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Original Research

Clinical characteristics and surgical outcomes of low-grade epilepsy-associated brain tumors

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Abstract

Background: Low-grade epilepsy-associated brain tumors (LEATs) are found to be the second most common lesion-related epilepsy. Malignant potential of LEATs is very low and the overall survival is good, so the focus of treatment is focused more on seizure outcome rather than oncological prognosis.

Objectives: This study was conducted to evaluate the risk factors of seizure outcomes after resection in patients with LEATs.

Design: A retrospective study.

Methods: A retrospective analysis of patients with LEATs who underwent resective surgery in our three epilepsy centers between October 2010 and April 2023 with a minimum follow-up of 1 year. Demography, clinical characters, neurophysiology, and molecular neuropathology were assessed for association with postoperative seizure outcomes at 1-, 2-, and 5-year follow-up. Synthetic minority oversampling technique (SMOTE) algorithm model was performed to handle the imbalance of data distribution. Gaussian Naïve Bayes (GNB) algorithms were created as a basis for classifying outcomes according to observation indicators.

Results: A total of 111 patients were enrolled in the cohort. The most common pathology was ganglioglioma ($n = 37$, 33.3%). The percentage of patients with seizure freedom was 91.0% (101/111) at 1-year follow-up, 87.5% (77/88) at 2-year follow-up, and 79.1% (53/67) at 5-year follow-up. Partial resection had a significantly poor seizure outcome compared to total resection and supratotal resection ($p < 0.05$). The epileptiform discharge on post-resective intraoperative electrocorticography (ECoG) or postoperative scalp electroencephalography (EEG) were negative factors on postoperative seizure freedom at 1-, 2-, or 5-year follow-ups ($p < 0.05$). The area under the receiver-operating characteristic curve value of the GNB-SMOTE model was 0.95 (95% CI, 0.876–1.000), 0.892 (95% CI, 0.656–0.934), and 0.786 (95% CI, 0.491–0.937) at 1-, 2-, and 5-year follow-up, respectively.

Conclusion: The partial resection, post-resective intraoperative ECoG, and postoperative scalp EEG were valuable indicators of poor seizure outcomes. The utilization of post-resective intraoperative ECoG is beneficial to improve seizure outcomes. Based on the data diversity and completeness of three medical centers, a multivariate correlation analysis model was established based on GNB algorithm.

Keywords: electroencephalography, epilepsy, epileptic surgery, low-grade epilepsy-associated brain tumor, seizure control

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Introduction

The terminology 'long-term epilepsy-associated tumors' was proposed in 2003, which was related to the rare solid tumor in patients with long-term drug-resistant epilepsy. The duration of 'long-term drug-resistant epilepsy' generally lasted for 2 years or more according to definition.[1] Most of long-term epilepsy-associated tumors were glioneuronal

tumors with WHO (World Health Organization) Grade I, localized in temporal lobe, and early-onset seizures (mean age, 16.5 years).[2] However, some patients with epilepsy and low-grade neuroepithelial tumors do not meet the diagnosis of 'long-term epilepsy' at the early stage of the disease. In 2020, the terminology 'low-grade epilepsy-associated brain tumor' (LEAT) came out, which presented the same characteristics as long-term epilepsy-associated tumors. LEATs consisted of a spectrum of brain tumors with morphological abnormalities.[3] Ganglioglioma (GG), dysembryoplastic neuroepithelial tumor (DNT), low-grade astroglioma (LGAG), oligodendroglioma, angiocentric glioma, isomorphic diffuse glioma, and the papillary glioneuronal tumor are commonly reported types of LEATs.[4,5] However, common pathogenic gene mutations have not been found among them.[3] LEATs accounted for 20–22% of postoperative pathological findings in epilepsy surgery; moreover, about 33.3% of these patients involved uncontrolled seizures despite anti-seizure medications (ASMs) treatment.[4] It was the most common pathological finding of lesion-related epilepsy expect for hippocampal sclerosis in adults, and secondly common lesion-related epilepsy after malformations of cortical development in children.[6,7] The annual period prevalence of LEATs with epilepsy surgery was about 9.56/100,000 in adults and 4.35/100,000 in children, and incidence was 1.14/100,000 in adults and 0.77/100,000 in children, respectively.[8] The location, histopathology, the somatic gene mutation of tumor cell, and the imbalance of excitatory and inhibitory amino acids in the peritumoral region contributed to the epileptogenicity of brain tumor.[9] For the LEATs, the dysmorphism neurons in tumor can produce spontaneous abnormal discharge and induce seizure attack.[9] Most of the patients with LEATs exhibited drug-resistant epilepsy, and surgical treatment is the most important therapeutic approach among them.[10] Notably, different from high-grade brain tumors, the postoperative seizure freedom are exclusive or major purpose in the patients with LEATs. There is still debate on the role of electroencephalography (EEG), resection region, and operation opportunity. Especially, the applications of EEGs, including preoperative and postoperative scalp EEG, stereo-EEG, and intraoperative electrocorticography (ECoG), are controversial. Some neurosurgeons tended to conform the epileptogenicity of LEATs with scalp EEG or SEEG, and conducted excision of tumor under ECoG monitoring, while other neurosurgeons preferred to resect the LEATs with the guidance of preoperative EEG examination instead of using intraoperative ECoG. Therefore, we performed this retrospective research to study the effect of using different types of EEG or other influence factors on the postoperative seizure freedom with data from these three centers to increase the number of samples and reduce the bias in patients' selection in single-center study.

Methods

Study population

All patients underwent resective surgery in our epilepsy centers. The patients were enrolled retrospectively according to the following inclusion criteria: (1) patients with lesion-associated epilepsy; (2) postoperative pathology was diagnosed as LEAT and tumor were classified as grade WHO I or grade WHO II[4]; (3) children or adults with at least 1-year follow-up. The patients with following exclusion criteria were excluded from the group: (1) subjects undergoing other neurosurgical operations for reasons other than epilepsy; (2) patients without outcome of seizure control at 1-year follow-up; (3) cases with incomplete clinical data.

