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## **Predictive factors of surgical outcome in frontal lobe epilepsy explored with stereo-electroencephalography**

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1 **Predictive factors of surgical outcome in frontal lobe epilepsy explored**  
2 **with stereo-electroencephalography**

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6  
7 **ABSTRACT**

8  
9 **Background:** Resective surgery is a well-established treatment for pharmaco-resistant frontal lobe  
10 epilepsy (FLE), but seizure outcome and prognostic indicators are poorly characterised and vary  
11 between studies.

12 **Objective:** To study long-term seizure outcome and identify prognostic factors.

13 **Methods:** We retrospectively analysed 42 FLE patients having undergone surgical resection, mostly  
14 preceded by invasive recordings with stereo-electroencephalography (SEEG). Post-surgical outcome  
15 up to 10 years' follow-up and prognostic indicators were analysed using Kaplan-Meier analysis,  
16 multivariate and conditional inference procedures.

17 **Results:** At the time of last follow-up 57.1% of patients were seizure-free. The estimated chance of  
18 seizure freedom was 67% (95% CI 54-83) at 6 months, 59% (95% CI 46-76) at 1 year, 53% (95% CI  
19 40-71) at 2 years and 46 % (95% CI 32-66) at 5 years. Most relapses (83%) occurred within the first  
20 12 months. Multivariate analysis showed that completeness of resection of the epileptogenic zone (EZ)  
21 as defined by SEEG was the main predictor of seizure outcome. According to conditional inference  
22 trees, in patients with complete resection of the epileptogenic zone, focal cortical dysplasia as  
23 aetiology and focal EZ were positive prognostic indicators. No difference in outcome was found in  
24 patients with positive versus negative MRI.

25 **Conclusion:** Surgical resection in drug-resistant FLE can be a successful therapeutic approach, even  
26 in the absence of neuroradiologically visible lesions. SEEG may be highly useful in both non-lesional  
27 and lesional FLE cases, since complete resection of the EZ as defined by SEEG is associated with  
28 better prognosis.

29  
30 **Running title:** Outcome in frontal lobe epilepsy surgery

31  
32 **Keywords:** Frontal lobe epilepsy; epilepsy surgery; outcome; Stereo-electroencephalography; MRI-  
33 negative; Focal Cortical Dysplasia

## 1 INTRODUCTION

2 Surgical resection of the epileptogenic tissue is a well-established treatment for pharmacoresistant  
3 patients<sup>1,2</sup>. Frontal lobe epilepsy (FLE) accounts for 6 to 30% of all epilepsy surgery and represents  
4 the second most common partial epilepsy after temporal lobe epilepsy (TLE)<sup>3-7</sup>. However, surgical  
5 outcome is considered less favourable and long-term success rates are more variable. Favourable  
6 seizure outcome ranges from 20.0 to 77.8% depending on series, with the majority of more recent  
7 studies reporting seizure freedom rates of around 50%<sup>5,8-12</sup>. The causes of post-operative seizure  
8 recurrence are poorly characterised, as are potential prognostic indicators. Assessing the probability of  
9 seizure freedom and determining prognostic factors is crucial to select candidates for epilepsy surgery  
10 and to drive the complex decision-making process from pre-surgical evaluation to definition of  
11 cortectomy.

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

17

## 18 METHODS

### 19 Patient selection

20 We reviewed patients evaluated in the Epilepsy Unit, XXXXXX Hospital, XXXXXX, France, with a  
21 diagnosis of drug-resistant frontal lobe epilepsy, who underwent resective FLE surgery from 2000 to  
22 2013. Most patients underwent pre-surgical evaluation with intracerebral EEG. Exclusion criteria were  
23 hemispherotomy, callosotomy, radiosurgery and follow-up duration  $\leq 6$  months. Collected clinical,  
24 radiological, electrophysiological and histopathological data are presented in table 1.

