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CRITICAL REVIEW

Tumor-related epilepsy in glioma: A multidisciplinary overview

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Abstract

Seizures are a common and challenging symptom in brain tumors, affecting approximately 60% of patients. Tumor-related epilepsy (TRE) in glioma patients requires personalized and dynamic management in a multidisciplinary

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environment, especially for its intricate pathophysiology and unpredictable disease evolution. This investigation provides an updated overview about the pathophysiological mechanisms and treatment options of TRE associated with gliomas, based on expert contributions belonging to different areas. By combining the most recent discoveries and expert opinions, this study seeks to provide useful advice for TRE management in glioma patients. To improve patient outcomes and quality of life, prospective, standardized, multicentric studies should be promoted to optimize TRE patient care and refine therapeutic approaches.

KEYWORDS

antiseizure medications, cerebral tumors, chemotherapy, epilepsy, epilepsy surgery, radiotherapy

1 | INTRODUCTION AND GENERAL REMARKS

Seizures are a frequent and difficult-to-treat symptom of cerebral neoplasms, occurring in approximately 60% of brain tumors (BTs) and often requiring complex and multidisciplinary management.[1,2] Overall seizures are the presenting symptom in approximately one third of patients with cerebral tumors. On the other hand, BTs account for 3.5% of all epilepsies. The incidence of epilepsy and seizure semiology, however, vary widely and depend on tumor type and location. Among patients with primary BTs, seizures are more prevalent in cases of low-grade tumors compared to high-grade ones.[2,3] It is not unusual that patients with high-grade tumors experience at least one seizure as first symptom of the condition or during the course of the disease and present uncontrolled epileptic seizures during tumor evolution. However, chronic epilepsy points to the presence of brain neoplasms with distinct features, which have been denominated "low-grade epilepsy-associated tumors" (LEATs) and mainly include glioneuronal and neuronal tumors (GNTs).[4–8]

Despite the variable frequency of seizures as a function of histologic type, an important factor associated with the development of seizures is tumor location. Seizures occur much more frequently in supratentorial (30%–70%) than infratentorial (6%) lesions. Moreover, the incidence of seizures increases as the site of tumor approaches the primary sensorimotor cortex, the temporal cortex, and the supplementary motor areas. Similarly, seizure development is much more common with cortical than with noncortical deep lesions (63% vs. 29%).[2]

Antiseizure medications (ASMs) are usually prescribed, either to control seizures or to prevent seizure occurrence, for example, after surgical treatment. Each of the modalities for tumor therapy (i.e., surgery, radiotherapy, chemotherapy) contributes to seizure control, but specific problems may arise when combined with ASMs.[9]

Key points

- Antiseizure medications, surgery, chemotherapy, and radiotherapy all contribute to controlling seizures and require a cooperative and multidisciplinary approach.
- Maximal safe surgical resection, in both low- and high-grade gliomas, implies a double benefit, in terms of both survival and seizure control.
- In glioneuronal tumors, lesionectomy with removal of the adjacent epileptogenic zone provides the best outcomes.
- Preoperative long-term monitoring, intraoperative monitoring and mapping and electrocorticography in selected cases improve the postoperative seizure outcome.
- Third-line antiseizure medications are commonly preferred because of their better tolerability profile and lack of drug–drug interactions.

Approximately one third of tumor-related epilepsy (TRE) patients, however, exhibit pharmacoresistance to ASMs, complicating their quality of life. Epilepsy and ASMs also contribute to cognitive decline, which remains a significant concern for BT patient management.[10,11]

This paper provides a comprehensive, multidisciplinary review of TRE, addressing its pathophysiology, classification, and management within the clinical context of high-grade gliomas (HGGs), diffuse low-grade gliomas (DLGGs), and GNTs.

2 | MECHANISMS OF EPILEPTOGENESIS IN BTs

Epileptogenesis in individuals with BTs refers to a complex and multifactorial process involving various mechanisms such as alterations in neuronal excitability, abnormal neural network activity, and changes in the tumor microenvironment (Figure 1). Over the past decade, there has been a notable expansion in the literature concerning the pathophysiology of TRE, highlighting shared mechanisms of epileptogenesis and tumor growth in glial tumors, as well as mechanisms of intrinsic epileptogenicity in LEATs.[12,13]

Recently, advancements in understanding tumor intrinsic molecular properties have shed light on how they create an environment susceptible to and supportive of hyperexcitability mechanisms. Genetic mutations and associated molecular pathways have emerged as pivotal factors sustaining both BTs and epilepsy, potentially elucidating tumoral and peritumoral hyperexcitability in specific tumor types.[14,15]

Recent experimental studies provide evidence linking the B-Raf proto-oncogene (BRAF) V600E mutation in epileptogenic developmental BTs to their intrinsic epileptogenicity.[16,17]

Mutations in isocitrate dehydrogenase (IDH), in particular IDH1, are commonly found in DLGGs, correlating with improved tumor prognosis while also serving as an independent risk factor for increased seizure susceptibility.[18,19] These mutations result in the accumulation of D-2-hydroxyglutarate in tumors, which can increase neuronal excitation in a glia-dependent manner through various mechanisms recently explored in experimental models.[20]

Furthermore, recent research has highlighted the role of mechanistic target of rapamycin (mTOR) signaling pathway activation in IDH mutant glioma epileptogenicity and tumor progression.[21,22]

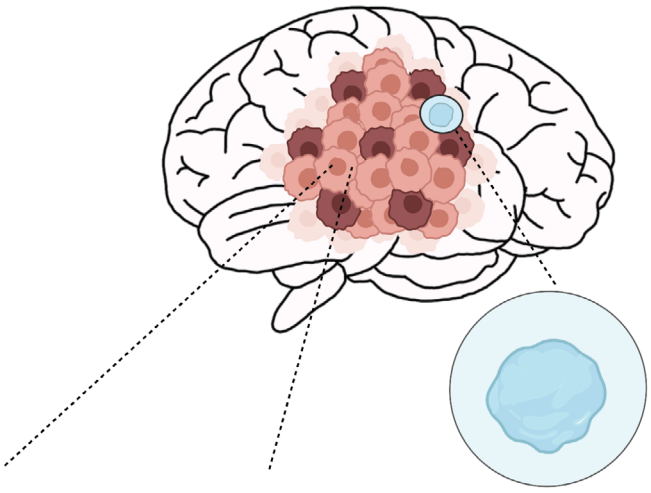

FIGURE 1 Epileptogenesis in brain tumors. It involves a multifactorial interplay between tumor-intrinsic genetic mutations (e.g., BRAF, IDH1), disrupted excitatory–inhibitory balance, neuron–glioma synaptic communication, neuroinflammation, and vascular/metabolic dysfunction. These alterations promote hyperexcitability and seizure susceptibility while also driving tumor growth. ADK, adenosine kinase; BBB, blood–brain barrier; BRAF V600E, B-Raf proto-oncogene, serine/threonine kinase v600e mutation; Cl^-, chloride ion; D-2-HG, D-2-hydroxyglutarate; ECM, extracellular matrix; GABA, γ-aminobutyric acid; IDH1/2, isocitrate dehydrogenase 1 and 2; mTOR, mechanistic target of rapamycin; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α; PNN, perineuronal net; RAS, rat sarcoma (a family of related proteins involved in cell signaling); RTK, receptor tyrosine kinase; system Xc, cystine/glutamate antiporter.

