BACKGROUND
CHAPTER 1

BACKGROUND

1.1 IMPACT OF MEDICALLY REFRACTORY EPILEPSY

Epilepsy affects approximately 1% (point prevalence in 2009) of the total population (i.e. 50 million people) and is classified as the most common serious neurological disorder by the World Health Organization ("Epilepsy fact sheet," 2011; Reynolds, 2002). The estimated proportion of the general population with active epilepsy is between 4 and 10 per 1000 people ("Epilepsy fact sheet," 2011). In developing countries, this is estimated between 6 and 10 per 1000 people ("Epilepsy fact sheet," 2011). The annual incidence rate is between 40 and 70 per 1000 people in developed countries and almost twice as high in developing countries ("Epilepsy fact sheet," 2011). Epilepsy is more prevalent in childhood with about 700 affected per 100,000 (twice as common than in adults) (Moshe, 2000; Neville, Chin, & Scott, 2007). Seizures tend to decrease in severity and frequency with age. Patients with epilepsy are at a threefold higher risk of cognitive decline as compared to the general population (Dodson, Kinsbourne, & Hitbrunner, 1991). In addition, epilepsy is associated with significant psychosocial harm including social isolation, depression and stigmatization (Baker et al., 1998).

In the United States, the direct average cost of epilepsy is $10,000 a year for patients with uncontrolled epilepsy and $2,000 a year for patients with controlled epilepsy.
The annual indirect costs for approximately 2.3 million prevalent cases are $12.5 billion; costs are eightfold higher in patients with intractable epilepsy (Begley et al., 2000; King, Sperling, Justice, & O’Connor, 1997; Silvenius, 2000). A Canadian modelling study suggested that epilepsy surgery in children is associated with a higher immediate cost that becomes cheaper (5% discounting accounted for) than medical therapy after 14 years due to the number of seizure-free patients and the decreased cost of drug therapy (Keene & Ventureyra, 1999).

1.2 TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis complex (TSC) is a genetic, variably expressed and multisystem disorder with a prevalence of 1 in 10,000 (Wiederholt, Gomez, & Kurland, 1985). It results from mutations in 1 of 2 genes, TSC1 on chromosome 9p34 which codes for hamartin and TSC2 on chromosome 16p13 which codes for tuberin (Curatolo, Bombardieri, & Jozwiak, 2008). The TSC1/TSC2 complex plays an important role in cortical development and growth control. Mutation in one or both of these genes results in dysregulated cell size control, abnormal differentiation and cellular migration (Napolioni, Moavero, & Curatolo, 2009).

TSC is one of the leading causes of genetic epilepsy with seizures affecting almost 90% of children (Curatolo, et al., 2008). These seizures often begin in the first year of life as infantile spasms which are commonly treated with Vigabatrin. After a period of remission, focal seizures usually return in late childhood and are often
severe and unremitting (Sugita et al., 1985). Only a third of these patients will achieve seizure freedom with antiepileptic drugs (AEDs) (Chu-Shore, Major, Camposano, Muzykewicz, & Thiele, 2010). Neurodevelopmental delay and cognitive dysfunction are strongly linked to early seizure onset, perhaps due to frequent seizures hindering normal development through childhood (O'Callaghan et al., 2004).

1.3 DETERMINATION OF SURGICAL CANDIDACY

In privileged parts of the world, children who remain with medically refractory epilepsy may be referred to a regional epilepsy surgery center to determine surgical candidacy (Ibrahim et al., 2012). The primary goal of the presurgical workup is to localize the epileptogenic zone (EZ) (i.e. the cortex that generates the epileptic seizures the removal or disconnection of which will result in seizure freedom), and the surrounding eloquent cortex to ensure that resective surgery can be done safely without creating new neurological deficits. The ideal candidate for surgery has convergent clinical, electroencephalographic (EEG) and magnetic resonance imaging (MRI) data. Various ancillary tests are available to help localize the EZ: video electroencephalography (vEEG), interictal Alpha-methyl-l-tryptophan-positron emission tomography (PET), ictal single-photon emission computed tomography (SPECT) and magnetoencephalography (MEG)/magnetic source imaging (Chandra et al., 2006; Jacobs et al., 2008; Jansen et al., 2006; Jansen, van Huffelen, Bourez-Swart, & van Nieuwenhuizen, 2005; Wu et al., 2006). Even when multiple tubers are
present, the epileptogenic activity can often be localized to 1 or 2 tubers (Bye, Matheson, Tobias, & Mackenzie, 1989).

If an EZ associated with one or more tubers in non-eloquent cortex can be localized, resective surgery may be offered; the remaining children may be candidates for palliative surgical procedures (i.e. insertion of a vagal nerve stimulator or corpus callosotomy) or the ketogenic diet. With resective surgery, 57% of children achieve seizure freedom and another 18% experience a reduction (>90%) in seizure frequency at 1-year follow-up (Jansen, van Huffelen, Algra, & van Nieuwenhuizen, 2007). Other benefits include the possibility of decreasing or discontinuing AEDs, ability to obtain/retain employment, ability to drive, improved independent functioning and improved social relationships with family and friends.

1.4 RISKS OF PEDIATRIC EPILEPSY SURGERY

Resective surgery, however, still leaves a large proportion of children (>40%) who have incurred the risks of brain surgery, with ongoing seizures. In general, complications of resective epilepsy surgery can be divided into surgical complications (infection, hemorrhage, cerebral edema, hydrocephalus, arterial or venous vascular compromise) and neurological impairment as a result of injury to eloquent brain (hemiparesis, hemiplegia, visual field deficit, aphasia, alexia and neuropsychological impairment resulting in deficits in cognition, memory, language, concentration and attention) (Gonzalez-Martinez & Bingaman, 2008).
Approximately 3% of patients suffer major surgical morbidity (Behrens, Schramm, Zentner, & Konig, 1997; Spencer & Huh, 2008). Mortality rates, including early postoperative death (secondary to hemorrhage, infection and hydrocephalus) and late postoperative death (unexplained or related to seizures) are between 1 to 2% (Nashef, Fish, Garner, Sander, & Shorvon, 1995; Spencer & Huh, 2008; Vining et al., 1997; Wyllie et al., 1998). Patients with TSC often undergo a diagnostic surgery, insertion of an invasive EEG, to more accurately localize the EZ prior to determination of resective epilepsy surgery candidacy; this is associated with infection and subdural hematoma formation which may lead to neurological deficits, intracranial hypertension and even death (Cahan et al., 1984).

1.5 CLINICAL PROBLEM

To date, there is no predictive instrument for seizure outcomes in patients with TSC undergoing resective epilepsy surgery. This makes surgical patient selection challenging and results in less informed discussions between the physicians and parents/child.

1.6 LITERATURE REVIEW

1.6.1 COHORT STUDIES

Small retrospective cohort studies (Range: 17 to 22 participants) have suggested that less developmental delay and concordance of EEG and MRI abnormalities may be associated with a greater chance of seizure freedom following resective surgery
Guerreiro et al.’s multicenter retrospective study of 18 participants has the following limitations: 1) MRI, which is now considered part of the routine investigations prior to undertaking advanced imaging techniques to determine surgical candidacy, was performed only on some participants (Guerreiro, et al., 1998); and 2) The cohort includes participants who have undergone palliative epilepsy surgery and has a variable follow-up length - as little as 1 month in some participants (Guerreiro, et al., 1998).

Lachhwani et al. reported their institutional experience using contemporary techniques of presurgical work-up (Lachhwani, et al., 2005). They concluded that EEG and MRI concordance is a predictor of good seizure outcomes. They did not find an association between age at time of surgery with seizure outcomes (Lachhwani, et al., 2005). Although this may be true, the somewhat arbitrarily chosen dichotomy of children less than 12 years of age compared to children over 12 years of age may hide the true effect of age. This may have also occurred due to the study being underpowered to find the effect of age at time of surgery on postoperative seizure outcomes.

A multicenter retrospective study identified younger age at seizure onset, a history of infantile spasms and interictal focality (unilateral vs. bilateral) predictive of a poor seizure outcome (Madhavan et al., 2007). Seizure outcomes in this study were
dichotomized to Engel Class I and Engel Class II to IV. The classification of Engel Class II as a poor seizure outcome may not be widely accepted by most epileptologists and epilepsy surgeons (Madhavan, et al., 2007). In addition, age at seizure onset was dichotomized to greater than 12 months and less than 12 months with no justification for the chosen cut-point (Madhavan, et al., 2007). Infantile spasms but not interictal focality remained a statistically significant predictor of seizure outcomes in multivariate analysis (Madhavan, et al., 2007).

1.6.2 SYSTEMATIC REVIEWS

A meta-analysis of 47 articles comprising 3336 adults and 175 children identified febrile seizures and EEG/MRI concordance as predictors of good seizure outcomes, and use of invasive EEG as a predictor of poor seizure outcomes (Tonini et al., 2004). This study included participants with all epilepsy syndromes, had a predominantly adult population and a large representation of mesial temporal sclerosis, a distinct epilepsy syndrome with favourable surgical outcomes. Therefore, there is minimal transferability of this knowledge to patients with TSC. Tonini et al. identified several limitations of undertaking studies in this field: largely retrospective study designs, variable follow-up lengths of studies, scarcity of pre-operative seizure data, absence of blinding in outcome assessors and forced dichotomization of variables (Tonini, et al., 2004). Nevertheless, it successfully identified variables of prognostic significance for resective epilepsy surgery.
A systematic review of predictors of seizure outcomes following epilepsy surgery for TSC identified the presence of tonic seizures, moderate or severe intellectual disability (IQ<70) and multifocal SPECT findings as significantly associated with seizure recurrence (Jansen, van Huffelen, Algra, et al., 2007). This first attempt at summarizing the relevant literature has important limitations: studies were not evaluated for risk of bias, p value for statistical significance was set at 0.05 despite the large number of predictors that were tested, seizure outcomes were pooled and analyzed by the last reported outcome (i.e. not adjusted for the variable follow-up length), participants with less than 1 year follow-up (i.e. inadequate follow-up) were included in the analysis, and participants who had undergone palliative surgical procedures were also included in the analysis (the goal of palliative epilepsy surgery is not seizure freedom).