25

### 26 Pre-operative protocol

27 Patients underwent non-invasive pre-surgical assessment including prolonged scalp video-EEG  
28 monitoring (International 10-20 system). Interictal and ictal EEG abnormalities were classified into 3  
29 categories: lateralised frontal, lateralised hemispheric or bilateral. MRI in patients up until 2010 was  
30 performed with a 1.5 T machine; in 14 patients explored from 2010 onwards, MRI was performed  
31 with a 3 T Siemens Magnetom scanner (Siemens AG, Erlangen, Germany). MRI epilepsy protocol  
32 included transverse diffusion images, transverse T2-weighted images, coronal T1-weighted inversion  
33 recovery images, coronal fluid-attenuated inversion recovery (FLAIR) images and a three-dimensional  
34 T1-weighted acquisition. Acquisition plans were referred to the bi-hippocampal plane for the  
35 transverse acquisitions and to the AC-PC plane for the coronal and axial acquisition. Reconstructions  
36 of the 3D T1 images were obtained as well. The multi-channel head coil allowed the use of matrix  
37 acquisition, isotropic 1mm 3D T1 images, with reasonable acquisition time especially for inversion-

1 recovery, FLAIR and 3D sequences. MRI findings were classified as normal or pathological and,  
2 when pathological, as showing a lesion limited to the frontal lobe, or a lesion extending beyond the  
3 frontal lobe. Positron emission tomography (PET) and interictal single photon emission computer  
4 tomography (SPECT) were obtained in all but 12 patients. If results of non-invasive investigations did  
5 not lead to the formulation of a single hypothesis about the localization of the epileptogenic zone (EZ)  
6 or if they pointed close to functional cortex, patients were selected for SEEG. SEEG exploration was  
7 carried out during long-term video-EEG monitoring and recordings were performed using  
8 intracerebral multiple contact electrodes (10–15 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm  
9 apart) placed intracerebrally according to Talairach's stereotactic method<sup>8</sup>. Number of electrodes per  
10 patients varied from a minimum of 5 to a maximum of 13 electrodes in present series (mean  $9,3 \pm 2$ ).  
11 Electrodes were implanted bilaterally in all but nine patients. All patients gave their informed consent  
12 prior to exploration and the study was approved by the Institutional Review Board of the French  
13 Institute of Health. Based on SEEG seizure recordings the EZ was defined as the regions involved in  
14 primary organization of the seizure, classified into focal (the seizure onset being limited to one  
15 anatomical area, lesional or not) or widespread (the seizure onset was not limited to a single functional  
16 region)<sup>9</sup>. This definition was based on visual analysis +/- a quantitative measure of epileptogenicity,  
17 the Epileptogenicity Index (EI)<sup>10</sup> implemented on Coherence Natus/Deltamed software.  
18 Neuropsychological test data before and after surgery were available for 25/42 patients. All these  
19 patients were administered a comprehensive battery of standardized neuropsychological tests,  
20 exploring intelligence and memory (immediate and delayed verbal and visual memory). The standard  
21 clinical measures of intelligence retained for IQ evaluation was Wechsler Intelligence Scale; according  
22 to the age, Wechsler intelligence scale for children – fourth edition (WISC IV) 6 to 16 years and  
23 Wechsler Adult Intelligence Scale third edition (WAIS-III) from 16 years (Wechsler, D. 2005;  
24 Wechsler, D. 2000). Memory abilities with verbal and/or visual material and attention/working  
25 memory were assessed with the score of the Wechsler Memory Scale (MEM III from 16 years, CMS 6  
26 to 16 years) (Wechsler, D. 2001; Wechsler, D. 2006).

27

28

### 29 **Surgery and post-operative protocol**

30 All patients underwent unilateral frontal lobe surgery, including lesionectomy, subtotal frontal  
31 lobectomy or frontal lobectomy. Resection area was classified based on anatomical landmarks into  
32 premotor, prefrontal, premotor + prefrontal and fronto-temporal (when extended to the anterior  
33 temporal lobe). Tissue specimens were analysed for histopathological diagnosis. Following surgery,  
34 patients were managed in the neurosurgery or intensive care unit and the occurrence of acute post-  
35 operative seizures (APOS) was noted. Surgical resection of the EZ was classified into complete or  
36 incomplete based on SEEG criteria allowing the identification of the EZ: a complete resection was  
37 defined as the total removal of the cortical tissue covered by intracerebral electrodes of the EZ, while

1 resection was considered incomplete if not all cortical tissue **belonging** to the EZ was removed.  
2 Additionally, in lesional cases, definition of complete resection also required the removal of the entire  
3 lesion, based on pathological data and, in cases with preoperative MRI lesion, on postoperative MRI.  
4 Possible causes of incomplete resection of the EZ included: a limited resection in order to preserve  
5 functional cortex (namely the primary motor cortex and Broca's area) and minimize postsurgical  
6 deficits; the involvement of contralateral cortex; remote epileptogenicity extending beyond the frontal  
7 lobe or the anterior temporal lobe; from histopathological analysis, the presence of residual  
8 pathological tissue within the border of the removed cortical tissue and/or of residual lesion visible on  
9 MRI.

