The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study

Jane de Tisi, Gail S Bell*, Janet L Peacock, Andrew W McEvoy, William F J Harkness, Josemir W Sander, John S Duncan*

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*Joint first authors

Department of Clinical and Experimental Epilepsy, University College London Institute of Neurology, National Hospital for Neurology and Neurosurgery, London, UK (J de Tisi BA, G S Bell MD, A W McEvoy FRCS, W F J Harkness FRCS, Prof J W Sander FRCP, Prof J S Duncan FRCP)**; Epilepsy Society, Chalfont St Peter, Buckinghamshire, UK** (G S Bell, Prof J W Sander, Prof J S Duncan)**; Department of Primary Care and Public Health Sciences, King's College London, London, UK** (Prof J L Peacock PhD)**; and Stichting Epilepsie Instellingen Nederland (SEIN)–Epilepsy Institute in the Netherlands Foundation, Heemstede, Netherlands** (Prof J W Sander)

Correspondence to: Prof John S Duncan, Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK
j.duncan@ucl.ac.uk

Summary

Background **Surgery is increasingly used as treatment for refractory focal epilepsy; however, few rigorous reports of long-term outcome exist. We did this study to identify long-term outcome of epilepsy surgery in adults by establishing patterns of seizure remission and relapse after surgery.**

Methods **We report long-term outcome of surgery for epilepsy in 615 adults (497 anterior temporal resections, 40 temporal lesionectomies, 40 extratemporal lesionectomies, 20 extratemporal resections, 11 hemispherectomies, and seven palliative procedures [corpus callosotomy, subpial transection]), with prospective annual follow-up for a median of 8 years (range 1–19). We used Kaplan-Meier survival analysis to estimate time to first seizure, and investigated patterns of seizure outcome.**

Findings **We used survival methods to estimate that 52% (95% CI 48–56) of patients remained seizure free (apart from simple partial seizures [SPS]) at 5 years after surgery, and 47% (42–51) at 10 years. Patients who had extratemporal resections were more likely to have seizure recurrence than were those who had anterior temporal resections (hazard ratio [HR] 2·0, 1·1–3·6; p=0·02); whereas for those having lesionectomies, no difference from anterior lobe resection was recorded. Those with SPS in the first 2 years after temporal lobe surgery had a greater chance of subsequent seizures with impaired awareness than did those with no SPS (2·4, 1·5–3·9). Relapse was less likely the longer a person was seizure free and, conversely, remission was less likely the longer seizures continued. In 18 (19%) of 93 people, late remission was associated with introduction of a previously untried antiepileptic drug. 104 of 365 (28%) seizure-free individuals had discontinued drugs at latest follow-up.**

Interpretation **Neurosurgical treatment is appealing for selected people with refractory focal epilepsy. Our data provide realistic expectations and indicate the scope for further improvements in presurgical assessment and surgical treatment of people with chronic epilepsy.**

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Introduction

Surgical treatment for focal epilepsy has been increasingly used.[1] The only randomised controlled trial[2] of surgery established the short-term benefits of anterior temporal lobe resection compared with medical treatment for refractory temporal epilepsy. Chances of seizure remission after surgery in an individual with concordant data are generally about 60–70%.[1] In one study[3] of long-term outcome in 325 people having anterior temporal resection, the rate of seizure freedom was 41% at 10 years. Patients who were seizure free 2 years postoperatively had a 74% (95% CI 66–81) probability of seizure freedom by 10 postoperative years. Late recurrence after initial seizure freedom was not uncommon, and risk factors associated with such recurrence are unknown.

Our aim was to follow up patients postoperatively to identify patterns of seizure remission and relapse after surgery, to enable individuals considering surgery to make informed choices.

