CHAPTER 6

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Prognosis after temporal lobe epilepsy surgery: The value of combining predictors.

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Abstract

Although many independent predictors of seizure freedom after temporal lobe epilepsy surgery have been identified, their combined predictive value is largely unknown. Using a large database of operated patients, we assessed the combined predictive value of a multivariable model including previously reported independent predictors.

The database comprised a cohort of 484 Dutch patients who underwent temporal lobe surgery for drug resistant temporal lobe epilepsy. Good outcome was defined as Engel class 1, one year after surgery. All predictors previously reported in the literature were assessed; independent predictors had to have a multivariable p-value of <0.20 to be included.

The final multivariable model included independent predictors obtained from the patient's history (absence of tonic-clonic seizures, absence of status epilepticus), and MRI (ipsilateral MTS, space occupying lesion), video EEG (absence of ictal dystonic posturing, concordance between MRI and ictal EEG), and FDG-PET (unilateral temporal abnormalities) findings. The model had an expected ROC area of 0.63 (95%CI 0.57 to 0.68) for new patient populations. Intracranial monitoring and surgery-related parameters (including histology) were not independent predictors of seizure freedom after surgery. Of the patients with a high probability of seizure freedom, 85% were seizure free one year after surgery; however, of the patients with a high risk of not becoming seizure free, 40% were seizure free one year after surgery.

In conclusion, preoperative and intraoperative findings were only moderate predictors of postoperative seizure freedom after temporal lobe epilepsy surgery, in spite of many predictors that are associated with outcome. It is particularly difficult to predict who will not become seizure free after surgery.

Introduction

Epilepsy surgery is an effective treatment for medically intractable epilepsy, especially in patients with temporal lobe epilepsy (TLE). After TLE surgery, 60% to 70% of patients become seizure free and 90% of patients achieve a worthwhile reduction in seizure severity.[13;14] The presurgical work-up for epilepsy surgery is stepwise and complex, and contradictory findings from standard tests (history, seizure semiology, EEG, and MRI) with regard to lateralization or localization of the seizure focus necessitate additional tests of increasing invasiveness and cost (e.g. ictal SPECT, PET, intracranial EEG recordings). To be able to inform candidates for TLE surgery about their chances of postoperative seizure freedom, it is important to define which characteristics are true or independent predictors of seizure freedom after surgery. This requires a multivariable study approach.[67] The ultimate goal would be to develop a simple clinical prediction model or rule to predict the chance of seizure freedom after surgery for individual patients undergoing TLE surgery.

Previous studies of predictors of postoperative seizure freedom using multivariable analysis differ in their methodology and results.[47;114-129] Although potential independent predictors have been identified, the predictive value of combinations of these independent predictors (i.e., the value of these predictors combined in a single prediction model) has been investigated in only one study, which included patients with all types of epilepsy and not only TLE.[47] The aim of the present study was therefore to use a large homogeneous database of patients who underwent TLE surgery to quantify the predictive accuracy of the combination of previously reported predictors of seizure freedom. Thus, in contrast to the previous chapters of this thesis, this chapter focuses solely on patients who underwent epilepsy surgery.

Patients and methods

Patients

In the Netherlands, all patients referred for epilepsy surgery enter the Dutch

Collaborative Epilepsy Surgery Program, a nationwide tertiary referral program, in which each referred patient undergoes the same step-wise presurgical work-up. Decisions are taken by a multidisciplinary team. The present retrospective prognostic cohort study included a consecutive cohort of 484 patients (in 16 years) who underwent temporal lobe resection.

Surgery consisted of temporal lobe resection, tailored by acute electrocorticography including amygdalohippocampectomy (79%),[73] a standard resection (first two to three centimeters from the temporal pole) with amygdalohippocampectomy (15%), or a tailored lesionectomy without amygdalohippocampectomy (6%).

Prognostic predictors

We selected previously reported pre- and intraoperative predictors of seizure freedom after TLE surgery (see table 6.1).[47;114-129] We also included four potential predictors suggested by the members of the Dutch Collaborative Epilepsy Surgery Program, namely, absence of atypical features for TLE in videotaped seizures, defined as a somatosensible aura or a tonic, hypermotoric or atonic seizure; posterior temporal ictal onset during EEG monitoring; (ipsilateral) delayed anterior temporal theta onset in ictal EEG as described by Risinger et al.[63]; and the side of surgery (left versus right). These potential predictors have not been investigated before.