Preoperative evaluation

The non-invasive preoperative evaluations consisted of neurological physical examinations, computed tomography, magnetic resonance imaging (MRI), 2-h scalp video EEG recordings, and neuropsychological tests. MRI scans included 3.0T axial T1- and T2-weighted, diffusion-weighted routine images, sagittal T1-weighted, and axial and coronal T2-flair high-resolution images with 1-mm thickness at zero intervals. 2-Deoxy-2-[18F]fluoro-D-glucose positron emission tomography was selectively used in patients with unclear tumor boundaries or classifications. Long-term scalp video EEG recordings were used in cases with lack of congruence between location of tumor on MRI and symtomatogenic zone according to the seizure semiology. For invasive stage evaluation, intracranial electrodes were implanted in patients with lack of congruence between location of tumor on MRI and seizure onset zone based on ictal EEG symtomatogenic zone according to the seizure semiology.

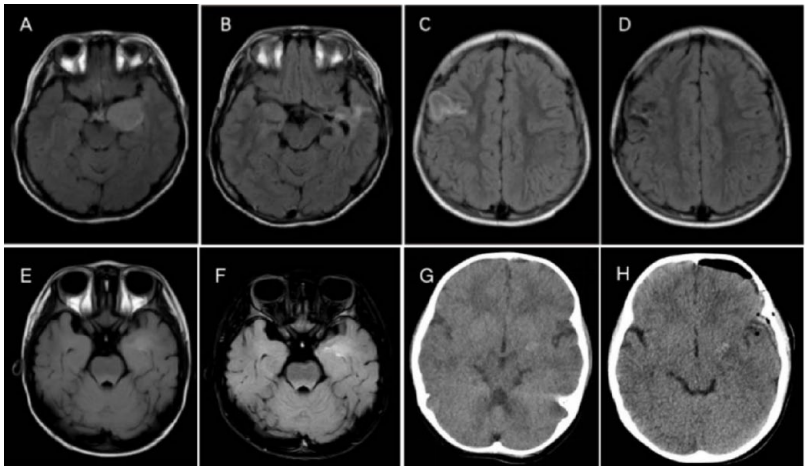

Figure 1. Pre- and postoperative MRI (T2-flair) of three patients with oligodendroglioma (a, b), dysembryoplastic neuroepithelial tumor (c, d), and ganglioglioma (e–h), respectively. (a) Preoperative axial MRI (T2-flair) showed a hyperintense lesion located in the left temporal lobe. (b) Eight-month postoperative axial MRI showed no recurrence of tumor. (c) Preoperative axial MRI (T2-flair) showed an iso- and hyperintense lesion located in the right frontal lobe. (d) Four-month postoperative axial MRI showed complete resection and no residual tumor. (e, f) Preoperative axial plain and enhanced MRI (T2-flair) showed a hyperintense lesion located in the left temporal lobe. (g, h) Preoperative CT showed calcification in the lesion, and postoperative CT showed partial resection of lesion and spot calcification left. All patients achieved seizure freedom after resection at the last follow-up.
CT, computed tomography; MRI, magnetic resonance imaging.

Each long-term video scalp EEG recording and intracranial electrodes EEG should include one or more habitual seizures.

Surgical methods

Resective surgery was performed with or without intraoperative ECoG. Intraoperative ECoG was used to localize epileptogenic area and also was used for functional cortical mapping in the condition of the tumor near to eloquent area when neurosurgeons thought it was necessary. Using standardized method, ECoG was reviewed real-time by the neurophysiological technician for interictal epileptiform discharges in recording areas, including focal spike, polyspike, spike and slow wave complex, and ictal epileptiform discharge occasionally. When the cortex with epileptiform discharges on intraoperative ECoG was consistent with or near to tumor location on preoperative MRI, resective operation was performed with more extensive excision, including the tumor and peritumoral epileptogenic zone. Resective surgery included partial resection (partial tumor was resected according to the region on Flair-image), total resection (total removal of tumor according to the region on Flair-image and postoperative MRI showed no residual tumor), and supratotal resection (the resection cavity larger than the region on Flair-image) (Figure 1).[9,11] For the tumor in the temporal lobe, the removal of hippocampus depended on whether the tumor involved the hippocampus or the intracranial electrode EEG confirmed that the hippocampus is the origin of epileptic discharge in the patients whose LEATs did not involve the hippocampus. For the patients with tumor in or clearly involving the structure of mesial temporal lobe, anterior temporal lobectomy was performed.

Follow-up

All patients were asked to visit the hospital at 1 year after the operation, the last follow-up was finished from January to April 2023. The removal extent was confirmed by two neurosurgeons by comparing tumor on the preoperative MRI T2-flair image and the resective region on the postoperative MRI at 6–12 months after surgery. Seizure outcomes were assessed according to the International League Against Epilepsy (ILAE) outcome classification.[2] Patients were divided into two groups – ILAE type 1 and ILAE types 2–6 – to ascertain predictors of seizure freedom.

Complications were described as transient or permanent. Transient complications were documented in hospital, and permanent complications were recorded by caregivers.

Statistical analysis

Statistical analysis was performed using SPSS (version 25.0; SPSS, Inc., Chicago, IL, USA). Outcomes are presented as percentages, mean ± standard deviation and median or IQRs (quartile 1–quartile 3). Chi-square and Fisher's exact tests were performed for univariate analysis of categorical variables. We used *t*- and *f* tests for comparison of continuous variables. Significance was defined as two-tailed error probability less than 0.05 ($p < 0.05$). Python software (version 3.11.4; Python Software Foundation) was applied for model development and statistical analysis.