Methods

Study design and participants

We identified the long-term outcome and patterns of seizure remission and relapse up to Nov 19, 2009, in 649 consecutive people undergoing epilepsy surgery at the National Hospital for Neurology and Neurosurgery (NHNN), London, UK, from Feb 15, 1990, to Oct 30, 2008. Two consultant neurosurgeons specialising in epilepsy (WFJH and AWMcE) did more than 90% of operations. For every person, clinical and investigatory data were considered in detail (ie, clinical history; examination; seizure semiology; interictal and ictal electroencephalogram; MRI; neuropsychological and psychiatric assessment; and when location of the epileptogenic zone was unclear, and to help predict risk of deficit, functional MRI [language and motor], carotid amytal, single-photon-emission CT, and PET were investigated). The optimum surgical approach was then derived to provide the best chance of seizure freedom with the lowest risk of complications.[4] The general principles of presurgical assessment in our unit were established in 1990, and, although advances have been made in MRI and video electroencephalography-recording technology, the principles for establishing a consensus of data for the zone of seizure onset and the relation to eloquent cortex have not changed.[4]

Information for yearly updates of seizure status was obtained from review of contemporaneous NHNN

notes and from notes of other hospitals people were attending. We supplemented these data with direct annual inquiry by a neurology consultant and clinical data manager who contacted the individuals and their general practitioners and, in cases of uncertainty, patients' next of kin. Specific questions were the occurrence of simple partial seizures (SPS), seizures with loss of awareness, and antiepileptic drugs taken. When there were discrepancies between sources, further inquiries were made until a consensus was reached. We classified seizure outcomes for each postsurgical year (outcome classification) with the International League Against Epilepsy (ILAE) surgery outcome scale[5] (panel 1). We use the term SPS throughout, which incorporates all events that are sometimes classified as auras. We noted the use of antiepileptic drugs and changes within each previous year. An outcome classification of class 3 (OC3) or greater defined the occurrence of seizures other than SPS. Distinction between OC4 and OC5 might be more difficult and this distinction was not analysed. This study was approved by the Joint Ethics Committee of the National Hospital for Neurology and Neurosurgery and University College London Institute of Neurology. The Research Ethics Committee classified this work as a service evaluation, therefore individual consent from patients was not needed.

Statistical analysis

Survival analysis with Cox proportional hazard regression was used for all time-to-event outcomes and to compare time to first seizure (≥OC3). Hazard ratios (HRs) were calculated with 95% CIs. Age at surgery was included in the analyses when appropriate. We used the Kaplan-Meier method to estimate the proportion of individuals remaining seizure free at various time-points. Analyses were done comparing different pathological changes in people with similar surgical procedures, and different surgical procedures in people with similar changes. For one analysis, we selected those who had no seizures or SPS only in the first 2 postoperative years and analysed time to first seizure (≥OC3). See webappendix for analysis of time to first seizure including SPS (≥OC2).

We did statistical analysis using Stata version 10, and 95% CIs for proportions were obtained from Confidence Interval Analysis software (version 2.1.2).[6]

See Online for webappendix

Role of the funding source

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Results

No yearly outcome scores were available for 34 of 649 (5%) people because of death (n=5) or loss to follow-up (27) within 1 year of surgery (15 of these 27 lived overseas), or because they had subsequent surgery within 1 year of the first operation (2). Thus, 615 people (287 men, aged 16–63 years at surgery, median duration of epilepsy before surgery 20·7 years [IQR 13·9–28·6]) are considered further. Table 1 shows pathological changes and surgical procedures. For 15 people who had two surgical procedures for epilepsy, data were censored at the time of the second procedure. We included 19 people who had had previous neurosurgical procedures (17 biopsy or partial lesion removal, one meningioma removal, one partial corpus callosal section). With 5241 person-years of follow up, data for outcome classifications were available for a median of 8 years (range 1–19). Data were not available for the 2 years before the audit date (Nov 19, 2009) in 127 (21%) people for whom the last verified follow-up data were obtained before Nov 19, 2007. The median duration of follow-up for these 127 people was 6 years (range 1·2–17·5).

We estimated by survival analysis the probability of being entirely seizure free at 2 years as 49% (webappendix). 63% (95% CI 59–67) of the whole cohort remained seizure

Panel 1: Outcome after epilepsy surgery[5]

- OC1: seizure free
- OC2: SPS only—ie, no other seizures
- OC3: Seizures on less than 4 days per 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

OC=outcome classification. SPS=simple partial seizures.

