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NAVIGATING BRAIN TUMORS: A COMPREHENSIVE INSIGHT INTO EPIDEMIOLOGY, MECHANISMS, DIAGNOSIS, AND EMERGING THERAPEUTIC FRONTIERS

Shehla Akbar[1*], Memoona Tahira[2], Saima Noreen[2], Mehvish Javeed[3]

[1]College of Pharmacy, University of Sargodha, Sargodha, Punjab, Pakistan
[2]Department of Zoology, Wildlife and Fisheries, Faculty of Veterinary and Animal Sciences, Muhammad Nawaz Sharif University of Agriculture, Multan
[3]Department of Pathobiology and Biomedical Sciences, Muhammad Nawaz Sharif University of Agriculture, Multan, Punjab, Pakistan

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ABSTRACT

Brain tumors are a heterogeneous group of neoplasms with diverse histopathological, molecular, and clinical features. Despite advances in diagnosis and treatment, malignant brain tumors continue to cause significant morbidity, mortality, recurrence, and therapeutic resistance. Genetic and epigenetic alterations, metabolic reprogramming, tumor microenvironment, and immune evasion play important roles in tumor progression and treatment response. This review summarizes current advances in brain tumor epidemiology, classification, molecular biology, diagnosis, treatment, and precision medicine. Molecular markers including IDH1/2, 1p/19q, MGMT, EGFR, TERT, ATRX, TP53, H3, and BRAF contribute to tumor classification, prognosis, and therapeutic decision-making. Conventional management includes surgery, radiotherapy, and chemotherapy, while emerging approaches include targeted and immune-based therapies, cancer vaccines, CAR-T/CAR-NK cells, oncolytic viruses, nanotechnology, gene/RNA therapies, ferroptosis-based strategies, and artificial intelligence-assisted precision oncology. Advanced neuroimaging, liquid biopsy, radiomics, and molecular profiling are also improving diagnostic and prognostic assessment. However, intratumoral heterogeneity, blood–brain barrier limitations, recurrence, treatment resistance, and toxicity remain major challenges. Integrating molecular classification, advanced diagnostics, and individualized therapies may improve brain tumor management and support the development of more effective and durable treatment strategies.

Keywords: Brain tumor, Glioblastoma, Meningioma, Intracranial neoplasm, Neurosurgery, Radiation therapy, Immunotherapy

[*]**Corresponding Author.** E-mail: shehla.akbar@uos.edu.pk

INTRODUCTION

A brain tumor diagnosis carries immense clinical weight, directly affecting the structural substrate of human identity, cognition, and motor function. Defined as an abnormal mass of uncontrolled cellular proliferation, these lesions encompass a diverse spectrum of pathologies. This range spans from slow-growing, benign meningiomas to highly aggressive, malignant glioblastomas. Epidemiological modeling indicates that roughly 700,000 individuals in the United States manage a primary central nervous system (CNS) diagnosis, with nearly 87,000 fresh cases recorded every year. On a global scale, the annual incidence surpasses 300,000 cases, cementing these neoplasms as leading causes of cancer-related mortality **[1]**.

Recent clinical decades have seen rapid progress driven by innovations across molecular biology, neuroimaging, and surgical methodologies. Notably, the updated World Health Organization (WHO) classification framework established a paradigm shift by integrating molecular criteria alongside conventional tissue histology. While targeted

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treatments and immunotherapy options show long-term promise, the prognosis for high-grade malignancies remains a critical challenge. This review systematically covers the transition from underlying bench science to active clinical application, offering an integrated overview of modern neuro-oncological management **[2]**.

Classification of Brain Tumors

There are two major types of brain tumors, Primary and Secondary Brain Tumors. Primary brain tumors develop directly from native intracranial elements, including glial entities, neurons, meningeal layers, or the choroid plexus. Conversely, secondary (metastatic) brain tumors develop when malignant cells colonize the brain via hematogenous or lymphatic pathways from primary cancers like lung, breast, colorectal, or melanoma sites. In adult cohorts, secondary lesions significantly outnumber primary tumors. Differentiating between these groups is critical because it dictates subsequent systemic staging, treatment selection, and overall prognosis **[2]**. Gliomas are the most frequent primary intra-axial tumors in adults, originating from supportive glial elements. This category includes astrocytomas, oligodendrogliomas, and ependymomas **[3]**. Glioblastoma (GBM)—defined as an IDH-wildtype, Grade 4 astrocytoma—represents the most aggressive and common primary malignant brain tumor in adults **[2]**. Meningiomas arise from the protective arachnoidal membranes and represent approximately 37% of primary adult tumors. Most are classified as Grade 1, though atypical (Grade 2) and anaplastic (Grade 3) variants can occur. Other specialized variants include pituitary adenomas, pediatric medulloblastomas situated in the posterior fossa, vestibular schwannomas, craniopharyngiomas, and primary central nervous system lymphomas **[3]**.

