RESEARCH ARTICLE

Magnetic Resonance–Guided Focused Ultrasound Thalamotomy in a Prospective Cohort of 52 Patients with Parkinson's Disease: A Possible Critical Role of Age and Lesion Volume for Predicting Tremor Relapse

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ABSTRACT: **Background:** Magnetic resonance–guided focused ultrasound (MRgFUS) thalamotomy of ventral intermediate (Vim) nucleus is useful to treat drug-resistant tremor-dominant Parkinson's disease (TdPD), but tremor relapse may occur. Predictors of relapse have been poorly investigated so far.

Objective: The aim of this study is to evaluate the role of clinico-demographic, procedural, and neuroradiological variables in determining clinical response, relapse, and adverse events (AEs) in TdPD after MRgFUS Vim-thalamotomy.

Methods: Fifty-two TdPD patients who consecutively underwent unilateral MRgFUS Vim-thalamotomy were prospectively evaluated at baseline and after 24 hours, 1 month, 6 months, and 12 months using MDS-UPDRS-III in *off* and *on* medication conditions. AEs were collected at each evaluation. Lesion volume was calculated at 24-hour magnetic resonance imaging (MRI). Patients with tremor improvement <30% in *off* medication were considered nonresponders (when detected after 24 hours) or relapsers (if detected from 1-month visit onward).

Results: All patients showed tremor improvement >30% at 24 hours. Tremor relapse occurred in 12 patients (23%), exclusively during the first month after thalamotomy. Relapse was associated with younger age ($P = 0.030$) and smaller lesion volume ($P = 0.030$). At 1 month, 22 patients (42%) had AEs; at 6 and 12 months, AEs persisted in 19% and 6% of cases. AEs at 6 months were associated with larger lesions ($P = 0.018$). All AEs were mild.

Conclusions: MRgFUS Vim-thalamotomy is effective in treating tremor in TdPD. Relapse is associated with younger age and smaller lesion volume, but larger lesions make AEs more likely to persist. We suggest that a lesion volume between 145 and 220 mm^3 on T1-weighted MRI may be the therapeutic window that ensures tremor control without long-lasting AEs. © 2025 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: MRgFUS; Parkinson's disease; thalamotomy; focused ultrasound; tremor

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Among subjects with tremor-dominant Parkinson's disease (TdPD), tremor is the most disabling motor sign, often unresponsive to pharmacological therapy.[1] Magnetic resonance–guided focused ultrasound (MRgFUS) is a minimally invasive ablative technique that employes acoustic energy to generate lesions under real-time magnetic resonance imaging (MRI) guidance.[2] The immediate and long-lasting efficacy of ventralis intermediate (Vim) nucleus MRgFUS thalamotomy for the treatment of essential tremor (ET) has been widely demonstrated,[3-5] whereas a lot fewer TdPD patients have currently undergone this procedure.[6] Accordingly, predictors of outcome have not been systematically studied in large and prospective TdPD cohorts.

A recent meta-analysis confirmed the efficacy and safety of MRgFUS in patients with TdPD, summarizing the results of 20 studies conducted in the last 10 years, of which 10 investigated Vim thalamotomy on about 150 patients.[6] More recently, three additional studies reported the outcome of unilateral MRgFUS Vim thalamotomy for patients with TdPD, outlining its overall efficacy but also warning about the risk of potential treatment failure.[7-9] Notably, it has been suggested that the best intrathalamic target for tremor control may differ between TdPD and ET patients.[10]

Data from cohorts of patients with ET showed a positive correlation between tremor control and lesion volume.[11,12] This association has been investigated in nine patients (of whom three had TdPD) presenting tremor recurrence within 1 month after MRgFUS Vim thalamotomy[13]; however, the authors did not find significant differences in lesion size between responders and relapsers.

To date, data on lesion size are quite heterogeneous due to different methodological approaches: in some studies, lesion volumes were calculated using T2-weighted (T2w) MRIs,[8] whereas in others, T1-weighted (T1w) images were used[9]; in one case, volume had been inferred according to the diameter of the lesion.[14]

Tremor relapse in TdPD after MRgFUS Vim thalamotomy has been reported with various degrees of severity and timing.[6,8,9,13,15-17] To the best of our knowledge, no study specifically investigated prospectively the timing, frequency, and predictors of this phenomenon.

The aim of this study was to investigate the frequency and predictors of efficacy (focusing on tremor response and relapse) and safety (adverse events [AEs]) of unilateral MRgFUS Vim thalamotomy in a large cohort of TdPD.

Patients and Methods

Patients

We included consecutive patients with a diagnosis of established PD according to the Movement Disorder Society diagnostic criteria[18] and a tremor-dominant motor phenotype[19] who underwent MRgFUS Vim thalamotomy at Fondazione IRCCS Istituto Neurologico Carlo Besta (Milan, Italy) from January 2, 2019, to June 30, 2023.

Each patient's eligibility to MRgFUS thalamotomy was evaluated by a multidisciplinary team consisting of neurologists, neurosurgeons, neuropsychologists, and neuroradiologists. Detailed inclusion and exclusion criteria have been previously reported[20] and are provided as Supporting Information.

