

Long-term and late seizure outcome after surgery for temporal lobe epilepsy

José Pimentel¹, Carla Bentes^{1,2}, Alexandre Campos³,
A. Gonçalves Ferreira³, and the Epilepsy Surgery Group

¹ Department of Neurology; Institute of Molecular Medicine

² EEG/Sleep Laboratory

³ Department of Neurosurgery

CHLN, EPE - Hospital de Santa Maria/Lisbon Faculty of Medicine, Lisbon, Portugal

Received February 6, 2009; Accepted February 3, 2010

ABSTRACT – *Aim.* Although surgery for temporal lobe epilepsy (TLE) harbours a good prognosis, post-operative seizures may occur. Long-term, post-operative seizure follow-ups are rare but necessary to properly define outcome. *Methods.* Longitudinal, long-term, post-operative seizure follow-up in TLE patients with outcome analysed using Engel's classification. Three groups were considered according to the type of resection: isolated amygdalo-hippocampectomy (IAH), further divided into anterior and complete, AH plus focal neocortical resections (AH + FR) and focal neocortical resections (FR). *Results.* Eighty-nine patients were enrolled (61 in the IAH group, 24 in the AH + FR group, and four in the FR group), with a mean follow-up time of 46.7 months. For the three groups together, 90.9% and 86.7% of the patients were in Engel class I for six months and five years, respectively. Kaplan-Meier analysis of the IAH and AH + FR groups showed that, while 82.2% of patients of the IAH group tended to remain in class I within 84 months after surgery, 86.7% of the AH + FR group tended to remain in class I within 12 months. Kaplan-Meier analysis of the IAH sub-groups showed that more patients (91.0%) with anterior resection tended to remain in class I, although for a longer period of time (36 months), compared to those with complete resection (84.0% of patients and 12 months, respectively). For the IFR group, only three patients were in Engel class I for long-term follow-up. *Conclusions.* High rates of seizure freedom were obtained and stably maintained for years. The reasons for better long-term prognosis of the anterior IAH group are so far unclear, the IFR group was too small to draw any conclusive data.

Key words: surgery, temporal lobe epilepsy, seizure recurrence

Surgery for temporal lobe epilepsy (TLE) is the most frequent surgery performed when treating epilepsies, usually harbouring a very good prognosis (Engel, 1987). Despite the low rates of post-operative seizure recurrence, the

outcome is not similar for neocortex and mesial lesions, the first ones presenting higher seizure rates (Schwartz *et al.*, 2006). Furthermore, although many factors have been linked to post-operative prognosis, there are

Correspondence:

J. Pimentel
Department of Neurology,
Hospital de Santa Maria,
Av. Egas Moniz,
1649-035, Lisbon, Portugal
<josepimentel@fm.ul.pt>

This work was presented at the 8th European Congress on Epileptology, Berlin, 2008

still no consensual predictors of seizure recurrence (Hennessy *et al.*, 2001; Yun *et al.*, 2006; Janszki *et al.*, 2006). Finally, most studies concerning the post-operative outcome of seizures in patients with TLE present short or medium follow-up periods and are based on cross-sectional methods of analysis (McIntosh *et al.*, 2004).

The results of our series of TLE patients, who have undergone surgery, are presented through a prospective, longitudinal evaluation. The aim of this study was to identify long-term and late post-operative seizure outcome by examining extended follow-up data based on a surgical cohort.

Material and methods

One hundred patients (79.5% of the total) underwent TLE surgery in our department between 1993 and 2007, of which 71 were evaluated according to the Epilepsy Surgery Group's comprehensive pre-surgical protocol, institutionalized since 2000. The types of resections performed were as follows:

- isolated amygdalohippocampectomy (IAH), for allocortex lesions only, clinically and neuropathologically corresponding to mesial sclerosis (MS). Whenever the amygdala and a significant amount of the hippocampus (generally right mesial temporal lesions) were resected, the resection was referred to as "complete". In contrast, partial, usually anterior hippocampal resections (generally left mesial temporal lesions) were referred to as "anterior";
- amygdalohippocampectomy plus focal neocortical lesion resections (AH + FR), corresponding to a variable pathology (of which the majority were neuroepithelial tumours, vascular malformations and cortical dysplasias), other than MS, arising either from the neocortex or the allocortex;
- isolated focal lesion resections (IFR), also corresponding to a variable pathology arising from the neocortex only.

