

## Magnetic resonance imaging–guided focused ultrasound thalamotomy for essential tremor: 5-year follow-up results

G. Rees Cosgrove, MD,<sup>1</sup> Nir Lipsman, MD, PhD,<sup>2</sup> Andres M. Lozano, MD, PhD,<sup>3</sup> Jin Woo Chang, MD, PhD,<sup>4</sup> Casey Halpern, MD,<sup>5</sup> Pejman Ghanouni, MD, PhD,<sup>6</sup> Howard Eisenberg, MD,<sup>7</sup> Paul Fishman, MD, PhD,<sup>8</sup> Takaomi Taira, MD, PhD,<sup>9</sup> Michael L. Schwartz, MD, MSc,<sup>2</sup> Nathan McDannold, PhD,<sup>10</sup> Michael Hayes, MD,<sup>11</sup> Susie Ro, MD,<sup>12</sup> Binit Shah, MD,<sup>13</sup> Ryder Gwinn, MD,<sup>14</sup> Veronica E. Santini, MD, MA,<sup>15</sup> Kullervo Hynnen, PhD,<sup>16</sup> and W. Jeff Elias, MD<sup>17</sup>

Departments of <sup>1</sup>Neurosurgery, <sup>11</sup>Neurology, and <sup>10</sup>Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; Departments of <sup>2</sup>Neurosurgery and <sup>16</sup>Radiology, Sunnybrook Health Sciences Centre, University of Toronto, Ontario, Canada; <sup>3</sup>Department of Neurosurgery, Toronto Western Hospital, University of Toronto, Ontario, Canada; <sup>4</sup>Department of Neurosurgery, Yonsei University College of Medicine, Seoul, Korea; Departments of <sup>5</sup>Neurosurgery, <sup>15</sup>Neurology, and <sup>6</sup>Radiology, Stanford University School of Medicine, Stanford, California; Departments of <sup>7</sup>Neurosurgery and <sup>8</sup>Neurology, University of Maryland School of Medicine, Baltimore, Maryland; <sup>9</sup>Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan; Departments of <sup>14</sup>Neurosurgery and <sup>12</sup>Neurology, Swedish Neuroscience Center, Seattle, Washington; and Departments of <sup>17</sup>Neurological Surgery and <sup>13</sup>Neurology, University of Virginia School of Medicine, Charlottesville, Virginia

**OBJECTIVE** The objective of this study was to evaluate, at 4 and 5 years posttreatment, the long-term safety and efficacy of unilateral MRI-guided focused ultrasound (MRgFUS) thalamotomy for medication-refractory essential tremor in a cohort of patients from a prospective, controlled, multicenter clinical trial.

**METHODS** Outcomes per the Clinical Rating Scale for Tremor (CRST), including postural tremor scores (CRST Part A), combined hand tremor/motor scores (CRST Parts A and B), and functional disability scores (CRST Part C), were measured by a qualified neurologist. The Quality of Life in Essential Tremor Questionnaire (QUEST) was used to assess quality of life. CRST and QUEST scores at 48 and 60 months post-MRgFUS were compared to those at baseline to assess treatment efficacy and durability. All adverse events (AEs) were reported.

**RESULTS** Forty-five and 40 patients completed the 4- and 5-year follow-ups, respectively. CRST scores for postural tremor (Part A) for the treated hand remained significantly improved by 73.3% and 73.1% from baseline at both 48 and 60 months posttreatment, respectively (both  $p < 0.0001$ ). Combined hand tremor/motor scores (Parts A and B) also improved by 49.5% and 40.4% ( $p < 0.0001$ ) at each respective time point. Functional disability scores (Part C) increased slightly over time but remained significantly improved through the 5 years ( $p < 0.0001$ ). Similarly, QUEST scores remained significantly improved from baseline at year 4 ( $p < 0.0001$ ) and year 5 ( $p < 0.0003$ ). All previously reported AEs remained mild or moderate, and no new AEs were reported.

**CONCLUSIONS** Unilateral MRgFUS thalamotomy demonstrates sustained and significant tremor improvement at 5 years with an overall improvement in quality-of-life measures and without any progressive or delayed complications.

Clinical trial registration no.: NCT01827904 (ClinicalTrials.gov)

<https://thejns.org/doi/abs/10.3171/2022.6.JNS212483>

**KEYWORDS** focused ultrasound; thalamotomy; essential tremor; MRI; functional neurosurgery

**T**RANSCRANIAL MRI-guided focused ultrasound (MRgFUS) thalamotomy of the ventral intermediate (Vim) nucleus for the treatment of essential tremor (ET) is a recently developed, incisionless technique incorporating intraprocedural MRI, real-time ther-

mometry, and submillimeter adjustments based on patient feedback prior to lesioning.<sup>1</sup> The ExAblate 4000 system (InSightec Ltd.) and the procedure used for unilateral MRgFUS Vim thalamotomy have been previously described.<sup>1–3</sup>

**ABBREVIATIONS** AE = adverse event; CRST = Clinical Rating Scale for Tremor; DBS = deep brain stimulation; ET = essential tremor; MRgFUS = MRI-guided focused ultrasound; QUEST = Quality of Life in Essential Tremor Questionnaire; Vim = ventral intermediate.

