Minimally invasive techniques for epilepsy surgery: stereotactic radiosurgery and other technologies

A review

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Minimally invasive surgical techniques for the treatment of medically intractable epilepsy, which have been developed by neurosurgeons and epileptologists almost simultaneously with standard open epilepsy surgery, provide benefits in the traditional realms of safety and efficacy and the more recently appreciated realms of patient acceptance and costs. In this review, the authors discuss the shortcomings of the gold standard of open epilepsy surgery and summarize the techniques developed to provide minimally invasive alternatives. These minimally invasive techniques include stereotactic radiosurgery using the Gamma Knife, stereotactic radiofrequency thermocoagulation, laser-induced thermal therapy, and MRI-guided focused ultrasound ablation.
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THE lesions encountered in epilepsy surgery are often physiologically defined rather than discrete structural lesions; therefore, physicians involved with the evaluation leading up to and performance of epilepsy surgery are always pushing technology to determine what minimal extent of a surgical lesion can interrupt the critical circuits that define an epileptic network, what techniques can minimize invasive procedures required in defining these epileptic networks, and what surgical techniques can perform modification to or ablation of the target with the least morbidity and invasion. This review outlines the ongoing development of techniques of minimally invasive epilepsy surgery, including stereotactic radiosurgery (SRS), stereotactic radiofrequency thermocoagulation (SRT), laser-induced thermal therapy (LITT), and MRI-guided focused ultrasound ablation (FUS).

Abbreviations used in this paper: ATL = anterior temporal lobectomy; AVM = arteriovenous malformation; CM = cavernous malformation; FUS = focused ultrasound ablation; HH = hypothalamic hamartoma; LITT = laser-induced thermal therapy; MTLE = mesial temporal lobe epilepsy; SEEG = stereo-electroencephalography; SRS = stereotactic radiosurgery; SRT = stereotactic radiofrequency thermocoagulation; SUDEP = sudden unexpected death in epilepsy.

Open Surgery

Before discussion of minimally invasive techniques, a brief rationale for looking past open surgery is necessary. After all, craniotomy and anterior temporal lobectomy (ATL) are the gold standards established by Wiebe et al. in their randomized controlled trial of surgery versus “best medical therapy” for mesial temporal lobe epilepsy (MTLE).⁷⁹ This study showed that whereas only 8% of patients achieved seizure freedom for a year’s duration—with 1 death—almost 60% achieved seizure freedom after ATL with no clear surgical morbidities (beyond expected visual field cuts after ATL).²⁸

A reasonable question is, “Why should SRS be used when standard techniques may be good enough?”

One answer is utilization. ATL remains underutilized because of perceived risk, cost, and lack of willingness to seek specialized centers.^{6,40} Despite clear standards guiding physicians in the consideration of epilepsy surgery,¹⁹ and despite the proliferation of epilepsy centers, the actual number of surgeries has stayed flat.²⁰ Patients and referring physicians may be reluctant to invoke invasive surgery, leading to delays of definitive treatment.

Medical care costs, especially for open surgery re-

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quiring intensive care, are considerable. For example, the average cost per patient for treatment of arteriovenous malformations (AVMs) with open microsurgery is nearly 50% more than that with minimally invasive SRS.⁷⁸

Primary morbidities of open surgery are admittedly low but remain significant because epilepsy surgery is often considered an elective procedure; surgical risks include a 0.24% chance of death, a 2% chance of serious permanent complications, and a 6% chance of transient complications.⁷³ Secondary morbidities, especially in neurocognition, also remain significant. For example, impairments of verbal learning and memory have been demonstrated in 10%–60% of patients who undergo open ATL on the dominant hemisphere,^{10,29,30,71} whereas less consistent declines in visual memory are associated with ATL on the nondominant hemisphere.⁴⁷ In a multicenter prospective epilepsy surgery trial, an overall 38% prevalence of verbal memory decline after ATL was documented, with the greatest predictor being side of surgery.⁷¹ Of dominant-hemisphere surgery patients in this series, 40% declined in 1 measure of verbal memory and another 20% declined in 2 measures, for an overall prevalence of 60%.⁷¹

Therefore, underutilization of surgery, attributable to patient and physician reluctance, high costs, and perceived as well as measurable morbidities, drives the search for minimally invasive alternatives to open epilepsy surgery.

