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Evaluation for epilepsy surgery – Why do patients not proceed to operation?

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ABSTRACT

Purpose: To investigate the reasons for not proceeding to surgery in patients undergoing presurgical evaluation for epilepsy.
Methods: A retrospective cohort study of 401 consecutive patients who were evaluated for but did not proceed to surgery for epilepsy between 1990 and 2016 at three Swedish epilepsy surgery centers was performed. Reasons for not proceeding to surgery were categorized as inconclusive investigation, seizure onset within eloquent cortex, evidence of multiple seizure foci, infrequent seizures, risk of postoperative severe cognitive decline, patient or caregiver declining surgery or invasive investigation, severe psychiatric or somatic comorbidity, patient death during evaluation and complications during the evaluation. Chi-square tests were performed to compare ordered categorical variables.
Results: During the entire time period the main reasons for rejection were inconclusive investigation (34,4%) and multifocal seizure onset (20,0%). The risk for severe cognitive decline postoperatively was more often a cause for rejection in more recent years. Patients declining invasive EEG or surgery accounted for a minor but not insignificant proportion (14,2%) of rejections.
Conclusions: Inconclusive results from the presurgical evaluation and multifocal epilepsy were the main causes for not proceeding to surgery. The proportion of patients opting to abstain from surgery was low compared to other recent studies.

1. Introduction

Surgical treatment for epilepsy is an effective and safe procedure for selected patients in drug resistant focal epilepsy. [1–3] The presurgical evaluation is time consuming and costly and entails a multidisciplinary approach including neuroimaging, video-EEG recordings, neuropsychiatric assessment and neuropsychological assessment. Recent studies have demonstrated the cost-effectiveness and health economic gains of successful surgery [4]. Most studies of epilepsy surgery focus on the outcome of patients who proceed to surgery. Studies specifically addressing the reasons for not performing epilepsy surgery are scarce. Such studies are of importance for health economic analyses and for counselling before an operation. The proportion of evaluated patients not proceeding to epilepsy surgery varies substantially between studies. Fois et al. reported that two-thirds had not proceeded to surgery in a consecutive cohort of patients [5]. In a retrospective study by Mansouri et al. just over half of the patients did not undergo surgery [6]. In contrast, in a large retrospective study by Cloppenborg et al. surgery was not performed in one-third of patients [7]. The main reasons for not proceeding to surgery in these studies were inconclusive findings, inability to define the epileptogenic zone, presence of multiple foci, and patient (or caregiver) declining surgery. Overlap between the epileptogenic area and eloquent cortex was less often reported as a reason for refraining from surgery. Patients declining to undergo invasive investigation and surgery seems to be a rather frequent reason, ranging from 21,3% to 42,0% in the abovementioned studies [5–7].

Regardless of increasing numbers of presurgical evaluations, recent studies have reported a decrease or stable numbers of resective surgeries over the last two decades. [7–9] Our aim was to analyse the reasons for not proceeding to invasive evaluation and therapeutic surgery in a multicenter, population-based cohort from three Swedish epilepsy centers.

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2. Methods

2.1. Patients

Data was obtained from the Swedish National Epilepsy Surgery Register (SNESUR), which is a prospective nationwide register including all epilepsy surgery procedures performed since 1990. [3] We invited all six Swedish epilepsy surgery centers and three centers (Gothenburg, Lund, Uppsala) accounting for majority of surgical procedures (˜70%) were able to participate. We analyzed data from 401 consecutive adults (≥18 years) who underwent presurgical investigations without proceeding to surgery from January 1990 to December 2016. We included patients who had been discussed and accepted for surgical evaluation at a multidisciplinary team (MDT) conference. Patients were excluded if nonepileptic seizures were detected or if major part of the investigation had been performed in another hospital. The study period was divided into three time periods, 1990–1998, 1999–2007 and 2008–2016, to determine if there were any significant differences over time.