**SUBMITTED** November 14, 2021. **ACCEPTED** June 15, 2022.

**INCLUDE WHEN CITING** Published online August 5, 2022; DOI: 10.3171/2022.6.JNS212483.

A multicenter, randomized, double-blind, sham-controlled trial of unilateral MRgFUS Vim thalamotomy in patients with medication-refractory ET demonstrated significant tremor reduction in the treated hand and significant disability reduction, which led to FDA approval for this indication.<sup>2</sup> That same cohort was reported on by Chang et al.<sup>4</sup> and Halpern et al.<sup>3</sup> at 2 and 3 years post-treatment, respectively, detailing continued tremor reduction and disability improvement. In the current open-label study, the largest prospective, long-term follow-up study of unilateral thalamotomy for ET, we evaluated that same population for tremor reduction, disability, and treatment-related side effects at the 5-year follow-up.

## Methods

This long-term postinterventional observational clinical trial (registration no.: NCT01827904; <http://www.clinicaltrials.gov>) was designed to follow device-related safety, long-term effectiveness, and quality of life for participants who had undergone MRgFUS thalamotomy under an investigational device exemption. Written informed consent was obtained from all study participants according to the protocol approved by FDA and the institutional review board of each participating center.

Patients with moderate to severe ET, diagnosed by a neurologist with expertise in movement disorders, were enrolled in the original protocol. The disorder in all participants was medication refractory, and all patients exhibited significant disability resulting from their ET. Full eligibility criteria have been described previously.<sup>2</sup> Study participants were evaluated at baseline and 1, 3, 6, and 12 months posttreatment under the original protocol.<sup>2</sup> Annually, at years 2 through 5, assessments were performed to assess long-term safety, effectiveness, and quality of life. Any study participant who underwent a subsequent intervention for ET (not including medication changes) on their treated side at any point during the 5-year follow-up period was excluded from further analysis.

After patient preparation and positioning, stereotactic targeting with the use of MRI and patient neurological feedback was utilized to identify the Vim nucleus of the thalamus. Acoustic energy was gradually titrated to achieve thermal ablation, with peak voxel temperatures of 55°C–60°C in the target region. Real-time MR thermometry was monitored, and patients were continually assessed for safety and tremor response throughout the procedure.

Treatment effectiveness was assessed primarily using the Clinical Rating Scale for Tremor (CRST),<sup>15</sup> which was administered and scored by a qualified neurologist. The tremor severity score, evaluated by the postural component of tremor (CRST Part A, range 0 to 4), was reported. The combined tremor/motor score of the treated hand, contralateral to the thalamotomy (range 0 to 32), was calculated as the sum of CRST Part A (resting, postural, and action components of tremor) and CRST Part B (handwriting, drawing, and pouring tasks). The CRST Part C was used to evaluate the patient functional/disability status (range 0 to 32). The CRST was assessed at baseline and at all follow-up visits.

A secondary measure of effectiveness was the Quality

of Life in Essential Tremor Questionnaire (QUEST), a 30-item, self-reported questionnaire that assesses the effect of tremor symptoms on activities of daily living.<sup>5</sup>

To evaluate safety, the long-term incidence and severity of adverse events (AEs) were noted at all study follow-ups. All AEs were categorized by the investigators as definitely, probably, possibly, or not related to the device or study procedure. All events categorized as definitely or probably related to the procedure or device and sustained up to 3 years or later are reported here. The standard Code of Federal Regulation definitions were used to assess for serious AEs.

## Statistical Analysis

All patients who had undergone MRgFUS thalamotomy were included in the safety analysis. All observed data collected at follow-up visits through the 5-year time point were analyzed for effectiveness. Effectiveness was measured at each annual visit by the CRST and QUEST score reduction from baseline and by the mean percent of change from baseline, calculated for the patients who attended these visits.

Descriptive statistics were applied to calculate the significance of the mean score reduction per visit: paired t-tests were used to calculate p values to show the likelihood of the observed differences between baseline and each long-term follow-up time point (12 months and 2, 3, 4, and 5 years). GraphPad Prism version 9.2.0 software (GraphPad Software) was used. A p value < 0.05 was considered statistically significant. Mean values are expressed with the standard deviation.