Stereotactic Radiosurgery

SRS, either with the Gamma Knife (Elekta AB) or with various linear accelerators (Novalis Tx, Varian Medical Systems) and CyberKnife (Accuray, Inc.) deliver ionizing radiation to a focal target. The Gamma Knife consists of about 200 separate radioactive cobalt-60 sources housed inside a hemispheric chamber and focused to a single target. The target, in turn, is determined and maintained with the patient positioned in a stereotactic frame. The linear accelerators move to deliver beams about various vectors to construct a focus point within the calculated center. Unless noted, most work cited below involves the Gamma Knife.

Of the techniques discussed in this review, SRS has the widest and deepest range of publications reflecting clinical experience and basic science investigations over the last 60 years. Only recently, however, has SRS been specifically studied for its anticonvulsant effects.

Lesional Epilepsies

The anticonvulsant effects of SRS were first noted in treatments of mass lesions: tumors, AVMs, cavernous malformations (CMs), and hypothalamic hamartomas (HHs).

Tumors. Given the variety of CNS tumors, studies of SRS for treatment of tumor-associated epilepsy (as opposed to numerous reports on the efficacy of this technique for use on tumors themselves) are few. Schröttner et al., however, concentrated on the dose absorbed by tissue in tumor penumbra, dividing patients into 2 groups according to the volume of tissue outside the tumor that had

received 10 Gy or more.⁶² Outcome was retrospectively ranked at a mean duration of about 2 years into “excellent” (Engel Class I–II) or not. Patients in the high-volume group achieved a 66% improvement rate compared with 42% for those in the low-volume group. Because all patients achieved tumor control with SRS (thus removing tumor response as a confounder), the differing rates of seizure improvement suggest that higher SRS volumes delivered to tumor penumbra are important in treating tumor-associated epilepsy.

Arteriovenous Malformations. The anticonvulsant efficacy of SRS is most evident in the treatment of AVMs, with an across-study mean seizure remission rate of 70%.^{25,27,38,61,70} Representative is the large series accumulated by Steiner et al., who reported that seizures cease after SRS in 69% of patients with an AVM and epilepsy.⁷⁰ A recent update from the same center reported that 89% of patients achieved seizure remission (measured as Engel Class Ia/b outcomes), and 33% of patients were tapered off of pre-SRS anticonvulsant medications.⁵³ Obliteration of the AVM nidus is not a consistent marker for seizure remission among the above studies. The most recent found that there was some contribution of obliteration of the nidus to the ability to discontinue anticonvulsant medications; of the patients who experienced complete seizure remission, 54% with patent nidi remained on anticonvulsants compared with 19% with complete AVM obliteration.⁵³

Cavernous Malformations. The enthusiasm for the use of SRS for CMs remains mixed. The across-study proportion of seizure remission reported in retrospective case series is 50%.⁴ Representing the extremes in efficacy, Shih and Pan⁶⁶ reported mean margin doses of 13 Gy and central doses of 21 Gy for a remission rate of 25%, whereas Kim et al.³⁶ used a mean margin dose of 15 Gy and a central dose of 26 Gy for a remission rate of 70%. Retrospective studies of open resection suggest that removal of the hemosiderin-stained tissue surrounding the CM is associated with better outcome;⁵ therefore, variable outcomes following SRS may also stem from inconsistent inclusion of this potentially epileptogenic region in the treatment volume. With higher doses, however, radiation toxicity emerges as a concern.³⁴ In a recent retrospective comparison, the authors concluded that open resection resulted in better seizure control and hemorrhage avoidance than SRS.⁶⁶ This study, as well as comparisons to the approximately 70%–80% seizure remission rate seen after open surgery for CM,^{8,13} suggest that any benefits of noninvasive SRS over open surgery for CM must be weighed against risks of less efficacy and possibly increased toxicities.

