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Epilepsy Surgery: A Story of Diminishing Returns Over Time? Think Differently and Think Again

Beyond Seizure Freedom: Dissecting Long-Term Seizure Control After Surgical Resection for Drug-Resistant Epilepsy

Hsieh JK, Pucci FG, Sundar SJ, Kondylis E, Sharma A, Sheikh SR, Vegh D, Moosa AN, Gupta A, Najm I, Rammo R, Bingaman W, Jehi L. *Epilepsia*. 2023;64(1):103-113. doi:10.1111/epi.17445

Objective: This study was undertaken to better understand the long-term palliative and disease-modifying effects of surgical resection beyond seizure freedom, including frequency reduction and both late recurrence and remission, in patients with drug-resistant epilepsy. Methods: This retrospective database-driven cohort study included all patients with >9 years of follow-up at a single high-volume epilepsy center. We included patients who underwent lobectomy, multilobar resection, or lesionectomies for drug-resistant epilepsy; we excluded patients who underwent hemispherectomies. Our main outcomes were (1) reduction in frequency of disabling seizures (at 6 months, each year up to 9 years postoperatively, and at last follow-up), (2) achievement of seizure remission (>6 months, >1 year, and longest duration), and (3) seizure freedom at last follow-up. Results: We included 251 patients; 234 (93.2%) achieved 6 months and 232 (92.4%) experienced 1 year of seizure freedom. Of these, the average period of seizure freedom was 10.3 years. A total of 182 (72.5%) patients were seizure-free at last follow-up (defined as >1 year without seizures), with a median 11.9 years since remission. For patients not completely seizure-free, the mean seizure frequency reduction at each time point was 76.2% and ranged from 66.6% to 85.0%. Patients decreased their number of antiseizure medications on average by .58, and 53 (21.2%) patients were on no antiseizure medication at last follow-up. Nearly half (47.1%) of those seizure-free at last follow-up were not seizure-free immediately postoperatively. Significance: Patients who continue to have seizures after resection often have considerable reductions in seizure frequency, and many are able to achieve seizure freedom in a delayed manner.

Commentary

For patients with drug-resistant epilepsy (DRE); resective epilepsy surgery remains the treatment modality with the greatest chance of complete seizure freedom (SF).[1,2] Despite improvements in presurgical monitoring techniques, <1% patients are referred for epilepsy surgery. Possible reasons include misplaced expectations or misconceptions regarding outcomes of epilepsy surgery.[3] As Dr Engel once quoted, once the decision for epilepsy surgery is made; the expectation from epilepsy surgery is "no seizures, no side effects and as soon as possible."[4]

Let us further analyze the expectation and demand for ''no seizures,'' ''no side effects'' and ''as soon as possible'' a bit more . . . With advancing surgical techniques, the rate of complications has continued to drop-thus the "no side effects" demand seems within reach.

A: No seizures and no side effects after epilepsy surgery: Is 100% SF reasonable 100% of the time and to be expected?

In their recent article, authors Hsieh et al[5] have tried to address the above question by designing a retrospective study with a study design similar to one used in the publication on long-term outcome of patients who underwent neuromodulation in the initial responsive neuromodulation trials as published by Nair et al.[6]

Seizure freedom is defined as freedom from any seizures that cause impaired awareness—in keeping with the original definition used in the temporal lobe epilepsy surgery randomized controlled trial.[1]

We are now investigating more complex, nonlesional DRE. In a study that looked at evolution of epilepsy surgery across 9 surgical centers in the United States and Europe between 1991 and 2011; only one center reported peak mesial temporal sclerosis (MTS) related resections in 2011. While MTS was the main surgical substrate between 1991 to 2001 in most centers studied, MTS contributed to only 30% of total epilepsy surgery volume in 2011.[7] Thus, with more patients presenting with nonlesional MRIs, the proportion of patients undergoing invasive investigations has increased.[7] Bulacio et al published SF data of patients seen at a large surgical center in the United States with a median follow-up of 3.7 years (1-12 years); who underwent invasive EEG monitoring between 1998 and 2008. Authors found decreasing SF numbers with time: an estimated probability of complete SF of 61% at postoperative year one decreased to 42% at 5 years and to 33% at 10 years.[8] In another study from the United Kingdom[9] with a median follow-up of 5 years (1-27 years) after surgery (surgeries were performed between 1971 and 2014); SF rates were 47% at 5 years and 38% at 10 years after surgery.

