

Research progress in glioma-related epilepsy (Review)

XI CHEN*, JIN-ZHOU YANG*, LING-YUE KONG, ZHI-YU LI, FENG TANG and ZHI-QIANG LI

Brain Glioma Center, Department of Neurosurgery, Zhongnan Hospital of Wuhan University, Wuhan, Hubei 430071, P.R. China

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Abstract. Epilepsy is a frequently occurring complication in patients with gliomas that substantially impairs their quality of life. The onset of epilepsy in patients with gliomas is driven by multiple mechanisms, including tumour-induced compression of the peripheral neural network, the release of

neurotransmitters and inflammatory factors by tumour cells, alterations in the tumour microenvironment, and changes in gene expression. Collectively, these factors contribute to the abnormal excitability of local neurons, ultimately triggering seizures. Seizures occur in approximately 30 to 90% of patients with glioma, with a higher incidence observed in those with low-grade gliomas. The type and frequency of seizures are closely associated with tumour characteristics, such as tumour type, location, and growth rate. The current treatment strategies for glioma-related epilepsy (GRE) primarily involve antiepileptic drugs (AEDs) and tumour-directed therapies. While AEDs are effective in managing seizures, they show limited efficacy in some patients. Efforts have increasingly focused on identifying biomarkers and elucidating the molecular mechanisms underlying GRE, with the aim of developing more targeted and effective treatment approaches. The present review provides a comprehensive overview of the latest advancements in GRE research.

Correspondence to: Dr Feng Tang or Professor Zhi-Qiang Li, Brain Glioma Center, Department of Neurosurgery, Zhongnan Hospital of Wuhan University, 169 Donghu Road, Wuchang, Wuhan, Hubei 430071, P.R. China
E-mail: tf172126@163.com
E-mail: lizhiqiang@whu.edu.cn

*Contributed equally

Abbreviations: GRE, glioma-related epilepsy; AEDs, antiepileptic drugs; LGGs, low-grade gliomas; HGGs, high-grade gliomas; GBM, glioblastoma; BBB, blood-brain barrier; IDH, isocitrate dehydrogenase; MRI, magnetic resonance imaging; PET, positron emission tomography; MRS, magnetic resonance spectroscopy; CT, computed tomography; TME, tumour microenvironment; AMPAR, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NMDAR, *N*-methyl-D-aspartate receptor; KAR, kainite receptor; mGluR, metabotropic glutamate receptor; SLC7A11/xCT, solute carrier family 7 member 11; EAAT, excitatory amino acid transporter; IDHwt, IDH-wild-type; IDHmut, IDH-mutated; D-2HG, D-2-hydroxyglutarate; α -KG, α -ketoglutarate; TCA, tricarboxylic acid; GABA, gamma-aminobutyric acid; KCC2, K^+ -Cl⁻ co-transporter 2; MGMT, methylguanine methyltransferase; mTOR, mammalian target of rapamycin; ADK, adenosine kinase; ADA, adenosine deaminase; PTEN, phosphatase and tensin homologue; NF1, neurofibromin 1; TP53, tumour protein 53; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; BDNF, brain-derived neurotrophic factor; LE, leading edge; PFS, progression-free survival; EEG, electroencephalography; MEG, magnetoencephalography; ECoG, electrocorticography; LCM, lacosamide; LTG, lamotrigine; LEV, levetiracetam; TPM, topiramate; VPA, valproic acid; PER, perampanel; PHT, phenytoin; BRV, brivaracetam; CXB, celecoxib; SV2A, synaptic vesicle glycoprotein 2A; TMZ, temozolomide; PCV procarbazine, lomustine, and vincristine; DRE, drug-resistant epilepsy; BTRE, brain tumour-related epilepsy; AC, awake craniotomy; DES, direct electrical stimulation; EOR, extent of resection

Key words: glioma, epilepsy, seizure, antiepileptic drugs, anticonvulsants, treatment

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1. Introduction

Glioma-related epilepsy (GRE) refers to seizures that arise as a secondary symptom of gliomas. These seizures are not only a frequent complication during disease progression but also serve as the first noticeable sign of the condition (1). GRE is a variable and unpredictable disease closely related to the progression and recurrence of gliomas. Both seizures and antiepileptic drug (AED) treatment can cause cognitive impairment. The preoperative prevalence of anxiety or depression in adult patients with low-grade gliomas (LGGs) is markedly higher than that in patients without epilepsy (2). However, the interaction between AEDs and chemotherapy may have a direct impact on tumours, influencing the therapeutic effects on tumours, imposing a heavy economic and psychological burden on patients and their families, and significantly reducing the quality of life of patients (3,4). Therefore, understanding the pathogenesis and clinical features of epilepsy

is essential for the clinical management of brain tumours in affected patients. The present review summarises the findings of recent studies on this topic.

2. Clinical characteristics of GRE

Incidence of GRE. The occurrence of epilepsy in GRE is influenced by various factors such as tumour location, histological characteristics, the peritumoural microenvironment, and specific genetic changes. Seizures affect 30-90% of patients with glioma during the course of their disease (5), with approximately two-thirds manifesting at the onset and one-third emerging during treatment (6). Patients with diffuse LGGs often experience GRE in 60-90% of cases, whereas those with glioblastomas (GBMs) have seizures in 30-70% of cases (5). The cumulative incidence of brain tumour-related epilepsy (BTRE) has been shown to increase with tumour progression. Notably, ~50% of patients experience at least one seizure, with the proportion of cases increasing to 50-70% in the end-of-life phase (7). Isocitrate dehydrogenase 1 (IDH1) mutation, p53 overexpression (>40%), younger age (<38 years), male patients, cortical involvement, and large tumour volume are associated with a higher incidence of preoperative GRE in LGGs (3,4,8). A total of 75% of patients with grade 2 gliomas (astrocytomas or oligodendrogliomas) with IDH1/2 mutations and 25% of those with IDH wild-type (IDHwt) GBMs suffer from seizures, and patients with secondary GBMs carrying IDH1 mutations have an increased likelihood of seizures (8,9). Over 50% of patients exhibit preoperative GRE resistance, and postoperative seizure remission rates range from 43 to 87%, depending on the extent of resection (EOR). Subtotal resection, older age (>45 years), generalised seizures, shorter history of epilepsy (<1 year), and low Ki-67 expression are predictors of favourable postoperative seizure control (3,10). Notably, 70% of patients with GBMs and preoperative GRE are seizure-free early after tumour resection, and near-total resection remains a predictor of postoperative seizure control. In addition, GRE recurrence after resection of high-grade gliomas (HGGs) is usually associated with tumour recurrence/progression (3). Preoperative GRE is generally associated with prolonged overall survival in patients with LGG and GBM (3).

Clinical behaviour. The clinical manifestations of GRE predominantly encompass focal awareness seizures, focal impaired awareness seizures, generalised tonic-clonic seizures, and focal-to-bilateral tonic-clonic seizures (11). Research has highlighted the distinct seizure patterns in low- and high-grade gliomas. In patients with LGGs, 69.7% exhibited focal-to-bilateral tonic-clonic seizures. By contrast, HGGs were more commonly associated with focal motor-aware seizures (38%) or focal-to-bilateral tonic-clonic seizures (40%) (12). Secondary generalised epilepsy is common in patients with LGGs (40%), whereas simple partial seizures predominate in patients with HGGs (38.3%) (13). However, research suggests that LGGs frequently cause functional localisation-related focal seizures (45-95%) (4). HGGs are more frequently associated with generalised seizures and status epilepticus and are often triggered by factors such as medication non-adherence or infections (14-16). Tumour-associated status epilepticus typically manifests as complex focal seizures (74%) (17).