10

### 11 **Outcome definition and follow-up**

12 Seizure related-outcome was assessed based on 6 months then yearly (or as indicated by clinician)  
13 follow-up. Patients were classified as being either seizure-free (as defined by Engel class IA) or not-  
14 seizure-free<sup>11</sup>. The timing of the first postoperative seizure (beyond the first postoperative week for  
15 patients with APOS) was considered the time of recurrence and was set down for use in Kaplan-Meier  
16 analysis.

17

### 18 **Statistical analysis**

19 Univariate and multivariate statistics were used to test for predictors of outcome.

20 Descriptive statistics were obtained for each variable. As initial analysis, we performed Wilcoxon rank  
21 sum,  $\chi^2$  and Fisher's exact test to compare seizure-free to not seizure-free at 6 months up to 10 years  
22 after surgery. Individual patient differences between pre-surgical and post-surgical scores of  
23 neuropsychological tests were calculated. These were then analysed at group level using the Wilcoxon  
24 rank sum test, comparing the seizure-free and the non seizure-free groups.

25 Variables with a significant level at 5% on univariate analysis entered in a Multiple Correspondence  
26 Analysis (MCA). The MCA method projects multi-dimensional data - one dimension for each variable  
27 - into a bi-dimensional space (or more) and searches for patterns in the datasets<sup>12</sup>. The matrix of  
28 eigenvalues is determined to identify a combination of variables that present more stability in the  
29 factorial plan and explained the largest percentage of variability in the dataset. This allows  
30 identification of variable modalities that are more closely associated with different populations (i.e.  
31 with seizure-free patients). The MCA provides a visual representation regarding the conditions more  
32 strongly coupled with groups that helps to confirm associations or similarities between variable  
33 modalities. This method is suitable for population-based studies<sup>13</sup>.

34 Variables with a significant level at 10% on univariate analysis were entered into a survival multiple  
35 regression analysis, the Andersen-Gill counting process model, in order to identify predictors of  
36 outcome<sup>14</sup>. Statistical significance was set at the 5% level. This method aims to simultaneously

1 explore the effects of several variables on possibly recurrent outcome, while taking into account the  
2 relationship and possible dependency between the values of two or more variables.  
3 Finally conditional inference trees analysis was performed in order to identify subpopulations of  
4 patients susceptible to present seizure recurrence. Conditional inference trees are a supervised  
5 classification method for analyzing data that select covariates by permutation-based significance tests,  
6 thereby avoiding potential bias of the more traditional decision tree algorithms<sup>15</sup>. The results are  
7 displayed in a 'tree' graph, showing the hierarchy of significant variables, and the final groups and  
8 associated thresholds of response values following the binary splits.  
9 All statistics were performed using R software (version 2.13.1; R Core Development Team, 2013).

10

## 11 **RESULTS**

### 12 **Patient characteristics**

13 Within 54 patients with FLE who underwent epilepsy surgery, 42 patients (28 females) fulfilled  
14 inclusion criteria and were included in the study. Mean age at epilepsy onset was 7 years ( $\pm$  6 years,  
15 median 5), mean age at surgery was 23.4 years ( $\pm$ 12.3 years, median 23) and the mean epilepsy  
16 duration at the time of surgery was 16.4 years ( $\pm$ 10.7 years, median 15). Thirty-eight patients (90%)  
17 underwent SEEG prior to surgery and only four patients underwent surgical resection without previous  
18 SEEG (two because of young age, two because of patient refusal of invasive recording, all with  
19 lesional MRI).

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

24 Histopathology was available in all but five patients, who all had lesional MRI.

25 Aetiology, determined from combined histopathological and MRI findings, was focal cortical  
26 dysplasia in 25 patients (59.5%, 21 with FCD IIb and 4 with FCD Ib) (11 of whom with normal MRI),  
27 cryptogenic in 7 patients (16.7%) with normal MRI and normal or with mild gliosis on histopathology,  
28 and other pathological findings in 10 patients (24%) including encephalitis in 2, tuberous sclerosis in  
29 2, encephalomalacia from trauma or stroke in 3, vascular malformation in 2, and other malformation  
30 of cortical development in 1. Clinical patient characteristics are summarised in table 1.

