Volumetric analysis of magnetic resonance–guided focused ultrasound thalamotomy lesions

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OBJECTIVE Magnetic resonance–guided focused ultrasound (MRgFUS) thalamotomy was recently approved for use in the treatment of medication-refractory essential tremor (ET). Previous work has described lesion appearance and volume on MRI up to 6 months after treatment. Here, the authors report on the volumetric segmentation of the thalamotomy lesion and associated edema in the immediate postoperative period and 1 year following treatment, and relate these radiographic characteristics with clinical outcome.

METHODS Seven patients with medication-refractory ET underwent MRgFUS thalamotomy at Brigham and Women's Hospital and were monitored clinically for 1 year posttreatment. Treatment effect was measured using the Clinical Rating Scale for Tremor (CRST). MRI was performed immediately postoperatively, 24 hours posttreatment, and at 1 year. Lesion location and the volumes of the necrotic core (zone I) and surrounding edema (cytotoxic, zone II; vasogenic, zone III) were measured on thin-slice T2-weighted images using Slicer 3D software.

RESULTS Patients had significant improvement in overall CRST scores (baseline 51.4 ± 10.8 to 24.9 ± 11.0 at 1 year, $p = 0.001$). The most common adverse events (AEs) in the 1-month posttreatment period were transient gait disturbance (6 patients) and paresthesia (3 patients). The center of zone I immediately posttreatment was 5.61 ± 0.9 mm anterior to the posterior commissure, 14.6 ± 0.8 mm lateral to midline, and 11.0 ± 0.5 mm lateral to the border of the third ventricle on the anterior commissure–posterior commissure plane. Zone I, II, and III volumes immediately posttreatment were 0.01 ± 0.01 , 0.05 ± 0.02 , and 0.33 ± 0.21 cm³, respectively. These volumes increased significantly over the first 24 hours following surgery. The edema did not spread evenly, with more notable expansion in the superoinferior and lateral directions. The spread of edema inferiorly was associated with the incidence of gait disturbance. At 1 year, the remaining lesion location and size were comparable to those of zone I immediately posttreatment. Zone volumes were not associated with clinical efficacy in a statistically significant way.

CONCLUSIONS MRgFUS thalamotomy demonstrates sustained clinical efficacy at 1 year for the treatment of medication-refractory ET. This technology can create accurate, predictable, and small-volume lesions that are stable over time. Instances of AEs are transient and are associated with the pattern of perilesional edema expansion. Additional analysis of a larger MRgFUS thalamotomy cohort could provide more information to maximize clinical effect and reduce the rate of long-lasting AEs.

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KEY WORDS focused ultrasound; essential tremor; thalamotomy; MRgFUS; volumetric segmentation

ESSENTIAL tremor (ET) is the most common movement disorder, with an overall prevalence of 0.9%–4.6%.¹⁹ An estimated 25%–55% of ET cases are refractory to medical management.¹⁸ A subset of these patients are candidates for surgical intervention, which in-

cludes surgical lesioning and deep brain stimulation (DBS) of the ventral intermediate nucleus of the thalamus (Vim). More recently, MR-guided focused ultrasound (MRgFUS) thalamotomy has emerged as an alternative therapeutic option for medication-refractory ET.^{8,14}

ABBREVIATIONS AC = anterior commissure; AE = adverse event; AP = anteroposterior; CRST = Clinical Rating Scale for Tremor; ET = essential tremor; FRFSE = fast relaxation fast spin echo; MRgFUS = MR-guided focused ultrasound; PC = posterior commissure; PLIC = posterior limb of the internal capsule; ROC = receiver operating characteristic; SI = superoinferior; Vim = ventral intermediate nucleus of the thalamus.

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The landmark randomized controlled study by Elias et al. demonstrated the clinical efficacy of MRgFUS thalamotomy.⁸ The sham-controlled trial of 76 ET patients demonstrated a mean 47% improvement in the Clinical Rating Scale for Tremor (CRST; also referred to as the Fahn-Tolosa-Marin Tremor Rating Scale) in the treated arm at 3 months following treatment (9.6 vs 15.8, $p < 0.001$).⁸ These effects were sustained at the 1-year follow-up, with a mean 40% improvement. The patients also showed improvements in quality of life as measured by the Quality of Life in Essential Tremor Questionnaire (QUEST). Despite promising efficacy, the therapy was associated with nonnegligible rates of adverse events (AEs), which included 38% and 36% rates of paresthesia and gait disturbance, respectively. While these rates decreased to 14% and 9% by the 1-year follow-up time point, respectively, further fine-tuning of targeting and sonication parameters may yet improve both the clinical efficacy and the safety profile of this intervention.

