Predictive Factors of Surgical Outcome in Frontal Lobe Epilepsy Explored with Stereoelectroencephalography

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BACKGROUND: Resective surgery is a well-established treatment for pharmacoresistant frontal lobe epilepsy (FLE), but seizure outcome and prognostic indicators are poorly characterized and vary between studies.

OBJECTIVE: To study long-term seizure outcome and identify prognostic factors.

METHODS: We retrospectively analyzed 42 FLE patients having undergone surgical resection, mostly preceded by invasive recordings with stereoelectroencephalography (SEEG). Postsurgical outcome up to 10-yr follow-up and prognostic indicators were analyzed using Kaplan–Meier analysis and multivariate and conditional inference procedures.

RESULTS: At the time of last follow-up, 57.1% of patients were seizure-free. The estimated chance of seizure freedom was 67% (95% confidence interval [CI]: 54-83) at 6 mo, 59% (95% CI: 46-76) at 1 yr, 53% (95% CI: 40-71) at 2 yr, and 46% (95% CI: 32-66) at 5 yr. Most relapses (83%) occurred within the first 12 mo. Multivariate analysis showed that completeness of resection of the epileptogenic zone (EZ) as defined by SEEG was the main predictor of seizure outcome. According to conditional inference trees, in patients with complete resection of the EZ, focal cortical dysplasia as etiology and focal EZ were positive prognostic indicators. No difference in outcome was found in patients with positive vs negative magnetic resonance imaging.

CONCLUSION: Surgical resection in drug-resistant FLE can be a successful therapeutic approach, even in the absence of neuroradiologically visible lesions. SEEG may be highly useful in both nonlesional and lesional FLE cases, because complete resection of the EZ as defined by SEEG is associated with better prognosis.

KEY WORDS: Frontal lobe epilepsy, Epilepsy surgery, Outcome, Stereoelectroencephalography, MRI-negative, Focal cortical dysplasia

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Surgical resection of the epileptogenic tissue is a well-established treatment for pharmacoresistant patients.[1,2] Frontal lobe epilepsy (FLE) accounts for 6% to 30% of all epilepsy surgery and represents the second most common partial epilepsy after temporal lobe epilepsy (TLE).[3-7] However, surgical outcome is considered less favorable and long-term success rates are more variable. Favorable seizure outcome ranges from 20.0% to 77.8% depending on series, with the majority of more recent studies reporting seizure freedom rates of around 50%.[5,8-12] The causes of postoperative seizure recurrence are poorly characterized, as are potential prognostic indicators. Assessing the probability of seizure freedom and determining prognostic factors is crucial to selecting candidates for epilepsy surgery and to driving the complex decision-making process from presurgical evaluation to definition of cortectomy.

ABBREVIATIONS: CI, confidence interval; **EZ,** epileptogenic zone; **FCD,** focal cortical dysplasia; **FLE,** frontal lobe epilepsy; **GTCS,** generalized tonic-clonic seizure; **MCA,** multiple correspondence analysis; **MRI,** magnetic resonance imaging; **SEEG,** stereoelectroencephalography; **TLE,** temporal lobe epilepsy

Here, we studied long-term seizure outcome in a cohort of FLE patients having undergone surgical resection, preceded in most cases by intracerebral recording with stereoelectroencephalography (SEEG). We investigated potential indicators of outcome using univariate and multivariate statistical methods together with conditional inference procedures, which allow for evaluation of seizure recurrence over time, stability of predictors, and correlations and interactions among data.

METHODS

Patient Selection

We reviewed patients evaluated in the Epilepsy Unit, Timone Hospital, Marseille, France, with a diagnosis of drug-resistant FLE, who underwent resective FLE surgery from 2000 to 2013. Most patients underwent presurgical evaluation with intracerebral EEG. Exclusion criteria were hemispherotomy, callosotomy, radiosurgery, and follow-up duration ≤6 mo. Collected clinical, radiological, electrophysiological, and histopathological data are presented in Table 1.

