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Long-term outcome after temporal lobe epilepsy surgery in 434 consecutive adult patients

Clinical article

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Object. The aim of this study was to evaluate the long-term efficacy of temporal lobe epilepsy (TLE) surgery and potential risk factors for seizure recurrence after surgery.

Methods. This retrospective study included 434 consecutive adult patients who underwent TLE surgery at Bethel Epilepsy Centre between 1991 and 2002.

Results. Hippocampal sclerosis was found in 62% of patients, gliosis in 17.3%, tumors in 20%, and focal cortical dysplasia (FCD) in 6.9%. Based on a Kaplan-Meier analysis, the probability of Engel Class I outcome for the patients overall was 76.2% (95% CI 71–81%) at 6 months, 72.3% (95% CI 68–76%) at 2 years, 71.1% (95% CI 67–75%) at 5 years, 70.8% (95% CI 65–75%) at 10 years, and 69.4% (95% CI 64–74%) at 16 years postoperatively. The likelihood of remaining seizure free after 2 years of freedom from seizures was 90% (95% CI 82–98%) for 16 years. Seizure relapse occurred in all subgroups. Patients with FCD had the highest risk of recurrence (hazard ratio 2.15, 95% CI 0.849–5.545). Predictors of remission were the presence of hippocampal atrophy on preoperative MR imaging and a family history of epilepsy. Predictors of relapse were the presence of bilateral interictal sharp waves and versive seizures. Six-month follow-up electroencephalography predicted relapse in patients with FCD. Short epilepsy duration was predictive of seizure remission in patients with tumors and gliosis; 28.1% of patients were able to discontinue antiepileptic medications without an increased risk of seizure recurrence (hazard ratio 1.05, 95% CI 0.933–1.20).

Conclusions. These findings highlight the role of etiology in prediction of long-term outcome after TLE surgery.
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Key Words • epilepsy surgery • focal cortical dysplasia • gliosis • hippocampal sclerosis • long-term outcome • temporal lobe

Temporal lobe epilepsy is the most common type of epilepsy that requires surgical treatment.[32] The main goal of epilepsy surgery is to provide the patient with long-term freedom from seizures. Excellent short-term results of epilepsy surgery have been published.[66] However, there are relatively few studies on long-term postoperative outcome after surgery and little is known about what occurs in the subsequent 5–20 years.[43,72]

The few long-term outcome studies that exist have found that patients may relapse after many years of seizure freedom.[4,21] Initially, a rapid decrease in the proportion of seizure-free cases was followed by a slower decrease for at least several years afterward.[43] Some reports stated that the long-term outcome is worse than the short-term outcome and that 48–55% of patients continued to experience seizures 5 years after their operations.[32,44] In contrast, others reported that the long-term seizure-free rate following temporal lobe resection was similar to that reported in short-term controlled studies.[19]

One of the most obvious potential risks of seizure recurrence after surgery is the discontinuation of AEDs. This issue is highly pertinent, because patients commonly cite the hope of AED discontinuation as a reason for undergoing epilepsy surgery. Yet, there is little information about the risks of seizure recurrence posed by AED discontinuation.[70]

Most studies on long-term outcome are concerned

Abbreviations used in this paper: AED = antiepileptic drug; ECoG = electrocorticography; EEG = electroencephalography; FCD = focal cortical dysplasia; HR = hazard ratio; HS = hippocampal sclerosis; IED = interictal epileptiform discharge; MTS = mesial temporal sclerosis; TLE = temporal lobe epilepsy.

with HS and only a few studies focus on predictors of seizure remission after surgery for other temporal lesions.[27] An analysis of long-term outcome in a large number of patients with epilepsy who have undergone similar preoperative diagnostic studies and relatively uniform surgical procedures at a single institution may provide insight into the factors associated with improved postoperative outcomes.[12] We therefore reviewed the long-term results of surgical treatment of medically intractable TLE in a large surgical cohort of adults. Our aim was to evaluate preoperative, operative, and postoperative factors predicting postoperative outcome in the long term. It was also our objective to investigate AED discontinuation as a potential risk factor for seizures after surgery.

Methods

We retrospectively reviewed the records of all adult patients (16 years of age and older) who underwent TLE surgery at Bethel Epilepsy Centre in Bielefeld, Germany, between May 1991 and May 2002. There were 483 consecutive patients who met our inclusion criteria, which were adult patients with TLE, who underwent resective surgery, and a follow-up period of > 5 years. We excluded patients who underwent previous epilepsy surgery outside our clinic and patients who underwent reoperations for malignant tumors. We also excluded patients who did not come to the 6-month or 2-year follow-up examination. This process left 434 patients who were included in the study. Each patient had uniform preoperative evaluation (all followed the same protocol).

Preoperative Evaluation

The preoperative protocol developed at Bethel Epilepsy Centre to identify patients for surgery includes the patient's medical history and a physical examination; noninvasive video EEG monitoring and an invasive procedure if noninvasive results are insufficient; a neuropsychological evaluation; an ophthalmological assessment (visual field test); and MR imaging. Subdural grids were used in 6 patients. Patients were either examined using 1-T MR imaging (until 1998; Magnetom Vision, Siemens) or 1.5-T MR imaging (after 1998; Magnetom Symphony, Siemens) using a specific protocol for patients with epilepsy. In our study, 2 patients (0.5%) had normal MR imaging results, 160 patients (36.9%) had temporal lesions outside the hippocampus, and 272 patients (62.7%) had HS. Of these 272 patients with HS, 142 (52.2%) had both signs of sclerosis (atrophy and increased signal), 68 (25%) had only signal changes without hippocampal atrophy, and 62 (22.8%) had only hippocampal atrophy without signal changes. In addition, PET, SPECT, and functional MR imaging were performed. An intracarotid sodium amobarbital (Wada) test was used when appropriate.

