Z. Epileptol. 2020 · 33:50–61
<https://doi.org/10.1007/s10309-019-00302-x>
Published online: 7 January 2020
© The Author(s) 2019

Friedhelm C. Schmitt^{1,2} · H.-Joachim Meencke²

¹ Department of Neurology, University Otto-von-Guericke, Magdeburg, Germany

² Epilepsy Center Berlin Brandenburg at Ev. Krankenhaus Königin Elisabeth Herzberge, Teaching Hospital, Humboldt University, Berlin, Germany

Factors predicting 10-year seizure freedom after temporal lobe resection

A monocentric, continuous extra-long-term evaluation

Introduction

For patients with pharmacoresistant temporal lobe epilepsy (TLE), resective surgery has become a widely accepted, evidence-based, and advised [9] procedure to obtain seizure freedom. Cure, i.e., seizure freedom without medication, is a major motivation for patients to undergo presurgical evaluation [3, 37]. For a putative beneficial, yet irreversible, surgical procedure, prognostic factors based on long follow-up periods enhance the quality of patient counseling substantially.

The only randomized controlled study by Wiebe [42] has a follow-up period of 1 year. More than a decade later the Early Randomized Surgical Epilepsy Trial [8] added 2-year follow-up data, which supported the beneficial role of resective surgery compared with medical treatment. Yet, the study was prematurely finalized because of its slow recruitment rate. Studies using meta-analyses of several cohort studies [33, 38, 39], retrospective data acquisition in larger cohorts over a long time period [1, 20, 23, 27, 40], or statistical modeling methods [4] circumvented this recruitment matter.

In single-center studies, seizure freedom rates for anterior lobe resection vary between 58% after 1 year in 80 patients [42], to 59% after 2 years in 70 patients [1] and 55% after 5 years in 407 patients [40]. The last study is important because

of the large patient number and the long follow-up period of 5 years. Interestingly, similar results were reported for lesionectomies in this cohort (56%; [40]) and slightly lower rates for stereotactic laser thermoablation, a method increasingly used in North America [5, 19] because of its limited invasiveness in TLE (1-year follow-up, including repeat surgery, 53% [16] and 58% [44]).

Summarizing cohort studies (mono- and multicentric, retrospective and prospective data acquisition) in TLE:

1. In shorter follow-up periods, seizure outcome seems to be less dependent on the surgical method (2–5 years). These findings have been replicated for TLE for longer follow-up periods (e.g., [17]), even though there is a tendency for larger removal to be beneficial [21].
2. There is a constancy in the decrease in the rate of seizure-free patients with the time of follow-up, which progresses slower over the years.

Tellez-Zenteno et al. summarized the results of 40 studies with a mean/median follow-up period of at least 5 years: In almost 3900 TLE patients, the seizure-free rate of the last follow-up was 66% (independent of the surgical method; [39]). This number evidently summarizes the postsurgical seizure outcome of TLE patients with very variable follow-up periods and is, therefore, difficult to use for

patient counseling. It is, however, important for comparison with other epilepsy syndromes.

So far, the majority of observational seizure outcome studies do not focus on extended follow-up periods [28, 39], i.e., at least 5 years or even longer periods. It seems inevitable, therefore, that these studies report heterogeneous results [28, 33, 39] concerning the factors predicting seizure freedom. Interestingly, a cohort study by Janszky et al. [20] showed that prognostic factors may vary in the time course of the follow-up period [7].

The cohort of the present extra-long-term follow-up study has particular robust features such as a limited recruitment period of 5 years and successive, annual data acquisition for 10 years. The aim of this study was to determine prognostic factors for continuous seizure freedom over this period, with a particular focus on the time course of seizure freedom.

Methods

Subjects

The study group comprised 60 patients who underwent consecutively resective surgery for TLE over a period of 60 months beginning 1 March 1993 to 28 February 1998 at the Epilepsy Center Berlin-Brandenburg, Germany. Patients were not offered presurgical evaluation

Fig. 1 Summary of patient cohort

if they were not pharmacoresistant to at least one antiepileptic drug (AED) for a period more than 1 year. Patients with brain lesions requiring instant surgery, active severe psychiatric comorbidity, or a full-scale IQ lower than 70 were excluded. All patients underwent a standardized presurgical work-up including inpatient surface electroencephalographic (EEG) monitoring (10–20 system up to 32 electrodes, usually for 7 days), standardized epilepsy-specific magnetic resonance imaging (MRI; 1.5T), neuropsychological testing, psychiatric and social assessment. All findings were discussed in a multidisciplinary case conference, after which conclusions about the eligibility for resective surgery or further diagnostic steps were drawn. If considered necessary, additional diagnostic investigations were added (interictal positron emission tomography [PET], single-photon emission computed tomography [SPECT], Wada test, dichotic hearing test, or EEG

monitoring with foramen ovale/peg- or subdural grid-electrodes). Surgery was performed by two board-certified neurosurgeons (JNL or WRL). Surgical pathology was analyzed routinely. A neurological examination and a cranial computer tomogram scan were performed 1 day after surgery.

Study design

Complete medical history and current seizure frequency, seizure type, AEDs, potential adverse effects (AE), and non-adherence (NA) were assessed before the surgical intervention. During out-patient visits 6 months, 12 months, and annually after surgery, these parameters and the seizure outcome, defined by Engel's classification of postsurgical outcome [10], were followed up prospectively. The classification of the International League Against Epilepsy (ILAE; [43]) by Wieser et al. was not available at the beginning of this study. Seizure

types were classified according to the ILAE classification that was current at the time of data acquisition [47]. Seizures occurring less than 4 weeks after surgery were classified as perioperative as opposed to recurrence of seizures after this time period. Presurgical AEDs were continued after surgery for at least 2 years. Only in the case of AE or unprovoked recurrence of seizures was the dosage adjusted or an additional AED prescribed. Patients documented seizure-like events in seizure diaries and detailed oral descriptions were obtained from patients and, if possible, from witnesses during the yearly follow-up visits. If previous and current EEGs were not suggestive of an active epileptogenic focus, tapering of one AED for one third of the daily dosage was allowed. To minimize an observational bias error, all patients were seen by at least four of the following five certified epileptologists: CD, HJM (author), MM, FCS (author) and HBS. If a pre-scheduled follow-up (FU) visit failed, a semi-structured telephone interview was conducted and a new visit was scheduled.

