# SEIZURE AND THE RISK FOR SEIZURE RECURRENCE AMONG INDIVIDUALS WHO HAVE UNDERGONE SURGERY FOR EPILEPSY

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**Summary:** Epilepsy is a central nervous system disorder for which recurrent seizures are the main symptom. Seizures resulting from epilepsy may culminate in unpredictable and sudden incapacitation, and thus are of significant concern to those interested in driver safety. Surgical therapy is one of the main treatment options for patients who do not respond to pharmacotherapy. Although approximately two thirds of individuals who undergo the most common types of surgery for epilepsy become seizure free, a significant proportion of these individuals will experience seizure recurrence. A systematic review and meta-analysis was conducted to examine the likelihood of seizure recurrence among individuals who have undergone surgery for epilepsy. Specifically, we were interested in quantifying the relationship between time since last seizure and the likelihood that a seizure will occur within the following year. Our results indicate that the longer the time that has elapsed since the occurrence of the last seizure, the lower the risk for seizure recurrence in the following year. The average annual risk for experiencing seizure recurrence among individuals who have remained seizure free for ≥8 years is less than 2% and less than 1% for those who have remained seizure free for ≥10 years. These findings have important implications for regulatory agencies with responsibility for road safety; particularly those agencies that regulate safety sensitive industries.

## INTRODUCTION

Driving is a complicated psychomotor performance that depends on fine coordination between the sensory and motor systems. It is influenced by factors such as arousal, perception, learning, memory, attention, concentration, emotion, reflex speed, time estimation, auditory and visual functions, decision making and personality. Safe driving requires skills to maintain effective and reliable control of vehicles, the capacity to respond to the road, traffic, and other external clues, and the ability to follow the “rules of the road”. Many health conditions, including epilepsy, have the potential to impair perception, cognition (including alertness, attitude to risk, and recall) and/or motor function and, as a result, can make driving less safe.

Epilepsy is a central nervous system disorder characterized by recurrent involuntary seizures resulting from excessive hypersynchronous discharges of neurons in the brain. Epilepsy is not a distinct disease; rather, it is a group of disorders for which recurrent seizures are the main symptom. Seizures resulting from epilepsy may culminate in unpredictable and sudden incapacitation, and thus are of significant concern to those interested in driver safety as they have the potential to result in crash, injury, and death.

The typical treatment option for epilepsy is pharmacotherapy with anti-epileptic drugs (AEDs). Patients who do not respond well to AED therapy, however, may be candidates for surgical therapy, such as anterior temporal lobectomy and extra-temporal resection. The goal of epilepsy surgery is either to define and resect an area of epileptogenesis or disrupt the spread of seizure activity in order to reduce the likelihood of seizures or prevent certain seizure types. Although approximately two thirds of individuals who undergo the most common types of surgery for epilepsy become seizure free, a significant proportion of these individuals will experience seizure recurrence. Several studies have noted that the likelihood of an individual experiencing seizure recurrence following surgery decreases as a function of increasing time since last seizure (Folvary et al., 2000; Kim et al., 2005; Radhakrishnan et al., 1998; Salanova, Markand, & Worth, 1999; So et al., 1997; Spencer et al., 2005). In other words, an individual who has been seizure free for five years is less likely to experience seizure recurrence in the near future than an individual who has only been seizure free for one year. The purpose of this systematic review was to attempt to utilize published time-to-event data to quantify the relationship between time since last seizure and the likelihood that a seizure will occur within the following year in individuals who have been successfully treated with surgery.

## METHODS

In order to address our objectives, a systematic review of the literature was conducted utilizing the methodology described elsewhere.(Treadwell et al., 2006). In brief, we synthesized the available data from published studies that examined the relationship between seizure recurrence likelihood and the time since last seizure among individuals who have undergone surgery and are apparently seizure free. Formal *a priori* criteria for article retrieval and inclusion consisted of: 1) English language publications, 2) full-length articles, 3) enrolled ≥ 10 subjects, 4) 80% of subjects must be ≥ 18 years, 5) article may be prospective or retrospective with consecutive enrollment, 6) must have reported on time since last seizure, 7) minimum follow-up time must have been one year, 8) Studies of individuals on AEDs following surgery were eligible. Case reports and series of carefully selected patients chosen to demonstrate a particular point were excluded.

