International Journal of
Neurology and Neurotherapy

Wu et al. Int J Neurol Neurother 2016, 3:042
DOI: 10.23937/2378-3001/3/2/1042
Volume 3 | Issue 2

ISSN: 2378-3001

Review Article: Open Access

MR-Guided Laser Interstitial Thermal Therapy for the Treatment of Medically Refractory Epilepsy

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Abstract

Resective epilepsy surgery is highly effective in the treatment of medically refractory epilepsy. However, it involves an open craniotomy and carries the risks of permanent functional deficits and cosmetic concerns. Multiple minimally invasive surgical approaches have been attempted to destroy seizure foci with minimal damage to surrounding normal tissue. Here we review the currently available minimally invasive surgical approaches for epilepsy, with an emphasis on MR-guided laser interstitial thermal therapy (MRgLITT). The results from multiple centers are reviewed and our center's experiences with MRgLITT are reported to highlight the advantages and limitations of this new technology.

Keywords

Drug resistant epilepsy, Minimally invasive epilepsy surgery, Laser ablation, Laser coagulation, Laser amygdalohippocampectomy

Introduction

Epilepsy and seizures affect 1% of the population, which accounts for about three million Americans and 65 million people worldwide [1]. The mainstream treatment for epilepsy is drug therapy. Approximately 70-80% of patients are responsive to drug treatment, while the remaining 20-30% turns into medically refractory epilepsy (MRE) [2]. For the group of patients with MRE, epilepsy surgery not only brings a 34% to 74% chance of seizure freedom, but it also decreases seizure-related mortality and improves quality of life [3-5]. Therefore, all patients with MRE should be evaluated as candidates for epilepsy surgery. However, resective epilepsy surgery involves an open craniotomy and carries the risks of bleeding, infection, and permanent functional deficits, such as memory impairment, learning difficulties, and visual deficits [3,5]. Surgery also causes cosmetic concerns. Therefore, despite increasing in numbers of tertiary epilepsy centers nationwide where epilepsy surgeries are performed, epilepsy surgery is still underutilized [6].

Minimally invasive surgery starts a new era of epilepsy surgery. It avoids a craniotomy and attempts to destroy seizure foci with minimal damage to surrounding normal tissue. The minimally invasive surgical approaches include stereotactic radiosurgery (SRS), stereotactic radiofrequency thermocoagulation (SRT), magnetic resonance imaging (MRI)-guided focused ultrasound ablation (FUS), and magnetic resonance (MR)-guided laser interstitial thermal therapy (MRgLITT). Each of these approaches has some efficacy in reducing seizures, but they each have limitations.

Minimally Invasive Epilepsy Surgery

Stereotactic radiofrequency (SRS)

SRS involves delivering ionizing radiation using a gamma knife or linear accelerators to targeted brain tissue, which is determined and maintained with the patient positioned in a stereotactic frame [7]. Stereotactic radiosurgery does not require incision and is painless. Pilot studies show outcomes comparable to lobectomy in treatment of mesial temporal lobe epilepsy (MTLE): 58.8% and 76.9% seizure elimination at different radiation doses (20 vs 24 Gy) at two years of follow up [8]. However, radiation treatment may cause malignant edema which leads to increased intracerebral pressure [8]. In addition, SRS does not affect seizure outcome immediately: the earliest change in seizure frequency is seen at 2 months after treatment and the most dramatic drop in seizure frequency is between 12 to 18 months [9,10]. Moreover, radiation-induced necrosis and potential malignancy are the long term concerns attributable to stereotactic radiosurgery [7,11]. The Radiosurgery or Open Surgery for Epilepsy Trial (ROSE) was a multi-center, phase III study designed to compare SRS with standard temporal lobectomy as a treatment for patients with temporal lobe epilepsy [12]. The study started in 2006 at Gamma Knife centers, but is currently closed due to lack of enrollment, probably related to the prominent adverse effects such as malignant cerebral edema. Also it allowed only Gamma knife centers to participate excluding the majority of radiosurgery units.