Primary outcome was seizure freedom over a period of 10 years. The authors defined a “successful” surgery if the patient's condition was continuously classified as Engel Class I for this observation period. This approach was chosen because even rare seizure recurrence can be considered a failure in view of the high psychosocial impact of the seizures themselves.

Secondary outcome was the perpetuation of the individual patient's seizure class. To analyze the course of seizure freedom, patients were subdivided into five groups:

- Group 1 = “successful” surgery = retention of Engel Class I for the 10 years
- Group 2 = “running down” = continuous enhancement of seizure outcome with subsequent achievement of Engel Class I
- Group 3 = “running up” = initially Engel Class I, with successive worsening
- Group 4 = “mixed” = within the 10 years FU, at least 1 year of Engel Class I
- Group 5 = no seizure freedom for 10 years = Engel Class II–IV.

F. C. Schmitt · H. Meencke

Factors predicting 10-year seizure freedom after temporal lobe resection. A monocentric, continuous extra-long-term evaluation**Abstract**

Background. Resective surgery is an established and evidence-based treatment approach in pharmacoresistant temporal lobe epilepsy (TLE). Extra-long-term follow-up data are important to allow for good patient counseling. So far, only few trials provide prospective or retrospective data exceeding 5 years.

Objective. This study aimed to present data of continuous seizure outcome over an extended time period, with a particular focus on patients who remained seizure free for 10 years.

Methods. We analyzed seizure outcome after epilepsy surgery for TLE in 46 consecutive patients, who were seen on an annual basis

for 10 years in a single center (Epilepsy Center Berlin Brandenburg). Factors for remaining seizure free for 10 years were determined by univariate analysis.

Results. The class I outcome changed each year by 74–78%. Of the patients, 63% remained continuously in Engel class I (48% Engel Class IA for 10 years) for 10 years. Six patients were never seizure free (12.5%). After 10 years, 35% of the patients were cured (i.e., seizure-free without medication). A higher number of antiepileptic drugs and seizures before surgery as well as the indication for invasive presurgical monitoring were associated with “unsuccessful surgery.”

Conclusion. With almost half of the patients completely seizure free and more than a third “cured,” epilepsy surgery remains the mainstay of therapy for TLE patients. Analysis in larger cohorts with extra-long-term follow-up is needed to assess good prognostic factors and other postsurgical outcome issues such as neuropsychological, psychiatric, and psychosocial outcomes.

Keywords

Epilepsy · Long-term follow-up · Seizure outcome · Resective · Cure

Prognosefaktoren einer 10-Jahres-Anfallsfreiheit nach Temporallappenresektion. Eine monozentrische, kontinuierliche Extra-Langzeituntersuchung**Zusammenfassung**

Hintergrund. Die resective Epilepsiechirurgie ist ein etabliertes Verfahren zur Behandlung der pharmakoresistenten fokalen Epilepsie mit Ursprung im Temporallappen (TLE). Extra-Langzeitverlaufsdaten sind wichtig für eine gute Patientenberatung, allerdings sind bislang nur wenige prospektive oder retrospektive Untersuchungen mit einem Beobachtungszeitraum von länger als 5 Jahren publiziert worden.

Ziel der Arbeit. Ziel war die Präsentation der Ergebnisse bzgl. der Anfallsfrequenz bei operierten TLE-Patienten über einen längeren Zeitverlauf mit einem besonderen Schwerpunkt auf den Patienten, die über mindestens 10 Jahre anfallsfrei waren.

Material und Methoden. Die Autoren analysierten Daten zum Anfalls-Outcome von 46 aufeinanderfolgenden Patienten mit

Zustand nach Resektion, welche jährlich in einem tertiären Epilepsiezentrum (Epilepsie-Zentrum Berlin-Brandenburg) untersucht wurden. Faktoren für eine 10-jährige Anfallsfreiheit wurden durch eine univariate Analyse bestimmt.

Ergebnisse. In jedem einzelnen Jahr schwankte der Anteil von anfallsfreien Patienten zwischen 74 und 78 %. Während des gesamten Beobachtungszeitraums von 10 Jahren verblieben 63 % der Patienten in der Engel-Klasse I und 48 % in der Engel-Klasse IA. Kein Jahr mit Anfallsfreiheit wurde bei 6 Patienten (12,5 %) festgestellt. Nach 10 Jahren waren etwa 35 % der Patienten „geheilt“ (d. h. anfallsfrei ohne antiepileptische Behandlung). Eine erhöhte Anzahl von Antiepileptika oder Anfällen vor der Operation und die Indikationsstellung für

ein invasives Verfahren waren signifikante Faktoren für eine nicht erfolgreiche Operation.

Schlussfolgerung. Das Ergebnis von fast 50 % komplett anfallsfreien und mehr als ein Drittel „geheilte“ Patienten belegt, dass die Epilepsiechirurgie eine wichtige therapeutische Maßnahme bei pharmakoresistenter TLE ist. Analysen von größeren Kohorten mit einem Extralangzeitverlauf sind notwendig, um relevante Faktoren für das Ziel „Anfallsfreiheit“ und andere Parameter aus neuropsychologischen, psychiatrischen und psychosozialen Befunden bestimmen zu können.