## Results

Seventy-six patients were enrolled in the original protocol, 56 in the treatment arm and 20 in the sham arm. After unblinding at the 3-month follow-up, patients from the sham arm could cross over and undergo MRgFUS thalamotomy. One patient in the sham arm chose to exit the study prior to treatment, and 19 chose to proceed with treatment. Therefore, 75 patients underwent unilateral MRgFUS thalamotomy. While attempts were made to complete all study visits specified by the long-term protocol, some patients exited the study earlier. Ultimately, 70 patients were observed at 12 months, 50 at 2 years, 52 at 3 years, 45 at 4 years, and 40 at 5 years. Patient dropout during the first 3 years posttreatment has been previously described and discussed.<sup>3,4</sup> One patient underwent deep brain stimulation (DBS) because of tremor during the 3rd year and another one during the 4th year of follow-up. All other patients exited the study because of unrelated medical conditions (Table 1).

Of the 40 patients who completed the 5-year follow-up, 30 are male and 10 are female; 29 are White and 11 are Asian. The mean age at the 5-year follow-up was 75 ± 8.4 years.

## Efficacy Results

The tremor severity score (postural component of CRST Part A) for the treated side remained improved between baseline and each time point (p < 0.0001). The mean postural tremor scores were 3 ± 0.97 at baseline,

TABLE 1. Patient disposition

| Factor                            | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|-----------------------------------|--------|--------|--------|--------|--------|
| No. of patients (at start n = 75) | 70     | 50     | 52     | 45     | 40     |
| Unwilling to return               | 3      | 8      | 2      | 1      | 4      |
| Lost contact                      | 0      | 2      | 0      | 1      | 0      |
| Alternative procedure             | 1      | 2      | 1      | 1      | 1      |
| Unrelated new medical condition   | 1      | 1      | 1      | 0      | 4      |
| Missed observation                | 0      | 7      | 1      | 5      | 1      |

$0.84 \pm 1.0$  at the 1-year time point,  $0.68 \pm 0.84$  at the 2-year time point,  $0.77 \pm 0.96$  at the 3-year time point,  $0.8 \pm 1.1$  at the 4-year time point, and  $0.8 \pm 1.0$  at the 5-year time point (Fig. 1A). These values represent a mean percent of change of 72.6%, 77.0%, 76.1%, 73.3%, and 73.1% from baseline to the 1-, 2-, 3-, 4-, and 5-year time points, respectively (Fig. 1B).

The observed mean composite tremor/motor score (CRST Parts A and B), the primary endpoint of the original randomized controlled trial,<sup>2</sup> remained improved between baseline and each time point ( $p < 0.0001$ ). The mean composite motor scores were  $20 \pm 4.7$  at baseline,  $8.9 \pm 4.8$  at the 1-year time point,  $8.3 \pm 5.0$  at the 2-year time point,  $9.5 \pm 5.4$  at the 3-year time point,  $9.6 \pm 5.8$  at the 4-year time point, and  $11 \pm 6.5$  at the 5-year time point (Fig. 2A). These values represent a mean percent of change of 54.7%, 56.2%, 52.1%, 49.5%, and 40.4% from baseline to the 1-, 2-, 3-, 4-, and 5-year time points, respectively (Fig. 2B).

The observed mean disability scores (CRST Part C) remained improved between baseline and each time point ( $p < 0.0001$ ). The mean disability scores were  $16 \pm 4.6$  at baseline,  $5.6 \pm 5.4$  at the 1-year time point,  $6.5 \pm 5.0$  at the 2-year time point,  $7.5 \pm 6.1$  at the 3-year time point,  $8.4$

$\pm 6.9$  at the 4-year time point, and  $8.9 \pm 6.6$  at the 5-year time point (Fig. 3A). These values represent a mean percent of change of 67.4%, 60.1%, 56.1%, 49.0%, and 44.5% from baseline to the 1-, 2-, 3-, 4-, and 5-year time points, respectively (Fig. 3B).

The total QUEST scores remained improved between baseline and each time point ( $p < 0.0001$  for years 1–4,  $p < 0.0003$  for year 5). The mean total QUEST scores were  $43 \pm 18$  at baseline,  $20 \pm 17$  at the 1-year time point,  $25 \pm 21$  at the 2-year time point,  $26 \pm 21$  at the 3-year time point,  $28 \pm 19$  at the 4-year time point, and  $30 \pm 20$  at the 5-year time point (Fig. 4).