Preoperative Protocol

Patients underwent noninvasive presurgical assessment including prolonged scalp video-EEG monitoring (International 10-20 system). Interictal and ictal EEG abnormalities were classified into 3 categories: lateralized frontal, lateralized hemispheric, or bilateral. Magnetic resonance imaging (MRI) in patients up until 2010 was performed with a 1.5-T machine; in 14 patients examined from 2010 onwards, MRI was performed with a 3 T Siemens Magnetom scanner (Siemens AG, Erlangen, Germany). MRI epilepsy protocol included transverse diffusion images, transverse T2-weighted images, coronal T1-weighted inversion recovery images, coronal Fluid Attenuated Inversion Recovery (FLAIR) images, and a 3-dimensional T1-weighted acquisition. Acquisition plans were referred to the bihippocampal plane for the transverse acquisitions and to the anterior commissure–posterior commissure plane for the coronal and axial acquisition. Reconstructions of the 3-D T1 images were obtained as well. The multichannel head coil allowed the use of matrix acquisition, isotropic 1-mm 3-D T1 images, with reasonable acquisition time especially for inversion recovery, FLAIR, and 3-D sequences. MRI findings were classified as normal or pathological and, when pathological, as showing a lesion limited to the frontal lobe or a lesion extending beyond the frontal lobe. PET and interictal SPECT were obtained in all but 12 patients. If results of noninvasive investigations did not lead to the formulation of a single hypothesis about the localization of the epileptogenic zone (EZ) or if they pointed close to functional cortex, patients were selected for SEEG. SEEG exploration was carried out during long-term video-EEG monitoring, and recordings were performed using intracerebral multiple contact electrodes (10-15 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm apart) placed intracerebrally according to Talairach's stereotactic method.[8] Number of electrodes per patient varied from a minimum of 5 to a maximum of 13 electrodes in the present series (mean 9.3 ± 2). Electrodes were implanted bilaterally in all but 9 patients. All patients gave their informed consent prior to exploration, and the study was approved by the Institutional Review Board of the French Institute of Health. Based on SEEG seizure recordings, the EZ was defined as the regions involved in primary organization of the seizure, classified into focal (the seizure onset being limited to 1 anatomic area, lesional or not) or widespread (the seizure onset was not limited to a single functional region).[9] This definition was based on visual analysis ± a quantitative measure of epileptogenicity, the Epileptogenicity Index,[10] implemented on Deltamed Coherence software (Natus Medical Incorporated, Pleasanton, California).

TABLE 1. Characteristics of the Overall Cohort, With Comparison Between Seizure-Free and Not-Seizure-Free Group

		N	Recurred n (%)	*P*
Epilepsy side	Left	16	7 (44)	.75
	Right	26	14 (54)	
Aetiology	Cryptogenic	7	6 (86)	.02
	FCD	25	8 (32)	
	Other	10	7 (70)	
MRI	Normal	18	8 (44)	.76
	Not normal	24	14 (54)	
MRI	Extrafrontal extension	11	9 (82)	.03
	Frontal lesion	13	4 (31)	
	Normal	18	8 (44)	
GTCS occurrence	No	20	6 (30)	.03
	Yes	22	15 (68)	
Interictal EEG Abnormalities	Bilateral	14	6 (43)	.85
	Frontal	15	8 (53)	
	Hemispheric	11	6 (55)	
Ictal EEG discharge	Bilateral	10	7 (70)	.35
	Frontal	22	9 (41)	
	Hemispheric	9	4 (44)	
Surgery	FT	4	2 (50)	.93
	PreF	19	9 (47)	
	PreM	14	8 (57)	
	PreM+preF	5	2 (40)	
PET/SPECT	Bilateral	7	2 (29)	.10
Extrafrontal	extension	6	5 (83)	
	Ipsilateral	14	4 (29)	
	Normal	3	2 (67)	
Polymorphic seizures	No	36	16 (44)	.18
	Yes	6	5 (83)	
EZ	Focal	24	8 (33)	.02
	Widespread	14	11 (79)	
APOS	No	37	17 (46)	.34
	Yes	5	4 (80)	
Risk factors	No	38	18 (47)	.61
	Yes	4	3 (75)	
Extent of resection	Complete	24	6 (25)	<.001
	Incomplete	14	13 (93)	

N = overall group, n = number of not seizure-free patients; FCD: focal cortical dysplasia; EZ: epileptogenic zone; APOS: acute postoperative seizures.
Polymorphic seizures are defined as different type of seizures in the same patients, thus presenting variable ictal clinical pattern.

Neuropsychological test data before and after surgery were available for 25 of 42 patients. All of these patients were administered a comprehensive battery of standardized neuropsychological tests, exploring intelligence and memory (immediate and delayed verbal and visual memory). The standard clinical measure of intelligence retained for IQ evaluation was the Wechsler Intelligence Scale; the Wechsler Intelligence Scale for Children—Fourth Edition was used for patients aged 6 to 16 yr, and the Wechsler Adult Intelligence Scale—Third Edition was used from 16 yr (Wechsler, D. 2005; Wechsler, D. 2000). Memory abilities with verbal and/or visual material and attention/working memory were assessed with the Wechsler Memory Scale (Wechsler Memory Scale III from 16 yr, Children's Memory Scale 6 to 16 yr; Wechsler, D. 2001; Wechsler, D. 2006).

