Factors affecting seizure outcome after epilepsy surgery; an observational series

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ABSTRACT

Importance. Surgical treatment can bring seizure remission in people with focal epilepsy, but requires careful selection of candidates.

Objectives. To determine which preoperative factors are associated with post-operative seizure outcome.

Design. We audited seizure outcome of 693 adults who had resective epilepsy surgery between 1990 and 2010 and used survival analysis to detect preoperatively identifiable risk factors of poor seizure outcome.

Results. Seven factors were significantly associated with increased probability of recurrence of seizures with impaired awareness post-surgery: MRI findings (eg hazard ratio adjusted for other variables in the model 2.5; 95% CI 1.6 to 3.8 for normal MRI compared with hippocampal sclerosis (HS)), a history of secondarily generalised convulsive seizures (2.3; 95% CI 1.7 to 3.0 for these seizures in the previous year vs never), psychiatric history (1.3; 95% CI 1.1 to 1.7), learning disability (1.8; 95% CI 1.2 to 2.6), and extratemporal (vs temporal) surgery (1.4; 95% CI 1.02, 2.04). People with an older onset of epilepsy had a higher probability of seizure recurrence (1.01; 95% CI 1.00, 1.02) as did those who had used more anti-epileptic drugs (1.05; 95% CI 1.01, 1.09). Combinations of variables associated with seizure recurrence gave overall low probabilities of 5-year seizure freedom (eg a normal MRI and convulsive seizures in the previous year has a probability of seizure freedom at five years of approximately 0.19).

Conclusions and Relevance. Readily identified clinical features and investigations are associated with reduced probability of good outcome and need consideration when planning presurgical evaluation.

INTRODUCTION

Surgery is an option for people with focal epilepsy not controlled with antiepileptic drugs (AED). Numerous uncontrolled studies and two small randomised controlled trials[1;2] showed that, in appropriately selected people, surgery can bring prolonged remission and improved quality of life. Some individuals, however, do not attain seizure freedom[3] and careful selection is crucial.

Since 1990, we have systematically evaluated our epilepsy surgery outcomes to clarify long-term results and identify predictive factors, to help advise potential candidates. We previously estimated seizure freedom probability (ILAE class 1 or 2)[4] as 0.52 at 5 years and 0.47 at 10 years. We found that age at surgery, operation type and pathology were independent seizure recurrence predictors[3]. We have now extended the cohort and incorporated other potential predictors.

Two recent studies predicted outcome using pre-identified pre-surgically available variables. The first[5] gave 0/1 scores for six predictors (seizure frequency, history of secondarily generalised tonic clonic seizures (SGTCS), MRI abnormality, epilepsy duration, intracranial-EEG use, temporal or extratemporal resection), and found that the total score predicted outcome. The other used outcomes of nine predictors of which six remained following stepdown selection (sex, duration, seizure frequency, SGTCS, operation type and pathology) and constructed a nomogram to predict outcome[6]. These studies started with a few predefined predictors and did not consider many of the variables we incorporated. In another study of 121 people with temporal epilepsy, duration for <10 years, positive preoperative MRI, history of febrile seizures, not having SGTCS, and concordant EEG findings predicted good outcome[7].

METHODS

We identified long-term seizure outcome to the end of 2011 in consecutive people undergoing resective epilepsy surgery between February 1990 and November 2010. Two neurosurgeons specialized in epilepsy surgery carried out > 90% of operations. For people

having two surgical procedures for epilepsy (18 people), we censored data at the time of the second procedure.

We searched contemporaneous medical records and notes from other hospitals people were attending for presence or absence of seizures with loss of awareness and classified outcome (ILAE outcome group 1 = entirely seizure free, outcome group 2 = auras only, outcome groups 3-6 = occurrence of seizures with loss of awareness)[4] for each 12 month period after surgery, ignoring seizures within four weeks of surgery. Data were supplemented by annual direct enquiry to individuals, primary care teams and next of kin by a neurologist and clinical manager[3]. Any discrepancies between sources were investigated with further inquiries. We aimed to establish potential risk factors of poor outcome (demographic details, results of preoperative investigations, clinical history, AED use, surgical procedures, psychiatric/psychological history) that were available preoperatively. Details are available in the supplementary methods.

Analysis was performed using Stata 13.1. Cox proportional hazard regression was used to analyse time to event outcomes and compare the probability of a seizure impairing awareness (ILAE outcome group 3-6)[4] after surgery. Hazard ratios (HRs) were calculated with 95% CIs. The main multivariable analysis included adults who had resections (ie temporal resection or lesionectomy, extratemporal resection or lesionectomy) and a secondary analysis included only those who had temporal procedures. Informal comparison of univariable HRs between those with temporal and those with extratemporal procedures was performed.

We checked proportionality for Cox regression. The main analysis included 371 seizure events and 27 potential predictor variables while those with temporal resections had 319 seizure events.