These studies provide support for exploring the use of IDH inhibitors to control seizures, and simultaneously investigating the efficacy of mTOR inhibitors for seizure management could further advance research on mTOR inhibition targeting tumor growth. Genetic alterations in the RTK/RAS/PI3K pathway are a prevalent driver of tumorigenesis in IDH wild-type glioblastomas. Using a mouse model of glioblastoma, it has been demonstrated that several driver variants of PIK3CA promote neuronal activity, thereby identifying GPC3 (a secreted member of the glypican [GPC] family) as a contributor to both glioma tumorigenesis and network hyperexcitability.[23]

Interestingly, the patterns of cortical network activity are strongly influenced by tumor genetics.[15]

One pivotal aspect of epileptogenesis involves a disruption in the balance between excitation and inhibition, resulting from the loss of physiological homeostatic function of glioma cells and peritumoral astrocytes. This encompasses dysregulated potassium homeostasis, alterations in gap–junction expression, compromised glutamate transport, and disrupted neurotransmitter supply, all contributing to circuit hyperexcitability.[24,25]

In addition to glutamatergic dysfunction, which involves an increase in extracellular glutamate levels and promotes glioma cell proliferation, evidence supports defective inhibitory signaling in TRE. This includes the degradation of perineuronal nets surrounding fast-spiking interneurons,[26,27] as well as perturbed chloride homeostasis due to changes in the expression of neuronal chloride cotransporters, leading to depolarizing γ-aminobutyric acidergic activity.[28–30] Furthermore, intra- and peritumoral inflammatory changes, mediated by astrocytes and microglia, may also contribute to the disruption of the excitatory–inhibitory balance, thereby promoting epileptogenesis.[31,32]

Recently emerging insights from cancer neuroscience have provided a valuable framework for understanding epileptogenesis in BTs.[33] In experimental models of glioma, the activity of glutamatergic neurons has been shown to drive tumor growth of gliomas,[34,35] involving both paracrine signaling[23,35] and direct electrochemical communication, neuron-to-glioma synapses.[35–37] These studies give support to bidirectional interactions between neurons and glioma cells, with neuronal activity driving glioma and gliomas increasing neuronal activity.[35,38] Glial tumor cells electrically integrate into neural circuitry and may employ mechanisms of adaptive neuroplasticity to strengthen these growth-promoting neuron–glioma interactions. Interestingly, neuronal activity-regulated brain-derived neurotrophic factor signaling to the TrkB receptor in glioma cells may play a crucial role in such plasticity.[39] Another recent study underscores the complexity of the dysfunctional network in gliomas, revealing network-wide rhythmic intercellular Ca^{2+} waves that selectively activate the mitogen-activated protein kinase (MAPK) and NF-κB pathways, thereby driving BT growth[40] and potentially contributing to epileptogenesis.[41] Moreover, activity-dependent dysregulation of myelin plasticity may contribute to aberrant circuit function and pathological network activity, potentially supporting pathological cell proliferation[42] as well as epileptogenesis.[43]

Gliomas also disrupt functional hemodynamics, resulting in disturbed neurovascular coupling and seizure-induced hypoxia in affected cortical regions,[44] as well as blood–brain barrier breakdown.[45] This may serve as an additional mechanism contributing to the pathological network underlying tumor growth and epileptogenesis.

3 | ADVANCES IN THE CLASSIFICATION SYSTEM

Primary neoplasms of the central nervous system are rare and represent a small part of the much larger and more diverse cancer landscape.

Continuing the path started with the 2016 World Health Organization (WHO) classification, the new WHO 2021 classification of central nervous system tumors has further integrated molecular data into the typing, subtyping, and classification of primary tumor groups (Table 1).[46]

Why push on molecular data? The reason for this emphasis on molecular genetic diagnosis is the superiority of this approach in terms of tumor classification and correlation with prognosis. Moreover, diagnosis based on morphology can be more subjective, with high variability among pathologists. Molecular genetics is then required to perform investigations (e.g., IDH1 R132H, TP53, ATRX, and 1p/19q codeletion).[47]

Until 2016, the diagnosis of these neoplasms was based on histology alone. Starting with the WHO 2016 classification and then more extensively with the WHO 2021 classification, molecular biological data were integrated with anatomopathological data to provide an integrated diagnosis.[48]

With the WHO 2021 classification, some entities we have worked with before (e.g., gliomatosis) have disappeared and new, often very rare entities have appeared (Table 2).

The cornerstone of the new classification is the IDH mutation.[49] The identification of this mutation makes it possible to subdivide glial tumors into IDH mutant and wild-type neoplasms, with very different biological and clinical characteristics. A more aggressive clinical course and a worse prognosis characterize wild-type IDH tumors. The glioblastomas were diffuse grade 4 IDH1/2 wild-type

TABLE 1 Neuroepithelial tumors associated with epilepsy according to 2021 WHO classification.

Tumor histology according to CNS WHO 2021	WHO grading	LEAT entities[a]	Molecular profiles and key genetic alterations
Adult diffuse gliomas			
Astrocytoma, IDH mutant	2–4	No	IDH1- IDH2, ATRX, TP53, CDKN2A/B
Oligodendroglioma, IDH mutant, 1p/19q-codeleted	2–3	No	IDH1-IDH2, 1p-19q codeletion
Glioblastoma	4	No	IDHwt, EGFR, TERT, LOH10q, gain 7p, CDKN2A/B
Pediatric diffuse low-grade gliomas			
Diffuse astrocytoma, MYB- or MYBL1-altered	1	Yes	MYB, MYBL1
Angiocentric glioma	1	Yes	MYB
Polymorphous low-grade neuroepithelial tumor of the young	1	Yes	BRAF, FGFR
Diffuse low-grade glioma, MAPK pathway-altered	nd	nd	FGFR1, BRAF
Circumscribed astrocytic gliomas			
Pilocytic astrocytoma	1	Yes	KIAA1549-BRAF, BRAF, NF1
High-grade astrocytoma with piloid features	nd	No	BRAF, NF1, ATRX, CDKN2A/B (methylome)
Pleomorphic xanthoastrocytoma	2–3	No	BRAF, CDKN2A/B
Subependymal giant cell astrocytoma	1	No	TSC1, TSC2
Astroblastoma	nd	No	MN1
Chordoid glioma	2	No	PRKCA
Glioneuronal and neuronal tumors			
Ganglioglioma	1–3	Yes	BRAF
Gangliocytoma	1	No	BRAF
Desmoplastic infantile ganglioglioma/astrocytoma	1	No	nd
Dysembryoplastic neuroepithelial tumor	1	Yes	FGFR1
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters	nd	nd	Monosomy of chromosome 14 (methylome)
Papillary glioneuronal tumor	1	Yes	PRKCA
Rosette-forming glioneuronal tumor	1	No	FGFR1, PIK3CA, NF1
Myxoid glioneuronal tumor	nd	No	PDFGRA
Diffuse leptomeningeal glioneuronal tumor	nd	No	KIAA1549-BRAF fusion, 1p (methylome)
Multinodular vacuolating neuronal tumor	1	Yes	MAPK pathway
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	1	No	PTEN
Central neurocytoma	2	No	nd
Extraventricular neurocytoma	2	No	FGFR (FGFR1-TACC1fusion), IDHwt
Cerebellar liponeurocytoma	2	No	nd

Note: CDKN2A/B homozygous deletion is a frequent and clinically relevant alteration in high-grade gliomas, associated with poor prognosis and aggressive tumor behavior. Methylome: The analysis of the DNA methylation profile (methylome) is currently necessary for a definitive diagnosis.

