

Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis

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Summary

Assessment of long-term outcomes is essential in brain surgery for epilepsy, which is an irreversible intervention for a chronic condition. Excellent short-term results of resective epilepsy surgery have been established, but less is known about long-term outcomes. We performed a systematic review and meta-analysis of the evidence on this topic. To provide evidence-based estimates of long-term results of various types of epilepsy surgery and to identify sources of variation in results of published studies, we searched Medline, Index Medicus, the Cochrane database, bibliographies of reviews, original articles and book chapters to identify articles published since 1991 that contained ≥ 20 patients of any age, undergoing resective or non-resective epilepsy surgery, and followed for a mean/median of ≥ 5 years. Two reviewers independently assessed study eligibility and extracted data, resolving disagreements through discussion. Seventy-six articles fulfilled our eligibility criteria, of which 71 reported on resective surgery (93%) and five (7%) on non-resective surgery. There were no randomized trials and only six studies had a control group. Some articles contributed more than one study, yielding 83 studies of which 78 dealt with resective surgery and five with non-resective surgery. Forty studies (51%) of resective surgery referred to temporal lobe surgery, 25 (32%) to grouped temporal

and extratemporal surgery, seven (9%) to frontal surgery, two (3%) to grouped extratemporal surgery, two (3%) to hemispherectomy, and one (1%) each to parietal and occipital surgery. In the non-resective category, three studies reported outcomes after callosotomy and two after multiple subpial transections. The median proportion of long-term seizure-free patients was 66% with temporal lobe resections, 46% with occipital and parietal resections, and 27% with frontal lobe resections. In the long term, only 35% of patients with callosotomy were free of most disabling seizures, and 16% with multiple subpial transections remained free of all seizures. The year of operation, duration of follow-up and outcome classification system were most strongly associated with outcomes. Almost all long-term outcome studies describe patient cohorts without controls. Although there is substantial variation in outcome definition and methodology among the studies, consistent patterns of results emerge for various surgical interventions after adjusting for sources of heterogeneity. The long-term (≥ 5 years) seizure free rate following temporal lobe resective surgery was similar to that reported in short-term controlled studies. On the other hand, long-term seizure freedom was consistently lower after extratemporal surgery and palliative procedures.

Keywords: epilepsy surgery; long-term outcome; seizure free; meta-analysis; prognosis

Abbreviations: AED = anti-epileptic drug; CI = confidence interval; MST = multiple subpial transection

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Introduction

The short-term efficacy and safety of epilepsy surgery for temporal lobe epilepsy have been established through one randomized controlled trial (Wiebe *et al.*, 2001) and a systematic review and meta-analysis of the literature that

included 32 studies and 2250 patients (Engel *et al.*, 2003). In the study by Engel and colleagues, 65% of patients with anteromesial temporal resections were seizure free, while 21% improved and 14% did not improve. A sub-analysis

of a smaller data set in that study suggested that outcomes were similar in patients with longer follow-up (2–5 years), 63% of whom remained seizure free. Evidence for extratemporal surgery was weaker and management recommendations were less certain.

Assessment of long-term outcomes is essential, in general, in epilepsy because it is a chronic condition, and in brain surgery for epilepsy specifically because its effects are irreversible. While earlier studies traditionally focused on relatively short outcomes, epilepsy surgery centres are now reporting long-term outcomes in cohorts of patients with epilepsy following a variety of surgical interventions. Admittedly, the strength of inference that can be derived from these studies is less robust than that from randomized controlled trials. Nonetheless, data from cohort studies still inform clinical practice in many areas, including epilepsy. Furthermore, the question of long-term outcomes may not be amenable to randomized trials due to feasibility and ethical issues.

We performed a systematic review and meta-analysis of the evidence on long-term outcomes with different types of epilepsy surgery. Our aim was to provide clinicians with a coherent summary of the best current evidence and to explore whether reasonable pooled estimates of surgical effectiveness and safety can be obtained from the literature, the extent to which results vary among studies, and the sources of variation in results. In this analysis, we focus on seizure freedom, which is always a relevant outcome and also the one most consistently reported.

Methods

Data sources

A medical librarian performed a comprehensive literature search of Medline, Embase, Index Medicus and the Cochrane databases (the search used with Medline is given in Appendix 1). We also searched bibliographies of reviews, original articles and book chapters, and consulted experts about other studies. Searches were restricted to full-length English articles published between 1991 and 2003.

Study selection and classification

Two reviewers independently applied the following study inclusion criteria: (i) reports of ≥ 20 patients of any age undergoing resective or non-resective epilepsy surgery; (ii) outcomes reported after a mean/median follow-up of ≥ 5 years; (iii) quantitative report of seizure and other outcomes; and (iv) a description of the type of surgery and number of patients undergoing each intervention. We excluded duplicate publications, i.e. studies with any overlapping patient populations from the same centre.

Studies were categorized by type of surgery into resective (e.g. lesionectomy, corticectomy, lobectomy, hemispherectomy) and non-resective procedures (e.g. multiple subpial transections and callosotomy). We further classified studies by surgical topography into:

- (i) Temporal lobe surgery: studies reporting outcomes of temporal lobe surgery.
- (ii) Grouped temporal and extratemporal surgery: studies reporting results globally, without lobe specification.