	ATLRx	Tlesx	ETlesx	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 (81%)	40 (7%)	40 (7%)	20 (3%)	11 (2%)	7 (1%)	615

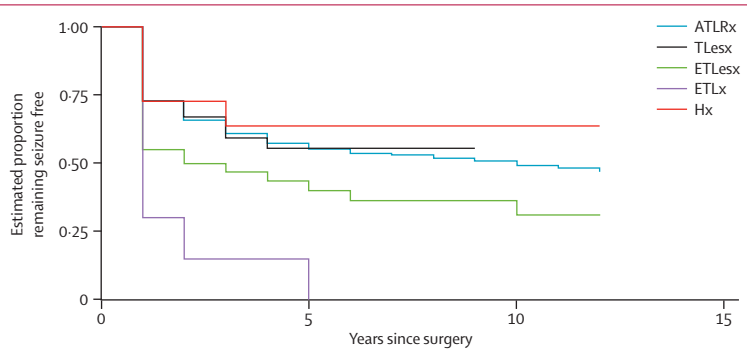
Data are number (%). ATLRx=anterior temporal lobe resection. Tlesx=temporal lesionectomy. ETlesx=extratemporal lesionectomy. ETLx=extratemporal lobe resection. Hx=hemispherectomy.

Table 1: **Surgical procedures and pathological findings in study population**

	Univariable analysis (unadjusted)		Estimated percentage seizure free at 10 years (unadjusted)	Multivariable analysis* (p=0·0003)
	HR (95% CI)	p value	% (95% CI)	HR (95% CI)
Age at surgery (1-year increment)	1·01 (1·00–1·02)	0·039	..	1·01 (1·00–1·03)
Age at surgery (5-year increment)	1·06 (1·00–1·13)	..	..	1·07 (1·01–1·14)
Operation type (n=615)		0·0004		
Anterior temporal 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 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)
Pathological findings (n=615)		0·012		
Hippocampal sclerosis (n=407)	1 (..)	..	51% (45–56)	1 (..)
DNT (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)
Glioma (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)

We estimated percentages from the survival curve. ≥OC3=Outcome classification class 3. HR=hazard ratio. DNT=dysembryoplastic neuroepithelial tumour. *All other factors in the model—ie, age at surgery, operation type, and pathology. †Dual pathology, no abnormalities, malformations, other focal abnormalities, and other abnormalities.

Table 2: **Univariable and multivariable survival analysis of time to first seizure (≥OC3)**



Number at risk

ATLRx	497	200	107
TLesx	40	14	6
ETLesx	40	12	7
ETLx	20	1	0
Hx	11	7	2

Figure 1: **Kaplan-Meier analysis of time to first seizure (excluding SPS), by operation type**
Palliative procedures not shown because of small numbers of patients. SPS=simple partial seizures. ATLRx=anterior temporal resection. TLesx=temporal lesionectomy. ETLesx=extratemporal lesionectomy. ETLx=extratemporal resection. Hx=hemispherectomy.

	HR (95% CI)
Hippocampal sclerosis (n=407)	1 (..)
Dysembryoplastic neuroepithelial tumour (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)
Focal cortical dysplasia (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)

HR=hazard ratio.

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

free (other than SPS) 2 years after surgery, 52% (48–56) after 5 years, and 47% (42–51) after 10 years. Table 2 shows univariable and multivariable survival analysis of time to first seizure (≥OC3) after surgery, and the probability of seizure freedom after 10 years. Multivariable results include all factors that were statistically significant in univariable models. Age at surgery had a significant effect on outcome (table 2) and was included in all subsequent analyses. 5 years after surgery, the seizure-free rates (excluding SPS) were 55% (95% CI 51–60) for anterior temporal resection, 56% (38–70) for temporal lesionectomy, 40% (24–55) for extratemporal lesionectomy, and 64% (30–85) for hemispherectomy (figure 1).

A difference in outcome was noted for the various pathological changes after anterior temporal resection (p=0·02; table 3). Those with focal cortical dysplasia and those with other changes, including other malformations and no detected abnormality, had significantly earlier relapses than did those with hippocampal sclerosis. 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% (45–77) for those with dysembryoplastic neuroepithelial tumour.

