

Current Literature

In Clinical Science



Long-Term Outcome After Epilepsy Surgery: Relapsing, Remitting Disorder?

The Long-Term Outcome of Adult Epilepsy Surgery, Patterns of Seizure Remission, and Relapse: A Cohort Study.

de Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WFJ, Sander JW, John S Duncan JS. *Lancet* 2011;378:1388–1395.

BACKGROUND: Surgery is increasingly used as treatment for refractory focal epilepsy; however, few rigorous reports of long-term outcome exist. We did this study to identify long-term outcome of epilepsy surgery in adults by establishing patterns of seizure remission and relapse after surgery. **METHODS:** We report long-term outcome of surgery for epilepsy in 615 adults (497 anterior temporal resections, 40 temporal lesionectomies, 40 extratemporal lesionectomies, 20 extratemporal resections, 11 hemispherectomies, and seven palliative procedures [corpus callosotomy, subpial transection]), with prospective annual follow-up for a median of 8 years (range 1–19). We used Kaplan-Meier survival analysis to estimate time to first seizure, and investigated patterns of seizure outcome. **FINDINGS:** We used survival methods to estimate that 52% (95% CI 48–56) of patients remained seizure free (apart from simple partial seizures [SPS]) at 5 years after surgery, and 47% (42–51) at 10 years. Patients who had extratemporal resections were more likely to have seizure recurrence than were those who had anterior temporal resections (hazard ratio [HR] 2.0, 1.1–3.6; $p=0.02$); whereas for those having lesionectomies, no difference from anterior lobe resection was recorded. Those with SPS in the first 2 years after temporal lobe surgery had a greater chance of subsequent seizures with impaired awareness than did those with no SPS (2.4, 1.5–3.9). Relapse was less likely the longer a person was seizure free and, conversely, remission was less likely the longer seizures continued. In 18 (19%) of 93 people, late remission was associated with introduction of a previously untried antiepileptic drug. 104 of 365 (28%) seizure-free individuals had discontinued drugs at latest follow-up. **INTERPRETATION:** Neurosurgical treatment is appealing for selected people with refractory focal epilepsy. Our data provide realistic expectations and indicate the scope for further improvements in presurgical assessment and surgical treatment of people with chronic epilepsy.

Commentary

There are now two prospective, randomized trials showing that temporal lobectomy is far superior to medical management for appropriate candidates for both seizure freedom and quality of life (1, 2). However, these studies had only 1- or 2-year outcome, and longer-term trials of this sort are not practical. Longer-term outcome from observational studies has shown that about two-thirds of patients will be seizure free 5 to 10 years after temporal lobectomy (Table 1). Good prognostic factors include hippocampal atrophy, focal lesions, and lack of secondarily generalized tonic-clonic seizures.

In the current study, the authors report on a large, single-center surgical experience. About 600 patients and 5,200 person-years of follow-up were included. More than 200 patients had 5 years of follow-up, and over 100 had 10 years. The majority of patients had temporal lobe surgery and hippocampal sclerosis; thus, conclusions should not be extrapolated to other groups. Perhaps the greatest strength of the study

was the careful evaluation of patterns of remission and relapse using annual seizure outcome status.

There are many clinically useful points that can be gleaned from the data; here are my top 12:

1. Despite the good long-term outcome for anterior temporal lobectomy seen in patients with hippocampal sclerosis (sustained seizure freedom with or without simple partial seizures [SPS] of 57% at 5 years and 51% at 10 years), there remains substantial room for improvement.

Comment: This finding is similar to prior studies (Table 1; [3, 4]) once it is recognized that this study looks at sustained seizure freedom throughout the follow-up period, not just seizure freedom for the past 1 to 2 years (as with the commonly used outcome scales). The importance of the outcome scale should not be underestimated; in a large systematic review of long-term outcome after epilepsy surgery (4), the only two multivariate predictors of outcome were year of surgery (worse if prior to 1980) and the outcome scale (better if Engel scale used).

2. Similarly, for patients with discrete lesions typically thought to be associated with high seizure-freedom rates,

such as cavernous malformations and dysembryoplastic neuroepithelial tumors, 10-year estimated sustained seizure-freedom rates were only 40 to 45 percent.

Comment: We should continue to investigate reasons for failure in these groups of patients in detail. Only a prospective multicenter randomized trial of lesionectomy, lesionectomy with electrocorticography, and lesionectomy guided by implantation of intracranial electrodes could determine the best approach to these patients.

3. Seizure freedom at 2 years (with or without auras) was associated with an 80% chance of seizure freedom at 5 years and 72% at 10 years.