When looking individually at each dimension of the QUEST, the physical and psychological subscores improved from baseline to the 1-year follow-up ( $p < 0.0001$ ), and these levels of significance were maintained over 5 years of follow-up. Specifically, the physical dimension subscore was  $73 \pm 19$  at baseline and decreased to  $32 \pm 27$  at 12 months,  $35 \pm 24$  at 2 years,  $40 \pm 25$  at 3 years,  $44 \pm 26$  at 4 years, and  $46 \pm 25$  at 5 years ( $p < 0.0001$  for all comparisons; Fig. 5A). The psychological dimension was  $41 \pm 24$  at baseline and decreased to  $13 \pm 17$  at 12 months and to  $18 \pm 21$ ,  $17 \pm 19$ ,  $18 \pm 17$ , and  $19 \pm 19$  at the 2-, 3-, 4-, and 5-year visits, respectively ( $p < 0.0001$  for all comparisons; Fig. 5B).

The QUEST work and finance dimension was improved from baseline at 1 year. The improvement from baseline was maintained over the 5 years with various levels of significance. At 4 and 5 years, the follow-up scores were improved from a baseline of  $28 \pm 31$  to  $18 \pm 25$  ( $p < 0.0001$ ) and  $20 \pm 26$  ( $p = 0.0076$ ), respectively (Fig. 5C).

The hobbies and leisure dimension subscore improved from baseline to 1 year, but the improvement gradually decreased over the years. Furthermore, the change from baseline was not significant at year 5 of follow-up ( $p = 0.4460$ ). There was little change from baseline in the communication dimension throughout the follow-up.

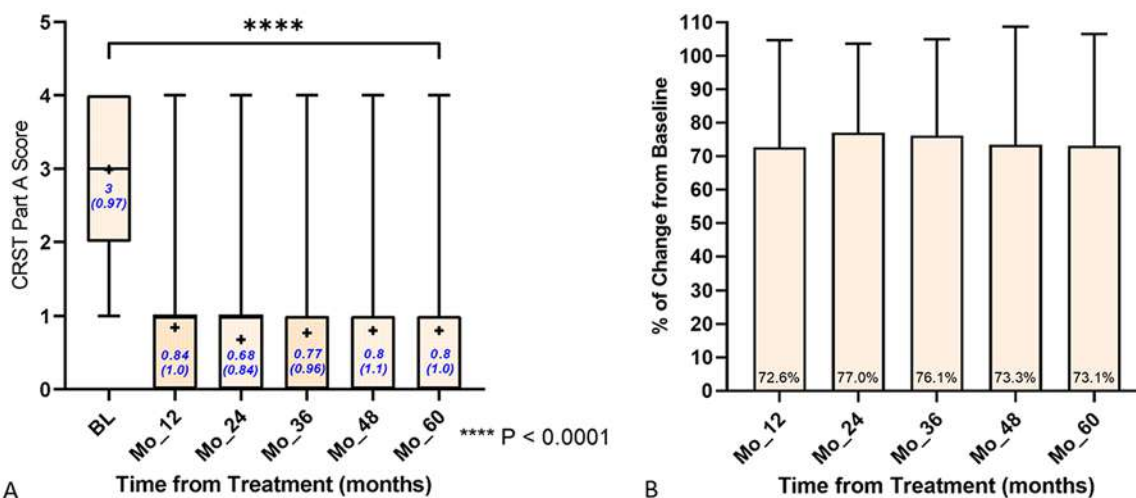
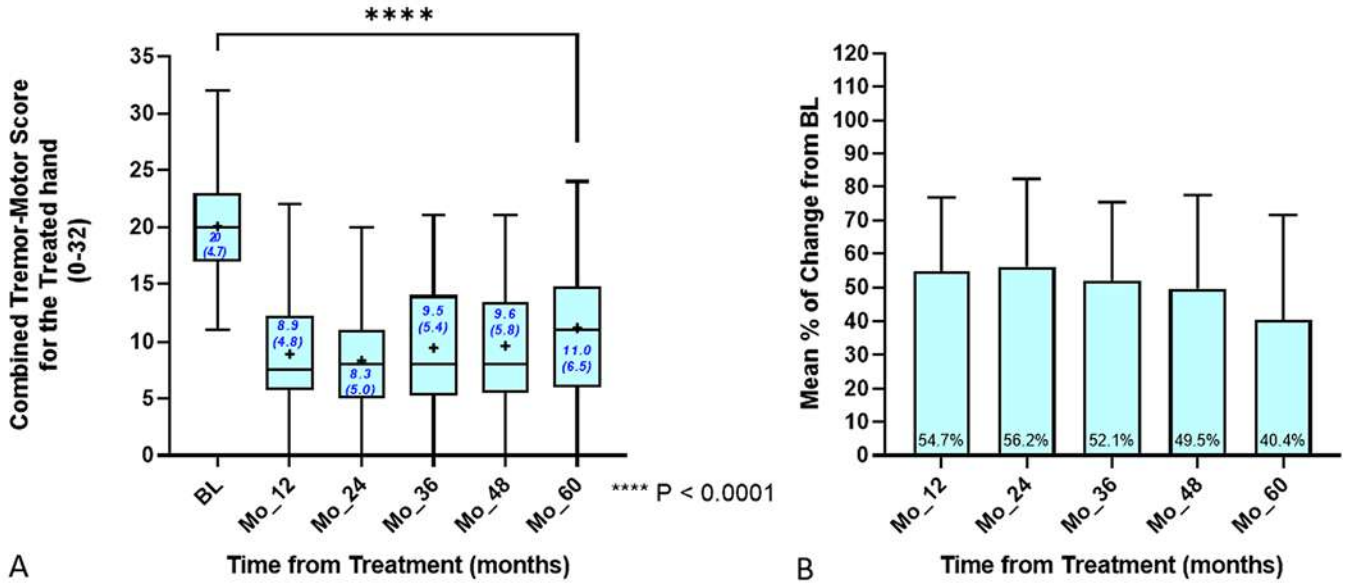