Surgical Procedure

MRgFUS Vim thalamotomy was performed using an MRI machine including the ExAblate 4000 device (InSightec, Haifa, Israel).[19] Patient preparation, target identification, and execution of the procedure followed the previously described standards.[3,20]

During the procedure, the effective target for each patient was optimized based on periodic clinical assessments of tremor and monitoring for the appearance of any adverse effects. The patient was examined in the baseline state (before the first sonication) and after each sonication, with particular attention to the possible appearance of transient side events at moderate temperatures (50°C–54°C), which could induce a change in the target. The protocol for intraoperative clinical testing is reported in the Supporting Information.

Data Collection and Clinical Evaluations

For all patients, we collected data about sex, disease duration, age at surgery, dominant hand, tremor side (unilateral or bilateral), and skull density ratio (SDR). In this open-label prospective study, all patients were evaluated in person by neurologists with extensive training in movement disorders (A.B., N.G.A., R.T., F.C., and G.G.) at each time point of the study (baseline, 24 hours, 1 month, 6 months, and 12 months after thalamotomy). All patients were asked to come to the study visits after discontinuation of dopaminergic medications for at least 12 hours (*off* medication-condition). The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[21] Parts I–IV were administered, and the motor score (MDS-UPDRS Part III) was collected in both *off* and *on* medication-conditions, after levodopa challenge test (90 minutes after oral intake of 150% of the patients' usual morning dose of levodopa).

AEs were carefully evaluated at every postoperative time point and classified by severity using Clavien-Dindo criteria.[8,22]

Levodopa-equivalent daily dose (LEDD) was collected at each time point, using conversion formulae previously published.[23-25]

During surgery, for each patient we recorded the total number of sonications, the number of sonications with average and maximum temperatures >55°C, the average duration of sonications with temperature >55°C, the average energy and power supplied, and the average temperature and the maximum temperature reached during sonications >55°C.

Image Acquisition and Lesion Analysis

All patients underwent 3-Tesla magnetic resonance at baseline (preprocedural condition), 24 hours, 1 month, 6 months, and 12 months after the procedure. Lesion volumes were calculated by two expert imaging analysts (F.G. and A.P.S.) on T1w and T2w sequences.

The center of the lesion was determined in the 24-hour T1w postcontrast images, following a previously described methodology[26] using multiplanar images obtained by the Radiant software (https://www.radiantviewer.com/).

Thalamic lesions were manually segmented in the axial plane of 24-hour and 1-month T1w sequences (F.G.) using MRIcron software (https://www.nitrc.org/projects/mricron) on postcontrast volumetric sequences (isotropic voxel size: 0.9 mm), and the volume has subsequently been calculated.

We additionally calculated lesion volumes using 24-hour T2w sequence (A.P.S.) after manual segmentation using ITK-SNAP (www.itksnap.org)[27]; the hypointense core (zone I, coagulation necrosis) and the strongly hyperintense surrounding rim (zone II, cytotoxic edema) were included in the segmentation.[8,27]

Outcomes

Subscores for tremor (MDS-UPDRS-III items 3.15–3.18), rigidity (items 3.3), and bradykinesia (sum of items 3.4–3.8) for the treated side and the postural instability/gait difficulty (PIGD) score (sum of items 2.12, 2.13, and 3.10–3.12)[19] were computed.

Tremor improvement in *off* medication condition was calculated using the following formula: (baseline tremor score – follow-up tremor score)/baseline tremor score × 100. Patients were classified according to clinical response as follows: (1) cases with an immediate (24-hour follow-up) change of tremor score <30% were considered *non-responders*; (2) cases with an immediate (at 24 hours) and sustained (after 1 and 6 months) improvement of tremor scores ≥30% were considered *responders*; and (3) patients with good response (>30%) at 24-hour visit but progressive worsening of tremor response, dropping below the 30% threshold, at either 1- or 6-month follow-up visit were considered *relapsers*.

The primary outcome of this study was to investigate the frequency of relapsers at the 6-month follow-up visit and to identify predictors of tremor relapse among clinicodemographic, intraprocedural, and radiological factors.

The threshold of 30% was chosen because it is commonly used to identify a significant improvement in tremor disorders,[29,30] including PD.[31]

Secondary outcomes included the evaluation of changes in other PD-related motor features (see later), LEDD, frequency of AEs, and factors predicting AEs.

Statistical Analysis

Data distribution was evaluated with the Shapiro–Wilk test. Comparison of baseline characteristics (demographic, clinical, sonication parameters, lesion volumes) and incidence of AEs between responders and relapsers were computed with the Mann–Whitney *U* test or Fisher's exact test as appropriate. Longitudinal evaluations of continuous clinical variables were evaluated with repeated measures ANOVA (rmANOVA), with time and outcome (responder vs. relapser) as factors. The sphericity assumption was evaluated using Mauchley's test, and the Greenhouse–Geisser correction was applied in case of violation of that assumption. Longitudinal differences in the proportions of patients with one or more AEs at any time point were evaluated with the McNemar test. Bonferroni correction for multiple comparisons was applied when necessary. Stepwise multivariable binary logistic regression models based on Akaike information criterion were used to verify the relationship between outcome (responder vs. relapser or patients without AEs vs. patients with one or more AEs) and clinicodemographic and radiological explanatory variables. For clinical usefulness, in the regression model, we used volume/50 to show the difference in odds ratio (OR) for every 50 mm^3 of change in lesion volume. Receiver operating characteristic (ROC) curve analysis was subsequently performed to identify cut-off thresholds for the outcome of interest. Statistical significance was set at $P < 0.05$. Statistics were computed with SPSS v.25.0 (IBM, Armonk, NY, USA) and R.[32-36]

Ethics

All patients gave their written informed consent to participate in this study. The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee (CE n.59/2020).

