



## Original Articles

## Epilepsy Surgery for Children With Low-Grade Epilepsy-Associated Tumors: Factors Associated With Seizure Recurrence and Cognitive Function



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## ABSTRACT

**OBJECTIVE:** Low-grade epilepsy-associated tumors (LEATs) are associated with childhood seizures that are typically drug-resistant, necessitating surgical interventions. In this study, we aimed to investigate the efficacy of surgical intervention in children with LEATs and to identify factors associated with seizure and cognitive outcomes.

**METHODS:** We reviewed 58 children less than 18 years of age who underwent epilepsy surgery due to histopathologically confirmed LEATs and had a minimum postoperative follow-up duration of 24 months.

**RESULTS:** Of the 58 patients who were followed for a median duration of 5.6 (IQR 3.2 to 10.0) years, 51 (87.9%) were seizure-free after surgery. In univariate analysis, shorter epilepsy duration, fewer antiepileptic drugs at time of surgery, gross total resection, and unilobar tumor involvement were associated with seizure freedom. In multivariate analysis, gross total resection was independently associated with seizure freedom. The preoperative and postoperative full-scale intelligence quotient (FSIQ) scores were  $78.9 \pm 27.1$  and  $80.9 \pm 28.7$ , respectively. In univariate analysis, younger age at seizure onset, longer epilepsy duration, more antiepileptic drugs at time of surgery, multilobar tumor involvement, and presence of generalized epileptic discharges were associated with lower preoperative FSIQ. In multivariate analysis, longer epilepsy duration was independently associated with lower preoperative FSIQ scores. Postoperative FSIQ scores were significantly influenced by preoperative FSIQ scores.

**CONCLUSIONS:** Epilepsy surgery for LEATs in children resulted in excellent seizure outcome. Gross total resection was the only independent factor associated with favorable seizure outcome. Preoperative and postoperative cognitive abilities were significantly influenced by epilepsy duration, so early surgical intervention should be considered.

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## Introduction

Low-grade epilepsy-associated tumors (LEATs) encompass a diverse spectrum of tumors that are slow-growing, low-grade, cortically based tumors of neuronal, glial, or mixed origins, which are associated with epilepsy. These tumors are characteristically represented by glioneuronal tumors (GNTs).<sup>1</sup> LEATs commonly present with focal seizures that are longstanding and typically drug-resistant. Moreover, they occur more frequently in children and young adults.<sup>2</sup> Therefore, although comprising only a small portion of all brain tumors (2% to 5%) and of total pediatric epilepsy patients (1% to 3%), LEATs are the second-most frequent etiology for epilepsy surgery, after focal cortical dysplasia, in children.<sup>2–4</sup>

Because LEATs rarely exhibit malignant transformation, surgical resection of these tumors is usually dependent upon associated epilepsy, and the morbidity of LEATs mostly derives from the epilepsy, rather than the tumors themselves.<sup>5,6</sup> The focal epilepsy associated with LEATs is extremely responsive to surgical treatment, and approximately 80% of patients, both adults and children, achieve seizure freedom after surgery.<sup>7–9</sup> Surgical treatment, therefore, should be considered as a therapeutic choice for LEATs. Nevertheless, medical treatments are preferred in some clinical practices and the optimal timing for surgery remains controversial.

We investigated the surgical outcomes of LEATs, and attempted to identify possible predictors of surgical outcomes regarding seizure control and cognitive function.

## Methods

### *Patients and clinical characteristics*

A retrospective single-center study was conducted for children with LEATs who received surgical treatment. Inclusion criteria were as follows: (1) children less than 18 years of age with epilepsy; (2) who underwent surgery in Severance Children's Hospital between 2006 and 2015; (3) who exhibited histopathologically confirmed LEATs; and (4) who had a postoperative follow-up duration of more than 24 months. The following patients were excluded: (1) patients who were undergoing a second surgery due to a prior incomplete resection; (2) patients whose surgeries were performed for reasons other than epilepsy.

This study was approved by the Institutional Review Board of Severance Hospital.