2.2. Data collection

Demographic and investigational data included age; sex; mean monthly seizure frequency during the year preceding the presurgical investigation; anti-epileptic drug (AED) treatment; the results from EEG, MRI, fMRI (functional MRI), FDG-PET (fluorodeoxyglucose-positron emission tomography), and SPECT (single-photon emission tomography); and presence or not of neurological, intellectual or neuropsychiatric disability. When MRI showed presence of an epileptogenic pathology congruent with the seizure semiology it was denominated “localizing”. Functional neuroimaging was considered “localizing” when congruent with other modalities (semiology, MRI or ictal EEG). The decision to offer or not to recommend surgery was made at a MDT conference (MDT neurologists, neurophysiologist, neurosurgeons, neuroradiologists, neuropsychologist). The reasons for not proceeding to surgery or invasive evaluation were documented at the MDT conference. For this study, the reasons were retrospectively categorized into nine groups.

The categories were inconclusive investigational results, evidence of multiple foci, seizure onset within eloquent cortex, risk of severe postoperative cognitive decline, patient’s or caregiver’s decline of invasive investigation, patient’s or caregiver’s decline of surgery, infrequent seizures; complications during the evaluation, patient deceased, or severe somatic and psychiatric comorbidity. The investigation was considered inconclusive when the clinical, neuroradiological and/or neurophysiological findings were discordant or when there was no localizing information. The risk of postoperative cognitive decline was based on baseline neuropsychological test results in relation to findings on neuroimaging.

2.3. Statistics

For comparisons between two groups, a Chi-square test was performed for ordered categorical variables. Bonferroni correction was used to reduce the probability of type I errors that resulted from multiple comparisons. In the case of expected frequencies less than 5, Fisher’s exact test was used to determine the significance level. All tests were conducted at the 5% significance level. Statistical analyses were performed using IBM SPSS Statistics 24 (Armonk, New York, USA).

2.4. Ethics

This study was approved by the Regional Board of Medical Ethics at the University of Gothenburg.

Table 1
Baseline data of the nonoperated patients. Values are n (%), mean (SD) or median (range). Abbreviation: AED = antiepileptic drug.

Characteristics	n (%, mean ± SDs or median (Range)
Female sex	209 (52,1 %)
Age at the start of the investigation	34,4 ± 11,9, 33,0 (18-70)
Disability	
Neurological	55 (13,7 %)
Intellectual	118 (29,4 %)
Neuropsychiatric	13 (3,2 %)
Any disability	160 (39,9 %)
Prior neurosurgery	51 (12,7 %)
Prior epilepsy surgery	25 (6,2 %)
Number of AED trials at the start of the investigation	
1-2	40 (10,2 %)
3 or more	354 (89,8 %)
Missing data	7 (1,7 %)
Seizure type and frequency	
Focal with preserved awareness	100 (24,9 %), 28,7 ± 58,4, 11,0 (0,1-500)
Focal with impaired awareness	279 (69,6 %), 14,8 ± 35,1, 5,0 (0,1-380)
Focal to bilateral tonic-clonic	156 (38,9 %), 6,8 ± 23,1, 1,0 (0,1-160)
Mean seizure frequency	21,6 ± 46,3
Not classified	5 (1,2 %)
Missing data	2 (0,5 %)

3. Results

3.1. Patient characteristics

A total of 401 nonoperated patients (n = 209, 52,1% female) were included. The number of operated patients at the three centers during the study period was 619, consequently 39,3% of the investigated patients did not proceed to surgery. The mean age was 34,4 years (± 11,9 SD), the mean seizure frequency per month was 21,6 ± 46,3, and the median seizure frequency was 7,0 (range 0,1–504). Three hundred and fifty-four (89,8%) patients had been treated with 3 or more AEDs (Table 1).

