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A Systematic Review Comparing Focused Ultrasound Surgery With Radiosurgery for Essential Tremor

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BACKGROUND: Focused ultrasound (FUS-T) and stereotactic radiosurgery thalamotomy (SRS-T) targeting the ventral intermediate nucleus are effective incisionless surgeries for essential tremor (ET). However, their efficacy for tremor reduction and, importantly, adverse event incidence have not been directly compared.
OBJECTIVE: To present a comprehensive systematic review with network meta-analysis examining both efficacy and adverse events (AEs) of FUS-T vs SRS-T for treating medically refractory ET.
METHODS: We conducted a systematic review and network meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, using the PubMed and Embase databases. We included all primary FUS-T/SRS-T studies with approximately 1-year follow-up, with unilateral Fahn-Tolosa-Marin Tremor Rating Scale or Clinical Rating Scale for Tremor scores prethalamotomy/post-thalamotomy and/or AEs. The primary efficacy outcome was Fahn-Tolosa-Marin Tremor Rating Scale A+B score reduction. AEs were reported as an estimated incidence.
RESULTS: Fifteen studies of 464 patients and 3 studies of 62 patients met inclusion criteria for FUS-T/SRS-T efficacy comparison, respectively. Network meta-analysis demonstrated similar tremor reduction between modalities (absolute tremor reduction: FUS-T: −11.6 (95% CI: −13.3, −9.9); SRS-T: −10.3 (95% CI: −14.2, −6.0). FUS-T had a greater 1-year adverse event rate, particularly imbalance and gait disturbances (10.5%) and sensory disturbances (8.3%). Contralateral hemiparesis (2.7%) often accompanied by speech impairment (2.4%) were most common after SRS-T. There was no correlation between efficacy and lesion volume.
CONCLUSION: Our systematic review found similar efficacy between FUS-T and SRS-T for ET, with trend toward higher efficacy yet greater adverse event incidence with FUS-T. Smaller lesion volumes could mitigate FUS-T off-target effects for greater safety.

KEY WORDS: HIFUFUS, MRgFUS, SRS, Thalamotomy, Essential tremor

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Essential tremor (ET) is the most common movement disorder, with a prevalence of 0.5% to 5%.[1,2] Although neuromodulation surgery such as deep brain stimulation (DBS) of the thalamus can be highly effective to reduce symptoms of medically refractory ET,[3-7] incisionless lesion-based approaches may be needed in cases where patients have contraindications to DBS. Circumstances include medical comorbidities that increase complication risks for implantation surgery, limited access to DBS programming, and patient preference.[8,9] Two common incisionless thalamotomy surgeries are stereotactic radiosurgery thalamotomy (SRS-T), also known as Gamma Knife thalamotomy, and more recently, focused ultrasound thalamotomy (FUS-T).

SRS-T and FUS-T are both permanently ablative surgeries, most commonly targeting the ventral intermediate nucleus (Vim) of the thalamus. In SRS-T, multiple radiation beams are delivered to create the lesion,[10] although real-time monitoring of symptom improvement is precluded because of delay of symptom improvement by up to 6 months.[11] By contrast, for FUS-T, ultrasound waves are delivered to heat and ablate tissue with real-time monitoring of tissue temperature using MR thermometry and clinical assessment for tremor improvement.[12,13]

ABBREVIATIONS: AEs, adverse events; **CRST,** Clinical Rating Scale for Tremor; **ET,** essential tremor; **FTM-TRS,** Fahn-Tolosa-Marin Tremor Rating Scale; **FUS-T,** focused ultrasound thalamotomy; **PRISMA,** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **SDR,** skull density ratio; **SRS-T,** stereotactic radiosurgery thalamotomy.

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Given these methodological differences, it is important to compare the relative efficacy of these incisionless modalities. Prior systematic reviews and meta-analyses comparing the 2 modalities have reported percent tremor reduction[14] and composite efficacy.[11] However, neither of these measures directly compares tremor reduction using the same rating scale, limiting conclusions.

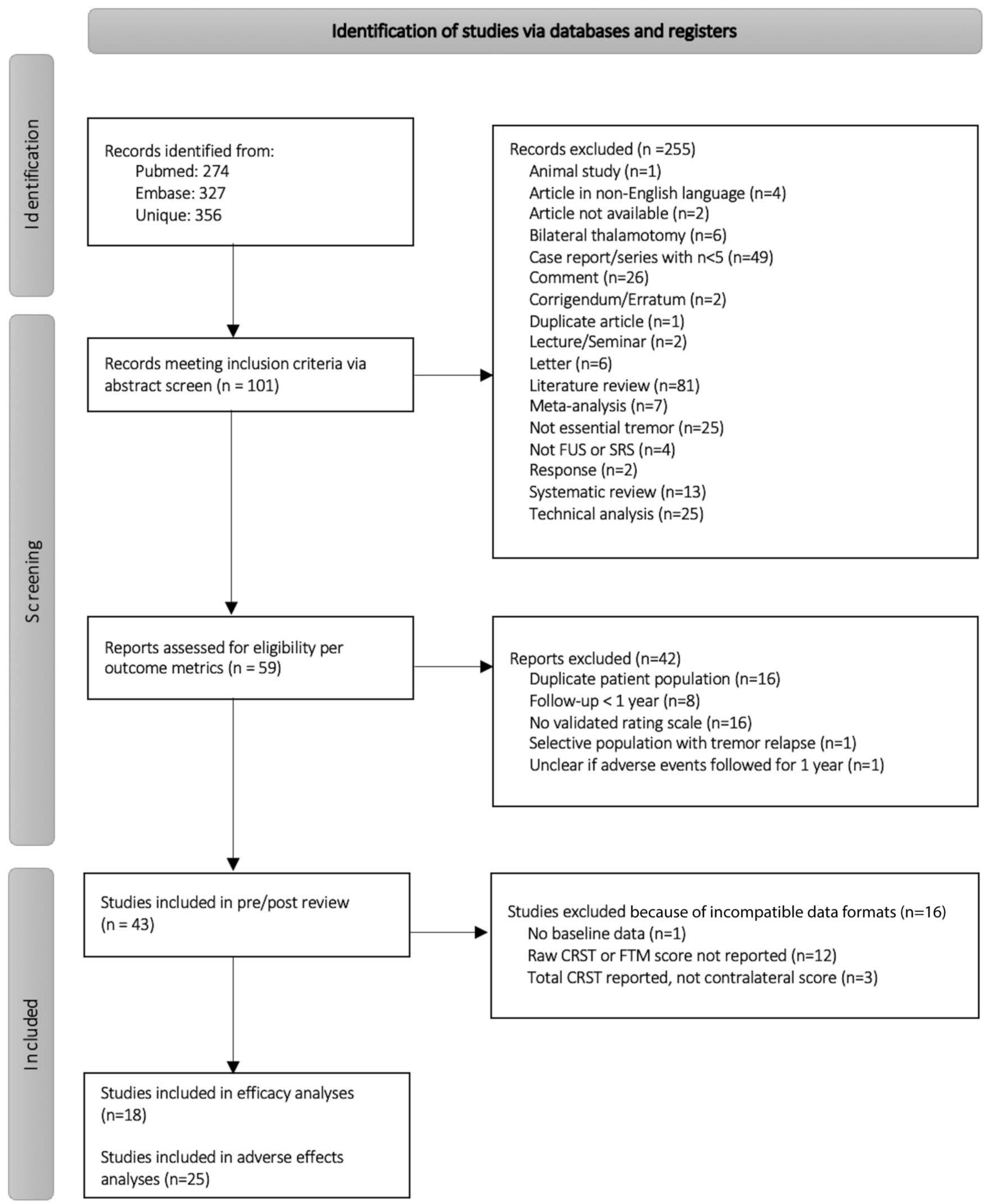

FIGURE 1. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of study identification, screening, and inclusion. CRST, Clinical Rating Scale for Tremor; FTM, Fahn-Tolosa-Marin; FUS, focused ultrasound; SRS, stereotactic radiosurgery.*

TABLE 1. Pooled Demographics for Prethalamotomy vs Post-Thalamotomy Studies with ∼12 Month Follow-up

