The long-term outcome of adult epilepsy surgery, patterns of seizure remission and relapse in a large cohort.

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Abstract

Background

Surgery is increasingly used as treatment for refractory focal epilepsy, but there are few rigorous reports of long-term outcome.

Methods

We report long-term outcome of epilepsy surgery in 615 adults (comprising 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 median 8 years (range 1 - 19 years). Survival analysis (Kaplan Meier method) was used to estimate time to first seizure, and patterns of seizure outcome were investigated.

Findings

The percentage of people remaining seizure-free apart from simple partial seizures (SPS) since surgery was estimated as 52% (95% CI 48%, 56%) at five years and 47% (95% CI 42%, 51%) at ten years. Those having extratemporal resections were more likely to have seizure recurrence than were people having anterior temporal resections (Hazard Ratio [HR] 2·0, 95% CI 1·1, 3·6), while those having lesionectomies were not significantly different in this regard.

Those with SPS in the first two years had a greater chance of a subsequent seizure with impaired awareness than those who had no SPS (HR 2·4, 95% CI 1·5, 3·9). The longer a person was seizure-free, the less likely was a relapse. Conversely, if seizures continued after surgery, seizure remission became less likely the longer seizures continued. In 19 people, late remission was associated with introduction of an antiepileptic drug not previously tried. At latest follow-up 28% (104 of 367) of seizure-free individuals had discontinued drugs.

Interpretation

Neurosurgical treatment is an attractive option for selected people with refractory focal epilepsy. These data provide realistic expectations and indicate the scope for further improvements in the pre-surgical evaluation and surgical treatment for people with chronic epilepsy.

INTRODUCTION

Surgical treatment for focal epilepsy has been increasingly used.[1] The only randomised control trial of surgery established the short-term benefits of anterior temporal lobe resection over medical treatment for refractory temporal epilepsy.[2] It is generally held that chances of seizure remission after surgery in an individual with concordant data are up to 60-70%. In one study of long-term outcome in 325 people having anterior temporal resection, the seizure freedom rate was 41% at ten years.[3] Those seizure-free two years postoperatively had a 74% (95% CI 66%, 81%) probability of seizure freedom by ten post-operative years. Late recurrence after initial seizure freedom was not rare and risk factors associated with this are unknown. Accurate long-term follow-up data are necessary to determine patterns of seizure remission and relapse following surgery and to enable individuals considering it to make informed choices.

METHODS

We determined the long-term outcome and patterns of seizure remission and relapse up to November 2009 in 649 consecutive people who had epilepsy surgery at the National Hospital for Neurology & Neurosurgery (NHNN) from February 1990 to October 2008. Two experienced consultant neurosurgeons specializing in epilepsy (WFH, AWM) carried out over 90% of the surgeries. For each person, the clinical and investigatory data (Box 1) were considered in detail and the optimal surgical

approach was derived for each individual, to give each person the optimal chance of seizure freedom, with the lowest risk of complications.[4] The general principles of presurgical evaluation in our Unit were established in 1990, and, whilst there have been advances in MRI and video-EEG recording technology, the principles of establishing a consensus of data regarding the seizure onset zone and relation to eloquent cortex have not changed.[4]

Information for annual updates of seizure status was obtained from review of contemporaneous NHNN notes and notes of other hospitals people were attending. These data were supplemented by direct annual enquiry by a neurology consultant and clinical data manager who contacted the individuals and their General Practitioners and, in cases of uncertainty, next of kin. Specific questions included the occurrence of simple partial seizures (SPS), of seizures with loss of awareness, and antiepileptic drugs (AED) taken. In the event of discrepancies between sources, further enquiries were made until a consensus was reached. At each post-surgical year seizure outcomes were classified (Outcome Classification - OC) using the ILAE Surgery outcome scale[5] (Box 2). The term SPS is used throughout, and incorporates all events that are sometimes classified as auras.

The use of AEDs and changes within each previous year were noted. OC3 or higher defined the occurrence of seizures other than SPS. Survival analysis using Cox proportional hazards regression was used for all time-to-event outcomes and to compare time to first seizure (OC3 or more). Hazard ratios (HRs) were calculated with 95% confidence intervals (CIs). Age at surgery was included in the analyses when appropriate. The Kaplan Meier method was used to estimate the percentage remaining seizure-free at various time points. Analyses were carried out comparing different pathologies in people with similar surgical procedures, and different surgical procedures in people with similar pathology. Those who had no seizures at all or SPS

only in the first two post-operative years were selected, and analysis was performed of time to first seizure (OC3+) thereafter.

Analysis of time to first seizure including SPS, (OC 2 or more), is available on-line. Statistical analysis was performed using Stata v10 (Statacorp LP, Texas). Confidence intervals for proportions were obtained from Confidence Interval Analysis software.[6]

This study was approved by the Joint Ethics Committee of the National Hospital for Neurology and Neurosurgery and UCL Institute of Neurology.

To place our research in context, we carried out a review to ascertain results of previous studies of the outcome after epilepsy surgery. We searched for published papers reporting outcome in electronic databases MEDLINE and EMBASE (up to March 2011) using the key words: epilep* surgery outcome.

Role of the funding source

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RESULTS

Demographics and procedures

In 34 of 649 people no yearly outcome scores were available, because of death (N = 5), or loss to follow-up (N = 27) within one year of surgery (15 of these lived overseas) or because they had subsequent surgery within one year of the first operation (N=2). Thus 615 people (287 male, aged 16 to 63 years at surgery, median [IQR] duration of epilepsy prior to surgery 20·7 [13·9, 28·6] years) are considered further; pathology and surgical procedure are in Table 1. Fifteen people

had two surgical procedures for epilepsy; in these, data were censored at the time of the second procedure. Nineteen people who had had previous neurosurgical procedures (17 biopsy/partial lesion removal, 1 meningioma removal, 1 partial corpus callosal section) are included.

