Targeting for stereotactic radiosurgical thalamotomy based on tremor treatment response

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OBJECTIVE Stereotactic radiosurgery (SRS) treats severe, medically refractory essential tremor and tremor-dominant Parkinson disease. However, the optimal target for SRS treatment within the thalamic ventral intermediate nucleus (VIM) is not clearly defined. This work evaluates the precision of the physician-selected VIM target, and determines the optimal SRS target within the VIM by correlation between early responders and nonresponders.

METHODS Early responders and nonresponders were assessed retrospectively by Elements Basal Ganglia Atlas autocounting of the VIM on the pre–SRS-treatment 1-mm slice thickness T1-weighted MRI and correlating the center of the post–SRS-treatment lesion. Using pre- and posttreatment diffusion tensor imaging, the fiber tracking package in the Elements software generated tremor-related tracts from autosegmented motor cortex, thalamus, red nucleus, and dentate nucleus. Autocounting of the VIM was successful for all patients.

RESULTS Among 23 patients, physician-directed SRS targets had a medial–lateral target range from +2.5 mm to −2.0 mm from the VIM center. Relative to the VIM center, the SRS isocenter target was 0.7–0.9 mm lateral for 6 early responders and 0.9–1.1 mm medial for 4 nonresponders (p = 0.019), and without differences in the other dimensions: 0.2 mm posterior and 0.6 mm superior. Dose–volume histogram analyses for the VIM had no significant differences between responders and nonresponders between 20 Gy and 140 Gy, mean or maximum dose, and dose to small volumes. Tractography data was obtained for 4 patients.

CONCLUSIONS For tremor control in early responders, the Elements Basal Ganglia Atlas autocontour for the VIM provides the optimal SRS target location that is 0.7–0.9 mm lateral to the VIM center.

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KEYWORDS stereotactic radiosurgery; tremor; thalamic ventral intermediate nucleus; autocontouring; isocenter target location; functional neurosurgery

Abbreviations: AC = anterior commissure; DBS = deep brain stimulation; DRTT = dentato-rubro-thalamic tract; DTI = diffusion tensor imaging; DVT = dose volume histogram; ET = essential tremor; FA = fractional anisotropy; FTM = Fahn-Tolosa-Marin; GKS = Gamma Knife surgery; IQR = interquartile range; LINAC = linear accelerator; PC = posterior commissure; QUEST = Quality of Life in Essential Tremor Questionnaire; SRS = stereotactic radiosurgery; VIM = ventral intermediate nucleus of the thalamus.

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Frameless LINAC-based SRS thalamotomy has been performed at our facility since 2012, generating one of the largest single-institution experiences. We previously showed in end-to-end analysis in patients that the 3D alignment accuracy was 1.1 mm and provided submillimeter accuracy within each axis. 7 An interim analysis of our clinical results shows success comparable to GKS, with approximately 80% of patients showing objective clinical improvement.11 Multiple published GKS case series show that 10%–25% of patients have an inadequate response.12-15 A likely reason for this lack of efficacy is target inaccuracy. The thalamic Vim target is based on anatomical measurements and these vary within a range of several millimeters among the published case series, typically determined by the neurosurgeon’s and radiation oncologist’s experience based on Schaltenbrand atlas coordinates.16 We hypothesize that the precise target isocenter position within the Vim correlates with response to treatment. We further hypothesize that an optimal target selection based on individual anatomical detail will correlate with good treatment response and provide a more consistent targeting system that will improve the reliability of clinical outcomes.

Responses to SRS typically occur during the first 12 months after treatment and are stable for years.5,13 In this project, we sought to determine the ideal target location within the Vim by using an automated neuroanatomy contouring system. We retrospectively studied early clinical responders showing significant improvement at 3 months and compared them to nonresponders whose tremor did not improve during 12 months after SRS. We determined the relationship between the autocontoured Vim structure and the target isocenter location, including the posttreatment brain lesion seen on MRI. We also investigated the potential implementation of diffusion tensor imaging (DTI) MRI to assist in finding the optimal target location, as well as study the impact of SRS on the white matter tracts that are involved in the generation of tremor.