The WHO Classification System

The classification of central nervous system tumors underwent a significant shift with the release of the updated 2021 WHO guidelines. Previous diagnostic standards focused primarily on light microscopy and histopathological features. The current framework mandates an integrated diagnostic model that combines tissue morphology with distinct molecular markers, such as Isocitrate dehydrogenase (IDH1/2) mutation profiles, chromosomal 1p/19q codeletion status, TERT promoter alterations, and MGMT promoter methylation statuses. Malignancy grading uses a scale from Grade 1 (indolent, benign lesions) up to Grade 4 (highly invasive, fast-growing malignancies). This scale reflects cellular proliferation indices, microvascular changes, and tissue necrosis. Under the revised guidelines, a tumor's grade is treated as an intrinsic biological feature tied directly to its molecularly defined entity **[2]**.

EPIDEMIOLOGY

Incidence and Prevalence

Statistical registers show an age-adjusted incidence rate for primary CNS tumors of roughly 24 cases per 100,000 individuals in the United States, with malignant presentations accounting for 7 per 100,000. Globally, approximately 308,000 new diagnoses are logged each year. While their total numbers are lower than breast or colorectal cancers, brain tumors carry a disproportionate clinical burden due to their direct impact on neurocognitive function and patient independence **[4]**.

Age and Sex Distribution

Incidence patterns vary widely across different age groups and sexes. In children, CNS malignancies represent the second most common cancer type overall and stand as the leading cause of cancer-related pediatric death. Common pediatric presentations include medulloblastomas, pilocytic astrocytomas, and ependymoma. In adult populations, the incidence curve rises steeply with age, peaking in the sixth and seventh decades. For instance, glioblastoma presents at a median age of 64 years. Regarding sex distributions, most malignant tumors occur more frequently in men, whereas benign meningiomas are significantly more common in women **[5].**

RISK FACTORS

The underlying causes of most primary brain tumors remain poorly understood, showing few verified links to lifestyle choices, diet, or tobacco exposure. The most clearly verified environmental risk factor is exposure to therapeutic ionizing radiation. Genetic factors contribute to a small percentage of cases, including syndromes like Neurofibromatosis Type 1 and Type 2 (NF1 / NF2), Li-Fraumeni syndrome (TP53 mutations), tuberous sclerosis, and von Hippel-Lindau disease. Large-scale epidemiological studies have found no reproducible, statistically significant causal links between brain tumor development and mobile phone usage **[6]**.

MOLECULAR BIOLOGY AND PATHOPHYSIOLOGY

Genetic Alterations in Brain Tumors

Large-scale genomic sequencing efforts have clarified the molecular mechanisms driving brain tumors. A key molecular marker is mutation of the isocitrate dehydrogenase (IDH1 or IDH2) genes. These mutations occur in most lower-grade gliomas and secondary glioblastomas, and they correlate with better overall survival compared to IDH-wildtype variants. Mechanistically, mutant IDH enzymes catalyze the conversion of alpha-ketoglutarate into the oncometabolite 2-hydroxyglutarate (2-HG) **[7]**. Another important biomarker is epigenetic silencing via MGMT promoter methylation. The MGMT gene encodes a DNA repair enzyme that removes alkyl

Table 1: Major brain tumor types: Clinical features, and prognostic characteristics.