Wintermark et al. recently described the 2D characteristics of FUS thalamotomy lesions on MRI up to 3 months after treatment.²⁸ The authors separated the thalamotomy lesion into 3 concentric zones on T2-weighted imaging—a hypointense center (necrotic core); a strongly hyperintense zone with a hypointense rim (cytotoxic edema); and a fuzzy, slightly hyperintense zone at the periphery (vasogenic edema)—and noted their similarity to stereotactic radiosurgery thalamotomies. They reported a relationship between lesion size, amount of perilesional edema, location, and tremor response in a series of 15 patients. Their study was limited by 2 major factors: follow-up time (3 months) and an evaluation of the lesion solely in the axial plane. Others have examined the volume of the necrotic core over the first 6 months after treatment, but the extent of edema was not evaluated.^{2,15}

The efficacy of and AEs associated with MRgFUS Vim thalamotomy are directly correlated with lesion location and volume. Imprecise lesioning and/or the transient development of perilesional edema can affect other thalamic nuclei and the adjacent structures, such as the posterior limb of the internal capsule (PLIC).¹⁰ A better understanding of the 3D characteristics of the MRgFUS thalamotomy lesion and surrounding transient edema would help to decrease the rate of AEs, inform patients regarding transient and permanent effects, and enable technique optimization for improved clinical outcomes. In this

paper, we report a quantitative MRI volumetric analysis of MRgFUS thalamotomy lesions and their evolution during the 1st year posttreatment.

Methods

Patient Selection

Between March and August 2016, 7 patients who underwent MRgFUS thalamotomy at Brigham and Women's Hospital as part of a larger Phase III clinical trial under IRB approval were included in this study. All patients had a preoperative diagnosis of medication-refractory ET. Details regarding eligibility criteria have been previously described.⁸ Briefly, patients were eligible if they had ET refractory to at least 2 trials of first-line medical therapy, as well as significant tremor severity (≥ 2 points in any of the components of the CRST for the upper extremity of interest) and disability (≥ 2 points on any of the 8 items in the CRST disability section). Clinical effect was evaluated using the CRST,²⁷ in which tremor severity in each body part is rated from 0 to 32 (higher score indicates more severe tremor), with a maximum total patient tremor score of 152. Five patients were male and 2 were female, with a mean age of 67.7 ± 6.3 years (SD) at the time of treatment (Table 1).

Procedure

A detailed operative summary of the FUS thalamotomy procedure can be found elsewhere.^{7,8} Briefly, the patient's head was shaved, and a modified Cosman-Roberts-Wells (CRW) frame (Radionics Inc.) was placed low on the head to accommodate a waterproof rubber seal. The patient was positioned on the 3-T MRI table (GE Medical Systems) and connected to the ExAblate 4000 MRgFUS hemispheric transducer, operating at 650 kHz (InSightec Inc.). The interface space between the head and the transducer was filled with circulating, cooled, degassed water. The Vim sonication target was localized using anatomical landmarks and stereotactic coordinates. Subthreshold sonications were conducted and monitored using MR thermometry. Interpretation of MR thermometry heat signature alongside clinical effects in the awake patient was used to finalize the target. Therapeutic sonications were delivered using a stepwise increase in power until a thalamotomy focus (i.e., Vim) goal temperature of 55°C – 60°C

TABLE 1. Patient characteristics

Pt No.	Age (yrs), Sex	Time Since Onset of Sxs (yrs)	Time Since Dx (yrs)	Laterality of Intervention	Baseline CRST Score
1	58, M	47	19	Lt	64
2	65, F	36	26	Lt	39
3	78, M	10	6	Rt	50
4	72, F	56	15	Rt	68
5	64, M	40	2	Rt	42
6	69, M	14	8	Rt	47
7	68, M	20	10	Lt	50
Mean $\pm$ SD	68 $\pm$ 6	32 $\pm$ 17	12 $\pm$ 8		51 $\pm$ 11