Prognostic outcome

Outcome was classified according to the Engel classification, one year after surgery. The outcome was dichotomized as Engel class 1 (including all subcategories), i.e. absence of disabling seizures, versus Engel class 2 or higher.[98]

Data collection

Predictors and outcome were retrieved for all 484 patients. Because each step of the presurgical work-up and the postsurgical follow-up is registered, we were able to

Table 6.1. Potential predictors of postoperative seizure freedom, investigated in our study.

History	*MRI*	*Video EEG*	*Additional tests*	*Surgery*
Female sex[128]	Abnormal MRI[46;116;122;126;129]	No ictal dystonic posturing[118]	Unilateral temporal abnormalities on FDG_PET[116]	Larger resection size (in cm)[129]
Febrile seizures[129]	MTS ipsilateral to resection side[119;120;125-129]	No bilateral interictal spikes[46;114;115]	Intracranial monitoring performed[46;114;129]	Postoperative discharges during acute eectrocorticography[129]
Shorter epilepsy duration (in years)[118;124]	Space occupying lesion ipsilateral to resection side[117;122;129]	No extratemp interictal spikes[123]		MTS on histology[128]
Higher age at start epilepsy (in years)[121]	Concordance of MRI & EEG results (both unilateral temporal)[129]	Concordance of interictal & ictal EEG results (both unilateral temporal)[127]		No cortical dysgenesis on histology[115]
No tonic clonic seizures[118;120;123;126] [a]				
No status epilepticus[122]				
Higher total IQ score[121;124] [b]				
Younger age at surgery (in years)[119;125;128]				

[a] *Including secondary generalized tonic clonic seizures;* [b] *Total IQ used as indicator for mental retardation[121] or need for special schooling[124]*

build a research database in which all information on predictors and outcome was coded as described above. During encoding, kappa analyses were performed between the two scoring researchers (SU and AC) and two independent experts (FL, JA), to ensure uniformity. As previously described, only variables with kappa values of 0.70 or higher were included.[18;19;130]

Data analysis

After univariable analysis, the predictors of postoperative seizure freedom were included in an overall multivariable logistic regression model. We assessed whether continuous predictors needed to be transformed, using restricted cubic splines.[67] This model included all predictors from basic preoperative work-up (i.e., from patient history, MRI, and video EEG monitoring). Predictors were excluded from this overall model if the sign of the multivariable regression coefficient was not considered plausible compared to the performance of the predictor in earlier studies, according to the sign OK method.[67;131] Furthermore, the model was reduced by step-wise exclusion of the least contributory predictors (defined as a p-value higher than 0.20, based on the log likelihood ratio test), to determine which predictors independently contributed to the prediction of seizure freedom (model 1). We then assessed the value of additional presurgical tests. In model 2, we added unilateral temporal abnormalities on FDG-PET to model 1, to assess its incremental predictive value, and in model 3 we additionally included intracranial monitoring. In model 4, we also included operative predictors identified from the literature.

The ability of each model to discriminate between postoperative seizure freedom or not was quantified using the area under the receiver operating characteristic curve (ROC area). Agreement (calibration) between the predicted and observed rates of seizure freedom was assessed with the Hosmer-Lemeshow statistic (high p-values indicating good calibration) and a calibration plot.

To prevent optimistic predictions in new patient populations, the internal validity of the prognostic models was studied with bootstrapping

techniques (100 samples).[67] The average difference in performance between the bootstrap samples and the original data gives an impression of the optimism of the model in new patients. Based on these bootstrap results, the ROC area and regression coefficients (odds ratios) of the predictors were corrected for optimism.

As some values were missing and missing values usually do not occur at random, we imputed the missing values to prevent bias, using single imputation by linear regression with the addition of a random error term.[66;83] FDG-PET was not performed in all patients, but was usually performed in patients with inconclusive results after MRI and video EEG monitoring. Imputation of FDG-PET results in patients in whom FDG-PET was actually not performed enabled us to assess the independent value of FDG-PET, as described previously.[66;83;130]

Statistical analyses were performed with S-plus version 6.2 (Insightful Corporation, Seattle, Washington, USA).