Patient Characteristics

Our analysis included 220 (50.7%) male patients and 214 (49.3%) females. The mean age (± SD) at epilepsy onset was 12.2 ± 9.2 years (range 0–55 years), and the mean age at the time of surgery was 33.8 ± 10.8 years (range 16–61 years). The mean duration of epilepsy was 21.5 ± 11.2 years (range 1–57 years). The mean duration of follow-up was 9 ± 3.1 years (range 2–16 years). Patient characteristics are summarized in Table 1.

Surgical Procedure and Postoperative Evaluation

All resections were performed by a single neurosurgeon (H.P.), who made consistent measurements of resection parameters during surgery. All patients underwent resective surgery according to the following protocol. 1) Anterior temporal lobe resection included the pole of the temporal lobe. The laterodorsal resection line was delineated by EEG as well as abnormalities noted on MR imaging. The size of resection was 2.5–4 cm in the language-dominant hemisphere and 3–6 cm in the nondominant hemisphere. Part of the procedure was to remove the parahippocampal gyrus, hippocampus, and amygdala. As a rule, intraoperative ECoG was not used in MTS. Figure 1 show the extent of resection in apical resection and in anterior temporal resection. 2) Apical temporal resection: tailored resection of the lesion in the apex of the temporal lobe with amygdalectomy, and maximal 4 cm laterodorsal cortex from the pole, extension of the resection was guided by using intraoperative ECoG. 3) Temporal lesionectomy included only a singular lesion resection as defined by EEG and MR imaging, but saved the eloquent cortex. In the case of dual pathology, a lesionectomy and a selective amygdalohippocampectomy were performed, and the dorsal resection was guided by means of intraoperative ECoG. 4) Selective amygdalohippocampectomy included only a resection of the hippocampus or mesial structures based on MR imaging and intraoperative findings. Only 5 patients underwent operations using this procedure.

Postoperative follow-up examinations occurred 6 months and 2 years after the operation, including EEG, MR imaging, and neurological and psychological evaluation. After the 2-year follow-up examination, each patient was sent questionnaires at 3, 5, 10, and 15 years after surgery.

Data Collection

Data were extracted from patients' medical records, the clinic's electronic files, recorded video EEG monitoring, and rehabilitation program files. Long-term outcome data were extracted from the clinic follow-up program, outpatient reports, and mailed questionnaires. Our questionnaire included detailed questions about auras, seizures, general quality of life, and medication. Histopathological information was obtained from histopathological reports in the patients' files. Dual pathology was diagnosed if the resected temporal lobe specimen contained 2 different pathologies.

Patients Lost to Follow-up

As previously stated, there were 434 patients in our study who complied with at least 2 years of follow-up. To complete the data missing in the follow-up databank, a total of 305 questionnaires were mailed (55 for the 5-year follow-up, 103 for the 10-year follow-up, and 147 for the 16-year follow-up). Of 305 patients who were mailed

TABLE 1: Summary of clinical characteristics and risk factors in 434 adult patients who underwent TLE surgery

Variable	Males (220)	Females (214)	All (434)
risk factor*			
age at seizure onset (yrs)	13.4 ± 10.1	11 ± 8.2	12.2 ± 9.2
epilepsy duration (yrs)	20.2 ± 11.2	22.9 ± 11.0	21.5 ± 11.2
age at surgery (yrs)	33.6 ± 10.78	33.9 ± 10.9	33.8 ± 10.8
duration of follow-up (yrs)	9.1 ± 3.2	8.91 ± 2.9	9 ± 3.1
pathological category†			
temporal sclerosis	124 (56.4)	145 (67.8)	269 (62)
FCD	15 (6.8)	15 (7)	30 (6.9)
tumor	46 (20.9)	41 (19.2)	87 (20)
gliosis	48 (21.8)	27 (12.6)	75 (17.3)
predisposing factors†			
history of febrile seizures	49 (22.3)	62 (29)	111 (25.6)
family history of epilepsy	16 (7.3)	7 (3.3)	23 (5.3)
history of status epilepticus	4 (1.8)	2 (0.9)	6 (1.4)
history of head trauma	17 (7.7)	9 (4.2)	26 (6)
history of CNS infection	19 (8.6)	12 (5.6)	31 (7.1)
history of psychiatric symptoms	13 (5.9)	11 (5.1)	24 (5.5)

* Values are means ± SD.
† Values are numbers of patients (%).

questionnaires, 52 (17%) did not return them. The number of patients included in the analysis was therefore 419 (97.7%) of 429 at 5 years, 366 (95.1%) of 385 at 10 years, and 147 (86.5%) of 170 at 16 years. Twenty-one (40.3%) of the 52 patients who did not reply had changed addresses and could not be reached.

During the follow-up period, 10 patients (2.3%) died of various medical causes; 3 of these patients died unexpected epileptic deaths, and 1 committed suicide.

