Title
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Journal
Epilepsy Currents, 13(5)

ISSN
1535-7597

Author
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Publication Date
2013-09-01

DOI
10.5698/1535-7597-13.5.198

Peer reviewed

EPILEPSY CURRENTS

Current Review
In Clinical Science

Why Is There Still Doubt to Cut It Out?

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Surgical treatment for epilepsy has made tremendous strides in the past few decades as a result of advances in neurodiagnostics—particularly structural and functional neuroimaging—and improved surgical techniques. This has not only resulted in better outcomes with respect to epileptic seizures and quality of life, and reduced surgical morbidity and mortality, but it has also increased the population of patients now considered as surgical candidates, particularly in the pediatric age range, and enhanced cost-effectiveness sufficient to make surgical treatment available to countries with limited resources. Yet surgical treatment for epilepsy remains arguably the most underutilized of all accepted medical interventions. In the United States, less than 1% of patients with pharmacoresistant epilepsy are referred to epilepsy centers.

Although the number of epilepsy surgery centers has increased appreciably over the past two decades, the number of therapeutic surgical procedures performed for epilepsy has not increased at all. For patients who are referred, the average delay from onset of epilepsy to surgery is more than 20 years—too late for many to avoid a lifetime of disability or premature death. Not only has there been no consistent message to convince neurologists and primary care physicians to refer patients for surgery, but the increase in epilepsy surgery centers in the United States has appeared to result in a divergence of approaches to surgical treatment. Efforts are still needed to further improve the safety and efficacy of surgical treatment, including the identification of biomarkers that can reliably determine the extent of the epileptogenic region; however, the greatest benefits would derive from increasing access for potential surgical candidates to epilepsy surgery facilities. Information is needed to determine why appropriate surgical referrals are not being made. Consensus conferences are necessary to resolve controversies that still exist regarding presurgical evaluation and surgical approaches. Standards should be established for certifying epilepsy centers as recommended by the Institute of Medicine's report on epilepsy. Finally, the epilepsy community should *not* be promoting epilepsy surgery per se but instead emphasize that epilepsy centers do more than epilepsy surgery, promoting the message: All patients with disabling pharmacoresistant seizures deserve evaluation by specialists at epilepsy centers who can provide a variety of advanced diagnostic and therapeutic services.

The modern era of surgical treatment for epilepsy began in the late nineteenth century. The epileptogenic region was originally localized on the basis of seizure semiology and identification of a structural lesion, which was then superseded by the advent of EEG in the mid-twentieth century (1). Introduction of advanced neuroimaging by the end of the twentieth century—first PET and then MRI—returned presurgical evaluation to a more lesion-directed approach, with EEG often playing a confirmatory role. SPECT, MEG, and fMRI also contribute to the identification of previously invisible lesions, such as hippocampal sclerosis in patients with mesial temporal lobe epilepsy (MTLE), as well as malformations of cortical development (MCD), particularly in infants and young children. Advances in operative techniques have greatly improved the safety, as well as the efficacy, of epilepsy surgery. As a result, not only are we achieving better outcomes today, but many patients are receiving surgery who would not have been considered surgical candidates a decade ago. Furthermore, procedures are now sufficiently cost-effective to permit establishment of epilepsy surgery programs in countries with limited resources (2). A major remaining challenge is establishment of biomarkers that reliably localize and determine the extent of the epileptogenic region, particularly in patients without obvious structural lesions (3).

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Surgical Approaches

Various therapeutic surgical procedures are performed for intractable epilepsy today (Table 1), depending upon the type of epilepsy and the location of the epileptogenic region. Approaches to presurgical evaluation vary according to the type of surgical procedure to be performed. These procedures can be categorized into standardized resections, tailored resections, disconnections, and stereotactic ablations. Deep-brain stimulation (4) and responsive cortical stimulation (5) are beyond the scope of this discussion.