Results

Of the 484 patients, 356 patients (incidence 74%, 95% confidence interval (CI): 0.69-0.77) were seizure free (Engel class 1) one year after surgery.

The univariable associations between predictors and outcome are presented in figure 6.1. In the multivariable model, the two continuous predictors 'age at time of surgery' and 'duration of epilepsy' were each included as square root. Reduction of the original model based on history, MRI, and video EEG monitoring findings yielded six independent predictors of seizure freedom (model 1, table 6.2): age at time of surgery, absence of tonic-clonic seizures or status epilepticus in the patient's history, presence of ipsilateral MTS or a space occupying lesion on the MRI, and absence of ictal dystonic posturing. None of the extra predictors proposed by the members of the Dutch Collaborative Epilepsy Surgery Program were of added predictive value to this reduced model.

FDG-PET abnormalities was an independent predictor of seizure freedom (OR = 1.47; 95% CI 0.95 to 2.29; p-value: 0.09) (model 2), whereas intracranial monitoring (OR = 1.14; 95% CI 0.62 to 2.07; p-value 0.68) and operative

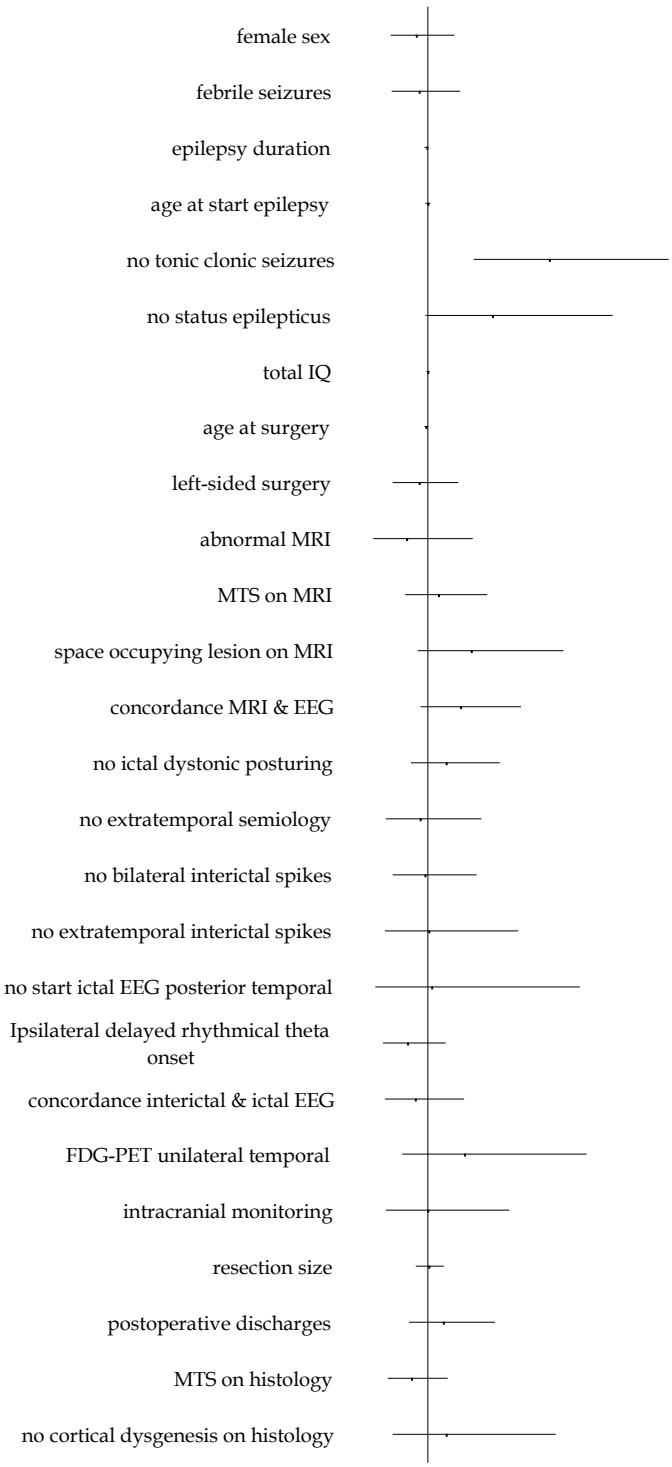

Figure 6.1. Univariable associations of each potential predictor with Engel class 1 (yes / no) as outcome. Lines represent odds ratio's with 95% confidence intervals, reference line at 1

