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Magnetic resonance-guided focused ultrasound treatment for essential tremor shows sustained efficacy: a meta-analysis

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ORIGINAL ARTICLE

Magnetic resonance-guided focused ultrasound treatment for essential tremor shows sustained efficacy: a meta-analysis

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Abstract

Although magnetic resonance-guided focused ultrasound (MRgFUS) is a viable treatment option for essential tremor, some studies note a diminished treatment benefit over time. A PubMed search was performed adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies were included if hand tremor scores (HTS), total Clinical Rating Scale for Tremor (CRST) scores, or Quality of Life in Essential Tremor Questionnaire (QUEST) scores at regular intervals following MRgFUS treatment for essential tremor were documented. Data analyses included a random effects model of meta-analysis and mixed-effects model of meta-regression. Twenty-one articles reporting HTS for 395 patients were included. Mean pre-operative HTS was 19.2 ± 5.0. Mean HTS at 3 months post-treatment was 7.4 ± 5.0 (61.5% improvement, $p < 0.001$). Treatment effect was mildly decreased at 36 months at 9.1 ± 5.4 (8.8% reduction). Meta-regression of time since treatment as a modifier of HTS revealed a downward trend in effect size, though this was not statistically significant ($p = 0.208$). Only 4 studies included follow-up ≥ 24 months. Thirteen included articles reported total CRST scores with standardized follow-up for 250 patients. Mean pre-operative total CRST score decreased by 46.2% at 3 months post-treatment ($p < 0.001$). Additionally, mean QUEST scores at 3 months post-treatment significantly improved compared to baseline ($p < 0.001$). HTS is significantly improved from baseline ≥ 24 months post-treatment and possibly ≥ 48 months post-treatment. There is a current paucity of long-term CRST and QUEST score reporting in the literature.

Keywords Essential tremor · Focused ultrasound · MRgFUS · Thalamotomy · Meta-analysis

Introduction

Essential tremor (ET) is a relatively benign condition characterized by an idiopathic, progressive tremor of the upper extremities [17]. Yet, patients suffering from ET (particularly medication-refractory ET) report debilitation and embarrassment and have high concomitant rates of depression and anxiety [20, 31, 44]. Thus, patients seek treatment to improve daily life. First-line treatment includes medications such as propranolol and primidone [17]. If medical management fails, patients may be referred for radiofrequency thalamotomy, gamma knife thalamotomy, or deep brain stimulation (DBS). These procedures are relatively low risk, but the associated adverse events can be severe (e.g., hemiparesis, paresthesias, and intracranial hemorrhage) [11, 26, 43]. Additionally, DBS electrode placement requires skin incision and confers risk of soft tissue infections and hemorrhage [11, 26]. Approved by the United States Food and Drug Administration (FDA) in 2016, magnetic resonance-guided focused ultrasound (MRgFUS) is a stereotactic modality that mitigates many surgical risks. However, the long-term benefit of this treatment remains undetermined.

Ultrasound is gaining favor across many medical specialties for its low cost, availability, and lack of ionizing radiation. Previous inability of ultrasound to traverse the calvarium traditionally limited its utility in neurosurgery; however, advanced algorithms coordinate multiple emission points via

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a phased transducer array to enable ultrasound waves to be effectively focused through bone to a single anatomic location [24]. The kinetic energy of focused ultrasound waves elevates tissue temperature and causes cell death within a well-defined lesion. Magnetic resonance targeting of focused ultrasound confers significant lesioning accuracy. Additionally, MRgFUS does not require craniotomy, skin incision, or general anesthesia, and thereby minimizes surgical complications, recovery periods, and resource utilization [18].

Despite these advantages, MRgFUS has several notable weaknesses. MRgFUS thalamotomy is only FDA approved for unilateral treatment of essential tremor. This limitation is intended to prevent serious adverse effects, though bilateral MRgFUS thalamotomy is performed (in small samples) safely and effectively for research [1, 21]. A series of stereotactic thalamotomy describes persistent dysarthria in 6% of unilateral procedures and 27% bilaterally, suggesting an effect-modifying relationship. Interestingly, a recent meta-analysis by Giordano et al. describes a similar value of speech disturbances (5.5%) for unilateral focused ultrasound thalamotomies [13]. Giordano et al.'s comparisons of unilateral DBS and MRgFUS showed no significant difference in treatment effect but a difference was observed between unilateral MRgFUS and bilateral DBS. Additionally, thalamotomy is a static and permanent procedure, whereas DBS electrodes may be adjusted or turned off as needed. Patients with low skull density ratios (SDR) may not benefit from MRgFUS due to ultrasound wave impedance. The American Society for Stereotactic and Functional Neurosurgery listed SDRs < 0.4 as a contraindication to MRgFUS in their position statement published December 2019 [40]. Interestingly, data published the same year suggests that SDR is a poor predictor of MRgFUS outcome and that skull shape and volume are more relevant indicators of patient response [2, 5, 6].