### *Presurgical evaluations and surgical procedures*

All of the patients had undergone a presurgical evaluation in Severance Children's Hospital, comprising a thorough documentation of clinical history including current and past seizure semiology, scalp video-electroencephalography monitoring (V-EEG), brain MRI, and neuropsychologic testing. Full-scale intelligence quotient (FSIQ) or mental developmental index (MDI) was assessed using one of the following scales, based on the patient's age: Bayley scales of infant development (second edition) for patients less than 42 months old, Wechsler preschool and primary scale of intelligence for individuals three to seven years old, Wechsler intelligence scale for children for children six to 16 years of age, and the Wechsler adult intelligence scale for those greater than 16 years old.

In selected patients, two-stage surgery with intracranial EEG monitoring (iEEG) was performed, following placement of subdural

grid electrodes. The remaining patients, and during the second stage for patients receiving two-stage surgery (i.e., all patients), were subjected to intraoperative electrocorticography (ECoG). All surgical procedures were performed by the same team of neurosurgeons (E.K.P., K.W.S., and D.S.K.) at Severance Children's Hospital.

Sites of resection were divided into three groups: temporal, unilobar extratemporal, and multilobar. The extent of surgical resection—complete or incomplete—was evaluated via postoperative brain MRI.

### *Pathology*

The tumors were classified pathologically according to the revised World Health Organization classification, then divided into three groups: gangliogliomas, dysembryoplastic neuroepithelial tumors, and other LEATs.<sup>1</sup>

### *Assessment of surgical outcomes*

Postoperative brain MRI was performed for every patient at mean of two (standard deviations [SD] 1.1) months postsurgery to evaluate whether gross total resection was achieved.

To assess seizure outcome, patients were divided into seizure-free and seizure-recurrence groups. The seizure-free group included patients who did not show any clinical seizures from two weeks after the surgery through the last follow-up, for more than 24 months. All other patients were included in the seizure-recurrence group.

### *Statistical analysis*

Data from statistical analyses are expressed as means and SD, medians and interquartile ranges (IQRs), or counts and percentages. Clinical characteristics of the seizure-free and seizure-recurrence groups were compared using univariate logistic regression. Multivariate logistic regression was then used for selected parameters. For univariate analysis to see the effects of clinical characteristics on neuropsychologic scores, linear regression, Mann-Whitney *U*, or Kruskal-Wallis *H* tests were used. Multivariate linear regression was then used for selected parameters. A *P* value of <0.05 was considered to be significant. The Statistical Package for the Social Sciences (version 23.0; IBM, Armonk, NY) was used for all analysis.

## Results

### *Demographics*

A total of 58 patients received epilepsy surgery related to LEATs in Severance Children's Hospital between 2006 and 2015. Twenty-nine of these (50.0%) were male (Table 1). Mean age at surgery was 10.2 (IQR 6.2 to 14.3) years old, and mean age at seizure onset was 6.0 (3.1 to 9.9) years old. Median lead time from seizure onset to surgery was 1.3 (IQR 0.3 to 5.3) years, and 39 (67.2%) patients exhibited drug-resistant epilepsy. Seventeen (29.3%) patients showed focal seizures only without secondary generalization, 30 (51.7%) patients showed focal seizures or focal-to-bilateral tonic-clonic seizures, and 11 (19.0%) patients showed generalized onset seizures. Median duration of follow-up was 5.6 (IQR 3.2 to 10.0) years. Preoperative V-EEG was performed for a median of four (IQR 3 to 6) days; in 17 (29.3%) patients, EEGs revealed generalized epileptiform discharges. Brain MRI showed findings consistent with LEATs in all patients (Fig 1). Fifty (86.2%) patients were investigated preoperatively with 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission

**TABLE 1.** Clinical Characteristics of Patients and Seizure Outcomes After Surgery

	Total (n = 58)	Seizure-free (n = 51)	Seizure-recur (n = 7)	P
Sex (male)	29 (50.0%)	26 (51.0%)	3 (42.9%)	0.688
Age at surgery (years)	10.2 (6.2-14.3)	10.0 (6.0-14.2)	12.0 (8.5-16.3)	0.180
Age at seizure onset (years)	6.0 (3.1-9.9)	6.3 (2.3-10.0)	4.3 (3.3-8.3)	0.563
Lead time (years)	1.3 (0.3-5.3)	1.2 (0.4-4.2)	7.8 (0.2-13.0)	<b>0.032</b>
Follow-up duration (years)	5.6 (3.2-10.0)	4.9 (2.9-9.6)	9.6 (5.6-12.8)	0.084
Initial seizure frequency (/day)	1.00 (0.14-3.00)	1.00 (0.14-3.00)	1.00 (0.03-10.00)	0.137
Seizure types				0.209
Focal only	17 (29.3%)	16 (31.4%)	1 (14.3%)	
Focal-to-bilateral	30 (51.7%)	27 (52.9%)	3 (42.9%)	
Generalized	11 (19.0%)	8 (15.7%)	3 (42.9%)	
Drug-resistant epilepsy	39 (67.2%)	33 (64.7%)	6 (85.7%)	0.289
Number of AEDs before surgery	2 (1-3)	2 (1-3)	3 (2-4)	<b>0.045</b>
Video EEG duration (days)	4 (3-6)	4 (3-6)	5 (3-6)	0.883
Generalized epileptiform discharges on EEG	17 (29.3%)	13 (25.5%)	4 (57.1%)	0.101
Gross total resection	51 (87.9%)	48 (94.1%)	3 (42.9%)	<b>0.002</b>
Tumor location				<b>0.029</b>
Temporal	31 (53.4%)	30 (58.8%)	1 (14.3%)	
Extratemporal unilobar	21 (36.2%)	18 (35.3%)	3 (42.9%)	
Multilobar	6 (10.3%)	3 (5.9%)	3 (42.9%)	
Side of tumor (right)	30 (51.7%)	26 (51.0%)	4 (57.1%)	0.760
Two-stage surgery	40 (69.0%)	34 (66.7%)	6 (85.7%)	0.327
Pathology				0.189
Ganglioma	27 (46.6%)	27 (52.9%)	1 (14.3%)	
Dysembryoplastic neuroepithelial tumor	28 (48.3%)	21 (41.2%)	6 (85.7%)	
Others	3 (5.2%)	3 (5.9%)	0 (0.0%)	
Focal cortical dysplasia on pathology	6 (10.3%)	5 (9.8%)	1 (14.3%)	0.731

AED, antiepileptic drug; EEG, electroencephalogram.

$p < 0.005$  are shown in bold.

tomography scan, of which 45 (90.0%) patients showed decreased fluoro-D-glucose uptake suggesting low-grade tumor and four patients showed nonspecific findings. Preoperative interictal single photon emission computed tomography (SPECT) was done in 44 (75.9%) patients, and 40 (90.9%) patients of them showed decreased blood flow to the tumor while the rest four (9.1%) patients showed no specific findings. Twenty-four of 44 (54.5%) patients who were investigated with interictal SPECT did successful ictal SPECT, and all of them showed increased blood flow at peritumor areas. The tumor was located solely at the temporal lobe in 31 (53.4%) patients, at the extratemporal lobe (unilobar) in 21 (36.2%) patients, and involved greater than two lobes (multilobar) in six (10.3%) patients. Histological classifications of tumors were ganglioma in 27 (46.6%) patients, dysembryoplastic neuroepithelial tumor in 28 (48.3%) patients, pilocytic astrocytoma in two (3.4%) patients, and papillary GNT in one (1.7%) patient. Cortical dysplasia associated with tumor was documented in six (10.3%) patients on pathology (Fig 2). Forty (69.0%) patients underwent a two-stage surgery with iEEG monitoring for a median duration of six (IQR four to seven) days, and all patients were subjected to ECoG. Gross total resection was achieved in 51 (87.9%) patients, whereas the remaining seven (12.1%) patients exhibited residual tumor on postoperative brain MRI. A surgical complication occurred in one (1.7%) patient, which comprised insidious prolonged hemorrhage that necessitated surgical intervention.