In those who had a lesionectomy, the risk of seizure recurrence did not significantly differ in patients with

a glioma (n=18) or dysembryoplastic neuroepithelial tumour (36) compared with those with a cavernoma (14) (HR 1·42, 95% CI 0·58–3·47). No difference in probability was noted between patients with glioma, dysembryoplastic neuroepithelial tumour, or cavernoma, compared with those with focal cortical dysplasia (n=7; HR 0·77, 0·27–2·17).

In people with glioma, dysembryoplastic neuroepithelial tumour, cavernoma, or focal cortical dysplasia, time to first seizure did not differ between those who underwent anterior temporal resection (n=62) or temporal lesionectomy (36; HR for lesionectomy 0·92, 0·49–1·73). Results were similar for individual pathological changes, but numbers were small.

40 people had temporal lesionectomies and 40 had extratemporal lesionectomies. The time to first seizure was not different between the two groups (HR for extratemporal lesionectomy 1·7, 0·9–3·1). This finding was not materially altered (1·8, 0·95–3·5) when type of pathological change was included in the analysis.

296 people with further follow-up had anterior temporal surgery and no seizures (or SPS only) in the first 2 years after surgery. The 73 individuals who had SPS in this time were significantly more likely to have a seizure (≥OC3) in the subsequent years than were those who had no SPS (HR 2·4, 1·5–3·9; figure 2, table 4).

At each annual review 68–73% of people were seizure free or had SPS only. Although the overall proportion remaining seizure free was fairly stable, 3–15% changed between groups each year (figure 3). Table 5 shows the probability of remaining seizure free after initial seizure freedom—the longer a person stayed seizure free, the less likely they were to relapse. The latest relapse in somebody previously seizure free was at 15 years after surgery. In people with postoperative seizures (table 6), subsequent remission was less likely the longer seizures continued.

Patterns of seizure remission and relapse in the total cohort (N=615) were stratified into eight groups (A–G, table 7). Deaths were noted and classified as not epilepsy related or probably epilepsy related. 451 (73%) patients had at least 1 year of absolute seizure freedom, and 505 (82%) had at least 1 year with no seizures or SPS only. In ten of 47 people (group C) who relapsed after 1 year or more without seizures, the relapse was preceded by tapering or omission of antiepileptic drugs. In a further nine, relapse was associated with stress or intercurrent illness. In 36 of 49 (73%) people with seizures initially continuing postsurgically (group B), remission occurred with no changes in antiepileptic drugs. 30 of these 49 (61%) people who continued to have seizures after surgery went into long-term remission 2 years after surgery, and the remainder did so after 3–14 years. A further 44 went into remission, 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 after surgery following the introduction of a previously unused antiepileptic drug (14 levetiracetam, one clobazam, one pregabalin, one topiramate, one valproate). A further 14 people from group D who had seizures after withdrawal of antiepileptic drugs went into long-term remission after restarting the drugs.

For people who were seizure free after surgery, the possibilities of reductions in antiepileptic drugs were discussed in accordance with their circumstances. At latest follow-up, 104 of 365 (28%) seizure-free individuals

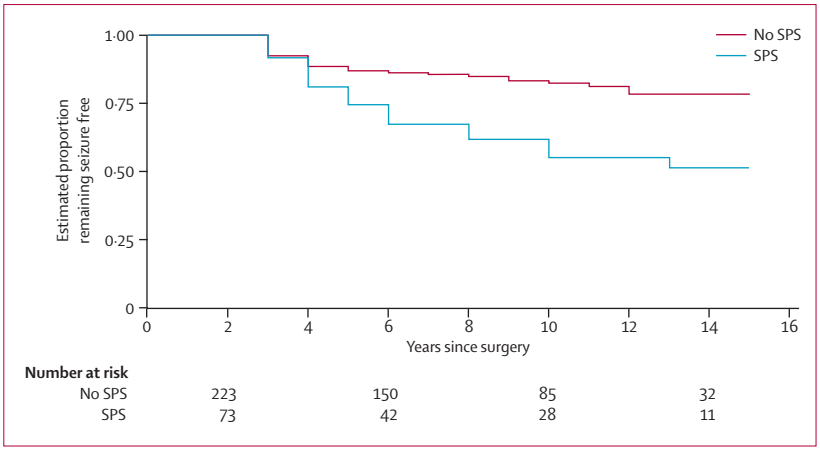


Figure 2: **Time to first seizure after temporal lobe surgery in people who had no seizures at all, or who had SPS only, in the first 2 postoperative years**
SPS=simple partial seizures.