Initial reports suggest a possibly diminished effect of MRgFUS after greater follow-up periods. This decrease may be clinically important and especially apparent between 3 months and 1 year post-operatively [8, 9, 28, 46]. Several scales have been designed to measure efficacy of treatment and quality of life in patients suffering from ET. The Clinical Rating Scale for Tremor (CRST) is a reliable and sensitive tool for evaluating ET severity [7]. CRST consists of part A (assessing global tremor severity), part B (action tremors of the upper extremity), and part C (tremor interference with daily activities). Hand tremor score (HTS) is a modified 32-point score derived from parts A and B of the CRST. HTS is used to standardize the pre- and post-operative evaluation of hand-specific ET symptoms [9]. The Quality of Life in Essential Tremor Questionnaire (QUEST) score is a standardized number that quantifies ET's impact on patient well-being. Though QUEST scores are subjectively dependent on an individual patient's experience, they are an important tool for evaluating ET severity, particularly before and after treatment [7]. Previously published meta-analyses did not evaluate MRgFUS effects beyond 1 year. Therefore, existing evaluation of treatment efficacy beyond 1 year is limited to individual studies.

Our primary goal is to evaluate the prevalence of worsening tremor after treatment with MRgFUS via longitudinal analysis of CRST, QUEST, and HTS metrics. We pool reported effects at commonly reported follow-up time points and utilize a meta-regression technique to explore long-term trends. To our knowledge, this is the first meta-analysis to include several years of follow-up data. Our results are intended to inform movement disorder specialists and neurosurgeons when selecting appropriate treatment modalities for medication-refractory ET.

Materials and methods

Database query and study selection

We searched the PubMed database using the search string "("magnetic resonance guided focused ultrasound" OR "MRgFUS" OR "focused ultrasound") AND ("essential tremor")." We followed Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines for meta-analysis [36] to systematically review titles, then abstracts, and eventually full texts of returned articles based on the following inclusion criteria:

1) At least some of the reported data must describe patients who received MRgFUS treatment for patients with a diagnosis of ET.
2) The data for ET patients must be presented separately from the data for patients with other included diseases (chiefly, Parkinson's disease).
3) Reported relevant data must include total CRST scores, QUEST scores, or HTS prior to and at regularly scheduled intervals after MRgFUS lesioning.
4) Data must be presented alongside measures of variance to enable calculation of Hedges' g as a measure of effect size.

Only one report from studies with multiple associated publications was included in the analyses at each time point, to eliminate duplicated data. For these studies, data was only included if separate cohorts or time points were distinct from other overlapping studies. We relied on clear author disclosure of association, identical reported values with common authors, and database searches for reported clinical trial associated publications to identify studies with multiple publications. Several studies reported "hand tremor scores" that

were not consistent with the previously described 32-point scale. We excluded these studies from the analysis.

Statistical analysis

Statistical analyses were conducted using the R programming language and software environment for statistical computing and graphics (R core team 2013). We grouped and separated data based on follow-up time points and clinical scales (HTS, CRST, QUEST). Means and standard deviations of clinical scale values were pooled via the method included in Cochrane Handbook for Systematic Reviews of Interventions ("7.7.3.8 Combining Groups"), separate from our random effects model [19]. For the random effects model, all MRgFUS treatment effect sizes were calculated from reported data as the standardized mean difference (Hedges' g) at 3 months, 12 months, and 24 months post-operatively where data and statistical power permitted. We estimated between-study variance using the DerSimonian-Laird method and between-study heterogeneity using Cochran's Q (χ^2) and I^2 values. Univariate meta-regression was performed using a mixed-effects model to evaluate whether time since MRgFUS treatment (in months) is a significant moderator of treatment effect size. Meta-regression was performed for HTS values from 3 to 48 months post-treatment, as well as for a sub-cohort of HTS values from 12 to 48 months post-treatment. Meta-regression was not performed for CRST and QUEST values due to lack of long-term data (≥ 12 months follow-up) for these values. P values ≤ 0.05 were considered significant.

Results

Literature search

Details of our literature search may be reviewed in Fig. 1. Our literature search returned 173 articles from the PubMed database. Examination of sources cited in other studies identified 4 additional publications meeting inclusion criteria. The abstract/title review eliminated 123 articles; 54 articles underwent subsequent full-text review. Final meta-analyses included 21 articles. A failure to report data in a usable format or reporting of HTS/CRST/QUEST scores without corresponding pre-MRgFUS controls eliminated 21 studies. Additionally, our search identified 2 studies focusing on Parkinson's disease rather than ET. Poorly defined follow-up periods for individual patients eliminated 1 additional study, as this prevented data aggregation into precise time points for meta-analysis. Failure to report standard deviations

