The long-term outcomes of epilepsy surgery

Midhun Mohan¹, Simon Keller¹,², Andrew Nicolson¹, Shubhabrata Biswas¹, David Smith¹, Jibril Osman Farah¹, Paul Eldridge¹, Udo Wieshmann¹*

¹ The Walton Centre, NHS Foundation Trust, Liverpool, Merseyside, United Kingdom, ² Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, Merseyside, United Kingdom

* udo.wieshmann@thewaltoncentre.nhs.uk

Abstract

Objective

Despite modern anti-epileptic drug treatment, approximately 30% of epilepsies remain medically refractory and for these patients, epilepsy surgery may be a treatment option. There have been numerous studies demonstrating good outcome of epilepsy surgery in the short to median term however, there are a limited number of studies looking at the long-term outcomes. The aim of this study was to ascertain the long-term outcome of resective epilepsy surgery in a large neurosurgery hospital in the U.K.

Methods

This a retrospective analysis of prospectively collected data. We used the 2001 International League Against Epilepsy (ILAE) classification system to classify seizure freedom and Kaplan-Meier survival analysis to estimate the probability of seizure freedom.

Results

We included 284 patients who underwent epilepsy surgery (178 anterior temporal lobe resections, 37 selective amygdalohippocampectomies, 33 temporal lesionectomies, 36 extratemporal lesionectomies), and had a prospective median follow-up of 5 years (range 1–27). Kaplan-Meier estimates showed that 47% (95% CI 40–58) remained seizure free (apart from simple partial seizures) at 5 years and 38% (95% CI 31–45) at 10 years after surgery. 74% (95% CI 69–80) had a greater than 50% seizure reduction at 5 years and 70% (95% CI 64–77) at 10 years. Patients who had an amygdalohippocampectomy were more likely to have seizure recurrence than patients who had an anterior temporal lobe resection (p = 0.006) and temporal lesionectomy (p = 0.029). There was no significant difference between extra temporal and temporal lesionectomies. Hippocampal sclerosis was associated with a good outcome but declined in relative frequency over the years.

Conclusion

The vast majority of patients who were not seizure free experienced at least a substantial and long-lasting reduction in seizure frequency. A positive long-term outcome after epilepsy surgery
surgery is possible for many patients and especially those with hippocampal sclerosis or those who had anterior temporal lobe resections.

**Introduction**

Epilepsy is the most common serious neurological disorder with medical treatment failing to control seizures in up to 30% of patients [1]. Temporal lobe epilepsy (TLE) is the most common pharmaco-resistant focal epilepsy disorder [2,3] and thus, temporal lobe resections are the most common operations done in adults with epilepsy, and has class I evidence for its short-term efficacy compared to continuing medical treatment [4,5]. Other operations done for epilepsy include extratemporal resection, [6] and hemispherectomy [7] to name a few, however there are several other operations that can be performed with their indications being multi-factorial. Surgery can be extremely effective for patients with TLE, significantly reducing seizure frequency and improving quality of life in the majority of patients. However, there are contrasting reports regarding the proportion of patients attaining seizure freedom after temporal lobe surgery for refractory epilepsy, which may range from 35–80%[4,8–12]. The length of time to follow up assessment after surgery and whether seizure freedom is defined as freedom from all kinds of seizures and aura or disabling seizures only, are the factors that likely explain the previously reported differences in postsurgical seizure outcomes after short follow up periods [13].

In the only randomised controlled trial of surgery for refractory TLE, it was reported that 58% of patients were free from seizures impairing awareness and 38% were free from any seizure related symptom one year after surgery [4]. This contrasted to 8% who became seizure-free in the non-surgical control group. Given that the majority of patients who are potential candidates for surgery are relatively young adults, long-term postoperative seizure freedom data is crucial and arguably more significant than short-term outcomes. Long-term outcome data is also necessary so that patients can make an informed decision regarding invasive neurosurgery from a risk-benefit perspective. However, long-term outcomes of epilepsy surgery are less frequently documented and seizure freedom rates range from 21% - 91% at 5 years [9,12,14–17] and 41% - 81% at 10 years [9,12,16,18]. Several studies have been published looking at predictors of both short-term and long-term outcomes after epilepsy surgery. The predictors of good short-term postoperative seizure freedom include: complete surgical resection, presence of hippocampal sclerosis, MRI positive (abnormal pre-operative MRI), no intracranial monitoring being performed, concordance with EEG and pre-operative MRI, no evidence of focal cortical dysplasia, no evidence of malformation of cortical development, a history of febrile seizures, presence of a tumour, unilateral interictal spikes and a right sided resection [19–21]. The predictors of bad postoperative seizure freedom include: long duration of epilepsy prior to surgery [18,22–26], higher age at surgery [9,16,27,28], high seizure frequency at baseline (pre-surgery) [22,29], generalised convulsive seizures at baseline (pre-surgery) [12,27,30], early postoperative seizures [31–33] and postoperative interictal epileptiform discharges [34–36]. However it is important to note there are some studies that found no predictors even after using multivariate analysis approaches [14,37,38].

There is currently a paucity in the literature of prospective studies investigating long-term outcomes after epilepsy surgery, therefore the primary aim of this study was to ascertain long-term postoperative seizure freedom rates at a large neurosurgery hospital in the United Kingdom.
Materials and methods

Overview and ethics

The study was approved by the clinical audit group at the Walton Centre NHS Foundation Trust, Liverpool who classified the work as a service evaluation and thus the study was exempt from requiring individual patient consent and did not require ethics approval. The Walton Centre is a tertiary referral centre covering a catchment area of approximately 3 million people in the North West of England and additionally treats people with refractory epilepsy referred from Northern Ireland, Wales and Yorkshire.

