Rates and Predictors of Success and Failure in Repeat Epilepsy Surgery: A Meta-Analysis and Systematic Review

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Summary

Objective—Medically refractory epilepsy is a debilitating disorder that is particularly challenging to treat in patients who have already failed a surgical resection. Evidence regarding outcomes of further epilepsy surgery is limited to small case series and reviews. Therefore, our group performed the first quantitative meta-analysis of the literature from the past 30 years to assess for rates and predictors of successful reoperations.

Methods—A PubMed search was conducted for studies reporting outcomes of repeat epilepsy surgery. Studies were excluded if they reported fewer than 5 eligible patients or had average follow ups < 1 year, and patients were excluded from analysis if they received a non-resective intervention. Outcomes were stratified by each variable of interest and quantitative meta-analysis was performed to generate odds ratios (OR) and 95% confidence intervals (CI).

Results—782 patients who received repeat resective epilepsy surgery from 36 studies were included. Engel I outcome was observed in 47% (N=369) of patients. Significant predictors of seizure freedom in included congruent over non-congruent electrophysiology data (OR 3.6, 95% CI 1.6–8.2), lesional over non-lesional epilepsy (OR 3.2, 95% CI 1.9–5.3), and surgical limitations over disease-related factors associated with failure of the first surgery (OR 2.6, 95% CI 1.3–5.3). Among patients with at least one of these predictors, seizure freedom was achieved in 58%. Conversely, the use of invasive monitoring was associated with worse outcome (OR 0.4, 95% CI

Conflicts of Interest

The authors declare we have no conflicts of interest

Ethics Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure

None of the authors has any conflict of interest to disclose

0.2–0.9). Temporal lobe over extratemporal/multilobe resection (OR 1.5, 95% CI 0.8–3.0) and abnormal over normal pre-operative MRI (OR 1.9, 95% CI 0.6–5.4) showed non-significant trends toward seizure freedom.

Significance—This analysis supports considering further resection in patients with intractable epilepsy who continue to have debilitating seizures after an initial surgery, especially in the context of factors predictive of a favorable outcome.

Keywords

Seizure; reresection; reoperation; secondary; redo

Introduction

Medically refractory epilepsy is a debilitating disorder that is challenging to treat. Surgical resection has been shown to provide long term seizure control in about 40–80%[1] of operative candidates (60–80% in temporal lobe epilepsy[2–5] and 40–60% in extratemporal lobe epilepsy[6]). However, in patients who continue to have seizures after surgery, treatment becomes even more difficult[7] and can frustrate both patients and clinicians. Further therapeutic options include continued antiepileptic drug (AED) modifications[8] while awaiting seizure "run down"[9–11], vagus nerve stimulation (VNS)[12,13], responsive neurostimulation (RNS)[14], or a second surgery. While some of these options are palliative, repeat surgical intervention may still provide an opportunity for seizure freedom. Since seizure freedom is the strongest predictor of quality of life[15,16], and continued seizures are known to increase morbidity, mortality, neurocognitive decline, and psychosocial problems[16–18], it is important to explore which patients might have the best chance of success with further resection.

Current evidence regarding outcomes from repeat surgery is limited to a number of small case series and reviews[19–22], and results are often inconclusive. As such, drawing clear conclusions regarding predictors of success can be challenging. Furthermore, our group is unaware of any plans for large, prospective, randomized trials in this patient population. As such, here we provide a systematic review and the first quantitative meta-analysis of outcomes following repeat epilepsy surgery. We analyze published literature on this topic from the past 30 years and examine patient demographics, diagnostic data, epilepsy characteristics, and surgical factors as possible predictors of outcome. Our results suggest that repeat surgery for intractable epilepsy can be efficacious for properly selected patients.

Methods

Literature Search

A PubMed search for peer-reviewed articles containing outcomes of repeat epilepsy surgeries was conducted using the following query guidelines: (epilepsy OR seizure) AND ((surgery OR resection OR resective OR lobectomy OR amygdalohippocampectomy) AND ((repeat OR redo OR failed) OR (reresection OR reoperation))). This resulted in 1123 titles and abstracts that were examined for the following inclusion criteria: reported primary outcomes of repeat epilepsy surgery, published between 1986 and April 2017, and available

in the English language. 92 manuscripts met such criteria and were examined thoroughly for the following exclusion criteria: mean or median post-operative follow up less than 1 year, insufficiently disaggregated outcomes, or fewer than 5 eligible patients reported. Ultimately, 36 eligible studies were identified and included in our analysis (see Figure 1 for a summary of this process). Individual patients were disqualified from analysis if they received a non-resective intervention prior to or instead of a resection (e.g. VNS, corpus callosotomy, or radiation). This literature search and study design were guided by PRISMA recommendations[23].

Data Collection

Outcomes following repeat surgery were classified as free of disabling seizure (Engel class IA–D) or not seizure-free (Engel class II–IV). To assess for possible relationships with outcome, data for the following variables were collected when available: age of seizure onset, epilepsy duration prior to 1st surgery, age at 1st surgery, age at last surgery, time between surgeries, gender, laterality of surgeries, imaging abnormalities, use of invasive monitoring, congruency of electrophysiological data, predominant seizure type, seizure generalization, anatomical site of surgeries, underlying pathology, and cited reason for failure of the initial surgery. If more than 2 surgeries were performed on a patient, only outcome data relating to the final surgery were included. Any cited complications (or lack thereof) from the repeat surgery were also noted.