With a total of 5,241 person-years of follow up, OC data were available for median 8 years, range 1-19 years. Data were not available for the two years prior to the audit date (19 November 2009) in 127 (21%) people for whom the last verified follow-up data were obtained prior to 19 November 2007. The median duration of follow-up for these 127 people was six years.

Survival analysis of time to first seizure following surgery

In the whole cohort the estimated percentage remaining seizure-free (other than SPS) was 63% (95% CI 59%, 67%) two years post surgery, 52% (95% CI 48%, 56%) after five years and 47% (95% CI 42%, 51%) after ten years. Table 2 shows univariable and multivariable survival analysis of time to first seizure (OC3+) following surgery, including the probability of seizure freedom after ten years. Multivariable results in this table include all factors that were statistically significant in univariable models. Age at surgery had a significant effect on outcome (table 2, one year HR 1.01, 95% CI 1.00, 1.02, five year HR 1.06, 95% CI 1.00, 1.13) and was included in all subsequent analyses. Five years following surgery, the seizure free rates (excluding SPS) were 55% (95% CI 51%, 60%) for anterior temporal resection, 56% (95% CI 38%, 70%) for temporal lesionectomy, 40% (95% CI 24%, 55%) for extratemporal lesionectomy, and 64% (95% CI 30%, 85%) for hemispherectomy (figure 1).

Outcome with respect to pathology in people who had similar operations

There was a difference in outcome for the various pathologies after anterior temporal resection (p=0·02) (table 3). Those with focal cortical dysplasia and those with "other pathologies" including other malformations and no detected abnormality had

significantly earlier relapses. The 5 year seizure free rates (excluding SPS) for anterior temporal resection were 57% (95% CI 52%, 62%) for those with hippocampal sclerosis and 63% (95% CI 45%, 77%) for those with DNT.

In those who had a lesionectomy the risk of seizure recurrence was not significantly different in those who had a glioma (N=18) or dysembryoplastic neuroepithelial tumour (N=36) compared with those with a cavernoma (N=14) (HR 1·42, 95% CI 0·58, 3·47). There was no difference in probability between those with glioma, dysembryoplastic neuroepithelial tumour or cavernoma compared with focal cortical dysplasia (N=7; HR 0·77, 95% CI 0·27 2·17).

Outcome of different surgical procedures in people with similar temporal pathology

In people with glioma, dysembryoplastic neuroepithelial tumour, cavernoma or focal cortical dysplasia, there was no significant difference in time to first seizure in those who underwent anterior temporal resection (N=62) or temporal lesionectomy (N=36) (HR for lesionectomy 0·92, 95% CI 0·49, 1·73). Results were similar for individual pathologies, but numbers were small.

Time to first seizure in people having temporal and extra-temporal lesionectomies

Forty people each had temporal or extra-temporal lesionectomies. The time to first seizure was not different between the two groups (HR for extra-temporal lesionectomy 1·7, 95% CI 0·9, 3·1). This was not materially altered (HR 1·8, 95% CI 0·95, 3·5) if pathology type was included in the analysis.

Time to first seizure in people with temporal surgery following 2 years of seizure freedom

296 people with further follow-up had anterior temporal surgery and no seizures (or SPS only) in the first two post-surgical years. The 73 who had SPS in this time were

significantly more likely to have a seizure (OC3+) in the subsequent years than those who had no SPS (HR 2·4, 95% CI 1·5, 3·9) (Figure 2, table 4).

Seizure remission and relapse

At each annual review 68 to 73% of people were seizure-free or had only SPS. Whilst overall percentage that remained seizure-free was fairly stable, each year 3-15% changed between groups (figure 3).

Probability of seizure freedom after an initial period of post-surgical seizure freedom, or of continuing seizures

Table 5A shows the probability of remaining seizure-free after initial seizure freedom; the longer a person was seizure-free; the less likely there was to be a relapse. The latest relapse in somebody previously seizure-free was at 15 years post-surgery. In people with post-operative seizures (table 5B), the longer seizures continued, the less likely was a subsequent remission.

Patterns of seizure remission and relapse following epilepsy surgery.

Patterns of seizure remission and relapse were stratified into eight groups (A to G) (table 6). Deaths were noted, and classified as not or probably, epilepsy-related. Almost three quarters (73%, 95% CI 70%, 77%; n=451) had at least one year of absolute seizure freedom and 82% had at least one year with no seizures or only auras.

In ten of 47 people (group C) who relapsed after a year or more without seizures, the relapse was preceded by tapering or omission of AEDs. In a further nine, relapse was associated with stress or intercurrent illness.

In 36 of 49 people with seizures initially continuing post-surgically (group B), remission occurred without any AED changes. Long-term remission developed in 30 at two years following surgery and in 19 people from years 3-14. A further 44 went into remission after 2-14 years, had a subsequent short-lived relapse, and then terminal remission (group D).

In 18 people from groups B and D, seizure remission occurred at 2-12 years following surgery after the introduction of an AED not used previously (14 Levetiracetam, 1 Clobazam, 1 Pregabalin, 1 Topiramate, 1 Valproate). A further 14 people from group D who had seizures on withdrawal of AEDs went into long-term remission on recommencing them.

Antiepileptic drug reduction

For people seizure-free following surgery the possibilities of AED reduction were discussed with each individual according to their circumstances. At latest follow-up, 104 of 365 (28%) of seizure-free individuals were off AEDs. Four of 65 (6%) people with SPS at last follow-up and five (2.7%) of 185 with continuing seizures were taking no AEDs.

