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ORIGINAL ARTICLE

"Laser and the Tuber": thermal dynamic and volumetric factors influencing seizure outcomes in pediatric subjects with tuberous sclerosis undergoing stereoencephalography-directed laser ablation of tubers

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Abstract

Purpose Tuberous sclerosis (TSC) is a well-known cause of medically refractory epilepsy (MRE). Stereoencephalography-directed magnetic resonance-guided laser interstitial thermal therapy (SEEG-directed MRgLITT) is an emerging minimally invasive technique that appears aptly suited for the surgical management of TSC. Our aims are to present our experiences with patients who had undergone SEEG-directed MRgLITT to identify and treat cortical tubers responsible for clinical seizures and to perform an in-depth analysis of volumetric and thermal dynamic factors that may be related to seizure outcomes.

Methods We studied all pediatric patients with MRE due to TSC who underwent SEEG-directed MRgLITT, investigating seizure outcomes in relation to thermal dynamic and volumetric factors.

Results Eight cortical tubers from three pediatric patients were analyzed. Two of three patients had Engel I outcomes at last follow-up (median 18 months). Average A/T (ablation volume/tuber volume) ratio for Engel I outcomes was 1.28 (variance, 0.16) and 0.84 (variance, < 0.01) for all other outcomes ($P = 0.035$). There was a moderate positive correlation when comparing ablation energy to ablation volume ($R^2 = 0.65$) in cortical tuber tissue. When the calcified tuber is excluded, the correlation is stronger ($R^2 = 0.77$). Thus, the calculated energy needed to ablate 1 cm^3 of cortical tuber tissue is 1263.6 J (calcified tuber) or 1089.5 J (non-calcified tuber).

Conclusions SEEG-directed MRgLITT appears to be a safe and effective technique in the management of pediatric patients with MRE due to TSC. The A/T ratio may be a useful indicator in predicting seizure outcomes.

Keywords Tuberous sclerosis · TSC, minimally invasive epilepsy surgery · MIES, stereotactic electroencephalography · SEEG, magnetic resonance guided laser interstitial thermal therapy · MRgLITT

Introduction

Tuberous sclerosis (TSC) is a well-known cause of pediatric epilepsy with upwards of 90% of patients with this condition suffering from seizures. [9] Approximately 60% of these patients continue to suffer from frequent seizures despite maximal medical therapy. [6] Data supports that early surgical management improves long-term seizure outcomes and cognitive development in toddlers with medically refractory epilepsy (MRE) due to TSC. [13]

Magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) is becoming an established technique in the field of neurosurgery, especially in epilepsy surgery. [27] The MRgLITT technique is well-suited for conditions like TSC in which several disparately located cortical tubers can be sources of epilepsy requiring treatment (resection and in the case of MRgLITT, ablation) which may be needed at different points in the patient's life. This minimally invasive technique

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obviates the need for extensive open surgery in these patients and allows the surgeon to focus treatment on only the epileptogenic lesions. [27]

This unique advantage of MRgLITT is being utilized with increasing application to TSC. Anecdotal evidence suggests that its clinical utility in this scenario is increasing; however, there is very little published data in this regard. To the best of our knowledge, there are only a handful of published cases of MRgLITT used in pediatric patients suffering from MRE due to TSC. [7, 10, 16, 21, 35]

Of these previously listed, only two had undergone previous invasive intracranial monitoring using stereotactic electroencephalography (SEEG). The remaining studies used video EEG (VEEG). To date, including those previous two patients, there are only a few additional published cases detailing the use of SEEG in TSC. [7, 24, 30, 33] Similar to MRgLITT, SEEG allows for local surveillance of cortical tubers to assist with determination of epileptogenicity. There has not been a fundamental analysis of SEEG-directed ablation of cortical tubers considering the effects of the amount of terminal energy used, volume of ablation achieved related to volume of the tuber, and seizure outcomes.

In this paper, we present our experience with patients who had undergone prior SEEG invasive intracranial monitoring to identify cortical tubers responsible for clinical seizures followed by directed MRgLITT. We also performed an in-depth analysis of volumetric and thermal dynamic factors that may be related to seizure outcomes.

