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REVIEW ARTICLE

Surgery for extratemporal nonlesional epilepsy in adults: an outcome meta-analysis

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Abstract
Purpose To better evaluate surgery for extratemporal lobe epilepsy (ETLE) in adults, we conducted a meta-analysis of previous studies that analyzed postoperative seizure outcomes for ETLE.
Methods After searching PubMed for appropriate studies, patient data were reviewed, and data on patients who fit the authors' criteria were extracted. Statistical analysis compared each variable with surgical outcome to determine if an association existed.
Results For the 131 patients who were included in the analysis, the age at surgery, age of seizure onset, and duration of epilepsy were not found to be statistically and significantly related to seizure outcome. Similarly, seizure semiology, abnormality on magnetic resonance imaging, lateralization of the seizures, the need for intracranial monitoring, pathological findings, and the type and location of surgery did not appear to be associated with outcome.
Conclusions This meta-analysis confirms the findings of other centers: ETLE surgical outcomes are less desirable than those for temporal lobe epilepsy. None of the factors studied in adults showed significant association with outcome. Contrary to some reports, shortening the duration of epilepsy by pursuing surgery as early as possible also does not appear to improve outcomes. The creation of standard protocols among epilepsy centers is needed to allow for a detailed evaluation of outcomes across different centers and, ultimately, to better assess the factors associated with improved outcomes.

Keywords ETLE · ETLE surgery · ETLE surgery outcome · Epilepsy

Introduction

Extratemporal lobe epilepsy (ETLE) is a chronic seizure disorder originating in an area of the brain outside the temporal lobe. ETLE is less common than temporal lobe epilepsy (TLE) and is more prevalent in children than adults [5, 26, 27], as the pathology involved in ETLE is often a congenital malformation of brain development, such as cortical dysplasia, that results in a more diffuse epileptic focus [15]. When compared to surgery for ETLE, surgery for temporal lobe epilepsy is associated with more desirable outcomes [28]. This analysis considers the outcomes of ETLE surgery in adults without structural lesions.

Complicating the treatment for ETLE is the difficulty in diagnosing the condition and differentiating it from TLE or from other medical conditions. Depending on the actual location of the epileptogenic focus, localization by scalp EEG may prove impossible—some frontal lobe epilepsies may not show any change at all on EEG, for example [43]. In addition, extratemporal onset seizures spread rapidly to other parts of the brain, obscuring the focus on EEG, which often shows a great deal of overlap with eloquent areas of

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the cortex, making complete resection of the focal region more difficult, if not impossible [18]. There are, however, certain characteristic semiological elements that can localize the origin of seizures. Swartz et al. described several characteristics of seizures that originate in various parts of the brain: parietal lobe seizures present with gustatory aura, swallowing movements, or tonic posturing; frontal lobe seizures may manifest as psychological disturbances (which could be mistaken for a psychiatric condition rather than a seizure) or complex motor movements. Seizures originating at the parieto-occipital junction may involve tinnitus, vertigo, or auditory hallucinations [23, 36].

This study was undertaken because there is currently no large-scale analysis of postoperative outcome of nonlesional ETLE surgery in adults. The primary concern in this analysis was to determine which of the variables under consideration demonstrate a strong association with postoperative seizure outcome. The available studies have been typically small-scale experiences of individual centers that often contained no more than 20–30 patients, among whom those who fit our criteria (listed below) were even fewer in number. In order to paint a clearer picture of the outcome of ETLE surgery and the reasons associated therewith, the authors investigated the experiences of the international epilepsy surgery community available in the English literature in dealing with nonlesional ETLE in adults.

The studies that report extratemporal surgical outcomes routinely exclude the patients who undergo disconnective procedures. Patients may undergo a disconnective procedure (such as corpus callosotomy) for a number of reasons such as atonic seizures. These patients often suffer from a heterogeneous class of epileptogenic pathologies that are not well understood. Since the introduction of vagus nerve stimulation, disconnective procedures are less commonly used. Therefore, we have excluded the patients who have undergone disconnective procedures.