Table 6.2. Models including only the independently contributing predictors for postoperative seizure freedom. Model 1 includes predictors from history, MRI and video EEG; model 2: model1+ FDG-PET result; model 3: model 2 + intracranial monitoring; model 4: model 3 + surgical predictors.

	Model 1		*Model 2*		*Model 3*		*Model 4*	
	Odds Ratio (95% CI)	*P-value*	*Odds Ratio (95% CI)*	*P-value*	*Odds Ratio (95% CI)*	*P-value*	*Odds Ratio (95% CI)*	*P-value*
no tonic clonic seizures	2.24 (1.40-3.58)	0.001	2.31 (1.44-3.70)	0.001	2.32 (1.45-3.73)	<0.01	2.32 (1.45-3.73)	<0.01
no status epilepticus	1.62 (0.88-2.98)	0.12	1.54 (0.83-2.84)	0.17	1.52 (0.82-2.82)	0.18	1.45 (0.78-2.71)	0.24
age at surgery [a]	0.84 (0.68-1.04)	0.10	0.83 (0.67-1.03)	0.09	0.83 (0.67-1.03)	0.09	0.84 (0.68-1.05)	0.12
MTS	1.63 (1.03-2.58)	0.04	1.61 (1.02-2.57)	0.04	1.59 (0.99-2.55)	0.06	1.80 (1.05-3.08)	0.03
space occupying lesion on MRI	1.67 (0.92-3.02)	0.09	1.68 (0.93-3.03)	0.09	1.63 (0.89-2.99)	0.11	1.57 (0.85-2.90)	0.15
no ictal dystonic posturing	1.34 (0.87-2.05)	0.19	1.36 (0.89-2.10)	0.16	1.35 (0.88-2.08)	0.18	1.36 (0.87-2.12)	0.17
FDG-PET unilateral temporal	na [b]		1.47 (0.95-2.29)	0.09	1.47 (0.95-2.29)	0.09	1.50 (0.96-2.35)	0.07
intracranial monitoring performed	na		na		1.14 (0.62-2.07)	0.68	1.14 (0.62-2.13)	0.67
resection size	na		na		na		1.02 (0.86-1.20)	0.86
postoperative discharges	na		na		na		1.15 (0.76-1.77)	0.51
MTS on histology	na		na		na		0.78 (0.46-1.34)	0.37
no cortical dysgenesis on histology	na		na		na		1.17 (0.55-2.49)	0.68

[a] *included as square root, see text;* [b] *na = not applicable*

predictors (model 4) were not.

The Hosmer-Leweshow test indicated good calibration, with a p-value of 0.79 for model 1, 0.35 for model 2, 0.47 for model 3, and 0.57 for model 4. This was confirmed by the calibration plots (not shown).

Model 2, based on predictors from the patient's history, and MRI, video EEG, and FDG-PET findings, was the best prediction model, with an ROC area of 0.66 (0.60-0.70). After correction for optimism, based on bootstrapping, this ROC area was reduced to a ROC area of 0.63 (95% CI 0.57 to 0.68), a value that can be expected if this model is used with other similar patient populations.

Table 6.3 shows the number of patients with and without seizure freedom after one year, across the probability categories predicted by model 2. The observed incidence of seizure freedom increased from 40% in the lowest probability group to 85% in the highest probability group. The risk of not becoming seizure free ranged from 15% in the group with the highest probability of seizure freedom to 60% in the lowest. This means that 40% of patients with the highest risk of not achieving seizure freedom were nevertheless seizure free one year after surgery.

Table 6.3. Number (%) of patients with or without seizure freedom after one year over the probability categories estimated by model 2 (see table 2). N=484.