Anatomical site of surgery was categorized as temporal or extratemporal (including multilobar), pathology as lesional (tumor, cyst, or vascular malformation) or non-lesional (all other pathologies), and electrophysiology results as congruent (focal, localizing) or incongruent (bilateral, widespread, or non-localizing patterns). Studies varied in terms of which electrophysiological data was obtained and/or presented for each patient (e.g. ictal, interictal, scalp electroencephalography [EEG], subdural electrocorticography [ECoG], or depth electrode data). Therefore, if any data suggested a non-localizing, bilateral, widespread, or incongruent pattern, the patient's data was categorized as incongruent.

Additionally, authors often cited a known or suspected reason that the primary epilepsy surgery failed. Such explanations were dichotomized into "surgery-related" (e.g. extension of epileptogenic zones into functional areas, missed lesions, sub-total resections, lesional recurrence, improperly categorized epileptogenic areas, or residual mesiotemporal structures) or "disease-related" (e.g. emergence of new epileptiform areas postoperatively, known widespread/bilateral disease, or palliative cases) factors, as explained more fully in the Discussion.

Statistical Analysis

For preliminary analysis, outcomes from repeat surgeries were stratified by each variable of interest. For summary purposes and to help identify factors for meta-analysis, potential outcome predictors were compared using unpaired, two-way Student's t-tests for continuous variables and Pearson's chi-squared (X^2) tests for categorical variables. Variables potentially associated with seizure outcome (p-value 0.05) were subjected to formal meta-analysis. Heterogeneity across studies was examined using both Cochran's Q and I^2 tests, which

identified a fixed effects model as appropriate in all cases. Cochran–Mantel–Haenszel (CMH) testing was used to calculate odds ratios (OR) and 95% confidence intervals (CI). All statistical analyses were computed using Wizard Pro 1.8.28 (207), MATLAB® R2016b, and Review Manager v5.3 (The Nordic Cochrane Centre, Rigshospitalet 2008).

Results

Data from 782 patients across 36 case series were analyzed (Table 1). No randomized or controlled trials were identified. The overall seizure freedom rate after repeat epilepsy surgery was 47% and did not change significantly over time (r = 0.14, p = 0.33) (Figure 2). Table 2 displays all summary data. Patient demographics displayed in Table 2a were not significantly associated with outcome. Factors found to be potentially associated with positive outcome after repeat surgery during preliminary analysis included abnormal imaging (p=0.03), congruent electrophysiology data (p<0.01), predominantly focal onset seizures with impaired awareness (i.e. complex-partial seizure) semiology (p=0.01), surgery-related limitation as the cited reason for failure of initial surgery (p<0.01), lesional pathology (p<0.01), temporal lobe resection in the initial surgery (p=0.04), and temporal lobe resection in the final surgery (p<0.01) (Table 2). The use of invasive monitoring correlated with a worse outcome (p<0.01). The presence of generalized seizures showed a trend toward worse outcomes, but this association did not reach statistical significance (p=0.08).

Formal meta-analysis was conducted on factors identified as potentially predictive of outcome (Figure 3). Higher odds of seizure freedom after a repeat surgery were identified with congruent over non-congruent electrophysiological data (OR 3.6, 95% CI 1.6–8.2), lesional over non-lesional epilepsy (OR 3.2, 95% CI 1.9–5.3), and surgical limitations over disease-related factors as the cited reason for failure of the initial surgery (OR 2.6, 95% CI 1.3–5.3). For patients with at least one of these positive factors, the rate of seizure freedom increased to 58% (N = 282 out of 485). The use of invasive monitoring was associated with worse outcome (OR 0.4, 95% CI 0.2–0.9). Temporal lobe over extratemporal/multilobe (OR 1.5, 95% CI 0.8–3.0) and abnormal over normal pre-operative MRI (OR 1.9, 95% CI 0.6–5.4) showed non-significant trends toward better outcomes. Meta-analysis was unable to be conducted for seizure semiology due to a paucity (<4) eligible studies.

Reported complications across all studies included neurological deficits (e.g. weakness, visual field cut, aphasia), vascular injury (e.g. hemorrhage, stroke), infection, and cerebrospinal fluid (CSF) disturbances (e.g. CSF leak, pseudomeningocele, or hydrocephalus). There were no short term surgical mortalities reported from repeat surgeries. When reported, complication rates varied widely across studies, as shown in Table 3.