1.7 RESEARCH QUESTION

We performed an individual participant data (IPD) meta-analysis addressing the following study question:

‘Among children with Tuberous Sclerosis Complex and intractable epilepsy undergoing resective epilepsy surgery, what variables are independently associated with good seizure outcomes?’
INDIVIDUAL PARTICIPANT DATA META-ANALYSIS
CHAPTER 2

METHODS

2.1 STUDY POPULATION

The population of interest is children (under 19 years of age at the time of surgery) who have medically intractable epilepsy, TSC and have undergone resective epilepsy surgery with the preoperative goal of seizure freedom. This includes tuberectomies, lobectomies, multilobar resections and hemispherectomies. We did not exclude studies based on geographic location or time.

Participants who have undergone palliative surgical procedures such as insertion of vagal nerve stimulators or corpus callosotomy were not included in this study as these are not intended to cure seizures. We also excluded participants who have undergone previous epilepsy surgery or present with status epilepticus or epilepsia partialis continua as they are more likely to have a poor seizure outcomes and likely represent a clinically different population.

2.2 DESCRIPTION OF STUDY OUTCOME

Our primary outcome was seizure status following resective epilepsy surgery. We dichotomized the outcome into ‘Good seizure outcome’ (i.e. Engel Class I or II) and ‘Poor seizure outcome’ (i.e. Engel Class III or IV) at the last reported follow-up time (Appendix A) (Jehi, Martinez-Gonzalez, & Bingaman, 2010). This method captures a clinically important distinction as patients with Engel Class I or II outcomes are
generally considered as having had a successful operation (van der Heide et al., 2010). The Engel instrument is the most commonly used instrument to determine postoperative seizure burden. However, the 4-tiered classification system is based on expert opinion and not an evidenced-based approach. The cutpoints between various Engel Classes are arbitrarily chosen. If Engel Classification was not stated in the manuscript but a description of the seizure outcome was used, we translated this information into an Engel Class using Appendix A as a guide. We adjusted for the variable length of follow-up using a multivariate regression model.

2.3 TYPE OF STUDY DESIGN USED

IPD meta-analysis is recognized to be the gold standard methodology for conducting meta-analysis (Stewart & Tierney, 2002). It will allow us to: 1) Address questions not addressed in the original publications (e.g. determining predictors of outcomes in a study that had an alternative objective); 2) Use common definitions, coding and cutpoints; 3) Ensuring accuracy of aggregate study data; 4) Account for the variability in clinical follow-up times; and 5) Enhance statistical power in identifying participant covariates that predict seizure outcomes.

2.4 QUALIFICATIONS OF REVIEW TEAM

The literature search strategy was designed in consultation with 2 experienced academic librarians (Laura Banfield and Neera Bhatnagar). Our reviewers had clinical epidemiology expertise (Shanil Ebrahim), neurosurgical expertise (George
Ibrahim, Alireza Mansouri) or both (Aria Fallah, Deven Reddy). The investigators of our research team have content expertise (James Rutka - pediatric epilepsy surgeon); (Carter Snead – pediatric epileptologist), and methodological/statistical expertise (Gordon Guyatt – clinical epidemiology, IPD meta-analysis); (Mohit Bhandari – clinical epidemiology, surgical outcome studies); (Abhaya Kulkarni – clinical epidemiology, surgical outcome studies); (Stephen Walter – biostatistics).

2.5 INFORMATION SOURCES AND SEARCH STRATEGY

We used multiple strategies to identify potentially eligible studies: 1) We conducted electronic literature searches of MEDLINE, EMBASE, CINAHL and Web of Science (Appendix B) for relevant articles. These databases were chosen based on the greatest likelihood to cite the relevant articles for our review and upon the recommendation of the two consulting information specialists (Laura Banfield and Neera Bhatnagar). We used the following search terms: “tuberous sclerosis”, “epilepsy surgery”, “seizure outcomes”, “Engel classification”, “predictors”. The search was restricted to humans but with no time or language limitations (Articles not in English were translated); 2) One reviewer (Aria Fallah) hand searched all abstracts of the American Epilepsy Society, American Neurological Association, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Canadian Neurological Sciences Federation and European Association of Neurosurgical Societies meetings from 2000 to 2011 for any relevant unpublished literature; and 3) a manual search of the bibliography of our included studies as well
as using the “related articles” feature of PubMed were performed. The search was completed on October 15th, 2011.

2.6 INCLUSION CRITERIA

Articles were included if they met the following criteria:

[1] Case-control or cohort methodology
[2] Consecutive participants
[3] At least 90% of participants are less than 19 years of age at the time of surgery
[4] At least 90% of participants have TSC
[5] At least 90% of participants have undergone resective epilepsy surgery
[6] Seizure outcomes reported
[7] When etiology is not reported in the title or abstract for a pediatric cohort of greater than 10 participants undergoing resective epilepsy surgery, a full-text review of these articles was performed to determine if they met eligibility criteria

2.7 EXCLUSION CRITERIA

Articles were excluded if they met the following criteria:

[1] Single case reports
[2] Reviews
[3] Only participants with anomalous features. (This was determined on an individual study basis through discussion by both reviewers. No standardized definition was used.)
Only participants who have undergone previous epilepsy surgery

Only participants who have undergone resective epilepsy surgery while in status epilepticus or epilepsia partialis continua

Only participants with normal MRI

Only participants who have undergone palliative surgical procedures (i.e. corpus collosotomy, multiple subpial transection or vagal nerve stimulator insertion)

Mixed adult and pediatric epilepsy surgery studies that do not mention TSC in the title and abstract

2.8 ARTICLE SCREENING

Two teams, each consisting of 2 reviewers, 1 with methodological expertise (graduate students in clinical epidemiology) (Shanil Ebrahim, Aria Fallah, Deven Reddy) and 1 with content expertise (neurosurgery residents) (Aria Fallah, George Ibrahim, Deven Reddy, Alireza Mansouri) screened in duplicate and independently the titles and abstracts of identified citations for potential eligibility. Prior to conduct of full screening, pilot training exercises in 200 article aliquots were performed to ensure at least substantial agreement was achieved (Kappa >0.61) (Cyr & Francis, 1992). Disagreements were resolved through discussion. We obtained the full text of citations judged as potentially eligible.
The reviewers independently and in duplicate applied the eligibility criteria to full texts. The reviewers checked agreement (calibration exercises were performed in 3 to 5 article aliquots) and resolved disagreements through discussion.

2.9 EFFORT TO INCLUDE ALL AVAILABLE STUDIES
Any article that was identified as eligible for full-text review was retrieved using the University of Toronto, McMaster University or Hospital for Sick Children library. Articles that were unavailable in electronic format were retrieved in photocopied format through interlibrary loans. If the article was still unavailable, we attempted to electronically contact the corresponding author for study data.

Two reviewers (Aria Fallah and George Ibrahim) independently attempted to obtain the corresponding author or co-author's electronic mailing address before we marked an article as 'unable to retrieve'.

2.10 SEARCH SOFTWARES USED
Reviewers performed title and abstract screening, full text review and data abstraction in ‘RefWorks’ and ‘Endnote X5’ softwares.

2.11 USE OF HAND SEARCHING
Handsearching of included articles was performed by one reviewer to identify additional eligible studies. We also reviewed the included studies of the only systematic review on this topic (Jansen, van Huffelen, Algra, et al., 2007).

2.12 LIST OF CITATIONS LOCATED AND THOSE EXCLUDED
We maintained a list of all citations as well as those articles that were excluded after full text review. We also maintained a list of reasons for excluding articles upon full text review.

2.13 METHOD OF ADDRESSING ARTICLES PUBLISHED IN LANGUAGES OTHER THAN ENGLISH
We did not impose any language restrictions for the conduct of this systematic review. We had two strategies to address articles published in languages other than English: 1) We attempted to find a translator for the article; 2) We attempted to contact the corresponding author in order to obtain the relevant information in English. We excluded articles if we were unsuccessful at both.

2.14 METHOD OF HANDLING ABSTRACTS
We contacted primary authors of eligible abstracts through electronic mail to obtain IPD. If this failed, we contacted any other co-author through electronic mail to obtain the same. If this was unsuccessful, we excluded the abstract.
2.15 SELECTION AND CODING OF DATA
We recorded all preoperative factors reported in the articles that may plausibly predict seizure outcomes at an individual participant level. A list of biologically plausible predictors was developed \textit{a priori} using a small set or articles in consultation with our content experts (James Rutka and Carter Snead) (Appendix C). We recorded continuous data where appropriate to minimize discarding of potentially important quantitative information.

Data abstraction was performed by one author (Aria Fallah) and verified by a second author (Alireza Mansouri), using predefined data fields. When necessary, corresponding authors of the studies were contacted for clarification of unclear data, missing data or inconsistencies. Data received from corresponding authors was checked for 1) missing data; and 2) plausibility. Participants with missing outcome data (i.e. length of follow-up and Engel classification) were excluded. We planned to contact authors to clarify implausible data.

