Classifications and Treatments for Gliomas

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Gliomas pose a significant challenge to neurosurgical oncology because of their diverse histopathological features, genetic heterogeneity, and clinical manifestations. Despite significant advances in understanding the molecular pathways of glioma, translating this knowledge into effective long-term solutions remains a challenge.

Keywords: gliomas ; LITT ; brain tumors ; FUS ; classification ; functional neurosurgery

1. Introduction

Gliomas, primary brain tumors that originate from glial cells, represent a significant challenge in the field of neuro-oncology. These intra-axial tumors exhibit high variability in their histopathological features, genetic profiles, and clinical manifestations, aspects that make it crucial to take an integrated, multidisciplinary approach to effectively combat their annihilating effect on patients [1].

Over the years, extensive research has shed light on the molecular basis of gliomas, offering promising possibilities for targeted therapies. In addition, advances in neurosurgical techniques have opened new horizons in the management of these tumors, providing more precise and personalized therapeutic options [1][2].

Despite these significant advances in understanding the complexity of glioma molecular pathways, the current standard of care, which includes maximal safe resection followed by radiotherapy and chemotherapy, often fails to provide patients with long-term survival and optimal quality of life. New therapeutic strategies are still needed to address the complexity of glioma biology and improve patient outcomes [2].

2. Epidemiology and Classification of Gliomas

Gliomas account for about 80% of all malignant brain tumors, with an incidence that increases with age and peaks in individuals older than 65 years. In the United States, the age-adjusted glioma incidence rate is 6.16 per 100,000 person-years in subjects aged 65 and older, compared with 0.50 per 100,000 person-years in subjects aged 20–44 years [3][4]. Another relevant factor is the origin of the patients. In Europe, the highest incidence rates have been reported in Denmark and Finland, with age-standardized rates of 6.8 and 5.5 per 100,000 person-years, respectively [5]. In the United States, the incidence of gliomas is higher among whites compared with other racial/ethnic groups [6]. Genetic predispositions, such as specific markers associated with glioma susceptibility, contribute to these disparities [7]. Environmental factors, including exposure to ionizing radiation, are implicated in the etiology of GBM [8].

Differences in health infrastructure and diagnostic accessibility also influence reported incidence rates. Developed countries with advanced diagnostic capabilities can detect and report cases more accurately, potentially contributing to higher incidence rates. Conversely, underdiagnosis in some regions may lead to biased reporting [9].

Lifestyle and diet-related factors may further contribute to the complex epidemiological landscape of GBM. Emerging research suggests potential links between certain dietary components and glioblastoma risk. [10]

In essence, the global distribution of glioblastoma involves a complex interplay of genetic, environmental, and health factors. Unraveling these complexities is essential to advancing our knowledge of glioma epidemiology and ultimately improving prevention and treatment strategies on a global scale.

Gliomas can be classified into grades based on their histological features and molecular characteristics. Grade I gliomas are considered benign tumors, while grades II, III, and IV are malignant. The most common malignant gliomas, approximately 50% of all, are grade IV glioblastomas (GBMs), which are most frequently diagnosed in individuals older

than 65 years. In the United States, the age-adjusted incidence rate of GBM is 3.21 per 100,000 person-years in subjects aged 65 and older, compared with 0.23 per 100,000 person-years in individuals aged 20–44 years [3].

Recent advances in molecular profiling have led to a better understanding of the underlying genetic alterations that drive the development of gliomas and can be used to classify them into molecular subtypes, which are characterized by different clinical outcomes and responses to treatment.

Among the most important genetic variants, mutations in the isocitrate dehydrogenase (IDH) gene identify IDH-mutant gliomas that demonstrate a better prognosis than wildtype IDH gliomas [11][12]. Other molecular alterations include mutations in the tumor-suppressor gene tumor protein 53 (TP53), the alpha-thalassemia/mental retardation x-linked (ATRX) syndrome, and the epidermal growth factor receptor (EGFR) pathway [13]. However, even taking into account this valuable genetic profiling, establishing glioma prognosis is more complicated because it is associated with a complex network of factors that contribute to determining the likelihood of patient survival [14].

