Long term outcomes after epilepsy surgery - a retrospective cohort study. in a stable population

7 years’ time and beyond. Are our epilepsy surgery patients still seizure free? A retrospective cohort study.

The Wales Epilepsy Unit, University Hospital Wales

Ben Kansu, Owen Pickrell, Arron Lacey, Georgiana Samolia, Mark Rees, Liam Gray, Khalid Hamandi

Author affilaitions

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Abstract

**Objective:** To assess the long-term outcomes of epilepsy surgery between 1995–2015 in South Wales, UK, linking case note review, postal questionnaire and routinely-collected healthcare data.

**Aims:** To determine: changes in seizure outcomes and dosing and type of anti-epileptic drugs (AEDs), time to surgery from initial diagnosis, patients’ reported interpretations of their health and their relation with clinical outcomes, changes in hospital admission rates using linked routinely-collected data.

**Method:** We identified patients from a departmental database and collected outcome data from patient case notes, an in-house questionnaire, the QOLIE-31-P and linked routinely-collected data within the Secure Anonymised Information Linkage (SAIL) databank.

**Results:** 57 patients had resective surgery with sufficient clinical information to be included in the study. The median age at surgery was 34 years (11­–70); a median 24 years (2-56) after onset of habitual seizures. The median follow-up was seven years (2–19). 28 (49%) patients were free from disabling seizures (Engel Class 1), 9 (16%) experienced rare disabling seizures (Class 2), 13 (23%) had worthwhile improvements (Class 3) and seven (12%) no improvement (Class 4). There was a 30% mean reduction in total AED load at five years post-surgery. 38 (66.7%) patients experienced tonic-clonic seizures pre-surgery verses 8 (14%) at last review. Seizure-free patients self-reported a greater overall quality-of-life over those not achieving seizure freedom. On the QOLIE-31-P, those seizure-free scored a mean of 67.6/100 (100 is best), whereas those with continuing seizures scored 46.0/100 (p<0.006). There was a significant decrease in the rate of hospital admissions for any cause after epilepsy surgery a median of X days per 1000 patient days compared with X before p<0.005)

**Significance:** Following epilepsy surgery 58% of patients were free of disabling seizures, there was a reduced AED load and an improved quality-of-life that closely correlated with seizure outcomes. We, as others have reported, note a long delay from diagnosis to surgery. The importance of long term follow-up is emphasized in terms of evolving medical needs and health and social care outcomes.

**Introduction:**

Epilepsy is a chronic condition with a prevalence of 50 million worldwide and an incidence of 2.4 million per annum (1). In Wales, approximately 30000 people suffer with epilepsy (2). The main treatment of epilepsy is pharmacological intervention with antiepileptic drugs (AEDs). However, a third to a half of patients develop seizures that are resistant to AEDs, or drug resistant epilepsy (DRE) (3). DRE is defined as a failure to achieve sustained seizure freedom after treatment with at least two appropriately chosen and appropriately used AEDs, in monotherapy or in combination (4-6). The reasons why DRE develops remains unknown (7). Delineation and surgical resection of epileptogenic brain tissue is a curative treatment option in selected cases, with a strong evidence base for reducing or halting seizures and reducing AED dependence, along with beneficial outcomes on quality of life (QOL) (8-12).

Delay from onset of habitual seizures and drug resistance to surgical treatment is well recognized with intervals of several decades in most case series (11-14). One reason for this delay may be poor knowledge of the available surgical options to patients, carers and treating physicians. This time to surgery likely impacts on morbidity and mortality (15), and those not proceeding to surgery have been found to be 2.4 times more likely to die than those who did have surgery (16). Life expectancy itself has also been shown to be on average five years longer in operated drug resistant epilepsy compared to those who stayed on medical therapy (17).

A small number of studies have looked at epilepsy surgery outcomes beyond five

years (18-23) {de Tisi, 2011, The long-term outcome of adult epilepsy surgery`, patterns of seizure remission`, and relapse: a cohort study;Reid, 2004, Epilepsy surgery: patient-perceived long-term costs and benefits;Wiebe, 2016, Epilepsy: Does access to care influence the use of epilepsy surgery?;Reid, 2004, Epilepsy surgery: patient-perceived long-term costs and benefits;Reid, 2004, Epilepsy surgery: patient-perceived long-term costs and benefits}with many others only reporting outcomes at 3 years or less (9, 10, 13). An important outcome, in addition to seizure freedom is change in AED treatment load post-surgery; one review of published outcome studies with more than five years follow up found that less than a quarter of these reports included outcomes on AED changes and the patient QOL measures (21).