Mortality after epilepsy surgery

Mortality in this group was reported previously.[7] Nineteen of the 615 people died (5 epilepsy-related and 11 non-epilepsy related; 3 cause unknown), as well as the five people who died within a year of surgery (1 cancer, 1 infection, 1 suicide, and 2 SUDEP). This approximates to one death per 218 patient-years of follow-up.

Morbidity after epilepsy surgery

Clinically evident morbidity consequent to the surgical procedures comprised: 46 superior quadrant visual field defects (8% of temporal lobe procedures), 28 (4.5%) wound infections requiring antibiotics, 3 (0.5%) hemiparesis, 15 (2.5%) frontalis muscle weakness, 6 (1%) dysphasia, 19 (3%) cerebrospinal fluid leaks requiring resuturing, and one deep venous thrombosis requiring anticoagulation.

DISCUSSION

We established long-term outcome and AED use in a large adult epilepsy surgery cohort, with over 5,200 person-years of follow-up. Previous studies of seizure outcome at the first and second year and at last follow-up do not capture the

spectrum of seizure control following surgery. A meta-analysis of long-term seizure outcome after surgery noted that few studies report how many people have sustained seizure freedom from the time of surgery.[8] Previous studies have used different outcome classifications and seizure freedom definitions[1,8] We used the ILAE classification[5] and analysed both OC1 (entirely seizure-free in the previous year – available on line) and OC1 & 2 (including SPS). Individuals were accustomed to keeping prospective seizure diaries and would know if they had seizures on more than 3 days in a year. Distinction between OC 4/5 may be more difficult and this distinction was not analysed.

Complete seizure freedom since surgery

Fifty one percent of individuals were 'seizure-free' in terms of the usually quoted criteria (entirely seizure-free or only SPS) for the duration of follow-up and 40% were completely seizure-free throughout follow-up. At any one time point, approximately 70% of people were 'seizure-free' for the last year (figure 3). One study had a 60% response to a questionnaire on average seven years after temporal surgery.[9] 48% had not experienced seizures since surgery, somewhat better than the 38% entirely seizure-free in our cohort ten years after anterior temporal resection as estimated by survival analysis; the poor response rate raises the possibility of bias. A retrospective review of 199 people following surgery found that 43% were seizure-free or had SPS throughout a mean seven year follow-up.[10] Other studies of people with temporal surgery, followed for mean 5 to 10 years, reported seizure freedom (with or without SPS) of 41 to 63%.[3,11,12]

In this study, age at surgery had a small effect (HR 1·01), showing a 6·6% increased risk of seizure recurrence in people five years older at surgery, and a 13·6% increased risk in people ten years older.

In the whole cohort the probability of remaining seizure-free (no seizures with loss of awareness) was 63% (95%CI 59%, 67%) at 2 years. (The probability of being

entirely seizure-free at two years was 49% (online). By ten years the probability of remaining seizure-free or with SPS was 47%, or 37% entirely seizure-free. A similar study in 134 consecutive people with temporal resection for hippocampal sclerosis estimated that 77% were seizure-free at two years and 74% at five years.[13] Their success rate seems higher, but numbers are small and CIs not provided. Not unexpectedly, a short interval between surgery and seizure recurrence was associated with a worse longer term prognosis than if there was a longer interval between surgery and initial recurrence.[14]

One year remission

Almost three quarters of people had at least one year of absolute seizure freedom at some stage, rising to 82% if discounting SPS. 18% had no single year of seizure freedom. A study of 102 people following surgery found that by two years 70% had had a remission (with or without SPS) of one year, 74% by three years and 77% by five years.[12]

Outcome after temporal and extra-temporal surgery

People having extra-temporal resections had a greater probability of seizure recurrence than did those having anterior temporal resection. A long-term follow-up of 399 people following surgery reported similar findings, with those with temporal resections having a greater chance of seizure freedom.[15]

Outcome according to pathology

For people having anterior temporal resection, those with focal cortical dysplasia and those with 'other' pathology, including other malformations and no detected abnormality, were more likely to have recurrent seizures than those with hippocampal sclerosis, although numbers are small. The 5 year seizure free rates (excluding SPS) for anterior temporal resection were 57% (95% CI 52%, 62%) for those with hippocampal sclerosis and 63% (95% CI 45%, 77%) for those with

dysembryoplastic neuroepithelial tumour. The numbers having lesionectomies for the different pathologies were too small to identify any difference in time to first seizure.

A comparison of post-operative outcome with abnormalities identified on preoperative MRI, reported that a two-year terminal remission was obtained in 16 of 20 people with tumours and vascular malformations, in 58% of 85 people with hippocampal sclerosis and 29% of those with normal MRI.[16] An evaluation of 368 consecutive people who had anterior temporal resection, however, found that pathology (defined as gliosis, mesial temporal sclerosis, normal or other) did not influence the time to subsequent seizure.[17] Others have reported a more favourable outcome in people with hippocampal sclerosis.[10,15] The presence of ganglioglioma or dysembryoplastic neuroepithelial tumour, and absence of dysplasia were associated with good post-operative seizure control[18]

Outcome according to operative procedure in people with temporal surgery

For equivalent pathologies (glioma, dysembryoplastic neuroepithelial tumour, cavernoma or focal cortical dysplasia), temporal lesionectomies and anterior temporal resection had similar rates of seizure freedom. Caveats include the fact that numbers are small, the decision was not randomised and those with more extensive pathology and lesions closer to the hippocampus were more likely to have anterior temporal resection.