- (iii) Grouped extratemporal: studies reporting globally on extratemporal surgery, without lobe specification (e.g. occipital, parietal, and frontal together).
- (iv) Specific extratemporal: reporting on individual lobes (occipital, parietal and frontal).
- (v) Other types of surgery: reporting separately for each procedure (callosotomy, multiple subpial transection and hemispherectomy).

Data gathering

Two reviewers independently abstracted all data, resolving disagreements through discussion. The primary outcome was seizure freedom, as defined by authors in each study at the last reported follow-up.

Analysis

Studies were the unit of analysis. We assessed inter-study variability (heterogeneity) in outcomes by plotting each study's point estimate and its 95% confidence intervals (CI) within four groups of studies: (i) temporal lobe surgery using Engel's outcome classification (Engel *et al.*, 1993); (ii) temporal lobe surgery using author-specific outcome classification; (iii) studies that grouped temporal and extratemporal studies using Engel's classification; and (iv) those using author-specific classification.

For each group, we obtained the median proportion of seizure-free patients and the 25th and the 75th percentiles. Studies whose results were outside of these percentiles were judged to be clinically heterogeneous, and a potential source for heterogeneity was sought in each instance. Within each surgical category, we also pooled the proportion of seizure free patients, weighting each study by the inverse of its variance (fixed effects model) and calculated 95% CI for the pooled estimate. To compare outcomes between groups of interest, we calculated the risk ratio and its 95% CI. A multivariate linear regression model explored the impact on seizure freedom of the following dichotomous explanatory variables: (i) surgery before or after 1980; (ii) < 40 or ≥ 40 patients; (iii) follow-up of 5–10 years or > 10 years; and (iv) seizure outcome using Engel's class I system (Engel *et al.*, 1993) or other systems.

Results

Evidence base

The literature search yielded 1500 references, of which 142 (9.4%) were potentially eligible and were reviewed in full text independently by two reviewers. Seventy-six studies (54%) fulfilled the eligibility criteria and constitute our data set (Fig. 1). Some articles contributed more than one study, i.e. more than one surgical procedure was reported separately and contained ≥ 20 patients. This yielded 83 studies, of which 78 dealt with resective surgery and five with non-resective surgery. Among studies of resective surgery, 40 (51%) reported outcomes after temporal lobe surgery, 25 (32%) grouped patients with temporal and extratemporal surgery, seven (9%) reported on frontal lobe surgery, two (3%) on extratemporal procedures, two (3%) on hemispherectomy, and one (1%) each on parietal and occipital lobe surgery. In non-resective surgery, three studies reported outcomes after

SEARCH STRATEGY AND EVIDENCE BASE

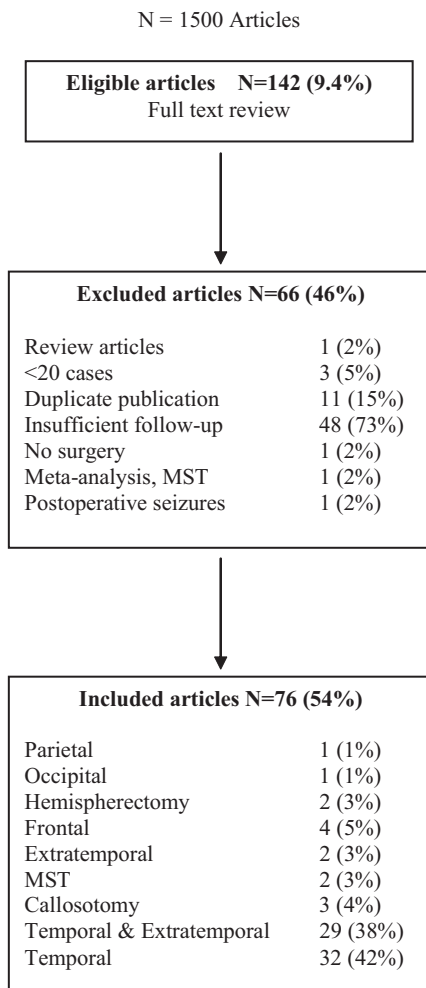


Fig. 1 Search strategy and evidence base (n = 1500 articles).

callosotomy and two after multiple subpial transections (see Appendix 2 for specific references).

Definitions of seizure-freedom in the included studies fell into two main categories. One required freedom of all seizure types, without specific reference to anti-epileptic drug (AED) discontinuation. Seventy-five percent of these studies focused on seizure freedom at the last follow-up, 11% did not specify a timeframe, and 14% used the last year before the final evaluation. The other category used Engel’s system (Engel *et al.*, 1993). This was used in 21 (53%) studies of temporal lobe surgery, and in 10 (40%) studies reporting grouped temporal and extratemporal surgery. In studies on callosotomy, authors defined seizure freedom as freedom from the most disabling type of seizures (typically drop attacks).

