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Management of glioma-associated epilepsy in the molecular era: a review of the literature and an institutional experience

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Seizures following resection for glioma can significantly impact patient quality of life. Resection and antiseizure medications have been first-line treatments for glioma-associated epilepsy since the survival benefit of maximizing the extent of resection was established. Given recent advances in tumor molecular profiling and neuron-glioma circuit interactions, should the management of tumor-associated epilepsy change? Here the authors present a literature review of the current state of the surgical and medical management of postoperative seizures in patients with glioma, summarize key findings from investigations of the molecular processes governing tumor-associated seizures, and provide a retrospective review correlating tumor mutational profiles obtained from next generation sequencing with seizure history in patients from a single institution. This paradigm of comparing clinical seizure outcomes and tumor genetics may broaden the understanding of glioma-associated epilepsy and prognostic factors, potentially leading to new therapeutic strategies.

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KEYWORDS diffuse glioma; seizures; next generation sequencing; tumor-associated epilepsy

Seizures are a frequent presenting symptom for patients with adult-type diffuse gliomas, as well as a major source of morbidity affecting patient quality of life postoperatively.[1–6] While the incidence of seizure varies by tumor size, location, histopathological type, and grade, *IDH*-mutant tumors are thought to be more epileptogenic than *IDH*-wildtype tumors, with > 80% of them presenting with seizure in some cohorts.[1] Seizure control following resection is a core aspect of disease management for patients with glioma, as there is a tradeoff between mitigating the deleterious effects of seizures and minimizing the adverse effects associated with the use of antiseizure medication. Several associations between postoperative seizures and tumor progression as well as worse survival outcomes have been reported, underscoring the importance of seizure freedom as an oncological consideration.[1,2,7,8] As new developments in cancer neuroscience have shed light on the tumor biology underpinning tumor-associated epilepsy, exploring molecular alterations in gliomas through methods such as next generation sequencing could reveal novel therapeutic opportunities and optimize the clinical management of seizures in glioma. Here we summarize the current literature on the surgical and postoperative medical management of tumor-associated epilepsy, review relevant biological pathways implicated in tumor-related epileptogenesis, and present our own institution's experience with the use of next generation sequencing to identify molecular alterations associated with preoperative and postoperative seizures.

Methods

We performed a literature search of PubMed for articles published before March 1, 2025. The search terms "glioma", "glioblastoma", "seizure", "epilepsy", "resection", "hippocampectomy", "lobectomy", "laser", "glioma associated epilepsy", "targeted inhibitor", "antiepileptic", "antiseizure", and "AED" were used with a combination of AND/OR restrictions to identify relevant articles. These articles were included as references on the basis of a review of the abstract.

Patient records from our institution were also retrospectively reviewed with approval from the University of California, San Francisco Institutional Review Board. Patients were included in our analysis if they were 18 years of age or older at the time of primary resection, underwent resec-

ABBREVIATIONS AED = antiepileptic drug; D2-HG = D-2-hydroxyglutarate; ECoG = electrocorticography; GBM = glioblastoma; GTR = gross-total resection; LITT = laser interstitial thermal therapy; KPS = Karnofsky Performance Status; STR = subtotal resection.

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tion of pathology-confirmed diffuse supratentorial glioma, and had next generation sequencing profiling of their tumor tissue with a gene panel of 529 cancer-related genes. For patients with multiple resections or multiple next generation sequencing panels, preoperative and postoperative seizure history was indexed from the first resection and results of the first next generation sequencing were used.

Clinical and demographic variables included age, sex, past medical history, preoperative Karnofsky Performance Status (KPS), seizures at presentation, tumor size, tumor location, extent of resection, and postoperative seizure history. Only seizures 72 hours after surgery and beyond were considered, as seizures before this time point could be more associated with surgical factors. To stratify patients by postoperative seizure burden, those who experienced postoperative seizures at an approximately monthly frequency or more at any point in their postoperative course were considered to have recalcitrant seizures; those who did not experience any seizures, a single seizure, or rare seizures were considered to not have recalcitrant seizures. Glioma grade and subtype were assessed using the WHO CNS tumor 2021 guidelines. Only mutations present in more than 5% of each cohort (*IDH*-wildtype and *IDH*-mutant) were included in the analysis. All statistical analysis was performed using R (version 4.2.2, The R Foundation for Statistical Computing). Predictors that had $p < 0.1$ on univariate analysis were included in a multivariate model. The threshold for statistical significance was set at $p < 0.05$ for all analyses.

Results

Surgical Strategies to Maximize Seizure Freedom and Prognostic Associations

Resection plays an important role in long-term seizure freedom, particularly for patients with low-grade gliomas of the insular or temporal lobe, near the cortical surface, or near eloquent areas. In several reports, a greater extent of resection has been found to predict increased seizure freedom in patients with low-grade glioma.[1,4,9–15] For example, in a multicenter study of 1509 patients with low-grade glioma, Pallud et al.[1] found that total or subtotal resection (STR), as compared to partial resection or biopsy, resulted in significantly greater rates of complete seizure freedom at 6 months. In a meta-analysis of 2641 patients with low-grade glioma, Shan et al.[4] found that gross-total resection (GTR) as compared to STR was associated with a significantly higher rate of Engel class I seizure freedom (complete freedom from disabling seizures); Nandoliya et al.[11] reported a similar conclusion for seizure freedom in a meta-analysis of 1628 patients. Some studies have suggested an extent of resection threshold of > 80% for total seizure freedom in low-grade glioma and 81% for Engel class I seizure freedom in insular glioma.[10,16]

While fewer studies have assessed postoperative seizure freedom in high-grade gliomas, there is evidence of a similar benefit in postoperative seizure control from a greater extent of resection. In a cohort of 1006 patients with glioblastoma (GBM), Pallud et al.[2] showed that while seizure rates increased from diagnosis to after standard of care treatment to tumor progression to finally end of life, supramarginal and total resection compared to STR or biopsy predicted greater seizure freedom during the disease course. Li et al.[8] found that GTR compared to STR produced a higher rate of seizure freedom in a cohort of 449 patients with high-grade gliomas.