In the separate sections (as above, and A to F in table 1 and supplementary methods), we first performed univariable analysis and then separate manual backward stepwise multivariable analyses of each variable in the group which had p<0.2 on univariable analysis; this was to be inclusive and to make sure that every potential variable was tested in a

multivariable model. We then performed further manual backward stepwise multivariable analysis including all variables significant at p<0.2 in the separate subgroup (A to F) multivariable analyses. We used the Kaplan Meier method to estimate the probability of seizure recurrence at 2 and 5 years in different groups. Two predictors (the individual anxiety and depression scores from the preoperative Hospital Anxiety and Depression Scale; HADS) were only performed in 362 people so the final multivariable analysis was performed with and without these variables.

We plotted predicted probability of seizure freedom based on the regression models for different combinations of covariates to help visualise the impact of covariates on seizure remission following surgery. We used the lincom command (linear combinations of estimators) in Stata to estimate hazard ratios of various linear combinations of risk factors based on the analysis. This was approved by the Research Ethics Committee as a service evaluation; individual consent was, therefore, not required.

RESULTS

We considered 734 adults, but excluded 23 who had hemispherectomy or palliative procedures, and 18 with insufficient preoperative data or loss to follow-up before the first year after surgery, leaving 693 people. In 1-22 years of follow-up (mean 10 years, median 10 years) 371 had at least one seizure impairing awareness. Table 1 indicates demographics and the variables considered. The overall probabilities of remaining free of these seizures, together with the number of people followed for those durations, are shown in table 2 with higher probabilities following temporal resections. Table 3 shows the initial univariable analysis for all 18 variables significant at p<0.02 that were entered into subgroup multivariable analysis.

Table 1. Potential predictive variables (N=693 unless otherwise stated). (NO (%)

unless otherwise stated)

A. DEMOGRAPHY	
Age of onset of epilepsy, yrs, mean (SD) median	12.2 (9.2) 11
Duration of epilepsy before surgery, yrs, mean (SD) median	21.9 (11.1) 20.6
Female	379 (55)
Handedness	
Right	592 (85)
Left	83 (12)
Ambidextrous	12 (1.7)
Unknown	6 (0.9)
B. INVESTIGATIONS	
Intracranial electrodes used	108 (16)
Pathology as defined by MRI	
HS	426 (61)
Discrete pathologies (Dysembryoplastic neuroepithelial tumour (76), cavernoma (37), glioma (23), focal cortical dysplasia (17))	153 (22)
Dual pathology	31 (4.5)
Other (eg gliosis, non-specific, brain damage)	54 (7.8)
Normal MRI	29 (4.2)
Background EEG changes	
Concordant for hemisphere and lobe	169 (24)
Contralateral discordant (ie any abnormality in contralateral hemisphere)	268 (39)
Ipsilateral discordant (ie any abnormality in ipsilateral hemisphere but different lobe)	44 (6.4)
Normal	117 (17)
Abnormal, location not indicated	49 (7.1)
No videotelemetry, or no results available	46 (6.6)
Interictal epileptiform discharges	
Concordant for hemisphere and lobe	282 (41)
Contralateral discordant (ie any discharge in contralateral hemisphere, but ipsilateral predominance)	247 (36)
Ipsilateral discordant (ie any discharge in ipsilateral hemisphere but different lobe)	63 (9.1)
No interictal discharge recorded	47 (6.8)
Abnormal, location not indicated	8 (1.2)
No videotelemetry, or no results available	46 (6.6)
EEG ictal onset	
Concordant for hemisphere and lobe	379 (55)
Contralateral discordant (ie apparent onset in contralateral hemisphere)	97 (14)
Ipsilateral discordant (ie apparent onset in ipsilateral hemisphere but different lobe)	52 (7.5)
No scalp EEG change	34 (4.9)
No seizure recorded	42 (6.1)
Abnormal, location not indicated	43 (6.2)
No videotelemetry, or no results available	46 (6.6)
MRI location of lesion	
Concordant with resection	625 (90)
Discordant (any abnormality outside resected area)	39 (5.6)
Normal MRI	29 (4.2)
C. CLINICAL HISTORY	
Prior neurological insult	52 (7.5)
Prolonged early childhood convulsions (>20 minutes, aged five yrs or younger)	155 (22)
History of status epilepticus	94 (14)
First degree relative with history of epilepsy	75 (11)
Head injury prior to epilepsy onset	

