metastases in other regions of the body, the cerebral barrier could impede the eradication of CNS micro metastases by chemotherapy.[42]

Growth in CNS

For a brain proliferation to develop and turn noticeable through clinical examination or imaging, conducive conditions must exist in the brain for the neoplastic cell, and the neoplastic cell itself must produce molecules that support its development in the brain. An instance of this is the association between the availability of the membrane receptor P75 neurotrophin receptor (NTR) on neoplastic cells and the enhanced capability of melanocytic cells to colonize the brain.[43] Nevertheless, the infiltration of tumor cells into the brain is facilitated by exploiting its vascular network, yet their capacity to proliferate and establish metastases relies on numerous factors inherent to both the tumor and the brain environment.

Diagnosis

For diagnosing a cerebral tumor, cranial MRI is the sole essential test. CT might fail to spot structural abnormalities, specifically in the posterior cranial cavity, or the non-aggressive tumors such as low-malignancy gliomas. Thus, when evaluating a potential cerebral neoplasm diagnosis, gadolinium-based contrast MRI is the preferred imaging modality; a normal MRI effectively eliminates the likelihood of a cerebral tumor.

Liquid Biopsy

With liquid biopsy, pathology-derived material in blood can be found and analyzed without the need for invasive procedures like open surgery. It might offer a unified platform for cancer diagnosis, guide treatment choices by identifying tumor variations that are sensitive or resistant, and track disease response.[44–47] With the creation of numerous clinically authorized assays for circulating tumor DNA (ctDNA) and circulating tumor cells, among other things, this strategy has made enormous progress in the treatment of systemic malignancies. However, because it stops biomarker shedding, the

BBB restricts its application for malignancies of the CNS.[48] A new technique called low-intensity MR-guided focused ultrasound (MRgFUS) creates a temporary BBB opening (BBBO) to allow non-invasive access to brain diseases.[49] The sonicated brain regions can be selected with flexibility and spatial precision thanks to MRI guidance. Patients with neuro-oncology and neurodegenerative diseases have shown safety and viability in early-phase clinical trials.[50–54]

Conventional MRI

Diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC), susceptibility-weighted or gradient echo imaging, pre- and post-contrast T1-weighted, T2-weighted, and T2-based fluid attenuation inversion recovery (FLAIR) are examples of conventional MRI sequences. Tumor analysis measures in conventional MRI have been set by the Response Assessment in Neuro-Oncology (RANO) working group. For a disease to be measurable, a contrast-enhancing lesion must be measured in two dimensions with easily identifiable boundaries. At least two axial slices should show the measurements, which should be perpendicular and at least 10 mm long. Lesions smaller than 10 mm, with ambiguous surgical margins, or where only one dimension may be measured, are considered non-measurable diseases.[55]

Magnetic Resonance Spectroscopy (MRS)

Water-soluble brain metabolites are detected non-invasively using MRS, an analytical technique that measures their precession frequency. These different signature resonance frequencies can be identified and examined because MR creates a distinctive magnetic field in nuclei with varying electron counts. Creatine (Cr), *N*-acetyl aspartate (NAA), choline (Cho), lactate, lipids, alanine, glutamine, glutamate, 2-hydroxyglutarate, citrate, and myo-inositol are among the chemical species commonly measured on MRS.[56] Cho's presence in the cell membrane makes it a sign of cell growth.[57,58] Anaerobic glycolysis is shown by lactate, which may indicate hypoxia adaptability in higher-grade tumor tissue.[59] Gliomas with isocitrate dehydrogenase (IDH) mutations can be identified by their oncometabolite 2-HG, which is a significant biomarker that can forecast tumor grade, tumor growth, and treatment response.[60] Low-grade gliomas may have elevated myo-inositol, a sign of gliosis.[61,62]

Magnetic Resonance Diffusion-weighted Imaging

Important physiological and functional data on brain tumors and the peri-tumoral milieu are provided by DWI. Since water mobility depends on cellularity, viscosity, and the tortuosity of the extracellular space, it can be directly measured and used as an imaging biomarker of tissue pathology.[63] Given the weaker ADC signal of the tumor, DWI can also be helpful in determining the response to treatment and distinguishing changes brought on by chemotherapy and radiation from the tumors.[64] In the postoperative context, restricted diffusion aids in the detection of cytotoxic edema. In the subacute phase, the associated parenchyma may enlarge and may be mistaken for the growth of the tumor. Within 3 weeks of starting treatment, DWI has been demonstrated to predict the outcome.[65]