Machine-learning algorithms and model development

Synthetic minority oversampling technique (SMOTE) model was performed to handle the imbalance of data distribution. Gaussian Naïve Bayes (GNB) algorithms were created in Python. GNB was a supervised learning algorithm that utilized Bayes' theorem as a basis for classifying observations and dealing with insufficient capacity of the classical linear regression.[12] The accuracy rate, error of mean square, and the correlation coefficient of test data were interpreted to judge the goodness of fit of the model. The area under the receiver-operating characteristic curve (AUC) and 95% confidence interval (CI) were calculated.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary material.

Results

Baseline information of the study population

Clinical data from 125 patients with LEATs who underwent epilepsy surgery at our centers were collected. Fourteen patients without enough clinical data were excluded from the study. A total of 111 patients (M: F = 69:42) were enrolled in this study. All patients underwent surgery during October 2010 to April 2023.

Age at surgery was 16.85 ± 15.69 years (range: 0.3–48, median: 9.8), and age at seizure onset was 15.30 ± 15.66 months (range: 0.1–49, median: 8.2). Duration of epilepsy ranged from 0.3 to 276 months (18.77 ± 39.91, median: 4). There were 60 patients (54.1%) with age at seizure onset ⩽10 years, 83 patients (74.8%) with duration of seizure ⩽12 months, and 73 cases (65.8%) with age at surgery ⩽18 years.

Types of seizure onset included focal to bilateral tonic-clonic seizure (37 patients, 33.3%), focal impaired awareness seizure (37 patients, 33.3%), focal awareness seizure (19 patients, 17.1%), generalized tonic-clonic seizure (18 patients, 16.2%). Seizure frequency included daily (11 patients, 9.9%), weekly (63 patients, 56.8%), and monthly (37 patients, 33.3%) during the baseline period. ASMs were used in 98 (88.3%) cases before surgery.

Preoperative evaluation and surgical approach

All of patients finished MRI examinations and 103 (92.8%) cases performed scalp EEG examination. The tumor localized in right hemisphere in 54 patients (48.6%) and left side in 57 cases (51.4%). There were 13 (11.7%) patients with tumors in parietal lobe, 23 (20.7%) patients with frontal lobe tumors, 49 (44.2%) cases with temporal lobe tumors, 4 (3.6%) cases with tumors in occipital lobe, 4 (3.6%) cases with tumors in insular lobe, and 18 (16.2%) patients with tumors in multiple lobes. Eleven cases presented preoperative low IQ with full IQ less than 70. Preoperative scalp EEG uncovered interictal epileptiform discharges in 95 (85.6%) patients, including ipsilateral epileptiform discharges in 67 (60.4%) patients, contralateral epileptiform discharges in 11 (9.9%) cases, and bilateral epileptiform discharges in 17 (15.3%) patients. Ictal discharges were recorded in 39 (35.1%) patients, and 29 (26.1%) cases presented focal ictal EEG onset consistent with the location of tumor on MRI. Intracranial EEG was performed on 11 patients (9.9%), with 6 patients (5.4%) monitored by subdural electrodes and 5 patients (4.5%) monitored by stereo-EEG electrodes.

All patients underwent resective surgery, and intraoperative ECoG was applied in 89 (80.2%)

cases, and pre-resection epileptiform discharges and post-resection epileptiform discharges were found in 81 cases and 21 cases, respectively. The resective surgery consisted of partial resection in 10 (9.0%) cases, total resection in 33 (29.7%) cases, and supratotal resection in 68 (61.3%) patients (Table 1).

Postoperative follow-up and complications

All patients finished 1-year follow-up, and 88 (79.2%) patients and 67 (60.3%) cases finished 2- and 5-year follow-up, respectively. Around the 6–12 months after resection, 97 (87.4%) cases accepted scalp video EEG examinations, and 35 (36.1%) cases found interictal epileptiform discharge. Transient complications were found in 13 (11.7%) cases, including seven cases with hemiplegia, five patients with aphasia, and one with intracranial infection. Permanent complication consisted of two patients with light hemiplegia.

Seizure outcomes

The percentage of patients with seizure freedom was 91.0% (101/111) at 1-year follow-up, 87.5% (77/88) at 2-year follow-up, and 79.1% (53/67) at 5-year follow-up. Seizure outcomes are shown in Figure 2.

The age at surgery, age onset, history of preoperative seizure, gender, seizure onset type, seizure frequency, interictal epileptiform discharge pattern on preoperative scalp EEG, ictal discharge captured during preoperative scalp EEG monitor, and application of intracranial EEG or pre-resective intraoperative ECoG had no influence on seizure control at 1-, 2-, or 5-year follow-ups. However, the epileptiform discharge on post-resective intraoperative ECoG or postoperative scalp EEG and partial resection of tumor were negative factors on postoperative seizure freedom at 1-, 2-, or 5-year follow-ups ($p < 0.05$) (Tables 1 and 2). The patients with tumors localized in multiple lobes presented poorer seizure control than those with temporal lobe tumors at 5-year follow-up.

Clinical characters and pathology findings in patients

The pathological findings included GG in 37 patients, DNT in 19 patients, 29 in LGAG (20 diffuse astrocytomas, 6 pilocytic astrocytomas, and 3 pleomorphic xanthoastrocytomas), and 26 with oligodendroglioma. Also, there were significant differences in different location of tumor, cystic degeneration, calcification of tumor, and isocitrate-dehydrogenase 1 (IDH1) gene mutation among four kinds of tumors ($p < 0.01$). The GG was the most common in temporal lobe than other tumors, and the tumor with GG or DNT presented high percentage of cysts in tumor and less IDH1 gene mutation compared with LGAG or oligodendroglioma ($p < 0.05$). Besides, the GG and oligodendroglioma had higher percentage of calcification than DNT or LGAG ($p < 0.05$). The age at surgery ($p < 0.05$) and age at seizure onset ($p < 0.05$) in GG and DNT is younger than LGAG or oligodendroglioma. The history of preoperative seizure in DNT was longer than GG, LGAG, or oligodendroglioma. Nevertheless, significant differences in percentage of postoperative seizure-free were not found among four kinds of tumor at 1-, 2-, and 5-year follow-ups (Table 3).