Materials and methods/case material

Study design

Following IRB approval from the Children's National Medical Center in Washington, DC, a single-center retrospective cohort study was performed to identify all pediatric patients diagnosed with TSC who underwent SEEG-directed MRgLITT over a 20-month period. All patients were treated at Children's National Medical Center in Washington DC by the senior author (C.O.O). Demographic, preoperative, intraoperative, and outcome data were analyzed.

Patient selection

All patients with TSC were referred to neurosurgery at Children's National Medical Center after meeting the requirements for MRE, defined by the International League Against Epilepsy (ILAE) as "the failure of adequate trials of two appropriately chosen and used anti-epileptic drug schedules to achieve sustained seizure." [20] Cases were discussed at a multidisciplinary epilepsy conference to determine optimal management. Patients with multiple lesions, as seen in TSC, were felt to be more amenable to minimally invasive surgery (MIS) strategies, in this case, SEEG followed by MRgLITT, to target these lesions. Each patient underwent MRI of the brain using our 3 T high-resolution epilepsy imaging protocol and invasive intracranial monitoring with SEEG prior to ablation. When indicated, patients underwent other ancillary studies, including functional MRI, magnetoencephalography (MEG), and FDG-PET.

Surgical technique

Stereoencephalography

Surgical techniques used in this study have been documented in detail previously. [7] To summarize, following appropriate imaging, target tubers were identified; then, either BrainLAB VarioGuide (Brainlab, Munich, Germany) or the ROSA neurosurgical robot (Medtech, Montpellier, France) was used for stereotaxy. Trajectories were planned, and depth electrodes were placed. Postoperative volumetric head CT scans were obtained to show electrode location which was merged with preoperative volumetric MR images by the ROSA proprietary fusion software. Accurate placement of each SEEG depth electrode was confirmed for every patient. Patients were admitted and monitored until sufficient localizing data were collected. Following invasive intracranial monitoring, the data was further discussed at a multidisciplinary epilepsy conference to identify epileptogenic foci that have a clinical correlate. Once identified, a consensus was reached that these cortical tubers were to be ablated if they were not excessively calcified. Tubers that were excessively calcified were surgically resected via craniotomy and were not included in this study. Excessive calcification was determined during SEEG electrode placement. If tubers were calcified such that electrodes could not be placed within the tuber, then that tuber was determined to be unamenable to MRgLITT and would be better suited for surgical resection via craniotomy. Patients were then returned to the operating room for removal of the electrodes and the laser ablation procedure, if indicated.

Magnetic resonance-guided laser interstitial thermal therapy

All MRgLITT procedures were performed using the Visualase system (Medtronic, Minneapolis, Minnesota). Stereotactic systems used included BrainLAB Neuronavigation and the ROSA neurosurgical robot. After planning safe trajectories, laser cooling tubers were carefully inserted to pre-measured distances within the targeted cortical tuber and affixed to bone anchors on the skull. Once done, the laser wire was inserted. This was repeated for all epileptogenic cortical tubers with clinical correlates. The patient was then moved to the 1.5 T intraoperative MRI scanner. Initial scans (T1-weighted and spoiled gradient-recalled acquisition (SPGR) and T2-weighted) were obtained to confirm accurate placement of laser probes. Laser ablation was performed with real-time MRI thermography. Following that, gadolinium was administered for postablation T1-weighted MRI to assure adequate ablation of cortical tubers. Probes were then removed, and a final MRI was obtained to assess for post-operative hemorrhages. Patients were discharged home the following day after ablation.

Imaging and thermal dynamic analysis

Post-operative T1-weighted MRI images were used to assess post-ablation volumes. OSiriX DICOM Viewer (Pixmeo SARL, Geneva, Switzerland) which has an established high interrater reliability was used for volumetric measurements. Two independent raters (K.C. and M.S.) assessed post-ablation volumes by leveraging the ROI draw and volume functions (Fig. 1). These measurements were averaged and used in the thermal dynamic analysis of each tuber. Total energy per each ablation was calculated using the laser Watt setting multiplied by the amount of time the laser was on, yielding total joules of energy. In addition, linear regression analysis was done to identify thermal dynamic properties of cortical tuber tissue. These data were used to calculate the amount of energy needed to ablate 1 cm^3 of cortical tuber tissue.