Seizure semiology is location-dependent; for example, precentral gyrus lesions cause focal motor seizures, whereas left frontal or right temporal lesions lead to seizures with or without consciousness disturbances (18). Patients may also experience additional symptoms such as visual disturbances, changes in mental status, or signs of elevated intracranial pressure, including headaches and nausea. Additionally, patients may exhibit postictal phenomena such as Todd's paralysis and psychosis (19).

Diagnosis. Tumour-related epilepsy is characterised by the occurrence of at least one seizure resulting from a brain abnormality, such as a glioma (20). The diagnosis of GRE requires confirmation of both glioma and epilepsy, as well as evidence of their correlation (3). Magnetic resonance imaging (MRI) is crucial for preoperative diagnosis, and is supplemented by magnetic resonance spectroscopy (MRS), computed tomography (CT), and positron emission tomography (PET). For cortical tumours, diffusion tensor imaging and functional MRI can help localise functional areas and track fibres (3). Notably, seizure history duration is correlated with intratumoural T1-weighted hyperintensity, styloid signs, and regional atrophy in angiocentric gliomas (21). Definitive glioma diagnosis requires surgery/biopsy and pathological evaluation, including histopathological and molecular analyses, with an emphasis on the IDH1 mutation status (3,22). Patients with IDH1-mutated gliomas, which are common in LGGs (>80%) and secondary GBM (73%), are more prone to preoperative seizures than those with IDH1 wild-type (IDH1wt) gliomas (22-24). Previous studies have used MRI-based radiomics to identify the IDH mutation status (25) and the occurrence of GRE (26,27). A research team recently explored the potential connection between the two to develop a novel radiomics approach that reduces the risk of overfitting, enhances model performance, and may be used to identify valuable generalised biomarkers for various clinical issues (28). Seizures are defined as transient symptoms of abnormal neuronal activity (9). For patients with glioma, epilepsy history and seizure signs should be documented, with a diagnosis typically made after a single seizure and classified according to the 2017 International League Against Epilepsy guidelines (3,9).

3. Underlying mechanisms in GRE

The mechanisms underlying GRE are multifactorial and involve tumour-related changes and the tumour microenvironment (TME) (Fig. 1). Seizure mechanisms vary between LGGs and HGGs and may differ between preoperative and postoperative seizures, with surgical complications potentially contributing postoperatively (4,29). Regardless of the glioma grade, epilepsy onset and tumour progression may share a dual relationship. Neuronal hyperexcitability and glutamate release during seizures can promote tumour growth, indicating common underlying mechanisms (4,30). The current research on GRE mechanisms are subsequently summarised and reviewed.

Tumor characteristics. GRE is affected by the mechanical effects of the tumour, including its location, size, and growth rate. Cortical tumours, particularly in the frontal, temporal,

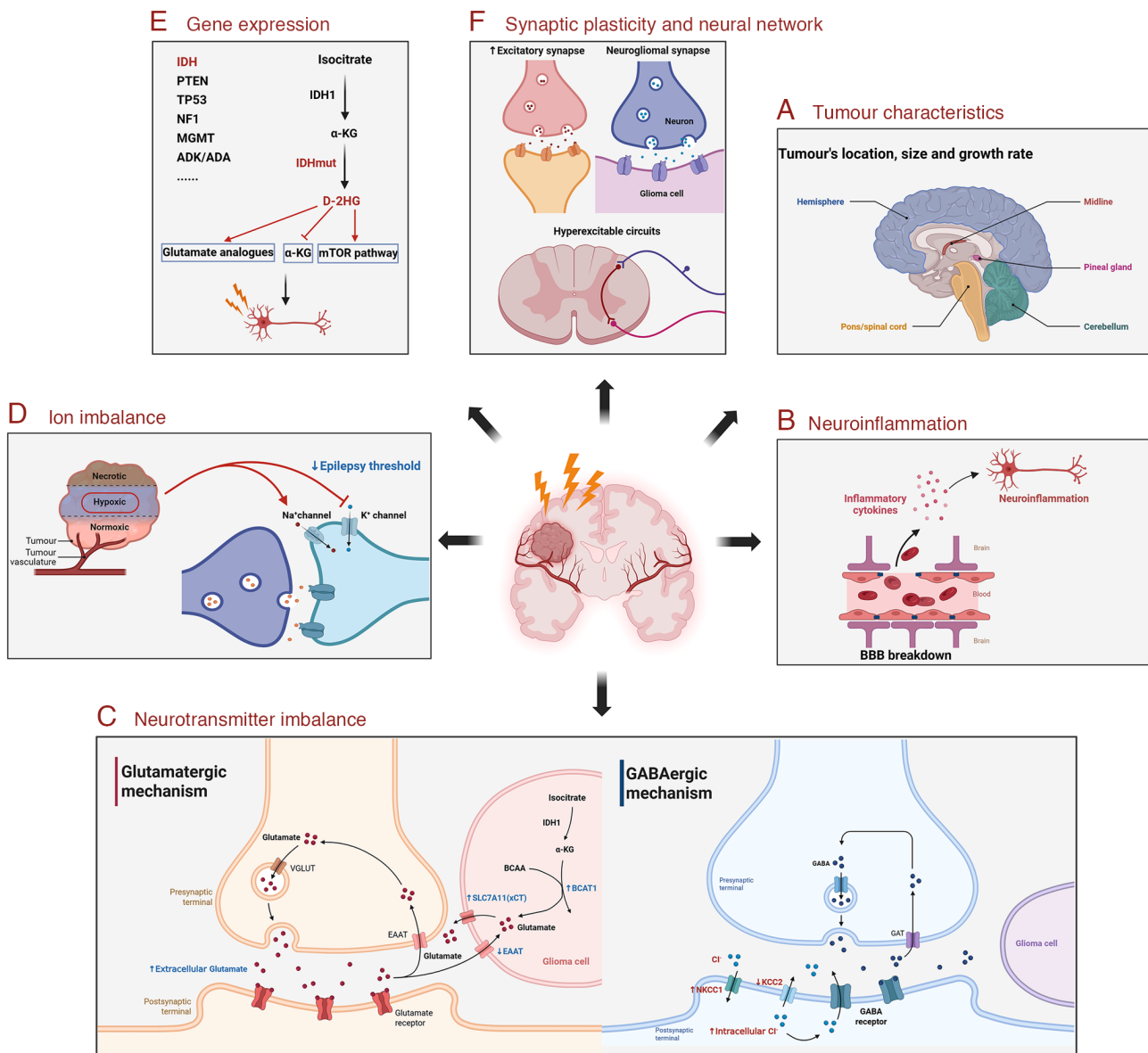


Figure 1. Underlying mechanisms in GRE. The mechanisms underlying GRE are multifactorial and involve tumour-related changes and the TME. (A) GRE is affected by the tumour characteristics, including its location, size, and growth rate. (B) Gliomas disrupt the BBB and cause neuroinflammation to induce seizures. (C) Excitation-inhibition imbalance of glutamate and GABA in the TME induces neuronal excitation and seizures. (D) Abnormal Na^+ and K^+ concentrations in the TME reduce seizure thresholds. (E) The aberrant expression of enzymes and proteins in the TME drives GRE through changes in the surrounding neuronal environment. (F) Gliomas can form neuroglial synapses, promote excitatory synapses and hyperexcitable circuit formation, thereby mediating seizures. GRE, glioma-related epilepsy; TME, tumour microenvironment; BBB, blood-brain barrier; VGLUT, vesicular glutamate transporter; EAAT, excitatory amino acid transporter; IDH, isocitrate dehydrogenase; α -KG, α -ketoglutarate; BCAA, branched-chain amino acids; BCAT1, branched chain amino acid transaminase 1; SLC7A11/xCT, solute carrier family 7 member 11; GABA, gamma-aminobutyric acid; GAT, GABA transporter; NKCC1, Na^+ - K^+ - 2Cl^- co-transporter 1; KCC2, K^+ - Cl^- co-transporter 2; PTEN, phosphatase and tensin homologue; TP53, tumour protein 53; NF1, neurofibromin 1; MGMT, methylguanine methyltransferase; ADK, adenosine kinase; ADA, adenosine deaminase; IDHmut, IDH-mutated; D-2HG, D-2-hydroxyglutarate; mTOR, mammalian target of rapamycin. The figure was created using BioRender (<https://www.biorender.com/>).

and parietal lobes (18,31), are significantly related to seizures, while deep-seated or infratentorial tumours are less frequently associated with epilepsy (4). LGGs involving the neocortex, especially oligodendrogliomas (10), have a higher seizure risk, while GBMs are associated with a lower incidence of epilepsy owing to shorter survival times and fewer epileptogenic origins (32,33). For subcortical and cortical brain regions, a significantly decreased risk has been reported in tumours within the left frontomesial and dorsal voxels (A3C1S1), and an increased seizure risk has been found in tumours located in the left supramarginal and posterior insular voxels (A4C2S3) (34).