Dx = diagnosis; Pt = patient; Sxs = symptoms.

was reached. Sonication was conducted with continuous clinical monitoring of the patient. Once the clinical team determined that the treatment was complete according to clinical and radiographic metrics, the head frame was removed, and the patient underwent immediate posttreatment MRI before being transported to the postoperative recovery unit. A T1-weighted sequence and a thin-slice fast-relaxation fast spin-echo (FRFSE) T2-weighted sequence were acquired immediately posttreatment, 24 hours posttreatment, and later at the 1-year follow-up.

Image Analysis

Image analysis and volumetric segmentation were performed using open-source software (3D Slicer). For each patient, the reference sequence (immediate posttreatment T2-weighted image) was transformed using the ACPC Transform module to adjust head tilt, bringing the anterior commissure–posterior commissure (AC-PC) plane parallel to the axial plane. The AC point was defined on the reference sequence as the posterior border of the AC, and the PC point was defined at the most anterior border of the PC (resulting in the shortest intercommissural distance). The remaining sequences were each transformed manually to roughly approximate the reference sequence, and then coregistered to the reference sequence using the General BRAINSfit Registration module (Center-of-Head alignment, Rigid+Scale(7-DOF) registration phase) (<http://www.insight-journal.org/browse/publication/180>). The accuracy of the registration was visually confirmed by the investigators. The thalamotomy MR signal on the 24-hour posttreatment image was separated into the following 3 volumes as described by Wintermark et al. (Fig. 1):²⁸ zone I, the necrotic lesion core (T2 hypointense); zone II, the rim of cytotoxic edema (markedly T2 hyperintense); and zone III, the surrounding vasogenic edema (moderately T2 hyperintense). Volumetric segmentation was done using the Level Tracing Effect feature in the Editor module,

FIG. 1. Lesion zones. Zone I, necrotic core. Zone II, cytotoxic edema. Zone III, vasogenic edema. Based on a representation by Wintermark et al.²⁸

followed by manual correction with the Paint Effect tool. The centroid of the lesion was defined on T2-weighted imaging as the center of zone I in the AC-PC plane, irrespective of the extension of zone I in the superoinferior (SI) direction. Distances were measured using the Annotation module. Segmentation was done independently on each imaging sequence on the thin-slice FRFSE T2-weighted images. Image analysis was performed by a single reviewer (M.H.). The T1-weighted sequence was only used for anatomical representation purposes.

Data Analysis

Statistical analysis was performed using IBM SPSS (version 23, IBM Corp.). For the comparison of CRST scores over time, a 1-way repeated-measures ANOVA test was used. For the comparison of lesion location and volume at different time points, a paired-sample t-test was used. A chi-square statistic was used to evaluate the relationship between AE and volume; $p < 0.05$ was considered statistically significant.

Results

Clinical Outcomes

At baseline, patients had a mean $\pm$ SD overall CRST score of 51.4 ± 10.8 and treated upper-extremity CRST tremor and motor scores of 6 ± 3.1 and 11.6 ± 2.9 , respectively. At the 1-month, 3-month, 6-month, and 1-year follow-ups, the mean overall CRST scores were 17.6 ± 7.6 , 19.3 ± 10.1 , 20.1 ± 7.4 , and 24.9 ± 11.0 , respectively (Fig. 2A). The mean CRST scores were significantly different ($F(2,28) = 34.9$, $p < 0.001$), with each of the posttreatment scores significantly different from baseline. The overall improvement in CRST score at the 1-year mark spanned from 10% to 73%, with a mean of $51.6\% \pm 21.1\%$. Excluding the 1 outlier (patient 3) with 10% improvement, the mean was $58.6\% \pm 11.4\%$. Similarly, significant improvement was also seen in the tremor and motor subscores for the treated upper extremity ($p \leq 0.001$, Fig. 2B and C). While there is a trend of increase in CRST scores from the posttreatment score trough at 1-month follow-up, the scores at each time point were not statistically different from one another. QUEST scores improved by a mean of $38.2\% \pm 16.7\%$ over the 1st year (88.7 ± 20.5 at baseline to 55.4 ± 22.1).