Methods

SRS was performed using the Novalis Tx (Varian) LINAC. The treatment target was identified by a single neurosurgeon (J.S.N. or H.Y.) and verified by a single radiation oncologist (A.J.C. or A.N.K.). The target location was selected by an atlas-based coordinate system derived from the Schaltenbrand atlas,16 further refined from an in-house database of patients receiving deep brain stimulator implantations with good response, and manually adjusted by the neurosurgeon and radiation oncologist. The in-house database was created by deep brain stimulator implantation imaging fused to MR images with a system-selected, best matching anatomy. The location of the active electrode was used as the treatment target. The target location is expressed in the axial system aligning the anterior commissure and posterior commissure in a single plane. The target is typically 6 mm anterior to the posterior commissure, 11 mm lateral from the third ventricle wall, and 4 mm superior. The coordinate system (X, Y, Z) is defined with the patient’s head in a neutral head holder (“A style” for men and “B style” for women [Silverman, Civco]), wearing a custom-fit thermoplastic head SRS mask (#F706B; Innovative Oncology Solutions). All patients were treated with 145- to 160-Gy maximum point dose using noninvasive thermoplastic SRS mask–based immobilization; 0.75-mm thickness CT simulation (resolution 512 × 512) on a Philips Brilliance Big-Bore scanner (Philips); 3D high-resolution T1-weighted brain MRI (voxel size 0.5 mm × 0.5 mm × 1 mm); iPlan treatment planning software (Brainlab AG); the Novalis Tx LINAC with 4-mm circular cone applicator; and ExacTrac stereoscopic kV imaging performed at every table angle with treatment alignment tolerances of 0.5-mm translational and 0.5° rotational. The ExacTrac isocenter is calibrated to be within 0.3 mm to radiation isocenter of the LINAC based on the Winston-Lutz test.7

Patients underwent assessments by quality of life questionnaires (Quality of Life in Essential Tremor Questionnaire [QUEST] or the 39-Item Parkinson Disease Questionnaire [i.e., the PDQ-39]) and objective tremor-rating assessment by the Fahn-Tolosa-Marin (FTM) scale at baseline (pretreatment) and 3 months after SRS.11,17-20 Compared to pretreatment baseline, early clinical responders were defined as patients who had improved at 3 months after SRS by at least 10 scale points in the following 4 items on the QUEST questionnaire: dominant hand tremor severity, writing ability, using a computer, and drinking liquids; and/or had improved ≥ 3 scale points in tremor rating severity in writing and pouring liquids on the FTM assessment. Nonresponders had no change in the QUEST and FTM assessments (0–2 scale points) at 3 months after SRS and did not improve by 12 months. Judging from these standards, 6 patients (cases 1, 2, 3, 5, 25, and 27) were early responders and 4 patients (cases 12, 13, 16, and 20) were nonresponders (Supplementary Table 1).

Elements software (Brainlab) was used to analyze all imaging, including CT and pre- and posttreatment MRI. The MRI scans were also processed with the Elements distortion correction cranial algorithm based on the MR–CT registration, and new MRI data sets with correction were generated. The Vim was autocontoured using the Elements Basal Ganglia Atlas (version 3.5.0.41 beta) on all uncorrected and corrected pretreatment MRI scans. Pretreatment DTI sequences were available for the patients in cases 24–27, who underwent scanning with the Philips MRI scanner with 32 directions and a resolution of 2 mm × 2 mm × 2 mm. Relevant tracts were created by the fiber tracking package in the Elements software with deterministic algorithm. Research has shown that increased activity involving the dentato-rubro-thalamic tract (DRTT) plays an important role in tremor.21-23 The related regions of interest, including the unilateral motor cortex, thalamus, red nucleus, and contralateral dentate nucleus were autosegmented with the Elements Basal Ganglia Atlas software package, and then fiber tracking was performed with the following settings: minimum fractional anisotropy (FA) 0.2, minimum length 40 mm, and maximum angulation 90°.