Authors	Year	FUS or SRS	n	F/M	Age at baseline, mean, ± SD (range)	Disease duration (y), mean ± SD (range)	FTM-TRS Baseline, mean ± SD	Follow-up time (mo)	FTM-TRS at follow-up, mean ± SD	Post-treatment lesion size: volume, mm^3	ROBINS-I risk of bias assessment
S Kato, et al.[27]	2022	FUS	15	4/11	72.8 ± 5.39 (64-81)	27.6 ± 20.9 (6-65)	19 ± 3.4	6	7.7 ± 5.4	∼	Confounding
C Pae, et al.[28]	2022	FUS	85	18/67	65.3 ± 8.7 (45-86)	13.8 ± 10.6 (1-40)	18.2 ± 5.3	6	5.1 ± 5.5	242 ± 91	Confounding Selection of participants
V Purrer, et al.[29]	2022	FUS	37	12/25	69.4 ± 12.2	19.1 ± 12.0	19.2 ± 4.2	12	6.2 ± 5.0	∼	Confounding
K Yamamoto, et al.[26]	2022	FUS	53	31/69[a]	38.1 ± 20.6[a]	∼	20.4 ± 5.1[a]	12	10.7 ± 6.5	175.3 ± 93.4	Confounding Missing data
K Fukutome, et al.[32]	2021	FUS	15	4/11	62.9 ± 11.3	21.5 ± 14.0	18.5 ± 5.8	12	4.6 ± 5.7	68.0 ± 29.8	Confounding
P Wu, et al.[30]	2021	FUS	48	17/31	59.14 ± 13.5	19.2 ± 13.6	14.7 ± 4.9	12	7.0 ± 5.5	∼	Confounding
G Zur, et al.[31]	2020	FUS	22	8/14	72 ± 6	13 ± 8	19.2 ± 6.9	6	4 ± 4	∼	Confounding Selection of participants
A Sinai, et al.[33]	2019	FUS	24	17/27[a]	70.5 (63-87)[a]	16.3 ± 10.4[a]	19.5 ± 7.2[a]	12	7.0 ± 5.8	297.1 ± 128.0	Confounding Missing data
YS Park, et al.[34]	2019	FUS	15	2/10	61.7 ± 8.1	17.8 ± 13.03	17.4 ± 3.8	12	5.3 ± 3.4	82.6 ± 29.0	Confounding
C Gasca-Salas, et al.[35]	2019	FUS	23	6/17	∼	∼	16.6 ± 4.6	12	6.1 ± 4.1	∼	Confounding Selection of participants
Q Tian, et al.[36]	2018	FUS	8	∼	∼	∼	18.9 ± 2.4	12	11.0 ± 4.8	∼	Confounding
NY Jung, et al.[37]	2018	FUS	20	3/17	64.1 (47-77)	21.2 (5-54)	18.2 ± 4.0	12	5.8 ± 4.5	∼	Confounding Selection of participants
WJ Elias, et al.[38]	2016	FUS	76	24/52	70.8 ± 8.7	16.4 ± 13.1	18.1 ± 4.8	12	10.9 ± 4.5	∼	Confounding
WS Chang, et al.[39]	2015	FUS	8	1/7	66.1 ± 5.25	32.1 ± 16.1	18.1 ± 3.2	6	4.0 ± 3.5	97.9 ± 41.9	Confounding
WJ Elias, et al.[40]	2013	FUS	15	5/10	66.6 ± 8.0	32.0 ± 21.3	20.4 ± 5.2	12	5.2 ± 4.8	∼	Confounding
FUS aggregate			464	152 (29.2%)/ 368 (70.8%)[b]	63.3[b]	59.9[b]	18.3 ± 5.2[a]	10.3	7.3 ± 5.7	200.2[b]	

TABLE 1. Continued.

Authors	Year	FUS or SRS	n	F/M	Age at baseline, mean, ± SD (range)	Disease duration (y), mean ± SD (range)	FTM-TRS Baseline, mean ± SD	Follow-up time (mo)	FTM-TRS at follow-up, mean ± SD	Post-treatment lesion size: volume, mm³	ROBINS-I risk of bias assessment
TAW Bolton, et al.[41]	2022	SRS	34	17/17	70.1 ± 9.1	35.5 ± 18.3	20.4 ± 5.5	12	6.3 ± 7.7	120 ± 130	
C Tuleasca, et al.[42]	2017	SRS	17	12/5	70.1 ± 9.8	38 ± 19.5	18.6 ± 5.5	12	7.2 ± 4.1	125 ± 162	
SY Lim, et al.[43]	2010	SRS	11	2/9	75.8 ± 5.9	21.1 ± 12.7	22.0 ± 5.7	24	20.1 ± 8.4	~	Confounding
SRS aggregate			62	31 (50.0%)/ 31 (50.0%)[b]	71.1[b]	33.6	20.2 ± 5.6	14.1	9.0 ± 8.7	121.7[b]	

CRST, Clinical Rating Scale for Tremor; FTM-TRS, Fahn-Tolosa-Marin Tremor Rating Scale; FUS, focused ultrasound; SRS, stereotactic radiosurgery.
[a]From initial enrolment, exact demographics of specific sample not available.
[b]From data available. ~not reported.
CRST scores were relabeled as FTM-TRS scores.

In addition, no study has complemented analysis of tremor reduction with direct comparison of adverse effect profiles of SRS-T and FUS-T. Thus, we performed a systematic review and network meta-analysis to directly compare SRS-T and FUS-T efficacy in tremor reduction for patients with medically refractory ET, with comprehensive characterization of adverse effects for each therapy.

METHODS

Retrospective Review

Literature Search

The systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[15] This study answered the following questions: (1) What is the effect of FUS-T vs SRS-T on tremor reduction in patients with ET? (2) What are the long-term adverse effects of FUS-T vs SRS-T in patients with ET? The PubMed database search was conducted on October 6th, 2022, from inception of the database to October 2022 using the following search: "(((ET OR essential tremor) AND thalamotomy) AND ((SRS OR stereotactic radiosurgery OR GK OR gamma knife) OR (focused US OR focused ultrasound)))." We repeated this query on the Embase database on October 10th, 2022, with the same time period and search terms. In accordance with guidelines for meta-analyses comprising publicly available research reports, written informed consent from participants was not required. The data sets supporting the current study are available from the corresponding author upon reasonable request.

Study Selection

Two researchers (S.K. and A.B.S.) independently screened all titles and abstracts based on the following inclusion and exclusion criteria.[16] The inclusion criteria were (1) the study population comprised patients with only ET, (2) the patients received either unilateral SRS-T or FUS-T, and (3) tremor severity in the study was scored using a validated tremor scoring scale. Exclusion criteria were (1) all articles not available in English; (2) studies that involved animals, without any human participants; (3) technical analyses; (4) editorials; (5) literature or systematic reviews; (6) case reports or series with <5 patients; and (7) follow-up ≤3 months (Figure 1). In the case of studies with mixed patient populations (eg, patients with either ET or Parkinson disease), studies were included only when ET patient data could be reliably separated from the larger cohort. In the case where multiple studies reported the same or overlapping patient data, the study with most recent and comprehensive patient population was included.

Given the difficulty in directly comparing across different tremor scales, we then further subselected studies that used the unilateral tremor score (parts A and B) from the Fahn-Tolosa-Marin Tremor Rating Scale (FTM-TRS) or Clinical Rating Scale for Tremor (CRST), also noted as the tremor score for the treated hand (TSTH). Although referred to with different names, each of these scales record information about subcomponents of tremor on the same numerical scale; the maximum possible unilateral tremor score is 58. For inclusion in network meta-analysis, total score with standard deviation for each group needed to be reported. If a study included the median and interquartile range, the data were converted to mean and standard deviation.[17] Studies that did not meet criteria for inclusion in the network meta-analysis of efficacy were still considered for analysis if there was characterization of adverse events (AEs) after 1 year of follow-up. The results of the full process for study selection are presented in Figure 1.

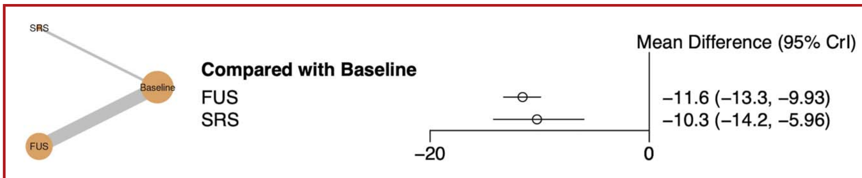

FIGURE 2. *Network meta-analysis results comparing reduction in tremor score from baseline for FUS vs SRS thalamotomy.* ***Left****, Network plot of FUS vs SRS thalamotomy.* ***Right****, Forest plot of frequentist model for network meta-analysis. FUS, focused ultrasound; SRS, stereotactic radiosurgery.*

Data Extraction

Two reviewers (S.K. and A.B.S.) independently extracted data for the systematic review on study design, patient population (whether inclusion and exclusion criteria were met, lesion area, and number of patients), and outcomes (unilateral tremor scores). All reviewers (S.K., A.B.S., and D.D.W.) verified accuracy of study inclusion or exclusion, study metrics, and outcomes.

