Advances in the Surgical Management of Epilepsy

Drug-Resistant Focal Epilepsy in the Adult Patient

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KEYWORDS

• Epilepsy • Drug-resistant • Neuroimaging • Surgical treatment

KEY POINTS

- *Pharmacoresistant* seizures may occur in nearly one-third of people with epilepsy, and Intractable epilepsy is associated with an increased mortality.
- Medial temporal lobe epilepsy and lesional epilepsy are the most favorable surgically remediable epileptic syndromes.
- Successful epilepsy surgery may render the patient seizure-free, reduce antiseizure drug(s) adverse effects, improve quality of life, and decrease mortality.
- Surgical management of epilepsy should not be considered a procedure of "last resort."
- Epilepsy surgery despite the results of randomized controlled trials remains an underutilized treatment modality for patients with drug-resistant epilepsy.

INTRODUCTION

Epilepsy is one of the most common chronic neurologic disorders affecting nearly 65 million people in the world.[1] It is estimated that approximately 1.2% of individuals in the United States, or approximately 3.4 million people, have seizure disorders.[1] This includes almost 3 million adults and 470,000 children.[1,2] More than 200,000 individuals in the United States will experience new-onset seizure disorders each year. Nearly 10% of people will have 1 or more seizures during their lifetime.[1–3] The 2012 Institute of Medicine of the National Academy of Sciences report indicated that 1 in 26 Americans will develop a seizure disorder during their lifetime; this is double the risk of those with Parkinson disease, multiple sclerosis, and autism spectrum disorder *combined*.[3] The diagnosis of epilepsy may include patients with 2 or more unprovoked seizures or

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those with single seizures with biomarkers that indicate an increased likelihood of seizure recurrence, that is, greater than 60% chance for an additional seizure.[4] Factors that may indicate an increased risk for seizures following a single seizure include the presence of developmental delay or a focal neurologic deficit, autoimmune neurologic disorder, a history of remote symptomatic neurologic disease, and an MRI-identified pathologic substrate or epileptogenic lesion, for example, mesial temporal sclerosis (MTS). The devastating effect of seizure disorders in part relates to the peak onset for the development of new-onset seizure disorders that include the very young (neonates and children) and very old (older than 65 years).[1–4] Approximately one-third of patients with recurrent seizures will have physically, medically, and socially disabling seizure disorders that adversely affect the individual's quality of life, that is, drug-resistant epilepsy (DRE) or *pharmacoresistant* epilepsy.[5] The most common seizure disorder in adults is focal epilepsy associated with focal impaired awareness seizures, also known as complex partial seizures or focal dyscognitive seizures. Such patients are at increased risk for comorbidities and mortality, including cognitive disorders, mood disorders like anxiety and depression, physical trauma related to seizures, and sudden unexpected death in epilepsy (SUDEP).[6–8] Patients with intractable epilepsy may have significant issues obtaining an education, becoming gainfully employed, and living independently. A seizure disorder is considered in remission if the patient is seizure-free for 10 years and has been off antiseizure medication for the past 5 years.[6] Importantly, the psychosocial debilitation associated with epilepsy may be unique compared with other neurologic disorders because of the wide range in age of seizure onset, the variability in response to medical therapy, and the presence of potentially devastating comorbidities.

The most effective medical treatment of epilepsy is the initial antiseizure drug (ASD). The first 2 ASDs are the most likely to be of benefit in rendering the patient seizure-free if the appropriate medication(s) is selected for the seizure type. Most individuals who will be rendered seizure-free and respond to ASD therapy in the initial 2 years of treatment if the patient has *pharmacoresponsive* epilepsy. Perhaps fewer than 10% of individuals with DRE will be rendered seizure-free with additional ASD trials.[6,7] Overreliance on use of antiepileptic drug levels may undermine the success of an ASD. In general, treat the *patient* and not the *drug level*. Patient tolerance and response to ASD medication dosing may be highly variable. Patients who do not respond favorably to 2 antiseizure drugs used appropriately are likely to have DRE and should be investigated for surgery and other alternative forms of treatment. Individuals who fail to respond satisfactorily to 2 or more ASDs would be considered to have DRE.[7] Importantly, medication nonadherence is a significant concern for all individuals with suspected DRE and needs to be carefully assessed in reviewing the efficacy of therapeutic modalities. An estimated one-third of people with epilepsy may have medically refractory seizure disorders and should be considered for alternative forms of treatment such as epilepsy surgery.[6,7]

The goals of treatment for individuals with DRE are to render the patient seizure-free (*No Seizures*), avoid treatment-related adverse effects (*No Side Effects*), and to improve the individual's quality of life allowing the patient to become a participating and productive member of society (*No Lifestyle Limitations*).[9] Often an important rationale for patients considering alternative treatments to ASD therapy is the inability to legally and safely operate a motor vehicle. This may be a significant disability for obtaining an education and being gainfully employed. Potential treatment options for these patients include continued ASD trials, neuromodulation, diet therapy, and surgical management, that is, epilepsy surgery.[8,9] The most effective treatment of DRE is surgical resection of the epileptic brain tissue and the pathologic substrate.

Unfortunately, epilepsy surgery remains a significantly underutilized, but highly effective therapeutic modality.[9] Only a small percentage of patients with focal DRE are referred for surgical treatment. This article discusses the advances in surgical treatment of DRE in adults with focal seizures.

BENEFICIAL EFFECTS OF SURGERY

The rationale for surgical treatment of DRE in patients with focal seizures is to render the individual seizure-free while avoiding neurologic morbidity.[9,10] The putative beneficial effects of surgery may include a reduction in ASD medication and potential adverse effects of medical therapy.[10] Discontinuance of ASD, however, may not be feasible in all patients who have a seizure remission following epilepsy surgery. Successful surgery has been shown to decrease the risk of physical trauma associated with seizures and SUDEP.[11] The overall mortality associated with epilepsy may be reduced following surgical treatment.[11,12] Epilepsy surgery may also improve the symptoms of depression and anxiety that are common comorbidities associated with DRE. A reduction in seizure tendency following surgical treatment in women has also been associated with an apparent increase in fertility and pregnancy.[13] Ultimately, the most common rationale for considering surgical treatment is the improvement in the patient's quality of life allowing them to become more independent and engaged in society.