No	584 (84)
Minor head injury	68 (9.8)
Clinically important head injury	18 (2.6)
Unclear	23 (3.3)
Previous secondarily generalised seizures	
Yes, in yr prior to surgery (or > 50% probability of occurring in yr prior to surgery)	317 (46)
Yes, but not in yr prior to surgery (or <50% probability)	204 (29)
No	172 (25)
Focal seizures with loss of awareness (LOA) in year prior to surgery (per month), median (IQR)	8 (4,15)
<4 focal seizures with LOA per month	172 (25)
4 to <8 focal seizures with LOA per month	155 (22)
8 to <15 focal seizures with LOA per month	186 (27)
>15 focal seizures with LOA per month	180 (26)
D. AED USE	
AEDs at time of surgery (excluding prn drugs), mean (SD) median	2.3 (0.9) 2
AEDs ever taken before surgery (including at time of surgery), mean (SD) median	7.1 (2.7) 7
E. SURGICAL DETAILS	
Operation type	
Temporal resection	567 (82)
Temporal lesionectomy	52 (7.5)
Extratemporal resection	32 (4.6)
Extratemporal lesionectomy	42 (6.1)
Side of surgery	
Left	373 (54)
Right	320 (46)
Year in which the surgery was performed	
1994 or earlier	107 (15)
1995 to 1998	164 (24)
1999 to 2002	133 (19)
2003 to 2006	135 (19)
2007 to 2010	154 (22)
F. PSYCHIATRY AND PSYCHOLOGY	
Psychiatric history recorded	246 (35)
Non-epileptic attack disorder prior to surgery	16 (2.3)
Learning disability	39 (5.6)
Preoperative verbal IQ	
Verbal IQ <70	16 (2.3)
Verbal IQ >70	617 (89)
Not tested or results not available	60 (8.7)
Preoperative performance IQ	
Performance IQ <70	20 (2.9)
Performance IQ >70	601 (87)
Not tested or results not available	72 (10)
Hospital Anxiety & Depression scale (HADs) anxiety scale preoperative (N=362)	
No symptoms of anxiety	199 (55)
Some symptoms of anxiety	163 (45)
HADs depression scale preoperative (N=362)	
No symptoms of depression	279 (77)
Some symptoms of depression	83 (23)

Legend: HS; Hippocampal sclerosis, LOA: loss of awareness

Table 2. Probability of remaining free of seizures causing loss of awareness (Kaplan Meier probabilities) at 5, 10 and 15 years after surgery in the whole cohort, in those who had temporal surgery and in those with extratemporal surgery

Probability of remaining seizure free at:	Whole cohort (N=693) (95% CI) (Number at risk)	Temporal lobe surgery (N=619) (95% CI) (Number at risk)	Extratemporal surgery (N=74) (95% CI) (Number at risk)
5 years	0.50 (0.46, 0.54) (284)	0.52 (0.48, 0.56) (267)	0.33 (0.22, 0.44) (17)
10 years	0.45 (0.41, 0.49) (165)	0.47 (0.43, 0.52) (158)	0.26 (0.15, 0.38) (7)
15 years	0.42 (0.38, 0.46) (71)	0.45 (0.40, 0.49) (68)	Not estimated

Table 3. Factors associated with seizure recurrence on initial univariable

analysis (p<0.2) and which were entered into subgroup (A to F) analysis (n=693)

	Univariable HR
Predictive factors	**HR (95% CI)**
Age of onset of epilepsy (yrs) (HR for one yr increase)*	**1.009 (0.998, 1.020)**
Pathology as predicted by MRI (vs HS)	
Dysembryoplastic neuroepithelial tumour, cavernoma, glioma or focal cortical dysplasia	1.43 (1.11, 1.83)
Dual pathology	1.83 (1.16, 2.90)
Other pathology	2.01 (1.41, 2.85)
Normal MRI	2.96 (1.94, 4.53)
Background EEG changes (vs concordant)	
Contralateral discordant	1.50 (1.14, 1.98)
Ipsilateral discordant	1.67 (1.07, 2.60)
Normal	1.27 (0.91, 1.77)
Abnormal, location not indicated	1.48 (0.96, 2.27)
No videotelemetry, or no results available	1.69 (1.09, 2.60)
Interictal epileptiform discharges (vs concordant)	
Contralateral discordant	1.35 (1.07, 1.71)
Ipsilateral discordant	1.43 (0.99, 2.06)
No interictal epileptiform discharges	0.88 (0.55, 1.41)
Abnormal, location not indicated	1.91 (0.84, 4.34)
No videotelemetry, or no results available	1.49 (0.99, 2.24)
Use of intracranial electrodes	1.75 (1.35, 2.26)
MRI location of lesion (vs concordant with resection)	
Discordant	1.18 (0.76, 1.83)
Normal MRI	2.51 (1.65, 3.80)
Prolonged childhood convulsions	**0.72 (0.55, 0.93)**
History of status epilepticus	**1.39 (1.06, 1.82)**
Previous secondarily generalised seizures (vs No)	
Yes, in yr prior to surgery	2.27 (1.72, 2.99)
Yes, but not in the yr prior to surgery	1.37 (1.00, 1.88)
Focal seizures with LOA in the year prior to surgery (vs <4)	
4 to <8 focal seizures with LOA per month	0.80 (0.59, 1.09)
8 to <15 focal seizures with LOA per month	0.92 (0.69, 1.23)
>15 focal seizures with LOA per month	1.12 (0.85, 1.48)
AEDs taken at the time of surgery*	**1.125 (0.996, 1.272)**
AEDs ever taken*	**1.059 (1.020, 1.099)**
Extratemporal surgery (vs temporal)	**1.84 (1.37, 2.47)**
Year in which surgery was performed (vs 2007 to 2010)	
1994 or earlier	1.04 (0.75, 1.44)
1995 to 1998	0.76 (0.56, 1.03)