Results

Seventy-three patients with TdPD underwent MRgFUS Vim thalamotomy during the study period, of whom 52 completed 6 months of follow-up and were included in this study. A subgroup of 36 patients also reached 12-month follow-up. The flowchart of the

study population is provided in the Supporting Information. Clinicodemographic characteristics are reported in Table 1.

Median lesion volume 24 hours after the procedure, estimated using T1w MRI sequences, was 205 mm^3 (interquartile range [IQR] = 152; 258), whereas median lesion volume calculated using T2w sequences (available on only 39 patients) was significantly larger with a value of 299 mm^3 (IQR = 234; 365; $P < 0.001$, Wilcoxon signed rank test). Lesion coordinates are reported in the Supporting Information.

At 24 hours, all patients showed an improvement of tremor scores of the treated side >30%: mean improvement of tremor in the *off* medication condition was 92% ± 11% (range 50%–100%). According to our a priori definition, no patient was classified as non-responder. Considering the whole sample, a significant improvement in tremor scores persisted at 1 and 6 months (Supporting Information).

Forty patients (77%) maintained satisfactory tremor control (improvement >30%) at 1 and 6 months and were therefore classified as responders. The clinical benefit dropped below the threshold of 30% for 12 patients (23%), defined as relapsers.

Demographic, clinical, and radiological information of responders versus relapsers at baseline, 1 month, and 6 months are detailed in Table 2. Notably, all relapsers manifested worsening of tremor during the first month after thalamotomy; tremor recurrence occurred within the first 15 days after the procedure in 10 of 12 relapsers (80%). A mild, albeit statistically significant, worsening of tremor was observed between the 24-hour assessment and 1 month also in the responders' group ($P < 0.01$; see Supporting Information). A transient improvement of rigidity was noticed among responders (Table 2).

Predictors of Relapse

Relapsers were significantly younger, with shorter disease duration and lower total MDS-UPDRS-III scores (albeit showing similar tremor severity), and presented a smaller lesion volume 24 hours postprocedure than responders. No differences were found in SDR, sonication parameters, T1w lesion volume at 1-month follow-up, and lesion coordinates (Table 2).

Over time we did not observe significant modifications in MDS-UPDRS Parts I, II, and IV, PIGD score, Hoehn and Yahr stage, or LEDD (Table 2).

Interestingly, a subanalysis within the subgroup of responders demonstrated higher improvement of action compared with rest tremor (median improvement for action tremor was 75% [IQR = 60; 100], whereas for rest tremor it was 55% [IQR = 33; 92]; $P = 0.008$, Wilcoxon signed rank test).

Considering the whole cohort of patients, multivariable binary logistic regression analysis (outcome

TABLE 1 *Baseline clinicodemographic characteristics of the 52 patients with tremor-dominant Parkinson's disease enrolled in this study*

Variable	Value
Woman, n (%)	10 (19.2%)
Disease duration, y	5 [4; 9]
Woman, n (%)	10 (19.2%)
Disease duration, y	5 [4; 9]
Age, y	64.2 ± 9.8
Dominant hand, n (%)	
Right-handed	47 (90.4%)
Left-handed	3 (5.8%)
Ambidextrous	2 (3.8%)
Unilateral tremor, n (%)	24 (46.2%)
SDR	0.56 ± 0.1 (min = 0.35, max = 0.79)
Left Vim, n (%)	28 (53.8%)
MDS-UPDRS-I	4 [2; 9]
MDS-UPDRS-II	8 [5; 11]
MDS-UPDRS-III (*off* medication)	
Total score	38 [27; 42]
Tremor score treated side[a]	8 [6; 9]
Rigidity score treated side[b]	2 [2; 3]
Bradykinesia score treated side[c]	7 [5; 9.5]
MDS-UPDRS-III (*on* medication)	
Total score	22 [17; 31]
Tremor score treated side[a]	5 [4; 7]
Rigidity score treated side[b]	2 [1; 2]
Bradykinesia score treated side[c]	5 [2; 6]
PIGD score *off* medication[d]	1 [0; 2]
MDS-UPDRS-IV	0 [0; 2]
H&Y stage	2 [2; 2]
LEDD[e]	450 [300; 607.5] (min = 0, max = 1500)

Data are expressed as median [IQR] or mean ± standard deviation unless otherwise specified.