Radiomics-based Predictive Modeling

A new area of study in neuro-oncology called "radiomics" uses quantitative characteristics to identify small spatial and textural patterns in medical pictures that are invisible to the human eye. Despite its enormous potential for glioma classification and prognosis prediction, methodological inconsistency and difficulties integrating machine-learning algorithms continue to impede practical translation. In order to increase repeatability and clinical application, imaging techniques must be standardized and validated across multicenter datasets. In the future, radiomics may be used with genomes and artificial intelligence to improve neuro-oncology's precise diagnosis and individualized care.[66]

Positron Emission Tomography (PET)

PET imaging provides dynamic functional molecular imaging by detecting photons released by intravenously positron-emitting radiotracers. Biological activities, including glucose consumption and amino acid/analog uptake, can be quantitatively and non-invasively observed, depending on the molecule to which the radionuclide is attached. To get estimates of the patient's radioactivity distribution, a PET scanner uses annihilation coincidence detection to find pairs of 511 keV photons that are released. Tumor in the brain PET data are presented as the mean and maximum tumor-to-brain ratio and are based on the standard uptake value. High sensitivity and quantitation, as well as the capacity to co-register with other imaging modalities, are among PET's benefits. Lower spatial resolution, radiation exposure, and comparatively high equipment costs are some of PET's drawbacks.[67]

PET–MRI

PET combined with MRI offers a powerful hybrid imaging technique that integrates functional and anatomical information for improved diagnostic accuracy. PET provides metabolic and molecular data, while MRI offers high-resolution structural and soft tissue contrast. Despite these advantages, challenges persist in harmonizing data due to differences in imaging physics and acquisition methods. Recent advances in deep learning, particularly convolutional neural networks (CNNs), have shown promise in optimizing PET–MRI data fusion. These approaches enhance image quality, improve lesion detection, and hold potential for more precise characterization of brain tumors and other neurological disorders.[68]

Functional MRI (fMRI)

fMRI, which was first used in the early 1990s, has grown to be an essential technique for mapping brain activity and directing neurosurgery planning, especially for tumors close to eloquent cortical areas. Preoperative planning and intraoperative navigation are facilitated by fMRI, which helps surgeons maximize tumor excision while maintaining vital brain function by pinpointing crucial regions responsible for activities like movement and language.[69]

Fluorodeoxyglucose PET (FDG-PET)

Modifications to the technique have tried to eliminate non-specific uptake in other processes, like inflammation, and counteract the challenge of using FDG to define tumor borders. Recently, multiphase FDG PET/CT has been utilized to assess metastatic lesions and high-grade gliomas. While FDG activity in malignant tissue either stays constant or rises with time, normal brain FDG activity gradually declines.[70]

Amino Acid PET

For the evaluation of primary high-grade malignant brain gliomas, international working groups advise using amino acid PET imaging in addition to MRI. Amino acid PET is suggested for the following purposes: prognostication, post-resection evaluation, radiation therapy planning, baseline monitoring for chemo-radiation, diagnosis of treatment-related changes versus progression/recurrence, baseline imaging for adjuvant treatment monitoring, delineation of tumor extent for resection or re-resection planning, and hot-spot localization for biopsy planning.[71]

Diffusion Tensor Imaging (DTI)

Neuronal fiber architecture and brain microstructure may be visualized by mapping the diffusion of water molecules using a non-invasive MRI method called DTI. Because it evaluates the microstructural impact of various intracranial malignancies on surrounding neural tissues, it offers vital insights into pathological alterations, including brain metastases, and helps with diagnosis and therapy planning. DTI helps distinguish between vasogenic edema and tumor infiltration and permits the early identification of white matter abnormalities. For tracking the course of the disease and the effectiveness of treatment in individuals with brain tumors, their quantitative measures, such as mean diffusivity and fractional anisotropy, are useful biomarkers.[72]

BBB

BBB serves as both a physical and physiological obstacle that controls the passage of molecules into the brain. This intricate system effectively safeguards the CNS from a range of harmful substances and variations in overall chemical levels in the body; however, in the presence of cancer cells, this framework becomes disrupted as tumor cells alter endothelial integrity, secrete permeability-enhancing factors (like VEGF), and facilitate metastasis or drug resistance within the brain microenvironment (Figure 4). Additionally, it presents a formidable obstacle to the entry of active ingredients such as chemotherapeutic drugs and anti-microbials or anti-bacterial. The vascular lining cells forming the BBB are characterized by occluding junctions, the absence of apertures, and minimal fluid-phase endocytic vesicles. These specific cells receive reinforcement from perivascular end-feet, which cover approximately 90% of cerebral capillaries; additionally, a high density of Rouget cells enhances the close alignment of