Comment: This finding is fairly similar to prior studies that reported this type of analysis. Spencer et al. (5) found that if patients were 2 years seizure free, 25% eventually relapsed at some point. McIntosh et al. (6) found that if patients were 2 years seizure free, 86% were seizure free at 5 years and 74% at 10 years. Elsharkawy et al. (7) (N=434 temporal lobe surgeries) found better results: if patients were 2 years seizure free, 95% were seizure free at 5 years, and 92% at 10 years. Cohen-Gadol et al. (8) found that if patients were 1 year seizure free, 92% were seizure free at the 10-year mark.

4. Those with persistent auras were significantly more likely to relapse than those who were completely seizure free. More specifically, if a patient had no seizures at all (including no auras) for the first 2 years, there was an 86% chance that they would still be free of seizures with loss of awareness 5 years later, with a 78% chance 10 years later. In comparison, for those seizure free but with persistent auras in the first 2 years, there was a 67% chance of remaining seizure free 5 years later, with a 55% chance 10 years later.

Comment: This finding is similar to prior smaller studies. The only other large study that investigated the prognostic value of persistent auras was The North American Multicenter Study (N = 339) (5), which found that of those free of disabling seizures at 2 years, 32% of those with persistent auras relapsed versus 24% of those without auras (not significant).

5. It was common for patients to move in and out of the seizure-freedom category; this occurred in 3 to 15 percent of patients each year. The same percentage of patients (8%) went from initially seizure free to relapse as did the reverse. At any given time point, about 70% of patients were seizure free (with or without SPS) for the past year, and

TABLE 1. Summary of Large Epilepsy Surgery Series With Long-Term Surgical Outcome*

Ref, Year	N, Population	Median Length Of Follow-Up	Outcome Measure	Results: Seizure Freedom	Predictors Of Seizure Freedom
Spencer et al. 2005 (5)	339 (7 centers); 297 medial temporal	4.6 years	2-year remission	66% at last follow-up	HC atrophy; lack of GTCs
Cohen-Gadol et al. 2006 (8)	399, no lesions except HC sclerosis, 93% temporal	6 years	Engel I	76% at 2 years, 74% at 5 years, 72% 10 years	Positive pathology; female; no prior surgery; temporal
McIntosh et al. 2004 (6)	325, temporal only	9.6 years	Sustained seizure freedom	55% at 2 years, 48% at 5 years, 41% at 10 years	Lesion; HC atrophy; lack of GTCs
Elsharkawy et al. 2009 (7)	434, temporal only	9 years	Engel I	72% at 2 years, 71% at 5 years, 71% at 10 years	HC atrophy; family history; lack of bilateral spikes; lack of versive seizures
Téllez-Zenteno et al. 2005 (4)	Systematic review of literature	Variable	Variable	Temporal group: 66% at 5 years, 45% at 10 years	Surgery after 1980; use of Engel scale
de Tisi et al. 2011 (current study)	615, 81% temporal (407 with HC sclerosis)	8 years	Sustained seizure freedom	52% at 5 years, 47% at 10 years	Temporal resection; younger age at surgery; HC sclerosis; lack of cortical dysplasia; lack of negative or "other" pathology

Abbreviations: Ref, reference; HC, hippocampal; GTC, secondarily generalized tonic-clonic seizure.

*Includes studies with >200 patients and >3 years of follow-up; and one systematic review.



overall, 82% of patients had at least 1 year free of seizures with loss of awareness.

6. In those who were not seizure free, the chances of becoming seizure free were better than might be expected. For example, for those with persistent seizures at 2 years after surgery, the chance of becoming seizure free for at least one year was 13% 2 years later, 24% 5 years later, and 38% 10 years later.
7. Only a minority (10/47) of delayed relapses could be explained by lowering or withdrawal of medication.
 Comment: This finding is similar to most but not all prior studies. McIntosh et al. ($N = 325$) (6) looked at this specifically and found no association of relapse with anti-epileptic drug (AED) discontinuation.
8. A significant minority of delayed seizure freedom (>2 years after surgery) was achieved by adding an antiepileptic medication that had not been tried previously; this was most commonly levetiracetam. However, it was more common for delayed seizure freedom to occur without any change in medications.
9. Age at surgery had a small but significant effect: an increase in age of 5 years was associated with a 6% greater risk of seizure recurrence, and an increase of 10 years was associated with a 13% increased risk.
 Comment: This small but measureable effect of age at surgery on univariate analysis is similar to prior studies (4).
10. Safety was quite good, with 5% of patients having wound infections requiring antibiotics, 3% having CSF leaks requiring repair, <1% with hemiparesis, and 1% with dysphasia.
11. At the latest follow-up, 104 (28%) of 365 seizure-free patients were off medication and therefore “cured” of their epilepsy. Many never attempted to stop medication.
 Comment: This finding is similar to prior studies. In seizure free patients who attempt AED withdrawal after surgery, 60 to 80 percent of patients remain seizure free (9–11).
12. Of importance, the median duration of epilepsy at time of surgery was 20 years.
 Comment: This large delay to surgery is remarkably consistent in the literature and has led to multiple official statements on the importance of early referral to specialty centers, typically after failure of two medications or >1 year of seizures.