Data Bias

No study included in the network meta-analysis directly compared FUS-T vs SRS-T with 2 groups of participants, precluding assessment of bias during treatment allocation between the 2 modalities. There was also no bias due to selective reporting because we only included studies reporting the total unilateral FTM-TRS score. However, we have used the ROBINS-I risk of bias assessment[18] for each study to examine quality of outcome assessment (Table 1).

Data Ethics Characterization

We assessed each study for whether it met the criteria for ethical data collection per the Declaration of Helsinki. Twenty one studies provided explicit statements with institutional review board (IRB)/local ethics committee (LEC) approval and written consent. Seven studies stated IRB/LEC approval, and 5 studies stated informed consent for the procedure. Four studies implied consent through statements such as "enrolled" and "enrollment in clinical trials." Finally, 6 studies had no mention as to whether the data were collected ethically or with patient consent.[19-24]

Data Synthesis and Statistical Analysis

Meta-analysis

First, we conducted independent meta-analyses for FUS-T and SRS-T tremor reduction. A pooled weighted mean distribution and 95% CI of FTM-TRS A+B scores relative to preprocedure baseline were determined for studies that had follow-up close to 12 months. We assessed heterogeneity using the I^2 statistic. For meta-analysis calculations and visual result display, we used MetaXL (version 5.3, EpiGear).

Network meta-analysis

For comparing tremor reduction after FUS-T or SRS-T, a network meta-analysis was conducted to compute a pooled weighted mean distribution and 95% CI of FTM-TRS A+B tremor reduction. This was also compared with preprocedure baseline, using the same studies that were included in the prior meta-analyses. We assessed transitivity by examining age of cohorts at baseline, disease duration, difference in sex distributions, and average follow-up times. Network meta-analysis calculations and visual display of results were conducted using MetaInsight (version 3.1.14, NIHR CRSU), which uses frequentist models from the R package "netmeta."[25]

Failure rate analysis

For each study that met inclusion criteria for either efficacy or adverse event comparison, we characterized whether authors explicitly described a subpopulation of treated patients where the outcome was below a prespecified efficacy threshold. Descriptions included "failure," "nonresponse," "poor response," "relapse," or "recurrence." Cohorts were then descriptively pooled across FUS-T and SRS-T treatment modalities.

Adverse events analysis

We compiled AEs reported in the literature for all studies that included follow-up from FUS-T or SRS-T for at least 1 year. Incidences of AEs were estimated by summing the count of AEs across all included studies and dividing by the total number of patients summed over all studies. We additionally compared the difference in AEs between FUS patient populations with "classic" Vim targeting (ie, at the z-level of the intercommissural (AC-PC) plane) vs those with "modified" Vim targeting (ie, noted in the respective Methods sections to be superior to the AC-PC plane). In addition to each category of AEs, we included a "maximum AE rate" category, defined by the maximum AE rate of the categories included, for subanalyses given that multiple AEs could be present in a single patient. Statistical analysis was performed using the 2-sample z-test for proportions or linear regression where appropriate.

TABLE 2. Comparison of All Treatments for FTM-TRS A+B Tremor Reduction

Condition	Baseline	FUS	SRS
Baseline	Baseline	−11.57 (−13.3, −9.93)	−10.26 (−14.21, −5.96)
FUS	11.57 (9.93, 13.3)	FUS	1.31 (−2.96, 5.99)
SRS	10.26 (5.96, 14.21)	−1.31 (−5.99, 2.96)	SRS

FTM-TRS, Fahn-Tolosa-Marin Tremor Rating Scale; FUS, focused ultrasound; SRS, stereotactic radiosurgery.

TABLE 3. Ranking Table for All Studies, With Probability for Each Treatment to be the Best

Condition	Rank 1	Rank 2	Rank 3
Baseline	0	7.5E-05	0.9999
FUS	0.7281	0.2719	0
SRS	0.2719	0.7280	7.5E-05

FUS, focused ultrasound; SRS, stereotactic radiosurgery.

Data Availability

The data sets supporting the current study are available from the corresponding author on reasonable request.

RESULTS

Patient Demographics of Included Studies for Efficacy Comparison

The full study selection process for inclusion in this analysis is detailed in the PRISMA flow diagram (Figure 1). Fifteen studies (n = 464) with FUS-T[26-40] and 3 studies (n = 62) with SRS-T[41-43] met inclusion criteria for pre-thalamotomy vs post-thalamotomy efficacy analyses. The weighted average follow-up times were 10.3 months and 14.1 months for FUS-T and SRS-T groups, respectively. Full pooled patient demographics by paper are detailed in Table 1.

Assessment of Risk of Bias

Sixteen of 18 of the studies did not explicitly address confounding factors, such as age, duration of symptoms, or lesion volume, that could have compromised the results. Four of 18 studies had risk of bias in selection of participants in the study because they did not explicitly detail both inclusion and exclusion criteria. Two studies across all analyses demonstrated attrition bias from initial enrollment baseline statistics; these are marked by superscript a in Table 1. In addition, low skull density ratio (SDR) was an exclusion criterion for the FUS cohorts, whereas this was not the case for the SRS cohorts. As we subselected those studies that reported the contralateral FTM-TRS A+B raw scores at baseline and follow-up, there was no risk of bias arising from measurement of exposure or outcome or in selection of the reported result. Finally, as only studies that had FUS-T or SRS-T without additional intervention were included, there was no risk of bias due to postexposure intervention.

TABLE 4. Reported Failure Rates for Prethalamotomy vs Post-Thalamotomy Studies Included in Either Efficacy or Adverse Outcome Analyses

Authors	Year	FUS or SRS	n	Failure definition	Failure rate
C Pae et al.[28]	2022	FUS	72	<50% contralateral CRST improvement at 6 mo	0.18
J Torii et al.[44]	2021	FUS	61	<50% contralateral CRST improvement at 3 mo	0.51
K Yamamoto et al.[51]	2019	FUS	6	Recurrence at 3 mo	0.33
Y Meng et al.[52]	2018	FUS	35	<50% tremor improvement at 1 y	0.54
FUS aggregate			174		0.37[b]
C Tuleasca et al.[42]	2017	SRS	17	≤50% improvement in TSTH	0.35
A Niranjan et al.[20]	2017	SRS	91	No improvement in any FTM scores	0.12
C Ohye et al.[60]	2012	SRS	53[a]	≤50% improvement in tremor	0.15[a]
SY Lim et al.[43]	2010	SRS	17	Lack of tremor suppression	0.12
D Kondziolka et al.[9]	2008	SRS	27	Lack of tremor improvement	0.11
C Ohye et al.[61]	2002	SRS	11	<75% tremor reduction	0.22
RF Young et al.[22]	2000	SRS	51	Criteria not described, "treatment failure"	0.079
A Niranjan et al.[23]	2000	SRS	8	<50% tremor improvement	0.00
RF Young et al.[24]	1998	SRS	27	Little or no reduction in tremor	0.11
SRS aggregate			302		0.13[b]

CRST, Clinical Rating Scale for Tremor; FTM, Fahn-Tolosa-Marin; FUS, focused ultrasound; SRS, stereotactic radiosurgery; TSTH, tremor score for the treated hand.
[a]Includes both essential tremor and Parkinson disease patient populations.
[b]From studies that explicitly reported failure rates, poor responses, or nonresponder cohort.