Abbreviations: CNS WHO, WHO Classification of Tumors of the Central Nervous System; LEAT, low-grade epilepsy-associated tumor; MAPK, mitogen-activated protein kinase; nd, not yet fully determined; WHO, World Health Organization; wt, wild type.

[a]LEAT entities: tumors well-recognized as being typically associated with epilepsy.

gliomas with microvascular proliferation and/or intertumoral necrosis. At the same time, a grade 2–3 IDH1/2 wild-type astrocytic glioma can now be classified as a glioblastoma if it has at least one of the following molecular features: telomerase reverse transcriptase (TERT) promoter mutation, epidermal growth factor receptor (EGFR) amplification, or concomitant gain of chromosome 7 and loss of chromosome 10.

2016 WHO classification	Revised term 2021 WHO classification
Diffuse astrocytoma, IDH mutant	Astrocytoma, IDH mutant; CNS WHO grade 2
Anaplastic astrocytoma, IDH mutant	Astrocytoma, IDH mutant; CNS WHO grade 3
Glioblastoma, IDH mutant	Astrocytoma, IDH mutant; CNS WHO grade 4
Diffuse midline glioma, H3 K27M mutant	Diffuse midline glioma, H3 K27-altered
Astroblastoma	Astroblastoma, MN1-altered
Ependymoma, RELA fusion-positive	Supratentorial ependymoma, ZFTA fusion-positive
Chordoid glioma of the third ventricle	Chordoid glioma
Embryonal tumor with multilayered rosettes, C19MC-altered	Embryonal tumor with multilayered rosettes
Melanotic schwannoma	Malignant melanotic nerve sheath tumor
Solitary fibrous tumor and hemangiopericytoma	Solitary fibrous tumor

TABLE 2 Revised CNS tumor nomenclature in CNS WHO 5.

Abbreviations: CNS, central nervous system; CNS WHO, WHO Classification of Tumors of the Central Nervous System; IDH, isocitrate dehydrogenase; WHO, World Health Organization.

The term IDH mutant glioblastoma was changed to WHO grade 4 astrocytoma, IDH mutant in the 2016 WHO classification. Astrocytoma consisted only of diffuse IDH mutant glioma and was divided into three grades (2, 3 or 4) based on histological findings and CDKN2A/B homozygous deletion status. Following this classification, we understood how an astrocytoma of histological grade 2 could have a prognosis similar to that of a glioblastoma if it had a deletion for the CDK2NA mutation or a deletion of chromosome 10 or a gain of 7.10.

In IDH-mutated neoplasms, codeletions on chromosomes 1 and 19 allow the differentiation of oligodendrocytes from astrocytic tumors. Within oligodendroglial tumors, grades 2–3 are maintained; WHO grade 3 (anaplastic) is assigned to an IDH mutant oligodendroglioma, with 1p/19q codeletion, dense cellularity, microvascular proliferation, necrosis, and significant mitotic activity.

IDH-wildtype diffuse gliomas affecting pediatric patients are classified separately from IDH-wildtype diffuse gliomas occurring in adults. Diffuse, MYB- or MYBL1-altered astrocytomas (WHO Classification of Tumors of the Central Nervous System grade 1) are responsible for refractory epilepsy (LEATs).[50] These tumors can arise in any brain lobe and have both cortical and subcortical localization. They are characterized by moderate hypercellularity and diffuse infiltration by monomorphic cells with ovoid to elongated nuclei. Mitotic activity is very low or absent. They are characterized by fusion between the MYB or MYBL1 genes.

Another tumor responsible for LEAT is the polymorphous low-grade neuroepithelial tumor of the young (PLNTY), almost always present in refractory epilepsy.[51] It is a grade 1 neuroepithelial tumor that mainly affects young and female patients but is also described in adults.

The usual localization is cortical or subcortical in the temporal lobe, with well-delineated tumor margins, extensive calcifications, and cystic tumor morphology with little or no enhancement.

PLNTYs have oligodendrogliomalike features with extensive CD34 expression. Genetic alteration of the MAPK pathway (including alterations in FGFR2/3 and BRAF) is characteristic. A classification of LEAT entities in presented in Table 3.[52]

4 | HGGs AND EPILEPSY

Epilepsy represents the onset symptom in approximately 40%–64% of HGG patients (Figure 2). Few studies have evaluated the prognostic effects of seizures that occur in the posttreatment scenario, although numerous papers have examined the influence of surgery on seizure outcome.[53,54]

Seizures at initial presentation in HGG were found to be associated with improved overall survival; a meta-analysis of 1836 glioblastoma multiforme patients showed reduced mortality in the subset of patients with positive seizure history (hazard ratio [HR] = .71, $p \leq .00001$),[55] and a 2018 meta-analysis of 2088 patients showed increased mortality with negative seizure history (HR = 1.73, $p \leq .001$).[56] Current theories for the underlying mechanism behind a possible protective effect of seizures in HGG include both cellular theories (such as slower growth rate and favorable molecular features, i.e., an association with IDH1 mutation) and clinical theories (such as early detection of HGG through seizure workup).[55–57]

Seizure semiology in HGG was clearly described in a prospective study enrolling 72 patients (the vast majority

TABLE 3 LEATs in the 2021 WHO classification.

Histology, according to the 2021 WHO classification	Grading	LEAT entities[a]	Molecular profiles and key genetic alterations
Pediatric diffuse low-grade gliomas			
Diffuse astrocytoma, MYB- or MYBL1-altered	1	Yes	MYB, MYBL1
Angiocentric glioma	1	Yes	MYB
Polymorphous low-grade neuroepithelial tumor of the young	1	Yes	BRAF, FGFR
Diffuse low-grade glioma, MAPK pathway-altered	nd	nd	FGFR1, BRAF
Circumscribed astrocytic gliomas			
Pilocytic astrocytoma	1	Yes	KIAA1549-BRAF, BRAF, NF1
Glioneuronal and neuronal tumors			
Ganglioglioma	1–3	Yes	BRAF
Dysembryoplastic neuroepithelial tumor	1	Yes	FGFR1
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters	nd	nd	Monosomy of chromosome 14 (methylome)
Multinodular and vacuolating neuronal tumor	1	Yes	MAPK pathway

Note: Methylome: The analysis of the DNA methylation profile (methylome) is currently necessary for a definitive diagnosis.

Abbreviations: LEAT, low-grade epilepsy-associated tumors; MAPK, mitogen-activated protein kinase; nd, not yet fully determined; WHO, World Health Organization.

[a]LEAT entities: tumors well-recognized as being typically associated with epilepsy.

having HGG) in which seizures were the first symptom of the tumor. Overall, the initial seizures were tonic–clonic (48%; without clear initial focal signs in more than half of the patients), focal motor (26%), focal with impaired awareness (10%), somatosensitive (8%), aphasic (4%), and other types (4%). The majority of cases (60%) had isolated seizures or a low seizure frequency at the onset of the disease, whereas a high seizure frequency or status epilepticus (SE) was observed in 18% and 12% of cases, respectively. After tumor removal, with a mean follow-up of 5 months, 39 patients (57%) were seizure-free, four (6%) had a marked improvement of seizure frequency, 14 (20%) were unchanged, and 12 (17%) had a worsening of seizure frequency.