Assessment of tuber volume

A board-certified pediatric neuroradiologist (M.W.) assessed cortical tuber volumes using the OSiriX DICOM Viewer ROI draw and ROI volume functions on pre-operative T2-weighted images (Fig. 2). The demonstrated interrater reliability of OSiriX combined with his experience made this the best approach to accurately identify tuber margins in our cohort.

Statistical analysis

All statistical analysis was conducted using the Data Analysis tool on Microsoft Excel (Redmond, Washington). ANOVA was done to confirm high interrater reliability when measuring post-ablation volumes. Linear regression analysis was conducted to determine the amount of energy needed to ablate one cubic centimeter of cortical tuber. A/T (ablation volume/tuber volume) ratio and seizure outcomes were analyzed using a two-sample *t* test and Chi-square tests comparing outcomes of Engel I vs Not Engel I. Statistical significance was defined by $P < 0.05$.

Results

Patient demographics

A total of eight cortical tubers in three pediatric patients with medically intractable epilepsy were investigated in this study. Patient demographic data are presented in Table 1. All patients underwent invasive intracranial monitoring via SEEG followed by ablation of epileptogenic cortical tubers using MRgLITT at CNMC from January 2017 to September 2018.

Imaging and analysis

Information regarding each tuber can be found in Table 2. Pre-operative tuber volumes and post-ablation volumes were compared for each tuber and an A/T ratio was developed (A = ablation volume, T = tuber volume) (Table 3). Interrater differences with respect to post-ablation volumes were determined to be insignificant ($P = 0.93$). In patients with Engel I outcomes, average A/T ratio was 1.00 and 1.47. In the patient with an Engel III outcome, average A/T ratio was 0.84. When investigating each tuber independently with patient outcomes,

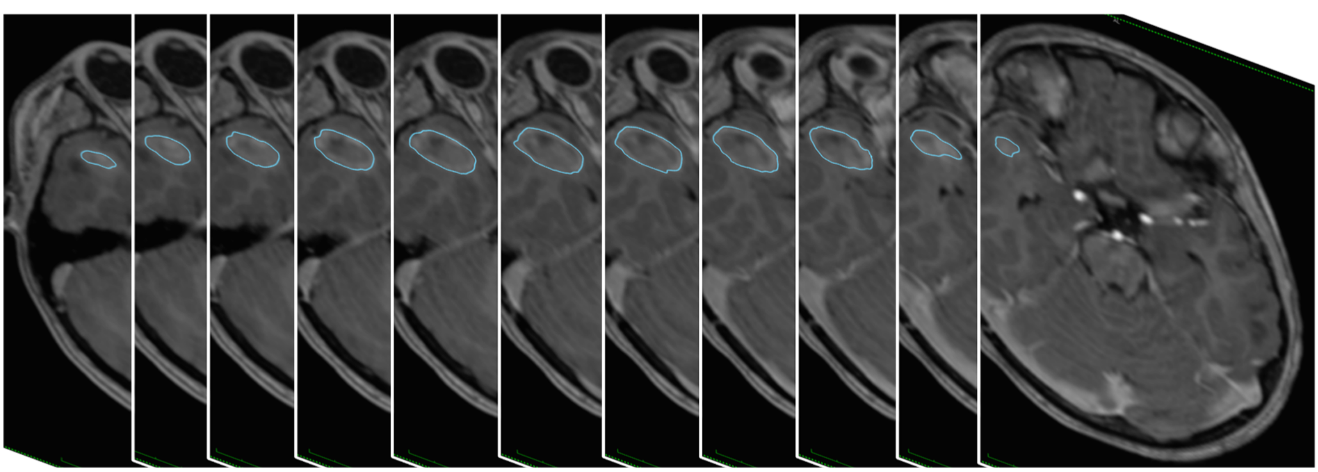

Fig. 1 Overlay of post-operative T-1 weighted MRI images in OSiriX demonstrating how post-ablation volumes were calculated using the ROI draw and ROI volume functions