Analysis of four different procedures (anterior temporal resection, amygdalohippocampectomy, and lesionectomy and corticectomy with or without hippocampectomy) for temporal epilepsy performed in 321 people found no significant difference in postoperative outcome.[18] In a paediatric population, however, amygdalohippocampectomy gave significantly lower seizure freedom rates than did standard anterior temporal resection.[19] In 18 people with dysembryoplastic neuroepithelial tumour, those with temporal resection were more likely to be seizure-

free than those who had lesionectomy.[20] In most, however, the lesion was not temporal.

Relapse following seizure freedom

The probability of remaining seizure-free increased with the number of years of seizure freedom already experienced (table 5). In the study of outcome following temporal surgery in 102 people,[12] individuals seizure-free (or with SPS) for any one year had a 90% probability of having no seizures in the following year and those with two successive years of seizure freedom had a 94% chance of seizure freedom in the subsequent year. The probability of remaining seizure-free throughout a mean of 5·6 years follow-up in those who were seizure-free for the first year following temporal surgery was 83%, and 92% in those seizure-free for the first two post-operative years.[11] A study of people seizure-free, with or without SPS, for one year after surgery estimated that the probability of then having a seizure was 18% at five years and 33% at ten years.[21]

Outcome in people with and without SPS in the first two years after temporal surgery

Those with SPS in the first two years were twice as likely to have subsequent seizures with impaired awareness as those entirely free. Another study considered people who had had SPS associated with complex partial or secondarily generalized seizures prior to temporal resections. In that study there was no difference in subsequent freedom from complex partial or secondarily generalized seizures in those free of these seizures- for two years after surgery, between those who did and did not have SPS post-operatively.[22]

Seizure freedom following initial seizures

Few people had continuing seizures each year for two and five years, so estimates are imprecise. Nevertheless, even in people with a prolonged period of continuing seizures, the possibility of remission remains (table 5). Forty-nine people (8%) had

seizures initially and then became seizure-free, while 7% were initially seizure-free, relapsed and were then free again. Small numbers of individuals became seizure-free following the introduction of new AEDs. These AEDs introduced following surgery had not been tried previously, and it is not possible to know whether they may have controlled seizures if used pre-operatively. It is worth trying previously unused AEDs if seizures continue after surgery.

Follow-up of 276 people who had at least one seizure after the immediate post-operative period noted that 77% would have further seizures within 12 months; after a second seizure 86% would have further seizures within 12 months. One third subsequently had one or more seizure free years[23] A study of 86 people with temporal epilepsy who still had seizures six months after surgery found that 32% had been seizure-free for at least one year, by two years.[24] Of 51 people who had anterior temporal resection, 14 had seizures during the first two years; four became seizure-free during the third and fourth postoperative years.[25]

Antiepileptic drug reduction and addition

Almost one fifth (and 28% of those who were seizure-free at last follow-up) stopped AEDs. Others may have been suitable for drug reduction, but have been reluctant to do so, often for social reasons, such as permission to drive. A future analysis will consider AED reduction and factors affecting this. With the small numbers and the observational nature of the study we cannot comment strongly but note that if seizures continue after surgery, it is worth considering new AEDs.

Mortality and morbidity after epilepsy surgery

The incidence of mortality and new morbidity after epilepsy surgery was low and compares favourably with the annual mortality rate of severe epilepsy.[7] The occurrence of visual field defects detected with Goldmann perimetry, which is more sensitive than clinical evaluation, following temporal lobe resection at NHNN was

reported recently.[26,27] The effects of surgery on cognitive function, psychiatric status and employment will be the subject of separate reports.

Conclusion

Our cohort was inevitably highly selected. Whilst the great majority showed a marked reduction in seizures, only 40% entered long-term remission by virtue of having no seizures from the time of surgery, and only 28% of people seizure-free at last follow-up had discontinued AEDs and so could be regarded as being "cured".

The procedures and process of epilepsy surgery at NHNN are similar to those at other major epilepsy surgery centres, and so are likely to be generalisable, but replication at other centres would be valuable.

Obtaining a driving licence and consideration of pregnancy seem major factors in an individual's decision-making, and there has been no prospective randomised trial of cessation or continuation of AEDs following surgery.

We are currently addressing psychological, social, economic and psychiatric aspects of surgery in this cohort. In terms of seizure outcome, surgery is successful for many individuals for whom AEDs have not been successful but further improvements need to be made to the presurgical evaluation, to improve further success rates.

Research in context

Previous studies of epilepsy surgery outcome were summarized in a meta-analysis[8]. which reported that 66% of people were seizure-free in the long-term after temporal resections with poorer results for those with other types of surgery.[8] It was noted that many studies reported seizure freedom at the end of follow-up rather than sustained seizure freedom.

We have reported long-term results and have looked at strictly long-term outcomes in terms of time to first seizure and ongoing seizure patterns. We have shown that

40% are entirely seizure-free from surgery; while at any time point about 70% are free of disabling seizures, each year up to 15% change their seizure status.

The clinical messages are:

1. Following epilepsy surgery 40% have long-term complete seizure freedom, with a further 11% only having SPS. Whilst 82% had at least one year with no seizures or only SPS, this does not indicate cure. No one had a significant worsening of epilepsy. Clinical practice needs to change to refer appropriate patients sooner for surgical consideration.
2. There is a need to improve the selection process and surgical methods to increase success rates and to identify more accurately those who will not be helped by surgery. Some studies may have implied over-optimistic expectations.
3. If SPS continue in the first 2 years after surgery, the probability of seizures recurring was twice that if the person is entirely seizure-free, but we note that previous studies have not reported this. This important information may influence the decision to taper or continue AEDs.
4. Anterior temporal resection was associated with a higher probability of seizure freedom than resections in other parts of the brain.
5. The majority of people who are seizure-free following surgery choose to remain on an AED. Further studies need to address the factors that affect risk of relapse.