2.1. Classification of Gliomas

In 2021, the World Health Organization (WHO) provided a new classification of tumors of the central nervous system, which is based on a more comprehensive understanding of the molecular and genetic characteristics of tumors and suggests the use of a combination of histology and molecular markers to predict patient outcomes and guide the choice of appropriate treatments (**Table 1**).

Table 1. Comparison of overall survival and progression-free survival of various types of gliomas.

Glioma Classification	Molecular Markers	Histology	Malignancy	OS	PFS	References
Diffuse astrocytic and oligodendroglial tumors	IDH-mutant	Diffuse astrocytoma	Low grade	>5 years	Variable	[15]
		Anaplastic astrocytoma	Intermediate grade	2–5 years	6–12 months	[15]
		Oligodendroglioma with 1p/19q co-deletion	Low grade	>5 years	Variable	[15][16]
Anaplastic astrocytic and oligodendroglial tumors	IDH-mutant	Anaplastic astrocytoma	Intermediate grade	2–5 years	6–12 months	[15][16]
		Anaplastic oligodendroglioma with 1p/19q co-deletion	Intermediate grade	2–5 years	Variable	[15][16]
Glioblastoma	IDH-wildtype	Glioblastoma	High grade	15 months	7–9 months	[15]
	IDH-mutant	Glioblastoma	High grade	31–46 months	11–20 months	[15]

Abbreviations: OS, overall survival; PFS, progression-free survival.

In particular, the document identifies four categories of gliomas: (1) diffuse astrocytic and oligodendroglial tumors, which include diffuse astrocytoma IDH-mutant, anaplastic astrocytoma IDH-mutant, oligodendroglioma IDH-mutant, and 1p/19q co-deleted tumors; (2) anaplastic astrocytic and oligodendroglial tumors, including anaplastic astrocytoma IDH-mutant, anaplastic oligodendroglioma IDH-mutant, and 1p/19q co-deleted tumors; (3) GBMs, including GBM IDH-wildtype and GBM IDH-mutant; (4) and other gliomas, such as ependymoma, choroid plexus tumors, and embryonal tumors.

The WHO classification does not automatically associate histological type with the grade of malignancy. For example, in the past, anaplastic astrocytoma was automatically considered a grade III glioma, as was anaplastic meningioma.

Therefore, it was expected that these two tumors, although biologically different, would have similar survival times. However, this is a simplistic approach, and today, the method is to stratify the various histological types as much as possible and to study their characteristics in more detail [15].

2.2. Molecular Signature of Gliomas

Accurately classifying the different types of gliomas by combining specific genetic and molecular features is critical to mitigating the difficulties of treating such a heterogeneous group of malignancies [16][17] and maximizing the chances of success [18].

Indeed, the molecular signature is strongly associated with the pathogenesis and prognosis of several tumors. Glioma pathogenesis is no exception, as it is closely dependent on genetic and epigenetic alterations, cellular signaling pathways, and the tumor microenvironment. The PI3K-Akt-mTOR pathway, which modulates cell growth, proliferation, survival, and metabolism, is one of the most important signaling pathways in glioma pathogenesis. As suggested by Wang et al., this pathway leads to increased activity in downstream effectors that promote glioma growth and progression through the amplification of growth factor receptors or the loss of negative regulators, promoting the processes of invasion and metastasis and resistance to chemotherapy and radiotherapy [19]. Of note, according to Cancer Genome Atlas (TCGA) data, approximately 88% of diffuse gliomas, which include GBM and lower-grade gliomas (LGGs), have genetic alterations in at least one component of the PI3K-Akt-mTOR pathway [15]. Specifically, mutations in the gene encoding the catalytic subunit of PI3K (PIK3CA) and the regulatory subunit of PI3K (PIK3R1) were found with a frequency of 17% and 18%, respectively. Less frequent are mutations in the downstream effector Akt (AKT1) and the gene encoding the component of the mTOR complex (MTOR), identified in 2% and 3% of diffuse gliomas, respectively. In addition, amplification of the gene encoding the epithelial growth factor receptor (EGFR), a potent activator of the PI3K-Akt-mTOR pathway, observed in approximately 50% of GBMs, further underscores the importance of this pathway in glioma pathogenesis [20][21][22]. As a result, targeting this signaling pathway is now considered a promising therapeutic strategy for treating gliomas, with several drugs currently in clinical trials [23][24]. **Table 2** summarizes the most studied mutations in gliomas with their relative frequency and etiopathogenetic roles. The frequency of each genetic variant is represented by a wide range because of the different grades and histological types of gliomas considered.