Stereotactic radiofrequency thermocoagulation (SRT)

SRT involves delivering high frequency current (> 250 kHz) which results in thermal injury to the tissue when the temperature rises above 45°C [13]. The electrodes used for thermal therapy can also be used for monitoring and stimulation. Several pilot studies show 72%-78% Engel class I outcome in patients with medically refractory MTLE after two years of surgery [14,15]. No patients had surgery-related permanent morbidity. However, SRT generates very small lesions. Pilot studies reveal that a larger destruction size is associated with a better outcome [14,16]. An amygdalohippocampectomy requires 16-38 lesions to achieve therapeutic efficacy (median = 25) [15]. The other drawbacks of SRT are imprecise radiofrequency energy delivery and lack of real time monitoring with MRI as the electrodes are not MRI-compatible [7].

Citation: Wu S, Tao JX, Issa NP, Rose S, Warnke P (2016) MR-Guided Laser Interstitial Thermal Therapy for the Treatment of Medically Refractory Epilepsy. Int J Neurol Neurother 3:042. doi.org/10.23937/2378-3001/3/2/1042

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Received: January 21, 2016: **Accepted:** February 29, 2016: **Published:** March 02, 2016

MRI-guided focused ultrasound ablation (FUS)

FUS uses a transcranial array of ultrasonic emitter sources, allowing differential frequency delivery ranging from 230 to 1000 kHz to stereotactically targeted structures for thermo coagulation [17]. The location and volume of the lesion is monitored under real time MRI. The technology has been used in the treatment of brain tumors, essential tremor and neuropathic pain [18-21]. However, the application of FUS in neurosurgery, including epilepsy surgery, remains largely experimental at this stage and is still very time consuming [22].

MR-guided laser interstitial thermal therapy (MRgLITT)

Laser-induced thermal therapy (LITT) is a technology that delivers laser light to targeted tissue via optic fibers where the light energy is absorbed and converted to thermal energy and causes thermocoagulation [23]. It has been used in neurosurgery for many years in the treatment of brain neoplasms [24,25]. The recent advances in imaging and stereotactic neurosurgery allows laser ablation under MRI real-time monitoring, which makes it controlled and highly precise [26]. In 2007, the Food and Drug Administration (FDA) cleared MR-guided stereotactic laser interstitial thermal therapy (MRgLITT) in neurosurgery for the treatment of metastatic brain tumors [27]. MRgLITT is a minimally invasive procedure that the LITT is performed steretactically under the real-time MR thermography monitoring. In 2012, Curry et al. [28] first performed MRg LITT on five pediatric patients with MRE secondary to different etiologies (two hypothalamic hamartomas, one MTLE, one cortical dysplasia, one cingulate tuber). All patients were seizure free at 2-13 months of follow-up with no complications [28]. Since then, there have been several case series reporting the application of MRgLITT in epilepsy surgery showing promising results [29-31].

MRgLITT is a minimally invasive procedure. It does not require a craniotomy and therefore reduces craniotomy related morbidities, requires less pain control and shortens hospital stays [32]. Compared to SRT, laser light delivers heat faster, generating a sharper margin between the affected and unaffected tissue and its effectiveness starts immediately [28]. The MRgLITT system has several measures to ensure the safety and precision of the therapy. 1) Monitoring the temperature of the target and the surrounding area during the ablation. 2) Automatic termination so the system shuts down laser delivery immediately if a preset temperature has been reached in a defined target structure. 3) A cooling cannula surrounding the optic fibers allows a sharp falloff in temperature between the exposed tip of the fiber and the rest of the laser fiber so that the lesion size is limited. At the center of the ablation, an irreversible damage zone is generated when the temperature rises above 60°C. The transitional zone is the margin between the affected and unaffected tissue, and is only 1 mm in width [28]. 4) The procedure is real-time monitored under MR-thermography using phase shift imaging. As a result, the location and the size of the lesion are precisely determined. 5) At the end of the ablation, the size and location of the ablation is confirmed immediately with a T1-weighted MRI with contrast.