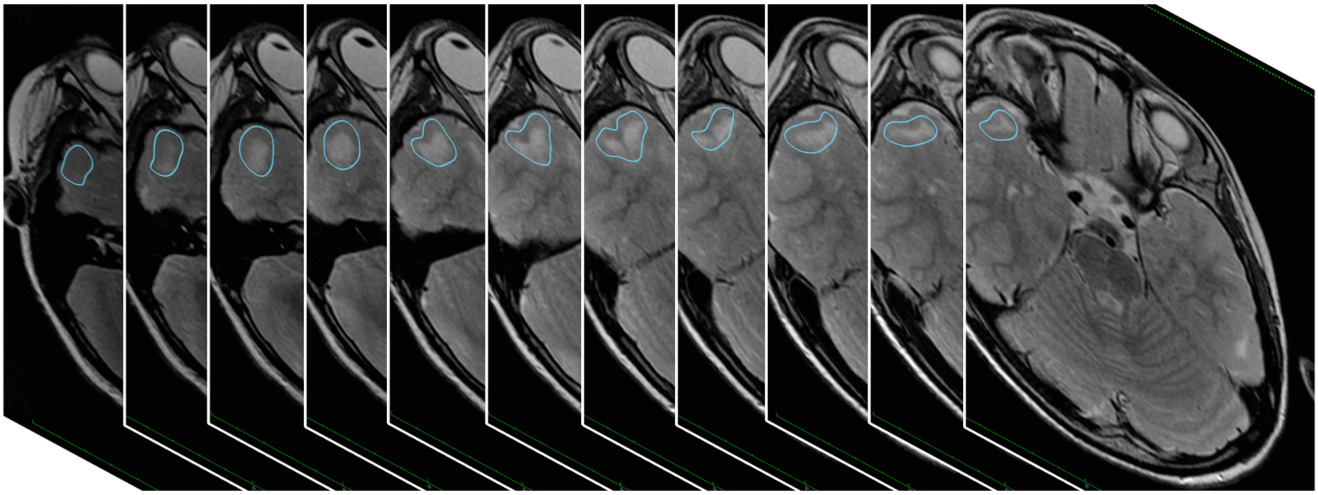

Fig. 2 Overlay of pre-operative T-2 weighted MRI images in OSiriX demonstrating how cortical tuber volumes were calculated using the ROI draw and ROI volume functions

Engel I outcomes had a mean (variance) A/T ratio of 1.28 (0.16) whereas tubers without Engel I outcomes had a mean A/T ratio of 0.84 (< 0.01). There was a statistically significant difference in mean A/T ratio in these two groups ($P = 0.035$) (Table 4). χ^2 analysis also yielded a significant difference between A/T ratio and Engel classification ($P = .025$).

Thermal dynamics

Ablation volume was compared to total ablation energy. Linear regression analysis yielded an R^2 value of 0.65 for all tubers and 0.77 if the calcified tuber was excluded from analysis (Figs. 3 and 4). Therefore, the amount of energy required to ablate 1 cm^3 of cortical tuber is 1263.60 J when all tubers are analyzed; 1089.45 J if the calcified tuber is excluded.

Patient outcomes and complications

Two out of 3 patients were completely seizure free following laser ablation of epileptogenic cortical tubers with Engel IA outcomes. One patient had worthwhile reduction in seizure frequency but did not achieve complete seizure freedom; therefore, this patient was classified as Engel IIIA. All patients made a full and rapid recovery following invasive intracranial monitoring and MRgLITT. Patients were discharged next day following MRgLITT. There were no post-operative complications observed in this cohort.

Table 1 Patient demographics

Patient identifier	A	B	C
Gender	Female	Male	Female
Age at seizure onset (month)	4	3	18
Duration of seizures (month)	19	71	36
Seizure frequency (#/day)	5–8	5–10	4–6
Previous interventions	Prior left frontal cortical tuber excision via craniotomy followed by Visualase LITT of left lateral frontal cortical tuber at 1 year of age without significant change in seizure semiology	Prior right occipital cortical tuber resection at 2 years of age with no significant change in seizure semiology	No prior interventions
Age at current surgery (years)	2	6	5
Total # tubers monitored	5	8	6
Duration SEEG monitoring (days)	4	3	6
# tubers causing clinical seizures	2	3	3
Outcome	Engel I	Engel III	Engel I
Complications	None	None	None
Length of stay post-ablation (days)	1	1	1
Length of follow-up (years)	1.94	1.52	0.55