Table 2. Genes affecting GBM tumor growth with their related mutation frequencies.

Gene	Role in GBM Tumor Growth	Mutation Frequency	References
EGFR	**Amplification or mutation of EGFR leads to increased proliferation and invasion of tumor cells.**	**40–60%**	**[22][23][24]**
PTEN	**Loss of PTEN function promotes tumor cell survival and proliferation.**	**20–40%**	**[15][25][26]**
TP53	**Mutation of TP53 is associated with a more aggressive phenotype.**	**25–30%**	**[27][28][29]**
IDH1	**Mutation of IDH1 is associated with a better prognosis.**	**5–10%**	**[25][30].**
MGMT	**Methylation of the MGMT promoter is associated with increased sensitivity to chemotherapy and better patient outcomes.**	**30–40%**	**[31][32][33]**
VEGF	**Overexpression of VEGF promotes angiogenesis and tumor growth in GBM.**	**50–80%**	**[34][35][36]**
PDGF	**Overexpression of PDGF and its receptor promotes tumor cell proliferation and migration.**	**15–20%**	**[37][38]**
CDK4	**Amplification of CDK4 promotes cell cycle progression and tumor growth.**	**5–10%**	**[39][40]**

Abbreviations: OS, overall survival; PFS, progression-free survival; EGFR, epidermal growth factor receptor; PTEN, phosphatase and tensin homolog; TP53, tumor protein 53; IDH1, isocitrate dehydrogenase 1; MGMT, O6-methylguanine-DNA methyltransferase; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; CDK4, cyclin-dependent kinase 4.

Lei et al. developed a model using transcriptome data from two cohorts of patients with GBM. They identified 341 metabolic genes that showed significant differences between normal brain and GBM tissues, among which, 56 genes were found to be correlated with the patients' overall survival (OS). In the end, the model was constructed using a Lasso regression model with 18 genes and showed high accuracy in predicting the OS of the patients. In particular, the high-risk group of patients included in this model had a significantly shorter OS than the low-risk group in the training cohort ($p < 0.0001$) and in the independent external validation ($p < 0.001$). The study by Lei et al. showed that the prognosis of GBM is closely related to metabolic pathways and that, by using a model, it is possible to predict the prognosis of patients with GBM [41]. As is evident in contemporary neuro-oncology, searching for better diagnostic and therapeutic strategies for glioblastoma has led to a deep exploration of prognostic and predictive biomarkers. Increasingly, the evidence allows us to make a targeted choice regarding the type of treatment in relation to the molecular profile of the tumor.

In fact, these biomarkers may now influence the choice of therapeutic approach. For example, the presence of the mutated IDH1 gene is associated with a better prognosis, and patients carrying this mutation may benefit from more aggressive surgical resection aimed at maximal tumor excision [42].

MGMT promoter methylation status is another crucial biomarker. Glioblastoma patients with MGMT promoter methylation tend to respond better to chemotherapy [43], and knowledge of this status may influence the decision on the extent of surgical resection and the subsequent use of adjuvant therapies. The expression of certain molecular markers, such as EGFR, may also impact the choice of treatment. Elevated EGFR expression may suggest a more aggressive tumor phenotype, influencing the decision for a more extensive surgical approach or the inclusion of targeted therapies [44]. Montano et al. observed significantly longer OS in GBM patients with high levels of EGFR treated with total resection and standard radiochemotherapy involving temozolomide [45].