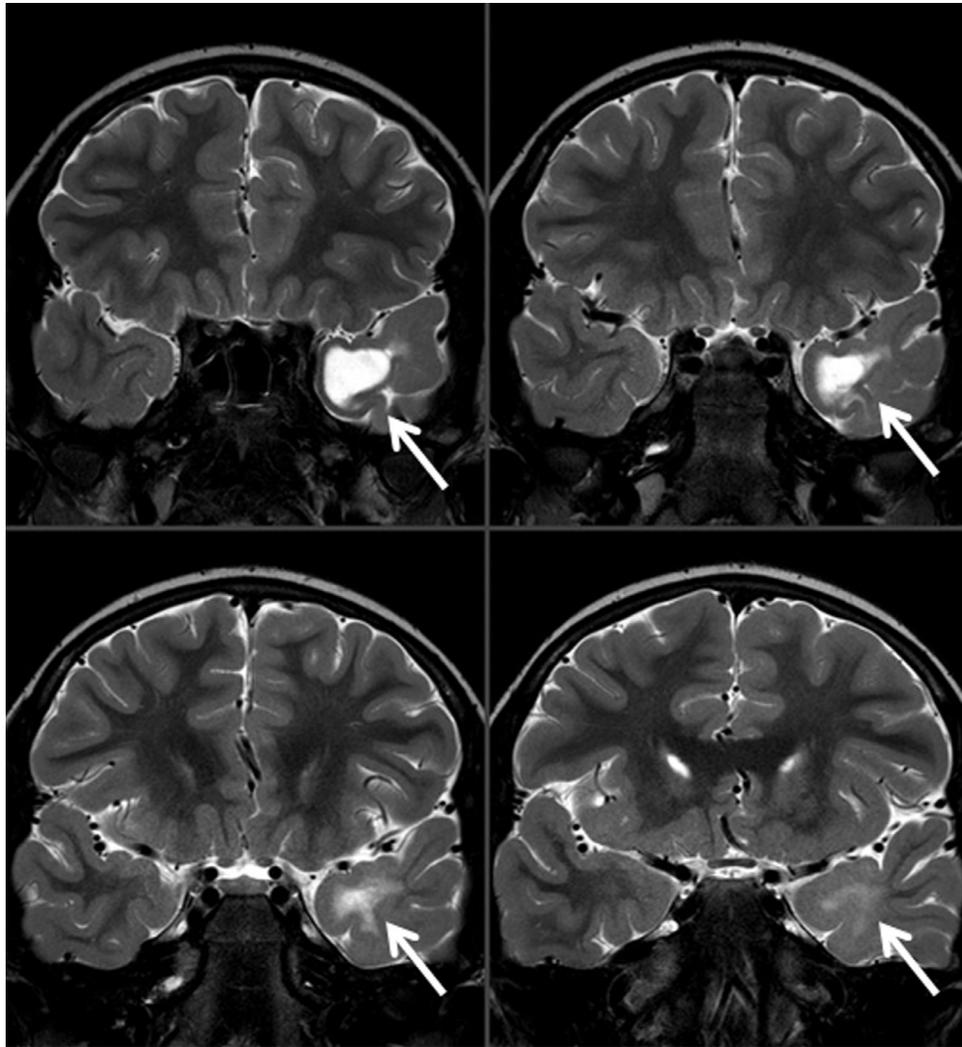
#### Surgical (seizure) outcome

Of 58 patients, 51 (87.9%) patients remained seizure-free for more than 24 months, until the last follow-up, and seven (12.1%) patients experienced seizures after

surgery. Seizures recurred at median of six (IQR 4 to 11) months after the surgery, and only one patient experienced seizure recurrence after 24 months. Fifteen patients (25.9%) were taking antiepileptic drugs (AEDs) until the last follow-up visits, eight of whom belonged to seizure-free group (15.7% of 51 seizure-free patients), and seven of whom belonged to seizure-recurrence group (all of the seven seizure-recurrence patients). Of the clinical variables listed in Table 1, longer lead time from seizure onset to surgery ( $P = 0.032$ ), more AEDs taken before surgery ( $P = 0.045$ ), incomplete resection ( $P = 0.002$ ), and multilobar involvement of the tumor ( $P = 0.029$ ) conferred increased risk for seizure recurrence in the univariate analysis. Sex, age at surgery, age at seizure onset, follow-up duration, initial seizure frequency at the time of surgery, seizure types, presence of drug-resistant epilepsy, duration of V-EEG monitoring, presence of generalized epileptiform discharges on V-EEG, side of tumor (left or right), performance of two-stage surgery with iEEG, histopathology, and associated cortical dysplasia were not associated with seizure outcome. However, when multivariate analysis was performed with the parameters that demonstrated  $P$  values of  $<0.010$  (i.e., lead time, follow-up duration, number of AEDs, gross total resection, and multilobar involvement) in univariate analysis, incomplete resection was the only independently significant factor associated with seizure recurrence (odds ratio 16.579, 95% confidence interval 1.501 to 183.159,  $P = 0.022$ , Table 2).