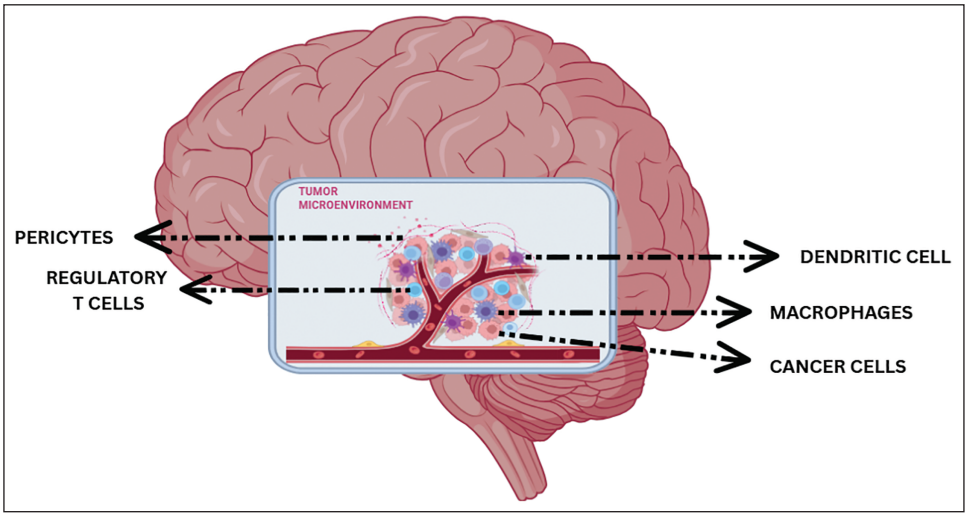


Figure 4. Framework of the Blood–Brain Barrier (BBB), Featuring Cancer Cells.

endothelial cells. Absorptive phagocytosis hinges on the interaction of electrically charged molecules, primarily facilitating the transportation of plasma proteins into the CNS. This process heavily relies on ionic interactions between proteins with a positive charge and the BBB. Ongoing research is exploring its potential for delivering linked large immunotherapies and gene therapy using nanoparticles.[73] The intact BBB poses a significant challenge for the passage of maximum drugs from the bloodstream into the brain.

Targeted Arterial Infusion with BBB Modulation

The purpose of intra-arterial (IA) drug delivery is to enhance the therapeutic agent concentration in a specific vascular area by bypassing first-pass metabolism. Nevertheless, drugs with rapid CNS transit may experience short dwell times, leading to reduced effectiveness. To date, IA administration alone has not demonstrated enhanced outcomes for patients with brain cancer.[74,75] Experimental models have demonstrated that IA chemotherapy combined with BBB disruption (BBBD) enhances drug levels within brain tissue.[76] A prevalent method involves employing osmotic BBBD using substances such as mannitol, followed by IA chemotherapy. Standard radiation therapy employed for the management of both primary and metastatic brain cancer has been demonstrated to elevate BBB penetrability in *in vivo* models and in clinical settings involving individuals.[77]

Enhanced Fluid Delivery

Enhanced fluid delivery, also known as convection-enhanced delivery, entails placing flexible tubes near a neoplasm to deliver anti-cancer agents immediately using hydrostatic pressure. This approach is especially beneficial for substances that are too big to penetrate the BBB or too harmful for whole-body use.[78,79] The main limitation of this is the range of active ingredient delivery, so imaging techniques such as FDG-PET, MRI, and single photon emission CT are increasingly utilized to visualize substances in the brain after enhanced fluid delivery.[80]

Infusion into CSF Cavities

Apart from the BBB, another barrier known as the blood-CSF (B-CSF) barrier exists. This barrier consists of a perforated endothelial layer on its interior side and strongly interconnected surface cells devoid of perforations on its lateral surface. Multidrug efflux pumps are similarly present within the B-CSF barrier, restricting the passage of active ingredients from the peripheral blood flow to the CSF while also aiding in the elimination of active ingredients passing into the CSF from the brain. With CSF carcinomatosis impacting 5%–15% of individuals having compact tumors, significant efforts have been undertaken to elevate drug infusion to the CSF compartments.