Surgery and Postoperative Protocol

All patients underwent unilateral frontal lobe surgery, including lesionectomy, subtotal frontal lobectomy, or frontal lobectomy. The resection area was classified based on anatomic landmarks into premotor, prefrontal, premotor + prefrontal, and frontotemporal (when extended to the anterior temporal lobe). Tissue specimens were analyzed for histopathological diagnosis. Following surgery, patients were managed in the neurosurgery or intensive care unit, and the occurrence of acute postoperative seizures was noted. Surgical resection of the EZ was classified into complete or incomplete based on SEEG criteria allowing the identification of the EZ. A complete resection was defined as the total removal of the cortical tissue covered by intracerebral electrodes of the EZ, while resection was considered incomplete if not all cortical tissue belonging to the EZ was removed. Additionally, in lesional cases, definition of complete resection also required the removal of the entire lesion, based on pathological data and, in cases with preoperative MRI lesion, on postoperative MRI. Possible causes of incomplete resection of the EZ included a limited resection in order to preserve functional cortex (namely, the primary motor cortex and Broca's area) and minimize postsurgical deficits; the involvement of contralateral cortex; remote epileptogenicity extending beyond the frontal lobe or the anterior temporal lobe; and from histopathological analysis, the presence of residual pathological tissue within the border of the removed cortical tissue and/or of residual lesion visible on MRI.

Outcome Definition and Follow-up

Seizure-related outcome was assessed based on 6-mo and yearly (or as indicated by clinician) follow-up. Patients were classified as being either seizure-free (as defined by Engel class IA) or not seizure-free.[11] The timing of the first postoperative seizure (beyond the first postoperative week for patients with acute postoperative seizures) was considered the time of recurrence and was set down for use in Kaplan–Meier analysis.

Statistical Analysis

Univariate and multivariate statistics were used to test for predictors of outcome. Descriptive statistics were obtained for each variable. As initial analysis, we performed Wilcoxon rank sum, χ^2, and Fisher's exact test to compare seizure-free to not seizure-free at 6 mo up to 10 yr after surgery. Individual patient differences between presurgical and postsurgical scores of neuropsychological tests were calculated. These were then analyzed at group level using the Wilcoxon rank sum test, comparing the seizure-free and the nonseizure-free groups.

Variables with a significant level at 5% on univariate analysis were entered in a multiple correspondence analysis (MCA). The MCA method projects multidimensional data—1 dimension for each variable—into a bidimensional (or greater) space and searches for patterns in the datasets.[12] The matrix of eigenvalues is determined to identify a combination of variables that present more stability in the factorial plan and explained the largest percentage of variability in the dataset. This allows identification of variable modalities that are more closely associated with different populations (ie, with seizure-free patients). The MCA provides a visual representation regarding the conditions more strongly coupled with groups that help to confirm associations or similarities between variable modalities. This method is suitable for population-based studies.[13]

Variables with a significant level at 10% on univariate analysis were entered into a survival multiple regression analysis, the Andersen-Gill counting process model, in order to identify outcome predictors.[14] Statistical significance was set at the 5% level. This method aims to simultaneously explore the effects of several variables on possibly recurrent outcome, while taking into account the relationship and possible dependency between the values of 2 or more variables.

Finally, conditional inference tree analysis was performed in order to identify subpopulations of patients susceptible to present seizure recurrence. Conditional inference trees are a supervised classification method for analyzing data that select covariates by permutation-based significance tests, thereby avoiding potential bias of the more traditional decision tree algorithms.[15] The results are displayed in a "tree" graph, showing the hierarchy of significant variables and the final groups and associated thresholds of response values following the binary splits.

All statistics were performed using R software (version 2.13.1; R Core Development Team, 2013).

RESULTS

Patient Characteristics

Within 54 patients with FLE who underwent epilepsy surgery, 42 patients (28 females) fulfilled inclusion criteria and were included in the study. Mean age at epilepsy onset was 7 yr (±6 yr, median 5), mean age at surgery was 23.4 yr (±12.3 yr, median 23), and the mean epilepsy duration at the time of surgery was 16.4 yr (±10.7 yr, median 15). Thirty-eight patients (90%) underwent SEEG prior to surgery and only 4 patients underwent surgical resection without previous SEEG (2 because of young age, 2 because of patient refusal of invasive recording, all with lesional MRIs).

MRI was normal in 18 patients (43%). Patients having undergone 3 T MRI did not have more positive findings compared to patients having undergone 1.5 T MRI. Lesional cases on MRI presented with a lesion limited to the frontal lobe (13 patients, 31%) or a lesion with extrafrontal extension (11 patients, 26%).

Histopathology was available in all but 5 patients, who all had lesional MRIs.

Etiology, determined by combined histopathological and MRI findings, was focal cortical dysplasia (FCD) in 25 patients (59.5%, 21 with FCD IIb and 4 with FCD Ib; 11 with normal MRI), cryptogenic in 7 patients (16.7%, with normal MRI and normal or with mild gliosis on histopathology), and other pathological findings in 10 patients (24%), including encephalitis in 2, tuberous sclerosis in 2, encephalomalacia from trauma or stroke in 3, vascular malformation in 2, and other malformation of cortical development in 1. Clinical patient characteristics are summarized in Table 1.