TABLE 5. Pooled AEs for Thalamotomy Studies with ~12 Month Follow-up

Authors Year FUS or SRS	Follow-up length maximum (mo)	Targeting method (classic or modified Vim, or other [coords: x, y, z])[a]	Post-treatment lesion size: volume (mm^3)	n	Adverse effects	Imbalance/ gait disturbance	Sensory disturbance	Dysmetria	Dysgeusia	Motor weakness	Dysarthria	Others
K Yamamoto[26] 2022 FUS	24[b]	Modified x: 11 mm y: 1/4 AC-PC distance z: 2 mm	175.3 ± 93.4[d]	56		8	6	n/a	n/a	3	0	n/a
V Purrer[29] 2022 FUS	12	Classic	n/a	37		4	8	n/a	10	1	n/a	6 (dyskinesia/ dystonia)
J Torii[44] 2022 FUS	24[b]	Modified x: 11.5 to 12.0 mm y: 1/3 AC-PC distance minus 1.5 mm z: 1.5 to 2.0 mm	n/a	64		n/a	n/a	n/a	n/a	n/a	n/a	None
K Abe[45] 2021 FUS	12	Classic	n/a	35		0	0	n/a	n/a	0	0	None
DJ Segar[46] 2021 FUS	12	Modified x: 11 mm y: 1/4 AC-PC distance minus 1.5 mm z: 1.5 to 2.0 mm	288.98 ± 137.72[d]	100		15[c]	17[c]	7[c]	3[c]	3[c]	6[c]	N/A
P Wu[30] 2021 FUS	24[b]	Classic	n/a	48		0	3	n/a	n/a	2	0	3 (not detailed)
E Tommasino[47] 2021 FUS	12	Modified x: 11 mm y: 1/4 to 3/10 AC-PC distance z: 0 to 2 mm	n/a	30		n/a	n/a	n/a	n/a	n/a	n/a	None
H Ito[48] 2020 FUS	24[b]	Classic	n/a	10		n/a	n/a	n/a	n/a	n/a	n/a	None
K Fukutome[32] 2020 FUS	12	Classic	68.0 ± 29.8	15		0	1	n/a	n/a	n/a	n/a	n/a
MN Gallay[49] 2020 FUS	12	Other: cerebellothalamic tract between red nucleus and subthalamic nucleus at the level of the AC-PC plane	n/a	10		3	1	n/a	n/a	1	0	n/a
AN Kapadia[50] 2020 FUS	12	n/a	180.8 ± 91.5	94		27[c]	8[c]	9[c]	n/a[c]	9[c]	9[c]	n/a
A Sinai[33] 2019 FUS	60[b]	n/a	297.1 ± 128.0[d]	24		2	2	n/a	2	n/a	n/a	n/a
YS Park[34] 2019 FUS	48[b]	Classic	82.6 ± 29.023	15		n/a	n/a	n/a	n/a	n/a	n/a	None

TABLE 5. Continued.

Authors Year FUS or SRS	Follow-up length maximum (mo)	Targeting method (classic or modified Vim, or other [coords: x, y, z])[a]	Post-treatment lesion size: volume (mm^3)	n	Adverse effects	Imbalance/ gait disturbance	Sensory disturbance	Dysmetria	Dysgeusia	Motor weakness	Dysarthria	Others
K Yamamoto[51] 2019 FUS	12	n/a	n/a	6		2	n/a	n/a	n/a	n/a	n/a	n/a
Y Meng[52] 2018 FUS	24	n/a	220.2 ± 112.3	35		5[c]	2[c]	0	n/a	2[c]	0	1 (lethargy)[c]
M Harary[53] 2018 FUS	12	n/a	300 ± 100	7		3	1	n/a	n/a	n/a	n/a	n/a
NY Jung[37] 2018 FUS	12	Classic	n/a	20		0	n/a	n/a	n/a	n/a	n/a	n/a
DG Iacopino[54] 2018 FUS	12	Modified x: 12 to 14 mm laterally from the intercommissural plane y: 1/4 AC-PC distance z: 0 to 2 mm	n/a	13		1	0	n/a	n/a	n/a	n/a	n/a
M Zaaroor[19] 2018 FUS	12	Classic	n/a	18		0	0	n/a	n/a	n/a	n/a	n/a
M Kim[55] 2017 FUS	12	Classic	n/a	10		n/a	0	n/a	n/a	n/a	0	none
WJ Elias[38] 2016 FUS	12	n/a	n/a	56		5	8	2	2	1	0	1 (disequilibrium)
MN Gallay[56] 2016 FUS	12	Other: Cerebellothalamic tract x: 8 mm lateral to the thalamo-ventricular border y: 5 mm posterior to the midcommissural line z: 3 mm below the intercommissural plane	n/a	21		1	n/a	n/a	n/a	n/a	n/a	n/a
DS Huss[57] 2015 FUS	24[b]	Classic	n/a	15		0	3	n/a	n/a	0	0	n/a
FUS aggregate				724		76 (10.5%)	60 (8.3%)	18 (2.5%)	17 (2.3%)	22 (3.0%)	15 (2.1%)	11 (1.5%)
MH Khattab[58] 2022 SRS	12	Modified x: 11 mm y: 1/4 AC-PC distance z: 2 to 4 mm	n/a	33		n/a	n/a	n/a	n/a	n/a	n/a	2 (headache)

TABLE 5. Continued.

Authors Year FUS or SRS	Follow-up length maximum (mo)	Targeting method (classic or modified Vim, or other [coords: x, y, z])[a]	Post-treatment lesion size: volume (mm^3)	n	Adverse effects	Imbalance/ gait disturbance	Sensory disturbance	Dysmetria	Dysgeusia	Motor weakness	Dysarthria	Others
A Niranjan[20] 2017 SRS	152[b]	Modified x: 11 mm y: 1/4 AC-PC distance z: 2 mm	n/a	73		n/a	n/a	n/a	n/a	n/a	n/a	n/a
T Witjas[59] 2015 SRS	12	Modified x: 11 mm y: 3.9 to 9.9 mm z: 2.5 mm	n/a	39		n/a	n/a	n/a	n/a	n/a	n/a	None
C Ohye[60] 2012 SRS	24[b]	Modified x: 15 to 17 mm from midsagittal plane y: 7 mm z: 4 mm	n/a	13		n/a	n/a	n/a	n/a	n/a	n/a	None
RF Young[21] 2010 SRS	12	n/a	n/a	172		n/a	2	n/a	n/a	9[a]	9[a]	n/a
SY Lim[63] 2010 SRS	30[b]	Modified x: 11 mm y: 1/4 AC-PC distance +1 mm z: 2 to 3 mm	n/a	11		n/a	2 (18, 19 mo)	n/a	n/a	n/a	n/a	1 (thalamic hemorrhage with speech difficulty and right hemiparesis at 14 months)
D Kondziolka[9] 2008 SRS	96[b]	Modified x: 11 mm y: 1/4 AC-PC distance +1 mm z: 2 to 3 mm	n/a	26		n/a	n/a	n/a	n/a	1[c] (6 mo -)	1[c] (6 mo -)	n/a
C Ohye[61] 2002 SRS	96[b]	n/a	(~125-750, 1-10 mo)	11		n/a	n/a	n/a	n/a	n/a	n/a	None
RF Young[22] 2000 SRS	96[b]	n/a	166 (0-523, 3 mo)	25		0	1	n/a	n/a	1	n/a	n/a
A Niranjan[23] 2000 SRS	11	Modified x: 11 mm y: 1/4 AC-PC distance z: 2 mm	n/a	12		n/a	n/a	n/a	n/a	1[c]	1[c]	n/a
RF Young[24] 1998 SRS	50[b]	n/a	245 (30-910, 3 mo)[d]	27		n/a	n/a	n/a	n/a	n/a	n/a	None
SRS aggregate				449		0 (0.0%)	5 (1.1%)	0 (0.0%)	0 (0.0%)	12 (2.7%)	11 (2.4%)	3 (0.7%)

AEs, adverse events; FUS, focused ultrasound; n/a, not discussed within the paper; none, paper explicitly stated no adverse effects with 1 year or greater follow-up; SRS, stereotactic radiosurgery.

[a]Classic AC-PC = targeting at 0 mm in the z-direction relative to the AC-PC plane. Modified AC-PC = targeting at 1 to 2 mm above the AC-PC plane. Coordinates deviating from - x: 11 to 12 mm lateral to wall of third ventricle; y: 1/4 to 1/3 AC-PC distance anterior to the front of the PC; z: 0 mm above the intercommissural plane are noted.

[b]If follow-up length exceeded 12 months, the adverse effects at close to 12 months were included here for comparison.

[c]Multiple AEs within the same individual explicitly stated or deduced from total numbers.

[d]Lesion volume of initially enrolled population, with adverse event population demonstrating attrition.

