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RESEARCH ARTICLE

Clinical characteristics of low-grade tumor-related epilepsy and its predictors for surgical outcome

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Abstract

Objectives: Low-grade tumors are the most common neoplasms inducing focal epilepsy; however, the short- and medium-term efficacy of surgery in epilepsy patients with low-grade tumors remains underappreciated. This study aims to summarize the clinical characteristics of epilepsy patients with low-grade tumors and to identify factors associated with postsurgical seizure-free outcomes. **Methods**: We retrospectively reviewed consecutive patients with low-grade tumors who underwent subsequent epilepsy surgery in our epilepsy center, between 2012 and 2018 with a minimum follow-up of 1 year. Using Engel's classification and Kaplan–Meier survival analysis, we assessed postoperative seizure freedom over time. Demographical, electroclinical, and other presurgical evaluations were then evaluated for association with postoperative seizure outcome. **Results**: The cohort included a total of 132 patients: 79 males and 53 females. Among them, 110 (83.33%) were seizure-free through their last follow-up. The Engel class I outcomes were 90.15%, 87.76%, 85.53%, 82.46%, and 73.17% at the end of the 1st, 2nd, 3rd, 4th, and 5th postoperative years, respectively. Multivariate logistic analysis revealed that longer epilepsy duration ($p < 0.001$, OR 1.091, 95% CI 1.040–1.144) and incomplete resection ($p = 0.009$, OR 3.673, 95% CI 1.393–9.684) were independently associated with seizure recurrence through the last follow-up. **Conclusions**: Surgical treatment for seizure control in patients with low-grade tumors provides excellent short- and median-term outcomes.

Introduction

Low-grade tumors (LGT) are benign and slow-growing neuroglial elements and common causes of focal epilepsy in both children and adults.[1–4] According to the 2016 World Health Organization (WHO) classification of tumors of the central nervous system:[5] LGT specifically include ganglioglioma, dysembryoplastic neuroepithelial tumor, oligodendroglioma, and astrocytoma, which are most common in the temporal lobe.[2,6,7] Unlike malignant brain tumors, the morbidity of LGT is derived primarily from induction of repeated seizures, rather than the tumors themselves.[8–10] About 33.3% of these patients suffer from uncontrolled seizures despite antiepileptic drug (AED) treatment.[11] Surgical intervention is therefore considered to be the optimal approach, leading to better seizure control and quality of life.[7,9,12]

Long-term postoperative seizure freedom rates in LGT patients vary from 64.6% to 86.7% in most developed countries.[1,13,14] The positive predictors for seizure freedom in LGT patients remain hotly debated; some studies suggested that shorter durations and younger ages at surgery yielded good seizure outcomes,[12,15,16] whereas others failed to find such correlations.[3,14] Moreover, to our knowledge, most studies on LGT have been limited to children or a single type of LGT,[3,7,8,14,17] with few studies focusing on the clinical characteristics and seizure outcomes of a wide spectrum of epileptic tumors across a wide age group, especially in developing countries. This study aims to clarify the aforementioned controversies

and knowledge gaps, by systematically analyzing the clinical characteristics and seizure outcomes of epilepsy patients with different LGT types and identifying their surgical prognostic factors via our China-based Epilepsy Center.

Materials and Methods

Patient selection and evaluation

We retrospectively reviewed the records of consecutive focal epilepsy patients with LGT who were admitted to the Epilepsy Center, Second Affiliated Hospital of Zhejiang University from 2012 to 2018. This study was approved by the institutional review boards of Second Affiliated Hospital of Zhejiang University.

The inclusion criteria were as follows: (1) focal epilepsy patients; (2) postoperative pathology was designated as tumor grade I or grade II based on WHO classification;[5] (3) with at least 1-year follow-up.

Data collection, surgical procedure, and postoperative follow-up

Clinical, imaging, EEG, histopathology, and surgical outcome data were collected. Long-term video-EEG (VEEG) monitoring during wakefulness and sleep was performed using the international 10–20 system of electrode placement, including anterior temporal electrodes and sphenoidal electrodes if appropriate. Interictal EEG patterns were classified as no focal EEG features or any focal EEG features (focal slowing or /and focal epileptic discharges). Ictal EEG patterns were coded as any regional EEG changes and no regional EEG changes. The seizure types based on history and VEEG were classified as focal aware seizure, focal impaired awareness seizure, and focal to bilateral tonic-clonic seizure according to the ILAE 2017 Classification.[18]

Preoperative evaluation of the selected patients included: history, symptomatology, scalp EEG, MRI, and other examinations if necessary. The findings of the noninvasive evaluations were discussed in a routine multidisciplinary patient management conference and the surgical strategy was determined collectively by the neurosurgeons and epileptologists. Epilepsy classifications were grouped into temporal lobe, frontal lobe, parietal lobe, occipital lobe, insular lobe, or multilobe epilepsy based on multidisciplinary panel consensus as well as the postoperative MRI scan. The extent of resection was defined as "complete resection" if residual tumor tissue was not identified on postoperative MRI, and "incomplete resection" if >80% of the tumor was removed. The pathological diagnoses were then categorized according to the WHO definitions:[5] ganglioglioma, pilocytic astrocytoma, diffuse astrocytoma, pleomorphic xanthoastrocytoma, dysembryoplastic neuroepithelial tumor, angiodendroglioma, oligodendroglioma, and unclassified low-grade tumors.