Overall Recurrence

Mean follow-up duration was 4.6 yr (±2.7 yr, median 4.5 yr, range 0.5-10 yr). At the time of last follow-up, 24 patients were seizure-free (57.1%), while in 18 patients, seizures recurred without subsequent remission (42.9%). Within the seizure-free group, a run-down phenomenon was observed in 2 patients (who became seizure-free at 1 and 1.5 yr for a subsequent follow-up period of, respectively, 10 and 10.5 yr); in another patient, seizures recurred with abrupt discontinuation of antiepileptic drugs and ceased after resuming antiepileptic drug intake. Nonetheless, in order to evaluate longitudinal outcome changes and explore the effects of variables on outcome upon time, their seizure recurrence was taken into account for statistical analysis.

Seizure outcomes using Engel criteria at 6 mo and at 1 to 5 yr postoperatively are reported in Table 2. The majority of relapses (17 total, when including patients with a run-down) occurred during the first year. Of the 4 patients without SEEG, 2 were seizure-free and 2 were not seizure-free at the end of their participation (respectively, 0.5, 2.5, 2, and 1.5 yr).

Longitudinal seizure-free outcome estimated using Kaplan–Meier survival analysis reveals that the probability of remaining in Engel class I varies with postsurgical time (Figure 1). The chance of being seizure-free was 67% (95% confidence interval [CI]: 54-83) at 6 mo, then fell to 59% (95% CI: 46-76) at 1 yr, 53% (95% CI: 40-71) at 2 yr, 50 (95% CI: 36-68) at 3 yr, and 46% (95% CI: 32-66) at 5 yr and beyond. The median time to seizure recurrence was 36 mo.

Neuropsychological Outcome

Concerning neuropsychological outcome, we found that patients assigned an Engel class I outcome compared to not-seizure-free patients who had a higher full-scale IQ postsurgically ($P = .029$) as well as a higher verbal IQ ($P = .017$). Conversely, there was no significant difference comparing presurgical to postsurgical scores between the groups on performance IQ and for working memory scores.

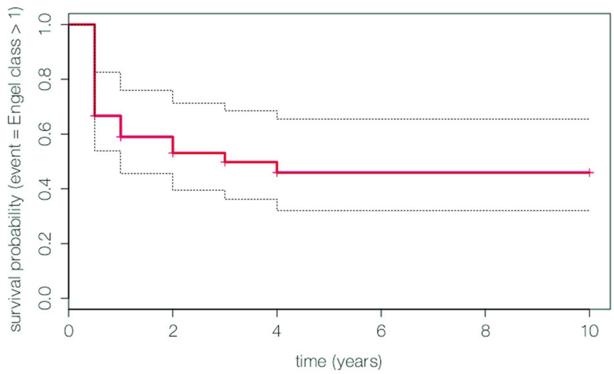

FIGURE 1. *Kaplan–Meier "survival" probability estimate (red line) with 95% confidence bounds (dotted lines) in the overall population, where event is transition to an Engel class greater than 1. Censored data are marked by crosses. Median survival time estimate = 3 yr.*

Outcome Predictors

Univariate Analysis

Results of univariate analysis for categorical variables are shown in Tables 1 and 3. For statistical purposes, MRI findings were twice grouped into 2 modalities to compare: normal vs lesional MRI and then MRI with extrafrontal extension MRI vs MRI (either normal or lesional) without extrafrontal extension. Similarly, etiology was doubly grouped into FCD, cryptogenic, and other, and then into FCD vs not-FCD.

Variables significantly ($P < .05$) associated with seizure recurrence were incomplete resection of the EZ, cryptogenic and not-FCD as etiology, extrafrontal extension lesional MRI, and widespread EZ as defined by SEEG. No significant difference in outcome was found in MRI-lesional patients compared to MRI-normal patients. When categorizing surgical outcome based on field strength, we found no difference for patients having undergone 3 T MRI compared to 1.5 T MRI. Combining etiology with MRI findings, the poorest outcomes were associated with normal or nonspecific histopathological findings associated with normal MRI on one hand, and etiology other than FCD associated with extrafrontal extension MRI on the other hand.

Concerning continuous variables (namely, age at epilepsy onset, age at surgery, and epilepsy duration), none of them proved to be correlated to surgical outcome ($P > .1$).