Conflicts of Interest

J De Tisi, J Peacock and A McEvoy have no conflict of interest to disclose. G Bell's husband works for, and has shares in, GSK. W Harkness has been consulted by and received research grants and fees for lectures from Forth Medical. J Sander has been consulted by and received fees for lectures and research grants from Eisai, GSK,

MedTronic, Pfizer and UCB. JS Duncan has been consulted by and received fees to his Institution for lectures from Eisai, GE Healthcare, Pfizer, GSK, Sanofi Aventis, and UCB; he has had departmental and grant support from MedTronic, Cyberonics, and VSM MedTech.

Authors' Contributions

J De Tisi: data collection and presentation, bibliography; G Bell, data analysis, first draft; J Peacock: data analysis; A McEvoy & W Harkness: surgical procedures: J Sander: data interpretation, editing; JS Duncan: conceived study, data interpretation, editing.

NHNN Epilepsy Surgery Programme

Many colleagues contributed to the multidisciplinary epilepsy surgery programme at NHNN since 1990, initiated by Prof SD Shorvon. Contributions were made by colleagues in Neurology, Neurophysiology, Neuropsychology, Neuroimaging, Psychiatry, Counselling, and Epilepsy Nursing. Also all those people who have had surgery and have contributed their follow-up data, and those who spoke with those who were considering surgical treatment.

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Box 1. Presurgical assessment

All individuals:

Clinical history

Examination

Seizure semiology

Interictal and ictal EEG

MRI

Neuropsychological evaluation

Psychiatric assessment

Additional investigations (used when there was lack of clarity of the location of the epileptogenic zone, and to help predict the risk of deficit):

fMRI: language and motor

Carotid amytal

SPECT and PET

Box 2.

Outcome following epilepsy surgery[5]

OC1: Seizure-free

OC2: Simple partial seizures (SPS) only – no other seizures

OC3: Seizures on less than 4 days / year, with or without SPS

OC4: More than 50% reduction in numbers of days affected by seizures with or without SPS

OC5: No significant change in seizures with up to 50% reduction ranging to 100% increase in days affected by seizures

OC6: More than 100% increase in days affected by seizures

Table 1: The surgical procedures and pathology

	Surgical procedure						
Pathology	ATLRx	Tlesx	ET lesx	ETLx	Hx	Palliative	Total
Hippocampal sclerosis	407	0	0	0	0	0	407
Dysembryoplastic neuroepithelial tumour	36	20	16	7	0	0	79
Cavernoma	18	6	8	1	0	0	33
Glioma	5	7	11	1	0	0	24
Focal cortical dysplasia	3	3	4	5	0	0	15
Gliosis	9	2	1	4	5	1	22
Other	19	2	0	2	6	6	35
Total (%)	497 (80.8%)	40 (6.5%)	40 (6.5%)	20 (3.3%)	11 (1.8%)	7 (1.1%)	615

Legend: ATLRx – anterior temporal lobe resection

Tlesx – temporal lesionectomy

ET lesx – extratemporal lesionectomy

ETLx – extratemporal lobe resection

Hx – hemispherectomy

Table 2: Univariable and multivariable survival analysis of time to first seizure (N=616)

	Univariable variableanalysis (unadjusted)			Estimated percentage seizure-free at 10 years (unadjusted)		Multivariable variableanalysis (p = 0.0003)	
	HR*	95% CI	P-value	Percentage	95% CI	HR	95% CI
Age at surgery (1yr increment)	1.01	1.00, 1.02	0.039			1.01	1.00, 1.03
Age at surgery (5 yr increment)	1.06	1.00, 1.13				1.07	1.01, 1.14
Operation type			0.0004				
Anterior temporal lobe resection (N=497)	1			49%	44%, 54%	1	
Temporal lesionectomy (N=40)	0.93	0.57, 1.52		56%	38%, 70%	0.78	0.44, 1.37
Extratemporal lesionectomy (N=40)	1.55	1.03, 2.32		31%	16%, 48%	1.37	0.82, 2.31
Extratemporal lobe resection (N=20)	2.79	1.69, 4.59				2.00	1.12, 3.59
Hemispherectomy (N=11)	0.73	0.27, 1.96				0.47	0.16, 1.38
Palliative (N=7)	3.35	1.57, 7.14				2.03	0.86, 4.76
Pathology			0.012				

Hippocampal sclerosis (N=407)	1		51%	45%, 56%	1	
Dysembryoplastic neuroepithelial tumour (N=79)	1.17	0.83, 1.64	42%	29%, 55%	1.15	0.76, 1.74
Cavernoma (N=33)	1.25	0.75, 2.08	45%	25%, 63%	1.08	0.61, 1.90
Gliomia (N=24)	1.37	0.79, 2.35	42%	20%, 62%	1.26	0.66, 2.40
Focal cortical dysplasia (N=15)	2.34	1.27, 4.31			1.88	0.93, 3.82
Gliosis (N=22)	1.95	1.17, 3.26			1.90	1.07, 3.37
Other (N=35)	1.82	1.18, 2.81			1.81	1.08, 3.01

Legend: Multivariable analysis includes all other factors in the model – ie age at surgery, operation type and pathology

Other pathology includes: dual pathology, no abnormalities, malformations, other focal abnormalities and other abnormalities.

*1 year HR provided

Table 3: Effect of pathology on time to first seizure after temporal lobe resections, allowing for age at surgery.