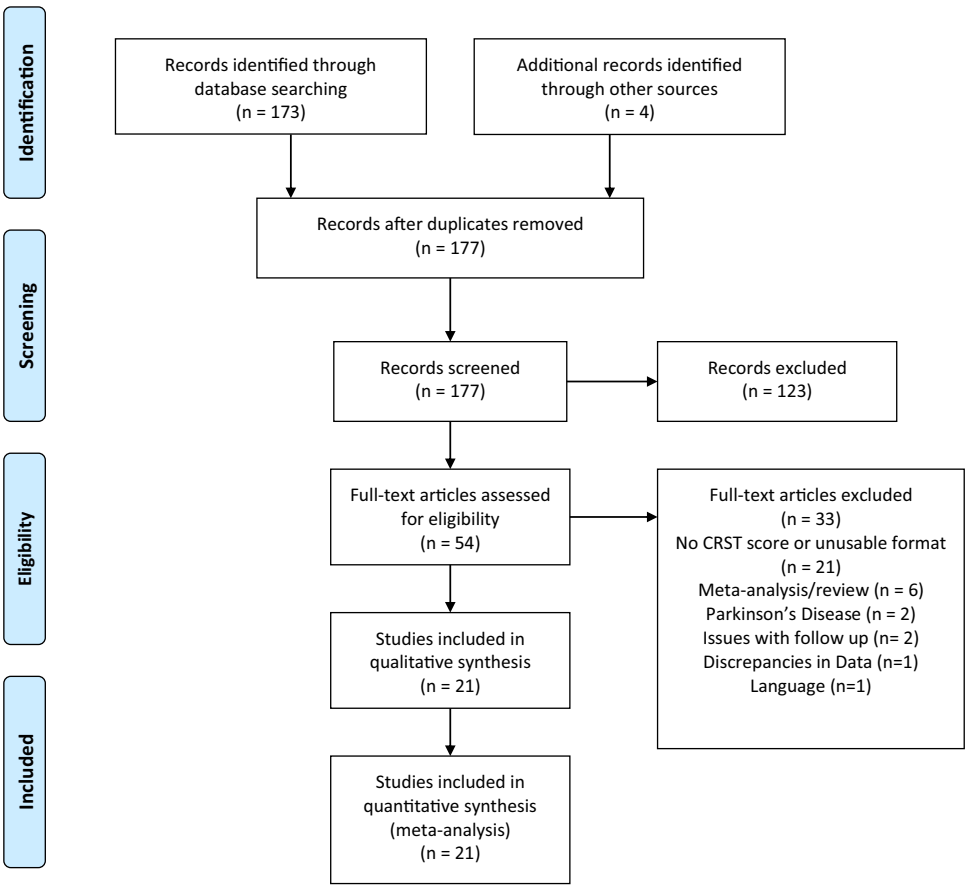

Fig. 1 Displays the PRISMA flow-chart describing the results of the literature search performed

with CRST scores and minor discrepancies between values reported in the manuscript body and study tables also excluded 1 study each. Two studies reported hand tremor scores inconsistent with the 32-point scale outlined in our methods; of these, 1 study reported total CRST scores which permitted its inclusion in total CRST analysis only.

Of the studies included, one (Elias et al. 2016) was a prospective, randomized controlled trial representing level II evidence. Twenty studies used pre-treatment values as controls; seventeen were prospective and three were retrospective, each representing level III evidence [32]. Papers included featured primary authors (in alphabetical order) from Argentina, Canada, Israel, South Korea, Spain, Switzerland, and the USA.

Baseline information

The baseline and demographics data from included studies is displayed in Table 1. The analysis included 395 patients after removal of duplicate data. The majority of treated patients were male (70%). The mean age of treated patients was 70.2 ± 8.9 years and the mean symptom duration before MRgFUS treatment was 21.2 ± 16.9 years. During MRgFUS treatment, the mean maximum peak tissue temperature was 56.5 ± 2.5 °C and the mean peak energy was 15.57 ± 7.4 kJ.

Hand tremor scores

Six studies reported HTS follow-up data after 3 months, 9 studies after 12 months, and 4 studies after 24 months (Table 2). After removal of duplicate data, we included 8 studies at the 12-month time point and 3 studies at the 24-month time point. Weighted mean pre-operative HTS values (19.2 ± 5.0) decreased to 7.4 ± 5.0 after 3 months; subsequently, weighted mean HTS increased to 7.8 ± 4.9 after 6 months, 8.3 ± 5.3 after 12 months, 9.0 ± 5.3 after 24 months, and 9.1 ± 5.4 after 36 months. Halpern et al. and Park et al. each reported 36 months of follow-up data, but only Park et al. published HTS data at the 48-month time point (7.7 ± 4.1). This 48-month value is lower than our calculated HTS means for earlier time points but is elevated over their reported intra-study values for earlier time points.

The crossover and sham procedure arms of Elias' 2016 study and follow-up studies (Chang and Halpern) are included in this table. However, these studies (denoted by *) were not included in meta-analyses at overlapping follow-up times. Similarly, these values were not used in calculating the pooled mean and standard deviations.

The pooled standardized mean difference of the random effects model (overall effect) compared to pre-treatment HTS values was 2.68 (95% CI: 1.94–3.41; $\chi^2 = 19.34$, $p < 0.01$) at the 3-month time point, 2.44 (95% CI: 1.97–2.91; $\chi^2 = 17.31$, $p < 0.01$) at the 12-month time point, and 2.18 (95% CI: 1.50–2.86, $\chi^2 = 5.77$, $p = 0.06$) at the 24-month time point (Fig. 2A–C). All p values for pooled effects were < 0.001, indicating a significant difference in HTS from baseline to follow-up at all analyzed time points. Calculation of Cochran's Q-statistic (χ^2) suggested significant between-study heterogeneity at both the 3- and 12-month time points ($p < 0.01$). χ^2 was not significant at the 24-month time point ($p = 0.06$), but this measure is significantly dependent on sample size, which was quite small for this time point (4 individual studies, $n = 146$ patients). I^2 values further supported moderate to significant heterogeneity at all time points (65–79%) (Fig. 2).

We conducted meta-regression analysis of HTS values to further investigate a correlation between MRgFUS effect size and time from 3 to 48 months post-treatment (Fig. 3). Univariate analysis suggested a statistically non-significant trend of decreased effect size (Hedges' g) with increased follow-up times ($p = 0.208$). A separate meta-regression investigating effect size trend from 12 to 48 months post-treatment revealed a similar result and failed to demonstrate a statistically significant correlation ($p = 0.489$). This subcohort analysis was performed to assess sustained effects specifically after the 12-month time point as suggested by recent literature [33].