TABLE 2. Engel Outcome Classification of Our Cohort at 6 mo to 5 yr Follow-up

	6 mo	1 yr	2 yr	3 yr	4 yr	5 yr
Patients available for follow-up	42	40	36	31	26	19
Engel I (%)	28 (66.7)	24 (60)	20 (55.6)	17 (54.8)	15 (57.7)	10 (52.6)
Engel II (%)	6 (14.3)	4 (10)	4 (11.1)	4 (12.9)	4 (15.4)	4 (21.1)
Engel III (%)	4 (9.5)	8 (20)	7 (19.4)	7 (22.6)	5 (19.2)	3 (15.8)
Engel IV (%)	4 (9.5)	4 (10)	5 (13.9)	3 (9.7)	2 (7.7)	2 (10.5)

TABLE 3. Variables Significantly Correlated With Postsurgical Seizure Outcome on Univariate Analysis

		N	Recurred n (%)	P
Etiology (1)	Cryptogenic	7	6 (86)	.02
	FCD	25	8 (32)	
	Other	10	7 (70)	
Etiology (2)	FCD	25	8 (32)	.001
	Not-FCD	17	13 (76)	
MRI	Extrafrontal extension	11	9 (82)	.03
	No extrafrontal extension	31	13 (42)	
Etiology MRI	cryptogenic_normal	7	6 (86)	.004
	FCD_extra-frontal extension	3	2 (67)	
	FCD_frontal lesion	11	4 (36)	
	FCD_normal	11	2 (18)	
	other_extra-frontal extension	8	7 (88)	
	other_frontal lesion	2	0 (0)	
GTCS occurrence	No	20	6 (30)	.03
	Yes	22	15 (68)	
EZ	Focal	24	8 (33)	.02
	Widespread	14	11 (79)	
Extent of resection	Complete	24	6 (25)	<.001
	Incomplete	14	13 (93)	

N = overall group; n = number of not seizure-free patients; FCD: focal cortical dysplasia; EZ: epileptogenic zone.

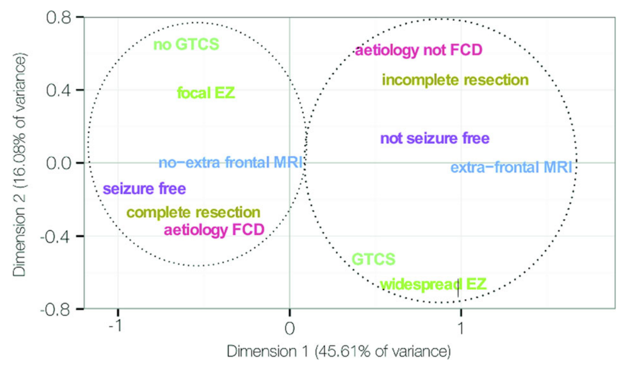

FIGURE 2. *Factorial plan of association of clinical variables with seizure outcome. The graphic is created by the 2 dimensions derived from the MCA. The horizontal axis represents the first dimension, while the vertical axis represents the second dimension.*

TABLE 4. Variables Correlating With Outcome After Multivariate Analysis on Variables With P < .1 on Univariate Analysis

Variable	Coef	HR	95% CI	P-value
Extent of resection: incomplete	1.39	4.00	1.10-14.58	.04
Etiology: not-FCD	0.27	1.30	0.40-4.21	NS
EZ: widespread	0.26	1.29	0.37-4.48	NS
GTCS occurrence: yes	0.56	1.76	0.51-6.10	NS
Ictal EEG discharge: lateralized	−0.23	0.79	0.25-2.51	NS
MRI: no extrafrontal extension	0.06	1.06	0.31-3.65	NS
Polymorphic seizures: yes	0.24	1.27	0.30-5.40	NS

coef = coefficient estimates; HR = hazard ratios; CI = 95% confidence intervals; NS = nonsignificant

Multiple Correspondence Analysis

Variables with $P < .05$ on univariate analysis were entered in the MCA. For a principle of parsimony, FCD vs not-FCD was chosen for 3 modalities etiology because of its lower P value, and the combined variable etiology/MRI was not included in the MCA.

As a result, the 2 first dimensions in the factorial plan explained 61.7% of the variance. This indicated that such an obtained 2-dimensional plan furnishes a reliable representation of the 5-dimensional reality, where 5 is the number of considered variables. Variables' proximity to the seizure-free group or to the not-seizure-free group indicates the characteristics that each group is more likely to present (Figure 2). The factorial plan illustrates the characteristics associated to each other and contributing the most to describing the group not seizure-free: incomplete resection of the EZ, not-FCD as etiology, widespread EZ, lesional MRI with extrafrontal extension, and presence of generalized tonic–clonic seizure (GTCS). Conversely, variable modalities associated with the seizure-free group were complete resection of the EZ, FCD as etiology, focal EZ, not extrafrontal extension MRI, and absence of GTCS.