The Engel classification of post-surgical seizure outcome was used (Engel, 1987). We performed a prospective, longitudinal study of all cases with a known post-surgical follow-up of six or more months. The variables of gender, age and type of surgery were extracted from the patients' epilepsy surgery database. Patients followed at our out-patient clinic were seen at 3, 6, 12, and 24 months after surgery and, from that time on, once a year or whenever necessary. They were asked to bring a seizure diary for each visit. For those who had undergone surgery in the previous four years, an effort was made not to change pre-surgical anticonvulsive treatment for five years. For those who had undergone surgery more than four years ago, the period of treatment was seldom shorter than two years. The great majority of patients followed at

other institutions were so by epileptologists, retaining the same pre- and post- surgical treatment for at least two years. For those few who left the out-patient clinic, data was obtained by telephone. When appropriate, and at the doctors' discretion, antiepileptic (AE) serum concentrations were required.

Results

The number of patients enrolled in the study was 89 (11 were lost during follow-up or had post-operative follow-up periods of less than six months), 48 women and 41 men, with a mean age (known for 87 patients) of 35 years (range: 1 to 66). Forty-eight lesions were identified from the left temporal lobe and 41 from the right temporal lobe. Epileptogenic lesions were identified for all patients by magnetic resonance imaging (MRI). The mean length of follow-up for post-operative seizures was 46.7 months (ranging from 6 to 180 months). IAHs were performed in 61 patients, anterior and complete resections in 36 and 25, respectively. AH + FR were performed in 24 patients, with 12 for epileptogenic lesions arising from the allocortex and 12 from the neocortex. IFRs were performed four times (*figure 1*).

Overall, 76 patients (85.3%) were in Engel class I for a mean follow-up period of 46.7 months (ranging from 6 to 168 months), while 54 (85.5%) (ranging from 6 to 168 months), 19 (79.1%) (ranging from 24 to 192 months), and 3 out of 4 (ranging from 48 to 84 months) belonged to the IAH, AH + FR and IFR groups, respectively.

In particular, for only those patients not in Engel class I: a) IAH group: three patients were and remained in Engel class II with no change in anticonvulsive therapy (one was lost during follow-up at 24 months, one died at 48 months, and one had a follow-up of 84 months). One patient, who shifted from Engel class I to class II at 12 months, had a follow-up of 24 months with no change in anticonvulsive therapy. Two other patients shifted from Engel class I to

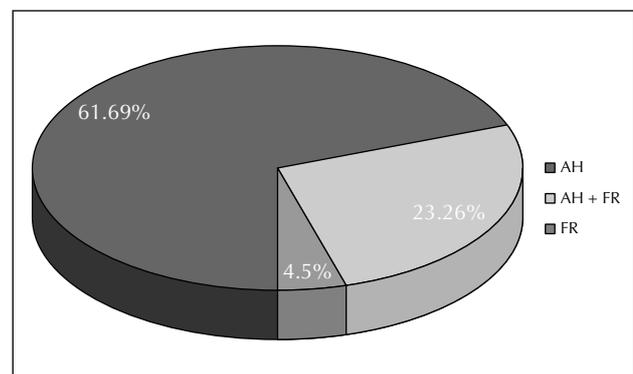


Figure 1. Type of surgical resections.

IAH: isolated amygdalohippocampectomy; AH + FR: amygdalohippocampectomy plus focal resection; IFR: isolated focal resection.