Estimated probability based on model 2 in table 2	*Seizure freedom* N=356	*No seizure freedom* N=128
<0.45 (N=5; 1% of 484)	2 (40%)	3 (60%)
0.45-0.60 (N=52; 11%)	31 (59%)	21 (41%)
0.60-0.70 (N=112; 23%)	74 (66%)	38 (33%)
0.70-0.80 (N=161; 33%)	118 (73%)	43 (26%)
> 0.80 (N=154; 32%)	131 (85%)	23 (15%)

Discussion

We assessed all 22 predictors found in earlier multivariable studies on seizure freedom after TLE surgery[47;114-129] and identified seven independent predictors of postoperative seizure freedom, i.e., younger age at time of surgery, a history without tonic-clonic seizures, a history without status epilepticus, MRI with ipsilateral MTS, MRI with space occupying lesion, no dystonic posturing during the seizure, and unilateral temporal abnormalities on FDG-PET. The other predictors from the basic diagnostic work-up, additional diagnostic tests, and opertive data did not independently contribute to the prediction of postoperative seizure freedom. Our final model included all predictors reported by Janszky et al., Jeong et al. and Spencer et al..[117;119;120]

Our study presents an overall predictive value, i.e., a measure of how the use of such a model would discriminate between postoperative seizure freedom or not. This overall predictive value of the combination of predictors was moderate, with a ROC area 0.63. This means that we were unable to formulate a simple and stable prediction rule to predict seizure freedom that could be used to inform patients. The model can be used to indicate 'risk' categories for postoperative seizure freedom, however, it performs insufficiently to be used for individual patients to discriminate between becoming and not becoming seizure free.

Of earlier studies, only the one by Armon et al. included a measure of the performance of their model in predicting postoperative seizure freedom.[47;118] Armon et al. found a Somers' D of 0.47, or a ROC area of 0.74 without correction for optimism, on the basis of five preoperative predictors: ipsilateral imaging abnormality, ipsilateral EEG localization (ictal and interictal), intracranial EEG recordings, temporal lobe resection, and age.[47] Since their study involved patients who had undergone temporal or extratemporal resections, their model is not directly comparable to ours. However, the predictors 'ipsilateral imaging abnormality' and 'age' were also included in our model.

Unfortunately, other studies predicting postoperative seizure freedom did not present the overall accuracy of their model (nor could this be reconstructed

with the data provided). The wide variation of preoperative predictors reported in the literature and the moderate overall predictive value of our own model indicate that it is difficult to predict of postoperative seizure freedom one year after TLE surgery. In prognostic medical research, as in all areas of life, prediction becomes more difficult the further ahead we want to predict.[132] This means that the presence or absence of an independent predictor in an individual patient cannot directly be associated with an increased or decreased chance of becoming seizure free after surgery.

To appreciate our results, some methodological aspects need to be discussed. First, the study outcome measure was Engel class 1, one year after surgery. We reanalyzed the data with the outcome absolute seizure freedom (Engel class 1A) one year after surgery, which led to the same results, i.e., the same independent predictors were identified. Secondly, we wanted to include ancillary tests, such as FDG-PET, which were not performed in all patients. FDG-PET was performed in 188 of 484 patients, mostly when MRI and video EEG monitoring results were inconclusive. Imputation of FDG-PET results in patients in whom FDG-PET was not performed, as described earlier, enabled us to assess the independent value of FDG-PET in the complete patient population.[130] We reached the same conclusion when we restricted our analysis to the subgroup of 188 patients in whom FDG-PET was performed. Thirdly, the predictors were necessarily reduced to essentials for categorization. Since the number of predictors that can be included a prognostic model is limited, we only included previously reported predictors of seizure freedom. This obviously does not fully reflect the subtle nuances of interpretation that often arise in clinical practice, and thus the model does not comprise all possible information; these complexities necessarily have been obscured.

In conclusion, whereas the results of many preoperative tests in TLE surgery have a statistically significant association with postoperative seizure freedom, in combination they are only moderate predictors of postoperative

seizure freedom. It is particularly difficult to predict the absence of postoperative seizure freedom. Unfortunately, currently available data do not yet allow the development of a robust prediction rule for postoperative seizure freedom. More refined (software) analysis of existing tests, new diagnostic tests such as EEG-fMRI, and even genetic analysis, may provide future opportunities to improve the prediction of postoperative seizure freedom.