Contours, image scans, and image registrations were exported from the Elements software to the Eclipse treatment planning system (Varian) to analyze dose–volume...
cohort, patient demographics showed no significant differences between 6 early-responding patients and 4 non-responders, with median age 76.4 (12.8 IQR) years versus 81.8 (9.3 IQR) years (p = 0.32), male sex in 83% versus 75% (p = 0.81), and ET in 67% versus 75% (p = 0.78).

The patient-specific autocontour for the VIM was successfully generated on the pretreatment high-resolution T1-weighted native MRI series, as well as on the distortion-corrected MRI series. Among 23 patients studied, the VIM volume was 0.125 ± 0.020 cm³ (range 0.090–0.170 cm³), which did not differ significantly from the VIM volume of 0.129 ± 0.021 cm³ (range 0.091–0.179 cm³) on the distortion-corrected MR images (p = 0.55).

At 3 months after SRS, 15 patients had qualified MRI scans showing a lesion whose mean volume was 0.075 ± 0.049 cm³ (range 0.010–0.170 cm³) on native MR images, which did not differ significantly from the mean lesion volume of 0.080 ± 0.055 cm³ (range 0.008–0.18 cm³) on the distortion-corrected MR images (p = 0.65). Next, an analysis was performed for the overlapping volumes between the posttreatment SRS lesion and pretreatment VIM by registering pre- and posttreatment MRI scans. The SRS lesion intersects with 25.9% ± 13.9% of the VIM volume on the uncorrected MRI scans, which was not significantly different from the distortion-corrected MR images showing that the SRS lesion occupies 27.1% ± 16.4% of the VIM volume (p > 0.55). Fig. 1 shows the pretreatment VIM volume, the DRTT fiber tracked from DTI and the post-SRS-treatment lesion volume, and percentage of the VIM volume (p > 0.55). Fig. 1 shows the pretreatment VIM volume, the DRTT fiber tracked from DTI and the post-SRS lesion fused together for the patient in case 25, who was one of the early responders.

Reproducibility in the physician-derived SRS target isocenter was analyzed. Relative to the geometrical center of the VIM autocontour, the average treatment isocenter coordinates were 0.3 ± 0.2 mm lateral, 0.6 ± 0.3 mm anterior, and 0.1 ± 0.3 mm inferior (mean ± SEM). However, there was a large range of these relative coordinates, extending up to 2.5 mm laterally, 2.0 mm medially, 2.8 mm anteriorly, 2.4 mm posteriorly, 2.0 mm superiorly, and 2.5 mm inferiorly. The 3D distance for the relative position between the VIM center and the treatment isocenter was 2.0 mm on average, with a range of 3.3–6.6 mm. No statistically significant differences in relative coordinates were found between physicians. Analyses using the data from the distortion-corrected MRI series showed similar findings compared to the uncorrected MRI series (data not shown).

We hypothesized that early responders versus non-responders may have differences related to the VIM. Data from 6 clinically early-responding patients and 4 non-responding patients were compared. First, no significant differences were identified in autocontoured VIM volume, post-SRS-treatment lesion volume, and percentage of
overlap between the two volumes. Next, the radiation dose coverage of the autocontoured VIM structure was studied. DVHs at 20-Gy dose increments between 20 Gy and 140 Gy were analyzed, as well as the dose to 0.1, 0.05, and 0.035 cm³; maximum point dose; and mean dose to the VIM structure. The dose to 0.1 cm³ of the autocontoured VIM is significantly higher in the responders (3002 cGy) than nonresponders (1986 cGy), for the native MRI data set (p = 0.04). The data are listed in Table 1.

Examining the coverage of the autocontoured VIM at 20-Gy dose intervals, no statistically significant differences were found for VIM coverage at any DVH level between responders and nonresponders (Fig. 2A). The distortion-corrected MRI series were similarly analyzed using the autocontoured VIM, and showed no significant differences in the VIM DVH between responders and nonresponders (Fig. 2B). However, there was a trend for superior coverage in the responders versus nonresponders at the 20-Gy isodose level, both in the native MRI (p = 0.08 and p = 0.11) and the distortion-corrected MRI (p = 0.06 and p = 0.11), by 2-way ANOVA and Mann-Whitney U-test, respectively.