Tumour volume also plays a role: Smaller HGGs exhibit a higher propensity to present with seizures, whereas larger LGGs are more epileptogenic. Slow-growing tumours, such as LGGs, are more prone to epilepsy due to complex cellular reorganisation and vascularisation, unlike fast-growing HGGs, in which seizures are often triggered by necrosis or bleeding (18,33). Additionally, specific glioma cell subpopulations, such as astrocyte population C in GBM models, may contribute to epileptogenicity through synaptic gene expression and tumour progression (35). Another study showed that patients with lower anaplastic oligodendroglioma/anaplastic

oligoastrocytoma exhibited more frequent instances of post-operative seizures (36).

Neuroinflammation. Gliomas disrupt the blood-brain barrier (BBB), causing vasogenic oedema, inflammation, hypoxia, and necrosis. These changes alter the TME, leading to sodium-calcium imbalances, abnormal ion concentrations, acidosis, and glutamate pathway activation, all of which contribute to neuronal hyperexcitability and seizures (8,18,37,38). Inflammatory reactions and reactive astrogliosis, which are characteristic of the GBM micro-environment, play critical roles in BBB injury-induced epileptogenesis (37). Research using translocator protein-PET imaging have shown higher contralateral hemisphere neuro-inflammatory signals in individuals with persistent seizures, which are associated with shorter survival (39). Despite the immunosuppressive TME, pro-inflammatory cytokines [such as interleukin (IL)-1 β , IL-6, and TNF- α] and chemokines play roles in tumour progression and seizures (37,38). IL-6, in particular, promotes glioma cell proliferation and invasion, while contributing to seizure development (40-44). Recent findings have suggested that IL-6 levels predict poor post-resection seizure control in patients with LGGs (45). Over the past 20 years, studies have shown the presence of cytomegalovirus (CMV) in GBMs (46), and the degree of infection has been shown to be related to the survival rate of patients (47,48). Valganciclovir treatment can significantly prolong survival in patients with GBM (49-51). Recent research has confirmed that high CMV infection levels can promote epileptic seizures through a pro-inflammatory microenvironment (52).

Neurotransmitter imbalance

Glutamatergic mechanism. Glutamate, the primary excitatory neurotransmitter, plays a key role in BTRE through aberrant signalling in gliomas and peritumoural tissues (53). Elevated glutamate levels (>100 μ M) in these regions promote tumor progression, cognitive impairment, epilepsy, and neurodegeneration by hyperactivating α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA receptors)/N-methyl-D-aspartate receptors (NMDARs), causing neuronal hyperexcitability and excitotoxic cell death, while also stimulating glioma proliferation and invasion (1,4,6). Glutamate imbalance arises from disrupted regulation by glial cells, which normally maintain homeostasis via proteins such as solute carrier family 7 member 11 (SLC7A11 or xCT), excitatory amino acid transporter 1 (EAAT1), and excitatory amino acid transporter 2 (EAAT2). In gliomas, high xCT and low EAAT expression lead to excessive glutamate release, triggering seizures (1,54). xCT expression was not elevated in the peri-pain region of human tumour samples; however, in a mouse xenograft tumour model, primary central nervous system (CNS) tumours were found to release massive amounts of glutamate due to high xCT expression, thereby triggering epileptic activity in the peritumoural region (54). Notably, IDHwt HGGs exhibit heightened activity of the Xc-cysteine glutamate transporter system in comparison with IDH-mutated (IDHmut) diffuse low-grade gliomas (DLGGs) (55). This indicates distinct mechanisms underlying glutamatergic-mediated epileptogenicity in these tumour types, wherein glutamate release through the Xc-cysteine glutamate transporter

system from HGGs plays a key role, whereas in DLGGs, epileptogenicity is driven by extracellular accumulation of D-2-hydroxyglutarate (D-2HG), which acts as a glutamate receptor agonist (4). While xCT is highly expressed in tumour cells, EAAT1 and EAAT2 are significantly downregulated in gliomas across cell lines, animal models, and human GBMs (54), causing impaired reuptake of glutamate from the extracellular space (1). Additionally, hypoxia-induced overexpression of branched chain amino acid transaminase 1 further elevates glutamate levels by producing glutamate from branched-chain amino acids, exacerbating extracellular glutamate accumulation and epileptogenicity (56,57).

Extracellular glutamate activates glutamate receptors on tumour cells (autocrine) or neighbouring neurones and astrocytes (paracrine). The glutamate receptors include ionotropic [AMPA receptors, kainite receptors (KARs), and NMDARs] and metabotropic glutamate receptors (mGluR). Ca²⁺-permeable AMPARs, which are frequently expressed in gliomas, promote tumour proliferation and migration (58), and their antagonist perampampanel (PER) may suppress seizures and tumour growth (1). KARs may also contribute to GRE, with astrocyte-released glutamate specifically activating GluK1-containing KARs in interneurons (59). NMDARs, particularly the NR2B subunits, are highly phosphorylated in periglioma neurones, enhancing Ca²⁺ influx and neuronal overexcitation (60), which may be counteracted by PER by reversing GluN2B phosphorylation (1). mGluRs 1-8 have been less extensively studied but may influence glioma progression. For example, mGluR1/5 have been shown to promote tumorigenesis (1); low levels of mGluR3 have been shown to be correlated with longer survival (61,62); and mGluR4 signalling may affect tumour growth (63). However, no evidence linking mGluRs to glioma-associated seizures has been reported to date.

GABAergic mechanisms. Gamma-aminobutyric acid (GABA), a key inhibitory neurotransmitter, plays an important role in epileptogenesis. Peritumoural structural and functional changes reduce GABAergic inhibition and decrease inhibitory interneurons and synapses in pyramidal cells, leading to excitation-inhibition imbalances and seizures (4,8). Dysregulated chloride transporters [Na⁺-K⁺-2Cl⁻ co-transporter 1 upregulation and K⁺-Cl⁻ co-transporter 2 (KCC2) downregulation] in peritumoural neurones increase intracellular chloride levels, causing GABA receptor activation and reducing chloride efflux and neuronal excitation (64-66). Glutamate in the TME further reduces KCC2 expression. Antagonists such as picrotoxin and gabazine suppress epileptic discharges, thus confirming this mechanism (66). Additionally, proteolytic enzymes released by tumours disrupt neural networks, reducing GABAergic inhibition, whereas an acidic hypoxic environment further impairs GABA signalling and increases seizure susceptibility (18,67).

Ion imbalances. Ion imbalances contribute to tumour progression and seizures. The acidic, hypoxic environment around astrocytomas activates voltage-gated sodium channels and inhibits inward-rectifying potassium (KIR) channels, lowering the seizure threshold (67). BBB disruption and serum exposure downregulate astrocyte Kir4.1 channels, disrupting K⁺ homeostasis (37). Additionally, immunoglobulin superfamily

member 3, a mediator of glioma progression, interacts with Kir4.1 to impair K⁺ buffering in peritumoural areas and increase extracellular K⁺ levels and neuronal excitability, which can lead to seizures (68).

