HHS Public Access

Author manuscript

Curr Opin Neurol. Author manuscript; available in PMC 2019 April 01.

Published in final edited form as:

Curr Opin Neurol. 2018 April ; 31(2): 192–197. doi:10.1097/WCO.0000000000000528.

THE CURRENT PLACE OF EPILEPSY SURGERY

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Abstract

Purpose of Review—Three randomized controlled trials demonstrate that surgical treatment is safe and effective for drug resistant epilepsy (DRE), yet fewer than 1% of patients are referred for surgery. This is a review of recent trends in surgical referral for DRE, and advances in the field. Reasons for continued underutilization are discussed.

Recent Findings—Recent series indicate no increase in surgical referral for DRE over the past two decades. One study suggests that decreased referrals to major epilepsy centers can be accounted for by increased referrals to low-volume nonacademic hospitals where results are poorer, and complication rates higher. The increasing ability of high-resolution MRI to identify small neocortical lesions and an increase in pediatric surgeries, in part, explain a relative greater decrease in temporal lobe surgeries. Misconceptions continue to restrict referral. Consequently, advocacy for referral of all patients with DRE to epilepsy centers that offer specialized diagnosis and other alternative treatments, as well as psychosocial support, is recommended. Recent advances will continue to improve the safety and efficacy of surgical treatment and expand the types of patients who benefit from surgical intervention.

Summary—Surgical treatment for epilepsy remains underutilized, due in part to persistent misconceptions. Rather than promote referral for surgery, it would be more appropriate to advocate that all patients with DRE deserve a consultation at a full-service epilepsy center that offers many options for eliminating or reducing disability.

Introduction

A recently published study by the Center for Disease Control and Prevention, based on data collected from 2010 to 2015, indicates that the prevalence of epilepsy in the U.S. is significantly higher than previously determined. Three million adults and 475 children reported active epilepsy (doctor-diagnosed epilepsy under treatment, or seizures within the past twelve months), comprising 1.2% of the population (1). Given that antiseizure medication fails to control seizures in approximately 40% of people with epilepsy, there are well over a million people in the United States whose lives continue to be compromised by drug-resistant epilepsy (DRE). Whereas thousands of published surgical series, and three

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Conflicts of Interest

There are no conflicts of interest with respect to this paper, other than the fact that the author is the director of an epilepsy center.

randomized controlled studies (2, 3, 4), have confirmed the safety and efficacy of surgical treatment for selected cases of DRE, only a small fraction of potential surgical candidates actually receive surgery (5, 6). Although the percentage of people with DRE who might be considered candidates for surgery cannot be adequately determined, it could be as small as 10% or over 50%, the more serious issue is that less than 1% of patients with DRE are referred to full-service epilepsy centers annually, where multidisciplinary epilepsy specialists can determine whether surgery might be beneficial (7). Furthermore, when patients are referred and undergo surgery, the delay from onset of epilepsy averages over 20 years (8), often too late to reverse psychological and social comorbidity responsible for dependence on family and society. There is no argument that early surgical intervention for appropriately chosen patients with DRE offers the best opportunity to avoid a lifetime of disability, and premature death, and that this therapeutic option is underutilized. The degree of underutilization, and the reasons for it, remain unclear.

Current Trends in the Surgical Treatment for Epilepsy

The National Association of Epilepsy Centers (NAEC), whose membership consists of most of the epilepsy centers in the US, analyzed their data from 2003 to 2012 (5). During this time the number of US epilepsy centers offering surgical therapy increased from 37 to 189, and the number of monitoring beds per center increased from 7 to 8. They estimated that a low of 0.35% to a high of 0.63% of persons with DRE underwent a surgical procedure per year, the high being in 2009 with a decrease since then. The rate of neocortical resections remained stable while there was a decrease in temporal lobe resections, which traditionally have been the most common surgical procedures performed for epilepsy.

A more recent study of surgical procedures, derived from the Centers for Medicare and Medicaid Services, Part B, and the American College of Surgeons National Surgical Quality Program, between 2000 and 2013, identified a total of 6,200 cases of epilepsy surgery, 59% of which were temporal lobe resections (6). In this study, rates of temporal and extratemporal resections remained constant over time.

A third study attempted to define the evolution of epilepsy surgery between 1991 and 2011 by analyzing data collected from seven major epilepsy centers in the US, plus one in Germany and one in Australia (9). Five centers reported a reduction in surgical treatment for mesial temporal sclerosis (MTS) since 1991, three reported a reduction since 2001, and one continued to see an increase in surgery for this condition.