Study subjects and inclusion criteria

Patients with medically refractory focal epilepsy who had undergone epilepsy surgery were included in the present study. All patients who were offered surgery had epilepsy that failed to respond to at least two anti-epileptic drugs for a minimum of two years.

Presurgical evaluation

All patients underwent comprehensive standardised presurgical evaluation including documentation of seizure semiology, scalp electroencephalography (EEG), video EEG telemetry, high resolution magnetic resonance imaging (MRI) and neuropsychological evaluation. From the year 1996, all patients had dedicated MRI scans with coronal gradient echo T1 sequence with continuous slices in the highest available resolution and T2 imaging perpendicular to the longitudinal axis of the hippocampus. All MRI negative patients, and patients in whom there was a concern regarding the concordance of non-invasive results had invasive EEG investigations. Until the year 2000, foramen ovale electrodes were typically used [39,40]. After 2000 we used bitemporal depth electrodes. Grid and strip electrodes were implanted if required. Selected patients had the sodium amytal procedure (Wada test) and single photon emission computed tomography (SPECT).

Operative details

Epilepsy surgery was performed by three functional neurosurgeons (PE, TV, JF) who specialised in the surgical treatment of epilepsy. Operations were performed between 1971 and 2014. In patients with non-dominant (usually right) temporal lobe epilepsy, a standard en-bloc resection was performed. In dominant (usually left) temporal lobe epilepsy a selective amygdalohippocampectomy (AHE) was performed by the trans-middle temporal gyrus approach as described by Niemeyer [41], but with the use of image guidance. Hippocampal head, and at least a part of hippocampal body and the amygdala were removed. The aim was a selective operation leaving other mesiotemporal structures including the parahippocampal gyrus intact. Later in the series, because of a perception that the selective operation had a poorer seizure outcome, the practice was changed to a standard lobe resection. Some of the patients who had relapsed following the selective procedure were offered a standard temporal lobe resection as a second procedure.

All patients had a post-operative MRI which confirmed adequate removal of the intended target. We did not measure the extent of the resection or the volume. However, the limited resections in our case of amygdalohippocampectomy were less successful than standard temporal lobe resections. All patients who had seizure recurrence had MRI scanning to confirm the extent of the resection. One of three neurosurgeons experienced in epilepsy surgery resected a maximum of 6.0cm to 6.5cm of the anterior lateral non-dominant temporal lobe or 4.0cm to 4.5cm of the dominant temporal lobe. The mesial resection included the amygdala...
and, at a minimum, the anterior 1.0cm to 3.0cm of the hippocampus. Patients undergoing selective an amygdalohippocampectomy had only a very limited resection of the amygdala and the hippocampal head leaving the parahippocampal gyrus intact.

All patients remained on antiepileptic drugs unless they had signs of intoxication for at least 2 years following surgery. Following this, the dose was slowly reduced to achieve a low dose monotherapy. All patients apart from one remained on anti-epileptic drugs in the long term.

**Outcome measures and follow up**

This study is a retrospective analysis of prospectively collected data. Patients were followed up prospectively at three months after surgery and then between six and 12 months. Patients who were referred from outside the catchment area were followed up by the local hospitals 12 months after surgery. Long-term outcomes were ascertained from the case notes, the electronic record system of the hospital and from general practitioners. We used the International League Against Epilepsy (ILAE) [42] outcome classification scale. The ILAE outcome scale includes six classes of outcome: Class 1 = seizure free; Class 2 = auras only; Class 3 = one to three seizure days/year and auras; Class 4 = four seizure days/year to 50% reduction in baseline and auras; Class 5 = <50% reduction in baseline number of seizure days to 100% increase in baseline number of seizure days and auras; Class 6 = >100% increase in baseline number of seizure days and auras. Other clinical data collected included age, sex, age of onset of epilepsy, duration of epilepsy, pre-operative MRI diagnosis and surgical approach. We looked at the effect of structural abnormalities as detected by pre-operative MRI rather than post-operative histology since pre-operative MRI is more clinically useful. All authors had access to patient identifiable information and all data was stored locally at the hospital in a secure database on password protected computers.

**Statistical analysis**

We used Kaplan-Meier survival analysis[43] to estimate the chance to be free of seizures with loss of awareness (ILAE Class 1 and 2) at various timepoints after surgery. This particular statistical technique was used to address the issue of patients in the study having different lengths of follow up. Patients reach either the endpoint (i.e. seizure recurrence) or are "censored" and the "survival probability" estimated with the remaining "numbers at risk" for a given time point. Kaplan-Meier estimates are used routinely in high impact studies to estimate survival probability and was used in the Lancet publication on the topic of outcomes after epilepsy surgery by de Tisi et al[44].

To ascertain clinical significance, we used the Log Rank (Mantel-Cox) test. This nonparametric test is commonly used to compare survival distributions and when censoring of data is involved. A p-value of less than or equal to 0.05 was deemed as statistically significant.