The most common AEs reported in the early postoperative period (1 month) were gait disturbance (6 patients) and paresthesia (3 patients). With the exception of 1 instance of gait disturbance that started on posttreatment day 28, all events started on posttreatment day 0 or 1. Five AEs (gait disturbance, $n = 3$; paresthesia, $n = 2$) resolved by 3.5 months posttreatment. At the 1-year follow-up, gait disturbance persisted in 3 patients and paresthesia persisted in 1 patient. With respect to gait disturbance, 2 patients had a subjective sense of imbalance, and in the remaining 4 patients there was gait abnormality on examination. With the exception of 1 case rated as moderate, the other cases of gait disturbance were all mild. In all cases, the gait disturbance diminished over time. In addition, there was one report of dysgeusia and another of dysarthria, both transient. No patients experienced any serious AEs.

FIG. 2. Mean overall (A), tremor (B), and motor (C) CRST scores in treated and untreated upper extremities. Pretreatment scores are those at the 0-month mark. Error bars represent SD. * $p \leq 0.01$ relative to pretreatment score.

Lesion Location

The thalamotomy lesions and associated segmented volumes for each patient on early postoperative imaging are shown in Fig. 3.²⁸ Immediately posttreatment, the centroid of zone I was located at a mean 6.1 ± 0.9 mm anterior to the PC, 14.6 ± 0.8 mm lateral to the midline, and 11.0 ± 0.5 mm lateral to the border of the third ventricle at the level of the AC-PC plane (Table 2). At 24 hours posttreatment, the centroid of zone I appeared slightly more medial with a mean of 14.2 ± 0.6 mm ($p = 0.015$) lateral to the midline and 11.7 ± 0.6 mm ($p = 0.009$) lateral to the border of the third ventricle on the AC-PC plane.

At 1-year follow-up, the cytotoxic edema (zone II) and vasogenic edema (zone III) had subsided; however, there was a variable appearance of the residual thalamotomy lesion (Fig. 3). In 1 patient, there was no discernable lesion. In 4 patients, there was a small T2 hyperintense lesion, and in 2 patients there was a small and faint T2 hypointense lesion. The location in the 6 patients with a discern-

able lesion was at a mean 6.9 ± 0.7 mm anterior to the PC, 14.3 ± 0.8 mm lateral to the midline, and 11.3 ± 0.7 mm lateral to the border of the third ventricle at the level of the AC-PC plane (Table 2). The location of the lesion at 1 year was comparable in the left-right and anteroposterior (AP) planes to that of the centroid of zone I immediately posttreatment.

Lesion Volume

The mean volumes immediately posttreatment on T2-weighted FRFSE sequences were 0.01 ± 0.01 cm³, 0.05 ± 0.02 cm³, and 0.33 ± 0.21 cm³ for zones I, II, and III, respectively (Table 3). All 3 zones grew significantly within the first 24-hour period: 0.03 ± 0.01 cm³ ($p = 0.003$), 0.18 ± 0.05 cm³ ($p = 0.001$), and 1.25 ± 0.28 cm³ ($p = 0.001$), respectively. At 24 hours posttreatment, the mean total volume was 1.46 ± 0.40 cm³, with zone III accounting for the majority of the lesion, with a mean of $84.8\% \pm 5.1\%$ of the overall volume. Immediately posttreatment, the volume was relatively spherical, with a mean of the total volume below ($51\% \pm 8.3\%$), posterior to ($49\% \pm 8.3\%$), and lateral to ($62.9\% \pm 14.5\%$) the centroid of zone I in the AC-PC plane, respectively. In contrast, at the 24-hour posttreatment mark, the total volume was not evenly distributed, with a mean below ($37.4\% \pm 21.7\%$), posterior to ($48.3\% \pm 7.4\%$), and lateral to ($64.2\% \pm 9.6\%$) the center of zone I at the AC-PC plane. The shape of zone I at 24 hours was ellipsoid, with the long axis lying along the SI plane.

The mean volume of the lesion at 1 year was 0.02 ± 0.01 , which is not significantly different in size to the zone I volume immediately posttreatment but, as expected, is significantly smaller than the zone I volume at the 24-hour time point ($p = 0.02$).

