FULL-LENGTH ORIGINAL RESEARCH

# Cost-effectiveness analysis of epilepsy surgery in a controlled cohort of adult patients with intractable partial epilepsy: A 5-year follow-up study

[1,2]Marie-Christine Picot, [1]Audrey Jaussent, [3,4]Dorine Neveu, [5,6]Philippe Kahane, [7]Arielle Crespel, [7]Philippe Gelisse, [8]Edouard Hirsch, [9]Philippe Derambure, [10]Sophie Dupont, [11]Elizabeth Landré, [11]Francine Chassoux, [12]Luc Valton, [13]Jean-Pierre Vignal, [14]Cécile Marchal, [15]Catherine Lamy, [9,11,15]Franck Semah, [16]Arnaud Biraben, [17]Alexis Arzimanoglou, [18]Jérôme Petit, [19]Pierre Thomas, [1]Valérie Macioce, [1,3,4]Pierre Dujols, and [20,21,22]Philippe Ryvlin

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**Dr. Marie-Christine Picot**, is head of the clinical epidemiology unit at Montpellier University Hospital.

## Summary

**Objective:** **Despite its well-known effectiveness, the cost-effectiveness of epilepsy surgery has never been demonstrated in France. We compared cost-effectiveness between resective surgery and medical therapy in a controlled cohort of adult patients with partial intractable epilepsy.**

**Methods:** **A prospective cohort of adult patients with surgically remediable and medically intractable partial epilepsy was followed over 5 years in the 15 French centers. Effectiveness was defined as 1 year without a seizure, based on the International League Against Epilepsy (ILAE) classification. Clinical outcomes and direct costs were compared between surgical and medical groups. Long-term direct costs and effectiveness were extrapolated over the patients' lifetimes with a Monte-Carlo simulation using a Markov model, and an incremental cost-effectiveness ratio (ICER) was computed. Indirect costs were also evaluated.**

**Results:** **Among the 289 enrolled surgery candidates, 207 were operable—119 in the surgical group and 88 in the medical group—65 were not operable and not analyzed here, 7 were finally not eligible, and 10 were not followed. The proportion of patients completely seizure-free during the last 12 months (ILAE class 1) was 69.0% in the operated group and 12.3% in the medical group during the second year ($p < 0.001$), and it was respectively 76.8% and 21% during the fifth year ($p < 0.001$). Direct costs became significantly lower in the surgical group the third year after surgery, as a result of less antiepileptic drug use. The value of the discounted ICER was 10,406 (95% confidence interval [CI] 10,182–10,634) at 2 years and 2,630 (CI 95% 2,549–2,713) at 5 years.**

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[1]Clinical Research and Epidemiology Unit, CHU Montpellier, Montpellier, France; [2]INSERM, Clinical Investigation Center 1411, Montpellier, France; [3]INSERM U 1058, Montpellier, France; [4]University Montpellier, Montpellier, France; [5]Department of Neurology, GIN, CHU Grenoble, Grenoble, France; [6]INSERM U836, UJF, Grenoble Alpes University, Grenoble, France; [7]Epilepsy Unit, CHU Montpellier, Montpellier, France; [8]Department of Neurology, CHU Strasbourg, Strasbourg, France; [9]Lille University Medical Center, CHU Lille, EA 1046, University of Lille2, Lille, France; [10]Epileptology Unit, Assistance Publique-Hôpitaux de Paris, an UPMC University Paris 06, Paris, France; [11]Department of Neurosurgery, AP-HP and University Paris Descartes, Paris, France; [12]Department of Neurology, University Hospital, and UMR 5549, CNRS, Toulouse, France; [13]Clinical Neurophysiology and Epileptology Department, University Hospital of Nancy, Nancy, France; [14]Epilepsy Unit, CHU Bordeaux, Bordeaux, France; [15]Department of Neurology, AP-HP and University Paris Descartes, Paris, France; [16]Department of Neurology, University Hospital of Rennes, Rennes, France; [17]Epilepsy, Sleep and Paediatric Neurophysiology Department (ESEFNP), University Hospitals of Lyon (HCL) and DYCOG Team, Lyon Neuroscience Research Centre (CRNL), INSERM U1028, CNRS UMR 5292, Lyon, France; [18]La Teppe Epilepsy Center, Tain l'Hermitage, France; [19]Department of Neurology, University Hospital of Nice, Nice, France; [20]Department of Functional Neurology and Epileptology and the Institute of Epilepsies, Hospices Civils de Lyon, Lyon, France; [21]Lyon 1 University; Lyon's Neuroscience Research Center, Lyon, France; and [22]Department of Clinical Neurosciences, CHUV, Lausanne, Switzerland

Address correspondence to Marie-Christine Picot, Département de l'Information Médicale – Unité de Recherche Clinique, CHRU Montpellier, Hôpital La Colombière, 39 Avenue Charles Flahaut, Montpellier Cedex F-34 295, France. E-mail: mc-picot@chu-montpellier.fr

**Surgery became cost-effective between 9 and 10 years after surgery, and even earlier if indirect costs were taken into account as well.**

**Significance: Our study suggests that in addition to being safe and effective, resective surgery of epilepsy is cost-effective in the medium term. It should therefore be considered earlier in the development of epilepsy.**

**KEY WORDS: Prospective study, Refractory epilepsy, Direct medical costs, Indirect costs, Incremental cost-effectiveness ratio.**

## Key Points

- Seizure freedom rate (ILAE class 1) at 2 and 5 years was, respectively, 69% and 77% in surgical patients and 12% and 21% in medical patients
- Direct costs became lower in surgical patients compared with medical patients 3 years after surgery
- At 2 years, the mean direct medical cost per patient and per year was 2,990 € in surgery group and 3,550 € in medical group, resulting in an ICER of around 10,500 € per seizure-free patient
- Epilepsy surgery is cost-effective compared to medical treatment after a time interval between 9 and 10 years