Total CRST scores

Nine studies reported follow-up total CRST scores at the 3-month time point, 5 studies at the 6-month time point, and 6 studies at the 12-month time point (Table 3). No included studies reported total CRST scores after 12 months. The pooled mean for pre-operative total CRST scores was 53.6 ± 16.3 which decreased to 28.8 ± 13.6 at 3 months. Contrary to HTS, a diminished effect from 3 months follow-up was not observed in the mean CRST values at 6 and 12 months (25.7 ± 15.5 and 26.8 ± 14.6, respectively).

The pooled standardized mean difference of the random effects model (overall effect) of the total CRST scores was 1.86 (95% CI: 1.51–2.21; $\chi^2 = 10.25$, $p = 0.17$) after 3 months and 2.24 (95% CI: 1.55–2.94; $\chi^2 = 21.79$, $p < 0.01$) after 12 months (Fig. 2D–E). Again, pooled effect sizes were significant for both 3- and 12-month periods ($p < 0.001$), indicating a significant difference between pre- and post-MRgFUS total CRST scores.

QUEST scores

Six studies reported QUEST scores as a quality of life measure in patients with ET (Table 4). Pooled pre-operative QUEST score was 48.2 ± 22.4 which improved to 24.9 ± 18.2 at 3 months. The pooled standardized mean difference of our random effects model (overall effect) of QUEST scores at 3 months follow-up was 1.67 (95%

Table 1 Displays the baseline and demographic data and their pooled means and standard deviations (not from our random effects model)

Study	Mean age (years)	N =	Prospective/ retrospective	Lesion site	% male	Symptom duration (years)	Mean sonication number	Mean peak temperature (°C)	Mean peak energy (KJoules)
Lipsman 2013 [30]	70.8 ± 9.0	4	Prospective	ViM	100	17.8 ± 8.2	22.5 ± 7.6	59.3 ± 2.9	
Elias 2013 [8]	66.6 ± 8.0	15	Prospective	ViM	66.7	32 ± 21.3	17.9 ± 4.6	58.5 ± 2.5	10.30 ± 4.55
Wintermark 2014 [47]	67 ± 8.0	15	Prospective	ViM	66.7		18	59 ± 3.0	
Wintermark 2014 [48]	67 ± 8.0	14	Prospective	ViM	66.7				
Gallay 2016 [12]	69.1 ± 9.2	21	Prospective	CTT	71	29.9 ± 15.0			16.07 ± 6.04
Elias 2016 [9]	70.8 ± 8.7	56	Prospective*	ViM	66	28.3 ± 16.4	18.5 ± 5.2	55.6 ± 2.2	14.50 ± 6.70
Crossover/ Sham	71.4 ± 7.3	20			75	27.9 ± 14.9	N/A	N/A	
Zaroor 2018 [49]	68.9 ± 8.3	18	Prospective	ViM		12.1 ± 8.9	21.0 ± 6.9	56.5 ± 2.2	12.50 ± 4.27
Federau 2018 [10]	78.0 ± 6.0	7	Retrospective	ViM	71		18.6 ± 5.7		
Chang, JW 2018 [4]	71.0 ± 8.3	76	Prospective	ViM	68	16.8 ± 12.3	18.5 ± 5.2	55.6 ± 2.3	14.50 ± 6.70
Harary 2018 [15]	67.7 ± 6.3	7	Prospective	ViM	71	32 ± 17			
Iacopino 2018 [22]	65.2 ± 11.9	13	Prospective	ViM	76.9	22.4 ± 22.6			
Jung 2018 [25]	64.1	20	Prospective	ViM	85	21.2	16.8	57.9	15.91 ± 5.70
Krishna 2019 [27]	70.8	10	Prospective	ViM	60	34.3 ± 22.1	13.9 ± 4.5		
Tian 2018 [46]		8	Prospective	ViM					
Meng 2018 [33]	71.4	37	Prospective	ViM	21.6	22.3 ± 14.0			
Boutet 2018 [3]	72.4 ± 8.4	66	Retrospective	ViM	71	23		56.6 ± 2.3	
Park 2019 [37]	61.7 ± 8.1	12	Prospective	ViM	83.3	17.8 ± 13.0	17.3 ± 1.6		15.55 ± 6.57
Pineda-Pardo 2019 [39]	68.0 ± 10.1	24	Prospective	ViM	70.8	18.6 ± 12.8			
Miller 2019 [34]		4	Retrospective	DRT					
Krishna 2019 (post-pivotal cohort only) [29]	71 ± 9.5	114	Prospective	ViM	70	15.4 ± 13.3	17.1 ± 5.3	56.7 ± 2.5	16.91 ± 8.34
Halpern 2019 [14]	71.0 ± 8.3	75	Prospective	ViM		16.8 ± 12.3			
Total/mean	70.2 ± 8.9	580, 395 with duplicates removed		19 ViM, 1 CTT, 1 DRT	70	21.2 ± 16.9	17.8 ± 5.4	56.5 ± 2.5	15.40 ± 7.20

CTT = cerebellothalamic tract, DRT = dentato-rubro-thalamic tract, ViM = ventral intermediate nucleus of the thalamus, *represents a randomized, controlled trial.

Only data with standard deviations were included in the mean calculations if standard deviations were calculated. Suspected duplicate data were also removed from calculations of the mean and standard deviation.