Outcome Evaluation

Outcome was evaluated using a modified Engel seizure classification.[18] Patients in Engel Class 1 were considered seizure free. Seizures that occurred within 1 month after surgery were not included in this analysis. Seizure types were classified according to the semiological seizure classification suggested by Lüders et al.[40,41]

According to our protocol for the withdrawal of AEDs, patients generally continued their preoperative levels of AEDs for 2 years after surgery. If a patient remained seizure free and wished to discontinue his or her medication, then the AEDs would be systematically reduced. If the patient had a seizure during AED withdrawal, then AEDs were restarted. Many seizure-free patients refused to stop taking AEDs.

Statistical Analysis

Due to the variation in duration of the patients' follow-up (ranging from 6 months to 16 years), time-to-event methods were used to associate various risk factors with the maintenance of Engel Class I outcome after surgery. Kaplan-Meier methods were used to estimate the probability of remaining in Engel Class I as a function of time. Cox proportional hazards models were used to estimate HRs with 95% CIs for each risk factor. We reported seizure recurrence by obtaining survival estimates at 0.5, 2, 5, 10, and 16 years after surgery. Univariate analysis was used to detect the factors affecting long-term outcome and the Cox stepwise logistic regression model was used to evaluate the predictor. Variables of interest in this analysis were preoperative, operative, and postoperative factors. These variables are summarized in Tables 1 and 2.

Results

Overall Outcome

The majority of seizure recurrences occurred during the first 6 months after surgery (Fig. 2). Overall, 330 of 434 patients were seizure free after 6 months. The number of patients in each Engel Class at 5 different time points after surgery is summarized in Table 3.

The probability of remaining in Engel Class I was 76.2% (95% CI 71–81%) at 6 months, 72.3% (95% CI 68–76%) at 2 years, 71.1% (95% CI 67–75%) at 5 years, 70.8% (95% CI 65–75%) at 10 years, and 69.4% (95% CI 64–74%) at 16 years postoperatively. The rate of Engel Class I outcome remained 69.4% for the 102 patients evaluated after > 16 years.

Late Seizure Recurrence

After surgery, seizures recurred between 2 and 5

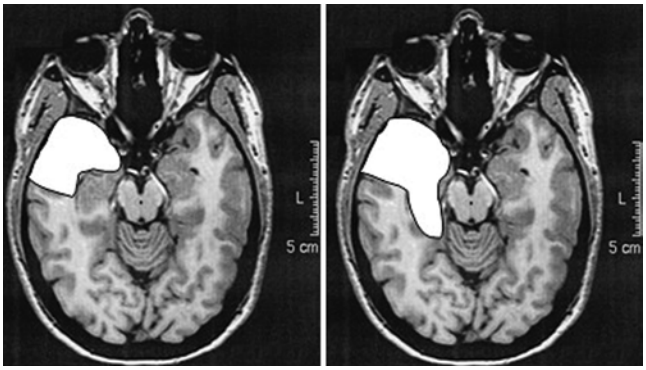

FIG. 1. Axial MR images showing the extension of resection in apical resection *(left)* and in anterior temporal lobe resection *(right)*.

years in 13 patients (4.5%), between 5 and 10 years in 17 patients (6.7%), and between 10 and 16 years in 4 patients (4.1%). Among patients who were seizure free 2 years postoperatively, the probability of freedom from seizure at 5 years after surgery was 95.5% (95% CI 92–98%), at 10 years was 92.1% (95% CI 86–98%), and at 16 years was 90% (95% CI 82–98%).

Pathological Subgroups

Histopathological examination of the resected specimens revealed HS in 269 patients (62%), gliosis in 75 (17.3%), tumor in 87 (20%), FCD in 30 (6.9%), vascular lesion in 18 (4.1%), and dual pathology in 54 (12.4%). Kaplan-Meier curves illustrating the probability of Engel Class I outcome for the pathological subgroups are shown in Fig. 3. Almost all patients with MTS who were seizure free at the 2-year follow-up evaluation remained in the Engel Class I group through their last follow-up review. The likelihood of remaining in Engel Class I for patients with HS was 75.8% (95% CI 71–79%) at 6 months, 73.4% (95% CI 69–84%) at 2 years, 72.2% (95% CI 68–76%) at both 5 and 10 years, and 75.5% (95% CI 67–83%) at 16 years.

In the group with tumors, the likelihood of remaining in Engel Class I was 78.2% (95% CI 70–88%) at 6 months, 73.3% (95% CI 69–77%) at 2 and 5 years, 68.3% (95% CI 58–78%) at 10 years, and 65.4% (95% CI 55–75%) at 16 years after surgery. In the group in which gliosis was diagnosed, the likelihood of remaining in Class I after 0.5, 2, 5, 10, and 16 years was 71.7% (95% CI 65–77%), 67.8% (95% CI 61–72%), 63.2% (95% CI 55–71%), 69.6% (95% CI 60–78%), and 66.7% (95% CI 60–72%), respectively.

Similarly, among the cohort in whom FCD was diagnosed, FCD showed the highest risk of recurrence (HR 2.15, 95% CI 0.849–5.545). The likelihood of remaining in Class I after 0.5, 2, 5, 10, and 16 years was 66.7% (95% CI 60–72%), 56.7% (95% CI 50–62%), 51.7% (95% CI 42–60%), 54.5% (95% CI 44–64%), and 33.3% (95% CI 23–43%), respectively.