Schlüsselwörter

Epilepsie · Langzeitverlauf · Anfalls-Outcome · Resektiv · Heilung

Patient selection is delineated in **Fig. 1** and detailed data, before presurgical evaluation (e.g., clinical details and etiology according to MRI), the mode of presurgical and surgical procedures (e.g., surface vs. invasive monitoring; resection methods) of the patient cohorts are summarized in **Table 1**.

The analyzed variables obtainable before and after the presurgical evaluation and after surgery are summarized in **Table 2**. They were chosen according

to the generally accepted decision process for resective surgery. Presurgical occurrence of auras and focal to bilateral tonic-clonic seizures were regarded as a separate variable. For baseline seizure frequency, focal impaired awareness seizures (according to ILAE classification from 1981: complex partial seizures) and focal to bilateral tonic-clonic seizures (according to ILAE classification from 1981: secondarily generalized seizures) from the last 3 months prior to surgery

were averaged. The authors consider the term “aura” as important in the context of epilepsy surgery, therefore they will use “aura” in this manuscript, even though the current classification [12–15] would classify this seizure-type as “focal aware seizure.” Electroclinical, neuropsychological, psychiatric, and social outcome parameters are not addressed in this study.

Table 1 Clinical details of whole cohort (including extratemporal lobe epilepsies) and of study group (only temporal lobe epilepsies without re-resection)

		All = 67		Study group = 46	
		Mean	SD	Mean	SD
Minimum follow-up		9.2	2.5	10.3	0.1
Sex	Female	33	–	25	–
Age	Age at surgery	30.5	12.7	2.4	12.5
	Younger than 18	16	–	9	–
	Epilepsy duration	17.6	13.4	19.3	13.8
	First seizure	13.2	9.8	13.0	10.3
Side	Left	38	–	26	–
Location	FLE	4	–	0	–
	Multifocal epilepsy	3	–	0	–
	mTLE	32	–	26	–
	Temporal epilepsies (other)	28	–	20	–
Invasiveness	Surface	43	–	27	–
	Peg/foramen ovale electrode	5	–	4	–
	Grids	19	–	13	–
OP region	Temporo-anterior	46	–	37	–
	Temporo-lateral	9	–	7	–
	Temporal others	5	–	2	–
	Frontal	6	–	0	–
OP procedure	Hemispherical	1	–	0	–
	aTLR	52	–	40	–
	aTLR extended	3	–	3	–
	Lesionectomy	5	–	1	–
	Partial cortectomy	2	–	1	–
	Partial frontal lobectomy	2	–	0	–
PMHx	Others	3	–	1	–
	Febrile seizures	10	–	8	–
	Epilepsy in family	10	–	7	–
	Psychiatric illness	20	–	9	–
Seizure frequency		8.6	12.2	7.4	8.6
AEDs	No AED after 10 years	22	–	21	–
	Non-adherence	18	–	12	–
	Number in lifetime	3.6	1.9	3.6	1.8
Semiology	Auras	38	–	29	–
	BTCS	47	–	33	–
	SE	2	–	2	–

Statistical analysis

For the Kaplan–Meier event-free survival, curves were determined and differences between subgroups were evaluated with the generalized Wilcoxon test. Patient outcome was classified into “successful” surgery (Group 1) and “unsuccessful” surgery (Groups 2–5). Differences in metric variables between the “successful” surgery group vs. the cumulated “unsuccessful” surgery groups

were analyzed with the Mann–Whitney-U-test (non-parametric distribution) or Student’s *t*-test (parametric distribution). For multiple group comparison of metric variables, the Kruskal–Wallis-test with a post-hoc-Tamhane-test (non-parametric distribution) or a one-way ANOVA- with a post-hoc Tukey-test was used (parametric distribution). Categorical variables were compared with the chi-square- or Fisher’s exact-test. The Kolmogorov–Smirnov-test was used to

assess the parametric vs. non-parametric distribution. Differences were considered significant at $p < 0.05$. Data are given as mean $\pm$ SD. Statistical calculations were performed using PASW 19.0.

Results

Altogether, 60 consecutive patients (29 female, 48.3%) had surgery between 1 March 1993 and 28 February 1998. Surgical procedures comprised classic anterior or extended temporal lobe resection (91.7%), lesionectomy (5.0%), partial lobectomy or cortectomy (1.6%), and others (1.6%). A total of 37 patients (61.7%) had surgery on the left hemisphere. The age range was from 10 years to 57 years (mean 32.1 years, SD = 12.2).

Patients lost to continuous follow-up

One patient (1.7% of 60 TLE patients) died after the sixth follow-up visit. Death was unexpected and unexplained and therefore “sudden unexpected death in epilepsy” (SUDEP) was suspected. Post-surgical outcome had steadily been classified as Engel Class II before. One patient did not attend follow-up visits, since the first visit 6 months after surgery.

Continuous study participation failed in ten patients (16.7% of 60 TLE patients; [Fig. 1](#)). Seven (11.7% of 60 patients) of these patients attended follow-up visits for 2 years (details [Fig. 2](#)), so that a fairly robust approximation of seizure outcome was not available for the remaining three patients (5.0% of 60 TLE patients). The median continuous follow-up of the then patients lost to follow-up was 3.16 years (SD = 2.7), and five out of nine (55.6%) patients achieved Engel Class I at the last outcome visit ([Fig. 2](#)).