Sensitive search strategies, developed and refined by an information specialist, were applied to six electronic databases (Medline, PubMed (pre Medline), EMBASE, CINAHL, TRIS, and the Cochrane library). Additional hand searches of the published literature (i.e., bibliographies of identified relevant articles) and “gray literature” resources (e.g., Web searches) were also performed. The quality of all included studies was determined using the ECRI Quality Scale X, which was designed specifically for the assessment of the validity of time-to-event studies.

Time-to-event (survival) data were pooled using non-linear regression techniques. We determined the function that best fit data extracted from each included study by fitting mathematical models based on several plausible probability distributions (exponential, Weibull, etc). We then tested the goodness of fit of the resulting survival functions to the available data and chose the model that best described these data. Relevant parameters that described each resulting mathematical function (and their 95 percent confidence intervals) were then pooled as described above.

## RESULTS

Our searches identified a total of 227 articles that appeared relevant to the purpose of this study. Following application of the retrieval criteria, 35 full-length articles retrieved and read in full. Of these articles, 12 were found to meet our inclusion criteria.

All twelve studies that met our inclusion criteria were case series in which data on seizure status, recorded over a period of several years, was analyzed using typical survival analysis techniques. Data on seizure status was usually drawn retrospectively from medical records (only one study was prospective). Sometimes this information was supplemented by telephone interviews of the patient or a close family member. All of the included studies were designed to assess the long-term effectiveness and safety of surgery for medically intractable localized epilepsy. The majority of included studies examined the long-term effectiveness of temporal lobectomy; three included studies evaluated the effectiveness of other surgical procedures in addition to temporal lobectomy (Rougier et al., 1992; Spencer et al., 2005; Yoon et al., 2003). Other procedures assessed by these studies included frontal, occipital, and parietal lobectomies. As a consequence, the findings of our analysis are generalizable only to individuals who become seizure free following one of these procedures. Our assessment of the quality of the studies that comprise the present evidence base found that the overall quality of the included studies was low (Median Quality Score=6.25; Quality=Low). Aside from poor reporting which made evaluation of study quality difficult in many cases, the primary reasons for the low quality scores was due to the fact that all studies were case-series (single arm observational studies), and that data was collected retrospectively in 11 of the 12 studies.

Data on the cumulative probability for seizure recurrence extracted from the 12 included studies are presented in Table 1.

A summary time-to-event (survival) function was determined from the data extracted from the 12 included studies using curve fitting software. Several probability distributions were examined including exponential, Weibull, and log-normal distributions. Time-to-event data from each study were well fit using a non-linear regression model in which the underlying probability distribution was exponential.

The hazard function for a survival curve with an exponential probability distribution is described by a single constant, the hazard rate ($\lambda$).
Table 2 presents our calculated hazard function estimates and 95% confidence intervals. A hazard rate could not be determined for one of the 12 studies because too few data points were available for a curve to be reliably fitted.

The hazard rate data from the 11 remaining studies were found to be heterogeneous (($Q=137.27$, $P<0.0001$; $I^2=92.72$). This heterogeneity could not be explained using maximum-likelihood meta-regression. Because of the observed heterogeneity, we pooled the hazard rate data from the individual studies using a random-effects model which incorporated the between studies variance into the summary estimate of the hazard rate and its confidence intervals (Figure 1). The random-effects summary hazard rate was found to be 0.39 (95 percent CI: 0.26 to 0.53).