The most common standardized surgical resection and, indeed, the most common type of surgery performed for

TABLE 1. ***Common Surgical Procedures for Epilepsy***

Anterior temporal lobe resection
Amygdalohippocampectomy
Neocortical resection
Lesionectomy
Hemispherectomy/Hemispherotomy
Multilobar resection
Corpus callosotomy
Multiple subpial transection
Stereotactic ablation

pharmacoresistant epilepsy, is anterior temporal lobe resection. Originally, this included 5 to 6 cm of the lateral temporal cortex; more recently, many centers prefer an anteromesial temporal resection that includes the pole and mesial temporal structures, sparing most of the lateral cortex (6). Selective amygdalohippocampectomy is a smaller standardized resection used by some centers (7). The other common standardized resection is hemispherectomy or, more recently, hemispherotomy, usually performed in infants and young children with diffusely epileptogenic abnormalities limited to one hemisphere (8). Presurgical evaluation for these procedures need only determine that the epileptogenic region is within the boundaries of the intended standardized resection.

Neocortical resections are always tailored, meaning that the presurgical evaluation must not only localize the epileptogenic region but determine its extent (9). Some centers still prefer to perform tailored anterior temporal resections for MTLE, and tailored multilobar resections can also be performed in lieu of hemispherectomy or hemispherotomy when a portion of cortex in the affected hemisphere has retained important function and appears not to be epileptogenic. Lesionectomies are tailored resections that spare cortical margins to preserve essential function. Gelastic seizures with hypothalamic hamartomas are a unique epilepsy condition in that seizures clearly originate within the tumor and not from adjacent cortex (10, 11).

The prototypic disconnection surgery is corpus callosotomy, which can be effective in controlling drop attacks in patients with diffuse bilateral epileptogenic abnormalities (12). Presurgical evaluation for this procedure need only confirm that the patient is not a candidate for a more definitive resective procedure. Corpus callosotomy is rarely performed today because vagus nerve stimulation (VNS) has a similarly beneficial effect. Multiple subpial transection (MST) is a localized disconnection procedure, usually performed in association with cortical removal when the epileptogenic region includes essential cortex that cannot be resected (13). Presurgical evaluation for this procedure is the same as for tailored resections. Hemispherotomy includes a disconnection procedure (8).

The most common stereotactic ablative procedure is gamma knife surgery (GSK), which uses stereotactic radiosurgery to destroy epileptogenic tissue (14). There is initial edema, which can produce unwanted side effects; the therapeutic effect, if it occurs, takes months or sometimes more than a year. A more recent invasive approach requires temporary implantation of a probe to create laser ablations; the antiseizure effect, if it occurs, is more immediate (15). These techniques are particularly useful for patients who have medical contraindications to open surgery.

Presurgical Evaluation

The key to determining successful resective surgical treatment is delineation of the epileptogenic region, defined as the area necessary and sufficient for generation of habitual seizures, and the smallest amount of tissue that can be removed to achieve a seizure-free outcome (9). The epileptogenic region is a theoretical concept, and there is no diagnostic procedure that definitively determines its location and extent. This can only be approximated through use of a variety of EEG, MRI, neurocognitive, and other measures (Table 2). Tremendous advances in neurodiagnostics, particularly in neuroimaging, have made it possible for the majority of surgical candidates to proceed to surgery today based on noninvasive presurgical evaluation, with or without intraoperative recording, but some still require long-term monitoring with intracranial electrodes: stereotactically implanted depth electrodes and/or subdural grid and strip electrodes.

Prior to the late 1980s, different schools preferred different invasive approaches to presurgical evaluation: Some chose to use depth electrodes only, others to use subdural electrodes only, others chose to invasively explore all or almost all patients, and still others not to use chronic invasive studies at all but to only do direct recordings intraoperatively (16). General consensus was reached during two Palm Desert conferences (17, 18) regarding when and how to use all the various invasive recording approaches. As a result of this and the advent of high-resolution MRI, invasive studies became necessary in only a minority of patients, with depth electrodes recommended for evaluation of deep epileptogenic regions, as in mesial temporal lobe epilepsy, and subdural electrodes for evaluation of superficial neocortical epilepsies.

