Stereoelectroencephalography followed by combined electrode removal and MRI-guided laser interstitial thermal therapy or open resection: a single-center series in pediatric patients with medically refractory epilepsy

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OBJECTIVE Stereoelectroencephalography (SEEG) and MRI-guided laser interstitial thermal therapy (MRgLITT) have emerged as safe, effective, and less invasive alternatives to subdural grid placement and open resection, respectively, for the localization and treatment of medically refractory epilepsy (MRE) in children. Reported pediatric experience combining these complementary techniques is limited, with traditional workflows separating electrode removal and ablation/resection. The authors describe the largest reported series of pediatric epilepsy patients who underwent MRgLITT following SEEG contrasted with a cohort that underwent craniotomy following SEEG, combining ablation/resection with electrode explantation as standard practice.

METHODS The medical records of all patients with MRE who had undergone SEEG followed by MRgLITT or open resection/disconnection at Boston Children’s Hospital between November 2015 and December 2020 were retrospectively reviewed. Primary outcome variables included surgical complication rates, length of hospital stay following treatment, and Engel classification at the last follow-up.

RESULTS Of 74 SEEG patients, 27 (median age 12.1 years, 63% female) underwent MRgLITT and 47 (median age 12.1 years, 49% female) underwent craniotomy. Seventy patients (95%) underwent SEEG followed by combined electrode removal and treatment. Eight MRgLITT cases (30%) and no open cases targeted the insula (p < 0.001). Complication rates did not differ, although trends toward more subdural/epidural hematomas, infarcts, and permanent unanticipated neurological deficits were evident following craniotomy, whereas a trend toward more temporary unanticipated neurological deficits was seen following MRgLITT. The median duration of hospitalization after treatment was 3 and 5 days for MRgLITT and open cases, respectively (p = 0.078). Seizure outcomes were similar between the cohorts, with 74% of MRgLITT and craniotomy patients attaining Engel class I or II outcomes (p = 0.386) at the last follow-up (median 1.1 and 1.9 years, respectively).

CONCLUSIONS MRgLITT and open resection following SEEG can both effectively treat MRE in pediatric patients and generally can be performed in a two-surgery workflow during a single hospitalization. In appropriately selected patients, MRgLITT tended to be associated with shorter hospitalizations and fewer complications following treatment and may be best suited for focal deep-seated targets associated with relatively challenging open surgical approaches.

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KEYWORDS MRI-guided laser interstitial thermal therapy; laser ablation; stereoelectroencephalography; medically refractive epilepsy; minimally invasive epilepsy surgery; pediatrics

PEDIATRIC epilepsy affects approximately 1% of children,1 and nearly one-third of these children have seizures that are incompletely controlled with antiseizure medications (ASMs).2,3 Drug-resistant epilepsy has been defined by the International League Against Epilepsy as a failure of adequate trials of 2 (or more) tolerated, appropriately chosen and used antiseizure drug regimens to achieve seizure freedom.4 Children with medically refractory epilepsy (MRE) are at an increased risk of premature death,5,6 psychiatric illness,7 injuries,8 and reduced quality

ABBREVIATIONS ASM = antiseizure medication; MRE = medically refractory epilepsy; MRgLITT = MRI-guided laser interstitial thermal therapy; SDG = subdural grid; SEEG = stereoelectroencephalography.


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of life. These risks are exacerbated when surgical treatment for seizure control is delayed or underutilized.

Well-established surgical options for pediatric MRE include resection, disconnection, neurostimulation, invasive monitoring via subdural grid (SDG) electrodes, or some combination thereof. In many cases, resection is effective in disrupting the epileptogenic zone, controlling patient seizures, and improving quality of life. However, open resections are invasive, associated with risks, and often unsuitable for patients with deep-seated foci. Similarly, SDG electrodes placed on the cortical surface via craniotomy provide wide coverage of superficial cortex but do not access deeper lesions.

