Surgical Treatment of Epilepsy

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ABSTRACT

Purpose of Review: This article outlines indications for neurosurgical treatment of epilepsy, describes the presurgical workup, summarizes surgical approaches, and details expected risks and benefits.

Recent Findings: There is class I evidence for the efficacy of temporal lobectomy in treating intractable seizures, and accumulating documentation that successful surgical treatment reverses much of the disability, morbidity, and excess mortality of chronic epilepsy.

Summary: Chronic, uncontrolled focal epilepsy causes progressive disability and increased mortality, but these can be reversed with seizure control. Vigorous efforts to stop seizures are warranted. If two well-chosen and tolerated medication trials do not achieve seizure control, an early workup for epilepsy surgery should be arranged. If this workup definitively identifies the brain region from which the seizures arise, and this region can be removed with a low risk of disabling neurologic deficits, neurosurgery will have a much better chance of stopping seizures than further medication trials.

REASONS FOR EPILEPSY SURGERY

About one-third of epilepsy patients have seizures that cannot be controlled with medication. This has severe consequences, including interference with school and work, loss of independence and social isolation, and increased risk of injury, depression, and suicide. Patients with uncontrolled epilepsy also have a significantly increased long-term mortality rate (1.59% per year), with sudden unexpected death in epilepsy (SUDEP) being the most common cause. Furthermore, uncontrolled temporal lobe epilepsy is associated with slowly progressive cortical atrophy and cognitive deterioration.

For selected patients, resection of epileptogenic brain has a far better chance of controlling drug-resistant seizures than further medication trials. There is also class I evidence for the efficacy of temporal lobectomy and evidence that successful neurosurgical treatment reverses much of the disability and increased mortality of chronic epilepsy. For all of these reasons, clinicians treating chronic epilepsy must recognize which patients to refer for epilepsy surgery and what it can accomplish.

CANDIDATES

Resective surgery is a consideration in patients with drug-resistant, uncontrolled, disabling focal epilepsy if the seizures originate from a region that can be removed with minimal risk of disabling neurologic or cognitive dysfunction. Epilepsy is termed drug-resistant when two tolerated, appropriately chosen and used antiepileptic drugs (AEDs)
fail to achieve sustained seizure freedom.\textsuperscript{12} Response to an additional medication trial ranges from 4\% to 16\% in different studies\textsuperscript{2,13} but depends on epilepsy syndrome and etiology.\textsuperscript{14,15} Patients with drug-resistant seizures should have an epilepsy center evaluation to confirm the diagnosis and determine the epilepsy syndrome and possible candidacy for neurosurgery. Vagus nerve stimulation is not more effective than AEDs and has a very low chance of achieving seizure freedom in drug-resistant epilepsy, so it should not be considered before resective surgery, and should be reserved for patients who are poor candidates or who refuse surgery.\textsuperscript{16}

Patients with lesional epilepsy respond more poorly to AEDs than those with cryptogenic/idiopathic epilepsy but have a better chance of seizure freedom with surgery.\textsuperscript{14,15} Therefore, those with chronic, intractable epilepsy due to discrete lesions such as mesial temporal sclerosis (MTS), low-grade neoplasms, vascular malformations, encephalomalacia from stroke or trauma, and focal cortical dysplasias are common surgical candidates. Good surgical outcomes are also possible in patients with normal MRI if the seizures are electrographically well localized to the temporal lobe.\textsuperscript{17–20}

Identifying the seizure focus in patients with normal MRI and neocortical epilepsy is much more difficult. They may still be surgical candidates if electrographic seizures are clearly localized, and other tests, such as invasive video-EEG monitoring, positron emission tomography (PET), or ictal single-photon emission computed tomography (SPECT) confirm the location of the epileptic focus. Sometimes focal cortical dysplasia is documented postoperatively in such seemingly nonlesional cases. Because the chance of seizure freedom with surgery is lower in these patients,\textsuperscript{21,22} and the chances of achieving seizure control with medication is somewhat higher with cryptogenic epilepsy,\textsuperscript{14,15} these individuals typically will receive more than two medication trials before surgery is considered.

Patients who are typically not surgical candidates include those with clear evidence of bilateral onset of habitual seizures (Case 9-1), those with severe psychiatric or medical comorbidities increasing surgical risk or compromising recovery, those with rapidly progressive CNS disease, and those with primary generalized epilepsy.