Descriptive Data Pertaining to AED Discontinuation

In this analysis, 122 patients (28.1%) had stopped tak-

TABLE 2: Variables of interest in the analysis*

Variable	No. of Patients (%)
duration of epilepsy (range 1–57 yrs)	
<20 yrs	212 (48.8)
>20 yrs	222 (51.2)
age at surgery (range 16–61 yrs)	
<30 yrs	170 (39.2)
>30 yrs	264 (60.8)
MR imaging findings	
hippocampal atrophy (visual assessment)	204 (47)
hippocampal signal change	210 (48.4)
temporal lesion (not HS)	160 (36.9)
presurgical EEG interictal evaluation	
absence of epileptic discharges	54 (12.4)
presence of epileptic discharges	380 (87.6)
EEG interictal findings according to MR imaging	
ipsilateral IEDs	233 (53.7)
bilateral IEDs	147 (33.9)
EEG seizure pattern	
concordance with MR imaging	302 (69.6)
nonconcordance with MR imaging	100 (23)
no EEG seizure pattern recorded	32 (7.4)
aura	
absent	95 (21.9)
present	339 (78.1)
aura classification	
abdominal	220 (50.7)
somatosensory	23 (5.3)
psychic	62 (14.3)
visual	15 (3.5)
unspecific	82 (18.9)
vegetative	18 (4.1)
combined form	81 (18.7)
seizure classification	
psychomotor	399 (91.9)
clonic	36 (8.3)
GTCS	206 (47.5)
versive	34 (7.8)
hypermotor	18 (4.1)
combined form	53 (12.2)
side and type of surgery	
right-sided resection	233 (53.7)
left-sided resection	201 (46.3)
anterior resection	219 (50.5)
apical resection	49 (11.3)
lesional resection	161 (37.1)
selective amygdalohippocampectomy	5 (1.1)
postop complications	
yes	22 (5.1)
no	412 (94.9)
EEG at 6-month follow-up	
presence of IEDs	51 (11.8)
no IEDs	383 (88.2)
EEG at 2-year follow-up	
presence of IEDs	55 (12.7)
no IEDs	379 (87.3)

continued

TABLE 2: Variables of interest in the analysis* (continued)

Variable	No. of Patients (%)
AEDs	
discontinuation	122 (28.1)
continuation	306 (70.5)
AEDs after surgery	
changed	137 (31.6)
not changed	297 (68.4)
postoperative GTCS	
>1/year	5 (1.2)
=1/year	17 (3.9)
postoperative focal seizure	
≥3/month	18 (4.1)
<3/month	33 (7.6)

* GTCS = generalized tonic-clonic seizures.

ing their AEDs by the date of the last follow-up examination. Data relevant to AED discontinuation were missing in 6 patients. All patients who discontinued their medication had been seizure free for 2 years after surgery when the AED was discontinued. There was no risk of seizure recurrence after AED discontinuation. The HR was 1.05 (95% CI 0.933–1.200) and there was no difference between patients who discontinued their AEDs and patients who continued their AEDs in regard to recurrence of seizures ($p = 0.375$). Moreover, the median time until medication discontinuation was 4.2 years after surgery (range 2–11 years). Of the patients who continued taking AEDs, 137 (31.6%) were prescribed a change in the AED they had been taking; 181 (41.7%) were receiving monotherapy, and 129 (29.7%) were receiving polytherapy.

Duration of Epilepsy and Age at Surgery

Preoperative epilepsy duration (HR 1.38, 95% CI 1.01–1.87; $p = 0.043$) and age at surgery (HR 1.08, 95% CI 0.79–1.46; $p = 0.013$) showed a significant relationship to outcome in the univariate analysis (Table 4). In our cohort there were 32 patients (7.4%) who underwent operations within 5 years after the onset of epilepsy, 48 (11.1%) within 6–10 years, 132 (30.4%) within 11–20 years, and 222 (51.2%) after > 20 years. These numbers reflect the common practice of delaying patient referral to epilepsy surgery for many years. Patients undergoing surgery soon after epilepsy onset showed better outcome. Due to the small number of patients who underwent operations early, we used an epilepsy duration of < 20 years as our reference in the multivariate analysis. Figure 4 shows the Kaplan-Meier curve for the outcome of patients (Engel Class I) in relation to epilepsy duration. This curve clearly shows that longer epilepsy duration correlated with less satisfactory outcome.

Size of Resections

In our analysis, the right-sided operations had a significantly better outcome compared with the left-sided operations. For patients who underwent operations on the left side, the probability of remaining in Engel Class I at 6 months, and 2, 5, and 10 years after surgery was 74.6, 67.0, 66.5, and 66.9%, respectively.

However, in the group who underwent operations on the right side, the probability of remaining in Engel Class I at 0.5, 2, 5, and 10 years after surgery was 77.3, 78.2, 75.2, and 74.3%, respectively (Fig. 5). There were the following significant differences between left- and right-sided resections: males had more right-sided operations ($p = 0.033$); there were more lesions on the right side other than HS ($p = 0.002$); and those with resections on the left side had HS more often ($p = 0.01$).

Univariate Analysis

On the initial univariate analysis, the following variables were correlated with good outcome: presence of regional hippocampal atrophy on preoperative MR imaging ($p = 0.012$); history of febrile seizure ($p = 0.031$); EEG unilateral seizure onset ($p = 0.006$); age < 30 years at surgery ($p = 0.013$); exclusively unilateral sharp waves ($p = 0.048$); right-sided resection ($p = 0.042$); short epilepsy duration ($p = 0.043$); and a family history of epilepsy ($p = 0.001$).