The subjects can be divided into WHO-I group and WHO-II group, and the 66 (59.5%) tumors in WHO-I group consisted of GG, DNT, and 10 cases with LGAG. The patients with WHO-II tumors had significantly older age at seizure onset and age at surgery, shorter history of preoperative seizure ($p < 0.01$), and lower percentage of postoperative seizure freedom at 5-year follow-up ($p < 0.05$) compared to WHO-I tumors. Furthermore, the WHO-II tumor presented significant lower percentage of cystic degeneration and higher percentage of IDH1 gene mutation ($p < 0.01$) (Table 3).

Development and evaluation of the novel predictive model

SMOTE model was used to solve the imbalance of data distribution. The data was split into 80% training and 20% testing partitions. Different seeds were chosen for each set to maintain the training and testing set distributions. For each trial, combinations of variables of subset were selected and utilized with Gaussian random function fully used for classification. In binary classification, patient labels were determined through postoperative seizure outcome (seizure attack or seizure freedom), which were considered as the classification category in GNB model. Within the GNB model, the 10-fold cross-validation was implemented, and the patients were categorized into seizure attack group or seizure freedom group

Table 1. Preoperative influence factors and extent of resection for postoperative seizure freedom [*n* (%)].

Factors	1-Year follow-up (*n* = 111)		2-Year follow-up (*n* = 88)		5-Year follow-up (*n* = 67)	
	SF	No-SF	SF	No-SF	SF	No-SF
Age at onset						
⩽10 years	57 (95.0%)	3 (5.0%)	35 (87.5%)	5 (12.5%)	22 (91.7%)	2 (8.3%)
>10 years	44 (86.3%)	7 (13.7%)	42 (87.5%)	6 (12.5%)	31 (72.1%)	12 (27.9%)
Duration of epilepsy						
⩽12 months	75 (90.4%)	8 (9.6%)	56 (84.8%)	10 (15.2%)	39 (76.5%)	12 (23.5%)
>12 months	26 (92.9%)	2 (7.1%)	21 (95.5%)	1 (4.5%)	14 (87.5%)	2 (12.5%)
Age at surgery						
⩽18 years	69 (94.5%)	4 (5.5%)	45 (90.0%)	5 (1.0%)	25 (86.2%)	4 (13.8%)
>18 years	32 (84.2%)	6 (15.8%)	32 (84.2%)	6 (15.8%)	28 (73.7%)	10 (26.3%)
Gender						
Male	60 (87.0%)	9 (13.0%)	48 (85.7%)	8 (14.3%)	21 (65.6%)	11 (34.4%)
Female	41 (97.6%)	1 (2.4%)	29 (90.6%)	3 (9.4%)	11 (78.6%)	3 (21.4%)
Seizure type at onset						
Generalized epileptic spasms	14 (77.8%)	4 (22.2%)	12 (75.0%)	4 (25.0%)	9 (69.2%)	4 (30.8%)
Focal seizure	53 (94.6%)	3 (5.4%)	41 (93.2%)	3 (6.8%)	29 (85.3%)	5 (14.7%)
Focal to bilateral tonic-clonic seizure	34 (91.9%)	3 (8.1%)	24 (85.7%)	4 (14.3%)	15 (75.0%)	5 (25.0%)
Seizure frequency						
Daily	9 (81.8%)	2 (18.2%)	7 (77.8%)	2 (22.2%)	5 (62.5%)	3 (37.5%)
Weekly	58 (92.1%)	5 (7.9%)	43 (87.8%)	6 (12.2%)	30 (81.1%)	7 (18.9%)
Monthly	34 (91.9%)	3 (8.1%)	27 (90.0%)	3 (10.0%)	18 (81.8%)	4 (18.2%)
Preoperative IQ						
Full IQ ⩾ 70	90 (90.9%)	9 (9.1%)	68 (87.2%)	10 (12.8%)	48 (77.4%)	14 (22.6%)
Full IQ < 70	11 (91.7%)	1 (8.3%)	8 (88.9%)	1 (11.1%)	5 (100.0%)	0 (0.0%)
Location of tumor						
Temporal lobe	49 (100.0%)	0 (0.0%)	33 (97.1%)	1 (2.9%)	23 (100.0%)	0 (0.0%)
Frontal lobe	22 (95.7%)	1 (4.3%)	20 (95.2%)	1 (4.8%)	14 (82.4%)	3 (17.6%)
Parietal/occipital lobe/insular	18 (85.7%)	3 (14.3%)	17 (85.0%)	3 (15.0%)	12 (75.0%)	4 (25.0%)
Multiple lobe	12 (66.7%)	6 (33.3%)	7 (53.8%)	6 (46.2%)	4 (46.4%)*	7 (63.6%)
Resection approach						
Partial resection	4 (40.0%)$	6 (60.0%)	3 (33.3%)$	6 (66.7%)	2 (25.0%)$	6 (75.0%)
Total resection	30 (90.9%)	3 (9.1%)	23 (85.2%)	4 (14.8%)	17 (73.9%)	6 (26.1%)
Supratotal resection	67 (98.5%)	1 (1.5%)	51 (98.1%)	1 (1.9%)	34 (94.4%)	2 (5.6%)

*$p < 0.05$, percentage of postoperative seizure freedom in this group *versus* the data in temporal lobe group (Chi-square test)
$$p < 0.05$, the percentage of seizure freedom in this group *versus* the other two group (Chi-square test).
SF, seizure freedom.