Seizure outcome and postsurgical AEDs treatment were evaluated according to the last visit or telephone interviews. Seizure outcome was rated during the 1st, 2nd, 3rd, 4th, and 5th year as well as the last follow-up, according to Engel classification,[19] and further classified as either in the favorable outcome group (Engel class I) or the unfavorable outcome group (Engle class II–IV).

Statistical analysis

The data are presented as median (percentiles 25%–75%) or mean ± standard deviation (SD) via SPSS version 23.0. Student's *t*-test and nonparametric Mann–Whitney *U* test were used to compare group differences on continuous variables. Categorical variables were analyzed by Pearson's chi-square test or Fisher's exact test. Univariate analysis results were then entered into a Cox regression model with statistical significance at $p < 0.05$. A Cox regression model was applied to determine the unique predictive value of several variables on surgical favorable outcomes with statistical significance set at $p < 0.05$. Odds ratios (OR) and 95% confidence interval (CI) were also calculated for each of these parameters. The Kaplan–Meier survival analysis was used to calculate the seizure-free duration probability after surgery. To identify the threshold of continuous variables that could predict seizure outcomes, continuous variables were stratified and the cutoff values were determined according to the Youden index in a receiver operating curve (ROC) analysis.

Results

Cohort characteristics

Of the 141 patients with LGT-related epilepsy meeting the inclusion criteria, nine patients were excluded due to missing follow-ups (Fig. 1). Collectively, a total of 132 patients were enrolled (79 male, 53 female); 86 (65.15%) were pediatric patients (age <18 years at surgery). The mean age at seizure onset was 23.18 ± 15.46 years and the median duration was 1.75 years (interquartile range 0.42–5 years). Seventy-two patients (54.55%) had left-sided surgery (Table 1). Tumors classified as WHO grade I and WHO grade II were 50.76% and 35.61%, respectively (Fig. 2; Table 1). Tumor location was temporal in 74 patients (56.06%) and extratemporal in 58 (43.94%). The most frequent extratemporal location was frontal (21.21%), followed by parietal (5.30%), occipital (3.79%), and insular (0.76%). Seventeen patients (12.88%) had multilobar extension (Table 1).

We also compared the differences between children and adults with LGT-related epilepsy and found that children had a higher prevalence of refractory epilepsy ($p = 0.002$) and a longer epilepsy duration ($p = 0.013$). However, the rate of seizure-free patients did not show a difference (children: 82.56%, adults: 84.78%) between the two groups. Regarding the tumor types, only diffuse astrocytoma was more common in adults ($p = 0.015$). Other variables, such as gender, tumor location, seizure type, seizure frequency, and tumor grade, displayed no difference between children and adults with LGT (Table S2).

Seizure characteristics and scalp VEEG findings

Based on history and VEEG, focal impaired awareness seizure was found in 112 cases (84.85%), focal to bilateral tonic-clonic seizure in 46 (34.85%), and focal aware seizure in 45 (34.09%). Among these patients, 14 patients experienced all three types of seizures. Twenty-five patients had both focal aware seizures and focal impaired awareness seizures. Seventeen patients had both focal impaired awareness seizures and focal to bilateral tonic-clonic seizures. One patient had both focal aware seizures and focal to bilateral tonic-clonic seizures. Fifty-six patients had only focal impaired awareness seizures. Fourteen patients had only focal to bilateral tonic-clonic seizures. Five patients had only focal aware seizures (Fig. S1). Nineteen patients (14.39%) had daily seizures. Long-term VEEG monitoring was available in 94 patients (71.21%). Among these patients, interictal EEG patterns were distributed as no focal features (31.91%), any focal features (68.09%). During VEEG monitoring, 63 patients (67.02%) had seizures recorded, with ictal EEG patterns including any regional EEG changes (49.21%) and no regional EEG changes (50.79%; Table 1).