**Table 1. Cumulative Probability of Seizure Recurrence**

| Authors | Year | Type of Surgery | Landmark event | Followup time (Years) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 15 | 20 |
| Jeha et al. | 2006 | TL | Surgery | - | 0.24 | - | - | 0.34 | - | - | 0.42 | - | 0.47 | - | - |
| Kelly et al. | 2005 | TL | 1 year | 0.00 | 0.33 | 0.48 | 0.52 | 0.58 | | | | | 0.63 | 0.67 | 0.67 |
| Spencer et al. | 2005 | TL or ONR | 2 years | - | 0.00 | 0.13 | 0.23 | 0.30 | - | - | - | - | - | - | - |
| McIntosh et al. | 2004 | TL | Surgery | 0.29 | 0.45 | - | - | 0.52 | - | - | - | - | 0.59 | 0.63 | - |
| Yoon et al. | 2003 | TL, FL, PL, or OL | 1 year | 0.00 | 0.11 | 0.16 | - | 0.27 | - | - | - | - | 0.43 | - | - |
| Jutila et al. | 2002 | TL | 1 year | 0.00 | 0.34 | 0.42 | 0.46 | 0.50 | - | 0.55 | - | - | - | - | - |
| Salanova et al. | 1999 | TL | Surgery | 0.31 | 0.34 | 0.37 | 0.37 | 0.37 | 0.37 | 0.40 | 0.42 | 0.42 | 0.42 | - | - |
| So et al. | 1997 | TL | Surgery | 0.35 | 0.34 | 0.35 | 0.35 | 0.41 | - | - | - | - | - | - | - |
| Eliashiv et al. | 1997 | TL | Surgery | 0.02 | 0.04 | 0.10 | 0.14 | 0.18 | 0.2 | 0.2 | 0.2 | 0.22 | 0.24 | - | - |
| Foldvary et al. | 2000 | TL | Surgery | 0.37 | 0.47 | - | - | 0.48 | - | 0.50 | - | - | 0.50 | - | - |
| Luders et al. | 1994 | TL | Surgery | 0.25 | 0.34 | - | - | - | - | - | - | - | - | - | - |
| Rougier et al. | 1992 | TL, FL, PL, or OL | Surgery | 0.38 | 0.45 | 0.50 | 0.53 | 0.55 | 0.58 | - | - | - | - | - | - |

FL = frontal lobectomy; OL = occipital lobectomy; ONR = other neocortical resections; PL = parietal lobectomy; TL = temporal lobectomy

**Table 2. Hazard Function Estimates and 95% Confidence Intervals for Included Studies**

| Reference | Jeha et al. | Kelly et al. | Spencer et al. | McIntosh et al. | Yoon et al. | Jutila et al. | Salanova et al. | So et al. | Eliashiv et al. | Foldvary et al. | Luders et al. | Rougier et al. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| λ | 0.29 | 0.72 | 0.30 | 0.09 | 0.17 | 0.44 | 1.02 | 2.12 | 0.16 | 1.54 | NC | 1.03 |
| **Lower 95 % CI** | 0.00 | 0.51 | 0.04 | 0.05 | 0.03 | 0.35 | 0.51 | 0.00 | 0.11 | 0.22 | NC | 0.39 |
| **Upper 95% CI** | 0.58 | 0.93 | 0.56 | 0.13 | 0.31 | 0.53 | 1.53 | 4.24 | 0.21 | 2.86 | NC | 1.67 |

γ = hazard ratio; CI = confidence limit; NC = not calculated

The summary hazard rate and its 95 percent confidence intervals were used to construct a summary time-to-event curve which in turn was used to determine a conservative estimate of the likelihood that a surgically treated individual will experience seizure recurrence within the following year given that they have been seizure free for a specified period of time (Figure 2).

According to guidelines from Austroads, an annual seizure risk of 20 percent–50 percent for private license holders and 1 percent–2 percent for commercial drivers are considered acceptable risk levels for allowing an individual to drive. Consequently, we used the summary survival curve constructed above to determine a conservative estimate of the likelihood that a surgically treated individual will experience seizure recurrence within the following year given that they have been seizure free for a specified period of time. The findings of our model suggest that individuals who have been seizure free following surgery for at least 1 year have an annual risk for seizure recurrence of ≤20 percent, individuals who have been seizure free for at least 8 years have an annual risk for seizure recurrence of ≤2 percent, and individuals who have been seizure free for at least 10 years have an annual risk for seizure recurrence of ≤1 percent.

| Study name | Statistics for each study | | | | | | |
|---|---|---|---|---|---|---|---|
| | Mean | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
| Jeha | 0.291 | 0.126 | 0.016 | 0.043 | 0.539 | 2.300 | 0.021 |
| Kelly | 0.720 | 0.092 | 0.008 | 0.540 | 0.900 | 7.850 | 0.000 |
| Spencer | 0.300 | 0.113 | 0.013 | 0.078 | 0.522 | 2.646 | 0.008 |
| McIntosh | 0.090 | 0.018 | 0.000 | 0.055 | 0.125 | 5.102 | 0.000 |
| Yoon | 0.170 | 0.061 | 0.004 | 0.050 | 0.290 | 2.788 | 0.005 |
| Jutila | 0.440 | 0.039 | 0.002 | 0.363 | 0.517 | 11.193 | 0.000 |
| Salanova | 1.020 | 0.223 | 0.050 | 0.583 | 1.457 | 4.579 | 0.000 |
| So | 2.120 | 0.926 | 0.857 | 0.305 | 3.935 | 2.290 | 0.022 |
| Eliashiv | 0.160 | 0.022 | 0.000 | 0.118 | 0.202 | 7.383 | 0.000 |
| Foldvary | 1.540 | 0.577 | 0.332 | 0.410 | 2.670 | 2.671 | 0.008 |
| Rougier | 1.030 | 0.280 | 0.078 | 0.482 | 1.578 | 3.682 | 0.000 |
| | 0.396 | 0.068 | 0.005 | 0.263 | 0.528 | 5.852 | 0.000 |