**SURGICAL WORKUP**

**Initial Evaluation**

Upon referral, the patient undergoes a detailed neurologic history and examination, neuroimaging, video-EEG monitoring, and neuropsychological testing. MRI at 3 Tesla should include coronal fine cuts of T1- and T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences to detect signal change and atrophy or loss of internal structure with hippocampal sclerosis, and detailed imaging of other regions suspected as sites of seizure origin from history or other tests.\textsuperscript{23} Focal cortical dysplasia may be subtle; sometimes meticulous inspection will reveal mild cortical thickening or an unusually deep sulcus, but special image analysis techniques can help.\textsuperscript{24}

Long-term video-EEG monitoring with scalp electrodes is essential to confirm and localize focal epilepsy. If possible, several seizures should be captured to confirm a single focus. Interictal spikes also aid localization. Standard 10:10 scalp electrode placement is performed, sometimes with bilateral infratemporal electrode chains or other additional electrodes over the likely seizure-onset region. Dense array video-EEG monitoring, usually with 256 electrodes, also improves localization, especially in neocortical epilepsy (Figure 9-2).\textsuperscript{25}

**KEY POINTS**

- About one-third of patients with epilepsy have seizures that cannot be controlled with medication.
- Uncontrolled epilepsy causes progressive disability and increased mortality risk.
- Resective epilepsy surgery requires definite demonstration that the seizures originate from a region that can be removed with minimal risk of disabling neurologic or cognitive dysfunction.
- Epilepsy is termed drug-resistant when two appropriate, tolerated medications fail to control seizures.
- Epilepsy surgery should be considered in drug-resistant cases before the vagus nerve stimulator.
- Lesional epilepsy has a poorer response to medications than cryptogenic/idiopathic epilepsy but a better chance of seizure freedom with epilepsy surgery.
Neuropsychological testing establishes baseline measurements of any cognitive deficits, sometimes giving insight into the epileptic focus location. It also allows comparison with postoperative testing to measure cognitive outcomes. Predictors of higher risk of cognitive decline after temporal lobectomy include intact baseline cognitive ability, dominant temporal lobe resection, later age of epilepsy onset, normal MRI results, female gender, and loss of memory function during injection of amobarbital into the carotid artery on the side of planned surgery (the intracarotid amobarbital procedure [Wada test] is discussed below under “Functional Localization”).

Case 9-1
A 44-year-old, right-handed man had cryptogenic epilepsy since age 18, with weekly seizures refractory to eight antiepileptic drug trials. His seizures were nocturnal (he made noises, thrashed, and wandered around), and convulsions were infrequent. Scalp EEG showed independent left and right anterior temporal epileptiform abnormalities in equal proportions, and three seizures with right anterior temporal ictal EEG changes. Repeat EEG monitoring captured three left temporal seizures and a right temporal seizure with different semiology. Single-photon emission computed tomography (SPECT) injection during a seizure with right temporal EEG changes showed right temporal hyperperfusion (Figure 9-1). The patient’s MRI results were normal.

Comment. While this patient has focal onset epilepsy, there is no clear evidence all seizures are arising from a single focus (in fact, the data suggest otherwise). The normal MRI results do not provide any evidence to localize the seizures, and the EEG indicates that the seizures arise independently from the right and left temporal lobe. This patient is not a surgical candidate since only unilateral resections can be safely performed. Bilateral mesial temporal lobe resection or injury may lead to devastating global amnesia.
FIGURE 9-2

Right temporal secure on 256-channel scalp EEG recording. The underlying recording shows a subset of the recorded channels with the black arrow pointing to a cursor placed shortly after the seizure onset. Activity on all channels at the time of the cursor is displayed in the insert on upper left corner, with the orange arrow pointing toward the right temporal ictal discharge. The insert at the bottom left shows source localization of the ictal activity at the time of the cursor to the right mesial temporal region (white arrow).
Further Noninvasive Assessment
Localization of the epileptic focus requires that different tests give congruent information. 18F-fluorodeoxyglucose (FDG) PET, which measures interictal cerebral glucose, is particularly useful for additional confirmation (Figure 9-3). Unilateral temporal lobe hypometabolism on 18F-FDG-PET strongly predicts seizure freedom with resection of that temporal lobe, independent of MRI findings.\(^{28}\) Another approach is ictal SPECT, which images cerebral blood flow with a radioactive tracer (usually 99mTc–hexamethylpropylene amine oxime [HMPAO]). This tracer is injected intravenously as early as possible during a seizure and is taken up by tissue on its first pass through the brain, producing a “snapshot” of ictal blood flow. Imaging is enhanced by digital subtraction of a second image taken after an interictal injection; this subtracted image can be coregistered with MRI.\(^{29}\) SPECT is a powerful method for confirming localization of both mesial temporal and cortical seizures.\(^{30}\) Other imaging modalities include PET with other tracers, including agents binding to opioid, benzodiazepine, dopamine, or serotonin receptors, and magnetic resonance spectroscopy that can detect decreased N-acetylaspartate (NAA) concentration in mesial temporal epilepsy. Magnetoencephalography can better localize interictal spikes in three dimensions, but is not suitable for recording and localizing actual seizures.\(^{31,32}\)