1999 to 2002	0.68 (0.49, 0.95)
2003 to 2006	0.67 (0.48, 0.94)
Psychiatric history recorded	**1.39 (1.13, 1.71)**
Learning disability recorded	**1.70 (1.15, 2.51)**
Non-epileptic attack disorder prior to surgery	**1.54 (0.84, 2.80)**
Performance IQ (vs >70)	
Performance IQ <70	1.39 (0.80, 2.42)
Not tested or results not available	1.37 (0.98, 1.91)

*3 decimal places given for HRs for discrete variables to allow accurate estimation of

changes greater than one

Legend: LOA; loss of awareness. HS; Hippocampal sclerosis

Multivariable analysis of each separate subgroup gave 14 variables with p <0.2 that were

included in the final multivariable analyses. One variable, a history of status epilepticus,

violated proportionality assumptions on univariable analysis, but inspection of the graphs

suggested that this was due to three people with such a history who had a first seizure

recurrence 13 to 16 years after surgery, when only 12 people were at risk; we thus kept this

variable in the analysis unaltered. Duration of epilepsy prior to surgery was not significant in

univariable analysis (HR 0.999; 95% CI 0.989, 1.008) and so was not considered in the

multivariable analysis. The final multivariable analysis showed that MRI lesion, SGTCS

history, extratemporal or temporal surgery, a psychiatric history, learning disability, age of

epilepsy onset, and number of AEDs ever taken, were significantly related to the probability

of postsurgical seizure recurrence (table 4).

Table 4. Multivariable predictors of probability of seizure recurrence in 693 people having resective epilepsy surgery.

Predictive factors	Adjusted for other variables in the final model
	HR (95% CI)
Age of onset of epilepsy (yrs) (HR for one yr increase)*	1.012 (1.000, 1.024)
Number of AEDs ever taken*	1.048 (1.008, 1.090)
Pathology as predicted by MRI (vs HS)	
Dysembryoplastic neuroepithelial tumour, cavernoma, glioma or focal cortical dysplasia	1.22 (0.91, 1.64)
Dual pathology	1.79 (1.13, 2.84)
Other pathology	1.71 (1.16, 2.52)
Normal MRI	2.45 (1.57, 3.84)
History of secondarily generalised seizures (vs never)	
Ever	1.47 (1.07, 2.01)
In yr prior to surgery	2.26 (1.71, 2.99)
Other history	
Psychiatric history (yes)	**1.34 (1.08, 1.66)**
Learning disability (yes)	**1.75 (1.17, 2.63)**
Extratemporal surgery (vs temporal)	**1.44 (1.02, 2.04)**

Legend: HS; hippocampal sclerosis

Higher HRs are associated with a worse outcome – ie a greater probability of seizure recurrence

*3 decimal places given for HRs for discrete variables to allow accurate estimation of changes greater than one

Those with HS did better than any other pathology groups and recurrence risk was over twice as high in those with normal MRI as in those with HS. The HR of those with discrete pathologies was above 1 but did not reach statistical significance (table 4). SGTCS showed a gradient with those who had SGTCS in the year prior to surgery having twice the risk of recurrence of those who never had them; those with SGTCS longer ago had intermediate risk. When HADS scores were included, neither anxiety nor depression was significant on multivariable analysis.

Combinations of variables

Figure 1 shows the impact of preoperative variables on the probability of remaining free of seizures affecting awareness. Visual inspection of the graphs suggests that, compared with the best case scenario of probability of seizure freedom at 5 years following surgery of approximately 0.74, a normal MRI reduced this to about 0.48, SGTCS in the year prior to surgery to about 0.51, learning disability to about 0.59, a psychiatric history to about 0.66, and extratemporal surgery to about 0.63. A normal MRI and SGTCS in the last year was associated with a seizure freedom rate at 5 years of about 0.19 (figure 1B), reducing to <0.10 if there was also learning disability or extratemporal surgery (figure 1C).

Linear combination of estimators showed that, compared with somebody with no history of SGTCS and with HS on MRI, the HR for an individual with SGTCS in the previous year and a normal MRI would be 5.5 (95% CI 3.3 to 9.3). Having extratemporal rather than temporal surgery would increase this HR to 8.0 (95% CI 4.4, 14.4). The addition of learning disability instead would increase it to 9.7 (95% CI 5.0, 19.0) and a psychiatric history instead to 7.4 (95% CI 4.2 to 13.1). By extrapolation, individuals with recent SGTCS, normal MRI, extratemporal surgery, learning disability and a psychiatric history would have an 18-fold increased risk of post-surgical recurrence compared with individuals with no SGTCS, HS, temporal surgery and neither learning disability nor a psychiatric history. This would suggest an estimated probability of seizure freedom at 5 years of <1%; none in our cohort had all these characteristics.