Next, the physician-selected SRS target isocenter was compared to the geometrical center of the VIM autocontour for the early-responding patients versus the nonresponding patients. Relative to the center of the VIM, the treatment isocenter was 0.9 ± 0.2 mm lateral in the early-responding patients compared to 0.9 ± 0.5 mm medial (mean ± SEM) (p = 0.019) (Fig. 3A). There were no statistically significant differences in the other dimensions: 0.2 ± 0.5 mm posterior and 0.6 ± 0.4 mm superior, compared to 0.4 ± 0.4 mm posterior and 0.2 ± 0.8 mm superior for responders and nonresponders, respectively (mean ± SEM). Analysis of the distortion-corrected MRI showed similar findings, with treatment isocenter being 0.7 ± 0.2 mm lateral to the VIM center in the responders compared to 1.1 ± 0.5 mm medial in the nonresponders (p = 0.019), and no significant differences for the other dimensions (mean ± SEM) (Fig. 3B).

A confirmatory analysis was performed by comparing the geometrical center of the posttreatment lesions for the responders and nonresponders as manually contoured on the 3-month posttreatment MRI scan relative to the autocontoured VIM geometrical center on the pretreatment MRI. Relative to the VIM center, the posttreatment lesion center was 0.5 ± 0.1 mm lateral in responders compared to 1.1 ± 0.5 mm medial in nonresponders (mean ± SEM) (p = 0.014) (Fig. 3C). The anteroposterior and superoinferior directions did not show significant differences for the posttreatment lesion center relative to the VIM center between responders and nonresponders. The distortion-corrected MRI showed similar findings, with the posttreatment lesion center 0.6 ± 0.1 mm lateral in responders compared to 1.1 ± 0.5 mm medial in nonresponders (mean ± SEM) (p = 0.010) (Fig. 3D).

To explore additional methods of determining the optimal treatment isocenter, DTI MRI series were acquired before and after SRS in the patients in cases 24–27. The DRTT structure was generated from the autocontoured regions of interest. The characteristics of the tracked fibers, including average FA, mean fiber length, and volume of the tracked fibers are listed in Table 2 for pretreatment

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**Table 1. Autocontoured VIM data for treatment responders and nonresponders**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Native MRI</th>
<th>Distortion-Corrected MRI</th>
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<tbody>
<tr>
<td>VIM vol in cm³ (range)</td>
<td>0.133 ± 0.016 (0.114–0.150)</td>
<td>0.131 ± 0.039 (0.097–0.170)</td>
</tr>
<tr>
<td>Post-Tx lesion vol in cm³ (range)</td>
<td>0.081 ± 0.054 (0.010–0.170)</td>
<td>0.065 ± 0.037 (0.020–0.109)</td>
</tr>
<tr>
<td>% VIM overlap w/post-Tx lesion</td>
<td>26.8 ± 14.9</td>
<td>24.1 ± 12.2</td>
</tr>
<tr>
<td>Max dose ± SD (cGy)</td>
<td>15669 ± 298</td>
<td>15884 ± 124</td>
</tr>
<tr>
<td>Dose to 0.1 cm³ of VIM ± SD (cGy)</td>
<td>1986 ± 753</td>
<td>0.04</td>
</tr>
<tr>
<td>Dose to 0.05 cm² of VIM ± SD (cGy)</td>
<td>5402 ± 861</td>
<td>0.61</td>
</tr>
<tr>
<td>Dose to 0.035 cm² of VIM ± SD (cGy)</td>
<td>7175 ± 938</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Max = maximum; Tx = treatment.