Epilepsy surgery is known to be clinically effective[1–3] and is recommended as the treatment of choice for medically refractory temporal lobe epilepsy.[4] However, it is mainly restricted to patients with severe drug-resistant epilepsy and is often used as a last resort. Indeed, mean duration of epilepsy prior to temporal lobe epilepsy surgery is >20 years and has remained stable over the last decade.[5] One reason is limited access to presurgical explorations that require highly specialized techniques, with cost as a major restriction on use of surgery. Across health pre-surgical care systems, patients with active epilepsy receive about four to nine times more health care than patients with well-controlled epilepsy.[6] Direct cost estimates of refractory epilepsy are 2.1–10.6 times higher than those for controlled epilepsy.[7,8] Moreover, health pre-surgical care costs of epilepsy increase with the number of comorbidities.[9] The highest cost is for antiepileptic drugs (AEDs), which account for about 50% of the total cost according to recent Italian[10] and Chinese studies.[11] AEDs available in the last decades are somewhat effective but much more expensive. It remains unclear whether surgery for refractory epilepsy is a more cost-effective approach than continued medical management. Few prospective studies have yet provided good evidence of cost-effectiveness in drug-resistant epilepsy.[12] Most economic evaluations are retrospective and have been conducted in the United States, Canada, and Sweden, with different health pre-surgical care systems.[13–17] Their models include parameter estimates extracted from the literature or based on expert opinions and provide weak evidence. However, the hypothesis that epilepsy surgery may be cost-effective in the long term is supported by a reduction in health pre-surgical care costs after disappearance of seizures and in indirect costs by 50–90% after a simulation over a lifetime in drug-resistant epilepsy.[7,18]

First, we assessed whether epilepsy surgery is cost-effective as compared with medical treatment in patients with drug-resistant partial epilepsy. Second, we compared clinical outcomes, costs of medical care, and indirect costs between surgical and medical strategies.

## Population and Methods

### Study design and population

We conducted a prospective observational cohort study from January 1, 2001 to December 31, 2013. Patients were recruited between January 1, 2001 and December 31, 2003 at all of the 15 epilepsy units in France. For patients referred for an opinion on surgical indication, the inclusion criteria were the following: (1) age between 15 and 60 years; (2) drug-resistant epilepsy with focal seizures defined as a persistence of seizures for at least 2 years on appropriate treatment and acceptable adherence, and at least two AED schedules; and (3) no contraindication to surgery and potential candidate for epilepsy surgery on the basis of available data at inclusion. Patients with a severe and progressive illness other than epilepsy (e.g., heart or respiratory failure) or malignant or progressive vascular cerebral lesion were not included; nor were those who could not be followed up regularly for at least 2 years. All participants provided written informed consent before enrollment. Patients were excluded from the study if they withdrew their consent or received a therapeutic alternative (thermocoagulation, vagus nerve stimulation, and so on).

After presurgical evaluation, participants were allocated to one of the following groups: surgical arm with operated patients (surgical group), medical arm with operable but nonoperated patients (control group), and medical arm with inoperable patients. Inoperable patients were not considered in the present analysis because they were suspected to have forms of epilepsy that might differ from the other two groups. Patients were followed for 5 years, with clinical

visits scheduled every 6 months (±3 months) during the first 2 years after screening (control group) or surgery (surgical group), and at 36 (±6) and 60 (±12) months thereafter.

The protocol was approved by the ethics committee (*Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé, CCTIRS*) and the French Data Protection Authority (*Commission nationale de l'informatique et des libertés* or CNIL).

**Preoperative explorations and surgery**

At inclusion, history of epilepsy, etiologic factors, seizure semiology, electroencephalography (EEG) findings, computed tomography (CT) scan and magnetic resonance imaging (MRI) done before inclusion, current treatments and treatments prescribed since epilepsy onset were recorded.,

Preoperative explorations included first video-EEG monitoring and MRI, then ictal or interictal SPECT (single-photon emission computed tomography), positron emission tomography (PET), functional MRI, or the Wada test. In more than two thirds of cases, these explorations localized the epileptic focus precisely enough for surgery, which consisted mostly of temporal lobectomy, or, more rarely, lesionectomy. Otherwise, an intracranial exploration with deep or subdural electrodes complemented the previous explorations and surgery consisted of tailored corticectomy guided by the results of intracranial explorations.

Biochemical assays and neuropsychological tests were also done. Surgery was assigned by adjudication of a panel of experts in epilepsy, based on the findings of preoperative explorations. At every follow-up visit, the type and seizure frequency, clinical symptoms, and AEDs together with tapering and discontinuation were recorded. Physicians were recommended to continue AEDs for at least 2 years after surgery.[19] Patients who missed a visit were contacted by phone in order to limit losses to follow-up. These data were collected with a case report form (CRF) filled out by the neurologist and then, completed and validated with the patient record on site by the coordination team (project manager or coordinating investigator).

**Clinical outcome**

The effectiveness was defined as complete seizure freedom for the last 12 months, as defined by ILAE class 1.[20] This classification reports the patient's outcome on an annual basis at each anniversary date after surgery. Classes 1–3 refer to absolute postoperative seizure events, where class 1 refers to complete seizure freedom (no aura), and classes 4–6 refer to relative changes with respect to the preoperative seizure constellation. Secondary end points were seizure freedom defined by Engel class 1A (completely seizure-free since surgery) and class 1 (free of disabling seizures),[21] and seizure-free patients according to the ILAE in patients on and off AEDs. Seizure frequency was assessed by the physician and the patient to limit information bias. In case of discordance, the seizure frequency was reassessed by the physician.

