American Society for Stereotactic and Functional Neurosurgery
Position Statement on Laser Interstitial Thermal Therapy for the Treatment of Drug-Resistant Epilepsy

[ASSFN Position Statement on LITT for Epilepsy]

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Executive Summary

Purpose of the Statement

1. To provide an evidence-based, best practices summary to guide health-care providers in the use of Magnetic Resonance-guided Laser Interstitial Thermal Therapy (MRgLITT) in the management of epilepsy
2. To report consensus opinion of the American Society for Stereotactic and Functional Neurosurgery (ASSFN) regarding the use of MRgLITT for intractable epilepsy

Importance of the American Society of Stereotactic and Functional Neurosurgery (ASSFN) Statement

1. Stereotactic and functional neurosurgeons are domain-specific experts in the specialty literature and the practical use of stereotactic and open procedures for the surgical management of drug-resistant epilepsy (DRE).
2. Stereotactic and functional neurosurgeons are domain-specific experts in the comparative assessment of benefits, risks, and alternatives of surgical procedures for the management of patients with DRE.

Indications for the Use of MRgLITT as a Treatment Option for Patients With DRE Include All of the Following Criteria:

1. Failure to respond to, or intolerance of, at least 2 appropriately chosen medications at appropriate doses for disabling, localization-related epilepsy AND
2. Well-defined epileptogenic foci or critical pathways of seizure propagation accessible by MRgLITT.

Contraindication to Use of MRgLITT:

1. Inability to identify the epileptogenic focus (or foci) or critical pathways within epileptogenic networks.
2. Inability to undergo magnetic resonance imaging (MRI) because of medical reasons.
3. Medical contraindications to surgery, e.g., unstable cardiac or respiratory conditions, anticoagulants that cannot be stopped, bleeding diatheses

Recommendations Are Based On:

1. Safety and efficacy demonstrated in multiple peer reviewed large case series demonstrating the safety and efficacy of MRgLITT in reducing seizure frequency in patients with DRE that is nearly comparable to data obtained from cases series of open surgical procedures.
2. Published literature demonstrates that MRgLITT is a less invasive option for many types of focal DRE that involves a shorter hospital stay and less surgical and neurologic morbidity as compared to open surgical resection for such common epilepsy etiologies as mesial temporal epilepsy, hypothalamic hamartomas, and focal cortical dysplasia/periventricular nodular heterotopia.

3. Some published studies indicate that MRgLITT may better preserve cognitive functions as compared to open epilepsy surgery.

4. When offered a choice between open surgery and MRgLITT, patients increasingly prefer LITT to open surgery and many will otherwise refuse surgical treatment at all. Moreover, MRgLITT has also become the first choice procedure of many epilepsy teams for treatment of many focal epilepsies and has essentially completely supplanted open surgery for epilepsy due to hypothalamic hamartomas. These trends make it unlikely that any randomized trials between MRgLITT and open surgery will be performed.
Background and Supporting Literature

Prevalence and Impact of Drug-Resistant Epilepsy

Epilepsy is the fourth most common neurological disease with approximately 1.2% of the population in the United States suffering from active epilepsy.\(^1\) This is equivalent to about 3.4 million people with epilepsy nationwide, consisting of 3 million adults and 470,000 children. Approximately 1 in 26 people will develop epilepsy during their lifetime.\(^2\) For patients with epilepsy, 25-40% will suffer from persistent seizures despite maximal medical management – otherwise known as drug-resistant epilepsy (DRE) \(^3,4\)

Persistent seizures and associated neurologic comorbidities lead to an approximately 3 times higher mortality rate than the general population with an estimated decreased life expectancy of 10 years in people whose epilepsy has a known cause.\(^5,6\) Furthermore, epilepsy has a significant detrimental impact on employment, social relationships, and overall quality of life for both the patient and their families.\(^7,8\)

However, despite the clear benefits of open epilepsy surgery in reducing mortality and morbidity,\(^4,6,9\) only about 4% of eligible patients undergo this surgery in the United States annually. There was a decreasing rate of epilepsy surgery in the United States from 2003 to 2014, despite the publication of “Epilepsy Across the Spectrum” by the Institute of Medicine in 2012,\(^6,10\) which strongly advocated for epilepsy surgery. Reasons for this underutilization have been attributed to knowledge gaps (inappropriate optimism about seizure reduction), inability of humans to accurately assess risk, barriers to specialists, and fear of surgery.\(^11\)

Medical and Surgical Management of Drug-Resistant Epilepsy

The International League Against Epilepsy has defined DRE as the “failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.”\(^12\) As such, by definition, definitive medical treatment for patients with DRE is inadequate.