Given the propensity of temporal and insular lobe tumors to cause seizures, some authors have also compared GTR to supratotal resection for survival and seizure freedom. In a systematic review of 1181 low-grade gliomas and glioneuronal tumors, Englot et al.[9] reported not only a higher rate of Engel class I seizure freedom at 6 months in the patients who had undergone GTR versus STR, but also greater seizure control among the patients who had undergone hippocampectomy or anterior temporal lobe corticectomy in addition to GTR versus GTR alone. In a meta-analysis of supratotal resection with anterior temporal lobectomy and GTR alone for temporal lobe GBM in 286 patients, Zheng et al.[17] reached a similar conclusion.

Laser interstitial thermal therapy (LITT) is another surgical approach for treating gliomas that are difficult to access.[18] Although the data on seizure outcomes following LITT for glioma are sparse, one series comparing LITT to resection in 14 patients with insular low-grade epilepsy-associated tumors demonstrated a similar rate of approximately 50% with freedom from disabling seizures at 12 months.[19] However, one review of LITT for insular tumors and epilepsy documented complete seizure freedom in only 1 of the 7 patients who had undergone the procedure.[20]

While maximal safe resection is important, so too is the need for further work to understand the value of targeting epileptogenic tissue beyond the tumor margin. Intraoperative electrocorticography (ECoG) can be used in epilepsy surgery to identify seizure foci.[21] And while the technique is commonly used to monitor for discharge potentials in glioma resection, there is no consensus on its value in improving seizure outcomes following surgery, primarily due to a lack of data, although individual studies have reported no significant impact on seizures.[14,15] One recent meta-analysis comprising 1115 patients with low-grade brain tumors and medically refractory epilepsy has revealed that the use of intraoperative ECoG to guide resection improves postoperative seizure freedom and seizure control more than lesionectomy alone,[22] although there is a need to replicate these analyses specifically in glioma to reflect the growing understanding of the mechanism of glioma-associated epilepsy.

Similar to patient quality of life considerations, postoperative seizure control may be relevant prognostically. Many studies have reported that a history of seizures at initial diagnosis confers a favorable overall survival benefit.[1,2,6,7,23] Moreover, some have shown that postoperative seizures confer an improved prognosis as compared to their absence in both high- and low-grade gliomas.[1,2,7,8,23] However, others have reported worse survival[3,24] or a correlation between seizures and disease progression.[25] We have also found a strong correlation between the timing of the first postoperative seizure and tumor progression as well as improved overall survival in patients with greater seizure freedom for both *IDH*-wildtype and *IDH*-mutant gliomas.[26]

Antiepileptic Drug Therapy

Antiepileptic drugs (AEDs) are a cornerstone of managing seizures in patients with diffuse gliomas in both the pre- and postoperative setting, and the optimal strategy for regimen selection and timing has been the subject of much study and discussion.[27–31] The consensus among clinicians is to begin AEDs after a single verified seizure before or after surgery,[27,31] although quality data on the benefit of seizure prophylaxis are lacking.[30] These opinions are reflected in the 2021 practice guidelines from the Society for Neuro-Oncology (SNO) and European Association of Neuro-Oncology (EANO), which advise against prophylactic AEDs in seizure-naive patients with newly diagnosed brain tumors (level A) and insufficient evidence to support preventative peri- or postoperative AEDs (level C).[32–34]

Determining the best agent for glioma-associated epilepsy is made difficult by a lack of focused studies.[31,35,36] Generally, first-generation antiepileptics are avoided out of concern for side effects and drug-drug interactions with steroids or chemotherapy.[28,29,31] Levetiracetam is commonly favored among clinicians in part because of its favorable side-effect profile and has the largest body of evidence supporting its use as a first-line agent in this population.[28,30,32,35,37,38] Other potential agents include lacosamide, which has been shown to significantly reduce seizures in patients with brain tumor–related epilepsy, including those with glioma, either as monotherapy or an add-on agent.[39–41] Valproic acid, once a popular treatment option, has fallen out of favor due to concerns about side effects and a lack of evidence of superiority in this patient population.[27,42,43] Newer AED options, such as brivaracetam and perampanel, show promise in this clinical context but require more robust study.[31]

The optimal duration of antiepileptic treatment is not well defined,[44] and there is currently no widely accepted schedule for the tapering of medication in patients with glioma-associated seizures, primarily due to a lack of data specific to this population. Consideration must be given to the adverse effects of long-term AED use, primarily cognitive and mood disturbances, which can significantly impact quality of life.[28,45,46] A review by Koekkoek et al. suggested that stopping AEDs may be considered in patients with stable low-grade glioma and long-term seizure freedom.[47] Withdrawal timing can range from 2 weeks after surgery to lifelong use depending on the preoperative and postoperative seizure burden, extent of resection, and tumor- and surgery-related risk factors.[48]

Randomized trials of AEDs in patients with glioma-associated epilepsy, such as the STING (first-line levetiracetam versus valproic acid in glioma patients with epilepsy, NCT030480) and SPRING (prophylactic levetiracetam versus no prophylactic AED in seizure-naive glioma patients) trials, might identify optimal agents and regimens.[36,49] Additional work could identify subgroups of patients with glioma who are more predisposed to seizures and warrant a more aggressive or prophylactic AED regimen.[29]

Institutional Experience

We performed univariate and multivariate logistic regression analyses of clinical and genomic factors to identify correlates of seizures at initial presentation and diagnosis of glioma, as well as postoperative seizures. Patients were stratified by their *IDH* mutation status to control for the distinct tumor biology of these two subsets of glioma.