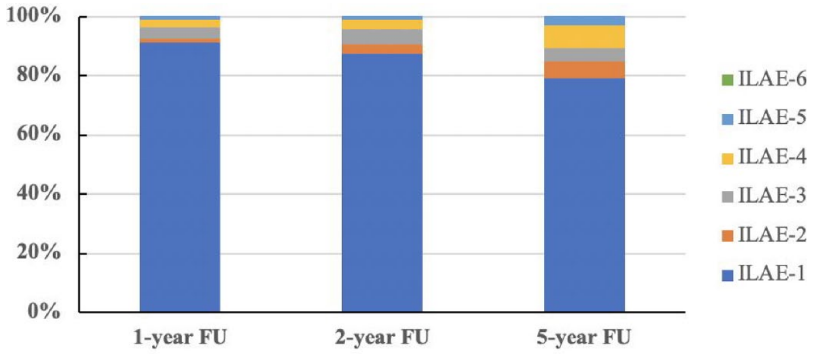

Figure 2. Postoperative seizure outcomes according to ILAE classification at 1-, 2-, or 5-year follow-up. 91.0%, 87.5%, and 79.1% of patients reach ILAE-1 after surgery at 1-, 2-, or 5-year, respectively. 1.8%, 3.4%, and 5.9% of patients reach ILAE-2 after surgery at 1-, 2, or 5 years, respectively. 3.6%, 4.6%, and 4.5% of patients reach ILAE-3 after surgery at 1-, 2-, or 5 years, respectively. 2.7%, 3.4%, and 7.5% of patients reach ILAE-4 after surgery at 1-, 2-, or 5 years, respectively. 0.9%, 1.1%, and 3.0% of patients reach ILAE-5 after surgery at 1-, 2-, or 5 years, respectively. There is no patient reaching ILAE-6 after surgery.
FU, follow-up; ILAE, International League Against Epilepsy.

according to the extraction of the feature importance parameter. Besides, the variables were fragmented, combined, and analyzed to obtain the correlation matrix heatmap (Figure 3). Pearson correlation coefficient was used to test the degree of correlation between two random variables. The color of squares on the correlation matrix heatmap became deeper as the correlation between two variables got stronger. The extent of resection, location of tumor, postoperative ECoG, and postoperative EEG might have a strong association with postoperative seizure control compared with other factors at 1-, 2-, and 5-year follow-up. After internal validation, the predictive accuracy rate of 1-, 2-, and 5-year follow-up data was 0.95, 0.81, and 0.77, separately. Besides, the AUC value of the GNB-SMOTE model was 0.95 (95% CI, 0.876–1.000), 0.892 (95% CI, 0.656–0.934), and 0.786 (95% CI, 0.491–0.937), respectively. The results showed that the values by use of the algorithm approximate well to real ones. To synthesize the predictive performance and clinical utility, the GNB-SMOTE model was chosen as the final prediction model of postoperative seizure control.

Discussion

This study provided comprehensive and multicentral epidemiological statistics for the surgical LEATs for both children and adults. Based on the data diversity and completeness of multiple medical centers, a multivariate correlation analysis model was established based on GNB algorithm. Furthermore, the factors associated with LEATs were presented and discussed as follows.

Clinical characteristics to seizure outcome

This study involved 73 children and 38 adults, 69 males and 42 females, from our three epilepsy centers, in which patients with different kinds of LEATs had distinct characteristics. The most common location of LEATs ($n=49$, 44.1%) occurred in the temporal lobe, and the most common pathology finding was GG ($n=37$, 33.3%). Tumor located in temporal lobe had a better seizure outcome than multi-lobe at 5-year follow-up; in addition, the potent correlation between tumor location and seizure outcome was shown in the correlation matrix heatmap (Figure 3). The confined tumor and the tumor in temporal lobe were more likely to total resection, which was in line with the result of previous research.[13] There was no statistically significant difference in seizure control and different types of LEATs. Furthermore, patients with WHO-II LEATs showed a lower percentage of postoperative seizure freedom at 5-year follow-up compared to WHO-I tumors. The potential of natural proliferation in the developing central nervous system may complicate assessments of tumor malignancy.[14] The higher rate might possibly be associated with the higher grade of low-grade tumors, which can be more infiltrative.[15] Higher-grade tumors were more aggressive and likely to relapse, and the microenvironment and release of

Table 2. Electroencephalography for postoperative seizure freedom [*n* (%)].

Factors	1-Year follow-up (*n* = 111)		2-Year follow-up (*n* = 88)		5-Year follow-up (*n* = 67)	
	SF	No-SF	SF	No-SF	SF	No-SF
Interictal discharge (IID) pattern on preoperative scalp EEG						
Ipsilateral IID	64 (95.5%)	3 (4.5%)	46 (93.9%)	3 (6.1%)	33 (89.2%)	4 (10.8%)
Contralateral IID	9 (81.8%)	2 (18.2%)	8 (80.0%)	2 (20.0%)	6 (60%)	4 (40%)
Bilateral IIDs	14 (82.4%)	3 (17.6%)	11 (78.6%)	3 (21.4%)	7 (70%)	3 (30%)
No IIDs or no EEG	14 (87.5%)	2 (12.5%)	12 (80.0%)	3 (20.0%)	7 (70%)	3 (30%)
Ictal discharge captured during preoperative scalp EEG monitor						
Yes	34 (87.2%)	5 (12.8%)	23 (79.3%)	6 (20.7%)	11 (73.3%)	4 (26.7%)
No	67 (93.1%)	5 (6.9%)	52 (91.2%)	5 (8.8%)	42 (80.8%)	10 (19.2%)
Intracranial EEG						
Yes	8 (72.7%)	3 (27.3%)	6 (66.7%)	3 (33.3%)	3 (42.9%)	4 (57.1%)
No	93 (93.0%)	7 (7.0%)	71 (89.9%)	8 (10.1%)	50 (83.3%)	10 (16.7%)
Pre-resection electrocorticography						
No electrocorticography	20 (90.9%)	2 (9.1%)	16 (88.9%)	2 (11.1%)	11 (84.6%)	2 (15.4%)
No epileptiform discharge	7 (87.5%)	1 (12.5%)	6 (85.7%)	1 (14.3%)	4 (80.0%)	1 (20.0%)
Epileptiform discharge	74 (91.4%)	7 (8.6%)	55 (87.3%)	8 (12.7%)	38 (77.6%)	11 (22.4%)
Post-resection electrocorticography						
No electrocorticography	20 (90.9%)	2 (9.1%)	16 (88.9%)	2 (11.1%)	11 (84.6%)	2 (15.4%)
No epileptiform discharge	67 (98.5%)	1 (1.5%)	51 (98.1%)	1 (1.9%)	37 (90.5%)	4 (9.5%)
Epileptiform discharge	14 (66.7%)$^{\$}$	7 (33.3%)	10 (55.6%)$^{\$}$	8 (44.4%)	5 (38.5%)$^{\$}$	8 (61.5%)
Postoperative scalp EEG						
No electrocorticography	14 (100.0%)	0 (0.0%)	10 (100.0%)	0 (0.0%)	8 (88.9%)	1 (11.1%)
No epileptiform discharge	60 (96.8%)	2 (3.2%)	47 (97.9%)	1 (2.1%)	34 (94.4%)	2 (5.6%)
Epileptiform discharge	27 (77.1%)$^{\$}$	8 (22.9%)	20 (66.7%)$^{\$}$	10 (33.3%)	11 (50.0%)$^{\$}$	11 (50.0%)