Table 2 Displays the total hand tremor scores defined for studies meeting inclusion criteria

Study	Pre-op n =	Pre-op	3 months	6 months	1 year	2 years	3 years	4 years
Elias 2013 [8]	15	20.4 ± 5.2	4.3 ± 3.5		5.2 ± 4.8			
Wintermark 2014* [48]	14	19.8 ± 5.0	4.6 ± 3.5					
Elias 2016 [9]	56	18.1 ± 4.8	9.6 ± 5.1	10.1 ± 5.3	10.9 ± 4.5			
Sham*	20	16 ± 4.4	15.8 ± 4.9					
Crossover*	21	16.5 ± 4.2	7.43 ± 3.9	8 ± 3.9	6.71 ± 4.7			
Federau 2018 [10]	6	21.5 ± 2.0			9.7 ± 5.2			
Chang 2018* [4]	76	19.8 ± 4.9		8.6 ± 4.5	8.9 ± 4.8	8.8 ± 5.0		
Krishna 2019 [27]	9	18.3 ± 4.5	6.5 ± 3.7					
Tian 2018 [46]	8	18.9 ± 2.4	9.1 ± 0.9	11 ± 3.7	11 ± 4.8			
Meng 2018 [33]	37	20.3 ± 5.0			11.7 ± 6.6	11.5 ± 6.7		
Krishna (post-pivotal group) 2019 [29]	114	19.3 ± 5.0	7.0 ± 5.0	7.4 ± 5.0	7.4 ± 4.8			
Park 2019 [37]	12	17.4 ± 3.8		5 ± 3.3	5.3 ± 3.4	6.9 ± 3.6	7.5 ± 5.3	7.7 ± 4.1
Halpern 2019* [14]	75	20.1 ± 4.7			8.9 ± 4.8	8.4 ± 5.0	9.5 ± 5.4	
Weighted mean	271 patients (with duplicates removed)	19.2 ± 5.0	7.4 ± 5.0	7.8 ± 4.9	8.3 ± 5.3	9.0 ± 5.3	9.1 ± 5.4	7.7 ± 4.1

*Denotes suspected duplicate data which were not included in meta-analyses at overlapping times.

CI:1.09–2.25, $\chi^2 = 9.65$, $p = 0.05$) (Fig. 2F). The p value for the pooled effect at 3 months was < 0.001, indicating significant improvement in QUEST score from baseline. Additionally, Halpern et al. detailed a mean 23.8 ± 19.6 QUEST score at 36 months follow-up, an increase of 2.2 over 30 months.

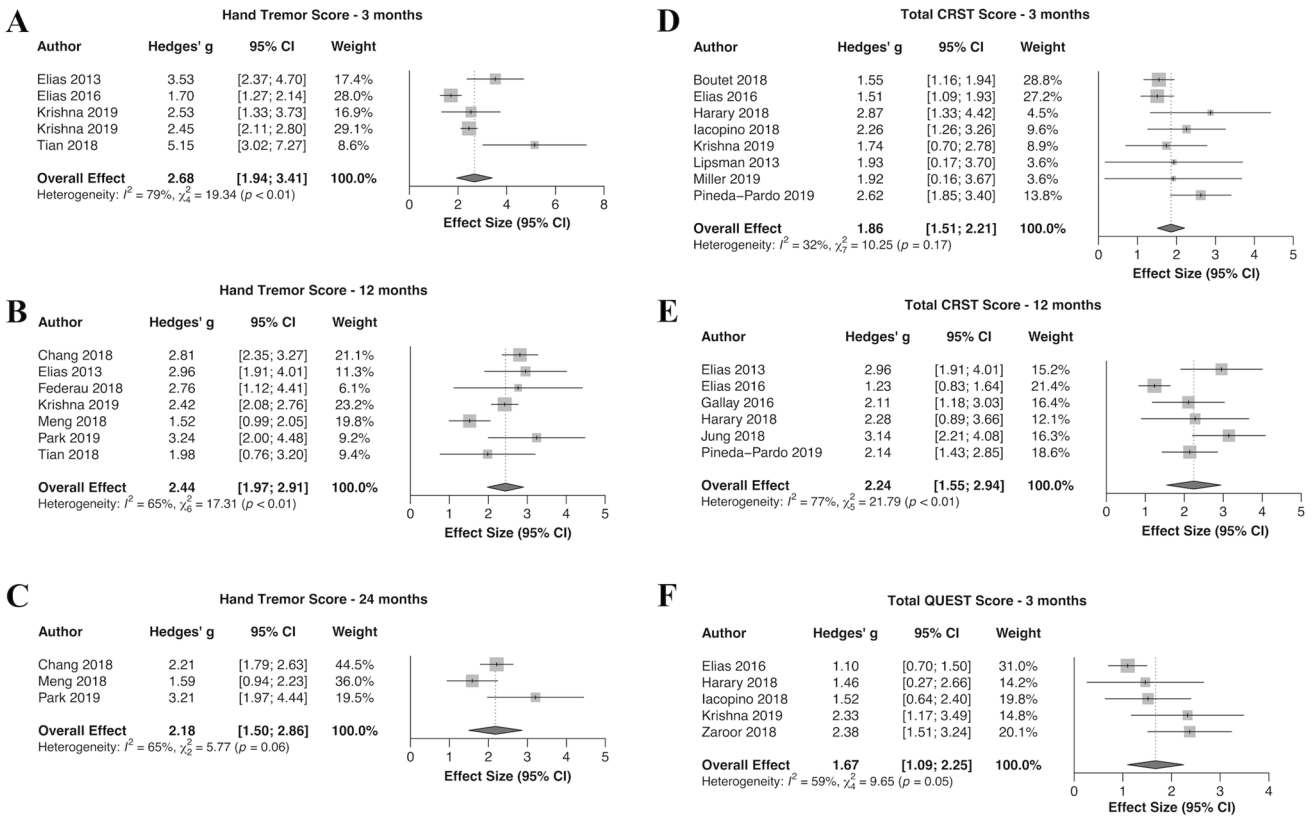

Fig. 2 Displays forest plots for; 2a. HTS at 3 months, 2b. HTS at 12 months, 2c. HTS at 24 months, 2d. Total CRST score at 3 months, 2e. Total CRST scores at 12 months and 2f. QUEST scores at 3 months post-operatively compared to baseline scores