Goals of Epilepsy Surgery

- Render the patient seizure-free or significantly reduce seizure tendency
- Avoid operative morbidity
- Reduce antiseizure drug(s) adverse effects
- Improve the patient's quality of life
- Decrease risk of seizure-related mortality and SUDEP

DIAGNOSTIC EVALUATION

The care and management of people with focal DRE begins with confirming the classification of the seizure disorder and seizure type(s), determining the presence of an underlying or symptomatic etiology, and evaluating seizure precipitating factors. A comprehensive neurologic history and examination is performed to elucidate the potential underlying etiology, identify the seizure type(s) and precipitating factors, recognize comorbidities and discuss important psychosocial issues including patient education, employment history, and current living situation.[9,14] The presence of a mood disorder such as anxiety and depression should be assessed, as these psychiatric illnesses are overrepresented in people with epilepsy and may significantly impair quality of life. Also, inadequately treated mood disorders may increase seizure tendency. The prior ASD medication and other potential treatment options, for example, diet or neuromodulation, would be reviewed in detail with careful attention to patient compliance and adverse effects of therapy. The presence of dose-related and idiosyncratic side effects associated with ASD need to be recognized. Not uncommonly, patients and their family members may identify certain situations that exacerbate the seizure tendency. These are highly variable but often include ASD noncompliance, sleep deprivation, psychosocial stress, inadequately treated anxiety or depression, or correlation with menstrual cycle. Attempts to manage the precipitating factors that are reversible, for example, irregular ASD intake, may be pivotal to the success of any therapeutic intervention. Patients with cognitive impairment may be at high risk for ASD noncompliance with complicated ASD protocols.

Diagnostic studies obtained initially in the evaluation of suspect DRE include routine electroencephalogram (EEG), neuroimaging procedures, and neuropsychological testing.[8,9,14] Admission to a dedicated epilepsy monitoring unit (EMU) for scalp-recorded long-term video-EEG recordings would be required for evaluation of focal epilepsy to classify seizure type(s) and permit adequate surgical localization. The presence of interictal and ictal epileptiform discharges may assist in localization of the epileptogenic zone, that is, the epileptic brain tissue important for focal seizure activity. The seizure semiologies and behavioral assessment during the seizure activity may be critical in lateralizing and localizing the site of seizure onset. Selected patients with focal epilepsy based on history, seizure type(s), and comorbidities may require additional diagnostic studies including an autoimmune neurology evaluation (serum and cerebrospinal fluid autoantibody determinations) and medical genetics consultation with genetic testing.

Diagnostic Studies for Epilepsy Surgery (Variably performed, indicating these studies may or may not be performed depending on the clinical picture)

- Routine awake-sleep EEG
- MRI head seizure protocol
- Video-EEG monitoring in EMU
- Neuropsychological studies
- 2-Deoxy-2–^{18}F-deoxyglucose (FDG)-PET scan*
- Subtraction ictal single-photon emission computed tomography (SPECT) coregistered to MRI*
- Functional MRI (fMRI)*
- Magnetoencephalography*
- Chronic intracranial EEG monitoring*
- Intraoperative electrocorticography*

Electrophysiological Studies

Scalp-recorded EEG studies are performed to record interictal and ictal epileptiform patterns.[15,16] While in the EMU the patients ASD medication may be tapered or withdrawn to increased seizure tendency. Video-EEG monitoring during the individual's habitual clinical seizure type(s) is usually considered pivotal in surgical decision making. Rarely, interictal EEG epileptiform discharges concordant with a structural neuroimaging abnormality may be sufficient for surgical localization. High-density array of EEG electrodes (10–10 electrode placement) may be useful in patients with extratemporal focal seizures; especially involving the mesial frontal lobe such as supplementary motor area seizures. Clinical examination during focal seizures may include language and memory assessments.

Neuroimaging Studies

High-resolution MRI is an essential structural neuroimaging procedure to assess surgical candidacy for patients with DRE and focal seizures.[17] The finding of an MRI-identified pathologic substrate concordant with the site of seizure onset is a major determinant of operative strategy and has significant prognostic importance.[9,17] Specific imaging protocols have been developed to increase the diagnostic yield of these studies. The MRI should include coronal or oblique-coronal T1-weightedd and T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences (**Box 1**).[18–21] A 3-T MRI study is routinely performed in patients with seizure disorders.[17] MRI almost invariably reveals an abnormality indicating the focal epileptogenic pathology in patients with low-grade neoplasms like dysembryoplastic neuroepitheliomas tumors (DNET), vascular anomalies including cavernous malformations, large vessel cerebral

Box 1
Standard MRI epilepsy protocol "3D Epilepsy Study" used at Mayo Clinic (3.0-T, 1.5-mm temporal lobe sections)

Imaging sequences:

Scout

Sagittal T1-weighted fluid-attenuated inversion recovery (FLAIR)

Axial 2D T2-weighted fast spin echo with fat saturation

Coronal 2D T2-weighted FLAIR with fat saturation

Sagittal Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (SPACE) double inversion recovery (DIR)

Sagittal magnetization prepared rapid acquisition gradient echo (MPRAGE)

Small Field of View Coronal SPACE T2-weighted FLAIR

Axial diffusion-weighted imaging (DWI)

Axial susceptibility-weighted imaging (SWI)

infarctions, and encephaloceles.[17,22] MRI may reveal hippocampal atrophy and an FLAIR and T2 signal hyperintensity in patients with MTS (**Fig. 1**).[18–21] Quantitative measures of hippocampal volume may be useful in selected patients with bilateral symmetric hippocampal atrophy or subtle unilateral volume loss with MTS.[18–21] Loss of internal structure of the hippocampus may also be seen in these patients. An MRI finding of MTS is predictive of better seizure and memory outcomes following surgery.[17,21] A significant percentage of patients with the common developmental pathologies such as focal cortical dysplasia (FCD) type IIb also may have an imaging alteration.[21] In patients with FCD, MRI findings may be subtle and include mild cortical thickening, a prominent deep sulcus, a cortical signal intensity change, blurring of the gray-white junction, or aberrant cortical architecture, focal atrophy, and hyperintense signal in T2/FLAIR sequences (**Fig. 2**).[21] FCD is characterized by disorganization of the cortical lamination associated with bizarre (dysplastic neurons). The introduction of a 7-T MRI scanner may increase the sensitivity and specificity of selected pathologies. Unfortunately, a significant number of patients referred for epilepsy surgery have MRI-negative focal epilepsy. Additional neuroimaging procedures need to be considered in these individuals and many will require chronic intracranial EEG monitoring for surgical planning (see later in this article).