Outcome in temporal lobe surgery

The weighted pooled proportion of long-term seizure free patients in 40 studies of temporal lobe surgery was 66% (95% CI = 62, 70) (Table 1). This was slightly higher and

Table 1 Long-term seizure freedom: overall proportion by type of surgery

Type of surgery (number of studies)	Number of patients	% seizure free (pooled if ≥2 studies)	95% CI
Temporal (n = 40)	3895	66	62, 70
Hemispherectomy (n = 2)	169	61	54, 68
Grouped temporal and extratemporal (n = 25)	2334	59	56, 62
Parietal (n = 1)	82	46	35, 57
Occipital (n = 1)	35	46	29, 63
Callosotomy* (n = 3)	99	35	26, 44
Grouped extratemporal (n = 2)	169	34	28, 40
Frontal (n = 7)	486	27	23, 30
Multiple subpial transections (n = 2)	74	16	8, 24

*In this group, freedom from the most disabling seizure type, i.e. drop attacks.

less heterogeneous in studies using Engel’s classification (66%; 95% CI = 64, 69) than in those using other classifications (61%; 95% CI = 59, 64) (Fig. 2A and 2B; Table 2). In univariate analyses, long-term seizure freedom was highest in patients with tumoral epilepsy (76%; 95% CI = 73, 79), and lowest in studies of patients older than 50 years at time of surgery (41%; 95% CI = 29, 53), in older studies (54%; 95% CI = 48, 60), and in those with follow-up >10 years (45%; 95% CI = 41, 49) (Table 2).

Other resective surgery

In studies reporting grouped temporal and extratemporal surgery, the average percentage seizure-free was 71% (95% CI = 68, 74) in those using Engel’s classification, and 48% (95% CI = 45, 51) in those using other outcomes systems (Fig. 3A and 3B; Table 3). In univariate analyses, the odds of being seizure free were significantly higher in patients with vascular malformations, in children, in those with follow-up >10 years, and in those operated on after 1980. Conversely, the odds were significantly lower in patients with cortical malformations (Table 3). Long-term seizure freedom with other types of surgery was as follows: 27% with frontal lobe resections (95% CI = 23, 30), 46% with occipital lobe resections (95% CI = 29, 63), 46% with parietal resections (95% CI = 35, 57), 61% with hemispherectomy (95% CI = 54, 68) and 34% in grouped extratemporal resections (95% CI = 28, 40) (Table 1).

Seizure outcome in non-resective surgery

The pooled proportion of long-term seizure-free patients was 16% with multiple subpial transections (MSTs) (95%