A relative increase in tailored neocortical resections in recent years derives from improved high-resolution MRI that can identify previously invisible lesions, such as focal cortical dysplasia (FCD) in adults, as well as a variety of MCDs in infants and young children (19). PET-MRI fusion has helped to localize these very subtle structural abnormalities (20). Ictal SPECT has also been useful in localizing hard-to-characterize areas of ictal onset, particularly when co-registered with MRI (21). MEG and EEG source localization of interictal spikes and ictal discharges helps confirm localization and plan the placement of invasive electrodes (22). Simultaneously recorded EEG and fMRI localizes blood flow changes related to interictal spikes and offers another approach to identifying the epileptogenic region (23).

Considerable effort is now directed toward potential biomarkers that might reliably delineate the epileptogenic region (24). Alpha-methyl-tryptophan (AMT) PET is one candidate (25), but to date, the most promising biomarker is pathological high-frequency oscillations (pHFOs) (26–28), which appear to define epileptogenic tissue more reliably than interictal spikes (29) or ictal onset (30). Currently, however, these biomarkers

TABLE 2. ***Definition of Abnormal Brain Areas***

Zone	Definition	Measures
Epileptogenic zone	The area of brain that is necessary and sufficient for initiating seizures and whose removal or disconnection is necessary for abolition of seizures	Theoretical concept
Irritative zone	Area of cortex that generates interictal spikes	Electrophysiological (invasive and non-invasive)
Ictal onset zone	Area of cortex where seizures are generated (including areas of early propagation under certain circumstances)	Electrophysiological (invasive and non-invasive)
Epileptogenic lesion	Structural abnormality of the brain that is the direct cause of the epileptic seizures	Structural imaging and tissue pathology
Symptomatogenic zone	Portion of the brain that produces the initial clinical symptomatology	Behavioral observation and patient report
Functional deficit zone	Cortical area of non-epileptic dysfunction	Neurological examination, neuropsychological testing, EEG, PET, SPECT

EEG, electroencephalogram; PET, positron emission tomography; SPECT, single photon emission computed tomography. From Ref. 14, with permission.

can be identified only with direct brain recordings. Future non-invasive identification of pHFOs may be possible with scalp EEG (31), MEG, or EEG-fMRI.

Presurgical evaluation is necessary not only to identify the epileptogenic region but also to ensure that the planned surgical procedure will not result in unacceptable additional neurological deficits. For standardized anterior temporal resections, this requires confirmation that the contralateral hemisphere can support memory, which can usually be determined by neurocognitive testing and the intracarotid amobarbital procedure (IAP) (32). When the epileptogenic region includes, or abuts upon, essential neocortex that cannot be resected, functional mapping is necessary, which can be achieved with intraoperative or extraoperative ECoG and with functional imaging using fMRI, PET, and MEG (33).

In the 20 years since the second Palm Desert conference (18), there has been a substantial increase worldwide in the number of epilepsy centers performing surgical treatment, and this appears to have been accompanied by a return to increased divergence among centers in their approaches to surgical and presurgical evaluations. Most centers continue to do more anterior temporal resections than other therapeutic procedures, but some are now performing many more tailored neocortical resections; the reasons for this divergence are not clear. In addition, there are growing differences from one center to another concerning the need for invasive recording, and many centers today rely entirely on subdural recording, even for epileptogenic regions in mesial temporal and other deep structures. There is also no agreement internationally on how to perform IAP or when it is necessary; approaches range from centers that never use IAP to those who use it in all cases, often bilaterally. Given so many conferences and publications on epilepsy surgery during the past two decades, it is difficult to understand why such divergent schools have arisen, but there appears to be a need for consensus on standards.