Abbreviations: SDR, skull density ratio; min, minimum; max, maximum; Vim, ventral intermediate; MDS-UPDRS-I, Movement Disorder Society Unified Parkinson's Disease Rating Scale Part I, non-motor aspects of experiences of daily living; MDS-UPDRS-II, Movement Disorder Society Unified Parkinson's Disease Rating Scale Part II, motor aspects of experiences of daily living; MDS-UPDRS-III, Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III, motor score; PIGD, postural instability/gait difficulty; MDS-UPDRS-IV, Movement Disorder Society Unified Parkinson's Disease Rating Scale Part IV, motor complications[21]; H&Y, Hoehn and Yahr; LEDD, levodopa equivalent daily dose.

[a]Sum of items 3.15–3.17 relative to the treated side.

[b]Sum of items 3.4–3.8 relative to the treated side.

[c]Sum of item 3.3 of upper and lower limbs relative to the treated side.

[d]Sum of items 2.12, 2.13, and 3.10–3.13.[18,19]

[e]LEDD was calculated using previously published conversion formulae.[23–25]

TABLE 2 *Demographic, clinical, and radiological characteristics of patients with tremor-dominant Parkinson's disease divided into responders (n = 40) and relapsers (n = 12) at baseline and follow-up*

	Baseline		1 mo		6 mo	
Characteristics	**Responders**	**Relapsers**	**Responders**	**Relapsers**	**Responders**	**Relapsers**
Sex, female, n (%)	7 (18%)	3 (25%)				
Disease duration, y	5 [4; 9]##	4 [3; 5]##				
Age, y	66 ± 7###	57 ± 13###				
SDR	0.56 ± 0.10	0.55 ± 0.13				
Left Vim, n (%)	24 (60%)	4 (33%)				
Clinical outcomes						
MDS-UPDRS-I	4 [2; 8]	9 [4; 11]	3 [2; 7]	9 [3; 10]	5 [2; 8]	9 [3; 11]
MDS-UPDRS-II	8 [5; 12]	6 [5; 9]	7 [3; 11]	5 [4; 11]	7 [3; 13]	5 [2; 7]
MDS-UPDRS-III (*off* medication)						
Total score	39 [29; 44]#	28 [22; 34]#	29 [20; 36]***	26 [21; 35]	27 [21; 33]***	29 [23; 34]
Tremor score treated side[a]	8 [6; 9]	7 [6; 9]	2 [1; 4]***	6 [5; 8]*	2 [1;4]***	7 [5; 9]
Tremor improvement, (%)[b]	—	—	67 [50; 83]#	14 [0; 17]#	65 [50; 81]##	5 [0; 17]##
Rest tremor treated side[c]	4 [3; 5]	4 [4; 5]	2 [1; 2]***	4 [3; 4]	2 [1; 3]***	4 [3; 5]
Action tremor treated side[d]	4 [3; 5]	3 [2; 4]	1 [0; 1]***	2 [2; 4]	1 [0; 2]***	3 [2; 4]
Rigidity score treated side[e]	3 [2; 3]	2 [1; 3]	2 [1; 2]***	1 [1; 3]	2 [1;3]	2 [1; 3]
Bradykinesia score treated side[f]	8 [5; 10]	6 [5; 8]	7 [5; 9]	6 [4; 8]	6 [5;8]	7 [4; 9]
MDS-UPDRS-III (*on* medication)						
Total score	24 [19; 31]	20 [13; 23]	17 [12; 20]***	18 [12; 23]	16 [11; 21]***	17 [12; 22]
PIGD score *off* medication[g]	1 [0; 3]	1 [0; 2]	1 [1; 2]	1 [0; 2]	1 [1; 2]	1 [1; 1]
MDS-UPDRS-IV	0 [0; 1]	0 [0; 3]	0 [0; 0]	0 [0; 3]	0 [0; 0]	0 [0; 1]
H&Y stage	2 [2; 2]	2 [2; 2]	2 [1; 2]	2 [2; 2]	2 [2; 2]	2 [1; 2]
LEDD (mg)[h]	473 [300; 608]	300 [175; 575]	460 [340; 582]	300 [175; 500]	473 [310; 620]	325 [175; 600]
Sonication parameters						
Total no. of sonications	11 [9; 13]	12 [8; 15]				
Sonications with T mean ≥55°C	2 [2; 3]	2 [1; 4]				
Sonications with T max ≥55°C	4 [3; 4]	3 [2; 6]				
Sonication duration, s[i]	21 [17; 27]	21 [14; 25]				
Energy, Joules[i]	14,963 [10,817; 22,096]	16,570 [10,749; 30,403]				

(Continues)