Pathology	HR*	95% CI
Hippocampal sclerosis (N=407)	1	
DNT (N=36)	0.89	0.51, 1.53
Cavernoma (N=18)	1.18	0.58, 2.40
Glioma (N=5)	1.22	0.39, 3.82
FCD (N=3)	3.60	1.15, 11.3
Gliosis (N=9)	2.05	0.96, 4.37
Other including malformations and no detected abnormality (N=19)	2.09	1.21, 3.61

*1 year HR provided

Table 4. Probability of remaining free of seizures with loss of awareness (with 95% CIs) at intervals following temporal lobe surgery in patients who did, and did not, have simple partial seizures in the first two years after surgery.

	No seizures in first 2 yr	SPS only in first 2 yr
2 years later	0.89 (0.84, 0.92)	0.81 (0.70, 0.89)
5 years later	0.86 (0.80, 0.90)	0.67 (0.54, 0.77)
10 years later	0.78 (0.71, 0.84)	0.55 (0.41, 0.67)

Table 5A. Percentage of people remaining seizure-free after continuous periods of post-surgical seizure freedom, estimated by survival analysis. Seizure freedom or continuation was defined annually, on the anniversary of surgery.

Subsequent follow up (years)	Duration of seizure freedom from surgery		
	2 years (N=323) Estimated percentage (95% CI)	5 years (N=208) Estimated percentage (95% CI)	10 years (N=100) Estimated percentage (95% CI)
1 year	92% (88%, 94%)	97% (94%, 99%)	99% (93%, 100%)
2 years	87% (82%, 90%)	97% (93%, 98%)	97% (90%, 99%)
5 years	80% (75%, 85%)	89% (83%, 93%)	92% (79%, 97%)
10 years	72% (65%, 77%)	82% (71%, 89%)	Not estimable

Table 5B Percentage of people gaining one year of seizure freedom after continuous periods of ongoing seizures, estimated by survival analysis. Seizure freedom or continuation was defined annually, on the anniversary of surgery.

Subsequent follow-up	Duration of ongoing seizures since surgery	
	2 years (N=108) Estimated percentage (95% CI)	5 years (N=69) Estimated percentage (95% CI)
1 year	6% (3%, 13%)	1% (0%, 10%)
2 years	13% (8%, 21%)	8% (3%, 18%)
5 years	24% (16%, 34%)	20% (12%, 33%)
10 years	38% (28%, 51%)	30% (17%, 50%)

Table 6. Patterns of seizure remission and relapse following surgery in 615 people

	Description		N (%)	Median (range) duration follow-up (years)
A	Seizure-free, or SPS only, since surgery		51% (315)	7 (1-17)
		Entirely seizure-free since surgery	40% (245)	7 (1-17)
		SPS only since surgery	11% (70)	10 (1-17)
B	Seizures initially, then terminal remission		8% (49)	9 (2-19)
C	Initial seizure freedom, then relapse		8% (47)	11 (2-17)
D	Seizure freedom, with transient relapse, then terminal remission		7% (44)	10 (3-18)
E	Never seizure-free		18% (110)	7 (1-19)
F	Complex pattern of remissions and relapses		6% (37)	12 (4-17)
G	Seizures initially, then a period of seizure freedom, then relapse		2% (13)	11 (3-15)

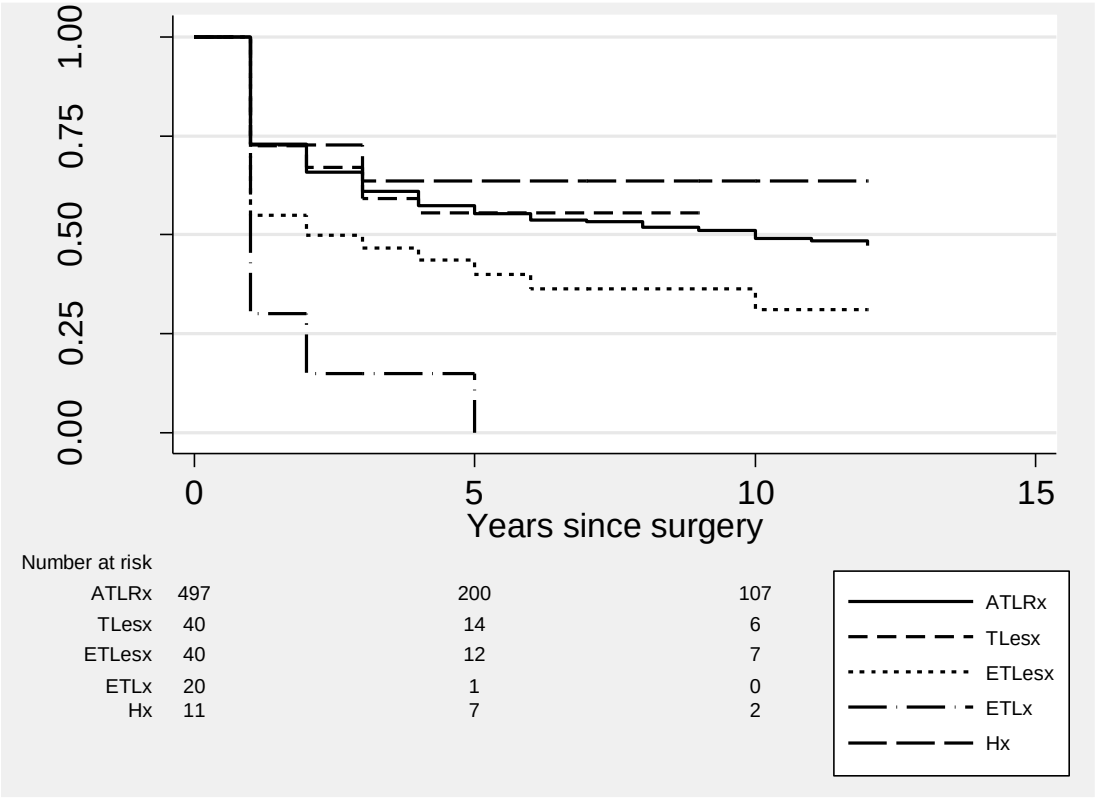


Figure 1. Kaplan Meier analysis of time to first seizure (excluding SPS), by operation type. Palliative procedures not shown, due to small numbers performed.