FIG. 1. A: Observed change in CRST Part A (postural tremor) scores from baseline (BL) at the annual follow-up, calculated by separate t-tests per visit. Boxes indicate medians with interquartile ranges; whiskers, ranges; and plus signs, means. The mean score values (standard deviations) are noted in blue type. B: Mean observed change in CRST Part A (postural tremor) scores from baseline at the annual follow-up. Mo = month. Figure is available in color online only.

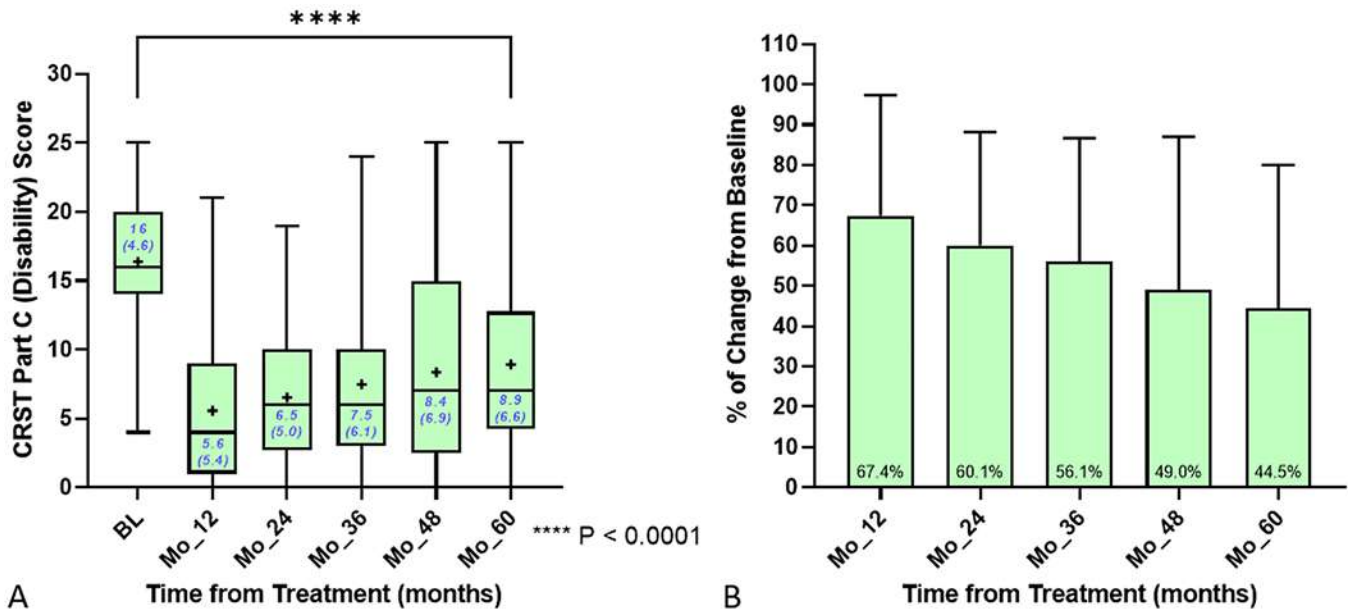


**FIG. 2. A:** Observed change in CRST Parts A and B (tremor/motor) scores from baseline at the annual follow-up, calculated by separate t-tests per visit. Boxes indicate medians with interquartile ranges; whiskers, ranges; and plus signs, means. The mean score values (standard deviations) are noted in blue type. **B:** Mean observed change in CRST Parts A and B (tremor/motor) scores from baseline at the annual follow-up. Figure is available in color online only.