Outcome

There is no doubt that the past two decades have seen marked improvement in the safety and efficacy of surgical treatment for epilepsy. Not only have outcomes with respect to seizures improved (34, 35), but we now have measures of health-related quality of life (HRQOL) that can quantify the beneficial effects of seizure freedom on patients' lives (36). Two randomized controlled trials (RCTs) of anterior temporal resections for MTLE have confirmed that surgery is superior to continued pharmacotherapy. The first included subjects with long-standing epilepsy who were randomized before presurgical evaluation, so some in the surgical arm were not necessarily the best surgical candidates (37). Nevertheless, 64 percent of those undergoing surgery were seizure free and experienced a significant improvement in HRQOL at one year. Based on this study and a review of the literature, the American Academy of Neurology (AAN) published a practice parameter recommending surgery as the treatment of choice for pharmacoresistant temporal lobe epilepsy, and suggested that surgery should be performed early to avoid adverse psychological and social consequences that lead to irreversible disability (38). Consequently, the second RCT enrolled subjects within two years of failure of two antiseizure drugs, performing presurgical evaluation to establish surgical candidacy prior to randomization (39). In this group of early refractory patients with relatively pure MTLE, 85 percent of those who underwent surgery and completed the study were free of all seizures in the second postoperative year and had a statistically significant improvement in HRQOL. Numerous noncontrolled surgical series have duplicated these findings and also revealed the beneficial

effects of other surgical procedures (34, 35). Surgical benefit is long-lasting for most patients (40).

A recent meta-analysis documented that mortality with epilepsy surgery is exceedingly rare, and that complications are, for the most part, minor or temporary (41). Material-specific memory deficits do usually occur with anterior temporal resections in patients who do not have memory deficit preoperatively. Such deficits are likely to be of clinical significance when surgery is in the language-dominant hemisphere, and this remains a particular concern for early surgical therapy. However, one study revealed that HRQOL improves when patients are seizure free, even if they experience postoperative memory deficit (42), indicating that seizure freedom is a fair tradeoff for memory loss. In this study, HRQOL only declined in 8 percent of patients: those who were not seizure free and also experienced memory loss.

Underutilization

Despite the unequivocal benefits of surgical treatment—now demonstrated with two RCTs for temporal lobe epilepsy (36, 37)—with recognition that very few patients become seizure free after failing two appropriate antiseizure drugs (43) and evidence that pharmacoresistant epilepsy often causes progressive adverse psychological and social consequences leading to irreversible disability, or premature death (44), surgical treatment for epilepsy remains arguably the most underutilized of all accepted therapies in the field of medicine. If one considers one-third of people with epilepsy to have pharmacoresistant seizures, there should be approximately one million people in the United States with epileptic seizures who have not adequately been controlled by medication. Somewhere between 10 and 50 percent of these (100- to 500,000 people) are potential surgical candidates, yet only 2,000 therapeutic surgical procedures per year are performed, in the United States, according to the National Association of Epilepsy Centers. Although there has been an increase in the number of patients with epilepsy referred to hospitals over the past two decades, there has not been an increase in the number of surgical procedures performed; in fact, there has been a decrease in referrals to full-service epilepsy centers where surgical treatment is offered (45, 46). A large multicenter study indicated that when patients are referred for surgery, this referral is made on average more than 20 years after onset of epilepsy (47), often too late to avoid irreversible disability. Although such patients usually become seizure free after surgery, they are likely to remain dependent on families and society. Two studies have demonstrated no change in the delay from diagnosis to referral after the first RCT and the AAN practice parameter (48, 49).

Recent publications have commented on what appears to be a decrease in numbers of uncomplicated cases of MTLE with hippocampal sclerosis referred for surgery (50, 51), suggesting that this might reflect a general decrease in the incidence of this condition. Given that such a small percentage of patients with medically refractory epilepsy are ever referred to epilepsy centers, there would be no justification for drawing conclusions about the incidence or prevalence of hippocampal sclerosis based only on experience at these centers. More likely, this observation reflects the possibility that many community hospitals are operating on straightforward cases of MTLE themselves, without bothering to refer them to epilepsy centers. Another explanation is that the reduction in the number of referrals of patients with MTLE merely reflects the overall reduction in surgical referrals in general, while there has been a relative increase in referrals of neocortical epilepsies as a result of the ability of high-resolution MRI to identify MCDs, and the increase in surgery for infants and young children who do not have MTLE.