From the remaining 50 patients, a complete postsurgical follow-up could be obtained. If presurgical re-assessment was suggestive of possible improvement of seizure control by re-resection, patients were offered another resection. Therefore, four patients had to be excluded, because re-resection was per-

Table 1 (Continued)

		All = 67		Study group = 46	
		Mean	SD	Mean	SD
Etiology by MRI	HS	18	–	13	–
	FCD	8	–	5	–
	Cortical malformations (other)	8	–	7	–
	Oligodendroglioma	1	–	0	–
	Ganglioglioma	3	–	2	–
	DNET	3	–	2	–
	Hamartoma	4	–	3	–
	Tumor (other)	5	–	4	–
	Cavernoma, single	2	–	1	–
	Cavernoma, multiple	2	–	1	–
	Posttraumatic	1	–	1	–
	Post-stroke	1	–	0	–
	Others	11	–	7	–
HS confirmed in pathology	–	22	–	15	–

LE frontal lobe epilepsy, mTLE mesial temporal lobe epilepsies, aTLE anterior temporal lobe resection, OP resective surgery, PMHx past medical history, AED antiepileptic drugs, BTCS bilateral tonic-clonic seizures, SE status epilepticus, MRI magnetic resonance imaging, HS hippocampal sclerosis, FCD focal cortical dysplasia

Table 2 *p*-Values for all analyzed variables comparing the “successful” surgery group (i.e. patients experiencing postsurgically exclusively auras or continuous seizure freedom) and the “unsuccessful” surgery groups (i.e. patients with seizures others than auras after the resection)

Variables before presurgical work-up	<i>p</i>
Sex	1
Age at surgery	0.211
Age at 1st seizure	0.157
Duration of epilepsy	0.998
Previous psychiatric illness	1
Family history of epilepsy	0.517
Febrile seizures	0.431
Mean number of AEDs before surgery	0.005 ^a
Non-adherence	0.722
Hippocampus sclerosis on MRI	0.516
Mean number of seizures 3 months before surgery	0.049 ^a
Seizure semiology includes aura	0.336
Seizure semiology includes focal to BTCS	1
Known status epilepticus	0.137
Variables during and after presurgical work-up	
Invasive monitoring (i.e., peg/foramen ovale electrodes and/or grid)	0.0279 ^a
Left vs. right	1
Operation site (mTLE vs. others TLE)	0.443
Variables during and after surgery	
Transient surgical complications	0.493
Etiology in pathology	0.5949
Hippocampal sclerosis in pathology	1

MRI magnetic resonance imaging, BTCS bilateral tonic-clonic seizure, mTLE mesial temporal lobe epilepsies

^aStatistically significant value

formed within the 10-year follow-up period.

A total of 46 patients (76.7% of 60 TLE patients) were included in the final statistical analysis of this study. For further patient details, see [Table 1](#).

The distribution of the Engel classification in each consecutive year is shown in [Fig. 3](#). The proportion of patients classified as Engel Class I ranged from 70.0 to 72.0% (median: 70%, SD = 0.97), Engel Class II from 6.0 to 10.0 (median 8.0%, SD = 1.75), Engel Class III from 6.0 to 14.0% (median 8.0%, SD = 2.07), and Engel Class IV from 0 to 4.35% (median 0.87%, SD = 0.82).

Seizure freedom over 10 years

Kaplan–Meyer survival rate

Out of 46 patients, 29 (63.1%) remained continuously in Engel class I (group 1) ([Fig. 4a](#)). The survival rate for seizure freedom of all 60 patients with TLE (i.e., including the patients lost to continuous follow-up) is shown in [Fig. 4b](#). For the latter analysis, patients who were lost to continuous follow-up were censored after their last follow-up visit and patients who had had a re-operation were censored before this intervention. Another three patients achieved continuous seizure freedom after 1–5 years (mean: 3 years; group 2).

Successful vs. unsuccessful surgery

As outlined in the Method section, the cohort was divided into two groups: the “successful” surgery (i.e., group 1) sustaining Engel Class I classification for 10 years and the “unsuccessful” surgery group (i.e., groups 2–5). The following preoperative factors predicted seizure freedom over 10 years: the number of AEDs that had been taken by the patients prior to surgery (mean 3.2 ± 1.3 in the successful group vs. 4.7 ± 1.3 in the unsuccessful group, $p < 0.05$) was significantly lower, the number of seizures prior to surgery (median 5.3 ± 2.3 in the successful surgery group vs. 11.9 ± 3.5 in the unsuccessful surgery group, $p < 0.01$) was significantly lower, and patients who needed invasive recordings had a significantly lower chance of obtaining complete seizure freedom (41% in patients

Fig. 2 ▲ Follow-up of patients without study participation

Fig. 3 ◀ Year-by-year follow up of patients with temporal lobe epilepsy

with invasive recordings vs. 76% in patients without invasive recordings; see [Fig. 5](#)). The latter results were supported by a significant difference in the survival rate toward seizure freedom during the 10-year follow-up period in patients who had to have invasive recordings (see [Fig. 6](#)).

The *p* values for all analyzed variables comparing the “successful” surgery group

and the “unsuccessful” surgery groups are summarized in [Table 2](#).

Perpetuation of postoperative seizure class

From the 29 patients classified as having successful surgery (i.e., retention of Engel Class I), 22 patients (47.8% from 46 patients) had no seizure including auras

(Engel Class IA). Three patients (“running down” = group 2) showed a continuous improvement reaching Engel Class I (mean 6.3 ± 2.5 years of Engel Class I, from 4 to 9 years). In three patients there was an opposite phenomenon: They were initially classified Engel Class I (mean 4.17 ± 1.16 years of Engel Class I, from 4 to 6 years), with successive seizure recurrence. Six patients (group 4 = “mixed”)

Fig. 4 ◀ Kaplan-Meier survival analysis: years of continuous seizure freedom (Engel Class I). TLE temporal lobe epilepsy

were classified as Engel Class I for at least 1 year (mean 5.5 ± 2.6 years of Engel Class I, from 1 to 8 years); there was, however, neither terminal remission of seizures nor constant worsening. Five patients never achieved a year of seizure freedom (group 5 = no seizure freedom).