Discussion

Medically refractory epilepsy is a debilitating disease and can be particularly challenging to treat after an initial surgical intervention has failed. Existing data to help select candidates for repeat surgery have been limited to small case series and reviews[19–22]. Here, our group

analyzed outcomes from 782 patients across 36 case series to provide the first quantitative meta-analysis of seizure outcomes following repeat epilepsy surgery. We found that 47% of patients across the literature achieved seizure freedom after further resection – a percentage higher than appreciated in a recent review[19]. We also found these outcomes to be positively correlated with electrophysiological congruency, lesional epilepsy, and surgical limitations as the cause of initial surgical failure. For patients who have at least one of these predictors, the seizure freedom rate after repeat surgery increased to 58%. It should be noted that this percentage does not include Engel II outcomes, which some consider a good result[58]. While temporal lobe surgery and MRI abnormalities were positively associated with seizure freedom in summary analysis, these traits did not reach statistical significance in quantitative meta-analysis. Similarly, predominantly focal onset seizures with impaired awareness showed a favorable association but was unable to undergo formal meta-analysis due to a paucity of studies with patients in both categories (seizure free and not seizure free, with and without predominantly focal onset seizures with impaired awareness). Perhaps intuitively, the amalgam of the attributes that predict seizure freedom here resemble those that predict good outcomes for an initial surgical resection[59]. Poorer outcomes were seen in patients who required invasive monitoring, possibly because this intervention is pursued in the more challenging cases. Ultimately, our findings demonstrate a previously underappreciated efficacy of repeat surgery in properly selected patients and supports evaluation for further surgical resection in patients who have failed an initial operation.

Predictors of Successful Repeat Surgery

Our group's analysis demonstrated higher odds of seizure freedom in patients with lesional pathology, electrophysiological congruence, and surgical limitations as the cited reason for failure of the initial surgery. While the predictive value of the first two factors seems intuitive, not all studies have found them to be associated with favorable outcome[36,40]. The third factor, cited reasons for failure of the primary surgery, was divided into "surgical limitations" and "disease-related factors" for our analysis. Surgical limitations included reasons that implied an incomplete initial resection, such as errors in preoperative planning (e.g. wrong diagnosis or incomplete characterization of epileptogenic focus), overlap of functional and epileptogenic zones preventing complete resection, sub-optimal execution of surgical plan (e.g. sub-total resection), and regrowth or recurrence of a lesion (which also implies a sub-total resection). Disease-related factors suggested failure due to disease processes that maybe too widespread or evolving to cure, including emergence of new epileptiform areas postoperatively and widespread, multifocal, progressive, or bilateral disease (including palliative surgeries). The categorization of each result into the two groups relied completely on the description provided by the authors of the cited studies. While these two categories admittedly contain some overlap, the overall purpose of the dichotomy was to divide patients with foci that may have been amenable to complete resection were it not limited by surgical/diagnostic factors from those who have disease processes that may never be amenable to complete resection. The finding that surgical limitations portend higher odds of success with a repeat resection than disease-related factors is consistent with findings from Ramantani et al. and Sacino et al. demonstrating that when functional limitations prevented a complete primary resection, patients had better outcomes after further surgery[46,48]. Munari et al. have suggested that persistent seizures after resection of eloquent

epileptogenic regions may not always represent a true failure, if the intent is a palliative operation aimed at reducing seizure frequency or severity[43]. Ultimately, our result illustrates the principle that those with epileptogic foci amenable to complete resection have a greater chance of success from a second surgery than those with progressive disease that may never be completely resected.

Factors Not Predictive of Outcome

Gender, epilepsy duration, age at either surgery, time between resections, laterality of resections, and seizure generalization showed no statistically significant association with outcome (although seizure generalizations did show a non-significant trend toward worse outcomes). While summary data suggested a significant association between temporal lobe resection and MRI abnormalities with better outcomes, formal meta-analysis did not demonstrate significant relationships for either of these variables. The lack of a clear distinction between temporal and extratemporal outcomes may be due to underappreciated heterogeneity in the temporal group, as it has been reported in multiple studies that the discovery of extratemporal epileptogenic foci (i.e. "temporal-plus" epilepsy) is correlated with initial surgical failure[24,60–62]. Therefore, failed temporal lobe-only resections may be due an inaccurate classification of temporal lobe epilepsy in these patients. Furthermore, after a temporal lobe resection, whether residual mesiotemporal structures cause continued seizures is not clear, as there is evidence for[63–65] and against[24,47,66] this finding. This makes it difficult to focus the target of re-resection after a failed temporal lobe resection. Ramos et al. argue that failure after temporal lobe surgery is most likely due to dual pathological entities, scar tissue, or contralateral temporal epileptogenesis, and that incomplete resection of the epileptogenic zones in the form of residual hippocampus is not the most likely cause for surgical failures[47]. Similarly, Hennessey et al. suggest that extrahippocampal or extratemporal epileptogenesis accounts for the majority of temporal surgical failures, regardless of the underlying pathology[60]. Abosch et al. argue that failure of selective amygdalohippocampectomy is usually because patients were improperly identified as having unilateral temporal lobe epilepsy[24]. Even so, the latter authors still include inadequate resection of mesial structures in their differential diagnosis of a failed resection. Furthermore, epileptogenic structures found surrounding the resection may have arisen postoperatively[47] or were always present but not properly resected[24,63] – a topic that remains in debate[67].