Once the diagnosis of HGG is suggested on the basis of neuroradiological features, the first step of treatment consists in gross total removal, which leads to complete seizure control in the vast majority of patients. Over the past decade, increasing evidence has demonstrated that the degree of HGG resection translates to improvements in overall survival and progression-free survival. An extended resection above the anatomical limits of the enhanced area (supramarginal resection) after complete microsurgical resection is an emerging topic, whenever possible with respect to functional integrity, with potential survival and TRE benefit.[58] However total or supratotal removal is not always possible due to the extension and location of the tumor.[59] In these cases, one should consider different surgical strategies (including no surgery, biopsy, or partial removal).

After surgery, additional treatment modalities include radiotherapy and chemotherapy. Fractionated radiotherapy (54–60 Gy in 30 daily fractions) combined with chemotherapy is an essential part of the management of any grade glioma aiming to improve local tumor control, preserve and/or improve patient's functioning, and increase overall survival. Koekkoek et al.[60] reviewed the effects of radiotherapy on seizure control and reported an improved seizure outcome after radiotherapy in 72%–77% of patients, with seizure freedom rates ranging from 20% after focal radiotherapy to 80% at 6 months after brachytherapy. Nevertheless, seizure frequency increases occasionally after surgery or radiotherapy, secondary to complications such as edema, bleeding, or radiation necrosis.

The alkylating chemotherapeutic agent temozolomide (TMZ) is commonly used in combination with

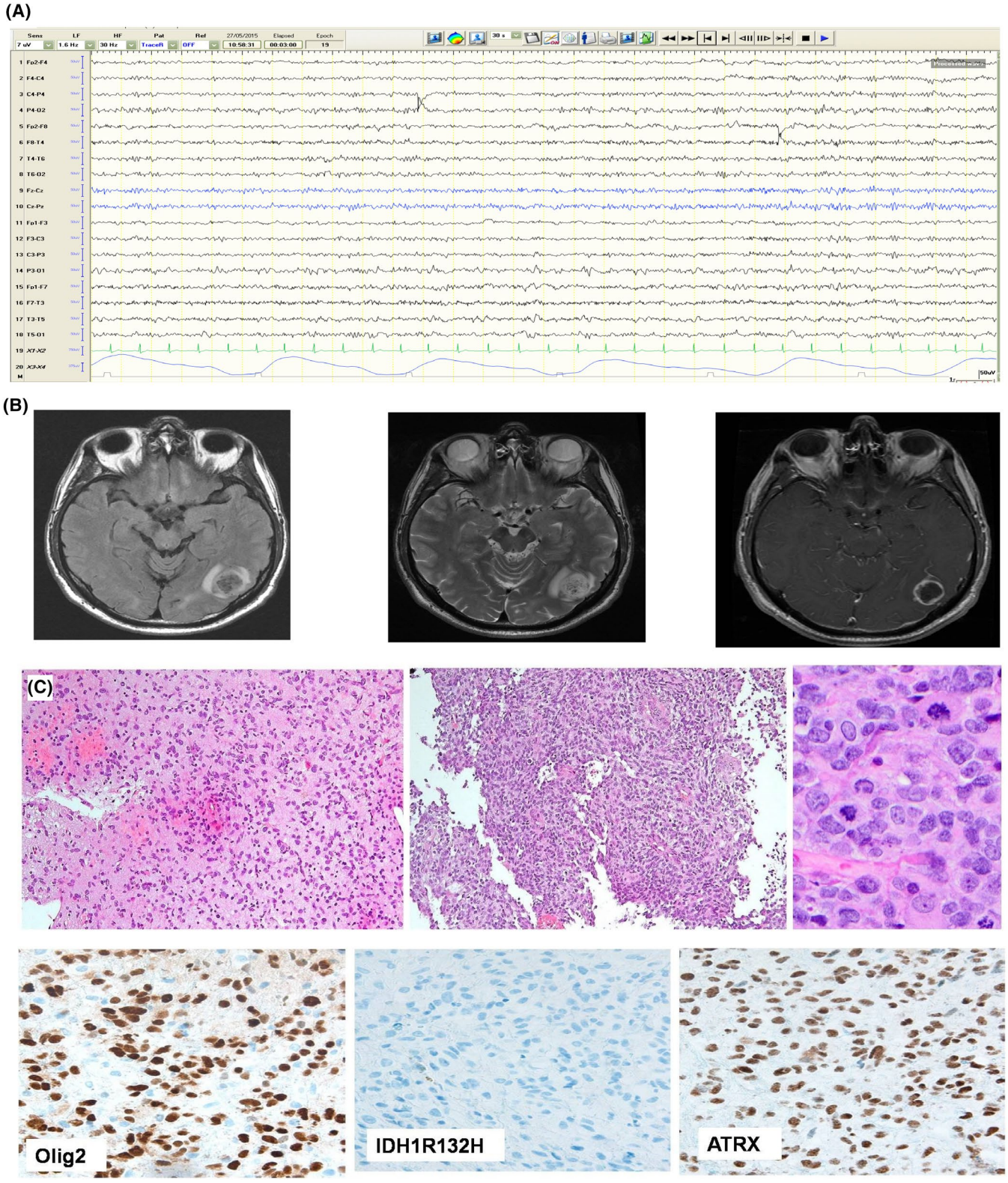

FIGURE 2 Tumor epilepsy case history: male, aged 50 years. Two-month history of focal seizures characterized by the sudden onset of visual hallucinations (scenes of his life flowing back in quick succession from adulthood to infancy) strictly confined to the right visual hemifield, sometimes evolving to tonic–clonic seizures. (A) Electroencephalogram showing left posterior slow activity intermingled with rare slow spikes. (B) Magnetic resonance imaging showing left posterior high-grade glioma. (C) Neuropathological examination: diffuse astrocytic glioma, isocitrate dehydrogenase (IDH) wild-type, and H3 wild-type, showing high mitotic activity and microvascular proliferation, and a TERT promoter mutation (c.-146C>T; C250T, VAF 59%), corresponding to a glioblastoma, IDH wild-type, grade 4, according to World Health Organization 2021.

radiotherapy to increase the overall survival time in HGGs. The benefit of the addition of temozolomide to radiotherapy in people with newly diagnosed glioblastoma was first demonstrated in 2005 in the pivotal EORTC 26981/22981-NCIC CE3 randomized clinical trial[61] and later confirmed in elderly patients with glioblastoma.[62] In both studies, the clinical benefit of TMZ treatment was largely confined to patients with glioblastomas with a methylated O6-methylguanine DNA methyltransferase (MGMT) promoter. In the CATNON trial, the efficacy of the addition of TMZ during and after radiotherapy was investigated in patients with grade 3 astrocytoma. In this study, the TMZ benefit was found to be restricted to patients with astrocytoma grade 3 with IDH1/2 mutations and as adjuvant treatment; there was no TMZ clinical benefit in patients with IDH1/2 wild-type gliomas, now referred to as glioblastoma, regardless of MGMT promoter status.[63,64]

Additional targets for personalized medicine are also available (ESMO Scale for Clinical Actionability of Molecular Targets [ESCAT] 1–2, BRAF, NTRK, FGFR). Dabrafenib plus trametinib showed clinically meaningful activity in patients with $BRAF^{V600E}$ mutation-positive recurrent or refractory HGG and DLGG, so that $BRAF^{V600E}$ testing could potentially be adopted in clinical practice for patients with glioma.[65]