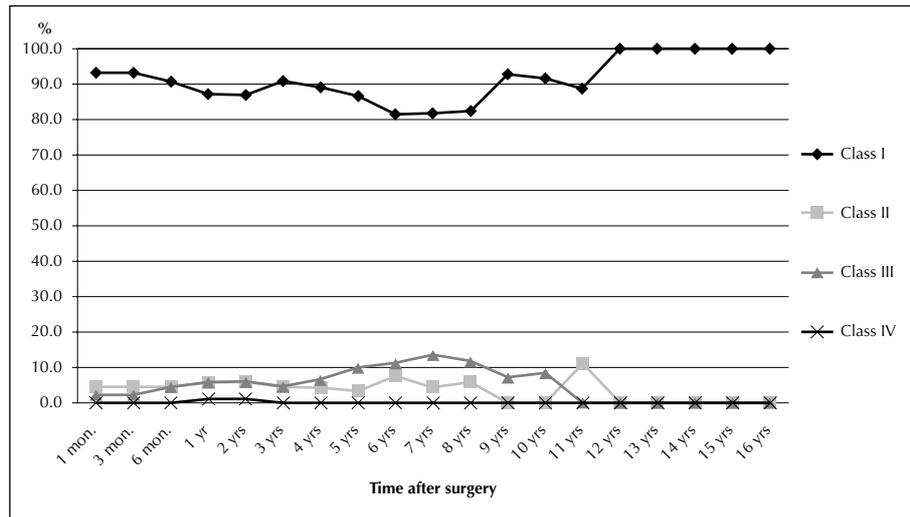


Figure 2. Post-surgery seizure outcome. Engel classification: Class I: seizure-free patient, Class II: rare seizures, Class III; worthwhile seizure reductions, Class IV: no improvement.

class III at six months (and for a further 24 months until death) and 96 months, respectively, also with no change of anticonvulsive therapy. Finally, one patient shifted from Engel class I to II at 12 months, returning to class I at 36 months of follow-up, again with no change of therapy; b) AH + FR group: one patient shifted from Engel class I to class II at three months and subsequently to class III at 12 months during a 24-month follow-up period. The last clinical data suggested the existence of pseudo-seizures but there was no account of change of anticonvulsive treatment. Another patient shifted from Engel class I to class IV at 12 months and subsequently to class II at 132 months, although with low compliance. Finally, one patient remained in Engel class III following surgery during a 24-month follow-up period, with no change in anticonvulsive therapy;

c) IFR group: one patient was in Engel class III at three months but shifted to class II at 96 months, with a change in anticonvulsive therapy.

For the three groups together, 90.9% and 86.7% of the patients were in Engel class I at six months and five years of post-operative follow-up, respectively (figure 2). Regarding the IAH and AH + FR groups only, 91.8% and 89.0% of patients in the IAH group were in Engel class I at six months and five years, respectively, whereas 91.3% and 88.8% of the patients in the AH + FR group were in the same class for a similar period of time. According to Kaplan-Meier's survival analysis, after a period of 84 months post-surgery, 82.2% of patients of the IAH group tended to remain in class I, whereas 86.7% of patients in the AH + FR group tended to remain in class I within 12 months (figure 3). Of the IAH isolated group, 97.2% of patients with anterior resections and 89.0% of the patients with complete resections were in Engel class I at six months post-surgery. At five years post-surgery,

90.0% of patients with anterior resections and 88.9% of the patients with complete resections of the patients were in the same class. According to Kaplan-Meier's survival analysis, more patients (91.0%) in the anterior resection sub-group tended to remain in class I, although for a longer post-surgical period (36 months), compared with the complete resection sub-group (84.0% of the patients and 12 months, respectively) (figure 4). Finally, for the IFR group, 3 patients were in Engel class I at six months and four years of follow-up and 1 patient was in Engel class III for similar, elapsed follow-up periods. None of these differences were statistically significant ($p > 0.05$). Data concerning post-surgical maintenance or withdrawal of AE was obtained for 79 of the 89 patients enrolled. Of these, 25 (31.6%) were free of medication, and were evaluated as Engel class I.