Values are expressed as the mean ± SD (range). Boldface type indicates statistical significance. There were no significant differences between early responders and nonresponders, using the native MRI or distortion-corrected MRI, for the autocontoured VIM volume, posttreatment lesion volume, or percentage of VIM overlap with the posttreatment lesion. For dose parameters, there were no differences between categories for the maximum radiation dose as well as dose to 0.05 cm³ and 0.035 cm³ of the VIM, but the dose to 0.1 cm³ of VIM was significantly different for the native MRI for early responders and nonresponders.
and at least 2 posttreatment MRI scans. For the patients in cases 24 and 26, fiber tracking was unsuccessful at 3 months posttreatment, whereas for the patients in cases 25 and 27, fiber tracking was unsuccessful starting at 6 months posttreatment, showing the response patterns over several months after SRS.

**Discussion**

Successful delivery of SRS thalamotomy requires a 2-fold approach: the appropriate location of the isocenter target and the accurate delivery of radiation to the planned target position. For the delivery accuracy, we demonstrated that our delivered isocenter is within 1.1 mm of the intended target by overlapping the posttreatment lesion to the planned isocenter.\(^7\) Given that response from radiation therapy is a delayed reaction, predetermination of the treatment target is more crucial for SRS thalamotomy than for DBS or radiofrequency ablation procedures, in which the target can be adjusted according to a patient’s response during the procedure. In our current treatment protocol, the location of the target is initially derived from historical atlases, refined by a database of patients with deep brain stimulator implants, and then adjusted at the physician’s discretion. Although our current practice can benefit most patients, we aim to improve the treatment outcome by locating the optimal target directly from MR images with comparison of the early clinical responders and nonresponders.

Numerous studies have shown that the VIM is the target for successful deep brain stimulator implantation and radiofrequency ablation. Autocontouring of brain substructures was successfully performed by the Elements software on all the qualified imaging series. The VIM was appropriate in location, size, and shape, according to accepted neuroanatomical information.\(^{24,25}\)

After mapping the isocenter to the autocontoured VIM, we found that our treated patients had a large range of isocenter positions relative to the VIM center—up to 2.8 mm in a single direction. The differences in all 6 directions (lateral–medial, anterior–posterior, and superior–inferior) were compared for groups of early responders and nonresponders. The only direction that appears to be associated with patient response is the medial–lateral position. Specifically, relative to the autocontoured VIM center, the responders had an isocenter position that was 0.9 ± 0.2 mm lateral and a posttreatment lesion center that was 0.5 ± 0.1 mm lateral (mean ± SEM). In contrast, nonresponders had a relative isocenter position that was 0.9 ± 0.5 mm medial to the VIM center and a posttreatment lesion that was 1.1 ± 0.5 mm medial (mean ± SEM). This statistically significant finding suggests that the optimal isocenter position for clinical response is 0.5–0.9 mm lateral to the autocontoured VIM geometrical center. Very similar results were obtained for both native and distortion-corrected MR images. It is likely that our MRI scanners were appropriately optimized to minimize geometrical distortion, especially near the center of the head where the echo planar spin echo MR scan is minimally distorted.

We investigated whether there were any correlations between early responders and nonresponders for DVH values, including volumes at 20-Gy intervals up to 140 Gy, mean dose, maximum dose, and dose to small volumes of the VIM. The only statistically significant difference was identified in the dose to 0.1 cm\(^3\) of autocontoured VIM structure, being slightly higher (at 30 Gy) in the responders compared to 20 Gy in the nonresponders. No correlations were found in any other of these parameters, although there was a trend toward significance at the 20-Gy isodose level. This finding may be due to the fact that the high-dose region resulting from a 4-mm cone is relatively small compared with the volume of the VIM structure. Therefore, as long as the isocenter is not too far from the center of VIM, the DVH at the high-dose level to VIM will be within the VIM and therefore similar on analysis of dosimetric parameters. In other words, once the maximum dose exceeds a certain threshold, the key correlation with tremor-control outcome appears to be the precise location where the high dose is deposited, not how much VIM is irradiated. Except for the low-dose range (20–30 Gy), the DVH-related values are not sensitive to where the isocenter is located and cannot be used as a predictor for good patient outcome.
The DTI fiber tracking can potentially provide another way of locating the isocenter. In this project, DRTTs were created by the Elements software with a deterministic algorithm for a few patients. A logical speculation is that the optimal location should be situated where the DRTT overlaps with the VIM contour. Even though this is true (as shown in Fig. 1 for the patient in case 25) and for the patient in case 27 (not shown), we cannot make a definitive conclusion due to limited data from only 2 patients with pretreatment DTI data in the early responders and non-responders cohort. We therefore expanded the analysis to include 4 patients: 2 early responders and 2 late responders. In all cases, the DRTT appears to be disrupted by 6–8 months after SRS, which suggests that the treatment-related outcome mechanism involves this tract. Furthermore, the DRTT passes the VIM laterally and inferiorly, which could explain why all the early responders have an isocenter located laterally to the VIM center. The expected white matter damage is consistent with decreased DTI fiber length in all patients analyzed posttreatment, although this includes early responders and late responders.