	No seizures in first 2 years (95% CI)	SPS only in first 2 years (95% CI)
2 years later	89% (84–92)	81% (70–89)
5 years later	86% (80–90)	67% (54–77)
10 years later	78% (71–84)	55% (41–67)

SPS=simple partial seizure.

Table 4: **Estimated percentage of patients remaining free of seizures with loss of awareness (with 95% CIs) at intervals after temporal surgery in patients who did, and did not have, SPS in first 2 years after surgery**

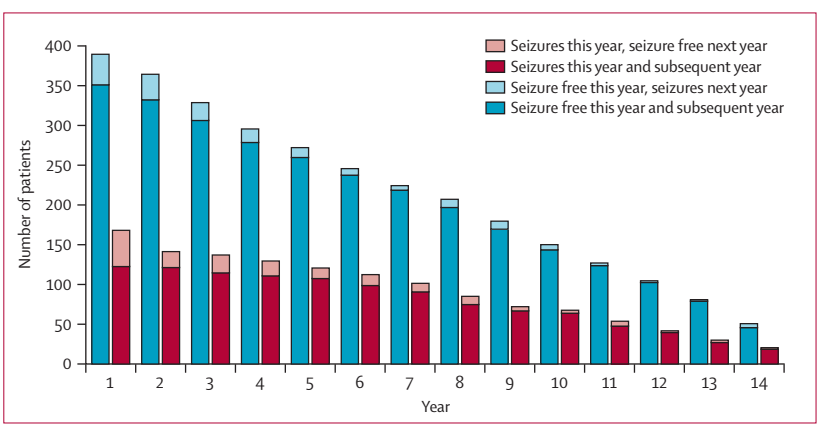


Figure 3: **Patients seizure free (OC1 and OC2) and not seizure free (≥OC3) after epilepsy surgery**
Darker blocks represent patients who remained in the same seizure status (seizure free or not seizure free) in the subsequent year. Lighter areas represent those who changed seizure status (from seizure free to having seizures, or from continuing seizures to seizure freedom) in the subsequent year. OC=outcome classification.

	Seizure free for 2 years after surgery (n=323)	Seizure free for 5 years after surgery (n=208)	Seizure free for 10 years after surgery (n=100)
1-year SFU	92% (88–94)	97% (94–99)	99% (93–100)
2-year SFU	87% (82–90)	97% (93–98)	97% (90–99)
5-year SFU	80% (75–85)	89% (83–93)	92% (79–97)
10-year SFU	72% (65–77)	82% (71–89)	Not estimable

Data are estimated percentage (95% CI). Seizure freedom or continuation was defined every year on the anniversary of surgery. SFU=subsequent follow-up.

Table 5: **People remaining seizure free after continuous periods of postsurgical seizure freedom, estimated by survival analysis, at each subsequent follow-up**

	Ongoing seizures for 2 years after surgery (n=108)	Ongoing seizures for 5 years after surgery (n=69)
1 year SFU	6% (3–13)	1% (0–10)
2 year SFU	13% (8–21)	8% (3–18)
5 year SFU	24% (16–34)	20% (12–33)
10 year SFU	38% (28–51)	30% (17–50)

Data are estimated percentage (95% CI). Seizure freedom or continuation was defined every year on the anniversary of surgery. SFU=subsequent follow-up.

Table 6: **People gaining 1 year of seizure freedom after continuous periods of ongoing seizures, estimated by survival analysis, at each subsequent follow-up**

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

SPS=simple partial seizure.

Table 7: **Patterns of seizure remission and relapse after surgery**

were off these drugs. Four of 65 (6%) people with SPS at last follow-up, and five of 185 (3%) with continuing seizures were taking no antiepileptic drugs.