**Health care utilization**

Because the national databases of the French health pre-surgical care system were not accessible before 2009, information about health pre-surgical care utilization was collected at inclusion (over the previous 12 months) and then prospectively at each visit (6, 12, 18, 24, 36, and 60 ± 12 months) by the patient and his (or her) relatives, with a detailed self-administered questionnaire. Patients reported hospitalizations, outpatient visits, prescribing treatments as well as the visits to the emergency, work stoppages, job status changes, welfare, and family status, among others. To limit recall bias, the patients had a notebook to report continuously seizures (severity and frequency) and all the seek care due to epilepsy between the visits. The general practitioner and the neurologist had also to fill a clinical report form on medical resource use. Clinical research assistants (CRAs) made reminders by phone. The information provided by the patient and the doctor were crossed for validation and, if available, validated with the patient record on-site by the CRA.

**Cost evaluation**

Costs were estimated from a societal point of view. Unit costs, expressed in euros, and respective sources used to calculate the total cost per patient are reported in Table 1. Costs were estimated using a bottom-up approach, in which information about each element of service used was multiplied by its unit cost and summed to provide an overall total cost. Direct medical costs included hospitalizations, complementary examinations, outpatient visits, and medical treatments related to epilepsy. The cost of hospitalization was assessed using daily rates and packages set by prefectural orders of 01/01/2006. The medical procedures performed outside the hospitalizations were valued according to the quotation of the general classification of treatments (general classification system for the medical professional activities [NGAP]) and the rates of 2006. Direct nonmedical costs related to transportation were estimated using type of transportation and distances traveled, and valued according to legal conditions, JO published in the Official Journal in 2006. Unit costs evolved very little during the past decade. Indirect costs (or production losses) were measured in physical units (e.g., employment rate, number of working days lost) but not valued.

**Statistical analysis**

Data were analyzed using SAS (SAS Institute, Cary, NC, USA), package V9.2. Baseline sociodemographic data, characteristics of epilepsy, treatments, and health pre-surgical care costs were compared between the two groups using the chi-square test or Fisher's exact test for qualitative parameters and the *t*-test or Mann-Whitney test for quantitative parameters.

**Table 1. Unit costs employed to calculate costs of health presurgical care use and respective sources**

| | Unit costs (€) | Sources |
|---|---|---|
| Outpatient visit | | |
| GP visit | 20.0 | NHS (NGAP) 2006 |
| Medical specialist visit | 23.0 | |
| Neurosurgical, psychiatric visit | 34.3 | |
| Occupational medicine | 34.3 | |
| Neurologic examinations | | |
| EEG | 57.6 | NHS (NGAP) 2006 |
| EEG 48 h | 107.9 | |
| Video-EEG <4 h | 178.8 | |
| Video-EEG >4 h | 345.6 | |
| CT scan | 136.0 | |
| MRI | 274.1 | |
| SPECT | 318.6 | |
| FGD-PET | 295.5 | |
| Visual field | 25.0 | |
| Electrocardiography/lung examination | | |
| Lung radiology | 30.7 | NHS (NGAP) 2006 |
| ECG | 12.5 | |
| ECG during visit | 45.7 | |
| Blood sample | | |
| AED dosage | 18.9 | NHS (NGAP) 2006 |
| Blood cell count | 10.8 | |
| Ionic balance | 5.4 | |
| Liver tests (transaminases gamma-GT, LDH, CPK) | 25.65 | |
| Neuropsychological evaluation | | |
| Language therapy assessment | 7.7 | NHS (NGAP) 2006 |
| Neuropsychological assessment | 103.7 | |
| Wada test | 172.8 | |
| Speech therapy assessment | 71.1 | |
| Total cost epilepsy surgery evaluation (mean, min.–max.) | | |
| Operated patients (N = 119) | 9 073 (275– 44 497) | Present study |
| Nonoperated patients (N = 73) | 6 089 (19–25 057) | |
| Hospitalization (mean of main hospitals) | | |
| Emergency SMUR/SAMU | 589.0 | Prefectural orders 2006 |
| General hospital (per bed day) | 180.0 | |
| Medical department (per bed day) | 1017.8 | |
| Surgery department (per bed day) | 1366.6 | |
| Intensive care unit (per bed day) | 3054.6 | |
| Day hospitalization (outpatient) | 968.2 | |
| Surgery: intervention costs | | |
| Lesionectomy/epileptic focus resection | 647.9 | NHS (NGAP) 2006 |
| Cortectomy amygdalohippocampectomy | 647.9 | |
| Temporal lobectomy | 689.7 | |
| Lobectomy+ amygdalohippocampectomy | 971.9 | |
| Ganglioma resection+ amygdalohippocampectomy | 1013.7 | |
| Cortectomy+ amygdalohippocampectomy | 971.9 | |
| Total costs for epilepsy surgery (N = 119) | | |
| Mean (min.–max) | 12,643 (6,757–25,050) | Present study |

GP, general practitioner; NGAP, general classification system for the medical professional activities; NHS, National Health Service; EEG, electroencephalography; SPECT, single-photon emission computed tomography; FDG-PET, fluorodeoxyglucose–positron emission tomography; AED, antiepileptic drug; GT, glutamyltransferase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; SMUR/SAMU, Emergency medical service in France.

In order to assess the medical and economic impact of surgery, we compared the two arms with respect to clinical status, costs related to epilepsy, and occupational status.

The incremental cost-effectiveness ratio (ICER) was defined as the ratio of the difference in mean costs ($\overline{C_{Surgical}} - \overline{C_{Medical}}$) between the two arms to the difference in mean effectiveness ($\overline{E_S} - \overline{E_M}$).[22] Direct medical costs were first taken into account and then cumulated to the direct nonmedical costs. Indirect costs were not included in ICER because the method used to estimate production losses is controversial.[22,23] ICER is the extra cost paid for every extra year without seizure gained by using surgery instead of continued medical care.