#### Pre- and postoperative FSIQ

Preoperative FSIQ scores were available for 54 (93.1%) patients while MDI scores were available for the



**FIGURE 1.** MRI (T2 images) scan of a patient with LEAT showing a cystic and solid mass (arrows) in the left mesial temporal lobe involving uncus, parahippocampal, and inferior temporal gyri with possible overlying focal cortical dysplasia. LEAT, low-grade epilepsy-associated tumor.

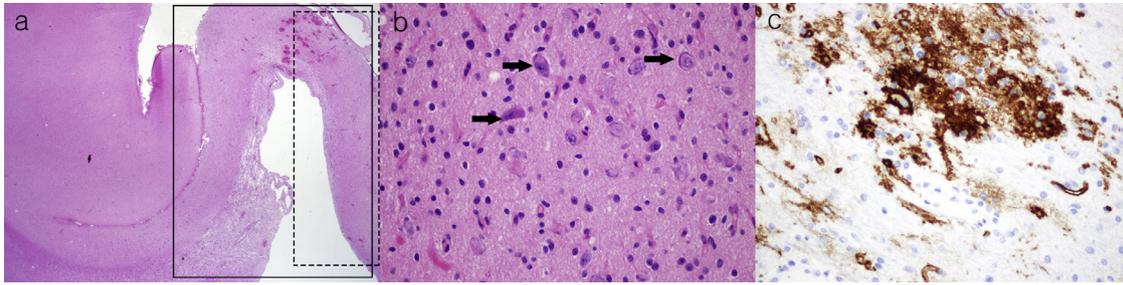
remaining four (6.9%) patients; the 54 patients with preoperative FSIQ scores were subjected to analysis. The mean preoperative FSIQ score was 78.9 (SD 27.1). In a univariate analysis to characterize the relationships between clinical variables and preoperative FSIQ, younger age at seizure onset ( $P = 0.001$ ), longer lead time from seizure onset to surgery ( $P < 0.001$ ), more AEDs taken before surgery ( $P = 0.037$ ), multilobar involvement of the tumor ( $P = 0.018$ ), and presence of generalized ED on V-EEG ( $P = 0.033$ ) were statistically significant factors associated with lower preoperative FSIQ scores (Supplementary Table 1). However, when multivariate regression was performed with these parameters, the only statistically significant factor associated with FSIQ was lead time from seizure onset to surgery, with longer lead time resulting in lower FSIQ scores (coefficient  $\beta = -3.067$ ,  $P < 0.001$ , Table 3). When the four excluded MDI scores were included for analysis together with the FSIQ scores, the statistical results remained the same. Figure 3 is a simple

scatter plot that represents the correlation between lead time from seizure onset to surgery and preoperative FSIQ (coefficient  $\gamma = -0.670$ ,  $P < 0.001$ ).

The postoperative FSIQ scores were available for 42 (77.8%) of the 54 patients with preoperative FSIQ scores; these patients were evaluated at median of 21.0 (IQR 13.2 to 31.0) months after the surgery. The mean postoperative FSIQ score was 80.9 (SD 28.7). The postoperative FSIQ was significantly influenced by preoperative FSIQ (coefficient  $\beta = 0.790$ ,  $P < 0.001$ ), with median change from preoperative to postoperative FSIQ of 0.0 (IQR  $-5.8$  to 14.0).

