Surgical Management of Intractable Epilepsy

Neurosurgical techniques are effective and underutilized for patients with drug-resistant epilepsy.

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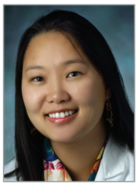

Epilepsy is one of the most common neurologic disorders affecting 2.2 million people in the US. Approximately 70% to 80% of these patients achieve acceptable seizure control with antiepileptic drugs, while the remaining 20% to 30% have drug-resistant epilepsy.[1] Patients with epilepsy are at increased risk of serious morbidity and mortality including cognitive and mood disorders and sudden death in epilepsy (SUDEP). Although for many patients with drug-resistant epilepsy, neurosurgery is the most effective treatment to control seizures and significantly improve quality of life,[2] epilepsy surgery remains one of the most underutilized therapeutic interventions.[3] The reasons for this underutilization are not clearly defined but may include underrecognition of potential surgical candidates and concerns about further morbidity from surgery.

In the past decade, there has been significant advancement and refinement of imaging and surgical techniques. Although surgical resections are still the most common epilepsy surgery, the focus of this article is indications for epilepsy surgery and newer and less invasive surgical techniques and outcomes.

Recommendation and Referral for Surgery

The epilepsy community has made efforts to promote epilepsy surgery as a treatment option for patients with drug-resistant epilepsy. In 2010, the International League Against Epilepsy (ILAE) proposed the following definition for drug-resistant epilepsy: "failure of adequate trials of 2 tolerated and appropriately chosen and used anticonvulsant schedules (whether as monotherapies or in combination) to achieve seizure freedom."[4] In a landmark, randomized controlled trial, epilepsy surgery was superior to continued medical therapy for patients with drug-resistant temporal lobe epilepsy; 58% of patients who had surgery were free from seizures that impaired awareness compared with 8% of patients with drug-resistant epilepsy who continued medical management.[2] Greater improvement in quality of life was also seen in patients who had surgery. Based on this, along with an additional 24 class IV studies, in 2003, the American Academy of Neurology (AAN) published the first practice parameters for epilepsy surgery in adults. The panel recommended that "patients with disabling complex partial seizures, with or without secondarily generalized seizures, who have failed appropriate trials of first-line antiepileptic drugs should be considered for referral to an epilepsy surgery center."[5]

Despite the previously mentioned efforts, the overall number of epilepsy surgery procedures has remained stable. A patient with epilepsy may wait on average 17 to 22 years from the time of diagnosis to referral to an epilepsy center for presurgical evaluation.[6,7] This prolonged duration has devastating consequences for the patient. By the time the patient is considered a surgical candidate, it may be too late to reverse disabling effects of uncontrolled seizures, including psychosocial disability and SUDEP. Surgical outcome may also depend on the duration of the epilepsy; 90% of patients who had epilepsy less than 10 years became seizure free, whereas approximately 30% of patients with epilepsy for more than 30 years became seizure free postoperatively.[8]

Presurgical Evaluation

The success of epilepsy surgery depends largely on the results of the presurgical evaluation. The overall goal of the presurgical evaluation is to identify the epileptogenic zone and to determine which surgical procedure would be appropriate and beneficial for the patient.[9] The core components of a presurgical evaluation include a neuropsychologic evaluation, high-resolution structural MRI and video scalp EEG to capture and localize seizures. Depending on the clinical scenario, additional testing such as task-based functional magnetic resonance imaging (MRI), interictal F-fluorodeoxyglucose (F-FDG) PET scan, and magnetoencephalography (MEG) may be utilized.

Concordance of data in the presurgical evaluation to a resectable brain region often allows the patient to proceed directly to the surgery; otherwise, an invasive investigation is needed.[10] Subdural electrodes in the form of grids and strips are the most common invasive method used in the US.[11] Electrodes embedded in sheets of polyurethane or other material are implanted over suspected epileptogenic regions. The limitation of the subdural methodology is that subcortical structures such as the insula and cingulate regions cannot be investigated adequately. Robot-assisted stereo-electroencephalography (S-EEG) is a minimally invasive method using depth electrodes to sample the epileptogenic network in 3-D anatomical space and is increasingly utilized in specialized surgical epilepsy centers in the US. Compared to subdural electrodes, S-EEG seems to have reduced potential for complications such as hemorrhage and infections and is generally better tolerated by patients.[12]

Epilepsy Surgery

There is an overall trend in neurosurgery toward minimally invasive techniques and several improved surgical methods for achieving precisely targeted destruction of subcortical structures. Recent advances in neuroablative techniques in epilepsy include MRI-guided laser interstitial thermal therapy (MRgLiTT), stereotatic radiosurgery, radiofrequency (RF) thermocoagulation, and MRI-guided focused ultrasound (MRgFUS).