Temporal and extratemporal surgery

Those having temporal surgery (N=619) had a longer duration of epilepsy prior to surgery (mean 22.3 years) than those with extratemporal surgery (N=74; mean 18.8 years). Those with extratemporal surgery had taken more AEDs at the time of surgery and ever. A greater percentage of those with temporal surgery had had prolonged childhood convulsions (24% vs 5.4% for those with extratemporal surgery). More with extratemporal surgery (23%) had had a prior head injury than those with temporal surgery (11%). Fewer with

extratemporal surgery had concordant results for background EEG abnormality, interictal or ictal onset; numbers are small for most categories in the group with extratemporal surgery. Those with extratemporal surgery were more likely to have had intracranial recordings (46% compared with 12%). More people with extratemporal surgery had lesionectomies (42; 57%) than those with temporal surgery (52; 8%). There was no difference in the groups in respect of a history of status epilepticus: 14% of those with temporal surgery and 11% of those with extratemporal surgery.

The results of the multivariable analysis for those with temporal surgery was similar to the whole group (table 5).

Table 5. Multivariable predictors of probability of seizure recurrence in 619 people who had temporal lobe procedures

Predictive variable (N)	HR (95% CI)
Age at onset of epilepsy (yrs) (HR for one year increase)*	**1.014 (1.002, 1.027)**
Pathology as predicted by MRI (vs HS; n=425)	
Dysembryoplastic neuroepithelial tumour, cavernoma, glioma or focal cortical dysplasia (105)	1.09 (0.79, 1.49)
Dual pathology (30)	1.71 (1.07, 2.76)
Other pathology (34)	1.90 (1.24, 2.92)
Normal MRI (25)	2.55 (1.60, 4.07)
History of secondarily generalized seizures (vs never; n=154)	
Ever (187)	1.48 (1.06, 2.08)
In the year prior to surgery (278)	2.30 (1.70, 3.11)
Psychiatric history (yes) (225)	**1.42 (1.13, 1.77)**
Learning disability (yes) (31)	**1.97 (1.24, 3.13)**

*3 decimal places given for HRs for discrete variables to allow accurate estimation of changes greater than one.

The number of individuals with extratemporal surgery was insufficient for multivariable analysis. We had insufficient power to use interaction tests to investigate differences between the extratemporal and temporal groups, but informal inspection of univariable HRs (of potential predictor variables with at least 10% of people in each group positive) suggested that a history of status epilepticus had stronger association with seizure recurrence in those with extratemporal surgery (HR 2.84 vs 1.33 in the temporal group). Use

of intracranial electrodes was of lower prognostic significance in the group with extratemporal surgery (HR 1.03 vs 1.78 in the temporal group). Those who had a lesionectomy (rather than resection) did better in both groups, but the difference appeared more marked in the extratemporal group (HR 0.55 vs 0.93). The effect of age at epilepsy onset appeared different between groups, as did psychiatric history (HR 1.13 in the extratemporal group vs 1.47). Learning disability and a history of SGTCS in the year prior to surgery had similar effects in both groups.

Epoch in which surgery was performed

The epochs with relatively lower seizure free outcome (pre 1995 and 2007-2010 – Table 3) had a higher incidence of normal MRI at 7.5% and 7.8% respectively, compared with 1.8-2.3% in the intervening years. In the 2007-2010 epoch there was a higher incidence of psychiatric comorbidity identified (45%), compared with 29-32% for pre1995-2002.

DISCUSSION

We have followed a large cohort who had epilepsy surgery at our centre over a long period. We included 27 variables in univariable, followed by multivariable, analysis to establish predictors of long-term outcome. Our results confirm that the probability of seizure recurrence following surgery is associated with MRI pathology and those with HS had the best outcome, and those with normal MRI did least well. We found that those with no history of SGTCS fared better. People with a learning disability or a psychiatric history had higher probability of seizure recurrence. We also found that extratemporal surgery was more strongly associated with seizure recurrence than temporal lobe surgery.

In the current study we found that the overall probabilities of freedom from seizures with loss of awareness (ILAE class 1 or 2)[4] at 5 and 10 years were marginally lower than we previously estimated[3]. Previously a small study estimated the probability of seizure freedom of 0.67 at five years and 0.51 at ten years post-operatively[8]; the apparently higher rates of seizure freedom may be due to their more liberal definition of Engel group

classification I for seizure freedom, which incorporates the occurrence of some seizures with loss of awareness.

Previous studies using a variety of methods following excision for HS found a probability of seizure freedom of 0.60[9] and 0.64[10] at 5 years and 0.43[9] and 0.65[11] at ten years and beyond; however, numbers were small, and two used questionnaires years after surgery[9;10]. It is likely that our results of people with temporal excision (75% had HS) are lower because of our practice of prospectively obtaining contemporaneous outcome data each year.