The CSF spaces can be accessed for drug delivery using three main techniques: into the thecal sac, within the cerebral ventricles, and intraluminal. Intraspinal delivery typically involves infusing the medication into the arachnoid cavity in the lumbosacral area. This approach necessitates several operations, and the distribution of the active ingredient throughout the CSF pathways might be restricted. Conversely, intraventricular drug administration requires specific hardware but is likely to enhance the drug's distribution volume throughout the CSF pathways.[81]

Systemic Delivery

Presently, the majority of anti-neoplastic medications for brain neoplasms are administered via the bloodstream, either through an intravenous (IV) or by mouth, based on the medication's systemic availability. While some drugs possess properties facilitating access to brain tumors, the constraints discussed earlier hinder the dissemination of the majority of chemotherapy agents. High-potency IV oncolytic treatment has been explored for numerous medications; however, it is typically restricted due to its accompanying body-wide adverse effects. Medication level escalation has proven beneficial for methotrexate in managing primary brain hematologic cancer, leading to elevated cranial concentrations and subsequently better treatment outcomes.[82,83] There have been considerations of elevating the dose to enhance the transport of other substances across the BBB, like etoposide and carboplatin, yet such endeavors are still in the experimental stage.[84]

Epidermal Growth Factor Receptor (EGFR)-targeted Therapies

When treating glioblastoma (GBM) with EGFR as the target, two approaches are typically taken into consideration: using EGFR inhibitors and limiting the amount of EGFR with antibodies, vaccinations, chimeric antigen receptor T (CAR-T), and other therapies. One of the most prevalent oncogenic mutation sites in IDH-wild-type (WT) GBM is EGFR, which is related to tumor cell motility,[85] proliferation, and resistance to apoptosis.[86] EGFRvIII is the most prevalent EGFR gene mutation and may be used as a therapy indicator for GBM. Patients with EGFR-amplification GBM do not respond well to EGFR inhibitors, such as gefitinib and dacomitinib, which is thought to be connected to BBB obstruction.[87,88]

PI3/AKT/mTOR Pathway

One of the most prevalent mutation pathways in IDH-WT GBM patients is the PI3K/mTOR.[85] Phosphatase and tensin homolog mutations on chromosome 10 are the primary cause of PI3K activation in GBM.[89,90] Although the results of a recent phase I clinical trial examining Temsirolimus and the AKT inhibitor perifosine together were disappointing, it was noted that patients exhibited a greater tolerance to Temsirolimus,

which was thought to be connected to the experiment's use of corticosteroids.[91] An ongoing trial is testing the combination of Temsirolimus and perifosine for recurrent GBM (rGBM).

Neurotrophic Tyrosine Receptor Kinases

NTRK1, NTRK2, and NTRK3 are the three distinct genes that encode NTRK. Gene fusion results from the NTRK gene's genomic rearrangement.[92] It appears that GBM rarely exhibits NTRK gene fusion.[93] A female patient with juvenile GBM also received larotrectinib, and the treatment had a notable curative impact.[94] Infantile GBM was also successfully treated with entrectinib, suggesting that NTRK fusion may have both therapeutic and diagnostic use for GBM.[95]

Nanotechnology Against Tumor

A potent instrument in the arsenal of cancer treatments is nanotechnology, which encompasses the research and production of materials utilizing atomic and molecular constituents. Rapid advances in our understanding of how to create and characterize extremely tiny particles underpin the potential of nanotechnology.[96] Since the initial evidence of using nanotechnology for glioma MRI, research on nanodevices for brain tumor diagnosis and treatment has advanced quickly.[97] One major obstacle to therapeutic drug delivery to the CNS is the BBB, which limits the passage of hydrophilic substances, tiny proteins, and charged molecules. Accurate drug delivery to tumor sites is necessary for the effective treatment of brain cancers, especially aggressive ones like GBM multiforme. Although infiltrative regions are protected, high-grade tumors have aberrant vasculature and partial BBB disruption at initial locations, whereas low-grade cancers are frequently treated with surgery or radiation. Drug delivery methods must take advantage of these variations in permeability while navigating the BBB's detoxification and drug-resistance systems.[98] Nanoparticles' small size (less than 100 nm), biocompatibility, and blood stability make them perfect for medication administration across the BBB. They avoid immunological activation, stop platelet aggregation, avoid the reticuloendothelial system, and demonstrate selective administration via receptor-mediated endocytosis. They are also scalable and economical, provide extended circulation, regulated drug release, and are appropriate for a range of treatments.[99,100]