There are multiple challenges to determine the optimal treatment target inside the VIM with either autosegmentation or DTI. For example, the autosegmentation of VIM with Elements software is atlas based, not directly imaged, and that can impose some uncertainty. There are other imaging modalities and techniques that can be used to directly map subthalamic structures, including susceptibility-weighted...
imaging with stronger magnetic fields.26–31 However, even if direct imaging of the VIM is clinically available, this work shows that the 0.7–0.9 mm lateral to geometrical center of the VIM is probably the optimal target location. DTI fiber tracking can potentially provide another way to locate the optimal treatment isocenter, because the DTTT fibers probably intersect with the target. The challenge with DTI, however, is that resolution is somewhat limited given the current clinical equipment and software available at most medical facilities. We suspect that improved imaging modalities in the future will continue to enhance the ability to identify the optimal target location.

Although the treatment outcome data are acquired prospectively to identify responders and nonresponders, the weakness of this study includes the limited and unparallelized sample sizes. Unfortunately, the DTI data are available for very few patients in our study. For future study, we will standardize the imaging process to improve the completeness of data sets for every patient. Other probabilistic fiber tracking algorithms can also be used to analyze our data.

Conclusions

SRS for tremor is a high-dose radiation treatment that requires extreme precision in selecting the optimal target location for clinical success. For early clinical response, the patient-specific autocontour of the thalamic VIM using Elements software identifies the optimal isocenter that is 0.7–0.9 mm lateral to the VIM geometrical center. DTI data can also potentially aid with deriving the treatment location for clinical success. For early clinical response, the patient-specific autocontour of the thalamic VIM using Elements software identifies the optimal isocenter that is 0.7–0.9 mm lateral to the VIM geometrical center. DTI data can also potentially aid with deriving the treatment location for clinical success.

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table 2. DRTT fiber characteristics for SRS-treated patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 24</th>
<th>Case 25</th>
<th>Case 26</th>
<th>Case 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Tx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average FA</td>
<td>0.49</td>
<td>0.43</td>
<td>0.47</td>
<td>0.37</td>
</tr>
<tr>
<td>Mean fiber length (mm)</td>
<td>125</td>
<td>151</td>
<td>110</td>
<td>138</td>
</tr>
<tr>
<td>Vol (cm³)</td>
<td>2.62</td>
<td>1.69</td>
<td>1.86</td>
<td>0.5</td>
</tr>
<tr>
<td>Post-Tx group 1 (3 mos)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average FA</td>
<td>NA</td>
<td>0.47</td>
<td>NA</td>
<td>0.38</td>
</tr>
<tr>
<td>Mean fiber length (mm)</td>
<td>NA</td>
<td>132</td>
<td>NA</td>
<td>121</td>
</tr>
<tr>
<td>Vol (cm³)</td>
<td>NA</td>
<td>2.55</td>
<td>NA</td>
<td>0.78</td>
</tr>
<tr>
<td>Post-Tx group 2 (6–8 mos)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average FA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mean fiber length (mm)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vol (cm³)</td>
<td>NA</td>
<td>NA</td>
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</tr>
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</table>

NA = not applicable.

Tracts could not be generated (i.e., NA) for all 4 patients at 6–8 months after SRS, suggesting that the lesion successfully interrupted the DRTT.

References