PET is a functional neuroimaging modality that may localize a focal abnormality for surgical planning in patients with pharmacoresistant epilepsy.[23,24] PET is the most important *interictal* functional neuroimaging procedure in patients with DRE being considered for epilepsy surgery. PET scans use ^{18}F-deoxyglucose (FDG-PET) as a ligand to measure differential glucose consumption as a surrogate for metabolism. A key concept is that FDG-PET measures *interictal* brain metabolism and that the region of seizure onset is *hypometabolic*. FDG-PET has been found to be most useful in temporal lobe epilepsy. In patients with medial temporal lobe epilepsy, temporal hypometabolism may accurately lateralize to the temporal lobe of seizure origin and is associated with favorable surgical outcomes, even when MRI is negative.[23] FDG-PET is less sensitive in patients with extratemporal epilepsy.

SPECT measures cerebral blood flow via the injection of a radiotracer such as technetium-99m-hexamethylpropylene amine oxime (99mTc-HMPAO) with rapid uptake within the brain (30–60 seconds from injection) but a long half-life.[25,26] SPECT

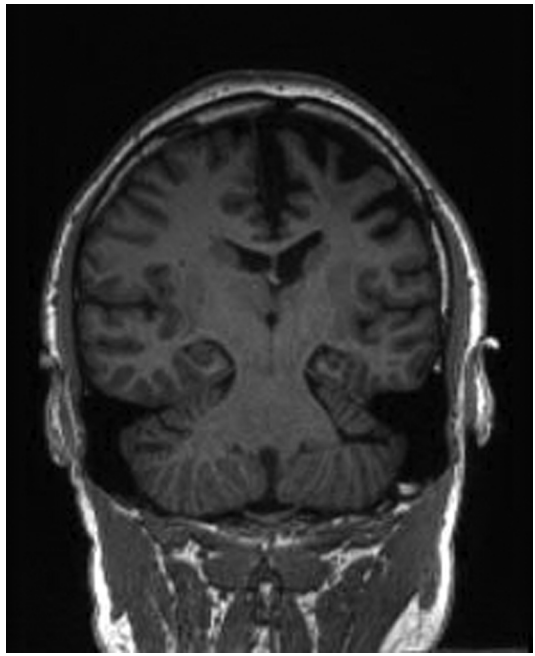

Fig. 1. Patient with left medial temporal lobe epilepsy. MRI head seizure protocol T1-weighted image in the oblique-coronal plane shows volume loss involving the left hippocampal formation and left mesial temporal lobe compatible with MTS. Encephalomalacia within the posterior superior left frontal lobe presumably related to remote meningioma resection. Patient is seizure-free after a left selective amygdalohippocampectomy. Note the left temporal lobe is on the right side of the figure.

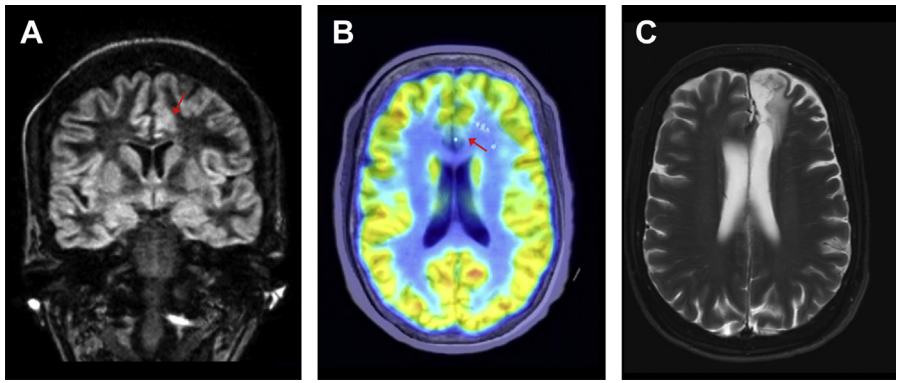

Fig. 2. Patient presenting with focal seizures related to FCD, with scalp EEG maximal over the midline frontal area at onset. (*A*) Double inversion recovery MRI head reveals thickened cortex with blurring of the gray-white matter border over the anterior cingulate (*red arrow*). (*B*) FDG-PET shows bilateral hypometabolism in the anterior cingulate (*red arrow*), and SEEG monitoring shows seizures arising from the left anterior cingulate. (*C*) Focal resection of the FCD lesion including the locations of the seizure onset electrodes rendered the patient seizure free as of 25 months follow-up.

identifies the location of *ictal* activity, which is characterized by *increased* cerebral perfusion. Subtraction ictal SPECT coregistered to MRI (SISCOM) is a modification of the ictal SPECT technique that superimposes ictal and interictal SPECT images and brain MRI. Statistical parametric mapping is a more recent innovation that permits comparison of focal or regional areas of hyperperfusion to a control group that increases the diagnostic yield of the technique in patients with DRE being considered for focal cortical resection.[26]

fMRI is a noninvasive imaging study that may localize selected neurologic clinical functions, for example, language.[27] fMRI detects relative changes in focal blood oxygen levels that occur over time while the patient is given a protocolled computerized task testing specific brain functions and which is alternated with rest or control tasks. Language function can be lateralized and localized to guide surgical resection. This imaging technique may obviate the need for an invasive procedure such as intracarotid amobarbital study.

Neuropsychological Studies

Neuropsychological studies are performed to evaluate the presence of verbal or nonverbal learning and memory deficits in patients with DRE being considered for surgical treatment.[28] These studies may be of highest diagnostic yield in individuals with focal seizures of temporal lobe origin. This is most commonly a standard protocol permitting comparison of results before and after surgery. The preoperative memory assessment may allow appropriate counseling of patients regarding memory outcome following surgery. Neuropsychological studies are often performed to provide a baseline determination of cognitive performance before surgery that can be compared with a postoperative examination.