Successful surgery in relation to AED medication

Out of the 29 patients with successful surgery (i.e., 10 years of Engel Class I), 16 (34.8% of all 46 study patients) experienced not only full remission but at least a “resolution” or likely a “cure” [11]: They did not take any AED during the last 3–10 years of continuous follow-up (mean 6.6 ± 2.4 years). Four of these pa-

tients (25.0% of 16 cured patients) did not adhere to the treatment plan and discontinued AED medication abruptly. They were seizure free and AED free for 8–10 years (mean 9.3 ± 0.7 years). Non-adherence was prevalent in the successful surgery group at a rate of 24.1% (seven patients) and at a rate of 35.3% (six patients) in the unsuccessful surgery. Univariate analysis for patients with successful surgery on AED and cured patients did

Fig. 5 ▲ Left: Number of antiepileptic drugs (AEDs) and seizure before surgery in “successful” surgery (dark blue) and “unsuccessful” surgery (light blue) groups. Right: Proportion (absolute numbers in column) of patients with or without invasive presurgical monitoring in successful surgery (dark blue) and unsuccessful surgery groups (light blue)

Fig. 6 ▲ Kaplan–Meier survival analysis

not reveal any discriminating factors. An additional three patients (group 2, “running down”) achieved continuous seizure freedom within 5–9 years, all of them by adding an additional AED and never without AEDs.

Discussion

The presented cohort of TLE patients who received resective surgery was followed up clinically on an annual basis. The primary outcome of seizure freedom over a period of 10 years was deliberately chosen because even rare seizure recurrence is a failure in view of the potential negative psychosocial impact. Most importantly, factors predicting a successful surgery on a long-term basis are important for patient counseling.

This monocentric extra-long-term follow-up study observed a homogeneous patient group with robust features, because:

1. Of the rather short recruitment period of 5 years, the same diagnostic and surgical techniques were used.
2. The recruitment period ended in February 1998, so that all patients had a comparable history of previously available AEDs excluding the so-called new second- and third-generation medications [25].
3. The 60 TLE patients were prospectively invited to an outpatient follow-up visit annually, a management procedure that has had the advantage of obtaining regular data and probably added to this robust data set.

The main five findings were:

- A. The change of seizure freedom for TLE patients after resective surgery is 63% (49% strictly including all patients for follow-up).
- B. The chance to become seizure free for 1 year (annual follow-up) ranged solidly between 76 and 80%.
- C. In a univariate analysis the number of seizures and the number of AEDs prior to surgery were a negative predictive factor for achieving 10 years of seizure freedom.
- D. In this particular cohort the decision in the multidisciplinary case conference to advise for invasive monitoring (peg or foramen ovale electrodes or grids) because of a more complex network disturbance was associated with a noticeable drop in the seizure rate from 76 to 41%.
- E. More than one third of patients were cured in the sense of obtaining seizure freedom without AED medication.

Patients lost to follow-up and postoperative long-term seizure outcome

Most of the findings are in line with previous publications on resective surgery.

Concerning the rate of patients lost to follow-up, both de Tisi et al. [40] with more than 500 TLE patients and Asztely et al. [1] with their predominantly extra-long-term study (mean follow-up of 12.4 years) had a similar rate of 5% of pa-

tients, where no data at all were available. Both study groups obtained their data from a prospectively maintained central database, suggesting that a monocentric prospective data collection—similar to our cohort—supports extra-long-term data acquisition. Aszetyl et al. presented data with extra-long-term follow-up of at least 8.6 years from 65 patients after resective surgery (both temporal and extratemporal epilepsies). The rate of patients lost to follow-up who did not reach the 10-year margin was slightly higher at 18%, compared with our rate of 12%. In their cohort the last follow-up had a seizure-free rate in patients with temporal lobe resection of 65%, comparable to the 63% in our study. The de Tisi cohort of 537 TLE patients achieved Engel Class I outcome either by temporal lobe resection (55%) or lesionectomies (56%) after 5 years [40]. In view of the expected decrease within the following 5 years, this seizure rate estimate seems rather conservative. However, apparently most of their TLE patients were lost to follow-up in the first year after surgery, so that a recruitment deficit might explain the lower number. Interestingly, they also found a high rate of 82% of patients who achieved Engel Class I for at least 1 year at some stage of their extended long-term follow-up period.

Prognostic factors for successful surgery assessed before presurgical work-up

Téllez-Zenteno et al. [39] in their meta-analyses found that for all resective types of surgery, the long-term seizure freedom was highest in patients with tumoral epilepsy, lowest in studies of patients older than 50 years at the time of surgery, as well as in older studies and in those with and extra-long-term follow-up of 10 years. Several studies suggest that the age (i.e., the duration of uncontrolled epilepsy; [6, 34, 45]), the severity (e.g., preoperative seizure frequency; [6, 22, 27]), and the functional extent of the epileptogenic network (EEG data or existence of focal to bilateral tonic-clonic seizures; cortical malformation; [6, 20, 34]) have an impact on seizure outcome. It is well accepted that a difficult-to-local-

ize or a non-lesional epileptogenic network (e.g., the lack of an epileptogenic lesion on the preoperatively MRI) is a stable negative predictor [6, 20, 22, 23, 27, 34, 35, 45]. Concerning the predictive factors for long-term seizure freedom, several factors have been suggested; unfortunately, in most cases with a follow-up period of less than 5 years. In Sweden, all epilepsy surgery procedures after 1989 are reported to a central database, so that Edelvik et al. [6] were able to analyze the long-term follow-up seizure outcome (minimum 5 years) after resective surgery in a large cohort of 190 patients with temporal and extra-temporal epilepsies. In their multivariate analysis, they found that:

1. The detection of an epileptogenic lesion on the MRI and a temporal site of the epileptogenic network are good prognostic factors.
2. And more importantly, the duration of the epilepsy, the preoperative seizure frequency, and the existence of cortical malformation or gliosis are negative predictors for seizure outcome.