3.2. Investigational characteristics

All patients were investigated with EEG and MRI. Functional neuroimaging was performed in 194 (48,4%) patients. 119 (29,7%) had SPECT, 98 (24,4%) had FDG-PET and 31 (7,7%) had fMRI investigations. MRI was localizing in 118/401 (29,5%), FDG-PET and/or SPECT in 61/189 (32,2%). Ictal EEG was localizing in 132 (33,0%) patients. Intracranial EEG registration was performed in 94 (23,4%) patients. The investigational characteristics are further described in Table 2.

3.3. Main reasons for abstaining from surgery

The most common reason for not proceeding to surgery was inconclusive investigation, comprising 138 (34,4%) patients. Other reasons were multiple foci (80 patients, 20,0%), patients declining surgery (38 patients, 9,5%), infrequent seizures (38 patients, 9,5%), risk of postoperative severe cognitive deterioration (36 patients, 9,0%), and seizure onset within the eloquent cortex (35 patients, 8,7%). Less common reasons were patient abstaining from invasive investigation (19 patients, 4,7%), severe somatic comorbidity (7 patients, 1,7%), patient deceased during evaluation (6 patients, 1,5%), severe psychiatric comorbidity (4 patients, 1,0%), and complications from evaluation (1 patient, 0,2%).

In total, risk of severe cognitive decline was the reason for rejection

Table 2
Investigational characteristics divided into the three time periods. All patients had EEG and MRI.

		1990–1998	1999–2007	2008–2016	Total
FDG-PET investigation	n (%)	20 (22,5 %)	37 (26,1 %)	41 (24,1 %)	98 (24,4 %)
SPECT investigation	n (%)	56 (62,9 %)	24 (16,9 %)	39 (22,9 %)	119 (29,7 %)
fMRI investigation	n (%)	1 (1,1 %)	7 (4,9 %)	23 (13,5 %)	31 (7,7 %)
Intracranial EEG investigation	n (%)	34 (38,2 %)	30 (21,1 %)	30 (17,6 %)	94 (23,4 %)
Localizing MRI	n (%)	15 (16,9 %)	52 (36,9 %)	50 (29,4 %)	117 (29,3 %)
Localizing functional imaging	n (%)	19 (25,7 %)	23 (39,7 %)	19 (30,6 %)	61 (31,4 %)
Localizing ictal EEG	n (%)	24 (27,0 %)	42 (29,6 %)	52 (30,6 %)	118 (29,4 %)

Table 3
The main reasons for not proceeding to epilepsy surgery in the three time periods. *The risk of severe cognitive decline as a reason for not proceeding to surgery was more frequent in 2008–2016 than in 1999–2007, p = 0,007. After adjustment for Bonferrroni correction for three pairwise comparisons p = 0,021.

		1990–1998	1999–2007	2008–2016	Total
Inconclusive investigation	n (%)	30 (33,7 %)	47 (33,1 %)	61 (35,9 %)	138 (34,4 %)
Seizure onset within eloquent cortex	n (%)	8 (9,0 %)	15 (106 %)	12 (7,1 %)	35 (8,7 %)
Evidence of multiple foci	n (%)	23 (25,8 %)	30 (21,1 %)	27 (15,9 %)	80 (20,0 %)
Infrequent seizures	n (%)	7 (7,9 %)	16 (11,3 %)	14 (8,2 %)	37 (9,2 %)
Risk of postoperative severe cognitive decline	n (%)	8 (9,0 %)	6 (4,2 %)*	22 (12,9 %)*	36 (9,0 %)
Patient/caregiver declining surgery	n (%)	6 (6,7 %)	13 (9,2 %)	19 (11,2 %)	38 (9,5 %)
Patient/caregiver declining invasive investigation	n (%)	2 (2,2 %)	7 (4,9 %)	10 (5,9 %)	19 (4,7 %)
Severe psychiatric comorbidity	n (%)	1 (1,1 %)	2 (1,4 %)	1 (0,6 %)	4 (1,0 %)
Severe somatic comorbidity	n (%)	1 (1,1 %)	3 (2,1 %)	3 (1,8 %)	7 (1,7 %)
Patient deceased during evaluation	n (%)	2 (2,2 %)	3 (2,1 %)	1 (0,6 %)	6 (1,5 %)
Complications from evaluation	n (%)	1 (1,1 %)	0 (0,0 %)	0 (0,0 %)	1 (0,2 %)
Total	n	89	142	170	401