2.16 ASSESSMENT OF RISK OF BIAS
Two reviewers (Aria Fallah and George Ibrahim) independently and in duplicate evaluated the risk of bias of each included study (Appendix 3). We evaluated 5 criteria with response options as “definitely yes”, “probably yes”, “probably no” and “definitely no”. ‘Definitely yes’ and ‘probably yes’ responses were assigned a ‘low
risk of bias’ while ‘definitely no’ and ‘probably no’ were assigned a ‘high risk of bias’. Reviewers resolved all disagreements through discussion.

2.17 ASSESSMENT OF HETEROGENEITY

We aimed to assess heterogeneity through two methods: 1) Using a Forest plot; and 2) Calculating the $I^2$ statistic from the Cochran Q. An $I^2$ score of 0% to 40% was considered as “might not be important”; 30% to 60% as “may represent moderate heterogeneity”; 50% to 90% as “may represent substantial heterogeneity” and; 75% to 100% as “considerable heterogeneity” (Deeks, Higgins, & D.G., 2008). The importance of the $I^2$ value depended on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity) (Deeks, et al., 2008). If heterogeneity was greater than 30%, we planned to conduct the following subgroup analyses at the study level to explain heterogeneity: risk of bias (low, moderate or high) and availability of IPD (studies with IPD or studies without IPD).

2.18 PUBLICATION BIAS

We intended to assess publication bias (i.e. small studies and those studies that demonstrate exceptionally poor or good seizure outcomes are potentially less likely to be published) for each potential predictor using two techniques: 1) Visual assessment for symmetry in a funnel plot; and 2) A funnel plot regression using the treatment effect as the dependent variable and the reciprocal of the pooled variance for each study as the independent variable (Macaskill, Walter, & Irwig, 2001).
2.19 STATISTICAL METHODS

We calculated Cohen's Kappa to determine the strength of agreement for full-text review, using a computer software (Measurement of clinical agreement for categorical data: The Kappa Coefficients by Louis Cyr and Kennon Francis, 1992) with the following thresholds for interpretation: <0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and >0.81 as almost perfect agreement.

For continuous data, we reported median, interquartile range and total range. For dichotomous outcomes, we reported frequencies and percentages. We excluded independent variables with less than 20 observations per value from inferential statistics. We log transformed non-normally distributed continuous variables. We performed a bivariate logistic regression for each eligible independent variable, adjusting for the length of follow-up by including this in the multivariate regression model. We reported our findings using odds ratios (OR), 95% confidence intervals (CI) and p values. Data permitting, we planned a multivariable analysis including adjustment for the study effect to identify independent predictors of outcome. We set the alpha level for accepting statistical significance at 0.05.

2.20 TABLES AND FIGURES
We created a PRISMA 2009 flow diagram to track the process of article identification, screening, eligibility and inclusion. We also created a histogram to present the proportion of participants at each Engel Class at the time of last follow-up. Tables were created to describe study characteristics, assessment of risk of bias, descriptive statistics and inferential statistics for potential predictor variables.
CHAPTER 3

RESULTS

3.1 ARTICLE IDENTIFICATION

We identified 9863 citations from our electronic database search of Medline, Embase, CINAHL and Web of Science with duplicates removed (Figure 1). We identified 30 additional citations after reviewing conference abstracts. We reviewed 241 articles in full text (unweighted Kappa = 0.55; 95% CI 0.50-0.60; moderate strength of agreement in selecting articles for full text review). We included 20 articles reporting on 185 participants (181 participants had seizure outcome data and were used in the meta-analysis). Appendix E presents the excluded articles after full text review, with reasons for exclusion.

We obtained IPD in 20 of the eligible 25 articles (80%) (Aboian et al., 2011; Asano et al., 2000; Avellino, Berger, Rostomily, Shaw, & Ojemann, 1997; Baumgartner et al., 1997; Bebin, Kelly, & Gomez, 1993; Guerreiro, et al., 1998; Jansen, et al., 2006; Jansen et al., 2007; Kagawa et al., 2005; Kamimura et al., 2006; Karenfort, Kruse, Freitag, Pannek, & Tuxhorn, 2002; Koh et al., 2000; Lachhwani, et al., 2005; Liang et al., 2010; Major et al., 2009; Perot, Weir, & Rasmussen, 1966; Teutonico et al., 2008; van der Heide, et al., 2010; Weiner et al., 2006; Wen et al., 2009). This includes 3 articles comprising of 32 participants, for which we obtained IPD after contacting the corresponding authors. We unsuccessfully contacted authors of 5 additional articles to obtain IPD. We did not contact any authors for implausible or missing data after
receiving IPD. One hundred and twenty-six (70%) of participants achieved a good surgical outcome (i.e. Engel Class I or II) (Figure 2). The median duration of follow-up was 2.3 years (IQR=1.3-4.3). Table 1 and 2 present the summary descriptive statistics for all independent variables. We excluded size of predominant tuber, invasive interictal and ictal evaluation, PET, SPECT and MEG findings due to the low frequency of observations per variable (n<20).

3.2 STUDY CHARACTERISTICS

*Descriptive information for each study included*

There were a total of 20 studies with 3 to 25 participants per study (Table 1). The majority of these studies were performed in the United States of America (10) followed by Netherlands (3), Canada (2), China (2) Germany (1) and Japan (1). Another study included participants both from Italy and USA. The predictors that were most commonly reported include age at surgery (17 studies), presence of infantile spasms (15 studies) and presence of moderate/severe developmental delay (14 studies). Most studies performed tuberectomy/lobectomies and multilobar resections (8), followed by tuberectomy/lobectomy alone (4), tuberectomy/lobectomy, multilobar resection and hemispherectomy (2), and multilobar resection alone (1). Five studies did not report the type of operations that were performed. Nine studies reported outcomes with at least 1 year of follow-
up following surgery while the other 11 studies included participants with less than 1 year follow-up data.

All studies were judged to have high confidence in outcome assessment (Table 2). Confidence in outcome assessment was based on participants having frequent postoperative visits. Nineteen studies were thought to have a representative sample of participants and 17 studies were thought to have well-defined prognostic variables as well as standardized surgical strategies. We assessed representativeness of participants by evaluating whether children were deemed medically refractory and had undergone a resective epilepsy procedure with the goal of seizure freedom. We assessed standardization of treatment by determining whether there was a change in diagnostic tool availability or epilepsy surgeon throughout the study. Thirteen studies were judged to report adequate follow-up.

3.3 PREDICTORS OF OUTCOME

3.3.1 STATISTICALLY SIGNIFICANT PREDICTORS OF OUTCOME

Table 5 presents the OR, 95% confidence interval and p-value for each variable from our logistic regression analyses. Due to the small sample sizes of individual studies (median: 7; range 3-25 patients), and the variable inclusion of predictors across studies, we were unable to conduct a multivariable analysis or adjust for study effects. When adjusting for length of follow-up, statistically significant predictors of
good seizure outcomes following resective epilepsy surgery in TSC included absence of generalized seizure semiology (OR=3.1; 95% CI=1.2-8.2, p=0.022), no or mild developmental delay (OR=7.3; 95% CI=2.1-24.7, p=0.001), unifocal scalp ictal EEG abnormality (OR=3.2; 95% CI=1.4-7.6, p=0.008) and EEG/MRI concordance (OR=4.9; 95% CI=1.8-13.5, p=0.002).

3.3.2 ASSESSMENT OF COVARIATION BETWEEN STATISTICALLY SIGNIFICANT PREDICTORS OF OUTCOME

From the four predictors identified, it is clinically plausible that Unifocal scalp ictal EEG abnormality could demonstrate covariation with EEG/MRI concordance and Absence of generalized seizure semiology. Multivariable regression including Unifocal scalp ictal EEG abnormality, EEG/MRI concordance and duration of follow-up demonstrated these variables as independently predictive of seizure outcome (Unifocal scalp ictal EEG abnormality OR=4.1, 95% CI=1.2-14.1, p=0.024; EEG/MRI concordance OR=4.1, 95% CI=1.2-13.8, p=0.022). Similarly, multivariable regression including Unifocal scalp ictal EEG abnormality, Absence of generalized seizure semiology and duration of follow-up demonstrated these variables as independently predictive of seizure outcome (Unifocal scalp ictal EEG abnormality OR=5.4, 95% CI=1.3-22.6, p=0.020; Absence of generalized seizure semiology OR=4.2, 95% CI=1.1-16.3, p=0.036). The data did not allow us to enter all four predictors of seizure outcomes in the multivariable model.
3.4 ASSESSMENT OF HETEROGENEITY

Assessment of heterogeneity using Forest plots may involve unreliable odds ratios and confidence intervals. This issue was discussed at a biostatistical meeting at McMaster University. The summary estimates were thought to be misleading as we were underpowered to calculate a study effect. A minimum number of participants are required by study to have a reliable summary effect. We decided not to report the heterogeneity plots given these limitations.

3.5 ASSESSMENT OF PUBLICATION BIAS

For the same reasons mentioned above, we were unable to address publication bias.
CHAPTER 4
DISCUSSION

In our review of 20 studies, 56% of participants with TSC undergoing resective epilepsy surgery achieved Engel Class I outcomes and another 13% Engel Class II outcomes. We identified absence of generalized seizure semiology, no or mild developmental delay, unifocal scalp ictal EEG abnormality and EEG/MRI concordance as predictive factors of good seizure outcome.

4.1 GENERALIZED SEIZURE SEMIOLOGY

Generalized seizure semiology may be associated with a poor seizure outcome following resection as it may indicate a widespread epileptic network in the brain that may not be amenable to a focal resection. Alternatively, generalized seizure semiology may result from focal epilepsy that spreads very rapidly to both cerebral hemispheres. Generalized seizure semiology may make the determination of the epileptogenic zone more challenging and often times misleading. It is plausible that the absence of generalized seizure semiology is associated with a unifocal scalp ictal EEG abnormality. However, multivariable regression demonstrated that these two variables were independently associated with seizure outcome.