Mortality was reported previously in patients who were, and were not, seizure free after surgery.[7] 19 of the 615 (3%) people died (five deaths were epilepsy related, 11 non-epilepsy related, and three of unknown cause), in addition to the five people who died within 1 year of surgery (one cancer death, one infection-related death, one suicide, and two sudden expected deaths in epilepsy [SUDEP]). These results approximate to one death per 218 patient-years of follow-up. Clinically evident morbidity caused by the surgical procedures consisted of 46 superior quadrant visual field defects (8% of temporal lobe procedures); 28 (5%) wound infections needing antibiotics; three (<1%) hemipareses; 15 (2%) cases of frontalis muscle weakness; six (1%) cases of dysphasia; 19 (3%) cerebrospinal fluid leaks needing resuturing; and one deep venous thrombosis needing anticoagulation.

Discussion

We established long-term outcome and use of antiepileptic drugs in a large adult epilepsy surgery cohort with more than 5200 person-years of follow-up. Half the individuals were seizure free in terms of usually cited criteria—ie, entirely seizure free or SPS only—for the duration of follow-up, and 40% were completely seizure free throughout follow-up. At any time, nearly three-quarters of people were seizure free in the previous year (figure 3). Age at surgery had a small effect (HR 1·01) with about a 6% increased risk of seizure recurrence in adults who were 5 years older at surgery, and a 13% increased risk in people 10 years older.

Previous studies of seizure outcome at year 1, year 2, and at last follow-up do not capture all the outcomes of seizure control after surgery.[8] Other workers[1,8] have used differing outcome classifications and definitions of seizure freedom. We used the ILAE classification[5] and analysed OC1 (entirely seizure free in the previous year, panel 1, webappendix), and OC1 and OC2 (including SPS). Individuals kept prospective seizure diaries and would have known if they had had seizures on more than 3 days in a year.

One study[9] had a 60% response to a questionnaire done on average 7 years after temporal surgery, and showed that 48% of patients had not had seizures since surgery, which is somewhat better than the 38% entirely seizure-free individuals in our cohort 10 years after anterior temporal resection, as estimated by survival analysis. The poor response rate of the questionnaire raises the possibility of bias. Another study[10] has shown that, after surgery, 43% of patients were seizure free or had SPS throughout a mean 7-year follow-up, whereas others[3,11,12] of people with temporal surgery followed up for a mean of 5–10 years reported seizure freedom (with or without SPS) of between 41% and 63%.

In our cohort, the probability of remaining seizure free (no seizures with loss of awareness) was 63% at 2 years. By 10 years the probability of remaining seizure free or with SPS was 47%, or 37% entirely seizure free. A study[13] in consecutive people with temporal resection for hippocampal sclerosis estimated that 77% were seizure free at 2 years, and 74% at 5 years. Although the success rate in that study seems higher than that in our study, numbers were small and 95% CIs not provided. Unsurprisingly, others[14] have noted that a short interval between surgery and first seizure recurrence was associated with a worse longer-term prognosis than a longer interval.

We showed that almost three-quarters of people had at least 1 year of absolute seizure freedom at some stage, which increased to 82% if SPS were discounted. 18% had no seizure freedom for 1 year, at any time. Another study[12] noted that by 2 years, 70% had a remission (with or without SPS) of 1 year, 74% by 3 years, and 77% by 5 years.

We found that people with extratemporal resections had a greater probability of seizure recurrence than did those with anterior temporal resection. Similar findings were reported in a long-term follow-up study[15] of patients after surgery in which those who had temporal resections were at an increased chance of seizure freedom.

In our study, in people who had anterior temporal resection, those with focal cortical dysplasia, and those with other pathological changes, including other malformations and no detected abnormality, were more likely to have recurrent seizures than were those with hippocampal sclerosis, although numbers are small. Other studies[10,15] have also reported a more favourable outcome in people with hippocampal sclerosis. Our 5-year rates of seizure freedom (excluding SPS) for anterior temporal resection were 57% for patients with hippocampal sclerosis, and 63% for those with dysembryoplastic neuroepithelial tumour. A study[16] of postoperative outcome in patients with pathological changes identified with preoperative MRI showed that a 2-year terminal remission was obtained in 80% of patients with tumours and vascular malformations, 58% with hippocampal sclerosis, and 29% of those with normal MRI. However, an assessment[17] of people who had anterior temporal resection showed that the underlying pathological changes did not determine time to subsequent first seizure. The presence of ganglioglioma or dysembryoplastic neuroepithelial tumour, and absence of dysplasia have been associated with good postoperative control of seizures.[18]