Relationship Between MR Characteristics and Clinical Outcomes

Patients 2 and 3 were the best and worst responders in this series, experiencing a 74.4% and 10% improvement in overall CRST score over a 1-year period, respectively. Patient 3 had the largest percentage of the volume lateral to the centroid of the lesion immediately (88.7%) and at the 24-hour time point (81.7%). Meanwhile, patient 2 had the second lowest percentage of the volume lateral to the centroid of the lesion immediately posttreatment (57.5%) and the lowest at the 24-hour time point (54.3%). Patient 2 also had the largest necrotic core volume at the 24-hour time point and the largest residual volume at 1 year. In contrast, patient 3 was the only patient who had no discernable lesion at the 1-year mark. However, in the group as a whole, there was no statistically significant correlation between lesion location or lesion volume of any zone at any time point and overall clinical efficacy, which undoubtedly relates to the small series size.

In patients that experienced gait disturbance, greater than 0.21 cm³ of the total volume at the 24-hour time point was below the AC-PC plane ($\chi^2 = 7.0$ [df = 1], $p = 0.008$). There was no statistically significant relationship between postoperative paresthesia and the volume distribution in the AP, left-right, or SI plane.

FIG. 3. Axial T2-weighted MR images of the thalamotomy lesion at the AC-PC plane at 24 hours and 1 year posttreatment, and volumetric segmentation of the lesion at 24 hours posttreatment (represented on T1-weighted sequences). Axial (Ax) are views bounded by AC, PC, midline, and insular cortex. *Orange* indicates zone I (necrotic core); *yellow*, zone II (cytotoxic edema); and *blue*, zone III (vasogenic edema). All axial images are shown at the AC-PC plane. *Horizontal line* across coronal (Cor) images represents the AC-PC plane. *Arrows* indicate the residual lesion at 1 year. Pt = patient.

Discussion

MRgFUS has only recently become a viable tool for clinical treatment. Potential applications include treatment of Parkinson's disease, obsessive-compulsive disorder, pain syndromes, and brain tumors.³ Phase III studies have demonstrated the efficacy of MRgFUS thalamotomy in the treatment of medically refractory ET and have highlighted the need for precise lesioning. It is therefore of paramount importance to understand the way these thermal lesions develop over time in 3D space. Better understanding

of the imaging characteristics of MRgFUS thalamotomy will help inform and fine-tune MRgFUS ablative interventions with the aim of minimizing AEs, improving prognostication of AE course, and improving overall clinical outcomes. Building on prior work that evaluated MRgFUS thalamotomy lesions and associated edema in 2D space over a follow-up period of 6 months posttreatment, we describe the 3D volumetric imaging characteristics of MRgFUS thalamotomy lesions over a follow-up period of 1 year and how volumetric assessment of these lesions correlates with AEs and clinical outcomes.

TABLE 2. Location of the centroid of the lesion (zone I) immediately, 24 hours, and 1 year posttreatment as measured on T2-weighted images in the AC-PC plane

Variable	Location (mm)*		
	Immediately Posttreatment	24 Hrs Posttreatment	1 Yr Posttreatment
Anterior to PC	6.1 ± 0.9	5.9 ± 1.1	6.9 ± 0.9
Anterior to PC as ratio of AC-PC length	0.22 ± 0.4	0.22 ± 0.4	0.3 ± 0.3
Lat to midline	14.6 ± 0.8	14.2 ± 0.6*	14.3 ± 0.8
Lat to border of 3rd ventricle	11.0 ± 0.5	11.7 ± 0.6†	11.3 ± 0.7

Values are presented as the mean ± SD.

* p < 0.05 relative to location immediately posttreatment.

† p < 0.01 relative to location immediately posttreatment.