Effect of pathology (MRI)

We found that those with pathologies other than HS as detected by MRI were more likely to have seizure recurrence, and those with normal MRI did particularly badly. A study of neocortical resections found that pathology did not influence outcome, but a visible MRI lesion was associated with good outcome[12]. A study of temporal excision using survival analysis found that those with normal or 'other' pathology, as judged by a combination of histopathology and MRI findings, had a worse outcome than those with HS or foreign tissue lesions[13]. A recent study of 109 people with unremarkable MRI found 54% to be seizure free one year post-surgically[14]. Caveats with the interpretation of this study are that a more liberal definition of seizure freedom was used (Engel group 1) than in our studies and pathologies such as focal cortical dysplasia and dysembryoplastic neuroepithelial tumour would be expected to be detected by contemporary MRI. Other studies using outcome at specific time points found no effect of lesional vs non-lesional epilepsy (largely HS)[15] or of pathology (normal, gliosis or atrophy, hamartomas, arteriovenous malformations, non-specific) almost 30 years post-surgery[16]. A review of surgery for epilepsy found that an abnormal MRI was associated with better outcome[17]. In conclusion, the weight of evidence is that if a discrete MRI-visible pathology, particularly HS, is resected, the chances of long-term remission is better than if the MRI is normal.

History of SGTCS

A history of SGTCS in our cohort had a gradient of effect. Those who had SGTCS in the year prior to surgery had the greatest risk of recurrence, and those with SGTCS longer ago had intermediate risk compared with those with no SGTCS, with similar effects in the whole cohort and those with temporal surgery, and those with extratemporal excision. A systematic review found that SGTCS before temporal surgery predicted poorer outcome[18]. Follow-up of 325 people with temporal resections found a similar gradient of response to ours[13]; it was speculated that this might reflect more widespread epileptogenic zones. In a smaller group with temporal excision, a history of SGTCS reduced the probability of being seizure free[11]. Others found that, in various extratemporal resections (in apparent contrast to our results), SGTCS were not associated with outcome; numbers were also small[19-21]. In conclusion, the occurrence of SGTCS is an adverse factor when predicting post-operative seizure freedom.

Psychiatric history, learning disability and IQ

People with a psychiatric diagnosis and those with learning disability had higher probability of recurrence, while IQ above or below 70 was not predictive; having a psychiatric disorder was previously shown in a subsection of this cohort to influence seizure outcome[22]. Another study found that people with low IQ were less likely to have surgery, but those who did achieved short term outcome comparable to those with higher IQ[23]. Some people with epilepsy perform progressively less well on IQ measures over time; this is not the same as having learning disability which, in this series, required it to be present from early childhood. A study found that IQ was an independent predictor of seizure freedom at two years, with more of those with IQ $\geq$70 seizure free[24]. In summary, psychiatric pathology and learning disability were associated with reduced chance of seizure remission, and the combination with extratemporal surgery, normal MRI and SGTCS was associated with very low chance, <1%, of remaining seizure free 5 years after surgery.

EEG findings and MRI concordance

A systematic review found that unilateral interictal epileptiform abnormality on scalp-EEG was associated with good outcome after temporal resection, while scalp-EEG ictal characteristics were inconclusive[18]. We found no evidence that background, interictal or ictal EEG findings affected seizure recurrence. For this analysis, we regarded finding any contralateral spikes as indicating bilateral involvement, which is stricter than usual clinical interpretations.

Multivariable analysis found no evidence that concordance of MRI with other findings predicted outcome, although few had discordant findings. It is the nature of the selection process to try to establish concordance, with the consequence that few people with discordant features on EEG or MRI go forward to surgery.

Those needing intracranial EEG monitoring to define the site of onset of seizures had worse outcome on univariable analysis in the whole cohort and in those with temporal surgery; this was no longer significant once other variables were included, suggesting that other factors explain its apparent association. This is not a surprising finding and reflects the selection process for intracranial EEG; those who require invasive monitoring generally have a less clear-cut situation than those in whom intracranial EEG is not deemed necessary and hence might be expected to have poorer outcome. Others have shown no association between invasive recordings and outcome[19;25], while some found that, in certain situations, those who required intracranial monitoring had worse outcome[16;26;27]; differences in cohort selection, surgical procedures and small numbers may all influence findings.

Era of surgery

In univariable analysis the era of surgery was significant, with those having surgery between 1999 and 2006 having a higher probability of seizure freedom than those operated since. This association, whilst weaker on multivariable analysis, suggests that people with less favourable prognostic features are now being taken forward for surgery. In particular, the pathology as predicted by MRI appears to be slightly different over the years with a lower percentage of people with HS, and a higher percentage of those with normal pathology

being having surgery in the earlier (before 1995) and later (after 2007) years, the years associated with poorer outcome. A likely explanation for this is that pre-1995 MRI was less sensitive than in later years, so some pathologies were not detected and in the current era, more challenging cases with normal optimal MRI and with evidence of psychiatric comorbidities are being considered for surgery. This underpins the importance of careful selection, whilst recognizing that some individuals with refractory epilepsy may wish to pursue surgical treatment, even if there is a low chance of seizure freedom.

Number of AEDs ever taken

A higher number of AEDs ever tried was associated with worse chance of a seizure free outcome. This had a positive correlation with duration of epilepsy (data not shown) and we interpret the number of AEDs taken to be a surrogate for epilepsy severity.

Age of onset and duration of epilepsy

For each year older at epilepsy onset, the probability of seizure recurrence increased by 1%. A study that dichotomised into age of onset <10 year and >20 years found that age of onset was not significantly associated with outcome after temporal surgery[28]. We did not find that duration of epilepsy prior to surgery was significant; and note that results from other groups have been inconsistent in this regard [6;7;13;15;19;29].