Brain tumor type	Major characteristics / molecular classification	Common clinical presentation	Typical location	General prognostic considerations
Glioblastoma, IDH-wildtype	Aggressive adult-type diffuse glioma; frequently associated with molecular alterations such as TERT promoter mutation, EGFR amplification and chromosome +7/−10 pattern	Headache, seizures, cognitive changes, focal neurological deficits	Cerebral hemispheres	Highly aggressive; recurrence is common despite multimodal therapy
Astrocytoma, IDH-mutant	Adult-type diffuse glioma characterized by IDH mutation; ATRX and TP53 alterations are frequent	Seizures, headache, cognitive or focal neurological deficits	Cerebral hemispheres	Prognosis varies with grade, molecular features and extent of resection
Diffuse midline glioma, H3 K27-altered	Pediatric/young-adult high-grade diffuse glioma with characteristic H3 alteration	Cranial nerve deficits, weakness, gait abnormalities, raised intracranial pressure	Midline structures, particularly brainstem	Aggressive tumor with poor prognosis
Medulloblastoma	Embryonal tumor; molecular groups include WNT-activated, SHH-activated and non-WNT/non-SHH groups	Headache, vomiting, ataxia, hydrocephalus	Cerebellum/posterior fossa	Prognosis varies substantially according to molecular group, age and disease dissemination
Ependymoma	Molecularly diverse CNS tumor with distinct anatomical and molecular subgroups	Headache, hydrocephalus, nausea/vomiting, neurological deficits	Ventricular system or spinal cord	Outcome depends on location, molecular subtype, grade and extent of resection
Meningioma	Usually extra-axial tumor arising from meningothelial cells; molecular alterations vary among subtypes	Headache, seizures, visual or focal neurological deficits	Meninges/extra-axial compartment	Many are slow-growing, but higher-grade tumors have increased recurrence risk
Schwannoma	Benign peripheral nerve sheath tumor, frequently involving the vestibular nerve	Hearing loss, tinnitus, balance disturbance	Cerebellopontine angle/cranial nerves	Usually slow-growing; prognosis is generally favorable

Table 2: Major molecular alterations and signaling pathways in brain tumorigenesis.

Molecular alteration/pathway	Biological function	Associated brain tumors	Major consequence	Potential clinical/therapeutic relevance
IDH1/IDH2 mutation	Alters cellular metabolism and produces the oncometabolite 2-hydroxyglutarate	Astrocytoma, IDH-mutant; oligodendroglioma	Epigenetic and metabolic reprogramming	Diagnostic classification, prognostic significance and therapeutic targeting
TP53 alteration	Disrupts DNA-damage response and cell-cycle regulation	Astrocytoma and other gliomas	Genomic instability and impaired apoptosis	Potential therapeutic and prognostic relevance
ATRX alteration	Affects chromatin remodeling and telomere maintenance	Astrocytoma, IDH-mutant	Alternative lengthening of telomeres and genomic instability	Useful in integrated molecular diagnosis
TERT promoter mutation	Promotes telomerase activity	Glioblastoma and other diffuse gliomas	Sustained cellular replicative capacity	Diagnostic and prognostic relevance
EGFR amplification/mutation	Activates growth and survival signaling	Glioblastoma, particularly IDH-wildtype	Increased proliferation, invasion and survival	Target for molecularly directed therapies
PI3K/AKT/mTOR pathway	Regulates proliferation, metabolism and survival	Multiple glioma subtypes	Increased tumor growth and treatment resistance	Potential target for pathway inhibition
H3 K27 alteration	Alters histone modification and chromatin regulation	Diffuse midline glioma	Epigenetic dysregulation and aggressive tumor behavior	Important diagnostic and therapeutic biomarker
BRAF alteration/fusion	Activates MAPK signaling	Selected pediatric and low-grade gliomas	Enhanced proliferation	BRAF/MEK-directed treatment may be applicable to selected tumors
MGMT promoter methylation	Reduces MGMT-mediated DNA repair	Particularly relevant to glioblastoma	Increased sensitivity to alkylating chemotherapy	Predictive biomarker for response to temozolomide
WNT signaling	Regulates developmental and proliferative processes	WNT-activated medulloblastoma	Tumor-specific transcriptional activation	Molecular classification and prognostic stratification
VEGF signaling	Promotes angiogenesis	High-grade gliomas	Tumor vascularization and edema	Antiangiogenic strategies
p53/RB pathways	Regulate cell-cycle arrest and genomic integrity	High-grade gliomas	Uncontrolled cell-cycle progression	Potential therapeutic vulnerability

groups added by chemotherapies like temozolomide. When the promoter region is methylated and silenced, tumor cells cannot repair this chemotherapy-induced DNA damage, which occurs in 45% to 55% of glioblastoma cases [**8**].

Blood-Brain Barrier

The blood-brain barrier (BBB)—formed by continuous endothelial tight junctions, pericytes, and astrocytic end-feet—restricts the delivery of systemic therapeutic agents into the central nervous system. In high-grade malignancies, this barrier is often partially disrupted, creating a highly variable blood-tumor barrier (BTB). While the vascular core of a glioblastoma may allow some drug penetration, the invasive cells at the tumor margin typically remain protected behind an intact BBB, driving recurrence **[10]**.