Unfortunately, there was not enough disaggregated data to formally address the question of whether residual temporal structures on a postoperative MRI predicts success of a secondary surgery. Similarly, while abnormal MRIs showed an association with seizure freedom in our summary data, meta-analysis did not find a significant difference. This, too, is likely due to the heterogeneity of the abnormal MRI group. The fact that lesional versus non-lesional epilepsy did show significance whereas abnormal versus normal MRI did not suggests that the underlying pathology is more prognostic. In our analysis, abnormal MRIs included some cases that were considered non-lesional (e.g. mesiotemporal sclerosis [MTS] and cortical dysplasia [CD]), thus creating enough of an overlap to diminish its significance (see above discussion regarding temporal lobe epilepsy). González-Martínez et al. suggest that MTS and CD are the most likely pathologies to be associated with dual pathology, hence leading

to worse outcomes after surgery[32]. There is also evidence that CD is associated with worse outcomes in temporal lobe epilepsy[4]. This is consistent with our finding that non-lesional epilepsy (which included these pathologic diagnoses in our analysis) portends lower odds for success than its counterpart. Although some studies classify focal CD and nodular heterotopias as lesional[34,54], our group did not because it was often difficult to tell which CDs were focal versus widespread, and CD was often part of a dual pathology or presented at distant locations. Ultimately, the lack of significant association with outcome for abnormal MRIs and temporal resections may be due to the confounders explored in this section, or simply a result of underpowering.

Predictors of Failed Repeat Surgery

Previously cited predictors of poor outcome after repeat epilepsy surgery have included: distant or multifocal epileptiform discharges (i.e. widespread disease)[30,46,51,52], history of encephalitis after 4 years of age[36], inadequate second surgery (e.g. lesional excision or volume of temporal lobe taken)[36,51], pathology consistent with CD or MTS[32], recurrent or new epileptiform areas despite adequate achievement of primary surgical targets[52], history of central nervous system (CNS) infection[36], history of traumatic brain injury (TBI)[40], and palliative procedures[52]. Most of these variables were not reported at a high enough rate to be quantitatively analyzed in our study. However, odds of negative outcomes were higher with the use of invasive monitoring and a disease-related failure in the initial surgery. The former association is controversial in the literature. While some studies suggest that invasive recording is associated with a higher rate of primary surgical seizure failure[50,68], other studies advocate for its necessity[34,52,57,69–71]. The most likely explanation for invasive monitoring's association with worse outcomes is its use in more complex cases. In some cases, invasive monitoring may enable surgery to be performed on patients who would otherwise not be considered surgical candidates. Some authors argue that lack of invasive monitoring during an initial surgery leaves room for improvement on the repeat surgery, thus predicting a successful reoperation[52]. Therefore, our data suggest that if the first surgery failed despite the use of invasive monitoring and due to disease-related factors, caution should be taken when considering a second intervention.

Morbidity and Complications

The overall complication rate of repeat epilepsy surgery was most recently reported as 13.5%[19], but as we have shown, it varies greatly across studies (Table 3). For example, Germano et al. published a series where 39 of 40 patients had no neurological complications, and one patient experienced only temporary worsening of preoperative visual deficit[30]. Awad et al. and Holmes et al. report 0% complication rates[25,36]. However, Bower et al. cite a complication rate as high as 50% including cases of hydrocephalus causing pseudomeningoceles requiring shunt placement (mostly after functional hemispherectomies)[28], and Ramantani et al. report that 57% of their patients had some form of adverse event[46]. The large discrepancy in complication rate is most likely related to the breadth of surgical interventions offered. If primary surgeries failed due to an overly conservative resection, a higher risk of neurological deficits such as visual field cuts, motor weakness, or aphasias might be expected from repeat, larger resections that extend into eloquent areas to control exceptionally difficult seizures[46]. Neurocognitive decline after

secondary surgery has been reported as well, but it is also often followed by late neurocognitive improvements in patients who ultimately achieve seizure freedom[34,40,45]. Of note, there was no acute surgical mortality reported in any of the studies reviewed.

Reasons for Failure of Initial Surgery

Defining failure for epilepsy surgery can be challenging and should be analyzed on an individual basis and in the context of the patient and family's expectations and goals. A broad definition of surgical failure might be the return to a state of medically intractable seizures, or a non-achievement of preoperative goals. While not all postoperative seizures predict true failure[9], there is some evidence that latency to first seizure is related to long-term outcome in temporal lobe epilepsy[72]. Current evidence suggests that having 2 unprovoked seizures within 6 months of surgery and recurrence of ipsilateral epileptiform discharges on a 6 month postoperative evaluation constitutes a very high probability (>95%) of continuing into persistent medically refractory seizures[73]. Therefore, it is reasonable to consider a second surgery on this subset of patients.