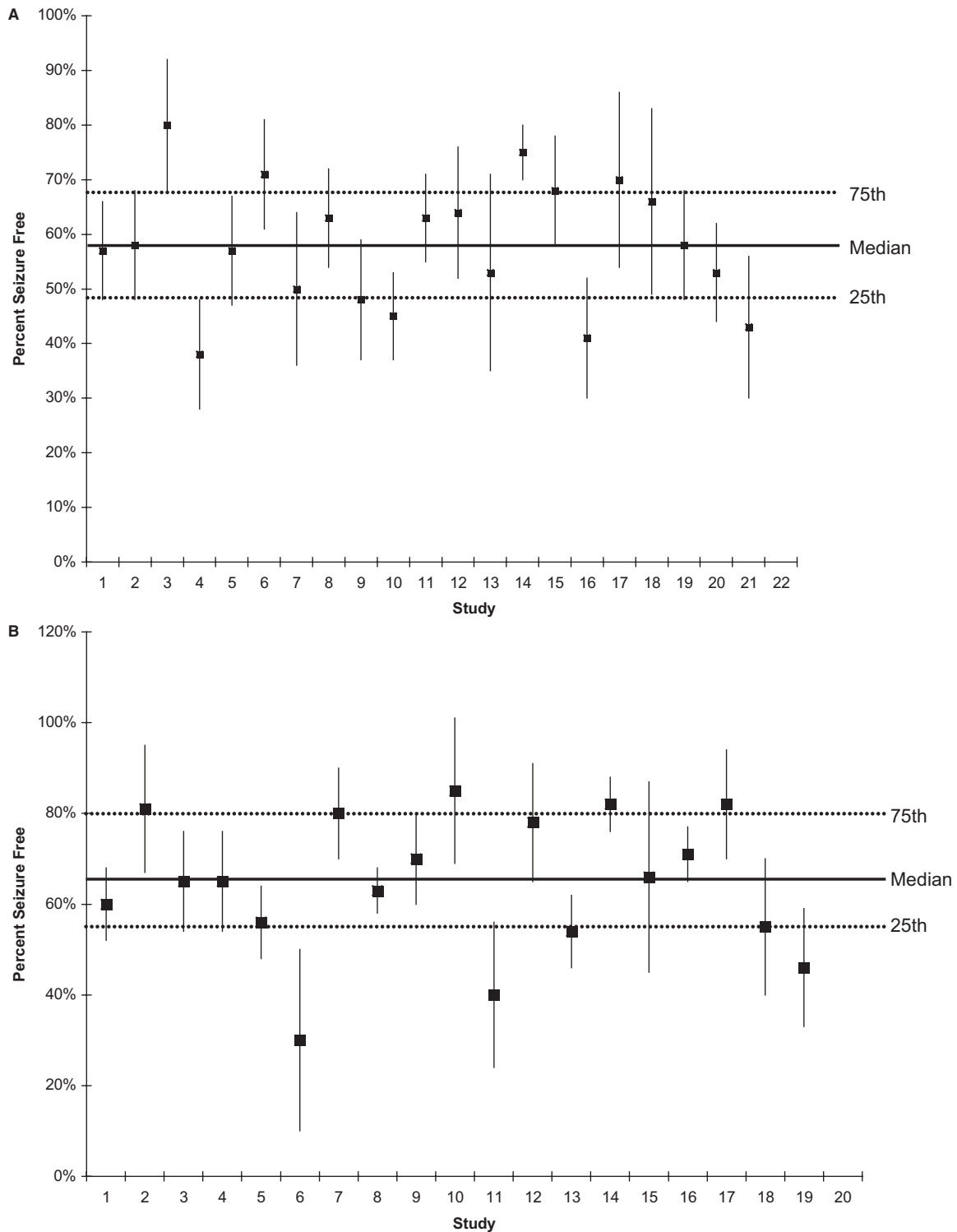


Fig. 2 Proportion of patients with long-term seizure freedom in various groups of studies. Individual studies are depicted with their corresponding 95% CI. Solid lines represent the median proportion and dotted lines the 25th and 75th percentiles. Studies outside these percentiles were judged as clinically heterogeneous and are described for each group. **(A)** Temporal lobe surgery: seizure freedom defined by author ($n = 21$). The median proportion (25th, 75th percentiles) was 58% (49%, 67%). Four studies below the 25th percentile reported follow up >10 years (one), surgery before 1980 (two), or non-specific patient groups (one). Four studies above the 75% percentile reported on focal lesions (one), patients younger than 50 years (one), children (one), or non-specific patient groups (one). The pooled proportion of seizure free patients was 61% (95% CI = 59, 64). **(B)** Temporal lobe surgery: seizure freedom using Engel's class I ($n = 19$). The median proportion (25th, 75th percentiles) was 65% (55%, 80%). Four studies below the 25th percentile reported follow up >10 years (three) or surgery before 1980 (one). Four studies above the 75% percentile reported on patients with tumours (two), familial hippocampal sclerosis (one) or children (one). The pooled proportion of seizure free patients was 66% (95% CI = 64, 69).

Table 2 Temporal lobe surgery: seizure free rates by prognostic variable (40 studies involving 3895 patients)

Group of studies	Number of patients	Pooled (%)	95% CI	Risk ratio†	95% CI
Studies with patients operated after 1980 (<i>n</i> = 35)	3512	64	61, 67	1.1	0.9, 1.5
Studies with patients operated before 1980 (<i>n</i> = 5)	383	54	48, 60		
Studies with five to ten years of follow-up (<i>n</i> = 35)	3407	61	59, 63	1.3	1.0, 1.7
Studies with more than ten years of follow-up (<i>n</i> = 5)	488	45	41, 49		
Studies in adults (<i>n</i> = 30)*	2947	63	61, 65	1.0	0.7, 1.3
Studies in children (<i>n</i> = 9)*	444	62	57, 67		
Studies using Engel's outcome classification (<i>n</i> = 19)	1803	66	64, 69	1.0	0.8, 1.4
Studies using other classification systems (<i>n</i> = 21)	2092	61	59, 64		
Other groups					
Studies including patients older than 50 years (<i>n</i> = 2)**	50	41	29, 53	0.6	0.4, 0.8
Studies including patients with tumours (<i>n</i> = 3)**	269	76	73, 79	1.1	0.9, 1.4

*One out of 40 studies did not specify the age group. **Ratio of probability of being seizure free in these studies relative to all other studies of temporal lobe epilepsy. †Ratio of probability of being seizure free in one group relative to its comparison; <1 denotes lower and >1 higher chance of being seizure free.

CI = 8, 24). With callosotomy, 35% (95% CI = 26, 44) of patients were free of the most disabling seizures, i.e. drop attacks (Table 1).

Other outcomes

Outcomes other than seizure freedom were reported in 22 of the 32 studies (68%) of temporal lobe surgery (Appendix 2). Six studies explored AEDs outcome (18%), seven studies explored psychological aspects (22%) and nine explored cognition (28%). Three of the 29 studies (10%) reporting grouped temporal and extratemporal surgery explored AED use, and one explored psychosocial outcomes. Only one study in the other categories (callosotomy) explored psychosocial outcome and one in hemispherectomy explored AED use. Six studies had a control group (non-randomized), four in temporal lobe and two in grouped temporal and extratemporal surgery.

Heterogeneity and predictors of outcome

Assessment of clinically important heterogeneity in temporal lobe surgery disclosed potential explanatory factors, such as studies with >10 years of follow-up, studies of surgery performed before 1980, age (children or patients >50 years old), specific aetiologies (tumours, familiar mesial temporal sclerosis and focal lesions) (Fig. 2; Table 2). In studies reporting grouped temporal and extratemporal surgery, potential sources of heterogeneity were similar to those in temporal lobe surgery, but also included neuronal migration disorders, and studies of patients with vascular malformations (Fig. 3; Table 3).

Only two factors emerged as important predictors of seizure freedom in the linear regression model, i.e. the year of operation ($P = 0.001$) and the outcome classification system ($P = 0.018$). Accordingly, an earlier year of surgery was associated with studies reporting lower seizure-free rates and using Engel's system to define seizure

freedom correlated with studies reporting higher seizure-free rates.