In terms of seizure control, a systematic review showed that TMZ reduced seizure frequency in 29%–89.7% of patients with glioma, and the percentage of patients with complete seizure control after TMZ ranged from 19.4% to 72%.[66] These good results were mostly obtained in patients with DLGG; TMZ seemed to have little effect on seizure control in elderly patients with glioblastoma. Chemotherapy with the alkylating agents procarbazine, lomustine (CCNU) or TMZ in DLGG has demonstrated, in retrospective series, a seizure reduction in >50% of the patients in most studies and seizure freedom ranging from 13% to 60%.[60] Moreover, an Italian prospective study focused on the use of TMZ in DLGG requiring treatment after surgery has reported seizure reduction in 85% of patients, regardless of the radiological response.[67]

The mechanism of action by which TMZ shows this antiepileptic effect is unclear. It has been speculated that TMZ may be exerting its effect by killing glioma cells that may be actively irritating surrounding neurons or altering the peritumoral microenvironment to trigger seizures.[66]

Approximately two thirds of HGG patients show a recurrence or worsening of seizures after first-line treatment, which marks disease progression.[1,68] In DLGG, however, the association between seizure worsening and tumor evolution is poorly documented.[69]

5 | LOW-GRADE GLIOMAS AND EPILEPSY

Supratentorial DLGGs, classified as WHO grade 2 tumors, are a heterogeneous group of slowly growing BTs derived from glial cell lines.[46]

DLGGs are relatively rare tumors, accounting for 6.4% of all adult primary central nervous system tumors.[70] They typically affect patients at a younger age compared with HGGs, with the peak incidence between ages 35 and 44 years.[70] Median survival for patients with low-grade gliomas (LGGs) ranges from 5 to 13 years and depends on specific histology and molecular features.[70]

The majority of patients diagnosed with DLGG develop TRE, often as the clinical onset of the disease.[71] Surgery plays a central role in achieving both oncological benefit and seizure control.[72,73]

Tumor site, extent of resection (EOR), adjuvant radiotherapy or chemotherapy, length of preoperative seizures, and number of ASMs required to control seizures are among the potential predictors of postoperative seizure outcome in DLGG patients. EOR emerges as one of the independent predictors of epileptic outcome in DLGG.[73–76] A large multicenter study by Still et al.[75] showed that postoperative seizure control in individuals with supratentorial DLGG was more likely when EOR was 91%. Ius et al.[73] emphasized the importance of combining volumetric resection thresholds (e.g., >90%) with molecular profiling (e.g., IDH1/2 mutation, 1p/19q codeletion) to stratify patients and predict seizure outcomes. Their findings indicate that early and extensive resection, when feasible, offers optimal seizure control, particularly in tumors with favorable molecular profiles.

Overall, in this clinical setting the impact of surgery on postoperative seizure control can be attributed to the shared pathogenic mechanisms underlying glioma growth and glioma-related epileptogenesis, as well as the presence of epileptogenic foci within the neocortical regions surrounding the glioma core.[77] Notwithstanding, approximately 40% of DLGG patients have persistent seizures following maximal resection.[6,8] Epileptogenic focus and tumor area are not always completely overlapping; epileptic activity is found mainly in peritumoral tissues, and sometimes it may extend beyond the tumor site. The refinement of the epileptogenic zone by means of preoperative long-term video-electroencephalographic (EEG) monitoring (LTVEM) intended to record the seizures may be necessary for surgical strategy.

Although it is well known that recurrent seizures after a seizure-free period may herald malignant progression, the implications of seizure relapses for clinical outcome have not been systematically studied. Also, the exact

temporal relationship between seizures and tumor progression in DLGG remains unclear.[78]

In a recent investigation, Mazzucchi et al.[79] highlighted the importance of understanding the impact of posttumor resection seizures on survival outcomes in DLGG patients. Through their clinical retrospective study, the authors described an association between the persistence of seizures after tumor removal and decreased survival rates in this patient population. Furthermore, postsurgical seizure control could be a relevant factor to consider during follow-up of TRE, in particular when gross total resection is not achieved. Pathological findings on intraoperative electrocorticography (iECoG) may suggest a "hidden" propensity to malignant progression, strictly related to the persistent neuronal hyperexcitability.[78] Similarly, the study by Englot et al.[80] suggested that seizures may influence glioma biology, potentially affecting tumor growth and progression. Patients who continued to experience seizures postoperatively exhibited markedly poorer survival rates compared to those who became seizure-free following surgery. These results highlight the detrimental effect of persistent seizures on the prognosis of DLGG patients, emphasizing the importance of comprehensive seizure management strategies in the treatment of DLGG patients, not only for improving quality of life but also for potentially extending survival outcomes.

6 | GNTs AND EPILEPSY

GNTs originate from neuroepithelial cells that form the wall of the neuronal tube during early embryonic development. They are increasingly recognized as a cause of focal epilepsies, particularly in children and young adults.[48] GNTs account for .1%–1.3% of all BTs and are more common in infancy, with an incidence of 7.6%.[68] These tumors comprise a mixture of glial and neuronal elements and are most commonly observed in the temporal lobe, particularly at the temporoanterobasal mesial site.[81] GNTs are classified among LEATs (Table 3), whose most frequent symptom is drug-resistant epilepsy. The occurrence of seizures is reported in up to 100% of dysembryoplastic neuroepithelial tumors (DNETs), 80%–90% of gangliogliomas, and 60%–85% of low-grade astrocytomas and oligodendrogliomas.[12]

Seizures associated with GNTs are extremely responsive to surgical treatment. Early surgical intervention seems to be significantly associated with improved seizure control.[82] The best seizure outcome results are obtained with resection of the tumor and the adjacent epileptogenic zone as identified by noninvasive presurgical neurophysiological study. GNTs are frequently associated with cortical dysplasias (40%–80% of cases) and rarely with hippocampal sclerosis (2%–25% of cases).[83]

The use of an epilepsy surgery-oriented strategy may result in an excellent seizure outcome (Engel I outcome up to 80%), thus enabling surgical treatment to be offered at an early stage.[84] This approach can help to avoid the consequences of uncontrolled seizures and the side effects of prolonged pharmacological therapy, while also reducing the risk of tumor growth or malignant transformation. Although there is a paucity of evidence and no current treatment guidelines, adjuvant therapies such as radiotherapy and chemotherapy are mainly reserved for the setting of anaplastic gangliogliomas/malignant transformations. It is possible that immunotherapy could be employed in the treatment of BRAF-mutated high-grade lesions.[85]

7 | DIAGNOSTIC WORKUP OF TRE

TRE represents a peculiar etiology-specific epilepsy,[86] requiring a multidisciplinary approach from the onset of the condition.

Diagnostic work-p of TRE includes a detailed epileptological medical history encompassing description of seizure types, seizure frequency and duration, presence of epileptic auras, possible triggers, post- and interictal manifestations, and current and/or previous ASMs, including doses and any side effects.

Neurological examination carried out according to the Neurological Assessment in Neuro-Oncology scale and the Karnofsky Performance Score (KPS) is crucial to obtain baseline data and assess neurological and global function at each further visit.[87,88]

In case of cognitive disturbances, comprehensive neuropsychological testing should be performed, and Mini-Mental State Examination or the Montreal Cognitive Assessment are useful to evaluate patients before and after treatments.

