



In Epilepsy Surgery, Pathology Matters, and Lesions Need to Go

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Seizure Outcome and Use of Antiepileptic Drugs After Epilepsy Surgery According to Histopathological Diagnosis: A Retrospective Multicenter Cohort Study

Lamberink HJ, Otte WM, Blümcke I, et al; European Epilepsy Brain Bank writing group; study group; European Reference Network EpiCARE. *Lancet Neurol.* 2020;19(9):748-757. doi:10.1016/s1474-4422(20)30220-9

Background: Surgery is a widely accepted treatment option for drug-resistant focal epilepsy. A detailed analysis of longitudinal postoperative seizure outcomes and use of antiepileptic drugs for different brain lesions causing epilepsy is not available. We aimed to analyze the association between histopathology and seizure outcome and drug freedom up to 5 years after epilepsy surgery, to improve presurgical decision-making and counselling. **Methods:** In this retrospective, multicenter, longitudinal, cohort study, patients who had epilepsy surgery between January 1, 2000, and December 31, 2012, at 37 collaborating tertiary referral centers across 18 European countries of the European Epilepsy Brain Bank consortium were assessed. We included patients of all ages with histopathology available after epilepsy surgery. Histopathological diagnoses and a minimal data set of clinical variables were collected from existing local databases and patient records. The primary outcomes were freedom from disabling seizures (Engel class I) and drug freedom at 1, 2, and 5 years after surgery. Proportions of individuals who were Engel class I and drug-free were reported for the 11 main categories of histopathological diagnosis. We analyzed the association between histopathology, duration of epilepsy, and age at surgery, and the primary outcomes using random effects multivariable logistic regression to control for confounding. **Findings:** A total of 9147 patients were included, of whom seizure outcomes were available for 8191 (89.5%) participants at 2 years, and for 5577 (61.0%) at 5 years. The diagnoses of low-grade epilepsy-associated neuroepithelial tumor (LEAT), vascular malformation, and hippocampal sclerosis had the best seizure outcome at 2 years after surgery, with 77.5% (1027 of 1325) of patients free from disabling seizures for LEAT, 74.0% (328 of 443) for vascular malformation, and 71.5% (2108 of 2948) for hippocampal sclerosis. The worst seizure outcomes at 2 years were seen for patients with focal cortical dysplasia type I or mild malformation of cortical development (50.0%, 213 of 426 free from disabling seizures), those with malformation of cortical development-other (52.3%, 212 of 405 free from disabling seizures), and for those with no histopathological lesion (53.5%, 396 of 740 free from disabling seizures). The proportion of patients being both Engel class I and drug-free was 0% to 14% at 1 year and increased to 14% to 51% at 5 years. Children were more often drug-free; temporal lobe surgeries had the best seizure outcomes; and a longer duration of epilepsy was associated with reduced chance of favorable seizure outcomes and drug freedom. This effect of duration was evident for all lesions, except for hippocampal sclerosis. **Interpretation:** Histopathological diagnosis, age at surgery, and duration of epilepsy are important prognostic factors for outcomes of epilepsy surgery. In every patient with refractory focal epilepsy presumed to be lesional, evaluation for surgery should be considered.

Commentary

Deciding whether to offer surgical intervention for drug resistant epilepsy and counseling patients about the likelihood of success are both critically important processes influenced by many factors. These factors include the presumed epilepsy etiology, level of confidence in the presurgical localization, and personal experiences of the individual center and provider. It is commonly understood that patients harboring a pathological lesion are more likely to achieve seizure freedom than those

with nonlesional epilepsy. However, this knowledge is mostly informed by small cohort studies published over several decades and meta-analysis of multiple heterogeneous investigations. Although randomized controlled trials supply the highest level of evidence, these are rare in epilepsy surgery and typically include a small patient sample. Thus, there is value in large, multicenter, longitudinal studies where data collection is fairly organized and homogenous, and confidence in the reliability of results is relatively high. Prior to the presently



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highlighted investigation, only 5 studies relating surgical pathology to seizure outcome in epilepsy surgery have included more than 500 patients, and none included more than 2000 individuals. Also, these prior large investigations did not evaluate drug freedom after surgery.