In this series, the lesion was accurately located within the traditional stereotactic coordinates for Vim thalamotomy, which once again provides consistent data regarding the spatial accuracy of MRgFUS thermal lesioning.^{4,21} The location of the lesion was stable between the immediate postoperative and 1-year time point, but our data showed a small medial shift in lesion location at the 24-hour time point. This finding is likely due to transient edema, which is more noticeable at the 24-hour time point than at the immediate postoperative time point but fully resolves by the 1-year time point. The location of the center of the necrotic core (zone I) in the axial plane was not correlated to clinical outcome at any time point during the 1st year posttreatment. This is consistent with prior work on lesion characteristics in radiofrequency thermal thalamotomy.¹¹

Earlier imaging studies have reported that the thalamotomy lesion might disappear by 6 months posttreatment. In this study, the majority of patients did have discernable lesions at 1 year posttreatment.^{2,15} At the 1-year time point, the lesions were either T2 hypointense or T2 hyperintense, likely a lacuna of fluid that remained after the absorption/breakdown of tissue at the centroid of necrosis. Interestingly, the 1 patient in whom the lesion completely disappeared at the 1-year time point also had the lowest clinical improvement in CRST score. This variability in appearance (i.e., T2 hyperintense vs T2 hypointense) may or may not be of clinical significance, but the presence of a discernible lesion (i.e., T2 hyper-/hypointense vs no lesion) on MRI may inform the utility of future repeat unilateral treatment.

The volume of the MRgFUS lesion grew significantly by the 24-hour time point, which is in agreement with previous studies.^{2,15,22,28} This volume change was seen for all 3 zones individually, with the growth of perilesional edema being particularly significant. Interestingly, the edema did not expand equally in all directions. Specifically, it spread more widely in the lateral and SI directions relative to the AP plane. This might suggest a more significant spread along white matter tracts into the PLIC laterally and then along the PLIC in the SI direction. This rapid expansion in edema 24 hours posttreatment gradually dissipates over approximately 1 month and completely disappears by 3 months posttreatment.^{2,15,22,28} These imaging findings are correlated with the natural history of several AEs.^{2,15,22,28} As edema dissipates, the majority of initially reported AEs also subside, suggesting that at least some AEs are attrib-

utable to mass effect and/or microenvironment disruptions due to transient perilesional edema on neighboring fiber tracts and nuclei rather than direct ablative effects. In our patients, the spread of edema inferiorly was significantly associated with incidence of gait disturbance, which is most likely due to involvement of cerebellothalamic connections. In this study, receiver operating characteristic (ROC) analysis showed that a volume greater than 0.21 cm³ below the AC-PC plane at the 24-hour time point was associated with postoperative gait disturbance, with diagnostic capabilities. It is important to note that these values are based on a small cohort, and analysis on a larger cohort is required to draw more definitive conclusions. The posterior spread of edema, involving the ventral posterolateral nucleus, or laterally into PLIC, was not associated with the incidence of paresthesia.

The volume of zone I significantly expanded at the 24-hour time point but contracted to a comparable size by the 1-year time point. The lesion volume, ranging from 0.01 to 0.03 cm³ at 1 year, was on average smaller than the le-

TABLE 3. Volumes of individual zones immediately and 24 hours posttreatment

Variable	Vol	
	Immediately Posttreatment	24 Hrs Posttreatment
Zone		
I	0.01 ± 0.01	0.03 ± 0.01*
II	0.05 ± 0.02	0.18 ± 0.05†
III	0.33 ± 0.21	1.25 ± 0.28†
Total vol	0.39 ± 0.22	1.46 ± 0.40†
Vol below AC-PC plane	0.13 ± 0.06	0.53 ± 0.28
% total vol	51.0 ± 8.3%	37.4 ± 21.7%
Vol posterior to centroid of zone I	0.18 ± 0.1	0.71 ± 0.23
% total vol	49.0 ± 8.29%	48.3 ± 7.45%
Vol lat to centroid of zone I	0.25 ± 0.14	0.95 ± 0.35
% total vol	62.9 ± 14.5%	64.2 ± 9.6%

All values are presented as the mean ± SD. Volume values are presented in cubic centimeters. All volumes were measured on a thin-slice FRFSE T2-weighted sequence.

* p < 0.01 relative to volume immediately posttreatment.