4.2 NO OR MILD DEVELOPMENTAL DELAY

Patients with a lower IQ often have a more severe form of epilepsy compared to those with normal intelligence. Intellectual disabilities are more often associated
with bilateral or diffuse brain damage and therefore, more likely to have multifocal or diffuse epilepsy. Contrary to this review, Gleissner et al. suggest that when adjusting for the severity of epilepsy, children who are intellectually disabled, learning disabled and those with normal intelligence have similar seizure outcomes following surgery (Gleissner, Clusmann, Sassen, Elger, & Helmstaedter, 2006). They suggest that the decision to operate on a child with a low level of intelligence should not be different than those with normal intelligence as long as the EZ can be confidently localized and that the resection of which does not result in an unacceptable neurological deficit. However, the vast majority of children in their study had neuronal migrational disorders, tumours and mesial temporal sclerosis. Therefore, the finding of this study is not easily transferable to our study. Whether or not developmental delay predicts a poor response following surgery should be evaluated in future studies.

One explanation for children with no or mild developmental delay experiencing improved seizure outcomes may be due to the ease in accurately localizing the EZ. These children may be better at describing the seizure semiology (e.g. auras) and for epileptologists to classify their seizure disorder. Therefore, this may be a confounding factor and the true predictive factor being, the degree of difficulty in identifying the EZ. Failure to perform multivariate analysis precludes controlling for confounding.
4.3 UNIFOCAL SCALP ICTAL EEG ABNORMALITY

Since the seizure onset zone is the cortical area responsible for generation of the seizures and is closely related to the EZ, identification of this area consistently during VEEG monitoring may facilitate accurate localization and resection with confidence that seizures are not being generated elsewhere in the brain. However, it is well known that tubers that were not previously epileptogenic may become epileptogenic once other epileptogenic tuber(s) are resected. In this scenario, unifocal scalp ictal EEG abnormality may not predict a good seizure outcome. Extrapolating this to unifocal invasive ictal EEG abnormality should be done cautiously for 2 reasons: 1) Children who undergo invasive EEG evaluation are likely more challenging in determination of the EZ. This presents a selection bias; and 2) invasive EEG evaluation requires a hypothesis of the location of the EZ which if incorrect, could result in misleading conclusions. This represents a sampling error as invasive EEG evaluation only records from selected cortical areas. We were unable to conclude the predictive value of invasive ictal EEG abnormality for seizure outcomes as we were underpowered.

4.4 EEG/MRI CONCORDANCE

When an EEG abnormality spatially corresponds to a tuber, there is a greater likelihood that resection of that tuber will result in seizure freedom. However, due to the difference in spatial resolution between an EEG and MRI, it may be difficult to attribute an EEG abnormality to a particular tuber. This becomes especially
problematic when there are multiple tubers. As the number of tubers increase, it becomes increasingly likely to conclude EEG/MRI concordance on the basis of a focal EEG abnormality. However, multivariable regression demonstrated that these two variables were independently associated with seizure outcome. In this study, we examined the concordance of ictal EEG findings to MRI. Perhaps the positive predictive value of a good outcome would be different if concordance between interictal EEG and MRI was examined. Last, we did not record instances of EEG abnormality with other imaging modalities such as PET and SPECT. To determine the predictive value of EEG concordance with these imaging modalities, long term studies with a large sample are required.

4.5 STUDY STRENGTHS

Strengths of this review include: 1) We developed our study protocol in advance of conducting the review; 2) We developed and performed a comprehensive search; 3) We did not exclude studies based on language of publication or date of publication; 4) We obtained individual data and performed an IPD meta-analysis; and 5) We adjusted for the length of follow-up, thereby eliminating bias that would have resulted if putative predictive variables were associated with length of follow-up.

4.6 STUDY LIMITATIONS

The review also has limitations: 1) Although an exhaustive search strategy was utilized, it is possible that some studies were not identified due to inappropriate
indexing or errors in screening. Given this, we screened articles in duplicate and independently. Also, we attempted to identify studies for inclusion also through reviewing the bibliography of other relevant articles. Inaccurate indexing of articles could compromise the validity of our results. The previous review did not publish their search strategy; 2) Non-standardized reporting affects the validity of data abstraction and assessment of risk of bias. Although we performed these tasks in duplicate, the extent to which this was inaccurate could compromise the validity of our results; 3) There is a lack of recognized criteria for assessment of bias in prognostic cohort studies. This required us to develop and utilize our own instrument which was not validated. Therefore, we may have missed other important criteria to assess, failed to appropriately evaluate criteria which we identified as important or evaluated a criteria that may not be important for assessment of bias. No attempt was made by the previous review to assess risk of bias; 4) Criteria for surgical acceptability as (a worthwhile chance of seizure freedom) may have differed between centers and co-varied with predictive factors; 5) Failure to obtain IPD from 5 studies after contacting the corresponding author. The surgical outcomes of these studies may have differed from other studies for which IPD was available thus presenting a selection bias. The authors of the previous review did not contact studies to obtain IPD; and 6) The data did not allow us to perform multivariable regression to ascertain whether variables were independently predictive. Therefore, we were unable to state whether the predictors we identified in univariate analysis are independently predictive of
seizure outcomes. Given these limitations, cautious interpretation is required in applying the findings of this study to patient care.

4.7 SOURCES OF BIAS

There are two potential sources of bias:

1) Determination of surgical candidacy and operative plan: The determination of surgical candidacy, technique and risks of surgery is a complex process requiring multidisciplinary collaboration. The groups’ recommendation is presented to the child and/or parent who must ultimately be willing to accept the risks of the proposed operation in hopes of attaining a good seizure outcome. The intricacies of management decision, although based on similar principles of epilepsy surgery, are variable at each center, influenced by individual patient values and preferences, and too complex to be accurately captured from retrospective observational studies.

2) Degree of resection of the EZ: an extensive resection of the EZ is associated with better seizure outcomes than a subtotal resection of the EZ. Degree of resection was difficult to ascertain accurately as it was not consistently reported in studies. However, it is reasonable to assume that an extensive resection of the EZ was performed in almost all cases for the following reasons: 1) it is not justifiable to plan a subtotal resection of the EZ if the preoperative goal is attaining seizure freedom; and 2) the vast majority of surgical cases go according to plan. We excluded cases that were documented to not have had a complete surgical resection of the hypothesized EZ from this review.
4.8 ASSESSMENT OF QUALITY OF INCLUDED STUDIES

Generally, the studies had low risk of bias with respect to sample representativeness and outcome assessment. There was moderate risk of bias with respect to well defining prognostic variables, adequacy of length of follow-up and standardization of treatment (Table 2). However, assessment of risk of bias should be interpreted cautiously as we did not validate the assessment tool that we developed. Also, as these characteristics were inconsistently reported in articles, we were frequently required to make inferences regarding the risk of bias.

Future observational studies aimed at determining predictors of seizure outcome in surgery for TSC should explicitly state their methodology in selecting surgical candidates to allow comparison between studies, report on consecutive participants to minimize selection bias, collect data prospectively to ensure accuracy, in duplicate and independently to minimize errors, report greater than 1 year follow-up data and prepare their manuscript in concordance to the MOOSE criteria (Stroup et al., 2000).

4.9 APPROPRIATENESS OF STUDIES ASSEMBLED FOR ASSESSING THE HYPOTHESIS

A requirement for reliable prognostic studies is to choose a cohort of participants who are relatively similar with respect to stage of their disease. In this study,
selecting participants who are medically refractory and have undergone resective epilepsy surgery will satisfy this criterion. However, this excludes an important group of patients: those with medically refractory epilepsy who are deemed to be poor candidates for resective surgery who either undergo a palliative surgical procedure or do not undergo surgery. Therefore, it is important to note that the participants we identified are likely deemed to have at least a ‘worthwhile’ chance to have a satisfactory seizure outcome after surgery. To the extent that criteria for resectability differ across centers could compromise the generalizability of the results.

One study, was conducted in the pre-MRI era and prior to the advances of modern micro-neurosurgical technique, therefore it is of questionable value to include it (Perot, et al., 1966). Since an a priori decision was not made to exclude old studies, we chose to include it in our analysis. We did perform a post-hoc sensitivity analysis (not presented) that did not affect the conclusions of this review. We also limited inclusion to studies that at least 90% of the participants had TSC. We did not have the resources to identify and extract data from articles that had a significant number of participants with TSC which did not comprise at least 90% of the study sample. This approach may have provided additional useful information.

4.10 COMPARISON TO PREVIOUS LITERATURE
The systematic review by Jansen et al. of 170 participants also reported on IPD obtained from full-text review of the articles. However they did not contact authors when IPD was not available. Although 10 of their articles were also included in our review, the participant composition is different as we selectively chose participants within articles to be included in the review. For example, they included participants who had undergone a corpus callosotomy (Guerreiro, et al., 1998) or had a pathological diagnosis other than TSC (Bebin, et al., 1993). They excluded participants from studies for unclear reasons (Avellino, et al., 1997). Similar to this review, they identified that moderate or severe developmental delay was associated with poor seizure outcomes (Jansen, van Huffelen, Algra, et al., 2007). The point estimate for no or mild developmental delay predicting a good seizure outcome was lower: OR=4.1 (Jansen et al.) vs. OR=7.3 (current study). However in contrast to our review, the authors found no statistically significant difference with respect to generalized seizure semiology and unifocal scalp ictal EEG abnormalities and seizure outcome (Jansen, van Huffelen, Algra, et al., 2007). The authors did not evaluate EEG/MRI concordance as a potential predictor of seizure outcome (Jansen, van Huffelen, Algra, et al., 2007).