Table 2 Tuber information

Tuber number	Pt	Location of tuber	Ca?	Pre-ablation volume (MW)	Ablation volume (Avg)	A/T ratio	W*s	Total time	Joules	Outcome
1	A	R Anterior Superior Frontal	N	2.77	1.60	0.77	10.5 W × 150 s	150.00	1575.00	Engel I
2	A	L Inferior Frontal	N	1.04	2.24	1.23	10.5 W × 165 s	165.00	1732.50	Engel I
3	B	R Posterior Superior Frontal	N	3.62	3.63	0.82	11.25 W × 150 s + 11.25 W × 135 s	285.00	3206.25	Engel III
4	B	R Medial Temporal	N	3.97	3.31	0.85	11.25 W × 135 s + 11.5 W × 150 s	285.00	3206.25	Engel III
5	B	R Posterior Temporal	N	3.61	3.00	0.85	11.25 W × 135 s + 11.25 × 135 s	270.00	3037.50	Engel III
6	C	L Insular	N	0.95	1.96	1.59	11.25 W × 150 s	150.00	1687.50	Engel I
7	C	L Superior Frontal	N	0.57	0.92	1.05	11.25 W × 165 s	165.00	1856.25	Engel I
8	C	Lateral Medial Frontal	Y	1.48	5.61	1.77	11.25 W × 148 s + 11.25 W × 135 s	283.00	3183.75	Engel I

Discussion

We present an analysis of the volumetric and thermal dynamic factors influencing seizure outcomes in our cohort of patients following SEEG-directed cortical tuber laser ablation. To the best of our knowledge, this is the first study that analyzes these factors in laser interstitial therapy for cortical tuber ablation.

MRgLITT is becoming a popular technique, especially in the field of epilepsy surgery. However, there is a paucity of literature on its use. This technique appears to be well-suited for tuberous sclerosis as it allows for minimally invasive ablation of multiple disparately located cortical tubers even at different points in a patient's life with this lifelong condition. Since its relatively recent introduction, there has been an expected increase in publications on the experience of different centers with this technique. [10, 11, 17, 21, 35] However, most of the these studies have been limited to case series that focus on clinical outcomes with very little consideration of laser energy deployment factors that influence seizure control outcomes.

MRgLITT offers numerous advantages compared to previous techniques used in epilepsy surgery. Compared to radiofrequency ablation, MRgLITT allows for real-time monitoring of the extent of tissue ablation, and thus allows for immediate visual feedback. [3, 23, 28, 31] This allows one to ensure that all target epileptogenic foci are completely ablated prior to completion of the procedure. When compared to the use of the gamma knife for epilepsy surgery, clinical seizure control effects do not appear for approximately 3–18 months whereas for MRgLITT, they are immediately apparent. [25, 32] Compared to tuberectomies or lobectomies for the treatment of MRE due to TSC, MRgLITT offers numerous advantages, such as lower complication rates and decreased length of hospital stay, where average hospital length of stay was 7 days when TSC therapy necessitated a craniotomy. [36] In this study, all patients were discharged the next day following MRgLITT and there were no short or long-term complications observed. Similar to MRgLITT, data supports that complete removal of cortical tubers is associated with improved seizure control. [19] In general, MRgLITT appears to be a safe and effective technique that is well suited for this application. Studies that treated TSC with tuberectomy or lobectomy saw Engel I outcomes in 55–70% of their patients. [1, 13, 19, 22] Though this is a small study, Engel I outcomes were observed in 2 out of 3 patients at last follow-up; thus, the seizure outcomes appear to be similar when a more minimally

Table 3 A/T ratio of each cortical tuber with patient outcomes

Tuber number	A/T ratio	Outcome
1	0.77	Engel I
2	1.23	Engel I
3	0.82	Engel III
4	0.85	Engel III
5	0.85	Engel III
6	1.59	Engel I
7	1.05	Engel I
8	1.77	Engel I

