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 ≥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 coauthors1 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 every 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 al5 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. Stereoele-
troencephalography 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 recur-
cence 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 Reo-
peration would be even more attractive if adverse effects prove
not to be bad. Yardi et al1 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 tem-
poral resections, with some increased neurological risk near
eloquent cortex.6 Furthermore, the preferred method for relo-
calization for possible reoperation is now sEEG,7 which is safer
than the use of subdural grids

Nevertheless, the authors highlight two negative preopera-
tive 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. Surpris-
ingly, lesions on MRI were not predictive. Pathology was also
not predictive, although most failures involved “gliosis.” With
modern subpial resection and laser or radiofrequency tech-
niques, 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 postopera-
tive 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 consider-
ing 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 mea-
sured 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 al1 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.

By Edward Faught

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