**Safety Results**

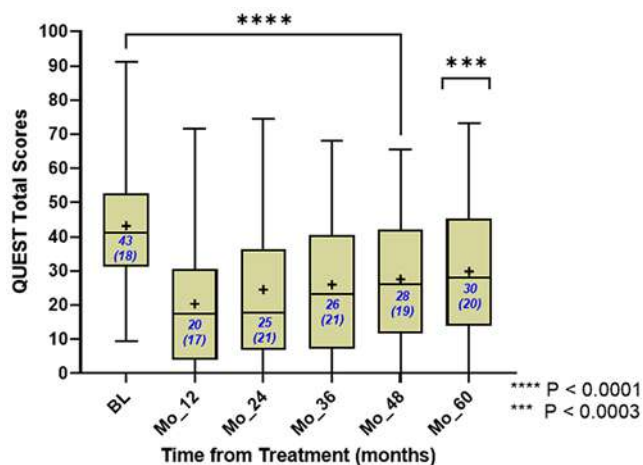
AEs were collected and recorded for all 76 study patients who had enrolled and randomized in the original trial.<sup>2</sup> At each follow-up visit, patients were evaluated for any new AEs and the severity of existing AEs was assessed. Two of the patients in the original ExAblate treatment group<sup>2</sup> underwent an additional (open label) MRgFUS

procedure during the 1st follow-up year because of technical issues that had prevented completion of the first procedure, and one of the sham-group patients did not cross over to the treatment arm (n = 19). The number of treatments (n = 77) was used to evaluate safety, rather than the number of enrolled patients (n = 76) or the number of patients who underwent MRgFUS as part of the study (n = 75).



**FIG. 3. A:** Observed change in CRST Part C (disability) scores from baseline at the annual follow-up, calculated by separate t-tests per visit. Boxes indicate medians with interquartile ranges; whiskers, ranges; and plus signs, means. The mean score values (standard deviations) are noted in blue type. **B:** Mean observed change in CRST Part C (disability) scores from baseline at the annual follow-up. Figure is available in color online only.





**FIG. 4.** Observed change in total QUEST scores from baseline at the annual follow-up, calculated by separate t-tests per visit. Boxes indicate medians with interquartile ranges; whiskers, ranges; and plus signs, means. The mean score values (standard deviations) are noted in blue type. Figure is available in color online only.

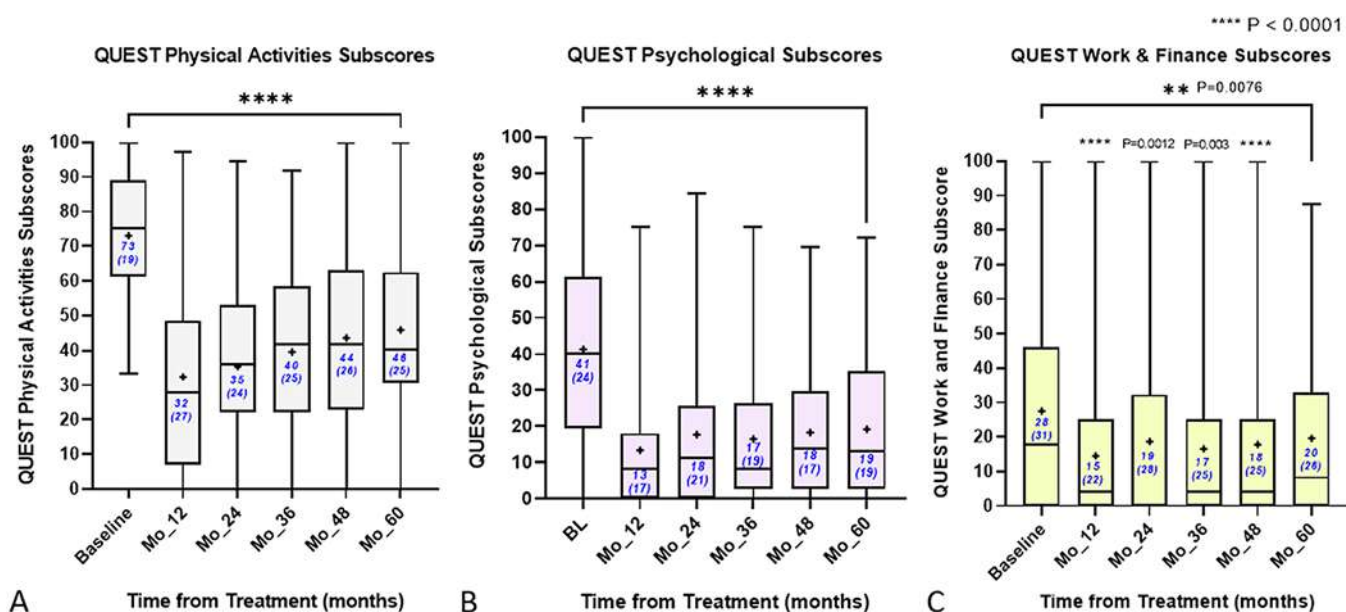
There were no serious AEs recorded at 5 years. All recorded AEs at the 4- and 5-year follow-ups were classified as mild (71%) or moderate (29%) by the study investigators. There were no new AEs related to or probably related to the procedure from the 12-month time point to the last follow-up at 5 years. Overall, at completion of the 5-year follow-up, the remaining AEs included paresthesia (8 patients), imbalance (6), unsteadiness (2), gait disturbances (2), limb weakness (2), dysmetria (2), dysgeusia (2), slow movements (1), and head pressure (1).