significantly more often in 2008–2016 (22 patients, 12,9%) than in 1999–2007 (6 patients, 4,2%), p = 0,007. After adjustment for Bonferrroni correction for three pairwise comparisons p = 0,021. No other significant difference was seen over time regarding the main reason for rejection (see Table 3).

Patients with a nonlocalizing MRI were more often rejected due to inconclusive investigation (114 patients, 40,3%) compared to patients with a localizing MRI (24 patients, 20,5%), p < 0,001. Corresponding findings were seen in patients with a nonlocalizing interictal and ictal EEG and rejection due to inconclusive investigation (interictal EEG, 112 patients, 41,8% compared to 26 patients, 19,7% and ictal EEG, 118 patients, 41,7% compared to 20 patients, 16,9%), p < 0,001.

Patients evaluated invasively were less often rejected because of inconclusive investigation in comparison to patients with only extracranial evaluation (23 patients, 24,5% compared to 115 patients, 37,5%), p < 0,05. They were more frequently rejected due to overlap between the epileptogenic area and eloquent cortex or multifocal seizure onset (overlap with eloquent cortex; 13 patients, 13,8% vs. 22 patients, 7,2% and multifocal epilepsy; 35 patients, 37,2% vs. 45 patients, 14,7%), p < 0,05 and p < 0,001, respectively.

Patients who declined surgery had a lower initial mean seizure frequency compared to patients rejected for other reasons (9,7 vs. 22,8 seizures per month), p < 0,01.

4. Discussion

In this study, the aim was to investigate the main motives for not proceeding to epilepsy surgery in patients undergoing presurgical evaluation. The most frequent reason was inconclusive investigation (34,4%) followed by multifocal seizure onset (20,0%). This is in line with other studies reflecting the knowledge that inconclusive investigations reduce the chance of successful surgery. [10,11] During the study period, the proportion of inconclusive cases remained stable. In a large European study comparing epilepsy surgery between 1997–1998 and 2012–2013, the postsurgical seizure outcome had improved despite increasing complexity of procedures. This finding suggests improvement of investigational methods, possibly reducing the number of inconclusive investigations. However, the number of rejected patients in the European study is not reported [12].

Among the 1020 patients undergoing epilepsy surgery investigation at the three centers during the time period January 1990 to December 2016, 60.7% proceeded to operation. This proportion is compatible to the study by Cloppenborg et al. (66,8% operated) but differs substantially from the reported proportions by Mansouri et al. (48,7% operated) and Fois et al. (33,3% operated)· [5–7] Cloppenborg et al. proposed that increasing thoroughness over time when counselling about potential surgical risks might have been a driving factor for the increasing gap between increased presurgical volumes and decreased number of surgeries. [7] In this register-based study we have not been able to explore this in detail, although we acknowledge that also in our centers counselling has developed and includes much more factual information about potential adverse effects. Different selection criteria for offering presurgical work-up may result in increasing or decreasing numbers of patients declining epilepsy surgery and may also be an explanation for the differences between the numbers of rejections.

In Sweden there are recommendations for neurologists concerning whom to consider for epilepsy surgery evaluation. According to these, patients with focal epilepsy who have failed two adequate and well-tolerated AEDs should be referred to an epilepsy specialist center. Conversely, we have no specific criteria for selecting which patients who should proceed to presurgical investigation. To our knowledge, there are no validated criteria for entering presurgical evaluation and this decision is individualized.