Follow-up, seizure outcome, and pathological findings

In this study, 127 patients (96.21%) continued with anticonvulsant therapy after surgery. After a median follow-up of 44.5 months (interquartile range 21.25–63 months), 110 patients (83.33%) had favorable outcomes through the last follow-up. Thirteen patients had seizure recurrence within the first year after surgery. The seizure outcomes during each follow-up year are given in Table 2. Engel class I outcome was 90.15%, 87.76%, 85.53%, 82.46%, and 73.17% at the end of the 1st, 2nd, 3rd, 4th, and 5th postoperative year, respectively. Whether the lesion was completely resected depended on postsurgical MRI (Fig. 3). Histologic examination of surgical specimens revealed 46 gangliogliomas (34.85%), 24 oligodendrogliomas (18.18%), 13 diffuse astrocytomas (9.85%), 12 dysembryoplastic neuroepithelial tumors (9.09%), 10 pleomorphic xanthoastrocytomas (7.58%), 8 pilocytic astrocytomas (6.06%), 1 angiodendroglioma (0.76%), and 18 unclassified astrocytomas (13.64%). Figure 4 showed the relationship between tumor types and tumor locations. We found that ganglioglioma (84.78%) and pleomorphic xanthoastrocytoma (90%) were the most common tumors that occurred in the temporal lobe, and oligodendroglioma (50%) was predisposed to occur in the frontal lobe.

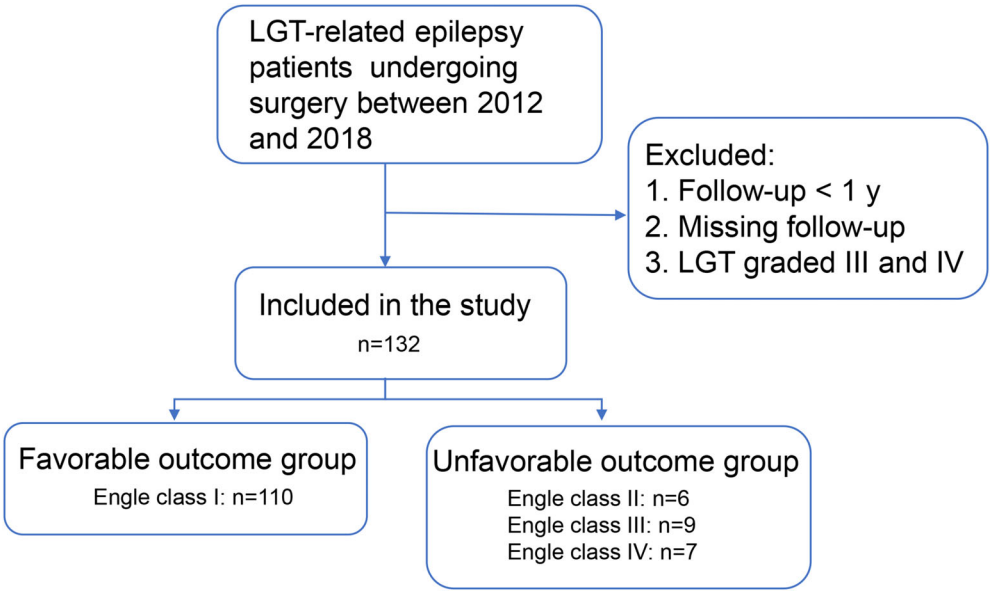

Figure 1. Study flowchart.

Table 1. Clinical characteristics and seizure outcome at the last follow-up.

	Final seizure outcome			
Variables (%)	Total (n = 132), %	Engle Class I (n = 110)	Engle Class II-IV(n = 22)	p-value
Sex, male	79 (59.85)	62	17	0.068[3]
Refractory epilepsy	40 (30.30)	30	10	0.090[3]
Children	86 (65.15)	71	15	0.744[3]
Age at onset, Y	23.18 ± 15.46	22.93 ± 14.73	24.45 ± 19.05	0.725[2]
Age at Surgery, Y	27.05 ± 15.49	26.15 ± 15.11	31.57 ± 16.93	0.135[2]
Epilepsy duration, Y	1.75 (0.42–5)	1.5 (0.25–5)	3.5 (0.86–15)	0.044[4]
Temporal	74 (56.06)	65	9	0.117[3]
Frontal	28 (21.21)	24	4	0.924[3]
Parietal	7 (5.30)	5	2	0.728[3]
Occipital	5 (3.79)	5	0	0.589[1]
Insular	1 (0.76)	0	1	0.167[1]
Multilobe	17 (12.88)	11	6	0.027[3]
Hemispheric lateralization, left	72 (54.55)	62	10	0.348[3]
Seizure type				
Focal aware seizure	45 (34.09)	39	6	0.334[3]
Focal impaired awareness seizure	112 (84.85)	101	11	1.000[3]
Focal to bilateral tonic-clonic seizure	46 (34.85)	42	4	0.985[3]
Seizure frequency, daily	19 (14.39)	15	4	0.579[3]
Had the VEEG monitoring	94 (71.21)	78	16	0.863[3]
Interictal EEG pattern (94 patients)				
No focal EEG features	30 (31.91)	25	5	0.373[3]
Any focal EEG features	64 (68.09)	53	11	
Ictal EEG pattern (63 patients)				
Any regional EEG changes	31 (49.21)	25	6	1.000[3]
No regional EEG changes	32 (50.79)	25	7	
Incomplete resection	18 (13.64)	11	7	0.006[3]
Sparing eloquent cortical areas	29 (21.67)	21	8	0.074[3]
Postsurgical AEDs treatment	127 (96.21)	106	21	0.838[3]
Pathology				
Ganglioglioma	46 (34.85)	40	6	0.414[3]
Oligodendroglioma	24 (18.18)	17	7	0.069[3]
Diffuse astrocytoma	13 (9.85)	10	3	0.794[3]
Dysembryoplastic neuroepithelial tumor	12 (9.09)	11	1	0.685[3]
Pleomorphic xanthoastrocytoma	10 (7.58)	9	1	0.883[3]
Pilocytic astrocytoma	8 (6.06)	7	1	1.000[3]
Angiocentric glioma	1 (0.76)	1	0	1.000[1]
Unclassified	18 (13.64)	15	3	1.000[3]
WHO grade				
Grade I	67 (50.76)	59	8	0.139[3]
Grade II	47 (35.61)	36	11	0.122[3]
Unclassified	18 (13.64)	15	3	1.000[3]