Stereoencephalography (SEEG) and MRI-guided laser interstitial thermal therapy (MRgLITT) have emerged as safe and effective minimally invasive techniques for localizing and treating drug-resistant seizures. SEEG is especially beneficial for identifying seizure origins in deep regions such as the medial cortex, depths of sulci, insula, and mesial temporal lobe. Some studies have shown either MRgLITT or SEEG to be useful in the pediatric population, but few small case series have analyzed these complementary approaches in combination. Moreover, there is currently no consensus on when to use SEEG, SDG, or a combination of surface and depth electrodes as opposed to open resection. Finally, the traditional SEEG workflow involves 3 surgical steps performed at separate times: implantation, electrode removal, and treatment. Combining electrode removal and treatment surgery into a single step creates a more efficient 2-step workflow and eliminates a potential third exposure to general anesthesia. To our knowledge, this is the largest series describing periprocedural and postoperative outcomes and complication rates of SEEG followed by MRgLITT or open resection in a pediatric population and implementing a standard 2-step workflow, and the only to do so in a patient population with mixed seizure etiologies and locations. This study aims to establish current outcomes following MRgLITT and resection in pediatric patients investigated using SEEG in a real-world setting and the factors that may lead epilepsy surgery teams to choose one surgical approach over the other to better inform future clinical decision-making.

Methods

Study Design

This study, approved by the Boston Children’s Hospital Institutional Review Board, is a single-center retrospective review of all pediatric patients who underwent initial SEEG followed by MRgLITT or open surgical treatment between November 2015 and December 2020.

Clinical Methods and Surgical Techniques

Patients with MRE were deemed surgical candidates following review at a multidisciplinary epilepsy surgery conference. The neurosurgeon (S.S.D.S.) created SEEG implantation schemes with input from epilepsy neurologists with advanced SEEG training and experience. Stereotactic planning was performed using fused pre-operative MRI and CTA images and stereotactic software (Neuroinspire, Renishaw). SEEG electrodes (Adtech Medical Instrument Corp. and PMT Corp.) and MRgLITT fibers (Visualase, Medtronic) were placed using frame-based stereotaxy (CRW, Integra) and robotic assistance (Neuramate, Renishaw). SEEG analysis and stimulation testing/mapping were performed by epilepsy neurologists during the implantation period, and treatment decisions were made by consensus upon review at a multidisciplinary epilepsy surgery conference prior to the end of the SEEG implantation. MRgLITT treatments were performed using standard methods, including high and low temperature safety cutoffs of 87°C and 47°C, respectively, and laser firing times of ≤ 3 minutes per ablation position. Peri-ablation steroid treatment was used to minimize postablation edema. Craniotomies for resection employed standard surgical techniques augmented in some cases with electrocorticography and intraoperative MRI. All patients were transferred to the intensive care unit for initial postoperative recovery.

Data Collection and Analysis

Patient records were reviewed to identify demographics and preoperative data including age at seizure onset and surgery, sex, prior invasive monitoring and epilepsy treatment, number of preoperative ASMs, and primary seizure etiology. In cases with multiple etiologies, the primary etiology—decided by the senior author—was included in the analysis.

Operative data, including staged operative workflow, robot assistance, treatment laterality and sites, electrode and contact counts, and duration of surgeries, were analyzed. In a two-stage operation workflow, epilepsy treatment surgery occurred under the same anesthetic as SEEG removal. Three-stage operation workflows required separate surgeries for SEEG removal and epilepsy treatment. Complications such as intraparenchymal hemorrhage, extraaxial hematoma, infection, infarct, CSF leakage, anesthesia-related complications, temporary and permanent unanticipated neurological deficits, and additional complication-related operations were noted.

The duration of invasive monitoring, length of hospitalization following epilepsy treatment, and total length of hospital stay were compared between treatment groups. For patients who had undergone three-stage treatments, the length of stay, days between electrode removal/treatment and discharge, and operation durations were the sums of both hospital admissions and surgeries.