$^{\$}p < 0.05$, the percentage of seizure freedom in this group *versus* the other two group (Chi-square test).
EEG, electroencephalography; SF, seizure freedom.

neurotransmitter around the tumor can be changed, contributing to epileptogenic discharge extends to the surrounding area.[11,16] Furthermore, tumor recurrence is clearly relevant to seizure and the reappearance of epilepsy is an important indicator of tumor recurrence.[7,17,18]

Compared with other studies, more patients with oligodendroglioma and LGAG were enrolled in this study, and there were 23% of patients with oligodendroglioma and 26% cases with LGAG. The possible reason is that one center participated in this study is also a comprehensive glioma

Table 3. Characters and postoperative seizure freedom of different tumors [*n* (%)].

Factors	Pathological finding				WHO-I *versus* WHO-II grade	
	GG (*n* = 37)	DNT (*n* = 19)	LGAG (*n* = 29)	Oligodendroglioma (*n* = 26)	WHO-I (*n* = 66)	WHO-II (*n* = 45)
Age at onset	4.04 ± 4.07&&,##	7.84 ± 10.42&&,##	21.07 ± 15.83##	30.33 ± 13.63	7.18 ± 9.99**	27.20 ± 14.77
Duration of epilepsy	17.76 ± 33.75$	44.16 ± 69.99	7.52 ± 12.28$$	14.20 ± 31.84$	23.92 ± 46.71**	11.20 ± 25.73
Age at surgery	5.47 ± 5.76&&,##	11.53 ± 12.22&&,##	21.70 ± 15.91##	31.51 ± 13.43	9.15 ± 10.95**	28.13 ± 14.81
Location of tumor						
Temporal lobe	27 (55.1%)^^	7 (14.3%)	10 (20.4%)	5 (10.2%)	39 (78.0%)	11 (22.0%)
Frontal lobe	1 (4.3%)	6 (26.1%)	6 (26.1%)	10 (43.5%)	6 (28.6%)	15 (71.4%)
Parietal/occipital lobe/insular	5 (22.8%)	3 (13.6%)	7 (31.8%)	7 (31.8%)	11 (55.0%)	9 (45.0%)
Multiple lobes	4 (23.5%)	3 (17.7%)	6 (35.3%)	4 (23.5%)	7 (41.2%)	10 (58.8%)
Cystic degeneration in tumor						
Yes	27 (47.4%)	15 (26.3%)	11 (19.3%)	4 (7.0%)	43 (75.4%)**	14 (24.6%)
No	10 (18.5%)	4 (7.4%)	18 (33.3%)	22 (40.8%)	23 (42.6%)	31 (57.4%)
Calcification in tumor						
Yes	18 (40.9%)^^	3 (6.8%)	3 (6.8%)	20 (45.5%)	22 (50.0%)	22 (50.0%)
No	19 (28.4%)	16 (23.9%)	26 (38.8%)	6 (8.9%)	44 (65.7%)	23 (34.3%)
High expression of Ki67						
Yes	9 (47.4%)	0 (0.0%)	6 (31.6%)	4 (21.0%)	9 (47.4%)	10 (52.6%)
No	28 (30.4%)	19 (20.7%)	23 (25.0%)	22 (23.9%)	57 (62.0%)	35 (38.0%)
IDH1 gene mutation						
Yes	2 (6.5%)^^	0 (0.0%)	13 (41.9%)	16 (51.6%)	5** (16.1%)	26 (83.9%)
No	35 (43.8%)	19 (23.7%)	16 (20.0%)	10 (12.5%)	61 (76.3%)	19 (23.7%)
Postoperative seizure control at 1 year						
Seizure free	35 (34.7%)	18 (17.8%)	27 (26.7%)	21 (20.8%)	63 (62.4%)	38 (37.6%)
No seizure free	2 (20.0%)	1 (10.0%)	2 (20.0%)	5 (50.0%)	3 (30.0%)	7 (70.0%)
Postoperative seizure control at 2 years						
Seizure free	19 (24.7%)	13 (16.9%)	25 (32.5%)	20 (25.9%)	41 (53.2%)	36 (46.8%)
No seizure free	4 (%)	0 (%)	2 (%)	5 (%)	4 (36.4%)	7 (63.6%)
Postoperative seizure control at 5 years						
Seizure free	9 (17.0%)	10 (18.9%)	19 (35.8%)	15 (28.3%)	27 (50.9%)*	26 (49.1%)
No seizure free	2 (14.3%)	0 (0.0%)	4 (28.6%)	8 (57.1%)	2 (14.3%)	12 (85.7%)

&&$p < 0.01$, the mean age in this group *versus* the low-grade astrocytoma group (*F* test).
##$p < 0.01$, the mean age in this group *versus* the oligodendroglioma (*F* test).
$$p < 0.05$, $$$p < 0.01$, the data in this group *versus* the data in DNT group (*F* test).
^^$p < 0.01$, the percentage of different tumor in different groups (Chi-square test).
*$p < 0.05$, **$p < 0.01$, the percentage of seizure freedom in patients with this group *versus* the data in WHO-II group (Chi-square test).
DNT, dysembryoplastic neuroepithelial tumor; GG, ganglioglioma; IDH1, isocitrate-dehydrogenase 1; LGAG, low-grade diffusive astroglioma; WHO, World Health Organization.