Abbreviations: AEDs, anti-epileptic drugs; EEG, electroencephalogram; VEEG, video-electroencephalographic monitoring; WHO, World Health Organization; Y, year.

[1]Fisher's exact test, statistically significant difference ($p < 0.05$).

[2]Student's t-test.

[3]Chi-square test.

[4]Nonparametric Mann–Whitney U test.

Predictors of seizure outcome

Univariate analysis found longer epilepsy duration ($p = 0.044$), multilobe lesions ($p = 0.027$), and incomplete resection of the lesion ($p = 0.006$) through the last follow-up to be predictors of seizure recurrence (Table 1); although, there were no statistical differences at 1-year and 2-year follow-up (Table S1). Histological subtype analysis exhibited no significant impact on recurrence. Interictal and ictal EEG patterns between the favorable

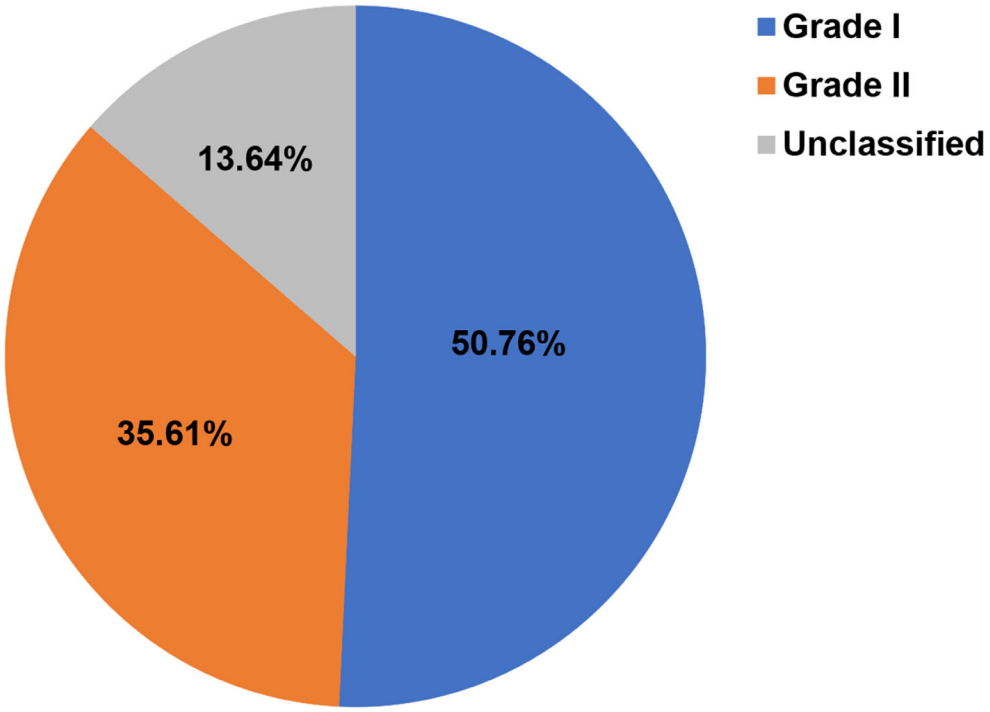

Figure 2. Patient distribution by tumor WHO grade.

outcome and unfavorable outcome groups were not significantly different at the 1-year follow-up, 2-year follow-up, and the last follow-up (Table 1, Table S1). Cox regression analysis revealed long epilepsy duration ($p < 0.001$, OR 1.091, 95% CI 1.040–1.144) and incomplete resection ($p = 0.009$, OR 3.673, 95% CI 1.393–9.684) to be statistically significant negative predictive factors for surgery outcomes through the last follow-up (Table 3).