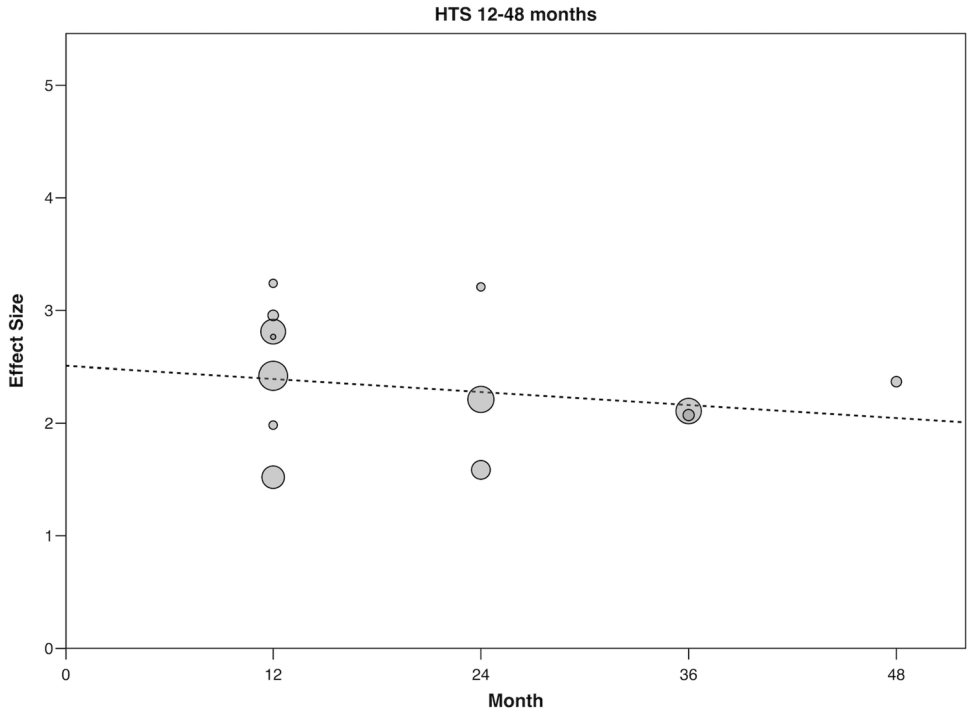

Fig. 3 Displays the meta-regression bubble plots depicting the time since treatment on the X-axis and the effect size on the Y-axis. Two meta-regressions were performed; 3a. includes measurements from 3 to 48 months ($p = 0.208$) while 3b. includes only measurements 12–48 months ($p = 0.489$)

Discussion

Elias et al.'s 2013 pilot study of MRgFUS for ET unveiled a promising addition to the functional neurosurgeon's repertoire [8]. They hoped this incisionless procedure would prove safer than DBS and current stereotactic modalities while providing long-term clinical benefit. Although numerous studies have presented MRgFUS to be a relatively safe procedure, conclusions of sustained efficacy have been limited by low sample sizes and incongruent methods.

Table 3 Displays the overall CRST scores for each study with pooled means and standard deviations (not from our random effects model)

Study	Pre-op n =	Pre-op	3 months	6 months	1 year
Lipsman 2013 [30]	4	70.8 ± 19.7	35.3 ± 11.0		
Elias 2013* [8]	15	54.9 ± 14.4			24.3 ± 14.8
Wintermark 2014* [47]	15	54.9 ± 14.4	20.3 ± 11.0		
Elias 2016 [9]	56	50.1 ± 14.0	29.6 ± 13.0	31.7 ± 14.4	32.4 ± 14.5
Sham*	20*	44.1 ± 12.7	43.1 ± 13.1		
Crossover*	21**	45.4 ± 12.6	23.5 ± 11.0	25.0 ± 11.1	18.7 ± 16.0
Gallay 2016 [12]	13	57.6 ± 13.2			25.8 ± 17.6
Zaroor 2018 [49]	18	40.7 ± 11.6		8.2 ± 5.0	
Harary 2018 [15]	7	51.4 ± 10.8	19.3 ± 10.1	20.1 ± 7.4	24.9 ± 11.0
Iacopino 2018 [22]	13	40.2 ± 11.8	17.3 ± 7.3	17.7 ± 8.8	
Jung 2018 [25]	20	44.8 ± 9.6			14.7 ± 9.2
Krishna 2019 [27]	10	59.3 ± 17.3	29.0 ± 16.0	32.0 ± 15.9	
Boutet 2018 [3]	66	59.7 ± 17.4	34.8 ± 14.4		
Pineda- Pardo 2019 [39]	24	52.9 ± 13.0	23.8 ± 8.3		26.4 ± 11.3
Miller 2019 [34]	4	57.5 ± 16.8	29.5 ± 6.4		
Weighted mean	250 patients (with duplicates removed)	53.6 ± 16.3	28.8 ± 13.6	25.2 ± 15.5	26.8 ± 14.5

*Denotes suspected duplicate data that was not included in the analysis of this paper.