Hypothalamic Hamartomas. These lesions frequently cause medically intractable gelastic and other seizures that are usually accompanied by behavioral and cognitive decline. SRS has an advantage of noninvasive access. Series of SRS treatment of HH^{1,44,56,60,64,75} demonstrate a seizure remission rate of 27% across studies. Although this rate appears low, seizure remission alone underestimates the benefits seen with respect to improved behavior and

the need for less custodial care required in these cases of severe epilepsy. A European multicenter, prospective trial of SRS for HH enrolled 60 patients, 27 of whom exceeded 3 years of follow-up.⁶⁰ Morbidity was low, with no ill effects except for one instance of poikilothermia noted among the above reports. Some reports emphasize the importance of the margin dose of radiation,⁶⁰ as noted for tumors and AVMs. Patients treated with doses exceeding 17 Gy to the margin of the HH had greater rates of seizure remission than those receiving less than 13 Gy.⁵⁶

Physiological Epilepsies

Mesial Temporal Lobe Epilepsy. Extensive study has centered on focal epilepsies not caused by a discrete mass. MTLE consists of atrophy, gliosis, and selective neuronal loss within the hippocampus and associated limbic system. Régis et al. were the first to systematically evaluate SRS for treatment of MTLE in 1995,⁵⁸ and they then conducted a subsequent trial of 7 MTLE patients.⁵⁷ In this series, a target comprising the parahippocampal gyrus, head and anterior body of the hippocampus, and amygdala, with an approximately 6.5-ml 50% isodose volume, was treated with 25 Gy. Since this publication, 9 studies treating a total of 83 patients have been reported. These studies demonstrate a wide range of efficacies of seizure remission, ranging from 0% to 86%,^{2,12,31,35,46,52,57,59,68} with an across-study average of 51%. In comparison, the rate of seizure remission in the prospective, randomized trial of open surgery for MTLE was 58%.⁷⁹

The wide range of outcomes in seizure remission arose from the developing understanding of the anticonvulsant mechanism of ionizing radiation, dose/volume considerations, and patient selection.

Hypotheses on mechanisms of the anticonvulsant effect of ionizing radiation have centered on neuromodulation versus ablation.⁵⁵ Animal models of focal epilepsy suggested that nondestructive neuromodulation was sufficient for seizure reduction.^{11,41} Single-center case series of SRS with “low-dose protocols” (dose < 24 Gy) informed by this work showed poor results.^{12,31,35,52,68} In contrast, 2 larger, prospective multicenter studies, 1 European⁵⁹ and 1 American,² used doses at or above 24 Gy. The European trial demonstrated a 2-year postoperative seizure remission rate of 62% with the use of a treatment protocol identical to that used in the group’s earlier studies. Barbaro et al., in the US Multicenter Pilot Study,² randomized 30 patients to a high (24 Gy, n = 13) or low (20 Gy, n = 17) dose delivered to the target as specified by Régis et al.,⁵⁹ with the added specification that 50% isodose volumes were restricted to 5.5–7.0 ml. Ten patients in each group were seizure free at 36 months of follow-up, resulting in a remission rate of 77% in the high-dose and 59% in the low-dose group, for an overall remission rate of 67%. Patients in the high-dose group had higher volumes of radiation-induced changes and had spectrographic evidence of necrosis in the target center, suggesting that higher doses caused ablations of the epileptic target.⁹

Patient selection is an important consideration in evaluating SRS treatment protocols. In fact, any minimally invasive surgical technique requires rigorous defi-

nition of the target. SRS is, in effect, a “superselective” amygdalohippocampectomy involving the destruction of the minimum volume and anatomy important in the pathophysiology of MTLE. Patients with epilepsies that may differ from the stereotypic unilateral MTLE lesion may not be suitable for SRS. For example, most patients in a long-term cohort in whom SRS failed also had evidence for extension of the “epileptic zone” beyond mesial structures.³ In another trial with poor SRS results, one explanation for poor rates of seizure remission was that the primary epileptic injury in some patients could be considered symptomatic “MTLE plus.”⁷⁶ Patients with evidence of involvement outside of the SRS target or with symptomatic etiologies may not experience seizure remission with the highly selective/minimally invasive techniques. Of course, this limitation is not unique to SRS.