Study Limitations

The use of retrospective studies in meta-analyses contains many inherent limitations.[74] In our case, although data from 782 patients were utilized, not all variables were reported for each patient. Therefore, each analysis comprised only a subset of the total study population. For example, data regarding secondary seizure generalization were available in 145 (18.5%) patients, predominant seizure type in 206 (26.3%) patients, MRI findings in 196 (25.1%) patients, electrophysiological congruency in 192 (24.6%) patients, invasive monitoring in 210 (26.9%) patients, pathology in 507 (65%) patients, initial surgical location in 447 (57.2%) patients, final surgical location in 496 (63.4%) patients, and reason for failure of initial surgery in 283 (36.2%) patients (see Table 2). The inconsistent availability of variables of interest across reports is a limitation inherent to any meta-analysis of previously published studies, and it is important to consider when interpreting our results. Furthermore, drawing conclusions from data across multiple case series is always subject to a positive skew from publication bias, as positive results may be more likely to be published than negative ones. However, in the absence of a prospective, randomized, controlled trial, these methods allow us to capture the largest amount of data possible to quantitatively analyze potentially prognostic relationships between variables of interest and patient outcomes after repeat epilepsy surgery. Unfortunately, only two randomized, controlled studies of epilepsy resection exist[75,76], and no controlled studies of repeat epilepsy surgery have ever been performed. Pursuing further randomized, controlled trials in epilepsy surgery remains a valuable future goal.

Additionally, this analysis contains patients, epileptologists, and surgeons from different countries and training backgrounds who utilize different diagnostic modalities and techniques. The included studies span over 30 years, an epoch that has seen advances in MRI techniques, positron-emission tomography (PET) scans[62], AEDs, surgical practices, and knowledge of disease entities[77,78], all of which can affect outcomes. However, our analysis found no significant trend in outcomes over time (Figure 2). To further ensure that the reported results were not skewed by older data, we repeated our analysis using only

studies from the past 20 years and found no notable differences. It should also be noted that, while this study analyzes repeat surgery for epilepsy, it does not directly compare these results to other treatment modalities, such as medication adjustments or VNS.

Furthermore, there was a great deal of heterogeneity in the electrophysiological work-ups reported across studies. Unfortunately, available data were insufficient to separately analyze ictal versus non-ictal, invasive versus non-invasive, and subdural versus stereo-EEG data in a meaningful way. Thus, combining information allowed us to assess for any evidence of localized or non-localized findings across electrophysiological studies reported, which may provide some insight into the importance of overall electrophysiology congruency in predicting outcome. Therefore, conclusions related to individual electrophysiological exams cannot be made from our data, making it an important focus for future studies.

Conclusion

Here we provide the first quantitative meta-analysis of rates and predictors of seizure freedom following repeat epilepsy surgery. Freedom from disabling seizures (Engel I outcome) was observed in 47% of patients after repeat surgery, a rate higher than the previously reported 37%[19]. Additionally, this rate increased to 58% in patients who had a least one factor associated with a favorable outcome. The higher rate of success found in our analysis compared to historically reported values[19] may be due to the inclusion of more patients and newer studies, or the exclusion of patients undergoing non-resective procedures like VNS or callosotomies. Significant predictors of seizure freedom in these patients resembled those for initial epilepsy surgery[59], and included lesional over non-lesional epilepsy, congruent over non-congruent EEG data, and surgical over disease-related factors as the cited reason for failure of the first surgery. Invasive monitoring was associated with worse outcomes, and temporal lobe resections and abnormal MRIs trended toward better outcomes but did not reach statistical significance. Ultimately, these data support considering a repeat resection in patients who fail an initial intervention, especially in the setting of predictors of a favorable response.

Acknowledgments

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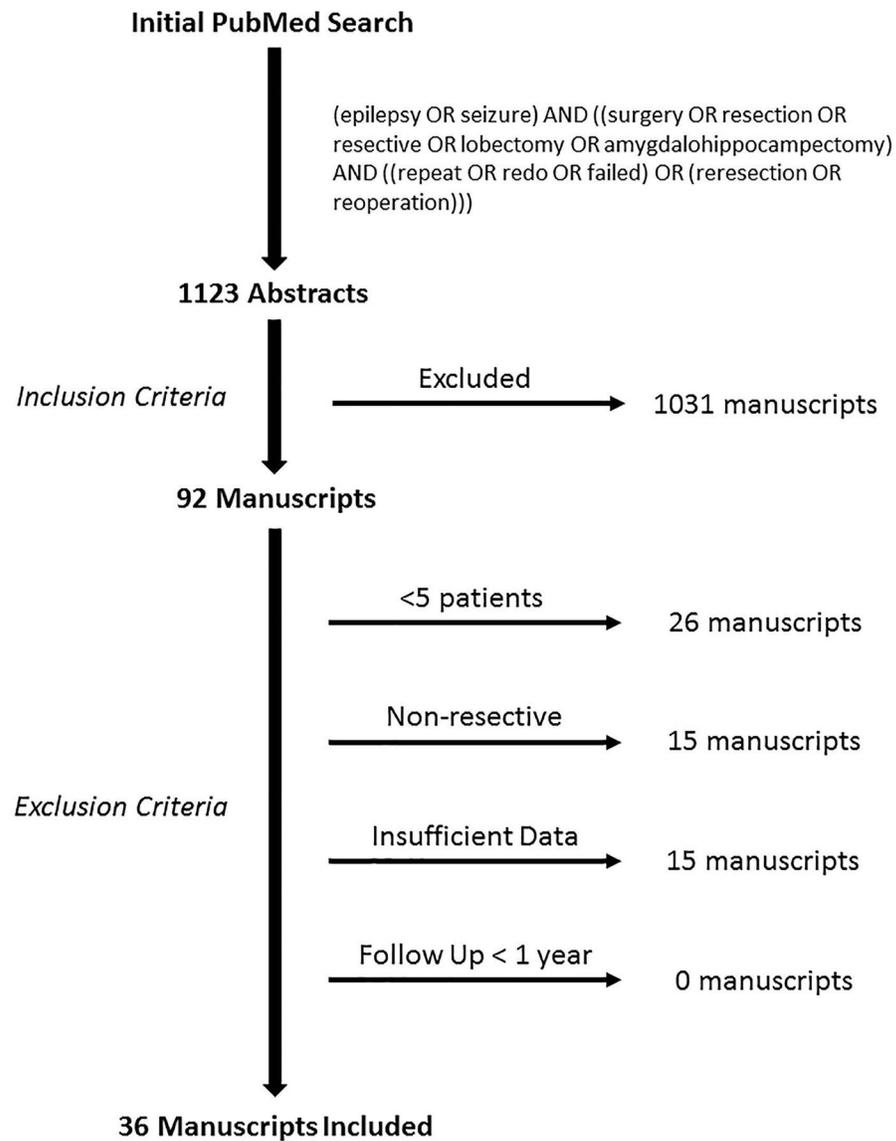
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Key Points