A Kaplan–Meier survival curve was used to illustrate post-surgery seizure freedom over time, across the study population (Fig. 5A). Compared to the complete resection group, the incomplete resection group showed a sharp decrease in the probability of seizure freedom (Fig. 5B). Furthermore, by ROC analysis we found that the epilepsy duration cut-off was 26.5 months; patients with longer durations (especially >26 months) were significantly more likely to have seizure recurrence (Fig. 5C). Of the seven patients who exhibited both factors, 42.86% (3/7) had experienced seizure recurrence at the last follow-up.

Table 2. Seizure outcome at 1-year, 2-year, 3-year,4-year, 5-year follow-up, and until the last follow-up.

Variable (%)	Patients (*n*)	Engle class I	Engle class II	Engle class III	Engle class IV
1 Y	132	119 (90.15)	3 (2.27)	6 (4.55)	4 (3.03)
2 Y	98	86 (87.76)	3 (3.06)	5 (5.10)	4 (4.08)
3 Y	76	65 (85.53)	2 (2.63)	6 (7.89)	3 (3.94)
4 Y	57	47 (82.46)	3 (5.26)	3 (5.26)	4 (7.02)
5 Y	41	30 (73.17)	3 (7.32)	3 (7.32)	5 (12.20)
Last follow-up	132	110 (83.33)	6 (4.55)	9 (6.82)	7 (5.30)

Abbreviations: Y, year.

Discussion

Studies on large series of LGT-related epilepsy patients remain rare in developing countries. Up to 75% of patients with LGT-experienced seizures; of these, one-third will become refractory to treatment. Recurrent epileptic attacks can seriously increase the economic burden and reduce the quality of life of patients. Surgical resection is currently the most effective method for seizure control in this group.[2,4,10,11,20,21] This retrospective study enrolled 132 LGT-related epilepsy patients, including both adults and children, with a wide spectrum of pathological conditions, who underwent surgical resection with at least 1-year of follow-up in China. Our study found that 83.33% of patients achieved complete seizure control through the last follow-up, which is consistent with literature-reported seizure-free rates of 64.6–