The situation in Europe is not much different than that in the US. A recently published representative study from Germany (10) evaluated patients admitted for presurgical evaluation between 1990 and 2011, and found an increase over time in patient referrals but a decrease after 2009 in surgical procedures. They attributed this to more complex cases and more reluctance on the part of patients to undergo surgery. Reasons for both of these trends are not apparent.

These data are consistent with prior studies demonstrating the tremendous underutilization of surgical treatment for DRE, and some confirm the experience of many epilepsy surgery

centers in the US and Europe of a specific consistent decrease in recent years of referral of candidates with mesial temporal lobe epilepsy (MTLE). The suggestion of some (9, 11), that this reflects a depletion of patients with classical MTS, is difficult to support. MTLE is the most common DRE in the adult population (12), and could constitute over half of the one million patients in the United States whose seizures are not controlled by medication; it would, therefore, be impossible to draw any conclusions regarding this large population based on the very small percentage who are referred to epilepsy centers. More likely, this represents a *general* decrease in surgical referrals that has disproportionately affected patients with MTLE compared to those with extratemporal epilepsy for two reasons: 1) increasing sensitivity of detection of focal cortical dysplasia and other small localized lesions by high-resolution magnetic resonance imaging (MRI); and 2) increasing acceptance of surgical treatment for pediatric patients with DRE, most of whom require extratemporal resections.

Another potentially important consideration is that an increasing number of patients with DRE may be operated on at community hospitals, particularly patients with MTS, which can often be easily identified on MRI. This was suggested by one of the studies mentioned previously (5); not only was there an increase from 2000 to 2013 in the percentage of surgeries performed at low-volume and non-academic centers, but this was associated with poorer outcome and an increased rate of minor and major complications.

One positive recent trend in referrals for surgical treatment of epilepsy is that disparities in the U.S., which disadvantage racial minorities (13), may have been reversed as a result of the implementation of the Affordable Care Act (14).

A final contribution to the recent decrease in resective surgical treatment for epilepsy is the advent of new approaches for focal ablative surgery. Two semi-invasive approaches are gaining popularity and are discussed below.

Why Aren’t More Patients with DRE Referred to Epilepsy Centers?

It is understandable that neurologists and patients maintain a healthy reluctance to consider brain surgery, particularly when they may be unaware that the risk of serious morbidity and mortality of DRE is considerably higher than that of surgical treatment (15). Cost may also be a consideration, but the outlay required for surgical treatment is considerably less than expenses incurred over a lifetime disabled by epileptic seizures. Despite many thousands of research papers, and tens of textbooks documenting the safety and efficacy of surgical treatment for epilepsy, primary care physicians and general neurologists, as well as patients and their families, continue to have serious misconceptions that make surgery appear to be an unattractive option (Table 1). For this reason, it has been suggested that recommendations should be for referral to an epilepsy center, rather than referral for epilepsy surgery (7). It is a tragedy when appropriate surgical candidates are not referred because their treating physician believes they would not benefit from surgery, or the patient does not wish to consider this alternative treatment. Rather, it could be argued that every patient with DRE deserves an evaluation by a multidisciplinary team of epilepsy specialists at a full-service epilepsy center, where advanced diagnostic approaches may determine that the patient is not

pharmacoresistant, does not have epilepsy, or is a candidate for other alternative therapies. Furthermore, whether or not evaluation at an epilepsy center results in elimination of seizures, services provided by psychiatrists, psychologists, counselors, and social workers experienced in daily life problems encountered by people with epilepsy, offer supportive care to greatly ameliorate or relieve epilepsy-related disabilities.

There have been several attempts to create on-line tools to quickly determine whether a patient with DRE may be a surgical candidate (16, 17). This well-intentioned effort may be useful for personnel at epilepsy centers, but would be counterproductive if advocated for primary care physicians and general neurologists, who might conclude patients not considered to be surgical candidates on the basis of such an index should not be referred to an epilepsy center (7, 18). Physicians should be encouraged, not discouraged, to make such referrals for *all* patients with DRE, whether they are surgical candidates or not, for reasons stated above; furthermore, it is quite likely that many patients deemed not to be surgical candidates on the basis of a simple grading scale will, in fact, benefit from surgery.

Recent Developments in Epilepsy Surgery

Advances in diagnostic approaches and surgical techniques continue to improve the safety and efficacy of surgical treatment for epilepsy, and also increase the types of epilepsy that can be treated by surgical means. It is not the intention of this review to provide a comprehensive discussion of these recent advances, but a few of the more promising developments are considered here.

