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Review Article

Brain Cancer: Pathogenesis, Diagnosis, and Emerging Therapeutic Strategies

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ABSTRACT:

Brain cancer remains one of the most challenging malignancies to diagnose and treat due to its heterogeneity, rapid progression, and the protective blood-brain barrier limiting therapeutic penetration. Despite advances in molecular biology, neuroimaging, and targeted therapies, prognosis remains poor for many patients, especially those with glioblastoma multiforme (GBM), the most aggressive form. This article reviews the epidemiology, pathology, risk factors, clinical manifestations, diagnostic modalities, and treatment strategies for brain cancer. It further highlights recent research directions including immunotherapy, nanomedicine, and precision oncology, while addressing ongoing challenges and future prospects.

KEYWORDS: brain cancer; glioblastoma multiforme; neuro-oncology; blood-brain barrier; immunotherapy; precision medicine

INTRODUCTION

Brain cancer encompasses a spectrum of malignant tumors arising from the brain's parenchyma, meninges, or associated structures. Unlike systemic cancers, brain tumors pose unique challenges due to their localization within the central nervous system (CNS), where even small lesions can cause profound neurological deficits (Ostrom et al., 2022). Brain cancers are broadly classified as primary tumors (originating in the brain) and secondary tumors (metastases from extracranial cancers). Among primary malignancies, gliomas, particularly glioblastoma multiforme (GBM), are the most prevalent and deadly (Louis et al., 2021).

Despite major strides in neuro-oncology, brain cancer continues to have high morbidity and mortality. Conventional treatments such as surgery, radiotherapy, and chemotherapy extend survival only modestly in high-grade gliomas. Therefore, research is increasingly focused on understanding tumors biology, developing novel therapies, and overcoming barriers to drug delivery in the CNS.

EPIDEMIOLOGY

Globally, brain and central nervous system (CNS) tumors account for approximately 1.6% of all cancers and 2.5% of cancer-related deaths (Sung et al., 2021). According to the Central Brain Tumor Registry of the United States (CBTRUS), around 88,000 new cases of primary brain and CNS tumors were diagnosed in the U.S. in 2022, with malignant tumors comprising 33% of cases (Ostrom et al., 2022).

1. Age and Gender: Brain cancer affects individuals of all ages. Pediatric populations most commonly present with medulloblastomas, while adults are more prone to gliomas and meningiomas

(Ramaswamy & Taylor, 2017). Men are slightly more predisposed to gliomas, whereas women more frequently develop meningiomas.

2. Survival Rates: Prognosis is poor in high-grade gliomas, particularly GBM, where median survival is around 14–18 months despite aggressive therapy (Stupp et al., 2009). Lower-grade gliomas and meningiomas typically show better outcomes.
3. Geographic Variation: Incidence rates are higher in developed countries, partly due to improved diagnostic imaging. Genetic and environmental factors may also play a role in regional variations (Sung et al., 2021).

PATHOPHYSIOLOGY AND MOLECULAR MECHANISMS

Brain cancers exhibit complex molecular and cellular heterogeneity. Key pathological types include astrocytoma's, oligodendrogliomas, ependymomas, meningiomas, and medulloblastomas. Glioblastoma, classified as WHO grade IV astrocytoma, is the most lethal subtype.

Genetic Alterations

1. IDH Mutations: Mutations in the isocitrate dehydrogenase (IDH1/IDH2) genes are commonly seen in lower-grade gliomas and are associated with better prognosis (Yan et al., 2009).
2. TERT Promoter Mutations: Found in GBM and associated with telomerase activation, leading to cellular immortality (Killela et al., 2013).
3. EGFR Amplification: Epidermal growth factor receptor amplification and mutations are common in GBM, driving tumour proliferation [Verhaak et al., 2010].
4. TP53 and PTEN Loss: Mutations in tumour suppressor genes contribute to uncontrolled growth and resistance to apoptosis.

Tumour Microenvironment

Brain tumours interact with a complex microenvironment, including stromal cells, immune cells, and extracellular matrix. The presence of tumour-associated macrophages and microglia creates an immunosuppressive milieu, facilitating tumour progression [Quail & Joyce, 2017].

Blood-Brain Barrier [BBB]

The BBB poses a major therapeutic obstacle by restricting entry of most chemotherapeutic drugs. Tumour-induced disruption of the BBB allows partial permeability, but heterogeneity in this disruption complicates treatment delivery [Arvanitis et al., 2020].

RISK FACTORS

Brain cancers are multifactorial in etiology, influenced by genetic, environmental, and lifestyle factors:

1. Genetic Predisposition: Syndromes such as Li-Fraumeni, Turcot's, and Lynch syndrome increase susceptibility.
2. Ionizing Radiation: Previous therapeutic cranial radiation increases risk, particularly in paediatric populations.
3. Environmental Exposure: Prolonged exposure to carcinogens such as vinyl chloride or pesticides has been implicated, though evidence remains inconsistent.
4. Mobile Phone Use: The role of electromagnetic radiation remains debated, with inconclusive findings [Carlberg & Hardell, 2017].
5. Family History: Having a first-degree relative with brain cancer increases risk marginally.