EEG recordings support the diagnosis of TRE and allow a better definition of the interictal and, more rarely, ictal features. These aspects are helpful for ASMs decision-making. Routine EEGs may be completely normal or exhibit normal background with focal slow activity and/or epileptiform activity. Continuous focal delta slowing is more often observed in HGGs, and it correlates with involvement of white matter tracts.[89]

Prolonged EEG recordings and ambulatory EEG permit a more thorough classification of seizure type and quantification of seizure frequency. However, the gold standard for EEG recording is LTVEM, especially in the case of refractory epilepsy associated with LEATs and

LGGs, with the aim of recording seizures and therefore disclosing the epileptogenic zone.[90] Preoperative invasive EEG (iEEG) recordings are preferentially performed in the case of LEATs, especially if they are located extratemporally. In patients with TRE secondary to LGGs, the role of iEEG is controversial. Rosenow and Menzler[91] consider preoperative iEEG only for subjects with extratemporal lesions, if the tumor cannot be largely resected because of adjacent or overlapping eloquent areas. They suggest mapping the peritumoral zone to determine its relationships to the lesion, and the irritative and seizure-onset zones to maximize the lesionectomy. However, the evolution of neuroimaging, noninvasive EEG techniques, intraoperative monitoring, and surgical approaches further limits the need for iEEG in the case of glioma-related epilepsy.[92]

Neuroimaging is crucial for the diagnosis of BT and the definition of the epileptogenic lesion. Brain magnetic resonance imaging (MRI) with T2-weighted, T2 fluid attenuation inversion recovery sequences and three-dimensional weighted sequences before and after contrast agent represents the diagnostic gold standard. Perfusion MRI, functional MRI with diffusion tensor imaging, and amino acid positron emission tomography are useful to define metabolic characteristics of the lesions and identify relations with white matter tracts.[93]

Finally, multimodal evoked potentials should be performed preoperatively in all patients undergoing surgery with intraoperative monitoring and mapping (IOM), to obtain data useful for surgical planning and comparison with intraoperatively recorded traces.

The use of IOM is essential to preserve the integrity of motor and sensory areas and is a gold standard for surgery of gliomas.

Different brain functions can be assessed during awake surgery using electrical stimulation alone or in combination with neuropsychological testing.[72] Motor, somatosensory, and visual functions can be successfully monitored in sleeping patients.[94]

Neurophysiologic monitoring techniques support the surgeon during resection by continuously assessing functional integrity of eloquent brain areas and subcortical pathways and warning about mechanical and/or vascular injury. IOM may contribute to maximizing the extent of resection, minimizing potential functional deficits, and optimizing both oncological and epileptological outcome.[95] Factors influencing the decision between an awake versus asleep intraoperative setting should be carefully considered, encompassing surgical goals, patient cooperation, team expertise, and neuro-oncological aspects.[95]

Thus, IOM should be performed in all glioma surgeries, regardless of their histology, when the lesion involves eloquent brain areas or white matter tracts, and in the presence of TRE. On the other hand, preoperative presence of severe neurological deficits may compromise the reliability of IOM and therefore make it useless.

The use of iECoG during glioma surgery is still controversial.[96] Increasing data show that iECoG can help in detecting epileptiform activity in tumoral and peritumoral tissues, aiding surgical resection and improving seizure outcomes.[97] Furthermore, iECoG allows recognition of intraoperative seizures (IOS), usually electric seizures without motor signs.[98] The occurrence of IOS may compromise patients' cooperation during awake craniotomy. Thus, a prompt detection of IOS prevents the possible evolution in tonic–clonic seizures and the need for benzodiazepines or propofol drips and allows patients to be fully cooperative during the procedure.[98]

Intraoperative stereo-EEG may contribute to improving seizure outcomes in TRE, especially in lesions involving deep brain structures and in the case of hippocampal sparing.

During the follow-up period, patients undergo MRI with contrast at periodic intervals (2–6 months usually, according to histology) to assess disease status and treatment response. However, in the case of more benign lesions, a longer timespan between neuroimaging can be considered.

Neurological assessments are crucial in cases of TRE, to evaluate recovery from possible postsurgical transient deficits, seizure outcome, and treatments benefits and to monitor the effectiveness of ASMs. Periodic EEG recordings are not needed, except in cases of ASM dose reduction, therapeutical changes, and seizure relapse in previously seizure-free patients. ASM tapering and withdrawal may be considered in selected cases and should always be performed under neurological and EEG control. However, no evidence exists for an optimal seizure-free period before ASM tapering in TRE patients.[90]

8 | SURGICAL APPROACH TO TRE

Surgical therapy represents the optimal treatment for TRE, irrespective of the specific histotype (HGG, DLGG, or LEAT) or brain site of the BT. Early surgical intervention is crucial in ensuring a precise diagnosis, delineating the molecular and genetic profile of the lesions, and guiding the subsequent sequence of chemoradiotherapy and targeted treatments. This approach is associated with a higher probability of achieving seizure freedom.

In the context of HGG- and DLGG-related epilepsy, the oncological aspects are of paramount significance. The objective of early surgery is to achieve maximal extent of tumor resection while preserving neurological and

neuropsychological functions. Awake surgery, MRI navigation, IOM, intraoperative confocal laser imaging, intraoperative ultrasound, and fluorescence-guided surgery (5-aminolevulinc acid and fluorescein) represent the main neurosurgical tools capable of guiding the surgeon, reducing surgical time, and decreasing the risk of permanent deficits.[99] When minor neurological deficits are predictable, they should be discussed with the patients and their caregivers, to evaluate together the best strategy to achieve good oncological and functional outcome.

A resection of >90% of the tumoral volume has been shown to offer the best long-term oncological prognosis for both HGG and DLGG,[100,101] along with optimal seizure control (65.5% in DLGG and 50% in HGG),[80,102] irrespective of tumoral locations.[103] In addition, there have been suggestions that supratotal resection of diffuse gliomas may result in improved seizure control and oncological treatment outcomes.[104] A particular focus of the current research is the investigation of whether anterior temporal lobectomy (a procedure routinely performed in patients with pharmacoresistant temporal lobe epilepsy) may constitute a supramarginal resection in temporal glioblastomas.[105] The aim is to determine whether this may have implications for epileptological and oncological outcomes. Furthermore, a recent meta-analysis proposed that seizure freedom is less likely to be achieved in patients with focal preoperative seizures and more likely to be achieved in patients with frontal lobe LGGs.[106]

Surgery is recommended for patients with IDH mutant and 10-19q codeleted oligodendrogliomas of WHO grade 2 and IDH mutated astrocytoma of WHO grade 2. EOR represents a prognostic factor for anaplastic oligodendrogliomas and astrocytomas; thus, surgery should be performed as feasible.[93] Surgery at tumor recurrence may provide therapeutic benefits, under a reasonable risk of postoperative complications. It is important to reevaluate histology and detect molecular information, in the light of potential targeted therapy.[107] Finally, surgery is advisable in the case of glioblastomas with KPS < 70; elderly patients should be considered candidates on an individual basis.