The following variables correlated with poor prognosis: bilateral sharp waves ($p = 0.004$); seizure onset bilateral ($p = 0.000$); versive seizures ($p = 0.034$); somatosensory aura ($p = 0.038$); EEG at 6 months with IED ($p = 0.001$); and EEG at 2 years with IED ($p = 0.002$; Table 4).

Long-Term Outcome Predictors

After applying forward stepwise Cox proportional-hazards regression modeling, the following variables retained their significance as independent predictors of outcome: a family history of epilepsy ($p = 0.009$); presence of preoperative MR imaging hippocampal atrophy ($p = 0.021$); bilateral sharp waves ($p = 0.001$); and versive seizures ($p = 0.007$). In patients with HS, predictors of outcome were the same as those previously found as independent predictors of outcome in all groups (see above). In patients with tumors and gliosis, preoperative epilepsy duration was the only independent predictor of outcome, whereas in patients with FCD, a 6-month EEG with IED was the only predictor (Table 5).

Postoperative Complications

In our analysis, 22 (5%) of the patients had postoperative complications; 10 (2.3%) had a permanent deficit, and 12 (2.7%) experienced a transient complication. All transient complications resolved within 6 months postoperatively.

Discussion

General Outcome

This study confirms the sustained, long-term benefit of surgery with long-term follow-up for the treatment of medically refractory TLE. The mean follow-up after TLE was 9.0 ± 3.1 years (range 0.5–16 years). Data were missing for very few of the patients. For the patient sample

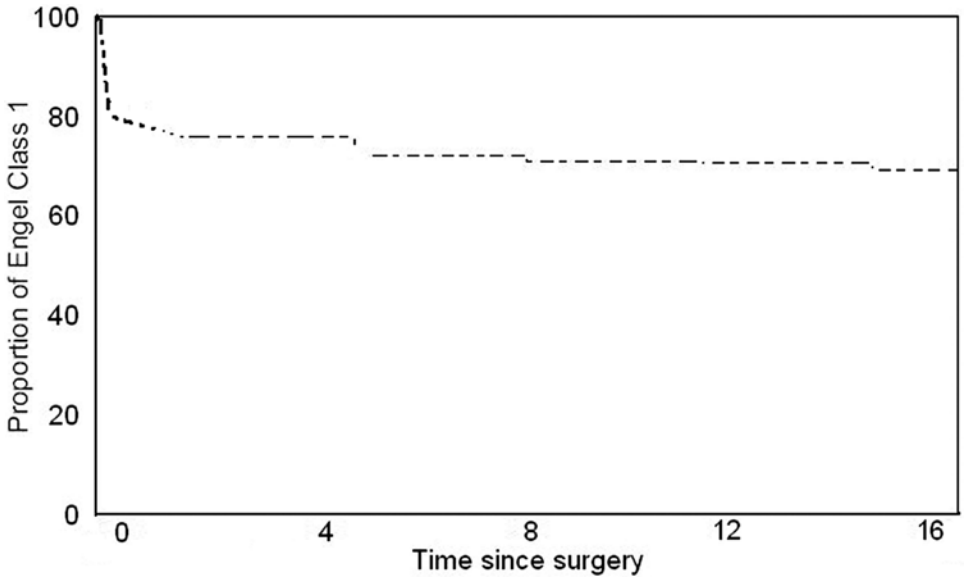

FIG. 2. Kaplan-Meier curve showing the overall percentage of patients remaining in Engel Class I over time.

as a whole, the likelihood of remaining seizure free was 76.2% at 6 months, 72.3% at 2 years, 71.1% at 5 years, 70.8% at 10 years, and 69.4% at 16 years postoperatively. These results are very consistent with those from other recent reports, which found a high rate of seizure-free outcome. Tellez-Zenteno and colleagues[66] reported in a meta-analysis that 66% of patients had long-term seizure freedom after epilepsy surgery. Cohen-Gadol and associates[12] reported a 72% seizure free rate at the 10-year follow-up in a group of non-lesional patients after temporal lobe surgery.

Some studies have reported poor long-term outcomes after TLE surgery.[19,21,27,43,61,63,72] These studies have certain elements that must be examined more closely, such as the variations in treatment protocols over the 20-year study period, during which neuroimaging, other seizure localization methods, and surgical procedures may have changed. Some results have been affected by patient attrition. It was reported that some of the patients who experienced seizure relief may have failed to return for their later office check-up.[59] This factor may affect the reported outcome, because the reason for patients losing or maintaining contact may be closely related to their outcome status.[44] Selection criteria in the preoperative diagnostic phase varies among centers, as well as the use of different definitions of seizure-free outcome in the published papers.[14] Such a drop-out bias may explain some of the discrepancies between the results of our study and other ones that report a worse long-term seizure outcome. Moreover, we cannot ignore the role of patient selection in the preoperative diagnostic phase that contributes to achieving such a high long-term outcome rate.