In total, 539 patients were analyzed in the seizure presentation analysis (Fig. 1). Of the 366 patients with *IDH*-wildtype glioma, 129 (35.2%; Table 1) presented with seizure. On multivariate analysis, KPS (OR 1.03, 95% CI 1.00–1.05, p = 0.025) and *EGFR* mutation (OR 2.23, 95% CI 1.38–3.65, p = 0.001) were associated with a greater likelihood of presenting with seizure, whereas tumor volume (OR 0.98, 95% CI 0.97–0.99, p < 0.001) and PI3K-mTOR pathway mutations (OR 0.58, 95% CI 0.35–0.96, p = 0.033; Table 2) were associated with less frequent seizure presentation. For the 173 *IDH*-mutant tumors, 116 (67.1%; Table 1) presented with seizure. Tumor volume was similarly associated with lower odds of seizure (OR 0.99, 95% CI 0.98–1.00, p = 0.01), whereas temporal lobe tumors (OR 7.29, 95% CI 2.11–34.5, p = 0.004) and those with *CIC* mutations (OR 4.07, 95% CI 1.21–17.0, p = 0.034; Table 2) were associated with higher odds of seizure presentation.

Patients were included for postoperative seizure analysis if they had had standard of care resection, radiation therapy to the resection cavity, and temozolomide for *IDH*-wildtype tumors and at least resection for *IDH*-mutant tumors (n = 403; Fig. 2, Table 1). Median overall survival for the 254 *IDH*-wildtype tumors included in the analysis was 20.2 months (IQR 12.9–35.4 months), 120 patients experienced at least 1 postoperative seizure (47.2%), and 50 (19.7%) experienced recalcitrant seizures. In a multivariate analysis of any postoperative seizures versus complete seizure freedom, male sex (OR 2.14, 95% CI 1.27–3.66, p = 0.005) and seizure at initial presentation (OR 1.8, 95% CI 1.04–3.13, p = 0.036; Table 3) were both associated with increased odds of seizure. On multivariate analysis, seizures at initial presentation (OR 2.43, 95% CI 1.18–5.08, p = 0.017), *CHEK2* mutation (OR 25, 95% CI 1.49–1.93, p = 0.05), and *TSC1* mutation (OR 10.5, 95% CI 1.20–132, p = 0.036; Table 4) were all associated with greater odds of postoperative recalcitrant seizures. Among the 149 *IDH*-mutant tumors included for analysis, median overall survival was 63.8 months (IQR 4.0–110.5 months), 70 patients (47.0%) experienced 1 or more postoperative seizures, and 38 (25.5%; Table 1) experienced postoperative recalcitrant seizures. Multivariate analysis for any postoperative seizures identified male sex (OR 2.13, 95% CI 1.06–4.36, p = 0.037; Table 3) as associated with seizures. No clinical or molecular factors were significantly associated with recalcitrant postoperative seizures in *IDH*-mutant tumors in our cohort.

Discussion

Key Molecular and Circuit Mechanisms

Gliomas are thought to cause seizures through several mechanisms (Fig. 3). Many reports from the basic science literature suggest not only that neurons and glioma cells form synaptic connections, but also that this signaling may promote tumor growth.[50–52] Glutamate-mediated calcium