An innovative approach to glioblastoma can be achieved not only through research on new biomarkers but also through new treatment technologies.

Among the innovative avenues gaining traction is the study of PROteolysis TAgeting Chimeras (PROTACs) as potential game-changers in glioblastoma therapy [46].

PROTACs represent a paradigm shift in drug development, harnessing the cellular machinery to induce targeted protein degradation. In the context of glioblastoma, this approach holds the promise of selectively eliminating specific oncogenic proteins, thereby disrupting key pathways implicated in tumor progression. Yang et al. used a therapeutic nanosystem created by combining the BRD4-degrading PROTAC ARV-825 with a complex micelle. This micelle was able to penetrate the blood–brain barrier and target brain tumors. The drug released by this system shows antitumor effects by reducing cell proliferation, inducing apoptosis, and suppressing M2 macrophage polarization. These effects are achieved through the inhibition of IRF4 promoter transcription and the phosphorylation of STAT6, STAT3, and AKT [47].

To contextualize these advancements, a comprehensive understanding of the molecular landscape of glioblastoma subtypes is imperative. This molecular intricacy necessitates a tailored approach, recognizing that one-size-fits-all interventions may fall short in addressing the diverse manifestations of the disease.

Neurosurgical approaches and treatment modalities are intrinsically linked to the molecular profile of the glioblastoma, and understanding these connections is pivotal in optimizing patient outcomes. The choice between maximal safe resection, adjuvant therapies, and targeted interventions hinges on a nuanced appreciation of the specific molecular signatures at play [48]. Given the complex interplay between biomarkers, neurosurgical strategies, and other therapeutic options, researchers approach a future in which personalized and precise interventions will redefine the trajectory of glioblastoma management.

3. Overview of Treatments for Gliomas

Surgery has been an important component of the management of gliomas since the late 19th century. The first surgical resection was performed in 1884 by Victor Horsley, who removed a frontal lobe glioma from a patient who had been experiencing seizures. On 25 November 1884, Mr. Rickman J. Godlee performed the first recognized resection of a primary brain tumor. The surgery was performed at the Hospital for Epilepsy and Paralysis in London, UK. The patient died postoperatively from apparent meningitis, but postmortem examination revealed no residuals of the excised glioma [49].

In the following decades, surgical techniques have continued to evolve, with the development of new tools and methods to access and remove brain tumors.

In the early 20th century, Harvey Cushing became one of the most prominent neurosurgeons contributing significantly to glioma surgery. He is credited with developing the transsphenoidal approach, a minimally invasive method of accessing tumors located at the base of the skull. He also introduced the use of the operating microscope, which enabled more precise and controlled surgical resections [50].

In the mid-20th century, the use of neuroimaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) revolutionized the diagnosis and management of gliomas. These techniques enabled more accurate preoperative planning and intraoperative visualization of the tumor and surrounding brain tissue [51].

Many advances in glioma surgery have been made in recent decades, including the development of intraoperative neurophysiological monitoring, which enables the real-time monitoring of neurological function during surgery. This technique has helped to minimize the risk of neurological deficits associated with the surgical resection of gliomas [52].

In addition, image-guided navigation systems and endoscopic techniques have expanded the range of accessible tumors and increased the precision of surgical resection [53][54].

Despite these advances, surgical resection of gliomas remains a complex and challenging procedure, particularly for high-grade tumors located in critical or eloquent areas of the brain. Furthermore, for these cases, the development of new surgical tools, such as ultrasonic aspirators and lasers, has enabled more effective and efficient tumor removal. In recent years, interest has grown in the use of less invasive approaches, such as stereotactic radiosurgery and laser interstitial thermal therapy (LITT). These approaches may offer a less invasive alternative to surgical resection for certain types of tumors [55][56].

The primary goal of surgery is to safely remove as much of the glioma as possible while preserving neurological function. The extent of surgical resection is a major determinant of patient survival and functional outcomes [57].