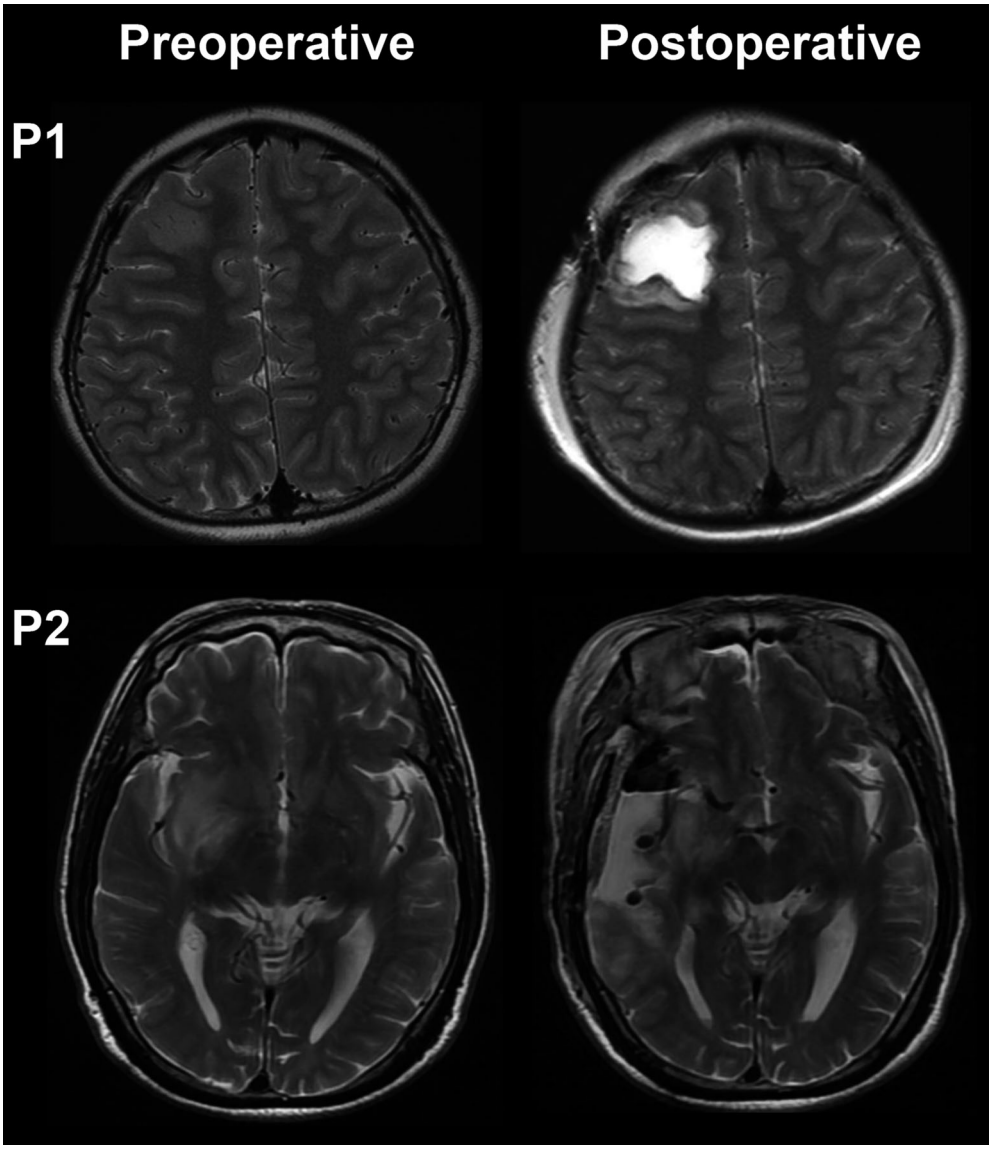

Figure 3. Preoperative and postoperative images of epilepsy patients with LGT. (P1) T2 preoperative MRI image (left) showing right frontal tumor of a 9-year-old boy with epilepsy. Postoperative MRI image (right) showing that the lesion was completely resected. The patient was seizure-free after a 3-year follow-up. (P2) T2 MRI image (left) of a 68-year-old male with a right temporal-insular tumor. The postoperative MRI image (right) showed residual tumor tissue in the right insular lobe, and the patient had recurrent seizures in the first year after surgery.

86.7%.[1,13,14] Among the 22 patients who experienced seizures post-surgery, 13 patients (59.09%) had seizure recurrence within 1 year after surgery, indicating that the majority of post-surgery seizure recurrence in LTG-related epilepsy occurs within the first year.

Our study revealed an association between longer epilepsy duration and poorer seizure outcomes following resective epilepsy. Chronic recurrent seizures may lead to a complicated epileptogenic network or give rise to a second epileptogenic focus.[22] This is one possible mechanism for epileptic seizure persistence in LGT patients even after the primary tumor has been removed. For LGT patients, earlier surgical intervention has been recommended even before the emergence of drug-resistant epilepsy; earlier surgery may not only avoid AEDs-related adverse events but also protect against impairment of brain function, such as worsening cognitive function from repeated seizures.[7] In contrast to our findings, several studies did not find the duration of epilepsy to be significantly related to seizure outcome; however, they did find a trend that patients with shorter epilepsy duration were more likely to have better prognoses.[3,9]