CLINICAL MANIFESTATIONS

Clinical presentation varies depending on tumour size, location, and growth rate. Common symptoms include:

1. Neurological Deficits: Weakness, sensory loss, aphasia, or visual field defects.
2. Increased Intracranial Pressure [ICP]: Headaches, nausea, vomiting, and papilledema.
3. Seizures: Common in low-grade gliomas and cortical tumours.
4. Cognitive and Behavioral Changes: Memory loss, personality alterations, or executive dysfunction.

Because symptoms are nonspecific, diagnosis is often delayed until tumours are advanced.

DIAGNOSIS

Accurate diagnosis relies on neuroimaging, histopathology, and increasingly, molecular profiling.

- **Neuroimaging**

1. Magnetic Resonance Imaging [MRI]: The gold standard for brain tumour imaging, with contrast-enhanced MRI providing superior resolution.
2. Functional MRI [fMRI] & Diffusion Tensor Imaging [DTI]: Help map eloquent brain regions and guide surgery.
3. Positron Emission Tomography [PET]: Assesses metabolic activity and distinguishes tumour recurrence from treatment-induced necrosis.

➢ Histopathology and Molecular Testing

Tissue biopsy remains the definitive diagnostic method. The 2021 WHO classification integrates molecular markers such as IDH mutation, 1p/19q codeletion, and MGMT promoter methylation into tumour grading [Louis et al., 2021].

➢ Liquid Biopsy

Emerging techniques detect circulating tumour DNA [ctDNA] and microRNAs in cerebrospinal fluid or blood, offering less invasive diagnostic approaches [Miller et al., 2019]

TREATMENT MODALITIES

➢ Surgery

Maximal safe surgical resection is the cornerstone of treatment. Techniques such as intraoperative MRI, awake craniotomy, and fluorescence-guided surgery [5-ALA] improve resection while minimizing neurological deficits.

Radiation Therapy

Fractionated external beam radiotherapy is standard for high-grade gliomas. Techniques like stereotactic radiosurgery [SRS] deliver focused doses to localized tumours.

➢ Chemotherapy

1. Temozolomide [TMZ]: The frontline alkylating agent, particularly effective in MGMT promoter-methylated tumours [Stupp et al., 2009].
2. Carmustine wafers: Implanted locally in the tumour bed post-surgery.
3. Resistance, however, remains a challenge due to tumour heterogeneity and drug efflux mechanisms.

➢ Targeted Therapies

1. Bevacizumab [anti-VEGF]: Approved for recurrent GBM, though survival benefits are limited.
2. EGFR inhibitors: Under investigation but hindered by BBB penetration.

➢ Immunotherapy

1. Checkpoint Inhibitors: Clinical trials with PD-1/PD-L1 inhibitors have shown limited efficacy, but combinational strategies are promising.
2. CAR T-cell Therapy: Engineered T-cells targeting EGFRvIII and other antigens are under evaluation.

3.Cancer Vaccines: Personalized neoantigen vaccines are emerging research directions.

➢ Emerging Strategies

1. Nanomedicine: Nanoparticle-based delivery systems enhance drug penetration across the BBB.
2. Gene Therapy: Viral vectors delivering tumour-suppressor genes or suicide genes are under development.
3. Tumour Treating Fields [TTFs]: Alternating electric fields disrupt tumour cell division and extend survival in GBM [Stupp et al., 2017].

PROGNOSIS AND CHALLENGES

Despite multimodal therapy, prognosis for aggressive brain cancers remains poor. Median survival in GBM is less than two years, with a 5-year survival rate of ~7% (Ostrom et al., 2022). Challenges include:

1. Tumour heterogeneity and adaptive resistance.
2. Limited drug penetration across the BBB.
3. Immunosuppressive tumour microenvironment.
4. Difficulties in early detection.

RESEARCH ADVANCES AND FUTURE DIRECTIONS

1. Precision Oncology: Molecular profiling is guiding personalized therapy selection.

2. Artificial Intelligence (AI): Machine learning models improve tumour detection, prognosis prediction, and treatment planning.
3. Liquid Biopsy & Biomarkers: Offer potential for real-time monitoring of disease progression.
4. Combination Therapies: Integrating surgery, radiotherapy, chemotherapy, and immunotherapy shows synergistic potential.

CONCLUSION

Brain cancer remains one of the most devastating malignancies due to its aggressive biology, diagnostic challenges, and therapeutic limitations. Advances in molecular characterization, precision oncology, and innovative treatment modalities are gradually improving outcomes. However, significant work remains to overcome therapeutic resistance, enhance drug delivery, and improve quality of life for patients. Multidisciplinary collaboration between neuroscientists, oncologists, geneticists, and bioengineers will be crucial in developing transformative therapies for brain cancer in the coming decades.

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