Surgical options for DRE depend on seizure type and characteristics of onset and propagation. Surgical procedures for DRE may be divided into ablative/resective (destructive) and neuromodulatory (nondestructive) categories. Complete surgical removal of the brain tissue responsible for seizures (epileptogenic zone, EZ) yields the best outcomes and are associated with the highest rates of seizure freedom. Meanwhile, incomplete removal of the EZ or disconnection of this tissue from the rest of the brain is associated with lower rates of seizure freedom or seizure reduction alone. Fortunately, patients with surgically-treated DRE have been shown to have normalization of overall mortality even without complete seizure freedom, as long as there is reduction of seizures with impaired awareness.\(^5\)
Since mesial temporal lobe epilepsy (MTLE) remains the most common form of DRE, overall surgical experience is greatest with this group of patients. Anterior temporal lobectomy (ATL) remains the gold-standard treatment with proven efficacy in two class I trials and rates of seizure freedom from 60-80% with 2-years of follow-up. Several approaches to selective amygdalohippocampectomy (SAH), with relative sparing of the lateral temporal neocortex, have also demonstrated benefit. In patients with extratemporal lobe epilepsy, surgery has been shown to be effective, albeit with lower rates of seizure freedom in the range of 30-60% with 2-years of follow-up. Despite overall benefits for quality of life, surgery remains underutilized, at least in part due to concerns regarding its invasiveness, procedural morbidity, and neurocognitive side effects.

Over the last decade, magnetic resonance guided laser interstitial thermal therapy (MRgLITT) has emerged as a less invasive option for stereotactic ablation rather than resection of the EZ. MRgLITT offers access to foci virtually anywhere in the brain with minimal disruption of the overlying functional cortex and white matter, promising fewer neurological side effects and less surgical morbidity and pain. Compared to other ablative techniques such as radiofrequency ablation or stereotactic radiosurgery, MRgLITT produces immediate, discrete lesions with real-time monitoring of temperature and damage estimates that allows for quantification of the ablation and minimization of injury to surrounding brain tissue. As more and more clinical experience has been gained with MRgLITT for DRE, it has become the procedure of choice for many types of epilepsy due to its efficacy, favorable side effect profile, short hospital stay and rapid return to normal activity as compared to open surgery.

**Efficacy of MRgLITT in Drug-Resistant Epilepsy**

Selective ablation of amygdalohippocampal complex is the most widely reported application of MRgLITT for DRE. Across several institutional series, MRgLITT has demonstrated seizure freedom rates of 44-78% with at least 1 year of postoperative follow-up. In general, patient selection was based on a diagnosis of DRE and clear evidence of mesial temporal lobe onset. Pre-operative evaluation typically included semiology, MRI, neuropsychology, and video EEG, as is done in determination of candidacy for open procedures. Mesial temporal sclerosis was a common finding on MRI, but was not necessary if other studies such as vEEG or intracranial EEG allowed for concordance. In the largest multi-center series to date, MRgLITT performed in 234 patients from 11 centers across the United States led to seizure freedom in 58% of patients at 1-year follow-up. Furthermore, 19% of patients benefited from significant seizure reduction – totaling 77% of patients with significant clinical benefit. Two recent meta-analyses have since reported overall rates of seizure freedom to be 55% and 58% in patients with MTLE. These rates of seizure freedom are mildly lower than that reported with ATL, as is seen with open selective amygdalohippocampectomy as well. The outcomes are certainly superior to continued medical management alone. Moreover, the typical length of stay for mesial temporal MRgLITT is one night, versus 3-4 nights for an standard open ATL. Importantly, when offered a choice between open
ATL and stereotactic MRgLITT, an increasing proportion of patients is either willing to sacrifice some of the chance of seizure freedom for the other benefits of the minimally invasive procedure or will simply refuse to consider any open surgery at all.

MRgLITT for the treatment of hypothalamic hamartomas (HH) associated with DRE is the next most reported application of this technology. In the largest two series consisting of a total of 129 patients, 81% were free of gelastic seizures at 6-months follow-up; and 93% were free of gelastic seizures at 1-year follow-up.39,40 While fewer patients experienced resolution of non-gelastic seizures (68% free of non-gelastic seizures)39,41, the overall efficacy of MRgLITT remains high for the treatment of HH. Specifically, a recent review reported that 78% of patients experienced favorable outcomes after MRgLITT, which is further strengthened with a relatively low overall complication rate of 8%.42 These outcomes are in contrast to open surgical options, in which seizure freedom rates range from 20-54%43-46 and permanent neurological and endocrinological complications occur in up to 30-59% of patients.42,45-48 Overall, published results with MRgLITT for HH are superior to those for cohorts treated by stereotactic radiosurgery, craniotomy, or neuroendoscopy.43 At this time, MRgLITT is the clear procedure of choice for treating hypothalamic hamartomas, having almost completely supplanted open surgery.