ICER was estimated with a Monte Carlo simulation based on a discrete-time Markov process with a 1-year cycle. In each arm, outcome of 10,000 patients, who were given the mean age of the surgical group, was simulated. Four health states were defined: (state 1) patients with seizures and AEDs, (state 2) seizure-free patients with AEDs, (state 3) seizure-free patients without AEDs, and (state 4) death. The state transition probabilities of the five first cycles were calculated from our data. As the risk of recurrence decreased with the time passed in remission,[24,25] the transition probability was estimated according to this time in remission. A schematic representation of the model structure is presented in supplementary data (Fig. S1). ICER was extrapolated over a lifetime in order to determine when surgery became cost-effective compared with continued medical treatment, that is, when the extra cost paid for every extra year without seizure gained by using surgery is lower than that related to continued medical care. Costs were extracted from study data. Mortality rates of states 2 and 3 were extracted from the World Health Organization (WHO) general population

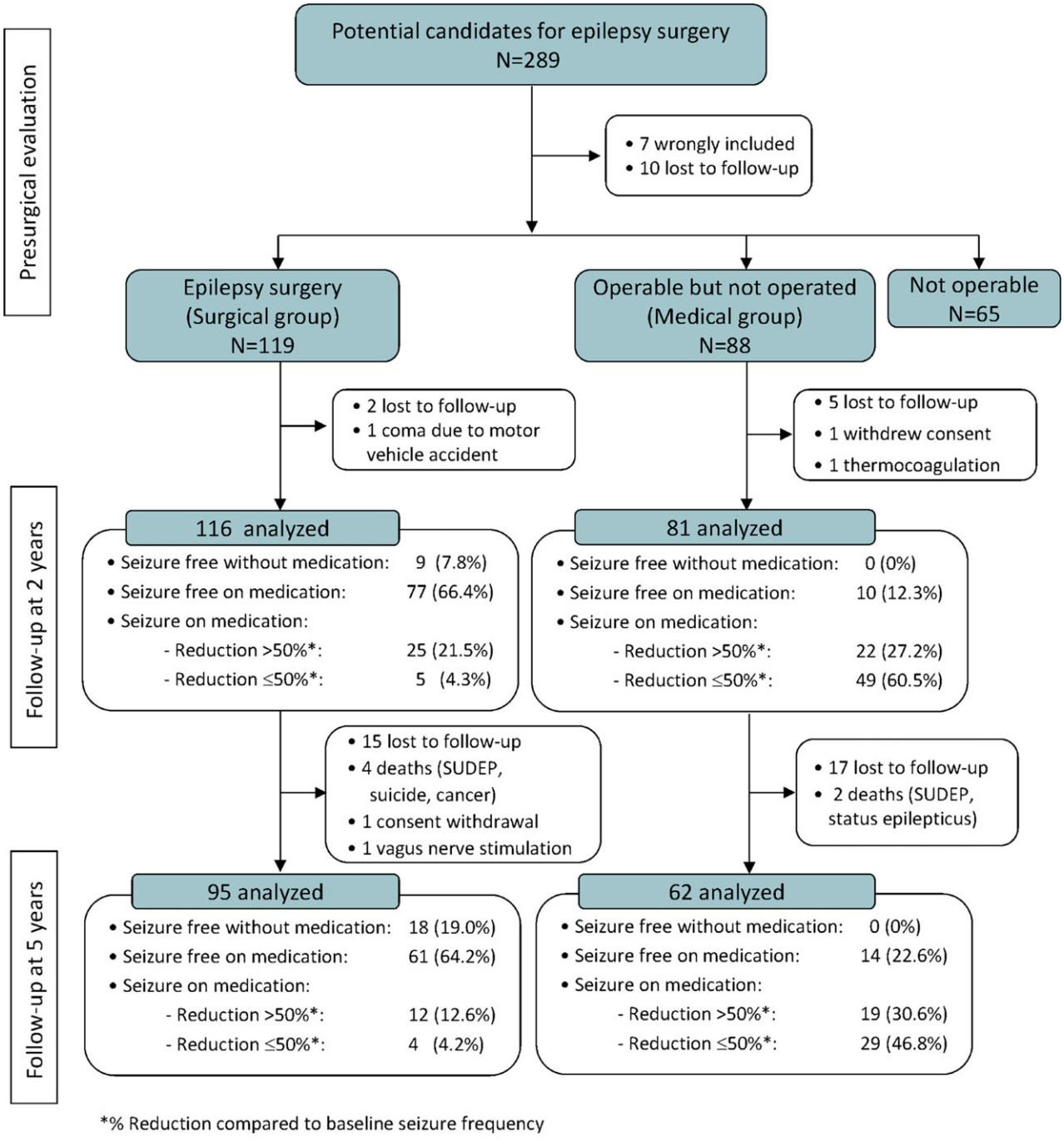


**Figure 1.**
Flow chart and clinical outcome in operated (surgical group) and nonoperated (control group) patients with intractable epilepsy.
*Epilepsia* © ILAE

archives (WHO Mortality Database 2005, http://www.who.int/healthinfo/statistics/mortality/en/index.html) according to age and sex. Because patients with seizures are more likely to die than seizure-free patients are,[26] the mortality rate of state 1 was given a multiplicative correction factor (4.7), equal to the standardized mortality ratio estimated in patients with epilepsy.[27] Both costs and health outcome were discounted at an annual rate of 3%. The 95% confidence intervals (CIs) of ICER were estimated with Fieller's method[28] using bootstrapping in a specific program computed with SAS.