Patients and methods

Data for this analysis were collected from past studies conducted to determine surgical outcomes of patients with nonlesional ETLE. Studies containing this data were found using PubMed searches with the following search terms: extratemporal epilepsy, extratemporal epilepsy treatment, extratemporal epilepsy surgery, extratemporal epilepsy surgery outcome, frontal lobe epilepsy, occipital lobe epilepsy, and parietal lobe epilepsy. Additional manual searching of the bibliographies of the available articles was also performed. Types of data collected included patient age at onset of seizures and at surgery, location of epileptic focus (as defined by the most specific type of monitoring used), postoperative seizure outcome (with at least 1 year of follow-up, classified using the Engel system) [14], pathology of the epileptic region, magnetic resonance imaging (MRI) findings (normal vs. abnormal), predominant seizure type (simple/complex partial, generalized), location of surgery, and whether the patient underwent intracranial monitoring (see Table 1) [4, 7, 8, 16, 19–22, 24, 25, 30, 32, 35, 37, 42]. Only patients with 1 year or more of follow-up were included because several groups have established that seizure status at 1 year is highly indicative of long-term seizure status [11, 39]. Adults were separated from children. Pediatric outcomes have been analyzed in a separate study [2]. In cases where outcome was not directly reported using the Engel system, the authors translated the study's system to the Engel system using the descriptions of outcomes given in the paper. Seizure type was divided into complex partial, simple partial, and generalized. Specific criteria for patient inclusion were outlined at the beginning of the study, and all accessible studies published after 1990 with available data were reviewed for patients who fit these criteria. The cutoff date of 1990 was chosen because most studies published after this year included MRI findings, which are an important part of this analysis.

The specific characteristics of the patients to be included in this analysis were as follows: only adults (patients aged 18 and over) with nonlesional ETLE were considered. Since this study focuses on ETLE, patients with purely temporal lobe foci were excluded, but all patients with multilobar foci that included the temporal lobe were included. Lesional status was determined by using pathology data provided in the studies; patients with tumors, vascular malformations/lesions, and tuberous sclerosis were excluded. All other pathologies, such as cortical dysplasia, malformations of cortical development, gliosis, chronic inflammation, polymicrogyria, ulegyria, and neuronal loss, among others, were included. Certain patients with focal cortical dysplasia displayed a “lesion” on MRI, with the true nature of these lesions determined on pathological examination; however, since these patients were consistently included among the patients with “nonlesional” epilepsy syndromes in the literature, they were also included in this analysis. Surgical procedures performed included topectomy, corticectomy, full/partial lobectomy, and focal resection. Patients who underwent multiple subpial transection (MST) alone were excluded. Patients who underwent corpus callosotomy or other disconnection surgeries were also excluded. Only studies which provided data broken down by individual patient were used, and the studies which provided only “general demographic” information for all the patients combined were by necessity excluded.

Statistical analysis was performed using R version 2.4.1. Each variable was analyzed for any association with postoperative outcome. Continuous variables (age at onset/surgery and duration) were summarized using mean and

Table 1 Patient and surgery characteristics by outcome class [11–25]

	Outcome class								
	I		II		III		IV		*P* value
	n		*n*		*n*		*N*		
Age at onset (years)	44	10.2 (8.0)	16	11.8 (13.0)	13	10.3 (10.9)	9	4.8 (5.2)	0.358
Age at surgery (years)	59	27.7 (9.0)	26	30.8 (8.9)	19	28.2 (8.7)	20	25.4 (7.1)	0.214
Duration (years)	44	17.4 (9.0)	16	19.0 (11.0)	13	19.3 (8.6)	9	23.9 (8.0)	0.287
Seizure type	37		11		8		8		0.397
Complex partial		16 (43.2%)		6 (54.6%)		3 (37.5%)		1 (12.5%)	
Generalized		12 (32.4%)		4 (36.4%)		4 (50.0%)		6 (75.0%)	
Other		9 (24.4%)		1 (9.1%)		1 (12.5%)		1 (12.5%)	
Pathology	54		25		16		20		0.352
Cortical dysplasia		23 (42.6%)		5 (20.0%)		4 (25.0%)		9 (45.0%)	
Gliosis		21 (38.9%)		11 (44.0%)		7 (43.8%)		6 (30.0%)	
Other		10 (18.5%)		9 (36.0%)		5 (31.3%)		5 (25.0%)	
Surgery type	31		25		11		14		0.620
Frontal resection		14 (45.2%)		10 (40.0%)		5 (45.5%)		5 (35.7%)	
Central resection		6 (19.4%)		4 (16.0%)		2 (18.2%)		7 (50.0%)	
Posterior cortical resection		5 (16.1%)		5 (20.0%)		1 (9.1%)		1 (7.1%)	
Other		6 (19.4%)		6 (24.0%)		3 (27.3%)		1 (7.1%)	
Lateralization	56		29		16		22		0.622
Bilateral		1 (1.8%)		0 (0.0%)		0 (0.0%)		1 (4.6%)	
Left		25 (44.6%)		17 (58.6%)		8 (50.0%)		13 (59.1%)	
Right		30 (53.6%)		12 (41.4%)		8 (50.0%)		8 (36.4%)	
MRI	33		15		9		4		0.208
Abnormal		16 (48.5%)		10 (66.7%)		6 (66.7%)		4 (100%)	
Monitoring	52		22		15		18		0.714
Yes		36 (69.2%)		15 (68.2%)		11 (73.3%)		15 (83.3%)	