Patient Selection

Diagnostic advances that improve our ability to accurately localize the epileptogenic region for surgical resection are making surgery an option for people with DRE who would not have been considered surgical candidates in the past. This is particularly important for patients with normal structural MRI scans (19) and those with multiple, or diffuse, lesions such as tuberous sclerosis, schizencephaly, or polymicrogyria, where only one of several lesions, or a part of a diffuse lesion, is epileptogenic.

It has been almost two decades since the discovery that brief pathological 100–600 Hz electroencephalogram (EEG) events characterize brain tissue capable of generating spontaneous seizures (20). These pathological high-frequency oscillations (pHFOs) are presumed to reflect summated action potentials from synchronously bursting neurons, which are known to underlie epileptogenesis. Numerous clinical studies have now demonstrated that pHFOs can be reliably recorded with clinical depth and subdural grid electrodes from both mesial temporal limbic structures, and neocortex during chronic intracranial monitoring, and that removal of brain areas generating pHFOs yields a high likelihood of a seizure free outcome (21–22). Most recently, studies carried out during intraoperative electrocorticography (ECoG) have revealed that the localization of pHFO activity is not necessarily the same after resection as before, and that seizure freedom is more likely when post-resection pHFOs are completely removed (23). At present, relatively few epilepsy surgery centers have developed the capacity to record pHFOs, either chronically or during

ECoG; however, as this technique becomes more widely available (24), it should greatly reduce the cost and increase the effectiveness of epilepsy surgery.

Structural MRI remains the mainstay of presurgical evaluation, and functional imaging, including positron emission tomography (PET) and ictal single photon emission computed tomography (SPECT), as well as various functional MRI (fMRI) approaches, provide additional information for localizing the epileptogenic region (25). MRI, PET, and SPECT are dealt with in more detail elsewhere in this volume. Combining techniques, for instance MRI/PET fusion, for delineation of small, difficult to identify lesions such as focal cortical dysplasias, EEG/fMRI for localizing BOLD signals associated with epileptiform discharges, and magnetoencephalography (MEG) with MRI and EEG, which offers the potential to record pHFOs noninvasively (26–27), are areas of active research. Resting fMRI is also being used to reveal functional network disturbances that can be correlated with diffusion tensor imaging (DTI), and EEG. Epilepsy is now appreciated to be a network disease where even focal seizures depend upon disturbances in discrete patterns of connectivity that are widely distributed throughout the whole brain. Patient-specific dynamical computational models are being constructed in which the connectivity matrices identify those areas with high epileptogenicity and predict which surgical resections are likely to be effective (28–30). Such functional connectivity studies can be combined with structural connectivity data utilizing DTI with the intention not only of planning initial surgery, but also determining why some surgical procedures fail and suggesting alternative second surgeries.

Surgical Approach

Advances in surgical approach involve issues related to techniques for invasive monitoring during presurgical evaluation, microscopic resective surgery, and alternative therapeutic intracranial procedures. With respect to invasive monitoring, there continues to be debate regarding the use of intracerebral depth electrodes, specifically stereo encephalography (SEEG) vs. subdural grids and strips. Up until the 1980s, centers tended to use only depth electrodes or only subdural electrodes when chronic intracranial monitoring was required, but by the time of the Second Palm Desert Conference (31), it was agreed that all centers should use both techniques, depth electrodes for deep epileptogenic regions such as those in mesial temporal lobe structures, and subdural electrodes for superficial neocortical epileptogenic regions. Since then, however, there has been a tendency to use only subdural electrodes in the United States, and only SEEG in Europe, although SEEG is now gaining popularity in the US, often using frameless robotic image guidance systems (32–34).

Resective surgery continues to be primarily lesion-directed, aided by advances in high resolution neuroimaging, as well as standardized pathological approaches (35) leading to formal definitions of two common pathological substrates, hippocampal sclerosis (36) and focal cortical dysplasia (37). As techniques for invasive monitoring and resective surgery have improved, interest has increased in identifying and removing epileptogenic regions in the insula, an area difficult to resect due to vascularity and location (see 38).

Neuromodulation in the form of recurrent deep brain stimulation (DBS) (39, 40), which is not yet approved in the United States but is in Europe, appears to be more effective than vagus nerve stimulation, but rarely renders patients seizure free.