Gene expression. The aberrant expression of enzymes and proteins in the TME drives GRE through changes in the surrounding neuronal environment. IDH1 mutations (60-72), 1p/19q co-deletion (73), and high Ki-67 expression have been linked to seizure occurrence (73,74), whereas 1p/19q loss of heterozygosity, p53 overexpression (<40%), and Ki-67 loss are correlated with reduced seizure frequency and remission (8). In addition, methylation of the methylguanine methyltransferase (MGMT) repair protein promoter can significantly increase the risk of postoperative epileptic seizures (75,76). In the following sections, the changes in gene expression that influence GRE are detailed.

IDH is a crucial enzyme involved in cellular metabolism, particularly in the tricarboxylic acid (TCA) cycle. It catalyses the conversion of isocitrate to α -ketoglutarate (α -KG), generating NADH or NADPH. IDH has three primary isoforms: IDH1, IDH2, and IDH3. Mutations in IDH1 and IDH2 are frequently observed in certain cancers, including GBM (77,78) and acute myeloid leukaemia (79-81). These mutations alter the enzyme activity, leading to the production of the onco-metabolite 2-HG, which contributes to tumourigenesis and progression (14). Notably, IDH mutations are strongly associated with GRE.

According to the Ivy Glioblastoma Atlas Project (<http://glioblastoma.alleninstitute.org>), IDH1 expression is low at the tumour leading edge (LE) but elevated in the tumour core, whereas IDH2 is upregulated in regions of microvascular proliferation (82). Additionally, IDH3A has emerged as a potential risk gene for epilepsy (83,84). IDH mutations are predictive of seizure occurrence and prognosis in adults with lower-grade gliomas (85). While 18-34% of patients with IDH1wt GBM experience preoperative seizures, this rate increases to 59-74% in patients with IDH1mut GBM (69). Multiple studies have shown that IDH1 mutations increase the risk of developing GRE before, during, and after surgery (14,22,69,86,87). However, some studies have suggested that IDH mutations are not related to postoperative epilepsy or are negatively correlated with postoperative seizure control (75,87,88). Similar predictive effects have been attributed to IDH2 mutations in studies on preoperative epilepsy (5,23,71). In WHO grade II and III gliomas, IDH1 mutations were revealed to be linked to epilepsy; however, this association was absent in patients with GBMs (14).

Among IDHmut lower-grade gliomas, seizure control and prognosis vary among subgroups. Grade 3 tumours are associated with improved seizure control throughout the disease course, and seizure freedom post-surgery and adjuvant therapy is correlated with longer progression-free survival (PFS), regardless of tumour grade (89). Notably, current evidence suggests that IDHwt and IDHmut genotypes differentially affect tumour metabolism and consequently have different pathological mechanisms that cause excitability in peritumoural neuronal populations. IDHwt tumours upregulate glycolysis and subsequently release excess glutamate and lactate into the peritumoural environment, both of which

can mediate hyperexcitability in surrounding neurons (90). The increased seizure risk in IDHmut gliomas may stem from the accumulation of D-2HG, an abnormal metabolite detected at elevated levels using MRS in IDHmut gliomas (91). Mechanistically, IDH1mut glioma cells produce D-2HG instead of α -KG, with D-2HG concentrations 100-300 times higher than that in normal tissues (14). Structurally similar to glutamate, D-2HG binds NMDARs, impairing glutamate clearance and increasing neuronal excitability (92,93). Furthermore, D-2HG competitively inhibits α -KG (94,95), an antiepileptic metabolite, and induces hypermetabolic changes in peritumoural neurones, including upregulated lactate dehydrogenase A, TCA cycle dysfunction, and activation of the mammalian target of rapamycin (mTOR) pathway, a known pro-epileptogenic mechanism (96). Preclinical studies have demonstrated that mTOR inhibitors, such as rapamycin, reduce neuronal excitability and suppress seizures (30,97,98), highlighting mTOR as a potential therapeutic target for GRE.

Adenosine, an endogenous regulator of the mammalian brain, plays a critical role in neuroprotection and seizure suppression (99,100). Adenosine levels increase during seizure activity (101), making the adenosinergic system a promising therapeutic target for epilepsy (102). Adenosine homeostasis is maintained through its metabolic clearance by adenosine kinase (ADK), which converts adenosine into 5'-adenosine-monophosphate, and adenosine deaminase (ADA), which deaminates adenosine to inosine (103). Notably, ADA levels increase during pentylentetrazole-induced seizures, as demonstrated in adult zebrafish models (104). Studies have shown that both ADA and ADK are upregulated in the peritumoural tissues of glioma patients with epilepsy in comparison with those without epilepsy, suggesting their involvement in glioma progression and epileptogenesis (105,106). Elevated ADA and ADK expression may lead to excessive adenosine degradation, reducing its inhibitory effects and contributing to seizure activity (105,106). Additionally, astrocytomas with high ADK expression exhibit lower extracellular concentrations of inhibitory neurotransmitters and increased aquaporin-4 levels, further decreasing the seizure threshold (107,108). Since ADK inhibition effectively treats epilepsy in animal models (109), the development of suitable experimental models for tumour-associated epileptogenesis is essential for evaluating the potential of adenosine augmentation therapies in patients with brain tumours and epilepsy.

Mutations in the tumour suppressor genes phosphatase and tensin homologue (*PTEN*) (110,111), neurofibromin 1 (*NFI*) (112-114), and tumour protein (*TP53*) (115-117) are frequently observed in primary GBM. These mutations disrupt downstream signalling pathways and play critical roles in tumourigenesis. These genes are also closely associated with epilepsy. Previous experimental studies have targeted these genes for deletion or mutation in rodent models, successfully generating reliable epileptogenic tumours (118,119).

Physiologically, *PTEN* inhibits the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mTOR pathway. However, mutations or deletions in *PTEN* in GBM have been shown to lead to the disinhibition of PI3K/Akt and hyperactivation of mTOR signaling (120,121). These alterations are associated with poor GBM prognosis and have been implicated in epilepsy syndromes. Conditional deletion of

PTEN in mice was shown to result in spontaneous seizures, with post-mortem analyses revealing features consistent with temporal lobe epilepsy (122-126).

NFI functions as a critical regulator of the Ras signalling pathway. It exerts its inhibitory effects by enhancing the GTPase activity of Ras, thereby converting active guanosine triphosphate-bound Ras into its inactive guanosine diphosphate-bound form (112,113). Mutations that impair the function of the *NFI* gene, which are often observed in GBM, disinhibit the Ras/MAPK pathway, resulting in hyperactivation of the mTOR pathway and uncontrolled cell proliferation, thereby promoting cancer development. In mouse models, *NFI* knockout was demonstrated to be associated with a reduced latency period before the onset of epilepsy and more severe seizures (127). Similarly, in patients with neurofibromatosis type 1, *NFI* mutations are correlated with increased seizure frequency (128). TP53 (p53) mutations disrupt the functioning of p53 in promoting cell cycle arrest, senescence, and apoptosis, enabling the uncontrolled proliferation of damaged cells (129). The gain-of-function mutant form of p53 is frequently overexpressed in GBM cells. This mutant p53 promotes invasive signalling pathways by increasing the expression of receptor tyrosine kinases (RTKs), including MET and epidermal growth factor receptor (EGFR) (116). Research has shown that the amplification of the RTK proto-oncogene MET can best predict intraoperative epileptic seizures (130). In addition, the high expression of platelet derived growth factor receptor- α can aggravate epilepsy, while inhibiting the RTK signalling pathway can reduce epileptic seizures (131), and tumour-related changes in EGFR may also increase the risk of intraoperative epilepsy and postoperative epilepsy (36,132). One possible mechanism is that activation of the RTK signalling pathway promotes the release of glutamate and enhances the excitability of the TME, thereby inducing epilepsy (133,134). Increased p53 levels, particularly in the hippocampal region, have been detected in both experimental models and clinical specimens obtained from individuals with drug-resistant temporal lobe epilepsy (135,136). In the context of seizures, high p53 expression has been linked to increased apoptosis and neuronal death, contributing to excitability imbalances (135). Furthermore, elevated p53 levels were revealed to be associated with epileptogenic GBMs (137). Additionally, the p53 signalling pathway has been demonstrated to be associated with drug resistance in epilepsy in diffuse astrocytoma and oligodendroglioma, but through a mechanism distinct from that of p53-ATRX (138). Notably, TP53 mutations alone are insufficient to drive GBM formation; they require concurrent mutations in other genes such as PTEN to promote GBM progression (139).