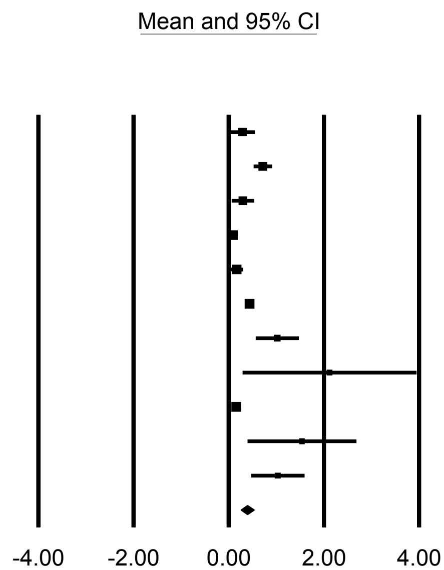


**Figure 1. Random Effects Meta-Analysis of Hazard Rate (λ) Data**

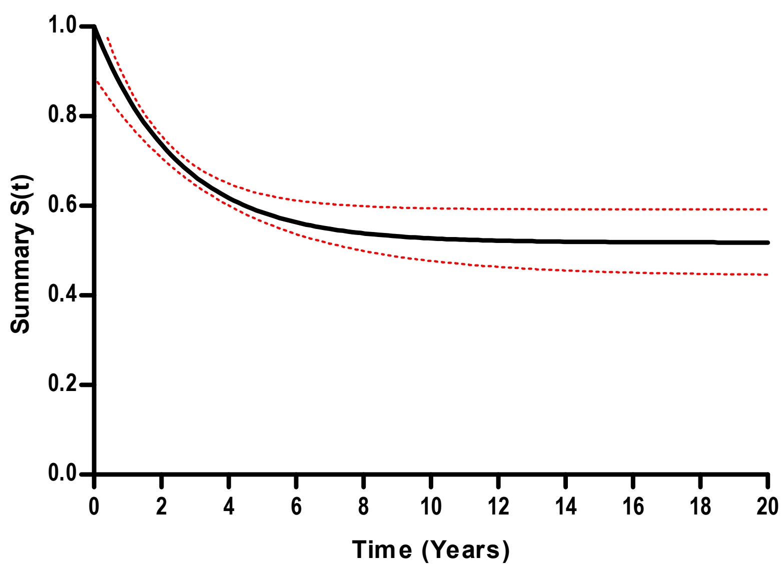


**Figure 2. Summary S(t) and 95% Confidence Interval**

## DISCUSSION

According to the results of our analyses, the longer the time that has elapsed since the occurrence of the last seizure in an individual who has undergone surgery for focal epilepsy (primarily temporal lobectomy), the lower the risk for seizures in the following year. The findings of our model suggest that the average annual risk for experiencing seizure recurrence among individuals who have remained seizure free for ≥1 year is less than 20 percent, ≥8 years is less than 2 percent, and ≥10 years less than 1 percent. These findings have important implications for regulatory agencies with responsibility for road safety; particularly those agencies that regulate safety sensitive industries. For example, if one were to accept the guidance from Austroads, one would disqualify individuals who have undergone surgery for refractory epilepsy from driving until they have been seizure free for a period of at least 1 year. Likewise, one would disqualify such individuals from driving a commercial vehicle until they have been seizure free for at least 8 years.

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## REFERENCES

Earle, C.C., Pham, B., & Wells, G.A. (2000). An assessment of methods to combine published survival curves. *Medical Decision Making, 20*(1),104-111.