In the case of GNTs and other LEATs, the epileptological aspects are found to be of greater significance than the oncological aspects. Surgery represents a curative treatment in almost the totality of these lesions. Early removal and a short seizure history offer the best chance to achieve Engel I seizure outcome (in approximately 80% of cases).[84] When faced with these tumors, an epilepsy-oriented presurgical workout is always suggested, including LTVEM to record seizures. The aims are to clearly define the anatomoelectroclinical correlation and to determine whether tumor resection (lesionectomy) is sufficient to cure the seizures or whether it is necessary to remove the lesion and the epileptogenic zone (tailored resection). Some shared opinions and consensus point out that lesionectomy alone provides good seizure outcome in GNTs located at extratemporal and temporolateral sites, whereas the results of lesionectomy alone appear to be disappointing at the temporomesial site. A resection of the temporomesial structures (hippocampal–parahippocampal complex), even if the hippocampus is not clearly invaded by the tumor, offers the most favorable epileptological outcome in mesial, especially long-lasting, temporal lobe epilepsy.[84,108]

In this context, iECoG monitoring has the potential to facilitate the identification and resection of the epileptogenic zone, a region that occasionally exhibits a greater extent than the primary tumor itself. The finding of continuous spiking, bursts, and recruiting discharges occur in almost 90% of patients with GNTs associated with focal cortical dysplasia, whereas they are rare in isolated GNTs.[109]

Table 4 presents the outcomes of surgical interventions for epilepsy according to histopathological classification.

TABLE 4 Surgical aspects of TREs across HGGs, DLGGs, and LEATs.

TRE group	Surgical indications	Postsurgical seizure outcome	Long-term follow-up
HGG	Surgery for oncologic purposes and molecular profiling; seizure relief is secondary	Limited; seizure-free rates typically <30% Strong association between seizure onset and longer survival	Short-term focus; seizure control has limited impact on prognosis
DLGG	Maximal safe resection aiming at seizure control and oncologic stability; strong correlation with extent of resection and molecular markers	Favorable; seizure-free rates 60%–80%; >90% if EOR >90% and favorable molecular profile	Long-term follow-up needed due to risk of seizure and tumor recurrence; seizure recurrence may indicate tumor recurrence and/or progression
LEAT	Curative intent even in small or asymptomatic lesions; early surgery recommended	Excellent; seizure-free rates >80%–90%	Generally stable long-term outcome; low risk of recurrence

Abbreviations: DLGG, diffuse low-grade glioma; EOR, extent of resection; HGG, high-grade glioma; LEAT, low-grade epilepsy-associated tumor; TRE, tumor-related epilepsy.

9 | ANTISEIZURE DRUGS, THERAPEUTIC PERSONALIZATION, AND INTEGRATION OF TREATMENTS

A preliminary issue concerns when to start antiseizures therapy in BT patients.

According to the updated Society for Neuro-Oncology and European Association of Neuro-Oncology (EANO) practice guideline on antiseizure prophylaxis, ASMs should not be prescribed to reduce the risk of seizures in newly diagnosed BT patients who have not had a seizure (level A class evidence). There is also insufficient evidence to recommend prescribing ASMs in seizure-naïve BT patients in the peri- or postoperative period to reduce the risk of seizures (level C class evidence).[110] Still, this topic is highly debated, mainly because current available evidence for the use of primary seizure prophylaxis is scanty and flawed.[111] The prescription patterns of primary ASM prophylaxis vary widely between physicians, ranging from 29% among EANO members to 78% among members of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons.[112,113]

Glioma patients who experience a first seizure usually necessitate ASM treatment due to the high risk of a recurrent seizure, which is common practice among a vast majority (86%) of European physicians.[112]

There are many variables that influence the choice of ASMs in patients with BT, including gender, age, tumor histology and molecular findings, chemotherapy, patients' perspectives and needs (e.g., license to drive or desire for pregnancy), disease stage, and comorbidities. Few randomized clinical trials have examined the efficacy of ASMs in TRE. Most have evaluated ASMs as add-on therapy rather than monotherapy. Sample sizes are often small and include variable tumoral pathologies. Therefore, evidence is usually scanty, and recommendations are inferred from expert opinions.

The type of the tumor plays an important role; whereas epilepsy secondary to LEATs such as gangliogliomas and DNETs may benefit from surgery, with high a chance of obtaining complete seizure remission and withdrawal of medications in the long term, seizures secondary to gliomas or cerebral metastases, irrespective of their frequency, need long-lasting antiseizure treatment without realistic possibility of complete recovery.[90,114]

First generation ASMs such as phenobarbital, carbamazepine, and phenytoin, although effective for reducing seizure frequency, are not usually recommended in TRE mostly because of increased risk for drug–drug interactions and potentially more frequently occurring adverse effects.[9,90,114] This is due to the inhibitory (valproate) or inducing (phenobarbital, carbamazepine, and phenytoin) effect on the hepatic drug-metabolizing enzymes, mostly involving the cytochrome P450 system. The enzyme-inducing agents may interfere with chemotherapy and increase the risk of severe allergic reactions during radiotherapy. Interactions with monoclonal antibodies such as irinotecan and bevacizumab used in the therapy of brain metastases have been also reported. Valproate was initially favored due to its potential antineoplastic effect as a histone deacetylase inhibitor.[115] However, a subsequent pooled analysis of 1869 patients from four randomized clinical trials in newly diagnosed glioblastoma found that valproate use at the start of chemoradiotherapy was not associated with improved progression-free survival or overall survival compared with all other patients.[116] Valproate use has therefore declined, although it is often prescribed as a second- or third-line agent. Overall, the interaction potential of first-generation ASMs has led to widespread use, in clinical practice, of second- or third-generation ASMs.

Among the newly introduced ASMs, levetiracetam is the most popular drug in the treatment of TRE, with prescription percentages ranging from 80% to 90%.[90,112,114] The reasons for its success are the ease of use, a rapid titration, the lack of inducing properties, the good safety profile, and the availability of an intravenous formulation. Specific caution is required regarding the frontal localization of the tumor for possible psychiatric reactions and thrombocytopenia.

Lamotrigine is an efficacious drug for seizure control, but the slow titration schedule limits its use in patients with rapidly progressive tumors and/or high seizure frequency.

Topiramate is a drug with multiple mechanisms of action, including action on sodium channels and antiglutamatergic and γ-aminobutyric acidergic effects. Despite preliminary data on a good tolerability profile and high efficacy in TRE,[117] its use is limited.

Lacosamide has recently been shown to achieve satisfactory rates of seizure freedom as monotherapy in TRE, with 64.4% of patients being seizure-free at 3 months and 55% at 6 months.[118]

Perampanel is a promising drug in the treatment of glioma-induced epilepsy, mostly because of its specific mechanism of action involving the glutamatergic pathways. Perampanel acts as a selective antagonist of glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors and may therefore play a role in both the reduction in tumor growth and the control of epileptiform activity. Salmaggi et al.[119] evaluated the impact of perampanel alone or in combination with temozolomide on the growth of a number of glioblastoma grade 3 astrocytoma cell lines. Perampanel showed antitumor activity in all cell lines, and the combination of

perampanel and temozolomide had a significant synergistic effect, the antitumor activity being related to a proapoptotic effect. In humans, a number of studies have highlighted its efficacy and tolerability as add-on therapy in drug-resistant TRE.[120]

In elderly patients, comorbidities need special attention to avoid possible interactions, particularly with the new direct oral anticoagulants. In these cases, not only the old generation ASMs are contraindicated but also levetiracetam, a recommendation however based only on in vitro studies and not on clinical evidence. In the elderly, hepatic and renal insufficiency may gradually develop, with clearance changes requiring ASMs dosage adjustments.