CLINICAL PRESENTATION

General Symptoms

Brain tumor symptoms vary widely based on the lesion's size, growth rate, and secondary mass effect. Headaches are reported by 35% to 50% of patients at diagnosis. The classic brain tumor headache is typically most severe in the morning due to nocturnal changes in intracranial pressure, is often accompanied by nausea or vomiting, and can improve when upright. However, many patients present with non-specific headache patterns, requiring careful evaluation for red flags like progressive worsening **[11]**.

Focal Neurological Deficits

Anatomical location determines specific focal symptoms: Frontal lobe lesions present with executive dysfunction and expressive aphasia; temporal lobe tumors cause memory impairment and auditory hallucinations; parietal lobe lesions cause corticosensory deficits and apraxia; occipital lobe tumors produce visual field deficits; and cerebellar lesions lead to ataxia and dysmetria **[12]**.

Seizures and Cognitive Effects

Seizures occur as a presenting symptom in 20% to 40% of patients, with the highest rates observed in slow-growing, lower-grade cortical gliomas. Any new-onset adult seizure, particularly with a focal onset, requires immediate neuroimaging to rule out a structural mass. Cognitive decline is also common, with deficits in memory, attention, and executive processing speed arising from direct tumor invasion or as a side effect of cranial treatments **[12]**.

DIAGNOSIS

Neuroimaging

Magnetic Resonance Imaging (MRI) is the gold standard for intracranial tumor evaluation. Standard clinical protocols include T1-weighted sequences before and after gadolinium contrast, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) profiles. High-grade malignancies typically demonstrate irregular ring-enhancement surrounding a central necrotic core, reflecting breakdown of the blood-brain barrier **[10]**. Advanced imaging modalities include MR Spectroscopy (MRS) to measure metabolic signatures, Perfusion MRI to assess relative cerebral blood volume, and Diffusion Tensor Imaging (DTI) to visualize white matter tracts **[13]**.

Histopathology and Molecular Diagnostics

Definitive diagnosis requires tissue analysis via stereotactic needle biopsy or surgical resection. Pathologists evaluate features such as cellular pleomorphism, mitotic activity, microvascular proliferation, and necrosis to establish tumor type and grade. Modern diagnostic protocols combine these morphological findings with molecular assays to formulate an integrated diagnosis under the WHO framework.

DIFFERENTIAL DIAGNOSIS

Several conditions can mimic brain tumors on neuroimaging and must be carefully differentiated. Pyogenic or fungal brain abscesses often present with ring-enhancing profiles similar to glioblastoma. Other key differentials include tumefactive multiple sclerosis, acute cerebral infarction, and localized radiation necrosis **[15].**

TREATMENT OF BRAIN TUMORS

Surgery

Surgical intervention is the standard initial step for accessible tumors, helping to establish tissue diagnosis, relieve mass effect, and achieve cytoreduction. For high-grade gliomas, maximizing the extent of resection (EOR) while preserving neurological function correlates with improved overall survival. Advanced intraoperative technologies include frameless neuronavigation, 5-Aminolevulinic Acid (5-ALA) fluorescence, and awake craniotomies **[16]**.

Radiation Therapy

Radiation therapy is a cornerstone of management for high-grade tumors. The standard protocol for newly diagnosed glioblastoma delivers a total dose of 60 Gy in 30 fractions over 6 weeks, combined with concurrent temozolomide chemotherapy. Advanced delivery techniques include Intensity-Modulated Radiation Therapy (IMRT), Stereotactic Radiosurgery (SRS), and Proton Beam Therapy **[17]**.

Chemotherapy

Temozolomide (TMZ), an oral alkylating agent, is the standard systemic therapy for glioblastoma. The landmark Stupp protocol demonstrated that adding concurrent and adjuvant temozolomide to radiotherapy extended median survival from 12.1 months to 14.6 months **[18]**. For recurrent glioblastoma, Bevacizumab—a monoclonal antibody targeting VEGF—is approved to help control

Table 3: Diagnostic approaches for brain tumors: principles, applications, and limitations.