We therefore set out to study the long-term outcomes of epilepsy surgery at our centre, that serves a relatively stable population in South Wales, UK. We focused on AED use and quality of life, as well as seizure outcome measures.

**Methods**

Approval for the study as a service evaluation was given by the hospital Continuous Service Improvement Office, Cardiff and Vale University Health Board, Wales, UK. We searched the departmental database searched for all patients who had epilepsy and neurosurgery between 1995–2015. We obtained information for 84 patients by reviewing paper case notes and the hospital’s online clinical portal [electronic front end for clinical investigations, attendances and letters (from 2008)]. We determined changes in seizure frequency and character, time to surgery from initial diagnosis, changes in epilepsy drugs and any record of adverse surgical events or psychiatric, cognitive and visual problems (pre-surgical baselines were noted). We used Engel classification to determine seizure outcome at most recent out-patient appointment, where one is the best outcome and four the worst, with subcategories for each class (appendix 1). A questionnaire was developed to identify the patient’s current perspective on having experienced epilepsy surgery including their report of seizure frequency (daily, weekly, monthly, yearly and none in the past year), employment and driving status (appendix 2). We also included the QOLIE-31-P which was originally developed by Crammer to specifically assess the QOL of people with epilepsy (24). The scale takes into account the patients’ perception of: levels of energy, emotional toll, daily activities, mental activity, medication effects, seizure attitudes and their feelings on quality of life overall (appendix 3). Responses to the QOLIE-31-P were scored according to standard instructions giving an overall score for each patient ranging from 1–100 (100 being the best QOL).

Given the large number, type and doses of AEDs to be assessed at different time points over a period of up to 20 years, comparison over time can be difficult. We developed a system to calculate a drug load or burden with respect to the maximum recommended daily dose, as well as recording the total number of AEDs. For each AED, we calculated a ratio of total daily dose taken compared to the maximum recommended daily dose [from British National Formulary, March 2017 (25)]. A patient taking the maximum recommended daily dose would score 1, a patient taking 50% of daily dose 0.5, and so forth. For example, a patient taking levetiracetam 1250mg BD would score 2500/3000=0.83 (3000mg being the highest recommended daily dose).

We used the Secure Anonymous Information Linkage databank (SAIL) [A,B] (Health Data Research UK, Swansea University) to anonymously link the list of patients having had resective epilepsy surgery to routinely-collected primary care and hospital admission records. We excluded patients who were not registered with a General Practice (primary care provider) for at least five years before and after the epilepsy surgery. We recorded the length of stay for all hospital admissions before and after surgery excluding the month/6 months immediately after surgery to exclude specific peri-operative related hospital stays. We compared the rates of admission before and after surgery using a signed Wilcoxon Signed-Rank test. We used X to estimate costs for hospital admission.

All studies using SAIL data need independent Information Governance Review Panel (IGRP) approval but do not require specific NHS research ethics committee approval. This study obtained IGRP approval ref 0565.

**Results**

We identified 406 cases as having epilepsy and neurosurgery, from which 84 were identified as having resective epilepsy surgery. 64 sets of case notes were available for review. We excluded a further seven cases [three had palliative not resective procedures, two insufficient case notes, and two did not have neurosurgery (incorrectly identified)], leaving a total of 57 patients.

40 patients had undergone anterior temporal lobectomy (27 left, 13 right) , seven had selective amygdalohippocampectomy (five left, two right) with the remaining ten having resective surgery for space occupying lesions. 49 were right handed, seven left and one ambidextrous. 51% (29) of patients had a history of febrile seizures, 47% were noted to have not suffered a febrile seizure and one was undocumented. Patients had a median age of 34 at surgery, with the time between onset of habitual seizures (median of one years of age) and surgery being 24 years (range 2-56). Median duration of follow up since surgery for this study was seven years, with a range of 1-19 years. Lateralisation and histopathological diagnoses are shown in figure 1.