Furthermore, the use of ASMs has specific implications that deserve special attention; ASMs may give rise to side effects, which may interfere with the clinical monitoring of the underlying pathology. Conversely, the underlying pathology may cause the appearance of subtle neurological symptoms that may be attributed erroneously to the last add-on drug, giving rise to delays of diagnosis.[9]

Specific clinical contexts in the field of TRE consist of the treatment of SE and therapeutic management in the end-of-life stage of the disease.

SE may occur in different stages of BT, either as the first manifestation or during the course, often heralding tumor progression and contributing to a decline in functional status.

Overall, a number of studies suggest that the treatment of SE in BT does not differ from that usually employed in non-BT patients, with treatment responsiveness and short-term clinical outcomes also showing comparable results, including mortality rate.[121–123] In a study by Tziakouri et al.[123] comparing SE treatment and outcomes in glioma, other neoplastic, and nonneoplastic patients, it was observed that refractoriness and short-term mortality were similar in all groups.

Although in the end-of-life stages SE bears a dismal prognosis in the short term and therapeutic choices are easier, the treatment of SE in near-terminal conditions (e.g., SE caused by long-standing glioblastoma) is a difficult issue, particularly regarding the acceptance of avoiding third-line therapies in patients who have not yet expressed end-of life decisions, with the risk of futile treatments in intensive care unit (ICU), including invasive mechanical ventilation (IMV).[124,125] In a multicenter retrospective study performed at four certified interdisciplinary BT centers in Germany, an in-hospital mortality rate of 60.6% was observed in 33 glioblastoma patients undergoing unplanned ICU treatment with IMV for a number of reasons, including SE.[126] In this condition, the mortality rate was 50%, highlighting the difficulties of the decision-making process and the need for frequent reassessment of goals during ICU stay. These observations suggest that a specific path to obtain anticipated decisions and advanced care planning from the glioblastoma patients should be pursued following Italian law (No. 219 of December 22, 2017).

10 | CONCLUSIONS

TRE management warrants a special attention within the realm of symptomatic epilepsies, due to the considerable challenges it poses, arising from its intricate pathophysiological mechanisms and its evolution over tumor progression.

This cooperative multidisciplinary overview provided a synthesis of key evidence and therapeutic advancements for TRE in BT patients (Table 5).

10.1 | Pathophysiology of TRE

TRE has a complicated and dynamic etiology that includes neurotransmitter imbalances, neuroinflammation, and genetic abnormalities. These processes affect the hyperexcitability of BTs by promoting tumor development and epileptogenesis. Understanding the intricate interplay of these mechanisms involved in epileptogenesis associated with BTs is essential for the development of precise therapeutic strategies aimed at enhancing seizure control and ultimately improving patient outcomes.

10.2 | WHO 2021 tumor classification

The latest WHO classification integrates molecular data, improving tumor subtyping, prognosis, and clinical trial design, particularly for gliomas. Tumor behavior and treatment response can be better understood with the help of this molecular approach with clear advantages in terms of prognosis refinement and designing clinical trials.

10.3 | Seizure control and surgery

The principle of maximal safe resection, in both LGG and HGG, implies a double benefit, in terms of both survival and seizure control. Supratotal resection is gaining attention for sustained seizure control. In cases of highly epileptogenic tumors, such as GNTs, lesionectomy with removal of the adjacent epileptogenic zone provides the best outcomes, especially in cases of mesial temporal lobe epilepsy. The refinement of the epileptogenic zone by means of preoperative LTVEM intended to record the seizures may be necessary for surgical strategy, at least

TABLE 5 Treatment of tumor-related epilepsy.

in selected cases. Use of IOM and iECoG allows identification of interictal electrographic highly epileptogenic patterns, improving the possibility of achieving a good postoperative seizure outcome.

10.4 | Radiotherapy and chemotherapy

In addition to their role in tumor progression, radiotherapy and chemotherapy (especially TMZ) can reduce seizure frequency in many patients, with the response rate being highest in DLGGs and IDH-mutated tumors.

10.5 | Seizure persistence and prognosis

Persistent or recurring seizures after an initial seizure-free period often signal tumor progression and are associated with poorer survival.

10.6 | Antiseizure medications

ASMs are commonly used in the treatment of TRE and are usually commenced after the first seizure. Prophylactic treatment in patients without a history of seizures is not recommended, and in any case is restricted to a brief postoperative period. Third-line ASMs are commonly preferred because of their better tolerability profile and lack of drug–drug interactions. Studies comparing the efficacy of individual drugs in TRE are not available, and the choice of ASMs mostly depends on individual patient factors and expert opinion, with levetiracetam being the most commonly used drug. Perampanel is a promising alternative due to its effects on glutamate transmission.

10.7 | Management of SE

Although the treatment of SE in BT does not differ from that usually employed in non-BT patients with comparable results, the management of SE in near-terminal conditions (e.g., SE caused by long-standing glioblastoma) is a difficult issue, particularly in patients who have not yet expressed their end-of-life decisions, with the risk of futile treatments in ICU including IMV.

10.8 | Multidisciplinary management

A cooperative, multidisciplinary approach is required, especially when seizures are linked to a progressing condition. Treatment options may include surgery, chemotherapy, radiotherapy, and ASMs. The value of each approach varies depending on the stage of disease evolution, and hence each patient should be evaluated by a team of specialists at tumor board meetings.

In conclusion, TRE presents significant challenges in the management of BT patients. To enhance patient outcomes and quality of life, further prospective, multicentric studies including multiple outcomes and complementary treatment strategies are needed.

AUTHOR CONTRIBUTIONS

Roberto Michelucci: Conception and design of the work; writing—original draft preparation; final draft preparation and editing. **Giada Pauletto, Tamara Ius, Matteo Martinoni, Antonio Silvani, Andrea Salmaggi, Carlo Alberto Castioni, Elena Pasini**, and **Eleonora Aronica:** Preparation of drafts of single sections of the paper. **Marta Maschio, Roberta Rudà, Tamara Ius, Giuseppe Minniti, Enrico Franceschi, Flavio Villani, Carlo di Bonaventura, Sofia Asioli**, and **Elena Pasini:** Review and critical revision of the final paper. **Paolo Vitali, Damiano Balestrini, Elisa D'Angelo, Lorenzo Bello, Marco Rossi, Marta Padovan, Anna Teresa Giallonardo, Francesco Toni, Angela La Neve, Simona Rizzato, Matteo Pugnaghi, Marco Vindigni**, and **Carmelo Sturiale:** Members of a discussion group on tumor epilepsy; contribution to the multidisciplinary network giving rise to the article; review of the article.

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CONFLICT OF INTEREST STATEMENT

R.M. has received speaker and consultancy fees from Angelini Pharma and Eisai. E.F. has served on a steering committee for GSK and advisory board for Genenta Science. E.A. has served on scientific advisory boards for UCB and Nutricia. R.R. has received speaker or consultancy fees from Novocure, Servier, Bayer, Genenta, and CureVac. A.L.N. has received speaker or consultancy fees from Eisai, Mylan, Sanofi, Bial, GW, UCB Pharma, Arvelle Therapeutics, Angelini Pharma, and Neuraxpharm. The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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