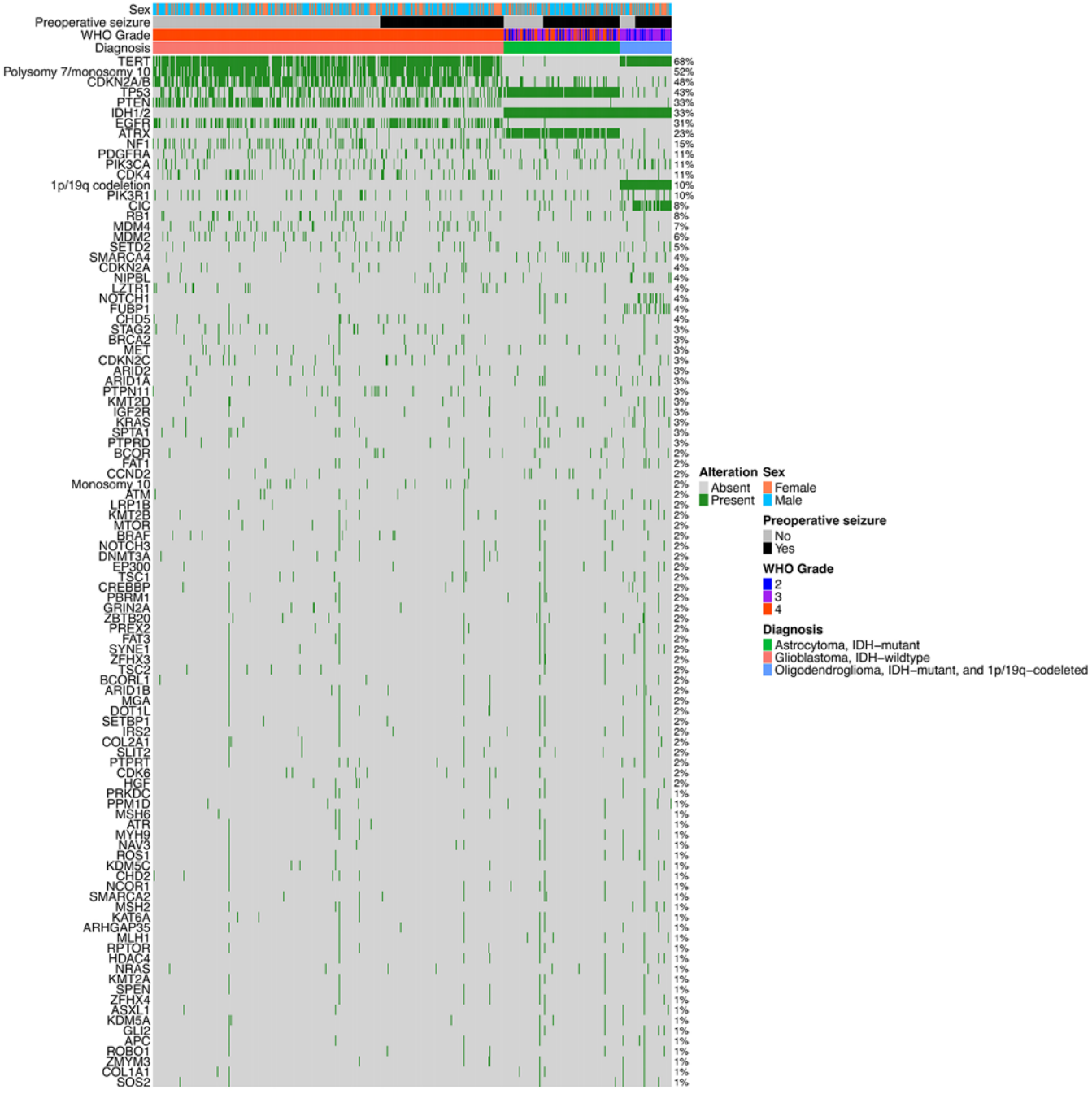

FIG. 1. Oncoplot of a cohort of adult diffuse gliomas (n = 539), including *IDH*-wildtype (n = 366) and *IDH*-mutant tumors (n = 173), depicting the 100 most common genomic alterations detected with next generation sequencing. Samples are grouped by diagnosis based on WHO 2021 criteria and by the presence of preoperative seizures.

signaling through AMPA receptors at the neuron-glioma interface and gap junctions among glioma cells can drive tumor progression.[50,51] Membrane depolarization of tumor cells via potassium currents may also have a similar effect.[50] Krishna et al. have also shown that gliomas that maintain high functional connectivity through local synaptic remodeling have a worse survival prognosis than less integrated gliomas.[52]

In turn, gliomas can influence neighboring neurons by increasing hyperexcitability via increased extracellular glutamate from upregulation of cysteine-glutamate exchange,[50,53] synaptic remodeling,[50,52] or dysregulated potassium and chloride ion homeostasis.[50,54,55] Tumor metabolomics may also play a role in glioma-associated epilepsy. Seizures are more common in patients with *IDH1*-mutated tumors, which may be attributable to the structural similarity between D-2-hydroxyglutarate (D2-HG), a Kreb's cycle metabolite that accumulates in *IDH1*-

TABLE 1. Baseline characteristics of a study cohort with glioma and results of logistic regression analysis

Variable	Patients Analyzed for Preop Sz				Patients Analyzed for Postop Sz			
	Overall	*IDH*-Mutant Tumor	*IDH*-Wildtype Tumor	p Value*	Overall	*IDH*-Mutant Tumor	*IDH*-Wildtype Tumor	p Value*
No. of patients	539	173	366		403	149	254	
Age at index op in yrs	54 (39–65)	35 (30–45)	61 (52–69)	**<0.001**	52 (38–63)	36 (30–44)	60 (52–66)	**<0.001**
Sex				>0.9				0.8
M	312 (57.9)	100 (57.8)	212 (57.9)		233 (57.8)	85 (57.0)	148 (58.3)	
F	227 (42.1)	73 (42.2)	154 (42.1)		170 (42.2)	64 (43.0)	106 (41.7)	
KPS				**<0.001**				**<0.001**
≥80	440 (81.6)	163 (94.2)	277 (75.7)		345 (85.6)	142 (95.3)	203 (79.9)	
<80	99 (18.4)	10 (5.8)	89 (24.3)		58 (14.4)	7 (4.7)	51 (20.1)	
Presented w/ Sz	245 (45.5)	116 (67.1)	129 (35.2)	**<0.001**	190 (47.1)	102 (68.5)	88 (34.6)	**<0.001**
FU in mos	27.4 (13.7–57.0)	65.4 (44.0–112.9)	18.4 (10.2–32.6)	**<0.001**	31.2 (16.5–58.9)	63.8 (44.0–110.5)	20.4 (12.9–35.4)	**<0.001**
Dead at FU	305 (56.6)	55 (31.8)	250 (68.3)	**<0.001**	221 (54.8)	43 (28.9)	178 (70.1)	**<0.001**
Tumor setting at time of UCSF500 sample collection				**<0.001**				**<0.001**
Primary	370 (68.6)	72 (41.6)	298 (81.4)		283 (70.2)	65 (43.6)	218 (85.8)	
Recurrent	169 (31.4)	101 (58.4)	68 (18.6)		120 (29.8)	84 (56.4)	36 (14.2)	
Tumor hemisphere				0.8				0.2
Rt	271 (50.3)	91 (52.6)	180 (49.2)		210 (52.1)	82 (55.0)	128 (50.4)	
Lt	259 (48.1)	80 (46.2)	179 (48.9)		192 (47.6)	66 (44.3)	126 (49.6)	
Bilat	8 (1.5)	2 (1.2)	6 (1.6)		1 (0.2)	1 (0.7)	0 (0.0)	
Midline	1 (0.2)	0 (0.0)	1 (0.3)		—	—	—	—
Tumor location				**<0.001**				**<0.001**
Frontal	224 (41.6)	101 (58.4)	123 (33.6)		170 (42.2)	88 (59.1)	82 (32.3)	
Temporal	151 (28.0)	30 (17.3)	121 (33.1)		114 (28.3)	29 (19.5)	85 (33.5)	
Parietal	98 (18.2)	23 (13.3)	75 (20.5)		74 (18.4)	18 (12.1)	56 (22.0)	
Insular	31 (5.8)	17 (9.8)	14 (3.8)		25 (6.2)	12 (8.1)	13 (5.1)	
Occipital	21 (3.9)	1 (0.6)	20 (5.5)		17 (4.2)	1 (0.7)	16 (6.3)	
Other	14 (2.6)	1 (0.6)	13 (3.6)		3 (0.7)	1 (0.7)	2 (0.8)	
Molecular grade				**<0.001**				**<0.001**
4	419 (77.7)	53 (30.6)	366 (100.0)		305 (75.7)	51 (34.2)	254 (100.0)	
3	74 (13.7)	74 (42.8)	0 (0.0)		59 (14.6)	59 (39.6)	0 (0.0)	
2	46 (8.5)	46 (26.6)	0 (0.0)		39 (9.7)	39 (26.2)	0 (0.0)	
Molecular classification				**<0.001**				**<0.001**
GBM, *IDH*-wildtype	366 (67.9)	0 (0.0)	366 (100.0)		254 (63.0)	0 (0.0)	254 (100.0)	
Astrocytoma, *IDH*-mutant	120 (22.3)	120 (69.4)	0 (0.0)		108 (26.8)	108 (72.5)	0 (0.0)	
OG, *IDH*-mutant & 1p/19q-codeleted	53 (9.8)	53 (30.6)	0 (0.0)		41 (10.2)	41 (27.5)	0 (0.0)	
Postop Szs	—	—	—		190 (47.1)	70 (47.0)	120 (47.2)	>0.9
Recalcitrant postop Szs	—	—	—		88 (21.8)	38 (25.5)	50 (19.7)	0.2