**Results**

**Demographics**

From a database containing 897 patients who were discussed at epilepsy surgery multidisciplinary team meetings, we identified 291 patients who had epilepsy surgery. Seven patients were excluded due to incomplete data leaving 284 patients for the study. 143 (50.4%) patients were male, the mean age of onset of epilepsy was 13.7 years (SD 9.91 years) and the mean duration of epilepsy was 19.6 years (SD 11.0 years). All patients were receiving four anti-epileptic drugs (AEDs) prior to surgery and were receiving at least two AEDs at the time of surgery. The
mean age when operated on was 33.0 years (SD 10.6 years). 178 (62.7%) patients had an anterior temporal lobe resection (ATL), 37 (13.0%) had an amygdalohippocampectomy (AHE), 33 (11.6%) had a temporal lesionectomy (TLesx), and 36 (12.7%) had an extra temporal lesionectomy (ETLesx). There were no perioperative deaths. One patient had a hemiparesis after a selective amygdalohippocampectomy. Fifteen patients died during the follow up period. The underlying cause of death was sudden unexpected death in epilepsy (SUDEP) in three patients and for the remaining twelve patients the underlying cause of death was unknown. The median duration of follow up was 5 years with a range from 1 to 27.0 years and a total of 1957 person-years. More than half of all surgeries performed were for hippocampal sclerosis (62.6%) and 14.0% were due to tumour: usually low grade gliomas and dysembryoplastic neuroepithelial tumours. There were two patients with meningiomas. The most common vascular abnormality were cavernous haemangiomas, there was only one patient with an arteriovenous malformation in this group. All malformations of cortical development were focal cortical dysplasias type II. MRI diagnosis was confirmed by post-operative histology. In MRI negative patients who had temporal lobe resections all had gliosis on post-operative histology. Table 1 shows pre-operative MRI findings and the operative procedure. For 49 patients, the pre-operative MRI finding was unknown or had various other pathologies (e.g. cystic lesion, middle cerebral artery infarct, meningeal fibrosis) and thus, were excluded from this particular analysis (see S1 Table for further details).

Seizure freedom
The overall mean number of years to remain seizure free after surgery was 8.4 years (95% CI 7.1–9.7) regardless of operative procedure. Further analysis showed that 47% (n = 133) (95% CI 40–58) remained seizure free at 5 years and 38% (n = 108) (95% CI 31–45) at 10 years after surgery (Fig 1).

Seizure freedom and operation type
The mean number of years remaining seizure free was 9.9 years (95% CI 8.1–11.6) for ATL, 5.3 years (95% CI 3.1–7.4) for AHE, 6.8 years (95% CI 4.0–9.6) for ETLesx and 8.9 years (95% CI 5.5–12.3) for TLesx. There was a statistically significant difference between ATL and AHE (p = 0.006) (Log Rank (Mantel-Cox) test), and AHE and TLesx (p = 0.029) (Log Rank (Mantel-Cox) test). There was no statistically significant difference between ATL and ETLesx (p = 0.189) (Log Rank (Mantel-Cox) test), AHE and ETLesx (p = 0.375) (Log Rank (Mantel-Cox) test), ETLesx and TLesx (p = 0.162) (Log Rank (Mantel-Cox) test). Further analysis showed that after 5 years 49% (n = 87) (95% CI 41–57) who had ATL, 31% (n = 11) (95% CI

| Table 1. Pre-operative MRI findings and the operative procedure. |
|-----------------|-----|-----|-----|-----|-----|
|                  | AHE | ATL | ETLesx | TLesx | Total |
| Hippocampal Sclerosis | 33  (22.4%) | 114  (77.6%) | 0 | 0 | 147 |
| MCD | 0 | 5  (41.7%) | 5  (41.7%) | 2  (16.7%) | 12 |
| MRI Negative | 0 | 19  (95.0%) | 0 | 1  (5.0%) | 20 |
| Tumour | 1  (3.0%) | 1  (3.0%) | 13  (39.4%) | 18  (54.5%) | 33 |
| Vascular | 0 | 1   (4.3%) | 15  (65.2%) | 7  (30.4%) | 23 |
| Total | 34 | 140 | 33 | 28 | 235 |

AHE = amygdalohippocampectomy, ATL = anterior temporal lobe resection, ETLesx = extra temporal lesionectomy, TLesx = temporal lesionectomy, MCD = malformations of cortical development.

https://doi.org/10.1371/journal.pone.0196274.t001
15–47) who had AHE, 42% (n = 15) (95% CI 25–59) who had ETLesx and 56% (n = 18) (95% CI 37–75) who had TLesx remained seizure free. At 10 years postoperatively, 44% (n = 78) (95% CI 35–53) who had ATL, 26% (n = 10) (95% CI 12–40) who had AHE, 31% (n = 11) (95% CI 9–53) who had an ETLesx and 34% (n = 11) (95% CI 10–58) who had TLesx remained seizure free (Fig 2).

Seizure freedom and underlying pathology as determined by preoperative MRI

The mean number of years remaining seizure free was 8.2 years (95% CI 7.0–9.5) for HS, 1.9 years (95% CI 1.0–2.8) for MCD, 4.7 years (95% CI 1.8–8.0) for MRI neg, 10.2 years (95% CI 6.9–13.6) for TM and 3.5 years (95% CI 2.2–4.9) for VSC. There was a statistically significant difference between HS and MCD (p = 0.011) (Log Rank (Mantel-Cox) test), HS and MRI Neg (p = 0.004) (Log Rank (Mantel-Cox) test), HS and VSC (p = 0.033) (Log Rank (Mantel-Cox) test), MCD and TM (p = 0.01) (Log Rank (Mantel-Cox) test), MRI neg and TM (p = 0.003) (Log Rank (Mantel-Cox) test), TM and VSC (p = 0.009) (Log Rank (Mantel-Cox) test). There
was no statistically significant difference between HS and TM (p = 0.361) (Log Rank (Mantel-Cox) test), MCD and MRI neg (p = 0.87) (Log Rank (Mantel-Cox) test), MCD and VSC (p = 0.74) (Log Rank (Mantel-Cox) test), MRI neg and VSC (p = 0.58) (Log Rank (Mantel-Cox) test). In the cohort with HS, 51% (n = 75) (95% CI 42–60) remained seizure free at 5 years and 44% (n = 65) (95% CI 35–53) at 10 years. For the MCD cohort 38% (n = 5) (95% CI 8–68) remained seizure free at 4 years 0% at 10 years. For the MRI neg cohort 20% (n = 4) (95% CI 2–38) remained seizure free at 5 years and 20% (n = 4) (95% CI 2–38) at 10 years. For the TM cohort 60% (n = 20) (95% CI 45–75) remained seizure free at 5 years and 44% (n = 15) (95% CI 21–67) at 10 years. For the VSC cohort, 36% (n = 8) (95% CI 14–58) remained seizure free at 5 years, 0% at 10 years (Fig 3).