† p = 0.001 relative to volume immediately posttreatment.

sion volumes reported after radiofrequency thalamotomy (0.004–0.16 cm³).¹¹ In Gamma Knife thalamotomy, the lesion only becomes apparent at approximately 3 months following treatment and, in some instances, continues increasing in volume up to 6 months following treatment, reaching 0.05–0.6 cm³.²³

In our series, MRgFUS Vim thalamotomy lesion location and volume(s) did not appear to correlate with overall clinical efficacy using standard CRST scales or explain/predict the incidence of persistent AEs.^{11,16} Performing a similar volumetric analysis in a larger cohort of patients, however, could provide important information on optimal lesion volume and location, especially in the SI plane. Our volumetric analysis was predictive of gait disturbance with respect to the inferior extension of the lesion and associated edema. Nevertheless, this study is underpowered to make recommendations regarding targeting.

Improvements in clinical efficacy and safety profile will require further investigation of how sonication parameters might affect the characteristics of the lesion. Early work in focused ultrasound thermal lesioning demonstrated that short sonications with rapid ramp-up to maximum intensity allow for the creation of discrete, small-volume lesions and minimal effect on surrounding tissue.²⁰ Longer duration of sonication, along with the additive effects of prior sonication, leads to a higher thermal dose, and concurrently more collateral effects.^{1,4,6,21} Literature on radiofrequency thalamotomy has suggested that while treatment parameters correlate with some of the lesion characteristics, these alone could not predict lesion volume, likely due to individual variation.¹² Sonication parameters needed to achieve goal temperatures and clinical effects vary between patients due to individual variation in factors, such as skull characteristics.² In this series, to achieve the desired clinical effect, patients had anywhere between 2 and 7 suprathreshold sonications (10 seconds each) and a total of 15–28 sonications (including subthreshold). Better characterization of the overall thermal dose in real time and the effect of individual variation may help guide the appropriate sonication protocol with the aim of reducing perilesional edema and the development of edema-related AE. Assessment of cumulative thermal dose may become particularly important in applications that have either bilateral targeting (e.g., bilateral capsulotomy) or a larger target volume.

Another method for improvement in the clinical efficacy and safety profile might involve improved targeting methods, such as tractography and low-intensity stimulation. White matter tractography based on diffusion tensor imaging (DTI) has been proposed as a tool to assist localization of targets based on their white matter connectivity and has been applied to the Vim, to identify cerebellar input to the Vim (dentate-rubro-thalamic tract) with improved clinical outcomes.^{9,13,17,25,26,29}

Low-intensity focused ultrasound has also been proposed as a method to assist intraoperative targeting.²⁴ These low-intensity focused ultrasound sonications, which create no histological damage and have no MR thermometry heat signature (i.e., do not cause heating), are able to stimulate neural tissue and generate somatosensory evoked potentials when targeting the ventral posterolateral

nucleus in an animal model.⁵ This technique might eventually be used to functionally map the Vim and surrounding structures without contributing to thermal dosing.

The major limitation of this study is its small sample size. This analysis could be expanded to the remaining Elias et al. cohort to allow for more rigorous ROC curve analysis, which may expand the present results or further uncover additional underlying imaging correlation between lesion characteristics and clinical outcomes. Despite these limitations, this study is the first to quantitatively analyze the 3D volume of the lesion along with its surrounding edema and to assess these in the context of clinical outcomes.

Conclusions

MRgFUS is an effective tool to create accurate, predictable, and precise thalamotomy lesions under real-time MRI guidance, with associated good clinical improvement for the treatment of medically refractory ET. Treatment-related AEs (e.g., gait disturbance and paresthesia) are likely attributable to the spread of perilesional edema along white matter tracts, and most resolve with the disappearance of this edema. This work provides a descriptive volumetric analysis of MRgFUS thalamotomy lesions over 1 year and examines the association between volumetric MRI characteristics, clinical outcomes, and transient and permanent AEs. Additional analysis of a larger MRgFUS thalamotomy cohort could provide more information to maximize clinical effect and reduce the rate of permanent side effects.

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Disclosures

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Author Contributions

Conception and design: Cosgrove, Harary, Essayed, McDannold. Acquisition of data: Harary, Essayed. Analysis and interpretation of data: Harary, Essayed, Valdes. Drafting the article: Harary. Critically revising the article: Cosgrove, Harary, Essayed, Valdes. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Cosgrove. Statistical analysis: Harary, Valdes. Study supervision: Cosgrove.

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