Durability of MRgLITT in DRE

Due to the relatively recent development of MRgLITT for MTLE, long-term outcomes data is limited. Cajigas et al provide the largest single center cohort with Engel scores with at least 2 years of follow up. They reported 62% seizure freedom with an average follow up of 43 months49. Other studies have published seizure freedom rates between 30-52% with 2-year follow-up.50-52 While a meta-analysis has suggested that seizure freedom rates may wane over time – with predicted seizure freedom rates of 64%, 47%, and 42% at 12, 24, and 36 months, respectively – real-world data consisting of larger cohorts with longer follow-up are needed.33 Long-term data for other DRE indications remain limited. Given that much of the current longer-term data represent patients operated on in the early experience with MRgLITT, it is expected that these outcomes will improve with time given the learning curve and the now extant literature regarding optimization of MRgLITT lesions.

Safety of MRgLITT

MRgLITT is significantly less invasive than open surgery, resulting in reduced pain and shorter length of stay, with patients routinely discharged on the first postoperative day in many reports. Furthermore, the ability to monitor the ablation in real-time along with the functionality of adding thermal limits allows surgeons to minimize unintended ablation of structures outside the target zone. Serious neurological
complications, such as hemiparesis, and wound infections have not been reported with MRgLITT for MTLE, and clinically significant hemorrhage is rare (<0.5%).

The most common complication with MRgLITT for MTLE is a visual field deficit, which has been reported to be clinically significant in 5-7% of all patients. This complication typically manifests as a contralateral superior quadrant anopsia, which results from posterolateral extension of the ablation into the optic radiations. Overall this morbidity occurs less frequently than when compared with those reported with standard ATL. Given the proximity of the cranial nerves to the mesial hippocampus. A small number of patients have experienced transient third and fourth cranial nerve palsies, leading to double vision, with MRgLITT for MTLE, but these also occur with open surgery.

Compared with open resection, MRgLITT for MTLE may better preserve neurocognitive functions supported by the lateral temporal neocortex and white matter; although there have been no direct comparisons and many series do not report formal neurocognitive outcomes. Specifically, MRgLITT appears to largely preserve naming and object recognition following language dominant ablations, functions that commonly decline following ATL or SAH. Verbal memory may decline following dominant hemisphere MRgLITT, however, the risk appears to be lower than with open surgery. Kang et al parsed out verbal memory changes and found a decline in non-contextual (word list) verbal memory, which is localized to the mesial structures, but preservation of contextual (narrative) verbal memory, which is supported by the temporal neocortex.

**Indications for MRgLITT in DRE**

While the most common published indications for MRgLITT have been MTLE and HH, the technique has been successfully demonstrated in case series for the treatment of DRE associated with localizable epilepsies such as focal cortical dysplasias, tuberous sclerosis, periventricular nodular heterotopias, and cavernous malformations, demonstrating the relative comfort of stereotactic and functional neurosurgeons with use of this technique for deep-seated lesions. Similarly, there have been several reports of MRgLITT used to perform a corpus callosotomy, but overall experience with this indication remains limited.

**Conclusion**

MRgLITT is an increasingly popular surgical option for DRE. It provides minimally invasive access to make immediate, well-demarcated lesions of the EZ virtually anywhere in the brain with minimal disruption to overlying white matter and cortex with real-time thermal monitoring. Compared to open surgery...
surgery, most reports note significantly less pain and shorter length of stay. While more evidence of safety and longer-term efficacy is needed, it is becoming a first-line surgical option for a variety of indications, particularly when the target is in a deep or difficult-to-access location. While rates of seizure freedom may be lower than with surgical resection for some indications, such as MTLE and extensive FCD, this must be weighed against potential neurocognitive side effects and morbidity associated with open surgery. In addition, MRgLITT does not preclude the option of subsequent more extensive ablations or open surgery. While long-term outcomes must be compared against proven surgical resection techniques, MRgLITT serves as a minimally-invasive option that clearly provides greater benefit in patients with DRE than medical management alone.
References