Risk Factors of Nanoparticles in Drug Delivery

Due to their non-specific distribution throughout the body, which affects both cancerous and healthy cells, conventional chemotherapeutic medicines limit the amount of the dose that can be administered inside the tumor and also lead to less-than-ideal treatment because of their high toxicities. One method to get around the traditional chemotherapeutic drugs' lack of specificity is molecularly targeted therapy.[101] Cancer nanotherapeutics are developing quickly and are being used to address a number of issues with traditional drug delivery methods, including low therapeutic indices, poor oral bioavailability, non-specific biodistribution and targeting, and lack of water solubility.[102,103]

Reproductive and Menstrual Factors

Females exhibit a decreased risk of glioma development, as indicated by incidence rates reported by the New York State Cancer Registry. This protective effect is observed during the period spanning from menarche to menopause, with a decline noted in postmenopausal age cohorts.[104] Meningioma occurrence is about two times as prevalent in females compared to males. Certain meningeal neoplasms exhibit progestin receptor expression, with this phenomenon being more pronounced in women.[105] Overall, there is a pattern of consistent findings indicating that premenopausal women face a higher risk of meningioma compared to their postmenopausal counterparts of the same age. However, research on the relationship between meningeal risk, menarche age, and gravidity has yielded contradictory outcomes.[106,107]

Cellular Telephone Use

The majority of initial investigations into the correlation between phone use and the risk of glioma typically yield unsupportive proof for such an association.[108] If the latency period extends to a minimum of 5 years, the initial studies lacked the requisite number of extended-duration mobile phone users to adequately assess the correlation. Conversely, several recent investigations offer indications of a potential link between prolonged cell phone usage and glioma, although such findings could potentially be influenced by selection bias.[109,110]

Genetic Factors

Many researchers have shifted their focus from ecological and lifestyle-related risk factors to genomic ones. This shift is partly due to numerous ambiguous outcomes regarding alterable ecological influences. Additionally, advancements in understanding the biochemical etiology of cerebral neoplasms, particularly glial tumors, and the availability of innovative methods for investigating relationships between genetic variants and illnesses have influenced this redirection. While familial clustering of glioma has been observed, distinguishing between shared environmental exposures and inherited traits can be challenging. Grossman et al.[111] demonstrated occurrences of cerebral neoplasms in bloodlines lacking known hereditary predispositions, suggesting environmental influences in many cases.

Uncommon Alterations in Expressive Genes and Family Clustering

Cerebral neoplasm is thought to emerge as a result of the gradual congregation of genomic and epigenomic changes,

Table 1. Molecular Diagnostics, Key Genetic Alterations, and Targeted Therapeutic Strategies in Central Nervous System (CNS) Tumors.

Tumor/Category	Key Molecular/Genetic Markers	Diagnostic/Molecular Approach	Targeted/Therapeutic Strategy	References
Glioblastoma (GBM), IDH-wildtype	EGFR amplification/EGFRvIII, TERT promoter mutation, +Chr7/−Chr10, PTEN loss, MGMT promoter methylation (predicts TMZ response).	MGMT methylation and EGFR/TERT testing per WHO CNS5.	Maximal resection + radiotherapy + temozolomide; trials with EGFR inhibitors, bevacizumab (anti-VEGF), immune checkpoint inhibitors, CAR-T therapy, and oncolytic viruses.	115, 116
Astrocytoma, IDH-mutant	IDH1/IDH2 mutations, ATRX loss, TP53 mutations.	IDH testing (IHC/NGS) essential for classification and prognosis.	IDH inhibitors (ivosidenib, vorasidenib) under clinical evaluation.	117, 118
Oligodendroglioma	IDH mutation + 1p/19q co-deletion (defining).	1p/19q testing by FISH or NGS.	Chemotherapy (PCV or temozolomide) and radiotherapy; strong prognostic and predictive value.	118
Meningioma	NF2, TRAF7, AKT1, SMO mutations.	Genomic profiling to stratify risk and recurrence.	Surgery ± radiotherapy; AKT and SMO inhibitors under study.	117, 119
Primary CNS lymphoma (PCNSL).	MYD88, CD79B mutations; B-cell markers (CD19, CD20).	Molecular and immunophenotypic analysis of CSF/tissue.	High-dose methotrexate regimens; emerging BTK inhibitors and immunotherapies.	120, 121
Tumors with actionable mutations (BRAF, NTRK, ALK, ROS1).	BRAF V600E, NTRK fusions, ALK/ROS1 rearrangements.	Comprehensive genomic testing via NGS panels.	Targeted agents (BRAF/MEK inhibitors, TRK inhibitors) showing intracranial efficacy.	122, 123
Tumor microenvironment, angiogenesis, and BBB.	VEGF overexpression, immune evasion pathways, BBB dysfunction.	Immunohistochemistry, perfusion MRI, PET imaging.	Anti-angiogenic therapy (bevacizumab); BBB modulation (MR-guided focused ultrasound); immunotherapy combinations.	124, 125