Table 4 Statistical analysis of mean A/T ratio of patients with Engel I outcomes vs those without Engel I outcomes and *P* value. A *P* value < 0.05 was determined to be significant

	Engel I	Not Engel I
Mean	1.28	0.84
Variance	0.16	< 0.01
P	0.035	

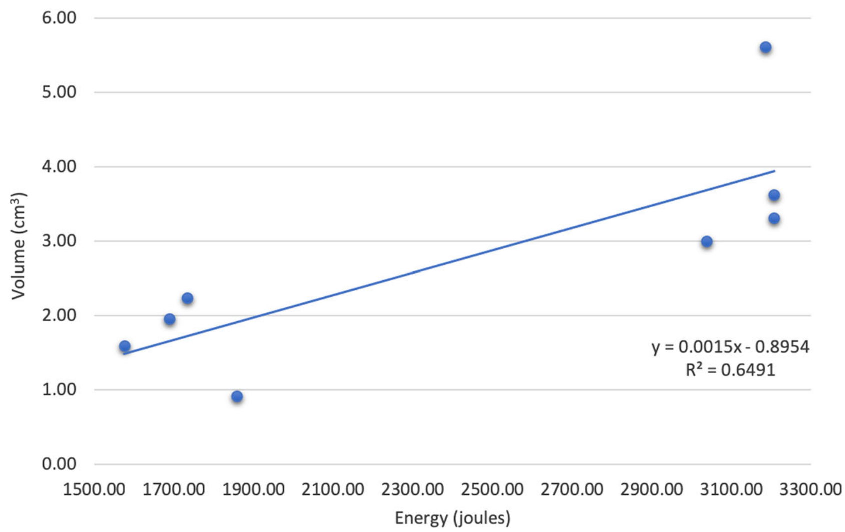

Fig. 3 Graph of cortical tuber ablation volume vs energy applied. A linear trendline is shown with formula and R^2

invasive treatment strategy is used. However, more patients are needed to better support these claims.

The data from our cohort of patients suggests that an increased proportion of tuber ablated may be associated with increased seizure control outcomes. In our analysis, the adopted A/T ratio was predictive of adequacy of ablation and seizure outcomes. In the small cohort of cortical tubers assessed, an A/T ratio greater than or equal to 1 appeared to be indicative of Engel I outcomes whereas an A/T ratio less than 1 indicated that the patient would likely not have Engel I outcomes. To the best of our knowledge, volumetric data using MRgLITT has only been applied in the setting of analyzing changes in measured ablation volume over time. [2, 5, 12, 29] There does not appear to have been an analysis of ablation volume compared to lesion volume in the field of epilepsy surgery. One study by Mohammadi et al. investigates this concept with respect to high grade gliomas and found that when ablation volumes resulted in a sufficiently small remaining lesion volume, progression free survival was significantly increased. [26] This concept agrees with the data presented in our study, where an A/T ratio greater than 1 appears to correlate with improved post-operative seizure outcomes.

Another unique aspect of this study was the attempt to define the amount of energy required to ablate a unit volume of cortical tuber tissue. At present, these values are chosen empirically at the surgeon's discretion based on clinical experience. Our data may help to provide some direction in this regard. We have identified that 1263 joules of energy are