FU = follow-up; OG = oligodendroglioma; PMH = past medical history; Sz = seizure; UCSF500 = UCSF 500 Cancer Gene Panel Test.
Values are expressed as the median (interquartile range) or number (percent), unless indicated otherwise. Boldface type indicates statistical significance.
* Wilcoxon rank sum test, Pearson's chi-square test, or Fisher's exact test.

TABLE 2. Clinical and molecular predictors of presentation with seizure

IDH-Wildtype Tumor	No. of Cases	Univariate Analysis			Multivariate Analysis		
		OR	95% CI	p Value	OR	95% CI	p Value
KPS	366	1.03	1.01–1.05	0.007	1.03	1.00–1.05	**0.025**
Tumor vol	351	0.98	0.97–0.99	<0.001	0.98	0.97–0.99	**<0.001**
Tumor location	366						
Frontal		—	—		—	—	
Insular		2.77	0.90–8.92	0.076	2.22	0.66–7.81	0.2
Occipital		0.52	0.14–1.52	0.27	0.39	0.10–1.22	0.13
Other		0.62	0.13–2.17	0.49	0.35	0.05–1.47	0.2
Parietal		0.98	0.52–1.80	0.94	1	0.50–1.96	>0.9
Temporal		1.46	0.87–2.47	0.15	1.24	0.69–2.23	0.5
EGFR mutation	366	2.05	1.33–3.17	0.001	2.23	1.38–3.65	**0.001**
PI3K mTOR pathway mutation	366	0.51	0.33–0.80	0.003	0.58	0.35–0.96	**0.033**
NIPBL mutation	366	3.8	0.99–18.3	0.062	2.21	0.48–12.1	0.3
RTK RAS pathway mutation	366	0.61	0.33–1.07	0.1	0.72	0.36–1.36	0.3
IDH-Mutant Tumor	No. of Cases	Univariate Analysis			Multivariate Analysis		
		OR	95% CI	p Value	OR	95% CI	p Value
Age	173	0.97	0.95–1.00	0.086	0.97	0.93–1.01	0.12
Tumor vol	139	0.99	0.99–1.00	0.003	0.99	0.98–1.00	**0.01**
Tumor location	173						
Frontal		—	—		—	—	
Insular		5.13	1.35–33.6	0.036	4.95	1.14–34.7	0.054
Occipital		3,934,505	0.00–NA	>0.99	541,134,605	0.00–NA	>0.9
Other		3,934,505	0.00–NA	>0.99	64,355,656	0.00–NA	>0.9
Parietal		1.06	0.43–2.77	0.9	0.56	0.14–2.03	0.4
Temporal		3.42	1.30–10.8	0.02	7.29	2.11–34.5	**0.004**
CIC mutation	173	2.84	1.23–7.43	0.021	4.07	1.21–17.0	**0.034**
Notch pathway mutation	173	10.3	2.04–188	0.025	77,368,378	0.00–NA	>0.9

NA = not available.
Boldface type indicates statistical significance on multivariate analysis.

mutant tumors,[56,57] and glutamate. D2-HG may also directly induce mTOR pathway activation as another route to seizure activity.[58]

