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Reoperations for Epilepsy: How Many Times Should We Bat?

Long-Term Outcomes of Reoperations in Epilepsy Surgery

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Objective: To analyze longitudinal seizure outcomes following epilepsy surgery, including reoperations, in patients with intractable focal epilepsy. Methods: Clinicoradiological characteristics of patients who underwent epilepsy surgery from 1995 to 2016 with follow-up of $\geq$1 year were reviewed. In patients undergoing reoperations, the latest resection was considered the index surgery. The primary outcome was complete seizure freedom (Engel I) at last follow-up. Potentially significant outcome variables were first identified using univariate analyses and then fit in multivariate Cox proportional hazards models. Results: Of 898 patients fulfilling study criteria, 110 had reoperations: 92 had one resection prior to the index surgery and 18 patients had 2 or more prior resective surgeries. Two years after the index surgery, 69% of patients with no prior surgeries had an Engel score of I, as opposed to only 42% of those with one prior surgery, and 33% of those with 2 or more prior resections ($P < .001$). Among surgical outcome predictors, the number of prior epilepsy surgeries, female sex, lesional initial magnetic resonance imaging, no prior history of generalization, and pathology correlated with better seizure outcomes on univariate analysis. However, only sex ($P = .011$), history of generalization ($P = .016$), and number of prior surgeries ($P = .002$) remained statistically significant in the multivariate model. Significance: Although long-term seizure control is possible in patients with failed prior epilepsy surgery, the chances of success diminish with every subsequent resection. Outcome is additionally determined by inherent biological markers (sex and secondary generalization tendency), rather than traditional outcome predictors, supporting a hypothesis of "surgical refractoriness."

Commentary

Enthusiasm for reoperation after an initial nonoptimal outcome from epilepsy surgery seems to be increasing. This is probably due to certain assumptions, which may or may not be true. We believe that both localization procedures, such as stereoelectroencephalography (sEEG,) and surgical procedures, such as selective ablations, have improved in both precision and safety. So why not take another swing at the baseball? (My apologies to football fans). Maybe things are better, but ultimately we need to know how many home runs we hit, that is, how many patients become seizure-free. Yardi and coauthors[1] measured the chance of seizure freedom among 110 patients who underwent a second or third therapeutic surgical procedure, relating this outcome to number of surgeries, gender, pathology from the first surgical specimen, proximity of the procedure to eloquent cortex, first surgery not done at the Cleveland Clinic, and a history of tonic–clonic seizures.

Not surprisingly, the strongest factor was the number of previous surgeries. The best batting average is often with the first swing of the bat. Easy pitches we knock out of the park 70% of the time. Hundred-mile-perhour fastballs, not so much. However, the epilepsy surgery game is changing in many ways. It is important to recognize that over the time period covered by this treatment series, many factors changed. This report is of a game played with radically different rules between 1995 and 2016. Over the same period of time, baseball batters became bigger and stronger. But pitchers became even bigger and stronger: the major league batting average is now 0.240, the lowest since 1908.[2] The analogy for us is that we physicians may be better and smarter, but we are seeing much tougher cases. The percentage of surgical candidates with obvious mesial temporal sclerosis is diminishing, for unclear reasons.[3] Yardi et al[1] mention the disconcerting fact that postsurgical seizure-free rates actually went down from the start to the finish of their case series.

Another big change is in electroencephalography (EEG) techniques. Their listing of 14 patients who underwent 3 procedures shows a clear progression from no invasive monitoring before the first surgery, to subdural electrodes before the second, to sEEG before the third. Of course, this does not prove that the combination of sEEG and smaller areas of tissue removal or ablation is either worse or superior to scalp EEG,

at least for the single outcome of seizure freedom. Stereoelectroencephalography might actually result in fewer successes with initial surgery. We can accept this because of superior surgical adverse event rates, as well as the option to proceed with second or third surgeries if the adverse event rates remain low. We can foul off a pitch or two if another ball is forthcoming.

This report should not be read as a cautionary tale against reoperation. A swing and a miss does not mean that you should sit down. Would we not be overjoyed if our third antiseizure medication trial resulted in a 33% seizure-free rate? The authors do not fall into the misperception, which became prevalent about medication, that the third try is bound to be futile. With regard to medication, this myth was recently corrected in a cogent letter.[4] Had these authors followed that line of thought, they would have reported misleadingly that there was only an 18 (2%) of 898 chance that a person with intractable epilepsy would become seizure-free with a third surgery. So, 1 of 3 sounds like a pretty good number, especially for home runs. Furthermore, the authors of reports of long-term recurrence rates often fail to note that many patients who relapse have had, or will have, long periods of remission, or renewed good seizure control with or without a new medication.[5] Reoperation would be even more attractive if adverse effects prove not to be bad. Yardi et al[1] do not report adverse effects of first versus third surgeries. However, most of the additional risk from repeat surgeries is to the visual fields after bigger temporal resections, with some increased neurological risk near eloquent cortex.[6] Furthermore, the preferred method for relocalization for possible reoperation is now sEEG,[7] which is safer than the use of subdural grids

Nevertheless, the authors highlight two negative preoperative prognostic factors which emerged from the multivariate analysis: male sex and a history of tonic–clonic seizures. We need to understand these factors in terms of both genetics and mechanisms of generalization. Of course, these same negative factors are relevant to prognosis after the first surgery. Surprisingly, lesions on MRI were not predictive. Pathology was also not predictive, although most failures involved "gliosis." With modern subpial resection and laser or radiofrequency techniques, good pathological specimens are unlikely in any case. Lobe of surgery was also nonpredictive, although most of these patients had temporal lobe epilepsy. One important postoperative factor is the occurrence of early versus late recurrence. Early recurrence may suggest that more surgery in the same region will be effective, with late recurrence suggesting that an epileptogenic process is ongoing. In that case, a remote focus or network may have been recruited. This series is not large enough for the timing of recurrence to be decisive in considering a second or third surgery, but late recurrence is an important phenomenon that we need to understand. It is ominous that Kaplan-Meier survival curves for seizure-freedom flatten but never truly level off even after 5 years, in this series or others.[1,5,8] Once we have a true antiepileptogenic drug—not an antiseizure medication—perhaps it could be administered to postoperative patients.

Finally, although seizure freedom is rightly considered our true goal, we should not minimize the importance of converting tonic–clonic seizures to focal seizures, an outcome not measured in this series. Medications are more effective at this than rendering patients totally seizure-free and that is also true of surgery. Neurostimulation is also an increasingly sophisticated option if destructive surgery is not chosen and may lessen the severity of seizures. Stopping tonic–clonic events may or may not improve quality of life, but it almost certainly reduces the chance of death.

The decision for surgical treatment of a person with epilepsy is one of the most complex in medicine. The decision to embark on reoperation is even more so. Yardi et al[1] have provided valuable data to guide us and especially to use in counseling our patients. However, because of the evolution of diagnostic and operative techniques, we need to revisit the question of reoperation very soon. This game, like baseball, has not stayed the same.

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