TABLE 2 *Continued*

Characteristics	Baseline		1 mo		6 mo	
	Responders	Relapsers	Responders	Relapsers	Responders	Relapsers
Power, watts[i]	779 [688; 844]	870 [729; 966]				
T mean (°C)[i]	57 [56; 58]	56 [55; 57]				
T max (°C)[i]	59 [58; 61]	59 [57; 61]				
Lesion coordinates[j]						
ACPC, mm	25.5 [25.0; 26.0]	25.3 [23.8; 26.0]				
x (laterolateral), mm	14.0 [13.0; 14.5]	13.6 [13.5; 14.5]				
y (anteroposterior), mm	7.5 [7.0; 8.5]	7.0 [6.0; 8.0]				
y (anteroposterior), % of ACPC	30 [27; 32]	28 [26; 31]				
z (superoinferior), mm	1.9 [1.3; 2.5]	1.5 [1.0; 1.7]				
Lesion volume, mm^3	24 h		1 mo			
T1w sequence	225 [173; 267][#] (min = 80; max = 500)	135 [86; 230][#] (min = 27; max = 300)	95 [60; 148]	50 [20; 145]		
T2w sequence[k]	308 [249; 384][##] (min = 143; max = 666)	196 [107; 263][##] (min = 48; max = 350)	NA	NA		
AEs[l]	24 h		1 mo		6 mo	
n (%)	27 (68%)	8 (67%)	18 (45%)	4 (33%)	8 (20%)	2 (17%)

Data are expressed as median [IQR] or mean ± standard deviation unless otherwise specified.
Abbreviations: SDR, skull density ratio; Vim, ventral intermediate; MDS-UPDRS-I, Movement Disorder Society Unified Parkinson's Disease Rating Scale Part I, non-motor aspects of experiences of daily living; MDS-UPDRS-II, Movement Disorder Society Unified Parkinson's Disease Rating Scale Part II, motor aspects of experiences of daily living; MDS-UPDRS-III, Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III, motor score; PIGD, postural instability/gait difficulty; MDS-UPDRS-IV, Movement Disorder Society Unified Parkinson's Disease Rating Scale Part IV, motor complications[21]; H&Y, Hoehn and Yahr; LEDD, levodopa equivalent daily dose; ACPC, anterior commissure-posterior commissure line; T1w, T1-weighted magnetic resonance imaging; min, minimum; max, maximum; T2w, T2-weighted magnetic resonance imaging; AE, adverse event.
★$P < 0.05$ compared with baseline values;
★★★$P < 0.001$ compared with baseline values.
[#]$P < 0.05$ between responders and relapsers;
[##]$P < 0.01$ between responders and relapsers;
[###]$P < 0.001$ between responders and relapsers.
[a]Sum of items 3.15–3.17 relative to the treated side.
[b](Tremor score at baseline − tremor score at 1- or 6-month follow-up)/tremor score at baseline; tremor score calculated as detailed in footnote a.
[c]Sum of items 3.15 and 3.16 relative to the treated side (postural and kinetic tremor of the upper limb).
[d]Sum of item 3.17 relative to the treated side (rest tremor of upper and lower limb).
[e]Sum of items 3.4–3.8 relative to the treated side.
[f]Sum of item 3.3 of upper and lower limbs relative to the treated side.
[g]Sum of items 2.12, 2.13, and 3.10–3.13.[19]
[h]LEDD calculated using conversion formulae previously published.[23–25]
[i]Only data of sonications with mean temperature ≥55°C were used to calculate these variables.
[j]Coordinates of the lesion are calculated on 24-hour T1w magnetic resonance imaging sequences; *x* (laterolateral) expresses the distance of the center of the lesion from midline; *y* (anteroposterior) expresses the distance of the center of the lesion from the posterior commissure in the anteroposterior axis calculated in absolute value and as a percentage of ACPC; *z* (superoinferior) expresses the distance of the center of the lesion from the axial plane passing through ACPC line (positive values indicate the *z* coordinate above the aforementioned axial plane).
[k]Lesion volume in T2 sequence was available for 39 patients.
[l]Thalamotomy-related AEs.[2]

[responders vs. relapsers] as dependent variable and age, disease duration, baseline MDS-UPDRS-III in *off* medication condition, SDR, and T1w lesion volume at 24 hours as explanatory variables) showed a significant association between type of outcome at 6 months (being classified in the responders' group) and age (OR = 1.13; 95% CI: 1.01–1.25; $P = 0.030$) and lesion volume (OR = 2.18; 95% CI: 1.08–4.43; $P = 0.030$). The relationship between T1w lesion volume at 24 hours and outcome is depicted in Figure 1A (black line), which shows the regression line for the predicted probability of being in the relapsers group (which decreases with the increase of lesion volume). ROC curve analysis showed that a lesion volume >145 mm^3