Temporal and extratemporal surgery

A review[17] reported that '55-70% of individuals undergoing temporal resection and 30-50% undergoing extratemporal resection become completely seizure-free', although the difference was less marked in their own analysis (62% 'good' outcome – which includes >1 year seizure free - for extratemporal resection and 69% for temporal). In contrast, using survival analysis, we found that at 5 years 33% remained seizure free in the extratemporal group compared with 52% in the temporal group (table 2).

Two studies from the same Australian centre showed 5-year seizure freedom rates (Kaplan Meier) of 47.7% (95% CI 42, 53) following temporal resection [13] and 14.7% (95% CI 8, 23) following extratemporal resections[19]. A recent review found that extratemporal vs temporal surgery was inconsistently associated with outcome.[30]. Overall, it appears that

extratemporal surgery is associated with less chance of long-term remission, than is temporal lobe surgery. The latter group of course is associated with HS, which has the best outcome. This is not to say that extratemporal surgery should not be pursued as some have good long-term outcome, particularly if there is a well-defined discrete pathology evident on MRI.

Combinations of covariates

Our findings suggest that the combination of normal MRI, recent SGTCS and extratemporal surgery is associated with a low probability of good outcome, especially if there is also a psychiatric history or learning disability. If these findings are replicated, we should consider our advice to potential surgical candidates with these combinations.

Complications of surgery are a very important aspect of outcome which we considered in our 1990-2008 cohort[3] and more recently for the 1990-2014 cohort[31].

Limitations

Our study has limitations. In this single centre observational series we obtained follow-up data on seizure outcome from records and enquiries to operated adults and their physicians and there is, therefore, the possibility of recall bias. Our practice is confined to adults, and so may not be generalizable to paediatric practice. Most had temporal excisions, so the results may also differ from those from centres with a different mix of procedures. A caveat is that the analysed EEG data were derived from written conclusions from presurgical EEG investigations that were previously undertaken. We recognize that a prospective and quantitative EEG evaluation might yield different results. Only about half our patients had HADS scores, limiting its use in analysis. There are many heterogeneous reasons why people did not have this performed including, in some cases, inability of the individual to understand the questions fully. There was no relationship between operation type and whether HADS scores were available. Additionally, HADS only assesses mood states in the previous week and may not reflect the individual's overall affective state.

We also only considered seizure outcome and we fully recognise that other outcomes such as cognitive changes and quality of life are important; these are being currently analysed and will be reported separately.

CONCLUSION

Resective surgery is confirmed as an effective treatment for individuals with medication-refractory focal epilepsy. We have shown that estimates of the probability of seizure freedom can be made from basic clinical and MRI data, and advice stratified (Fig 1). This should be discussed with individuals prior to embarking on intrusive, costly investigations, as some with low chance of a good result may elect not to undergo evaluation. A clinical judgment on the potential surgical need for an individual should, however, not be overruled by these estimates. A person with sufficiently severe seizures may elect to undergo a procedure despite a low probability of good outcome.

Author contributions

JSD conceived this evaluation. JDT collected the data. JCG designed and maintained the database. GSB did data analysis and drafted the report. JLP provided statistical support and data interpretation. BD, JWS and JSD selected people for the surgical procedures. AWMcE and WFH did the surgical procedures; JF and RP obtained psychiatric data. BD, JWS and JSD did data interpretation and editing. All approved the final version.

Conflicts of interest

GSB and her husband have shares in GlaxoSmithKline.

JdT, JLP, JF and RAP report no disclosures

AWMcE has received lecture fees and travel bursaries from Baxter, Eisai, UCB, Forth Medical, Fannin and Cyberonics. He has had departmental and research support from Cyberonics and Medtronic.

WFH has been consulted by and received research grants and fees for lectures from Forth Medical.

JWS has been consulted by and received fees for lectures from Eisai, GlaxoSmithKline, Teva, Lundbeck, and UCB. He has had departmental and research support from Eisai, UCB, NL Epilepsy Funds, and the Dr Marvin Weil Epilepsy Research Fund.

JSD has been consulted by and received research grants and fees for lectures from Eisai, GE Healthcare; he has had departmental and grant support from Medtronic, Cyberonics, NIHR, MRC and Wellcome Trust.

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FIGURE LEGENDS

Figure 1. Probability of seizure freedom in selected groups in the whole cohort (N=693). All assume age of onset of epilepsy of 11 years (median) and 7 (median) anti-epileptic drugs ever taken.

A. Those with 'best case scenario': hippocampal sclerosis (HS), no secondarily generalised tonic-clonic seizures (SGTCS), temporal surgery, no psychiatric history, no learning disability compared with single significant prognostic features
Legend:

B. Normal MRI combined with single significant prognostic features
Legend:

C. Normal MRI, SGTCS in the last year, combined with significant prognostic features
Legend:

Reference List

1. Wiebe S, Blume WT, Girvin JP,et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001;345:311-8.

2. Engel J, Jr., McDermott MP, Wiebe S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *JAMA* 2012;307:922-30.

3. de Tisi J, Bell GS, Peacock JL, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *Lancet* 2011;378:1388-95.