4.11 ALTERNATIVE EXPLANATIONS FOR OBSERVED RESULTS

The variables we identified, and their associated ORs, may represent an appropriate accounting of the optimal variables for predicting response to surgery. There may, however, be other variables that were either not collected or not well-reported in
the studies that may be more powerful variables predictive of seizure outcomes. We may also have been misled by the play of chance. Dealing with the former limitation requires each relevant study to collect data on all possible predictors. With respect to the latter limitation, spuriously positive findings are extremely unlikely given the low p values obtained for three of the variables (no or mild developmental delay, unifocal scalp ictal EEG abnormality and EEG/MRI concordance). Dealing with both limitations requires a larger sample size.

Given the non-uniform reporting of variables, our power in determining the significance of predictor variables varied across outcomes. For example, we were less powered to determine the significance of MEG abnormality, interictal invasive EEG abnormality and ictal invasive EEG abnormality compared to age at surgery and degree of developmental delay.

4.12 GENERALIZATION OF THE FINDINGS

Given our study's limitations, it may be unwise to use this data in isolation to counsel patients for or against undertaking epilepsy surgery. Serious consideration against resective epilepsy surgery should be made in a situation where there are multiple predictors of poor seizure outcome present. Similarly, multiple predictors of good seizure outcome may warrant the healthcare team to strongly advocate for surgical candidacy provided the EZ is identified and its resection is safe. However, the predictive power of each (and multiple) predictor(s) should be analyzed using a
a receiver operating characteristic analysis. Our findings can serve as a platform for hypothesis testing in future observational studies.

Currently, given the low quality of evidence, determining surgical candidacy should be based primarily of the experience of the epilepsy team while considering the results of this study. The individual success and risks of surgery should be quoted based on institutional experience.
FUTURE DIRECTIONS
CHAPTER 5

FUTURE DIRECTIONS AND DISCLOSURE OF FUNDING SOURCES

5.1 GUIDELINES FOR FUTURE RESEARCH

From this literature review, we have discovered several important challenges in identification of predictors of seizure outcomes in children with TSC who undergo resective epilepsy surgery. The two most important are: 1) Rare incidence of disease preclude the conduction of a feasible single-center prospective trial (Observational studies are superior to clinical trials in identification predictors of outcome); and 2) Variability between centers in determining epilepsy surgery candidacy. A large long-term, prospective multicenter observational study is warranted to further evaluate predictors of seizure outcomes. The population of interest would be children (18 years of age or younger) with TSC and medically refractory epilepsy who are being considered for epilepsy surgery. It is equally important to follow participants who do not undergo resective epilepsy surgery in addition to those who undergo resective epilepsy surgery. A small percentage of participants who do not undergo resective epilepsy surgery will eventually be seizure-free with additional AED trials. Determining variables associated with this outcome would also inform selection of surgical candidacy. The variables that predict a poor surgical outcome may not overlap with those that predict a good outcome with medical therapy. The variables to be studied would be best determined using the results of this study as well as a survey of an expert panel of epileptologists and epilepsy surgeons. Based on the variables selected for study, an
a priori sample size calculation should be performed. Prospective and consecutive enrolment of participants at participating centers should be performed until the target sample size is achieved. The results should be analyzed using time-to-event (event defined as seizure recurrence after the first postoperative week not including auras) methodology to account for the variable length of follow-up. Given the variability in available technology for selecting surgical candidates, experience of the epilepsy team and the epilepsy surgeon, the determination of surgical candidacy and the operative plan must be centrally adjudicated and be statistically adjusted for factors that cannot be controlled across centers.

5.2 DISCLOSURE OF FUNDING SOURCE

There was no funding source or other support for the conduct of this systematic review.
REFERENCES


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10.1016/S0140-6736(08)61279-9


range intelligence. [Comparative Study]. *Epilepsia, 47*(2), 406-414. doi: 10.1111/j.1528-1167.2006.00436.x


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10.1212/01.WNL.0000160389.93984.53


EPI2669 [pii]


10.1111/j.1528-1167.2007.01112.x


FIGURES AND TABLES
Figure 1. PRISMA 2009 Flow Diagram

Records identified through database searching
- Medline (n = 4752)
- Embase (n = 7264)
- CINAHL (n = 217)
- Web of Science (n = 656)

Additional records identified through conference abstracts (n = 30)

Records with duplicates removed (n = 9863)

Records screened (n = 9863)

Records excluded after title and abstract screening (n = 9624)

Full-text articles excluded (n = 221) for:
- Some patients (n = 7)
- Case report (n = 2)
- Less than 90% TSC (n = 190)
- No seizure outcome data available (n = 3)
- Patients with anomalous features (n = 1)
- No surgery (n = 1)
- Editorial (n = 2)
- Abstract only (n = 5)
- Duplicate publication (n = 5), eligible study based on abstract could not obtain IPD (n = 5)

Full-text articles assessed for eligibility (n = 241)

Studies included in qualitative synthesis (n = 20)

Studies included in quantitative synthesis (meta-analysis) (n = 20)
Figure 2. Engel Classification of participants with TSC undergoing resective epilepsy surgery
**Table 1.** Characteristics of included studies

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>No. of patients</th>
<th>Age at surgery range (years)</th>
<th>Study Location</th>
<th>Predictors reported*</th>
<th>Type of surgery performed</th>
<th>Range of follow-up duration (y)</th>
<th>Seizure free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboian (2011)</td>
<td>6</td>
<td>0.7-13.0</td>
<td>USA</td>
<td>b, d, e, f, h, i, j, k, l</td>
<td>Tuberecctomy/lobectomy Multilobar resection</td>
<td>2.0-9.5</td>
<td>3/6 (50%)</td>
</tr>
<tr>
<td>Asano (2000)</td>
<td>7</td>
<td>1.1-9.4</td>
<td>USA</td>
<td>a, d, e, f, i, j, l</td>
<td>N/A</td>
<td>0.3-2.3</td>
<td>5/7 (71%)</td>
</tr>
<tr>
<td>Avellino (1997)</td>
<td>8</td>
<td>3.0-46.0*</td>
<td>USA</td>
<td>a, b, e, f, h, i, j, l</td>
<td>Tuberecctomy/lobectomy Multilobar resection</td>
<td>0.7-10.6</td>
<td>4/8 (50%)**</td>
</tr>
<tr>
<td>Baumgartner (1997)</td>
<td>4</td>
<td>5.0-13.0</td>
<td>USA</td>
<td>a, b, c, d, e, f, h, i, j, k, l, o, p</td>
<td>Tuberecctomy/lobectomy Multilobar resection</td>
<td>1.0-11.0</td>
<td>1/4 (25%)</td>
</tr>
<tr>
<td>Bebin (1993)</td>
<td>7</td>
<td>0.8-19.7</td>
<td>USA</td>
<td>d, e, f, l</td>
<td>Tuberecctomy/lobectomy</td>
<td>0.8-6.0</td>
<td>5/7 (71%)</td>
</tr>
<tr>
<td>Guerreiro (1998)</td>
<td>11</td>
<td>1.7-54.0</td>
<td>Canada</td>
<td>a, b, d, e, f, g, h, i, j, k, l</td>
<td>Tuberecctomy/lobectomy Multilobar resection</td>
<td>0.1-47.0</td>
<td>8/11 (67%)**</td>
</tr>
<tr>
<td>Heide (2010)</td>
<td>6</td>
<td>2.0-29.0</td>
<td>Netherlands</td>
<td>b, c, d, e, f, i, j, k, l</td>
<td>Tuberecctomy/lobectomy Multilobar resection</td>
<td>2.8-7.0</td>
<td>4/6 (67%)</td>
</tr>
<tr>
<td>Jansen (2006)</td>
<td>3</td>
<td>6.0-20.0</td>
<td>Netherlands</td>
<td>b, c, d, e, f, g, h, i, l, n, o</td>
<td>N/A</td>
<td>2.0-4.0</td>
<td>2/3 (67%)</td>
</tr>
<tr>
<td>Jansen (2007)</td>
<td>6</td>
<td>3.0-36.0</td>
<td>Netherlands</td>
<td>b, c, d, e, f, i, j, k, l, n, o</td>
<td>Tuberecctomy/lobectomy Multilobar resection</td>
<td>1.2-6.3</td>
<td>4/6 (67%)</td>
</tr>
<tr>
<td>Kagawa (2005)</td>
<td>17</td>
<td>0.3-12.3</td>
<td>USA</td>
<td>a, b, d, f, i, j, k, l, p</td>
<td>Tuberecctomy/lobectomy Multilobar resection</td>
<td>0.4-4.8</td>
<td>12/17 (71%)</td>
</tr>
<tr>
<td>Kamimura (2006)</td>
<td>3</td>
<td>2.0-24.0*</td>
<td>Japan</td>
<td>a, c, d, e, f, k</td>
<td>N/A</td>
<td>3.0 (mean)</td>
<td>3/3 (100%)</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>N</td>
<td>Range</td>
<td>Country</td>
<td>Predictors</td>
<td>Surgery</td>
<td>Age</td>
<td>Outcome</td>
</tr>
<tr>
<td>-------------</td>
<td>---</td>
<td>-------</td>
<td>---------</td>
<td>------------</td>
<td>---------</td>
<td>-----</td>
<td>---------</td>
</tr>
<tr>
<td>Karenfort (2002)</td>
<td>8</td>
<td>0.5-34.0</td>
<td>Germany</td>
<td>a, b, f, i, j</td>
<td>Tubectomy/lobectomy</td>
<td>0.5-4.3</td>
<td>7/8 (88%)</td>
</tr>
<tr>
<td>Koh (2000)</td>
<td>11</td>
<td>0.5-7.5</td>
<td>USA</td>
<td>d, e, f, i, j, m</td>
<td>Multilobar resection</td>
<td>0.5-6.8</td>
<td>8/11 (73%) **</td>
</tr>
<tr>
<td>Lachhwani (2005)</td>
<td>17</td>
<td>0.2-31.0</td>
<td>USA</td>
<td>a, b, f, i, j, k, l</td>
<td>Tubectomy/lobectomy</td>
<td>1.0-15.0</td>
<td>12/17 (71%)</td>
</tr>
<tr>
<td>Liang (2010)**</td>
<td>17</td>
<td>6.0-23.0</td>
<td>China</td>
<td>a, b, d, g, h, l</td>
<td>Tubectomy/lobectomy</td>
<td>1.0-5.0</td>
<td>13/17 (76%)</td>
</tr>
<tr>
<td>Major (2009)</td>
<td>3</td>
<td>3.0-14.0</td>
<td>USA</td>
<td>a, c, d, e, f, h, i, j, k, l</td>
<td>Tubectomy/lobectomy</td>
<td>0.8-2.3</td>
<td>2/3 (67%)</td>
</tr>
<tr>
<td>Perot (1966)</td>
<td>7</td>
<td>1.7-26.0</td>
<td>Canada</td>
<td>a, b, c, d, e, f, g, h, i</td>
<td>Tubectomy/lobectomy</td>
<td>0.5-16.0</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td>Teutonico (2008)**</td>
<td>11</td>
<td>7.1 (median)</td>
<td>Italy/USA</td>
<td>b, h, j</td>
<td>Tubectomy/lobectomy</td>
<td>0.6-14.0</td>
<td>5/11 (45%)</td>
</tr>
<tr>
<td>Weiner (2006)</td>
<td>25</td>
<td>0.6-16.6</td>
<td>USA</td>
<td>f, o, p</td>
<td>N/A</td>
<td>0.5-6.0</td>
<td>23/25 (92%)</td>
</tr>
<tr>
<td>Wen (2009)**</td>
<td>4</td>
<td>8.0-12.5</td>
<td>China</td>
<td>a, b, d, f</td>
<td>N/A</td>
<td>1.8-6.0</td>
<td>3/4 (75%)</td>
</tr>
</tbody>
</table>