**Post-operative seizure outcomes**

49% of patients were at Engel class 1 (free from disabling seizures), 16% class 2(9), 23% class 3 (13) and 12% at class 4 (7) (no worthwhile improvement) (figure 2a) (11). A more detailed breakdown of seizure type and frequency before and at one year following surgery was also determined, see figure 2b and of seizure type and frequency at long term follow up (figure 2c).

**Post-operative morbidity outcomes.**

Six of the 57 patients suffered surgical site infections with three requiring cranioplasty and one requiring an ITU admission. 3 patients experienced de novo psychiatric events post-surgery that required inpatient stays. One of these required involuntary detention under the mental health act after attempting suicide by violent means. One other patient attempted suicide with no previous psychiatric history. 23 patients experienced at least mild visual impairment on formal testing.

**Anti-epileptic drug usage**

As time progressing since surgery, the number of patient follow up data reduced, and therefore, total drug consumption was calculated per capita (Figure 4). The mean average number of AEDs patients were on pre surgery was 2.35, at last OP appointment this figure had dropped to 1.83 a reduction of 22%. Of the 20 patients who stopped AEDs entirely only three remained seizure free with the remaining 17 returning to some form of medication to help with seizure control. Of the three patients who succeeded two stopped medications having previously taken 1500mg of levetiracetam for one patient and 300mg of pregabalin for the second patient. Both came off medication at one year post-op and were at three and five years post-op respectively at their last outpatient appointment. The third patient attempted to come off medication at four years

but unfortunately relapsed on this attempt and was placed back on a 1000mg dose of carbamazepine however, on their second attempt at eight years post-op they remained seizure free, at the time of writing 13 years since their operation. Of the remaining 54 patients, 33 were on an reduced total AED load compared to pre-surgery, 13 were on the same and unfortunately 8 were on a greater AED load.

**Postal survey**

Of the 84 patients identified, 34 (40%) completed questionnaires where returned. Results are surmised in table 1.

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Employment (Full or part time) | 12 | 22 |
| Driving | 7 | 27 |
| Seizures free on questionnare | 21 | 13 |

Table 1: Figures on the patient’s employment, driving and seizure status from the questionnaire.

In terms of the patient’s employment status 22 were unemployed with 12 in part or full time work. Seven of the 34 patients were currently driving with the mean average time beginning to drive after the surgery 3.5 years.

Patients’ responses to seizures frequency can be seen in figure 2d. Two (6%) patients of the 34 experienced no reduction in their frequency, with the rest experiencing at least a one class reduction. 13 (40%) patients reported seizure freedom. No patients reported worsening seizures however, 3 patients reported their QOL has decreased. 26 (76%) of the 34 patients expressed the view that their QOL has improved to some extent.

**QOLIE-P31 questionnaire**

Four responses were excluded due to incomplete responses to the questions. The remaining 30 scores were calculated. The final score is a scale ranging from 0, suggesting the patient has absolutely no QOL, with a score of 100 being the best possible QOL. The mean average of all respondents 55.2, with a standard deviation of 21.7. Those free of seizures scored a mean of 67.9 whereas those who did not achieve seizure freedom scoured 46.1, giving a difference of 21.6 (CI 7.0,37.9) and was statistically significant (using a 2 tailed hypothesis Mann-Whitney U) at p<0.006.

There was a significant decrease in the rate of hospital admissions for any cause when comparing the five years after surgery with the five years immediately prior to surgery (X vs Y, P<0.05) see figure 6.

**Discussion**

We conducted an evaluation of long term outcomes in patients having undergone epilepsy surgery in Cardiff, UK. We found that 48% of patients were free of disabling seizures (Engel class 1) at their most recent outpatient visit, a median of seven years post-surgery (Range 2-19).