Legend. ATLRx – anterior temporal lobe resection; Tlesx – temporal lesionectomy

ETlesx – extratemporal lesionectomy; ETLx – extratemporal lobe resection

Hx – hemispherectomy; sz free – seizure free

Figure 2. Time to first seizure in people after temporal lobe surgery who had had no seizures at all, or who had SPS only in the first two post-operative years

Legend. SPS - simple partial seizures

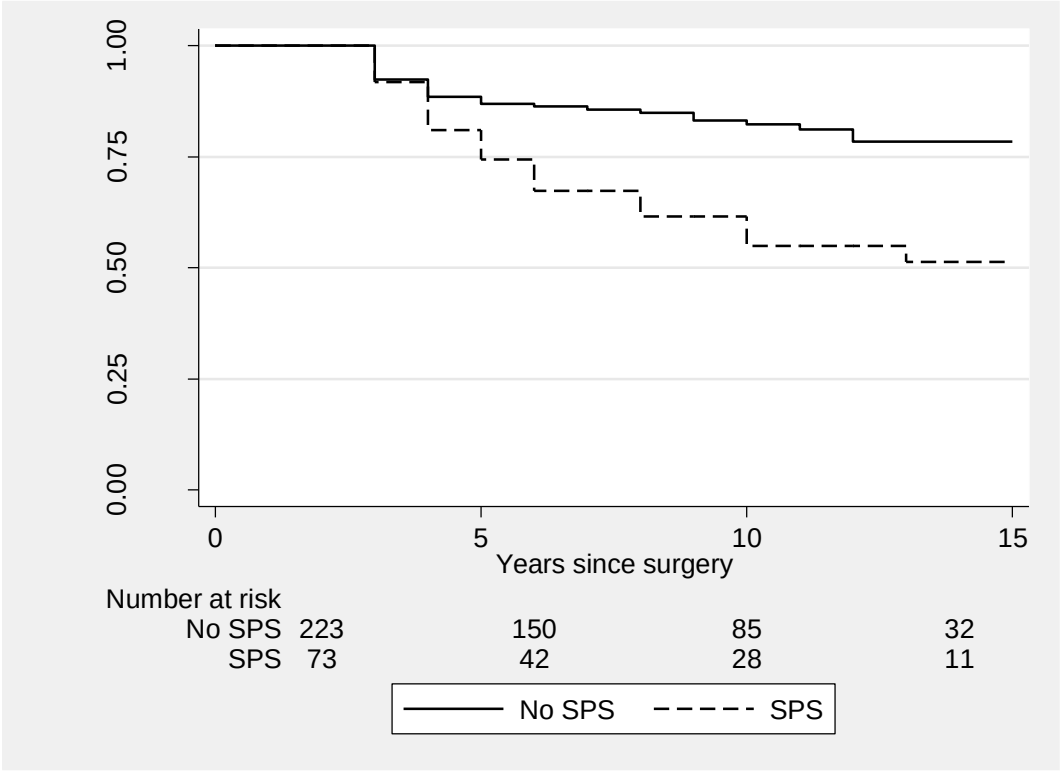
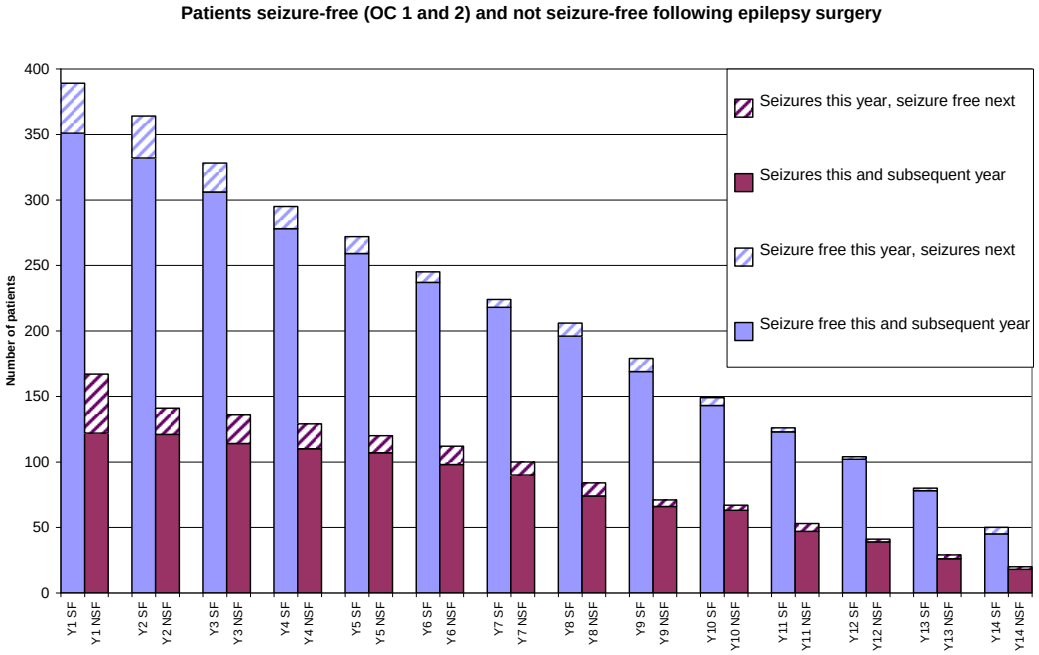


Figure 3: Seizure status, and change of seizure status, in people following epilepsy surgery. Those with a solid block remained in the same seizure status (seizure free or not seizure free) in the subsequent year. Those in the hatched areas changed seizure status (from seizure free to having seizures, or from continuing seizures to seizure freedom) in the subsequent year.