Discussion

Epilepsy outcomes following temporal lobe surgery have been studied extensively in recent years. A review of studies with 1–5 years of follow-up (Engel *et al.*, 2003) reported freedom of disabling seizures in 63.2% of patients (95% CI = 60, 66) and identified a trend for better outcomes in more recent reports. In contrast, our analyses focused on long-term outcomes (i.e. ≥ 5 years). Compared with Engel *et al.* (2003), long-term follow-up studies of temporal lobe epilepsy surgery revealed a slightly lower seizure free rate (median 58% in studies using author defined outcomes, and 65% in those using Engel's class I classification), and a narrower range of seizure-free rates (59–89%). However, the results are more similar than different. In fact, one of our most salient findings is that, overall, long-term surgical results were consistently similar to those of short-term studies, including those from a randomized trial (Wiebe *et al.*, 2001). This supports the durability of the benefits of surgery in general.

In carefully selected children, hemispherectomy results in seizure-free rates of 70–80% (Daniel *et al.*, 2001; Pulsifer *et al.*, 2004). The evidence from long-term reports indicates that the benefit of hemispherectomy is maintained over time; 60% remain seizure free after 5 years.

Surgical studies of extratemporal epilepsy comprise a heterogeneous group of patients and interventions, and long-term outcomes are reported less frequently in this group. The meta-analysis by Engel *et al.* (2003) reported on extratemporal resections as a group, and is not comparable with our analysis of extratemporal resections by specific lobe. We identified only one long-term study of parietal and one of occipital surgery, each reporting a 46% seizure-free rate. The single studies of parietal and occipital lobe surgery preclude any robust inferences. On the other hand, studies of frontal