SURGICAL MANAGEMENT OF FOCAL EPILEPSY

Several surgical strategies may be considered in the management of DRE in the adult patient.[10,29,30] Surgically remediable epileptic syndromes have been identified in patients with focal seizures that are medically, physically, and socially disabling. The patient candidacy and presurgical evaluation depends on the operative intervention. The timing of a consideration of surgical treatment begins with the diagnosis of DRE in individuals with focal seizures. The patients should undergo an appropriate diagnostic evaluation to determine seizure classification, underlying etiology, comorbid conditions, and effective treatment options. Unfortunately, the duration between the diagnosis of DRE and the neurosurgical procedure for epilepsy is often 20 years or longer.[31] This delay may adversely affect the patient's psychosocial development and opportunities to become a participating member of society.

Surgically Remediable Epileptic Syndromes
- Medial temporal lobe epilepsy
- Lesional epilepsy
- MRI-negative focal epilepsy

Medial Temporal Lobe Epilepsy

The most common surgical strategy for DRE is a focal cortical resection of the site of seizure onset and initial seizure propagation. In adult patients with focal seizures this most commonly involves the anteromedial temporal lobe including the amygdala and hippocampus.[9,10,16] The most common pathology is MTS with focal hippocampal neuronal loss.[9,10] The extent of surgical resection is determined by the preoperative

investigation including the ictal EEG recordings and the neuroimaging techniques. Selected institutions performed a "standard anterior temporal lobectomy" with the preoperative evaluation determining the operative margins of the focal cortical resection. The resection includes anterior temporal lobe neocortex and an amygdalohippocampectomy.[30,31] Preoperative interictal-ictal EEG recordings and MRI head studies are used for seizure lateralization and localization. The posterior extent of the anterior temporal resection is determined by potential adverse effects on language and vision. Other surgical epilepsy centers perform a "tailored" cortical resection that may use intraoperative electrocorticography and functional mapping of language cortex to guide the excision. Additional operative management of medial temporal lobe epilepsy includes selective amygdalohippocampectomy that limits the excision of the temporal lobe neocortex. There are conflicting results regarding the effectiveness of the specific operative strategies to render individuals with mesial temporal lobe epilepsy seizure-free. Importantly, most individuals experience a significant reduction in seizure tendency with either operative approach. More recently, MRI-guided laser interstitial thermal therapy (LITT) has been introduced in the management of medial temporal lobe epilepsy related to MTS (**Fig. 3**).[32] LITT may be a minimally invasive surgical procedure that is effective in these patients and compares favorably with anterior temporal lobectomy regarding neurocognitive outcome.[32,33]

Surgical management of medial temporal lobe epilepsy has been shown to be safe and effective in randomized clinical trials.[34–36] Surgery was superior in efficacy to "best medical therapy" in a pivotal study involving 80 patients with temporal lobe epilepsy.[34] At 1 year, the cumulative proportion of patients who were seizure-free (focal impaired awareness seizures) was significantly greater in the surgery group than the medical group (58% vs 8%).[34] Quality-of-life ratings were also higher in the surgical-treated group.

The consensus of randomized clinical trials and observational series with large patient cohorts is that approximately 75% of patients with medial temporal lobe epilepsy are seizure-free during long-term follow-up after surgical intervention if the MRI head

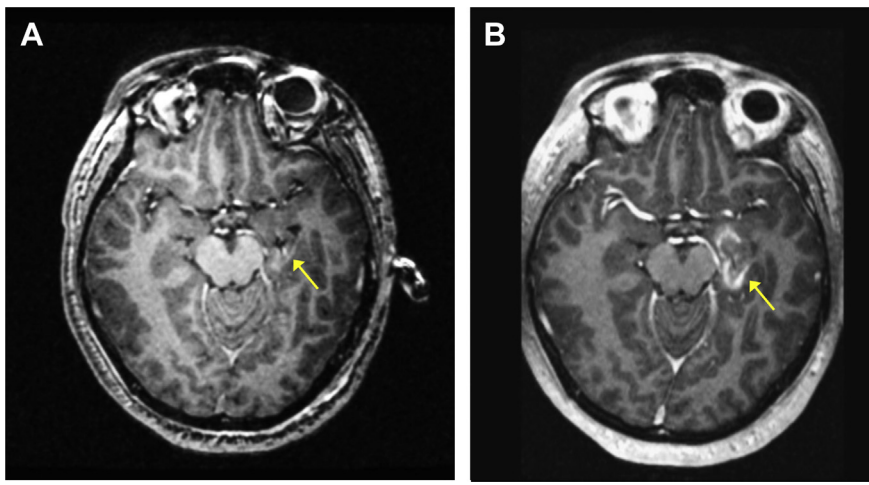

Fig. 3. LITT provides focal ablative therapy without damaging surrounding tissue. (*A*) Intraoperative MRI confirms placement of the water-cooled fiber optic applicator in the hippocampus (*arrow*), and laser energy is used to heat the tissue to ablative levels. (*B*) Gadolinium contrast forms a ring around the damaged tissue following ablation.

shows changes consistent with MTS (focal hippocampal formation atrophy with or without FLAIR-identified mesial temporal signal hyperintensity).[31] The best predictors of a favorable operative outcome include MRI-identified MTS, concordant scalp-recorded EEG and MRI findings, PET-identified hypometabolism concordant with the temporal lobe of seizure origin, and shorter seizure disorder duration.[16] Approximately 90% of patients with unilateral MRI-identified MTS concordant with the interictal epileptiform discharges will be seizure-free or experience auras only or seizures with ASD discontinuance following epilepsy surgery.[16] Poor predictors of operative outcome include normal MRI head study, bilateral MRI-identified MTS, bitemporal epileptiform discharges, normal PET study, and the presence of clinical semiology that suggests seizures emanating from outside the medial temporal lobe region. In a series of 87 patients with a normal MRI undergoing anterior temporal lobectomy, 55% had an excellent operative outcome (seizure-free or auras only).[37] The surgical outcome of patients with a localized temporal lobe PET abnormality and a normal MRI may be equivalent to individuals with MRI-identified unilateral hippocampal sclerosis. Seventy-six percent of patients in one series with temporal lobe PET hypometabolism and a normal MRI were seizure-free following surgery.[23]