Table 4 Displays the QUEST score data included in studies

Study	Pre-op n =	Pre-op	3 months	6 months	1 year	2 years	3 years
Elias 2016* [9]	56	42.6 ± 18.3	23.1 ± 16.9		21.7 ± 17.2		
Sham*	20	42.8 ± 19.5	41.4 ± 19.4				
Zaroor 2018 [49]	18	44.8 ± 12.9		12.3 ± 7.2			
Harary 2018 [15]	7	88.7 ± 20.5			55.4 ± 22.1		
Iacopino 2018 [22]	13	35.1 ± 12.3	17.1 ± 10.7				
Krishna 2019 [27]	10	81.7 ± 17.7	45.3 ± 11.6	45.6 ± 10.8			
Halpern 2019 [14]	75	43.1 ± 18.3		21.6 ± 17.6	20.0 ± 17.2	22.9 ± 19.6	23.8 ± 19.6
Weighted mean	123 patients (with duplicates removed)	48.2 ± 22.4	24.9 ± 18.2	24.7 ± 17.2	23.2 ± 20.3	22.9 ± 19.6	23.8 ± 19.6

Means and standard deviations were pooled and are not a result of our random effects model. Elias et al.'s sham procedure cohort is included for comparison but was not included in any calculations.

*Denotes suspected duplicate data that was not included in the analysis of this paper.

MRgFUS efficacy

Our analysis revealed a diminished effect from 3 to 12 and 24 months post-treatment (standardized mean difference of 2.68 to 2.44 and 2.18, respectively). Notably, Hedges' *g* (standardized mean difference) value is dependent on the standard deviation. Therefore, while the diminished effect above may seem large based on sample size (i.e., patients lost to follow-up), changes in individual outcomes may be less profound. Meta-regression illustrates a trending decrease ($p = 0.208$) which suggests a decreased treatment effect with time. Care should be taken when interpreting this trend; the insignificant *p* value indicates that time elapsed since treatment is not an accurate predictor of treatment effects but does not necessarily reflect a lack of decline over time. However, identification and control of other treatment parameters which may produce effect heterogeneity (skull shape, age, symptom duration, etc.) will theoretically enable more accurate analysis. CRST scores likely worsen with time; whether the culprit is diminished effect or disease progression is debatable. However, treatment benefit compared to pre-treatment symptoms is apparent at all follow-up times reported.

Elias et al. presented a randomized controlled trial in 2016 that demonstrated the efficacy of MRgFUS[9]; Chang et al. [4] and Halpern et al. [14] continued to follow this study cohort at 24 and 36 months post-treatment, respectively. Park et al. provided a separate analysis 48 months post-treatment [37]. Overall, these studies suggest significant benefit several years post-operatively and a small score increase with time (approximately 1–2.5 points). Extended analysis of data originally presented by Elias et al. [9] via Chang et al. [4] and Halpern et al. [14] is difficult since initial cohorts were combined in later studies and patients were lost to follow-up. Two meta-analyses recently compared MRgFUS for ET to other treatment modalities; Schreglman et al. [43] included radiofrequency and gamma knife techniques and Harary et al. [16] studied unilateral DBS placement. Both studies detail similar initial treatment effects across modalities, however, neither provide follow-up in the past 12 months.

Several studies report diminished effects of DBS over time. Rodriguez et al. report a mean tremor reduction of 71.5% within 6 months that worsened to 50.1% over ~ 7.5 years mean follow-up [41]. In a study of twenty patients, Paschen et al. report a mean tremor worsening of 0.37 points per month in CRST scores following DBS [38]. Their study included an interesting analysis of patient's CRST scores with stimulators on and off to determine 87% of decline was due to disease progression, while 13% was a result of habituation to DBS. Data presented by Park et al. suggest a 71% HTS reduction at 6 months which declined to 56% at 48 months [37]. Direct comparisons between studies are limited since they utilized different scores. Further head-to-head longitudinal comparisons of these two interventions past the 12-month time point are necessary.

Treatment parameters

We collected data regarding mean peak tissue temperature, age, and sonication numbers and performed a meta-regression based on these variables. However, few studies report uniform data; the model was fundamentally limited and therefore not included. These analyses are more appropriate for studies with individual patient data. Elias and colleague's 2016 study [9] accounts for the majority of data after 12 months, with follow-up data reported by Chang et al. [4] and Halpern et al. [14], and had a relatively low mean peak tissue temperature (55.6 ± 2.2). Interestingly, their data showed a relatively low treatment effect compared to prior studies. Therefore, long-term follow-up of patients with higher mean peak tissue temperatures may provide valuable information.

Krishna et al. recently analyzed data from 189 patients treated with MRgFUS (75 from the Elias et al. randomized trial [9] and 114 from their "post-pivotal" cohort) [28]. They identified lower sonication number, higher peak temperature, age, and disease duration as predictors of positive patient outcome. SDR was not a significant predictor and patients in the post-pivotal group (which experienced more successful outcomes) had a lower SDR (0.50 ± 0.1 vs. 0.55 ± 0.1, $p = 0.004$). Post-pivotal patients also experienced a higher number of adverse events (4 of 114, 3.5%), possibly resulting from higher tissue temperatures. However, improved outcomes in their post-pivotal cohort may also result from increased provider experience with MRgFUS. Additionally, higher mean peak tissue temperatures may reflect improved technology.