Changing underlying pathology

From the year 1997 onwards the number of operations performed for hippocampal sclerosis had decreased with 41 operations performed between the time period of 1997–1999 and four operations performed between 2012 and 2014 (Fig 4).
Improved epilepsy (ILAE Class 4 or better)

Seventy four percent (n = 210) (95% CI 69–80) had a >50% seizure reduction at 5 years and 70% (n = 199) (95% CI 64–77) at 10 years (ILAE Class 1 to 4) (Fig 5).

Discussion

The aim of this study was to determine long-term seizure outcomes after epilepsy surgery in a large cohort of patients from a dedicated neurosurgical hospital in the U.K. Our survival analysis estimated that 47% patients were free from debilitating seizures at 5 years and 38% at 10 years. These outcomes fall within the range of published long-term outcomes [9,14,16,17,22,28,32,37,45–52]. The reason for the heterogeneity in seizure outcomes are likely to be multifactorial. One reason may be due to how the authors defined seizure freedom and whether or not they included SPS in their definition. Another possible reason is the different post-surgical AED treatment and tapering methods used. The heterogeneity in the use of AEDs post epilepsy surgery is likely due to there being no consensus statement or robust evidence on the timeframes for when AEDs should be tapered or stopped post successful surgery. [53]. Furthermore, a
study conducted on patients with epilepsy who were medically treated showed that how the possible risks are conveyed to the patient greatly influences their decision whether to taper or stop the AEDs [54]. The study used a computer based predictive model to counsel patients about their individual risk of seizure recurrence and the majority of patients opted to continue with AEDs. Therefore, the way the risks associated with stopping and tapering AEDs are conveyed could have a significant impact on the patient’s decision and subsequently add to the heterogeneity seen in seizure freedom rates in the literature.

Interestingly, the reported long-term outcomes of surgery in the modern MRI era is similar to the outcomes of surgical therapy for temporal lobe seizures in patients with non-tumour lesions prior to the advent of modern imaging. In a study that ranged from 1930 to 1967, 49% of patients were completely seizure free or seizure free after some postoperative attacks with a follow-up ranging from 2–36 years (median 8 years) [55]. Tellez-Zenteno [6] observed only a trend for improved long-term seizure outcomes for patients with temporal lobe epilepsy operated after 1980, compared to patients operated prior to 1980 before MRI became available. There can be no doubt that MRI has enabled the pre-surgical detection of important structural abnormalities such as hippocampal sclerosis [56], however, the advent of MRI has not necessarily translated into a significant improvement of long-term outcomes.

In our study the Kaplan-Meier curve, very similar to other studies, [9,32] started to flatten after an initial steep decline at about 4 years and flattened to almost a plateau at about 6 years, although late recurrences did occur. It is unclear if patients can be considered to be completely
cured in the very long-term by epilepsy surgery or if the epilepsy is merely converted from a medical refractory to a medically treatable form and continue to require anti-epileptic medication. The reason for late recurrences is unclear. Interestingly, about 50% of patients who underwent supratentorial neurosurgery for a wide variety of reasons other than epilepsy also developed seizures within 5 years, suggesting the surgery itself could be the cause of seizure recurrence [57].

**Operation type and long-term outcome**

In the present study, those who had an ATL had a better long-term outcome than those who had AHE. Patients with AHE had a very limited resection of amygdala and hippocampal head but not including the parahippocampal gyrus. Although a limited resection did not always preclude a good long-term outcome in individual cases, overall a better outcome was achieved with larger resections [58,59]. Studies suggest that removal of the parahippocampal gyrus improved outcomes in keeping with the hypothesis for an amplifier role of the parahippocampal gyrus [60]. A recent study by Mathon et al [61] shows similar seizure outcome between ATL and trans-superior temporal gyrus AHE. Another study by Keller et al [62] reports superior outcomes in patients who had a greater resection of the uncinate fasciculus which runs through the temporal stem. Therefore, we speculate that disconnection of the temporal stem may also be a factor.
In keeping with a large multi-centre study the outcome of medial temporal resections was not significantly different to neocortical resections [48]. The study by de Tisi et al [9] reported that patients who had an ATL had better seizure freedom rates compared to ETLex. In our study the difference was not statistically significant.

**Underlying pathology and long-term outcome**

Our results showed patients with hippocampal sclerosis had a significantly greater chance of long-term postoperative seizure freedom compared to MRI negative patients. Hippocampal sclerosis had been identified as the cause of epilepsy in some patients with epilepsy over 100 years ago [63] and is a well-known predictor of good outcome [48]. However, our study showed that the prevalence of hippocampal sclerosis was declining relative to the prevalence of other pathologies or no structural abnormality on MRI over the study period. The exact prevalence of hippocampal sclerosis amenable to epilepsy surgery in the general epilepsy population is unknown. Post mortem studies have demonstrated a high prevalence of hippocampal or Ammon’s horn sclerosis (66%) in selected patients [64]. In a large study 160 of 450 patients (35.5%) with chronic epilepsy had Ammon’s horn sclerosis. However, only 68 (15%) had a unilateral Ammon’s horn sclerosis. Of the unilateral cases, 54 had other (more widespread) additional pathologies including hemiatrophy, cystic defects, tumours, arteriosclerosis, trauma, leaving only 14 (3%) “ideal candidates” for surgery [65]. MRI studies mirrored the pathological studies. A high prevalence of hippocampal sclerosis (between 24% [66] to 32% [67]) was found in selected patients with epilepsy attending a tertiary referral centre. However, in unselected patients after a first seizure the prevalence of hippocampal sclerosis was only 5% [68]. Gowers commented in 1893 that overall “no greater significance can be ascribed to the induration of the Cornu Ammonis (pes hippocampi) [as a pathological substrate of epilepsy]” [69]. The data suggest that the surge in cases with hippocampal sclerosis was due to a backlog of patients. It is quite likely that in the future the mix of underlying pathologies will significantly change. Our results suggest that the outcomes of patients with normal MRI or vascular abnormalities are not as favourable as the outcomes of patients with hippocampal sclerosis. Further studies are required for malformations of cortical development but our relatively short-term data are not promising. Our results on outcome predictors can therefore not be automatically transferred to other, future patient groups with a different mix of underlying pathologies.