FUS-T and SRS-T Tremor Reduction vs Prethalamotomy Baseline

From the pairwise meta-analysis, FUS-T demonstrated significant tremor reduction as measured by the unilateral FTM-TRS A+B score reduction at follow-up closest to 12 months (**Supplemental Figure 1**, http://links.lww.com/NEU/D755, absolute tremor reduction: −11.13 [95% CI: −12.74, −9.52]; relative tremor reduction, 60.8%). SRS-T also demonstrated significant absolute tremor reduction (**Supplemental Figure 2**, http://links.lww.com/NEU/D756, absolute tremor reduction: −11.41 [95% CI: −17.39, −5.44]; relative tremor reduction 56.5%).

Network meta-analysis demonstrated a trend toward greater absolute tremor reduction with FUS-T (Figure 2). FUS-T demonstrated 1.31 (95% CI: −2.96, 5.99) greater weighted mean difference in FTM-TRS A+B reduction relative to SRS-T (Table 2, FUS-T: −11.57 [95% CI: −13.3, −9.93]; SRS-T: −10.26 [95% CI: −14.21, −5.96]), resulting in a 72.8% probability that FUS-T is the more efficacious treatment for tremor reduction (Table 3).

For FUS-T and SRS-T, I^2 was 79% and 84%, Q statistic was 62.29 and 12.40, and $P < .01$ and $< .01$, respectively, indicating significant heterogeneity in study results among both therapies. We also note that there are differences in the FUS-T and SRS-T baseline demographics, with a greater proportion of men, younger age, greater disease duration, shorter follow-up time, and greater lesion volume in the FUS-T combined cohort, leading to decreased transitivity for comparison in the network meta-analysis. We used descriptive comparison as none of the demographics were reported across all studies for direct quantitative comparison.

Failure Rate

We assessed all papers meeting either efficacy or adverse event inclusion criteria for whether failure rates were explicitly characterized by the authors. Although 9 SRS-T papers explicitly did so, only 4 FUS-T papers did, possibly because of real-time feedback regarding tremor reduction that is available with FUS-T (Table 4). In addition, the definition of failure was most commonly <50% contralateral FTM-TRS improvement with FUS-T, whereas with SRS-T it was more commonly little or no reduction in tremor. Thus, although the failure rate was numerically higher for FUS-T (37%) than SRS-T (13%), this was confounded by differences in failure rate definitions, as well as no reporting of 0 failure rate in the FUS-T studies.

Adverse Events

Twenty three studies for FUS-T[19,26,29,30,32-34,37,38,44-57] and 11 studies for SRS-T[9,20-24,43,58-61] met inclusion criteria for comparison of AE incidence (Table 4). Seven hundred and twenty four FUS-T and 449 SRS-T cases were available for AE analysis. Long-term AEs for FUS-T in order of decreasing frequency were imbalance/gait disturbance (10.5%), sensory-related disturbance (8.3%), motor weakness (3.0%), dysmetria (2.5%), dysgeusia (2.3%), dysarthria (2.1%), and others (1.5%, including dyskinesia/dystonia, lethargy, and disequilibrium), as seen in Table 4. For SRS-T, adverse thalamotomy effects in order of decreasing frequency were motor weakness/hemiparesis (2.7%), dysarthria/speech impairment (2.5%), sensory disturbance (1.1%), headache (0.4%), and thalamic edema/hemorrhage (0.2%). Of note, many studies reported that different AEs could be present for the same patient; studies which either explicitly or implicitly (via frequency total) stated this are indicated in Table 5.

To address possible factors leading to high AE rate in the FUS cohorts, we compared lesion characteristics to AE rates in each study. First, we assessed contribution of initial lesion targeting coordinates (ie, classic at the level of the AC-PC plane or modified above the AC-PC plane). We found increased imbalance/gait disturbance (9.1% vs 1.9%, $P = .00054$, Bonferroni-corrected $\alpha = 0.0071$) with modified coordinates (Table 6). We next assessed whether lesion volume and AE rate were correlated for imbalance/gait disturbance. Eight studies had both lesion volume and AEs, demonstrating increased sensory disturbance with increased lesion size ($R^2 = 0.52$, $P = .045$), as well as trends toward increased imbalance/gait disturbance ($R^2 = 0.36$, $P = .12$) and maximum AE rate ($R^2 = 0.31$, $P = .15$) with increased lesion size (Figure 3). Subsequently, we found no correlation between rate of AEs and efficacy (n = 8 studies, $P = .63$ for imbalance/gait disturbance, $P = .74$ for sensory disturbance, $P = .85$ for maximum rate of any AE). Finally, we found no correlation between efficacy and lesion volume (n = 6 studies, $P = .63$).

DISCUSSION

Our study presents the first network meta-analysis of studies directly comparing FUS-T and SRS-T as incisionless treatment modalities for patients with ET. We found similar absolute contralateral FTM-TRS tremor reduction between FUS-T and

TABLE 6. FUS AE Rate by Thalamotomy Initial Coordinate Location with z-Test for Difference in Proportions

Thalamotomy coordinate location	Imbalance/gait disturbance	Sensory disturbance	Dysmetria	Dysgeusia	Motor weakness	Dysarthria	Others
Modified (n = 263)	**24 (9.1%)**	23 (8.7%)	7 (2.7%)	3 (1.1%)	6 (2.3%)	6 (2.3%)	0 (0.0%)
Classic (n = 223)	4 (1.9%)	15 (6.7%)	0 (0.0%)	10 (4.4%)	3 (0.0028)	0 (0.00)	**9 (4.0%)**
P-value	**.00054**	.41	.014	.023	.45	.023	**.001**

AE, adverse event; CRST, Clinical Rating Scale for Tremor; FUS, focused ultrasound.
Significance indicated in bold, with a Bonferroni-corrected α of 0.0071.

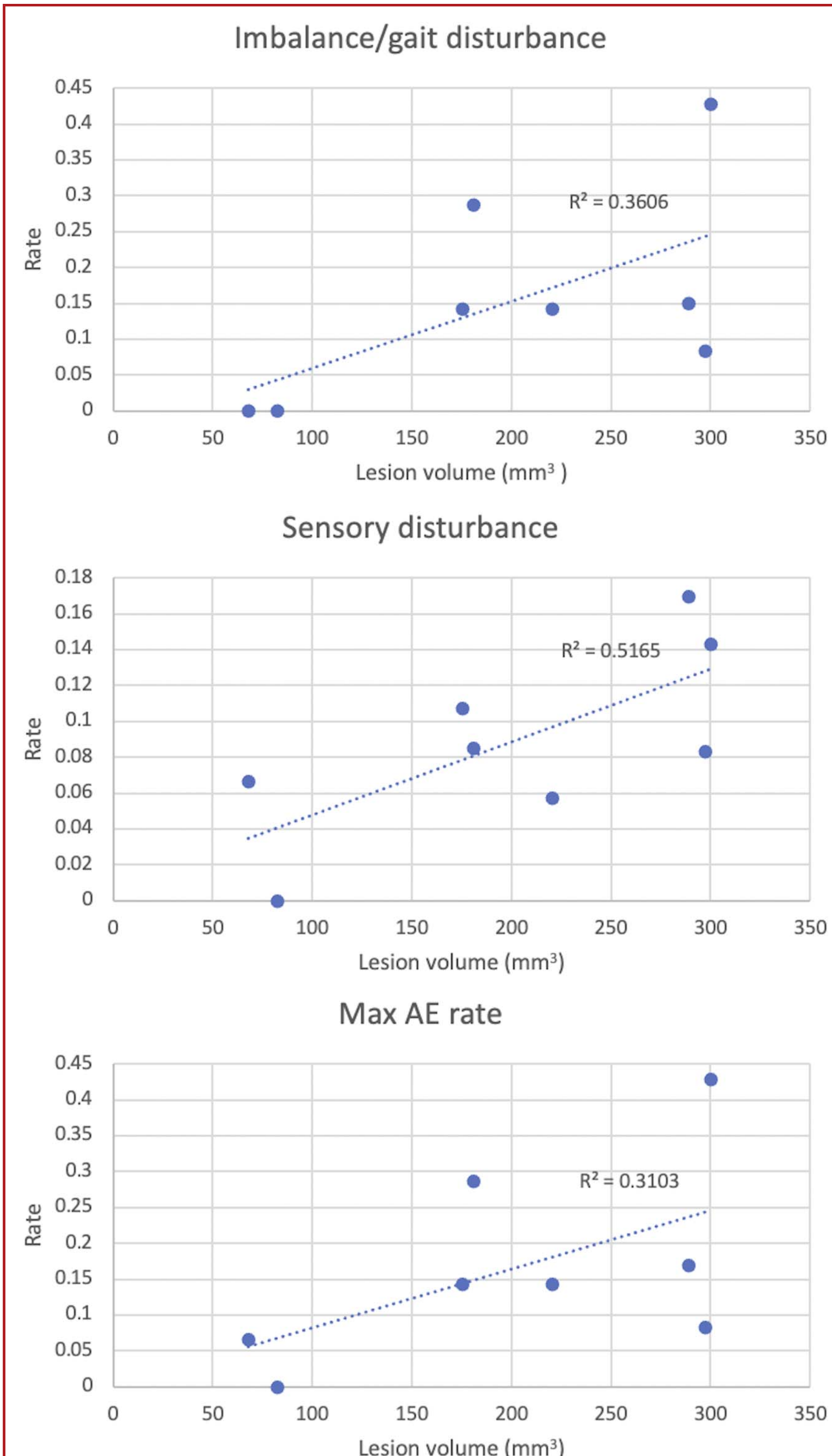

FIGURE 3. *Linear regression of lesion volume vs rate of adverse events across FUS studies: imbalance/gait disturbance (top), sensory disturbance (middle), and maximum AE rate (bottom). AE, adverse event; FUS, focused ultrasound.*