The question on how to best select patients who will benefit from invasive investigation is problematic. In our study, inconclusive investigation was a frequent cause for rejection, second only to multifocal seizure onset in patients who underwent invasive monitoring with intracranial EEG-electrodes. In comparison, Fois et al. found that seizure onset within eloquent cortex followed by multifocal epilepsy were the predominant reasons for rejection in this subgroup of patients. [5] The use of intracranial EEG was more frequent in the first time period compared to the second and third (38,2% vs. 21,1% and 17,6% respectively). An important reason for this difference is probably the improvement and increased availability of neuroimaging and other technical modalities. Furthermore, over the duration of the study period, the notion of whom to offer epilepsy surgery may have evolved due to increased knowledge from evidence-based studies.

Intracranial EEG was used less often in the study by Fois et al.

compared to our study (14,2% vs. 23,4%). A more appropriate selection of candidates for invasive investigation might lead to less inconclusive results. To our knowledge, there are no systematic studies addressing prediction modeling for this selection. However, there are detailed descriptions of experience-based approaches. [13]

A finding that merits special attention is that during the study period, rejection from surgery because of risk of severe cognitive decline was more common in the period 2008–2016 compared to 1999–2007. During the last decade there has been more focus on trying to identify patients where the risk of a pronounced cognitive loss is not counter-balanced by good odds for seizure freedom. [14] This has probably influenced our counselling process.

In our study, patients declining intracranial EEG or surgery accounted for a minor but not insignificant proportion of the total population (14,2%). Other studies have reported this to be more frequent at 21,3% (Cloppenborg et al.) and 24,0% (Fois et al.). [5,7] An even higher proportion, 42,0% was reported by Mansouri and colleagues [6]. The reasons for patients to refrain from surgery are probably multifactorial. The estimated chances of a good seizure outcome based on the presurgical evaluation should be weighed against the risk of any adverse outcome and patients have varying priorities. The way risk information is presented may also influence patients´ informed decision making. A number of methods have been empirically shown to improve patients´ understanding of risk and benefit information and/or their decision making. Introducing such methods could be one way to improve counselling [15]. Seizure frequency may have an impact on the decision to proceed to surgery. In this study, patients opting against surgery had a significantly lower initial mean seizure frequency than patients rejected for other reasons. However, the seizure frequency in this population was notably variable, with a range of 0,1–500 seizures per month. Therefore, the impact of seizure frequency is hard to establish. There is clearly a need to explore the specific motives of individual patients who decline surgery to make the best use of limited resources and to optimize the information and counselling to patients [16].

Thirty-seven (9,2%) patients were rejected because of infrequent seizures. In any epilepsy population pharmacoresistance can vary over time, which explains this proportion of withdrawals during the investigation. [17] However, even in cases with infrequent seizures but otherwise straightforward investigation, surgery might be an option. Seven patients (1,7%) had severe somatic comorbidity. This was not identified at the initiation of the investigation, but became obvious during evaluation *e.g.* cognitive deterioration, neurosarcoidosis, supervening cerebrovacular disease.

Our study has the limitations normally associated with retrospective investigations. It is heavily reliant on the data entered into the register (SNESUR) and data on potential confounding factors may be lost. Furthermore, the study population may be too small to detect differences over time regarding the reasons for rejection. The study is not population based since all operating centers were not represented. However, in Sweden, we work closely together in the epilepsy surgery network with regular case discussions and the non-participating centers have similar presurgical programs. A major advantage of the study is the consecutive recruitment of patients from regional referral within each operating center and the prospectively collected baseline data, minimizing sources of sampling bias and also allowing some generalizability of the results.

Patients who did proceed to operation were not included in this study. An opportunity for future research would be to use operated patients as a comparison group to discover factors that could reduce the number of patients who will ultimately be rejected for surgical treatment after a comprehensive workup.

In conclusion, we found that inconclusive evaluation and multifocal seizures were the prevailing causes for not proceeding to operation. The likelihood of not performing surgery because of risk of severe cognitive decline was higher in the later time period. The proportion of other possible reasons did not change over time. The number of patients abstaining from surgery was small, but not insignificant and merits further investigation.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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