Two semi-invasive ablation procedures have been recently introduced. Radio frequency thermocoagulation (41, 42), and laser intermittent thermal ablation treatment (LiTT), which is not yet approved in Europe, is increasingly used in the United States (43, 44). These approaches are effective for small discrete lesions such as hypothalamic hamartomas and heterotopias. Application of LiTT for MTLE is not as effective as open resection, but when patients are rendered seizure free there may be fewer neuropsychological deficits, and if seizures continue, open resection can be done as a second operation (45). The role these procedures will play in the future remains to be determined.

Responsive neurostimulation (RNS) (46, 47) involves implantation of a small computer in the skull connected to one or two epileptogenic brain regions by electrodes which permit detection of ictal onsets followed by abortive neurostimulations. This technique does not replace resective surgery, but widens the application of surgery by offering treatment when epileptogenic regions cannot be totally resected without producing unwanted neurological deficits, and when there are two independent epileptogenic regions, for instance bilateral MTLE. Patients usually experience a significant decrease in seizure frequency and severity, but rarely become seizure free. Results appear to improve over time.

Outcome

As surgical treatment is being carried out on increasingly more complicated forms of epilepsy, it is encouraging that overall outcomes continue to be highly beneficial, not only with respect to seizure frequency, but with improved quality of life. Studies show that patients experience improvement in anxiety, depression, and other adverse behavioral comorbidity following surgical treatment, whereas patients with DRE who do not undergo surgery tend to become worse in these domains (48).

An important perspective is that surgical treatment reduces the mortality rate among people with DRE, not only for those who become seizure free, but also for those who experience a significant decrease in generalized tonic-clonic seizure frequency and, therefore, are less susceptible to sudden unexpected death in epilepsy (SUDEP) (15). Retrospective analysis of a multi-institutional surgical registry that included data between 2006 and 2014 revealed a mortality rate for temporal lobe resections of only 1.4% (49). The major complication rate was 6.5% and the readmission rate was 11%. Typically, approximately half of surgical complications are transient. Data for intracranial monitoring have consistently shown more complications from subdural than from depth electrodes (50).

Whereas most surgical centers perform a version of the standardized anteromesial temporal resection as a treatment for MTLE, there remains interest in performing more selective amygdalohippocampectomies, with the belief that this yields fewer neuropsychological deficits. This view may be disputed by a recent study of 80 patients who were not seizure free following selective amygdalohippocampectomy, subsequently underwent anteromesial temporal resection, and more often experienced improvement rather than decline in psychological performance (51).

Conclusions

Surgical treatment for epilepsy remains underutilized, due, in part, to misconceptions about this alternative therapy. Rather than promote referral for surgery in the future, it would be more appropriate to advocate that all patients with DRE deserve a consultation at a full-service specialized epilepsy center where a multidisciplinary team of experts can offer advanced diagnostic and therapeutic approaches, as well as psychological and social support services to eliminate or reduce disability.

Acknowledgments

None

Financial Support and sponsorship

This work was supported in part by Grants NS-02808, NS-15654, NS-33310, NS-42372, NS80181, and NS100064 from the National Institutes of Health (NIH).

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Table 1

Common misconceptions about epilepsy surgery

Misconception	Fact
All drugs need to be tried.	Seizure freedom is unlikely after two drugs have failed.
Bilateral EEG spikes are a contraindication to surgery.	Patients with unilateral onset seizures usually have bilateral spikes.
Normal MRI is a contraindication to surgery.	Other techniques often detect a single epileptogenic one in patients with normal MRIs.
Multiple or diffuse lesions on MRI are a contra-indication to surgery.	The epileptogenic zone may involve only a part of the lesion.
Surgery is not possible if primary cortex is involved.	Essential functions can be localized and protected.
Surgery will make memory worse if there is an existing memory deficit.	Poor memory usually will not get worse and could get Better.
Chronic psychosis is a contraindication to surgery.	Patients will still benefit if seizures are eliminated.
I.Q. less than 70 is a contraindication to surgery.	Outcome depends on the type of epilepsy and the type of surgery.
Patients with focal epilepsy and a focal lesion can have the lesion removed without detailed pre-surgical evaluation.	Focal lesions can be incidental findings unrelated to the epilepsy; epileptogenicity of a lesion always needs to be confirmed.
My patient is too old.	Older patients do as well as younger ones.

Adapted from 52, with permission.

This was the original title of the table, which comes from the following volume: Engel J Jr. Seizures and Epilepsy, 2nd Edition. Oxford: Oxford University Press, 2013, p. 607.