In our study, the long-term seizure-free rate following temporal lobe resection was closely related to the short-

TABLE 3: Numbers and percentages of patients according to Engel Class*

Engel Class	6 Months	2 Years	5 Years	10 Years	16 Years
I	330 (76.2)	311 (72.3)	298 (71.1)	259 (70.8)	102 (69.4)
II	45 (10.4)	53 (12.3)	55 (13.1)	58 (15.8)	22 (15)
III	37 (8.5)	42 (9.8)	43 (10.3)	31 (8.5)	14 (9.5)
IV	21 (4.8)	24 (5.6)	23 (5.5)	18 (4.9)	9 (6.1)
Total analyzed	433/434 (99.8)	430/434 (99.1)	419/429 (97.7)	366/385 (95.1)	147/170 (86.5)

* Because of the differences among patients related to time of surgery, periods of follow-up, and missing data (52 did not reply to follow-up questionnaires and 10 died), the total number of patients was 433 for the 6-month follow-up, 430 for the 2-year follow-up, 419 for the 5-year follow-up, 366 for the 10-year follow-up, and 147 for the 16-year follow-up. All values are number of patients (%).

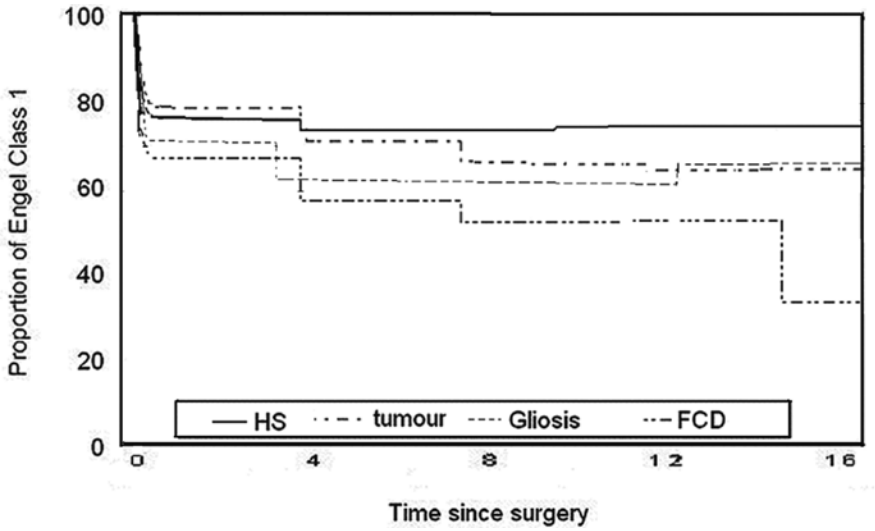

FIG. 3. Kaplan-Meier curves showing the percentage of patients in each pathological category who underwent temporal lobe resections and continued to remain in Engel Class I.

term outcome. This close relationship between short- and long-term outcome was also reported by other authors.[19,65]

Pathological Subgroups

Hippocampal Sclerosis. The best outcome in the pathological subgroups was in the group of patients with HS. In this group, the probability of remaining in Engel Class I at 16 years after surgery was 75.5% (95% CI 67–83%). Previous reports stated that the outcome in patients with HS ranges between 37 and 79%.[12,16,17,24,39,68]

Tumors, Gliosis, and FCD. In our study, similar to other studies, we reported favorable outcomes in patients with tumors; 65.4% (95% CI 55–75%) were seizure free 16 years after their operation.[42,45,60,74,76] Gliosis in older studies was associated with unfavorable results after TLE surgery.[13,29,75] Our results showed a favorable outcome in long-term follow-up, reaching 66.7% (95% CI 60–72%) in Engel Class I at the 16-year follow-up. A new report showed a favorable outcome similar to ours.[12] The difference between our study and older ones may have been due to the poor definition of gliosis in the latter studies.

The worst outcome in our study occurred in patients with FCD. The short-term outcome in the group of patients with FCD was favorable and in agreement with other authors reporting a short duration of follow-up.[20,62] The seizure-free rate in our study decreased over time; only 33.3% (CI 23–43%) of the patients remained seizure free at the 16-year follow-up. Our results are consistent with reports that suggest that the seizure-free outcome after surgery for FCD is less satisfactory than other focal pathologies.[10,15,47] Some authors reported a high seizure-free rate after FCD, but most of these studies included a combination of patients with temporal and extratemporal lobe

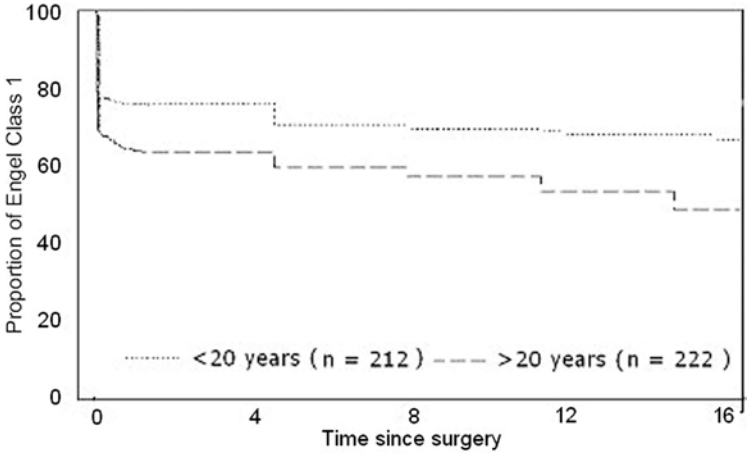

FIG. 4. Kaplan-Meier curves showing the percentage of patients in Engel Class I based on the preoperative duration of seizures.