Eliashiv, S.D., Dewar, S., Wainwright, I., Engel, J., & Fried, I. (1997). Long-term follow-up after temporal lobe resection for lesions associated with chronic seizures. *Neurology, 48*(5), 1383-1388.

Foldvary, N., Nashold, B., Mascha, E., Thompson, E.A., Lee, N., McNamara, J.O., et al. (2000). Seizure outcome after temporal lobectomy for temporal lobe epilepsy: a Kaplan-Meier survival analysis. *Neurology, 54*(3), 630-634.

Jeha, L.E., Najm, I.M., Bingaman, W.E., Khandwala, F., Widdess-Walsh, P., Morris, H.H., et al. (2006). Predictors of outcome after temporal lobectomy for the treatment of intractable epilepsy. *Neurology, 66*(12), 1938-1940.

Jutila, L., Immonen, A., Mervaala, E., Partanen, J., Partanen, K., Puranen, M., et al. (2002). Long term outcome of temporal lobe epilepsy surgery: analyses of 140 consecutive patients. *J Neurol Neurosurg Psychiatry, 73*(5), 486-494.

Kelley, K. & Theodore, W.H. (2005). Prognosis 30 years after temporal lobectomy. *Neurology, 64*(11), 1974-1976.

Kim, Y.D., Heo, K., Park, S.C., Huh, K., Chang, J.W., Choi, J.U., et al. (2005). Antiepileptic drug withdrawal after successful surgery for intractable temporal lobe epilepsy. *Epilepsia, 46*(2), 251-257.

Luders, H., Murphy, D., Awad, I., Wyllie, E., Dinner, D.S., Morris. H.H. 3rd, & Rothner, A.D. (1994). Quantitative analysis of seizure frequency 1 week and 6, 12, and 24 months after surgery of epilepsy. *Epilepsia, 35*(6), 1174-1178.

McIntosh, A.M., Kalnins, R.M., Mitchell, L.A., Fabinyi, G.C., Briellmann, R.S., & Berkovic, S.F. (2004). Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. *Brain, 127*(Pt 9), 2018-2030.

Radhakrishnan, K., So, E.L., Silbert, P.L., Jack, C.R., Cascino, G.D., Sharbrough, F.W., & O'Brien, P.C. (1998). Predictors of outcome of anterior temporal lobectomy for intractable epilepsy: a multivariate study. *Neurology, 51*(2), 465-471.

Rougier, A., Dartigues, J.F., Commenges, D., Claverie, B., Loiseau, P., & Cohadon, F. (1992). A longitudinal assessment of seizure outcome and overall benefit from 100 cortectomies for epilepsy. *J Neurol Neurosurg Psychiatry, 55*(9), 762-767.

Salanova, V., Markand, O., & Worth, R. (1999). Longitudinal follow-up in 145 patients with medically refractory temporal lobe epilepsy treated surgically between 1984 and 1995. *Epilepsia, 40*(10), 1417-1423.

Shore, T., Nelson, N., & Weinerman, B. (1990). A meta-analysis of stages I and II Hodgkin's disease. *Cancer, 65*(5), 1155-1160.

So, E.L., Radhakrishnan, K., Silbert, P.L., Cascino, G.D., Sharbrough, F.W., & O'Brien, P.C. (1997). Assessing changes over time in temporal lobectomy: outcome by scoring seizure frequency. *Epilepsy Res, 27*(2), 119-125.

Spencer, S.S., Berg, A.T., Vickrey, B.G., Sperling, M.R., Bazil, C.W., Shinnar, S., et al. (2005). Predicting long-term seizure outcome after resective epilepsy surgery: the multicenter study. *Neurology, 65*(6), 912-918.

Treadwell, J.T., Tregear, S.J., Reston, J.T., & Turkelson, C. M. A system for rating the stability and strength of medical evidence. *BMC Medical Research Methodology, 19*, 6-52. Also available: http://www.biomedcentral.com/1471-2288/6/52.

United States Department of Labor, Bureau of Labor Statistics. (2008). National census of fatal occupational injuries. Retrieved on November 20, 2008. Available at: http://www.bls.gov/iif/oshcfoi1.htm

Yoon, H.H., Kwon, H.L., Mattson, R.H., Spencer, D.D., & Spencer, S.S. (2003). Long-term seizure outcome in patients initially seizure-free after resective epilepsy surgery. Neurology, 61(4), 445-450.