SRS-T (FUS-T, −11.6; SRS-T, −10.3) and relative tremor reduction (FUS: 60.8%, SRS-T: 56.5%). In addition, we estimated rates of AEs with both modalities. FUS-T demonstrated a greater rate of AEs, in particular imbalance and gait disturbance (10.5%). Importantly, we found that rate of AEs in FUS-T, such as sensory disturbance, was correlated with lesion size, echoing observations seen in individual studies.[46,50,62] There was no relationship between lesion size and efficacy nor AE rate and efficacy, highlighting the importance of smaller, well-targeted lesions.

When examining the tremor reduction results further, we note that FUS-T trended toward greater efficacy than SRS-T, with FUS-T having a 72.8% probability of being the best treatment. The consistency of improvements with FUS-T was also greater, as evidenced by (1) the lower I^2 value, which is the fraction of variance that is due to heterogeneity among studies and (2) a smaller CI for tremor reduction, although we recognize more studies with FUS-T met criteria for this analysis. Despite the low number of SRS-T studies that met inclusion criteria, 1 of the 3 SRS-T studies (Lim 2010)[43] did not report significant improvements in a patient population blinded to treatment, demonstrating the greater variability with SRS-T in tremor reduction efficacy. Our result regarding SRS-T variability is consistent with a meta-analysis that included further subscore comparisons.[14] The wider tremor response range could partially be explained by the variability in lesion size seen with SRS-T because there is no way to tailor or assess lesion size during treatment.[63,64]

Why might FUS-T have a higher rate of side effects compared with SRS-T? SRS-T lesions evolve over time[63,64] and often can be quite small to undetectable on follow-up imaging[65] thus limiting off-target effects. In addition, the lesion shape created with SRS-T tends to be more spherical[9,21,66] because radiation energy can be emitted linearly to lesion at a precise target. By contrast, FUS-T lesions tend to be more ellipsoid,[46,53] with the long axis extending from the medial superior direction to the inferior lateral position because of convergence of ultrasound transducer elements off of the midline of the transducer array.[67] The resulting ellipsoid lesion may encroach onto the internal capsule, comprising corticospinal tract, resulting in off-target effects.[46] To mitigate these off-target side effects, many treating physicians target above the intercommissural plane. Interestingly, we found that superior targeting with modified coordinates (1-2 mm above the intercommissural plane) resulted in greater gait disturbance than classical targeting (at the level of the intercommissural plane). This is likely due to the fact that classically targeted lesions were smaller in volume compared with modified targets (classic, n = 2. 75.3 mm^3; modified, n = 2, 248.2 mm^3). Thus, we suspect that the greater gait disturbance seen with superior targeting both in our analysis and a recent cohort[68] could be due to greater lesion volume, extending below the AC-PC plane or inferolateral to the thalamus.[53,62,64] Although FUS-T enables real-time monitoring of both magnetic resonance-based thermometry and treatment effect and during thalamotomy,[12,53] further investigation into factors that could contribute to larger lesion volume, such as increased acceleration in power per sonication, higher skull density ratio, and increased distance between targets in multiple sonications, would improve an already efficacious incisionless thalamotomy option. Our analysis motivates future studies that model lesion size and use improved imaging techniques such as diffusion tractography imaging[69] to optimize lesion location, limit off-target side effects, and improve efficacy with FUS-T.

Limitations

A main limitation of this network meta-analysis is that many noteworthy studies from the literature search only reported subscores or percentage change instead of total unilateral FTM-TRS scores, and another small subset did not report standard deviation of scores. In particular, many FUS-T studies reported bilateral FTM-TRS scores or only A or B subscores, whereas SRS-T studies focused on part A and B subcomponents, such as kinetic tremor and handwriting. Thus, transparent and standardized reporting of FTM-TRS total scores, in addition to the subcomponents, would improve the power of this and subsequent comparative studies. Of note, although many studies were excluded in this analysis, tremor reduction from FUS matched findings from a recent meta-analysis.[70]

CONCLUSION

Both SRS-T and FUS-T have been used as incisionless stereotactic ablative surgeries for treatment of medically refractory ET. Although there is significant heterogeneity between studies in each modality, our network meta-analysis found that FUS-T and SRS-T demonstrated similar efficacy in tremor reduction in ET, with FUS-T having both a higher probability of being more efficacious and a higher incidence of adverse effects, correlated with increased lesion volume.