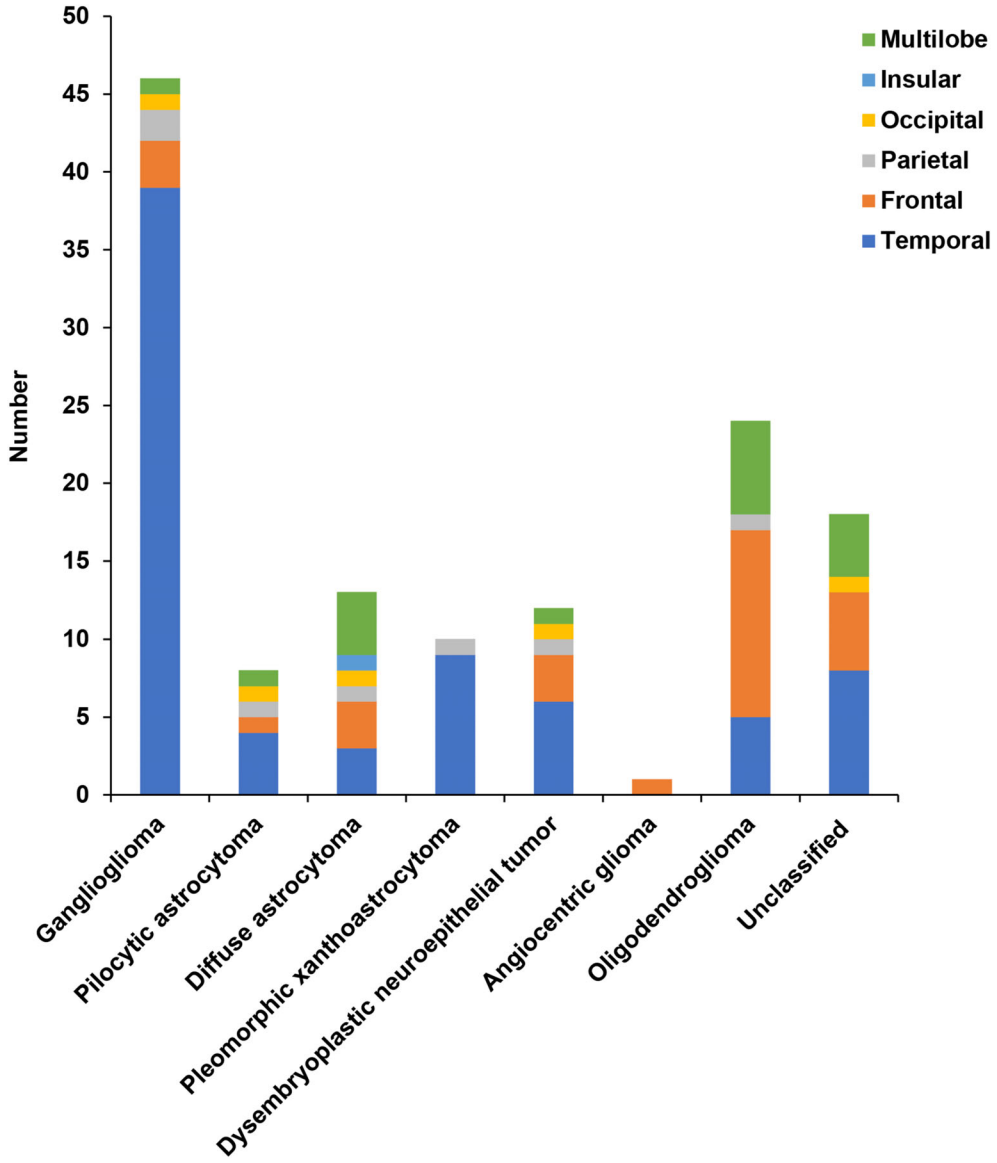

Figure 4. The relationship between tumor types and tumor locations.

Table 3. Factors associated with seizure-free outcome in epilepsy patients with low-grade tumors following a localized surgery until the last follow-up.

Variables	95% CI	OR	*p*-value
Epilepsy duration, Y	1.040–1.144	1.091	<0.001[1]
Incomplete resection	1.393–9.684	3.673	0.009[1]
Multilobe	0.475–5.723	1.649	0.431[1]

Abbreviations: CI, confidence interval; OR, odds ratio; Y, year.
[1]Cox regression analysis, statistically significant difference ($p < 0.05$).

Multivariate analysis also identified incomplete resection of residual tumor tissue as an independent predictor for postsurgical seizure recurrence in LGT-related epilepsy. It is well-known that the extent of tumor resection in LGT-related epilepsy correlates with the chances of postoperative seizure control.[7,13,14,23,24] Currently, the surgical strategies of epilepsy-related LGT include subtotal resection, gross-total lesionectomy, and tailored resection.[6,9,21,25] Subtotal resection is performed when the tumor cannot be removed entirely due to the involvement of functionally eloquent brain areas or vital structures, and its seizure-freedom rate is relatively low due to the remaining epileptogenic zone;[7,9,13,14,23,24] a previous study

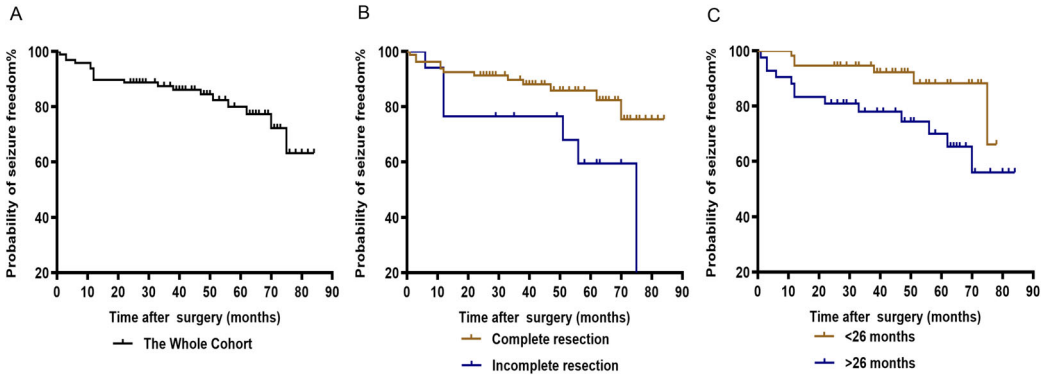

Figure 5. Kaplan–Meier curve among different groups. (A) Kaplan–Meier curve illustrating chances of postoperative seizure freedom in the overall cohort (132 patients). (B) Kaplan–Meier curves exhibiting distinct seizure outcomes depending on the complete or incomplete resection of tumors ($p = 0.009$). (C) Kaplan–Meier curves showing distinct seizure outcomes depending on epilepsy duration. In LGT epilepsy patients, long epilepsy duration and incomplete resection were independently associated with seizure recurrence through the last follow-up.