## Discussion

The most common surgical approach for intractable disabling tremor has been thalamic DBS. The obvious advantages of DBS include its adjustability for optimizing efficacy and minimizing adverse effects as well as its feasibility for bilateral treatment. However, some disadvantages of DBS include the need for ongoing adjustment, battery replacement, device-related issues, and the surgical risks of intracranial bleeding and infection. Patients with significant medical illness, elderly patients, or patients who are unwilling to have an invasive neurosurgical procedure with permanently implanted hardware might consider MRgFUS as an appropriate alternative to DBS if the safety and efficacy profiles were similar.

This study represents the longest follow-up reported for MRgFUS thalamotomy and one of the largest multicenter cohorts at 5 years for thalamotomy of any method. The CRST Part A (posture) scores and the combined Parts A and B (tremor/motor) scores represent a specific and relatively isolated assessment of overall tremor control. The significant and sustained improvements over this extended time period demonstrate the effectiveness and durability of the technique, results comparable in magnitude with the tremor control effectiveness reported 5 years after unilateral DBS.<sup>6,7</sup>

As in the 3-year report and consistent with our understanding of the mechanism of the technique, no latent AEs were reported during this additional 2 years of follow-up. Any persistent AEs remained mild or moderate with none rising to the level of serious. This safety profile appears similar to or at least no worse than that for DBS. Furthermore, this cohort represents the initial results of performing MRgFUS thalamotomy in these investigators' hands,



**FIG. 5.** Observed change in QUEST dimension subscores from baseline at the annual follow-up, calculated by separate t-tests per visit. Boxes indicate medians with interquartile ranges; whiskers, ranges; and plus signs, means. The mean score values (standard deviations) are noted in blue type. Graphs are shown only for the significant dimension outcomes. Figure is available in color online only.

and Krishna et al. have shown that, with experience, treatment outcomes and safety profiles improve.<sup>8</sup>

The improvement of the physical and psychological dimensions of the QUEST is consistent with the CRST Part A (posture) and CRST Parts A and B (tremor/motor) results and signals a clinically meaningful improvement in quality of life.

The results of the CRST Part C and other dimensions of the QUEST reflect a more global measure of function and quality of life, less specific to tremor control. While both showed persistent improvement from baseline, the gradual decline and decreasing statistical significance may be expected in an elderly cohort with comorbidities over 5 years. A gradual decline in DBS effectiveness and quality of life over time has also been reported.<sup>9</sup>

The primary limitation of the present study is the loss of patient follow-up at 4 and 5 years. However, only 1 of the 7 patients who exited the study at the 4th year underwent an alternative treatment (DBS); all others left because of concomitant unrelated health issues and an inability to travel because of the coronavirus disease 2019 outbreak.

Recent systematic reviews and meta-analyses have demonstrated that MRgFUS thalamotomy appears to be as effective as thalamic DBS in the treatment of unilateral tremor.<sup>10,11</sup> Investigation of bilateral staged MRgFUS thalamotomy for ET is ongoing, with small case series suggesting the feasibility of this approach.<sup>12,13</sup> Interestingly, as the adoption rate of MRgFUS has continued to rise, there has been no apparent reduction in DBS procedures for ET, suggesting that MRgFUS represents an appealing, noninvasive option among an underserved population.<sup>14</sup>

## Conclusions

Unilateral MRgFUS thalamotomy is an effective treatment for patients with intractable ET and demonstrates significant durability over the long term. The sustained therapeutic benefit reported herein versus the modest rate of persistent mild or moderate AEs makes MRgFUS an attractive treatment option for patients with disabling and medication-refractory ET.