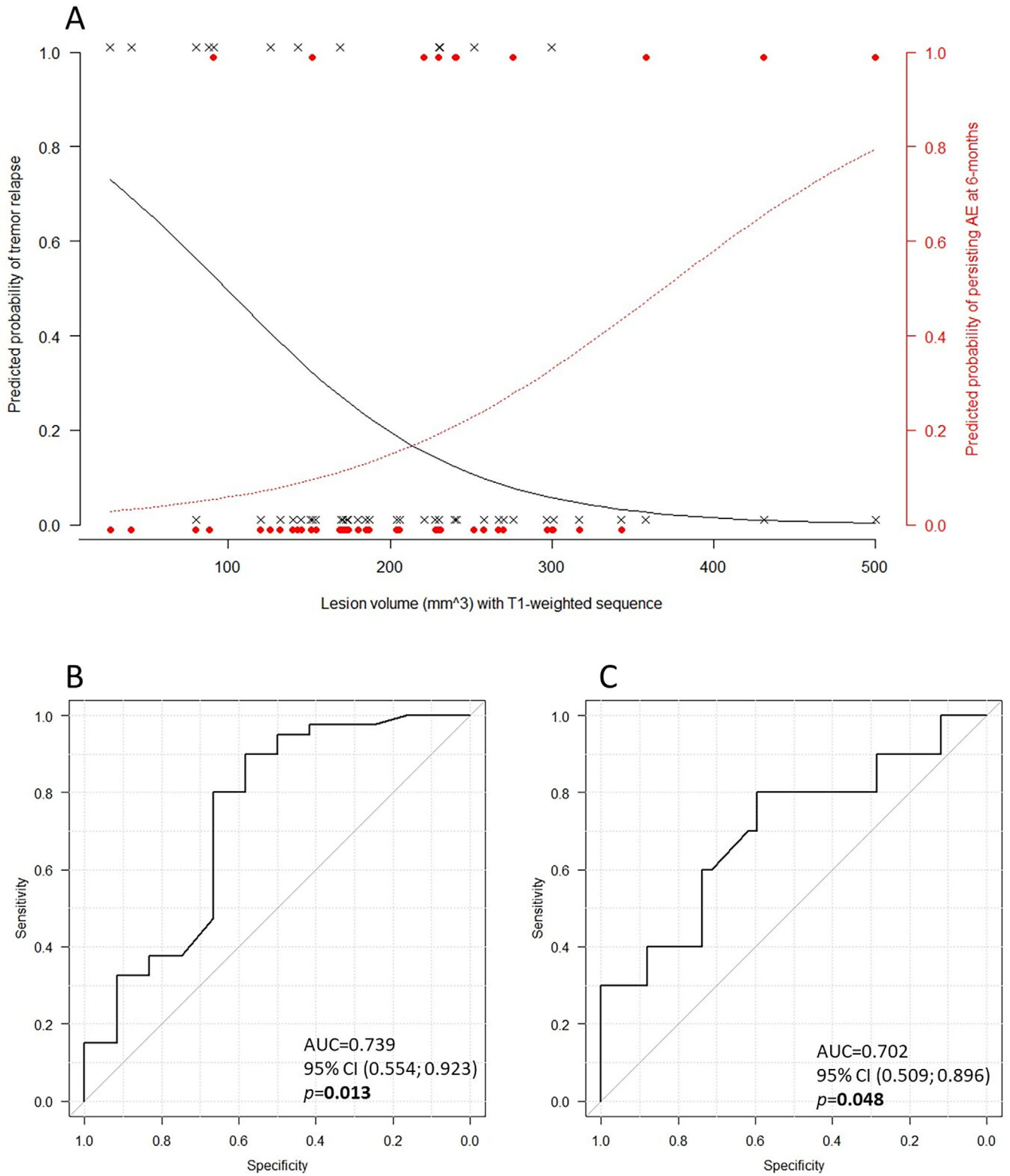

FIG. 1. (**A**) Regression lines for the predicted probability of tremor relapse (left *y* axis, black line; black crosses identify single patients) and for the persistence of adverse events (AEs) at 6 months (right *y* axis, red dotted line; red circles identify single patients). Receiver operating characteristic curves depict the relationship between lesion volume calculated on T1-weighted magnetic resonance imaging sequences at 24 hours postsurgery and type of outcome (responder vs. relapsers) at 6 months (**B**) and AEs (present vs. absent) at 6 months (**C**). AUC, area under the curve; CI, confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 *Thalamotomy-related[a] AEs at all time points*

	24 h (n = 52)	1 mo (n = 52)	6 mo (n = 52)	12 mo (n = 36)
Patients with one or more AEs, n (%)	35 (67%)	22 (42%)★	10 (19%)★★,#	6 (17%)★★,#
Type of AE, n (%)				
Imbalance	28 (54%)	12 (23%)	3 (6%)	2 (6%)
Perioral/hand paraesthesia	16 (31%)	11 (21%)	7 (13%)	4 (11%)
Motor weakness	7 (13%)	7 (13%)	3 (6%)	2 (6%)
Dysarthria	5 (10%)	4 (8%)	1 (2%)	0
Dysgeusia	4 (8%)	4 (8%)	2 (4%)	2 (6%)

Abbreviation: AE, adverse event.
★$P < 0.01$ compared with baseline value.
★★$P < 0.001$ compared with baseline value.
#$P < 0.01$ compared with 1 month.
[a]AEs due to the formation of the thalamic lesion (as reported by Bond et al[2]).

(calculated on 24-hour T1w sequences) has 90% sensitivity and 58% specificity in identifying responders (Fig. 1B). For age and outcome, the optimal cutoff value with 93% sensitivity and 58% specificity was 58 years of age (see Supporting Information for more details).

Using the lesion volumes in T2w sequences at 24 hours, we did not find statistically significant results in the multivariable logistic regression model (see Supporting Information for more details). The lesion volumes calculated on the 1-month T1w MRI did not significantly differ between responders and relapsers (see Table 2); accordingly, the univariate logistic regression model and ROC curve did not find statistically significant results (see Supporting Information).