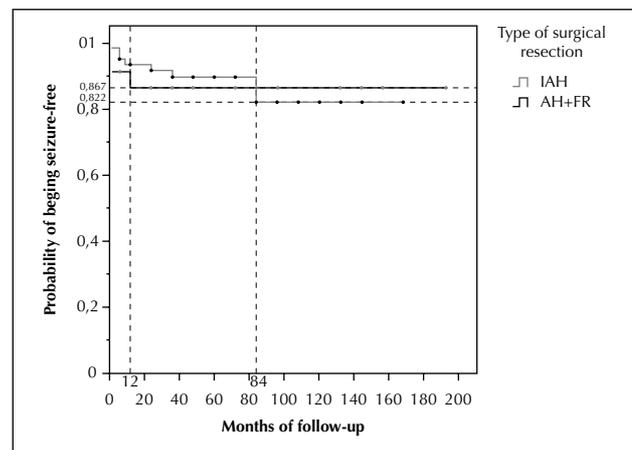


Figure 3. Kaplan-Meier cumulative survival in IAH and AH + FR types of surgery.

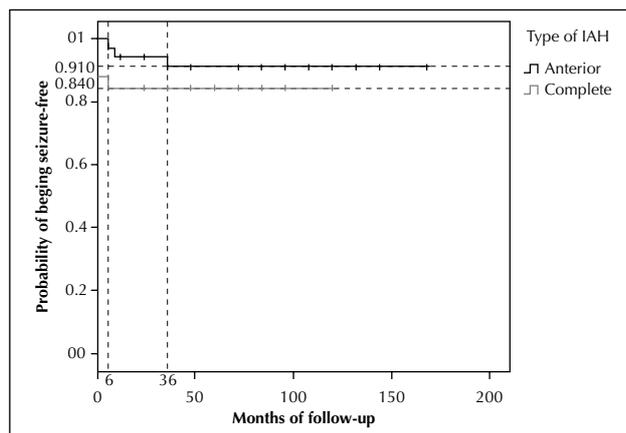


Figure 4. Kaplan-Meier cumulative survival in sub-groups of IAH type of surgery.

Discussion

The efficacy of surgery and its inferiority in prolonged therapy for TLE is widely accepted (Engel, 1987; Wiebe *et al.*, 2001), as is the type of surgical approach used in our department (Olivier, 1988). This efficacy is most frequently measured by seizure outcome, although many other parameters (for instance, surgery complications, memory outcome, social and professional achievements) may also account for the general post-operative outcome. Predictors of surgical outcome have been identified, although not always consensually, in patients with TLE, both pre-operatively (McIntosh *et al.*, 2004; Schwartz *et al.*, 2006; Yun *et al.*, 2006) as well as per-operatively (Clusmann *et al.*, 2004; Chen *et al.*, 2006; Bonilha *et al.*, 2007). Post-operatively, the type of pathology (Hennessy *et al.*, 2001) and time of withdrawal of antiepileptic medication (Berg *et al.*, 2006), among other factors, may be crucial. The patients' follow-up was performed by well-trained epileptologists, and more than 95% of our patient series had post-surgical treatment lasting for at least two years, increasing to five years for 60% patients, at the time the data was studied. Moreover, as we have described in detail, during the pre- and post-surgical period most of our patients complied with the number and dosage of anticonvulsive drugs that rarely changed. It is therefore highly unlikely that the time of post-surgical treatment and change in anticonvulsive drugs may be responsible for seizure recurrence. Finally, AE serum concentration performed in the selected cases was of no help in solving the cause of recurrence.