## References

- Elias WJ, Huss D, Voss T, et al. A pilot study of focused ultrasound thalamotomy for essential tremor. *N Engl J Med*. 2013;369(7):640-648.
- Elias WJ, Lipsman N, Ondo WG, et al. A randomized trial of focused ultrasound thalamotomy for essential tremor. *N Engl J Med*. 2016;375(8):730-739.
- Halpern CH, Santini V, Lipsman N, et al. Three-year follow-up of prospective trial of focused ultrasound thalamotomy for essential tremor. *Neurology*. 2019;93(24):e2284-e2293.
- Chang JW, Park CK, Lipsman N, et al. A prospective trial of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: results at the 2-year follow-up. *Ann Neurol*. 2018;83(1):107-114.
- Tröster AI, Pahwa R, Fields JA, Tanner CM, Lyons KE. Quality of life in Essential Tremor Questionnaire (QUEST): development and initial validation. *Parkinsonism Relat Disord*. 2005;11(6):367-373.
- Pahwa R, Lyons KE, Wilkinson SB, et al. Long-term evaluation of deep brain stimulation of the thalamus. *J Neurosurg*. 2006;104(4):506-512.
- Zhang K, Bhatia S, Oh MY, Cohen D, Angle C, Whiting D. Long-term results of thalamic deep brain stimulation for essential tremor. *J Neurosurg*. 2010;112(6):1271-1276.
- Krishna V, Sammartino F, Cosgrove R, et al. Predictors of outcomes after focused ultrasound thalamotomy. *Neurosurgery*. 2020;87(2):229-237.
- Paschen S, Forstenpointner J, Becktepe J, et al. Long-term efficacy of deep brain stimulation for essential tremor: An observer-blinded study. *Neurology*. 2019;92(12):e1378-e1386.
- Harary M, Segar DJ, Hayes MT, Cosgrove GR. Unilateral thalamic deep brain stimulation versus focused ultrasound thalamotomy for essential tremor. *World Neurosurg*. 2019;126:e144-e152.
- Giordano M, Caccavella VM, Zaed I, et al. Comparison between deep brain stimulation and magnetic resonance-guided focused ultrasound in the treatment of essential tremor: a systematic review and pooled analysis of functional outcomes. *J Neurol Neurosurg Psychiatry*. 2020;91(12):1270-1278.
- Martínez-Fernández R, Mahendran S, Pineda-Pardo JA, et al. Bilateral staged magnetic resonance-guided focused ultrasound thalamotomy for the treatment of essential tremor: a case series study. *J Neurol Neurosurg Psychiatry*. 2021;92(9):927-931.
- Iorio-Morin C, Yamamoto K, Sarica C, et al. Bilateral focused ultrasound thalamotomy for essential tremor (BEST-FUS Phase 2 Trial). *Mov Disord*. 2021;36(11):2653-2662.
- Iorio-Morin C, Hodaie M, Lozano AM. Adoption of focused ultrasound thalamotomy for essential tremor: why so much fuss about FUS? *J Neurol Neurosurg Psychiatry*. 2021;92(5):549-554.
- Fahn S, Tolosa E, Marin C. Clinical rating scale for tremor. In: Jankovic J, Tolosa E, eds. *Parkinson's Disease and Movement Disorders*. Williams & Wilkins; 1993:271-280.

## Disclosures

Drs. Cosgrove, Ghanouni, Eisenberg, and Santini received clinical or research support from InSightec for the study described. Dr. Lozano is a consultant for Medtronic, Abbott, Boston Scientific, and Insightec and the scientific director for Functional Neuromodulation. Dr. Ghanouni is a consultant for InSightec and SonALASense. Dr. Taira is a consultant for and receives honoraria from InSightec Japan. Dr. Santini receives support from Biogen and Genentech for non-study-related clinical or research effort and receives honoraria from the American Academy of Neurology and International Parkinson and Movement Disorder Society. Dr. Hynynen receives royalties from InSightec. Dr. Elias is a consultant for InSightec.

## Author Contributions

Conception and design: Elias. Acquisition of data: Cosgrove, Lipsman, Lozano, Chang, Halpern, Ghanouni, Eisenberg, Fishman, Taira, Schwartz, McDannold, Hayes, Ro, Shah, Gwinn, Santini, Elias. Analysis and interpretation of data: Cosgrove. Drafting the article: Cosgrove, McDannold. Critically revising the article: Cosgrove, Lipsman, Lozano, Halpern, McDannold, Hayes, Elias. Reviewed submitted version of manuscript: Cosgrove, Lipsman, Lozano, Chang, Halpern, Ghanouni, Eisenberg, Fishman, Taira, Schwartz, Hayes, Ro, Shah, Gwinn, Santini, Hynynen, Elias. Approved the final version of the manuscript on behalf of all authors: Cosgrove.

## Correspondence

G. Rees Cosgrove: Brigham and Women's Hospital, Harvard Medical School, Boston, MA. rcosgrove2@bwh.harvard.edu.