**Long-term outcome of non-seizure free patients**

It is well known that epilepsy surgery is far superior to standard anti-epileptic drug treatment in selected patients in the short-term [4]. For obvious ethical reasons there is a lack of randomised long-term studies with non-surgical control groups. However, observational studies suggested that with conventional anti-epileptic drug treatment only 21% of patients, who were considered for surgery but for a range of reasons were not operated, entered remission and remained seizure free for an average of 2.5 years [70]. Our study showed the vast majority of patients who were not completely seizure free experienced at least a substantial and long-lasting reduction in seizure frequency. Seventy percent of patients had at least a 50% reduction of seizure frequency 10 years after surgery. This finding is supported by Yoon et al [71] who found that half of the patients who relapsed after epilepsy surgery had at most one seizure per year. Epilepsy surgery therefore compared favourably to all new anti-epileptic drugs including Lamotrigine, Oxcarbazepine, Topiramate, Gabapentin [72] Levetiracetam, Remacemide, Zonisamide, [73] Eslicarbazepine, Retigabine, Carisbamate, Lacosamide, Brivaracetam, Perampanel, [74] and Cannabidiol [75]. Therefore, in patients who are refractory to conventional
antiepileptic drugs and who are candidate for resective epilepsy surgery, surgery appears to be preferable to trying the latest anti-epileptic drug. Further studies are required to determine if a mere reduction in seizure frequency as opposed to complete seizure freedom still results in an improved quality of life.

**Limitations.** This study has several limitations. Firstly our study is skewed towards temporal lobe resections. Unfortunately, this is an inevitable since ATL resection is always the most common form of epilepsy surgery performed in large neurosurgical centres. Our study design is pragmatic and we included all possible cases, thus providing a real world perspective on epilepsy surgery. Furthermore, high impact studies have been published with their data skewed towards ATL resection. For example in the Lancet study by de Tisi et al[76], over 80% of their operations were ATL (497 out of 615).

Secondly, we did not investigate the issue of outcomes and subsequent post-operative death due to lack of data being available. For 12 out of 15 patients that had died, we did not have any data for the underlying cause of death. We acknowledge this is a major limiting factor since if the deaths were due to SUDEP, this would be indicative of surgical failure. Nevertheless, the principal aim of this study was to investigate the seizure outcomes after epilepsy surgery which has been achieved.

**Conclusion**

Our study shows that surgery is effective in providing long-term seizure freedom in patients with refractory epilepsy; almost three quarters of patients had a greater than 50% seizure reduction in seizure frequency at five years and 70% had this reduction at 10 years. Almost half of all patients remained free from debilitating seizures at five years, and over a third of patients at 10 years. Hippocampal sclerosis and ATL was associated with positive long-term seizure outcome.

**Supporting information**

S1 Table. Clinical data on all patients.
(XLSX)

**Acknowledgments**

We would like to thank Carol Chadwick for proof reading the manuscript prior to submission, Dr. Shubhabrata Biswas and Dr. Radhika Manohar for undertaking the MRIs and EEGs. We would also like to thank Mr Thelekat Varma and Mr John Miles for operating on patients and Prof Chadwick for his contribution to the clinical management of the patients.

**Author Contributions**

Conceptualization: Simon Keller, Udo Wieshmann.

Data curation: Midhun Mohan, Andrew Nicolson, David Smith, Udo Wieshmann.

Formal analysis: Midhun Mohan, Udo Wieshmann.

Investigation: Midhun Mohan, Udo Wieshmann.

Methodology: Midhun Mohan, Simon Keller, Udo Wieshmann.

Project administration: Midhun Mohan, Udo Wieshmann.

Resources: Udo Wieshmann.
Software: Udo Wieshmann.
Supervision: Udo Wieshmann.
Validation: Udo Wieshmann.
Visualization: Udo Wieshmann.
Writing – original draft: Midhun Mohan, Simon Keller, Udo Wieshmann.
Writing – review & editing: Midhun Mohan, Simon Keller, Andrew Nicolson, Shubhabrata Biswas, David Smith, Jibril Osman Farah, Paul Eldridge, Udo Wieshmann.