Predictors reported* a) Gender; b) Age at seizure onset; c) Preoperative seizure frequency; d) Presence of infantile spasms; e) Presence of generalized seizures; f) Age at surgery; g) Preoperative intelligent Quotient score; h) Presence of moderate/severe developmental delay; i) Focal or generalized/multifocal interictal EEG abnormality; j) Focal or generalized/multifocal ictal EEG abnormality; k) Concordant electroencephalographic and radiological studies; l) Tuber burden; m) Focal or multifocal SPECT abnormality; n) Focal or multifocal MEG abnormality; o) Focal or generalized/multifocal interictal invasive EEG abnormality; p) Focal or generalized/multifocal ictal invasive EEG abnormality

** Remaining participants were lost to follow-up
*** Author contacted for IPD
**Table 2.** Assessment of risk of bias in included studies

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Sample representative?</th>
<th>Prognostic variables well defined?</th>
<th>Confidence in assessment of outcome</th>
<th>Was the follow-up adequate?</th>
<th>Was the treatment standardized?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboian (2011)</td>
<td>Probably yes</td>
<td>Definitely yes</td>
<td>Mostly yes</td>
<td>Definitely yes</td>
<td>Probably yes</td>
</tr>
<tr>
<td>Asano (2000)</td>
<td>Probably yes</td>
<td>Probably yes</td>
<td>Mostly yes</td>
<td>Probably yes</td>
<td>Probably yes</td>
</tr>
<tr>
<td>Avellino (1997)</td>
<td>Definitely yes</td>
<td>Definitely yes</td>
<td>Mostly yes</td>
<td>Probably no</td>
<td>Probably yes</td>
</tr>
<tr>
<td>Baumgartner (1997)</td>
<td>Definitely yes</td>
<td>Probably yes</td>
<td>Mostly yes</td>
<td>Probably no</td>
<td>Probably yes</td>
</tr>
<tr>
<td>Bebin (1993)</td>
<td>Probably yes</td>
<td>Probably no</td>
<td>Mostly yes</td>
<td>Probably yes</td>
<td>Probably yes</td>
</tr>
<tr>
<td>Guerreiro (1998)</td>
<td>Definitely yes</td>
<td>Probably yes</td>
<td>Mostly yes</td>
<td>Probably no</td>
<td>Probably no</td>
</tr>
<tr>
<td>Heide (2010)</td>
<td>Definitely yes</td>
<td>Probably yes</td>
<td>Mostly yes</td>
<td>Definitely yes</td>
<td>Probably yes</td>
</tr>
<tr>
<td>Jansen (2007)</td>
<td>Definitely yes</td>
<td>Definitely yes</td>
<td>Mostly yes</td>
<td>Definitely yes</td>
<td>Probably no</td>
</tr>
<tr>
<td>Kagawa (2005)</td>
<td>Definitely yes</td>
<td>Definitely yes</td>
<td>Mostly yes</td>
<td>Probably no</td>
<td>Probably yes</td>
</tr>
<tr>
<td>Kamimura (2006)</td>
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<td>Probably yes</td>
<td>Mostly yes</td>
<td>Definitely yes</td>
<td>Probably yes</td>
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<tr>
<td>Karenfort (2002)</td>
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<td>Definitely yes</td>
<td>Mostly yes</td>
<td>Probably no</td>
<td>Probably yes</td>
</tr>
<tr>
<td>Koh (2000)</td>
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<td>Mostly yes</td>
<td>Definitely not</td>
<td>Probably yes</td>
</tr>
<tr>
<td>Author</td>
<td>definitely yes</td>
<td>definitely yes</td>
<td>mostly yes</td>
<td>probably yes</td>
<td>probably yes</td>
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<tr>
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<td>------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
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<td>mostly yes</td>
<td>probably yes</td>
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</tr>
<tr>
<td>Liang (2010)</td>
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<td>mostly yes</td>
<td>probably yes</td>
<td>definitely yes</td>
<td>definitely yes</td>
</tr>
<tr>
<td>Major (2009)</td>
<td>probably yes</td>
<td>mostly yes</td>
<td>probably yes</td>
<td>probably yes</td>
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</tr>
<tr>
<td>Perot (1966)</td>
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<td>mostly yes</td>
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<td>probably no</td>
</tr>
<tr>
<td>Teutonico (2008)</td>
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</tr>
<tr>
<td>Wen (2009)</td>
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<td>mostly yes</td>
<td>definitely yes</td>
<td>probably yes</td>
</tr>
<tr>
<td>Independent variable</td>
<td>Frequency (Percentage) No</td>
<td>Frequency (Percentage) Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>52(48.1%) Female</td>
<td>56(51.9%) Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infantile spasms</td>
<td>79(69.9%)</td>
<td>34(30.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized seizures</td>
<td>49(59.8%)</td>
<td>33(40.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developmental Delay</td>
<td>34(57.6%)</td>
<td>25(42.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEG/MRI concordance</td>
<td>31(38.8%)</td>
<td>49(61.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Interictal EEG</strong></td>
<td>68(53.5%)</td>
<td>59(46.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ictal EEG</strong></td>
<td>69(65.1%)</td>
<td>37(34.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPECT</td>
<td>5(41.7%)</td>
<td>7(58.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEG</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive interictal EEG</td>
<td>24(70.6%)</td>
<td>10(29.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive ictal EEG</td>
<td>26(65.0%)</td>
<td>14(35.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.** Frequency table of dichotomous predictors of seizure outcome
**Table 4.** Summary table for continuous predictors of seizure outcome

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>N</th>
<th>Median (IQR)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first seizure (months)</td>
<td>126</td>
<td>8.0 (2.0-28.5)</td>
<td>0-216</td>
</tr>
<tr>
<td>Preoperative seizure frequency (per day)</td>
<td>30</td>
<td>1.0 (0.0-5.0)</td>
<td>0-35</td>
</tr>
<tr>
<td>Age at surgery (years)</td>
<td>174</td>
<td>7.0 (3.0-14.0)</td>
<td>0-46</td>
</tr>
<tr>
<td>IQ</td>
<td>28</td>
<td>77.5 (70.25-84.50)</td>
<td>48-119</td>
</tr>
<tr>
<td>Size of predominant tuber</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tuber burden</td>
<td>74</td>
<td>5.0 (1.0-15.0)</td>
<td>1-37</td>
</tr>
</tbody>
</table>
Table 5. Odds ratios, 95% confidence intervals and p values for preoperative predictors of good seizure outcome adjusted for duration of follow-up