Several factors should be considered when deciding on the optimal surgical approach to gliomas, including the location, size, and grade of the tumor, as well as the patient's age and general health status [58]. In general, surgical resection is recommended for patients with low-grade gliomas and for those with high-grade gliomas who can tolerate the procedure [59].

The goal of surgery for high-grade gliomas is typically to achieve a safe maximal resection (SMR), which involves removing as much of the visible tumor as possible while preserving neurological function [60]. The extent of resection is typically assessed using MRI and is classified as gross total resection (GTR), subtotal resection (STR), or partial resection (PR) [61][62].

Several studies have demonstrated that achieving a GTR is associated with improved OS and progression-free survival (PFS) in patients with high-grade gliomas. A meta-analysis of 37 studies found that patients who underwent GTR probably increased the likelihood of 1-year survival compared with STR by about 61% and increased the likelihood of 2-year survival by about 19% (GTR compared with STR at 1 year: RR, 0.62; 95% CI, 0.56–0.69; $p < 0.001$) [63].

However, achieving a GTR is not always possible or safe. Indeed, in the case of tumors located in critical or eloquent areas of the brain case, the goal of surgery may be to obtain a biopsy or to remove the tumor to alleviate symptoms. Increasing evidence has shown that the use of fluorescence-guided surgery, which involves the administration of a fluorescent contrast agent that accumulates in tumor tissue, can improve the extent of glioma resection and increase PFS in patients with high-grade gliomas [64][65]

These studies have demonstrated that patients undergoing fluorescence-guided surgery have a significantly higher rate of complete tumor resection than those undergoing conventional white-light surgery.

Another recent study investigated the impact of intraoperative MRI (iMRI) on the extent of resection and patient outcomes in glioma surgery [60]. The study found that the use of iMRI can improve the extent of tumor resection and increase PFS in patients with high-grade gliomas. In addition, the use of iMRI is associated with a lower risk of postoperative neurological deficits.

Advances in imaging technology have also led to the development of new tools for preoperative planning and intraoperative navigation. For example, diffusion tensor imaging (DTI) has been shown to provide valuable information on the location and orientation of white matter tracts in the brain, which can help surgeons avoid damaging these critical structures during tumor resection [66].

There has also been growing interest in the use of minimally invasive approaches for the treatment of gliomas, such as LITT and stereotactic radiosurgery (SRS). A recent study compared the effectiveness of LITT and SRS for the treatment of recurrent high-grade gliomas and found that both approaches were associated with similar rates of tumor control and survival [67]. The study suggested that LITT may be a less invasive alternative to SRS for certain types of recurrent gliomas.

In summary, recent studies have focused on refining surgical techniques for glioma resection and identifying the most effective surgical strategies to improve patient outcomes. Advances in imaging technology and the development of new

tools for operative navigation have also provided valuable insights into improving surgical precision and minimizing damage to surrounding brain tissue.

The Standard of Care for Gliomas

The standard of care for gliomas depends on various factors, including the grade of the tumor, the location and size of the tumor, and the patient's health status. However, the current standard of care typically involves a combination of surgery, radiation therapy, and chemotherapy.

Surgery is usually the first-line treatment and aims to remove as much of the tumor as possible while preserving critical brain functions. The extent of tumor resection is an important predictor of patient outcomes, and efforts to maximize resection while minimizing damage to the surrounding brain tissue have led to the development of various surgical techniques and technologies, such as intraoperative imaging and fluorescence-guided surgery [68].

Radiation therapy is typically used following surgery to kill any remaining tumor cells and prevent tumor regrowth. Various types of radiation therapy can be used for gliomas, including external beam radiation therapy, brachytherapy, and stereotactic radiosurgery [69]. The use of concurrent chemotherapy and radiation therapy has also been shown to improve outcomes in certain cases, such as for patients with high-grade gliomas [70].