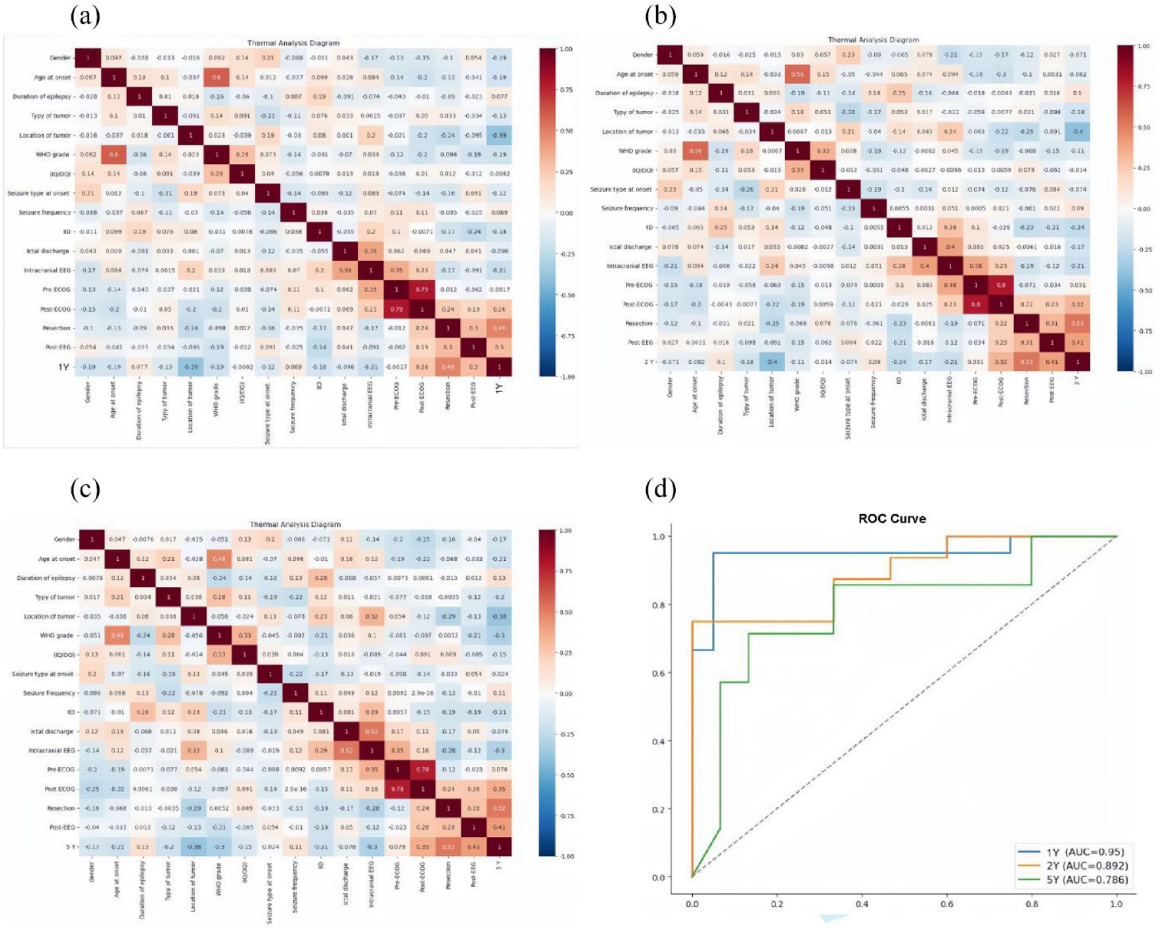

Figure 3. The correlation matrix heatmap (a–c) and receiver-operating characteristic curve (d) at 1-year (1Y), and 2-year (2Y), and 5-year (5Y) follow-up based on GNB learning algorithms. This figure showed the trend of correlation between every two random variables (correlation became stronger as the color getting deeper). The extent of resection, location of tumor, post-resective ECoG, and postoperative scalp EEG were the crucial variables in evaluation of postoperative seizure control. The GNB model is based on postoperative 1-year follow-up training data with the highest value (accuracy rate = 0.95; error of mean square = 0.048; AUC = 0.95).
AUC, area under the receiver-operating characteristic curve; ECoG, electrocorticography; EEG, electroencephalography; GNB, Gaussian Naïve Bayes.

center for adults and children, and more patients suffered with glioma were enrolled in the study.

Operative treatment to seizure outcome

Unlike intracranial malignant tumors, the prognosis and quality of life in patients with LEAT are mainly derived from seizure control rather than the tumors themselves.[4,18,19] The epileptogenesis of LEATs is multifactorial, including intratumor and peritumor mechanisms.[3,9,20–25] LEATs can also coexist with focal cortical dysplasia.[9,20,26,27] Fortunately, patients with LEATs can extremely benefit from surgical treatment, and most of them can achieve seizure freedom after surgery.[6,18] Patients were followed up for 1, 2, and 5 years, and reached postoperative seizure freedom in 91%, 88%, and 79%, respectively, which was in line with other research reporting.[18,28,29] In a review of the literature, in patients with tumor-associated epilepsy, the extent of tumor resection was correlated with postoperative seizure control and survival period.[6,18,30] Similarly, partial resection actuarially was a negative factor for seizure freedom after surgery in this study. GNB-SMOTE analysis verified that extent of resection of tumor was the principal factor that influenced postoperative seizure freedom in correlation matrix heatmap (Figure 3). Nowadays, intraoperative MRI, intraoperative fluorescent staining,

and neuronavigational systems are widely applied to improve complete anatomically total resection, other than total resection of epileptogenic zone.[31–36] Therefore, surgical strategies still need to be improved in identifying the residual epileptogenic zone.