standard deviation and compared across groups using ANOVA. Categorical variables were summarized using frequency and percentage and were compared across groups using Fisher's exact test.

Results

Seizure outcomes

Of the131 patients included in this study, 60 (45.8%) had Engel class I outcome, or complete seizure freedom, 30 (22.9%) had Engel II outcome (>90% seizure reduction or seizure freedom with medication), 19 (14.5%) had Engel III outcome (>75% seizure reduction), and 22 (16.8%) were Engel IV outcome, or no worthwhile seizure reduction. If Engel classes I, II, and III are to be considered "worthwhile" outcomes, then 109 (83.2%) had worthwhile outcome and 22 (16.8%) had no worthwhile reduction of their seizures.

Factors related to outcome

The mean age of the study group at the time of surgery was 28.06±8.7 years, and this variable had no association with seizure outcome (P=0.214, Table 1). Similarly, the mean age of seizure onset, which was 9.92±9.4 years, also did not show any significant association with outcome (P= 0.358). However, the patients with outcome class IV had the youngest reported mean age at seizure onset (4.8 years). In addition, the duration of epilepsy (time from onset of seizure to surgery), which had a mean of 18.72± 9.3 years, had no significant association with seizure outcome (P=0.287).

In this analysis, information regarding seizure type was available for 62 patients. Seizures were classified as complex partial, generalized, or "other" (which included simple partial, SMA seizures, and status epilepticus). Among these 62 patients, 37 (59.7%) had Engel class I outcome, 11 (17.7%) had class II, 8 (12.9%) had class III, and 8 (12.9%) had class IV outcome. Within the class I group, 16 (43.2%) had complex partial seizures, 12 (32.4%) had generalized seizures, and 9 (24.4%) had "other" seizures. There was no significant association between seizure type and outcome class (P=0.397). Notably, more than half of all the patients with complex partial seizures and the patients with "other" seizure type enjoyed favorable surgical outcomes (class I).

Sixty-one patients had MRI findings, which were listed as either normal or abnormal for simplicity in analysis. Of these patients, 33 (53.2%) had class I outcomes, and 16 (48.5%) of these 33 had an abnormal MRI; 15 (24.2%) patients had class II outcomes, and 10 (66.7%) of these patients had abnormal MRI; 9 (14.2%) had class III outcomes, with 6 (66.7%) of these showing an abnormality on MRI; and 4 patients had class IV outcomes, with all 4 of these showing an abnormal MRI. There was no significant association between MRI findings and seizure outcome class (P=0.208).

Invasive intracranial EEG monitoring is used in patients when a seizure focus cannot be determined by noninvasive means (MRI, EEG, PET, and SPECT). In this analysis, the information pertaining to intracranial monitoring was available for 108 patients. Of these, 77 underwent monitoring, with 36 (46.7%) showing a class I outcome, 15 (19.5%) showing class II, 11 (14.3%) with class III, and 15 (19.5%) with class IV. As with the MRI findings, there was no statistically significant association between the use of intracranial monitoring and seizure-free outcome (P=0.714).

The histopathological findings of the reviewed studies were categorized as cortical dysplasia (CD), gliosis, and "other" (including porencephaly, neuronal loss, malformation of cortical development, polymicrogyria, and minor morphological abnormalities). Pathological findings were available for 115 of the 131 patients: 54 (47.0%) patients had Engel class I outcomes with respect to postoperative seizures, 25 (21.7%) had class II, 16 (13.9%) had class III, and 20 (17.4%) had class IV outcomes. There was no significant association between the pathology of the epileptic region and seizure outcome (P=0.352). Among the patients with class I outcomes, 23 (42.6%) harbored CD, 21 (38.9%) harbored gliosis, and 10 (18.5%) harbored other pathologies.