Robustness of ICER estimates was tested with one-way sensitivity analyses by varying the annual discount rate (0%, 3%, and 5%), age at surgery to assess the impact of the duration of the intractability (20-, 30-, and 36-years-old) and the cost of surgery associated with presurgical

**Table 2. Baseline characteristics of operated and nonoperated epileptic patients**

| | Surgical group N = 119 | Control group N = 88 | p-Value |
|---|---|---|---|
| Age at epilepsy onset (year), mean ± SD | 13.7 (±9.2) | 13.9 (±10.7) | 0.62 |
| Gender, male, N (%) | 46 (38.7) | 34 (38.6) | 1.00 |
| Duration of epilepsy (year), mean (±SD) | 22.0 (±11.2) | 21.6 (±12.7) | 0.68 |
| Age at presurgical exploration (year), mean (±SD) | 35.7 (±8.8) | 35.7 (±10.3) | 1.00 |
| Seizure frequency during the last 12 months, N (%) | | | |
| <1/month | 1 (0.8) | 8 (9.1) | <0.0001 |
| 1–4/month | 35 (29.4) | 46 (52.3) | |
| 5–30/month | 75 (63.0) | 28 (31.8) | |
| >30/month | 8 (6.7) | 6 (6.8) | |
| Secondarily generalized seizures during the past 12 months | | | |
| Mean (±SD) | 5.4 (±15.5) | 3.3 (±8.6) | 0.48 |
| Median (min.–max.) | 0 (0–120) | 0 (0–48) | |
| Duration of seizure-free intervals (days), mean (±SD) | 31.3 (±67.0) | 33.7 (±42.7) | 0.21 |
| Location of epileptic focus, N (%) | | | |
| Temporal lobe | 100 (86.2) | 51 (61.5) | <0.0001 |
| Temporo-perisylvian | 1 (0.9) | 11 (13.3) | |
| Frontal lobe | 3 (2.6) | 8 (9.6) | |
| Frontotemporal | 8 (6.9) | 9 (10.8) | |
| Other | 4 (3.5) | 4 (4.8) | |
| MRI lesions, N (%) | | | |
| No lesion | 9 (7.6) | 31 (35.2) | <0.0001 |
| Limited lesion | 104 (87.4) | 51 (58.0) | |
| Large or multiple lesions | 6 (5.0) | 6 (6.8) | |
| Underlying pathology (MRI), N (%) | | | |
| Hippocampal sclerosis | 81 (68.1) | 30 (36.1) | <0.0001 |
| Dysplasia-dysgenesia | 21 (17.7) | 8 (9.6) | 0.11 |
| Cicatricial lesion (stroke, surgery, trauma) | 5 (4.2) | 8 (9.1) | 0.15 |
| Vascular | 3 (2.5) | 1 (1.2) | 0.65 |
| Perinatal lesion | 2 (1.7) | 1 (1.2) | 1.00 |
| Tumor | 1 (0.8) | 1 (1.2) | 1.00 |
| Other lesions | 12 (10.1) | 13 (15.7) | 0.24 |
| Comorbidities, N (%) | | | |
| Anxious disorder | 48 (40.3) | 27 (31.4) | 0.19 |
| Depressive disorder | 27 (22.7) | 15 (17.4) | 0.36 |
| Mental retardation | 5 (4.2) | 5 (5.8) | 0.75 |
| Cognitive disorder | 60 (50.9) | 30 (34.5) | 0.02 |
| Number of previous AEDs, median (min–max) | 6.0 (2.0–11.0) | 5.0 (2.0–10.0) | 0.09 |

explorations (interquantiles, IQ25 and IQ75). Multivariate sensitivity analysis were performed by varying costs: first, under the assumption of an underestimation of the costs, by taking the value of the 75th percentile of costs for each cycle in surgical group and, secondly, by taking the annual direct costs of patients treated mainly by newer AEDs in each group and for each cycle. The ICER was also calculated by taking the direct costs of the patients treated mainly with newer AEDs in both groups.

The impact of the variation of seizure-free patient rates in the surgical group was also tested taking the lower bound of 95% CI of the transition probabilities from state 1 to state 2: 64.2% of seizure-free patients the first year, 15.8 the second year, and 7.3% the third (in the base case approach, these probabilities were 72.3%, 32.3%, and 24%, respectively).

The method of the Last Observation Carried Forward (LOCF) method was used mainly for handling missing data. Our strategy consisted of replacing the missing value at 12 months by the non-missing value at 6 months, and missing value at 24 months by the non-missing one at 18 months. For the 3- to 5-year visit, missing data between two completed visits were replaced by the non-missing value of the previous visit. Finally, for the 5-year visit, we used the observation reported between 4 and 6 years.

## Results

Of 289 patients included in the study, 7 were wrongly included (drug responder, n = 4; nonepileptic psychogenic seizures, n = 1; idiopathic epilepsy, n = 1; age > 60 years, n = 1), and 10 were lost to follow-up (Fig. 1). Among the remaining 269 patients, 119 were operated on (surgical group) and 88 were operable although not operated (control group) because of fear of adverse effects or poor motivation (N = 44), testing a new AED therapy (N = 35), uncertain risk-benefit ratio (N = 7), or death before surgery (N = 2).

Sixty-five patients were considered inoperable because of a too-large epileptic focus or multiple foci (N = 46), epileptic focus located in highly functional areas (N = 13), or negative risk-benefit ratio (N = 3). The latter patients were not included in the present analyses.

### Baseline characteristics

Baseline characteristics of the two groups are reported in Table 2. As expected, more patients in the surgical group had temporal lobe epilepsy (86.2% vs. 61.5%) and hippocampal sclerosis (68.1% vs. 36.1%). Seizure frequency was higher (69.7% having more than five seizures per month vs. 38.6%) and cognitive disorders were more frequent (50.9% vs. 34.5%) in the surgical group. At inclusion, the two groups were similar with respect to number of previous AEDs, number of AEDs prescribed at inclusion, and employment. However, direct costs in the last 12 months were slightly higher in the surgical group.