The long-term outcomes of epilepsy surgery are, in the broad view, positive with a majority of patients taking fewer AEDs and experiencing fewer and less severe seizures. This is similar to the result reported at one-year post surgery by Wiebe et al (9). Reid demonstrated similar percentages (45%) up to six years post-surgery (18). This shows the longer term outcomes of epilepsy surgery are comparable to the shorter term outcomes. Previous long term studies that assess seizure outcomes beyond 5 years for temporal lobe epilepsy range from 45%-69% (18-20) with 3 studies focusing on resective surgery finding between 60-72% seizure freedom (21-23). These studies also reported similar ratios of those who achieved seizure freedom. QOLIE-P31 scores showed a significant difference in quality of life between those who achieved seizure freedom and those who did not. There was close correlation between seizure outcomes, subjective quality of life questionnaire responses and QOLIE-P31 scores. The majority of patients responded positively that they had undergone epilepsy surgery and that it had a positive outcome for them.

Using a novel measure of AED burden we found a measurable reduction in the total AED dosing following surgery, as a ratio of maximum recommended dose, along with the total number of AEDs taken per person. Although studies have reported AED use and seizure freedom (21, 26) what many studies failed to report on was how the patient’s medications evolved over time and sourced patients’ opinions on their decision to undergo surgery.

Our cohort was made up of those with lesional epilepsy, 76% (43 patients) had hippocampal sclerosist the remaining 24% (14 patients) had either focal cortical dysplasia or space occupying lesions. 89% (51 patients) underwent temporal lobe surgery with the remaining patients undergoing extra-temporal resections. It has previously been reported that extra temporal resections carry poorer outcomes with seizure freedom ranging between 27%-46% (21). Of our six patients who underwent extra temporal surgery three were still experiencing daily seizures with only two achieving seizure freedom. Although the number are too small to draw any significant conclusions it was interesting to note that the patients in our cohort who had extra temporal surgery had some of the poorest outcomes.

Another finding of note was there was a significant difference in the number of patients operated with left (n=28 ) and right (n=14) hippocampal sclerosis was significant at p<0.02 (one sample binomial test); this has also been reported by other centers (27) The reasons are unclear, and we do not have a denominator figure of prevalence of all HS in our epilepsy population. Two previous papers that investigated temporal lobe epilepsy found a majority of patients had left sided pathology however, the magnitude of the difference was smaller at 54% (28, 29). We postulate that that prevalence of left and right HS may be equal but that those with left HS suffer more debilitating seizures (with loss of awareness), compared to right HS and hence more likely to come to surgery (30).

The Engel classification is a commonly used outcome measure in epilepsy surgery. However, this does not always capture changes in seizure type or severity. Only 14% of patients showed no improvement in frequency of seizures and therefore received a class IV Engel’s score. The severity of seizures dropped, for example, 38 of the 57 patients experiencing at least yearly tonic clonic seizure (TCS) in comparison to eight at the most recent outpatient visit. One case developed de novo monthly bilateral to tonic clonic seizures following surgery, having previously suffered with weekly focal seizures and in 2 other patients, bilateral to tonic clonic seizure rate increased from annually to monthly in one case and monthly to weekly in the other. The cases were classified as Engel class II based on the fact the overall rate of disabling seizures however, the change to bilateral tonic clonic seizures was not captured by the scale.

The dosage of drugs also steadily dropped with a 30% reduction in drug dosage five years post-surgery, in comparison to pre-surgery. There appeared to be a levelling of AED decrease from eight years post-surgery and beyond. Previous literature has drawn associations with the AED’s themselves reducing QOL (31) and the cessation of them improves cognition (32). However, despite there being an overall reduction in AED’S only 20 of the 57 patients had a trial of complete AED withdrawal and of those only three remained off AEDs and seizure free with the remaining 17 returning to AED therapy. A recent paper found a higher percentage of patients (30%) successfully stopped their AED’s at 8 years’ post-surgery but, 50% of the patients were still on the same AED load or higher (23). Although only 5% (3) of our patients successfully stopped their seizure medication, only 36% (21) remained on the same AED load or higher. The variation in these result may be a reflection on the different practices between institution about stopping AED’s medication entirely. For example, 10 of our patients AED load had been reduced by 80% or greater.

Patients’ subjective interpretation of their health seems to correlate with their clinical picture, with 14.7% reporting no change or a decrease in their questionnaire responses with a similar percentage as those who class as Engel IV(Figure 2a), although these were not necessary the same individuals. Those completely seizure free reported a statistically significant difference (P<0.006) in their QOLIE-P31 showing seizure freedom is strongly correlated to better outcomes holistically. Of the 19 patients who returned their questionnaire who were still experiencing seizures 12 still described their QOL ‘much improved’ or ‘very much improved’ following surgery. This demonstrates the importance of recording patient’s opinions and QOL measures in addition to Engel scores.