In addition to *IDH1* mutations, tumor-specific molecular alterations may further influence epileptogenesis separately from the mechanisms above. In long-term epilepsy-associated tumors, the *BRAF* V600E mutation is thought to contribute to seizures due to decreased inhibition of the *RAS-RAF-MAPK* pathway and dysregulation of the transcription factors governing ion channel expression.[6,59–61] Mutations of the *PI3K-AKT-mTOR* pathway have also garnered interest for their potential role in mediating tumor-associated epilepsy. *PTEN*, *NF1*, and *TP53* are negative regulators of the *mTOR* or *MPK* pathways commonly mutated in GBM, and their loss of function has been associated with increased seizures in preclinical models.[62] Increased *mTOR* pathway activity has been seen in peritumoral tissues of patients with tumor-associated epilepsy,[63] *PI3K* pathway alterations have been found to mediate seizure phenotypes in cortical malformations,[64] and different mutations of *PIK3CA*, the catalytic subunit of *PI3K*, have been linked to a broad spectrum of epileptic activity in mouse models[65,66] and in correlation with tumor molecular profiles from humans.[67]

Transcriptomic and other methods to molecularly profile tumors may yield additional insights into the mechanisms of glioma-associated epilepsy[55,68] and reveal therapeutic opportunities. While *BRAF* and *MEK* inhibitors have not effectively controlled tumor-associated epilepsy in GBM, they may have a role in treating gangliogliomas.[6] The dual role of the *mTOR* pathway in promoting unregulated tissue growth and inducing epilepsy has motivated the use of the *mTOR* inhibitor everolimus in tuberous sclerosis.[31] The mutant *IDH* inhibitor vorasidenib improved progression-free survival compared to placebo in patients with WHO grade 2 oligodendroglioma in phase 3 testing. While not advanced to phase 3 testing,[69] another mutant *IDH* inhibitor, ivosidenib, has shown promising results in improving seizure control in patients with both high- and low-grade gliomas.[70,71]

Conclusions

Tumor-associated epilepsy is both a common present-

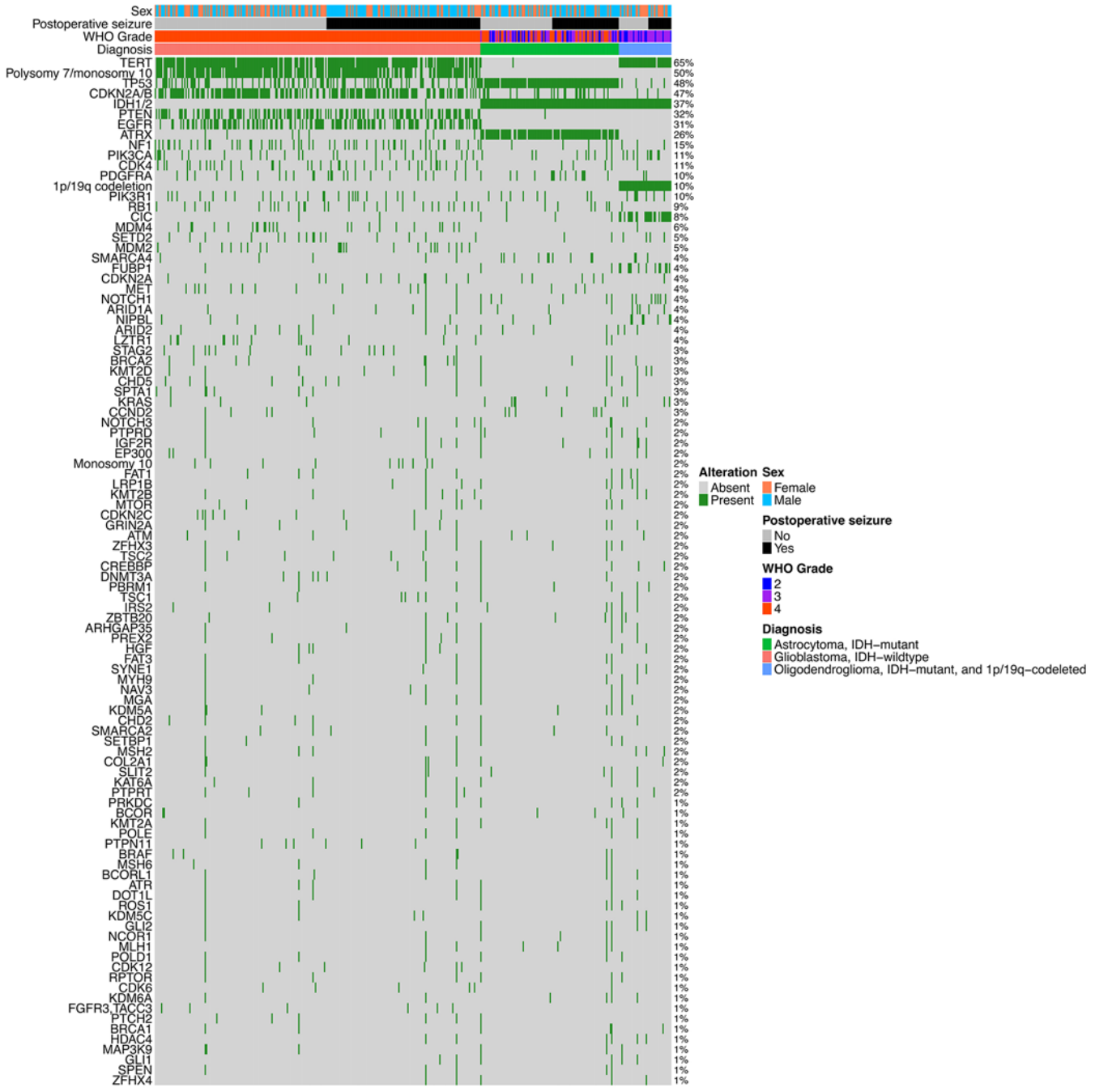

FIG. 2. Oncoplot of a subset of the cohort of adult diffuse gliomas treated with resection (n = 403), including *IDH*-wildtype tumors treated with standard radiotherapy and temozolomide (n = 254) and *IDH*-mutant tumors (n = 149), depicting the 100 most common genomic alterations detected with next generation sequencing. Samples are grouped by diagnosis based on WHO 2021 criteria and by the presence of seizures > 72 hours after resection.

ing symptom and a frequent complication following surgical treatment for adult diffuse gliomas. Maximizing the extent of resection is a mainstay of postoperative seizure control, with GTR providing the greatest seizure freedom over STR. In cases of temporal lobe involvement, supratotal resection involving temporal lobectomy may be preferred. Optimal medical management of antiseizure medications requires a patient-focused approach, as no strong guidelines exist for initiation and cessation of antiseizure regimens, and quality of life considerations must be weighed against seizure control and medication adverse effects.