Morbidities in the multicenter SRS protocols do not exceed those of open surgery and fall in line with those seen commonly after SRS. Superior quadrant field defects are an expected morbidity after standard temporal lobectomy, with rates of visual field defects between 52% and 100%.²⁸ Quantified visual fields were measured in the US Multicenter Study at 24 months after SRS, with the finding that 62.5% of patients had postoperative visual field changes, all homonymous superior quadrantanopsias.²⁸ Other morbidities consisted of headache, nausea, vomiting, and depression. Headache requires special comment as it coincides in some subjects with postoperative edema. Steroids, either in response to headache, visual field changes, or MRI changes, were used in 62% of patients.²

In the treatment of MTLE, one potential benefit of SRS—or indeed, of any minimally invasive surgery—is the sparing of neurocognitive function owing to the “superselectivity” of the minimally invasive lesion. The European prospective trial reported no mean neurocognitive changes through a 2-year follow-up period.⁵⁹ Detailed evaluation of neurocognitive outcomes was provided from the US Multicenter Trial.⁵⁴ Mean scores of tests of language and verbal memory at 24 and 36 months after SRS did not differ from preoperative baselines. Specifically, significant verbal memory impairment was seen in 25% of dominant-hemisphere surgery patients and in 7% of nondominant-hemisphere surgery patients. In fact, significant improvement was seen in 16% of dominant-hemisphere surgery and 7% of nondominant-hemisphere surgery patients. In comparison, rates of significant impairment following dominant-hemisphere temporal lobectomy range from 10% to 60%.^{10,29,30,63,71} Furthermore, mood remained stable, and quality of life scores improved in those patients who experienced seizure remission.

Neocortical Foci. There are no published reports on the use of SRS for nonstructural lesion neocortical foci. Régis has presented a small series of cases in which radiosurgery was delivered to perisylvian regions, including the insular cortex, following localization of the seizure focus with stereo-electroencephalography (SEEG) recordings (J. Régis, personal communication, 2012). Because localization of seizure foci in nonlesional neocortical epilepsies usually requires invasive techniques, the noninvasive nature of SRS loses some advantage. One

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may speculate that if noninvasive localization and brain mapping were rigorous enough to supplant invasive methods, then SRS might have a future role.

Corpus Callosotomy. Transection of the corpus callosum may decrease the severity and number of primary generalized or rapidly propagating secondarily generalized seizures in patients who are not otherwise good surgical candidates. In small case series, improvement in seizures following SRS resection of the corpus callosum was comparable to that reported after open callosotomy, with lack of notable complications.^{16,51}

Potential Problems Unique to SRS

Trials of SRS for HH and MTLE highlight one of the potential shortcomings of SRS relative to open surgery, the latency of development of the radiosurgical lesion.

In HH, changes in seizure frequency first occur at earliest 2 months after SRS. Seizures may transiently worsen in frequency before reduction and remission occur. Behavioral improvements, along with EEG normalization, tend to occur in a more linear fashion.⁶⁰

In the case of MTLE, clinical effects—typically headache and transient emergence of auras—begin to emerge around 6 months after SRS, and most clinical or neuroimaging changes occur between 9 and 15 months. The most dramatic drop in seizure rate occurs between 12 and 18 months,^{2,59} coinciding with the development and resolution of maximal MRI changes.⁹ Lower-dose protocols early in the SRS-MTLE experience were reported to be associated with marked seizure worsening and, in 3 cases, deaths associated with probable sudden unexpected death in epilepsy (SUDEP).^{52,68} One death, reported by Prayson and Yoder, occurred 2 weeks postradiation and was due to “persistent seizure complications.” Because radiographic changes occur within time intervals on the order of months, rather than days, it is unlikely that radiosurgery contributed to this patient’s outcome. An autopsy showing mesial temporal sclerosis but no radiation-induced pathology supports this interpretation.⁵² Additional mortality was reported by Srikiyvilakul et al., who described 1 death at 1 month and another at 1 year following radiosurgery.⁶⁸ Both were attributed to complications of seizures, consistent with SUDEP.

A notable “escape hatch” is available for patients who do not respond to SRS. For example, a protocol-defined severe event was reported in the US Multicenter Trial when, at 15 months after SRS, a patient underwent standard ATL for continuing seizures and persistent radiation edema.