There are of course some limitations to this study. It spanned multiple decades and is a single-center study; thus it is difficult to know how well it can be extrapolated widely. The determination of seizure freedom or of only SPS was based on patient report, as with virtually all other studies. It is now well known that patient report of seizure frequency or of their maintained awareness is highly inaccurate (12). There was no evaluation of driving, employment, mood, or overall quality

of life. There is an excellent discussion of the prior literature in both the main paper and the accompanying editorial (3). Yet somehow both overlooked the most rigorously performed study on this (5), which included a standardized protocol used at seven centers, prospectively acquired outcome determination every 3 months for a median of 4.6 years, and a similar analysis of late relapses.

In summary, this is a very large, carefully analyzed, and very useful study that will help us counsel patients at various time points before and after epilepsy surgery.

by Lawrence J. Hirsch, MD

References

1. Wiebe S, Blume WT, Girvin JP, Eliasziw M, for the Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001;345:311–318.
2. Engel J Jr, McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, Sperling MR, Gardiner I, Erba G, Fried I, Jacobs M, Vinters HV, Mintzer S, Kieburz K, for the Early Randomized Surgical Epilepsy Trial (ERSET) Study Group. Early surgical therapy for drug-resistant temporal lobe epilepsy: A randomized trial. *JAMA* 2012;307:922–930.
3. Sadek AR, Gray WP. Chopping and changing: Long-term results of epilepsy surgery. *Lancet* 2011;378:1360–1362.
4. Téllez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: A systematic review and meta-analysis. *Brain* 2005;128(pt 5):1188–1198.
5. Spencer SS, Berg AT, Vickrey BG, Sperling MR, Bazil CW, Shinnar S, Langfitt JT, Walczak TS, Pacia SV, for the Multicenter Study of Epilepsy Surgery. Predicting long-term seizure outcome after resective epilepsy surgery: The multicenter study. *Neurology* 2005;65:912–918.
6. McIntosh AM, Kalnins RM, Mitchell LA, Fabinyi GC, Briellmann RS, Berkovic SF. Temporal lobectomy: Long-term seizure outcome, late recurrence and risks for seizure recurrence. *Brain* 2004;127(pt 9):2018–2030.
7. Elsharkawy AE, Alabbasi AH, Pannek H, Ooppel F, Schulz R, Hoppe M, Hamad AP, Nayel M, Issa A, Ebner A. Long-term outcome after temporal lobe epilepsy surgery in 434 consecutive adult patients. *J Neurosurg* 2009;110:1135–1146.
8. Cohen-Gadol AA, Wilhelmi BG, Collignon F, White JB, Britton JW, Cambier DM, Christianson TJ, Marsh WR, Meyer FB, Cascino GD. Long-term outcome of epilepsy surgery among 399 patients with nonlesional seizure foci including mesial temporal lobe sclerosis. *J Neurosurg* 2006;104:513–524.
9. Kim YD, Heo K, Park SC, Huh K, Chang JW, Choi JU, Chung SS, Lee BI. Antiepileptic drug withdrawal after successful surgery for intractable temporal lobe epilepsy. *Epilepsia* 2005;46:251–257.
10. Rathore C, Panda S, Sarma PS, Radhakrishnan K. How safe is it to withdraw antiepileptic drugs following successful surgery for mesial temporal lobe epilepsy? *Epilepsia* 2011;52:627–635.
11. Berg AT, Vickrey BG, Langfitt JT, Sperling MR, Shinnar S, Bazil C, Walczak T, Spencer SS, for the Multicenter Study of Epilepsy Surgery. Reduction of AEDs in postsurgical patients who attain remission. *Epilepsia* 2006;47:64–71.
12. Hoppe C, Poepel A, Elger CE. Epilepsy: Accuracy of patient seizure counts. *Arch Neurol* 2007;64:1595–1599.