found that resection >80% was an independent positive predictor in subtotal resection surgery.[21] Gross-total lesionectomy, termed "complete resection" in this study, yielded a superior seizure outcome to incomplete resection in our evaluation (86.84% vs. 61.11%), analogous to previous researches.[7,13,14,23,24] Tailored resection is the removal of abnormal cortex tissue around the tumor using intracranial EEG (iEEG) or electrocorticogram (ECoG) as a guide, which stressed the importance of intracranial EEG monitoring, especially in temporomesial LGT.[1,3] In our study, only five patients had implanted iEEG. The first patient was recommended to have deep electrodes implanted for negative MRI imaging. In the second case, subdural electrodes and deep electrodes were implanted to assess whether functional areas were involved as the lesion was located in the left frontal lobe. The remaining three patients were recommended to perform iEEG because the origin of seizures on scalp EEG was unclear. Among these three patients, two had deep electrodes implanted and one had subdural electrodes and deep electrodes implanted. However, we found no difference in seizure outcomes between patients with and without iEEGs. That is not to say that iEEG or ECoG applications cannot facilitate seizure freedom, as iEEGs and ECoGs can identify abnormal spiking in peritumoral tissue. Blumcke and Wiestler found that seizure outcome was more associated with the resection of the epileptogenic lesion, which can be identified by iEEG, and less correlated with complete resection of the tumor.[26] Future research dedicated to evaluating the efficacy of iEEGs is needed.

Among the evaluated patients, focal impaired awareness seizure (84.85%) was the most common seizure type experienced by tumor-related epilepsy, which is consistent with previously published literature.[23] 34.85% of patients had focal to bilateral tonic-clonic seizures, which did not influence the rate of seizure outcome, in contrast to previous studies.[12,15] We found no statistically significant differences deriving from tumor location, contrary to one study which concluded that tumors in the temporal lobe were associated with better seizure outcomes.[27] This discrepancy might be due to the relative distributions of temporal lobe epilepsy (68% in the aforementioned vs. 56.06% herein).

Seizure outcome did not differ according to LGT subtype in our study. A previous study found that tumor type was the significant predictor for postsurgical seizure freedom, with the lowest rate (56.6%) in pilocytic astrocytoma, a slightly higher rate in pleomorphic xanthoastrocytoma (62.5%), and the highest rates in diffuse astrocytoma (77.8%), ganglioglioma (81.3%), and dysembryoplastic neuroepithelial tumor (89.3%); however, the scope of that study was limited to temporal lobe epilepsy only.[28] Other studies including only partial low-grade tumors found no relationship between tumor type and seizure outcome.[9,21,24] Our study found that patients with WHO grade II tumors had worse outcomes than those with WHO grade I tumors (76.60% vs. 88.06%), but not to a statistically significant extent. The effects of tumor type and tumor grade on patient outcome remain inconclusive and require further investigation.

Long-term VEEG monitoring is unquestionably valuable in epilepsy evaluation; notably, its capability to define paroxysmal events as epileptic or not, localize seizure onset, characterize epileptic syndrome, and even determine AEDs adjustments.[29] However, it is not the only preoperative evaluation methodology to determine the epileptogenic zone in LGT-related epilepsy. A detailed seizure history and/or MRI findings may suffice for establishing an anatomic connection between the tumor and

the origin of the seizure. Our findings suggest that VEEG might be less useful in focal LGT-related epilepsy when a lesion is fully concordant with seizure semiology and lateralized interictal discharges. Our results add important evidence to the debate of the value of VEEG evaluation in LGT-related epilepsy, potentially conserving medical resources and decreasing patient burden if VEEG evaluation proves unnecessary. However, these findings should be interpreted with caution and not be applied to LGT-related patients with bilateral, multifocal, MRI negative, or other types of epilepsies.

Important limitations cannot be disregarded in this single, large, respective study. The patient cohort was selected from those who had at least 1-year of postoperative follow-up and low-grade glioneuronal tumors pathologically identified; they cannot represent all LGT patients. In addition, not all patients included in our study underwent VEEG monitoring, reflecting the reality of everyday practice. Therefore, a direct comparison of yields should be interpreted with caution. Moreover, due to the lack of a control group who received no epilepsy surgery, this study is less reliable as an evaluation of the efficacy of surgery as a short- to medium-term seizure control in LGT-related epilepsy populations.

Conclusion

This study contributes comprehensive clinical characteristics and outcome data on LGT-related epilepsy. The surgical treatment of LGT provides epilepsy patients in developing countries with a high chance of seizure amelioration. Early surgical intervention and complete tumor resection were independently associated with seizure-free outcomes through the patients' last follow-up.

Acknowledgment

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Conflict of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. The distribution of seizure types.
Table S1. Clinical characteristics and seizure outcome at the 1-year follow-up, 2-year follow-up.
Table S2. Clinical characteristics between children and adults.