Based on the location of surgical resection, the surgery types were classified as frontal cortical resection (which included frontal focal cortical resections and full/partial frontal lobectomies), central cortical resection, posterior cortical resection (which included parietal and occipital lobectomies), and "other," which included all multilobar surgeries and MSTs. This degree of consolidation of categories was required for computation of the statistical tests. Eighty-one patients had data pertaining to their surgeries; 31 (38.3%) of these patients had Engel I outcomes, 25 (30.9%) had Engel II, 11 (13.6%) had Engel III, and 14 (17.3%) had Engel IV. The P value for the test comparing surgery location to outcome was 0.620, indicating no significant association between these variables. In the class I outcome group, there were 14 patients (45.2%) who underwent frontal cortical resection, 6 (19.4%) who underwent central cortical resection, 5 (16.1%) who underwent posterior cortical resection, and 6 (19.4%) who underwent other types of procedures (Table 1).

Discussion

The relatively poor surgical outcome of ETLE surgery as compared to TLE surgery has been reported by other groups [11–13, 18, 31, 39]. Adults with temporal lobe epilepsy experience a 63.2% seizure freedom rate, whereas patients with extratemporal epilepsy have a 27% seizure freedom rate for frontal lobe resections, and 46% each for parietal and occipital resections [39]. Our data demonstrate a similar outcome, with a combined 45.8% seizure freedom rate for all three lobes. Among the patients who present with ETLE, those with lesions have good outcomes when compared with those who have no well-defined lesion or a normal MRI [3, 6, 32, 40]. Some groups have claimed that negative outcomes can be predicted by the presence of generalized tonic–clonic seizures (although we did not find this to be significant in adults), history of a previous surgery for epilepsy, and focal cortical dysplasia on pathological exam (our data also found that this was not significant in adults) [13]. Another notable finding by Elsharkawy et al. is that the risk of recurrence of seizures is highest within the first 1–2 years following surgery [11–13]. After this time period, the patients who had Engel class I outcomes had a 92% chance of remaining in this class [11]. Our data show that, in adults, no one factor is associated significantly with postoperative seizure outcome.

The reasons for the poor outcomes in ETLE revolve around the pathology involved in the disease. Whereas epilepsy of the temporal lobe origin usually involves a discrete, well-defined lesion, this is often not the case in ETLE [15]. ETLE pathology is often congenital, such as cortical dysplasia [26]. Our analysis found that no pathology was significantly associated with postoperative outcome. Indeed, among those patients who were seizure-free postoperatively, almost equal numbers were found to harbor cortical dysplasia and gliosis. These data indicate that histopathology of the epileptogenic zone cannot be used to predict postoperative outcome in adults. Siegel et al. suggested that the reason for the higher incidence of ETLE among children is that maturation of the brain begins in the central area, and so congenital malformations manifest in the central area first [32]. As a result, the focus is more diffuse and infiltrates eloquent areas of cortex, such as those for speech, motor control, and visual and auditory processing. When resection is attempted, these eloquent areas must be spared, and this leads to subtotal resection, resulting in outcomes less favorable than those for TLE. Our data also support previous findings by Sinclair et al. [33] that showed the patients who underwent frontal lobe resection have better outcomes than those who underwent posterior cortical resection.

In the present analysis, the semiology of seizures (generalized, complex, or simple partial seizures) showed no significant association with postoperative seizure outcome. Unlike those patients with "generalized" seizures, the majority of patients with complex partial and "other" seizures had relatively favorable outcomes. When there is insufficient agreement among the clinical, radiologic, and electroencephalographic data to proceed with surgery, long-term intracranial monitoring may be used to more precisely localize the epileptogenic zone [34]. According to Centeno et al., long-term intracranial monitoring is valuable in localizing epileptogenic zones in adults and older children, but it may be of limited use for young children because the cortex is not as well developed, so localization of a precise focus is not possible [6]. Our data show that the use of intracranial monitoring had no significant association with postsurgical outcome. Due to the retrospective nature of our analysis, there is no random assignment of patients to a group with and without invasive monitoring. Therefore, selection bias plays a role in the results. Only those patients whose seizure foci could not be localized by noninvasive means underwent intracranial monitoring; these patients may have been destined for a negative outcome regardless of the monitoring used [6, 44].