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REFERENCES

1. Findley LJ. Epidemiology and genetics of essential tremor. *Neurology*. 2000;54(11 suppl 4):S8-S13.

2. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Mov Disord*. 2010;25(5):534-541.
3. Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R. Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. *Mov Disord*. 2001;16(3):464-468.
4. Rehncrona S, Johnels B, Widner H, Törnqvist AL, Hariz M, Sydow O. Long-term efficacy of thalamic deep brain stimulation for tremor: double-blind assessments. *Mov Disord*. 2003;18(2):163-170.
5. Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with essential tremor. *Lancet Neurol*. 2011;10(2):148-161.
6. Wharen RE, Okun MS, Guthrie BL, et al. Thalamic DBS with a constant-current device in essential tremor: a controlled clinical trial. *Parkinsonism Relat Disord*. 2017;40:18-26.
7. 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.
8. Elble RJ, Shih L, Cozzens JW. Surgical treatments for essential tremor. *Expert Rev Neurother*. 2018;18(4):303-321.
9. Kondziolka D, Ong JG, Lee JYK, Moore RY, Flickinger JC, Lunsford LD. Gamma knife thalamotomy for essential tremor. *J Neurosurg*. 2008;108(1):111-117.
10. Higuchi Y, Matsuda S, Serizawa T. Gamma knife radiosurgery in movement disorders: indications and limitations. *Mov Disord*. 2017;32(1):28-35.
11. Ravikumar VK, Parker JJ, Hornbeck TS, et al. Cost-effectiveness of focused ultrasound, radiosurgery, and DBS for essential tremor. *Mov Disord*. 2017;32(8):1165-1173.
12. Wintermark M, Druzgal J, Huss DS, et al. Imaging findings in MR imaging–guided focused ultrasound treatment for patients with essential tremor. *Am J Neuroradiol*. 2014;35(5):891-896.
13. Harary M, Segar DJ, Huang KT, Tafel IJ, Valdes PA, Cosgrove GR. Focused ultrasound in neurosurgery: a historical perspective. *Neurosurg Focus*. 2018;44(2):E2.
14. Dallapiazza RF, Lee DJ, De Vloo P, et al. Outcomes from stereotactic surgery for essential tremor. *J Neurol Neurosurg Psychiatry*. 2019;90(4):474-482.
15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
16. Kondapavulur S, Silva AB, Wang DD. Ventral intermediate nucleus of the thalamus versus posterior subthalamic area: network meta-analysis of DBS target site efficacy for essential tremor. *Stereotactic Funct Neurosurg*. 2022;100(4):224-235.
17. *Estimating the Mean and Variance from the Median, Range, and the Size of a Sample—PubMed*. Accessed August 7, 2022. https://pubmed.ncbi.nlm.nih.gov/15840177/
18. *ROBINS-I Tool | Cochrane Methods*. Accessed October 31, 2022. https://methods.cochrane.org/methods-cochrane/robins-i-tool
19. Zaaroor M, Sinai A, Goldsher D, Eran A, Nassar M, Schlesinger I. Magnetic resonance-guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson's disease and essential tremor cases. *J Neurosurg*. 2018;128(1):202-210.
20. Niranjan A, Raju SS, Kooshkabadi A, Monaco E, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for essential tremor: retrospective analysis of a 19-year experience. *Mov Disord*. 2017;32(5):769-777.
21. Young RF, Li F, Vermeulen S, Meier R. Gamma knife thalamotomy for treatment of essential tremor: long-term results. *J Neurosurg*. 2010;112(6):1311-1317.
22. Young RF, Jacques S, Mark R, et al. Gamma knife thalamotomy for treatment of tremor: long-term results. *J Neurosurg*. 2000;93(suppl_3):128-135.
23. Niranjan A, Kondziolka D, Baser S, Heyman R, Lunsford LD. Functional outcomes after gamma knife thalamotomy for essential tremor and MS-related tremor. *Neurology*. 2000;55(3):443-446.
24. Young RF, Shumway-Cook A, Vermeulen SS, et al. Gamma knife radiosurgery as a lesioning technique in movement disorder surgery. *J Neurosurg*. 1998;89(2):183-193.
25. Owen RK, Bradbury N, Xin Y, Cooper N, Sutton A. MetaInsight: an interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. *Res Synth Methods*. 2019;10(4):569-581.
26. Yamamoto K, Sarica C, Elias GJB, et al. Ipsilateral and axial tremor response to focused ultrasound thalamotomy for essential tremor: clinical outcomes and probabilistic mapping. *J Neurol Neurosurg Psychiatry*. 2022;93(10):1049-1058.
27. Kato S, Maesawa S, Bagarinao E, et al. Magnetic resonance-guided focused ultrasound thalamotomy restored distinctive resting-state networks in patients with essential tremor. *J Neurosurg*. 2023;138(2):306-317.
28. Pae C, Kim MJ, Chang WS, et al. Differences in intrinsic functional networks in patients with essential tremor who had good and poor long-term responses after thalamotomy performed using MR-guided ultrasound. *J Neurosurg*. 2023;138(2):318-328.
29. Purrer V, Borger V, Pohl E, et al. Transcranial high-intensity magnetic resonance-guided focused ultrasound (tcMRgFUS)—safety and impacts on tremor severity and quality of life. *Parkinsonism Relat Disord*. 2022;100:6-12.
30. Wu P, Lin W, Li KH, et al. Focused ultrasound thalamotomy for the treatment of essential tremor: a 2-year outcome study of Chinese people. *Front Aging Neurosci*. 2021;13:697029.
31. Zur G, Lesman-Segev OH, Schlesinger I, et al. Tremor relief and structural integrity after mri-guided focused us thalamotomy in tremor disorders. *Radiology*. 2020;294(3):676-685.
32. Fukutome K, Kuga Y, Ohnishi H, Hirabayashi H, Nakase H. What factors impact the clinical outcome of magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor? *J Neurosurg*. 2021;134(5):1618-1623.
33. Sinai A, Nassar M, Eran A, et al. Magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: a 5-year single-center experience. *J Neurosurg*. 2020;133(2):417-424.
34. Park YS, Jung NY, Na YC, Chang JW. Four-year follow-up results of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor. *Mov Disord*. 2019;34(5):727-734.
35. Gasca-Salas C, Guida P, Piredda R, et al. Cognitive safety after unilateral magnetic resonance-guided focused ultrasound thalamotomy for essential tremor. *J Neurol Neurosurg Psychiatry*. 2019;90(7):830-831.
36. Tian Q, Wintermark M, Jeffrey Elias W, et al. Diffusion MRI tractography for improved transcranial MRI-guided focused ultrasound thalamotomy targeting for essential tremor. *NeuroImage Clin*. 2018;19:572-580.
37. Jung NY, Park CK, Chang WS, Jung HH, Chang JW. Effects on cognition and quality of life with unilateral magnetic resonance-guided focused ultrasound thalamotomy for essential tremor. *Neurosurg Focus*. 2018;44(2):E8.
38. 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.
39. Chang WS, Jung HH, Kweon EJ, Zadicario E, Rachmilevitch I, Chang JW. Unilateral magnetic resonance guided focused ultrasound thalamotomy for essential tremor: practices and clinicoradiological outcomes. *J Neurol Neurosurg Psychiatry*. 2015;86(3):257-264.
40. Elias WJ, Khaled M, Hilliard JD, et al. A magnetic resonance imaging, histological, and dose modeling comparison of focused ultrasound, radiofrequency, and Gamma Knife radiosurgery lesions in swine thalamus: laboratory investigation. *J Neurosurg*. 2013;119(2):307-317.
41. Bolton TAW, Van De Ville D, Régis J, et al. Graph theoretical analysis of structural covariance reveals the relevance of visuospatial and attentional areas in essential tremor recovery after stereotactic radiosurgical thalamotomy. *Front Aging Neurosci*. 2022;14:873605.
42. Tuleasca C, Najdenovska E, Régis J, et al. Pretherapeutic functional neuroimaging predicts tremor arrest after thalamotomy. *Acta Neurol Scand*. 2018;137(5):500-508.
43. Lim SY, Hodaie M, Fallis M, Poon YY, Mazzella F, Moro E. Gamma knife thalamotomy for disabling tremor: a blinded evaluation. *Arch Neurol*. 2010;67(5):584-588.
44. Torii J, Maesawa S, Nakatsubo D, et al. Cutoff values for the best management strategy for magnetic resonance-guided focused ultrasound ablation for essential tremor. *J Neurosurg*. 2023;138(1):38-49.
45. Abe K, Horisawa S, Yamaguchi T, et al. Focused ultrasound thalamotomy for refractory essential tremor: a Japanese multicenter single-arm study. *Neurosurgery*. 2021;88(4):751-757.
46. Segar DJ, Lak AM, Lee S, et al. Lesion location and lesion creation affect outcomes after focused ultrasound thalamotomy. *Brain*. 2021;144(10):3089-3100.
47. Tommasino E, Bruno F, Catalucci A, et al. Prognostic value of brain tissues' volumes in patients with essential tremor treated with MRgFUS thalamotomy. *J Clin Neurosci*. 2021;92:33-38.
48. Ito H, Yamamoto K, Fukutake S, Odo T, Kamei T. Two-year follow-up results of magnetic resonance imaging-guided focused ultrasound unilateral thalamotomy for medication-refractory essential tremor. *Intern Med*. 2020;59(20):2481-2483.
49. Gallay MN, Moser D, Jeanmonod D. MR-guided focused ultrasound cerebellothalamic tractotomy for chronic therapy-resistant essential tremor: anatomical target reappraisal and clinical results. *J Neurosurg*. 134(2), 2021:376-385.
50. Kapadia AN, Elias GJB, Boutet A, et al. Multimodal MRI for MRgFUS in essential tremor: post-treatment radiological markers of clinical outcome. *J Neurol Neurosurg Psychiatry*. 2020;91(9):921-927.