Legend. SF – seizure-free; NSF – not seizure-free



Reference List

1. Engel J, Jr. Surgery for seizures. *N.Engl.J.Med.* 1996;**334**(10):647-52.

2. Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N.Engl.J.Med.* 2001;**345**(5):311-8.

3. 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):2018-30.

4. Duncan JS. Selecting patients for epilepsy surgery: synthesis of data. *Epilepsy & Behavior* 2011;**20**(2):230-2.

5. Wieser HG, Blume WT, Fish D et al. ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia* 2001;**42**(2):282-6.

6. Altman DG, Machin D, Bryant TN, Gardner MJ. Confidence interval analysis. Bristol: BMJ Books; 2000.

7. Bell GS, Sinha S, Tisi J et al. Premature mortality in refractory partial epilepsy: does surgical treatment make a difference? *J.Neurol.Neurosurg.Psychiatry* 2010;**81**(7):716-8.

8. Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain* 2005;**128**(Pt 5):1188-98.

9. Dupont S, Tanguy ML, Clemenceau S, Adam C, Hazemann P, Baulac M. Long-term prognosis and psychosocial outcomes after surgery for MTLE. *Epilepsia* 2006;**47**(12):2115-24.

10. Dunlea O, Doherty CP, Farrell M et al. The Irish epilepsy surgery experience: Long-term follow-up. *Seizure* 2010;**19**(4):247-52.

11. 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**(10):1417-23.

12. Elwes RD, Dunn G, Binnie CD, Polkey CE. Outcome following resective surgery for temporal lobe epilepsy: a prospective follow up study of 102 consecutive cases. *J.Neurol.Neurosurg.Psychiatry* 1991;**54**(11):949-52.

13. Paglioli E, Palmini A, Paglioli E et al. Survival analysis of the surgical outcome of temporal lobe epilepsy due to hippocampal sclerosis. *Epilepsia* 2004;**45**(11):1383-91.

14. Buckingham SE, Chervoneva I, Sharan A et al. Latency to first seizure after temporal lobectomy predicts long-term outcome. *Epilepsia* 2010;**51**(10):1987-93.

15. Cohen-Gadol AA, Wilhelmi BG, Collignon F et al. Long-term outcome of epilepsy surgery among 399 patients with nonlesional seizure foci including mesial temporal lobe sclerosis. *J.Neurosurg.* 2006;**104**(4):513-24.

16. Berkovic SF, McIntosh AM, Kalnins RM et al. Preoperative MRI predicts outcome of temporal lobectomy: an actuarial analysis. *Neurology* 1995;**45**(7):1358-63.

17. Burneo JG, Villanueva V, Knowlton RC, Faught RE, Kuzniecky RI. Kaplan-Meier analysis on seizure outcome after epilepsy surgery: do gender and race influence it? *Seizure* 2008;**17**(4):314-9.

18. 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**(5):1131-41.

19. Clusmann H, Kral T, Gleissner U et al. Analysis of different types of resection for pediatric patients with temporal lobe epilepsy. *Neurosurgery* 2004;**54**(4):847-59.

20. Chan CH, Bittar RG, Davis GA, Kalnins RM, Fabinyi GC. Long-term seizure outcome following surgery for dysembryoplastic neuroepithelial tumor. *J.Neurosurg.* 2006;**104**(1):62-9.

21. Schwartz TH, Jeha L, Tanner A, Bingaman W, Sperling MR. Late seizures in patients initially seizure free after epilepsy surgery. *Epilepsia* 2006;**47**(3):567-73.

22. Chandrasekar T, Sharan AD, Sperling MR. Postoperative auras and the risk of recurrent seizures. *Epilepsy Res.* 2008;**78**(2-3):195-200.

23. Jehi L, Sarkis R, Bingaman W, Kotagal P, Najm I. When is a postoperative seizure equivalent to "epilepsy recurrence" after epilepsy surgery? *Epilepsia* 2010;**51**(6):994-1003.

24. Janszky J, Pannek HW, Janszky I et al. Failed surgery for temporal lobe epilepsy: predictors of long-term seizure-free course. *Epilepsy Res.* 2005;**64**(1-2):35-44.

25. Lee SA, Yim SB, Lim YM, Kang JK, Lee JK. Factors predicting seizure outcome of anterior temporal lobectomy for patients with mesial temporal sclerosis. *Seizure* 2006;**15**(6):397-404.

26. Jeelani NU, Jindahra P, Tamber MS et al. 'Hemispherical asymmetry in the Meyer's Loop': a prospective study of visual-field deficits in 105 cases undergoing anterior temporal lobe resection for epilepsy. *J.Neurol.Neurosurg.Psychiatry* 2010;**81**(9):985-91.

27. Yogarajah M, Focke NK, Bonelli S et al. Defining Meyer's loop-temporal lobe resections, visual field deficits and diffusion tensor tractography. *Brain* 2009;**132**(Pt 6):1656-68.