While gliomas can cause seizures through increased extracellular glutamate release, local synaptic remodeling, metabolism, and dysregulated ion homeostasis overactivation of key biological pathways such as the *PI3K-AKT-*

TABLE 3. Clinical and molecular predictors of any postoperative seizures

		Univariate Analysis			Multivariate Analysis		
IDH-Wildtype Tumor	No. of Cases	OR	95% CI	p Value	OR	95% CI	p Value
Age	254	0.98	0.96–1.00	0.064	0.98	0.96–1.00	**0.04**
Sex	254						
F		—	—		—	—	
M		2.08	1.25–3.48	0.005	2.14	1.27–3.66	**0.005**
Sz at presentation	254	1.8	1.07–3.06	0.027	1.8	1.04–3.13	**0.036**
SETD2 mutation	254	0.35	0.10–1.04	0.076	0.45	0.12–1.50	0.2
SPTA1 mutation	254	0.15	0.01–0.87	0.081	0.17	0.01–1.12	0.11
LZTR1 mutation	254	0.32	0.07–1.07	0.088	0.32	0.07–1.18	0.11
		Univariate Analysis			Multivariate Analysis		
IDH-Mutant Tumor	No. of Cases	OR	95% CI	p Value	OR	95% CI	p Value
Sex	149						
F		—	—		—	—	
M		2.2	1.14–4.34	0.02	2.13	1.06–4.36	**0.037**
Location	149						
Frontal		—	—		—	—	
Insular		3.77	1.04–17.9	0.058	3.42	0.89–17.0	0.093
Occipital		7,234,175	0.00–NA	>0.99	3,450,922	0.00–NA	>0.9
Other		0		>0.99	0		>0.9
Parietal		1.26	0.45–3.51	0.66	1.65	0.55–5.04	0.4
Temporal		0.89	0.37–2.06	0.78	0.8	0.33–1.90	0.6
RT	149	1.83	0.94–3.61	0.079	1.53	0.74–3.17	0.2
Cell cycle pathway mutations	149	1.44	0.97–2.17	0.075	1.34	0.89–2.05	0.2

RT = radiotherapy.
Boldface type indicates statistical significance on multivariate analysis.

TABLE 4. Clinical and molecular predictors of multiple postoperative seizures

		Univariate Analysis			Multivariate Analysis		
IDH-Wildtype Tumor	No. of Cases	OR	95% CI	p Value	OR	95% CI	p Value
Age	254	0.98	0.95–1.00	0.086	0.98	0.95–1.01	0.3
Sex	254						
F		—	—		—	—	
M		1.88	0.98–3.74	0.063	1.96	0.95–4.27	0.078
Sz at presentation	254	2.24	1.19–4.21	0.012	2.43	1.18–5.08	**0.017**
Preop tumor vol at index op	252	0.99	0.98–1.00	0.032	0.99	0.98–1.00	0.2
CHEK2 mutation	254	13	1.62–265	0.028	25	1.49–1.93	**0.05**
TSC1 mutation	254	6.45	1.04–50.0	0.044	10.5	1.20–132	**0.036**
Cell cycle pathway mutation	254	0.29	0.07–1.21	0.072	0.58	0.12–3.25	0.5
KMT2B mutation	254	4.28	0.77–23.7	0.081	2.7	0.06–96.0	0.6
NOTCH3 mutation	254	4.28	0.77–23.7	0.081	0.26	0.01–11.2	0.5
GRIN2A mutation	254	4.28	0.77–23.7	0.081	3.89	0.45–27.0	0.2
ARID1A mutation	254	4.28	0.77–23.7	0.081	4.1	0.40–32.0	0.2
POLQ mutation	254	8.46	0.79–184	0.084	0.06	0.00–5.41	0.2
PTCH1 mutation	254	8.46	0.79–184	0.084	1.23	0.03–71.1	>0.9
PALB2 mutation	254	8.46	0.79–184	0.084	5.14	0.37–133	0.2
Polysomy 7/monosomy 10	254	0.55	0.28–1.13	0.095	0.58	0.26–1.35	0.2

Boldface type indicates statistical significance on multivariate analysis.