Invasive Video-EEG Monitoring
This is performed when noninvasive testing suggests a resectable epileptic focus with some uncertainty. Invasive video-EEG can also more precisely delineate the extent of a neocortical epileptogenic zone and its relationship to areas of eloquent functional cortex. Arrays of disk electrodes embedded in sheets or strips of silastic are usually subdurally implanted. Depth electrodes can also be inserted into the brain, typically to record from deeper structures, although some centers also use these for cortical recordings. Monitoring occurs in the patient’s room over several days to localize typical seizures.

Functional Localization
Defining speech and language dominance for temporal and some frontal resections is necessary. In addition, eloquent cortices essential for language, motor, or sensory functions must often be delineated so resection can be tailored to avoid causing deficits.

The intracarotid amobarbital procedure is the best validated method of determining the speech dominant hemisphere and can also assess risk of postoperative memory deterioration after temporal lobectomy.\(^{26,27}\) Amobarbital or another anesthetic is
injected into the internal carotid artery, temporarily disrupting function on that side, while language and memory tests are performed. In addition, functional MRI and magnetoencephalography are being developed as alternatives for lateralizing or localizing temporal language function.\textsuperscript{33,34}

Although functional MRI can be used to locate functional neocortex and associated connections, the standard approach in epilepsy surgery is mapping by electrical cortical stimulation. This can be carried out intraoperatively (during brief period of wakefulness during the operation) or at bedside with the same subdural electrodes used for invasive EEG monitoring. Mapping of temporal language cortex then is done with the patient naming objects displayed on a computer screen while the physician systematically maps cortex by stimulating various brain regions.

**COMMON SURGICALLY TREATABLE EPILEPSY SYNDROMES**

**Mesial Temporal Lobe Epilepsy**

Mesial temporal lobe epilepsy is the most common surgically treated epilepsy, with efficacy of lobectomy demonstrated in a randomized controlled trial.\textsuperscript{9} Seizures often begin with rising epigastric sensations, smells, fear, déjá vu or jamais vu, and progress to loss of responsiveness, often with behavioral arrest, orofacial automatisms, ipsilateral hand movements, and contralateral arm posturing. The most common associated pathology is MTS (Case 9-2), which may be associated with a history of early-life febrile seizures or neurologic insult, and is pathologically characterized by hippocampal neuronal loss in CA1 and CA3 as well as the dentate granule cell layer.\textsuperscript{35} Identical seizures can result from mesial temporal tumors, vascular malformations, and dysplasia. A few MTS patients have a second, ipsilateral cortical focus (i.e., “dual pathology”), with better surgical outcome if the second focus can also be resected.\textsuperscript{36}

The most common surgical procedure for mesial temporal epilepsy is the anterior temporal lobectomy, in which the temporal pole is removed to allow resection of the hippocampus and part of the amygdala. The anterior temporal resection may be measured (4.0 to 4.5 cm from the temporal tip on the dominant side, and 5.0 to 5.5 cm on the nondominant side).\textsuperscript{37} Cortical resection can also be tailored based on language mapping (because temporal language cortex location is variable)\textsuperscript{38} and intraoperative electrocorticography, and the extent of hippocampal resection may be determined by the presence of interictal epileptiform discharges along its length.\textsuperscript{39} Alternate techniques to amygdalo-hippocampectomy include approaches through the superior temporal gyrus, the middle temporal gyrus, the basal temporal cortex, or parahippocampal gyrus.\textsuperscript{40,42} Radiosurgery and MRI-guided laser ablation of the hippocampus are also being investigated as alternative approaches to treat hippocampal epilepsy while reducing injury to other nearby temporal structures.\textsuperscript{43}

**Neocortical Epilepsy**

The clinical manifestations of neocortical epilepsy depend on the region involved.\textsuperscript{44} Lateral temporal lobe seizures are more likely to have experiential auras and less likely to have epigastric auras and contralateral dystonia. Frontal lobe seizures tend to be shorter and more frequent than temporal lobe seizures, with manifestations varying from motionless staring to violent automatisms, and often may be confined to sleep. Parietal and occipital seizures often have complex sensory symptoms such as visual hallucinations.