Adverse Events

Overall, two-thirds of patients (67%) had at least one AE of any type. AEs are listed in Table 3. All AEs were categorized as mild according to the Clavien-Dindo scale, and their frequency significantly reduced over time ($P < 0.01$ at 1-, 6- and 12-month follow-up compared with the 24-hour assessment; see Table 3).

Comparison of AEs between responders and relapsers is reported in Table 2 (no significant difference was found between the two groups).

Multivariable logistic regression analysis for the presence or absence of AEs at any time point as independent variable and age, lesion volume in T1 and T2w sequences, and lesion coordinates showed the subsequent findings:

- 24 hours: The presence of a more dorsal lesion reduced the odds for AEs (OR = 0.45; 95% CI: 0.24–0.83; $P = 0.011$).
- 6 months: Larger lesion volumes were associated with increased odds for AEs (OR = 1.85; 95% CI: 1.11–3.08; $P = 0.018$).

Figure 1C shows ROC curve for the presence/absence of AEs at 6 months. Figure 1A (red dotted line) shows the regression line for the predicted probability of having persistent AEs at 6 months, which increases with the increase of lesion volume. Using 24-hour T1w sequences, a volume of 220 mm^3 has 80% specificity and 60% sensitivity in detecting patients with AEs persisting at 6 months.

Logistic regression analysis and ROC curves using the lesion volume calculated on 24-hour T2w and 1-month T1w sequences led to similar results (see Supporting Information).

Discussion

Our study overall confirms the effectiveness and safety of MRgFUS Vim thalamotomy for treating drug-resistant tremor in TdPD patients but highlights important findings on timing, frequency, and predictors of relapse.

All studies concerning PD patients undergoing MRgFUS Vim thalamotomy showed good efficacy in terms of tremor control[8,14,15,20,37-43]; however, poor response or tremor relapse has been described.[6,8,9,13,15,16,44] The heterogeneity in sample sizes, follow-up duration, timing of tremor recurrence, clinical scales used, and in some cases, the lack of information on patients' medication condition (*off* or *on* medication)[15,37,39,40] limit the interpretation and generalizability of the results to adequately improve clinical practice.

Frequency and Predictors of Tremor Relapse

In our cohort, we observed that 23% of TdPD patients experienced tremor recurrence within the first month after the procedure, and we found that the risk

of relapse is associated with smaller lesion volume at 24 hours and younger age at surgery.

On the contrary, lesion volume calculated 1 month after surgery did not differ between responders and relapsers and does not seem to be a good predictor of efficacy.

The rate and timing of tremor relapse that we observed may be similar to what was previously found in small series[13,15,17] and in a randomized controlled trial.[2] These data are in contrast with another study where tremor recurrence occurred in only 1 of 48 patients (2%) 3 months after MRgFUS Vim thalamotomy.[8] The definition of recurrence was different between our (loss of improvement below the 30% threshold) and these studies, and this may partially account for the different rates of tremor relapse.

Despite that lesion volumes 24 hours after surgery were significantly smaller in relapsers compared with responders, the lesions were still "sufficient" to guarantee an excellent immediate tremor control in all our patients.

Afterward, tremor score increased 1 month after surgery compared with the 24-hour evaluation (likely due to progressive reabsorption of postoperative edema),[12,28] although this phenomenon was clinically meaningful only in the relapsers.

We could postulate, first, that the early effect on tremor in relapsers was mainly associated with the presence of the perilesional vasogenic edema, which reduces in the first weeks, making the actual lesion of insufficient size to influence tremor circuitry; or second, that tremor relapse is sustained by an emerging pathogenetic contribution of areas beyond Vim.[1,45,46]

A small case series already suggested the probable relationship between tremor relapse after MRgFUS Vim thalamotomy and small lesion volume among TdPD patients.[38] Our lesion volume is, however, comparable with what has been found by other authors for both T1w[9] and T2w sequences images.[7,37] On the contrary, Chua et al[8] reported a mean lesion volume of $494.9 \pm 195.4\ mm^3$ the day after surgery (calculated on T2w sequences), which seems significantly larger compared with our study. Other studies measured only the diameter of the lesion,[14,15,38] and this does not allow direct comparison with our results.

So far, to the best of our knowledge, no studies reported a relationship between age at surgery and tremor control after MRgFUS Vim thalamotomy in TdPD patients. One possibility is that neural tissue in older patients could be more susceptible to sonications, favoring larger lesion volumes; a recent study found that the temperature during sonications correlated with the total volume of supratentorial gray matter, cerebrospinal fluid, and total intracranial volume, and these variables correlated with age.[47] Moreover, in younger patients, a lower responsiveness of tremor to dopaminergic treatment has been reported[48] and, similarly to our data, patients with better tremor improvement after dopaminergic therapy also had higher total baseline motor scores.[48] Sung et al[48] suggested that a different pathophysiology of tremor in younger compared with older PD patients could influence the response of tremor to different treatments.

Finally, a recent neurophysiological research study demonstrated higher neuronal plasticity in the motor cortex in younger compared with older individuals[49]; it is conceivable (albeit highly speculative) that younger patients may have greater neuronal plasticity also in subcortical structures and therefore may "restore" the tremor circuit more easily than older patients or may simply have a greater ability to self-repair the injured tissue.