### 31 **Overall recurrence**

32 Mean follow-up duration was 4.6 years ( $\pm$  2.7 years, median 4.5 years, range 0.5-10 years). At the  
33 time of last follow-up 24 patients were seizure-free (57.1%) while in 18 patients seizures recurred  
34 without subsequent remission (42.9%). Within the seizure-free group, a run-down phenomenon was  
35 observed in two patients (who became seizure-free at 1 and 1.5 years for a subsequent follow-up  
36 period of respectively 10 and 10.5 years) and in another patient, seizures recurred with abrupt  
37 discontinuation of AED, and ceased after resuming AED intake. Nonetheless, in order to evaluate

1 longitudinal outcome changes and explore the effects of variables on outcome upon a time, their  
2 seizure recurrence was taken into account for statistical analysis.  
3 Seizure outcomes using Engel criteria at 6 months and at 1 to 5 years post-operatively are reported in  
4 table 2. The majority of relapses (17, when including patients with a run-down) occurred during the  
5 first year. Of the four patients without SEEG, two were seizure free and two were not-seizure free at  
6 the end of their participation (respectively 0.5, 2.5, 2 and 1.5 years).  
7 Longitudinal seizure-free outcome estimated using Kaplan-Meier survival analysis reveals that  
8 probability of remaining in Engel Class I vary with post-surgical time (Figure 1). The chance of being  
9 seizure free was 67% (95% CI 54-83) at 6 months, then fell to 59% (95% CI 46-76) at 1 year, 53%  
10 (95% CI 40-71) at 2 years, 50 (95% CI 36-68) at 3 years and 46 % (95% CI 32-66) at 5 years and  
11 beyond. The median time to seizure recurrence was 36 months.

12

### 13 **Neuropsychological outcome**

14 Concerning neuropsychological outcome, we found that patients assigned an Engel class I outcome  
15 compared to not-seizure free patients had a post-surgical higher full scale IQ ( $P = 0.029$ ) as well as a  
16 higher verbal IQ ( $P = 0.017$ ). Conversely, there was no significant difference comparing pre-surgical  
17 to post-surgical scores between the groups on Performance IQ and for working memory scores.

18

### 19 **Outcome predictors**

#### 20 *Univariate analysis*

21 Results of univariate analysis for categorical variables are shown in table 1-3. For statistical purposes,  
22 MRI findings were twice grouped into two modalities to compare: normal versus lesional MRI and  
23 then MRI with extra-frontal extension MRI versus MRI (either normal or lesional) without extra-  
24 frontal extension. Similarly, aetiology was doubly grouped into FCD, cryptogenic, and other, and then  
25 into FCD versus not-FCD.

26 Variables significantly ( $P < .05$ ) associated with seizure recurrence were: incomplete resection of the  
27 EZ, cryptogenic and not-FCD as aetiology, extra-frontal extension lesional MRI and widespread EZ as  
28 defined by SEEG. Not significant difference in outcome was found in MRI-lesional patients compared  
29 to MRI-normal patients. When categorizing surgical outcome based on field strength, we found no  
30 difference for patients having undergone 3T MRI compared to 1.5T MRI. Combining aetiology with  
31 MRI findings, the poorest outcomes were associated with normal or non-specific histopathological  
32 findings associated with normal MRI on one hand, and aetiology other than FCD associated with  
33 extra-frontal extension MRI on the other hand.

34 Concerning continuous variables (namely, age at epilepsy onset, age at surgery and epilepsy duration),  
35 none of them proved to be correlated to surgical outcome ( $P > 0.1$ ).

36

1 *Multiple Correspondence Analysis*

2 Variables with  $P < .05$  on univariate analysis entered in the MCA. For a principle of parsimony, FCD  
3 versus not-FCD was chosen to three modalities aetiology because of its lower  $p$  value, and the  
4 combined variable aetiology/MRI was not included in the MCA.