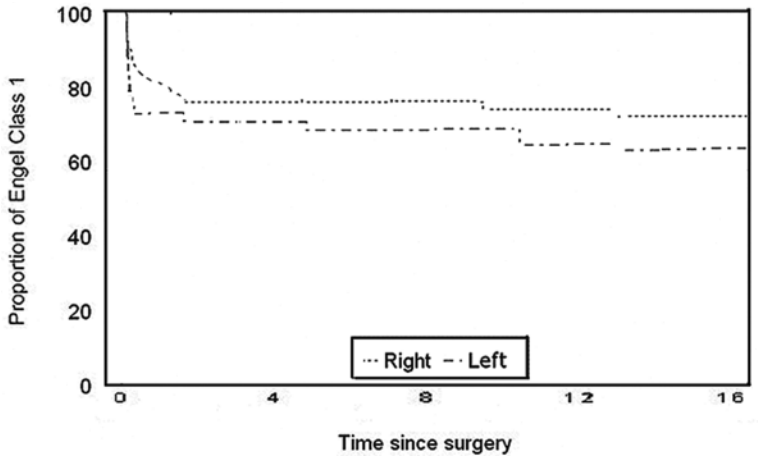

FIG. 5. Kaplan-Meier curves showing the percentage of patients in Engel Class I based on the side of operation.

resection as well as both pediatric and adult patients.[38] Many investigators have shown that the postoperative outcome in pediatric series is consistently better than in adult series of patients with FCD.[9,58] The unfavorable outcome in patients with FCD may be due to widespread pathological findings extending beyond the changes identified on MR imaging,[47,48,57] a different subtype of FCD,[20] and the extension of the epileptogenic zone beyond the lesional pathology.[11]

Side of Resection and Role of ECoG

In the univariate analysis, patients undergoing right-sided surgery had a significantly better outcome compared with those with left-sided resections, but right-sided surgery did not predict outcome in the multivariate analysis, meaning that this better outcome is attributable to many factors. In our study, right-sided operations were performed more often in males than in females; males were previously reported to show better outcomes.[8,52] From an etiological standpoint, the patients undergoing right-sided operations more often had lesions that were known as lesions with limited epileptogenic zones and capable of being completely resected. In a previous study from our institute, right-sided HS was associated with complex febrile seizures, and it has been shown that these seizures are a good predictor of outcome.[33] Moreover the right-sided resections tended to be more extensive.

TABLE 4: Results of the univariate analysis of significant variables

Variable	p Value	HR	95% CI
unilateral hippocampal atrophy on MR imaging	0.012	0.658	0.489-0.885
unilateral sharp waves	0.048	1.60	1.11–2.341
bilateral sharp waves	0.004	2.56	0.05–6.19
EEG unilateral seizure onset	0.006	0.26	0.07–0.98
EEG bilateral seizure onset	0.000	1.08	0.79–1.46
versive seizure	0.034	3.739	1.161–5.606
somatosensory aura	0.038	1.60	1.11–2.32
EEG at 6 months with IED	0.001	3.38	1.10–10.38
EEG at 2 years with IED	0.002	1.96	1.34–2.86
family history of epilepsy	0.001	0.450	0.285–0.711
history of febrile seizures	0.031	0.773	0.604–0.989
right-sided operation	0.042	1.06	1.11–2.32
duration of epilepsy (range 1–57 yrs)	0.043		
<20 years (212 patients)		reference	
>20 years (222 patients)		1.38	1.01–1.87
Age at surgery (range 16–57 yrs)	0.013		
<30 years (170 patients)		reference	
>30 years (264 patients)		1.08	0.79–1.46

TABLE 5: Predictors of outcome in different pathological subgroups

Pathology	Predictors of Outcome	p Value	HR	95% CIs
HS	bilateral sharp waves	0.004	1.507	1.143–1.987
	versive seizure	0.022	1.728	0.555–2.955
	preop MR imaging atrophy	0.021	0.347	0.08–1.504
	family history of epilepsy	0.001	0.445	0.346–0.857
tumor	duration of epilepsy	0.006	0.509	0.313–0.827
gliosis	duration of epilepsy	0.021	1.523	0.302–2.906
FCD	6-month EEG with IED	0.028	2.242	0.069–3.858

Electrocorticography

In our analysis, application of ECoG was not a predictor of outcome. In our clinic we stopped using ECoG in cases of HS/MTS. We found, like other authors, that ECOG has no role in this cases.[56] In temporal resection for other lesions, our neurosurgeon planned the resection based on preoperative MR imaging and the EEG field, which is 2D. The second step of planning was the intraoperative ECoG results. The ECoG results gave us the third dimension and led the surgeon to stop at the same line that had been constructed preoperatively or else to extend the resection guided by epileptiform discharges as recorded by ECoG. The effective role of ECoG in this type of surgery has been reported.[46] We consider it a useful diagnostic tool in all resections except for patients with HS.

Risk of Recurrence After Discontinuation of AEDs

In our study, 28.1% of the patients stopped taking AEDs and 41.7% were receiving monotherapy. Complete discontinuation of AEDs after 2 postoperative years was not associated with an increased risk of recurrence; the estimated HR was 1.05 (95% CI 0.933–1.20) and the probability value was 0.375.