During and after a typical epilepsy surgery conference, a cognitive assessment of potential SF is made on a case-by-case basis for every unique patient. This risk-benefit assessment of undergoing a craniotomy to attain the promise of total and durable SF is likely to color the ultimate decision to proceed with resective surgery or some other therapy for DRE like neuromodulation.

B: Do we have comparable SF data after neuromodulation?

In 2020, Nair et al published the long-term effectiveness of responsive neurostimulation (RNS) trial in 162 patients who completed all 9 years of follow-up.[6] Patients had a median of 10 plus seizures per month for an average of 19.7 years (range 2-58). This data also revealed diminishing SF rates at 6 months and 1 year of 28% and 18%, respectively, but improving median percent reduction in seizure frequency from 58% at year 3 to 75% by the end of year 9 of follow-up. Risk of infection per procedure was 4.1% and the average time to needing repeat craniotomy for battery replacement was 3.5 years. This data also supports improved quality of life (QOL) and decreased sudden unexpected death in epilepsy (SUDEP) risks. Changes in anti-seizure medications were not associated with eventual seizure frequency outcomes.

C: How does epilepsy surgery outcome in the Hsieh article compare to neuromodulation data published by Nair et al?

Hseih et al have responded to the need for valid comparative effectiveness assessment of resective surgery compared to RNS for long-term outcomes.[5] Authors chose 251 patients from their surgical database who had undergone resective surgery between 1994 and 2012 and had at least 9 years of postoperative follow-up. Patients were followed at 3 months, 6 months, and yearly after epilepsy surgery in clinic or via telephone using a standardized case review form. Like the Nair study, data were analyzed for postoperative complications and changes to anti-seizure medications over time. However, QOL assessments and SUDEP data were not analyzed/reported.

D: What were salient results from the Hsieh study?

Meaningful seizure reduction in terms of seizure frequency and durability: Prior to resective surgery; 71.8% patients had greater than weekly seizures for an average duration of 14.6 years; 96 patients (38%) had NO seizures after surgery and maintained this seizure free state over the course of >9 years of follow-up; 155 patients (61.75%) had postoperative recurrence of seizures: 38% within 6 months and 45.8% within the first year. However, the frequency of seizures was no longer debilitating in the majority; with 136 patients enjoying up to 1 year of SF and 86 of the 155 patients (55%) were seizure free at last follow-up. Looking at proportion of patients of the initial cohort of 251 patients who attained SF;182 (72.5%) were seizure free (>1 year of SF) at last follow-up. Of these two-thirds (119) achieved remission by 2 years after surgery. Median percent reduction of seizures at every time point was 100%; 20% of patients were able to come off their medications completely. Sixteen patients (6.4%) experienced serious peri/postoperative complications.

E: How might I use all this information to counsel my patients in clinic?

Our approach to epilepsy surgery has changed over time. We no longer offer epilepsy surgery so that patients can come off medications but do so because medications have failed our patients and medications alone are not sufficient to attain meaningful seizure control. We can no longer rely on "cut the lesion and be done with it" because there might not be such a lesion and when there is, it might not be the sole contributor to seizures. It may be more prudent to counsel patients in terms of meaningful seizure reduction (note that this term also includes SF) with SF discussed on a case-by-case basis. For those patients with less certain chances at SF, I now have more data with this paper. I would counsel my patients about variable times to SF ranging from 40% immediately after surgery to 70% within 2 years after surgery with additional medical management as necessary. The possibility of this outcome remains far superior to any other surgical or nonsurgical therapy available to our patients currently. Although it is clear from the original randomized control trial of temporal lobe resection[1] that QOL improved in the surgical group, authors Hsieh et al did not have consistent data to analyze in their retrospective study and future longer term outcome studies with focus on QOL are needed.

F: Might this data apply to children?

I am a pediatric epileptologist—In closing, Id venture that the above data, though adult focused, is applicable to my patient population as well. In children at risk for developmental delays with longer term ongoing seizures, surgical options without the promise of complete SF are better than no surgery at all.

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Declaration of Conflicting Interests

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