Four patients experienced wound infections requiring cranioplasty and most suffered from at least mild visual and mild cognitive impairment on formal testing one-year post surgery. Others reported adverse psychiatric effects (commonly depression) that were not present before surgery. 3 patients required inpatient psychiatric stays , one due to suicide by violent acts requiring a section. One other patient attempted suicide but, did not have an inpatient stay. These patients did not have evidence of a psychiatric history before surgery. Of these 4 patients with poor de novo psychiatric morbidity all 4 had anterior temporal lobectomies (3 left, one right). Two of these patients achieved seizure freedom and 2 unfortunately did not. Since 2011 a formal psychiatric evaluation has been part of the epilepsy pre-surgical evaluation for all out patients.

The goal of epilepsy surgery is to achieve long term seizure freedom. Despite the long term goals, few studies report seizure freedom beyond five years along with AED use and quality of life. The achievement of seizure freedom is not a static event. In our cohort eight patients who were seizure free at one-year post surgery experienced seizures in some capacity at five year post surgery and beyond. Some patients did not develop more severe psychiatric events until 5 years post-surgery and AED load continued to fall until eight years post-surgery.

Trying to ascertain why some in our cohort failed to achieve seizure freedom is limited by sample size and retrospective review. Trying to establish causality as to which pre-surgical factors could be a marker to surgical failure remains challenging. In a recent paper investigating psychiatric outcomes the only significant risk factor found for poor mental health outcomes was having a previous history of poor mental heath (33). As discussed earlier the anatomical location of the surgery may influence outcome with extra-temporal resections tending towards poorer outcomes (34). Unsurprisingly others have linked a history of bilateral to tonic clonic seizures with poorer post-surgical outcome (19).

As suggested in previous literature although the primary epigenic focus is correctly identified, it has been proposed that other neighboring regions that do not undergo resection may play some role in continuing to initiate complexes post-surgery, known as temporal lobe plus syndrome. Those who have been identified as have secondary focus’s were 59.7% less likely (14.8% vs 74.5%) to be seizure free at ten years post-surgery compared to those who had more clearly defined unilateral temporal lobe epilepsy (35).

8) SAIL DATA

9) overall summing up.

In summary, our findings are similar to previous studies, with positive long-term outcomes following epilepsy surgery, the majority: taking fewer AEDs, experiencing less frequent and less severe seizures, and reporting improved quality-of-life. We, as elsewhere, note a long delay from diagnosis to surgery. Some patient’s seizures returned years after surgery stressing the need for long term follow up. Research is needed to establish predictive markers of good or bad surgical outcome.

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**Table and figure legends**

**Figure 1.**

**Figure 2.** **a)**. Post-operative outcomes at most recent outpatient clinic - Engel classification. 1, Class 1 (Free from disabling seizures); 2, Class 2, Rare disabling seizures; 3, Class 3 (Worthwhile improvement); 4, Class 4 (No worthwhile improvement). Letters represent subclasses of categorization (see appendix 3), **b)** The type and frequency of seizures, pre surgery and one year after surgery. D, daily; W, weekly; M, monthly; Y, yearly; O, once- the patient had one seizure post surgery. PUT GRAPH WITH NUMBERS. **Figure 2c:** Type and frequency of seizures, against patient number and percentage at their last outpatient clinic. **2d.**  self reported seizure frequency (n = 34).

**Figure 3.** Drug use per capita in the years following surgery. The number on the Y axis refers to the average anti-epileptic drug score per capita. Please refer to the methods section for an explanation to how scores were calculated.

All epileptic medications patients were on were scaled, where 1 is the maximum dose of single drug as recommended by the British National formulary( March 2017). Patients scores were added together to give an overall number and per capita calculated.

**Figure 4.** Subjective QOL questionnaire responses ranging from one to thirteen years post-surgery.

**Figure 5.** Box and whisker plot showing the difference in quality of life of those who achieved seizure freedom following and those who did not.