### Clinical outcome

During the second year, 69.0% (N = 80) of operated patients were completely seizure-free (ILAE class 1) and 5.2% (N = 6) had only aura (ILAE class 2), whereas in the nonoperated group, they were, respectively, 12.3% (N = 10) and 0% ($p < 0.0001$). During the fifth year, 76.8% (N = 73) were completely seizure-free and 6.3% (N = 6) had aura only; in the nonoperated group, they were 21.0% (N = 13) and 1.6%, respectively ($p < 0.0001$).

After 2 years, 59.5% of operated patients were in Engel class 1A and 3.4% in class 1B, whereas these proportions were only 8.9% and 0%, respectively, in the nonoperated group ($p < 0.001$). For Engel class 1 (A to D), these proportions were 76.7% versus 12.6%, $p < 0.0001$.

Although the usual practice is to maintain patients on AEDs for 2 years postsurgery, patients in the surgical group received significantly fewer AEDs than nonoperated patients from the second year of follow-up (median, IQ range: 2[1–2] vs. 2 [2–3], $p < 0.001$). From the third year, the difference increased between the two groups (1 [1–2] vs. 3 [2–3], $p < 0.001$) and remained stable at 5 years of postoperative follow-up.

### Direct medical and nonmedical costs

The mean cost of presurgical explorations was 7,784 € in the whole cohort, 9,073 € (IQ25–75: 3,808–12,179 €) in the surgical group, and 6,089 € (IQ25–75: 2,356–8,592 €) in the control group ($p < 0.001$). These costs amounted, on average, to 21,517 € (IQ25–75: 15,060–26,875 €) in the surgical group if surgery was also included.

Compared with the control group, mean direct medical costs (Fig. 2) were significantly lower in the surgical group from the second year ($p = 0.02$), with a highly significant difference from the third year ($p < 0.001$). This was due mainly due to the sharp decrease in costs of AEDs and hospitalization in the surgical group from the second year (Fig. 3A), whereas costs of AEDs showed a continuous increase in the medical group (Fig. 3B). Direct medical and nonmedical costs during follow-up are detailed in Table S1. In the surgical group, mean direct medical and nonmedical costs were significantly lower in seizure-free patients than in patients who still had seizures from the third year after surgery ($p = 0.02$, Table S1).

### Incremental cost-effectiveness ratio

The value of the discounted ICER was 10,406 (95% CI 10,182–10,634) at 2 years and 2,630 (95% CI 2,549–2,713) at 5 years (Table S2). The extra cost paid for each extra year without seizures gained by using surgery became lower than that related to medical care continuation between 9 and 10 years considering all direct costs (Fig. 4).

In the sensitivity analysis, ICER was slightly influenced by discount rate (minus 1 year with 0% and delayed by 1 year with 5%, Fig. S2) and not by age at surgery, as shown

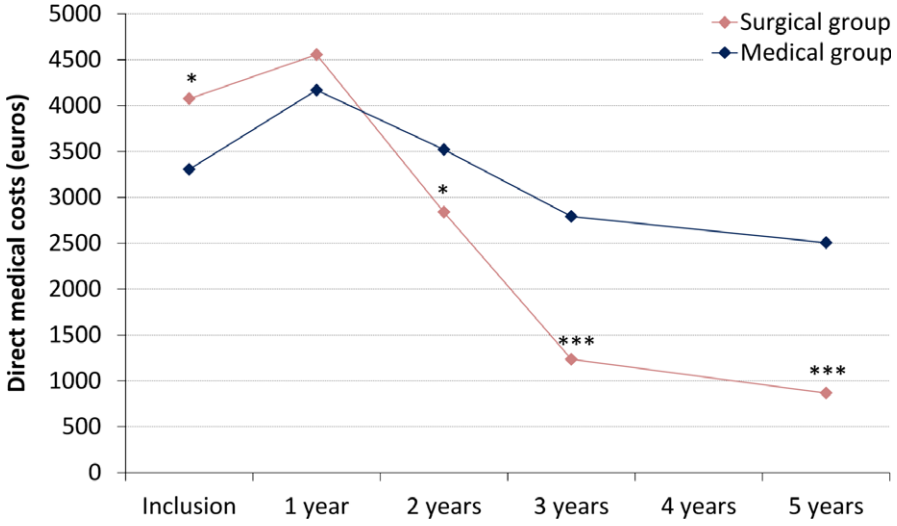


**Figure 2.**
Direct medical costs in operated (surgical group) and nonoperated (control group) patients (€). Statistical difference between the two groups: NS, not significant; $^{T}$, trend ($p < 0.10$); *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

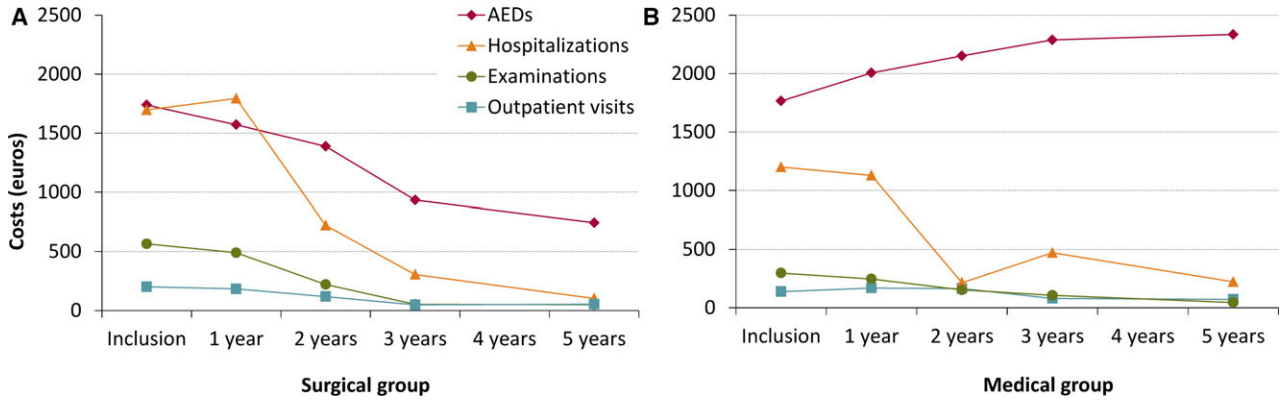


**Figure 3.**
Direct medical costs in the surgical group (€) (**A**) and in the control group (€) (**B**).
*Epilepsia* © ILAE