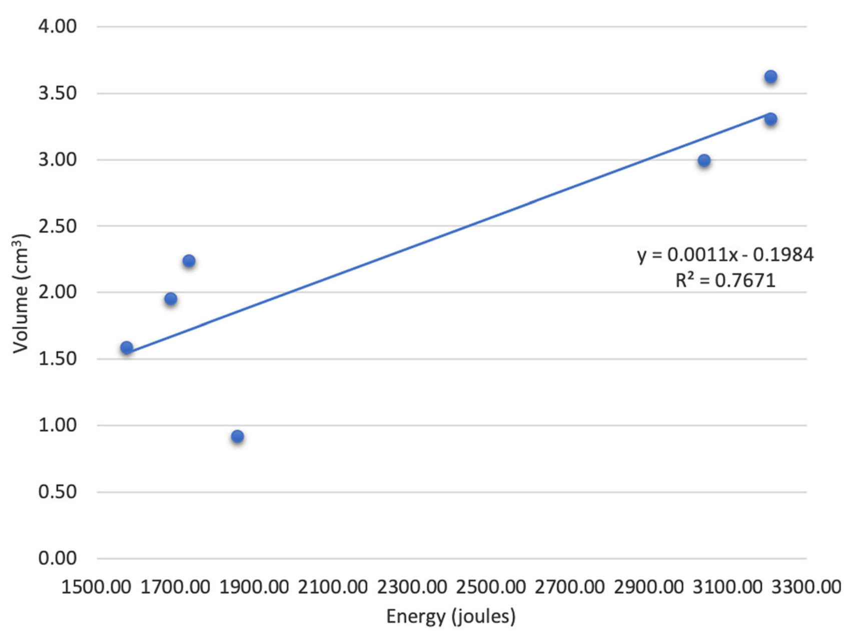

Fig. 4 Graph of cortical tuber ablation volume vs energy applied. The calcified tuber was removed from analysis in this figure. A linear trendline is shown with formula and R^2

required to ablate one cubic centimeter of cortical tuber tissue. This value, however, is changed when the calcified tuber was removed, indicating that calcification may alter the thermodynamic properties of the cortical tissue. A total of 1089 joules of energy are required to ablate one cubic centimeter of uncalcified cortical tuber tissue in this instance. It appears that calcification alters the thermal dynamic properties of cortical tuber tissue, requiring more energy to ablate a unit volume of calcified tissue compared to non-calcified tissue. Given the relatively high positive correlation in cortical tuber tissue, these data may prove beneficial in confirming adequacy of ablation.

With SEEG, we are gaining insight into the fact that, in some of these patients, multiple tubers form an epileptic network and it appears that ablation of specific tubers or "nodes" in these patients is required for effective disruption of this epileptic network. However, what appears to be most important is complete ablation of the "nodes." In each patient, SEEG was utilized to record potential epileptogenic activity from several cortical tubers, ranging from 5 to 8 tubers per patient that may have manifested as clinical seizures. Following a period of invasive intracranial monitoring, it was determined that only a fraction of those tubers were causing clinical seizures, ranging from 2 to 3 tubers per patient. Thus, in our cohort, SEEG proved instrumental in defining the epileptic network in each patient. A known benefit of SEEG is that it is able to help elucidate the 3D spatial field of seizure onset and progression. [18] There is still a paucity of data regarding the use of SEEG in TSC. SEEG, however, has been proven to be safe with a low complication rate of 0–3%, a rate similar to subdural electrodes. [4, 8, 14, 15, 34] However, subdural EEG has been associated with high morbidity in some pediatric series. [37] In addition, SEEG has an added benefit in that it avoids the need for a craniotomy and allows for the 3D investigation of complex epileptic networks with proven benefit in children with multifocal epilepsy, such as TSC. [8, 31]

There are several limitations of this study. First off, our cohort included only eight cortical tubers in three pediatric patients. Future studies that investigate a greater number of cortical tubers will be useful to increase study validity and further categorize the thermal dynamic properties of cortical tuber tissue. Second, measuring pre-ablation cortical tuber volume had some limitations including: adequate assessment of tuber margins, identifying where one tuber ends and another starts, identifying cortical tuber versus radial band, age-related myelination changes, and the thickness of T2-weighted MRI slices. However, we leveraged a board certified neuroradiologist to ensure accurate tuber volume measurements to help mitigate these limitations. With the laser technology, there exists a well-known limitation regarding the absence of pathological tissue as it cannot be attained with this technique. However, in these particular patients, the pathology is well understood and thus, would not add any useful information to this study.

Conclusions

To the best of our knowledge, this is the first study that utilizes SEEG-directed MRgLITT in the treatment of TSC. In addition, this study investigated the thermal dynamics and volumetric factors of this technique to better characterize it and guide future practice. It appears that the A/T ratio is a useful parameter for the prediction seizure outcomes. When tuber ablation is adequate, SEEG-directed MRgLITT appears to be a safe and efficacious method that is well designed for multifocal epilepsy. Further investigation with this technique is needed in both TSC as well as other forms of epilepsy to better qualify seizure outcomes and safety profiles.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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