Chemotherapy is usually reserved for cases where surgery and radiotherapy alone are not sufficient or in cases where the tumor recurs after initial treatment. Several chemotherapy agents can be used for gliomas, such as the DNA alkylating agents temozolomide (TMZ) and carmustine (BCNU) [71] TMZ is the most used drug in the treatment of high-risk gliomas after surgical resection. However, chemoresistance occurs in many patients, representing a substantial obstacle to successful therapy. A crucial role in chemoresistance is played by genes encoding for DNA repair proteins, such as DNA mismatch repair (MMR)-related proteins, O-6-methylguanine-DNA methyltransferase (MGMT), base excision repair (BER)-related proteins, AlkB homolog 2, alpha-ketoglutarate-dependent dioxygenase (ALKBH2), and proteins involved in homologous recombinational repair/non-homologous end joining (HRR/NHEJ), all of which correlate with TMZ efficacy [72].

Fortunately, today, it is possible to use a pharmacogenetically guided approach to predict the degree of sensitivity or resistance to a specific drug [73]. Although there are still barriers to overcome, pharmacogenetics, which studies responses to drug therapy based on a patient's genetic background, is very useful in personalizing drug therapy in all medical areas [73][74]. Regarding TMZ, pharmacogenetic testing based on the determination of MGMT methylation status is a useful tool for predicting responses to TMZ [71].

In 2016, Buckner et al. analyzed the clinical outcomes of 254 patients younger than 40 years randomized to receive radiotherapy (n. 128) or radiotherapy with chemotherapy (n. 126). The patients had astrocytoma, oligodendroglioma, or oligoastrocytoma and, after STR, were randomly separated into two treatment groups.

The results showed that, regardless of histologic type, patients who received radiotherapy with chemotherapy had a longer median OS than those who received chemotherapy alone (13.3 years vs. 7.8 years; $p = 0.003$). The two OS curves did not separate immediately but rather after one year in astrocytoma and about three years in oligoastrocytoma and oligodendroglioma.

The two curves, in all cases, remained well separated and distinct until the end of observation, about 12 years. The study showed that disease-free survival was also higher in patients who received chemotherapy and radiotherapy than those who received only radiotherapy, but the data are less reliable because these patients were promptly treated in various ways to improve prognosis [75].

The standard of care for gliomas is continuously evolving as new treatment options and strategies are developed. Recent studies have investigated the potential benefits of immunotherapy, targeted therapy, and other therapeutic approaches [76], and clinical trials are ongoing to determine the safety and efficacy of these new treatment options [77].

Table 3 gives a brief description of each of the treatments for gliomas.

Table 3. Treatments for gliomas.

Treatment	Description	Reference
Surgery	**First-line treatment to remove as much of the tumor as possible while preserving critical brain functions.**	**[68]**

Treatment	Description	Reference
LITT	A minimally invasive procedure that uses laser energy to heat and destroy tumor cells. It can be used as an alternative to traditional surgery or as a salvage treatment option for recurrent tumors.	[75]
FUS	A non-invasive procedure that uses focused ultrasound waves to heat and destroy tumor cells. It can be used as an alternative to traditional surgery or as a salvage treatment option for recurrent tumors.	[76]
Radiation therapy	Used following surgery to kill any remaining tumor cells and prevent tumor regrowth. Various types of radiation therapy can be used, including external beam radiation therapy, brachytherapy, and stereotactic radiosurgery.	[69]
Chemotherapy	Reserved for cases where surgery and radiation therapy alone are insufficient or for cases where the tumor recurs following initial treatment. Various chemotherapy agents can be used, such as temozolomide and carmustine (BCNU).	[71]
Concurrent chemotherapy and radiation therapy	Used in certain cases, such as for patients with high-grade gliomas, to improve outcomes.	[70]
Immunotherapy	Investigated as a potential treatment option for gliomas.	[77]
Targeted therapy	Investigated as a potential treatment option for gliomas.	[56]

Abbreviations: LITT, laser interstitial thermal therapy; FUS, magnetic resonance-guided focused ultrasound.

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