4. 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;42:282-6.

5. Garcia GC, Yardi R, Kattan MW, et al. Seizure freedom score: A new simple method to predict success of epilepsy surgery. *Epilepsia* 2015;56:359-65.

6. Jehi L, Yardi R, Chagin K, et al. Development and validation of nomograms to provide individualised predictions of seizure outcomes after epilepsy surgery: a retrospective analysis. *Lancet Neurology* 2015;14:283-92.

7. Sun Z, Zuo H, Yuan D,et al. Predictors of prognosis in patients with temporal lobe epilepsy after anterior temporal lobectomy. *Exp Ther Med* 2015;10:1896-902.

8. Kunieda T, Mikuni N, Shibata S, et al. Long-term seizure outcome following resective surgery for epilepsy: to be or not to be completely cured? *Neurol Med Chir (Tokyo)* 2013;53:805-13.

9. Dupont S, Tanguy ML, Clemenceau S, et al. Long-term prognosis and psychosocial outcomes after surgery for MTLE. *Epilepsia* 2006;47:2115-24.

10. Lowe AJ, David E, Kilpatrick CJ, et al. Epilepsy surgery for pathologically proven hippocampal sclerosis provides long-term seizure control and improved quality of life. *Epilepsia* 2004;45:237-42.

11. Hemb M, Palmini A, Paglioli E, 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;84:800-5.

12. Kim DW, Kim HK, Lee SK,et al. Extent of neocortical resection and surgical outcome of epilepsy: intracranial EEG analysis. *Epilepsia* 2010;51:1010-7.

13. McIntosh AM, Kalnins RM, Mitchell LA, et al. Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. *Brain* 2004;127:9-30.

14. Kim DW, Lee SK, Moon HJ, et al. Surgical Treatment of Nonlesional Neocortical Epilepsy: Long-term Longitudinal Study. *JAMA Neurol* 2017;74:324-31.

15. Wieser HG, Ortega M, Friedman A, et al. Long-term seizure outcomes following amygdalohippocampectomy. *Journal of Neurosurgery* 2003;98:751-63.

16. Kelley K, Theodore WH. Prognosis 30 years after temporal lobectomy. *Neurology* 2005;64:1974-6.

17. West S, Nolan SJ, Cotton J, et al. Surgery for epilepsy. *Cochrane Database Syst Rev* 2015;CD010541.

18. McIntosh AM, Wilson SJ, Berkovic SF. Seizure outcome after temporal lobectomy: current research practice and findings. *Epilepsia* 2001;42:1288-307.

19. McIntosh AM, Averill CA, Kalnins RM, et al. Long-term seizure outcome and risk factors for recurrence after extratemporal epilepsy surgery. *Epilepsia* 2012;53:970-8.

20. Aykut-Bingol C, Bronen RA, Kim JH, et al. Surgical outcome in occipital lobe epilepsy: implications for pathophysiology. *Annals of Neurology* 1998;44:60-9.

21. Kim CH, Chung CK, Lee SK. Longitudinal change in outcome of frontal lobe epilepsy surgery. *Neurosurgery* 2010;67:1222-9.

22. Cleary RA, Thompson PJ, Fox Z, et al. Predictors of psychiatric and seizure outcome following temporal lobe epilepsy surgery. *Epilepsia* 2012;53:1705-12.

23. Davies R, Baxendale S, Thompson P, et al. Epilepsy surgery for people with a low IQ. *Seizure* 2009;18:150-2.

24. Malmgren K, Olsson I, Engman E,et al. Seizure outcome after resective epilepsy surgery in patients with low IQ. *Brain* 2008;131:535-42.

25. Roberti F, Potolicchio SJ, Caputy AJ. Tailored anteromedial lobectomy in the treatment of refractory epilepsy of the temporal lobe: long term surgical outcome and predictive factors. *Clin Neurol Neurosurg* 2007;109:158-65.

26. Blume WT, Ganapathy GR, Munoz D, et al. Indices of resective surgery effectiveness for intractable nonlesional focal epilepsy. *Epilepsia* 2004;45:46-53.

27. Mathon B, Bielle F, Samson S, et al. Predictive factors of long-term outcomes of surgery for mesial temporal lobe epilepsy associated with hippocampal sclerosis. *Epilepsia* 2017 doi: 10.1111/epi.13831.

28. Asadi-Pooya AA, Sperling MR. Age at onset in patients with medically refractory temporal lobe epilepsy and mesial temporal sclerosis: impact on clinical manifestations and postsurgical outcome. *Seizure* 2015;30:42-5.

29. 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;104:513-24.

30. Jobst BC, Cascino GD. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. *JAMA* 2015;313:285-93.

31. Gooneratne IK, Mannan S, de Tisi J, et al. Somatic complications of epilepsy surgery over 25 years at a single center. *Epilepsy Res* 2017; 132:70-77.