We showed that for equivalent pathological changes (glioma, dysembryoplastic neuroepithelial tumour, cavernoma, or focal cortical dysplasia), temporal lesionectomies and anterior temporal resection had similar rates of seizure freedom. In an analysis[18] of people aged between 2 years and 62 years with temporal lobe epilepsy, no difference in postoperative outcome was noted between people who had anterior temporal resection with hippocampectomy, amygdalohippocampectomy, lateral temporal lesionectomy with corticectomy, or lesionectomy with corticectomy and hippocampectomy. However, in another study of children[19] those who had amygdalohippocampectomy had significantly lower rates of seizure freedom than did those who had standard anterior temporal resection. In patients with dysembryoplastic neuroepithelial tumour,[20] those with temporal resection were more likely to be seizure free than were those who had lesionectomy, but the lesion was not temporal in most patients.

The probability of patients in our study remaining seizure free increased with the number of years of seizure freedom already experienced (table 5). This finding is supported by results from a study[12] of outcome after temporal surgery in which individuals who were seizure free (or with SPS only) for any 1 year had a 90% probability of having no seizures in the next year, and those with 2 successive years of seizure freedom had a 94% chance of seizure freedom in the subsequent year. Others found that the probability of remaining seizure free for a mean of 5·6 years follow-up was 83% in those who were seizure free for the first year after temporal surgery, and 92% in those seizure free for the first 2 post-operative years.[11] In another study,[21] in people seizure free with or without SPS for 1 year after surgery, the probability of subsequently having a seizure was estimated to be 18% at 5 years and 33% at 10 years.

***Panel 2:* Research in context**

Systematic review

We did a review to ascertain results of previous studies of the outcome after epilepsy surgery. We searched Medline and Embase from Jan 1, 1990, to March 30, 2011 for published papers reporting outcome with the search term "epilepsy surgery outcome". We excluded articles not written in English.

Interpretation

A meta-analysis[8] summarised previous studies of epilepsy surgery outcome in which 66% of people were seizure free in the long term after temporal resections with poorer results for those with other types of surgery. 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; whereas at any timepoint about 70% are free of disabling seizures, and every year up to 15% change their seizure status.

There are five clinical messages. First, 40% have long-term complete seizure freedom after epilepsy surgery, with a further 11% having only SPS. Although 82% had at least 1 year with no seizures or only SPS, this does not indicate cure. No patient had substantial worsening of epilepsy. Clinical practice should change to sooner refer appropriate patients for possible surgery. Second, selection process and surgical methods need improvement to increase success rates and to more accurately identify those who will not benefit from surgery. Some studies could have implied overoptimistic expectations. Third, if SPS continue in the first 2 years after surgery, the probability of seizures recurring was twice that if the person was entirely seizure free; previous studies have not reported this finding. Such important information might affect the decision to taper or continue antiepileptic drugs. Fourth, anterior temporal resection was associated with a higher probability of seizure freedom than resections in other parts of the brain. Finally, most people who are seizure free after surgery choose to remain on an antiepileptic drug.

In our study, patients with SPS in the first 2 years were twice as likely to have subsequent seizures with impaired awareness as were those entirely SPS free. Another study[22] examined people who had SPS associated with complex partial or secondarily generalised seizures before temporal resections. In that study,[22] follow up of patients who were free of complex partial or secondarily generalised seizures for 2 years after surgery showed no difference in terms of subsequent freedom from these seizures between patients who did and did not have postoperative SPS.

Our findings show that even in people with a long period of continuing seizures, the possibility of remission remains (table 6), and a few individuals became seizure free after the introduction of new antiepileptic drugs. The antiepileptic drugs introduced after surgery in our study had not been tried previously, and we cannot know whether they could have controlled seizures if used pre-operatively.

Follow-up[23] of 276 people who had at least one seizure after the immediate postoperative period noted that 77% would have further seizures within 12 months and, after a second seizure, 86% would have further seizures within 12 months. A third of patients subsequently had one or more seizure-free years. A study[24] of 86 people with temporal epilepsy who still had seizures 6 months after surgery found that 32% had been seizure free for at least 1 year by 2-year follow-up. In another study,[25] of 51 people who had anterior temporal resection, 27% had seizures in the first 2 years and 29% of these became seizure free in the third and fourth postoperative years.