Reasons for the persistent reticence among physicians and patients to consider surgical therapy need to be elucidated. Suggestions include: 1) fear of surgery, yet morbidity and mortality from recurrent seizures is greater than that from epilepsy surgery (41, 44); 2) lack of information about improvements in safety and efficacy, yet countless books (for physicians and the lay public), two randomized controlled trials, and hundreds of surgical series have been published in recent years; and 3) the expense of surgery, yet the cost is considerably less than the cost of a lifetime of disability (52). It is understandable why uninformed patients might continue to consider surgery a last resort, but physicians, particularly neurologists, must certainly be aware that surgery offers hope for seizure freedom in a high percentage of properly chosen patients who otherwise would likely become irreversibly disabled or die prematurely.

One possible obstacle could be that physicians might feel they should refer only patients whom *they* consider to be good surgical candidates. There are countless misconceptions in the medical community concerning criteria for surgery (Table 3). Indeed, it is a common experience at epilepsy surgery centers to see self-referred patients who are excellent surgical candidates but were not referred by their neurologists who were certain they were not surgical candidates. A solution to this problem would be for the epilepsy community to stop promoting epilepsy surgery per se, which tends to "turn off" patients, and perpetuates the misconceptions of referring physicians. Instead, we should promote the fact that epilepsy centers have much to offer besides epilepsy surgery, and that *all* patients who continue to have epileptic seizures that interfere with work, school, or interpersonal relationships, despite two trials of appropriate antiseizure drugs, deserve a consultation at a specialized full-service epilepsy center. Then let center epileptologists decide who might be surgical candidates.

Conclusions

Tremendous advances in diagnostic technology have greatly improved the efficacy and safety of resective surgical treatment, but there is an overriding need to identify and validate reliable biomarkers, such as pHFOs, that can delineate the extent, as well as the location, of the epileptogenic zone.

Surveillance studies should be carried out to determine knowledge, attitudes, and practices of general neurologists toward epilepsy surgery: How many of their patients who meet the criteria for pharmacoresistant epilepsy have *not* been referred to an epilepsy center—and why?

Data should be collected to determine the extent of variation in approaches to epilepsy surgery from one epilepsy surgery center to another and, if possible, the reasons for this variation. If it is clear that significant controversies remain

TABLE 3. ***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 often have bilateral spikes.
Normal MRI is a contraindication to surgery.	Other techniques often detect a single epileptogenic zone in patients with normal MRIs.
Multiple or diffuse lesions on MRI are a contraindication 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.
IQ 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 presurgical evaluation.	Focal lesions can be incidental findings unrelated to the epilepsy; epileptogenicity of a lesion always needs to be confirmed.

From Ref. 54, with permission.

concerning appropriate approaches to surgery and presurgical evaluation, a consensus conference should be held.

The Institute of Medicine Report on *Epilepsy across the Spectrum* (53) recommended establishing accredited epilepsy centers, which would then work together to form an epilepsy care network. Accreditation would ensure that specific criteria for surgical treatment for epilepsy were met at all epilepsy centers and that every patient referred to an epilepsy center would have access to the best standard of surgical treatment, when appropriate.

The epilepsy community should replace its promotion of epilepsy surgery per se with promotion of the value of epilepsy centers for the diagnosis and treatment of pharmacoresistant epilepsy in general. The new message should be: All patients with disabling pharmacoresistant seizures deserve evaluation by specialists at epilepsy centers who can provide a variety of advanced diagnostic and therapeutic services.

Acknowledgments

Original research reported by the author was supported in part by Grants NS-02808, NS-15654, NS-33310, and NS-80181.

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