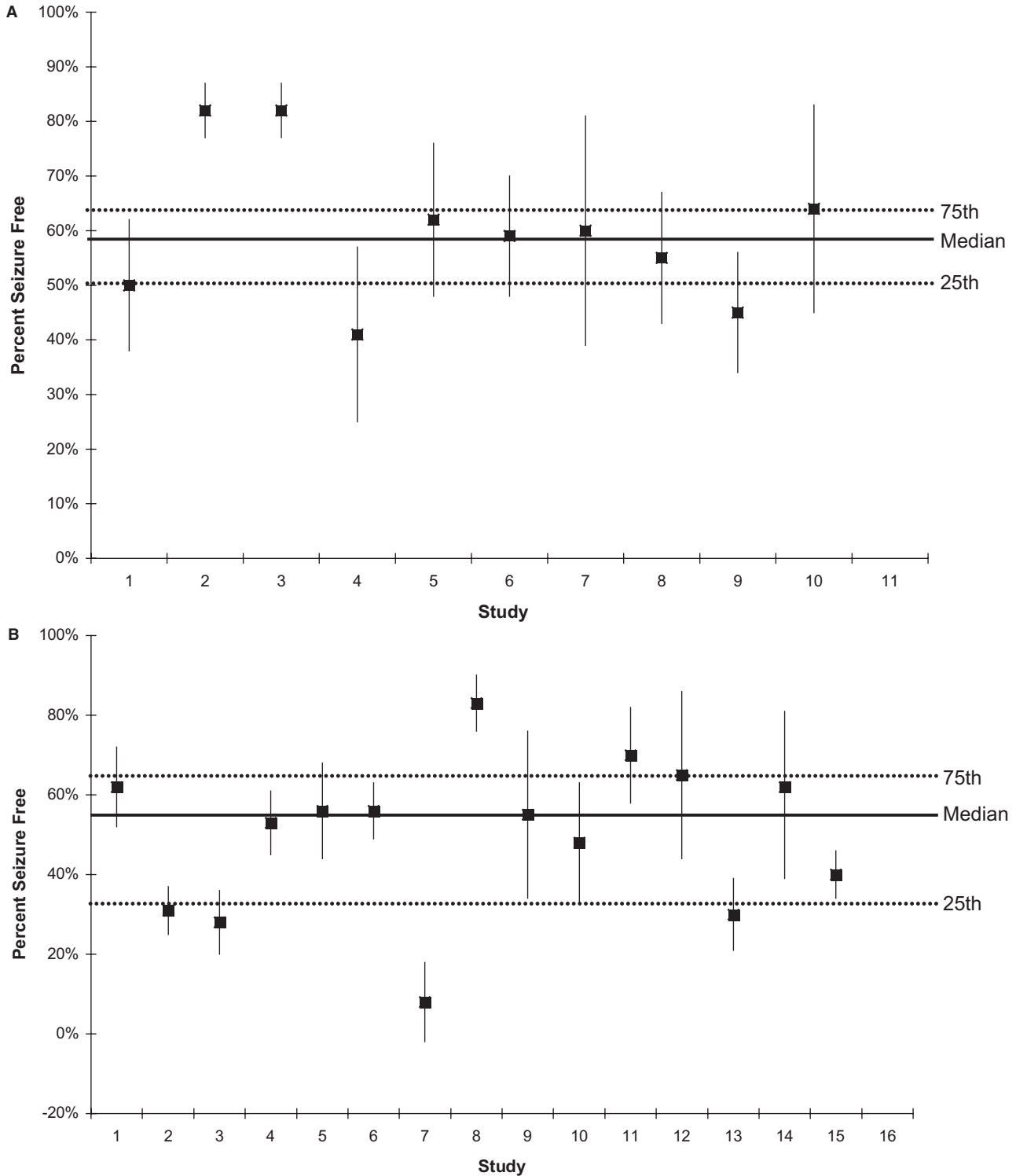


Fig. 3 Studies that grouped temporal and extratemporal surgery. Individual studies are depicted with their corresponding 95% CI. Solid lines represent the median proportion and dotted lines the 25th and 75th percentiles. Studies outside these percentiles were judged as clinically heterogeneous and are described for each group. **(A)** Studies of grouped temporal and extratemporal surgery: seizure freedom using Engel’s class I ($n = 10$). The median proportion (25th, 75th percentiles) was 59% (50%, 64%). Two studies below the 25th percentile reported follow up >10 years and surgery before 1980 (one) or surgery in cortical malformations (one). Two studies above the 75th percentile reported on patients with tumours (one) or children (one). The pooled proportion of seizure-free patients was 71% (95% CI = 68, 74). **(B)** Studies of grouped temporal and extratemporal surgery: seizure freedom defined by author ($n = 15$). The median proportion (25th, 75th percentiles) was 55% (33%, 62%). Four studies below the 25th percentile reported surgery before 1980 (three) or surgery in cortical malformations (one). Two studies above the 75th percentile both reported results in patients with vascular malformations. The pooled proportion of seizure free patients was 48% (95% CI = 45, 51).

Table 3 Grouped temporal and extratemporal surgery: seizure free rates by prognostic variable (25 studies involving 2334 patients)

Group of studies	Number of patients	Pooled (%)	95% CI	Risk ratio†	95% CI
Studies with patients operated after 1980 (<i>n</i> = 12)*	1125	68	66, 70	1.5	1.2, 2.0
Studies with patients operated before 1980 (<i>n</i> = 7)*	772	43	40, 46		
Studies with five to ten years of follow-up (<i>n</i> = 21)	1825	62	60, 64	1.6	1.2, 2.0
Studies with more than ten years of follow-up (<i>n</i> = 4)	509	38	34, 42		
Studies in children (<i>n</i> = 8)	777	59	56, 62	1.0	0.8, 1.4
Studies in adults (<i>n</i> = 17)	1557	54	52, 56		
Studies using Engel's outcome classification (<i>n</i> = 15)	1526	71	68, 74	1.4	1.1, 1.8
Studies using other classification systems (<i>n</i> = 10)	808	48	45, 51		
Other studies					
Patients with cortical dysplasia (<i>n</i> = 3)**	116	50	39, 61	0.8	0.6, 1.1
Patients with arteriovenous malformation (<i>n</i> = 2)**	156	79	73, 85	1.3	1.0, 1.6

*Six out of 25 studies did not specify the year of surgery. **Ratio of being seizure free in these studies relative to all other studies of temporal lobe epilepsy. †Ratio of probability of being seizure free in one group relative to its comparison; <1 denotes lower and >1 higher chance of seizure freedom.

lobe resections (seven studies) allow for somewhat stronger conclusions. These resections produced the worst long-term seizure-free rates among the resective surgeries (mean 27%, median 34%), but they were also highly heterogeneous (ranging from 9% to 80%). There are several possible explanations for poorer and heterogeneous outcomes. Poorer outcomes may relate to inability to resect the entire epileptogenic area due to its proximity to functionally important cortex. In addition, the epileptogenic area may be larger in the frontal lobe and seizure spread may be particularly rapid and extensive. Heterogeneity is probably explained by differences in outcome assessment, different aetiologies (e.g. better outcomes with tumoral epilepsy), whether the epileptogenic zone and surgical resection involve only the frontal lobe or adjacent structures as well, and the completeness of resection. These factors require systematic assessment in prospective studies.

A recent meta-analysis of 211 patients undergoing MST at six centres found similar results with MST alone (62–71% had >95% seizure reduction) and MST plus cortical resections (68–87% had similar outcome) (Spencer *et al.*, 2002). Our analysis supports concerns raised about the durability of seizure control following MST (Orbach *et al.*, 2001). MST had the lowest long-term seizure free rate of all procedures (16%). Regarding callosotomy, >65% of patients who undergo callosotomy experience a substantial decrease in or complete elimination of drop attacks in studies without prolonged follow-up (Sass *et al.*, 1988; Spencer *et al.*, 1988). However, as with MST, the long-term outcome for callosotomy is not as good; only 35% of patients had sustained seizure freedom of the most disabling type of seizures.

It is important to point out that few studies reported the proportion of patients with sustained seizure freedom from the time of surgery. Instead, most studies focused on the last year or the time of last follow-up. It is well known that some patients who are initially seizure-free can experience late seizure recurrence, while others who initially have seizures

may become seizure-free later. This ambiguity in expression of seizure outcome applies both to studies with author-defined outcomes and to those that used Engel's class I outcome. The latter can include complete seizure freedom since surgery, non-disabling simple partial seizures, and some initial disabling seizures but freedom of disabling seizures for at least 2 years ('running down' phenomenon). Therefore, the results of this meta-analysis should not be interpreted as the proportion of patients with sustained seizure freedom from the time of surgery. Instead, it largely represents the overall proportion of seizure-free patients at various points in time on long-term follow-up.