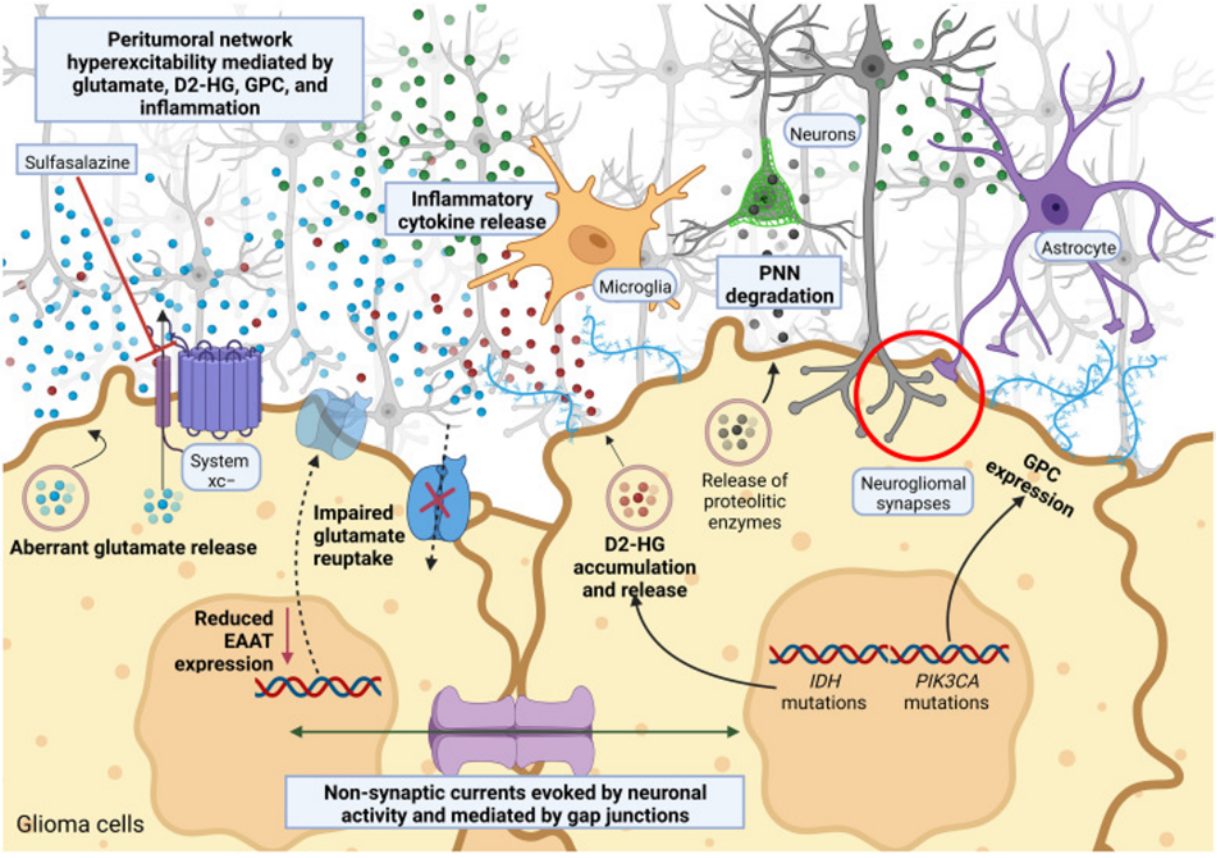

FIG. 3. Molecular and circuit mechanisms of glioma-associated epilepsy. Several glioma-neuron interactions are thought to contribute to glioma-associated epilepsy. These include both direct synaptic connections between tumor cells and neurons and nonsynaptic forms of signaling such as glutamate release from glioma cells, D2-HG accumulation resulting from *IDH* mutation, and *PI3K-mTOR* pathway mutations possibly mediated by glypican (GPC) expression, which may promote synaptogenesis. Depolarizing currents in glioma cells can also be transmitted to neighboring tumor cells via gap junctions formed within the tumor. EAAT = excitatory amino acid transporter; PNN = perineural network; System xc = cystine–glutamate antiporter. Modified from Aronica et al. *J Neurol Sci*. 2023;446:120584.[59] © The authors, published with permission. CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

mTOR and *RAS-RAF-MAPK* pathways may be implicated. Molecular profiling of tumors may yield further insights into the biology of glioma-associated epilepsy and lead to new therapeutic avenues, such as mutant *IDH* inhibitors, which could have combined antitumor and antiseizure effects.

The molecular alterations we found to be associated with seizures are consistent with the clinical and basic science literature. Previous studies[72] have reported an association between *EGFR* amplification and seizures at presentation in GBM, whereas in vitro work has shown *CIC* mutation contributing to increased extracellular glutamate.[73] *TSC1* mutation is seen in tuberous sclerosis and focal cortical dysplasia where it is thought to contribute to seizure activity via decreased inhibition of the *PI3K* pathway.[74] While no seizure associations with *CHEK2* have been reported, the gene may play a role in GBM progression, as its loss contributes to defective DNA damage repair.[75]

Large multicenter studies with long-term follow-up are needed to better quantify the burden of glioma-associated epilepsy in patients with all grades of glioma and to reveal how seizure frequency evolves over the course of treatment. These clinical studies should also consider whether certain AED regimens are more efficacious in preventing seizures and possibly influencing overall survival. These clinical data should be correlated with tumor molecular profiling performed at the time of resection to better discern the relationship between tumor mutational profile and postoperative seizure risk, which may yield therapeutic opportunities specific to certain patient populations.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Young, Shukla, Nguyen, Chang. Acquisition of data: Young, Shukla, Nguyen. Analysis and interpretation of data: Young, Shukla, Nguyen. Drafting the article: Shukla, Nguyen. Critically revising the article: all authors. Reviewed submitted version of manuscript: Young, Shukla, Nguyen, Lee. Approved the final version of the manuscript on behalf of all authors: Young. Statistical analysis: Shukla, Nguyen. Administrative/technical/material support: Young, Lee. Study supervision: Young, Chang.

Supplemental Information

Videos

Video Abstract. https://vimeo.com/1100301485.

Previous Presentations

The findings in this study were presented as an oral abstract at the CNS 2022 Annual Meeting held in San Francisco, CA, on October 8–12, 2022, and as an oral abstract and printed poster at the CNS 2023 Annual Meeting held in Washington, DC, on September 9–13, 2023.

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