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

14  
15 *Multivariate analysis*

16 Results of multivariate analysis after applying Andersen-Gill counting process model are reported in  
17 table 4. The variable “extent of resection” resulted in an independent predictor of outcome ( $P = .04$ ) in  
18 our series, with a hazard ratio equal to 4 for incomplete resection ( $\beta = 1.39$ ,  $p < 0.05$ ,  $e^\beta = 3.9998$ , CI  
19 95% [1.097, 14.582]), meaning that incomplete resection of the EZ as defined by SEEG led to a risk of  
20 seizure recurrence four times **greater** than for complete resection.

21 The Kaplan-Meier survival curve for this outcome predictor shows a less favourable outcome for  
22 patients with incomplete resection of the EZ ( $P < .001$ ), with 65% of patients recurring within the first  
23 six months post-operatively (CI 18-72) (Figure 3).

24  
25 *Conditional inference trees*

26 Recursive partitioning (Figure 4) confirmed extent of resection as the most important variable  
27 associated with outcome (first node). Secondly, aetiology was relevant in patients with complete  
28 resection (left branch of the tree), with not-FCD as aetiology associated with seizure  
29 recurrence. Thirdly, in the FCD branch, focal EZ predicted seizure freedom while widespread EZ  
30 predicted seizure recurrence.

31  
32  
33 **DISCUSSION**

34 In the present study we aimed to investigate post-surgical outcome in FLE and to identify potential  
35 predictors of seizure recurrence using different statistical techniques, combining the advantages of 1)  
36 univariate analysis to select the most relevant variables, 2) MCA to highlight the structure of the



1 population with respect to prognosis, 3) survival multiple regression analysis to derive significant parts  
2 of this structure and 4) conditional inference trees to refine this conclusion.

3 As a result 57.1% of patients were seizure freedom at last follow-up and the estimated chance of long-  
4 term (10 years) favourable outcome was 46%. Most relapses occurred within the first two post-  
5 operative years. Afterwards, likelihood of maintaining a good outcome following a prolonged period  
6 of seizure freedom was quite high.

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

10 Multivariate and Conditional Inference procedures showed that the complete resection of the EZ as  
11 defined by SEEG was the main predictor of favourable outcome. Additionally FCD predicted seizure  
12 freedom in patients with complete resection, and a focal EZ was associated with favourable outcome  
13 in patients with FCD. Importantly, patients with negative MRI had the same chance of favourable  
14 outcome as patients with lesional MRI in our series.

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

20 Our study shows a deterioration of outcome with time, as also observed after TLE surgery <sup>17,18</sup>.

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

34 Compared to our population predominantly explored with SEEG, the great majority of series studying  
35 long-term seizure outcome of FLE are characterised by the absence of invasive recording or by the use  
36 of subdural electrodes in about half of patients undergoing cortical resection (<sup>4,20,24-27,30-34</sup>). In these  
37 subdural guided series, the rate of negative MRI varies from 0% to 46% (39% on average <sup>4,20,24-26,30-</sup>

1 <sup>32,34,35</sup>). In the majority of epilepsy centres, invasive subdural electrodes have traditionally been the  
2 intracranial EEG method of choice including for evaluating non-lesional cases <sup>20,24,30–32,35</sup>. Until very  
3 recently the SEEG was almost exclusively used in France and Italy. In the last few years, international  
4 interest in SEEG as a potentially useful tool for presurgical evaluation, especially for extra-temporal  
5 and MRI-negative cases, has led to a rapid worldwide increase in centres adopting this method. For  
6 example, the Cleveland Clinic now prioritizes SEEG as first choice exploration method rather than  
7 grids for the majority of cases, and particularly for “suspected frontal lobe epilepsy in non-lesional  
8 MRI scenario” <sup>36</sup>(Alomar et al 2016). A recent report from an ILAE working party, evaluating  
9 different modalities of invasive EEG recordings, discusses the utility of subdural grid for extensive  
10 unilateral exploration with wide coverage of neocortical gyral surface<sup>37</sup> (Jayakar et al, 2016). On the  
11 other hand, authors recommend SEEG for bilateral exploration and for deep targets such as the  
12 cingulate cortex, the orbito-frontal cortex, the insular cortex and mesio-temporal structures<sup>37,38</sup>  
13 (Jayakar et al, 2016; Podkoryotova et al, 2016). These latter structures, because of their strong  
14 anatomo-functional connections with the prefrontal cortex, are particularly important to explore as  
15 potentially implicated in the EZ network in FLE. Although more often used in MRI-negative  
16 extratemporal epilepsies, invasive recording has been recommended for both MRI negative or positive  
17 cases<sup>37</sup> (Jayakar et al, 2016). In actual fact, with few exceptions<sup>24,30</sup> (Lazow et al, 2012; Lee et al,  
18 2008), most FLE surgical series do not use systematically intracranial EEG; however, such series  
19 without intracranial EEG are generally composed of cases with radiologically visible lesions.  
20 Conversely, we regularly used SEEG if clinically indicated, in both MRI positive and MRI negative  
21 cases, and found similar or better outcome than other reports.