The absence of controls in all but a few studies of long-term surgical outcome must be considered when interpreting our analyses. It is highly probable that the reported benefit is inflated to a considerable degree. In a randomized surgical trial of temporal lobe epilepsy in medically refractory patients, 10% of patients in the control group became seizure-free (Wiebe *et al.*, 2001). A similar if not greater effect can be expected for many of the interventions considered in this analysis. This is particularly germane in surgical procedures known to result in low rates of long-term seizure freedom even in the absence of controls, such as callosotomies, MST and some types of frontal lobe surgery. The logical question is whether the benefit of some of these interventions poses sufficient uncertainty to warrant assessment through randomized controlled trials.

We explored between-study variation of results in the two largest categories of studies (temporal lobe and mixed temporal/extratemporal) and identified a number of possible explanations in univariate analyses (e.g. older series, longer follow-up, aetiology and type of outcome system). However, only two variables remained significant in multivariate analyses; surgery performed after 1980 and outcomes assessed using Engel's system were associated with reports of higher rates of sustained seizure freedom. This suggests that improvement in patient selection, identification of seizure

focus and surgical techniques have favourably affected outcomes of epilepsy surgery. They also highlight the importance of standardizing surgical outcome assessment. The multitudinous ways in which authors define seizure improvement or seizure freedom produces unnecessary noise and differences in outcomes that are more apparent than real.

The association between length of follow-up and poorer outcomes (Tables 2 and 3) found in our review may relate to multiple factors and deserves comment. This finding is not an artefact of our meta-analysis. A sub-analysis of studies that performed year-by-year follow-up (Appendix 2) showed the same trend. Potential explanations include the following: (i) operations were performed before the era of modern diagnostic and surgical technology, which may contribute to poorer outcomes; (ii) AEDs are increasingly withdrawn years after surgery; (iii) pharmacoresistance worsens over time; (iv) or new seizure foci develop. One study in our systematic review reported on AED withdrawal at different times during follow-up (Wieser and Hane, 2003) and found a relationship between drug discontinuation and reduction in seizure-free rates. Similarly, a recent systematic review of studies exploring the association between use of AEDs and seizure freedom after epilepsy surgery in studies with <5 years of follow-up suggests that withdrawal or decrement of AEDs may relate to seizure recurrence (Schmidt *et al.*, 2004). Regardless of its cause, clinicians and patients need to be aware that, although seizure control remains high after many years of follow-up, it tends to decline over time.

The differential effect of several variables on outcomes in temporal versus grouped temporal/extratemporal studies are of interest, e.g. better outcomes in patients operated after 1980 in the grouped temporal/extratemporal studies, but not in the temporal studies (Tables 2 and 3). In our univariate analyses, the risk ratios were small (around 1.4) and their lower 95% CI were as low as 1.1. Nonetheless, it is possible that in studies including extratemporal surgery, the association of more recent surgery (i.e. after 1980) and better outcomes reflects the impact of modern, more precise imaging and seizure mapping techniques, which may not be as crucial in the more confined epileptogenic zone of pure temporal lobe surgery.

Importantly, some relevant variables may have been under-represented or excluded in the multivariate analysis due to small numbers and our results may underestimate their overall impact on long-term outcomes. Outcomes other than seizures are very important to patients with epilepsy, but these are infrequently reported in long-term studies. Less than a quarter of the studies in our analysis reported on psychosocial well-being, cognition and AEDs. This highlights the need for comprehensive outcome assessment in long-term studies.

Others have described the sources of heterogeneity we identified in analyses that did not focus on long term outcomes (McIntosh *et al.*, 2001). The nature of the available data does not allow for a more robust analysis of the sources of variability among studies and important variables such as aetiology or epilepsy syndrome may be under-represented.

However, our clinical analysis of heterogeneity consistently identified similar variables across different types of surgery, lending support to their validity. Therefore, analyses of other variables would enrich, but not invalidate, our observations.

Like others (McIntosh *et al.*, 2001), we identified a number of important variations among reports and several limitations in studies of long-term surgical outcomes. For example, seizure outcome assessment and interpretation is highly variable, seizure severity is not addressed, non-seizure outcomes are often neglected, surgical groups are often mixed and include several types of surgery, surgical techniques and extent of resection vary among centres, and patient selection and evaluation varies over time and among centres. Under these circumstances, heterogeneity of results comes as no surprise. What is remarkable is the finding that, after adjusting for some sources of heterogeneity, one can uncover consistent patterns of clinically meaningful results among the numerous surgical interventions for epilepsy.

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Appendix 1: Literature search strategy used with Medline

First step

'Epilepsy/surgery' (MESH) OR 'Epilepsy' (TW) AND 'Surgery' (TW)

Second step

'Incidence' (MESH) OR 'Mortality' (MESH) OR 'mortality' (SH) OR 'Follow-Up Studies' (MESH) OR 'Prognosis' (MeSH:NOEXP) OR 'prognos*' (TW) OR 'predict*' (TW) OR 'course' (TW) OR 'outcome' (TW) OR 'psychology' (TW) OR 'Quality of Life' (MESH) OR 'Quality of Life' (TW) OR memory (TW) OR 'Survival Analysis' (MH:NOEXP)