Diagnostic approach	Principal application	Major advantages	Important limitations	Clinical/molecular information obtained
Neurological examination	Initial assessment of neurological function	Rapid, inexpensive and non-invasive	Limited specificity	Identifies neurological deficits and guides further investigation
Computed tomography (CT)	Initial structural evaluation and emergency assessment	Rapid; useful for hemorrhage, calcification and bone abnormalities	Lower soft-tissue contrast than MRI; radiation exposure	Tumor location, mass effect, hemorrhage and calcification
Conventional MRI	Primary structural imaging	Excellent soft-tissue resolution; no ionizing radiation	Longer acquisition time; contraindications in some patients	Tumor location, size, edema, enhancement and anatomical relationships
Diffusion-weighted MRI	Assessment of tissue cellularity and water movement	Useful for characterizing tumor tissue	Interpretation can be affected by tumor heterogeneity	Cellular characteristics and differential diagnosis
Perfusion MRI	Assessment of tumor vascularity	Provides information on blood volume and perfusion	Requires specialized acquisition and interpretation	Tumor vascularity and treatment-response assessment
Magnetic resonance spectroscopy	Assessment of tumor biochemical composition	Provides metabolic information without tissue sampling	Lower spatial resolution and complex interpretation	Metabolite patterns that may support tumor characterization
PET imaging	Metabolic and molecular imaging	Provides functional information	Radiation exposure; tracer availability and specificity vary	Tumor metabolism and selected molecular characteristics
Stereotactic biopsy	Tissue acquisition when complete resection is unsuitable	Provides definitive tissue diagnosis	Invasive; sampling error may occur because of tumor heterogeneity	Histology, grade and molecular characteristics
Surgical resection	Diagnosis and maximal safe tumor removal	Provides large tissue sample and therapeutic benefit	Surgical morbidity; not suitable for all tumor locations	Histopathology, molecular testing and extent of resection
Histopathology	Morphological tumor classification	Established diagnostic method	Morphological overlap between tumors	Tumor type and histological characteristics
Immunohistochemistry	Detection of specific proteins/markers	Widely available and relatively rapid	Interpretation depends on antibodies and tumor context	Molecular surrogates and tumor classification
DNA/RNA sequencing	Molecular profiling	Identifies mutations, fusions and other alterations	Cost, tissue requirements and interpretation	Genomic alterations relevant to diagnosis/prognosis/therapy
DNA methylation profiling	Molecular tumor classification	Useful for difficult or ambiguous cases	Requires specialized platforms and reference classifiers	Epigenetic tumor classification
Liquid biopsy	Detection of tumor-derived material in body fluids	Minimally invasive and potentially useful for longitudinal monitoring	Sensitivity can be limited by the blood-brain barrier and low tumor shedding	Circulating tumor DNA/RNA and other biomarkers
Radiomics/AI-assisted imaging	Automated feature extraction and tumor characterization	Can identify complex imaging patterns	Requires validation, standardized datasets and clinical integration	Diagnostic, prognostic and potentially predictive imaging biomarkers

Table 4: Current and emerging therapeutic strategies for brain tumors.

Therapeutic strategy	Main mechanism/target	Current application	Advantages/potential	Major limitations/challenges
Maximal safe surgical resection	Physical removal of tumor while preserving neurological function	Resectable primary brain tumors	Reduces tumor burden and provides tissue for diagnosis	Infiltrative growth and eloquent brain locations limit complete removal
Radiotherapy	DNA damage induced by ionizing radiation	Primary and metastatic brain tumors	Effective local treatment	Neurotoxicity and recurrence; dose limitations
Chemotherapy	Cytotoxic or molecularly directed tumor-cell killing	Selected gliomas and other CNS tumors	Systemic treatment capability	BBB penetration, toxicity and resistance
Temozolomide	Alkylating DNA damage	Particularly glioblastoma	Oral administration and established clinical use	Resistance, recurrence and limited efficacy in some molecular contexts
IDH-targeted therapy	Inhibition of mutant IDH enzymes	IDH-mutant gliomas	Molecularly targeted approach	Applicable only to selected molecular tumors
BRAF/MEK inhibition	Blocks MAPK signaling	Selected BRAF-altered tumors	Molecularly directed treatment	Restricted to appropriate molecular alterations; resistance may develop
Antiangiogenic therapy	Inhibition of VEGF-mediated angiogenesis	Selected recurrent/high-grade tumors	May reduce edema and vascular signaling	Resistance and limited durable tumor control
Cancer vaccines	Tumor-antigen-specific immune activation	Clinical trials	Potentially personalized treatment	Antigen heterogeneity and immune escape
CAR-T cell therapy	Genetically engineered T cells recognize tumor antigens	Refractory brain tumors in clinical trials	Highly targeted cellular therapy	Antigen heterogeneity, trafficking and toxicity
CAR-NK therapy	Engineered natural killer cells target tumor antigens	Experimental brain tumors	Potentially favorable safety and off-the-shelf development	Tumor penetration and persistence
Oncolytic viruses	Selective infection/lysis of tumor cells with immune activation	Recurrent or refractory tumors in trials	Direct tumor killing plus immune stimulation	Delivery, antiviral immunity and tumor heterogeneity
Nanoparticle drug delivery	Improves drug stability, targeting and delivery	Experimental CNS tumors	Potential to improve BBB penetration and tumor accumulation	Manufacturing, toxicity and clinical translation
Gene/RNA therapy	Modulation or correction of tumor-associated molecular pathways	Experimental	Highly specific molecular intervention	Delivery, off-target effects and durability
Epigenetic therapy	Modifies abnormal DNA methylation/chromatin regulation	Molecularly selected experimental settings	Addresses epigenetic drivers of tumor biology	Toxicity and complex tumor epigenetics
Ferroptosis-based therapy	Promotes iron-dependent lipid peroxidation and regulated cell death	Preclinical/early translational research	May overcome some conventional resistance mechanisms	Selectivity, BBB penetration and toxicity