Multivariate Analysis

Results of multivariate analysis after applying the Andersen–Gill counting process model are reported in Table 4. The variable "extent of resection" resulted in an independent predictor of outcome ($P = .04$) in our series, with a hazard ratio equal to 4 for incomplete resection ($\beta = 1.39$, $P < .05$, $e^{\beta} = 3.9998$, CI 95%: 1.097-14.582), meaning that incomplete resection of the EZ as defined by SEEG led to a risk of seizure recurrence 4 times greater than for complete resection.

The Kaplan–Meier survival curve for this outcome predictor shows a less favorable outcome for patients with incomplete resection of the EZ ($P < .001$), with 65% of patients experiencing recurrence within the first 6 mo postoperatively (CI: 18-72; Figure 3).

Conditional Inference Trees

Recursive partitioning (Figure 4) confirmed extent of resection as the most important variable associated with outcome (first

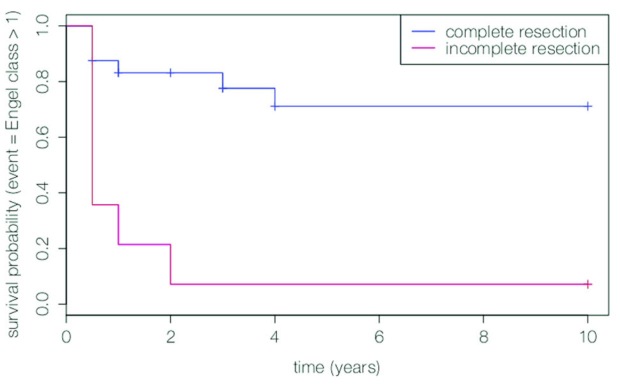

FIGURE 3. *Kaplan–Meier survival curve showing chances of postoperative seizure freedom depending on the completeness of the resection (Log-rank test: $\chi^2 = 18.5$, 1 df, $P < .001$). Median time of recurrence for incomplete resection is 6 mo (95% CI: 0.5-2). With complete resection, 67% of patients are seizure-free 10 yr after surgery.*

node). Second, etiology was relevant in patients with complete resection (left branch of the tree), with not-FCD as etiology associated with seizure recurrence. Third, in the FCD branch, focal EZ predicted seizure freedom, while widespread EZ predicted seizure recurrence.

DISCUSSION

In this study, we aimed to investigate postsurgical outcome in FLE and to identify potential predictors of seizure recurrence using different statistical techniques, combining the advantages of (1) univariate analysis to select the most relevant variables, (2) MCA to highlight the structure of the population with respect to prognosis, (3) survival multiple regression analysis to derive significant parts of this structure, and (4) conditional inference trees to refine this conclusion.

As a result, 57.1% of patients were seizure-free at last follow-up, and the estimated chance of long-term (10 yr) favorable outcome was 46%. Most relapses occurred within the first 2 postoperative yr. After that, the likelihood of maintaining a good outcome following a prolonged period of seizure freedom was quite high.

MCA distinguished a stable combination of variables associated with favorable outcome, which could help to identify optimal candidates for surgery: MRI normal, or showing a lesion limited to the frontal lobe; focal EZ; complete resection of the EZ; FCD as etiology; and no GTCS.

Multivariate and conditional inference procedures showed that the complete resection of the EZ as defined by SEEG was the main predictor of a favorable outcome. Additionally, FCD predicted seizure freedom in patients with complete resection, and a focal EZ was associated with favorable outcome in patients