Temporal Lobectomy

Mesial temporal lobe epilepsy is the single most common etiology of surgically treated epilepsy and comprises about two-thirds of epilepsy surgeries done in the US. Traditionally, anterior temporal lobectomy has been the gold standard surgical treatment for intractable temporal lobe epilepsy. Seizure freedom is achieved in up to 70% of patients after temporal resection, and another 20% have a significant reduction of seizure frequency.[13] However, temporal lobectomy has been associated with cognitive impairments such as verbal memory and naming deficits and is usually followed by a prolonged 2- to 3-month recovery period.[14]

MRI-Guided Laser Interstitial Thermal Therapy

The MRgLiTT technique is rapidly becoming an accepted alternative to surgical resection in patients with mesial temporal lobe epilepsy. The procedure utilizes laser heating via stereotatically inserted optic fiber to target and thermocoagulate mesial temporal structures. The extent of thermocoagulation is regulated by a real-time magnetically guided heat-mapping and cooling catheter.[14,15] Outcomes data are limited, follow-up times are short, but the initial evidence seems to suggest that MRgLiTT is a good alternative for anterior temporal lobectomy. Several case series report successful outcomes in about half of the patients.[16-21] Patients with mesial temporal sclerosis (MTS) seem to have better outcomes compared to those without MTS (60% of patients free of disabling seizures 1 year after surgery vs 33.3%).[21] The SLATE[a] trial, a prospective, multicenter study of MRI-guided laser ablation in patients with medically intractable mesial temporal lobe epilepsy is currently underway.

Compared to temporal lobectomy, MRgLiTT is well tolerated and is associated with fewer cognitive deficits in patients with mesial temporal lobe epilepsy.[22] Craniotomy is not required for MRgLiTT, which makes the recovery period much shorter. Patients often stay in the hospital for 1 day, usually in the neurologic intensive care unit or in a standard hospital unit and are then discharged to home the day following the procedure. Most activities, including work, can be resumed in 5 to 7 days. Complications reported usually include asymptomatic visual field deficits, cranial nerve palsy, and intracranial hemorrhage (Table).

A variety of epileptogenic lesions have been treated with MRgLiTT including mesial temporal sclerosis, hypothalamic hamartomas (HH), cortical dysplasia, cavernous heman-

TABLE. COMPLICATIONS OF MRI-GUIDED LASER INTERSTITIAL THERMAL THERAPY

Complications	Number of patients	Free of disabling seizures (All)	Free of disabling seizures (MTS)
VFD (N=5,58.6%), Symptomatic VFD, HH (N=1, 1.7%) H (N=2,3%), transient partial CN palsy (N=4,6.9%)[21]	58	31 (53.4%, CI 40.8-65.7%)	26 (60.5%, CI 45.6-73.7%)
No H, infection,CN deficits reported[20]	43	28 (67.4%)	17 (76.4%)
HH (N=1, 4%)[19]	23	15 (65.2%)	11 (73%)
VFD (N=7, 18%), CN deficit (N=2,5%), H (N=3,7.8%)[18]	38	18 (53%)	17 (60.7%)
VFD (N=1, 5%), CN deficit (N=1,5%), H(N=1,5%)[17]	20	11 (53%)	10 (59%)
HH (N=1,7.7%), H (N=1,7.7%)[16]	13	7 (54%)	6 (67%)

Abbreviations. CN, cranial nerve; H, hemorrhage; HH, homonymous hemianopia; MTS, mesial temporal sclerosis; VFD, visual field defect.

a Stereotatic laser ablation for temporal lobe epilepsy (NCT02844465).

giomas, and insular encephalomalacia.[23] There is increasing evidence that MRgLiTT may be an effective treatment for HH. A study reported that 12 (86%) of 14 patients who underwent ablation of an HH became seizure free. In a recent update, the same group reported that 66 (93%) of 71 patients were free of gelastic seizures at 1 year.[24]