Retrospectively, the detection of an MRI lesion was not prognostic in our cohort, probably due to the limited sensitivity and experience with technology available at that time instead of the new MRI technology. Concerning the severity of the individual patient's epileptogenic network disturbance, in our cohort we also found that the number of preoperative seizures was a predictor for negative outcome. It is conceivable that the number of AEDs in the patient's previous history are also an expression of the severity—and possibly of the age of—the individual epileptogenic network. To our knowledge, the number of AEDs prior to surgery has yet not been thoroughly investigated in the context of resective epilepsy surgery. There are, however, few studies that suggest that the postoperative AED regimen has an impact on the patients [20, 46].

Prognostic factors for successful surgery assessed during presurgical work-up

As outlined in **Table 2**, “invasive monitoring” (i.e., peg/foramen ovale electrodes and/or grid) was the only factor to have a negative impact on postsurgical outcome. The site of surgery—mesial vs. lateral or left vs. right—did not have an impact.

In our cohort, the chance of having a successful surgery was reduced almost by half from 76 to 41%, if the multidisciplinary case conference advised invasive monitoring (i.e., peg/foramen ovale electrodes and/or grids). Acknowledging the growing numbers of patients who both are advised to accept invasive monitoring and are reluctant to undergo invasive procedures [2], this aspect seems increasingly important for patient counseling. However, only a few cohort studies have provided comparative seizure outcome data of patients who were perceived to need invasive monitoring. Pooled data of different epilepsy syndromes and different follow-up periods showed that there was a 72% change of seizure freedom for patients without invasive monitoring and a 59% change with invasive monitoring [41]. Nevertheless, in 866 patients with non-lesional TLE, Mariani et al. did not find any difference in outcome in the univariate analysis whether stereo-EEG was used or not [26].

Generally, all monocentric resective surgery outcome studies have a center-specific bias concerning their decisions in the multidisciplinary case conference, especially regarding the choice of diagnostic measurements. Our result probably reflects the conservative approach of the epilepsy center with a general tendency toward noninvasive diagnostic tools, so that only patients with a difficult-to-localize epileptogenic network had invasive monitoring. This view was shared in a large meta-analysis of 782 patients from 36 studies who received repeat resective epilepsy surgery [24].

The chance of cure after temporal lobe epilepsy surgery

The chance of cure is an important motivation for patients to undergo presurgical evaluation, possibly invasive monitoring, and subsequent resection [18, 29, 36]. Of our 29 patients who remained seizure free for 10 years (group 1, “successful” surgery), 16 (35% of our 46 study and 55% of all patients in group 1) had a curative resection: They remained seizure free even though they did not take AEDs for 3–10 years of continuous follow-up. In view of the strict criteria of “10-year seizure freedom,” our finding (55% cured patients of all postsurgically seizure-free patients) can be viewed in line with those of Schmidt et al. [32]: In their literature review on predominantly TLE patients, AED discontinuation was successful (i.e. no seizure recurrence) in 66% of the patients, who were rendered seizure free by epilepsy surgery before (maximum follow-up of 1–5 years).

Limitations and outlook

Several limitations of the data presented in this study should be considered. Even though only a few patients were lost to follow-up and the continuous follow-up visits on an annual basis yielded a robust data set, the sample size is rather modest. Also, in this study we used only univariate statistics. Most importantly, we did not compare our results with best medical treatment group with AED treatment. Furthermore, the results are from a single center, so that—as discussed—center-specific decisions might be mirrored in the findings. However, only very few studies have carried out extra-long-term follow-up (i.e., 10 years) and all of them were single-center studies. In most follow-up studies, a considerable loss of patients to follow-up over time dominates the data, so that factors predicting seizure outcome are possibly flawed. The assessment of these factors—especially those relating to the time before or during the presurgical work-up—is of particular importance.

Follow-up visits are part of the national quality guidelines for presurgical epilepsy diagnosis and operative epilepsy

therapy [30, 31]. In our view, the collection of (extra-)long-term follow-up data enhance the quality management by every tertiary center performing resective (or other invasive or minimally invasive) procedures: Follow-up data over an extended period of time would allow more data to be collected about the proportions of patients who are cured (i.e., seizure-free without AED) after a surgical procedure. After all, cure is the best postsurgical result, followed by complete seizure freedom including auras. It would be beneficial to examine these endpoints on a regular basis, because:

1. From the perspective of the patients it is an important motivation to become not only seizure free but also medication free.
2. The concept of complete removal of the epileptogenic network requires this information.

In our cohort, resection led to complete removal of the epileptic network in nearly half of the patients. In view of these two key results, the authors regret that the postsurgical outcome classification of the ILAE [43] has not reached overall acceptance in the literature, because this outcome classification has—among others—the important advantage of accrediting “complete seizure freedom” its own category (Engel Class IA versus ILAE Class 1).

Conclusion

Our results underline that resective surgery of carefully chosen patients remains the mainstay of therapy and that a thorough follow-up with several periods should be the gold standard for non-reversible surgical procedures. There seem to be distinct subgroups of surgery failures (i.e., groups 2–5) and of surgery “winners” (i.e., “cured” patients). Further analysis is needed to also assess other outcome issues such as neuropsychological, psychiatric, and psychosocial outcome. Larger groups in a preferably controlled design are needed so as to assess factors that predetermine which patients might belong to which of the five aforementioned groups.

Corresponding address

PD Dr. med.
Friedhelm C. Schmitt, MD
Department of Neurology,
University Otto-von-Guericke
Leipzigerstr. 40,
39122 Magdeburg,
Germany
FC.Schmitt@gmx.net

Prof. Dr. med.
H.-Joachim Meencke, MD
Epilepsy Center Berlin
Brandenburg at Ev.
Krankenhaus Königin
Elisabeth Herzberge,
Teaching Hospital, Humboldt
University
Herzbergstr. 79, 10365 Berlin,
Germany
jo.meencke@web.de

Acknowledgements. We thank the following contributors for their participation: D. Meinken-Jäggi (data acquisition), F. Oltmanns, MA (data acquisition and manuscript proofreading), C. Dehnicke, MD (CD; data analysis and patient management), M. Merschhemke, MD, MBA (MM; patient management) and H. B. Straub, MD (HBS; patient management) (all Epilepsy Center Berlin Brandenburg). Surgery was performed by T.-N. Lehmann (TNL), MD, and W. R. Lanksch, MD (WRL) (both Department of Neurosurgery, Charité—University Medicine, Berlin, Germany).