Most studies addressing post-operative TLE short or long-term seizure follow-up periods have consistently shown high rates of seizure control for allocortical resections (Jeong *et al.*, 2005) and, although not consistently, lower rates for neocortical resections (O'Brien *et al.*, 1996; Schramm *et al.*, 2001). Furthermore, evidence has also

emerged of higher rates, than previously reported, of late recurrence, with seizures reappearing even as late as a decade after post-operative cessation (Yoon *et al.*, 2003; McIntosh *et al.*, 2004). This fact highlights the need for longitudinal rather than cross-sectional methods of analysis, allowing for pre- and post-operative counselling and management of patients (McIntosh *et al.*, 2004).

Our study has been conducted in such a way as to specifically evaluate post-operative seizure outcome, rather than the presence of any potential risk factors for recurrence. The rationale for this decision was based upon our sample size, which was the same or smaller than in previously reported studies that have addressed the same issue. The disparity regarding the prognostic value of risk factors was also a consideration.

Collectively, our results may be considered to be similar to other series, with either longitudinal (Salanova *et al.*, 1999; McIntosh *et al.*, 2004; Jeong *et al.*, 2005) or cross-sectional outcome (Paglioli *et al.*, 2004; Schwartz *et al.*, 2006; Jeha *et al.*, 2006). Indeed, we observed between 85% and 90% of patients in Engel class I at five years following surgery.

All patients in our series presented a lesion on MRI. Identification of an epileptogenic lesion by MRI may be one of the predictors of a seizure-free outcome for TLE patients (Clusmann *et al.*, 2002; Yun *et al.*, 2006), although absence of a lesion does not always predict a worse prognosis (Jeha *et al.*, 2006). Hence, although we may have introduced a bias for the selection of our patients, we are confident that this factor *per se* has not been a major factor in altering analysis of seizure outcome.

Unexpectedly, patients in the anterior resection sub-group of IAH seemed to have a better outcome than those in the complete resection sub-group. Despite the reported difference in outcome between a short and a longer resection in the so-called selective AH (Wyller *et al.*, 1995), which corresponds to our IAH resection type, this matter still seems to be debatable. Indeed, an extensive and critical review of many aspects of TLE surgery (Schramm, 2008) concluded that strong evidence is lacking concerning seizure outcome related to both the extension and the type of resection of mesial temporal structures. Furthermore, the majority of the authors concluded that the extent of mesial resection does not seem to be important with regards to outcome. In addition, the usual absence of post-operative MRI volumetry could prevent the correct estimation of the amount of resected hippocampus. Finally, we cannot exclude the fact that an unidentified seizure recurrence risk factor is significant, and this will only be addressed definitely by using appropriate methodology. Notwithstanding, at the time of our data analysis, around at least one third of the patients had already achieved full AE withdrawal. The relevance of this is endorsed by the fact that the median time of follow-up

of this series did not reach 48 months, indicating that a significant proportion of patients had not yet reached the ideal time for stopping medication.

Our series of neocortical TLE surgery is too small to draw any definitive conclusions. Nevertheless, overall, our results are generally in agreement with other series that have identified two thirds of patients being seizure-free following surgery (Janzky *et al.*, 2006; Yun *et al.*, 2006). In conclusion, we have confirmed that seizure outcome for TLE surgery is good. Furthermore, and despite the different methodologies and discontinuity of antiepileptic drugs, or any other risk factors, late recurrences in our series did not appear to be an issue of concern. We confidently believe, therefore, that patients with TLE should be proposed for surgery in the absence of any precluding potential risk factors for recurrence. The appropriate extent of mesial structure resectioning, in terms of seizure outcome, is still under debate. □

Disclosure.

None of the authors has any conflict of interest to disclose.