Oncogenesis attributable to radiation is another controversial aspect of SRS. Given that most use of SRS is for treatment of tumors, overall life expectancy and the confounder of preexistent tumor make the investigation of this aspect difficult. At the low end, a best estimate from 1 meta-analysis determined that 3 cases with reasonable evidence of oncogenesis occurred in 200,000 uses (0.0015%).²⁴ At the high end, of tumors seen in patients treated for AVM (eliminating the primary tumor confounder) in a single center, the cumulative rate of probably SRS-induced tumors in those with a minimum of 10-year follow-up was 3 in 4692 person-years (0.64%).⁶⁹

Summary

In summary, seizure remission rates following SRS vary, but the larger, multicenter trials with higher-dose protocols showed remission rates similar to the gold standard of open surgery. Favorable neurocognitive outcomes compared with open surgery suggest that the highly selective radiosurgical lesion may provide some benefit. Note that there are no studies that directly compare open surgery and SRS. However, the ROSE Trial (Radiosurgery or Open Surgery for Epilepsy), a prospective randomized trial of standard open surgery versus SRS, is currently underway. The ROSE Trial may provide further evidence regarding the effects of SRS on neuropsychological functioning and whether cognitive abilities may be less adversely affected by SRS relative to traditional open surgery.

Thermocoagulation Methods

The next 3 methods share the principle of causing a permanent lesion by heating brain tissue until proteins denature above 45°C.¹⁴ They differ in how focal heating is introduced to the target.

Stereotactic Radiofrequency Thermocoagulation

Stereotactic radiofrequency thermocoagulation is a procedure during which a monopolar needle, under stereotactic guidance, is inserted into the surgical target. Current at high frequency (i.e., radiofrequency above 250 kHz) is injected, resulting in heating of tissue at the electrode tip. Since recording and stimulation can be performed with the same electrode, recordings from the lesion, electrical stimulation to evoke seizures, and thermocoagulation can all be accomplished efficiently.

There is a long history of the use of SRT to induce focal lesions to interrupt epileptic networks reported in a variety of small case series performed before the mid-1990s. For brevity’s sake, we quote Neil Kitchen in his review of these studies: “in all instances follow-up has been short and success unpredictable, with not an insignificant risk of complications, and as a result the overall clinical impression of the procedures is that good outcomes are patchy and improvements unsustained.”⁷³ The experience perhaps is more demonstrative of the limitations of drawing conclusions from idiosyncratic case series and a lack of well-organized prospective trials than from the limitations of the technique itself.

Hypothalamic Hamartomas

Most recent uses of SRT in the treatment of epilepsy are reported in retrospective case reports and small case series of HH.^{22,23,32,33,39,72,77} Kameyama et al. reported the largest group, consisting of 25 patients, of whom 19 (76%) had seizure remission. As seen in the SRS group, substantial improvements in behavior also occurred.³³ Complications in this series included evidence of hypothalamic dysfunction in more than 50% of patients (poikilothermia, hyperphagia, hyponatremia, and Horner’s syndrome, all transient) as well as unexpected subdural hematoma in 2 patients.

Physiological Lesions

Selective lesions for MTLE and for neocortical epilepsies have also been performed with SRT.^{7,42,49,50} In an early series of 25 patients who underwent either unilateral or bilateral amygdalotomies performed for psychiatric surgery, comorbid psychomotor seizures fortuitously decreased or ceased in 9 subjects. Numerous subsequent studies on amygdalotomies or amygdalohippocampectomies have been published, but here we focus on 2 of the larger series. The earlier series, reported by Parrent and Blume,⁵⁰ is notable for its excellent review on SRT. In this study, 22 subjects with MTLE underwent SRT performed using 2 different techniques. In the first group of 5 patients, SRT lesions were confined to the amygdala and the anterior 13–21 mm of the hippocampus. Only 1 patient (20%) experienced improvement according to their criteria of remission or limited auras or > 90% seizure reduction. In the second group of 15 patients, “confluent” SRT lesions of the entire amygdala and anterior mid-hippocampus, extending up to 34 mm posteriorly, were performed, resulting in 9 patients (60%) with favorable outcome and 2 (13%) completely seizure free. Notably, the target did not include the entorhinal cortex, thought to be a key structure in evaluating the likelihood of seizure freedom following open surgery for MTLE.⁶⁷

The more recent series, reported by Guénot et al., is notable for the recording and creation of radiofrequency lesions with the same set of implanted SEEG depth electrodes.²⁶ This study comprised 20 patients with lesionless limbic and cortical epilepsies who had seizure foci localized with the use of SEEG depth electrodes. Radiofrequency lesions were created where focal seizures arose, with the number of coagulations ranging from 2 to 13. Three patients (15%) were seizure free short term, with another 8 experiencing > 80% improvement in seizure frequency. No permanent complications arose. Several patients reported transient symptoms corresponding to lesion location.