A board-certified pediatric neuroradiologist (S.P.P.) measured the total volume of ablated tissue on contrast-enhanced volumetric spoiled gradient echo or T1-weighted images obtained immediately upon completion of MRgLITT, and on a Synapse 3D workstation (Fuji Medical Systems).

The number of ASMs, Engel class, and the need for redo treatments were assessed at the last follow-up. Engel classifications were cross-checked with an epileptologist (J.B.) and a prospectively maintained epilepsy surgery outcomes database. If patients required redo operations, the date of the last follow-up before the redo operation was used to assess Engel classification.
Statistical Analysis

Continuous variables are presented within each group as medians and interquartile ranges, and categorical variables are presented as frequencies and percentages. Statistical testing was performed using the nonparametric Wilcoxon rank-sum test for continuous data and Fisher’s exact test for categorical data. Kaplan-Meier curves for freedom from failure over the follow-up were constructed with the numbers at risk presented, and group comparisons were performed using the log-rank test. Treatment failure was defined as an Engel class III or IV at the last follow-up. Statistical analyses were performed using Stata software (version 16.0, StataCorp). A two-tailed alpha less than 0.05 was considered statistically significant.

Results

Seventy-four patients underwent either MRgLITT or open surgery following SEEG. Three patients underwent multiple invasive monitoring and treatment operations, with the first SEEG and treatment sequence included in the analysis and subsequent treatments considered reoperations. Patients were a median age of 12.1 years (IQR 8.2–15.6 years) at surgery, and 54% were female. Age at seizure onset, age at surgery, sex, and primary seizure etiology did not significantly differ between treatment cohorts (Table 1). Trends toward a greater prevalence of cortical dysplasia in the MRgLITT cohort (70% vs 47%) and congenital malformations (11% vs 0%) and strokes/infarcts (13% vs 0%) in the open cohort were evident.

The 6 patients (13%) in the open cohort who had undergone invasive monitoring and epilepsy surgery prior to SEEG had had several prior resection/disconnection, vagus nerve stimulator insertion, and MRgLITT treatments (Table 1). Of the 2 patients (7%) in the MRgLITT cohort who had undergone prior invasive monitoring, 1 had had prior temporal resection of focal cortical dysplasia.

Seizures were captured by SEEG in all cases, with most patients (n = 70, 95%) subsequently undergoing combined SEEG removal and treatment surgery as the second stage of a two-operation workflow (Table 2). Of the 47 patients treated with open surgery, 46 underwent resection/disconnection of seizure foci, and 1 whose seizures were not focal underwent functional hemispherotomy.

Ablations treated a mean tissue volume of 8.8 cm³ (SD 5.02 cm³). MRgLITT more frequently targeted insular areas versus temporal and multilobar areas in open cases (p < 0.001). Hospital stay following open surgery trended a median 2 days longer than for MRgLITT (p = 0.078). The number of ASMs pre- and postoperatively did not significantly differ between cohorts.

Complication rates did not differ between cohorts (Table 2). Notably, however, 5 MRgLITT patients (19%) had temporary unanticipated neurological deficits including upper-extremity monoparesis and dysarthria, hemiparesis, absent proprioception, and facial droop. These deficits typically resolved over a period of days to weeks. The 1 MRgLITT patient who suffered an anesthesia-related complication had loosening of eyelid tape leading to a corneal abrasion and temporary ophthalmoalgalgia without permanent damage. Three patients (6%) in the open cohort developed epidural hematomas requiring additional emergency craniotomies, and 1 patient (2%) had a nonoperative subdural hematoma. Of the 3 open surgery patients (6%) with infarcts, 1 had permanent left-sided hemiparesis secondary to a right internal capsule infarct, and 1 had permanent hypoesthesia of the left arm and leg. The 3 patients (6%) in the open cohort with temporary unanticipated neurological deficits had facial droop (1 case), hemiparesis (1 case), and facial droop, hemihypesthesia, and hemiparesis (1 case). No patients in either cohort had a postoperative infection.