in the tornado diagram for the ICER at 5 years (Fig. S5). ICER was more sensitive to the cost of surgery including presurgical explorations (Fig. S3). Surgery was cost-effective between 6 and 7 years if the first quartile was used (15,060 €) and between 12 and 13 years with the third quartile (26,875 €). When the ICER was calculated by taking the direct costs of the patients treated mainly with newer AEDs (annual AEDs cost around 3,000 €) in both groups (Fig. S5), surgery was cost-effective between 10 and 11 years. By taking the lower bound of the 95% CI for the probabilities of transition from state 1 (seizure with treatment) to state 2 (seizure-free with treatment) in the surgical arm, surgery was cost-effective between 10 and 11 years (Fig. S4).

### Indirect costs: production losses

Employment rates remained stable throughout the 5-year follow-up in both groups (Table S3). Even if more patients had a driving license in the surgical group at inclusion (67.2% vs. 50.0%, p = 0.01), the gap is much larger at 5 years (78.2% vs. 45.1%, p = 0.0001). Among the patients with a driving license, 24 additional patients reported driving in the surgical group against only 4 in the medical group at the last follow-up. One in each group stopped driving.

## Discussion

In the present study, we first assessed whether epilepsy surgery was cost-effective as compared with continued medical treatment in patients with surgically remediable drug-resistant partial epilepsy. We found that the extra cost paid for each extra year without seizures gained by using surgery became lower than that related to medical care continuation in the medium term, around 9 years if all direct costs were taken into account.

Unlike most studies assessing cost-effectiveness of epilepsy surgery, the present study was prospective, included a control group on continued medical treatment, and had a rather long follow-up. Moreover, we used study data to estimate ICER through a Monte Carlo simulation based on a Markov model.

The balance of costs related to surgery and medical care in such a period of time was due mainly to the excellent clinical results of surgery and to high AED costs in the medical group. Although most surgical patients remained on AEDs after surgery, as recommended, the median number of AEDs became significantly lower in the surgical group from the second year. Reducing AEDs in patients who have been seizure-free for at least 1 year after surgery does not seem to increase the risk of relapse, after adjustment for immediate versus delayed remission.[29] Moreover, a review of retrospective studies did not suggest any benefit in waiting for >2 years to attempt AED discontinuation in seizure-free patients.[30] Furthermore, the clinical results of surgery observed in our study are consistent with the literature data. According to ILAE classification, 69% of operated patients were completely seizure-free during the last 12 months at 2 years, and 76.8% at 5 years. In the available literature, around 55–80% of patients with drug-resistant partial epilepsy, mainly temporal lobe epilepsy, are totally seizure-free 2 years after surgery,[2,31,32] and around 44–48% are totally seizure-free in the longer term.[1,32] A recent review reported that the median of seizure freedom across noncontrolled observational studies was 62.5%.[33] In a review of studies with >5 years of follow-up, 66% of patients were seizure-free at the last reported follow-up after temporal lobe surgery; in studies with >10 years of follow-up, the 45% were seizure-free.[34] In one of the two randomized controlled trials, 64% of operated patients were free of seizures that impaired awareness 1 year after a temporal lobectomy, and 42% were free of all seizures.[3] In the other randomized controlled trial, 11 (73%) of the 15 operated patients were free of disabling seizures after 2 years, versus 0% in the medical group.[35] The proportion of seizure freedom found in our medical group (12.3%) is consistent with that reported in two literature reviews.[1,36] Comparison of our study population with patients admitted to the same center

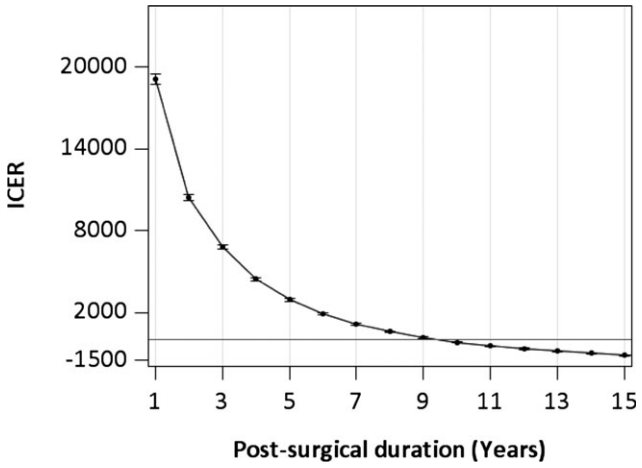


**Figure 4.**
Incremental cost-effectiveness ratio (ICER) according to post-surgery duration, estimated from Monte Carlo simulation based on a Markov model. The ICER, representing the extra cost paid for each extra year without seizures gained by using the surgery instead of medical care continuation, was calculated taking into account direct medical costs.


during the same period showed no significant difference, suggesting that the good results of surgery were not due to a selection bias (data not shown).