References
1. Sander JW, Shorvon SD. Epidemiology of the epilepsies. Journal of Neurology, Neurosurgery & Psychiatry. 1996; 61: 433–443. https://doi.org/10.1136/jnnp.61.5.433
2. Engel J. Mesial temporal lobe epilepsy: what have we learned? Neuroscientist. 2001; 7: 340–352. https://doi.org/10.1177/107385840100700410 PMID: 11488399
3. Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology. 1998; 51: 1256–1262. PMID: 9818842
4. Wiebe S, Blume WT, Girvin JP, Eliaszw M. 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. Massachusetts Medical Society; 2001; 345: 351–318. https://doi.org/10.1056/NEJM200108023450501 PMID: 11484687
5. Engel J, McDermott MP, Wiebe S, Langfitt JT, Stern JM, Langfitt JT, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA. 2012; 307: 922–930. https://doi.org/10.1001/jama.2012.220 PMID: 22396514
6. Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain. 2005; 128: 1188–1198. https://doi.org/10.1093/brain/awh449 PMID: 15758038
7. Schramm J, Delev D, Wagner J, Elger CE, Lehe von M. Seizure outcome, functional outcome, and quality of life after hemispherectomy in adults. Acta Neurochir (Wien). Springer Vienna; 2012; 154: 1603–1612. https://doi.org/10.1007/s00701-012-1408-z PMID: 22706972
8. Berkovic SF, McIntosh AM, Kalnins RM, Jackson GD, Fabinyi GC, Brazenor GA, et al. Preoperative MRI predicts outcome of temporal lobectomy: an actuarial analysis. Neurology. 1995; 45: 1358–1363. PMID: 7617198
9. de Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WFJ, Sander JW, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet. 2011; 378: 1388–1395. https://doi.org/10.1016/S0140-6736(11)60890-8 PMID: 22000136
10. Giuliani M, Marucci G, Martinoni M, Volpi L, Riguzzi P, Marliani AF, et al. Seizure outcome in surgically treated drug-resistant mesial temporal lobe epilepsy based on the recent histopathological classifications. J Neurosurg. American Association of Neurological Surgeons; 2013; 119: 37–47. https://doi.org/10.3171/2013.3.JNS122132 PMID: 23641822
11. Hemb M, Palmi M, Aglioli P, Aglioli EB, Costa da Costa J, Azambuja N, et al. An 18-year follow-up of seizure outcome after surgery for temporal lobe epilepsy and hippocampal sclerosis. Journal of Neurology, Neurosurgery & Psychiatry. 2013; 84: 800–805. https://doi.org/10.1136/jnnp-2012-304038 PMID: 23408065
12. McIntosh AM, Kalnins RM, Mitchell LA, Fabinyi GCA, Briellmann RS, Berkovic SF. Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. Brain. 2004; 127: 2018–2030. https://doi.org/10.1093/brain/awh221 PMID: 15215219
13. Keller SS, Glenn GR, Weber B, Kreilak BAK, Jensen JH, Helpen JA, et al. Preoperative automated fibre quantification predicts postoperative seizure recurrence in temporal lobe epilepsy. Brain. 2017; 140: 68–82. https://doi.org/10.1093/brain/aww280 PMID: 28031219
14. Aull-Watchinger S, Pataraia E, Czech T, Baumgartner C. Outcome predictors for surgical treatment of temporal lobe epilepsy with hippocampal sclerosis. Epilepsia. Blackwell Publishing Inc; 2008; 49: 1308–1316. https://doi.org/10.1111/j.1528-1167.2008.01732.x PMID: 18754943
15. Edelvik A, Rydenhag B, Olsson I, Flink R, Kumlien E, Källén K, et al. Long-term outcomes of epilepsy surgery in Sweden: a national prospective and longitudinal study. Neurology. Lippincott Williams & Wilkins; 2013; 81: 1244–1251. https://doi.org/10.1212/WNL.0b013e3182a6ca7b PMID: 23966252
16. Elsharkawy AE, Behne F, Oppel F, Pannek H, Schulz R, Hoppe M, et al. Long-term outcome of extratemporal epilepsy surgery among 154 adult patients. J Neurosurg. 2008; 108: 676–686. https://doi.org/10.3171/JNS/2008/108/4/0676 PMID: 18377245

17. Paglioli E, Palmi A, Paglioli E, da Costa JC, Portugal M, Martinez JU, et al. Survival analysis of the surgical outcome of temporal lobe epilepsy due to hippocampal sclerosis. Epilepsia. Blackwell Science Inc; 2004; 45: 1383–1391. https://doi.org/10.1111/j.0013-9580.2004.22204.x PMID: 15509239

18. Luken C, Blümcke I, Fimmers R, Urbach H, Elger CE, Wiestler OD, et al. The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects. Epilepsia. 2003; 44: 822–830. PMID: 12790896

19. Tonini C, Beghi E, Berg AT, Bogliun G, Giordano L, Newton RW, et al. Predictors of epilepsy surgery outcome: a meta-analysis. Epilepsy Research. 2004; 62: 75–87. https://doi.org/10.1016/j.eplepsyres.2004.08.006 PMID: 15509239

20. West S, Nolan SJ, Newton R. Surgery for epilepsy: a systematic review of current evidence. Epileptic Disord. 2016; 18: 113–121. https://doi.org/10.1684/epd.2016.0825 PMID: 27193634

21. Malmgren K, Edelvik A. Long-term outcomes of surgical treatment for epilepsy in adults with regard to seizures, antiepileptic drug treatment and employment. Seizure. 2016. https://doi.org/10.1016/j.seizure.2016.10.015 PMID: 27839670

22. Edelvik A, Rydenhag B, Olsson I, Flink R, Kumlien E, Källén K, et al. Long-term outcomes of epilepsy surgery in Sweden: a national prospective and longitudinal study. Neurology. Lippincott Williams & Wilkins; 2013; 81: 1244–1251. https://doi.org/10.1212/WNL.0b013e3182a6ca7b PMID: 23966252

23. Bien CG, Raabe AL, Schramm J, Becker A, Urbach H, Elger CE. Trends in presurgical evaluation and surgical treatment of epilepsy at one centre from 1988–2009. Journal of Neurology, Neurosurgery & Psychiatry. 2013; 84: 54–61. https://doi.org/10.1136/jnnp-2011-301763 PMID: 23055516

24. Menon R, Rathore C, Sarma SP, Radhakrishnan K. Feasibility of antiepileptic drug withdrawal following extratemporal resective epilepsy surgery. Neurology. 2012; 79: 770–776. https://doi.org/10.1212/WNL.0b013e31826447ed PMID: 22843256