51. Yamamoto K, Ito H, Fukutake S, Kamei T, Yamaguchi T, Taira T. Ventralis intermedius thalamotomy with focused ultrasound for patients with low skull density ratio. *Mov Disord*. 2019;34(8):1239-1240.
52. Meng Y, Solomon B, Boutet A, et al. Magnetic resonance-guided focused ultrasound thalamotomy for treatment of essential tremor: a 2-year outcome study. *Mov Disord*. 2018;33(10):1647-1650.
53. Harary M, Essayed WI, Valdes PA, McDannold N, Cosgrove GR. Volumetric analysis of magnetic resonance-guided focused ultrasound thalamotomy lesions. *Neurosurg Focus*. 2018;44(2):E6.
54. Iacopino DG, Gagliardo C, Giugno A, et al. Preliminary experience with a transcranial magnetic resonance-guided focused ultrasound surgery system integrated with a 1.5-T MRI unit in a series of patients with essential tremor and Parkinson's disease. *Neurosurg Focus*. 2018;44(2):E7.
55. Kim M, Jung NY, Park CK, Chang WS, Jung HH, Chang JW. Comparative evaluation of magnetic resonance-guided focused ultrasound surgery for essential tremor. *Stereotact Funct Neurosurg*. 2017;95(4):279-286.
56. Gallay MN, Moser D, Rossi F, et al. Incisionless transcranial MR-guided focused ultrasound in essential tremor: cerebellothalamic tractotomy. *J Ther Ultrasound*. 2016;4(1):5.
57. Huss DS, Dallapiazza RF, Shah BB, Harrison MB, Diamond J, Elias WJ. Functional assessment and quality of life in essential tremor with bilateral or unilateral DBS and focused ultrasound thalamotomy. *Mov Disord*. 2015;30(14):1937-1943.
58. Khattab MH, Cmelak AJ, Sherry AD, et al. Noninvasive thalamotomy for refractory tremor by frameless radiosurgery. *Int J Radiat Oncol Biol Phys*. 2022; 112(1):121-130.
59. Witjas T, Carron R, Krack P, et al. A prospective single-blind study of gamma knife thalamotomy for tremor. *Neurology*. 2015;85(18):1562-1568.
60. Ohye C, Higuchi Y, Shibazaki T, et al. Gamma knife thalamotomy for Parkinson disease and essential tremor: a prospective multicenter study. *Neurosurgery*. 2012; 70(3):526-536; discussion 535-536.
61. Ohye C, Shibazaki T, Zhang J, Andou Y. Thalamic lesions produced by gamma thalamotomy for movement disorders. *J Neurosurg*. 2002;97(5 suppl):600-606.
62. Boutet A, Ranjan M, Zhong J, et al. Focused ultrasound thalamotomy location determines clinical benefits in patients with essential tremor. *Brain*. 2018;141(12): 3405-3414.
63. De Salles AAF, Melega WP, Laćan G, Steele LJ, Solberg TD. Radiosurgery performed with the aid of a 3-mm collimator in the subthalamic nucleus and substantia nigra of the vervet monkey. *J Neurosurg*. 2001;95(6):990-997.
64. 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.
65. Moosa S, Elias WJ. Essential tremor: lesions. In: Pouratian N Sheth SA, eds. *Stereotactic and Functional Neurosurgery: Principles and Applications*. Springer International Publishing; 2020:297-310.
66. Frighetto L, Bizzi J, Oppitz P. Stereotactic radiosurgery for movement disorders. In: De Salles AAF, Gorgulho A, Agazaryan N, et al., eds. *Shaped Beam Radiosurgery: State of the Art*. Springer; 2011:209-218.
67. Miller TR, Guo S, Melhem ER, et al. Predicting final lesion characteristics during MR-guided focused ultrasound pallidotomy for treatment of Parkinson's disease. *J Neurosurg*. 2021;134(4):1083-1090.
68. Jackson LM, Kaufmann TJ, Lehman VT, et al. Clinical characteristics of patients with gait instability after mr-guided focused ultrasound thalamotomy. *Tremor Other Hyperkinet Mov*. 2021;11(1):41.
69. Feltrin FS, Chopra R, Pouratian N, et al. Focused ultrasound using a novel targeting method four-tract tractography for magnetic resonance–guided high-intensity focused ultrasound targeting. *Brain Commun*. 2022;4(6):fcac273.
70. Miller WK, Becker KN, Caras AJ, et al. Magnetic resonance-guided focused ultrasound treatment for essential tremor shows sustained efficacy: a meta-analysis. *Neurosurg Rev*. 2022;45(1):533-544.

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Supplemental Figure 1. Meta-analysis results for difference in pre-FUS vs post-FUS thalamotomy total unilateral FTM-TRS tremor scores at ∼12 months of follow-up. **Supplemental Figure 2.** Meta-analysis results for difference in pre-SRS vs post-SRS thalamotomy total unilateral FTM-TRS tremor scores at ∼12 months of follow-up.

COMMENTS

What's in a name? In the current days of DBS yet another systematic review of ventrolateral thalamic lesions for tremors may seem something of an anachronism. Is the same old Freiburg thalamotomy still with us[1a]—made sweeter once again by the allure of focused ultrasound?[2a] Perhaps not. New names and nuanced targets do make a difference.

This detailed comparison of modern stereotactic radiosurgery (SRS) and focused ultrasound (FUS) thalamotomy for ET asserts that there is a trend towards great efficacy with FUS. A brief glance at Supplemental Figures 1 and 2 (http://links.lww.com/NEU/D755 and http://links.lww.com/NEU/D756) shows that this may be a rosy claim. A well targeted thalamotomy by any other name is an effective thalamotomy.

But where is the safe target? By aiming a single 4 mm shot above the horizontal intercommissural plane—usually by about 4 mm—and contouring it to limit radiation exposure laterally towards the internal capsule, radiosurgeons have learned to minimize both gait disturbance and weakness. Although not mentioned by the authors, conforming a sonication centroid is also possible. Indeed early in sonication alignment phases an FUS case it is important to apply acoustic filters. These masks reshape the so-called "ellipsoid lesion" that will otherwise approach the internal capsule and cause weakness. Moving a focused ultrasound thalamotomy 2 to 4 mm above the horizontal plane, as with radiosurgery, will reduce (and not increase) the risk of gait disturbance. Energy dose within the target, as the authors note, is still something of an art for SRS and under ongoing refinement for FUS. Finally, it's worth remembering that the Vim is not spherical. Preplanning either procedure with tractography overlay can outline the nucleus as Krishna and others have elegantly shown.[3a,4a] Imaging the surrounding corticospinal and lemniscal fiber tracts may further mitigate risks that still accompany a thalamotomy of any sort.

As this paper nicely shows, the side effect profiles of these surgeries are quite different with SRS thalamotomy carrying less sensory and gait risk. Yet with either surgery the thornier risks of hemorrhage, infection, implant migration and failure are obviated. A rose by any other name... may yet be sweeter.

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1a. Hassler R, Riechert T. A special method of stereotactic brain operation. *Proc R Soc Med*. 1955;48(6):469-470.
2a. 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.
3a. Sammartino F, Krishna V, King NKK, et al. Tractography-based ventral intermediate nucleus targeting: novel methodology and intraoperative validation. *Mov Disord*. 2016;31(8):1217-1225.
4a. Krishna V, Sammartino F, Agrawal P, et al. Prospective tractography-based targeting for improved safety of focused ultrasound thalamotomy. *Neurosurgery*. 2019; 84(1):160-168.

These authors provide a meaningful contribution to the discussion of treatment options for ET. SRS-T and focused ultrasound thalamotomy (FUS-T) can both be used to perform incisionless ablations within the ventral intermediate (VIM) nucleus of the thalamus to treat ET. However, the relative efficacy and rate of AEs remain under investigation. This article is well-written and thoughtfully discussed. Rigorous inclusion and exclusion criteria allow for thorough characterization of efficacy and AEs but limit the number of studies included, especially for SRS-T. It principally finds that the 2 techniques have comparable efficacy, albeit with a trend towards greater tremor reduction with FUS-T, while FUS-T has a higher rate of persistent AEs, particularly gait and sensory disturbances.

While the trend towards better tremor reduction found with FUS-T may be influenced by the small number of included SRS-T studies, the authors suggest that SRS-T is hampered by the inability to tailer lesion size and/or location to beneficial or AEs during the procedure, leading to inconsistencies between reported results. Furthermore, in characterizing the increased AE rate with FUS-T they found a positive correlation between the rate of AEs in FUS-T and lesion size, and no relationship between lesion size and efficacy. Larger lesion size has been associated with degree and durability of symptoms control[1b]; this would suggest that smaller, more precisely localized lesions may minimize AEs while still suppressing tremor. Intriguingly, the authors also find an almost 5-fold increase in the rate of gait disturbance with lesions targeted above the AC-PC plane, a modification suggested to reduce the likelihood of these AEs.[2b,3b] The current study would suggest that this modification may need to be revisited.

Overall, FUS-T is likely to continue gaining popularity as a noninvasive alternative to open surgery that does not require radiation, provides real-time feedback on target location, and offers instant benefit to patients. Determining the ideal target and lesion volume will become more important, with increased attention on lesion size informing targeting to optimize benefit while limiting AEs. Tractography and connectomics may be useful in this process.

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1b. Young RF, Li F, Vermeulen S, Meier R. Gamma Knife thalamotomy for treatment of essential tremor: long-term results. *J Neurosurg*. 2010;112(6):1311-1317.
2b. Boutet A, Ranjan M, Zhong J, et al. Focused ultrasound thalamotomy location determines clinical benefits in patients with essential tremor. *Brain*. 2018;141(12):3405-3414.
3b. Segar DJ, Lak AM, Lee S, et al. Lesion location and lesion creation affect outcomes after focused ultrasound thalamotomy. *Brain*. 2021;144(10):3089-3100.