## Discussion

In this study, we presented seizure and cognitive outcomes of 58 children who received epilepsy surgery due to LEATs and were followed up for more than 24 months in Severance Children's Hospital. After median follow-up of 5.6 (IQR 3.2 to 10.0) years, 51 of 58 (87.9%) patients remained



**FIGURE 2.** Pathology of the patient with LEAT whose brain MRI scans are shown in Fig 1. (a) Low power view (x12) of ganglioglioma (box) with overlying focal cortical dysplasia (dotted box). (b) High power view (x 400) showing dysplastic ganglion cells (arrows) with glial cell proliferation. (c) Immunohistochemical staining showing CD34 expressing dysplastic ganglion cells. LEAT, low-grade epilepsy-associated tumor.

seizure-free. Achievement of gross total resection was significantly associated with seizure freedom after surgery, and longer duration of epilepsy was significantly associated with lower FSIQ before and after the surgery. This study is the first to assess and analyze preoperative developmental functioning status in LEATs for all patients included in the study without missing data.

In this study, 87.9% (51 of 58) patients showed seizure freedom after epilepsy surgery for LEATs. The tapering of AEDs after surgery was conducted variably among patients with inconsistent policy due to the retrospective nature of the study, but 74.1% (43 of 58) patients remained seizure free after discontinuation of AEDs. This favorable seizure outcome is comparable with other published studies, where the resection of LEATs led to excellent results in both adults and children.<sup>9–13</sup> Our cohort included 27 (46.6%) patients with ganglioglioma, 28 (48.3%) with dysembryoplastic neuroepithelium tumor, two (3.4%) with pilocytic astrocytoma, and one (1.7%) with a papillary GNT. Only patients who underwent epilepsy surgery were included. Patients who underwent resection surgery for other reasons, such as hydrocephalus or tumor resection itself, were not included; this may explain the small number of pilocytic astrocytoma patients in this cohort, because these tumors are common located in the cerebellum.

The reported factors associated with favorable seizure outcome after resective surgery of LEATs from various studies comprise gross total resection, lower age at surgery, shorter duration of epilepsy, temporal resection site, absence of secondary generalized seizures, and absence of spikes in postoperative EEG.<sup>9,10,14–19</sup> However, this is still controversial, as factors which are significant predictors in some studies are reported as insignificant in others. In this study, shorter duration of epilepsy, fewer

AEDs taken at the time of surgery, total gross resection, and unilobar involvement of tumor were all factors that were associated with seizure freedom; however, only gross total resection was an independent predictor for seizure freedom. This is consistent with several studies that reported gross total resection to be the only factor significant correlated with seizure outcome.<sup>9,15,16,18–20</sup> However, the small number of patients included in the seizure-recurrence group in our study (seven of 58 patients) may place some limitations on the analysis. Furthermore, longer duration of epilepsy was significantly associated with multilobar involvement of tumors ( $P < 0.001$ ), which in turn was significantly associated with incomplete tumor resection ( $P < 0.001$ ). Therefore, shorter duration of epilepsy and unilobar involvement of tumor act as significant predictors for the achievement of gross total resection; thus, they are significant in predicting seizure freedom after surgery, at least partly or indirectly.

The role of ECoG during epilepsy surgery for LEATs is still unclear. Some studies have emphasized the importance of ECoG in epilepsy surgery for LEATs to facilitate complete gross resection and increase the likelihood of seizure freedom, whereas other reports have found no significant differences in seizure outcome, regardless of whether ECoG was performed; these negative reports suggest that ECoG is only needed to delineate eloquent areas in extratemporal tumors, or to aid in repeated surgery after failing to control seizures during the previous surgery of temporal lobe tumors.<sup>11,20,21</sup> Another study showed that, in patients who underwent two-stage surgery, iEEG helped to define seizure-onset zones and improved seizure outcome.<sup>22</sup> It was difficult to assess the effect of ECoG on seizure outcome in this study because all patients underwent ECoG. Instead, when we investigated the effect of iEEG on seizure outcome, performance of iEEG was

**TABLE 2.** Multivariate Analysis of Factors Associated with Seizure Outcome

	Seizure-free (n = 51)	Seizure-recur (n = 7)	OR	95% CI	P
Lead time (years)	1.2 (0.4–4.2)	7.8 (0.2–13.0)	1.065	0.833–1.360	0.617
Follow-up duration (years)	4.9 (2.9–9.6)	9.6 (5.6–12.8)	1.246	0.894–1.737	0.194
Number of AEDs before surgery	2 (1–3)	3 (2–4)	1.446	0.512–4.088	0.487
Gross total resection	48 (94.1%)	3 (42.9%)	16.579	1.501–183.159	<b>0.022</b>
Multilobar involvement	3 (5.9%)	3 (42.9%)	17.911	0.452–709.697	0.124

AEDs, antiepileptic drugs; CI, confidence interval; OR, odds ratio.  
 $p < 0.005$  are shown in bold.