25. Simasathien T, Vadera S, Najm I, Gupta A, Bingaman W, Jehl L. Improved outcomes with earlier surgery for intractable frontal lobe epilepsy. Ann Neurol. 2013; 73: 646–654. https://doi.org/10.1002/ana.23862 PMID: 2349550

26. Phi JH, Kim S-K, Cho B-K, Lee SY, Park SY, Park S-J, et al. Long-term outcomes of surgical treatment for epilepsy in adults with regard to seizures, antiepileptic drug treatment and employment. Seizure. 2016. https://doi.org/10.1016/j.seizure.2016.10.015 PMID: 27839670

27. Schwartz TH, Jeha L, Tanner A, Bingaman W, Sperling MR. Late seizures in patients initially seizure free after epilepsy surgery. Epilepsia. 2006; 47: 567–573. https://doi.org/10.1111/j.1528-1167.2006.00469.x PMID: 16529623

28. Fauser S, Essang C, Altenmüller D-M, Staack AM, Steinhoff BJ, Strobl K, et al. Long-term seizure outcome in 211 patients with focal cortical dysplasia. Epilepsia. 2015; 56: 66–76. https://doi.org/10.1111/epi.12876 PMID: 25495786

29. Foldvary N, Nashold B, Mascha E, Thompson EA, Lee N, McNamara JO, et al. Seizure outcome after temporal lobectomy for temporal lobe epilepsy: a Kaplan-Meier survival analysis. Neurology. 2000; 54: 630–634. PMID: 10680795

30. Spencer SS, Berg AT, Vickrey BG, Sperling MR, Bazil CW, Shinnar S, et al. Predicting long-term seizure outcome after resective epilepsy surgery: the multicenter study. Epilepsy Research. 2005; 65: 912–918. https://doi.org/10.1012/j.epmr.2005.08.001 PMID: 16186534

31. Jeha LE, Najm I, Bingaman W, Dinner D, Widness-Walsh P, Lüders H. Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. Brain. 2007; 130: 574–584. https://doi.org/10.1093/brain/awl364 PMID: 17209228

32. McIntosh AM, Kalnins RM, Mitchell LA, Fabinyi GCA, Briellmann RS, Berkovic SF. Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. Brain. 2004; 127: 2018–2030. https://doi.org/10.1093/brain/awh221 PMID: 15215219

33. Ramesha KN, Mooney T, Sarma PS, Radhakrishnan K. Long-term seizure outcome and its predictors in patients with recurrent seizures during the first year after temporal lobe resective epilepsy surgery. Epilepsia. 2011; 52: 917–924. https://doi.org/10.1111/j.1528-1167.2010.02891.x PMID: 21219316

34. 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. https://doi.org/10.1111/j.1528-1167.2010.02890.x PMID: 21219315

35. Menon R, Rathore C, Sarma SP, Radhakrishnan K. Feasibility of antiepileptic drug withdrawal following extratemporal resective epilepsy surgery. Neurology. 2012; 79: 770–776. https://doi.org/10.1212/WNL.0b013e31826447ed PMID: 22843256
36. Di Gennaro G, Casciato S, D’Aniello A, De Risi M, Quarato PP, Mascia A, et al. Serial postoperative awake and sleep EEG and long-term seizure outcome after anterior temporal lobectomy for hippocampal sclerosis. Epilepsy Research. 2014; 108: 945–952. https://doi.org/10.1016/j.eplepsyres.2014.03.010 PMID: 24721201

37. Dupont S, Tanguy M-L, Clemenceau S, Adam C, Hazemann P, Baulac M. Long-term prognosis and psychosocial outcomes after surgery for MTLE. Epilepsia. 2006; 47: 2115–2124. https://doi.org/10.1111/j.1528-1167.2006.00852.x PMID: 17201711

38. Lazow SP, Morse RP, Bujarski KA, Kulandaiel K, et al. Outcome of frontal lobe epilepsy surgery. Epilepsia. 2012; 53: 1746–1755. https://doi.org/10.1111/j.1528-1167.2012.03582.x PMID: 22780836

39. Wiesmann UC, Denby CE, Eldridge PR, Roberts N, Mackay CE, Webb JA, et al. Foramen ovale recordings: a presurgical investigation in epilepsy. Eur Neurol. 2003; 49: 3–7. https://doi.org/10.1159/000067019 PMID: 12464711

40. Wieser HG, Elger CE, Stodieck SR. The “foramen ovale electrode”: a new recording method for the preoperative evaluation of patients suffering from mesio-basal temporal lobe epilepsy. Electroencephalogr Clin Neurophysiol. 1985; 61: 314–322. PMID: 2411510

41. Niemeyer P. The transventricular amygdalohippocampectomy in temporal lobe epilepsy. Temporal lobe epilepsy. Charles C Thomas Springfield, IL; 1958;: 461–482.

42. Wieser HG, Blume WT, Fish D, Goldman J, King D, et al. ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. 2001. pp. 282–286.

43. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. Journal of the American Statistical Association. 1958; 53: 457–481. https://doi.org/10.1080/01621459.1958.10501452

44. de Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WFJ, Sander JW, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet. 2011; 378: 1388–1395. https://doi.org/10.1016/S0140-6736(11)60890-8 PMID: 22000136

45. McIntosh AM, Averill CA, Kalnings RM, Mitchell LA, Fabinyi GCA, Jackson GD, et al. Long-term seizure outcome and risk factors for recurrence after extratemporal epilepsy surgery. Epilepsia. 2012; 53: 970–978. https://doi.org/10.1111/j.1528-1167.2012.03430.x PMID: 22417071

46. Téllez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain. 2005; 128: 1188–1198. https://doi.org/10.1093/brain/awh449 PMID: 15758038