Note: BBB: Blood–brain barrier; CAR-T: Chimeric antigen receptor T; CSF: Cerebrospinal fluid; EGFR: Epidermal growth factor receptor; IDH: Isocitrate dehydrogenase; MGMT: O6-methylguanine-DNA methyltransferase; MRI: Magnetic resonance imaging; PET: Positron emission tomography; PTEN: Phosphatase and tensin homolog; TERT: Telomerase reverse transcriptase; TMZ: Temozolomide; WHO: World Health Organization; VEGF: Vascular endothelial growth factor.

enabling cells to elude standard control processes or resist eradication by the immunological system. Epidemiological evidence strongly supports the association between genetic causes and the probability of developing cerebral neoplasms. Specifically, numerous abnormalities linked to uncommon variants in strongly expressive genes have been identified as increasing the likelihood of cerebral neoplasms.[112,113] In research involving 500 glioma patients, less than 1% were found to have a recognized hereditary syndrome.[114]

Molecular and Therapeutic Targeting in CNS Tumors

Different CNS malignancies, Table 1 offers a thorough summary of the molecular categorization, its significant genetic changes, and developing targeted therapy approaches. The table comprises data from the World Health Organization (WHO) classification for 2021, emphasizing clinically significant indicators such as O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, 1p/19q co-deletion, and IDH mutation. The focus is on how these molecular discoveries inform prognosis, diagnosis, and individualized therapy planning.

Conclusion

This study provides a comprehensive overview of cancer, covering various aspects from its molecular mechanisms to clinical manifestations and treatment options. Complex resistance mechanisms, such as adaptive signaling, genetic heterogeneity, and an immunosuppressive tumor microenvironment, are present in high-grade gliomas and restrict the effectiveness of long-term therapy. Knowing these elements and how they contribute to recurrence offers vital translational information for creating longer-lasting and more successful treatment plans. A more thorough translational knowledge is provided by discussing the processes behind therapy resistance and recurrence patterns in high-grade gliomas. This thorough revision enhances the manuscript's applicability to recent developments in neuro-oncology

research. As such, a multidisciplinary approach involving collaboration among neurosurgeons, oncologists, radiologists, pathologists, and other allied healthcare professionals is indispensable for delivering comprehensive and patient-centered care to individuals affected by intracranial tumors. Globally, the incidence of brain tumors shows notable regional variation, with higher rates observed in developed countries due to advanced diagnostic capabilities and reporting accuracy. Environmental, genetic, and healthcare accessibility factors further contribute to these geographic differences in tumor occurrences. Furthermore, the importance of early detection and prevention strategies cannot be emphasized enough, as they offer the best opportunity for successful treatment and improved survival rates. Public health campaigns aimed at raising awareness, advocating healthy lifestyles, and facilitating access to screening programs have the potential to significantly impact cancer incidence and mortality rates.

Abbreviations

ADC: Apparent diffusion coefficient; **BBB:** Blood–brain barrier; **BBBD:** Blood–brain barrier disruption; **B-CSF:** Blood-cerebrospinal fluid; **Cho:** Choline; **C-MET:** Mesenchymal-epithelial transition factor; **CNS:** Central nervous system; **Cr:** Creatine; **CSF:** Cerebrospinal fluid; **CT:** Computed tomography; **ctDNA:** Circulating tumor DNA; **DWI:** Diffusion-weighted imaging; **EGFR:** Epidermal growth factor receptor; **FLAIR:** Fluid attenuation inversion recovery; **fMRI:** Functional magnetic resonance imaging; **GBM:** Glioblastoma; **IA:** Intra-arterial; **MRgFUS:** MR-guided focused ultrasound; **MRI:** Magnetic resonance imaging; **MRS:** Magnetic resonance spectroscopy; **NAA:***N*-acetyl aspartate; **PET–MRI:** Positron emission tomography–magnetic resonance imaging; **RANO:** Response Assessment in Neuro-Oncology; **VEGF:** Vascular endothelial growth factor.

Acknowledgments

The authors would like to thank the respective institutions for their support of this project.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study did not require ethical approval.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Informed Consent

The participant has provided informed consent for the submission of the article to the journal.

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