Lesional Epilepsy

Patients with DRE due to focal foreign-tissue lesions, that is, lesional epilepsy, may be candidates for surgical treatment of epilepsy.[38–42] A comprehensive evaluation is required to determine the epileptogenicity of the structural-anatomical pathology. The pivotal diagnostic modality in these individuals is almost invariably an MRI head study with and without contrast. The surgical strategy in these patients most commonly involves excision of the pathologic substrate and resection of the epileptogenic tissue. Most individuals with lesional epilepsy become seizure-free or experience a marked reduction in seizure tendency.[38–42] Common pathologic entities responsible for DRE associated with lesional pathology include tumors, cavernous malformations, and FCD.[38–42]

Lesional Epilepsy
- Low-grade neoplasms like DNET and gangliogliomas
- Cavernous hemangiomas
- FCD
- Temporal lobe encephaloceles

The incidence of seizures among patients with primary brain tumors is related to tumor type and grade and cortical localization. Low-grade, slowly growing tumors are most commonly associated with a chronic seizure disorder (**Fig. 4**). Gangliogliomas and DNET together account for approximately three-quarters of all tumors found in adults undergoing epilepsy surgery.[38–41] Some studies have suggested that DNETs are associated with higher seizure relapse rates compared with other epileptogenic tumors. Most patients with DRE related to these low-grade neoplasms are rendered seizure-free with complete lesion resection and excision of the epileptic brain tissue.[38]

Cavernous malformations and arteriovenous malformations are the most common vascular lesions found in patients with focal epilepsy (**Fig. 5**).[42,43] Seizures are a common presenting feature of cavernous malformation. Resection typically leads to complete seizure control or significant improvement. In a case series of 168 patients with symptomatic epilepsy attributed to cavernous malformations, more than two-thirds of patients were seizure free at 3 years after surgery.[43] Predictors for a favorable seizure outcome included medial temporal location, size less than 1.5 cm, and the absence of tonic-clonic seizures.[42]

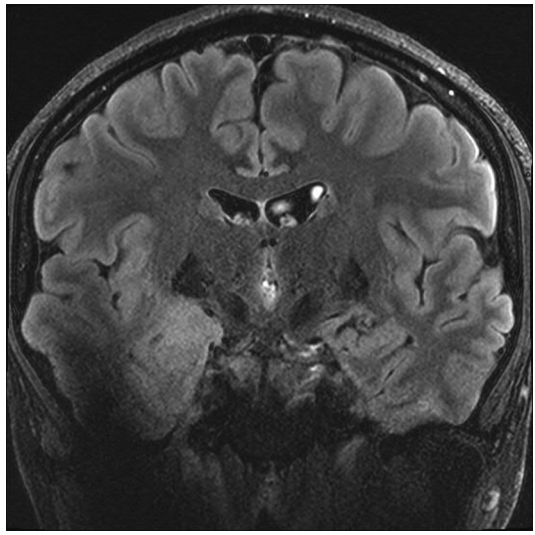

Fig. 4. Patient with right medial temporal lobe epilepsy. Seven-Tesla MRI head T2-weighted image in the oblique-coronal plane shows right medial temporal lobe lesion that is, consistent with a low-grade glial neoplasm. Note the right temporal lobe is on the left side of the figure.

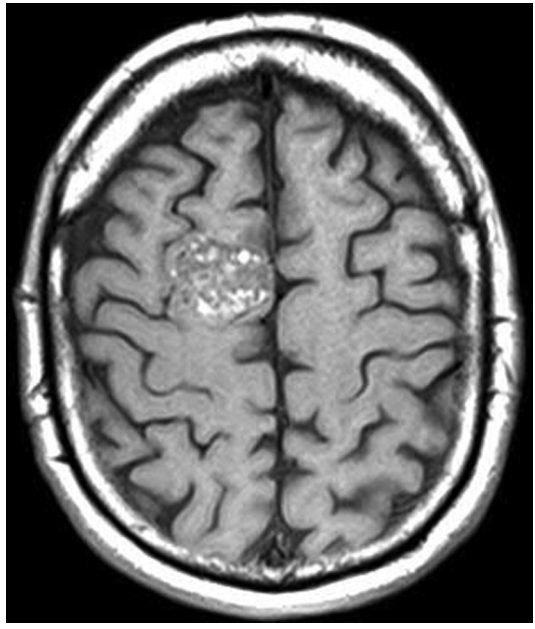

Fig. 5. Patient with right supplementary motor area seizures. MRI head T1-weighted image in the axial plane shows a right mesial frontal cavernous malformation. Note the right frontal lobe is on the left side of the figure.

FCDs are an important etiology for drug-resistant focal epilepsy.[44,45] Patients with MRI-negative focal epilepsy may have evidence of FCD at the time of surgery. Epilepsy surgery is less effective in patients with FCD than in patients with other lesional pathology (eg, tumors or cavernous malformations). Challenging issues in these patients include the difficulty identifying areas of FCD using MRI, the presence of extratemporal neocortical lesions, and multilobar pathology. One center reported that 57% of 166 patients with FCD followed for 2 years or longer after surgery were seizure free.[45] Success rates may be higher in patients with a specific form of focal cortical dysplasia type II in which dysplastic features are maximal at the bottom of the sulcus (referred to as a transmantle sign on MRI). FDG-PET/MRI may improve the surgical outcome in patients with FCD type II associated with balloon cells (Taylor-type focal cortical dysplasia). In a study that included 23 patients who underwent epilepsy surgery, and who had pathologically verified FCD type II, MRI was negative in 13 patients and showed subtle alterations in 10 patients. FDG-PET/MRI revealed a hypometabolic zone in 22 of 23 patients. Twenty of the 23 patients (87%) became seizure free following surgery.[24]

Temporal lobe encephaloceles are a more recently recognized etiology of DRE.[46,47] The encephaloceles may be idiopathic or related to congenital defects, prior head trauma, or surgery. Not all encephaloceles are epileptogenic; therefore, a preoperative evaluation would need to performed and correlate with the structural neuroimaging findings. Surgical strategy may include an encephalocele repair with or without a focal cortical resection.