Compliance with ethical guidelines

Conflict of interest F.C. Schmitt and H.-J. Meencke declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

Open Access. This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

- Asztely F, Ekstedt G, Rydenhag B, Malmgren K (2007) Long term follow-up of the first 70 operated adults in the Göteborg Epilepsy Surgery Series with respect to seizures, psychosocial outcome and use of antiepileptic drugs. *J Neurol Neurosurg Psychiatry* 78:605–609. <https://doi.org/10.1136/jnnp.2006.098244>
- Bien CG, Raabe AL, Schramm J et al (2013) Trends in presurgical evaluation and surgical treatment of epilepsy at one centre from 1988–2009. *J Neurol Neurosurg Psychiatry* 84:54–61. <https://doi.org/10.1136/jnnp-2011-301763>
- Bower CM, Hays RD, Devinsky O et al (2009) Expectations prior to epilepsy surgery: an exploratory comparison of men and women. *Seizure* 18:228–231. <https://doi.org/10.1016/j.seizure.2008.09.001>
- Choi H, Sell RL, Lenert L et al (2008) Epilepsy surgery for pharmacoresistant temporal lobe epilepsy: a decision analysis. *JAMA* 300:2497–2505. <https://doi.org/10.1001/jama.2008.771>
- Dorfer C, Czech T, Rössler K (2019) Chirurgie der Temporallappenepilepsie. *Z Epileptol*. <https://doi.org/10.1007/s10309-019-00297-5>
- Edelvik A, Rydenhag B, Olsson I et al (2013) Long-term outcomes of epilepsy surgery in Sweden. *Neurology* 81:1244–1251. <https://doi.org/10.1212/WNL.0b013e3182a6ca7b>
- Elwes RD, Dunn G, Binnie CD, Polkey CE (1991) Outcome following resective surgery for temporal lobe epilepsy: a prospective follow up study of 102 consecutive cases. *J Neurol Neurosurg Psychiatry* 54:949–952. <https://doi.org/10.1136/jnnp.54.11.949>
- Engel J Jr, McDermott MP, Wiebe S et al (2012) Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *JAMA* 307:922–930. <https://doi.org/10.1001/jama.2012.220>
- Engel J Jr, Wiebe S, French J et al (2003) Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. *Neurology* 60:538–547
- Engel J, Van Ness P, Rasmussen TB, Ojemann GA (1993) Outcome with respect to epileptic seizures. In: *Surgical treatment of epilepsies*, 2nd edn. Raven Press, New York, pp 609–621
- Fisher RS, Acevedo C, Arzimanoglou A et al (2014) ILAE Official Report: a practical clinical definition of epilepsy. *Epilepsia* 55:475–482. <https://doi.org/10.1111/epi.12550>
- Fisher RS, Cross JH, D'Souza C et al (2017) Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia* 58:531–542. <https://doi.org/10.1111/epi.13671>
- Fisher RS, Cross JH, D'Souza C et al (2018) Anleitung ("instruction manual") zur Anwendung der operationalen Klassifikation von Anfallsformen der ILAE 2017. *Z Epileptol* 31:282–295. <https://doi.org/10.1007/s10309-018-0217-7>
- Fisher RS, Cross JH, French JA et al (2017) Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE commission for classification and terminology. *Epilepsia* 58:522–530. <https://doi.org/10.1111/epi.13670>
- Fisher RS, Cross JH, French JA et al (2018) Operationale Klassifikation der Anfallsformen durch die Internationale Liga gegen Epilepsie: Positionspapier der ILAE-Klassifikations- und Terminologiekommision. *Z Epileptol* 31:272–281. <https://doi.org/10.1007/s10309-018-0216-8>
- Gross RE, Stern MA, Willie JT et al (2018) Stereotactic laser amygdalohippocampotomy for mesial temporal lobe epilepsy. *Ann Neurol* 83:575–587. <https://doi.org/10.1002/ana.25180>
- Hemb M, Palmieri A, Paglioli E et al (2013) An 18-year follow-up of seizure outcome after surgery for temporal lobe epilepsy and hippocampal sclerosis. *J Neurol Neurosurg Psychiatry* 84:800–805. <https://doi.org/10.1136/jnnp-2012-304038>
- Holtkamp M, Steinbrenner M (2016) Einstellungen zur (resektiven) Epilepsiechirurgie. *Z Epileptol* 30:93–97. <https://doi.org/10.1007/s10309-016-0091-0>
- Ilse A, Büntjen L, Schmitt FC (2017) Stereotaktische Laserablation für fokale Epilepsien – Eine Literaturübersicht. *Z Epileptol* 30:152–161. <https://doi.org/10.1007/s10309-017-0113-6>
- Janszky J, Janszky I, Schulz R et al (2005) Temporal lobe epilepsy with hippocampal sclerosis: predictors for long-term surgical outcome. *Brain* 128:395–404. <https://doi.org/10.1093/brain/awh358>
- Josephson CB, Dykeman J, Fiest KM et al (2013) Systematic review and meta-analysis of standard vs selective temporal lobe epilepsy surgery. *Neurology* 80:1669–1676. <https://doi.org/10.1212/WNL.0b013e3182904f82>
- Kanchanatawan B, Limthai C, Srikiatvithakul T, Maes M (2014) Clinical predictors of 2-year outcome of resective epilepsy surgery in adults with refractory epilepsy: a cohort study. *BMJ Open*. <https://doi.org/10.1136/bmjopen-2014-004852>
- Kelley K, Theodore WH (2005) Prognosis 30 years after temporal lobectomy. *Neurology* 64:1974–1976. <https://doi.org/10.1212/01.WNL.0000163998.01543.CF>