The median length of follow-up for all patients was 1.7 years (IQR 0.9–2.7 years). Overall, there was no statistically significant difference in seizure outcome between the cohorts, with 74.1% of MRgLITT patients and 74.5% of open surgery patients having an Engel class of I or II at the last follow-up (Table 2). Kaplan-Meier analysis estimated an Engel class of I or II in 52.8% of MRgLITT and 52.3% of open patients at 4 years postoperatively (p = 0.354; Fig. 1). There was no significant association between etiology and seizure outcomes (p = 0.445; Table 3). Of the 3 open surgery patients (6%) who underwent redo operations to treat their epilepsy, 1 had a corpus callosumotomy, 1 underwent redo SEEG and resection twice, and 1 underwent MRgLITT.
This study reports current real-world outcomes for pediatric epilepsy patients who underwent SEEG and were subsequently treated via open surgery or MRgLITT, in most cases in the same procedure as electrode explanta-

On the next page:

### TABLE 2. Perioperative data and clinical outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>MRgLITT</th>
<th>Open Surgery</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>27</td>
<td>47</td>
<td>0.999</td>
</tr>
<tr>
<td>Seizure captured</td>
<td>27 (100.0)</td>
<td>47 (100.0)</td>
<td>0.999</td>
</tr>
<tr>
<td>2-stage workflow</td>
<td>24 (88.9)</td>
<td>46 (97.9)</td>
<td>0.135</td>
</tr>
<tr>
<td>Robot-assisted SEEG</td>
<td>24 (88.9)</td>
<td>41 (87.2)</td>
<td>0.999</td>
</tr>
<tr>
<td>Treatment laterality</td>
<td>9 (33.3)</td>
<td>18 (38.3)</td>
<td>0.803</td>
</tr>
<tr>
<td>Right</td>
<td>18 (66.7)</td>
<td>29 (61.7)</td>
<td>0.803</td>
</tr>
<tr>
<td>Left</td>
<td>15 (12, 17)</td>
<td>14 (12, 17)</td>
<td>0.852</td>
</tr>
<tr>
<td>No. of contacts</td>
<td>168 (142, 206)</td>
<td>164 (144, 194)</td>
<td>0.633</td>
</tr>
<tr>
<td>Ablation/resection site†</td>
<td>Insular</td>
<td>8 (29.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Parietal</td>
<td>3 (11.1)</td>
<td>3 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>1 (3.7)</td>
<td>14 (29.8)</td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>12 (44.4)</td>
<td>11 (23.4)</td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td>0 (0)</td>
<td>3 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Multilobar</td>
<td>3 (11.1)</td>
<td>15 (31.9)</td>
<td></td>
</tr>
<tr>
<td>Hospital days w/ SEEG electrodes</td>
<td>7 (7, 8)</td>
<td>7 (7, 7)</td>
<td>0.805</td>
</tr>
<tr>
<td>Hospital days after treatment surgery</td>
<td>3 (2, 5)</td>
<td>5 (4, 7)</td>
<td>0.078</td>
</tr>
<tr>
<td>Total days in hospital</td>
<td>11 (10, 14)</td>
<td>12 (11, 14)</td>
<td>0.122</td>
</tr>
<tr>
<td>Complication</td>
<td>IPH</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>EDH/SDH</td>
<td>0 (0)</td>
<td>4 (8.5)</td>
<td>0.29</td>
</tr>
<tr>
<td>Infection</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.999</td>
</tr>
<tr>
<td>Infarct</td>
<td>0 (0)</td>
<td>3 (6.4)</td>
<td>0.295</td>
</tr>
<tr>
<td>CSF leakage</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.999</td>
</tr>
<tr>
<td>Anesthesia related</td>
<td>1 (3.7)</td>
<td>0 (0)</td>
<td>0.365</td>
</tr>
<tr>
<td>Permanent unanticipated neuro deficit</td>
<td>0 (0)</td>
<td>2 (4.3)</td>
<td>0.530</td>
</tr>
<tr>
<td>Temporary unanticipated neuro deficit</td>
<td>5 (18.5)</td>
<td>3 (6.4)</td>
<td>0.132</td>
</tr>
<tr>
<td>Complication requiring surgery</td>
<td>0 (0)</td>
<td>3 (6.4)</td>
<td>0.209</td>
</tr>
<tr>
<td>No. of ASMs</td>
<td>Preoperatively</td>
<td>3 (2, 3)</td>
<td>3 (2, 3)</td>
</tr>
<tr>
<td>At last FU</td>
<td>2 (1, 3)</td>
<td>3 (2, 3)</td>
<td>0.134</td>
</tr>
<tr>
<td>Operating time in mins</td>
<td>SEEG implant</td>
<td>196 (167, 298)</td>
<td>192 (167, 270)</td>
</tr>
<tr>
<td>SEEG implant per electrode</td>
<td>14.6 (10.6, 18.3)</td>
<td>13.8 (11.5, 18.7)</td>
<td>0.969</td>
</tr>
<tr>
<td>SEEG removal/treatment</td>
<td>334 (290, 397)</td>
<td>373 (332, 463)</td>
<td>0.078</td>
</tr>
<tr>
<td>SEEG removal/treatment per electrode</td>
<td>24.1 (19.1, 29.1)</td>
<td>26.6 (20.8, 37.8)</td>
<td>0.199</td>
</tr>
<tr>
<td>FU in yrs</td>
<td>1.1 (0.8, 2.2)</td>
<td>1.9 (0.9, 3.2)</td>
<td>0.257</td>
</tr>
</tbody>
</table>