Several cost-effectiveness evaluations of drug-resistant partial epilepsy have been conducted. One study was carried out in 1995 in Canada on current and literature data, with an intention-to-treat approach, that is, each evaluated patient, undergoing surgery or not, was analyzed in the surgical arm.[17] The incremental cost-effectiveness ratio was not calculated, but cumulated direct costs of each strategy were balanced after 9 years due to the decreased cost of AEDs in the surgical arm. A study conducted in 2002 using literature data simulated direct and indirect costs, taking the disappearance of seizures—with or without aura—as an effectiveness criterion.[16] Direct costs of the two strategies balanced each other 14.4 years after surgery and direct medical costs after 35 years of treatment. Direct nonmedical costs including special education, transportation, and residential care represented 56% of direct costs, which could explain the difference in time needed to balance costs between the two arms. These two studies are comparable to the present one, with the same effectiveness criterion and approximately the same costs included in the analysis, even if estimated retrospectively and in different health pre-surgical care systems. The time needed to reach balance between the two strategies was much longer in the Platt and Sperling study than in the present one. However, Wiebe et al. obtained results comparable to ours.

A multicenter study conducted in the United States during the same period as our study, showed in 68 patients much higher costs due to higher health pre-surgical care prices in the United States.[6,37] The only benefits concerned seizure-free patients, with a significant decline in costs of AEDs from the second year after surgery.

As regards indirect costs, the present study did not show a significant improvement in occupational activity in the surgical arm after 5 years of follow-up. However, it is difficult to draw conclusions regarding this outcome because of insufficient patients and follow-up. In a recent study evaluating 369 patients who had anterior temporal lobectomy for refractory epilepsy with a mean follow-up of almost 10 years, as well as in a recent systematic review of the literature, employment and driving status were improved after surgery and were positively correlated with seizure freedom.[38,39]

In a modeling study, Platt and Sperling found that at 10 years, reduction in indirect costs related to unemployment was 31% in the surgical group compared with the medical group.[16,40] The total costs—direct and indirect—were lower in the surgical group versus the medical one after 7.3 years, whereas direct costs were lower in the surgical group after twice this period of time. This study showed that production losses influence conclusions.

One limitation in most studies comparing surgical and medical treatments in epilepsy is lack of randomization, mainly for ethical reasons. Only two teams succeeded in implementing a randomized controlled study, but in the first one the follow-up was only 1 year, so that patients of the medical group could benefit from surgery when necessary,[3] and in the second one the surgery group included only 15 patients with a 2-year follow-up.[35] However, in our study, inoperable patients (group 3) were not included in the analysis, so as to limit indication bias: only patients who could benefit from both surgical and medical treatments were analyzed. Another limitation was sample size, which was small to enable conclusions to be drawn regarding secondary outcomes such as occupation.

The costs evaluation was based on information collected with a self-report questionnaire, which can generate recall bias. To limit this bias, the patient had to complete a notebook between the visits, and different sources of information were used as the general practitioner or the neurologist and the medical record. So, in our approach, the two groups to be compared were affected by a similar bias, which was relatively limited. Five-year outcomes were jeopardized because of frequent losses to follow-up. We encountered more difficulties in the medical group because patients were referred to a tertiary center for presurgical assessment, but if the intervention was refuted, most of them were followed by their private neurologist and did not come back to the center that included them in the study. Much effort has been developed to monitor these patients through their general practitioner or their private neurologist, and most of them had persistent seizures. Another difficulty was that, for some patients, surgery was temporarily postponed for several months to 1 or 2 years to test new AEDs or deepen explorations, which significantly increased the expected duration

of the study with an increased risk of loss to follow-up, particularly seizure-free patients out of the care system. Thus, the attrition bias would be rather at the expense of the surgical arm.

The results of the present study confirm those obtained in other countries.[16,17] Although this is an observational cohort study, it clearly shows the value of surgery in partial drug-resistant epilepsies, from clinical and economic points of views. Given the very good results of epilepsy surgery and its cost-effectiveness, adequate means should be implemented to develop this surgery, which is too often limited to the most severe cases. According to the results of the survey of Devaux et al.,[41] approximately 400 patients (including >100 children) underwent epilepsy surgery yearly in France from 2003 to 2008. The needs are therefore not fully covered to date in France. The proportion of noncontrolled epilepsy with at least one seizure per month for 18 months was estimated at 15.6% in a prevalence study,[42] and the localization-related epilepsy is around 60%. With an annual incidence of 50 per 100,000, among the 30,000 new cases per year, 3,000 patients could benefit from presurgical explorations and surgery would be indicated in 25–50% of them, corresponding, in theory, to 750–1,500 additional cases per year.

However, it is necessary to encourage physicians to consider a surgical strategy earlier. To limit or avoid psychological and social handicap related to frequent seizures, surgery should not remain a therapeutic last resort. Good candidates for surgery should be identified early and addressed to specialized centers as soon as drug resistance occurs.

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## Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Schematic structure of the Markov model.

**Figure S2.** ICER calculated with varying discount rates (0% for undiscounted, 3% for base case approach, and 5% sensibility analysis).

**Figure S3.** ICER calculated with varying costs of surgery with the presurgical explorations (costs equal to IQ25: 15,060 €, mean: 21,517 € for base case approach, and IQ75: 26,875 €).

**Figure S4.** ICER calculated with lower 95% CI of the probabilities of state transition from seizure with treatment (state 1, s1) to seizure-free with treatment (s2) in surgical group.

**Figure S5.** Tornado diagram for the ICER at 5 years.

**Table S1.** Annual direct medical and nonmedical costs at inclusion and during follow-up in surgical and medical groups (€).

**Table S2. (a)** Discounted and undiscounted cumulative costs from 1 to 5 years follow-up in each group (10,000 simulated patients). **(b)** Discounted and undiscounted cumulated differences in costs and in efficacy and value of ICER from 1 to 5 years follow-up (10,000 simulated patients).

**Table S3.** Patients' occupation at inclusion and during follow-up.