EEG to seizure outcome

EEG is the crucial examination for diagnosis of epilepsy and localization of epileptogenic zone. However, neither interictal epileptiform discharge pattern nor ictal epileptiform discharge on scalp EEG can exactly localize the boundary of epileptogenic zone and have no influence on the postoperative seizure freedom. Intracranial EEG is seldom applied as an invasive and expensive preoperative examination, and also did not have effect on the postoperative seizure control.[6,37] ECoG has been widely used in the operation of tumor-related epilepsy.[10,33,38–40] Due to short monitoring time, being influenced by anesthetic medications, and only monitoring of interictal epileptiform discharges, the clinical value of delineation in epileptogenic foci has been highly controversial.[39–41] In this cohort, ECoG examinations were performed on 81% of patients, and pre-resective ECoG utilization did not improve postoperative seizure freedom, while epileptiform discharge on post-resective ECoG might indicate the residue of epileptogenic zone contributing to postoperative continuous seizure. The epileptogenic zone was the area of the cerebral cortex that generated seizures, not limited to tumors itself and usually involving the surrounding cortex in LEATs. Therefore, resective surgery should not simply remove the part or all of the tumors without attention to the epileptogenic zone. The interictal epileptiform discharges on post-resective ECoG may have a negative association with postoperative seizure freedom at 1-, 2-, and 5-year follow-ups in correlation matrix heatmap and univariate analysis (Figure 3). If surgery is considered in patients with LEATs, tailoring resection including tumor and abnormal cortex tissue according to the finding of epileptiform discharges on ECoG. Notably, post-resective ECoG-detected spikes were useful to identify the residual epileptogenic area, which can help the prejudging of postoperative seizure freedom.[15,40] Intraoperative ECoG identified interictal epileptiform discharges to delineate region located on peritumor or even centimeters away from the tumor. When the epileptiform discharges area showed on intraoperative ECoG was close to eloquent cortex, we prioritized protecting the patient's function rather than performing an unlimited excision. Besides, when the epileptiform discharges zone showed on intraoperative ECoG outside of the tumor at a distant region, we prioritized conducting the resection of tumor and the surrounding cortex. The microenvironmental alteration contributing to the abnormality of epilepsy network was considered. This result was also consistent with the outcome of higher seizure freedom rate after an enlarging excision involving the tumor plus adjacent cortex. Postoperative scalp EEG was a routine examination during follow-up. Epileptiform discharge on postoperative scalp EEG is also an index for epileptogenic zone residue and was negative factor on postoperative seizure freedom at 1-, 2-, and 5-year follow-ups in this study.

Molecular neuropathology to seizure outcome

The IDH1 mutation can lead to the accumulation of 2-hydroxyglutarate, an excitatory neurotransmitter that has been implicated in the pathogenesis of onset of epilepsy of LEAT patients.[42,43] GG and DNT presented less IDH1 gene mutation compared with LGAG or oligodendroglioma respectively, which was in line with the previous studies reporting.[44,45] The majority of GG and DNT were enrolled in WHO-I group in this study. Thus, patients in grade WHO-II group showed more IDH1 gene mutation than those in WHO-I group. Few cases with IDH1 mutation were involved in this study, the correlation between IDH1 mutation and postoperative seizure outcomes was not found in this study. Notably, IDH1 gene mutation showed statistical significance in different types of LEATs.

Ki-67 was a biomarker to determine the growth fraction of a given cell population, and the expression of Ki-67 was a routine test to predict the level of malignancy of tumors and the prognosis.[46,47] Yuan *et al.* found that a higher Ki-67 index did have a poor impact on prognosis of seizure of patients with LEATs in WHO-II.[48] The complexity and heterogeneity of tumor and the cut-off point of Ki-67 index for prediction were controversial, Ki-67 did not assess malignancy as a single indicator.[14,46] This study did not find the above indicators associated with seizure outcomes.

Limitations

The are some limitations in this research. Firstly, we finished a retrospective analysis of LEATs; however, a prospective clinical trial should be performed to discuss the value of different kinds of EEG in preoperative evaluation, intraoperative monitoring, and postoperative examination. Secondly, the clinical research with more centers and subjects enrolled can present more accurate clinical information and results.

Conclusion

Patients with complete resection of LEATs, and without epileptiform discharge on post-resective ECoG and postoperative scalp EEG might provide patients with a high chance of seizure control in overall. The application of ECoG monitoring might be beneficial to improve postoperative seizure outcomes of patients with LEATs. The GNB-SMOTE algorithm was a good evaluation model of postoperative seizure control and stratified patients in clinical development.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Fourth Medical Center, PLA General Hospital (No. 2021KY039-KS-001), and written informed consent was obtained from each patient.

Consent for publication

Not applicable.

Author contributions

Suhui Kuang: Data curation; Methodology; Software; Writing – original draft.

Shaohui Zhang: Data curation; Methodology; Writing – original draft.

Zhiqiang Cui: Data curation; Formal analysis; Methodology; Writing – review & editing.

Ming Ge: Conceptualization; Methodology; Supervision.

Liu Yuan: Data curation; Formal analysis; Methodology.

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Zhirong Wei: Data curation; Software.

Jinshan Xu: Formal analysis; Methodology.

Feng Zhai: Formal analysis; Methodology.

Shuli Liang: Conceptualization; Funding acquisition; Methodology; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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