peritumoral edema **[19]**. Localized options include biodegradable carmustine wafers placed directly in the surgical cavity.

Tumor Treating Fields (TTFields)

Tumor Treating Fields represent a non-invasive treatment modality that uses alternating electric fields at intermediate frequencies (200 kHz for GBM) to disrupt mitotic spindle assembly during cell division. The EF-14 clinical trial showed that adding TTFields to maintenance temozolomide extended median overall survival in newly diagnosed GBM patients from 16.0 months to 20.9 months **[18]**.

EMERGING THERAPIES AND FUTURE DIRECTIONS

Immunotherapy

While immune checkpoint inhibitors have shown limited efficacy in glioblastoma due to the highly immunosuppressive tumor microenvironment, active research continues into alternative strategies like CAR-T Cell Therapy and personalized neoantigen vaccines **[21]**.

Targeted Therapies

The molecular profiling of central nervous system tumors has led to targeted therapies such as vorasidenib, a dual oral inhibitor of mutant IDH1 and IDH2 enzymes. In the landmark INDIGO clinical trial, vorasidenib significantly improved progression-free survival in patients with Grade 2 IDH-mutant gliomas [10]. For pediatric low-grade gliomas harboring BRAF V600E mutations, combinations of BRAF and MEK inhibitors have demonstrated clinical activity **[22]**.

Oncolytic Virotherapy and Gene Therapy

Oncolytic virotherapy uses genetically modified viruses, such as modified herpes simplex virus or poliovirus (PVSRIPO), to selectively infect and destroy malignant cells while inducing an anti-tumor immune response. Gene therapy approaches, including CRISPR-based interventions, are also being studied using advanced delivery methods like convection-enhanced delivery (CED) **[23]**.

Liquid Biopsy and Precision Medicine

Liquid biopsy platforms analyze circulating tumor DNA (ctDNA) and distinct methylation signatures in blood or cerebrospinal fluid (CSF) to offer a minimally invasive method to monitor tumor progression. Adaptive clinical trial designs, such as the GBM AGILE platform, are also being used to evaluate multiple targeted therapies simultaneously across specific molecular subgroups **[24]**.

PREVENTION AND EARLY DETECTION

There are currently no proven primary prevention strategies for brain tumors in the general population, as most cases lack modifiable lifestyle risk factors. For individuals with verified hereditary syndromes like Neurofibromatosis or Li-Fraumeni syndrome, targeted screening protocols using surveillance MRI may be utilized. While routine population-level screening is not currently viable, ongoing research into liquid biopsy technology and blood-based methylation profiling may eventually support earlier detection strategies **[25].**

CONCLUSION

Brain tumors remain a significant challenge in oncology due to their biological heterogeneity, protection behind the blood-brain barrier, and location within an irreplaceable organ. While aggressive malignancies like glioblastoma continue to carry a difficult prognosis, advances in molecular diagnostics, surgical techniques, and targeted therapies have helped refine clinical management. Improving patient outcomes will depend on continued research into precision medicine, multi-modality treatment strategies, and comprehensive supportive care.

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