The aforementioned studies demonstrate both the strengths and the weaknesses of SRT. On one hand, the small lesions confer little risk to normal brain function, can be performed quickly without large craniotomy, have short recovery times, and in the case of combined recording/coagulation electrodes, require a minimum of operative manipulation. On the other hand, the small size of radiofrequency lesions leaves patients vulnerable to poor outcomes, since the total volume of lesion may not be sufficient to interrupt the epileptic circuit. As experience with open surgery teaches (and as seen in long-term outcomes after SRS⁴), the total volume of resection (in the case of MTLE) correlates with surgical success⁶⁵ because either the epileptic network is unperturbed or regions of the epileptic zone remain outside the boundaries of the minimally invasive lesion.

Laser-Induced Thermal Therapy

The term “laser” is an acronym for “light amplification by stimulated emission of radiation.” Laser-induced thermal therapy, also designated as MRI-guided thermal

laser ablation (MTLA), refers to elevation of tissue temperature to a lethal level, producing tissue coagulation via laser delivery. When laser light is introduced into a tissue, the photons introduced into the tissue are either scattered (reflected to adjacent tissue components) or absorbed by the tissue components, or they exit the tissue. The mechanism of thermal therapy is that the photon energy is absorbed and transferred to molecules in the tissue, which leads to direct heating of the tissue. The optical properties of the target tissue determine the extent to which photons will penetrate to adjacent tissue components or absorb near the site of delivery, and both aspects relate to the eventual volume of the thermal ablation lesion. For LITT in human tissue, FDA-approved wavelengths for LITT technology are in the infrared 800- to 1064-nm range, just beyond visible light. For LITT use in epilepsy, the wavelength is generally 980 nm.⁷⁴

As with real estate, location in LITT matters; nearby tissue components such as blood, water, and melanin mainly absorb photon energy and may serve as a heat sink. Therefore, relatively homogeneous tissue structures, such as the amygdalohippocampal complex, with appropriate photon delivery, will ablate fairly uniformly, with a rapid drop-off of heat ablation as the LITT reaches surrounding cysternal, ventricular, and vascular structures.

LITT requires stereotactic intracranial placement of a laser applicator/guide in the operating room, followed by performance of the actual ablation under MRI guidance. The eventual ablation is confirmed by immediate post-ablation T1-weighted or FLAIR MR images. The transition zone—that is, the volume demarcating affected from unaffected tissue—is quite sharp, about 1 mm in depth. Therefore, LITT allows a highly selective structural application via a minimally invasive procedure.

Currently, 2 commercial entities provide LITT technology. The Visualase system (<http://www.visualaseinc.com/>) received FDA clearance in August 2007 for a variety of focal surgeries within and outside of the brain. The Monteris Medical system (www.monteris.com/) received FDA clearance in late 2010 (previous approval in Canada), with a product name change in 2012 to the NeuroBlate System for brain surgery.

Peer-reviewed studies on the use of LITT for epilepsy are still few in number. In a recent series of 13 patients with intractable temporal epilepsy treated with LITT, 9 of whom had mesial temporal sclerosis, the mean ablated amygdalohippocampal complex volume was 60%. The only complication was a visual field cut in 1 patient, which was associated with deviation of the applicator insertion and was not from LITT. The median hospital stay was 1 day, and 77% (10/13) of patients achieved meaningful seizure reduction; 54% (7/13) were free of disabling seizures during a follow-up period of 5–26 months (median 14 months).⁸⁰

LITT has been reported in the treatment of HH. In a recently reported study of medically refractory gelastic epilepsy due to HH in patients who underwent LITT ablation, 12 (86%) of the 14 patients achieved seizure freedom, with mean follow-up of 9 months.¹⁵ The authors reported that no permanent surgical complications, neurological deficits, or neuroendocrine disturbances occurred. The

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median hospital stay was 1 day. Additionally, 2 cases of periventricular nodular heterotopia with epilepsy treated successfully with LITT have been reported.²¹

In summary, the spectrum of appropriate use, expected outcomes, and complications for LITT in epilepsy appears to be evolving. The “immediate feedback” of the LITT lesion revealed by MRI and without a latency period of lesion development (as required in SRS) has appeal, but LITT has yet to be explored in a systematic fashion.