47. Luyskens B, Blümcke I, Fimmers R, Urbach H, Elger CE, Wiestler OD, et al. The Spectrum of Long-term Epilepsy-associated Tumors: Long-term Seizure and Tumor Outcome and Neurosurgical Aspects. Epilepsia. 2003; 44: 822–830. https://doi.org/10.1046/j.1528-1157.2003.56102.x PMID: 12790896

48. Spencer SS, Berg AT, Vickrey BG, Sperling MR, Bazil CW, Shinnar S, et al. Predicting long-term seizure outcome after resective epilepsy surgery: the multicenter study. Neurology. 2005; 65: 912–918. https://doi.org/10.1212/01.wnl.0000176055.45774.71 PMID: 16186534

49. Cohen-Gadol AA, Wilhelm BG, Collignon F, White JB, Britton JW, Cambier DM, et al. Long-term outcome of epilepsy surgery among 399 patients with nonlesional seizure foci including mesial temporal lobe sclerosis. J Neurosurg. 2006; 104: 513–524. https://doi.org/10.3171/jns.2006.104.4.513 PMID: 16619654

50. Asztely F, Ekstedt G, Rydenhag B, Malmgren K. Long term follow-up of the first 70 operated adults in the Goteborg Epilepsy Surgery Series with respect to seizures, psychosocial outcome and use of antiepileptic drugs. Journal of Neurology, Neurosurgery & Psychiatry. 2007; 78: 605–609. https://doi.org/10.1136/jnnp.2006.098244 PMID: 17237145

51. Jeha LE, Najm IM, Bingaman WE, Khandwala F, Widness-Walsh P, Morris HH, et al. Predictors of outcome after temporal lobectomy for the treatment of intractable epilepsy. Neurology. 2006; 66: 1938–1940. https://doi.org/10.1212/01.wnl.0000219810.7160.9b PMID: 16801667

52. Sperling MR, Saykin AJ, Roberts FD, French JA, O’Connor MJ. Occupational outcome after temporal lobectomy for refractory epilepsy. Neurology. 1995; 45: 970–977. PMID: 7746417

53. Jehi L. Medication management after epilepsy surgery: opinions versus facts. Epilepsy Curr. 2013; 13: 166–168. https://doi.org/10.5698/1535-7597-13.4.166 PMID: 24009479

54. Jacoby A, Baker G, Chadwick D, Johnson A. The impact of counselling with a practical statistical model on patients’ decision-making about treatment for epilepsy: findings from a pilot study. Epilepsy Research. 1993; 16: 207–214. PMID: 8119271

55. Vincken PJ, Bruyn GW. Handbook of Clinical Neurology. North-Holland Publishing Company; 1974.

56. Duncan JS. Imaging and epilepsy. Brain: a journal of neurology; 1997; 120 (Pt 2): 339–377.
57. Foy PM, Chadwick DW, Raigopal N, Johnson AL, Shaw MD. Do prophylactic anticonvulsant drugs alter the pattern of seizures after craniotomy? Journal of Neurology, Neurosurgery & Psychiatry. 1992; 55: 753–757.

58. Josephson CB, Dyken J, Fiest KM, Liu X, Sadler RM, Jetté N, et al. Systematic review and meta-analysis of standard vs selective temporal lobe epilepsy surgery. Neurology. Lippincott Williams & Wilkins; 2013; 80: 1669–1676. https://doi.org/10.1212/WNL.0b013e3182904f82 PMID: 23553475

59. Hu W-H, Zhang C, Zhang K, Meng F-G, Chen N, Zhang J-G. Selective amygdalohippocampectomy versus anterior temporal lobectomy in the management of mesial temporal lobe epilepsy: a meta-analysis of comparative studies. J Neurosurg. American Association of Neurological Surgeons; 2013; 119: 1089–1097. https://doi.org/10.3171/2013.8.JNS121854 PMID: 24032705

60. Siegel AM, Wieser HG, Wichmann W, Yasargil GM. Relationships between MR-imaged total amount of tissue removed, resection scores of specific mediobasal limbic subcompartments and clinical outcome following selective amygdalohippocampectomy. Epilepsy Research. 1990; 6: 56–65. PMID: 2357956

61. Mathon B, Bielle F, Samson S, Plaisant O, Dupont S, Bertrand A, et al. Predictive factors of long-term outcomes of surgery for mesial temporal lobe epilepsy associated with hippocampal sclerosis. Epilepsia. 2017; 58: 1473–1485. https://doi.org/10.1111/epi.13831 PMID: 28031219

62. Sommer W. Erkrankung des Ammonshorn als aetiologisches Moment der Epilepsie. Archiv für psychiatrie und nervenkrankheiten. Springer; 1880; 10: 631–675.

63. Wiesmann UC. Clinical application of neuroimaging in epilepsy. Journal of Neurology, Neurosurgery & Psychiatry. 2003; 74: 466–470.

64. Gowers WR. A Manual of diseases of the nervous system. P. Blakiston's Sons & Company; 1901.

65. Marson AG, Hutton JL, Leach JP, Castillo S, Schmidt D, White S, et al. Levetiracetam, oxcarbazepine, remacemide and zonisamide for drug resistant localization-related epilepsy: a systematic review of randomized placebo-controlled trials. Epilepsy Research. 2013; 103: 31–44. https://doi.org/10.1016/j.eplepsyres.2012.06.005 PMID: 22776828

66. Hess EJ, Moody KA, Geoffrey AL, Pollack SF, Skirvin LA, Bruno PL, et al. Cannabidiol as a new treatment for drug-resistant epilepsy in tuberous sclerosis complex. Epilepsia. 2016; 57: 1617–1624. https://doi.org/10.1111/epi.13499 PMID: 27696387

67. de Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WFJ, Sander JW, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet. 2011; 378: 1388–1395. https://doi.org/10.1016/S0140-6736(11)60890-8 PMID: 22000136