- Krucoff MO, Chan AY, Harward SC et al (2017) Rates and predictors of success and failure in repeat epilepsy surgery: a meta-analysis and systematic review. *Epilepsia*. <https://doi.org/10.1111/epi.13920>
- Landmark CJ, Patsalos PN (2010) Drug interactions involving the new second- and third-generation antiepileptic drugs. *Expert Rev Neurother* 10:119–140. <https://doi.org/10.1586/ern.09.136>
- Mariani V, Revay M, D'Orto P et al (2019) Prognostic factors of postoperative seizure outcome in patients with temporal lobe epilepsy and normal magnetic resonance imaging. *J Neurol*. <https://doi.org/10.1007/s00415-019-09394-x>
- McIntosh AM, Kalnins RM, Mitchell LA et al (2004) Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. *Brain* 127:2018–2030. <https://doi.org/10.1093/brain/awh221>
- McIntosh AM, Wilson SJ, Berkovic SF (2001) Seizure outcome after temporal lobectomy: current research practice and findings. *Epilepsia* 42:1288–1307
- Ozanne A, Graneheim U, Ekstedt G, Malmgren K (2015) Patients' expectations and experiences of epilepsy surgery—a population-based long-term qualitative study. *Epilepsia* 57:605–611
- Rosenow F, Bast T, Czech T et al (2014) Quality guidelines for presurgical epilepsy diagnosis and operative epilepsy therapy: 1st revised version. *Nervenarzt* 85:753–756. <https://doi.org/10.1007/s00115-014-0070-2>
- Rosenow F, Bast T, Czech T et al (2016) Revised version of quality guidelines for presurgical epilepsy evaluation and surgical epilepsy therapy issued by the Austrian, German, and Swiss working group on presurgical epilepsy diagnosis and operative epilepsy treatment. *Epilepsia* 57:1215–1220. <https://doi.org/10.1111/epi.13449>
- Schmidt D, Baumgartner C, Löscher W (2004) Seizure recurrence after planned discontinuation of antiepileptic drugs in seizure-free patients after epilepsy surgery: a review of current clinical experience. *Epilepsia* 45:179–186. <https://doi.org/10.1111/j.0013-9580.2004.37803.x>
- Schmidt D, Stavem K (2009) Long-term seizure outcome of surgery versus no surgery for drug-resistant partial epilepsy: a review of controlled studies. *Epilepsia* 50:1301–1309. <https://doi.org/10.1111/j.1528-1167.2008.01997.x>
- Schwartz TH, Jeha L, Tanner A et al (2006) Late seizures in patients initially seizure free after epilepsy surgery. *Epilepsia* 47:567–573. <https://doi.org/10.1111/j.1528-1167.2006.00469.x>
- Stefan H, Schmitt FC (2017) Ablation und Epileptogenizität – Zur Beziehung von Läsion und Funktion. *Z Epileptol* 30:129–137. <https://doi.org/10.1007/s10309-016-0097-7>
- Steinbrenner M, Kowski AB, Holtkamp M (2019) Referral to evaluation for epilepsy surgery: reluctance by epileptologists and patients. *Epilepsia* 60:211–219. <https://doi.org/10.1111/epi.14641>
- Taylor DC, McMackin D, Staunton H et al (2001) Patients' aims for epilepsy surgery: desires beyond seizure freedom. *Epilepsia* 42:629–633. <https://doi.org/10.1046/j.1528-1157.2001.34400.x>
- Téllez-Zenteno JF, Dhar R, Hernandez-Ronquillo L, Wiebe S (2007) Long-term outcomes in epilepsy surgery: antiepileptic drugs, mortality, cognitive and psychosocial aspects. *Brain* 130:334–345. <https://doi.org/10.1093/brain/awl316>
- Téllez-Zenteno JF, Dhar R, Wiebe S (2005) Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain* 128:1188–1198. <https://doi.org/10.1093/brain/awh449>
- de Tisi J, Bell GS, Peacock JL et al (2011) The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *Lancet* 378:1388–1395. [https://doi.org/10.1016/S0140-6736\(11\)60890-8](https://doi.org/10.1016/S0140-6736(11)60890-8)
- West S, Nolan SJ, Cotton J et al (2015) Surgery for epilepsy. *Cochrane Database Syst Rev*. <https://doi.org/10.1002/14651858.CD010541.pub2>
- Wiebe S, Blume WT, Girvin JP, Eliasziw M (2001) A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 345:311–318. <https://doi.org/10.1056/NEJM200108023450501>
- Wieser HG, Blume WT, Fish D et al (2001) Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia* 42:282–286. <https://doi.org/10.1046/j.1528-1157.2001.35100.x>
- Wu C, Jermakowicz WJ, Chakravorti S et al (2019) Effects of surgical targeting in laser interstitial thermal therapy for mesial temporal lobe epilepsy: a multicenter study of 234 patients. *Epilepsia* 60:1171–1183. <https://doi.org/10.1111/epi.15565>
- Yoon HH, Kwon HL, Mattson RH et al (2003) Long-term seizure outcome in patients initially seizure-free after resective epilepsy surgery. *Neurology* 61(4):445–450
- Zeng T, Li Y, An D et al (2014) Effectiveness of levetiracetam use following resective surgery in patients with refractory epilepsy: a prospective observational study. *Epilepsia Res* 108:1904–1911. <https://doi.org/10.1016/j.eplepsyres.2014.09.034>

-
47. Bancaud J, Henriksen O, Rubio-Donnadieu F, Seino M, Dreifuss FE, Penry JK (1981) Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 22:489–501. <https://doi.org/10.1111/j.1528-1157.1981.tb06159.x>

Hier steht eine Anzeige.