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>OR</th>
<th>Lower 95% CI</th>
<th>Higher 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female)</td>
<td>1.092</td>
<td>0.481</td>
<td>2.475</td>
<td>0.834</td>
</tr>
<tr>
<td>Log_{10}(Age at seizure onset)</td>
<td>1.520</td>
<td>0.772</td>
<td>2.993</td>
<td>0.226</td>
</tr>
<tr>
<td>Log_{10}(Preoperative seizure frequency)</td>
<td>2.295</td>
<td>0.340</td>
<td>15.512</td>
<td>0.394</td>
</tr>
<tr>
<td>Lack of infantile spasms</td>
<td>1.184</td>
<td>0.492</td>
<td>2.849</td>
<td>0.707</td>
</tr>
<tr>
<td>Lack of generalized seizures*</td>
<td>3.111</td>
<td>1.175</td>
<td>8.237</td>
<td>0.022</td>
</tr>
<tr>
<td>Log_{10} (Age at surgery)</td>
<td>1.211</td>
<td>0.560</td>
<td>2.617</td>
<td>0.626</td>
</tr>
<tr>
<td>Preoperative IQ</td>
<td>1.008</td>
<td>0.940</td>
<td>1.081</td>
<td>0.823</td>
</tr>
<tr>
<td>No or mild developmental delay*</td>
<td>7.285</td>
<td>2.145</td>
<td>24.739</td>
<td>0.001</td>
</tr>
<tr>
<td>No or unifocal interictal scalp EEG abnormality</td>
<td>1.538</td>
<td>0.726</td>
<td>3.257</td>
<td>0.260</td>
</tr>
<tr>
<td>Unifocal scalp ictal EEG abnormality*</td>
<td>3.205</td>
<td>1.351</td>
<td>7.576</td>
<td>0.008</td>
</tr>
<tr>
<td>Less tuber burden</td>
<td>1.011</td>
<td>0.958</td>
<td>1.068</td>
<td>0.684</td>
</tr>
<tr>
<td>EEG/MRI concordance*</td>
<td>4.882</td>
<td>1.763</td>
<td>13.522</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* Statistically significant predictors of postoperative seizure outcome
APPENDICES
APPENDIX A. Engel classification table

<table>
<thead>
<tr>
<th>Engel's classification of postoperative outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td>Free of disabling seizures(^a)</td>
</tr>
<tr>
<td>A</td>
<td>Completely seizure free since surgery</td>
</tr>
<tr>
<td>B</td>
<td>Nondisabling simple partial seizures only since surgery</td>
</tr>
<tr>
<td>C</td>
<td>Some disabling seizures after surgery, but free of disabling seizures for (\geq 2) years</td>
</tr>
<tr>
<td>D</td>
<td>Generalized convulsions with AED withdrawal only</td>
</tr>
<tr>
<td><strong>Class II</strong></td>
<td>Rare disabling seizures (‘almost seizure free’)</td>
</tr>
<tr>
<td>A</td>
<td>Initially free of disabling seizures but has rare seizures now</td>
</tr>
<tr>
<td>B</td>
<td>Rare disabling seizures since surgery</td>
</tr>
<tr>
<td>C</td>
<td>More than rare disabling seizures since surgery, but rare seizures for the last 2 years</td>
</tr>
<tr>
<td>D</td>
<td>Nocturnal seizures only</td>
</tr>
<tr>
<td><strong>Class III</strong></td>
<td>Worthwhile improvement(^b)</td>
</tr>
<tr>
<td>A</td>
<td>Worthwhile seizure reduction</td>
</tr>
<tr>
<td>B</td>
<td>Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not (&lt;2) years</td>
</tr>
<tr>
<td><strong>Class IV</strong></td>
<td>No worthwhile improvement</td>
</tr>
<tr>
<td>A</td>
<td>Significant seizure reduction</td>
</tr>
<tr>
<td>B</td>
<td>No appreciable change</td>
</tr>
<tr>
<td>C</td>
<td>Seizures worse</td>
</tr>
</tbody>
</table>

\(^a\)Excludes early postoperative seizures (first few weeks)
\(^b\)Determination of ‘worthwhile improvement’ will require quantitative analysis of additional data such as percentage seizure reduction, cognitive function, and quality of life.
APPENDIX B: Search strategy

Search strategy for MEDLINE, Embase, CINAHL and Web of Science

**Embase** <1980 to 2011 Week 41> (7264 citations)

**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to Present>** (4752 citations)

Search performed: October 15, 2011

1. exp Neurosurgical Procedures/
2. surg*.mp.
3. neurosurgery/
4. su.fs.
5. 1 or 3
6. 2 or 4
7. exp Epilepsy/
8. Epilepsy*.mp.
9. 7 or 8
10. tuberous*.mp.
11. 9 and 10
12. child*.mp.
13. infant*.mp.
14. teen*.mp.
15. toddler*.mp.
16. adolescent*.mp.
17. preschool*.mp.
18. 12 or 13 or 14 or 15 or 16 or 17
19. 5 or 6
20. 10 and 19
21. 9 and 18 and 19
22. 20 or 21
23. limit 22 to (article or conference abstract or conference paper or journal or report or case reports or classical article or clinical conference or comparative study or congresses or "corrected and republished article" or duplicate publication or english abstract or evaluation studies or historical article or journal article or multicenter study or retracted publication or twin study)

**CINAHL** (217 citations)
Search performed: October 16, 2011
1. (MM "Neurosurgery") OR "neurosurgery"
2. (MH "Epilepsy") OR "epilepsy" OR (MM "Epilepsy, Partial, Complex") OR (MM "Epilepsy, Temporal Lobe") OR (MM "Epilepsy, Partial, Focal") OR (MM "Epilepsy, Partial")
3. s1 and s2

Web of Science (656 citations)
Search performed: October 16, 2011

# 3 656
#2 AND #1
Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years Lemmatization=On
# 2 77,419
Topic=(epilepsy/)
Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years Lemmatization=On
# 1 11,489
Topic=(neurosurgery/)
Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years Lemmatization=On
APPENDIX C: Participant level data collection