22 The use of intracerebral electrodes allows the definition of the EZ and of surgical resection in the  
23 absence of a visible lesion. Furthermore it minimizes the risk of an incomplete removal of the EZ  
24 extending beyond a visible neuroradiological abnormality, since epileptogenicity can extend beyond  
25 the lesion and organizes as a large network with remote and even bilateral epileptogenicity <sup>9,39</sup>.

26 As described in other studies we report a relatively high incidence of FCD amongst operated patients  
27 with normal MRI (40% of patients with FCD)<sup>9,21,29,40–42</sup>. In this context the invisible underlying  
28 pathology, namely FCD, represented a favourable prognostic indicator in case of complete removal of  
29 the EZ, when compared with all other aetiologies, in agreement with previous SEEG studies <sup>29,43</sup>.

30 Moreover, the characteristics of the EZ (i.e. focal versus widespread) can predict surgical outcome in  
31 our series. **Indeed bilateral involvement and involvement of remote extra-frontal cortex were**  
32 **important causes of incomplete resection of the EZ. Since another main reason of incomplete resection**  
33 **of the EZ is the need to preserve functional cortex, SEEG allows on one hand to evaluate the**  
34 **involvement of such structures and, on the other hand, to predict surgical failure and guide palliative**  
35 **surgery <sup>43</sup> if indicated.**

36 This study aimed to provide outcome measures that could guide the complex decision-making process  
37 leading to surgical resection. The use of SEEG appears to be particularly effective in evaluating the

1 eligibility for epilepsy surgery in FLE patients. Of course its effectiveness depends on conditions of  
2 use, such as patient selection, electrode implantation strategy and team expertise, which might help  
3 explain variable results across series <sup>44</sup>. Here, the complete resection of the EZ defined with SEEG  
4 represents the strongest predictor of seizure freedom, both in negative and in lesional MRI. Of course  
5 the capability to totally remove the EZ can be constrained by possible overlap between the EZ and  
6 functional cortex. Indeed, extension of the EZ to the central cortex has been shown to have a poor  
7 prognostic value for surgical outcome <sup>45</sup>.

## 9 **CONCLUSION**

10 A number of clinical characteristics that may co-exist can indicate patients with better chance of  
11 favourable outcome in FLE, namely: focal EZ; normal MRI or with lesion limited to the frontal lobe;  
12 complete resection of the EZ; and FCD as aetiology. SEEG in FLE candidates for surgery, both in  
13 lesional and non-lesional cases, contributes above all to the definition of the EZ, whose complete  
14 resection is the major outcome predictors for FLE. Epilepsy surgery can represent a successful  
15 therapeutic approach in drug-resistant FLE patients, even in the absence of a neuroradiological lesion.

## 19 **Disclosure of Conflicts of Interest**

20 “None of the authors has any conflict of interest to disclose.”

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1 **Figure legends**

2

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

6

7 **Figure 2.** Factorial plan of association of clinical variables with seizure outcome. The graphic is  
8 created by the two dimensions derived from the multiple correspondence analysis. The horizontal axis  
9 represents the first dimension, while the vertical axis represents the second dimension

10

11 **Figure 3.** Kaplan-Meier survival curve showing chances of post-operative seizure freedom depending  
12 on the completeness of the resection (Log-rank test:  $\chi^2 = 18.5$ , 1 df,  $p < 0.001$ ). Median time of  
13 recurrence for incomplete resection is 6 months (95% CI 0.5-2). With complete resection, 67% of  
14 patients are seizure free 10 years after surgery.

15

16 **Figure 4.** Conditional inference tree predicting probability of seizure recurrence: the 'tree' graph  
17 shows the hierarchy of significant variables associated with outcome

18