As a tumour suppressor gene, promoter methylation of MGMT is an important molecular feature of gliomas. In the presence of IDH mutations, the methylation frequency of the MGMT promoter increases significantly: This phenomenon is particularly common in oligodendrogliomas and astrocytomas, with approximately 35-45% of gliomas exhibiting MGMT promoter methylation (140).

An increase in the chromosome 7 arm (7⁺) and the loss of the chromosome 10 arm (10⁻) are typical features of IDHwt epileptic LGG. This 7⁺/10⁻ chromosomal abnormality pattern is associated with the malignant progression of GBM: 59% of patients with GBMs carry such variations, and their survival

rate is significantly reduced (141). Subsequent studies have shown that gene expression on chromosome 10, including the expression of key genes encoding MGMT, PTEN, and vimentin (Vim), is generally downregulated in epileptic gliomas (142). Moreover, Vim is also a biomarker of epilepsy (76). Notably, MGMT promoter methylation not only affects the biological behaviour of tumours, but may also significantly increase the risk of postoperative epileptic seizures through epigenetic regulation (36,75,76). However, the specific molecular mechanisms underlying this phenomenon remain unclear.

One study investigated the spatial distribution and expression patterns of 358 clinically validated human epilepsy genes within the GBM transcriptome and compared them with datasets from non-tumour adults and developing cortices. Nearly half of these genes, including the dosage-sensitive genes strongly linked to monogenic epilepsy, were strikingly enriched and aberrantly regulated at the LE of the tumour. These findings support the complex epistatic basis of peritumoural epileptogenesis. The surrounding hyperexcitability, driven by intricate patterns of proepileptic gene expression, may explain the limited efficacy of narrowly targeted anti-seizure medications and the persistence of epilepsy even after tumour resection. This may also clarify why not all brain tumours provoke seizures (82). Additionally, 52 genes exhibiting differential expression in patients with lower-grade gliomas and seizures were identified (104). These genes span a wide range of biological functions, underscoring the complexity of the molecular processes underlying glioma-associated seizures. Differential expression analysis revealed that gliomas that induce epileptic activity are closely associated with genes involved in neuronal development. The key implicated pathways include the RhoGDI, Semaphorin Neuronal Repulsive, and the Ephrin B signalling pathways (143). Drug-resistant epilepsy (DRE) is associated with somatic gene mutations. In comparison with patients showing drug reactivity, patients in the DRE group exhibited mutations in glutamate receptor genes (GRIA1, GRIK5, GRIN2B, or GRIN2C), ATRX, and glutamate-S-transferase genes (144). Understanding the genetic and molecular characteristics of gliomas and their relationship with seizures can significantly reduce the substantial morbidity and mortality associated with these conditions.

Synaptic plasticity and neural network. Gliomas promote axonal branching and synapse formation, increasing neuronal excitability and seizure risk (145,146). They form microtubules resembling neuronal axons and dendrites, enabling functional glial synapses mediated by AMPARs (38). Glioma-derived prothrombin also facilitates excitatory synapse formation in the peritumoural cortex (96). Elevated MMP-9 levels around tumours convert pro-brain-derived neurotrophic factor (BDNF) to mature BDNF, activate tropomyosin receptor kinase B, and foster hyperexcitable circuits (146,147). Chronic NMDAR activation and increased extracellular glutamate levels further exacerbate these effects along with abnormal neuronal structures and impaired synaptic plasticity, thereby contributing to epileptogenesis.

Although it shows major structural and molecular changes, epilepsy is fundamentally a network disorder. Functional MRI, electroencephalography (EEG), and magnetoencephalography (MEG) have revealed disrupted connectivity networks in brain

tumours (148-156), with preoperative seizures linked to suboptimal network topology (157). In summary, GRE arises from diverse mechanisms that reflect pathological heterogeneity and complex molecular interactions. Understanding these pathways is crucial for developing targeted therapies.

4. Treatment of GRE

Treatment with AEDs. AED regimens should be promptly initiated upon seizure diagnosis in patients with gliomas. The guiding principles of these regimens include avoiding liver enzyme-inducing AEDs in patients undergoing chemotherapy and adopting individualised monotherapy with adequate dosing and duration (3,158). For cases involving preoperative seizures, rapid-acting AEDs without slow titration are preferred.

Conversely, in postoperative cases, AEDs with versatile formulations (including injections, tablets, and oral solutions) and minimal interactions with anti-infectives, glucocorticoids, and haemostatics are recommended for long-term use (159). Given the strong correlation between glioma progression and epileptic seizures (160), AEDs with antitumour effects are usually the first choice for GRE.

Usage principles of AEDs. AEDs are commonly used to manage seizures in patients with glioma. An ideal AED should effectively control seizures, minimise side effects, and potentially enhance the efficacy of chemotherapy while protecting healthy brain tissue. Currently, AED selection is not directly guided by tumour histology, location, WHO grade, or molecular markers, although non-enzyme-inducing AEDs are preferred (30,38). Commonly used non-enzyme-inducing AEDs include lacosamide (LCM), lamotrigine (LTG), levetiracetam (LEV), topiramate (TPM), valproic acid (VPA), and zonisamide (38). Evidence-based guidelines recommend LEV and VPA as first-line treatments for GRE, with LEV exhibiting superior efficacy and comparable tolerability in comparison with VPA (3,158). Phenytoin (PHT) and pregabalin monotherapies may also be used for GRE, although they exhibit lower efficacy than LEV (161). LEV is particularly effective for focal and bilateral tonic-clonic seizures and is often combined with antitumour therapies due to its additional benefits. Mechanistically, LEV interacts with synaptic vesicle glycoprotein 2A (SV2A), modulating the release of neurotransmitters and strengthening GABA-mediated inhibitory signaling (96). Its analogue, brivaracetam (BRV), has a higher SV2A affinity. LEV also enhances p53-mediated MGMT inhibition, sensitising GBM cells to temozolomide (TMZ), especially when combined with interferon- α (8,96,162). Previous research has suggested that LEV may improve overall survival, potentially by modulating the glutamate-to-GABA ratio (1).

Similar to LEV, VPA exhibits antitumour effects mediated through mechanisms such as the upregulation of BDNF and activation of the ERK/Akt, Akt/mTOR, and Wnt signalling pathways (96). VPA may enhance the survival of patients receiving TMZ therapy (8). Although adjuvant VPA with chemoradiotherapy improves the survival of patients with GBMs, this benefit has not been observed in patients with grade II gliomas (1). For patients with inadequate seizure control after monotherapy, combination therapy with LEV, VPA, or PHT may be considered (3,161). However, LEV

or VPA should not be used solely for non-seizure-related purposes in patients with glioma (3). In cases of poor seizure control with LEV or VPA, TPM, a KAR inhibitor with antitumour effects, is an alternative option (1).