**KEY POINT**

- The effectiveness of temporal lobectomy for mesial temporal epilepsy has been demonstrated in a randomized controlled trial.
Case 9-2
A 34-year-old, right-handed woman presented with a history of status epilepticus of unknown cause at age 3, and subsequent complex partial seizures with orofacial automatisms and postictal aphasia that were refractory to five antiepileptic drugs. EEG showed interictal left anterior temporal sharp waves and left temporal seizures, and MRI demonstrated left mesial temporal sclerosis (Figure 9-4). The patient became seizure free after a left temporal lobectomy.

Comment. Mesial temporal epilepsy is a highly surgically remediable epilepsy syndrome, with anterior temporal lobectomy often offering an excellent chance for seizure freedom.

FIGURE 9-4 MRI showing left mesial temporal sclerosis (arrow) with a smaller hippocampus with increased signal and loss of internal architecture.

FIGURE 9-5 Right inferior frontal ganglioglioma (arrow) in a 29-year-old man with lifelong intractable epilepsy that was later successfully treated with surgery.

Epilepsy Due to Tumors
Benign or low-grade neoplasms such as meningiomas, gangliogliomas (Figure 9-5), dysplastic neuroepithelial tumors, astrocytomas, and oligodendrogliomas may cause chronic but surgically remediable epilepsy. The goal is to completely remove the lesion and the surrounding epileptogenic brain, if possible. Sometimes invasive monitoring
with mapping of the seizure-onset region and of brain function is needed.

**Epilepsy Due to Developmental Abnormalities**

Type I focal cortical dysplasia is characterized by delamination in the temporal lobe, but only some patients develop drug-resistant epilepsy. On the other hand, type II (Taylor type) dysplasia contains dysmorphic neurons and is characterized by medically refractory extratemporal epilepsy. If the entire dysplastic area visible on MRI can be completely removed at surgery, good seizure outcome is possible (Case 9-3, Figure 9-6).

Tuberous sclerosis complex may result in medically intractable focal epilepsy, and resection of an epileptogenic tuber may sometimes palliate seizures. In patients with Sturge-Weber syndrome, seizures may be controlled with medication in about 50% of cases, or spontaneously remit. Resection of brain affected by the leptomeningeal venous angioma may control seizures. After partial resection of venous angiomas, however, intractable epilepsy often recurs. The most effective treatment is hemispherectomy in those who have developed severe hemiparesis.

Hypothalamic hamartomas are rare developmental lesions attached to the tuber cinereum or the mammillary bodies, sometimes resulting in intractable epilepsy with gelastic (laughing) seizures. Complete microdissection by an endoscopic technique, or radiosurgery, can be effective.

**Epilepsy Due to Vascular Malformations**

Arteriovenous malformations may cause intractable epilepsy. Treatment is with embolization, radiosurgery, or microsurgery. These last two approaches have been shown to have a good chance of seizure control. Symptomatic cavernous hemangiomas most commonly present with seizures. They can be resected when they cause drug-resistant epilepsy or, less frequently, clinically significant hemorrhages. Surgery consists of lesionectomy plus resection of surrounding epileptogenic cortex, often guided by invasive monitoring or intraoperative electrocorticography.

**Epilepsy Due to Atrophic Lesions**

Stroke is a significant cause of epilepsy, which is sometimes drug resistant. In the setting of remote congenital or early childhood middle cerebral artery infarctions, patients often have residual hemiplegia, and the imaging may show porencephalic cysts. Hemispherectomy or multilobar resection in such cases offers an excellent chance of seizure control. Posttraumatic epilepsy may be intractable as well. Some posttraumatic epilepsy has widespread or multifocal injury, making these patients...
poor surgical candidates. However, many have MTS or localized cortical encephalomalacia and may achieve good seizure control with resection.\textsuperscript{54}

**Hemispheric Syndromes**

In addition to Sturge-Weber syndrome and large congenital hemiplegic strokes, hemispherectomy is considered for hemimegalencephaly (ie, hemispheric dysplastic malformation and overgrowth), other forms of extensive unilateral cortical dysplasia with severe hemiparesis, and Rasmussen syndrome. In Rasmussen syndrome, a progressive hemispheric condition, hemispherectomy has a high chance of controlling seizures and improving cognition.\textsuperscript{55} The usual procedure is the functional hemispherectomy, in which the central region and temporal lobe are removed and the frontal and occipital lobes are disconnected.\textsuperscript{56} This eliminates the superficial cerebral hemosiderosis that complicated the original anatomical hemispherectomy procedure.