Abnormality on MRI was one of the variables considered for this analysis: The presence of an MRI abnormality had no significant association with postoperative seizure outcome. This may be due to the fact that MRI may not detect the entire extent of a congenital lesion such as cortical dysplasia, which can be quite diffuse, especially in younger patients [7]. Thus MRI cannot be used to predict outcomes in nonlesional epilepsy—only to determine the presence of a focal structural lesion. Surgery to disconnect the epileptogenic region may entail focal cortical resection, partial or more extensive lobectomy, or transaction of the horizontal fiber tracts (MST). Our analysis found that no particular surgery type or location was associated with improved seizure outcome although the patients undergoing frontal lobe resection fared better. This finding is in agreement with those of other investigators who have reported that patients undergoing parietal and occipital (posterior cortical) surgeries for epilepsy emerge with worse postoperative outcomes than the patients undergoing frontal lobe surgery, especially with respect to intellectual and social function [33]. However, others have not concluded similarly as Elsharkawy et al. demonstrated that patients who undergo frontal surgery may have worse outcomes with respect to seizure frequency than those who undergo surgery in the posterior cerebral cortex [13].

There is currently scant literature regarding how to improve surgical outcomes for the ETLE population. Several groups have suggested that the timing of surgery may be correlated with better outcomes, but the sample sizes in these reports are too small to draw any definitive conclusions [10, 40]. Still other groups have concluded that the duration of epilepsy (time between the onset of seizures and surgery) is the most important factor in predicting the outcome of surgery [1, 26, 32]. However, Fogarasi found no association between duration of epilepsy and postsurgical outcome [9]. Dlugos concluded that there is no definitive evidence indicating significant benefit from early surgery [9]. Our data support this second conclusion. There is no definitive data so far, based on the compiled experience of other centers, that a shorter duration of epilepsy in adults will predict a more favorable outcome. Additionally, the age of onset of epilepsy and the age of surgery have no association with postoperative outcome.

Others have suggested resection of nonlesional epileptic foci in multiple stages in order to improve outcomes [3]. Bauman et al. claimed that this method can provide seizure freedom in 60% of patients and worthwhile improvement (Engel I, II, and III) in up to 87% of patients. According to their study, multistage surgery is indicated when there is incomplete localization during invasive monitoring, when there are multiple foci, or when the focus is close enough to eloquent cortex. They also suggested that 50% of patients may improve from baseline after the second surgery [3]. Another group of authors advocated very careful selection of patients for surgical intervention in order to enhance the final surgical outcome. Specifically, this group recommended offering an operation only on those patients in whom a focal lesion is detected [31]. Certain authors have recently suggested that seizure freedom need not be the only goal of epilepsy surgery, especially outside the temporal lobe [17, 38, 41]. The basis of their argument is that since the outcomes of ETLE surgery are relatively poor, with regard to seizure freedom, that epileptologists should not expect to achieve total remission. However, the patients who are not seizure free still experience improvement in overall quality of life due to reduction in the number of their seizures.

Limitations of this analysis include a relatively small sample size (total 131 patients) and a lack of control groups in the constituent studies. The small sample size of the present study is a result of the combined effect of small sample sizes in the individual studies included; other studies could not be included in our meta-analysis due to their lack of inclusion of adequate data in the original study.

All studies in this analysis were retrospective and observational in nature; none had a control group showing the effect of no surgery. A study by Selwa et al., however, did discuss the outcomes of nonsurgical patients with medically refractory epilepsy. These authors found that 21% of their patients, chosen from the population who were deemed unsuitable candidates for surgery, attained seizure freedom for an average of 2.5 years [29]. However, this study was not a randomized controlled trial, and selection bias was possibly introduced from the retrospective selection of patients. Lastly, many studies in this analysis lacked important data, such as information on intracranial monitoring, pathological exam findings, location of the epileptic focus, and age of the patient at surgery and onset of seizures. This may have a confounding effect by introducing a selection bias, resulting in a sample that is not representative of the whole population under consideration.

Conclusions

When compared to TLE, ETLE surgery has a relatively worse rate of seizure freedom. In the adult patient population, we found that no one factor had a significant statistical association with postoperative seizure outcome. There are, however, trends in the data that suggest that frontal lobe resections may be associated with better outcomes. Furthermore, the previous finding that duration of epilepsy has a significant association with outcome is not supported by our data. Finally, the patients with generalized seizures may have worse outcomes. Although there have been suggestions as to how to improve these outcomes, such as careful patient selection and multistage resection, there is currently no firm protocol supporting a methodology to improve surgical outcomes in patients with extratemporal nonlesional epilepsy. It is important that various comprehensive epilepsy centers standardize their evaluation and reporting process to allow for worthwhile comparison of the results across different centers. This process may lead to evolution of our current methods in the surgical treatment of ETLE and ultimately to improvement in outcomes.

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