MRI-Negative Focal Epilepsy

The surgical management of MRI-negative focal seizures of neocortical origin (ie, extrahippocampal) can be challenging because of difficulty defining the boundaries of the epileptogenic zone that must be resected for seizure freedom.[48] There are also increased concerns regarding clinically functional cortex, which may increase the risk of perioperative neurologic deficits. The clinical manifestations of neocortical seizures depend on the localization of seizure onset and initial seizure propagation. Seizures arising from functional cortex can be localized based on neurologic symptoms that occur at seizure onset or during the postictal state. Compared with medial temporal lobe epilepsy, neocortical seizures of temporal lobe origin may have a unique aura and ictal semiology with an increased tendency for tonic-clonic seizures. Frontal lobe seizures tend to be shorter and more frequent than temporal lobe seizures, with ictal manifestations varying from staring to hypermotor behavior. Frontal lobe seizures may be confined to sleep. Parietal and occipital seizures typically have complex sensory symptoms, such as visual hallucinations of objects or scenes. Despite these general principles, extrahippocampal focal seizures often have varied clinical semiology and can be difficult to localize with scalp-recorded ictal EEG studies. In addition, ictal behaviors may relate to seizure propagation and provide few clues regarding the site of actual seizure onset. Another challenge to clinical localization in neocortical epilepsy is that seizures may be tonic-clonic without a clinically recognized focal seizure, or the focal seizure may be very brief or subtle, such as a brief stare with arrest of activity or hypermotor activity. To adequately localize seizures and tailor resections to spare eloquent cortex, the surgical evaluation in patients with neocortical epilepsy often includes functional or metabolic imaging and long-term intracranial EEG monitoring.[49,50]

MRI-negative focal epilepsy

- High-resolution MRI head seizure protocol study is negative for a pathologic substrate
- Patients may have focal seizures of temporal lobe or extratemporal origin

- Chronic intracranial EEG monitoring with stereoelectroencephalography (SEEG) or subdural grid-strip recordings are almost invariably used for surgical localization and functional mapping
- Surgical outcomes in these patients are less favorable than in individuals with an epileptogenic lesion or MTS
- Surgical pathology may reveal FCD

SEEG is an older intracranial EEG technique for seizure localization that has reemerged as a pivotal tool in evaluating patients with DRE being considered for surgical treatment (**Fig. 6**).[49–52] This method for intracranial monitoring does not require a craniotomy and may be a "minimally" invasive diagnostic technique. The overall morbidity and patient tolerance of SEEG compares favorably to subdural grid recordings.[51] SEEG may be preferred in patients with diagnostic uncertainty regarding the lateralization or localization of seizure onset and in seizures suspected to emanate from sequestered cortex, for example, insula.

Unfortunately, despite the use of functional neuroimaging and chronic intracranial EEG monitoring, the surgical outcome is less favorable in patients with MRI-negative compared with medial temporal lobe epilepsy and lesional epilepsy. Perhaps 30% to 40% of patients with MRI-negative focal epilepsy of extratemporal origin are rendered seizure-free following focal cortical resection.[48]

EPILEPSY SURGERY IN CONTEMPORARY PRACTICE

Epilepsy surgery is significantly underutilized despite randomized clinical trials demonstrating the superiority of surgery compared with "best" medical therapy.[34–36]

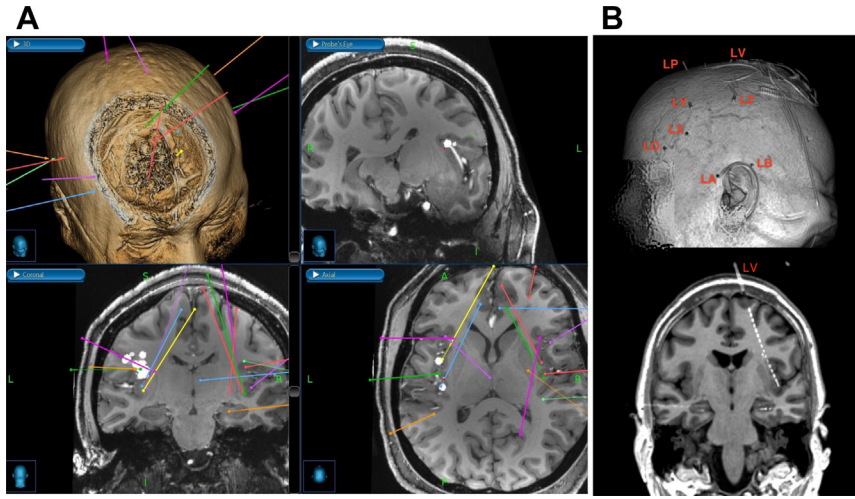

Fig. 6. Stereotactic implantation of electrodes enables invasive EEG monitoring with reduced invasiveness compared with grid and strip electrodes introduced via craniotomy. (*A*) Anatomic structures and functional features (magnetoencephalography dipoles, white spheres) are targeted with linear trajectories in a stereotactic planning system. Gadolinium (MRI) or iodine (CT) contrast-enhanced images (not shown) are used to visualize and avoid vessels when placing trajectories. (*B*) Following electrode implantation, CT images are acquired showing the locations of electrode contacts. The CT images are coregistered to preoperative MRI. Three-dimensional renderings (*top*) illustrate electrode entry points, and oblique slices (*bottom*) show the contact positions in relation to anatomic structures.