Radiofrequency Thermocoagulation

For patients who undergo invasive monitoring with intracranial electrodes, the same electrodes can be connected to a radiofrequency (RF) generator for focal themocoagulation (thermolesion). Although not widely performed in the US, thermocoagulation is thought to be a safe and well-tolerated procedure in Europe.[25] Multiple 5- to 7-mm-diameter thermolesions can be created by applying 100 to 110 mA bipolar current (50 V) for 10 to 50 seconds. There are several benefits to this technique. This procedure does not require additional surgery and can be performed at bedside without anesthesia. Multiple sites can be coagulated, with real-time electrophysiological feedback. However, unlike MRgLiTT, there is no real-time feedback on thermal energy delivery, with theoretical risk to surrounding structures.

Limited evidence so far suggests that RF thermocoagulation can be proposed as a palliative procedure if resection is not possible. Approximately one-third of patients experience significant reduction in seizure frequency; 15% to 18% of patients achieved seizure freedom after RF in 2 case series.[25,26] There were no reports of worsening seizures. Further randomized controlled trials are needed to determine the indications and efficacy of RF thermocoagulation.

Stereotatic Radiosurgery

Stereotatic radiosurgery (SRS) uses focused ionizing radiation to usually deep-seated lesions, such as epileptogenic HHs, arteriovenous malformations, and hippocampal sclerosis (HS).[27] The main advantage of SRS is that the patient is treated on an outpatient basis and does not require any surgery or anesthesia. There are several major disadvantages, however, including delayed efficacy (mean, 12 months),[28] significant brain edema, intracranial hypertension, and in some cases, a temporal increase in seizure frequency.[29]

In the past 20 years, there has been increasing interest in treating mesial temporal lobe epilepsy with SRS. In 2 prospective multicenter trials a seizure remission rate of 59% to 77%[30,31]; this prompted the randomized ROSE[b] trial comparing SRS to anterior temporal lobectomy (ATL). The recent results from the ROSE trial suggest that ATL is superior to SRS in terms of patients achieving seizure freedom (78% vs 52%). The SRS technique may be an alternative treatment for patients who may not be candidates or are reluctant to undergo ATL.[32]

Magnetic Resonance-Guided Focused Ultrasound Surgery

Magnetic resonance-guided focused ultrasound surgery (MRgFUS) is an emerging, transformative technology that has great potential to overcome the limitations of surgery, radiation, and drug therapy. It is a noninvasive method that can be integrated with MRI to enable targeted delivery of acoustic energy to thermally ablate tissue.[33] The MRgFUS technique offers significant advantage over current treatments because it does not require surgery or involve ionizing radiation and there is minimal collateral damage. Benign and malignant nonneurologic (eg, uterine fibroids, breast tumors, and liver cancers) have been treated successfully with MRgFUS. The need for craniotomy due to skull-bone heating and beam-phase aberration has significantly delayed feasibility of MRgFUS for intracranial lesions,[34] but recent advancements in transducer design and active cooling of the scalp have allowed for therapeutic application in movement disorders and neuropathic pain.[35]

Another potential capability of MRgFUS is the ability to increase drug delivery to targeted brain regions through a temporary disruption of the blood-brain barrier (BBB).[36] Combining sonications with microbubble agents may also enhance the increase focused bioeffects of FUS. MRgFUS is a promising noninvasive therapeutic option but needs further investigation before FUS can be translated to clinical practice. Several trials are currently underway to evaluate feasibility, safety, and initial effectiveness of MRgFUS for focal epilepsy.[c]

Conclusion

Epilepsy surgery can be an effective and safe treatment for patients with drug-resistant epilepsy. Although open resection still remains the standard for epilepsy surgery, early results suggest that minimally invasive surgical techniques may be an exciting and effective alternative treatment to open surgery. The potential for faster recovery time and reduced morbidity is certainly an attractive treatment option. Further larger prospective studies are needed to validate the safety, long-term efficacy, and cost effectiveness of the emerging procedures in epilepsy surgery. ■

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b Radiosurgery versus open surgery for mesial temporal epilepsy (NCT00860145)
c MR-guided focused ultrasound in the treatment of subcortical lesional epilepsy (NCT02804230).

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