**TABLE 3.** Multivariate Analysis of Factors Associated with Preoperative FSIQ

	Preoperative FSIQ (Coefficient $\beta$ )	P
Age at seizure onset (years)	1.072	0.140
Lead time (years)	-3.067	<b>&lt;0.001</b>
Number of AEDs before surgery	-1.298	0.619
Generalized epileptiform discharges on EEG	-8.328	0.174
Multilobar involvement	-11.905	0.068

AEDs, antiepileptic drugs; EEG, electroencephalogram; FSIQ, full scale intelligence quotient.

$p < 0.005$  are shown in bold.

neither associated with favorable seizure outcome nor with gross total resection. Whether iEEG facilitates better seizure outcome remains uncertain because more difficult patients may have been subjected to iEEG monitoring. Further randomized studies are needed to draw more decisive conclusions.

In this study, the mean preoperative FSIQ score was 78.9 (SD 27.1); younger age at seizure onset, longer duration of epilepsy, more AEDs taken at the time of surgery, multilobar involvement of the tumor, and presence of generalized epileptiform discharges on V-EEG were associated with lower preoperative FSIQ. However, longer duration of epilepsy was the only independent factor associated with lower preoperative FSIQ. Postoperative FSIQ was strongly influenced by preoperative FSIQ. In studies that investigated the cognitive outcomes following epilepsy surgery for LEATs, longer duration of epilepsy, younger age at seizure onset, and drug-resistant epilepsy were suggested as factors associated with poorer preoperative cognitive abilities.<sup>9,10,16,23</sup> However, longer duration of epilepsy is the only common risk factor for poorer cognitive function in all studies, which is consistent with our study. The cognitive decline observed in patients may be attributable to the longstanding effect of chronic seizures themselves or to long-term exposure to AEDs.<sup>24–26</sup> Longer duration of epilepsy results in more prolonged exposures to both; in our study, longer duration of epilepsy was also significantly associated with more AEDs taken at time of surgery ( $P = 0.048$ ), increasing the potential for adverse effects of AEDs on cognitive function. Therefore, early surgical intervention for

epilepsy, associated with LEATs, is important for both pre- and postoperative cognitive abilities.

This study was limited by its lack of a control group who did not undergo epilepsy surgery to more reliably assess the efficacy of epilepsy surgery in LEATs in terms of seizure control. Also, due to its retrospective nature, the postoperative developmental functions were assessed after various periods from surgery, and they were not assessed in all patients.

## Conclusions

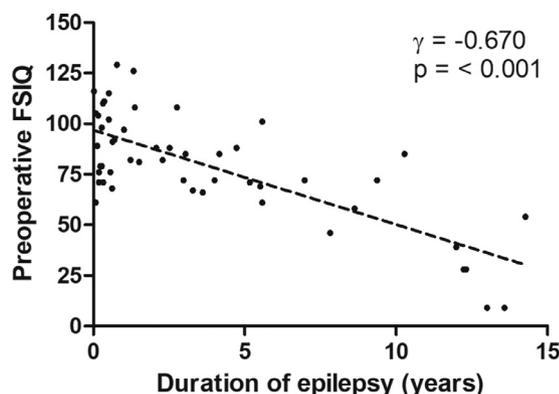
Epilepsy surgery for LEATs in children demonstrated excellent seizure outcomes, and 87.9% of patients who were followed up for more than 24 months achieved seizure freedom after surgery. Gross total resection was the only independent factor associated with favorable seizure outcome. Preoperative and postoperative cognitive abilities were significantly influenced by the duration of epilepsy, so early surgical intervention should be considered.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.pediatrneurol.2018.10.008](https://doi.org/10.1016/j.pediatrneurol.2018.10.008).

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**FIGURE 3.** Scatter-dot plot representing the correlation between epilepsy duration and preoperative FSIQ. FSIQ, full-scale intelligence quotient.

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