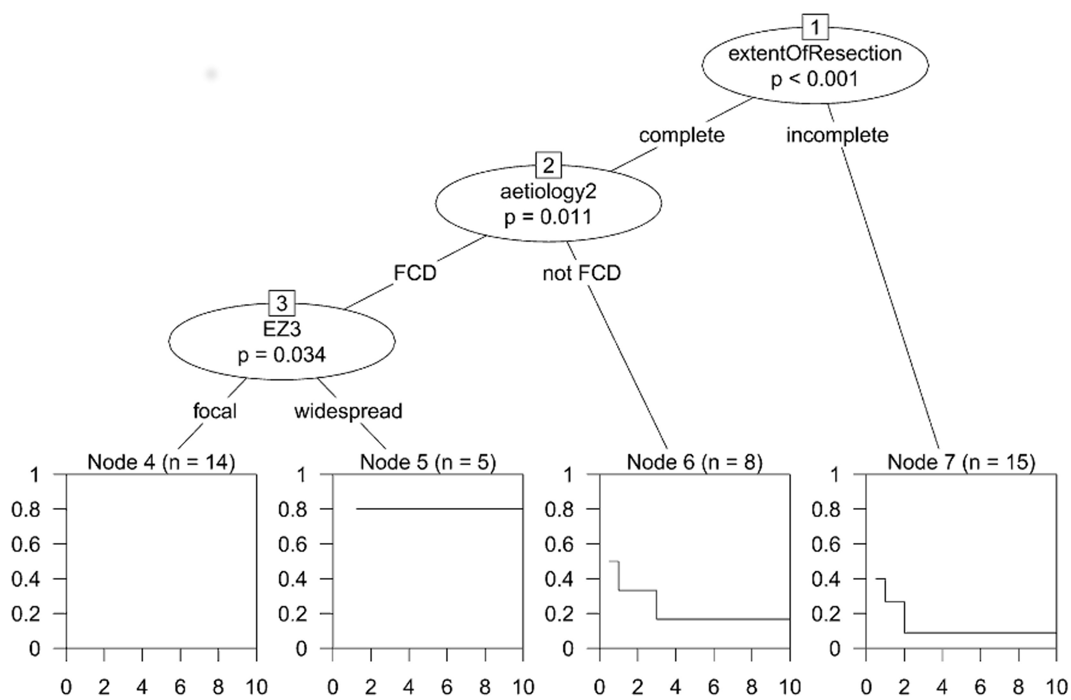

FIGURE 4. *Conditional inference tree predicting probability of seizure recurrence. The "tree" graph shows the hierarchy of significant variables associated with outcome.*

with FCD. Importantly, patients with negative MRI had the same chance of favorable outcome as patients with lesional MRI in our series.

Overall, present success rates are comparable or even slightly better than those reported in previous studies and in a recent meta-analysis,[5] indicating that a long-term success rate close to that of TLE[16] can be reached in FLE surgery investigated by SEEG. Indeed, TLE surgery has been recently reported to have long-term (5-15 yr) seizure freedom varying from 37% to 63%, often depending on pathology.[16-18]

Our study shows a deterioration of outcome with time, as also observed after TLE surgery.[17,18]

Reports on FLE surgery exhibit a great variability across studies, concerning both outcome rates and prognostic indicators.[5] This could be due to different statistical approaches, the evolution of neuroimaging techniques, selection bias, or the diverse and rather imprecise evaluation of some variables, namely the extension of the resection of the epileptogenic tissue. Indeed, the complete resection of the neuroimaging abnormality has been associated with higher success rate in several studies.[19-23] Consistently, the absence of a visible lesion on MRI is often reported as a negative predictor of outcome.[5,20,24-28] Here, the completeness of the resection was defined based upon SEEG criteria, and the total removal of the so-defined epileptogenic tissue was by far the main predictor of seizure outcome, confirming that it represents the sine qua noncondition to attain seizure freedom[8] Moreover, we found no difference in outcome when comparing patients with normal MRI to patients with lesional MRI. This is in agreement with a previous SEEG study[29] but is in contrast with other series[20,28] and indicates that SEEG is equally effective in MRI-negative and -positive cases.[29]

Compared to our population predominantly explored with SEEG, the great majority of series studying long-term seizure outcome of FLE are characterized by the absence of invasive recording or by the use of subdural electrodes in about half of patients undergoing cortical resection.[4,20,24-27,30-34] In these subdural guided series, the rate of negative MRI varies from 0% to 46% (39% on average[4,20,24-26,30-32,34,35]). In the majority of epilepsy centers, invasive subdural electrodes have traditionally been the intracranial EEG method of choice, including for evaluating nonlesional cases.[20,24,30-32,35] Until very recently, SEEG was almost exclusively used in France and Italy. In the last few years, international interest in SEEG as a potentially useful tool for presurgical evaluation, especially for extratemporal and MRI-negative cases, has led to a rapid worldwide increase in centers adopting this method. For example, the Cleveland Clinic now prioritizes SEEG as first-choice exploration method rather than grids for the majority of cases, and particularly for "suspected frontal lobe epilepsy in nonlesional MRI scenario."[36] A recent report from an International League Against Epilepsy working party, evaluating different modalities of invasive EEG recordings, discusses the utility of subdural grid for extensive unilateral exploration with wide coverage of neocortical gyral surface.[37] On the other hand, authors have recommended SEEG for bilateral exploration and for deep targets such as the cingulate cortex, the orbitofrontal cortex, the insular cortex, and mesiotemporal structures.[37,38] These latter structures, because of their strong anatomo-functional connections with the prefrontal cortex, are particularly important to explore as potentially implicated in the EZ network in FLE. Although more often used in MRI-negative extratemporal epilepsies, invasive recording has been recommended for both MRI-negative or positive cases.[37] In actual fact, with few exceptions,[24,30] most FLE surgical series do not use systematically intracranial EEG; however, such series without intracranial EEG are generally composed of cases with radiologically visible lesions. Conversely, we regularly used SEEG if clinically indicated, in both MRI-positive and MRI-negative cases, and found similar or better outcome than other reports.