Third step

'Randomized controlled trial' (PTYP) OR 'random*' (TW) OR ('double'(TW) AND 'blind*' (TW)) OR 'placebo' (TW) OR 'drug therapy' (SH) OR 'therapeutic use' (SH:NOEXP) OR 'cohort studies' (MESH) OR 'risk' (MESH) OR ('odds' (TW) AND 'ratio*' (TW)) OR ('relative' (TW) AND 'risk' (TW)) OR 'case control*' (TW) OR 'case-control studies' (MESH)

Fourth step: limits

Publication year 1991–2003
Human
Journal article

Appendix 2: Articles contributing to specific subgroups in the systematic review

Temporal lobe surgery

Walczak *et al.*, 1990; Elwes *et al.*, 1991; Feindel and Rasmussen, 1991; Guldvog *et al.*, 1991a, b; Erba *et al.*, 1992; Keogan *et al.*, 1992; McLachlan *et al.*, 1992; Nakasato *et al.*, 1992; Rougier *et al.*, 1992; Fish *et al.*, 1993; Kirkpatrick *et al.*, 1993; Polkey and Scarano, 1993; Garcia-Flores 1994; Sperling *et al.*, 1995, 1996; Holmes *et al.*, 1996; Wass *et al.*, 1996; Blume and Girving, 1997; Eliashiv *et al.*, 1997; Keene *et al.*, 1997; Altshuler *et al.*, 1999; Daniel and Chandy, 1999; Mathern *et al.*, 1999; Salanova *et al.*, 1999; Foldvary *et al.*, 2000; Iannelli *et al.*, 2000; Paolicchi *et al.*, 2000; Sirven *et al.*, 2000; Bien

et al., 2001; Boling *et al.*, 2001; Hennessy *et al.*, 2001; Jarrar *et al.*, 2002; Jones *et al.*, 2002; Jutila *et al.*, 2002; Helmstaedter *et al.*, 2003; Kobayashi *et al.*, 2003; Luyken *et al.*, 2003; Sinclair *et al.*, 2003; Wieser and Hane, 2003; York *et al.*, 2003; Zaatreh *et al.*, 2003.

Grouped temporal and extratemporal surgery

Garcia Sola and Miravet, 1991; Palmini *et al.*, 1991; Rougier *et al.*, 1992; Piepgras *et al.*, 1993; Yeh *et al.*, 1993; Guldvog *et al.*, 1994; Lehman *et al.*, 1994; Davies and Weeks, 1995; Liu *et al.*, 1995; Vickrey *et al.*, 1995; Wass *et al.*, 1996; Bizzi *et al.*, 1997; Keene *et al.*, 1997; Duchowny *et al.*, 1998; Koszewski *et al.*, 1998; Bourgeois *et al.*, 1999; Mathern *et al.*, 1999; Arzimanoglou *et al.*, 2000; Paolicchi *et al.*, 2000; Aronica *et al.*, 2001; Kloss *et al.*, 2002; Luyken *et al.*, 2003; Yoon *et al.*, 2003.

Frontal lobe surgery

Rasmussen, 1991a; Rougier *et al.*, 1992; Fish *et al.*, 1993; Swartz *et al.*, 1998; Ferrier *et al.*, 1999; Zaatreh *et al.*, 2002; Luyken *et al.*, 2003.

Grouped extratemporal mixed

Adler *et al.*, 1991; Rasmussen, 1991b.

Hemispherectomy

Vining *et al.*, 1997; Kossoff *et al.*, 2003.

Parietal lobe surgery

Salanova *et al.*, 1995.

Occipital lobe surgery

Aykut-Bingol *et al.*, 1998.

Callosotomy

Sakas and Phillips, 1996; Papo *et al.*, 1997; McInerney *et al.*, 1999.

Multiple subpial transection

Orbach D *et al.*, 2001; Schramm J *et al.*, 2002.

Psychosocial outcomes

Erba *et al.*, 1992; Sperling *et al.*, 1995, 1996; Sakas and Phillips, 1996; Wass *et al.*, 1996; Eliashiv *et al.*, 1997; Keene *et al.*, 1997; Sirven *et al.*, 2000; Jones *et al.*, 2002.

Cognitive outcomes

Keogan *et al.*, 1992; Kirkpatrick *et al.*, 1993; Sperling *et al.*, 1995, 1996; Bizzi *et al.*, 1997; Sirven *et al.*, 2000; Helmstaedter *et al.*, 2003; Sinclair *et al.*, 2003; York *et al.*, 2003.

Antiepileptic drug outcomes

Adler *et al.*, 1991; Guldvog *et al.*, 1991a, b; Mathern *et al.*, 1999; Salanova *et al.*, 1999; Schiller *et al.*, 2000; Bien *et al.*, 2001; Helmstaedter *et al.*, 2003; Kossoff *et al.*, 2003; Wieser and Hane, 2003.

Studies with year-by-year follow-up

Walczak *et al.*, 1990; Elwes *et al.*, 1991; Rougier *et al.*, 1992; Guldvog *et al.*, 1994; Sperling *et al.*, 1996; Eliashiv *et al.*, 1997; Mathern *et al.*, 1999; Salanova *et al.*, 1999; Foldvary *et al.*, 2000; Jarrar *et al.*, 2002; Jutila *et al.*, 2002; Schiller *et al.*, 2000; Luyken *et al.*, 2003; Wieser and Hane, 2003; Yoon *et al.*, 2003.