**Appendix 1: Engel classification score.**

|  |
| --- |
| Class I. Free from disabling seizures |
| A. Completely seizure free since surgery |  |
| B. Nondisabling simple partial seizures only since surgery |  |
| C. Some disabling seizures after surgery, but free from disabling seizures for ≥2 years |  |
| D. Generalized convulsions w/AED discontinuation only |  |

|  |
| --- |
| Class II. Rare disabling seizures (almost seizure free) |
| A. Initially free from disabling seizures, but still has rare seizures |
| B. Rare disabling seizures since surgery |
| C. Occasional disabling seizures since surgery, but rare seizures for the last 2 years |
| D. Nocturnal seizures only |
|  |

|  |
| --- |
| Class III. Worthwhile improvement |
| A. Worthwhile seizure reduction |
| B. Prolonged seizure-free intervals amounting to >50% of follow-up period, but not <2 years |

|  |
| --- |
| Class IV. No worthwhile improvement |
| A. Significant seizure reduction |
| B. No appreciable change |
| C. Seizures worse |

**Table and figure legends**

**Figure 1.**

**Figure 2a**

**49%**9%

**23%**9%

Number of patients

**12%**

**%**9%

**16%**9%

Engel score

**Figure 2b**

**Pre surgery 1-year post surgery**

Number of patients

**Figure 2c**

**42%**

**14%**

**26%**

**9%**

**17%**

Number of patients

**2%**

**Figure 2d**

Percentage of patients

**Figure 3.**

Anti-Epileptic

Drug

Dose

Per

capita

Years post-surgery

**Figure 4.**

Number of patients

**Figure 5.**

Experiencing seizures

No seizures

QOLIE-P31 score

**Figure 6. Hospital admission rates for any cause before and after surgery**

**Figure ## ?include:** Percentage of those seizure free 1 year post surgery, and last outpatient clinic (median 7 years). Y, year; OP, outpatients.

Probably leave out

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Design** | **Type of surgery** | **Follow up time (Medium)** | **Seizure freedom** | **QOL surveyed?** | **AED’s** |
| **(36)** | **Retrospective** | **Resective** | **9** | **Significant?** | **Y** | **N** |
| **(19)** | **Prospective** | **Temporal** | **18** | **62%** | **N** | **N** |
| **(18)** | **Prospective** | **Temporal** | **6** | **45%** | **Y** | **N** |
| **(32)** | **Prospective** | **Pediatric**  **Temporal** | **9** | **86%** | **Y** | **57% not on mediciation** |
| **(21)** | **Review** | **Resective** | **>5** | **65%** | **Y** | **Withdrawal may lead to sezuire reoccurance.** |
| **(22)** | **Prospective** | **Resective** | **6** | **72%** | **N** | **N** |
| **(20)** | **Retrospective** | **Temporal** | **16** | **69%** | **N** | **N** |

**Table 1: A brief summary of previous studies that followed up patients for 5 years or more who underwent curative epilepsy surgery.**

**Hello both,**

**Sorry for the slight delay. I have made most of the corrections.**

**I have looked at the author guidelines on Epilepsia. The max word count is 4000 which we are currently under. The abstract should be 300 words so I have trimmed down to suit (SAIL is still not included though). The intro should be less than 600 which we are under and the discussion should be less than 1500 which we are also currently under (Although do you still think it is worth trimming Owen?). The max number of references is 40 and we currently have 36. All tables of figures should be sent as TIFF files which I will convert them two when we are 100% happy with them.**

**Whilst looking at Epilepsia I came across this article https://onlinelibrary.wiley.com/doi/full/10.1111/epi.13654 it seems to be very similar to our paper but only focuses on parieoccipital cortex seizures.**

**Also, a few general questions about the paper,**

**1) What terms should I be using? Focal seizure, focal seizure with altered awareness and tonic clonic?**

**2) Do the QOLIE-P-31 and our questionnaire need to be added as appendices?**

**3) Khalid, you wanted to get names for the people who had poor physiatric outcomes. Could you send me the excel file (should still be in the epilepsy local S drive), I presume this should be a problem now I have an NHS email account and I can then give you names. If not all I can provide to DOB from my end.**

**Looking forward to hearing from you both**

**Best wishes**

**Ben**