References

- Berg AT, Vickrey BG, Langfitt JT, *et al.* Reduction of AEDs in post-surgical patients who attain remission. *Epilepsia* 2006; 47: 64-71.
- Bonilha L, Yasuda CL, Li LM, *et al.* Does resection of the medial temporal lobe improve the outcome of temporal lobe epilepsy surgery? *Epilepsia* 2007; 48: 571-8.
- Chen X, Sure U, Haag A, *et al.* Predictive value of electrocortigraphy in epilepsy patients with unilateral hippocampal sclerosis undergoing selective amygdalohippocampectomy. *Neurosurg Rev* 2006; 29: 108-13.
- Clusmann H, Kral T, Blümcke I, *et al.* Lesional mesial temporal lobe epilepsy and limited resections: prognostic factors and outcome. *J Neurol Neurosurg Psychiatry* 2004; 75: 1589-96.
- Clusmann H, Schramm J, Kral T, *et al.* Prognostic factors and outcome after different types of resection for temporal lobe epilepsy. *J Neurosurg* 2002; 97: 1131-41.
- Engel J Jr. Outcome with respect to epileptic seizures. In: *Engel J Jr. Surgical treatment of the epilepsies*. New York: Raven Press, 1987: 553-71.
- Hennessy MJ, Elwes RDC, Honavar M, *et al.* Predictors of outcome and pathological considerations in the surgical treatment of intractable epilepsy associated with temporal lobe lesions. *J Neurol Neurosurg Psychiatry* 2001; 70: 450-8.
- Janzky J, Pannek HW, Fogarasi A, *et al.* Prognostic factors for surgery of neocortical temporal lobe epilepsy. *Seizure* 2006; 15: 125-32.
- Jeha LE, Najm IM, Bingaman WE, *et al.* Predictors of outcome after temporal lobectomy for the treatment of intractable epilepsy. *Neurology* 2006; 66: 1938-40.
- Jeong S, Lee SK, Hong K, *et al.* Prognostic factors for the surgery for mesial temporal lobe epilepsy: longitudinal analysis. *Epilepsia* 2005: 1273-9.
- McIntosh AM, Kalnins RM, Mitchell LA, *et al.* Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. *Brain* 2004; 127: 2018-30.
- O'Brien TJ, Kilpatrick TC, Murrie V, *et al.* Temporal lobe epilepsy caused by mesial temporal lobe sclerosis and temporal neocortical lesions. *Brain* 1996; 119: 2133-44.
- Olivier A. Risk and benefit in the surgery of epilepsy: complications and positive results on seizures tendency and intellectual function. *Acta Neurol Scand* 1988; 78 (Suppl. 117): 114-21.
- Paglioli E, Palmieri A, Paglioli E, *et al.* Survival analysis of the surgical outcome of temporal lobe epilepsy due to hippocampal sclerosis. *Epilepsia* 2004; 45: 1383-91.
- Salanova V, Markand O, Worth R. Longitudinal follow-up in 145 patients with medically refractory temporal lobe epilepsy treated surgically between 1984 and 1995. *Epilepsia* 1999; 40: 1417-23.
- Schramm J. Temporal lobe epilepsy surgery and the quest for optimal extent of resection: A review. *Epilepsia* 2008; 49: 1296-307.
- Schramm J, Kral T, Grunwald T, *et al.* Surgical treatment for neocortical temporal lobe epilepsy: clinical and surgical aspects and seizure outcome. *J Neurosurg* 2001; 94: 33-42.
- Schwartz TH, Jeha L, Tanner A, *et al.* Late seizures in patients initially seizure free after epilepsy surgery. *Epilepsia* 2006; 47: 567-73.
- Wiebe S, Blum WT, Girvin JP, *et al.* A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001; 345: 311-8.
- Wyler AR, Hermann BP, Somes G. Extent of medical temporal resection on outcome from anterior temporal lobectomy: a randomized prospective study. *Neurosurgery* 1995; 37: 982-90.
- Yoon HH, Kwon HL, Mattson RH, *et al.* Long-term seizure outcome in patients initially seizure-free after resective epilepsy surgery. *Neurology* 2003; 61: 445-50.
- Yun C, Lee SK, Lee SY, *et al.* Prognostic factors in neocortical epilepsy: multivariate analysis. *Epilepsia* 2006; 47: 574-9.