Lamberink and colleagues retrospectively examined a large cohort of over 9000 surgical epilepsy patients across 37 European centers.¹ Histopathological diagnosis was related to postoperative seizure outcome and drug freedom, with outcome data available in more than 8000 individuals at 2 years and over 5000 patients at 5 years. Approximately two-thirds of the patients underwent temporal lobe surgery, while one-third received an extratemporal lobe resection. Overall, 68% of patients were free of disabling seizures 2 years after surgery, and 66% were seizure free at 5 years. Outcomes were more favorable in patients with a shorter duration of epilepsy and in individuals receiving temporal lobe surgery. The proportion of patients who were both seizure free and completely off anti-epileptic medication was 16% at 2 years and 33% at 5 years. Children were more likely than adults to be free of medications at 5 years, even though seizure freedom rates between the groups were similar, perhaps suggesting that providers are more aggressive in weaning medication in the pediatric age group.


The authors found striking differences in surgical outcome depending on pathology, as approximately 70% to 80% of individuals harboring low-grade neuroepithelial tumor, vascular malformation, or hippocampal sclerosis were seizure free at 5 years, while only 50% to 60% of patients with malformation of cortical development (including focal cortical dysplasia type 1), or no histopathological lesion achieved this outcome. Rates of complete medication discontinuation by the 5-year mark also differed among patients with low-grade neuroepithelial tumor (47%), vascular malformation (37%), hippocampal sclerosis (33%), malformation of cortical development (27%), and no clear pathological lesion (20%). Among category subgroups, the highest rate of medication discontinuation at 5 years was seen in patients with ganglioglioma (51%), while the lowest rates were observed in individuals with non-Rasmussen encephalitis (16%), focal cortical dysplasia type 1 (15%), and normal tissue without gliosis (14%).

Limitations of the highlighted study should be noted, including its retrospective nature, and limited clinical data points obtained from each center. Nevertheless, the findings of Lamberink and colleagues will help guide patient counselling regarding likelihood of seizure freedom based on suspected epilepsy etiology. They confirm that individuals with intractable epilepsy harboring a clear radiographic lesion are favorable surgical candidates, and if safe, surgery should be strongly considered. At our center, we unfortunately encounter many patients who have been treated for drug resistant epilepsy in the community for years and have never had a neuroimaging study. A 3T magnetic resonance imaging (MRI) with epilepsy-specific sequences is a critical part of the presurgical evaluation and should be obtained early. Although not yet widely


implemented, there is also some suggestion that 7T MRI may help uncover lesions not identified at 3T.²

It is interesting that patients with focal cortical dysplasia type 1 or mild malformation of cortical development have relatively similar rates of seizure freedom as individuals without any pathological lesion. This may reflect a more diffuse pathological process that is not fully delineated by MRI, or more complex brain network involvement than other pathologies. Nevertheless, an approximately 50% chance of long-term seizure freedom remains significantly higher than the likelihood of this outcome with continued medical therapy in drug-resistant patients.³ Prior studies have suggested that when identified, gross total resection of the radiographic lesion, if safely achievable, confers the most favorable seizure outcome.⁴ In addition, the highlighted study confirms that medication wean can be safely achieved in many patients who are stable and seizure free more than 1 to 2 years after surgery, although individual cases will differ. The short-term risk of breakthrough seizures should be considered and has been documented in individual cases series by others⁵ and in prior meta-analyses by the present group.⁶

The study by Lamberink and colleagues also confirms that seizure freedom is more likely in patients with a shorter duration of epilepsy, so surgical evaluation should be pursued early in drug-resistant patients. Unfortunately, epilepsy surgery continues to be underutilized, with only a minority of patients being referred for presurgical testing.^{7,8} Guidelines suggest that patients who continue to have seizures after one year despite 2 well-tolerated antiepileptic drug trials should be referred to a tertiary epilepsy center for evaluation.⁹ In temporal lobe epilepsy, the considerably improved efficacy of early surgery over continued medical therapy has been demonstrated in a randomized controlled trial.¹⁰ In short, if seizures are drug resistant, refer for early surgical evaluation. If a lesion is found, it likely needs to go.

By Dario J. Englot 

ORCID iD

Dario J. Englot  <https://orcid.org/0000-0001-8373-690X>

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