Jones et al. published an intriguing analysis of patients in whom peak temperatures greater than 55 °C could not be reached [23]. They employed multiple low temperature (50–54 °C) sonications to reach a goal accumulated thermal dose. Comparisons to their previous study yielded similar CRST hand tremor score improvements (notably, we did not include this study in our analysis due to minor discrepancies in data). However, they note that patients with the accumulated thermal dose method had smaller lesion volumes, which Meng et al. [33] correlate with lower improvements in CRST. Jones et al. suggest long-term follow-up is necessary to determine if this method is sustainable [23]. However, their technique may benefit patients traditionally considered poor candidates for MRgFUS.

Quality of life

Though relatively few studies included QUEST scores, the pooled effect size was quite large, suggesting MRgFUS significantly improves the quality of life for patients suffering from ET. We observed a bimodal distribution and large standard deviation of QUEST scores possibly emanating from their subjective nature (Table 4). Despite the challenges of subjective assessments, QUEST scores are important to consider since they reflect the patient's perspective (i.e., how has treatment improved the patient's quality of life). Mohammed et al. report a 46.5% improvement in QUEST scores in their meta-analysis (later updated to 50.7% post-publication after corresponding with Schreglman et al.) and 69.1% improvement in CRST part C (details tremor impact on daily activities) [35, 42]. Harary et al. suggest that QUEST scores are lower in patients undergoing DBS, indicating better quality of life [16]. Future studies may investigate long-term patient satisfaction after MRgFUS treatment.

Safety profile

We chose not to perform a meta-analysis of safety profiles since several meta-analyses already exist [18, 35, 43], and our primary focus was long-term follow-up. Mohammed et al. reported paresthesia (25.1%) and ataxia (32.8%) as common adverse events (AEs) at 3 months follow-up [35]. These percentages decreased to 15.3 and 10.5%, respectively, at 12 months. Schreglman et al. report persistent AEs after MRgFUS thalamotomy in 18.7% of patients [43]. Additionally, they analyzed AE rates for radiofrequency and gamma knife thalamotomy (9.3 and 1.8%, respectively). However, severe AE rates were lowest in the MRgFUS cohort (1.2% vs. 9.3% for radiofrequency and 1.8% for gamma knife).

Common perioperative complications of DBS include headache (4–15.0%), confusion (1.5–6.6%), and hallucinations (0.4–2.8%) [11, 26, 45]. Infection occurs in approximately 3.1–6.6% of cases and may require reoperation in 1.7–2.5% [11, 26]. Therefore, MRgFUS certainly has an advantage with regard to infection rates but AEs are more frequent with MRgFUS. Analysis by Harary et al. included a direct comparison of AEs; DBS resulted in speech and gait disturbances in 9.4 and 2.4% of cases at 6 months, respectively [16]. Gait disturbances occurred in 16.1% and lasted at least 12 months in 8.9% of patients undergoing MRgFUS.

Limitations

Our meta-analysis provides valuable insights into the future of MRgFUS. However, there are several notable limitations to this study. Many studies did not use uniform tremor scales or report standard deviations or confidence intervals, which prevented their inclusion in the pooled analysis. Several studies had overlapping authors and time frames. To the best of our ability, we did not include multiple studies with obvious patient overlap. Therefore, if two studies were suspected to include overlap, we did not include the study with a smaller sample size in our data analysis. However, these studies were often difficult to identify. It is possible that we included overlapping patient cohorts in our analyses despite these efforts. Power analyses of our data reported sufficient power up to 24 months, but meta-regression incorporated data past the 24-month time point. Not all time points were assessed based upon lack of sufficient reporting in the literature; namely, the lack of sufficient CRST and QUEST score reporting after 12 months post-treatment. Statistical analysis of differences in weighted mean HTS, CRST, and QUEST score values between time points was deferred due to more robust testing through pooled standardized mean difference and meta-regression analyses. Additionally, we report high levels of heterogeneity which reflect accurate modeling of a diverse population but cloud determination of effect size. We initially intended to evaluate and incorporate differences in treatment parameters (sonications, temperature, age, etc.); however, there was a lack of uniform reporting among studies. In an effort to address this variance, we utilized a random effects model of analysis. Defining factors which do predict treatment

outcomes will enable accurate determination of effect over time. Finally, meta-analyses provide valuable insights to treatment efficacies at a population level, but little information applicable to individuals. We urge providers to be cautious when applying our data to individual patients.

Conclusions

This is the first meta-analysis to examine long-term MRgFUS outcomes at follow-up time points greater than 12 months. We report HTSs are significantly improved from baseline at all follow-up points up to 24 months post-treatment, and likely up to 48 months post-treatment. Additionally, we found a decreasing trend in HTS over time. Recent data suggests skull shape, size, and accumulated thermal dose are predictors of treatment outcome. Treatment effects may theoretically be maximized by accounting for these variables. Existing data supports the hypothesis that MRgFUS benefits are sustained for several years.

Authors' contributions W.K.M.—project design, article review, data collection and manuscript composition. K.N.B.—statistical analysis, manuscript composition, and project design. A.J.C.—manuscript composition, project design, and assisted with statistical analysis. T.R.M.—manuscript composition, project design. M.T.M.—data verification and collection. M.R.—study design and manuscript editing. J.S.—study design and manuscript editing.

Data availability Not applicable

Code availability Not applicable

Declarations

Ethics Approval Not applicable

Consent to Participate Not applicable

Consent for Publication Not applicable

Conflict of interest Nothing to disclose.

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