- Medically refractory epilepsy is particularly challenging to treat after an initial surgical resection has failed

- Here we present the first quantitative meta-analysis of 30 years of literature to assess for rates and predictors of seizure freedom after reoperation

- Predictors of seizure freedom include lesional over non-lesional pathology and all congruent over any non-congruent electrophysiological data

- If the initial surgery failed due to surgical limitations versus disease-related factors, there are better odds of seizure freedom after reresection

- Invasive monitoring portends a worse outcome; abnormal MRIs and temporal lobe-only resections show non-significant trends toward seizure freedom

Initial PubMed Search

(epilepsy OR seizure) AND ((surgery OR resection OR
resective OR lobectomy OR amygdalohippocampectomy)
AND ((repeat OR redo OR failed) OR (reresection OR
reoperation)))

1123 Abstracts

Inclusion Criteria   Excluded   1031 manuscripts

92 Manuscripts

                              <5 patients   26 manuscripts

                              Non-resective   15 manuscripts

Exclusion Criteria

                              Insufficient Data   15 manuscripts

                              Follow Up < 1 year   0 manuscripts

36 Manuscripts Included

Figure 1.
Literature search guided by PRISMA[23].
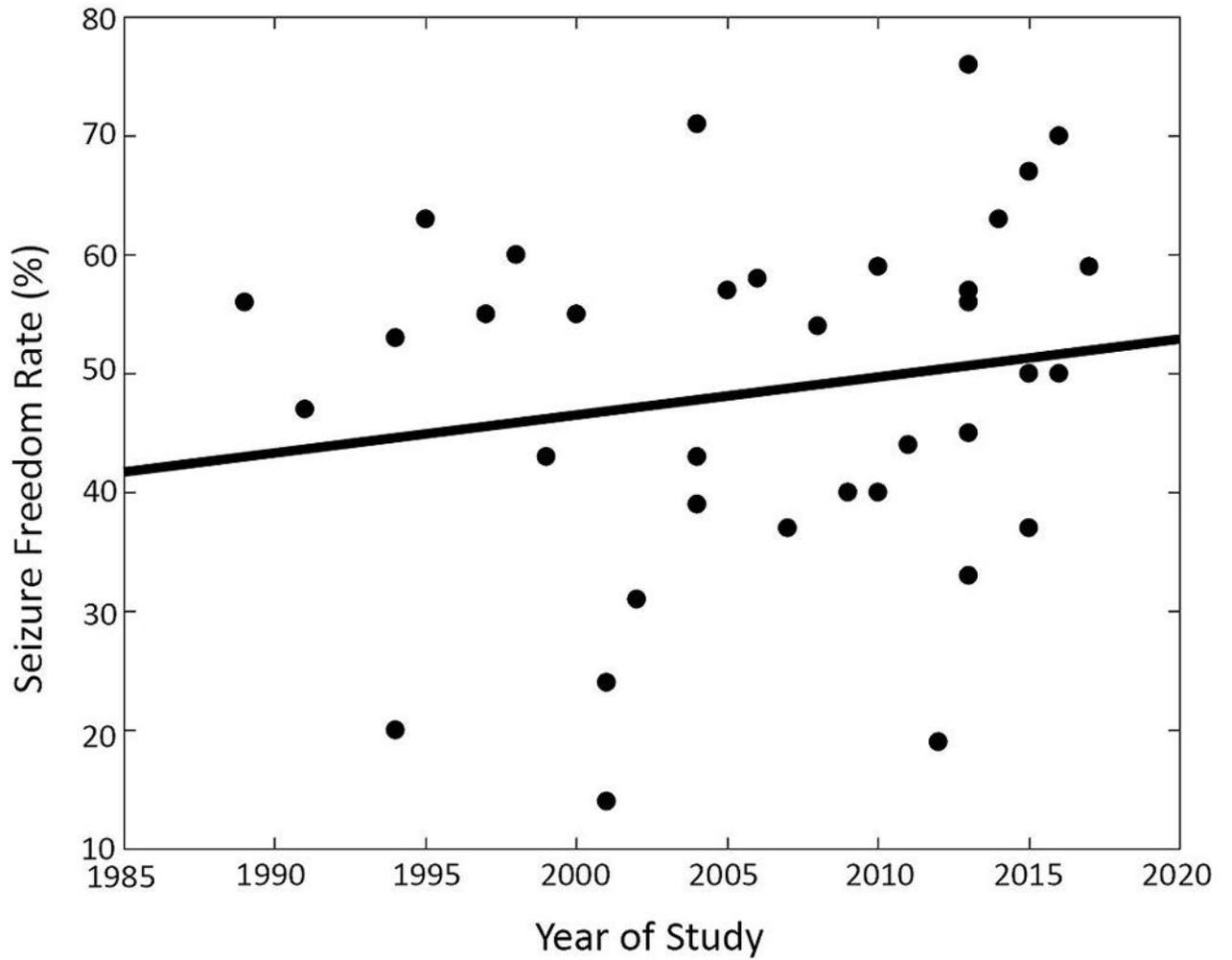
Figure 2.
Reported seizure free rates of repeat epilepsy surgeries over time. Linear regression revealed no significant trend (r = 0.14, p = 0.33).
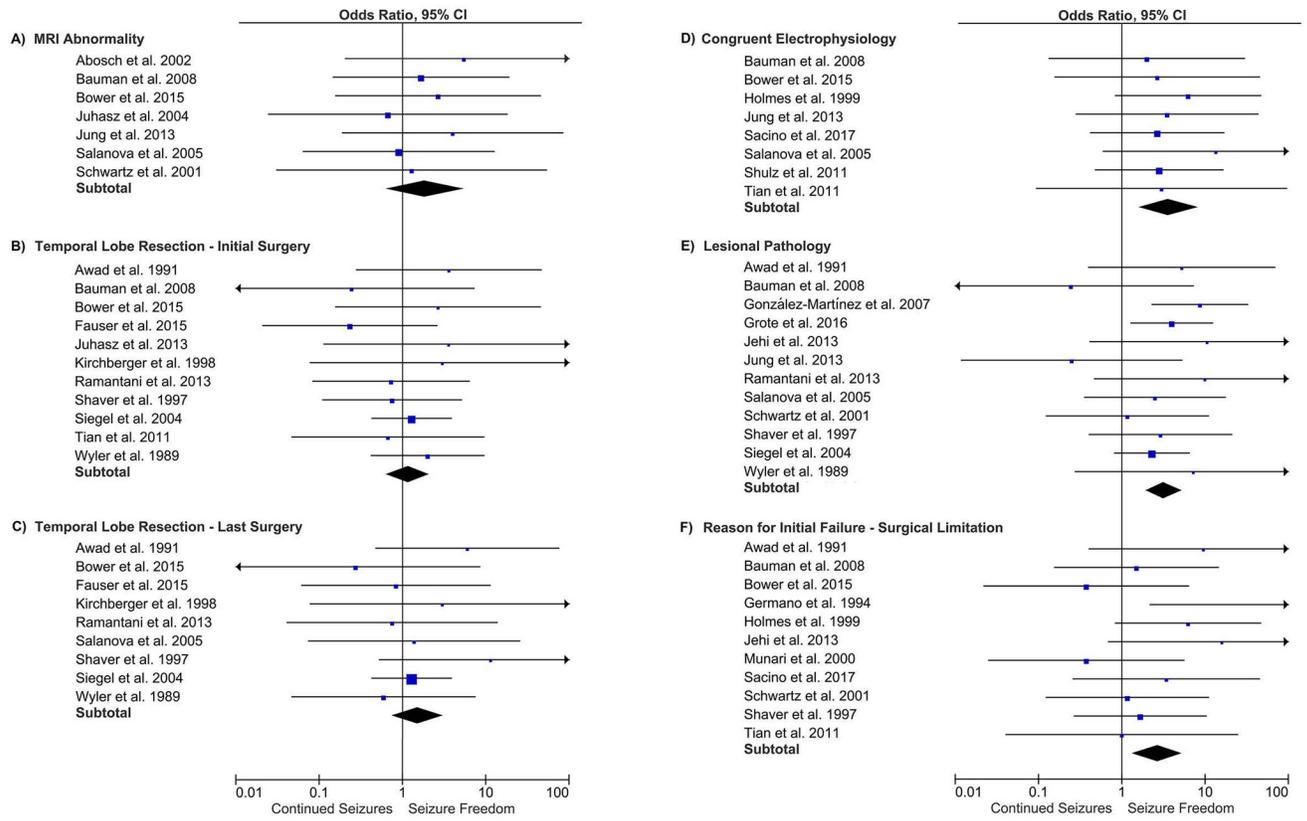
Figure 3.
Forest plots showing meta-analysis results.