<table>
<thead>
<tr>
<th>Variable name</th>
<th>Type</th>
<th>Values and coding</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authoryear</td>
<td>Text</td>
<td>Text</td>
<td>Uniquely identifies the study (First author, Year)</td>
</tr>
<tr>
<td>Id</td>
<td>Numeric (continuous)</td>
<td>Unique integer</td>
<td>Unique number for each record in each study</td>
</tr>
<tr>
<td>Case</td>
<td>Numeric (binary)</td>
<td>0 = control, 1 = case</td>
<td>Identifies cases and controls</td>
</tr>
<tr>
<td>Sex</td>
<td>Numeric (binary)</td>
<td>0 = female, 1 = male</td>
<td>Gender of the study participant</td>
</tr>
<tr>
<td>Ageszonset</td>
<td>Numeric (continuous)</td>
<td>Integer, 99 – missing data</td>
<td>Age of participant at seizure onset (years)</td>
</tr>
<tr>
<td>Is</td>
<td>Numeric</td>
<td>0 = no, 1 = yes, 8 = missing data</td>
<td>Identifies whether or not the child had infantile spasms</td>
</tr>
<tr>
<td>Psz</td>
<td>Numeric</td>
<td>0 = no, 1 = yes, 8 = missing data</td>
<td>Identifies whether or not the child had partial seizures</td>
</tr>
<tr>
<td>Gsz</td>
<td>Numeric</td>
<td>0 = no, 1 = yes, 8 = missing data</td>
<td>Identifies whether or not the child had generalized seizures (primary or secondarily)</td>
</tr>
<tr>
<td>Durationsz</td>
<td>Numeric</td>
<td>Integer</td>
<td>Presurgical duration</td>
</tr>
<tr>
<td>Variable</td>
<td>Type</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Agesurgery</td>
<td>Numeric</td>
<td>Age of participant at time of surgery (years)</td>
<td></td>
</tr>
<tr>
<td>Tscdx</td>
<td>Numeric</td>
<td>0 = yes, 1 = no, 8 = missing data. Uniquely identifies if the patient has been diagnosed with tuberous sclerosis complex</td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>Numeric</td>
<td>0 = not done, 1 = mutation, 2 = no mutation, 8 = missing data. Uniquely identifies if mutation analysis was done and if it was positive or negative</td>
<td></td>
</tr>
<tr>
<td>Ddelay</td>
<td>Numeric</td>
<td>0 = mild delay, 1 = medium delay, 2 = severe delay, 8 = missing data. Degree of developmental delay as determined by cognitive tests or by level of schooling</td>
<td></td>
</tr>
<tr>
<td>Surgerytype</td>
<td>Numeric</td>
<td>0 = focal lesionectomy/tuberectomy, 1 = lobectomy, 2 = multilobar resection, 3 = hemispherectomy, 8 = missing data. Uniquely identifies the type of operation performed</td>
<td></td>
</tr>
<tr>
<td>InterictalEEG</td>
<td>Numeric</td>
<td>0 = not performed, 1 = focal, 2 = multifocal or non-focal, 8 = missing data. Indicates if the interictal EEG had a focal or nonfocal or multifocal abnormality</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Type</td>
<td>Value</td>
<td>Description</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>--------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Eegabnormality</td>
<td>Numeric</td>
<td>0 = normal</td>
<td>Indicates if the interictal EEG was normal; mildly epileptogenic (focal spikes, sharp slow, or spike slow); severely epileptogenic (multifocal discharges, typical or modified hypsarrhythmia, or suppression burst)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = mildly abnormal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = severely abnormal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 = missing data</td>
<td></td>
</tr>
<tr>
<td>IctalEEG</td>
<td>Numeric</td>
<td>0 = not performed</td>
<td>Indicates if the ictal EEG had a focal or nonfocal or multifocal abnormality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = focal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = multifocal or non-focal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 = missing data</td>
<td></td>
</tr>
<tr>
<td>Ecog</td>
<td>Numeric</td>
<td>0 = not performed</td>
<td>Indicates if presurgical electrocorticography was localizing or non-localizing/multifocal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = localizing</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = non-localizing or multifocal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 = missing data</td>
<td></td>
</tr>
<tr>
<td>Mri</td>
<td>Numeric</td>
<td>0 = not performed</td>
<td>Indicates if the presurgical MRI showed a predominant tuber or not</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = predominant tuber</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = no predominant tuber</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 = missing data</td>
<td></td>
</tr>
<tr>
<td>Tuberburden</td>
<td>Numeric</td>
<td>Integer</td>
<td>Identifies the number of tubers on CT or MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99 = missing data</td>
<td></td>
</tr>
<tr>
<td>Ct</td>
<td>Numeric</td>
<td>0 = not performed</td>
<td>Indicates if the presurgical CT scan showed a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = predominant tuber</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Type</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>2 = no predominant tuber</td>
<td>numeric</td>
<td>Indicates if the preoperative MEG provided localizing or lateralizing data</td>
<td></td>
</tr>
<tr>
<td>8 = missing data</td>
<td>numeric</td>
<td>Indicates if the preoperative MEG provided localizing or lateralizing data</td>
<td></td>
</tr>
<tr>
<td>MEG</td>
<td>numeric</td>
<td>Indicates if the preoperative MEG provided localizing or lateralizing data</td>
<td></td>
</tr>
<tr>
<td>0 = not performed</td>
<td>numeric</td>
<td>Indicates if the preoperative MEG provided localizing or lateralizing data</td>
<td></td>
</tr>
<tr>
<td>1 = lateralizing or localizing</td>
<td>numeric</td>
<td>Indicates if the preoperative MEG provided localizing or lateralizing data</td>
<td></td>
</tr>
<tr>
<td>2 = non-lateralizing or non-localizing</td>
<td>numeric</td>
<td>Indicates if the preoperative MEG provided localizing or lateralizing data</td>
<td></td>
</tr>
<tr>
<td>8 = missing data</td>
<td>numeric</td>
<td>Indicates if the preoperative MEG provided localizing or lateralizing data</td>
<td></td>
</tr>
<tr>
<td>IctalSPECT</td>
<td>numeric</td>
<td>Indicates if the Ictal SPECT showed 1 or more than 1 areas of abnormality</td>
<td></td>
</tr>
<tr>
<td>0 = not performed</td>
<td>numeric</td>
<td>Indicates if the Ictal SPECT showed 1 or more than 1 areas of abnormality</td>
<td></td>
</tr>
<tr>
<td>1 = normal</td>
<td>numeric</td>
<td>Indicates if the Ictal SPECT showed 1 or more than 1 areas of abnormality</td>
<td></td>
</tr>
<tr>
<td>2 = 1 region of abnormal tracer uptake</td>
<td>numeric</td>
<td>Indicates if the Ictal SPECT showed 1 or more than 1 areas of abnormality</td>
<td></td>
</tr>
<tr>
<td>3 = more than 1 region of abnormal tracer uptake</td>
<td>numeric</td>
<td>Indicates if the Ictal SPECT showed 1 or more than 1 areas of abnormality</td>
<td></td>
</tr>
<tr>
<td>8 = missing data</td>
<td>numeric</td>
<td>Indicates if the Ictal SPECT showed 1 or more than 1 areas of abnormality</td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>numeric</td>
<td>Indicates if the PET study showed 1 or more than 1 areas of abnormality</td>
<td></td>
</tr>
<tr>
<td>0 = not performed</td>
<td>numeric</td>
<td>Indicates if the PET study showed 1 or more than 1 areas of abnormality</td>
<td></td>
</tr>
<tr>
<td>1 = normal</td>
<td>numeric</td>
<td>Indicates if the PET study showed 1 or more than 1 areas of abnormality</td>
<td></td>
</tr>
<tr>
<td>2 = 1 region of abnormal tracer uptake</td>
<td>numeric</td>
<td>Indicates if the PET study showed 1 or more than 1 areas of abnormality</td>
<td></td>
</tr>
<tr>
<td>3 = more than 1 region of abnormal tracer uptake</td>
<td>numeric</td>
<td>Indicates if the PET study showed 1 or more than 1 areas of abnormality</td>
<td></td>
</tr>
<tr>
<td>8 = missing data</td>
<td>numeric</td>
<td>Indicates if the PET study showed 1 or more than 1 areas of abnormality</td>
<td></td>
</tr>
<tr>
<td>Durationfu</td>
<td>numeric</td>
<td>Duration of last follow-up after surgery</td>
<td></td>
</tr>
<tr>
<td>99 = missing data</td>
<td>numeric</td>
<td>Duration of last follow-up after surgery</td>
<td></td>
</tr>
<tr>
<td>OutcomeLastVisit</td>
<td>numeric</td>
<td>Uniquely categorizes the seizure outcome at the last clinical follow-up</td>
<td></td>
</tr>
<tr>
<td>1 = Engel class I or II</td>
<td>numeric</td>
<td>Uniquely categorizes the seizure outcome at the last clinical follow-up</td>
<td></td>
</tr>
<tr>
<td>2 = Engel class III or IV</td>
<td>numeric</td>
<td>Uniquely categorizes the seizure outcome at the last clinical follow-up</td>
<td></td>
</tr>
<tr>
<td>8 = missing data</td>
<td>numeric</td>
<td>Uniquely categorizes the seizure outcome at the last clinical follow-up</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX D. Tool to assess risk of bias in prognostic cohort studies

1. **Was the sample of patients representative?**

<table>
<thead>
<tr>
<th>Definitely yes</th>
<th>Probably yes</th>
<th>Probably no</th>
<th>Definitely no</th>
</tr>
</thead>
<tbody>
<tr>
<td>(low risk of bias)</td>
<td></td>
<td></td>
<td>(high risk of bias)</td>
</tr>
</tbody>
</table>

   Examples of low risk of bias: Inclusion criteria is well-defined, sample selection is explained and is clear that it is consecutive, clinical and demographic characteristics fully described and sample is representative.

   Examples of high risk of bias: Inclusion criteria is poorly defined, sample selection is not explained and is unclear that it is consecutive, clinical and demographic characteristics are poorly described and sample is not very representative.

2. **Were the prognostic variables well defined and well characterized?**

<table>
<thead>
<tr>
<th>Definitely yes</th>
<th>Probably yes</th>
<th>Probably no</th>
<th>Definitely no</th>
</tr>
</thead>
<tbody>
<tr>
<td>(low risk of bias)</td>
<td></td>
<td></td>
<td>(high risk of bias)</td>
</tr>
</tbody>
</table>

   Examples of low risk of bias: The prognostic variables are well-defined, including the details of its measurement, are precisely measured, and available for all or a high proportion of patients.

   Examples of high risk of bias: The prognostic variables are poorly defined, lack of details regarding its measurements, are measured poorly and are not available for a high proportion of patients.

3. **Can we be confident in the assessment of outcome?**

<table>
<thead>
<tr>
<th>Definitely yes</th>
<th>Mostly yes</th>
<th>Mostly no</th>
<th>Definitely no</th>
</tr>
</thead>
<tbody>
<tr>
<td>(low risk of bias)</td>
<td></td>
<td></td>
<td>(high risk of bias)</td>
</tr>
</tbody>
</table>

   Examples of low risk of bias: Outcome is less subjective, fully defined and appropriate. E.g. Parents were asked to keep a seizure diary, follow-up appointments were frequent and the data was collected independently and in duplicate.

   Examples of high risk of bias: Outcome is more subjective, inadequately defined and inappropriate. E.g. No seizure diary was kept, long duration for follow-up appointments, and the data was collected by one data extractor.

4. **Was the follow-up adequate?**
Definitely yes  Probably yes  Probably no  Definitely no
(low risk of bias)             (high risk of bias)

Examples of low risk of bias: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring is unlikely to introduce bias); Missing outcome data balanced in numbers across different demographic groups, with similar reasons for missing data across groups.

Examples of high risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across demographic groups. E.g. Outcome data is not available for patients that have more severe seizures prior to surgery.

5. Can we be confident that the treatment was standardized?

Definitely yes  Probably yes  Probably no  Definitely no
(low risk of bias)             (high risk of bias)

Examples of low risk of bias: The treatment is described in detail and was standardized across patients. This means there has been no significant change in the philosophy of care for patients (i.e the same epilepsy surgery team, the same diagnostic tools utilized and the same surgeon).

Examples of high risk of bias: The treatment is adequately described and was non-standardized across patients. There have been significant changes in the philosophy of care for patients (i.e. a change in the epilepsy surgery team personnel, change in the diagnostic tools utilized and more than one surgeon).
APPENDIX E. List of excluded articles with reasons

Case reports (2)

2. Bye AM, Matheson JM, Tobias VH, Mackenzie RA: Selective epilepsy surgery in tuberous sclerosis. AUSTRALIA, Department of Paediatric Neurology, Prince of Wales Children's Hospital, Randwick, New South Wales, Australia, 1989, pp 243-245.

Patient overlap with another article (7)


**Less than 90% TSC participants (190)**


77. Hirsch LJ, Spencer SS, Spencer DD, Williamson PD, Mattson RH. Temporal lobectomy in patients with bitemporal epilepsy defined by depth electroencephalography. UNITED STATES: Department of Neurology, Yale University School of Medicine, New Haven, CT; 1991. p. 347-56.


surgery outcome in pediatric patients. United Kingdom: W.B. Saunders Ltd (32 Jamestown Road, London NW1 7BY, United Kingdom); 2009. p. 504-10.


of Women’s and Children’s Health, University of New South Wales, Sydney, Australia; 2006. p. 557-61.


184. van Empelen R, Jennekens-Schinkel A, van Rijen PC, Helders PjM, van Nieuwenhuizen O. Health-related quality of life and self-perceived competence of children assessed before and up to two years after epilepsy surgery. United States: Department of Pediatric Physical Therapy and Exercise Physiology, University Medical Center-Wilhelmina Children's


No seizure outcome data available (3)


Anomalous feature in presented participants (1)

Participants did not undergo surgery (1)

Editorial (2)
2. Mukawa J: Surgical treatment of epilepsy. JAPAN, Department of Neurosurgery, University of the Ryukyu School of Medicine, Okinawa, Japan, 1991, pp 201-211.

Abstract only (5)

**Duplicate publication (5)**


**Could not obtain IPD after contacting author (5)**