A previous study on LCM monotherapy reported seizure control rates of 65% at 3 months and 55% at 6 months. LTG and LCM exhibited comparable efficacy in reducing seizure frequency over 1 year (30). However, LTG is limited by its oral-only formulation, slow titration requirements, and potential interactions with antineoplastic agents (38).

Talampanel, a noncompetitive AMPAR antagonist, may reduce seizures and tumour growth. Although its combination with radiation and TMZ has been shown to improve median survival, talampanel alone has no significant antitumour effects (1,30). PER, another noncompetitive AMPAR antagonist, has a longer half-life and superior BBB penetration. Approved for focal and generalised epilepsy, PER is effective, safe, and well-tolerated in BTRE (163,164). It inhibits glioma cell proliferation, migration, and invasion, while reducing extracellular glutamate levels, although the precise mechanisms remain unclear (96). One case report described a GBM patient achieving 18 months of seizure freedom and survival with PER treatment (1,6). Cenobamate, which was recently approved for the treatment of focal epilepsy, has not yet been evaluated for GRE (38).

Notably, approximately one-third of patients with glioma continue to experience seizures despite AED monotherapy and dose escalation, although evidence regarding optimal AEDs for treatment-resistant cases is lacking (96). Patients with HGGs often require multiple AEDs for seizure control (18). Studies have suggested that LCM add-on therapy shows efficacy and tolerability comparable to those of LTG in patients with glioma (18,30). LCM, which is available intravenously, allows rapid titration, has minimal drug interactions, and causes fewer neuropsychiatric side effects, making it a preferred adjunct (38). Combining AEDs with different mechanisms of action, such as LEV with LCM, PER, or VPA, is recommended for multimodal therapy (9). A prior small-scale study reported a seizure remission rate of 57% with PER, add-on therapy (30). LEV combined with VPA was revealed to be particularly effective for seizure control (18). In a retrospective study, BRV add-on therapy reduced monthly seizures from seven to two (30). For status epilepticus in patients with brain tumours, first- (such as diazepam and midazolam) and second-line treatments (such as LEV, PHT, and VPA) should be initiated promptly (30).

Drug-resistant seizures occur in ~15% of patients with GBM and ~30% of patients with LGG (9,74). IDHmut gliomas exhibit a significantly higher trend toward pharmacoresistant seizures, whereas pharmacoresistance is rare in IDHwt tumours (165). Patients with IDHmut exhibited a higher 4-year cumulative incidence of DRE (18%) in comparison with patients with IDHwt (11%), although IDH mutations are not significantly associated with drug resistance (9). For patients with GRE who are resistant to other AEDs, LCM offers improved efficacy and fewer side effects (3).

Adverse effects of AEDs. Adverse effects are the leading causes of AED treatment failure and often limit effective dosing and patient adherence. Both first- and second-generation AEDs

exhibit similar rates of intolerable side effects. Patients with brain tumours are particularly vulnerable to adverse neurological effects, including cognitive decline, depression, anxiety, dizziness, headache, nausea, and somnolence, of which cognitive impairments are more common with first-generation AEDs (9,30). First-generation AEDs (such as carbamazepine, PHT, and VPA) often cause drug interactions such as accelerating dexamethasone metabolism. VPA is associated with coagulopathy, particularly thrombocytopenia, but it rarely causes adverse psychiatric effects. By contrast, second-generation AEDs, such as LEV, have minimal drug interactions and may improve neurocognitive function. However, LEV is associated with psychiatric side effects such as depression, agitation, or psychosis, especially in patients with frontal lobe tumours (9,30,38).

In patients with glioma undergoing chemoradiotherapy, the concomitant use of AEDs may have both beneficial and adverse effects. Although the combination of AEDs and chemotherapeutic agents can prolong patient survival, they carry potential risks, including thrombocytopenia and increased drug toxicity (166,167). Clinical studies have demonstrated that the combination of VPA and TMZ significantly extends the median survival in comparison with non-VPA treatment (168,169). Preclinical research has shown that VPA enhances the anti-glioma efficacy of TMZ in U87 cells, whereas celecoxib (CXB) combined with TMZ demonstrates optimal inhibitory effects in C6 and T98G cell lines. The combined use of VPA and CXB was revealed to synergistically enhance the antitumour effects of TMZ both *in vitro* and *in vivo*, significantly reducing tumour volume and prolonging survival (170).

In vivo and *in vitro* studies have shown that the combined use of PER and TMZ exerts a synergistic antitumour effect and significantly prolongs survival (171,172). However, the combination of AEDs and TMZ also has adverse effects. Chemotherapeutic drugs metabolised by the CYP450 system may reduce the serum levels of certain AEDs, while VPA, a CYP450 inhibitor, may increase the toxicity of some chemotherapeutic agents (173). Additionally, AED use during chemotherapy may induce thrombocytopenia (169,174).

The combination of AEDs and radiotherapy has primarily demonstrated synergistic effects. VPA, which possesses histone deacetylase inhibitor activity, exhibits synergistic anti-glioma effects during radiotherapy and may serve as a radiosensitiser (173,175). Both *in vitro* and *in vivo* research has shown that the combination of VPA and radiotherapy effectively inhibits tumour cells, while exerting minimal impact on normal neurons (176). However, a cohort study of 1,057 patients with GBM revealed that patients concurrently using AEDs for ≥ 14 days during chemoradiotherapy (AED group) had a significantly higher mortality risk than non-AED users. This adverse effect was dose-dependent, with VPA demonstrating pronounced detrimental effects (177).

Therefore, when selecting AEDs for GRE, key considerations include: i) Minimal drug interactions; ii) potential beneficial side effects (such as anxiety relief and mood stabilisation); iii) availability of multiple dosage forms (oral or intravenous); and iv) avoidance of adverse effects (38).

Prophylactic use of AEDs. The preventive administration of AEDs in patients with glioma is still a topic of debate, since

it cannot enhance PFS or decrease the likelihood of initial seizures occurring within 6 months post-diagnosis. Therefore, AEDs are not recommended for seizure prevention in newly diagnosed, seizure-free patients with brain tumours (30). The SNO and EANO guidelines state that the evidence supporting the use of prophylactic AEDs on the basis of tumour location, histology, or grade is currently insufficient (178). Perioperative or postoperative AED use is not advised in seizure-free patients (9,179), and a recent study revealed no reduction in postoperative seizures with preoperative AEDs (180). Although increased extracellular glutamate is linked to seizures in patients with glioma, most AEDs, including LEV, do not directly target the glutamatergic system, limiting their ability to prevent tumour-associated epilepsy (181). Nevertheless, 63% of neurosurgeons reported frequent perioperative AED use to reduce the risk of craniotomy-related epilepsy (181). Guidelines suggest postoperative AED use for patients with preoperative GRE, whereas prophylactic AEDs may only be considered for seizure-free patients in the presence of high-risk factors (3).

AED deactivation time. The discontinuation of AEDs in patients with GRE is complex due to the significant influence of tumour status and antineoplastic therapy on seizure risk, unlike idiopathic epilepsy. The psychosocial impact of seizure recurrence further complicates accurate risk prediction (3,10). Notably, 71% of seizure recurrences in patients with glioma occur within 6 months of post-AED discontinuation (30). Factors such as the adverse effects of AEDs, financial burden, and psychosocial implications must be weighed against benefits. Current guidelines recommend discontinuing prophylactic AEDs 2 weeks post-surgery for patients seizure-free before and after surgery (3). For patients with a single postoperative seizure, gradual discontinuation after 3 months is advised, whereas for patients with recurrent seizures, treatment should be continued for at least 1 year. In patients with preoperative GRE with a seizure history of <6 months and complete tumour resection, AEDs can be stopped after 1 year of seizure remission. Nevertheless, for individuals with a prolonged history of epilepsy, partial tumour removal, widespread epileptiform activity on EEG, preoperative drug-resistant seizures, or focal seizures accompanied by loss of consciousness, a seizure-free interval of at least 2 years after surgery is advisable before contemplating discontinuation of treatment. AED discontinuation is not recommended for: i) All patients with GBMs; and ii) other patients with HGG undergoing incomplete tumour resection or exhibiting postoperative refractory seizures (such as patients with anaplastic glioma).