**Corpus Callosotomy**

Corpus callosotomy is most often performed for palliation of atonic seizures

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**Case 9-3**

A 21-year-old, right-handed man experienced daily clusters of seizures with right arm elevation and head turning to the left since age 2. The patient’s seizures were refractory to four antiepileptic drugs and the ketogenic diet. Scalp EEG showed left frontotemporal interictal epileptiform discharges and ictal fast activity, MRI showed subtle left frontal cortical thickening (Figure 9-7), single-photon emission computed tomography (SPECT) demonstrated increased ictal blood flow in the left frontal pole, and positron emission tomography (PET) showed subtle left frontal hypometabolism (Figure 9-8). Invasive EEG demonstrated left frontopolar seizure onset (Figure 9-9), and the patient’s frontal dysplastic cortex was resected.

**FIGURE 9-7** MRI showing left lateral frontal cortical thickening (arrow) consistent with cortical dysplasia.

**FIGURE 9-8** Positron emission tomography (PET) showing left frontal decreased metabolism (arrow). The lateral cortical surface is orange, signifying hypometabolism, whereas the lateral cortical surface on the opposite side is bright yellow.

Continued on page 739
Comment. Detection of subtle cortical abnormalities is crucial to successful epilepsy surgery for cortical dysplasia.

**TABLE 9-1**  **Ongoing and Future Trends**

- Earlier consideration of epilepsy surgery
- Continued expansion of use of epilepsy surgery in children
- Wider geographic distribution of medical and surgical epilepsy centers
- Continuing efforts to improve MRI detection of occult cortical dysplasia
- Development of EEG signal analysis methods to better define the seizure-onset zone with scalp and invasive EEG monitoring
- Increased use of functional MRI for functional localization
- Continued development of less invasive methods of resection, such as stereotaxic surgery, laser ablation, and radiosurgery
- Development of devices to focally suppress seizures without resection
in patients with Lennox-Gastaut syndrome. The anterior two-thirds portion of the corpus callosum is sectioned; if this procedure is ineffective, the remaining posterior portion may be divided later.\textsuperscript{57}

**OUTCOMES**

The goal of resective epilepsy surgery is long-term seizure freedom. The best outcomes are for temporal lobectomy for MTS, lesional resections, and hemispherectomy. Seizure-free rates are lower in patients with nonlesional neocortical resections. Reported outcomes depend primarily on case selection and on the accurate and complete evaluation of postoperative seizures over a sufficient time. A multicenter study of 339 patients followed for at least 2 years found that 68\% of patients with mesial temporal resections and 50\% of patients with neocortical resections were seizure free except for possible auras.\textsuperscript{58}

This difference was not significant, and with multivariate analysis, only absence of convulsive seizures and presence of hippocampal atrophy in the mesial temporal group were independently associated with remission. While some patients are able to discontinue AEDs and remain seizure free, there are no randomized studies allowing prediction of the risk of seizure recurrence with drug withdrawal.\textsuperscript{59}

**CONCLUSIONS**

This review details the severe progressive consequences of uncontrolled epilepsy, the criteria determining epilepsy surgery candidacy, and the evidence for surgical efficacy. Despite these factors, the number of surgical lobectomies in the United States is less than 500 per year, with no significant change over almost 2 decades—far lower than expected from estimates of the prevalence of surgically remediable epilepsies.\textsuperscript{60}

In addition, the average delay from onset of habitual seizures to referral for surgical treatment is 17 to 18 years (Table 9-1).\textsuperscript{61} Chronic, uncontrolled epilepsy can be a malignant condition, and timely, systematic intervention to attain seizure freedom, including early consideration of epilepsy surgery, is the standard for neurologic practice.\textsuperscript{62}

**REFERENCES**


Surgical Treatment of Epilepsy