Table 1

Included Studies

First Author	Year	Patients
Abosch[24]	2002	13
Awad[25]	1991	15
Benifla[26]	2006	12
Bauman[27]	2008	13
Bower[28]	2015	10
Englot[6]	2014	16
Fauser[29]	2015	19
Germano[30]	1994	40
Goellner[31]	2013	11
Gonzalez-Martinez[32]	2007	57
Greiner[33]	2016	30
Grote[34]	2016	66
Hallbook[35]	2013	21
Holmes[36]	1999	21
Jehi[37]	2010	15
Jooma[38]	1995	8
Juhasz[39]	2004	7
Jung[40]	2013	17
Kirchberger[41]	1998	5
Koh[42]	2004	14
Munari[43]	2000	42
Otsuki[44]	2013	9
Pati[45]	2011	14
Ramantani[46]	2013	23
Ramos[47]	2009	5
Ryzi[7]	2015	6
Sacino[48]	2017	22
Salanova[49]	1994	35
Salanova[50]	2005	21
Schulz[51]	2011	22
Schwartz[52]	2001	17
Shaver[53]	1997	20
Siegel[54]	2004	64
Tian[55]	2011	9
Vadera[56]	2012	36
Wyler[57]	1989	27
Total		**782**

Table 2

Postoperative seizure outcomes stratified by patient characteristics

			Engel I	Engel II–IV	P value
	Total		369 (47%)	413 (53%)	
A) Demographics	Gender	Female	31 (56%)	24 (44%)	0.56
		Male	44 (52%)	41 (46%)	0.64
	Age of seizure onset, years (mean ± SEM)		7.1 ± 0.9 N = 78	6.6 ± 0.9 N = 67	0.57
	Age at initial surgery, years (mean ± SEM)		15.9 ± 1.3 N = 105	14.9 ± 1.3 N = 89	0.48
	Age at last surgery, years (mean ± SEM)		16.8 ± 1.4 N = 87	15.4 ± 1.3 N = 77	
B) Epilepsy characteristics	Pathology	Lesional	95 (61%)	62 (39%)	< 0.01 *
		Non-Lesional	145 (41%)	205 (59%)	
	Secondary seizure generalization	Yes	22 (38%)	36 (62%)	< 0.08
		No	46 (53%)	41 (47%)	
	Predominant seizure type	FOIA	54 (51%)	51 (49%)	0.01 *
		FOA	38 (45%)	46 (55%)	
		Other	2 (12%)	15 (88%)	
	Duration of epilepsy, years (mean ± SEM)		12.3 ± 1.9 N = 36	8.5 ± 1.9 N = 24	0.18
C) Diagnostics	MRI findings prior to 1st surgery	Normal	18 (35%)	34 (65%)	0.03 *
		Abnormal	76 (53%)	68 (47%)	
	Electrophysiology	Congruent	87 (69%)	39 (31%)	< 0.01 *
		Incongruent	31 (47%)	35 (53%)	
	Invasive Monitoring	Used	67 (52%)	61 (48%)	< 0.01 *
		Not used	62 (76%)	20 (24%)	
D) Surgical factors	Time between resections, years (mean ± SEM)		3.1 ± 0.3 N = 96	3.0 ± 0.3 N = 92	0.83
	Resection location – initial surgery	Temporal	94 (49%)	99 (51%)	0.04 *

		Engel I	Engel II–IV	P value
Resection location – last surgery	Extratemporal	99 (39%)	155 (61%)	
	Temporal	129 (54%)	112 (47%)	< 0.01 *
	Extratemporal	95 (37%)	160 (63%)	
Side of initial surgery	Left	47 (48%)	50 (52%)	0.26
	Right	68 (56%)	53 (48%)	
Side of last surgery	Left	46 (49%)	47 (51%)	0.34
	Right	65 (55%)	51 (45%)	
Reason for failure of initial surgery	Surgical limitation	100 (50%)	102 (50%)	< 0.01 *
	Disease-related	23 (32%)	48 (68%)	

*
Statistically significant value (p 0.05).

Data are reported as N values (with corresponding percent) unless otherwise indicated. SEM = standard error of the mean; FOIA = focal onset with impaired awareness (i.e. complex partial); FOA = focal onset aware (i.e. simple partial); MRI = magnetic resonance imaging.

Table 3

Complication Rates in Repeat Epilepsy Surgery

First author	Year	No. Patients	Overall Complication Rate	Neurological Complication Rate	Non-neurological Complication Rate
Awad	1991	15	0%	0%	0%
Bower	2015	10	50%	10%	40%
Germano	1994	40	8%	3%	5%
Gonzalez-Martinez	2007	57	11%	9%	2%
Grote	2016	66	29%	20%	9%
Holmes	1999	21	0%	0%	0%
Ramantani	2013	23	57%	44%	13%
Sacino	2017	22	36%	32%	5%
Salanova	1994	35	36%	36%	0%
Schulz	2011	22	9%	9%	NR
Shaver	1997	20	20%	10%	10%
Siegel	2004	64	20%	16%	5%
Tian	2011	9	22%	0%	22%
Vadera	2012	36	14%	0%	14%
Wyler	1989	27	11%	11%	0%

NR = not reported