A population-based study using the US Nationwide Inpatient Sample found that there were 6653 resective surgeries from 1990 to 2008, and there was no growth trend over this time period.[53] There are several potential reasons for the lack of referral of patients to comprehensive epilepsy centers that have been identified including concerns regarding operative morbidity and the attitude of the neurologists that surgical treatment is a procedure of "last resort."[54–57] Most perioperative complications are relatively "minor" or transient; significant treatment-related adverse effects are relatively uncommon.[57] The use of multiple ASDs in combination with neuromodulation, for example, vagus nerve stimulation, may be preferred to epilepsy surgery in clinical practice. Unfortunately, in patients with DRE medical therapy and neuromodulation are usually *palliative* and not *curative* treatments. An unnecessary delay in referring patients for epilepsy surgery with surgically remediable epileptic syndromes may have devastating effects on the individuals' psychosocial development and quality of life. There are strong compelling reasons to consider early and effective treatment of pharmacoresistant seizure disorders, as DRE can be a progressive and fatal illness.[58,59]

The patient population being referred for epilepsy surgery has changed in the past few years at major epilepsy centers.[60,61] People with medial temporal lobe epilepsy associated with MTS are less commonly being considered for surgical treatment.[60,61] There are a greater number of patients with MRI-negative focal epilepsy and multilobar seizures being considered. This would explain the increase interest in chronic intracranial EEG monitoring using SEEG.[49–51] Finally, an important challenge that remains is the patient disparities that remain regarding access to surgical epilepsy centers. There are racial disparities that have been identified that indicate that people of color are less likely to undergo epilepsy surgery.[62] Treatment gaps have been identified, which suggest that selected patient populations have barriers to access for surgical evaluations and treatment.[53]

RESOURCES

National Association of Epilepsy Centers: www.naec-epilepsy.org.
American Academy of Neurology: www.aan.com.
American Epilepsy Society: www.aesnet.org.
Epilepsy Foundation: www.epilepsy.com.

CLINICS CARE POINTS

- Patients with drug-resistant focal epilepsy should be evaluated for surgical treatment. For many patients surgical resection of a discrete seizure focus represents the best chance for seizure freedom.

REFERENCES

1. Zack MM, Kobau R. National and state estimates of the numbers of adults and children with active epilepsy — United States, 2015. MMWR Morb Mortal Wkly Rep 2017;66:821–5.
2. Russ SA, Larson K, Halfon N. A national profile of childhood epilepsy and seizure disorder. Pediatrics 2012;129:256–64.
3. Hesdorffer DC, Beck V, Begley CE, et al. Research implications of the Institute of Medicine report, epilepsy across the spectrum: promoting health and understanding. Epilepsia 2013;54:207–16.
4. Falco-Walter JJ, Scheffer IE, Fisher RS. The new definition and classification of seizures and epilepsy. Epilepsy Res 2018;139:73–9.

5. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the Ad Hoc task force of the ILAE Commission on therapeutic strategies. Epilepsia 2010;51:1069–77.
6. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55:475–82.
7. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia 2010;51:1069–77.
8. Jette N, Engel J Jr. Refractory epilepsy is a life-threatening disease: lest we forget. Neurology 2016;86:1932–3.
9. Jobst BC, Cascino GD. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. JAMA 2015;313:285–93.
10. Engel J Jr, Wiebe S, French J, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. Neurology 2003;60:538–47.
11. Sperling MR, Harris A, Nei M, et al. Mortality after epilepsy surgery. Epilepsia 2005;46:49–53.
12. Sperling MR, Barshow S, Nei M, et al. A reappraisal of mortality after epilepsy surgery. Neurology 2016;86:1938–44.
13. Fabris RR, Cascino TG, Mandrekar J, et al. Drug-resistant focal epilepsy in women of childbearing age: reproduction and the effect of epilepsy surgery. Epilepsy Behav 2016;60:17–20.
14. Junna MR, Buechler R, Cohen-Gadol AA, et al. Prognostic importance of risk factors for temporal lobe epilepsy in patients undergoing surgical treatment. Mayo Clin Proc 2013;88:332–6.
15. Cascino GD, Trenerry MR, So E, et al. Routine EEG and temporal lobe epilepsy: relation to long-term EEG monitoring, quantitative MRI, and operative outcome. Epilepsia 1996;37:651–6.
16. Radhakrishnan K, So EL, Silbert PL, et al. Predictors of outcome of anterior temporal lobectomy for intractable epilepsy: a multivariate study. Neurology 1998;51:465–71.
17. Jones AL, Cascino GD. Evidence on use of neuroimaging for surgical treatment of temporal lobe epilepsy: a systematic review. JAMA Neurol 2016;73:464–70.
18. Trenerry MR, Jack CR Jr, Ivnik RJ, et al. MRI hippocampal volumes and memory function before and after temporal lobectomy. Neurology 1993;43:1800–5.
19. Jack CR Jr, Rydberg CH, Krecke KN, et al. Mesial temporal sclerosis: diagnosis with fluid-attenuated inversion-recovery versus spin-echo MR imaging. Radiology 1996;199:367–73.
20. Kuzniecky RI, Bilir E, Gilliam F, et al. Multimodality MRI in mesial temporal sclerosis: relative sensitivity and specificity. Neurology 1997;49:774–8.
21. Cendes F, Theodore WH, Brinkmann BH, et al. Neuroimaging of epilepsy. Handb Clin Neurol 2016;136:985–1014.
22. Cascino GD, Jack CR Jr, Parisi JE, et al. Magnetic resonance imaging-based volume studies in temporal lobe epilepsy: pathological correlations. Ann Neurol 1991;30:31–6.
23. LoPinto-Khoury C, Sperling MR, Skidmore C, et al. Surgical outcome in PET-positive, MRI-negative patients with temporal lobe epilepsy. Epilepsia 2012;53:342–8.