Surgical treatment

Tumour resection extent. In patients with glioma, seizure control is being increasingly recognised as a critical goal, second only to tumour control. Maximal tumour resection significantly improves seizure outcomes, with the EOR being an independent predictor of postoperative seizure control (182-186). Surgical resection was shown to achieve seizure control in 36-100% of patients with LGGs (4), with 80% of patients with temporal lobe lesions achieving Engel class I outcomes following maximal resection (187,188). For patients with LGGs with preoperative epilepsy, resection

exceeding 91% significantly enhanced postoperative seizure control (3,4). Gross total resection has shown superior seizure reduction over other resection types (180), with near-total and subtotal resections achieving 87 and 55% seizure remission rates, respectively (18).

Maximal safe resection can not only improve seizure control but also enhance local tumour control and survival. In insular gliomas, maximal resection was demonstrated to prolong survival and improve seizure outcomes for both newly diagnosed and recurrent tumours (189,190). For GBMs, super-total resection, extending beyond the contrast-enhancing tumour margins, was revealed to improve overall survival and seizure control in comparison with near-total resection (9). Maximal resection with functional preservation is essential for tumours of the cerebral cortex. Advanced techniques such as ‘sculpting surgery’, which precisely target epileptic foci, can help reduce postoperative seizures when near-total resection is not feasible (3).

Location of epileptogenic foci. The epileptogenic zone in BTRE can be located within, adjacent to, or distant from the tumour. In two-thirds of patients with BTRE, it is found within or near the tumour (18). A previous electrophysiological study has revealed that epileptic activity primarily originates in the superior granular layer of the peritumoural neocortex, which is infiltrated by glioma cells, rather than in the tumour core (66). Animal studies have further indicated that the peritumoural area exhibits heightened spontaneous epileptiform activity, likely due to increased neuronal bursting in this region (4,191). In LGGs, epileptic foci are typically located at the tumour-neocortex interface, with the glioma-infiltrated peritumoural neocortex playing a key role in epileptogenesis (4).

Preoperative and intraoperative electrophysiological techniques, such as MEG, EEG, stereotactic EEG, and electrocorticography (ECoG), primarily detect epileptic activity in the peritumoural neocortex (4). While routine EEG can localise epileptic foci, intracranial EEG is often necessary for precise localisation and improved treatment outcomes (3,9,18). Intraoperative ECoG monitoring using strip or grid electrodes is recommended before and after tumour resection to identify residual epileptic activity that can be treated with electrocautery (192). Advances in biomedical engineering have introduced ‘circular grid’ electrodes, which enable 360° cortical monitoring and demonstrate higher seizure detection accuracy, tumour resection rates, and postoperative functional outcomes than conventional electrodes (192).

Awake craniotomy (AC), combined with direct electrical stimulation (DES) and ECoG, is effective for resecting gliomas in eloquent areas, reducing postoperative complications, and improving survival and quality of life (192,193). A previous study revealed no increase in seizure risk with AC in comparison with general anaesthesia (180). Recent research has highlighted the predictive value of transcranial magnetic stimulation for postoperative neurological outcomes, with ECoG-guided supratotal resection improving seizure control while preserving function (194). Emerging techniques for localising epileptogenic zones include PET with α -(11C) methyltryptophan, which selectively accumulates in epileptogenic foci, and proton MRS (1H-MRS), which non-invasively

assesses glutamate and GABA levels in tumour and peritumoural tissue (195-199). These advanced methods complement traditional imaging and electrophysiological tools, offering novel insights into the management of epilepsy in patients with glioma.

Management of intraoperative and early postoperative seizures. Near-total resection during glioma surgery can contribute to intraoperative seizures (158,193), particularly in high-risk patients with factors such as younger age, frontal lobe involvement (especially the supplementary motor area), preoperative epilepsy history, use of multiple AEDs, and IDH1 mutations. Prophylactic administration of LEV or VPA is recommended for these patients (3). During AC, DES under real-time ECoG monitoring, which is essential for functional localisation, carries a 3.2-15.5% risk of intraoperative seizures, typically partial seizures. However, this does not increase postoperative seizure risk (3,4,192). Minimising the intensity and frequency of electrical stimulation can reduce the incidence of seizures (193). In the event of a seizure, immediate cessation of stimulation and cortical irrigation with ice-cold Ringer's solution or saline is recommended. Persistent seizures may require benzodiazepine administration, with intraoperative electromyography facilitating early detection (3).

Early postoperative seizures that occur within the first week require prompt airway management and injury prevention (159). The diagnostic workup should include electrocardiography, blood tests (glucose, electrolytes, and liver/kidney function), and neuroimaging (CT/MRI) to exclude non-epileptic causes such as intracranial haemorrhage or metabolic disturbances. EEG monitoring for 2 h can help assess epileptiform discharges related to brain oedema or residual tumour (3). Seizures lasting over 5 min or clustered seizures (multiple brief episodes of interictal recovery) should be treated aggressively with midazolam or other AEDs to prevent progression to status epilepticus (159). Recurrent seizures warrant monitoring of AED blood levels and potential medication adjustments or substitution (3). Prophylactic AEDs are recommended for 1 week post-surgery, regardless of preoperative seizure history (158).

Postoperative seizures may result from preoperative epilepsy, surgical trauma, or metabolic disturbances (such as electrolyte imbalance and hypoglycaemia). Non-epileptic events should be distinguished using video EEG and AED-level testing to identify the underlying cause and guide appropriate management (159).

Postoperative epilepsy management. Postoperative MRI, including contrast-enhanced imaging, should be performed within 24-72 h to evaluate the EOR. MRI findings such as nodules, border blurring, or mass effect on T2 (FLAIR) or T1 sequences can predict postoperative epilepsy risk by reflecting tumour growth and seizure propensity (3,8). IDH mutations in gliomas are linked to more severe and refractory postoperative seizures, although glutamate concentrations in the LGG microenvironments are not correlated with seizure risk (4).

Seizure recurrence after a prolonged seizure-free period may result in tumour recurrence. In cases of tumour recurrence with drug-resistant seizures, surgery may be considered after a thorough evaluation. If seizures occur without evidence of

tumour recurrence, management should follow the refractory epilepsy guidelines. Surgical intervention is recommended for drug-resistant GRE when frequent seizures significantly impair the quality of life of a patient (3).

Radiation therapy and chemotherapy. Radiotherapy and chemotherapy are the cornerstone treatments for gliomas and are aimed at controlling tumour growth and improving survival. Their combined use enhances prognosis and quality of life, with research showing significant seizure reduction following these therapies in patients with LGGs (183). For instance, focal fractionated irradiation and TMZ chemotherapy have been associated with a 44-77% reduction in seizure frequency (200,201). Radiotherapy improves local tumour control, preserves neurological function, and extends survival (9). It also significantly reduces seizures in GRE, with remission rates ranging from 20% after focal radiotherapy to 80% after brachytherapy (3,9). Notably, seizure improvement often precedes tumour shrinkage on MRI, indicating a direct antiepileptic effect (4). For example, 76% of patients with WHO grade II glioma experienced a 50% reduction in seizure frequency within 3 months of radiotherapy, despite no apparent tumour changes on imaging (200,202). Early postoperative radiotherapy is recommended because earlier intervention is associated with improved seizure control. Neither seizure duration prior to radiotherapy nor radiation dose was found to significantly influence outcomes (3,4). Radiotherapy is also a viable option for patients with refractory seizures and surgical intolerance, regardless of tumour recurrence (3).