### Discussion

This study reports current real-world outcomes for pediatric epilepsy patients who underwent SEEG and were subsequently treated via open surgery or MRgLITT, in most cases in the same procedure as electrode explantation, at a high-volume pediatric epilepsy surgery center. Importantly, seizure outcomes and complications rates were comparable, and no MRgLITT patients underwent reoperation, supporting the recent trend toward MRgLITT in appropriately selected SEEG patients. Despite the rapid adoption of MRgLITT following SEEG, few reports have validated outcomes in this combined treatment context and, to our knowledge, none have done so in children with significantly mixed etiologies and treatment selections. In our experience, the less invasive nature of MRgLITT can be a strong influencer for patients and providers when making treatment decisions, and in some cases less invasiveness may be favored despite concern for potentially inferior seizure outcomes. Further research is needed to help epilepsy surgery programs balance procedural invasiveness, patient expectations, and seizure outcomes. Our data suggest that the current use of MRgLITT following SEEG in practices similar to ours is associated with generally favorable results.

Target regions for MRgLITT or open surgery differed, with MRgLITT employed exclusively for insular targets versus open surgery for temporal and multilobar regions more commonly. Given the absence of open surgery cases for insular targets, the study results do not permit comparison to inform treatment decisions in this brain region. The more common use of MRgLITT for insular lesions is not surprising, however, given its ability to target deep and relatively small foci while minimizing trauma to overlying cortex. Pediatric temporal lobe epilepsy often involves a relatively large volume of tissue with concomitant mesial and lateral temporal involvement and is generally associated with favorable seizure outcomes following traditional open surgery, both of which could explain our tendency toward open surgery in those cases. As one would expect, multilobar foci can be too extensive for MRgLITT.
and lend themselves to open surgical treatment. Despite these observed brain region differences between treatment selections, our nonrandomized data set does not permit examination of whether open resection or ablation results in better seizure outcomes for different brain targets.