MRI-Guided FUS Ablation

Focused ultrasound devices (for example, the ExBlate Neuro, Insightec) do exactly what the name suggests: high-energy sound waves of 230–1000 kHz, generated by 1024 emitters, are focused through techniques such as the spatial array of emitters, choice of frequency, and the manipulation of phase to direct energy to a central point at which temperature can be raised and lowered to create a transient or permanent lesion.⁴⁸ The location, volume, and change of temperature are monitored in real time with simultaneous MRI. Originally, because the skull diffuses ultrasound signals significantly, “minimally invasive” was a misnomer since craniotomies were required. However, subsequent work has largely overcome some of these challenges, and targets within homogeneous, deep regions of the brain allow reliable focusing without dispersal of signal and without unpredictable “radiator” effects of rapid heat transfer away from the target.

Accordingly, seminal trials of MRI-guided FUS have been conducted in the treatment of glioblastoma⁴⁵ and chronic neuropathic pain via medial thalamotomies,⁴³ and in the treatment of essential tremor through lesions of the ventral intermediate nucleus of the thalamus.¹⁷ Like SRS, FUS appears to be “the maximum of minimums,” because it (potentially) requires no craniotomies. Although patients require some sedation to comply with long procedure times, there is no need for general anesthesia, and with growing experience, the need for inpatient postoperative monitoring has decreased. Unlike SRS, results are presented in real time. One could imagine that the truly minimally invasive nature of FUS would allow a series of lesions across time based on interoperative periods of observation to determine the extent of seizure remission. However, technological limitations prohibit its current application to traditional limbic and neocortical epilepsies. Both amygdalohippocampal and neocortical targets currently are too close to the skull; critical heating of the skull and structures outside the target region can result. These limitations are being actively addressed.⁴⁸

Summary

The search for safe and effective minimally invasive neurosurgical techniques in epilepsy surgery has a long and largely successful history. The limitations of these techniques lie mainly within the limitations of the uncertain physiology of epilepsy rather than in the techniques themselves. Basic localization of the epileptic zone remains a critical challenge because, as demonstrated in several of the trials noted above, the very feature of mini-

minally invasive techniques that attracts us to their use—the superselectivity of the lesions caused by SRS, SRT, LITT, and FUS—often work against seizure remission since many patients have epileptic zones that defy definitive mapping or exceed volumes that can reasonably be called “minimally invasive.” However, many epileptologists may be too familiar with the limitations of open surgery. Often we feel that patients have “one good surgery” in them, and we find them reluctant to return to repeat open surgeries in the case of poor efficacy. What these techniques offer in common, especially LITT and FUS, is the ability to perform serial ablations in a segmented approach. In this paradigm, a minimally invasive technique is called upon to ablate the best-defined target, and the patient is observed for a period of time. If remission does not occur, then repeat ablation can be performed, perhaps following some additional localization.

As epileptologists who conduct epilepsy drug trials in addition to being involved in epilepsy surgery evaluations, we note that almost all of these studies have been conducted in a manner endemic in neurosurgical clinical research; single-center, retrospective case reports and small case series predominate. True comparisons among studies and even within reports are difficult since patient recruitment does not follow clear inclusion and exclusion criteria and methods are serially “tweaked” to accommodate patient inhomogeneity. Outcomes are usually cross-sectional rather than followed in a uniform time base. Primary outcomes—seizure remission—are judged in a variety of ways across studies, and secondary outcomes—patient disability, quality of life, cognition, and mood—are either ignored or qualitatively described rather than measured in accepted neurocognitive scales. To date, only 4 randomized, controlled trials of epilepsy surgery have been published,^{18,79,81} one of them the US Multicenter Study of SRS discussed above. A handful of publicly funded, prospective observational studies exist. Two publicly funded trials, the ERSET (Early Randomized Surgical Epilepsy Trial) study of the benefits of early ATL¹⁸ and the ongoing ROSE Trial evaluating open surgery versus SRS, were closed early because of insufficient recruitment. Although recent and ongoing studies of LITT and FUS have many of the features of a modern, well-conducted clinical trial, none achieve Class 1 evidence levels.

In short, it is difficult to conduct robust, unbiased trials in the field of epilepsy surgery. We challenge the researchers of future studies of minimally invasive techniques to design trials with unbiased judging, robust design, and common, validated outcome measures.

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