The use of intracerebral electrodes allows the definition of the EZ and surgical resection in the absence of a visible lesion. Furthermore, it minimizes the risk of an incomplete removal of the EZ extending beyond a visible neuroradiological abnormality, as epileptogenicity can extend beyond the lesion and organizes as a large network with remote and even bilateral epileptogenicity.[9,39]

As described in other studies, we report a relatively high incidence of FCD amongst operated patients with normal MRI (40% of patients with FCD).[9,21,29,40-42] In this context, the invisible underlying pathology, namely FCD, represented a favorable prognostic indicator in case of complete removal of the EZ when compared with all other etiologies, in agreement with previous SEEG studies.[29,43] Moreover, the characteristics of the EZ (ie, focal vs widespread) can predict surgical outcome in our series. Indeed, bilateral involvement and involvement of remote extrafrontal cortex were important causes of incomplete resection of the EZ. Because another main reason of incomplete resection of the EZ is the need to preserve functional cortex, SEEG allows, on one hand, evaluation of the involvement of such structures and, on the other hand, the ability to predict surgical failure and guide palliative surgery[43] if indicated.

This study aimed to provide outcome measures that could guide the complex decision-making process leading to surgical resection. The use of SEEG appears to be particularly effective in evaluating the eligibility for epilepsy surgery in FLE patients. Of course, its effectiveness depends on conditions of use, such as patient selection, electrode implantation strategy, and team expertise, which might help explain variable results across series.[44] Here, the complete resection of the EZ defined with SEEG represents the strongest predictor of seizure freedom, both in negative and in lesional MRI. Of course, the capability to totally remove the EZ can be constrained by possible overlap between the EZ and functional cortex. Indeed, extension of the EZ to the central cortex has been shown to have a poor prognostic value for surgical outcome.[45]

CONCLUSION

A number of clinical characteristics that may coexist can indicate patients with a better chance of a favorable outcome in FLE; namely, focal EZ, normal MRI or with lesion limited to the frontal lobe, complete resection of the EZ, and FCD as etiology. SEEG in FLE candidates for surgery, both in lesional and nonlesional cases, contributes above all to the definition of the EZ, whose complete resection is the major outcome predictor for FLE. Epilepsy surgery can represent a successful therapeutic approach in drug-resistant FLE patients, even in the absence of a neuroradiological lesion.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

Frontal lobe medically intractable epilepsies are challenging and difficult to localize, mainly in patients with nonlesional imaging studies, resulting in lower rates of seizure freedom following frontal lobe resections. The presence of a large amount of brain tissue, in addition to multiple eloquent cortical areas and their high connectivity with other brain regions may explain the relative suboptimal results in frontal lobe surgery in comparison with temporal lobe surgery. Stereo-electroencephalography (SEEG) is an efficient and safe invasive monitoring method that can be applied in frontal lobe epilepsy in order to more specifically define the anatomical boundaries of the epileptogenic zone. Due to its intrinsic features, which are based on anatomo-electroclinical correlations and 3-dimensional spatial-temporal conceptualization of the epileptic activity, the SEEG method may provide optimized views of the frontal lobe epileptogenic zones and, ultimately, improve seizure-free outcomes in a highly difficult and challenging group of patients. As described in the current manuscript, assessing the probability of seizure freedom and determining prognostic factors is crucial to select candidates for epilepsy surgery and to drive the complex decision-making process, from pre-surgical evaluation to definition of cortectomy. Despite its retrospective nature, the study brings evidence that SEEG may be highly useful in both non-lesional and lesional frontal lobe epilepsy cases, since complete resection of the epileptogenic zone, as defined by SEEG methodology, is associated with better prognosis. I commend the authors for their work.

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In epilepsy surgery cases in which location of seizure onset is unclear or very close to eloquent areas, stereo-electroencephalography (SEEG) can be a valuable tool to tailor extent of resection. The authors of this study analyzed a population of 42 patients undergoing surgery for frontal lobe epilepsy, most of whom underwent SEEG, to determine prognostic indicators for favorable seizure outcome. They found that about half had long-term seizure freedom and most relapses occurred within the first 12 months. Statistical analysis demonstrated that complete resection of the putative epileptogenic zone (EZ) as defined by SEEG correlated best with outcome, although cortical dysplasia and a focal EZ were also contributing factors. They conclude that SEEG is useful in this population.

The findings of this study are consistent with many previous reports that have established that extent of resection and focality of the EZ are strong prognostic factors for postoperative seizure freedom. As expected, incomplete resection of the EZ (presumably in cases where it is located in an eloquent area) leads to recurrence in a vast majority of patients, including all but 1 patient in this series. MRI-negative cases are not necessarily associated with worse outcome since SEEG is able to identify the region of seizure onset even in the absence of a visible lesion; this is precisely why SEEG is often employed for lesion-negative cases. While not entirely novel, these observations confirm that SEEG is able to identify seizure onset zone for preoperative planning purposes.

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