Previous studies showed that a successful AED discontinuation rate ranged from 8.8 to 32%.[5,14,25,32,43,54] Some authors reported a higher frequency of postoperative seizure recurrence in patients who discontinued their AEDs compared with the patients who continued AEDs.[54] Others reported a low risk of seizure recurrence with AED discontinuation.[14,43] Our results are consistent with a low risk of recurrence after 2 years of follow-up. It is likely that the protocol for AED withdrawal varies among surgical centers, which may account for the differences in findings. Most of the previous studies had a selection bias toward those individuals perceived as low risk. Additionally, there are differences between the cohorts in pathology, distributions of patients, surgical outcome, and the period of follow-up, which may have contributed to the differences in findings.[43]

The majority of patients had no side effects from AEDs (67.7%) and was receiving monotherapy. These results are in agreement with other studies that reported better efficacy of AEDs in patients after surgery compared with nonsurgical patients.[73]

Influence of Preoperative Duration of Epilepsy and Age at Surgery on Seizure-Free Outcome

Preoperative epilepsy duration and age at epilepsy surgery had a significant correlation with remaining in Engel Class I in the univariate analysis but failed to have predictive value in the stepwise multivariate Cox regression model. The significance in the univariate analysis but the lack of significance in the multivariate analysis may reflect an association between the variables hippocampal atrophy and/or bilateral sharp waves.

There is a controversial debate in the literature, with some previous studies showing a long duration of epilepsy associated with worse outcome after surgery.[27,34,69] Other studies have not found such an association.[35,42,50] Age at surgery has also been a controversial factor. Some authors did not regard it as a predictor of outcome,[43] whereas others found that younger age at surgery predicted good outcome,[27] and surgery at an older age predicted a poor outcome.[66] This controversy may be due to different statistical methods used and the type of study (longitudinal or cross-sectional). Moreover, in the literature there are confusing interpretations of statistical terms such as correlation, association, and prediction.[28] Most cited studies did not make statistical adjustments for other factors.[43]

Late Seizure Recurrence

The period of the greatest risk for seizure recurrence in our study was within the first 6 months after surgery, with a continued slow but steady decrease for as long as 16 years after surgery thereafter. In our study, the recurrence rate in patients who were seizure free for 2 years postoperatively was 4.5% at 5 years, 6.7% at 10 years, and 4.1% at 16 years. Late seizure recurrence occurred in all pathology subgroups. The recurrence rates were similar for patients with HS, tumors, and gliosis, ranging from 4.1 to 14.5% over 16 years. Patients with FCD showed the highest rate of recurrence (6.3%) within 5 years; this rate increased to 21.4% at 10 years and 33% at 16 years.

The relevant scientific literature shows greatly diversified rates for late seizure recurrence, with rates ranging from 10 to 28% at the 5-year follow-up[7,16] and from 10 to 44% at the 10-year follow-up.[43,72] Our results were in agreement with investigators who reported a lower rate of recurrence.[21,61]

Long-Term Outcome Predictors

In the univariate analysis, the factors correlated with outcome were in accordance with previous studies that documented this relationship of outcome to unilateral hippocampal atrophy on MR imaging,[22,34,50] concordant IED abnormalities,[4,7,50] history of febrile seizures,[7] presence of a known origin for epilepsy,[3] postoperative IEDs,[49] age at surgery,[7,23,34] and size of resection.[63] In the Cox stepwise regression model with regard to the postoperative interval, only 4 variables predicted outcome: a family history of epilepsy and preoperative MR imaging hippocampal atrophy predicted seizure freedom; bilateral sharp waves and versive seizures predicted non–seizure-free outcome.

In recent years, different syndromes with a strong genetic component and a genetic locus for familial mesial TLE have been identified.[26,53] It has also been reported that among patients with familial mesial TLE there is a higher proportion with hippocampal atrophy, a fact that was observed in 57% of patients in nonsurgical studies.[37] Familial mesial TLE has, in general, a benign course and good seizure outcome.[37]

Previous studies have shown that patients with hippocampal atrophy often have a good postoperative outcome, mainly when unilateral hippocampal atrophy is identified on MR imaging.[30,36] Versive seizures were more frequently associated with extratemporal lobe epilepsy (either frontal or posterior), which has a nonfavorable outcome.[6,31] However, this semiology has also been observed in seizures of temporal lobe origin.[1,71] Bilateral interictal sharp waves have been previously associated with a worse surgical outcome in TLE.[1,55,64]

Postoperative Complications

There were no surgery-related deaths. The 5% surgical complication rate compares favorably with the reported rate of 5.4% in larger studies.[2] There were 10 postoperative deaths unrelated to the operation, some of which were a consequence of uncontrolled epilepsy. This finding is in agreement with other studies that showed that continuing seizures are associated with an increased risk of death.[12,51,61,67] Sudden and unexplained death occurred in patients who did not become free of seizures after surgery due to complications related to the continuation of their epilepsy.[51] Suicide is another potential cause of death among these patients.

Conclusions

This study confirms the sustained long-term benefit of surgery for the treatment of medically refractory TLE. The long-term seizure-free rate after surgery in this study is very similar to the short-term seizure-free rate. The outcome for patients with MTS, tumors, and gliosis was satisfactory compared with patients with FCD. This study also implies that the seizure-free status of patients 2 years after surgery reasonably predicts the subsequent outcome for as long as 16 years thereafter. Furthermore, this study confirms the low risk of AED discontinuation, which may be important in the decision-making process regarding tapering of anticonvulsant medications postoperatively.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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