28% of our patients who were seizure free at last follow-up stopped antiepileptic drugs. Others might have been suitable for drug reduction but have been reluctant to do so (often for social reasons, such as permission to drive). In a future analysis, we will consider reduction of antiepileptic drugs and factors affecting this.

Our study had several limitations. Caveats to the assessment of outcome according to operative procedure in people with temporal surgery were the small numbers, that the decision was not randomly assigned, and that patients with extensive disease and lesions close to the hippocampus were more likely to have anterior temporal resection than were other patients. Additionally, because of the small numbers and the observational nature of our study we cannot comment strongly on use of antiepileptic drugs, but note that if seizures continue after surgery, new drugs could be considered.

In our study, incidence of mortality and new morbidity after epilepsy surgery was low and compares favourably with the annual mortality rate of severe epilepsy.[7] Goldmann perimetry is more sensitive than clinical assessment and visual field defects have been detected in up to 42% of patients after temporal resection at NHNN.[26,27] Separate reports will establish the effects of surgery on cognitive function, psychiatric status, and employment.

Our cohort was highly selected. Although most patients showed a substantial reduction in seizures, only 40% entered long-term remission by virtue of having no seizures from time of surgery, and only 28% of those who were seizure free at last follow-up had discontinued antiepileptic drugs and could therefore 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 as such could be generalisable, but replication at other centres would be valuable. Consideration of either pregnancy or obtaining a driving licence seem to be major factors in an individual's decision making, and no prospective randomised trial is available of cessation or continuation of antiepileptic drugs after surgery.

For seizure outcome, surgery is successful for many individuals in whom antiepileptic drugs have not been effective, but further improvements need to be made to presurgical assessment to further increase rates of success (panel 2).

Contributors

JDT did the data collection and presentation, and bibliography. GSB did the data analysis and compiled the first draft of the Article. JLP did the data analysis; AWMcE and WFH did the surgical procedures; JWS did the data interpretation and editing; and JSD conceived the study, and did the data interpretation and editing.

Conflicts of interest

JDT, JLP, and AWMcE declare that they have no conflicts of interest. GSB's husband works for, and has shares in, GlaxoSmithKline. 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 and research grants from Eisai, GlaxoSmithKline, MedTronic, Pfizer, and UCB. JSD has been consulted by and received fees to his institution for lectures from Eisai, GE Healthcare, Pfizer, GlaxoSmithKline, Sanofi- Aventis, and UCB; he has had departmental and grant support from MedTronic, Cyberonics, and VSM MedTech.

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References

1 Engel J Jr. Surgery for seizures. *N Engl J Med* 1996; **334:** 647–52.
2 Wiebe S, Blume WT, Girvin JP, Eliasziw M, for the Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001; **345:** 311–18.
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:** 2018–30.
4 Duncan JS. Selecting patients for epilepsy surgery: synthesis of data. *Epilepsy Behav* 2011; **20:** 230–32.
5 Wieser HG, Blume WT, Fish D, et al, for the Commission on Neurosurgery of the International League Against Epilepsy (ILAE). ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia* 2001; **42:** 282–86.
6 Altman DG, Machin D, Bryant TN, Gardner MJ. Statistics with confidence. 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:** 716–18.

8 Téllez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain* 2005; **128:** 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:** 2115–24.

10 Dunlea O, Doherty CP, Farrell M, et al. The Irish epilepsy surgery experience: long-term follow-up. *Seizure* 2010; **19:** 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:** 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:** 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:** 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:** 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:** 513–24.

16 Berkovic SF, McIntosh AM, Kalnins RM, et al. Preoperative MRI predicts outcome of temporal lobectomy: an actuarial analysis. *Neurology* 1995; **45:** 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:** 314–19.

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:** 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:** 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:** 62–69.

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

22 Chandrasekar T, Sharan AD, Sperling MR. Postoperative auras and the risk of recurrent seizures. *Epilepsy Res* 2008; **78:** 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:** 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:** 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:** 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:** 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:** 1656–68.