Common chemotherapy agents for gliomas include TMZ, procarbazine, lomustine, and vincristine (PCV), and lomustine. These drugs not only improve survival but also reduce seizures in 30-100% of patients with GRE (3). In LGGs, seizure remission rates range from 13 to 60% with PCV and from 13 to 50% with TMZ (9). TMZ, which is widely used in patients with LGGs and HGGs, was demonstrated to reduce seizure frequency by 50% in 48% of patients (203,204). However, evidence of the antiepileptic efficacy of TMZ remains inconclusive and warrants further research (205). The primary goal of TMZ is tumour control; however, its potential antiepileptic benefits should be leveraged if confirmed.

Emerging therapies

Targeting IDH and its related downstream pathways. Targeted therapies for IDHmut gliomas have shown significant promise in both preclinical and clinical settings. Vorasidenib (AG-881) and ivosidenib (AG-120), which are inhibitors of mutant IDH1/2 enzymes, specifically target D-2HG (97), a key driver of tumourigenesis and epileptogenesis. Vorasidenib, which effectively penetrates the BBB, demonstrated improved PFS in the INDIGO trial, although its direct impact on seizure control remains unclear (206-208). Ivosidenib, on the other hand, has shown potential antiepileptic benefits, as evidenced by reduced seizure frequency in a case of IDH1mut oligodendroglioma (209). Additionally, mTOR inhibitors such as rapamycin and everolimus, which counteract the activation of the mTOR pathway by D-2HG, may offer therapeutic benefits for patients with IDH1mut glioma with refractory epilepsy (30). Emerging therapies, including IDH1-targeted peptide vaccines currently under development, hold promise for mitigating the

seizure risk in GRE (8). These advancements highlight the potential of targeted approaches to not only control tumour growth, but also improve seizure outcomes in patients with IDHmut glioma.

Targeting metabolic abnormalities. The ketogenic diet has shown promise in inhibiting glioma proliferation and reducing seizure frequency and severity (3). Sulfasalazine, which inhibits glutamate release, has been associated with prolonged seizure-free survival, although its use is limited by its haematological adverse reactions (1). PPAR- λ agonists, such as glitazones, have been demonstrated to enhance glutamate reuptake, potentially reducing excitotoxicity (38). NMDAR antagonists have been shown to restore inhibitory GABA signalling in peritumoural neurones, offering another avenue for seizure control (6). Cannabidiol (CBD), known for its efficacy in refractory epilepsy, may also benefit patients with glioma, although its clinical effectiveness in GRE requires further validation (96).

Immune regulation. Bevacizumab, an anti-VEGF monoclonal antibody, has been demonstrated to reduce peritumoural oedema and may decrease the risk of seizures in patients with recurrent GBMs (8). While immune checkpoint inhibitors enhance antitumour immunity, they may also paradoxically increase the risk of status epilepticus in patients with brain metastases (56). Notably, disruption of the BBB has been shown in both patients with epilepsy and animal models of epilepsy (210-215). In patients with temporal lobe epilepsy, CCL2 upregulation was revealed to be associated with BBB disruption and epileptogenesis (211,212,216). Therefore, systemic delivery of immunotherapies may be a viable strategy for these patients, presenting an advantage over treating other CNS diseases not accompanied by BBB disruption.

Targeting ion channel. Enrichment analysis revealed conserved pathogenesis modules between epilepsy and glioma, including calcium-related pathways (217). Seizures have also been reported to be controlled by voltage-sensitive calcium channel antagonists and have been demonstrated in animal models of epilepsy (218). In addition, a new generation of calcium channel drugs has emerged for the treatment of epilepsy and chronic pain. ω -Taro spirotoxin is a potent blocker of presynaptic calcium channels in neurons. A synthetic derivative, ziconotide (Prialt), is administered intrathecally for the control of severe pain in patients with advanced cancer and other patients suffering from intractable pain (219). SCN3B is one of the hub genes involving ion channel regulation, and it is significantly overexpressed in patients with GRE (220). Upregulated SCN3B may influence cell excitability and contribute to epileptogenesis (221). Moreover, SCN3B is also a potential oncogenic factor, as the β 3 subunit could promote proliferation and suppress tumor cell apoptosis by promoting p53 degradation (222,223). SCN3B appears to have potential as a shared therapeutic target for both diffuse gliomas and GRE.

These emerging therapies represent innovative approaches to improving outcomes in GRE by targeting both tumour biology and epileptogenesis. In conclusion, although radiotherapy and chemotherapy remain central to glioma treatment,

emerging therapies and targeted agents offer promising avenues for improving seizure control and overall outcomes in patients with GRE. Further research is essential to validate their efficacy and optimise their clinical application.

5. Conclusion and perspectives

Gliomas are the most common primary brain tumours. Notably, 30-90% of patients with glioma experience epileptic seizures, especially those with LGGs, who exhibit an even higher incidence of epilepsy (60-90%). Epilepsy is not only an early symptom of glioma, but may also affect the quality of life, cognitive function and prognosis of patients. Its pathogenesis involves tumour-induced compression, destruction of peripheral neural tissue, and aberrant excitatory effects of tumour-derived chemicals. Furthermore, epileptic seizures (a symptom of GBM) promote tumour progression and exacerbate the increase in excitability. This establishes a reinforcing feedback loop that intensifies epileptic seizures (224). However, the detailed molecular, cellular, and electrophysiological mechanisms underlying seizure generation remain unclear, necessitating further research to develop precise therapeutic strategies. Patients with GRE present with diverse symptoms that complicate its diagnosis and treatment. Improving early diagnosis, accurate symptom analysis, and the use of predictive tools based on advanced imaging techniques such as MRI are crucial for improved patient outcomes. In addition, accurate and reliable diagnosis of glioma and prediction of glioma patient survival can provide valuable guidance for the diagnosis, treatment planning, and prognosis of subsequent complications such as epilepsy. A recent study proposed a method involving a standardised workflow of nanoparticle-enhanced laser desorption/ionisation mass spectrometry and paper-based dried serum spots to achieve sustainable metabolic diagnosis, which can diagnose multiple cancers within minutes at an affordable cost, with environmentally friendly, serum-equivalent precision, and user-friendly protocols (225). Another research team established a squeeze-and-excitation deep learning feature extractor for T1 contrast-enhanced images and histological sections and explored the significant cyclic 5-hydroxymethylcytosine profile for screening glioma survival through minimum absolute contraction and Cox regression (226).

Current treatments include surgical resection, radiotherapy, chemotherapy, and AEDs. However, challenges, such as surgical limitations, risks to the surrounding brain tissue, and AED resistance due to long-term use, persist. Future research should focus on elucidating the pathogenesis of GRE, including its seizure-initiation mechanisms, neuronal network abnormalities, and tumour-neuron interactions. Leveraging molecular biology, genomics, and cell biology techniques to identify seizure biomarkers can enhance the diagnostic and therapeutic precision. Additionally, exploring novel therapies, such as neuromodulation, immunotherapy, and next-generation AEDs, may address the limitations of existing treatment modalities.

Multidisciplinary collaboration and robust clinical research are essential to better understand the local and systemic effects of GRE and to accelerate the development of innovative therapies. Future research should integrate molecular pathology, radiomics, and artificial intelligence to promote individualised treatment and improve the quality of

life of patients. Although GRE research and treatment remain challenging, advancements in these areas hold promise for improving patient outcomes and quality of life. Continued exploration and collaboration are the keys to unlocking novel therapeutic possibilities.

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ZQL and FT were involved in the conception and the design of the review. XC, LYK and ZYL conducted the literature search and collation. XC and JZY wrote the manuscript. ZQL and FT reviewed the manuscript. All authors have reviewed the manuscript and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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