The most frequently performed MRgLITT procedure in epilepsy surgery is stereotactic laser amygdalohippocampectomy (SLAH). Temporal lobe epilepsy with mesial temporal sclerosis (MTS) is the most common medically refractory epilepsy which is surgically treated with standard anterior temporal lobectomy (ATL): resection 4.5 cm from the temporal tip in the dominant hemisphere and 5.5 cm in the nondominant hemisphere and 3 cm of hippocampus [33]. For patients with well-defined mesial temporal lobe epilepsy (MTLE), a selective amygdalohippocampectomy (SAH) can be performed to spare lateral neocortex which is not involved in seizure generation and mediates important functions [34]. Both ATL and SAH may bring 60-80% of seizure freedom in patients suffering from medically refractory MTLE [35]. However, both surgeries involve an open craniotomy and remove partially functioning brain tissue, therefore, are associated with risks of functional deficits such as visual field defects and memory impairment [3]. In contrast SLAH only involves a 3.2 mm twist drill trephination to insert the laser fiber and 1-3 lesions to destroy the target. The early case report demonstrated exciting surgical outcomes in terms of efficacy and safety: all five pediatric patients including one with MTLE were seizure free and had no complications at 2 to 13-month follow-up [28]. Several cohort studies suggested that the efficacy of MRgLITT may be less impressive compared to conventional resective surgery. The Emory group performed SLAH in 13 patients with medically intractable MTLE. Fifty four percent (7/13) of patients had an Engel class I outcome, although 67% (6/9) of the patients with MTS are seizure free [36]. Of 17 MRE pediatric patients with a variety of pathology who had MRgLITT, 41% (7/17) had Engel class I outcome [37]. Kang reported 53% (8/15) class I outcomes at six months in MTLE, but two initially seizure free patients had relapse at around 10 months after treatment; the study suggests that the likelihood of achieving long-term seizure freedom is modestly lower than with ATL in MTS [38]. The consensus is that MRgLITT is associated with shorter hospital stays, possibly less significant neurocognitive side effects and preserved memory function [32,36,39]. In Drane's study, 31/39 patients had either naming (dominant hemisphere) or face recognition (nondominant hemisphere) decline after ATL, while no patients in the MRgLITT treatment group (N = 19) had a decline in naming or recognition. However, no other cognitive domains were tested [40].

In our institution, 12 adult patients with medically intractable MTLE with and without lesions underwent SLAH from February 2014 to December 2015. Our cohort study is ongoing and the detailed methodology and outcomes will be described in a separate manuscript. Briefly, all 12 patients underwent MRI, PET, neuropsychological tests, and fMRI as part of their presurgical evaluation. The decision to pursue intracranial EEG monitoring was based on the noninvasive work up: If the noninvasive work up was non-concordant or the patient had a negative MRI brain, intracranial EEG monitoring with depth electrodes was performed to further define the seizure onset zone. Intracranial EEG may not be necessary if noninvasive workups congruently suggest mesial temporal onset. However, it can help to define the seizure onset zone precisely and help to decide how far back the ablation should be done along the longitudinal axial of the amygdala-hippocampal complex. Eleven of our MTLE patients (with or without MTS) underwent 5-10 days of intracranial monitoring with stereo-electroencephalography (SEEG) with 4 to 7 depth electrodes (each depth electrode has 12 contacts; AD-TECH, Racine, Wisconsin). After determination of the seizure onset zone, the depth electrodes were removed and MRgLITT was performed (Visualase Inc., Houston, TX). Two to three lesions were made for amygdalohippocampectomy. At the time of this manuscript, 58% (7/12) achieved Engel class I outcome at 4-16 months of follow up. Among them, 5 out of 6 (83%) patients who had MTS are seizure free (Table 1). Of note, the trajectory of the laser ablation was determined based on the SEEG findings and attempted to cover the seizure onset zone maximally, which might explain our more favorable results in MTS patients compared to the aforementioned publications which did not consistently use SEEG monitoring.

MRgLITT also shows advantages in the surgical treatment of medically resistant epilepsy associated with deep-seated or bihemispheric seizure foci, such as bilateral periventricular heterotopia [31]. Clarke reported one patient with bilateral occipital epilepsy secondary to bilateral occipital heterotopia who became seizure-free after ablating the bilateral heterotopia without disrupting the visual pathway [30]. Hawasli successfully treated a patient with

Table 1: Seizure outcomes in patients with and without MTS who underwent MRgLITT.

Outcomes	MTS	No MTS
Engel class outcome	N = 6	N = 6
I	5	1
II	1	2
III		3

MTS: mesial temporal lobe sclerosis; MRgLITT: magnetic resonance-guided stereotactic laser interstitial thermal therapy left insular epilepsy secondary to a previous ischemic stroke with MRgLITT, although the patient displayed mild verbal and memory symptoms requiring cognitive rehabilitation [41].