Our series demonstrates the feasibility of performing a two-stage surgical workflow, as 95% of our cases successfully employed SEEG followed by MRgLITT or open surgery under the same anesthetic. This highly efficient workflow includes extensive SEEG interpretation and consensus review along with patient counseling without eliminating the steps included in more traditional three-stage paradigms. Neither group had an infection, suggesting the possible safety of employing this strategy in centers with appropriate resource availability. The relatively small number of patients who had undergone a three-stage surgery in this study (n = 4) precluded direct comparisons of the hospitalizations, complications, and outcomes associated with each workflow. To inform selection of the treatment approach, a prospective randomized comparison may allow assessment of potentially meaningful differences such as length of implantation, infection rates, impacts of interval scar formation on subsequent surgical complications, and treatment targeting accuracy and precision.

Overall complication rates did not differ significantly between groups, although there was a trend toward more postoperative hemorrhages, infarcts, and permanent deficits with open surgery, whereas temporary unanticipated neurological deficits tended to be higher following MRgLITT. The latter trend may reflect the temporary effects of peri-ablation edema, which in our experience is occasionally more marked than anticipated, and/or differences in the proximity of resection/ablation targets to eloquent regions between groups. While the data do suggest that the safety of MRgLITT as applied here compares favorably to the open surgical experience, the study’s retrospective design and small sample size prevent any conclusion regarding relative safety.

Generalizing these results to guide treatment decisions in other practice environments warrants caution for several reasons. This is not a randomized comparison since decision regarding treatment modality was made based on considerations about target size, location, expected efficacy and safety, as well as the perceived utility of intraoperative electrocorticography. Data collection was retrospective via chart review rather than prospective, which also limited our ability to capture certain factors driving treatment selection. A larger sample size may uncover significant differences where trends were evident, such as differences in complication rates and the shorter hospital stay following MRgLITT. Indeed, our goal was not to conclude that one treatment strategy or workflow was superior to another. Instead, this study examined the role of MRgLITT following SEEG, as well as a two-stage workflow, in a consecutive pediatric surgical practice to establish baseline performance data and to describe some factors driving treatment selection to better inform future studies. This and other studies may ultimately point to potential areas of therapeutic equipoise warranting a prospective randomized study, such as relatively small epileptogenic foci that are considered accessible via either technique.

Conclusions

MRgLITT and open resection following SEEG can both effectively treat localized epileptogenic foci in pediatric patients and generally can be performed in a two-surgery workflow within the same hospitalization in contrast to electrode withdrawal and the need to schedule a future and additional operation. In appropriately selected patients, MRgLITT is associated with a tendency toward shorter hospitalizations and fewer complications following treatment and may be best suited for focal deep-seated targets associated with relatively challenging open surgical approaches.

References


Disclosures
Dr. Tsuboyama reports serving as a consultant for Neuroelectrics outside the submitted work.

Author Contributions
Conception and design: Stone, Bolton, Pearl, Madsen. Acquisition of data: Stone, Slingerland, Chua, Bolton, Prabhu, Pearl, Madsen. Analysis and interpretation of data: Stone, Slingerland, Bolton, Staffa, Tsuboyama, Prabhu, Pearl, Madsen. Drafting the article: Stone, Slingerland, Chua, Bolton, Staffa, Tsuboyama, Prabhu, Pearl, Madsen. Drafting the article: Stone, Slingerland, Chua, Bolton, Staffa, Tsuboyama, Prabhu, Pearl. Reviewed submitted version of manuscript: Stone, Slingerland, Chua, Staffa, Tsuboyama, Prabhu, Pearl. Approved the final version of the manuscript on behalf of all authors: Stone. Statistical analysis: Stone, Slingerland, Staffa. Administrative/technical/material support: Stone. Study supervision: Stone.

Supplemental Information
Previous Presentations
This work was presented as an in-person poster presentation at the American Epilepsy Society Annual Meeting held in Chicago, Illinois, on December 3–7, 2021, and as an e-poster at the 50th Annual Meeting of the AANS/CNS Section on Pediatric Neurological Surgery held in Salt Lake City, Utah, on December 7–10, 2021.

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