It has been shown that the best target for tremor control in TdPD may be more anterior than in ET patients.[10] Because we did not find significant differences in lesion coordinates between responders and relapsers, we may exclude that tremor relapse was due to inaccurate lesion placement.

Interestingly, among responders, we found a significantly higher improvement in action tremor (which comprises postural and kinetic tremor) compared with rest tremor, confirming a recent study.[50] We also observed that relapsers had a shorter disease duration than responders, albeit this difference did not remain significant in multivariable logistic regression analysis. Rest tremor severity tends to reach a plateau of severity a few years after disease onset, is not a reliable marker of disease progression, and does not correlate with severity of nigrostriatal dysfunction but has been linked to serotoninergic dysfunction.[51-54] The shorter disease duration among relapsers may imply the presence of an ongoing progression of tremor that still did not reach the aforementioned plateau of severity.

In our study, we used MDS-UPDRS-III,[21] which, compared with the Fahn-Tolosa-Marin scale[55] (used in most studies on TdPD treated with MRgFUS Vim thalamotomy), does not evaluate drawing, pouring, or postural and kinetic tremor of the lower limbs. The more prominent impact of rest tremor in evaluating tremor score with MDS-UPDRS-III may partly explain our rate of relapsers. The transient improvement in rigidity may be explained by the temporary involvement of the more anterior ventral oralis (Vo) thalamic nucleus due to perilesional edema[50]; the Vo, in fact, receives pallido-thalamic fibers that may be involved in the improvement of this symptom.[56] Other authors reported a persistent improvement in rigidity, which may be associated with a larger lesion volume compared with our study.[8]

Safety

All AEs observed in our study were mild, and the frequency of thalamotomy-related AEs decreased

significantly over time. The AEs profile in our patients is similar to other studies.[3,9] Taking into account the progressive reduction over time and the relatively low frequency of AEs,[2,3,8,9] in our study a possible lower frequency of AEs persisting in long-term follow-up compared with others could be noted, in particular for motor weakness, ataxia, and imbalance.[2,8] As outlined in the Results, the low frequency of AEs in long-term follow-up is likely due to the smaller lesion volume in our cohort compared with other studies.[8]

Strengths and Limitations

We report a large prospective cohort of patients, carefully evaluated in both *off* medication (limiting pharmacological interference) and *on* medication conditions, ensuring systematic and homogeneous data collection; we analyzed lesion volumes in both T1w and T2w sequences, allowing easier comparison with other studies, and we provided a definition of relapse that could be adopted in future studies.

Among the limitations, we include the limited follow-up time and the lack of advanced preoperative neuroimaging[41] and neurophysiological[57] data, which limited the identification of other possible preoperative predictive factors. Moreover, the evaluation of anatomical relationships between the lesion and surrounding structures (eg, posterior sensory thalamic nuclei, corticospinal tract, and dentato-rubro-thalamic tract) may be important in predicting clinical efficacy and AEs.[58,59]

Based on our results, we suggest that a lesion volume between 145 and 220 mm^3 (measured on T1-w sequences 24 hours after surgery) may be ideal to determine a stable effect on tremor without long-lasting AEs. In two previous studies in patients with ET,[12,58] a lower recurrence of tremor at 3 months was demonstrated in patients with greater lesion volume 1 day after treatment, and a volume of 170 mm^3 on T1w sequence was identified as a cutoff beyond which a greater incidence of AEs occurred.

Our data might suggest that we treated our patients in a more conservative way (ie, producing smaller lesions), to ensure the best possible safety profile in the long term, but, in turn, the small lesion volume predisposed subjects to a higher tremor recurrence rate compared with other studies. Indeed, lesion volume and the surrounding vasogenic edema need to be accurately titrated to achieve a low prevalence of AEs and, at the same time, to ensure a stable effect on tremor.[8] Techniques to predict lesion size directly during surgery[60] are warranted to optimize the intraoperative clinical decision-making process.

In conclusion, our data confirm the efficacy and safety of Vim thalamotomy in TdPD patients but highlight the presence of a possible early tremor relapse, especially in younger subjects, associated with a small lesion volume. We provided evidence on the importance of lesion size in predicting stability of clinical effect and persistence of AEs. Larger studies are needed to optimize safety and efficacy of MRgFUS Vim thalamotomy in TdPD; moreover, studies addressing direct comparison of different targets are warranted and may help to identify a "patient-specific target" based on pretreatment characteristics. ■

Author Roles: 1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.
A.B.: 1A, 1B, 1C, 2A, 2C, 3A, 3B
N.G.A.: 1A, 1B, 1C, 2A, 2B, 3A, 3B
F.G.: 1B, 1C, 2B, 2C, 3B
D.A.: 1B, 1C, 2C, 3B
A.P.S.: 1B, 1C, 2C, 3B
R.C.: 1A, 1B, 1C, 2A, 2C, 3B
R.T.: 1B, 1C, 2C, 3B
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M.S.: 1A, 1C, 2A, 2C, 3B
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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The anonymized dataset will also be available on https://zenodo.org.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.