24. Chassoux F, Rodrigo S, Semah F, et al. FDG-PET improves surgical outcome in negative MRI Taylor-type focal cortical dysplasias. Neurology 2010;75:2168–75.
25. O'Brien TJ, So EL, Mullan BP, et al. Subtraction ictal SPECT co-registered to MRI improves clinical usefulness of SPECT in localizing the surgical seizure focus. Neurology 1998;50:445–54.
26. Sulc V, Stykel S, Hanson DP, et al. Statistical SPECT processing in MRI-negative epilepsy surgery. Neurology 2014;82:932–9.
27. Szaflarski JP, Gloss D, Binder JR, et al. Practice guideline summary: use of fMRI in the presurgical evaluation of patients with epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2017;88:395–402.
28. Stroup E, Langfitt J, Berg M, et al. Predicting verbal memory decline following anterior temporal lobectomy (ATL). Neurology 2003;60:1266–73.
29. Engel J Jr, Wiebe S, French J, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy. Epilepsia 2003;44:741–51.
30. Jeha LE, Najm IM, Bingaman WE, et al. Predictors of outcome after temporal lobectomy for the treatment of intractable epilepsy. Neurology 2006;66:1938–40.
31. Cohen-Gadol AA, Wilhelmi BG, Collignon F, et al. Long-term outcome of epilepsy surgery among 399 patients with nonlesional seizure foci including mesial temporal lobe sclerosis. J Neurosurg 2006;104:513–24.
32. Brown MG, Drees C, Nagae LM, et al. Curative and palliative MRI-guided laser ablation for drug-resistant epilepsy. J Neurol Neurosurg Psychiatry 2018;89:425–33.
33. Shimamoto S, Wu C, Sperling MR. Laser interstitial thermal therapy in drug-resistant epilepsy. Curr Opin Neurol 2019;32:237–45.
34. Wiebe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 2001;345:311–8.
35. Engel J Jr, McDermott MP, Wiebe S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA 2012;307:922–30.
36. Spencer SS, Berg AT, Vickrey BG, et al. Predicting long-term seizure outcome after resective epilepsy surgery: the multicenter study. Neurology 2005;65:912–8.
37. Burkholder DB, Sulc V, Hoffman EM, et al. Interictal scalp electroencephalography and intraoperative electrocorticography in magnetic resonance imaging-negative temporal lobe epilepsy surgery. JAMA Neurol 2014;71:702–9.
38. Tassi L, Meroni A, Deleo F, et al. Temporal lobe epilepsy: neuropathological and clinical correlations in 243 surgically treated patients. Epileptic Disord 2009;11:281–92.
39. Bonney PA, Boettcher LB, Conner AK, et al. Review of seizure outcomes after surgical resection of dysembryoplastic neuroepithelial tumors. J Neurooncol 2016;126:1–10.
40. Giulioni M, Marucci G, Pelliccia V, et al. Epilepsy surgery of "low grade epilepsy associated neuroepithelial tumors": a retrospective nationwide Italian study. Epilepsia 2017;58:1832–41.
41. Nolan MA, Sakuta R, Chuang N, et al. Dysembryoplastic neuroepithelial tumors in childhood: long-term outcome and prognostic features. Neurology 2004;62:2270–6.
42. Kwon CS, Sheth SA, Walcott BP, et al. Long-term seizure outcomes following resection of supratentorial cavernous malformations. Clin Neurol Neurosurg 2013;115:2377–81.

43. Baumann CR, Acciarri N, Bertalanffy H, et al. Seizure outcome after resection of supratentorial cavernous malformations: a study of 168 patients. Epilepsia 2007; 48:559–63.
44. Blümcke I, Thom M, Aronica E, et al. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. Epilepsia 2011;52:158–74.
45. Kim DW, Lee SK, Chu K, et al. Predictors of surgical outcome and pathologic considerations in focal cortical dysplasia. Neurology 2009;72:211–6.
46. Giulioni M, Licchetta L, Bisulli F, et al. Tailored surgery for drug-resistant epilepsy due to temporal pole encephalocele and microdysgenesis. Seizure 2014;23: 164–6.
47. Urbach H, Jamneala G, Mader I, et al. Temporal lobe epilepsy due to meningoencephaloceles into the greater sphenoid wing: a consequence of idiopathic intracranial hypertension? Neuroradiology 2018;60:51–60.
48. Noe K, Sulc V, Wong-Kisiel L, et al. Long-term outcomes after nonlesional extratemporal lobe epilepsy surgery. JAMA Neurol 2013;70:1003–8.
49. Gonzalez-Martinez J, Mullin J, Bulacio J, et al. Stereoelectroencephalography in children and adolescents with difficult-to-localize refractory focal epilepsy. Neurosurgery 2014;75:258–68.
50. Serletis D, Bulacio J, Bingaman W, et al. The stereotactic approach for mapping epileptic networks: a prospective study of 200 patients. J Neurosurg 2014;121: 1239–46.
51. Tandon N, Tong BA, Friedman ER, et al. Analysis of morbidity and outcomes associated with use of subdural grids vs stereoelectroencephalography in patients with intractable epilepsy. JAMA Neurol 2019;76:672–81.
52. Englot DJ, Ouyang D, Garcia PA, et al. Epilepsy surgery trends in the United States, 1990-2008. Neurology 2012;78:1200–6.
53. Jette N, Sander JW, Keezer MR. Surgical treatment for epilepsy: the potential gap between evidence and practice. Lancet Neurol 2016;15:982–94.
54. Engel J Jr. Why is there still doubt to cut it out? Epilepsy Curr 2013;13:198–204.
55. Roberts JI, Hrazdil C, Wiebe S, et al. Neurologists' knowledge of and attitudes toward epilepsy surgery: a national survey. Neurology 2015;84:159–66.
56. Berg AT, Langfitt JT, Cascino GD. The changing landscape of epilepsy surgery: no longer the "last resort". Neurology 2018;91:55–6.
57. Hader WJ, Tellez-Zenteno J, Metcalfe A, et al. Complications of epilepsy surgery: a systematic review of focal surgical resections and invasive EEG monitoring. Epilepsia 2013;54:840–7.
58. Gomez-Alonso J, Cascino G. Temporal lobe epilepsy is a progressive neurologic disorder: time means neurons! Neurology 2010;74:347.
59. Engel J Jr. Evolution of concepts in epilepsy surgery. Epileptic Disord 2019;21: 391–409.
60. Jehi L, Friedman D, Carlson C, et al. The evolution of epilepsy surgery between 1991 and 2011 in nine major epilepsy centers across the United States, Germany, and Australia. Epilepsia 2015;56:1526–33.
61. Van Gompel JJ, Ottman R, Worrell GA, et al. Use of anterior temporal lobectomy for epilepsy in a community-based population. Arch Neurol 2012;69:1476–81.
62. Burneo JG, Black L, Knowlton RC, et al. Racial disparities in the use of surgical treatment for intractable temporal lobe epilepsy. Neurology 2005;64:50–4.