Hypothalamic hamartoma (HH) is a rare congenital lesion presenting with classic gelastic epilepsy, precocious puberty and developmental delay [42]. The gelastic seizures often start in infancy and progress into multiple types of seizures and patients develop epileptic encephalopathy. Gelastic seizures are characteristically resistant to medical treatment but are considered a surgically-remediable condition [43,44]. Surgical resection of HH not only reduces seizure frequency but also improves cognition and learning [45,46]. However, resective surgery is often difficult due to the location of the lesion and carries significant morbidities including post-operative diabetes insipidus, memory dysfunction, visual impairment and hemiparesis [47]. The Emory group performed MRgLITT in 14 patients with drug resistant epilepsy secondary to HH; 86% (12/14) were seizure free at a mean 9 months of follow up. One patient had asymptomatic subarachnoid hemorrhage. None developed diabetes insipidus or had memory complains [48]. Rolston et al. reported 2 patients with HH who underwent MRgLITT; both of them are seizure freedom at 5-7 months post-operation. One patient had transient amnesia and one had no complications [49]. Tovar-Spinoza reported the case of a 3-year old boy with MRE associated HH who was seizure free after MRgLITT without complication [29].

Recent publications suggest that MRgLITT is safe, feasible and well tolerated in treating MRE associated with cavernous malformation (CM) [50]. MRgLITT was performed in five consecutive patients with CM. Eighty percent (4/5) patients had class I outcomes and one patient had no improvement after the ablation and eventually had resective surgery. No neurological deficits or other complications were noted as a result of the MRgLITT [50].

Overall, MRgLITT is well tolerated and is associated with a low risk of morbidity. Patients are often discharged the next day after surgery. From our experience, mild headache is the most common complaint after surgery which often resolves in a few days and does not require medical treatment. Visual field deficits, such as homonymous hemianopia is the most frequently reported functional deficits. Two of seven patients had partial visual field deficit in Waseem's series and one of 13 patients in Willie's series had homonymous hemianopia [36,39]. In our series, one in 12 patients had homogenous hemianopia resulting from injury lateral geniculate nucleus (LGN) (unpublished data). In Kang's series, one of 20 patients had brain edema and mesial temporal lobe hemorrhage which lead to superior quadrantanopia. Another patient had a transient fourth nerve palsy without MRI evidence of abnormality. Another patient with preexisting depression committed suicide 4 months after MRgLITT [38]. Other rare MRgLITT surgery related complications include aseptic meningitis, brain edema, subdural hematoma, intracranial hematoma, subarachnoid hemorrhage and inaccurate fiber placement [36,37,51,52]. Amnestic syndrome from injury to the mammillary bodies following stereotactic laser ablation of a HH is reported [53]. In addition, the size of the ablation might sometimes be insufficient; some of the patients may need a second ablation [36,38].

Conclusions

The early series suggest that MRgLITT is safe, effective and is a promising new option for treating patients with MRE epilepsy without craniotomy. The outcome of MRgLITT is related to the precision with which the seizure focus can be defined, the accuracy of placement of laser fiber, and the volume of the ablation. Since only a limited brain volume can be ablated, the ideal candidates for MRgLITT are those with small and well-defined seizure foci such as MTS, HH, CM and heterotopia. Some patients may need a second ablation if the first one fails [37]. The possible mechanisms of treatment failure, similar to failure of ATL, could be related to incomplete ablation, dual pathology, and a wider seizure network [54,55]. MRgLITT can also be used in patients who have failed previous open surgery [36]. MRgLITT is associated with a superior neuropsychological outcome and less functional deficits compared to open surgery, likely because less brain tissue is damaged. Overall, the safety profile of MRgLITT significantly reduces the fear and anxiety of patients related to open brain surgery. As the procedure becomes more widely performed, it may increase epilepsy surgery referrals, which would help more patients to improve their quality of life.

Future Directions

More investigations are needed to better understand the indication of MRgLITT and to improve the application of laser ablation in epilepsy surgery. Several questions need to be further addressed: Does the volume of ablation correlate with surgical and cognitive outcomes? How does the procedure affect the epilepsy network? What is the mechanism of the ablation? Does the ablation have a disconnective or destructive effect on the seizure network? Prospective randomized trials to compare MRgLITT with conventional resective surgery are needed to determine the long term safety and efficacy of MRgLITT.

Disclosure

None of the authors has any conflicts of interest related to this topic to disclose.

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